Seizures in Critical Care
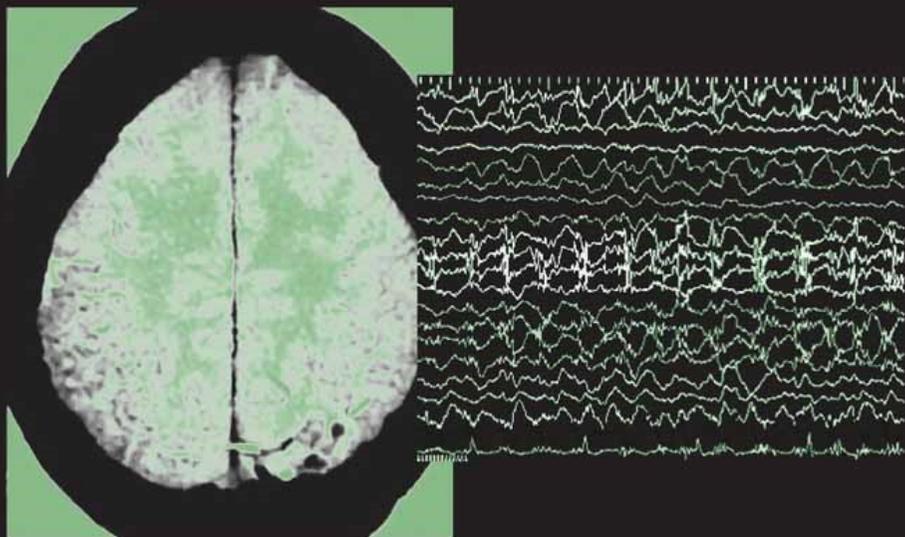
A Guide to Diagnosis and Therapeutics

Edited by

Panayiotis N. Varelas, MD, PhD

Seizures in Critical Care

CURRENT CLINICAL NEUROLOGY

Daniel Tarsy, MD, SERIES EDITOR

Seizures in Critical Care

A Guide to Diagnosis and Therapeutics

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Foreword by

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Series Editor's Introduction

   The evaluation and treatment of seizures in the very demanding environment of the critical care setting has not received sufficient attention in a focused monograph on the subject. *Seizures in Critical Care: A Guide to Diagnosis and Therapeutics* fills that need extremely well and serves as an indispensable companion to previous works in the Current Clinical Neurology Series, *Seizures: Medical Causes and Management* by Delanty, *Critical Care Neurology and Neurosurgery* by Suarez, and *Handbook of Neurocritical Care* by Bhardwaj, Mirski, and Ulatowski. The two volumes on critical care contain excellent chapters concerning management of status epilepticus. The current volume fills out the field by adding invaluable information concerning the wide range of specific critical care situations in which seizures of all types occur and how they are best managed in those contexts.

   Seizures are a very concerning and frightening event. As repeatedly pointed out in this volume, the incidence of seizures in various underlying medical and neurological disorders is astonishingly high. When they occur in the intensive care unit setting, they are nearly always symptomatic of serious underlying medical derangements and are often perceived, correctly or incorrectly, as heralding a significant downturn in the patient's clinical course. In the particular case of hypoxic–ischemic brain injury, they have been thought to be predictive of adverse outcomes that, as indicated by Drs. Koenig and Geocadin, may not necessarily be the case.

   Management of seizures begins with their prompt recognition and differentiation from other types of involuntary movements and changes in mental status which frequently occur in seriously ill patients. In particular, the surprising frequency with which nonconvulsive status epilepticus presents in the intensive care unit and how often it is missed underscores the need for careful clinical evaluation and the timely use of bedside electroencephalography in making this diagnosis. Because "seizures beget seizures" the urgency of prompt diagnosis and early effective treatment is paramount. Treatment of seizures begins with the identification and management of the usual suspects, such as metabolic, electrolyte, infectious, vascular, and pharmacologic contributors. The use of anticonvulsants requires particular skill in patients with organ failure and in patients being treated with numerous other drugs capable of interacting with anticonvulsants. All of these issues are addressed in great depth and with considerable sophistication by the impressive array of contributors to this volume.

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Foreword

Seizures and Critical Care: A Guide to Diagnosis and Therapeutics is a gem among monographs, as well as a tribute to the creativity, insight, and hard work of its editor. The idea itself is totally new. Now that it is complete and before me in finished form, I find myself wondering why this was never done before. It was a challenge to define all the issues, and then find a set of authors to soundly and comprehensively address the identified issues. The topic has been circumscribed for the first time.

In its final form, *Seizures and Critical Care: A Guide to Diagnosis and Therapeutics* is practically a text of epilepsy, even in a way a text of medicine. The number of situations in which seizures are precipitated, particularly in an intensive care unit (ICU) setting, recapitulates the systems of the body and the ways in which their altered functions affect the nervous system (and other systems). The brain responds to extreme malfunction of any system in a variety of ways, one of which is almost always the possibility of seizure. Understanding the manner in which this might occur, and the many approaches to diagnosis and treatment, is critical to progress in intensive care. This is all the more important because of the fragile situation often faced by the clinician caring for patients in an ICU setting, in which multiple other systems and derangements, as well as treatments and drug interactions, must be considered in the appropriate selection of therapy, monitoring, and followup. All of those aspects are recognized and addressed.

Just as the brain may respond to extreme malfunction of any and all systems with seizures, the clinician responds to seizures with a variety of approaches, some of which are inherently incorrect for some situations, even while preferred in others. Seizures in the intensive care setting may precipitate additional systemic or central nervous system compromise requiring compatible and thoughtful handling. If initial treatment fails, the steps to be followed may be novel, and require consideration of the myriad of other health risks in this setting. We need guidelines for diagnosis, selection of treatment, implementation of treatment, and assessment of outcome. Furthermore, where no answer exists, we need a balanced consideration of the areas of controversy.

Seizures and Critical Care: A Guide to Diagnosis and Therapeutics therefore fills a need we may not have even realized exists. It updates multiple antiquated misconceptions by discussing old controversies and finalizing some reasonable approaches and conclusions. It defines other controversies and objectively considers the data available, and the aspects that remain unknown.

The authoritative reviews with many references are welcome additions to our literature. The uniform format incorporating epidemiology and incidence, pathophysiology, diagnostic and treatment interventions, and outcome and its measure-

ment make it easy to read and approach each chapter. The reviews are comprehensive, accurate, well written, and unique in this field. The book will be of use to almost anyone who manages patients in a neurological or general medical or surgical intensive care setting.

I am proud to say that I had some part in the education and development of Dr. Varelas and was able to observe the formation of the idea, the process, and the completion of this most remarkable and useful work. It will certainly bring critical care neurology to a higher level, while identifying potential areas of fruitful and important research for the future.

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Preface

Seizures are devastating events in a person's life. Their very presence suggests that something is wrong with the brain. In some regions, seizures are believed to be caused by spirits; and in others, they are a "sacred illness," either a curse or a reason for awe. As a result of my training at Yale University, which has one of the best epilepsy centers in North America, and because I am married to an epileptologist, I have had extensive exposure to the study of seizures. Consequently, I could not escape their spell.

I became intrigued by the diversity of their presentation and fascinated by the possibility that various simple or complex behaviors, within the normal or abnormal range, could be explained by such an "obsolete" machine as the electroencephalograph (EEG). Later, after my training as a neurointensivist, my interest grew further as I was trying to find treatable causes in somnolent or comatose patients with various brain injuries in the intensive care unit (ICU). The simplistic and mechanistic suspicion that the patient's clinical status resulted from an electrical discharge of the brain led, I am sure, to several unnecessary requests for EEGs and trials of antiepileptics. Fortunately, I also had some unexpected successes.

I started looking at the issue of seizures more closely and had revealing discussions with my peers, especially those who were not neurointensivists. To my surprise, two facts emerged: first, many in the ICU community did not know what to seek, what to expect, and how and when to treat for seizure; and second, while reviewing the literature, I found little information. Most of the articles were reporting small, uncontrolled series or personal experiences. Few studies were conducted in the complex environment of an ICU. Very often, as with my personal experience, doubts regarding the epileptic nature of the phenomenon lingered. EEG, the gold-standard test, was difficult to interpret or inconsistently ordered. In many cases, seizures could be explained by more than one mechanism. In other cases, the response could be attributed not so much to the administration of the usual antiepileptics, but to the correction of more systemic derangements. Interactions between ICU medications and antiepileptics were frequent and puzzling to the treating physicians. Several antiepileptics either were not available for parenteral administration or were contraindicated because of specific organ failure. Finally, the newer antiepileptics were not well known and were seldom used in the ICU. It did not take me long to decide to edit a book regarding seizures in the ICU.

Seizures in Critical Care: A Guide to Diagnosis and Therapeutics is a collaborative effort. Experts in both the ICU and epilepsy fields from North America and Europe contributed chapters to this volume. I have tried to confine the content to the most common and interesting topics in the ICU. Norman Delanty's book, *Seizures: Medical Causes and Management*, served as the starting point in many

cases; however, the scope of this book is different. This book is much more balanced toward central nervous system insults, which can occur in the ICU. I encouraged authors to reference personal experiences and requested that they provide many authentic ICU cases with EEGs and neuroimages. Where data were lacking or information was contradictory—a very common situation indeed—the authors were advised to provide raw data and expert advice.

Our hope is that *Seizures in Critical Care: A Guide to Diagnosis and Therapeutics* can serve as a useful aid in the everyday ICU and in neurological practice for intensivists, neurologists, neurosurgeons, and any other healthcare professional or student in this expanding field. Most importantly in my mind, but less directly, it should constitute a testimony to the paucity of data in the field and become a starting point for well-organized research in the future.

I dedicate this effort to my parents, my grandfather (the shining star of my life), and all my teachers, who taught me the "ζειν" (living) and "ευ ζειν" (living well) of the ancients. I am also very grateful to all my coauthors, who did an excellent job, and especially to my wife, Marianna, for her indirect contribution and support.

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Presentation and Pathophysiology of Seizures in the Critical Care Environment

An Overview

Marek A. Mirski

SUMMARY

Seizures represent stereotypic electroencephalographic (EEG) and behavioral paroxysms as a consequence of electrical neurological derangement. Seizures are usually described as focal or generalized motor convulsions. Other, nonconvulsive seizure types are common as well and require vigilant patient evaluation for optimal detection. Owing to the admission diagnoses and physiological derangements common to critically ill patients, the intensive care unit (ICU) hosts conditions appropriate for the manifestation of the entire spectrum of seizure disorders. Common etiologies of seizures in the ICU entail primary neurological pathology or secondary to critical illness and clinical management. Alterations in neurotransmitter sensitivity via up- or down regulation of receptors, a decrease in inhibition, or alterations in membrane pump functions may contribute to the high incidence of seizures in an ICU. Particularly prevalent as precipitants of seizures are hypoxia/ischemia, mass lesions, drug toxicity, and metabolic abnormalities. For optimal treatment, early diagnosis of the seizure type and its cause is important to ensure appropriate therapy. Most seizures and their recurrence are easily treated, and attention is focused on ascertaining the cause and correcting any medical abnormality. Convulsive status epilepticus, which represents the most feared seizure state, requires emergent treatment to prevent irreversible brain injury and severe metabolic disturbances. Treatment of seizures with anticonvulsants in an ICU is not without risks, and appropriate judgment and selection of therapeutic drugs are important.

Key Words: Critical care; seizures; pathophysiology; GABA receptors; nonconvulsive status; convulsive status epilepticus.

INTRODUCTION

Over the past several decades, a collective attempt has been made to define the precise circuitry of brain elements important in seizure expression, together with the physiological mechanisms that ignite these paroxysms. Such answers, in theory, would provide the necessary clues to successfully inhibit and prevent the ictal process. Nature, of course, thwarts our attempts to simplify the human condition, and perhaps the most unsettling physiological constraint is our inability to comprehend the intricacies of brain function. Seizures lie within that neurological realm.

In a comparative manner, the complex care environment of the intensive care unit (ICU) is to clinical management as what the brain is to human physiology. We still remain appreciably uneducated about the fundamental physiology of the transitions from normal brain excitation to ictal behavior. Seizures may occur in any individual, given the appropriate triggers. Our brains normally have a "cloak" of inhibition that aids in protecting us from paroxysmal excitation. When a person is stricken with critical illness, such protective measures become less effective; given additional neurological injury such as trauma, ischemia, or inflammation, these protective measures work even less well. Coupled with the myriad physiological derangements that commonly occur in the ICU setting, our risk for seizures becomes unsettling high. The ICU is therefore both the best environment to gain an understanding into the nature of seizures—based on the incidence—and the worst—owing to the multiple and overlapping etiologic factors present. For intensivists, the complexities inherent in an ICU translate to the clinical truism that seizures may appear often and may manifest in severe form, with a few that are grossly refractory to routine inpatient management.

As we have come to appreciate, seizures that occur in the ICU are of many types, and the clinical characteristics of each are dependent on the region of brain involved. The term epilepsy, in fact, encompasses a wide variety of recurrent seizure disorders that have been classified in accordance to the location and extent of the seizure process within the brain. Fundamentally, seizures are of two types. Seizures may be partial (focal) or they may be generalized (Table 1). This distinction is appropriate for two reasons. First, the extent of cortical involvement differs between the groups. Second, and more important, each seizure type has a fundamentally distinct neuroanatomical mechanism. In the examination into the origin of seizures, many analytical tools and methods have been used. Surface and depth electroencephalographic recording have provided the majority of evidence to date, although radiographic techniques such as radionuclide autoradiography, positron emission tomography, computed tomography, and a variety of magnetic resonance sequence studies have proven to be of substantial value.

The greatest consideration into anatomical mapping has been given to the focal epilepsies, in which structural disease is frequently apparent. These seizures display electroencephalographic and clinical manifestations consistent with the involvement of only a portion of the cortex and its corresponding functional systems (Fig. 1). Such events are precipitated by local excitatory aberrations of the

Table 1
Common Presentation of Seizures in the ICU

Seizure type	Clinical expression
Focal motor	Face or limb motor seizure, no alteration of sensorium
Generalized tonic–clonic	Loss of consciousness, generalized convulsions
Complex–partial	Disturbed sensorium, automatisms common
Nonconvulsive status epilepticus	Disturbed sensorium or loss of consciousness
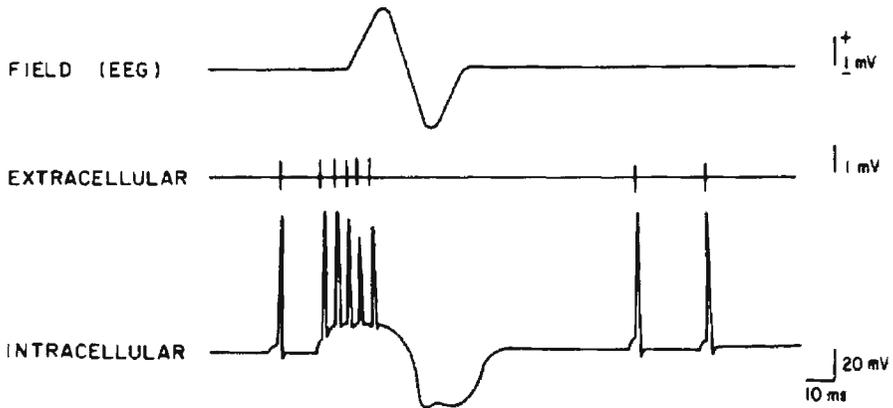
Fig. 1. Example of a focal seizure in a 49-yr-old man recorded by scalp EEG. The seizures begin in the left frontal region. (Used with permission from ref. *1*. Courtesy of R. P. Brenner.)

corresponding cerebral mantle, with spread typically to adjacent cortical regions via local synaptic connections. Such ictal events are exemplified by the classic "Jacksonian march," a focal seizure that spreads along the cortical motor strip to excite progressively the neurons that control topographically associated limb musculature.

Other partial seizures, such as many of the temporal epilepsies, are formally described as partial complex because conscious interaction with the environment is disturbed. The anatomy associated with this form of epilepsy is more complicated than that for a simple partial seizure because of the recruitment of deeper brain elements that affect our conscious behavior. Most commonly, elements of the limbic brain, usually the hippocampus or amygdala and their connections, play a major role in the expression of these seizures. Automatisms frequent such ictal events—speech or behavioral mannerisms such as lip smacking, blinking, or repetitive hand movements. Such seizures that affect nonmotor regions of the cerebral cortex may be difficult to diagnose unless suspicion is high. Such patients may only appear to be noninteractive, or in a "fugue" state.

At the other end of the spectrum are the generalized seizures, where consciousness is affected and convulsions may occur throughout the face and extremities.
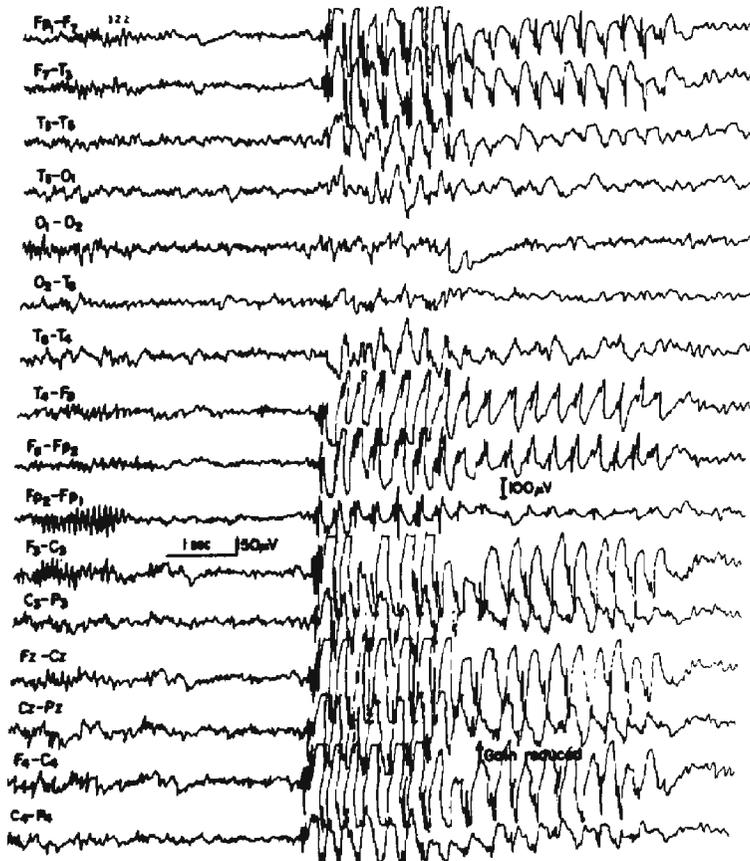
Fig. 2. Generalized and synchronous 3- to 3.5-s spike–wave EEG seizure having a frontal maximum, occurring during sleep. Note that all leads are rapidly incorporated into the seizure, although the occipital leads demonstrate only modest ictal changes. (Used with permission from ref. *2*. Courtesy E. Niedermeyer and F. Lopes Da Silva.)

Axial rigidity is not maintained, and the patient will fall if standing. Generalized seizures commonly begin with a focal cortical nidus, and ictal activity spreads rapidly. This "secondary" generalization may, in some circumstances, be too rapid for the electroencephalogram (EEG) to detect (Fig. 2). As a group, generalized seizures likely spread via cortical networks or cortical–subcortical circuits. The "primary" generalized seizures (e.g., absence epilepsy or primary tonic–clonic seizures) probably utilize brainstem/subcortical structures in the mediation and propagation of the paroxysmal activity *(3–7)*. No cortical nidus is identified, and the deeper cerebral elements are the likely culprits in the initiation, or at least early propagation, of these events *(8–15)*. These primary generalized seizures are exemplified by bilaterally synchronous and symmetrical epileptiform discharges on EEG and clini-

Table 2
Complications of Critical Illness Increasing Seizure Predisposition

Hypoxia/ischemia
Drug/substance toxicity
    Antibiotics
    Antidepressants
    Antipsychotics
    Bronchodilators
    Local anesthetics
    Immunosuppressives
    Cocaine
    Amphetamines
    Phencyclidine
Drug/substance withdrawal
    Barbiturates
    Benzodiazepines
    Opioids
    Alcohol
Infection and fever
Metabolic abnormalities
    Hypophosphatemia
    Hypocalcemia
    Hypoglycemia
    Renal/hepatic dysfunction
Surgical injury (craniotomy)

cal behavior characterized by a loss of consciousness and generalized convulsive or paralytic motor phenomena. In the majority of instances, no diffuse or focal brain disease or generalized metabolic disturbance can be convincingly demonstrated. Nonconvulsive generalized seizures may also occur and are more difficult to diagnose. As discussed later, such seizures often complicate the management of the comatose ICU patient.

In the intensive care unit setting, seizures are a common neurological complication in both medical and postsurgical patients; they commonly arise from comorbidities associated with the ICU experience (Table 2). Most ICU seizures occur in patients who have not had a prior episode or for whom neurological pathology was part of the primary admitting diagnosis. A review by Bleck et al. noted that approx 12% of patients admitted with a nonneurological primary diagnoses incurred neurological events during their critical illness *(16)*. Of these, seizures (28.1% incidence) closely followed metabolic encephalopathy (28.6%) as the leading neurological complication. Status epilepticus (SE), the diagnosis most associated with seizures and the ICU, is in fact a rare admission diagnosis (0.2%) compared with the incidence of seizures as a complication (3.3%). Since seizures occur most often in nonprimary neurological patients, it is important for the general

clinician, intensivist, and consulting neurologist to know about the potential for seizures in the ICU and to be aggressive in treating them.

Regardless of seizure type, the medical management in an ICU and the environment itself unfortunately present unique challenges and difficulties regarding the etiology, diagnosis, and treatment of seizures. Patients are critically ill, and the common scenario of multisystem organ dysfunction presents a variety of potential etiologies for cerebral disturbance, often predisposing to seizures. Also, hindering the neurological examination are treatment with sedatives, as a means to provide comfort to the patient, and administration of paralytic agents to optimize therapy *(17)*. Many pharmaceuticals used in an ICU, particularly psychotropic medications, antibiotics, and stimulants, may also lower seizure threshold *(18,19)*. Anti-convulsants and other medications may alternatively sedate the patient or enhance toxic responses, further delaying neurological recovery from the seizure episode *(20)*. Such difficulties may lead to additional diagnostic studies and a prolongation of ICU stay. Seizures also may accompany conditions that render the patient into coma, such as severe encephalopathy, trauma, or stroke *(21–26)*. Recurrent or continuous seizure activity may prevent arousal, and in such cases EEG assessment is necessary for correct diagnosis. More seriously, recurrent seizures and SE are more difficult to suppress than simple focal or generalized convulsions and can be life threatening when they occur as complications of primary neurological or other visceral organ disease. Finally, the ICU itself is an environment with considerable electrical field dispersion, often preventing optimal EEG recording.

The need to diagnose and effectively treat recurrent seizure activity is imperative. Multiple seizure events or convulsive SE may lead to acidosis, hyperthermia, rhabdomyolysis, and trauma, with consequent higher morbidity and mortality *(27)*. Loss of protective airway reflexes, which is common in patients with prolonged or recurrent seizures, promotes the likelihood of pulmonary aspiration. The duration of seizures of more than an hour is an independent predictor of poor outcome (odds ratio of almost 10) *(28)*. Prolonged seizures increase the risk of cerebral damage owing to excitotoxicity, intracellular Ca^{2+} accumulation and apoptosis, epileptogenic synaptic reorganization and sprouting, and the depletion of energy stores with inhibition of protein and DNA synthesis *(29)*.

CELLULAR PATHOPHYSIOLOGY OF ICU SEIZURES

Fundamentally, despite numerous phenotypic expressions of seizures and epilepsy syndromes, the manifestations of the ictal process emanate from a few common cellular mechanisms and brain loci. The cerebral cortex is the nidus for most clinically evident seizures, and into that category also falls the hippocampus, the most rudimentary cortical element of the medial temporal lobe. Regarding subcortical structures, it is well known that the thalamus plays a substantive role in mediating the paroxysms and supporting the hypersynchronous, rhythmic EEG activation. Specific research effort has prominently identified all three locations in seizure mechanisms and has implicated a variety of neuronal and glial functions *(12,30–33)*.
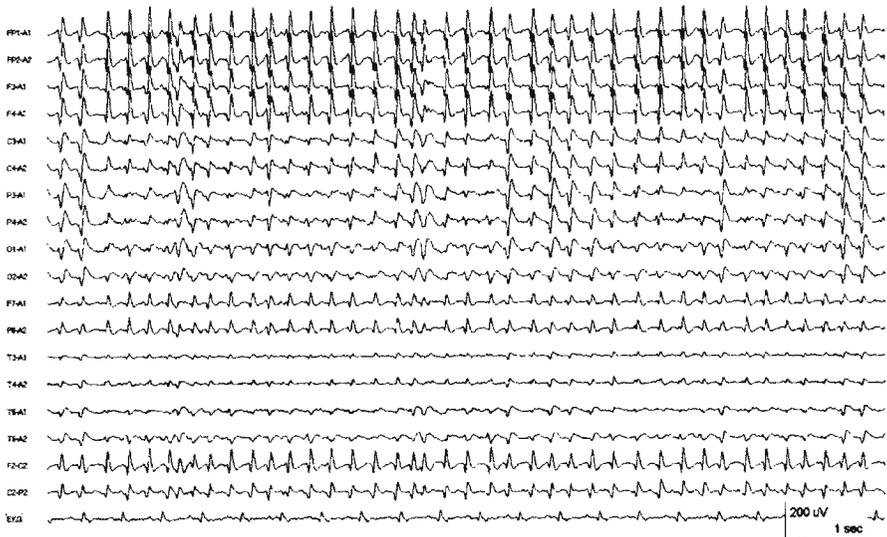
Fig. 3. Illustration of an intracellular PDS with both extracellular and field EEG correlations. Note intracellular depolarization triggers associated bursting of intracellular spikes leading to paroxysmal discharges on scalp EEG. (Used with permission from ref. *2*. Courtesy of E. Niedermeyer and F. Lopes Da Silva.)

As evidenced by the cortical EEG, the fundamental marker for an epileptic paroxysm is the interictal spike, which is the electrical fingerprint of the intracellular paroxysmal depolarizing shift or PDS (Fig. 3). The interictal spike is generated by a synchronous firing of a network of local neurons, coupled with periods of inhibition via K^+ current-activated hyperpolarization. Neurons in particular that are readily disposed to such activity are the pyramidal cells of cortical layer V and the CA3 neurons in the hippocampus *(34)*. These cells are synaptically linked to regional neurons that amplify the excitation within a synaptic network. The paroxysmal discharge may be induced by a local increase in excitation, a decrease inhibitory neurotransmission, or alteration in Na^+ or K^+ current conductance *(35)*. Excitation is classically derived from direct stimulation of *N*-methyl-D-aspartate receptors or enhancement of synaptic transmission via reduction of K^+ current. Reduced inhibition may stem from antagonism of γ-aminobutyric acid (GABA) activity at its receptor or decreasing GABA binding through chemical means, such as a reduction of local Mg^{2+} *(36–39)*.

The interictal spike may be effectively transitioned to an array of several spikes, or to a "burst," by the presence of local burst-generating cells. These are made possible by persistent Na^+ and Ca^{2+} slow-action potential currents that function primarily in the dendritic formations, promoting prolonged depolarizations in the neuron soma *(38,40)*. The bursts appear to further manifest when there is alternating depolarization between the dendrites and soma *(41)*. Network modeling of hippoc-
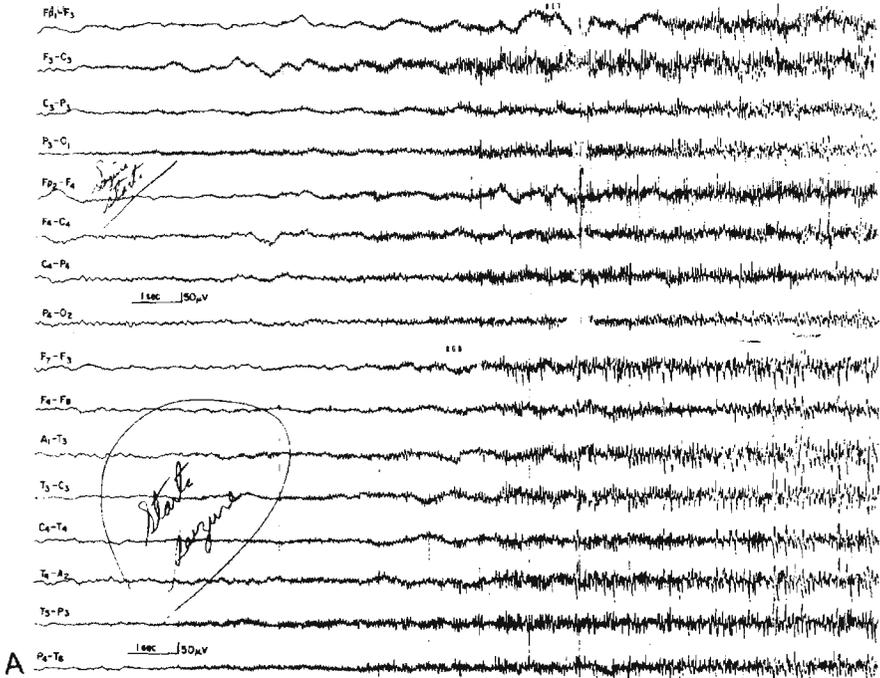
Fig. 4. Example of one of the few identified subcortical pathways participating in the early propagation of experimental generalized seizures. The expression of these seizures, induced by the chemical convulsant pentylenetetrazol, was modulated by the perturbation of neuronal activity within the path from the brainstem (ventral and dorsal tegmental nuclei) synaptically linked to the hypothalamus, anterior thalamus (AN), and cingulate gyrus *(33)*. Clinical trials of deep brain stimulation of AN for refractory epilepsy have been conducted.

ampal cells has reproduced the EEG events of a tonic–clonic seizure *(42,43)*. The high-frequency firing tonic component is triggered by prolonged somatic depolarizations, and the slower synchronous clonic seizure results from rhythmic bursting of slow-channel dendrite depolarizations. Continued depolarization of the neuronal membrane (contrast to the brief depolarization of a PDS) is responsible for the maintenance of successive rapid discharges inherent in a stereotypic seizure. Recurrent afterdischarges, as occur during a clonic seizure, are perpetuated by a reduction of the hyperpolarizations that follow aberrant paroxysms such as the interictal spike.

Now that the susceptible tissue has undergone epileptiform transformation, the propagation to larger cortical terrain, or even generalization, requires vital network pathways and connections *(44,45)*. On a regional scale, ictal events may spread by disruption of the local chemical environment, such as alterations in K^+ or Mg^{2+}. Such spread is not very rapid, estimated at 50–200 mm/s *(46)*. Clinically important

Table 3
Common Etiologies of Seizures in the ICU

Neurological pathology
Neurovascular
Stroke
Arteriovenous malformations
Hemorrhage
Tumor
Primary
Metastatic
CNS infection
Abscess
Meningitis
Encephalitis
Inflammatory disease
Vasculitis
Acute disseminated encephalomyelitis
Traumatic head injury
Contusion
Hemorrhage
Primary epilepsy
Primary CNS metabolic disturbance (inherited)

seizure propagation must clearly utilize synaptic transmission via networked connections. Even ectopic transmission has been proposed as a means to further enhance the spread or continuation of the ictal state *(47)*. Such cortico–cortico, or subcortico–cortico circuitry has only been occasionally identified *(12,32,48,49)* (Fig. 4).

We do know from clinical experience that many pathological conditions inherent in ICU patients, particularly those with primary cerebral disturbance, predispose to seizures (Table 3). However, very little is known concerning the contribution of regional pathology on the predisposition to seizures, despite ready acknowledgment that injured regions of brain following a stroke or head injury appear to be more prone to paroxysms than native cortex *(50)*. Similarly, brain tissue adjacent to "irritative elements" such as neoplasms or vascular malformations has been associated with a high risk of manifesting seizures. The mechanisms leading to enhanced susceptibility have only recently been forthcoming (Table 4) *(45,53)*.

It is clear from work on cerebral neoplasia that tumors may have intrinsic cellular properties inciting an epileptogenic focus *(55,56)*. Other consequences of a mass lesion that impacts regional blood flow and supply (such as tumors or arteriovenous malformations [AVMs]) are the potential for local tissue ischemia, denervation hypersensitivity, alteration in neural plasticity, and disequilibrium of the local micro-

Table 4
Proconvulsant Mechanisms Inherent in Cerebral Neoplastic and Vascular Malformations

Intrinsic epileptogenic cellular properties (tumors)
Local impaired vascularization/ischemia
Denervation hypersensitivity
Axonal and synaptic plasticity
Decrease in regional GABA
Increase in local glutamate
Alteration of electrolyte ions (Mg^{2+})
Increase in regional Fe^{2+}

Adapted from ref. *54.*

Table 5
Intracranial Pathology and Relative Risk for Seizures

Pathology	High risk
Stroke	Hemorrhagic
	Large cortical involvement
	Acute confusional state
Intracranial tumor	Cortical
	Primary
	Metastatic
Traumatic head injury	Cerebral contusion
	Acute subdural hemorrhage (SDH)
	Depressed skull fracture
	Penetrating missile injury
	Evacuation/chronic SDH

chemistry (GABA, glutamate, Mg^{2+}, etc.) *(57–60)*. Some evidence also suggests alterations in intercellular iron ions (Fe^{2+} or Fe^{3+}) may exist and predispose to seizures. Aside from the putative intrinsic epileptogenic characteristics of certain tumor types themselves, the proconvulsant features just listed that have been associated with tumors and AVMs may likely apply to cerebral tissue affected by head injury, stroke, and inflammatory conditions (Table 5). In the following chapters, there will be detailed discussion relating to the specific etiologies and therapies for seizures occurring in the ICU arena.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

A focal or generalized seizure commonly lasts for several seconds or up to 1–2 min. During this period, alterations in hemodynamics and respiratory indices are typical in generalized convulsions, with increases usually recorded in heart rate and blood pressure. Ventilation may be impeded in the latter seizure type, with

desaturation noted on pulse oximetry, often with excessive salivation. Interestingly, although grunting and gasping are encountered during a generalized tonic–clonic seizure, patients only rarely incur an aspiration event. If one should occur, it is almost always of the patient's oral secretions rather than gastric contents. Therefore, patient care during a violent convulsion is focused on protecting the patient from extremity injury and biting of the tongue, and maintenance of a clear airway during prolonged seizures. Brief desaturations are the rule, and these require no special intervention. For the vast majority of simple convulsive episodes, protection of the airway beyond what has been described, or frank ventilatory support, is not indicated. A depressed sensorium is common following a generalized convulsion and requires several additional minutes before baseline is reestablished. Focal or generalized seizures may also lead to postictal focal deficits (Todd's paralysis) lasting up to several hours. These deficits are especially common in patients with preexisting subtle weakness from a mass lesion or stroke, and seizures can accentuate these preconvulsive neurological impairments. In contrast to generalized convulsive episodes, patients with focal seizures are fully cogent during their attack, and those with complex–partial seizures typically return rapidly to their baseline neurological state.

Most seizures that occur in an ICU setting manifest as generalized tonic–clonic convulsions, including secondary generalization, with some reports observing approximately 90% of the presenting seizure as of this variety *(16,26)*. Focal seizures comprise the majority of remaining behaviorally disturbing seizure types. These data suggest that recognition of a seizure in the ICU is rarely a diagnostic dilemma. Patients who do present with complex–partial or other nonconvulsive seizures (9%) may be considerably more difficult to diagnose, especially in a critical care setting where sedative medication is often administered, but such patients are uncommon. Recent data suggest that in an ICU population, 5–10% of comatose patients were in nonconvulsive status epilepticus (NCSE) *(61)*. Other investigators have evidence to suggest that the incidence of nonconvulsive seizures is alarmingly high, up to 34% of neurological ICU patients, and only lack of monitoring prevents the detection of these seizures *(62)*.

Besides overt behavioral manifestations, the scalp EEG is the diagnostic test of choice. Even when a seizure is noted by obvious clinical expression, evaluating the treatment success according to the presence or absence of motor paroxysms or level of consciousness may be occasionally misleading. Treatment of motor convulsions alone may be insufficient to prevent the continuation of seizure activity. The persistence of electrographic status without convulsions (NCSE) has been observed in 14% of patients treated for convulsive SE *(63)*. Conversely, improvement in the neurological examination is often a poor clinical assessment tool, since 87% of patients successfully treated for convulsive SE and 100% of patients treated for NCSE remained comatose 12 h after the initiation of therapy *(64)*. Therefore, it cannot be over-emphasized that electrical monitoring of ICU patients is crucial in settings where seizures may be a complicating feature of critical illness. Unless a

seizure fully resolves and the patient returns to an alert, cognitive baseline, an EEG is highly useful, if not mandatory to exclude ongoing ictal activity.

OVERVIEW OF STATUS EPILEPTICUS

Status epilepticus represents a distinct seizure phenomenon. Not simply a prolonged seizure, SE represents a reconfiguration of the excitatory and inhibitory network of normal brain *(65)*. Most focal seizures do not secondarily spread to produce a generalized event because of local (GABA-mediated) inhibitory circuitry that prevents enlargement of the ictus. As seizures continue, it is known that a breakdown occurs within this cortical "inhibitory surround," thus making it easier for seizure activity to spread. In addition, the inhibitory events that assist in terminating the seizures also become disturbed. Thus, recurrent or prolonged seizures induce a positive feedback loop that help sustain ictal activity rather than inhibit it further. In essence, "seizures beget seizures" *(65)*.

Our understanding of the exact point at which a prolonged seizure or set of recurrent seizures is deemed to have become "SE" continues to evolve. Historically, since the 1960s, the minimum time of unremitting seizures before SE was said to occur by experts was arbitrarily set at 30 min. This included a single generalized seizure lasting longer than 30 min, or a group of repetitive seizures between which the patient had not fully recovered. Given the discussion regarding the risk of early neuronal injury, and a desire to adequately treat this disorder prior to irreversible cerebral insult, shorter seizure epochs have been more recently emphasized as SE. Based on the typical seizure duration of 1–2 min, it is reasonable to classify as SE any seizure events lasting longer than 5–10 min. Such is now the tenet of the American Academy of Neurology and the American Epilepsy Society. There are several reports describing seizures of 10–29 min duration that have had spontaneous resolution without therapy, but consensus is that these represent a small population. It is strongly felt that a high risk/benefit ratio exists in not treating such patients as SE. If treatment was required to "stop" the clinically obvious seizure, EEG correlation again is advocated for patients who have not returned to their preictal, alert condition.

There are three main subtypes of SE, two of which are prominent in the ICU. Generalized convulsive SE (GCSE) represents the classic motor SE (Fig. 5). The seizures may be overt, or they may have subtle motor manifestations, especially if the SE is prolonged. By far, GCSE is the most commonly reported SE subtype. Focal motor SE (FMSE), or epilepsia partialis continuans, is relatively uncommon and is rare in the ICU. Continuous motor twitching of a single limb or side of face is most frequently observed. These seizures can be difficult to control with medications. It is not clear whether prolonged FMSE results in substantive injury to the cerebral cortex. Thus, reasonable attempts at control are advocated, but high-risk therapies such as induced pharmacological coma are rarely used. Nonconvulsive SE is currently an umbrella term for a wide spectrum of continuous nonmotor seizures. As a group, the conditions may range from primary generalized SE, such as
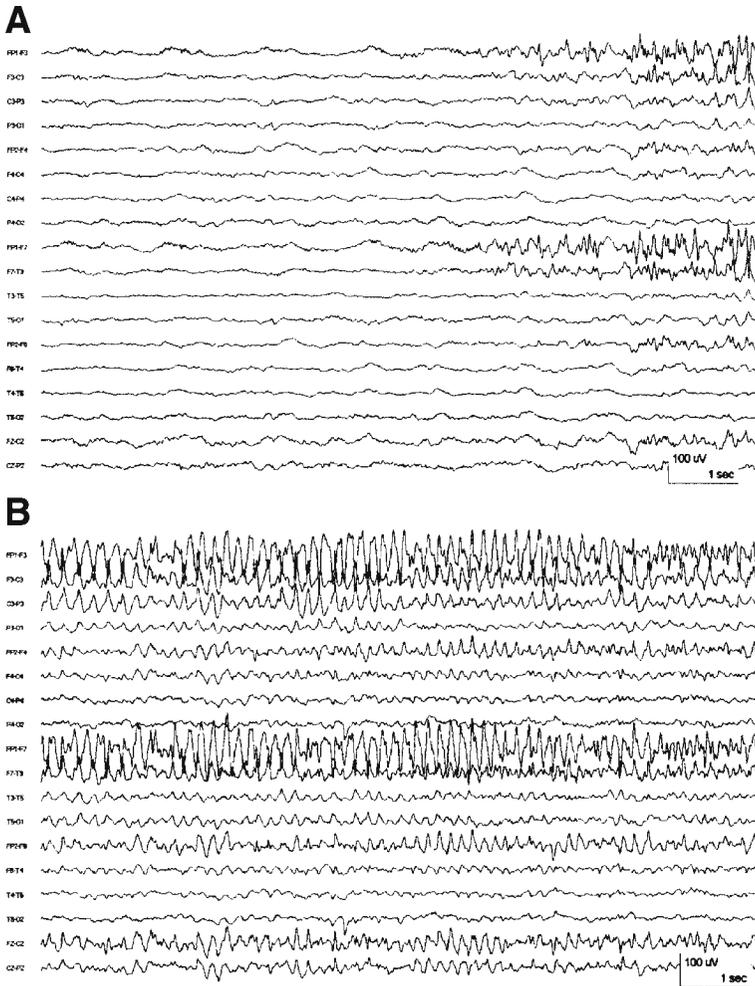
Fig. 5. Status epilepticus in a 20-yr-old female with no history of seizures. The seizure begins suddenly (A) and continues in a crescendo–decrescendo pattern with having an abrupt termination. A follow-up seizure began soon after the decrescendo phase (B). (Used with permission from ref. *2*. Courtesy of E. Niedermeyer and F. Lopes Da Silva.)

absence SE, which has a very stereotypic EEG to secondary generalized seizures with variable EEG features (Fig. 6). Other terms within NCSE are complex–partial SE, subtle SE, nontonic–clonic SE, and subclinical SE. The hallmark is a diminution of the neurological exam secondary to the seizure, but the patient may present clinically anywhere along the spectrum between awake/ambulatory and comatose. The true incidence of this subtype of SE is unknown and likely underrecognized. Pertinent to the ICU setting, a recent trend ascribes the label of NCSE to patients
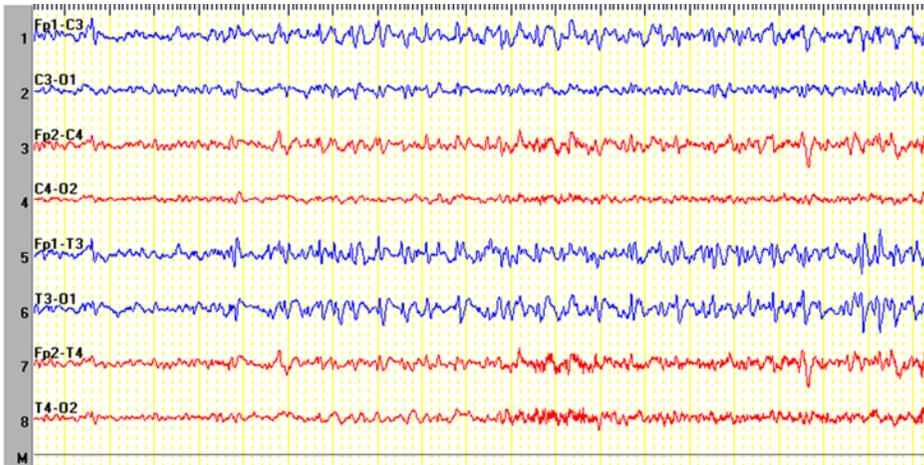
Fig. 6. Focal nonconvulsive status epilepticus a few hours after resection of a left tempo-ral lobe arteriovenous malformation. Onset of the seizure over the left fronto-temporal leads (dotted line). Patient was aphasic during the period of the seizure, but responded well to treatment with benzodiazepines.

having suffered from severe anoxic/ischemic encephalopathy, when characteristic EEG spikes are present. When such EEG findings, consisting of bilateral periodic lateralizing epileptiform discharges (PLEDs), are present along with the appropri-ate clinical history, they portend a poor neurological outcome *(66)*.

Although there is a strong consensus in aggressively treating GCSE, there is mixed opinion about the proper management of NCSE *(61,63)*. These seizures are diagnosed by recurrent paroxysmal or epileptiform bursts on the cortical EEG. In the purest form, without prior evidence of cerebral injury or mass lesion, NCSE is typically benign. Apart from altered cognition during a seizure that may be dis-abling, there is no evidence that permanent morbidity has been attributed to this form of SE. Thus, therapy should be directed toward chronic prevention of the attacks. In the ICU, however, most forms of NCSE are associated with a history of moderate to severe cerebral injury, for example, following an anoxic/ischemic event or trauma. Although associating the effects of NCSE with direct neuronal injury is difficult in this setting, most epileptologists would agree that in such scenarios the presence of continuous paroxysmal activity may accentuate injury incurred by the primary insult. Therefore, it is prudent to attempt therapy as rapidly as is feasible. It remains unclear to what degree one should attempt to abolish the EEG paroxysms, although even the induction of barbiturate coma has been performed.

As may be expected, monitoring by EEG is critical to achieving an accurate diagnosis of SE and for monitoring the therapeutic response itself. This is espe-cially true for both NCSE and prolonged convulsive SE, where physical findings are few and the EEG may be the only effective tool for diagnosis *(67–69)*. Table 6 lists common EEG features of GCSE and NCSE. For ongoing SE, EEG (preferably

Table 6
Typical EEG Presentation of Generalized Convulsive Status Epilepticus (GCSE) and Nonconvulsive Status Epilepticus (NCSE)

Classic GCSE	Generalized spike or sharp wave pattern—begins from a normal background rhythm. SE is characterized by an unremitting spike activity or, more commonly, a crescendo–decrescendo pattern of major motor ictal periods interspersed with lower voltage paroxysmal activity. No abrupt termination or "postictal depression" is observed, unlike the aftermath of simple seizures.
NCSE	EEG is variable, and a number of EEG patterns are recognized. Generally, seizures such as complex–partial status resemble their non-SE counterparts.

continuous) is mandatory to ensure effective treatment. Commonly, convulsive SE is incompletely treated with residual subtle EEG seizures or NCSE, despite cessation of motor ictal activity. Some clinical reports suggest residual electrographic seizures in almost 50% of patients with GCSE and a 10–20% incidence of NCSE in patients treated for GCSE with cessation of motor seizure activity *(63)*.

PAROXYSMAL LATERALIZING EPILEPTIFORM DISCHARGES (PLEDS)

The significance of PLEDs has been debated since their first designation in the early 1960s, but the fact not in dispute is their frequent appearance in ICU patients. Although not rigidly defined, PLEDs have been ascribed to the presence of spikes, sharp waves, or a mix of sharp–spike waves that may have coincident slow waves that together appear on the EEG at regular, periodic intervals (Fig. 7) *(70)*. Mostly described in patients with cortical injury, PLEDs have also been associated with patients with epilepsy syndromes and following bouts of severe seizures, such as SE. Ischemic stroke appears to be the most frequent etiology, but other brain conditions such as hemorrhage, neoplasms, cortical infection and inflammation, and even metabolic disturbances have been linked to this EEG phenomenon *(71)*.

The underlying pathophysiological mechanisms remain unclear, but the similarity of PLEDs to the interictal spike suggests that similar chemical/membrane disturbances underlying the PDS may be fundamental. In one interesting observation, clinically occurring PLEDs were linked to basal ganglia circuit function *(72)*. This is of interest because it links subcortical activity with PLEDs and thus connects this epileptiform phenotype with the basal ganglia association with seizures *(73)*.

Many consider PLEDs to be a cerebral response to an acute focal process, although these paroxysms may last for several years if a stroke or mass lesion remains a physiological irritant. Although structural injury is the greatest stimulant for development of PLEDs, metabolic or diffuse alteration of cerebral function may be an etiologic factor in some patients *(74)*. The presence or absence of coincident
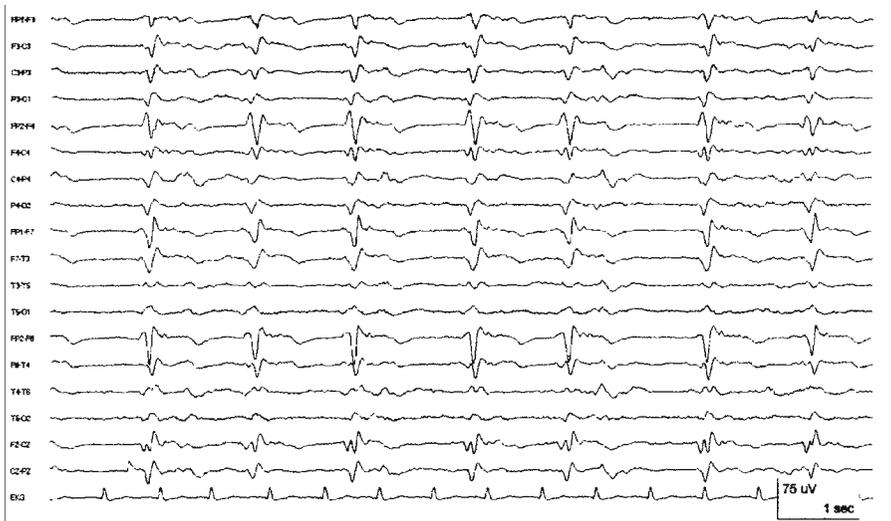
Fig. 7. A good example of PLEDs emanating from a largely quiet background EEG. (Used with permission from ref. *1*. Courtesy of R. P. Brenner.)

paroxysmal bursts leads to a subcategorization of "simple or proper PLEDs" or "PLEDs plus" *(75)*. The disappearance of PLEDs, either spontaneously or with anticonvulsant therapy, has been well documented *(76,77)*.

The attribution of PLEDs to an active ictal state is a position that lacks consensus. It is clear that these discharges may come in the setting of a diagnosis of seizures, or simply with a structural lesion. Data appear not to support definite conclusions that might be drawn from their presence about such matters as patient clinical outcome or further risk for seizures *(78)*.

CONCLUSION

Seizures occurring in the ICU setting are more difficult to prevent, diagnose, and treat effectively than those manifesting outside the ICU or hospital. Particularly challenging is the diagnostic component of seizure management, especially when only subtle clinical evidence is present and the EEG is not conclusive. The use of a variety of medications and the clinical management in an ICU all tend to lower seizure threshold rather than elevate it. A high index of suspicion is warranted by the intensivist, and early use of EEG surveillance can be vital in early detection. Treatment of seizures in an ICU setting can also be challenging, even in the absence of SE. The ability to recognize and treat seizures is critical, however, given the clear evidence for potential grave neurological injury when seizures persist as SE. However, the treatment of seizures itself may impose new patient toxicity, and there must be appropriate toxicity/benefit evaluation, as well as proper drug selection. Finally, confronting the etiology of the seizures, assessing the risk

for future episodes, and acquiring an understanding of the treatment options can greatly assist in formulating the acute ICU and future therapeutic management of these phenomena.

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Stroke and Critical Care Seizures

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SUMMARY

Patients with hemorrhagic stroke are usually admitted for observation to an intensive care unit (ICU). A smaller percentage of patients with ischemic stroke are also admitted, as well as patients with cerebral venous thrombosis or those who have undergone carotid endarterectomy. All these patients are at risk for seizures. Those with hemorrhagic stroke are usually at two to three times higher risk than those with ischemic stroke, but several characteristics of the stroke modify the risk for having a seizure. In most cases an early seizure (within the first few days after the ictus) has a different significance from a late seizure (after the patient has been discharged from the ICU or the hospital). In addition, a significant role is played by the treatment offered to these patients, either medical, surgical, or endovascular. Despite an abundance of studies examining the incidence and characteristics of poststroke seizures, there are several questions still to be answered regarding the institution and duration of the appropriate treatment.

Key Words: Ischemic; hemorrhagic stroke; sabarachnoid hemorrhage; arteriovenous malformation; caratoid endarterectomy; hyperfusion syndrome; cerebral sinus thrombosis.

INTRODUCTION

Seizures following stroke have been reported since the 19th century. Hughlings Jackson in 1864 reported convulsions in the paralyzed side after a middle cerebral artery (MCA) embolism *(1)*, and few years later, in 1885, William Gowers introduced the term "posthemiplegic epilepsy" *(2)*.

Seizures can occur early following a stroke (within the first 2 wk), or they can start at later stages. They can occur more than 24 h before clinical evidence of stroke ("antecedent" seizures) or within the 24-h period before or after the initial

neurologic deficit ("at-onset" or "acute phase" seizures) *(3,4)*. Early seizures may be seen during the index admission to the intensive care unit (ICU) for stroke, or they may occur later in the course of the event, justifying admission or readmission to the unit. Three major questions arise in the ICU when a patient with stroke develops one or more seizures.

(1) How do the seizures affect the stroke?
(2) Are the fits, especially the early ones, a mode of entrance into epilepsy?
(3) When is antiepileptic treatment appropriate?

While trying to address the importance of the problem, one may encounter several difficulties in reviewing the literature: many studies are older (from before the computed tomography [CT] era), retrospective, based on small numbers of patients, do not include all types of stroke, and do not consider the timing (not differentiating between early or late seizures). However, it is important to differentiate between early and late poststroke seizures because there are several clinical, etiological, and prognostic differences that justify a separate analysis *(5)*. Moreover, in several studies, the time between stroke onset and admission is unclear; and thus it is also unclear whether seizures occurred before a healthcare personnel encountered the patient, an important detail because many seizures occur during the very first hours after the onset of a stroke. Finally, many studies do not control effectively for the presence of antiepileptic medications when the seizures occur, potentially underestimating the natural history of poststroke seizures.

SEIZURES AFTER ISCHEMIC STROKE

Clinical Studies

The reported incidence of poststroke seizures varies between 4.4 and 13.8%, depending on the subgroups included in the analysis, the methods used to evaluate the stroke, and the follow-up period *(5–13)*. A male preponderance has been reported in two studies *(5,14)*. Early seizures (definition varying from the first 24 h to the first 4 wk poststroke) usually occur at the stroke onset in 1.8–15% of patients and constitute the majority of poststroke seizures *(5,6,8,9,11,12,15–18)*. The majority of early seizures occur immediately poststroke, and the majority of those are inaugural of stroke *(12)*. Late poststroke seizure occurrence also depends on the definition and the duration of follow-up, with a reported incidence of 2.5–15% of cases *(6,10,12,19–22)*. Recurrent seizures (epilepsy) after stroke can occur in 4–9% of patients *(23,24)*. Although some studies have reported that early seizures did not lead to the development of late seizures *(25,26)*, the cumulative risk for epilepsy may reach 19% by 6 yr, a figure 22 times higher than the expected age-specific incidence of epilepsy in the general population *(16)*. In a large epidemiological study from southwestern France, Loiseau et al. found that cerebrovascular disease was the most frequently recognized etiology of seizures in the aging population: it was the underlying cause in 36.6% of patients with spontaneous seizures

and in 53.9% of the patients with confirmed epilepsy *(14)*. Therefore, although only 5% of epilepsy is attributable to cerebrovascular disease (pre-CT data from Rochester, MN) *(16)*, because stroke incidence is high in the elderly, stroke may account for 25–50% of new epilepsy cases in this population segment *(14,27–31)*.

Most of the seizures after stroke have a focal onset and are of the simple partial type *(9–11,32,33)*. Almost half show secondary generalization, making it difficult in the ICU to differentiate between the two types unless the onset was witnessed or there is continuous video monitoring of electroencephalographic (EEG) data. Complex partial seizures are less frequent, although in one retrospective study their incidence reached 24% of all poststroke seizures *(33)*. The incidence of primary generalized seizures lies between the two, although this may be an overestimate, because most authorities agree that most of these events are secondary generalized *(34)*.

There have been very few studies conducted in a stroke unit or other ICU, because the majority of stroke patients are managed in an acute floor setting and are admitted to an ICU environment only if they have significant comorbidities or if their condition deteriorates. This chapter provides a review of all currently available data, so that readers may form their own opinions.

Several studies were conducted in the pre-CT era, the most notable being that by Louis and McDowell, who reviewed the records of 1000 patients who are presumed, based on clinical criteria, to have suffered thrombotic infarction *(10)*. The incidence of seizures was 7.7%. Early seizures were reported in 55% and late in 45% of 60 patients. Epilepsy developed in 3% of patients with early seizures and in 81% of patients with late seizures during an average follow-up period of 27 mo.

Another early report of a large stroke population admitted to an acute stroke unit in Toronto found that 83 of 827 (10%) patients had seizures during the first admission or during the 2- to 5-yr follow-up *(35)*. Seizures occurred only in patients with hemispheric lesions and were equally represented in those with infarcts and hemorrhages. Early seizures (within 1 wk) occurred in 57% of those patients (39% within the first day). By the first year 88% of those 83 patients had seizures. Mortality during the first week was not different in patients with and without seizures.

In a retrospective analysis of 90 patients with postischemic stroke seizures, immediate seizures (defined as occurring within 24 h) were observed in 30% and early seizures (within 2 wk) in 33% *(32)*. Overall, 98% of the initial poststroke seizures were observed within 2 yr. The authors could identify precipitating factors for initial seizures in four patients (one with hypoglycemia, one with hyponatremia, and two with fever resulting from pneumonia). Early seizures were more likely partial and late seizures generalized. Recurrent seizures occurred in 35 of 90 (39%) patients with a mean follow-up of 30 mo. Eighty-six percent of patients with recurrent seizures had identifiable precipitating factors, the major being noncompliance with the antiepileptic medication regimes. There was no difference in the recurrence rate between patients with early (40%) and late seizures (38%).

In a retrospective analysis of medical records from Taiwan, approx 2000 patients were admitted with presumed cerebral infarction and 118 of them had seizures *(33)*. A bimodal distribution of postthrombotic stroke seizures was found, with an early peak within 2 wk (early seizures) and a late peak between 6 and 12 mo *(33)*. Early seizures were reported in 13 of 118 (11%) patients, with seizures and late seizures in 66 of 118 (66%). However, this study has several limitations, including 42 of 118 patients with unknown interval between seizure and stroke onset. Twenty-three out of 118 patients (19.5%) with a first seizure had silent infarcts proven by CT of the head and no history of stroke. In patients with a single infarct (excluding lacunae and border zone infarcts), the frontal and the temporal lobes were the most commonly involved lobes, either solely or partially (58% each), followed by the parietal lobe (43%) and the occipital lobe (20%). Most of the seizures were simple partial (58%) or complex partial (24%), with or without secondary generalization. Status epilepticus (SE) occurred in 15% of the patients. For patients with ischemic stroke, epilepsy developed in 35% of patients after early seizures and in 90% of patients with late seizures.

In another hospital-based study from Buenos Aires, Argentina, 22 (10%) of 230 patients with stroke developed seizures, including 7.1% of those with ischemic stroke and 25% of those with intracerebral hemorrhage (ICH) *(6)*. The risk for seizures was higher in patients with ICH, cortical involvement, and large stroke (defined as a lesion involving more than one lobe). Early-onset seizures (within the first month) occurred in 54.5% and seizure recurrence in 6 of 22 (27%) of patients with seizures. There was no difference in the type, location, and size of stroke between patients with early and late seizures.

In a prospective study conducted in Birmingham, England, 230 patients were followed for at least 27 mo after acute stroke *(11)*. Early seizures at the onset of stroke (defined as within a 24-h period before or after the initial onset of neurological deficit) occurred in 13 (5.7%) of patients, all with strokes in the internal carotid artery distribution. The percentages were 4.3, 10.7, and in the subarachnoid hemorrhage (SAH) group 11.1% in the ischemic stroke subgroup, the ICH group, and the subarachnoid hemorrhage (SAH) group, respectively. Mortality in patients with seizures was significantly higher than the whole stroke group only during the first 48 h after admission. This study has several limitations. Only 86% of patients were admitted to the hospital within the first 48 h of stroke onset, and only 20% had confirmation of the stroke type by CT, angiogram, or necropsy. Six out of 13 patients with seizures had epilepsy or were taking antiepileptic medications before the onset of the stroke. None of the remaining patients with poststroke seizures who survived their stroke (5 of 7) had further seizures during a minimum follow-up of 30 mo. The authors concluded that antiepileptic agents failed to control seizures in these patients.

A large prospective study was conducted in Australia, following 1000 patients admitted for stroke *(9)*. The incidence of early seizures (within 2 wk) was 4.4% (44 patients) and occurred within the first 48 h in 43 of 44 subjects (97%). Four patients

had SE (0.4%), and 18 (1.8%) had multiple seizures. All patients who received antiepileptic treatment (77%) had readily controlled seizures. The highest incidence of early seizures (15.4%) was found in patients with supratentorial lobar or extensive (lobar and deep) ICH, followed by 8.5% in patients with SAH, 6.5% in patients with carotid territory infarcts, and 3.7% in patients with hemispheric transient ischemic attacks (TIAs). No early seizures were found in any patients with subcortical, lacunar, or vertebrobasilar distribution infarcts or deep cerebral or infratentorial ICHs. There was no difference in the incidence of seizures after cardioembolic infarct compared with large-vessel extracranial disease. In the ICH subgroup, arteriovenous malformation (AVM) as a cause of lobar ICH was found to have a strong association with early seizures ($p = 0.001$).

As a follow-up to the study from Australia, the same authors reported the incidence of late seizures (defined as seizures occurring after discharge) in 31 of 44 surviving patients who had had early seizures without TIA *(36)*. Late seizures occurred in 32% of these patients, compared with 10% of patients without early seizures from the same cohort and matched for age, sex, and type of stroke. In patients with ischemic stroke, late seizures occurred in 26 and 0%, respectively, and in patients with ICH in 62.5 and 25%, respectively. The mean time from early to late seizure was 12 mo (3 to 30 mo), and the type of seizure was not associated with seizure recurrence. Twenty-one patients were on antiepileptic treatment at discharge, but the authors could not draw conclusions about the usefulness of these medications to prevent late seizures because of the small sample size.

Early seizures (within 2 wk) occurred in 2.5% of 1200 patients admitted for acute stroke in a large, retrospective study from China *(15)*. The incidence of early seizures was 2.3% in infarction, 2.8% in ICH, and 2.7% in SAH. There was no association between the stroke subtype and early seizure occurrence. Carotid artery territory cortical infarctions had 10-fold increased incidence of seizures in comparison to noncortical infarctions, and lobar ICH had 20-fold increased incidence versus nonlobar ICH ($p < 0.001$). Two-thirds of early seizures were partial, 24% generalized, and 10% SE.

Another large retrospective hospital-based study was conducted in Marseilles, France *(12)*. Seventy-eight patients out of 2016 (3.9%) developed seizures after acute stroke and were followed for an average of 30.2 mo. The authors observed a biphasic chronological distribution of seizures: early seizures (within the first month) were observed in 28 of 78 (36%) of patients with seizures and late seizures (after the third month) in 64%. Among those with early seizures, two-thirds occurred within the first 24 h (23% of all seizures), and among the late seizures, two-thirds occurred between the 3rd and 12th mo (42% of all seizures). ICH was followed more frequently by early seizures than were ischemic strokes ($p = 0.05$). The proportion of seizures following cardioembolic stroke was analogous to that from other causes. Simple partial seizures (with or without secondary generalization) were observed in 64%, primary generalized in 32%, and complex partial in 4% of patients. SE presenting as first seizure occurred in 14% of cases. EEG was

performed in 97% of patients with seizures and showed focal slowing abnormalities in 63% and focal irritative abnormalities in 37% of cases. The earlier it was performed after stroke (within the first 48 h or not), the higher the percentage of irritative abnormalities found. Recurrent seizures occurred in 51% of 70 patients who survived the stroke, and no difference was found between those with early or late seizure onset.

In a retrospective, hospital-based study from Palermo, Italy, 217 out of 4425 (4.7%) patients with acute stroke had one or more seizures *(37)*. Seizures after ischemic stroke and ICH occurred in 4.7 and 5.7% of patients, respectively. In the ischemic group, seizures heralded the stroke in 10.7% of patients with seizures, were early (within 2 wk) in 44.3% and late in 44.9% of patients with seizures. The location of ischemic stroke was cortical in 45.5% of cases, subcortical in 32.6%, and mixed in 21.9%.

In a prospective hospital-based registry of 1099 patients with stroke conducted in Barcelona, Spain, 27 (2.5%) had early seizures (within the first 48 h) *(17)*. Younger age, confusional syndrome, hemorrhagic stroke, large lesion size, and involvement of parietal and temporal lobes were more frequently found in patients who developed early seizures. There was no increased frequency of early seizures in those patients with TIAs, embolic infarcts, and lacunar strokes. Patients with seizures had 33.3% mortality (vs 14.2% for those without seizures, $p = 0.02$). Presence of early seizures after stroke was an independent predictor of in-hospital mortality (odds ratio [OR] 6.17, 95% confidence interval [CI] 2.13–17.93). In a subsequent article, with an additional year of data included, the authors reported similar findings regarding early seizures: in the multivariate analysis, only cortical involvement (OR 6, 95% CI 2.5–14) and acute agitated confusional state (OR 4.4, 95% CI 1.4–13.8) were independent predictors for early poststroke seizures *(38)*.

In a prospective multicenter international study (Seizures After Stroke Study Group [SASS]), 1897 patients with acute stroke were admitted to teaching hospitals *(7)*. Seizures were present in 8.6% of patients with ischemic stroke and 10.6% of patients with ICH. Early-onset seizures (within 2 wk) occurred in 4.8% of patients with ischemic stroke. Forty percent of all seizures (3.4% of patients with ischemic stroke) occurred within the first 24 h. Recurrent seizures (epilepsy) occurred in 2.5% of all patients (28% of patients who had seizures) or 2.1% of patients with ischemic stroke (55% of patients with late-onset seizures). Partial seizures accounted for 52% of all seizures. The 1-yr actuarial risk for seizures was 20% for patients with ICH and 14% for patients with ischemic stroke. According to an analysis by means of a Cox proportional hazards model, late-onset seizures conveyed in the total cohort an almost 24-fold increased risk for epilepsy. In the ischemic stroke group, cortical involvement and stroke disability (as measured by the modified Canadian Neurological Score) were independent factors for development of seizures and late-onset seizures for the development of epilepsy (12-fold increased risk).

The only prospective hospital-based study conducted in the ICU examining the incidence of poststroke seizures was conducted at the University of California, Los Angeles; these investigators used continuous EEG (CEEG) monitoring *(39)*. None of the patients with ischemic stroke received prophylactic antiepileptic treatment (phenytoin, with therapeutic levels 14–18 mg/dL) unless they had had surgery, a ventriculostomy, or seizures. All patients with ICH were covered with such a regimen. Seizures occurred in 18 of 63 (28%) patients with ICH and 3 of 46 (6%) patients with ischemic stroke (OR 5.7, 95% CI 1.4–26.5; *p* < 0.004). Most seizures (89%) occurred within the first 72 h after the insult, and most (76%) were nonconvulsive (unresponsive patients with absence of overt convulsions).

Most of the aforementioned studies are hospital-based studies, introducing a potential bias for more severe stroke admissions. Such bias can be avoided by studying population-based cohorts. These studies give information for both acute-onset seizures after stroke (usually hospitalized patients) and the long-term risk (and thus influence the decision about prophylactic antiepileptic management).

The oldest population-based study was conducted in Rochester, Minnesota, and included 535 patients with first ischemic stroke *(40)*. Onset seizures (within 24 h) occurred in 4.8% of these patients and early seizures (within 1 wk) in 6%. The cumulative probability of developing late seizures (after the first week) in the first year was 3% (a risk 23-fold higher than for the general population); by 5 yr the probability was 7.4%, and by 10 yr it was 8.9%. In the multivariate analysis, anterior hemisphere location of the infarct was a strong predictor of early seizures (OR 4, 95% CI 1.2–13.7). Early seizures and stroke recurrence were independent predictors for late seizures and recurrent seizures (epilepsy). These results may be criticized because several patients had their first stroke in the 1960s, when CT was not available and might have had hemorrhagic instead of ischemic strokes as reported.

Another large prospective population-based study was performed in France between 1985 and 1992 *(5)*. Using the Stroke Registry of Dijon, the authors reported 90 (5.4%) patients with early seizures (within the first 15 d) out of 1640 patients with acute stroke, with an under-study population of 150,000. All patients had CT of the head, and all patients with seizures had an EEG evaluation. Patients with cerebral infarct resulting from atheroma, cardiogenic embolus, lacunae, and TIAs had seizures in 4.4, 16.6, 1, and in 1.9%, respectively. An interesting observation in this study is the high incidence of seizures with infarcts of the occipital lobe (11.3%). There were no seizures in patients with brainstem, thalamic, cerebellar, or retinal infarcts. The authors reported higher incidence of seizures after cardioembolic infarction (20.8%) than after infarction from atheroma (5%; *p* = 0.01) in the anterior circulation distribution. There was no such difference in the vertebrobasilar distribution. This study is also interesting because it reports male predominance as an independent factor for early seizures after stroke and also EEG findings. All patients with seizures had abnormal EEGs: nonspecific focal slow

waves in 43 patients, bilateral slow waves in 18, periodic lateralized epileptiform discharges (PLEDs) in 15, paroxysmal features in 10, and electrical partial SE in 4.

A second large, prospective, population-based study was conducted in Besançon, France *(21)*. Out of 3205 patients with first-time ischemic or hemorrhagic stroke, 159 (5%) had first-time seizures. Early-onset seizures occurred in 57 (1.8%) patients, and late seizures occurred in 102 (3.2%) patients. During a mean follow-up period of 47 mo, 68 of 135 (50%) patients with a first poststroke seizure experienced seizure recurrence. A second seizure occurred more often in patients with late as opposed to early seizures ($p < 0.01$). Occipital involvement and late-onset first seizure were independent predictors of multiple seizure recurrences.

A large European population study was conducted in England in the Oxfordshire community *(8)*. Over 4 yr, 675 patients with first stroke were registered from a study population of about 105,000. Onset seizures (within the first 24 h) occurred in 14 (2%) of acute stroke patients and were generalized in 7, simple partial in 6, and complex partial in 1. The risk for onset seizures was higher in patients with SAH (6%) and ICH (3%) than in patients with ischemic stroke (2%). Onset seizures conveyed a 7.5 times higher risk (95% CI 2.5–23) for subsequent seizures in comparison to patients with acute stroke but no onset seizures. In the actuarial analysis, the cumulative risk for seizures after ischemic stroke was 4.2% (2.2–6.2%) in the first year and 9.7% (3.7–15.7%) in 5 yr. The risks for seizures from ICH were 19.9% (1.5–38.3%) and 26.1% (0–54.8%) and from SAH 22% (2.6–41.8%) and 34.3% (0–100%), respectively. Survivors of total anterior circulation infarction had a 34% (12–57%) risk for poststroke seizures within 2 yr, a risk much higher than in those with other stroke subtypes. On the other hand, the lowest risk for seizures was found in those patients with lacunar strokes (only 3% developed seizures) and in those who were independent at 1 mo poststroke (actuarial risk at 5 yr 4.2% [0.1–8.3%]). Compared with the general population, ischemic stroke conveyed a 29-fold increased risk for seizures in the first year and a 21-fold increased risk in the second year. This difference was accentuated in the over-65 age group, where the risk for seizures in the first year was 76-fold increased compared with the general population without stroke. Interestingly, in this age group and during the second year, the risk for seizures, although still higher than for the general population, was lower than for the other age groups (17.2-fold increase vs 18.5 to 23.2-fold increase in patients age 65 yr and older). Thus, younger patients were noted to have a dramatically increased risk for seizures during the first year after stroke, which dropped during the second year.

Another population based study was conducted in Copenhagen, where 1195 patients with acute stroke out of a population of 240,000 inhabitants were followed for 3 yr *(18)*. Early seizures (within the first 14 d after stroke) occurred in 4.2% of patients, most within the first 72 h (86%). Early seizures were related to the severity of stroke only, as estimated by the Scandinavian Stroke Scale (SSS). For each 10-point increase in the SSS, the risk for early seizures increased by a factor of 1.65 (95% CI 1.4–1.9). This study did not include patients with SAH. Although ICH was more frequent in patients with early seizures than without (17 vs 7%), in the multivariate analysis it was not a predictor of seizures. Mortality in patients with

early seizures was 50% (vs 20% in patients without seizures), but seizures did not stand as an independent predictor of mortality in the multivariate analysis: only stroke severity predicted mortality. Indeed, in survivors this study found that early seizures were associated with a better outcome. The authors explained this finding by suggesting that seizures were emanating from a larger ischemic penumbra, which represents salvageable brain tissue.

In another population based study, the Northern Manhattan Stroke Study (NOMASS), seizures occurred in the first 7 d of the stroke onset in 4.1% of all 904 patients enrolled and in 3.1% of 704 patients with ischemic strokes *(41)*. The most common type was complex partial seizures (48.7%), followed by primary generalized (24.3%), simple partial (10.8%), and undetermined (16.2%) seizures. Compared with ischemic infarcts, seizures post-ICH conferred a 2.4-fold increased risk for subsequent seizures (95% CI 1.2–5.2). Compared with deep infarcts, lobar infarcts conferred an 11 times increased risk for seizures (95% CI 2.6–47.6). Deep and lobar ICH, as well as SAH also correlated with a significantly higher risk for seizures than deep ischemic infarcts (OR 7.9, 95% CI 1.4–43.6; OR 25.3, 95% CI 5.1–125.2; OR 13.2, 95% CI 2.7–86.4, respectively). In a subgroup with recorded National Institutes of Health Seizure Scores (NIHSS), seizures were more commonly associated with NIHSS > 15 on admission. Early seizures following ischemic stroke were not independently predictive of 30-d case fatality, a finding that was in conflict with results of earlier studies *(17)*.

Finally, a recent large prospective study from Lausanne, Switzerland, using the Lausanne Stroke Registry, reported 43 of 3628 (1.2%) patients with seizures *(42)*. The patients with seizures were matched for age, sex, and location/type of lesion with two controls without seizures from the same cohort. Early seizures (within the first 24 h) occurred in 23 of 3270 (0.7%) patients with ischemic stroke and 14 of 352 (3.97%) patients with ICH. Patients with infarcts were statistically less likely than those with ICH to develop seizures. Hemorrhagic infarcts were associated with seizures, but embolic infarcts were not. All lesions in patients with seizures involved the cortex, except for three (one deep posterior circulation infarct and two striatocapsular ICHs). In the multivariate analysis, a high blood cholesterol level was an independent predictor for decreased risk for early seizures (OR 0.18, 95% CI 0.06–0.54).

Table 1 summarizes the aforementioned studies of stroke and seizures, as well as percentages of early, late, recurrent (epilepsy), or total seizures.

Status Epilepticus

SE is defined as a seizure or a series of repetitive seizures that lasts more than 30 min without recovery between episodes *(43,44)*. SE may be an additional risk factor for increased mortality and morbidity after stroke through systemic metabolic changes, increased risk for herniation secondary to elevated intracranial pressure, cardiac arrhythmias leading to sudden death, or increased risk of aspiration pneumonia *(41)*. Thus, SE is an unquestionable reason for admission to the ICU.

Table 1
Studies With Reported Seizure Incidence After a Stroke

Study	Type of study	No. of patients	Type of stroke	Incidence			
				Total seizures	Early seizures	Late seizures	Epilepsy
Louis and McDowell (10)	R	1000	Isc	7.7%	3.3%	2.7%	3% early, 81% late
Black et al. (35)	R	827	Isc, hem	10%	57%[a]	43%[a]	
Gupta et al. (32)	R	90	Isc		33%[a]	1 yr 40%[a] 2 yr 24%[a]	39%[a]
Sung et al. (33)	R	118	Isc	5.9%	11%	66%[a]	35% early[a] 90% late[a]
Lancman et al. (6)	R	230	Isc, ICH	10%	5.4%	2.7%	
Shinton et al. (11)	P	230	Isc, ICH, SAH		5.7%		
Kilpatrick et al. (9)	P	1000	Isc, ICH, SAH		4.4%	32% early[a] 10% without early[a]	
Lo et al. (15)	R	1200	Isc, ICH, SAH		2.5%		
Milandre et al. (12)	R	2016	Isc, ICH	3.9%	1.4%	2.5%	1.7%
Daniele et al. (37)	R	4425	Isc, ICH	Isc 4.7% ICH 5.7%	Isc 2.6% ICH 3.6%	Isc 2.1% ICH 2.1%	
Arboix et al. (38)	P	1099	Isc, ICH, SAH		2.5%		
Bladin et al. (7)	P	1897	Isc, ICH	Isc 8.6% ICH 10.6%	Isc 4.8% ICH 7.9%	Isc 3.8% ICH 2.6%	Isc 2.1% ICH 2.6%
Vespa et al. (39)	P	109	Isc, ICH	Isc 6% ICH 28%			
So et al. (40)	R	535	Isc		6%	1 yr 3% 5 yr 7.4% 10 yr 8.9%	
Giroud et al. (5)	P	1640	Isc, ICH, SAH	Ath 4% Card 16.6%	5.4%		

Table 1 (continued)
Studies With Reported Seizure Incidence After a Stroke (continued)

Study	Type of study	No. of patients	Type of stroke	Total seizures	Incidence Early seizures	Incidence Late seizures	Incidence Epilepsy
Berges et al. (*21*)	P	3205	Isc, hem	Lac 1% TIA 1.7%	1.8%	3.2%	50%[b]
Burn et al. (*8*)	P	675	Isc, ICH, SAH	5% Isc 4.2/9.7% ICH 19.9/26.1% SAH 22/34.3%	2%		
Reith et al. (*18*)	P	1195	Isc, ICH	4.1%	Isc 3% ICH 8%		
Labovitz et al. (*41*)	P	904	Isc, ICH, SAH		Isc 3.1% ICH 7.3% SAH 8%		
Devuyst et al. (*42*)	P	3628	Isc, ICH	1.02%	Isc 0.7%[c] ICH 3.97%[c]		
Neau et al. (*78*)[d]	R	65	Isc	10.8%	2.4%	1 yr 3.1% 3 yr 5.5%	2.3%
Lamy et al. (*19*)[e]	P	581	Isc				

P, prospective; R, retrospective; Isc, ischemic; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; hem, hemorrhage; Ath, atheroma; Card, cardioembolic; Lac, lacunar; TIA, transient ischemic attack.

[a] Of patients with seizures.
[b] Of survivors with first seizure.
[c] Excluding six patients with prodromal seizures.
[d] Age group 15–45 yr.
[e] Age group 18–55 yr.

Acute stroke is the third most common cause for SE *(44)*, accounting for approx 20% of all SE cases *(45–47)*. In a retrospective study, 8% of all initial poststroke seizures presented as SE (6% focal and 2% generalized) *(32)*. SE was more common with early-onset seizures (14%) than with late (5%) but did not occur as recurrent seizures. This was demonstrated in the largest pre-CT retrospective study of seizures following nonembolic cerebral infarction, which found the majority of SE attacks to occur in the acute poststroke phase *(10)*.

In another retrospective study, SE occurred in 13% of 118 patients with thrombotic stroke and was generalized tonic–clonic (GTC) in 60%. This latter study reported only one patient with SE as the initial stroke manifestation and another three with SE in the acute stroke phase: 60% of patients had SE as late seizure manifestation postinfarction *(33)*. Milandre et al. found that 14% of their patients with initial poststroke seizures were in SE *(12)* and Lo et al. reported that 10% of early seizure patients were in SE *(15)*. In the first 7 d following an ischemic stroke, SE occurs in 0.9% of patients (NOMASS-population based study) and represents 15.8–27% of all seizures after stroke *(41,48)*.

In the large, prospective, population-based study conducted in Besançon, France *(48)*, out of 3205 patients with first-time strokes, 159 (5%) had first-time seizures. SE occurred in 31 of 159 (19%) patients with poststroke seizures. Partial SE occurred in 12 patients, nonconvulsive SE (NCSE) in 10, generalized seizures in 6, and unclassifiable events in 3 patients. SE occurred in 22 of 2742 (0.8%) patients with ischemic stroke and 22 of 116 (19%) patients with ischemic stroke who had poststroke seizures. SE occurred in 9 of 463 (1.9%) patients with ICH and 9 of 43 (21%) patients with ICH and poststroke seizures. There was no significant difference between the two etiologies of stroke (ischemic stroke or ICH) regarding the occurrence of poststroke SE. In 4 of 3205 (0.12%) patients, stroke initially manifested as SE, and in 17 of 159 (11%) SE occurred as the first poststroke epileptic symptom. In patients with SE, it manifested as the first epileptic syndrome in 17 of 31 (55%) patients (in 7 as "early" SE—within the first 2 wk—and in 10 as "late" SE), and in 14 patients it followed another seizure after the stroke (in 2 patients it was "early" SE, and in 12 patients it was "late" SE). In an average 47-mo follow-up of the 16 of 17 surviving patients with SE as the first epileptic symptom, only 3 (19%) developed additional episodes of SE and 50% were SE or seizure free. By contrast, all 14 patients with SE after one or more seizures had recurrences: 5 with SE (36%) and 9 (64%) with only seizures. Thus, SE as the first epileptic symptom was associated with a lower risk for subsequent seizures ($p < 0.01$). Such favorable association was not noted with early or late occurrence of SE. Fifteen out of 31 (48%) patients with poststroke SE died. In 5 patients (16%, all with infarction) SE was considered to be the direct cause of death. There was no significant difference in mortality for patients with poststroke seizures and poststroke SE. Permanent neurologic deterioration after SE occurred in 2 patients only, and transient deterioration occurred in 13 patients. However, there was no radiological change in these 15 patients. In another large, multicenter study of 346 patients with generalized

convulsive SE, mortality reached 11% in those patients with stroke as the precipitating cause *(45)*.

Another large, retrospective hospital-based study was reported from Turkey *(49)*. Out of 1174 patients with first-time stroke, 180 (15.3%) developed poststroke seizures, of which 17 (9%, or 1.45% of the whole cohort) developed SE. Twelve patients manifested SE after ischemic stroke and five after ICH. There were no differences between the group with SE and the group with poststroke seizures regarding sex, age, stroke risk factors, seizure types, EEG findings, stroke type (ischemic or hemorrhagic), topography or cortical involvement, or size of the lesion. However, SE occurred more frequently among more disabled patients (Rankin scale >3, $p = 0.002$). Early-onset (within the first week) SE was found in 7 of 17 patients, of whom SE occurred as the first epileptic symptom in 6 (stroke begun as SE in 2 patients) and as SE after at least one seizure in 1 patient. Late-onset SE was found in 10 of 17 patients, of whom SE occurred as the first epileptic symptom in 3. Five of seven patients with early onset SE and none with late-onset SE experienced recurrence of SE ($p = 0.003$). Mortality was not different among patients with SE (53%) and those with poststroke seizures (50%). However, it was higher in those patients with early-onset SE than in those with late-onset seizures ($p = 0.049$). Death was the direct consequence of SE in two patients (12%). Poor functional disability was the only independent clinical factor for developing poststroke SE; for mortality after poststroke SE, age was the only such factor.

In the large prospective study from Lausanne, Switzerland, SE was reported in 3 of 37 (8%) patients with early seizures after stroke but in only 0.08% of all patients with ischemic infarction or ICH in this cohort *(42)*.

Table 2 is a summary of the aforementioned studies reporting SE incidence after stroke.

Pathophysiology

Although the vast majority of seizures follow stroke, they can also precede it. Many studies excluded epileptic patients from the analysis if they suffered a stroke and had concurrent seizures. However, others reported the outcomes in these patients with "vascular precursor epilepsy" *(10,33)*. In one particular study from the United Kingdom, 46% of patients who developed seizures after acute stroke were epileptics, raising the possibility that epileptic patients may have more frequent seizures after a stroke than nonepileptic patients *(11)*. This could be explained either through recurrent or continuous focal ischemia capable of inducing an epileptogenic cortical focus or the activation of epileptiform discharges by regional hypoxia in patients with partial or primary generalized epilepsy, a mechanism not yet demonstrated in nonepileptic patients *(3)*.

In another study from Taiwan, 4 patients had seizures preceding the onset of thrombotic stroke by periods ranging from a few hours to 2–3 d *(33)*. In the Oxfordshire study, 2% of patients had a seizure in the year before the stroke, a threefold increase over the general population *(8)*. Another case-control study of 230 patients showed an eightfold increased risk of epilepsy before stroke *(50)*. More

Table 2
Studies With Reported SE Incidence After a Stroke

Study	Type of study	No. patients	Incidence of SE	Comments
Sung et al. *(33)*	R	118	15%	0.8% initial stroke manifestation
Kilpatrick et al. *(9)*	P	1000	0.4%	Patients with early seizures
Lo et al. *(15)*	R	1200	0.25%	Patients with early seizures
Milandre et al. *(12)*	R	2016	0.5%	
Gupta et al. *(32)*	R	90	8%	14% of patients with early seizures
				5% of patients with late seizures
Labovitz et al. *(41)*	P	904	0.9%	
Rumbach et al. *(48)*	P	3205	Isc 0.9%	0.12% initial stroke manifestation
			ICH 1.9%	19% of patients with SE had recurrent SE, when this was first epileptic symptom
				36% of patients with SE had recurrent SE when SE followed seizures
Velioglu et al. *(49)*	R	1174	1.45%	0.17% initial stroke manifestation
			Isc 1%	71% of patients with early-onset SE had recurrence
			ICH 0.45%	0% of patients with late-onset SE had recurrence
Devuyst et al. *(42)*	P	3628	0.08%	Excluding six patients with prodromal seizures
Lamy et al. *(19)*	P	581	0.34%	Age group 18–55 yr

P, prospective; R, retrospective; Isc, ischemic; ICH, intracerebral hemorrhage.

recently, the previously cited large prospective study from Switzerland reported 6 of 3628 (0.16%) patients with seizures within the week preceding the stroke onset *(42)*. Three patients had infarcts and three had ICH. The authors suggest that these prestroke seizures are caused by an initially preclinical lesion, which because of rebleeding, developing edema, or extension or dysfunction of adjacent or remote structures (diaschisis) evolves into a clinical stroke syndrome. Because of CTs revealing that up to 11% of patients with first clinical strokes have asymptomatic cerebral infarctions (half of which involve the cortex) *(51)*, it is conceivable that the preceding seizures arise from these asymptomatic lesions *(33)*. Two studies support this theory. In the first study, 15 of 132 (11.4%) patients with late-age-onset seizures and no history of stroke had infarcts on CT of the head vs 2 of age- and sex-matched controls ($p = 0.003$). However, 60% of these infarcts were lacunae *(52)*. In another study, 75 of 387 (19%) of patients older than age 50 yr with new-

onset seizures had ischemic lesions on CT of the head, making cerebral vascular disease the most frequently identified cause of late-in-life-onset epilepsy *(31)*.

Onset seizures after acute stroke have common features with acute seizures after traumatic brain injury and imply a common pathogenesis *(7,8)*. Because there may be a free-time interval between the development of late seizures after early poststroke seizures, the pathophysiologic mechanisms may differ between early and late seizures or may be evolving in time *(12)*. Early seizures are thought to emanate from electrically irritable tissue in the penumbra of the lesion *(53,54)*, as a result of regional metabolic dysfunction and excitotoxic neurotransmitter release, such as glutamate. Dysfunction of inhibitory circuits related to γ-aminobutyric acid (GABAergic) is another possibility. Accumulation of Ca^{2+} and Na^+ inside the cell results in depolarization of the cellular membrane and the activation of several intracellular cascades. This has been shown in animal models of stroke, where cortical neurons in the neocortex and hippocampus had altered membrane potentials and increased excitability *(55,56)*. In a rat model, Nedergaard and Hansen showed that the penumbral depolarization after middle cerebral artery (MCA) occlusion are either spreading depression waves (from K^+ or glutamate release from the core of the infarct) or ischemic depolarizations (because of blood flow fluctuations around the threshold of anoxic membrane failure) *(57)*. These derangements do not remain stationary but constitute an evolving process. In a rat model of forebrain ischemia a differential seizure threshold to infused proepileptic agents was seen to be changing over time *(58)*. Thus, it is suggested that after an initial critical period, estimated around 3 h, the progression of the penumbra tissue toward necrosis leads to lessened epileptogenic activity, which accounts for the decrease in seizure frequency between 3 and 24 h after stroke *(42)*. These findings are supported by another neurophysiological study using transcranial magnetic stimulation, where 6 of 84 patients with stroke showed a decrease in duration of the silent period in either the arm or leg of the affected side in comparison to the unaffected limb *(59)*. Five of these six patients had early or late poststroke focal seizures and no interictal epileptiform activity on the EEG. The authors suggested that this finding was the result of decreased cortical inhibitory activity related to functional or structural impairment of GABAergic interneurons.

Late seizures probably are caused by gliosis and the development of meningocerebral cicatrix, leading to persistent hypoperfusion and anoxia, dendritic deformation, and hypersensitivity or denervation supersensitivity *(3,32,54)*.

A summary of possible mechanisms for seizures in varying temporal relationships to stroke can be found in the work of Armon et al. *(3)* and Silverman et al. *(54)*. Poststroke seizures are associated with more severe brain ischemia as shown by positron emission tomography *(60)*. Seizures associated with migraine may be warning signs of an underlying cerebral infarction *(61)*. A causal relationship between TIAs and seizures has been difficult to establish. Repetitive involuntary movements in association with TIAs have been reported. EEG in these patients did

not show epileptiform activity, and the movements did not respond to phenytoin *(3,62)*.

Although the involvement of the cerebral cortex after ischemic stroke is thought to be necessary for the occurrence of seizures, there have been several reports of seizures associated with lesions involving subcortical structures. For instance, lacunar infarcts have been implicated in the development of seizures, either through more widespread cerebrovascular disease and involvement of adjacent cortex not apparent on the CT of the head or because subcortical lesions, such as those in the caudate head, may induce seizures *(5,26)*. In the prospective study from Birmingham, England, 4 of 13 patients with seizures after acute stroke had subcortical lesions *(11)*. Only 3 of 273 (1%) patients with lacunar infarcts had seizures in the previously quoted large prospective study from Dijon, France *(5)*. In the same population, the authors reported in a different study that 11 of 13 (85%) patients with seizures and CT-proven lenticulostriate strokes had an associated ipsilateral posterofrontal or anterotemporal cortical ischemic lesion demonstrated by magnetic resonance imaging (MRI). Inspection of single photon emission images showed that 13 of 13 (100%) patients had decreased cerebral blood flow (CBF) in the ipsilateral frontal area. Also, in patients with a lenticulostriate stroke, larger subcortical and ipsilateral cortical ischemic lesions were predictive of seizures *(63)*. In the Oxfordshire study, 5 patients (3%) with lacunae had seizures *(8)*, and another 5 patients with lacunal and grand mal seizures have been reported in a case series from Israel *(64)*. In the multicenter, prospective SASS study, 2.6% of patients with lacunae developed seizures, but 7 of 8 had also other identifiable reasons *(7)*.

Finally, in a prospective hospital-based registry, 113 patients with nonlacunar subcortical infarcts were studied. Seizures occurred in 4 (3.5%) of these patients, all with striatocapsular infarcts: two within the first 24 h, one within the first month, and one within the first year. Cardioembolic strokes were more common in patients with seizures *(65)*. Other large studies have not found an association between lacunae and seizures *(9)*.

Seizures associated with embolic infarcts may be caused by commonly seen hemorrhagic conversion, since iron deposition in rat brain tissue is known to be epileptogenic *(66)*. In the same way, iron deposition may play a significant role in seizure development after ICH, although this mechanism does not adequately explain the early onset frequently seen. In addition, thrombin is thought to play a significant role in seizures after ICH. In a rat model of ICH, thrombin injected into the brain at concentrations found in hematomas produced brain edema and immediate focal motor and electrographic seizures in all animals. When a-NAPAP, a thrombin inhibitor, was added to the thrombin injection, none of the animals had clinical or EEG seizure activity and brain edema was reduced *(67)*.

How much do seizures affect the evolution of the triggering stroke? The effect of seizures on the infarcted area, through hypoxia, lactic acidosis, ionic changes, and a higher metabolic demand of the brain, is thought to lead to persistent worsening of the neurologic deficits *(17,68)*. In one particular study, persistent partial

motor poststroke seizures led to persistent worsening of the prior neurologic deficit in 10 of 48 patients, without new CT or MRI findings *(68)*. However, several other studies have failed to demonstrate worsening of prognosis after poststroke seizures *(9,11,18,41)*.

EEG Findings

Occasionally, EEG may be helpful in the ICU in the evaluation of poorly defined poststroke neurological symptoms *(54)*, such as focal weakness (Todd's paralysis) or coma (resulting from NCSE) *(69)*. Conventional analog EEG, computer-assisted digitized EEG and CEEG recordings have all been used in the ICU *(69,70)*. Normal EEG after poststroke seizures has been reported in 4–15% of cases *(9,12,15,32)*. Vespa et al., who used CEEG monitoring in the ICU, concluded that electrographic poststroke seizures are four times more frequently detected than clinical poststroke seizures *(39)*.

Abnormalities on the EEG may have a differential predictive value regarding the development of seizures after cerebral infarction. Holmes found that 98% of poststroke patients with sharp waves, spikes, and PLEDs on the EEG developed seizures but did not correlate these findings with seizure recurrence *(13)*. Twenty-six percent of patients who developed poststroke seizures had PLEDs in this study, whereas only 2% of those never had one. The prognostic significance of poststroke PLEDs has also been emphasized in another retrospective study, which noted that all four patients with PLEDs on the initial EEG had recurrent seizures *(32)*.

Conversely, in patients with poststroke seizures, focal irritative abnormalities (electrographic seizures, epileptiform abnormalities, PLEDs) can be found on the average in one-fourth of cases and focal slowing in two-thirds *(12,15,32)*. Epileptiform abnormalities on EEG performed within the first 24 h ("unless the patient was critically ill") were found in 14% of patients with peristroke seizures in a large recent prospective study *(42)*. The specificity of the test is poor, because similar findings are not uncommon in patients with stroke without seizures *(12)*. The frequency of irritative abnormalities can be influenced by the timing and the repetition rate of the test. This may explain why in a prospective study from Denmark, epileptiform abnormalities were reported in only 2 of 77 (2.6%) patients with supratentorial strokes *(23)*. EEGs were obtained in all patients within the first week after the stroke and repeated at 3 and 6 mo. All seven patients who developed epilepsy in this series had focal δ and θ activity on the EEG. One patient who had epileptiform activity at 3 mo poststroke later developed epilepsy, and another had such activity on the first EEG recorded 6 d after stroke and 5 d after the first seizure. The authors conclude that EEG was not helpful in determining the risk for developing epilepsy.

Neuroimaging

Diffusion-weighted MRI (DWI) and apparent diffusion coefficient (ADC) changes have been well-described during acute ischemic stroke. In the acute phase, because of energy substrate depletion and Na^+, K^+-ATPase pump failure, ionic

changes lead to cytotoxic edema and decreased diffusion of water. On DWI, ischemic brain appears brighter (high signal) than normal brain, whereas it is darker on ADC maps (low ADC = decreased signal). Later, when the cells die and cellular membranes are disrupted, these changes reverse (decreased DWI signal and increased ADC signal). However, neuroimaging changes have also been reported after repetitive seizures or SE or NCSE *(71)*, making interpretation more difficult when these conditions coexist. Low-density changes on CT and high signals on T2-weighted MRI (that do not respect vascular territories), leptomeningeal contrast enhancement (indicative of alteration of the blood–brain barrier and vasogenic edema), local hyperperfusion on magnetic resonance angiography and cerebral activation on functional MRI, all reversible, have been well-associated with partial epilepsy and could help differentiate between ischemic stroke and seizure activity *(72,73)*. Senn et al. reported a patient with partial SE who had high DWI and ADC signal in the effected areas at the onset of seizures. Seven days later, DWI signal had regressed and ADC had further increased; 10 d later, there was marked regression of all signals and signs of focal atrophy *(72)*. These findings contrast with those of Lansberg et al., who reported three patients with complex partial SE and decrease in ADC on the first day *(73)*. These differences may be the result of timing of the MRI during SE. So far, to our knowledge, no data exist regarding neuroimaging findings of poststroke seizures, except for one patient with mitochondrial encephalomypathy–lactic acidosis syndrome and recurrent SE *(74)*.

Poststroke Seizures in the Young and Elderly

Nonhemorrhagic stroke in young patients (<45 yr) accounts for 3–10% of all infarctions and has low mortality (range: 1.5–8%) *(75–77)*. Only a few studies have examined the incidence of poststroke seizures in this younger population.

In a retrospective analysis of 65 young stroke patients (age 15–45 yr), followed for an average 32 mo (range: 12–59 mo), the incidence of seizures was 10.8%, and all occurred in patients with carotid artery territory infarction *(78)*.

In a prospective, multicenter European study (the PFO-ASA study), 581 patients with cryptogenic ischemic stroke, age 18–55 years, were followed for seizures for an average of 38 mo *(19)*. None of the six deaths was related to the occurrence of a seizure. Early seizures (within 1 wk poststroke) occurred in 14 of 581 (2.4%) of patients, 71% of them within the first 24 h. Two patients developed SE, one as an inaugural event. Rankin scale ≥3 (OR 3.9, 95% CI 1.2–12.7) and cortical involvement (OR 7.7, 95% CI 1–61.1) were the only clinical and radiologic independent variables associated with early seizures. Late seizures occurred in 20 of 581 (3.4%) with a mean delay of 12.9 mo poststroke. Six of these patients had early seizures and 4 of 6 were on antiepileptic treatment when the first late seizure occurred. Early seizures (OR 5.1, 95% CI 1.8–14.8), cortical signs (OR 4.5, 95% CI 1.6–13.1) and size of infarct larger than one-half hemisphere (OR 9.7, 95% CI 3.1–30.8) were independent predictors for late seizure development. Recurrent, unprovoked late seizures were found in 11 of 20 (55%) patients with late seizures, and the risk for epilepsy was 2.3% within 3 yr in this patient population.

The incidence of seizures in the elderly is close to that in the first decade of life. With increasing age, more patients have an identifiable cause for their seizures, and thus more seizures may have a focal onset *(79)*. Luhdorf et al. followed all patients within a definite area who developed seizures after age 60 yr. In 32% of these patients, the dominant cause of seizures was previous stroke *(29)*. In a retrospective population-based study from Saskatchewan, Canada, 46 of 84 (55%) patients age 60 yr and older with new-onset seizures had acute or remote cause identified (symptomatic). Of those, 22 of 46 (48%, or 26% of all patients with new seizures) resulted from acute or old stroke. All patients with non-life-threatening strokes had excellent prognosis, with seizures resolving in all but one patient. No information is provided about the number of elderly patients admitted to an ICU in these studies *(80)*.

Similar findings were noted in a large, prospective epidemiological study conducted in southwestern France *(14)*. The annual incidence of seizures in patients older than age 60 yr was 127 out of 100,000. Cerebrovascular disease was the most frequently recognized cause in this age group and represented 36.6% of patients with spontaneous seizures and 54% of patients with confirmed epilepsy.

Treatment of Post-Ischemic Stroke Seizures

Seizures at the onset of an ischemic stroke are considered to be a contraindication for intravenous administration of tissue plasminogen activator (t-PA) *(81)*, although data addressing this issue are missing. In a prospective study from Calgary, Canada, 230 patients were eligible for intravenous t-PA (admission within the 3-h window) but did not receive the treatment for various reasons *(82)*. Seizures at the stroke onset were the reason for the exclusion in 2 out of 230 (0.9%) of these patients. In a recent large prospective study, 60% of peristroke seizures occurred between the stroke onset and 3 h (during the IN t-PA treatment window) and only 26% between 3 and 24 h *(42)*. This study does not report the number of patients with stroke admitted within 3 h of stroke onset to estimate the percentage of the patients with seizures.

The most recent guidelines from the Stroke Council of the American Stroke Association recognized that the available data regarding poststroke seizures are derived from level III–V evidence (nonrandomized concurrent cohort studies to anecdotal case series) *(83)*. The authors concluded that there are no data about the utility of administering prophylactic antiepileptic treatments and few data concerning the efficacy of these drugs in the treatment of poststroke patients who have experienced seizures. Their recommendation was to base the treatment on the established management of seizures complicating any acute neurological illness. The following paragraphs summarize the data available and provide an in-depth look at the problem an intensivist faces.

It has been mentioned that there are no randomized-controlled trials evaluating specific treatment options in poststroke seizures. Bladin et al. argue that any such trial would pose extensive logistic challenges and would likely be unethical *(7)*. Prophylactic treatment for seizures after ischemic stroke is controversial. The dura-

tion of treatment is also unknown. Should these patients be admitted to an ICU when they present with a seizure in the context of an acute or subacute stroke?

Armon et al. have summarized the rationales for treating seizures at the onset of a stroke as follows: (a) control of persistent or recurrent seizures (SE), (b) prevention of seizures within the first day of stroke, (c) prevention within the first 2 wk poststroke, and (d) prevention of recurrence of seizures after the first 2 wk or the appearance of late seizures *(3)*. We suggest adapting the same rationale to the ICU setting by tailoring it to the following issues: (a) whether to treat or not treat a seizure that accompanies a stroke, (b) whether to treat recurrent seizures or SE, (c) whether to treat preventively poststroke seizures, (d) whether to prevent late seizures from occurring after an early seizure, and (e) whether to prevent epilepsy from developing after early or late seizures.

The current consensus in ischemic stroke management is not to treat patients unless they present with a first seizure or are known as pre-existing epileptics. For a patient who has had prestroke seizures, the rationale for covering with antiepileptic agents is based on the prevention of pre-existing epilepsy to manifest in its usual form poststroke or as SE *(3)*. However, even before the occurrence of the first seizure, some subgroups of nonepileptic patients may be at higher risk for seizure development. Large infarct size, cortical involvement, hemorrhagic stroke, and severe stroke *(5–7,15,18,19,32,36,38,40,41,84)* are typical situations in which a physician could consider covering the patient with antiepileptic treatment to prevent early seizures, especially if other comorbidities make a seizure manifestation an unacceptably high risk for complications.

The occurrence of one or more seizures may trigger the decision to use antiepileptics, although that decision may also depend on the type and location of stroke. Because of the risk of progression to SE, further damage to the ischemic penumbra leading to deterioration of the stroke or aspirating oral secretions or vomitus, we believe these patients should be admitted and treated in a neurological ICU (NICU) or a stroke unit. Are there any data that support this approach? In the series of Milandre et al., 51% of patients with seizures developed recurrent seizures (multiple in two-thirds) *(12)*. In the series by Gupta et al., 39% of patients had recurrent seizures (multiple in 57%) *(32)*. In neither study was there any difference in the recurrence rate that could be related to whether the seizures occurred early or late poststroke. In the Oxfordshire study, 3% of patients with cerebral infarction developed a single poststroke seizure and another 3% recurrent seizures, which overall occurred infrequently. The percentages for those with total anterior circulation infarction were 5 and 11% and 2 and 1%, in those with lacunae, respectively. However, 40% of patients with seizures within the first 24 h after an ischemic stroke and 50% post-ICH developed later seizures, although the numbers are very small *(8)*. Patients with lobar ICH or SAH had 14 and 8% incidence, respectively, of early seizures in the Manhattan population study, and the authors suggested prophylaxis for these subgroups for the first 24 h only, because almost 90% of seizures occurred within that time frame *(41)*.

Usually late poststroke seizures are not encountered in the ICU unless one is dealing with SE. Occasionally, however, a patient who is admitted to the ICU for another medical reason develops seizures that cannot be related to a drug or a metabolic derangement. Or, with a patient who develops seizures in the context of a recurrent stroke, it may be difficult (if there is no clear focality in the seizure onset or in the EEG) to associate the seizure with the new or the old stroke. As with early seizures, there are data supporting the use of antiepileptic coverage for these late seizures. From the SASS study, although late onset seizures (after the first 2 wk) occurred in only 3.8% of all patients with ischemic stroke, they led to epilepsy in 55% of these patients, and their presence was the only independent predictor for the development of epilepsy *(7)*. This has been also noted in other studies *(33,40)* and in younger patient populations *(19)*.

The role played by antiepileptic medications in preventing early or late poststroke seizures is also unclear *(9,11)*. In a retrospective study, 88% of patients with postinfarction seizures were controlled with monotherapy, mostly phenytoin, whereas smaller percentage was initially started on multidrug regimen *(32)*. An Israeli group retrospectively compared 35 patients with postischemic stroke treated immediately with antiepileptic medications for 2 yr after their first early seizure with 26 patients who were untreated until they developed a second seizure *(85)*. The assignment was made based on the admission service that had accepted the patients. The mean time for the development of a first seizure poststroke was 5.7 d, and for the second the mean time was 15.2 mo. During the initial 2-yr postevent period, the group that was treated immediately had lower relapse (14.3 vs 38.5%, *p* = 0.03) and higher seizure free rates (85 vs 61%, *p* = 0.042). However, after discontinuing the antiepileptic treatment, the treated group had the same seizure risk as the untreated group during the period between the first and second seizures (4.8 vs 6.2%, *p* = 0.6). This protective role of antiepileptic medications was not confirmed in other larger studies. In a recent multicenter prospective European study of younger patients (age <55 yr) with cryptogenic ischemic stroke, antiepileptic treatment did not prevent late seizures in patients with early seizures *(19)*.

Which antiepileptic agents are most effective in preventing poststroke seizures is also unknown. Overall, poststroke seizures seem to be easily controlled, and monotherapy usually suffices. Because the majority of seizures have a focal onset, first-line drugs in the ICU are parenteral agents, such as phenytoin (PHT) or fosphenytoin *(54)*. However, if the patient's mental status and swallowing ability allow oral administration of other agents, such as carbamazepine or oxcarbamazepine, those should be considered. Because of more favorable side effect profile and tolerability, newer agents such as lamotrigine, also should be considered as monotherapy. Other oral agents that are approved only for adjunctive treatment and are commonly used as monotherapy, such as topiramate, leviracetam, zonisamide, and tiagabine, could also be used in individual cases. Gabapentin has been used as monotherapy in 71 patients with late poststroke seizures, followed for an average of 30 mo, in an uncontrolled study from Barcelona, Spain *(86)*. The initial dose of

Table 3
Treatment With Antiepileptic Medications After Ischemic Stroke

1. Infarct and preexisting seizures: continue or restart antiepileptic regimen; keep therapeutic levels.
2. Infarct and no seizures
    Observe
    Consider treatment if large, cortical infarct, with hemorrhagic component or significant comorbidities (lung, heart, presence of aneurysm, etc.) for at least 2 wk.
3. Infarct and early first seizure
    Start monotherapy. If subcortical or lacune, continue for 2 wk. If anterior circulation cortical infarct, continue for 1–2 yr (seizure-free interval). Assess with EEG before discontinuation?
4. Infarct and SE
    Treat according to SE protocol in the NICU. Continue treatment for at least 4 yr (seizure-free interval) if SE was the first epileptic symptom. Assess with EEG before discontinuation and individualize. Treat indefinitely if SE followed early or late seizures.
5. Infarct and late first seizure
    Treat with monotherapy for at least 2 yr (seizure-free interval). Assess with EEG before discontinuation and individualize.

gabapentin was established based on weight: 900 mg/d for patients weighing under 75 kg and 1200 mg/d for patients weighing over 75 kg. If seizures recurred, the dose was increased by 300 mg/d. Thirteen patients (18.3%) experienced one or more recurrent epileptic seizures during follow-up, but only two patients (2.8%) discontinued the drug because of poor seizure control. Recurrence rate of seizures in the first year was 8.35%. A greater proportion of patients with no seizures was found among patients who had partial seizures than among those with generalized seizures ($p = 0.045$). Overall, these patients achieved better control than patients with newly diagnosed nonvascular partial epilepsy *(87)*.

The duration of the antiepileptic treatment is also unknown. Most experts use the EEG together with the clinical picture and stroke type to decide about the length of treatment. Armon et al. suggested for cortical ICH and seizures a 12-mo seizure-free interval and an EEG without epileptiform activity as grounds to consider withdrawing the treatment. For nonhemorrhagic stroke and one or more GTC seizures (at the onset or early on) they suggested a 1- to 2-wk course with PHT, then tapering if the EEG does not show an epileptogenic focus. If such a focus is present, they suggested a longer treatment. The same approach was used for epilepsia partialis continua, with the objective of minimizing the likelihood of secondary generalization *(3)*.

Table 3 represents a suggested algorithm for the treatment of poststroke seizures.

INTRACEREBRAL HEMORRHAGE

Clinical Studies

Although there are no widely accepted guidelines for ICH admission to an ICU, most physicians prefer to admit patients with moderate- to large-size (>30 cc) hematomas to the stroke unit or ICU for initial observation. One of the signs of ICH, which would make an admission to the ICU particularly likely, is early seizures, although there are no data supporting that approach. Seizures post-ICH can develop with the same crude incidence rate in the ICU and in other non-ICU services *(88)* but probably could be recognized earlier and managed more safely in a unit environment if they recur.

Several studies have reported the incidence of post-ICH seizures ranging between 0 and 28% *(5,7,26,37,39,88–95)*, with the highest incidence reported from a NICU in which patients were monitored with CEEG *(39)*. No particular sex association with seizures has been reported *(39,94)*. At least one study has reported lower frequency of post-ICH seizures in black patients *(94)*. Most studies have found that posthemorrhagic stroke seizures occur more frequently than postischemic stroke seizures *(5–7,9)*, although a few failed to find this association *(11,35)*. For at least 50 yr, since one of the earliest studies, by Richardson and Dodge, cortical involvement has been postulated to be more common in patients who develop seizures *(96)*. As with ischemic stroke, most post-ICH seizures are of the partial type with or without secondary generalization in 67–71% of cases *(26,39,91,95)*. Only one study found seizures to be more often generalized *(94)*.

Most of the studies providing information about the natural history of ICH have limitations.

Using the Besançon Stroke Registry, Tatu et al. identified 350 patients with primary ICH *(92)*. Seizures occurred in 39 of 350 patients (11.1%) and were the presenting symptom of ICH in 20 of 350 patients (5.7%), although their incidence varied with the location of the hematoma: 22.7% with lobar, 8% with putaminal, 1.8% with thalamic, and none with cerebellar ICH. Among 191 patients admitted within 12 h of onset, 51 (26.7%) experienced an early clinical worsening, but no data are presented about the subgroup with seizures. In another study, however, seizures were not found to be associated with neurological deterioration in noncomatose patients with ICH *(97)*.

The vast majority of studies after CT became available are hospital-based and retrospective investigations.

An interesting study with clinical and radiological details (through medical record review) was conducted in the Bronx, New York *(94)*. Seizures occurred in 19 of 112 (17%) patients with supratentorial ICH, all within 24 h from the ICH onset. A major limitation of this study is that in all but one patient, seizures manifested before arrival at the emergency room. This may account for a possible overrepresentation of generalized (68%) vs focal (32%) seizures. Another limitation is the short median follow-up period of 60 d. Patients with bleeding diatheses (anticoagulants or alcohol-induced thrombocytopenia) and cortical extension of the

hemorrhage were more likely to have seizures. No association was found between seizure occurrence and level of consciousness or Glasgow Coma Scale (GCS) score on admission, hemorrhage size, presence of midline shift, or subarachnoid or intraventricular extension.

Another large chart review study from Taipei, Taiwan, reported 126 patients with seizures out of 1402 patients with ICH (9%) *(91)*. However, the authors excluded from their analysis patients who had any type of surgery post-ICH. In those medically treated patients, who were followed for an average of slightly less than 2 yr, seizures occurred in 4.6%. More than half were early seizures (within 2 wk), and in 30% they were the first manifestation of ICH. Overall, 90% of seizures occurred within the first year post-ICH. The incidence of epilepsy after ICH was 2.5%. Twenty-nine percent of patients with early seizures developed epilepsy compared with 93% of those with late seizures; we calculated the OR for seizure recurrence for late vs early seizures (OR 29.4, 95% CI 5.9–146.4, $p < 0.001$). More patients with lobar vs deep-seated hematomas developed early seizures, late seizures, SE, or epilepsy.

One retrospective study from New Orleans examined the incidence of seizures after primary or secondary (neoplasms or vascular lesions) ICH *(93)*. Thirty-three out of 222 patients (15%) had seizures within 12 mo of follow-up. Hematoma location played a role: 32% of frontal ICH had seizures, 36% with parietal, 37% with temporal, and only 6% with occipital. None of the patients with caudate head involvement or intraventricular hemorrhage (IVH) had seizures. Of patients with immediate or early seizures (up to 72 h after onset of ICH), 70% had recurrent seizures. All patients with seizures after the first 72 h had recurrences, but no patient had seizures while on antiepileptic treatment after the first 4 mo.

In a retrospective, hospital-based study from Palermo, Italy, 217 out of 4425 (4.9%) patients with acute stroke had one or more seizures *(37)*. Seizures after ischemic stroke occurred in 4.7% of patients and after ICH in 5.7%. In the ICH group, seizures heralded stroke in 3.3%, were early (within 2 wk) in 60%, and were late in 36.7% of cases. Lobar ICH and seizures were found in 67% of cases, subcortical in 20%, and massive in 13%. In another retrospective study from Rome, Italy, the authors reported seizures in 55 of 298 (18%) patients with primary ICH *(95)*. A limitation of this study is that almost 40% of ICH was diagnosed before the CT era. In 42% of patients with seizures, these were the inaugural symptom of ICH, in 18% they were early (within 2 wk), and in 25% they were late. Seizures were seen in 35% of lobar ICH and only 8% of deep-seated hematomas. Epilepsy developed in 9% of patients with inaugural, in 29% with early, and in 93% of patients with late seizures.

In a series of 123 patients with primary ICH, followed for an average of 4.6 yr or until death, 31 (25%) patients from Birmingham, Alabama, had seizures according to retrospective chart review *(26)*. In 50% of patients with seizures, these occurred within 24 h of the ICH, and in 13% seizures were the inaugural symptom. Overall, two-thirds of seizures occurred within the first 48 h. Cumulative seizure incidence

was 50% within 5 yr. Seizure incidence was highest with bleeding into lobar cortical structures (54%), low with basal ganglionic hemorrhages (19%), and zero with thalamic hemorrhages. Within the basal ganglia, caudate involvement predicted seizures, and within the cortex, temporal or parietal involvement also predicted seizures. Although cumulative seizure incidence was high (50%) by year 5, prevalence of recurrent seizures (epilepsy) was much lower: 13% in 30-d to 2-yr survivors and 6.5% in 2- to 5-yr survivors. The authors estimated the incidence of post-ICH seizures to be 15 times higher than in the the general population within the first 2 yr and 8 times higher within years 3–5. Hematoma size in this *(26)* and other studies *(7)* was not found to be associated with seizures.

In the prospective study from Dijon, France, the authors reported a 16.2% incidence of seizures in patients with supratentorial ICH and none in those with infratentorial ICH *(5)*. Seizures were more frequent in patients with lobar ICH and cortical involvement (22.7%) than in those with deep ICH (2.5%) or those with cortical infarction (6.8%, $p = 0.001$).

In a prospective multicenter international study, 1897 patients with acute stroke were admitted to teaching hospitals and followed for an average of 9 mo *(7)*. Seizures were present in 10.6% of patients with ICH. Early-onset seizures (within 2 wk) occurred in 7.9% of patients, and 57% of these occurred during the first 24 h. The 1-yr actuarial risk for seizures was 20% for patients with ICH. Recurrent seizures occurred in all patients with late seizures (after the first 2 wk). Based on a Cox proportional hazards model, ICH conveyed an almost twofold increased risk for seizures (OR 1.85, 95% CI 1.3–2.7, $p = 0.002$). The only independent predictor for seizures was cortical involvement by the ICH. According to the authors, a combination of sudden development of a space-occupying lesion with mass effect, focal ischemia, and blood products is thought to play a role in the development of early seizures after ICH *(7)*.

A recent prospective hospital-based study from Siena, Italy, found that in 57 of 761 (7.5%) patients, seizures followed spontaneous supratentorial ICH *(88)*. The crude incidence rate of seizures in the ICU was 5.1%, not different from other services admitting ICH patients. An interesting finding was that patients with a history of stroke did not have a higher incidence of immediate (within 24 h) or early (within 30 d) seizures after the index ICH than those without a history of strokes. Thirty-two (4.2%) patients had immediate seizures, the majority (62.5%) being simple partial ones. In a multivariate analysis, lobar location of ICH and smaller volume of ICH (≤18 cc) were independent predictors of immediate seizures (OR 4, 95% CI 3.45–4.65, $p < 0.001$; OR 1.6, 95% CI 1.02–4.5, $p = 0.009$, respectively). Only one patient with immediate seizures had recurrent seizures. Twenty-five of 650 patients who survived the first ICH day (3.8%) had early seizures; the majority (52%) were generalized seizures. Lobar location (OR 2.8, 95% CI 1.6–4.8, $p = 0.0002$), neurologic complications (OR 2.2, 95% CI 1.5–3.3, $p = 0.0002$), and prophylactic antiepileptic treatment (in this study phenobarbital, which reduces the risk of early seizures €OR 0.58, 95% CI 0.39–0.87, $p = 0.009$) were the only independent pre-

dictors for early seizures. Immediate, early seizures or SE were not independent predictors of in-hospital mortality. The cumulative actuarial risk for seizures was 7.2% and 8.1% within 5 and 30 d of ICH onset, respectively. For those with seizures and a mean follow-up of 59 mo, the risk was 27% for relapse within 5 yr and was associated with clinical events such as infarct, hematoma enlargement, and discontinuation of medications.

Prophylactic antiepileptic treatment was given in 65.1% of patients based on the judgment of the responsible physician. Younger patients, with larger hematomas and midline shift, were more likely to be treated. The risk for early seizures was reduced with prophylactic treatment only in patients with lobar ICH (OR 0.62, 95% CI 0.4–0.96, $p = 0.033$). The authors reach the interesting conclusions that the likelihood of immediate seizures is influenced by predisposing factors that are inherent to the ICH and that the likelihood of early seizures correlates with additional unpredictable events, which may induce or favor seizures.

Another recent prospective ICU study examined the incidence of poststroke seizures by means of CEEG monitoring *(39)*. All patients with ICH were preventively covered with antiepileptic treatment (PHT, with therapeutic levels of 14–18 mg/dL). None of the patients with ischemic stroke received such prophylaxis unless they had surgery, ventriculostomy, or seizures. Seizures occurred in 18 of 63 (28%) of patients with ICH and 3 of 46 (6%) patients with ischemic stroke (OD 5.7, 95% CI 1.4–26.5, $p < 0.004$). Most seizures (89%) occurred within the first 72 h after the insult, and most of them (76%) were nonconvulsive (unresponsive patients with absence of overt convulsions). In the ICH subgroup, where there was a trend of more AVM representation in the seizures subgroup ($p = 0.07$), seizures occurred more frequently with intraventricular extension of blood ($p = 0.04$) and with lobar rather than subcortical location of the hematoma (2, 0.59–7). However, more than one-third of post-ICH seizures (38.9%) developed with subcortical ICH locations. The NIHSS score increased more in the seizure group than in the group of ICH without seizures ($p < 0.05$), and the same was true for the midline shift at the level of the septum pellucidum ($p = 0.03$). There was a weak tendency toward larger ICH volume during repeat CT in patients with seizures than in those without ($p < 0.16$). By the same token a nonsignificant correlation with higher mortality was found in the group of ICH patients with seizures (27.8%) vs those with ICH without seizures (15%). In the multivariate analysis, seizures were independently predicted by age, location of ICH, presence of IVH, initial volume tercile (<30, 30–60, or >60 cc), but not by the initial NIHSS score. Outcome in patients with ICH was predicted by the initial NIHSS score and age. Seizures had only a trend effect ($p < 0.06$) on outcome as measured by Glasgow Outcome Score.

SE Following ICH

SE occurs in 0.8–1.9% of patients with ICH. In patients with ICH who develop seizures, SE occurs in 14–21% *(12,88,91)*.

The incidence of SE after ICH was specifically addressed in the large prospective, population study from Besançon, France *(48)*. ICH triggered SE in 9 patients or SE occurred in 9 of 463 (1.9%) of patients with ICH. Among patients with first-time poststroke seizures, 9 of 43 (21%) had ICH and SE. Although SE was following ICH more than twice as frequently as ischemic stroke, etiology did not reach significance for SE in this cohort. ICH was more common among patients with SE as the first poststroke seizure symptom (6 of 17, 35.3%), than among those with SE occurring after one or more seizures (3 of 14, 21.4%). In another study from Taiwan, SE was found in 11 of 1402 (0.8%) patients with ICH. Among the patients who developed seizures, SE occurred in 11 of 64 (17%). SE was the first-ever seizure type post-ICH in 9 patients and the first manifestation of ICH in 6 patients. Mortality in this series reached 36% for patients with seizures and SE, whereas it was 24% in those with seizures without SE *(91)*. In a recent study from Italy, SE occurred in 1.1% of patients with ICH and 14% of those who developed seizures post-ICH *(88)*. SE occurred exclusively in patients with lobar ICH, but in the multivariate analysis alcohol abuse was the only independent predictor for SE (OR 3.4, 95% CI 1.2–9.6).

Pathophysiology of Post-ICH Seizures

In the pathophysiology of ischemic stroke, iron contained in the hemoglobin residing in the clot is a known trigger for cellular depolarization in animal models, and the theory of seizure development after ICH is based on this fact *(66)*. However, the mechanism does not adequately explain the early onset of seizures frequently seen after ICH. Another factor thought to play a significant role in seizure generation after ICH is thrombin. When thrombin was injected into a rat brain at concentrations found in hematomas, it produced brain edema and immediate focal motor and electrographic seizures in all animals. When the thrombin inhibitor a-NAPAP was added to the thrombin injection, none of the animals had clinical or EEG seizure activity and brain edema was reduced *(67)*.

Treatment of Post-ICH Seizures

The appropriateness of treating seizures that follow ICH has not been addressed specifically in the literature; the same is true of the usefulness of prophylactic treatment, knowledge about which is only inferred from observational studies because randomized trials are lacking. The guidelines published by the Stroke Council of the American Heart Association emphasize this lack of evidence but suggest antiepileptic treatment for 1 mo and then tapering and discontinuation of the treatment if no seizures occur *(98)*.

Immediate, early seizures or even SE do not appear to increase mortality after ICH *(88)*, but their effect on post-ICH morbidity is not known. In one retrospective study, which also included ICH from underlying vascular or neoplastic lesions, patients were followed for 1 yr *(93)*. All patients with ICH from an underlying

lesion that had earlier been causing seizures were noted to have seizure recurrences despite antiepileptic treatment, but none after the first 4 mo.

The only study of ICU stroke patients evaluated with CEEG monitoring found a higher incidence of post-ICH seizures than of seizures following ischemic stroke, although all ICH patients were systematically covered with antiepileptic medications upon admission and none of the ischemic stroke patients was on prophylactic treatment *(39)*. The results of this study make us and others *(88,94,99)* believe that antiepileptic treatment should be given prophylactically to all patients with lobar supratentorial ICH or with cortical ICH involvement. Among lobar ICH patients, the temporoparietal location appears to confer a higher seizure risk *(26,90)*. Other high-risk subgroups include the elderly and those with high initial ICH volume (>60 cc) *(39)*. If neurological complications (such as brain ischemia or rebleeding) occur after the ICH, early seizures may occur more often, and prophylactic antiepileptic treatment may indeed be effective *(88)*. If the seizures occur after the first 2 wk, most authorities recommend long-term antiepileptic treatment *(95,100)* because late seizures are strongly associated with epilepsy development *(91)*.

The effect of surgery on occurrence of seizures is also unknown. The study by Faught et al. did not find any increase in the incidence of seizures: in their series, 22 of 31 patients with post-ICH seizures were symptomatic before any surgery and 9 only after a surgical procedure *(26)*. In one retrospective study, patients who had surgical clot removal had a higher incidence of late than early seizures (43 vs 33%), but only 1 out of 15 patients eventually developed epilepsy *(95)*. Prophylactic treatment aimed at preventing postoperative seizures does not seem to be effective: 5 of 27 (18.5%) patients in a chart review analysis had seizures while still on antiepileptics after surgery, in comparison to 3 of 17 (17.6%) who were never treated *(26)*. A recent study agreed with these findings: the rate of surgery was not different in patients with immediate or early seizures and those without seizures *(88)*. Thus, we do not recommend prophylactic treatment in the ICU just because the patient underwent a surgical procedure, if there are no other high-risk factors present.

Because alcoholic patients have more than threefold increased risk for SE after ICH *(88)*, we recommend antiepileptic treatment in this patient subgroup in the ICU with agents that increase GABA-ergic inhibition (benzodiazepines or phenobarbital [PB]).

Table 4 represents a suggested algorithm for the treatment of ICH-related seizures.

SUBARACHNOID HEMORRHAGE

Clinical Studies

All patients with spontaneous SAH should be admitted to the NICU; most of them will stay there longer than patients with other types of stroke. It is not unusual to witness abnormal motor activity and loss of consciousness at the onset of SAH, usually preceding the ICU admission. Many patients have opisthotonos or tonic

Table 4
Treatment With Antiepileptic Medications After ICH

1. ICH and preexisting seizures: continue or restart antiepileptic regimen; keep therapeutic levels.
2. ICH and no seizures
   Observe
   Consider treatment for 1 mo if the patient is older or has lobar ICH (especially temporal-parietal) or ICH with cortical involvement.
   Treat if there is an underlying structural lesion (AVM or other lesion) or history of alcohol abuse.
3. ICH and early seizure
   Treat for at least 2 yr (seizure-free interval). Assess with EEG before discontinuation?
4. ICH and SE
   Treat according to SE protocol in the NICU. Continue long-term treatment. Consider discontinuing treatment after at least 2 yr (seizure-free interval) if there were concurrent etiologic factors such as alcohol abuse that are not present at time of discontinuation. Assess with EEG before discontinuation.
5. ICH and late seizures
   Treat indefinitely.

extension posturing of the arms and legs. Studies examining the incidence of seizures published in the pre-CT era had several limitations. The clinical phenomena that were witnessed were seldom described, and most of the articles were not focused on this subject, but rather on other aspects of SAH. In addition, several changes took place in the management of SAH in the 1990s. The most important are early angiography and surgery, endovascular treatment, and modern management in the NICU, leading to a decrease in mortality from 49% to between 20 and 30% *(101)*. As a result of the improvements in diagnosis and treatment, the earlier and more recent cohorts may have different characteristics. Early seizures after SAH have been reported in 1.1–16% of patients *(102–108)* and late seizures in 5.1–14% *(103,105,107–111)*, depending on the definition used and inherent biases to the sampling of patients. In studies with aneurysmal SAH, anterior cerebral or communicating artery aneurysms had the highest incidence of seizures, followed by middle cerebral artery aneurysms *(105,112)*.

Although several pathophysiologic mechanisms for seizure development have been considered in early studies (e.g., ICP elevation, intracerebral hematoma, infarction, vasospasm), most experts now agree that the majority of the seizures described earlier were indeed nonepileptic phenomena, consistent with either acutely released brainstem reflexes or preterminal events secondary to decreased cerebral perfusion or brain herniation *(106,113)*. The pathogenesis of post-SAH seizures remains speculative and most likely is multifactorial. For early seizures, direct irritation of the cerebral cortex by blood seems to be a more plausible mechanism than the vasospasm that usually develops 4–7 d later. However, an association

of onset seizures to brain ischemia from an "ultra-early arterial vasospasm" described by Qureshi et al. *(114)* remains a possibility *(107)*. For late seizures, factors such as cerebral infarction or operative trauma may play a more important role *(103)*.

One of the first systematic approaches to evaluate the incidence of seizures after SAH was the retrospective study by Hart et al. from the pre-CT era *(106)*. These authors evaluated 100 patients with SAH and based their results on clinical data and, in the majority of cases, on unwitnessed seizures. There were 30 episodes of seizure activity in 26 patients. Nineteen percent of patients experienced seizures at the onset or within the first 12 h after SAH, most during the first few minutes. There was no correlation between those seizures and the incidence of rebleeding or the prognosis. Late seizures (after the first 12 h) occurred in 11 of 93 (12%) patients who survived. In 73% of these survivors, seizures manifested during acute rebleeding. Patients with acute rebleeding had a 20% incidence of seizures, almost the same as those who experienced seizures at the onset of the initial bleeding (19%). Overall, 90% of all post-SAH seizures were temporally related to acute hemorrhage. The mortality of patients with late seizures was 64%, and the mortality of those who survived the first 12 h after the initial SAH without late seizures was 38%, but the difference did not reach significance. Neither of the authors did find any difference in the rebleeding rate or mortality between patients treated with antiepileptic medications and those who never received any.

In a chart review study from Saskatoon, Canada, seizures were observed in 31 of 131 (24%) patients with spontaneous SAH not related to AVMs *(103)*. Early seizures (within 2 wk) were found in 20% and late seizures (with a mean follow-up of 23 mo) in 4%. Nineteen out of 26 (73%) early seizures occurred during the first 24 h post-SAH, and only 2 (7.7%) patients with early seizures developed late seizures beyond 4 wk. There was no difference in mortality between patients with and without early seizures, nor was a difference found in the incidence of intracerebral hematoma or rebleeding. No specific predilection for seizures in relation to the location of supratentorial aneurysms was reported, but no seizures occurred with infratentorial ones. The authors question the need for routine prophylactic long-term antiepileptic treatment for patients with early seizures.

Another study, from Detroit, that randomly selected 100 charts for review, reported prehospital seizures in 17.9% of patients post-SAH, with an additional 7.4% having questionable seizures *(112)*. In-hospital seizures developed in 4.1% of patients, a mean 14.5 d from ictus, and in 8% of discharged patients (all with prehospital and none with in-hospital seizures). This study is interesting because it reports ICU length of stay, which was longer for patients with seizures (median 15 d vs 10 d for those without seizures, $p = 0.06$). Seizures were more frequent in men than in women. There were no other clinical or radiologic predictors of seizures, although there was a trend for higher Fisher scores and Graeb IVH scores to be associated with a seizure. Intracerebral hematomas induced by SAH were not associated with seizures regardless of size. No difference between groups with or without seizures regarding mortality or discharge disposition was found.

A limitation of the Detroit study is the absence of multivariate analysis. However, other studies have found an association between post-SAH seizures and increased mortality and disability. In a prospective hospital-based study from Lisbon, Portugal, onset seizures (within the first 12 h) occurred in 16 of 253 (6.3%) patients with SAH *(104)*. Rebleeding (OR 8.4, 95% CI 2.8–25.1), severe disability at discharge or death (OR 4.1, 95% CI 1.4–11.6) were significantly more frequent in the univariate analysis in patients with seizures. Because, however, rebleeding did not happen on the same day as the seizure, it was difficult to establish a cause-and-effect relationship. Only one patient in that series developed epilepsy 1 yr later.

A retrospective series from Melbourne, Australia, reported on SAH patients with seizures who were matched for age and sex with two control patients who did not have seizures *(107)*. Thirty-two out of 412 (7.8%) patients had onset seizures (defined as occurring within 24 h of the onset of headache), all generalized, and all but one within 1 h of onset. Late-onset seizures were those that occurred between 24 h and 6 wk, and those patients were matched with five controls without late seizures. Late seizures occurred in 17 of 412 (4.1%) patients and were generalized in 11 (in 8 of them related to a rebleed), and simple or complex partial in 6 (of whom 5 had multiple seizures recorded). All but one of the patients with late seizures were on antiepileptic treatment. Onset seizures were independently predicted by the total score of blood on the initial CT described by Hijdra et al. *(115)* but not by GCS, loss of consciousness >1 h, history of epilepsy or hypertension, or aneurysmal etiology of SAH. Disability 6 wk after admission was predicted by onset seizures (OR 7.8, 95% CI 1.1–13.9), initial GCS <6 (OR 13.7, 95% CI 2.2–228), and cisternal blood score (OR 1.1, 95% CI 1.08–1.18). The proportion of patients with onset seizures declined with increasing age (23% in those <31 yr and 4% in those >50 yr). Remarkably, 71% of patients age 31 yr and younger with fatal outcome had onset seizures, compared with only 4% in those older than age 50 yr. Late seizures were independently predicted by onset seizures (OR 27.4, 95% CI 2.3–330) and rebleeding (OR 94.4, 95% CI 4.1–186), but not by aneurysmal etiology, initial GCS, amount of blood on CT, vasospasm, or hydrocephalus.

Several studies have reported on the incidence of seizures in a stroke population, including but not specifically focusing on SAH. In a large prospective study from Victoria, Australia, Kilpatrick et al. reported 6 of 71 (8.5%) patients with post-SAH seizures *(9)*. None of the patients with early seizures had late seizures after discharge *(36)*. The authors of the prospective study from Dijon, France, reported seizures in 4 of 24 (16.4%) patients with SAH *(5)*. In the prospective study, from Birmingham, England, seizures at the onset of SAH (24 h before or after the development of the neurologic deficit) occurred in 1 of 9 (11.1%) patients *(11)*. In the large study from Barcelona, Spain, 1 of 28 (3.6%) patients with first-ever SAH developed early seizures *(38)*. Finally, two population-based studies reported on the incidence of seizures after SAH: in the one from Oxfordshire, England, where 6 of 33 (18%) patients had either single or recurrent seizures, 2 (6%) patients with seizure at the onset *(8)*, and in the one from Manhattan (New York City), 4 of 50 (8%) patients had early seizures and 1 of 50 (2%) had SE *(41)*.

The issue of long-term development of epilepsy after SAH has been examined in several studies. In the only population-based study on this topic, patients treated between 1958 and 1968 for aneurysmal SAH were compared with the general population of Iceland *(116)*. Eleven out of 44 (25%) patients with SAH developed epileptic seizures, 70% being the same patients who had a seizure within the first 2 wk following SAH (OR 7, 95% CI 2.3–21.6). In this study, which predates modern neuroimaging and neurosurgical and NICU care, the patients with the more severe neurologic residuals had also a higher risk for developing epilepsy.

In a retrospective study of 177 patients with aneurysmal SAH from Kuopio, Finland, early seizures occurred in only 2 (1.13%) patients, late seizures in 25 (14%), and recurrent seizures in 21 (12%) *(108)*. Most seizures were partial or secondary generalized, with a mean latency of 8.4 mo after the operation. Preoperative Hunt & Hess grade was a significant factor for epilepsy (33% of grade III–IV patients developed epilepsy), and middle cerebral artery aneurysm location, complications of SAH (hematoma, vasospasm with infarction, shunt-dependent hydrocephalus), or persistent neurological deficits (hemiparesis, dysphasia, visual field defects) were markers for late seizure occurrence.

In another retrospective hospital-based study from Rotterdam, the Netherlands, 35 of 381 (9%) patients were noted to have one or more epileptic seizures 12 h to 1761 d (median: 18 d) after the initial bleed *(105)*. In this study, patients with SAH were observed in the ICU for 28 d or until death or surgery (usually on day 12), and seizures that occurred within the first 12 h following either the initial or subsequent hemorrhage, surgery, or hyponatremia were excluded from the analysis. In the multivariate analysis, a high cisternal blood score (graded semiquantitatively from 0 to 30 points) and rebleeding were independent predictors of epilepsy (OR 2.06, 95% CI 1.03–4; OR 3.02, 95% CI 1.23–7.43, respectively), even after exclusion of patients who received perioperative antiepileptic treatment.

In a prospective study from Auckland, New Zealand, 24 of 123 (20%) patients followed 4–7 yr after SAH had seizures: 2 at the onset, 9 in the first 2 postoperative weeks, 10 after discharge during the first year, and 3 after the first year *(117)*. Seizures were related to aneurysmal SAH. Age was an independent predictor of seizures (the younger the patient, the more likely the seizure) and so was the GOS score at 10 wk (the worse the score, the higher the likelihood to experience a seizure).

The most recent published study, from Columbia Presbyterian Hospital, in New York, was a prospective evaluation of the frequency and predictors of epilepsy 12 mo after SAH *(118)*. All patients were initially managed in a NICU and had received a loading dose of fosphenytoin. Antiepileptic treatment was discontinued after discharge from the hospital, unless the patients had a seizure. Thirty-one out of 431 (7%) patients had in-hospital seizures and an additional 9 (2%) had NCSE evaluated with CEEG monitoring. Seizures were more common in patients with prior epilepsy (33%). In patients without a history of epilepsy, seizures were associated with a higher mortality rate at 12 mo (65 vs 23% in patients without seizures, $p < 0.001$) and a higher incidence of epilepsy (17 vs 7% in patients without seizures, p
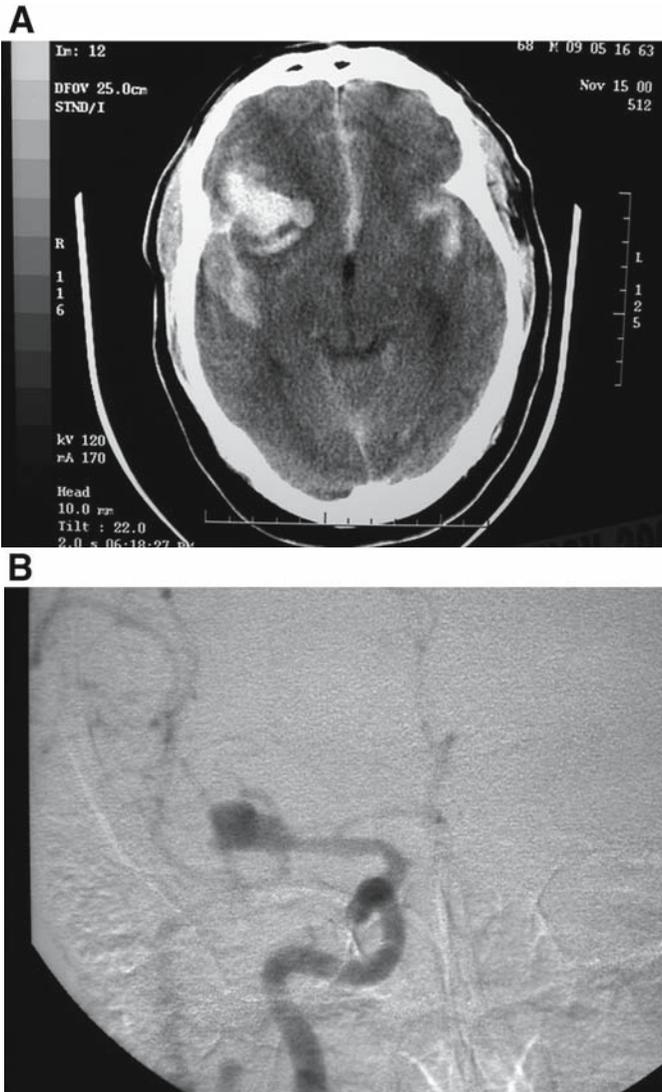
Fig. 1. This 68-yr-old African-American man was admitted with SAH and found to host a right MCA aneurysm, which was clipped on day 1. Six days later, the patient developed two episodes of left upper extremity shaking. (A) CT of the head demonstrating the SAH

= 0.36). Most (8 of 9, 89%) patients with NCSE were dead by 12 mo. New-onset epilepsy, defined as at lease 2 unprovoked seizures after discharge, occurred in 7% of patients with SAH (an additional 4% had only one seizure after discharge) and was independently predicted by the presence of subdural hematoma (SDH) or cerebral infarction at any time point. Most seizures were secondary generalized (76%).
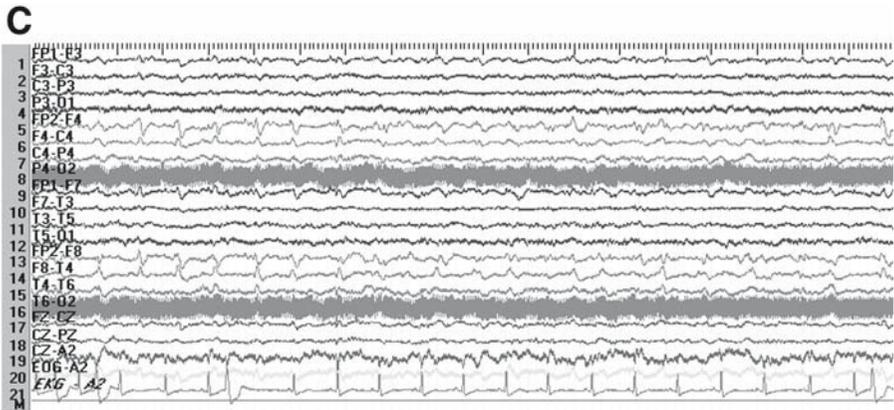
Fig. 1. *continued*

with a right frontotemporal large clot. (B) Cerebral angiogram revealing the right MCA aneurysm. (C) EEG recording obtained 1 h after the seizures, demonstrating semiperiodic sharp waves over the right frontal area and phase reversal over F8 on a θ–δ background. This interictal activity was partially affected by the iv administration of 2 mg of lorazepam. The patient was loaded with PHT and never experienced another seizure activity during the in-hospital period.

Patients who developed epilepsy at 12 mo were more severely disabled, had a reduced quality of life, and had increased anxiety, as measured by various scales.

Figure 1 presents an ICU patient who developed focal seizures, probably as a result of a combination of contralateral hematoma and surgical treatment of the aneurysm.

Treatment of Seizures After SAH

The main reason to use prophylactic antiepileptic treatment after SAH in the ICU is to decrease the likelihood of aneurysm rerupture, which usually has catastrophic consequences. Another reason is to avoid changes in the intracranial pressure (ICP) and cerebral blood flow (CBF), which could further compromise brain tissue perfusion in case of cerebral edema or vasospasm. Drugs that potentially reduce the seizure threshold, like ε-aminocaproic acid *(119)*, may be another reason of concern. Finally, the prevention of kindling effect of early seizures on the development of epilepsy may be another reason for prophylaxis, although recent data suggest that antiepileptics may only mask or suppress seizures, rather than preventing epilepsy from developing. Since there are no prospective, randomized trials, it is unclear whether antiepileptics can really do the job.

The chart review study from Detroit, revealed that 4 of 95 (4%) patients had an in-hospital seizure *(112)*. Three out of four patients were on antiepileptic medications (2 on phenytoin and 1 on carbamazepine) with therapeutic levels at the time of seizure. Seventy-three percent of the total cohort received a loading dose of

antiepileptic medication, and 99% of those a maintenance dose with phenytoin. Therapy was initiated within 24 h of hospitalization. The duration of therapy was not related to the occurrence of seizures. Antiepileptic therapy was prescribed at the time of discharge for 41% of patients with prehospital seizures and for all patients with in-hospital seizures. None of the in-hospital seizing patients had recurrent seizures after discharge, but 8 of 56 (14%) patients, all with prehospital seizures, had seizures after discharge (50% of them on treatment, with higher than therapeutic levels when the seizure occurred). The median time to discontinuation of antiepileptic treatment was 40 d (range: 12–730 d). Thus, most seizures in this study would be considered to be unpreventable because they occurred before admission to the ICU, and in three-fourths of the patients, those that occurred after admission to the ICU were not prevented with antiepileptics. The authors also suggest that because the incidence of in-hospital seizures (4%) was lower than the incidence of adverse effects from the antiepileptics (7%), long-term treatment may not be beneficial.

In the prospective hospital-based study from Portugal, onset seizures were more common in patients with hemiparesis (OR 5.2, 95% CI 1.6–16.6), Hunt & Hess (H&H) grade 4 or 5 (OR 5.3, 95% CI 1.5–18.6), Fisher grade 3 or 4 (OR 4.8, 95% CI 1.3–17.4) and when an aneurysm was found in angiography (OR 8.6, 95% CI 1.1–68.1) *(104)*. All patients with onset seizures were prescribed phenytoin (300 mg/d) and 4 of 16 of those had recurrent seizures between 12 and 24 h after SAH onset, but only one of the survivors had recurrent and difficult-to-control seizures at 1 yr of follow-up. Based on an early seizure recurrence rate of 25%, the authors find it reasonable to prescribe antiepileptic treatment during hospitalization to patients with onset seizures. Long-term prophylactic treatment did not seem successful to the authors, although the numbers in the study were too small to allow confident statements.

In the recently quoted prospective study from Columbia Presbyterian Hospital, 9% of patients had in-hospital seizures or NCSE after SAH *(118)*. At 12 mo 4% had one seizure, and another 7% had two or more seizures after discharge. Interestingly, 18% of the patients who developed epilepsy were on antiepileptic treatment at the time that their first posthospital seizure occurred, and 94% were treated at 12 mo. In the same study, in-hospital seizures after SAH were not identified as predictors of epilepsy. The authors mention the unpublished results of an American Association of Neurological Surgeons survey, where 24% of participants routinely treat patients with SAH with antiepileptic agents for 3 mo, regardless of whether in-hospital seizures occur, and suggest that prophylactic treatment after discharge is not warranted if there is neither cerebral infarction nor SDH, two independent variables predictive of epilepsy in this study. This statement was partially triggered by data supporting a negative influence of antiepileptic drugs like PHT on motor and cognitive recovery after stroke *(120)* or head trauma *(121)*. In another recent study from Australia, post-SAH onset seizures correlated with a large amount of blood on CT of the head and were independent predictors for both late seizures and disability at 6 wk *(107)*. Based on these results, the authors recommend early

antiepileptic treatment in patients with a large amount of blood on CT and long-term treatment for those with onset seizures.

In addition to the direct effect of SAH on seizure incidence, surgical or endovascular treatment of an aneurysm may contribute to early postprocedure seizures or epilepsy. Earlier studies reported a 10–25% incidence of epilepsy after aneurysm surgery *(108)*. More recent studies report a lower rate of early seizures of 1.9–5% *(108,111,122–124)*. The efficacy of antiepileptics in this patient population is also unknown. Postoperative PHT administration in mixed craniotomy patients at high risk for seizures was ineffective and was associated with toxicity *(125,126)*, and prophylactic administration of antiepileptic medications after supratentorial craniotomy is not routinely recommended *(127)*.

In the retrospective study of 177 patients surgically treated for ruptured aneurysms reported from Kuopio, Finland *(108)*, all patients were started on PHT treatment during surgery and maintained for 2–3 mo or longer (if they developed seizures). The authors conclude that low preoperative grade patients have a very low risk for epilepsy and treatment with PHT can be discontinued by 3 mo after the operation if no high-risk factors are present, such as high preoperative H&H grade, MCA aneurysm location, complications of SAH (hematoma, vasospasm with infarction, shunt-dependent hydrocephalus), or persistent neurological deficits (hemiparesis, dysphasia, visual field defects).

Sbeih et al. did not find any need for prophylactic phenytoin in a prospective study of 100 consecutive patients who survived aneurysm surgery and were followed for 4 yr *(123)*. In this series, only 3% of patients developed postoperative epilepsy, and there was no difference in seizure incidence between the groups with and without antiepileptic prophylaxis.

Bidzinski et al. reported a 7% risk for two or more seizures (epilepsy) in a prospective study of 121 patients operated on for cerebral aneurysms (only 3 with unruptured aneurysms) and followed for 12 mo after discharge *(110)*. Another three patients had a single seizure during the observation period. No prophylactic perioperative antiepileptic treatment was administered in this series unless epilepsy developed. Another eight patients had seizures during the perioperative period, but only one developed epilepsy during the follow-up period. None of these patients was treated with antiepileptic medications. Although a total of 18 of 121 (15%) patients had seizures during the perioperative or follow-up period, the authors concluded that prophylactic antiepileptic treatment is not justified after aneurysmal surgery.

A large retrospective study of perioperative short-term antiepileptic prophylaxis was conducted at Columbia Presbyterian Hospital in New York *(124)*. Patients at high risk for seizures (history of epilepsy, perioperative hematomas or infarction, concomitant AVMs) were excluded from the analysis. All patients with SAH were admitted to the NICU and those with unruptured aneurysms to the neurosurgical floor. All were loaded with antiepileptic medications and were maintained on a daily dose. Medications were then stopped within 7 d of surgery, on average after

3.1 d (or after 5.3 d of average total treatment duration). Postoperative seizures occurred in 5.4% of patients (4.5% for those with ruptured aneurysms, 6.9% for those with unruptured). Early postoperative seizures (within 14 d from surgery) occurred in 1.9% of patients (1.5% of ruptured and 2.6% of unruptured aneurysms) and late postoperative seizures in 3.5% (3% of ruptured and 4.4% of unruptured aneurysms). Two-thirds of early postoperative seizures occurred in patients with significant intracranial complications, such as hematomas or infarcts. Only 2 of 6 patients had therapeutic antiepileptic levels when the early seizures occurred, but all were reloaded and maintained on treatment for 1 yr without any further seizures. Late seizures developed in 8 of 11 patients within 3 mo of surgery and were easily controlled with antiepileptic medications. In the multivariate analysis, there was no association between total or postoperative duration of treatment and risk of early or late seizures. The authors concluded that early postoperative seizures should always be evaluated for ongoing intracranial pathology. They also recommend loading the patients the day before surgery, but not using antiepileptic medications for more than 7 d, if the patients are at low perioperative risk for seizures.

One would expect aneurysms treated with endovascular approaches to have a lower risk for seizures because there is no risk of additional injury from a craniotomy. The only published study at the time of this review examining the risk for seizures after endovascular treatment of cerebral aneurysms was conducted in Oxford, England *(128)*. The authors prospectively followed 243 patients treated with Gugliemi detachable coils for up to 7.7 yr (mean: 21.1 mo). Only 3 patients were epileptics and were already on an antiepileptic regimen when they developed SAH, and 33 other patients (12%) received prophylactic treatment after they bled. Ictal seizures (within 24 h from ictus) occurred in 26 of 243 (11%) patients and were independently predicted by loss of consciousness, MCA location of the aneurysm, and antiepileptic treatment. However, no distinction was made between loss of consciousness from SAH and seizure causing loss of consciousness. Moreover, antiepileptic treatment might have been prescribed because an individual patient experienced an ictal seizure. Seven out of 233 (3%) patients developed late seizures, but 3 already had epilepsy and only 4 (1.7%) had *de novo* seizures. None of the patients with late seizures presented during the periprocedural period (i.e., within 30 d), and none with ictal seizures experienced late seizures. Only half of patients with *de novo* siezures (0.85%) had recurrent seizures and required long-term antiepileptic treatment. Late seizures were independently predicted by a history of epilepsy before SAH, cerebrospinal fluid shunting, or drainage procedure and antiepileptic medications. This latter finding could probably be explained by noting that patients who experienced ictal seizures were covered with antiepileptic medications before referral. The authors concluded that there is no need for periprocedural seizure prophylaxis with antiepileptic medications and that the low incidence of *de novo* late seizures is also a reason for not using these agents prophylactically in long-term treatment.

In summary, a tentative algorithm for treating seizures after SAH is presented in Table 5.

Table 5
Treatment With Antiepileptic Medications After SAH

1. SAH and preexisting seizures: continue or restart antiepileptic regimen; keep thera-
    peutic levels.
2. SAH and no seizures
    Low-risk patients: Treat until aneurysm is secured.
    High-risk patients (high Hunt & Hess [H&H] grade, high Fisher grade, aneu-
    rysm found, hemiparesis):
        Treat during hospitalization: long-term treatment if subdural hematoma
        (SDH) (before or after surgery) or infarct.
        Postcraniotomy-clipping: treat for 7 d. Treat for at least 1–2 yr (seizure-free
        interval) if high H&H grade, MCA aneurysm, hematoma, infarct, shunt-
        dependent hydrocephalus or persistent neurological deficits. Assess with
        EEG before discontinuation?
    Post GDC: No treatment. Consider treatment for at least 1–2 yr (seizure-free
    interval) if patients were on antiepileptic medications before or have shunt-
    dependent hydrocephalus. Assess with EEG before discontinuation?
3. SAH and onset or early seizures
    Treat during hospitalization.
    Consider long-term treatment after discharge, for at least 1–2 yr (seizure-free
    interval) if large amount of blood on CT, infarct, hematoma, SDH, or hemipare-
    sis. Assess with EEG before discontinuation?
    Postcraniotomy-clipping: Treat during hospitalization. Treat for at least 1–2 yr
    (seizure-free interval) if high H&H grade, MCA aneurysm, hematoma, infarct,
    shunt-dependent hydrocephalus, or persistent neurological deficits. Assess with
    EEG before discontinuation?
    Post-GDC: Treat during hospitalization. Consider treatment for at least 1–2 yr
    (seizure-free interval) if patients were on antiepileptic medications before or
    have shunt-dependent hydrocephalus. Assess with EEG before discontinuation?

ARTERIOVENOUS MALFORMATIONS

Clinical Studies

AVMs are abnormal fistulas between arteries and veins in the brain without an
intervening capillary bed. They occur in 0.1% of the population and typically
present before age 40 yr, equally among men and women *(129)*. Although their
etiology is unknown, they are thought to arise from developmental derangements
of cerebral vessels and thus must be differentiated from arteriovenous fistulas
caused by trauma or occlusion of branch arteries or venous sinuses. The most com-
mon presentation is ICH (30–82%), which is also the most common reason for ICU
admission, other than AVM treatment (surgical, endovascular, or multidisciplinary)
or seizures (multiple or in succession). Seizures are the initial symptoms in 16–
53% of AVM cases. Most seizures are simple partial or partial complex. Although
focal seizure onset may be an indicator of the location of the lesion, in up to one-

third of patients, seizures are GTC. Headache, learning disabilities, and focal neurologic deficits unrelated to hemorrhage are less common *(130–136)*.

Seizures that occur in the ICU in a patient with an AVM may be related to the AVM itself (with or without a hemorrhage); alternatively, they may develop as a complication following surgical, endovascular, or radiosurgical treatment of the AVM. Factors associated with the development of pretreatment seizures were recently reported in a large series of AVMs from the Massachussets General Hospital. Seizures were statistically associated with male sex, age of less than 65 yr, AVM size of more than 3 cm, and temporal lobe AVM location ($p < 0.01$, $p < 0.05$, $p < 0.0001$, and $p < 0.01$, respectively). Posterior fossas and deep locations were statistically associated with the absence of seizures ($p < 0.0001$) *(137)*. Mechanisms thought to play a role in the pathogenesis of epilepsy in patients with AVMs include secondary epileptogenesis in the ipsilateral temporal cortex, gliosis from previous hemorrhage and hemosiderin deposition into the cortex, focal cerebral ischemia from a steal syndrome, and neurochemical changes on or around the lesion *(138–140)*.

Because of a higher incidence of rehemorrhage after the initial one (18% vs 2% for those without hemorrhage) *(133)*, aggressive treatment of AVMs is advocated to avoid hemorrhage rather than to control seizures *(141)*. This has also led to limited data regarding the natural history of seizures in these patients. In 138 conservatively managed patients with AVMs, Crawford et al. found a 19% risk of seizures at 20 yr, compared with 57% in 96 patients treated surgically; the authors used a life survival analysis in their study *(132)*. Similarly, other older studies showed poor control of seizures after surgical AVM removal and development of new seizures in patients who were seizure-free preoperatively *(142,143)*. Such findings were not reported in an older study, which noted no difference in seizures incidence between patients treated surgically and those treated medically *(134)*. Moreover, more recent studies indicate a lower risk of postoperative seizures that may depend on the history of seizures before the surgical intervention: <40% in patients with preoperative seizures and <10% in those without such history *(141,144,145)*. Factors that increase the incidence of postoperative seizures in AVM patients include age <30 yr at seizure onset, preoperative seizure duration >12 mo, AVM size >3 cm, location in the medial temporal or perirolandic cortex, and previous hemorrhage or hemosiderin deposition *(139–141,144)*. A recent prospective ICU study used CEEG monitoring to examine the effect of intracerebral hematomas on the incidence of poststroke seizures *(39)*. Seizures occurred in 18 of 63 (28%) of patients with ICH and 3 of 46 (6%) patients with ischemic stroke (OR 5.7, 95% CI 1.4–26.5, $p < 0.004$). In patients with ICH, there was a trend toward increased AVM representation in the seizures subgroup ($p = 0.07$).

Treatment of AVM-Related Seizures

Although there is a broad consensus to treat AVM-related epilepsy with antiepileptic medications (usually with a good response), many would also argue

for a prophylactic approach. More controversial is the need for and timing and duration of antiepileptic treatment after surgery, embolization, or radiotherapy, and there are no studies from which solid recommendations may be drawn *(130)*. Overall, there are data supporting a better prognosis with early seizures (within 30 d post-ICH or surgery) *(134,141)*, but most studies do not report details about the antiepileptic treatment used.

Piepgras et al. reported a series of 280 patients with surgically treated AVMs and a mean follow-up of 7.5 yr. Sixteen of 163 patients (10%) without preoperative seizures had perioperative seizures, and 6 of 117 patients (5%) with preoperative seizures had worsening of their seizures during hospitalization. At the last follow-up, 87.5 and 83%, respectively, of patients with early seizures were noted to be seizure free *(141)*.

In a large, recent, prospective study from Australia, 114 postoperative patients with AVMs were followed for a mean of 48 mo (22 mo–8.5 yr) *(146)*. Preoperative seizures were present in 53 patients (46%). Only 15 (13%) had seizures associated with an acute and newly diagnosed ICH. Postoperative seizures were defined as seizures occurring after the first month following AVM excision. Neither AVM size nor AVM localization to temporal cortex or other eloquent brain area was related to pre- or postoperative seizures. A total of 24 patients (21%) had postoperative seizures, including 14 of 53 (26%) of those with preoperative seizures and 10 of 61 (16%) of those who did not have them. Preoperative seizures were not associated with the development of postoperative seizures. All patients were put on antiepileptic medications (those with preoperative seizures being maintained on their current regimen) for at least 12 mo postresection. The majority of postoperative seizures in those 24 patients occurred during the first 12 mo while on antiepileptic treatment. In only 6 of 24 patients (25%) did the postoperative seizures appear after the first 12 mo. In 4 of these patients, the seizures developed after withdrawal of the antiepileptic regimen. Poor neurologic outcome at 12 mo was an independent predictor of postoperative seizures (OR 1.5, 95% CI 1.01–2.3, $p = 0.04$).

Figure 2 describes a patient who continued to have complex partial seizures even after resection of a frontal cavernous angioma.

The effect of radiosurgery on seizures has also been studied. Because of the delayed effect of this treatment, patients can be encountered in the ICU in the immediate posttreatment period or later, if admitted because of a seizure. A small risk for seizures as a complication of radiosurgery was reported in a large international study: 10 of 1255 (0.8%) patients with new-onset seizures and 12 of 1255 (1%) patients with seizures in addition to other symptoms *(147)*. It seems likely that the time of AVM obliteration does not correlate well with seizure control. In fact, seizures can be controlled quite rapidly—even before complete AVM obliteration has been confirmed *(148–150)*. The predominant theory suggests an independent effect of irradiation on epileptogenesis of cerebral tissue surrounding the AVM (owing to an effect on AVM thrombosis and reduction of a steal phenom-
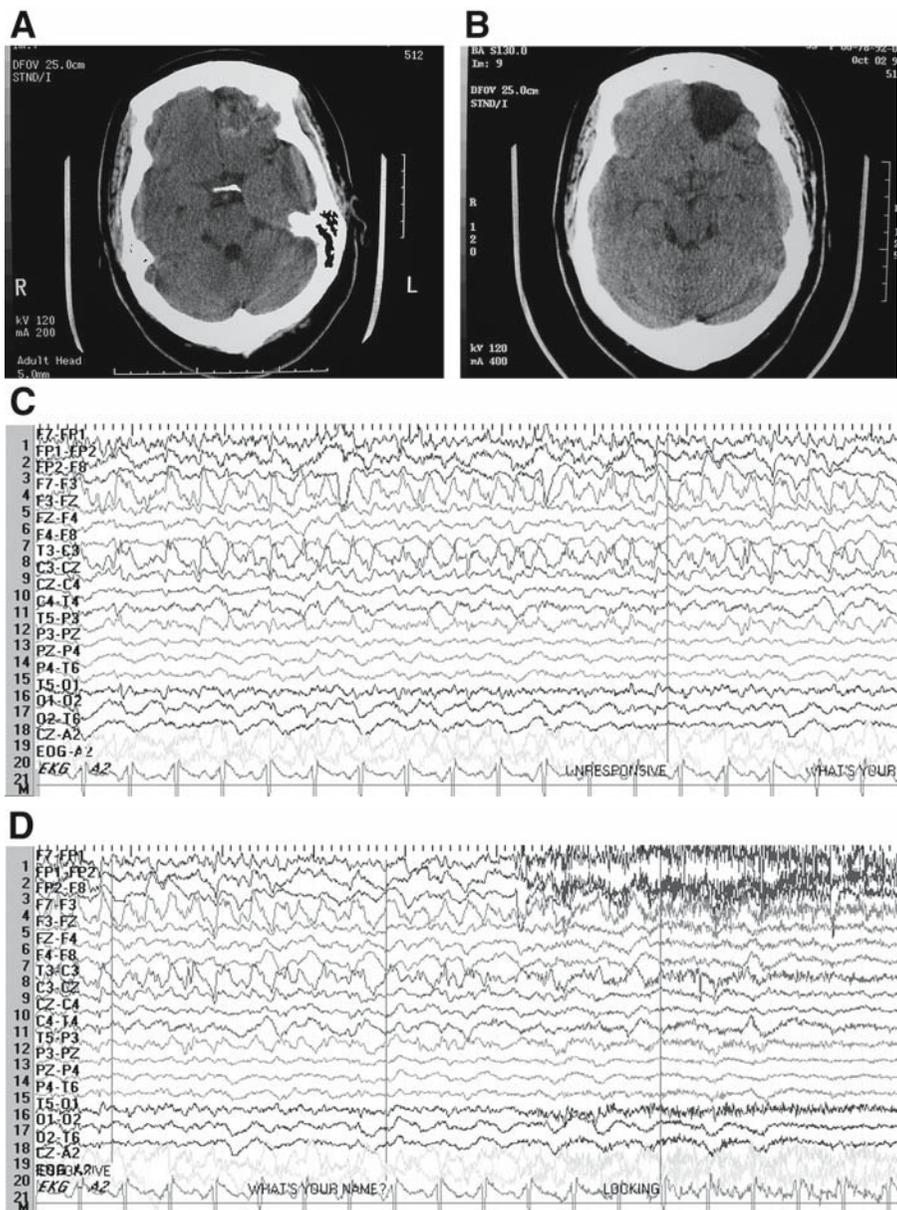
Fig. 2. This 32-yr-old African American female had complex partial seizures since age 17. CTs of the head (A) before and (B) after resection of a left frontal cavernous angioma. (C) EEG 3 mo after the resection showing an electrographic seizure over the left frontotemporal area. The patient had staring episodes and mouth automatisms during the event, while on therapeutic carbamazepine. (D) The same seizure activity later stopped abruptly (right side of the epoque).

enon from the surrounding ischemic areas) *(147,149)*. In a study from Finland, 129 patients with inoperable cerebral AVMs were treated by stereotactic proton beam irradiation from a linear accelerator *(149)*. Symptomatic epilepsy was present in 29 patients (22.5%) and was markedly relieved by radiosurgery, leading to cessation of the seizures in 16 (55.2%) patients, with a mean follow-up period of 4.5 yr. In another retrospective study, Kurita et al. reported the results of γ knife radiosurgery in 35 patients with unruptured epileptogenic AVMs (followed for a mean of 43 mo) and in another 22 patients with nonepileptogenic AVMs (followed for a mean of 30 mo). These authors found an association between the number and duration of pretreatment seizures and posttreatment seizure outcome: 92% of patients with ≤5 seizures before radiosurgery were seizure free after the treatment (vs 50% with >5 seizures: OR 2.8, 95% CI 0.09–0.7) and 94% of patients with seizures for ≤6 mo before radiosurgery were seizure-free after treatment (vs 64% with >6 mo of seizures: OR 2.2, 95% CI 0.046–0.58) *(150)*.

The largest series reporting seizure control after γ knife radiosurgery also comes from Japan *(148)*. Epilepsy presented in 79 or 462 (17.1%) patients: 58 cases presented with seizures as the initial symptoms (group A) and the other 21 mostly had seizures following ICH (group B). Before radiosurgery, seizures were predominantly generalized in both groups, followed by pure partial and complex partial seizures. Seizures decreased in most of the cases (mean follow-up: 24 mo) in relation to nidus obliteration: good seizure control was achieved in 94.7% of completely obliterated and 77.1% of incompletely obliterated AVMs ($p = 0.16$). Initial seizures (group A) were also more easily controlled than subsequent or secondary ones (group B) in the univariate analysis ($p = 0.0034$). Seizures either decreased or disappeared in 91.6% of group A and 62.5% of group B patients. The overall results of this study indicated that seizures improved in 85.5%, were unchanged in 11.6%, and deteriorated in 2.9% of patients. None of these studies mentions the details of antiepileptic treatment, so it is difficult for the intensivist to draw safe conclusions regarding when and how long to cover such patients.

There are not many data about embolization, usually considered to be an adjunctive treatment for AVMs. In an older study reporting data from the 1980s, 33 of 49 patients received embolization only and the rest additional surgery or radiosurgery *(151)*. Hours after treatment, four patients developed early focal seizures, which were easily controlled. None had CT-proven ICH. Long-term follow-up revealed that 9 of 21 (43%) patients who had presented with seizures experienced either a significant reduction in the frequency of their attacks or easier control of the seizures with medications.

Although most earlier reports were about single-modality treatments, now there are emerging data on multimodality approaches. The intensivist may encounter patients at various stages of treatment and should be aware of factors that may alter the risk for seizures or specific antiepileptic treatment needs. However, only scant data are available. A study from Stanford, California, reported on 33 patients who underwent radiosurgery followed by microsurgical resection 1–11 yr later. Embo-

lization was also offered to 25 patients prior to surgery. Out of 9 patients who already had seizures at the time the AVM was diagnosed, 3 improved, 4 became seizure-free, and 3 developed new-onset seizures after the combination of treatments *(152)*.

Another recent retrospective study from the Massachusetts General Hospital presented results between 1991 and 1999 *(137)*. The multidisciplinary neurovascular team treated 424 patients with cerebral AVMs with surgical resection, radiosurgery, or embolization, either alone or in combination. Of these 141 patients (33%) experienced seizures before treatment, and follow-up data were available on 110 (78%) of these patients for a mean period of 2.9 yr after treatment. On The Engel Seizure Outcome Scale there were 73 (66%) class I (free of disabling seizures), 11 (10%) class II (rare disabling seizures), 1 (0.9%) class III (worthwhile improvement), and 22 (20%) class IV (no worthwhile improvement) outcomes. Sixteen (5.7%) patients experienced new-onset seizures after treatment. A limited seizure history (<5 seizures before treatment), the association of seizures with ICH, GTC seizure type, deep and posterior fossa AVM locations, surgical resection, and complete AVM obliteration were statistically associated with class I outcomes. In the whole cohort, surgery resulted in seizure elimination in 81%, radiosurgery in 43%, and embolization in 50% of patients treated. When only completely obliterated AVMs were considered, there were no statistically significant differences between surgery, radiosurgery, and embolization.

Table 6 represents a suggested algorithm for the treatment of AVM-related seizures.

REPERFUSION–HYPERPERFUSION SYNDROME

First described by Sundt et al. *(153)*, the reperfusion syndrome is an uncommon constellation of symptoms usually encountered following carotid endarterectomy (CEA) (0.4–1.8% of cases) or other revascularization procedures, such as percutaneous transluminal angioplasty (PTA) *(154,155)* or innominate endarterectomy *(156)*. It comprises transient focal seizures (always emanating from the vascular territory ipsilateral to the treated artery), ipsilateral headache with atypical migrainous features, and ICH or brain edema, usually a few days to up to 3 wk after revascularization *(157)*. Occasionally, SE ensues *(54)*. Severe internal carotid artery (ICA) stenosis with preoperative ICA-to-common carotid artery pressure ratio under 0.7 leads to significant increase of CBF in both hemispheres after CEA more pronounced ipsilaterally *(158)*.

Seizures are thought to result from cerebral embolization from the operative site, hemorrhage secondary to the lack of autoregulation or simply to the reperfusion syndrome effect. If they occur during or early after surgery, they are more likely to be caused by intraoperative or immediate postoperative embolization or inadequate perfusion during clamping of the carotid. The predisposing role of preoperative strokes toward seizures in symptomatic patients is unclear. If seizures occur late during the postoperative course, especially when there is severe carotid stenosis and if

Table 6
Treatment With Antiepileptic Medications After an AVM

1. AVM and preexisting seizures: no AVM treatment
   Treat indefinitely or according to post-AVM regimen.
2. AVM and no seizures
   Observe.
   Consider treatment if patient is male, age <65 yr, has >3 cm AVM or an AVM in the temporal lobe.
3. AVM and surgical treatment
   Treat independently of presence of preoperative seizures for at least 2 yr (seizure-free interval) or indefinitely if poor neurologic outcome at 12 mo.
4. AVM and radiosurgery
   Treat for 1–2 wk, if no history of seizures.
   If AVM presented with seizures, treat up to 2 yr (seizure-free interval) if seizures were the initial symptom or up to 4 yr (seizure-free interval), if seizures were secondary symptoms (e.g., after ICH). Assess with EEG before discontinuation?
   Treat indefinitely if patient had preradiosurgery therapy >5 seizures, or the duration of seizures exceeded 6 mo.
5. AVM and embolization
   Treat for 1–2 wk, if no preexisting seizures.
   Continue treatment, if preexisting seizures or postprocedural seizures, for at least 1–2 yr (seizure-free interval). Assess with EEG before discontinuation?
6. AVM and multimodality treatment
   Treat for 1–2 wk if no preexisting seizures.
   If preexisting seizures, continue antiepileptic treatment for 1 yr (seizure-free interval) if low-risk factors for seizures are present (patient had <5 seizures before multimodality treatment, seizures were associated with ICH, seizures were GTC type, AVM was in the posterior fossa, AVM was surgically resected, or there was complete AVM obliteration). Assess with EEG before discontinuation? Continue antiepileptic treatment for at least 2 yr (seizure-free interval) if low risk for seizures factors are not present. Assess with EEG before discontinuation?

preceded by headache, they are most likely caused by the hyperperfusion syndrome *(157)*. The syndrome is attributed to impaired cerebral autoregulation as a result of chronic cerebral hypoperfusion distal to high-grade carotid stenosis *(159)*. The intracranial distal arterioles are maximally and chronically dilated and do not respond to the flush of blood by vasoconstriction after correction of the stenosis. Carotid baroreceptor insensitivity and the secondary hypertensive response after CEA are additional factors *(154)*, in as much as most patients have uncontrolled hypertensive blood pressure (BP) levels both before and after surgery *(157)*. The role played by various vasoactive peptides secreted from perivascular sensory nerves *(160)*, oxidants that develop before *(161)* or inflammatory cytokines (and the no-reflow phenomenon) after *(161)* revascularization is still unclear.

Pathological findings in the hyperperfusion syndrome resemble the findings in hypertensive encephalopathy and the reperfusion syndrome after cerebral AVM resection *(157)*. Sundt et al. reported an incidence of seizures after CEA in 11 of 1145 subjects (0.9%) *(153)*. A total of 20 (1.8%) patients in their series displayed the characteristic constellation of symptoms, which was given the name of hyperperfusion syndrome. Seizures presented between the fifth and seventh postoperative day. Five patients had a history of preoperative strokes and two developed postoperative ICH. Reigel et al. reported the lowest incidence of seizures so far in their large series from the Mayo Clinic (10 of 2439, 0.4%), which included some patients from Sundt's series *(162)*. Four patients had a history of preoperative strokes, and seven had a xenon CBF study during surgery, which demonstrated an increase in CBF ipsilaterally to the CEA. Nine of 10 patients had initial focal onset of seizures, which then generalized. Although all patients had PLEDs on EEG, all had complete resolution of their neurologic deficits. The authors suggested that patients with preoperative hypertension and high-grade bilateral carotid stenoses were at the greatest risk for developing seizures following CEA. They recommended caution with anticoagulant or antiplatelet agents in these patients and prompt treatment of blood pressure anomalies and seizures.

Kieburtz et al. described 8 patients with focal and generalized seizures following 650 CEAs (1.2%) *(163)*. Six patients had pre-CEA TIAs, and two were asymptomatic. Seizures occurred with a mean of 7.6 d (range: 6–13) after CEA. All patients initially had focal motor seizures contralateral to the side of the CEA, but six patients had seizures that became generalized. All patients had postictal hemiparesis. Lorazepam given initially and PHT/PB sodium for maintenance resulted in control of the seizures. CT showed old strokes in two patients (one ipsilateral to the CEA and the other contralaterally), diffuse cerebral edema ipsilateral to the CEA in another two, ICH in one, and no abnormalities in three patients. Five patients without CT evidence of stroke were normal at follow-up and had no further seizures. The other three patients had mild deficits. One developed a chronic seizure disorder.

Reversible cerebral edema was reported in 5 of 184 (2.7%) patients with severe carotid stenosis or occlusion who underwent CEA or bypass *(157)*. Headache, focal neurologic deficits, and white matter edema on CT developed after discharge from the hospital. Focal seizures occurred in four and generalized seizures in three of these patients, and EEGs showed PLEDs in two of the seven and ipsilateral slowing in another two. The authors suggested that hyperperfusion syndrome has been underreported and that many cases of cerebral edema, especially in older series, were misinterpreted as cerebral infarction.

The practice of PTA and stenting is gaining acceptance as a safe alternative to CEA in some patient subgroups. Seizures secondary to hyperperfusion syndrome have also been reported after PTA and stenting of the ICA *(154,155)*. Ho et al. reported two patients with high-grade bilateral ICA stenoses and preexisting hypertension who developed recurrent seizures with focal onset and secondary generali-

zation 7 h and 14 d, respectively, after successful endovascular treatment *(155)*. Seizures were controlled by intravenous diazepam and PHT, and by lowering the BP during the events. CT of the head did not reveal new infarcts, and follow-up angiograms showed widely patent ICAs. Two other patients reported by Schoser et al. developed seizures 16 h and 3 d, respectively, after the procedure, *(154)*. The first patient had diffuse basal SAH, swelling of the brainstem, and acute hydro-cephalus. He eventually herniated and died. The second patient had a small putaminal ICH and subcortical edema and recovered with hemiparesis. Although the management of seizures is not discussed in ref. *154*, marked increase of CBF volumes (CBFVs) was demonstrated by transcranial Doppler sonography (TCD).

TCD can be used in the ICU to evaluate patients with a suspicion of hyperperfusion syndrome. Thirty-six high-grade stenosis patients (>90% stenosis of ICA) were evaluated with TCD before and after intravenous infusion of 1 g of acetazolamide *(164)*. Thirty-three patients showed increased MCA CBFVs after the challenge (preserved reserve capacity) and 3 showed a decrease (loss of reserve capacity). After CEA, those 3 patients developed unilateral headache and an increase of mean MCA CBFVs, but the other 33 patients showed little difference. None of these patients developed seizures, suggesting a mild hyperperfusion syn-drome.

In a landmark paper, Jorgensen and Schroeder used TCD to evaluate 95 patients before and after symptomatic CEA *(159)*. Hyperperfusion syndrome developed in 18 of the 95 (19%), and two separate groups were identified: in 9 patients, symp-toms lasted for a mean of 3 h and in the other 9 for a mean of 12 d. The longer the duration of the symptoms of hyperperfusion, the more likely the preoperative find-ing of increased mean BP gradient across the stenosis, the lower the carbon dioxide (CO_2) reactivity index on both sides of the brain, and the more likely the absence of decrease of the pulsatility index during CO_2 inhalation. Following surgery in patients with symptoms of hyperperfusion, MCA CBFVs were shown to decrease with labetalol from a mean high of 104 cm/s to 68 cm/s ($p < 0.01$) on the side of CEA, a reaction not seen on the contralateral side. This asymmetric response diminished over time as the episodes of hyperperfusion subsided. At discharge, cerebral CO_2 reactivity improved bilaterally in these patients, a change not seen in patients without hyperperfusion syndrome. Interestingly, 2 of 9 (22%) patients with longer-lasting hyperperfusion symptoms developed seizures on the fifth to sixth postoperative day. MCA CBFVs on the side of the CEA in these 2 patients during seizures were 104 and 120 cm/s with mean arterial pressure (MAP) 130 and 120 mmHg, respectively. After labetalol was administered, MAP dropped to 100 and 67 mmHg and CBFVs to 38 and 60 cm/s, respectively, and the seizures stopped. In both patients, MCA CBFVs contralateral to the CEA remained unchanged, implying a defective cerebral autoregulation present only on the side ipsilateral to the CEA. Both patients who developed seizures had contralateral ICA occlusions, consistent with earlier observations *(162)*. None had postoperative infarcts on CT of the head, although they demonstrated patchy edema. These results prompted the authors to suggest that post-CEA patients should have their BP meticulously

Table 7
Treatment With Antiepileptic Medications After Revascularization

1. Revascularization and preexisting seizures
   Continue treatment.
2. Revascularization and immediate or early (less than day 5) seizure
   Neuroimaging to rule out ICH or artery-to-artery embolization.
   Treat seizures as after stroke.
3. Revascularization and late seizure (day 5–third week), with focal onset contralateral to procedure side
   Neuroimaging to rule out ICH.
   If preexisting high-grade stenosis and history of severe hypertension plus headache at present: treat hyperperfusion syndrome with lorazepam and PHT or PB or iv valproic acid and hypertension with iv labetalol or enalaprilat or clonidine to reduce systolic BP to a level where CBFVs by TCD are symmetrical. Continue treatment for at least 3 wk and discontinue if neuroimaging is negative.

controlled and that TCD may help identify patients at high risk for developing the hyperperfusion syndrome and seizures. If this eventuality is anticipated, a baseline study before or another immediately after surgery may be helpful *(157,159,165)*.

All this strongly suggests that high-risk patients (history of hypertension, bilateral high-grade stenoses, low CBFVs or CO_2 reactivity by TCD) should be monitored in the ICU for symptoms of hyperperfusion syndrome after revascularization of the cerebral vessels. The BP should be tightly controlled, and if symptoms develop, the first step of treatment should include further lowering of BP (to a level of equalization of ipsilateral and contralateral CBFVs) *(159)*. The ICU staff should be alerted to the possibility of seizures. Neuroimaging to exclude a new ICH or infarct should be considered if there is any change in the neurological exam.

Table 7 represents a suggested algorithm for the treatment of seizures related to the reperfusion–hyperperfusion syndrome.

CEREBRAL VENOUS AND DURAL SINUS THROMBOSIS

Clinical Studies

Several medical or surgical complications have been associated with the development of cerebral venous thrombosis (CVT). Also CVT is not infrequently encountered in ICU patients with the following conditions: various infectious processes (local or systemic), hematologic disorders (leukemia, thrombocytemia, paroxysmal nocturnal hemoglobinuria), cancer, noninfectious inflammatory disease, Behçet disease, nephrotic syndrome, dehydration and congestive heart failure, complications of pregnancy and the puerperium, and mechanical causes, such as lumbar puncture (LP) alone or associated with the diagnosis of multiple sclerosis and high-dose corticosteroids *(166–168)*. Patients with CVT are frequently also admitted to

the ICU for cerebral edema, signs of increased ISP (headache, papilledema), focal neurologic deficits, or seizures.

Outcomes after CVT in recent years have improved, with mortality in the 5–10% range and independent life in almost 80–86% of patients *(169–171)*. The outcome may be less favorable in hospitals without stroke units or early accessibility to MRI *(169)*. Seizures occur frequently after CVT, and in several cases they are the presenting sign. Indeed, seizures were present in the first clinical description of CVT in 1825 by Ribes *(172)*. In the angiographically proven cases reported by Bousser et al., Jacksonian or grand mal seizures occurred in 11 of 38 (29%) patients and were the fourth most common symptom, following headache (74%), papilledema (45%), and hemiplegia (34%) *(173)*.

It is interesting to note that several of the causative factors for CVT can also independently cause seizures (head trauma, intracranial surgery, CNS infection, primary or secondary brain tumors, vasculitis), although no attempt has been made to differentiate the relative roles of each *(173,174)*. Other common etiologies for CVT include the aforementioned conditions, but in up to a quarter of cases the etiology remains unknown. Because LPs are commonly performed in the ICUs, the reported association between CVT and LP is of special interest to the intensivist. All five patients reported by Wilder-Smith et al. developed a characteristic pattern of headache (initially postural, then continuous) and seizures after LP or complicated peridural anesthesia and were found to have CVT *(168)*. Three out of 4 tested had factor V Leiden deficiency. Other similar cases of CVT after LP complicated by seizure onset have also been reported *(175–177)*.

Several recent studies report on the incidence of early or late seizures, but all except for one from Portugal focus on the prediction of short- or long-term outcome after CVT. In a retrospective study of 78 patients with CVT, generalized seizures occurred in 24 (31%) patients and were the presenting symptom in 13 (17%); there were 7 with partial motor seizures and six with generalized seizures *(178)*. Seizures were associated with a poor outcome in the univariate analysis and were included in a prognostic scale (0–11 points) developed by the authors, with 0.98 positive prognostic value for good and 0.96 positive prognostic value for poor prognosis.

In another retrospective study from the Bronx, seizures were observed in 35 of 112 (31%) patients with acute CVT. Only 5% of patients had epilepsy after a mean follow-up period of 77.8 mo *(171)*. Among those patients with early seizures and follow-up records, 4 of 28 (14%) had epilepsy, all with focal signs in the acute stage of CVT. Those seizures manifested in 3 of 4 patients during the first year and in a single patient 2 yr after CVT. The authors concluded that because of the low risk of recurrent seizures and of late recurrences, antiepileptic treatment seems appropriate for no longer than a year post-CVT, after which it can be tapered off gradually, unless seizures recur.

The prospective, randomized Dutch–European Cerebral Sinus Thrombosis Trial compared nadroparin, the low molecular weight heparin, with placebo: for 3 wk,

the drug recipients received 180 antifactor Xa units/kg/d, followed by oral antico-agulation with a target international normalized ratio of 2.5–3.5 for 10 wk *(179)*. Seizures were reported in 28 of 59 (47%) patients, but the study did not comment on their relationship with outcomes at 12 wk *(170)*.

In a recent prospective French study, seizures occurred in 28 of 55 (50.9%) patients with CVT and were the presenting symptom in 1 (1.8%) patient *(169)*. The patients had been admitted to a stroke or an intensive care department, and all but one were treated with intravenous heparin. There is no mention of antiepileptic treatment in this series. With a median follow-up of 36 mo, recurrent seizures developed in 7 of 28 (25%) patients, with seizures in the acute stage (i.e., 14.5% of all 3-yr survivors from CVT). Focal or generalized seizures were not associated with outcome as measured with the modified Rankin disability score.

In a recent prospective study on CVT from Portugal (VENOPORT study), data were collected retrospectively for 51 patients and prospectively in another 91 patients (who were followed for an average of 1 yr) *(174,180)*. Early seizures (in the first 2 wk after the diagnosis) were observed in 31 of 91 (34%) patients. In 29 (31.9%) patients early seizures were the presenting feature of CVT (in 1 patient seizures evolved to grand mal SE). Two patients had seizures 2 and 6 d, respectively, after admission, and in 6 (6.6%) patients the early seizures recurred. The frequency of seizures was the same whether the superior sagital sinus (33%) or the lateral/sigmoid sinus (25%) was thrombosed, but no seizures were observed in the 7 patients with involvement of the deep venous system. Early seizures were independently predicted by sensory deficits (OR 7.8, 95% CI 0.8–74.8) and by the presence of a parenchymal lesion on admission, including focal edema, ischemic infarct, or hemorrhage (OR 3.7, 95% CI 1.4–9.4). Late seizures were found in 6 of 43 (14%) of survivors in the retrospective arm of the study *(180)* and in 8 of 84 (9.5%) of survivors in the prospective arm *(174)*, who were followed up to 10 mo from the onset of the CVT. Epilepsy developed in 4 of 84 (4.8%) patients. Seven out of 8 (87.5%) patients with late seizures were on antiepileptic treatment when the seizures occurred. Late seizures were generalized in almost two-thirds of patients and were independently predicted by the presence of hemorrhage on the neuroimaging study performed upon admission. Late seizures were more common in patients with early seizures (19% vs 5% in patients without early seizures, $p = 0.05$) but only in the univariate analysis. In the multivariate analysis early or late seizures were not independent predictors of increased mortality or dependency, although early seizures directly contributed to death in two patients (intractable SE and cardiorespiratory arrest after grand mal seizure). The authors concluded that prophylactic antiepileptic treatment during the first year after CVT is justified only in patients with hemorrhage on CT/MRI or early symptomatic seizures and probably could be avoided in patients without such high risk factors.

Another small prospective study from Lyon, France, recently reported a high percentage of prothrombotic states in patients with CVT admitted in a stroke unit *(181)*. Seizures were observed in 8 of 16 (50%) patients, 5 of whom had a hemor-

rhagic infarct. A prothrombotic state was detected in 6 of 8 (75%, a high factor VIII level in 4 patients), the same percentage as in patients without seizures.

Treatment of Seizures Related to CVT

The treatment of seizures that follow CVT (*see* Table 8 for an algorithm for treatment of CVT-related seizures) obeys to the same principles as the treatment of seizures not related to this condition (*see* Chapter 14). How does treatment, which is aimed at using various available options to recanalize the thrombosed venous channel, affect the incidence or severity of seizures? Few data are available to help answer that question. In the Dutch–European prospective study, seizures occurred in 16 of 30 (53%) patients on the nadroparin arm and in 12 of 29 (41%) patients on the control arm ($p > 0.05$). There were no new symptomatic hemorrhages in this study, including in the subgroup that presented with cerebral hemorrhage, which could account for the nonsignificant difference in seizures between the two treatment arms.

Are seizures in patients with CVT treated with iv heparin more likely to lead to fatal complications? One recent retrospective study from Freiburg, Germany analyzed 79 patients with CVT *(182)*. All patients received a 5000-IU iv bolus of heparin and a subsequent infusion with target activated partial thromboplastin time of 80–90 s. There was no difference in fatal vs nonfatal outcome in patients with seizures (58% of all patients) or in those patients with series of seizures or SE (28% of patients with seizures).

Other studies evaluating novel treatments for CVT usually do not report data regarding seizures, either because the numbers are too small to permit one to draw meaningful conclusions or because the investigations differ in their focus. Niwa et al. reported treating a woman in her 10th month of pregnancy and superior sagittal sinus thrombosis with direct t-PA instillation *(183)*. The patient presented with generalized seizure and tetraparesis but was discharged without neurologic deficit. Another interesting and informative case was reported by Gerszten et al., who treated an 18-yr-old man with deep cerebral venous system thrombosis secondary to antithrombin III deficiency *(184)*. The patient, who presented with a focal motor seizure, was started on antiepileptic medications and became comatose with fixed pupils before receiving endovascular treatment. He was treated with Urokinase delivered in the straight sinus and the vein of Galen 27 h after the onset and despite the presence of edema in both basal ganglia and thalami bilaterally, and a hemorrhage in the left thalamus. The procedure resulted in deep system recanalization, and subsequently continuous infusion of heparin was given. The patient remained in the ICU in a pentobarbital coma for 20 d for ICP control, but eventually improved to the point of independent living and was able to graduate from high school on time. In a series of 12 patients with CVT treated with a combination of intrathrombus recombinant t-PA and intravenous heparin, Frey et al. reported 5 (42%) patients who presented with seizures. Although patients with restored flow seemed to have a better prognosis, there is no mention of seizure control or recurrence *(185)*. Finally, in a series of five patients treated with a combination of intrathrombus Urokinase infusion and mechanical thrombolysis using the

Table 8
Treatment With Antiepileptic Medications After CVT

1. CVT and no seizures
    Observe.
    Consider treatment if there are focal sensory deficits or parenchymal lesions (focal edema, infarct, or hemorrhage) on the admission CT/MRI. Continue treatment for at least 1 yr (seizure-free interval). Assess with EEG before discontinuation?
2. CVT and onset or early seizures
    Treat with monotherapy first for 1 yr (seizure-free interval). Assess with EEG before discontinuation?

AngioJet rheolytic catheter, one patient presented with a seizure *(186)*. Four of the patients recovered without any residual deficits, but no details are given about seizure recurrence of antiepileptic treatments.

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3

Traumatic Brain Injury and Seizures in the ICU

Andrew Beaumont and Grant Sinson

SUMMARY

Seizures may occur in up to 22% of patients in the intensive care unit with severe traumatic brain injury. There is a relatively high risk of nonconvulsive seizures in this population. Seizures may exacerbate the injury process and disrupt both patient care and family coping. Therefore, seizures should be recognized quickly and treated promptly. The clinician should have a high index of suspicion for seizures, especially in patients with clearly defined risk factors for seizure development. Continuous electroencephalogram monitoring should be considered in patients who are considered to be at high risk of clinical or subclinical seizures. Seizure prophylaxis with antiepileptics is supported by the literature for the prevention of early seizures (defined as <7 d postinjury) but not for late seizures. Phenytoin and carbamazepine have been used in this setting, and both were efficacious in preventing early seizures. Phenytoin has several features that make it a best first-line agent. Anticonvulsants have not been found to reduce the incidence of developing late posttraumatic seizures, and, therefore, prolonged prophylaxis with antiepileptics is not currently supported.

Key Words: Traumatic brain injury; nonconvulsive seizures; seizures prophylaxis.

INTRODUCTION

Traumatic brain injury (TBI) is an important health problem. In the United States an estimated 1.5–2 million people experience TBI each year *(1)*. Nearly a quarter million of the patients require hospitalization *(2)*, and about 52,000 of the events result in death *(3)*. This incidence equates to one hospitalization per thousand people

each year *(2)*. Many of the patients are admitted to the intensive care unit (ICU) for initial stabilization and monitoring. The lifetime medical care costs of head injuries occurring in the United States in 1985 were estimated to total $4.5 billion, of which $3.5 billion was for hospital costs. Seizures are a well-known complication of TBI with reported incidences ranging from 2 to 12% *(4–14)*. The incidence of seizures is higher in severe TBI and also with penetrating injury *(5,15)*. Posttraumatic seizures are classified as immediate (<24 h), early, and late based on the relationship between the time of injury and time of seizure onset. The mechanisms that generate posttraumatic seizures are not known, and there may be differences in the pathophysiology of early and late seizures. Posttraumatic epilepsy, defined as two or more unprovoked seizures following injury, must be viewed in a different perspective as a single post-TBI seizure *(16)*.

One of the main goals of ICU care in TBI should be the prevention of physiological stresses that can worsen the injury. These secondary insults include hypoxia, hypotension, hyper/hypoglycemia, hypo/hyperperfusion, and neurotoxicity. Seizures cause intense metabolic stress and also release significant quantities of neurotransmitters. Therefore, seizures represent a potential for secondary insult, and some studies have demonstrated that seizures are associated with a worse outcome in TBI *(17,18)*. Therefore, it is important to recognize seizures in patients with TBI and to treat them aggressively; care must also be given to diagnose nonconvulsive seizures promptly. Their significance in affecting outcome post-TBI is unknown, but they may be a potential risk factor. In addition, patients with recognized risk factors for posttraumatic seizures should receive anticonvulsant prophylaxis.

This chapter reviews data regarding the incidence of posttraumatic seizures, particularly in the ICU population. Methods for diagnosing posttraumatic seizures are reviewed, along with experimental data and current hypotheses regarding their pathophysiology. Methods of treating seizures in TBI and current recommendations for seizure prophylaxis are discussed.

INCIDENCE OF SEIZURES IN TBI

Estimates of the incidence of posttraumatic seizures have varied widely, ranging from 2 to 12% *(6,10,14,19)*. Most of these studies are based on the civilian population and may be quite different from studies that addressed the problem in military populations. In the Vietnam Head Injury Study, 53% of veterans who had penetrating head injuries developed posttraumatic epilepsy, and half of those patients still had seizures 15 yr after injury. However, the relative risk of developing epilepsy in these patients dropped from 580 times higher than the general age-matched population in the first year after TBI to 25 times higher after 10 yr *(7)*. These studies used clinical evidence of seizure activity for establishing the diagnosis. In a more recent prospective, nonrandomized, nonblinded study, 22% of moderately to severely injured TBI patients experienced seizures: Vespa et al. *(20)* used continuous electroencephalograph (EEG) monitoring in the ICU in their examination of 94 patients

with moderate to severe TBI for up to 14 d postinjury. Of the 22% of patients with seizures, 52% had nonconvulsive or clinically silent seizures, and one-third of the group had status epilepticus (SE). Interestingly, except for one patient without any clinical seizure activity, the patients in SE had minimal clinical signs, which could easily have been missed (e.g., rhythmic facial twitching, eyelid fluttering, irregular myoclonus). All patients with SE died, compared with a 24% mortality rate in the nonseizure group. Other studies have indicated that seizures and nonconvulsive status epilepticus (NCSE) may occur more commonly than thought in the ICU. Young et al. *(21)* found that 43 of 127 (34%) critically ill non-TBI patients had seizures in the ICU based on continuous EEG monitoring. Seventeen out of 43 (39.5%) were found to be in nonconvulsive status.

The incidence of late seizures is reported to vary according to injury severity. Annegers et al. *(4)* followed 4541 patients who had experienced TBI in Olmsted County, Minnesota, from 1935 to 1984. The relative risk of seizures was 1.5 (95% confidence interval [CI] 1.0–2.2) after mild injuries, but with no increase after 5 yr; 2.9 (95% CI 1.9–4.1) after moderate injuries; and 17.2 (95% CI 12.3–23.6) after severe injuries. Significant risk factors for the development of posttraumatic seizures were brain contusion with subdural hematoma, skull fracture, loss of consciousness or amnesia lasting longer than 24 h, and age over 65 yr. Englander et al. found a 12% incidence of posttraumatic seizures in 647 TBI patients followed over 24 mo *(15)*. The highest cumulative probability for late seizures included biparietal contusions (66%), dural penetration (62.5%), multiple intracranial procedures (36.5%), multiple subcortical contusions (33.4%), evacuated subdural hemorrhages (27.8%), midline shift >5 mm (25.8%), and multiple cortical contusions (25%). In addition, Glasgow Coma Scale (GCS) values were correlated with seizure incidence: GCS 3–8 had a cumulative seizure probability of 16.8%, whereas GCS 9–12 had 24.3% and GCS 13–15 had 8.0%. In the large prospective, randomized, double-blind seizure prophylaxis studies from Seattle, Tempkin reported independent risk factors from Cox regression multivariate models: five factors emerged as increasing seizure risk in this population: early seizures (within 7 d), coma for over 1 wk, dural penetration, depressed skull fracture not surgically treated, and one or more nonreactive pupils *(22)*. These findings are in agreement with earlier results of Jennett, who described intracranial hemorrhage, linear and depressed skull fractures, focal/penetrating injuries, presence of focal neurological deficit, and prolonged amnesia (>24 h) as injury patterns associated with a higher incidence of seizures *(10)*. Figure 1 shows examples of injuries associated with significant seizures.

Other factors that can predispose to the development of posttraumatic seizures include age (incidence being higher in the pediatric population *[23]*), history of alcohol abuse, previous seizures, and a family history of seizures *(4,24)*. Genetic predisposition to post-TBI seizures is an interesting issue that has not been well addressed. Similar injuries lead to a wide variety of seizure incidence and frequency. Not all studies agree on the genetic predisposition. Jennett and Lewin found that
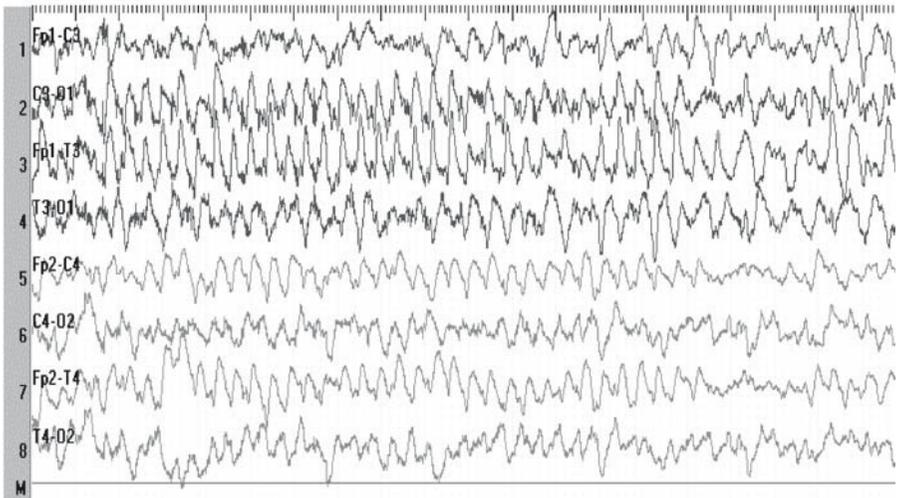
Fig. 1. Clinical examples of patients with TBI who developed seizures after being admitted to the neurological ICU.

Case 1: A 26-yr-old female involved in a rollover motor vehicle collision with prolonged extraction. The patient had a generalized tonic–clonic seizure on arrival in the trauma bay. She underwent an emergent craniotomy for large subdural hematoma and postoperatively remained in coma. At some point the next day, she was noted to have some involuntary left
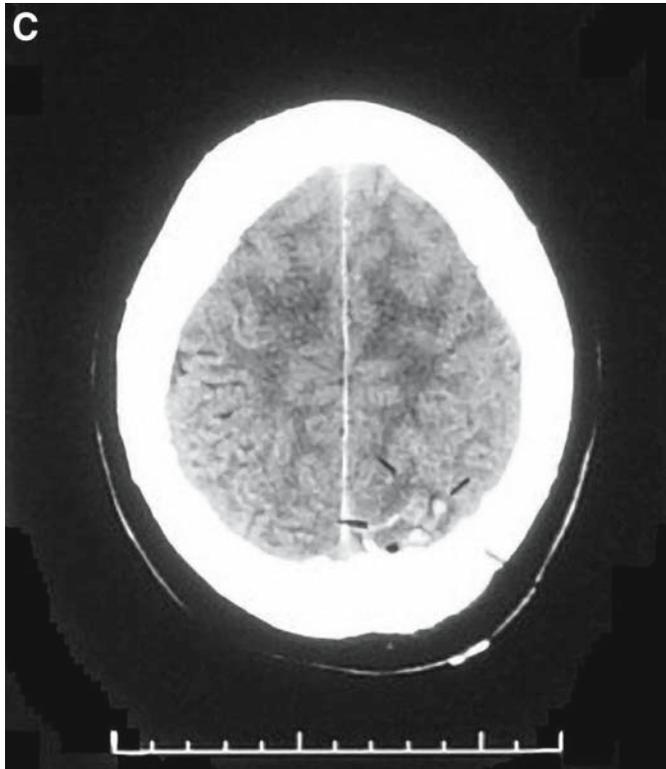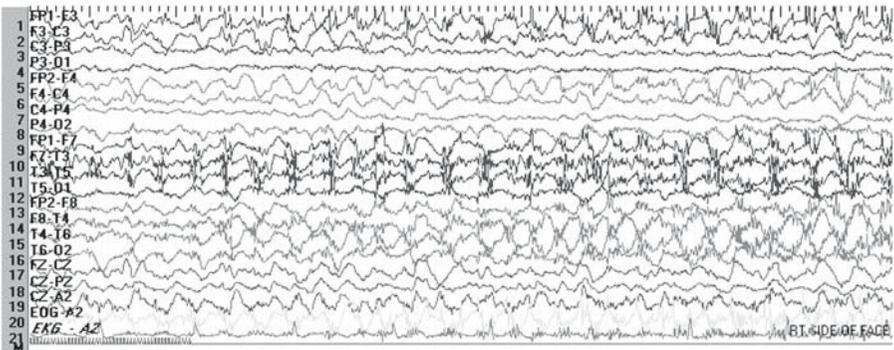
Fig. 1. *continued*

and right leg movements. A single routine EEG at that time showed generalized slowing. **(A)** Computed tomographic (CT) image of the head after the surgery demonstrates diffuse cerebral edema and midline shift. **(B)** A continuous EEG, started to exclude nonconvulsive seizures, shows sustained left-sided epileptiform activity (runs of spike–slow waves), which, interestingly, did not correlate with any clinical movements. The patient was treated with benzodiazepines and phenytoin and slowly regained function, to the level of walking with assistance.
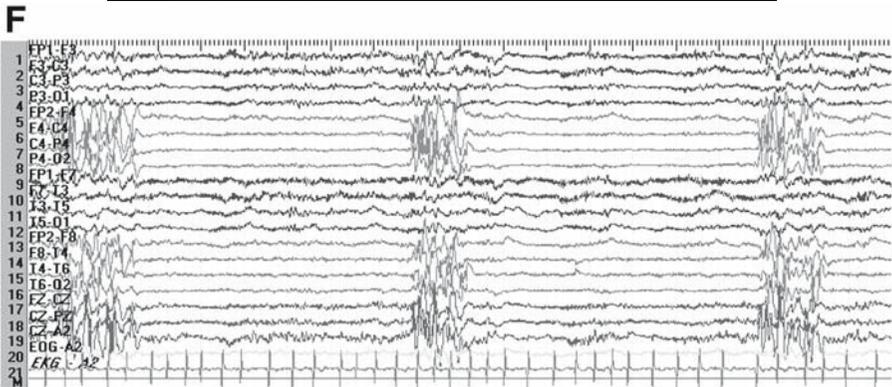
Fig. 1. *continued*

Case 2: A 20-yr-old male brought to the trauma center with a gunshot wound to the head. He had GCS of 15 both at the scene and in the trauma bay. **(C)** This CT image of the head shows that the bullet had barely penetrated the calvarium, but there is an area of contusion in the left parietal cortex (*arrow*). At one point after admission for observation, the patient was unresponsive. He quickly regained his level of consciousness but was found to have continued right-sided facial twitching. **(D)** A representative EEG strip from this patient shows left-sided epileptiform activity (runs of polyspikes–slow waves), correlating with right face and arm twitches. He was successfully treated with a load of phenytoin.

Case 3: A 59-yr-old female with a history of atrial fibrillation, hypertension, and Coumadin therapy was found on the ground, unresponsive, after an unwitnessed fall. On

family history of epilepsy was more common in young patients (<16 yr) with late post-TBI seizures *(25)*. In the Vietnam Head Injury Study, this factor was not predictive of either early or late seizures *(7)*. In another study examining genetic susceptibility to epilepsy, seizure incidence among relatives of patients with post-TBI seizures was not higher than among the general population *(26)*. In a recent prospective study of late posttraumatic seizures after moderate and severe TBI, 106 patients were examined for the ApoE locus by restriction fragment length polymorphism *(27)*. Twenty-one patients had at least one late post-TBI seizure. The relative risk of late post-TBI seizures for patients with the ε4 allele was 2.41 (95% CI 1.15–5.07, p = 0.03). The presence of this allele was not associated with an unfavorable outcome.

In studies examining posttraumatic seizures, arbitrary definitions of early and late are commonly used. Early seizures are defined as occurring in the first 7 d after injury, and late seizures occur after this point. Early seizure incidence ranges from 2.1 to 16.9% *(5,25,28)*. The incidence of late seizures ranges from 1.9 to 30% *(16)*. However, this classification is potentially too restrictive. Many TBI patients remain in critical condition in the ICU for longer than 7 d; it would be unreasonable to classify a seizure on the 10th hospital day as a "late" seizure. Some studies have extended the acute period to include the first month postinjury. However, this approach is not ideal, because the underlying cause of seizures in the first week after injury is most likely different from the cause of seizures occurring in the first month or indeed in the first year after injury. Seizures in the first week are more likely to be related to neurochemical and metabolic derangements, whereas later seizures may be related to the formation of glial scar leading to cortical irritation. Also, there is a significant occurrence of seizures at the scene of both mild and severe TBIs *(29,30)*. These immediate seizures are more likely to be related to the direct disruption of cortical and subcortical connections as a result of percussive forces on the brain, and less likely to be the result of neurochemical or metabolic derangements. However, classifying the timing of onset of posttraumatic seizures is important for trying both to understand their pathophysiology and to define factors that can predict their occurrence.

A second important goal of dividing seizures by time of occurrence is to evaluate whether early seizures can predict the occurrence of late seizures or the development of a long-term seizure problem. Early seizures are linked with late seizure

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Fig. 1. *continued*

arrival in the trauma bay, she was hypotensive, unresponsive, and flaccid to noxious stimuli, but with preserved brainstem reflexes. **(E)** This CT image of the head demonstrates a large right subdural hematoma (*arrow*). Following admission to the ICU, left-sided intermittent twitching was noted clinically. **(F)** This EEG demonstrates runs of right hemispheric polyspikes or spikes and slow waves, separated by periods of relatively depressed background activity. The patient developed extensive cerebral edema and brain death despite medical treatment.

development. The increased risk for late seizures after early seizures is independent of the actual number of seizures occurring during the first week after TBI *(16)*. However, not all studies report an increased incidence of late seizures after early post-TBI seizures. In the large retrospective study from Olmsted County, Minnesota, Annegers et al., who applied multivariate analysis to data from 1935 to 1984, found that early seizures are not an independent risk factor for late posttraumatic epilepsy, and most likely early seizures are a marker of injury severity sufficient to cause late epilepsy *(5)*. Another interesting observation is that the incidence of late seizures after early post-TBI seizures was dependent on the age of the patient. Children younger than 16 yr may not be at increased risk for late seizures regardless of the early seizure type *(4,16)*. Studies have also indicated that seizures at the scene of the trauma are not linked with any increased risk of developing late seizures *(10,29)*.

The incidence of posttraumatic seizures differs in the pediatric population. The overall incidence is higher than in adults *(5,23,24,28)*. Early posttraumatic seizures occur slightly more commonly *(13)*, with reported incidence rates of 9–15% *(13,23,31–33)*. As with adults, there is a close correlation between injury severity and the incidence of seizures of any type. Hahn et al. demonstrated that the incidence of posttraumatic seizures was seven times greater in children with severe TBI and GCS <8 than among children with milder injury and higher GCS *(31)*. Youth is also an important risk factor for seizures, with younger age having higher risk *(32–34)*. The occurrence of early seizures in severe TBI is also higher than in the adult population, with reported incidences as high as 38.7% in one study *(32)*. Furthermore, early seizures tend to occur even earlier in children: 50–80% of early seizures in the pediatric population occur in the first 24 h after injury *(24,35)*. Table 1 summarizes the risk factors for early and late seizures.

EXPERIMENTAL APPROACHES
TO POSTTRAUMATIC SEIZURES

Immediate posttraumatic seizures have been described in several experimental models of traumatic brain injury including the impact acceleration model of diffuse TBI and models of cortical contusion *(36,37)*. One study monitored EEG for 2 h postinjury in rodents exposed to a cortical contusion, and generalized seizure activity was recorded in 14 out of 17 cases at a mean time of 67 s after trauma. Concurrent microdialysis measured a consistent increase in aspartate, taurine, glutamate, and glycine; however, it is not clear whether this represented a cause or a consequence of the seizures. Longer-term behavioral studies in experimental TBI have not demonstrated any significant evidence of clinical seizure activity *(38,39)*. This finding is at odds with the clinical behavior of TBI, and it may relate to differences in seizure thresholds between rodents and humans.

The origin of posttraumatic seizures is not known, and improved understanding requires a good experimental model. Studies have evaluated in vivo seizure activity, in vitro seizure activity in brain tissue from injured animals, and in vitro seizure

Table 1
Risk Factors for Developing Early and Late Posttraumatic Seizures

Risk factor	Increased risk for seizures[b]	
	Early	Late
Acute intracerebral hematoma	+	+
Acute subdural hematoma	+	+
LOC[a] or post-TBI amnesia >30 min	+	
LOC[a] or post-TBI amnesia >24 h		+
Younger age (children)	+	
Older age (>65 yr)		+
Diffuse cerebral edema (children)	+	
Depressed/linear skull fracture	+	+
Metal fragment retention	+	+
Focal neurological deficits	+	+
Persistent EEG changes (>1 mo)		+
Early post-TBI seizures		+
Chronic alcoholism		+

[a]LOC, loss of consciousness.
[b]+, risk factor has been shown to increase the risk of seizures at the specified time-point.
(Adapted from ref. *16*.)

activity in brain tissue injured in vitro. In vivo models have focused on either direct observation of seizures or stimulation of seizures by cortical injection of ferrous chloride *(40)*; the latter technique, which is thought to mimic cortical accumulation of blood breakdown products, causes recurrent focal epileptiform discharges. One of the in vitro approaches isolated hippocampal slices from the brains of injured animals, followed by in vitro electrophysiological recording *(41)*. In vitro models of TBI have difficulty in reproducing a meaningful level of trauma. Models have included scraping hippocampal slices or stretching neurons grown in culture *(42, 43)*. Combining all these techniques, Golarai et al. examined changes in the rodent brain after weight drop injury to the somatosensory cortex *(44)*. They found an early selective cell loss in the dentate gyrus and area CA3 of the hippocampus, a persistently enhanced susceptibility to pentylenetetrazole-induced seizures for up to 15 wk after injury, and an abnormal hyperexcitability in the granule cell and molecular layers of the dentate gyrus.

PATHOPHYSIOLOGY OF POSTTRAUMATIC SEIZURES

The pathophysiological mechanisms causing posttraumatic seizures are not well understood, and there is likely some variation depending on the time of onset after injury. Posttraumatic seizures should be thought of as primary and secondary. Primary posttraumatic seizures are those caused by direct effects of the brain injury itself. Secondary seizures are caused by other epileptogenic factors not directly

related to the injury, such as fever, metabolic and electrolyte abnormalities, or drug reactions. Primary and secondary seizures are related in that the injury itself may contribute to a reduction in seizure threshold, therefore increasing the epileptogenicity of the factors that can cause secondary seizures.

Traumatic brain injury is characterized by a cascade of metabolic and neurochemical events that start at the time of injury and continue throughout the acute and subacute phases of injury, of which many are potentially epileptogenic. Examples include hyperglycolysis *(45)*, pH changes, extracellular elevation of glutamate (and other amino acids) *(46,47)*, transient flux of ions including sodium and potassium *(48)*, altered cerebral blood flow *(49)*, and loss of the inhibitory neuronal pool.

Elevations in extracellular excitatory amino acids can cause widespread depolarization that may reach seizure threshold. Loss of inhibitory neurons may promote generation of a seizure focus. Ionic transients may shift the cell membrane equilibrium potential, causing either action potential generation or a reduction in the stimulus threshold required to generate an action potential. Changes in extracellular pH also can shift the membrane potential; alkalosis tends to cause depolarization. Seizures arising in the more chronic phases of injury are less likely to be caused by acute changes in cellular physiology. These late seizures are more likely to be related to the influence of glial scars, breakdown products of hemoglobin, death of inhibitory interneurons, or disruption of neuronal connections with formation of abnormal neosynapses with greater excitatory potential *(50)*.

Epileptogenesis may not be entirely a neuronal phenomenon. It is known that glial membrane channels participate in ionic homeostasis *(51)*, especially at times of neuronal activity. In particular, glial cells buffer levels of extracellular potassium, and failure of this mechanism can result in increased neuronal excitability and seizures *(52)*. Electrophysiological recordings in hippocampal slices from experimentally injured brains have demonstrated reductions in inward and outward potassium currents and abnormal accumulation of extracellular potassium. Abnormal glial buffering of potassium may represent one mechanism of posttraumatic seizure development *(41)*.

Seizures themselves also place a stress on both the brain and the organism, and these stresses may contribute to injury, forming a vicious cycle of repeated injury and further seizure generation. In particular, seizures have been shown to cause hyperglycolysis; elevated extracellular amino acids including glutamate *(53)*; elevated extracellular glycerol levels, which are suggestive of cell membrane breakdown *(54)*; hyperperfusion *(55)*; changes in extracellular levels of bioactive lipids *(56)*; alterations in neurotransmitter receptor expression *(57)*; alterations in neurotransmitter uptake mechanisms *(58)*; and changes in synaptic morphology *(59)*.

The impact of seizures on macroscopic physiological parameters in TBI has not been well studied. In a study published in 1999 in which ICU patients with severe TBI received continuous EEG monitoring *(20)*, the incidence of raised intracranial pressure (ICP) was similar in seizure and nonseizure patients. The mean ICP was higher in the seizure group (15.6 vs 11.8 mmHg, $p < 0.001$); however, this finding

may simply reflect seizures occurring in the most severely injured patients. A separate analysis comparing ICP values in individual patients on seizure and nonseizure days demonstrated no significant difference. Furthermore, serial trends of ICP in the hours before and after seizure events did not demonstrate a clear seizure-related effect. Seizures can cause profound hypotension and hypoxia (in the nonventilated patient), and prolonged myoclonic and tonic–clonic activity can lead to excess tissue and serum lactate levels and acidosis. These factors may constitute secondary insults, known to worsen outcome after TBI *(60)*.

DIAGNOSIS OF SEIZURES

The occurrence of seizures can be suspected by clinical activity, but EEG confirmation is required. The clinical appearance of early seizures in the ICU includes generalized tonic–clonic and focal seizures. Complex–partial seizures may also occur, but documentation of these in an intubated, sedated patient is difficult. Focal seizures can appear as rhythmic myoclonic activity or as a more subtle finding, such as a facial twitch *(20)*. Seizures may also manifest as a decrease in mental status, and any workup for this problem after TBI should include an evaluation for seizures. Seizures may be masked in the ICU population by the use of neuromuscular blocking agents, and therefore, caution should be taken when these agents are used in patients who are at higher risk of posttraumatic seizures. If prolonged paralysis is needed, one should consider continuous EEG monitoring in high-risk patients.

The EEG can be used in different ways for diagnosing posttraumatic seizures. The simplest method is to obtain an EEG in a patient clinically suspected of having seizures. However, this EEG is a snapshot of the injured brain's electrical activity. If it does not capture a single seizure event or NCSE, then seizure diagnosis relies on being able to identify abnormal interictal activity. If there is a significant delay in obtaining the EEG, seizure activity may not be seen and the diagnostic yield of the study is compromised. Few studies have examined the benefit of frequent screening EEGs or continuous EEG monitoring. Dawson et al. obtained serial short-duration EEGs in 45 brain-injured patients every few days during the first 14 d after injury and found a 25% incidence of seizures by EEG criteria *(61)*. When Vespa et al. examined the role of continuous EEG monitoring in moderate to severe TBI, they found a 22% incidence of seizures among 94 patients admitted to the ICU *(20)*. More importantly, 52% of Vespa's patients with seizures had no clinical evidence of seizure activity. Additionally in this study's subgroup with no clinical or electro-graphic seizures, 10% of patients had epileptiform and nonepileptiform activity. Epileptiform activity included isolated spikes or sharp waves and/or repetitive sharp waves. Pseudoperiodic lateralized epileptiform discharges (PLEDs) were also seen in patients without other evidence of seizures. Nonepileptiform EEG abnormalities observed in these patients included symmetric disorganized slowing, asymmetrical disorganized delta waves with a focus, intermittent rhythmic delta activity, absence of sleep potentials, and progressive loss of EEG amplitude with

burst suppression. The latter was associated with impending brain death. Other EEG abnormalities were observed, including increased ß activity, amplitude suppression, and burst suppression. These patterns were seen in both the seizure and nonseizure groups and are related to the use of sedative hypnotics such as midazolam or propofol. Other studies have described a loss of EEG reactivity to external stimuli and loss of spontaneous variability *(62–65)*. "α Coma" is a term used to refer to coma in the presence of widespread α (8–12 Hz) activity in anterior–central cortical areas. This finding is associated with a poor prognosis in patients with TBI *(66–69)*.

Vespa's findings on continuous EEG monitoring in TBI support the use of continuous EEG monitoring in severely brain injured patients for early diagnosis and treatment of seizures *(20)*. Analysis of the EEG is also important in making determinations regarding seizures. Many studies have focused on compressed spectral array and other quantitative methods, whereas the highest yield of information comes from both trend analysis and examination of the raw EEG data. Vespa et al. used frequency analysis by fast Fourier transformation in the ICU, followed by examination of 2-min epochs that were evaluated for any increases in total power *(20)*. When increased spectral power was observed in an epoch, the raw EEG data were analyzed for evidence of seizures. Therefore, the trend analysis was used to flag periods in which seizures might have occurred, and this approach allowed a more focused examination of the raw EEG. Power spectral analysis has also been used to examine prognosis in TBI. Poor prognosis is frequently associated with unvarying activity, and a predominance of delta band activity (1–3 Hz) *(62)*. Variable spectral patterns are associated with better prognosis *(62,70)*, as are persistence or return of a peak in the α or θ frequency *(71,72)*.

Finally, one must consider the urgency of ordering the EEG when seizures are suspected after TBI. In one recent study, 23 emergent EEGs (EmEEGs), defined as a study performed less than an hour from request, were ordered mainly in post-TBI ICU patients *(73)*. The tests were ordered to rule out certain conditions: convulsive SE in 12 patients, NCSE in 6, and seizures in another 6 patients. Suspicious clinical activity was observed in 12 patients, and seizures before the test was performed were noted in a further 3 patients. The EmEEG showed convulsive status epilepticus in 3 patients, NCSE in 2 patients, and epileptiform activity or electrographic seizures in 4 patients. Half the patients were already on antiepileptic therapy when the test was performed.

TREATMENT OF POSTTRAUMATIC SEIZURES

There are two principal goals of treating posttraumatic seizures in the ICU. First, in the acute posttraumatic period the goal should be rapid cessation of seizure activity to prevent secondary physiological and biochemical insults and worsening injury. Second, further episodes of seizure activity should be prevented. There has been some debate about whether prevention of early seizures can result in lower

incidence of late posttraumatic seizures. Studies have also addressed whether long-term prophylaxis with antiepileptic agents is indicated *(11,74)*.

The initial management of seizures in the critically ill, brain-injured patient should include close observation of vital signs to ensure adequate oxygenation and end-organ perfusion, as well as adherence to advanced cardiac life support guidelines for assessment of airway, breathing, and circulation. In the nonintubated TBI patient, intubation should be considered, depending on the severity of the injury and on the duration of mental status change. An assessment of the seizure's origin should also be made. It should not always be assumed that seizures are primarily related to the brain injury. Critically ill patients are exposed to a wide variety of metabolic and pharmacological stressors that may trigger seizures independently of any brain injury. Such stressors include hypoglycemia, hyponatremia, hypocalcemia, hypophosphatemia, hypoxemia, hypocarbia, alcohol/recreational drug withdrawal, fever, meningoencephalitis, and hepatorenal failure. If seizures are newly diagnosed in a brain-injured patient, he or she should be evaluated for any of these complicating factors and appropriate measures introduced. Furthermore, a combination of these factors may interact in an additive fashion with the injury to trigger seizures, even if each factor by itself would not be sufficient.

A patient not currently on antiepileptics should be started on either phenytoin (15–18 mg/kg loading dose and 300–400 mg/d with frequent assessment of serum levels and a goal of 10–20 mg/dL), valproic acid (15–20 mg/kg loading dose, 600–3000 mg/d), or carbamazepine (600–1200 mg/d). Dilantin has benefits over other agents including the ability to load rapidly, the ability to titrate dose to effect, the widespread ability to follow serum levels, and long clinical experience with the agent. Patients already receiving seizure prophylaxis should have serum levels checked to ensure that they are in the therapeutic range; any who are subtherapeutic should be redosed, and their maintenance dose should be adjusted. Prolonged seizures should be stopped rapidly by using one of the sedative hypnotic agents at higher dose such as lorazepam (1–2 mg iv), diazepam (10–20 mg), midazolam (2–5 mg), sodium thiopentone (100–300 mg), or propofol (50–200 mg). These seizures and those that are recurrent or ongoing despite the foregoing measures should be treated as SE. Higher doses of benzodiazepines should be given (5–10 mg lorazepam, 20–40 mg diazepam, or 5–20 mg midazolam), and if the seizures remain refractory to this, then an infusion of propofol (150 µg/kg/min), thiopental (0.3–0.4 mg/kg/min), or pentobarbital (0.2–0.4 mg/kg/min) should be started with continuous EEG monitoring and a goal of achieving EEG burst suppression (*see* Chapter 2).

Several studies have examined the efficacy of antiepileptic agents in preventing early seizures. The largest prospective randomized, double-blind, placebo-controlled trial to date examined 404 brain-injured patients given phenytoin prophylaxis or placebo *(11)*. Follow-up was continued for 2 yr, and phenytoin levels were maintained in the high therapeutic range. A significant reduction in early seizures (<7 d) was observed.

Patients receiving phenytoin had a 3.6% incidence of seizures compared with 14.2% in the placebo group ($p < 0.001$, risk ratio [RR] 0.27, 95% CI 0.12–0.62). No

significant reduction in the development of late seizures was reported. By the end of the first year, 21.5% of phenytoin-treated patients and 15.7% of the placebo patients had seizures. By the end of the second year, these numbers had increased to 27.5 and 21.1%, respectively ($p > 0.2$). In addition, the incidence of adverse drug effects in the first 2 wk of treatment was low *(75)*. Hypersensitivity reactions occurred in 2.5% of the phenytoin-treated patients compared with 0% of the placebo patients ($p = 0.12$) during the first 2 wk of treatment. Based on these findings, the Seattle group advocates prophylactic phenytoin administration for the first 1–2 wk after injury. Other studies have also confirmed the ability of phenytoin to reduce the incidence of early seizures *(76)*.

Other antiepileptic agents have been evaluated. Glotzner et al. found in a group of 139 patients with TBI that carbamazepine can significantly reduce early seizure incidence *(77)*. Temkin et al. conducted another randomized, double-blind study comparing phenytoin with valproic acid for the prevention of post-TBI seizures. In this study, 132 patients were randomized to receive either phenytoin for 1 wk or valproic acid for 1 wk or 6 mo *(78)*. Incidence of early and late seizures did not differ between the phenytoin and valproic acid groups.

Several studies have examined the role of seizure prophylaxis in preventing late-onset posttraumatic seizures, and only one study has found a beneficial effect of long-term seizure prophylaxis *(76)*. However, this French study, conducted in a neurotraumatology ICU, was not blinded or placebo controlled. Thirty-four patients with severe TBI were randomized to receive phenytoin for 3 mo and were compared with 52 untreated severe TBI patients. After 2 yr, 6% of patients treated with phenytoin developed posttraumatic epilepsy compared with 42% of the untreated group. McQueen et al., who evaluated 164 patients in a prospective, randomized double-blind study comparing phenytoin and placebo, found no beneficial effect in the reduction of late seizures *(74)*. Temkin et al., in their large, well-controlled study of 404 patients, did not find any reduction in late posttraumatic seizures *(11)*. Studies of other agents, including carbamazepine *(77)* and phenobarbital *(79)*, have also failed to demonstrate any clear benefit on the incidence of late seizures. Glotzner et al. evaluated carbamazepine in a prospective, randomized, double-blind study of 139 patients and found no significant reduction in late posttraumatic seizures *(77)*. Manaka conducted a prospective, randomized, double-blind study of 126 patients receiving placebo or phenobarbital and found no reduction in late seizures in the treatment group *(79)*. A multiple regression analysis generated the following formula for prediction of epilepsy: $Y = 0.24433(x1) + 0.41753(x2) + 0.2185(x3) - 0.04639$, where $x1$ is presence of generalized neurological sign, $x2$ is early epilepsy, and $x3$ is computed tomography findings one month after the injury.

Clearly seizures occurring in brain-injured patients need to be rapidly treated. The clinical evidence at present supports the use of seizure prophylaxis for the prevention of early seizures (<7 d from injury) but does not support long-term administration of antiepileptic agents for the prevention of late-onset seizures *(80,81)* (Table 2). Specific risk factors for developing posttraumatic seizures have

Table 2
Summary of Randomized Studies in the Literature That Examine Prophylaxis Against the Risk of Early and Late Seizures Following Traumatic Brain Injury, and the Antiepileptic Drug Used: Values Represent Relative Risk With the 95% Confidence Interval in Parentheses

Study	Ref.	Drug used	Early seizures	Late seizures
Young et al. (1983)	*85*	DPH	0.99 (0.27–3.61)	
Young et al. (1983)	*82*	DPH		1.29 (0.56–3.0)
McQueen et al. (1983)	*74*	DPH		1.09 (0.41–2.86)
Glotzner et al. (1983)	*77*	CBZ	0.37 (0.18–0.78)[a]	0.71 (0.39–1.3)
Temkin et al. (1990)	*11*	DPH	0.25 (0.11–0.57)[a]	1.3 (0.82–2.08)
Pechadre et al. (1991)	*76*	DPH		0.14 (0.03–0.55)
Manaka (1992)	*79*	PB		1.38 (0.54–3.5)
Temkin et al. (1999)	*78*	VPA	2.9 (0.7–13.3)	1.4 (0.8–2.4)[a]

[a] Significant with $p < 0.05$.
DPH, phenytoin; CBZ, carbamazepine; PB, phenobarbital; VPA, valproic acid.

been identified including GCS <10, depressed skull fracture, cortical contusion, subdural/epidural hematomas, intracerebral hematoma, penetrating injury, focal deficit, and prolonged amnesia (>24 h) *(10,11,24)*. It is recommended that particular attention be given to seizure prophylaxis in the subgroup of brain-injured patients with these pathologies.

OUTCOME OF SEIZURES COMPLICATING TBI

It is pertinent to ask whether the benefits of seizure prophylaxis on early seizures reported in the literature translates into improved mortality or morbidity. Few studies have specifically addressed outcomes in relation to seizure prophylaxis *(11,74,76,77,82)*. No study to date has demonstrated any improvement in mortality as a result of administering anticonvulsants. A meta-analysis of several studies described a pooled relative risk of 1.15 (95% CI 0.89–1.51) for mortality in treated vs untreated patients, implying that treatment has no effect on mortality *(83)*. Two studies have examined outcome in surviving patients in relation to seizure prophylaxis. Glotzner et al. found a worse outcome in the treated group (RR 1.49, 95% CI 1.06–2.08, $p = 0.183$) *(77)* and Temkin et al. found no overall effect of seizure prophylaxis on patient outcome (RR 0.96, 95% CI 0.72–1.39, $p = 0.75$) *(11)*. One study comparing the efficacy of phenytoin and valproic acid actually found a trend to a higher mortality in the latter group (RR 2.0, 95% CI 0.9–4.1, $p = 0.07$), but it is unclear whether this is clinically significant *(78)*. A recent study using continuous EEG monitoring in critically ill ICU patients did not find any differences in either mortality or outcome at the time of discharge between the groups of patients with and without seizures *(20)*. However, six SE patients were identified, of whom three were found to be in NCSE. All six of the patients ultimately died, two as a result of sepsis after control of SE, three from progressive neurological deterioration and

brain death, and one from late respiratory arrest. Clearly the occurrence of SE is a grave prognostic sign in the traumatically brain-injured patient, and the high risk of NCSE suggests that EEG recording should be more frequently used in this patient population. Finally, the potential benefit for using antiepileptic drug prophylaxis after TBI must be weighed against the potential risk for impeding recovery of brain function from these compounds in addition to the aspects of safety and cost *(84)*.

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Brain Tumors and ICU Seizures

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SUMMARY

Seizures are a common presentation of brain neoplasms. Both primary brain tumors and metastases can present with seizures, which are more commonly focal depending on the location and the pathology of the lesion. In general, more benign tumors have higher incidence of seizures than more malignant ones. These patients are admitted to an intensive care unit either for preoperative monitoring or in the postoperative period. They should be treated with antiepileptics if seizures are witnessed. Whether they should be prophylactically treated with antiepileptic medications if seizures have not occurred yet in the pre- and postoperative period, and for how long, are questions that remain to be answered. More recent data do not seem to support such prophylactic administration.

Key Words: Brain tumors; seizures; intensive care unit; malignant; benign.

INTRODUCTION

Primary and metastatic brain tumors are frequently associated with epilepsy. Three categories of patients with brain tumors related to seizures may be brought to the intensivist's attention. In up to one-third of patients with brain tumors, seizures may be the initial presenting symptom, and some of these patients will be admitted to the intensive care unit (ICU) for monitoring for one day to few days, especially if the seizures recur or are associated with significant cerebral edema, hemorrhage, or signs of increased intracranial pressure or pending herniation. In all these cases, the members of the ICU team will be the first ones to address at least the acute, short-term management of the seizures. The second large category consists of postoperative patients after brain tumor resection, who spend at least 1 d in the ICU for observation. These patients may have one or more seizures in the ICU, and appropriate

treatment should be prescribed. An important issue to be addressed in the postoperative period, if patients are seizure-free, is whether they need prophylactic antiepileptic drug (AED) treatment during their ICU or hospital stay. The third category consists of patients with known and already treated brain tumors who are admitted because of refractory seizures or SE or have an unexplained change in mental status and are found to be in nonconvulsive status.

There are not many data regarding the ICU stay and management of these patients. A recent study by Ziai et al. addressed only postoperative issues. In this retrospective study, only 23 of 158 (15%) postoperative tumor patients stayed longer than 24 h in the Neurological Intensive Care Unit (NICU) at the Johns Hopkins Hospital *(1)*. Predictors of a stay longer than 1 d in the NICU in a logistic regression model were a tumor severity index, comprising preoperative radiologic characteristics of tumor location, mass effect, and midline shift (odds ratio [OR] 12.5, 95% confidence interval [CI] 3.1–50.5), an intraoperative fluid score, comprising estimated blood loss, total volume of crystalloid, and other colloid/hypertonic solutions administered (OR 1.8, 95% CI 1.2–2.6) and postoperative intubation (OR 67.5, 95% CI 6.5–702.0). Seizures were preoperatively present in 15 of 158 (9.5%) patients. There was no difference in the incidence between group 1 (≤24 h NICU stay) or group 2 (>24 h NICU stay) (11 of 135 vs 4 of 23, $p = 0.6$). Five patients (3.2%) had postoperative seizures. More patients who stayed longer had seizures postoperatively (2 of 135 patients in group 1 vs 3 of 23 patients in group 2, OR 10, 95% CI 1.6–62.5, $p = 0.02$). NICU resource use was reviewed in detail for 134 of 135 patients who stayed in the unit for a day or less. A total of 226 NICU interventions were performed in 69 (51%) patients. Fifteen (6.6%) were related to intravenous antiepileptic administration, but this was never done after the first 16 postoperative hours. This study provides valuable information regarding incidence of ICU seizures in brain tumor patients and use of ICU resources to treat them, but the results cannot necessarily be generalized to other ICUs.

INCIDENCE

Seizure occurrence remains a major morbidity problem in patients with intracranial tumors. Approximately 30–70% of patients with primary brain tumors will have seizures at some point throughout their disease *(2–5)*. About 40% of all the patients with metastatic brain tumors will have a seizure during their disease *(6,7)*. Half of these seizures will be simple or partial complex seizures and the other half secondary generalized seizures *(8,9)*. Brain tumors are rarely associated with primary generalized seizures.

Among the primary brain tumors, the higher incidence of seizures is found in patients with oligodendroglioma (92%). Astrocytomas and meningiomas have an incidence of about 70% and glioblastomas have an incidence of about 35% *(2)*. Other studies by Whittle and Beaumont *(10)*, Rasmussen and Blundell *(11)*, and Hoefer et al. *(12)* have reported oligodendrogliomas with seizure frequency of 89–90%, astrocytomas of 60–66%, glioblastomas of 31–40%, meningiomas of

29–41%, and metastatic tumors of 35%. Melanoma, choriocarcinoma, lung cancer, and breast cancer are tumors frequently metastasizing to the brain and associated with hemorrhage and seizures. Among metastatic tumors, melanoma seems to have the highest incidence of seizures. Conversely, based on a study from the Cleveland Clinic, the most common tumor types discovered among patients with intractable chronic epilepsy are ganglioglioma in 49 of 127 (39%) of cases and low-grade astrocytoma in 48 of 127 (38%) of cases *(13)*. Pleomorphic xanthoastrocytoma, dysembryoplastic neuroectodermal tumors (DNETs), and oligodendroglioma are also tumors frequently associated with chronic epilepsy. Overall, it seems likely that low-grade, well-differentiated gliomas have higher incidence of seizures than more aggressive glioblastomas or anaplastic astrocytomas *(14)*.

Different brain areas are also characterized by varying susceptibility to seizures. For example, among patients with gliomas, seizures occur in 59% of frontal tumors, 42% of parietal tumors, 35% of temporal tumors, and 33% of occipital tumors *(15)*. Similar observations suggest that the limbic and temporal lobe, primary and supplementary motor (M-I, M-II) areas, and primary and secondary somatosensory (S-I, S-II opercula and insula) areas have the lowest thresholds for seizures *(14)*. In contrast, the occipital lobe has a much higher threshold *(16)*. Tumors in the subcortical areas, such as thalamus and posterior fossa, are much less epileptogenic as well.

CLINICAL PRESENTATION

Besides focal neurological deficits, altered mental status, headache, and signs of increased intracranial pressure (ICP) (nausea, vomiting, papilledema), seizures are one of the most common presentations in patients with brain tumors. A first, unprovoked seizure in an adult is always suggestive of an intracranial tumor, until proven otherwise *(17)*. The timing of presentation is important to know. Seizure onset is usually within the first 24 h postoperatively *(18,19)* and, therefore, may be witnessed during the ICU patient stay. However, in a double-blind trial by North et al. of phenytoin vs placebo following craniotomy, 45% of the seizures occurred within the first week and 64% within the first month *(20)*. Patients who had seizures preoperatively are at a higher risk of developing postoperative seizures *(21)*. The type of seizure does not seem to be different pre- and postoperatively *(19,21)*.

Not all seizures have the same presentation: several seizure types have been reported and mainly reflect the location of the lesion. Most characteristic are the hypothalamic hamartomas, which are associated with gelastic seizures and precocious puberty. Parasagittal meningiomas may present with generalized seizures when located in the anterior one-third of the sagittal sinus, whereas meningiomas of the middle third usually present with focal seizures, at times following a Jacksonian marching pattern. Choroid plexus tumors in children may have seizures as the presenting symptom in 18% of the cases *(21a)*. Simple or partial seizures characterized by olfactory, gustatory, and epigastric auras, depersonalization, or feelings of fear or pleasure are usually an indication of temporal lobe pathology. Complex partial seizures with repetitive psychomotor movements (e.g., masticatory),

impairment of consciousness, or déjà-vu phenomena are also associated with the temporal lobe. Delusions and psychotic behavior have been reported with frontal lobe tumors *(22)*. Lesions involving the frontal eye fields are associated with turning of the eyes and head to one side (contraversive or ipsiversive, depending on the side of turning in relation to the lesion). Parietal lobe tumors are associated with sensory seizures, and occipital lobe tumors can cause seizures that are triggered by lights, colors, and geometric patterns *(17)*.

PATHOPHYSIOLOGY

The pathogenic mechanism of epileptogenesis in patients with brain tumors is not fully understood *(14)* and is beyond the scope of this chapter. Both the location and the histopathology, which correlates with the infiltrative potential, are important factors determining the clinical presentation of the tumors *(23)*. Tumors that tend to cause hemorrhage, necrosis, inflammation, and ischemia have a higher incidence of seizures. Focal hypoxia, mass effect and edema, and altered levels of excitatory amino acids all have been postulated to play a role in epileptogenesis. Tumors of different types may cause seizures through different mechanisms. Some tumors, like DNETs and gangliogliomas, with significantly higher seizure frequencies, have been associated with intrinsic epileptogenic properties.

Brain tumors are thought to alter the dendritic, axonal, and synaptic plasticity of the neurons and in this way to contribute to epileptogenesis *(24,25)*. Echlin proposed that brain tumors are causing partial isolation and deafferentation of the cerebral cortex, resulting in denervation hypersensitivity *(26)*, but there is no definite proof of that theory. Sodium channels in tumor cells may play a role in epileptogenesis, because these channels are responsible for generating action potentials more frequently than others *(27,28)*. Deregulation of inhibitory (γ-aminobutyric acid [GABA], taurine), as well as excitatory amino acid (glutamate, aspartate) may also contribute to the process *(29–31)*. Changes in extracellular Mg^{2+} ions and their effect on the ionotropic receptors for *N*-methyl-κ-aspartate also have been implicated *(32)*. Increased levels of Fe^{2+} in peritumoral brain tissue also convey a potential for paroxysmal epileptogenic activity. Alterations in the glial gap junctions have been observed in the cortex surrounding glial tumors *(14)*. Alkaline pH with increased lactate levels has also been observed in brain tumors *(33)*. Enzymatic changes and immune differences among individuals have also been implicated. Positron emission tomographic imaging has shown increased glucose metabolism and cerebral blood flow in epileptogenic cortex *(34)*.

All the foregoing mechanisms may be present and may work in parallel in the process of epileptogenesis. However, the individual's susceptibility to different homeostatic changes (systemic or regional) and their contribution in reducing the seizure threshold probably make up for the great variability noted in patients with similar findings, but different clinical presentations. An extensive review by Beaumont and Whittle of the implicated mechanisms has been published *(14)*.

Iatrogenic contribution is another entity that ICU specialists should be aware of. The route of ICU drug administration is important, beside their epileptogenic potential (*see* Chapter 12). For example, patients with primary brain lymphoma receiving intrathecal chemotherapy have a 47% incidence of seizures *(35)*. Even intravenous contrast has been implicated in the generation of seizures in a patient with primary brain tumor *(36)*.

Systemic cancer can metastasize to the brain and produce seizures as its first manifestation. The intracranial metastases usually originate from embolization of neoplastic cells to the brain, commonly in terminal arterial supply territories, such as the gray–white matter junction. However, systemic cancer may induce seizures through additional noninvasive mechanisms; coagulopathy and stroke (sinus thrombosis), nonbacterial thrombotic endocarditis with cerebral emboli, systemic metabolic derangements such as hypomagnesemia *(37)* or hyponatremia *(38)*, opportunistic infections after chemotherapy, and direct toxicity of chemotherapeutic agents to the brain *(39,40)* are a few of the potential pathogenetic mechanisms for which treatment is available. Paraneoplastic syndromes, such as limbic encephalopathy with anti-Hu antibodies can be associated with seizures preceding the diagnosis of cancer *(41)*. Some patients with cancer and altered mental status may be in nonconvulsive status epilepticus (NCSE) (Fig. 1). Drislane reported six patients with systemic cancer, whose electroencephalograms (EEGs) showed NCSE. Three patients were confused, and the others were stuporous or comatose. The possibility of paraneoplastic encephalopathy was raised in three patients. Antiepileptic treatment led to an improved mental status in four of these patients *(42)*. Five patients out of 84 (6%) with cancer and altered mental status (coma or delirium) were found to be on NCSE by EEG in an Italian study. None of these patients had brain metastases: 1 had aphasic, 2 patients treated with ifosfamide absence, and 2 patients treated with cisplatin complex partial status epilepticus. All experienced rapid recovery after antiepileptic treatment *(43)*.

EVALUATION OF PATIENTS WITH ICU SEIZURES

Most of the seizures associated with primary or metastatic tumors of the central nervous system (CNS) are of focal onset (Figs. 2 and 3) with or without secondary generalization. These patients may progress to convulsive (SE) and permanent neurologic damage. Brain tumors are not intrinsic and can lead to seizures associated with increased blood volume, intracranial pressure, and tissue displacement, resulting in cerebral herniation. Posturing in this case must be differentiated from a seizure. Seizures caused by brain tumors must also be differentiated from intermittent episodes of increased intracranial pressure with plateau waves, which cause headaches, diplopia and other visual disturbances, fluctuation of mental status, motor deficits, or dystonic or opisthotonic postures.

A patient who has a sudden postoperative change of mental status after brain tumor resection will need to be evaluated for hemorrhage, edema, and infarction, as well as seizures, clinical or subclinical. In parallel with head imaging studies—
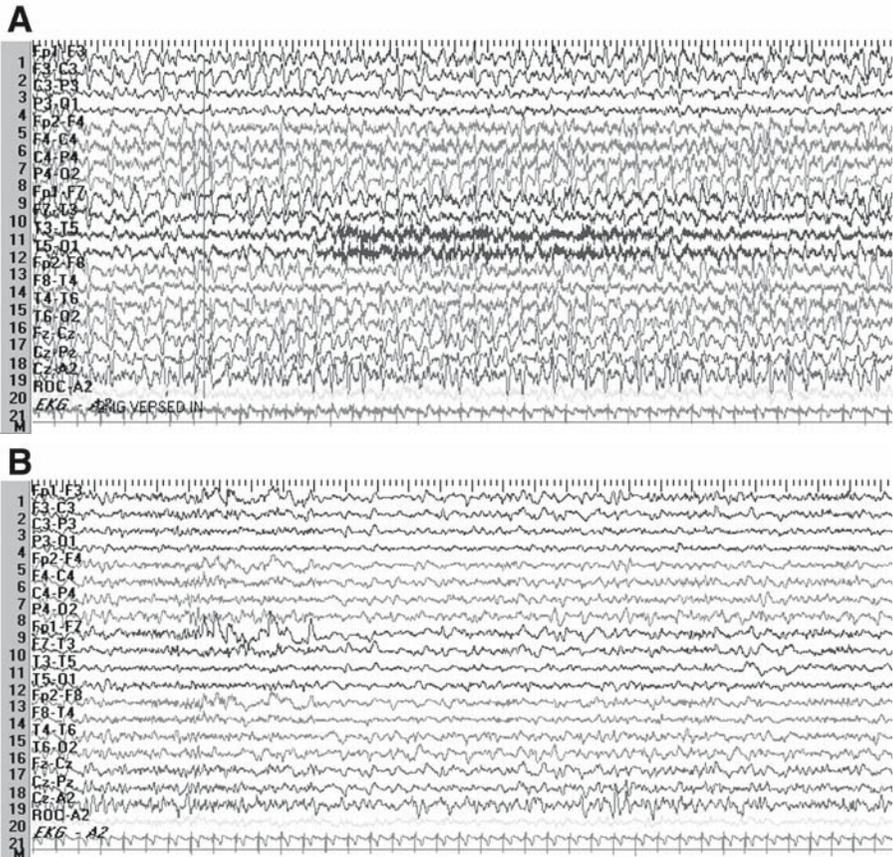
Fig. 1. This patient, a 63-yr-old man with metastatic squamous cell carcinoma of the tonsils to the brain, had two large metastases, one in the right parieto-occipital area (resected, with recurrence) and one in the left frontal area; SE was noted after whole-brain irradiation and chemotherapy. The patient was admitted to the NICU for observation prompted by change in mental status: drowsy, able to say only "Eeeh" with minimal stimulation, moving all four extremities, but not following commands. He was receiving phenytoin at therapeutic levels, but no evidence of toxic or metabolic reasons for his condition appeared in the work-up. The patient was placed on lorazepam (1 mg po three times a day). Two days later his mental status had improved and he was able to carry on some conversation. He was then transferred to palliative care, where he expired 9 d later. EEGs showed **(A)** nearly continuous triphasic waves over both frontal regions on a θ/δ background and **(B)** after administration of 2 mg of midazolam intravenously.

such as head computed tomography (CT)—magnetic resonance imaging (MRI), or MR spectroscopy, and the appropriate workup for other common critical care causes of encephalopathy as just noted, an EEG will confirm whether the patient is having nonconvulsive seizure activity and may also help in assessing the appropriate
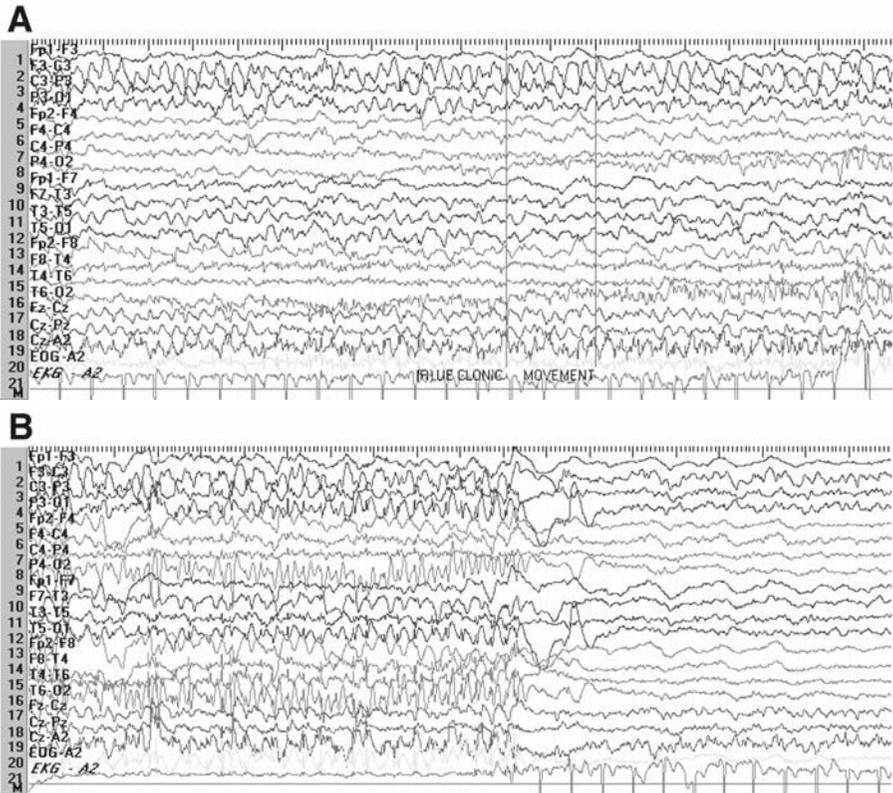
Fig. 2. This 59-yr-old man was readmitted to the NICU 7 d after a left frontal oligoden-droglioma resection because of significant edema. He presented with intermittent episodes of right upper extremity clonic activity lasting for 15–60 s. The patient responded to 1 mg of lorazepam and extra phenytoin to correct the low levels. EEGs show **(A)** left frontocentral epileptiform discharges at a frequency of 2–3 Hz progressing to involve the right occipital head region (right side of the epoque) and **(B)** abrupt cessation 30 s later of spike and slow–wave activity with subsequent attenuation of the record.

response to treatment. The role of continuous EEG monitoring (CEEGM) in this ICU population has not been well-established, but there is growing evidence of its use in diagnosing NCSE in tumor patients. Jordan monitored 124 NICU patients with CEEGM and reported that 34% of them had nonconvulsive seizures and 27% were in NCSE. Among the 11 patients with brain tumors, 6 (54%) had nonconvulsive seizures. Overall, CEEGM played a decisive or contributing role in the ICU management in 13 of 16 (81%) of patients with brain tumor in a later report with additional patients by the same author *(44,45)*. NCSE was reported in 2 patients with non-Hodgkin lymphoma presenting with mutism and confusional state after infusion with ifosfamide (an alkylating agent, structurally an isomer of cyclophos-
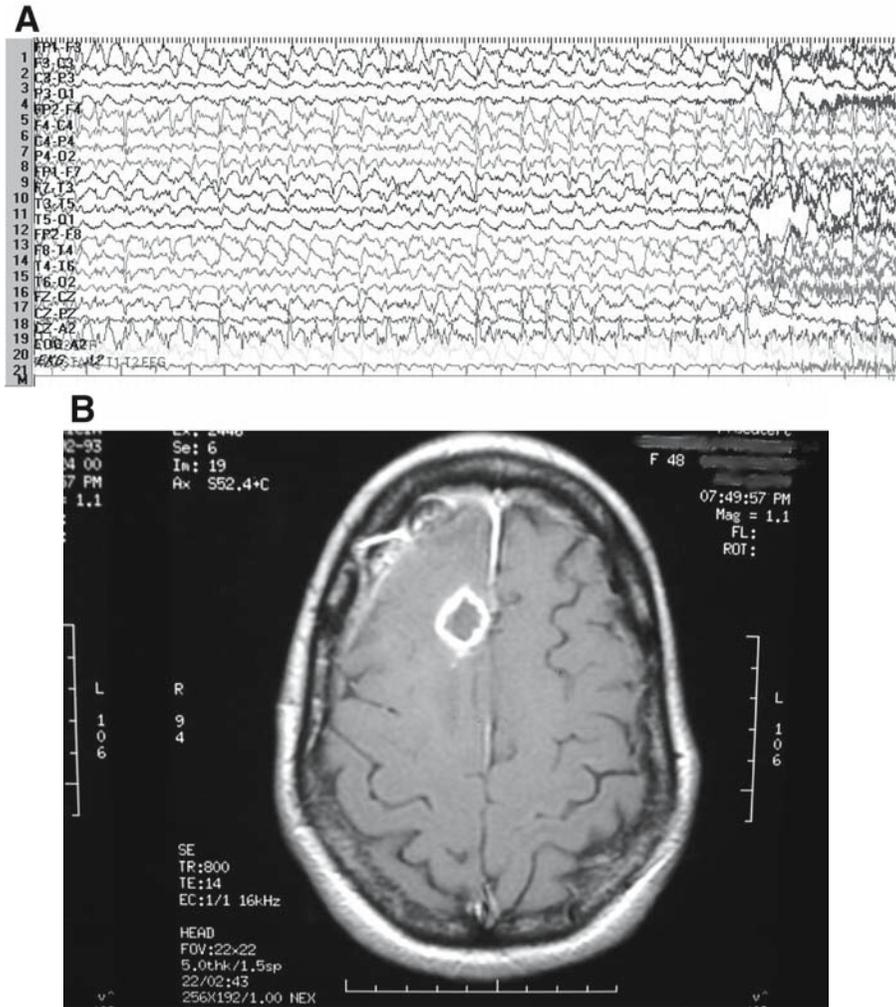
Fig. 3. This 48-yr-old woman, admitted for frequent paroxysmal episodes of staring, was examined by CT and found to host a lesion in the head. **(A)** EEG showing rhythmic sharp waves maximally over the right frontocentral region. The patient was unresponsive with head and eyes turned to the left during this event. **(B)** Gadolinium-enhanced T1-weighted MR image of the head showing a ring-enhancing lesion on the right frontal lobe. The lesion was resected and found to be a metastasis.

phamide) *(46)*. Another patient with glioblastoma multiforme was treated with intravenous tirapazamine and brain irradiation. After CT scan was performed with intravenous contrast medium, the patient became aphasic and the EEG showed NCSE. Intravenously administered lorazepam and a loading dose of phenytoin returned the patient to normal state the next morning *(36)*.

These results emphasize the need for emergent EEG evaluation of tumor patients who manifest unexplained change upon neurological examination in the ICU.

TREATMENT

Prophylactic Administration of Antiepileptics

The issue of prophylactic treatment of patients with brain tumors is very complex. If a seizure has already occurred, there is little doubt about the value of antiepileptic agents *(47)*; however, when the patient has never exhibited epileptic phenomena, such a treatment becomes more controversial. Efficacy of the treatment must be balanced with adverse events associated with the chosen drugs. Despite the best efforts, a significant percentage of patients still have breakthrough seizures, and their response to the treatment is very unpredictable. Several reasons must be considered: examples include lack of antiepileptics having an effect on a vast range of physiologic derangements induced by brain tumors and difficulty of maintaining appropriate antiepileptic levels and tumor progression or recurrence *(14,48)*. On the other hand, antiepileptic treatment is not without adverse effects, some of them potentially serious. The case report by Cockey et al. is revealing of our inability to predict complications in those medically complex patients: severe Stevens–Johnson syndrome, documented by biopsy, occurred in a patient with metastatic squamous cell carcinoma who had been receiving phenytoin, whole-brain radiation therapy, and a tapering steroid dose *(49)*. Moreover, there is growing evidence supporting increased frequency and severity of side effects from antiepileptic medications in this population: in a meta-analysis of studies examining prophylactic treatment in patients with newly diagnosed brain tumors, 23.8% (range: 5–38%) of treated patients experienced side effects that were severe enough to lead to change or discontinuation of the medications. This incidence is higher than that in the general population and should make physicians skeptical about the real need for using these drugs for all patients with brain tumor *(47)*. The bottom line remains that personal preference and training or experience of physicians may be more important in making the decision than clinical evidence of benefits and drawbacks. According to a study conducted in Rhode Island, 55% of participating physicians gave antiepileptic prophylaxis, but the percentage differed according to the subspecialty: 33% of radiation oncologists, 50% of oncologists, 53% of neurologists, and 81% of neurosurgeons *(47,50)*.

Additional morbidity by the treatment directed at the tumor may be of some help in making the appropriate decision. Tumor resection is still the cornerstone of brain tumor management. Seizures after tumor resection may pose a serious problem. Extensive intraoperative retraction and cortical injury associated with tumor invasion and aggressive resection are probably associated with increased seizure frequency postoperatively. Residual anesthetic agents may prevent early diagnosis of seizures, as well as neurologic complications. Seizures may compromise the airway and cause limb injuries or structural brain injury, possibly predisposing the patient to more seizures or even SE *(51)*. Seizures can also cause cerebral acidosis, cere-

bral edema, and increased ICP (which may already be elevated), all conditions that challenge the compensatory mechanisms of the brain (*52*). Metabolic disturbances, such as hyponatremia or hypernatremia, hypoxia, pain-induced hyperventilation, and hyperglycemia are frequently noted postoperatively and may also contribute to increased seizure frequency; hence, they should be treated aggressively. Lee et al. found that metabolic acidosis and hyponatremia had been present in 80 and 20%, respectively, of patients who then had seizures (*19*). The altered rate of metabolism during surgery, especially by the liver, also affects the levels of anticonvulsants. More than one study has shown that inadequate levels of phenytoin were the leading cause of postcraniotomy seizures (*6,20*).

The effect of surgery on seizures has been studied in numerous trials. Overall, surgical excision of a brain tumor results in improved control of seizures, and the more extensive the resection of gliomas, the lower the postoperative seizure frequency, although this last notion is not supported by all studies (*14*). The effect on seizure occurrence of craniotomy *per se*, with the meningeal or parenchymal injury that ensues, cannot be easily separated from the very effect the tumor induces. Most of the available studies were performed in mixed tumor and nontumor patients; therefore, the conclusions may not be applicable to the former. In the next sections, we will mention some of the most important studies regarding craniotomy, all including tumor patients, because these data are pertinent to the decisions an intensivist faces. Subsequently we will present the data regarding prophylactic antiepileptic use specifically in patients with brain tumors.

Kvam et al. showed that out of 538 postcraniotomy patients, 23 had postoperative seizures. Among these 23 patients, only 5 had seizures preoperatively. The authors suggested a preoperative loading dose of 10 mg/kg of phenytoin (PHT), followed by a postoperative dose of 5 mg/kg/d (*18*). In a more pertinent follow-up to the ICU study conducted in Taiwan (*52*), 374 craniotomy patients were randomized to receive 15 mg/kg of PHT intravenously during surgery, followed by 3–6 mg/kg/d for 3 d, or placebo. The group receiving phenytoin had two early postoperative seizures and the placebo nine, but the difference was not statistically significant. Eighty percent of the seizures occurred within 20 min after surgery. Thus, the authors recommended that prophylactic anticonvulsant medication be given at least 20 min before completion of wound closure. This view was not shared by the authors of a subsequent large prospective study, who did not recommend prophylactic treatment with antiepileptics after supratentorial craniotomy. In this study, 276 postcraniotomy patients were randomized to receive carbamazepine or phenytoin for 6 or 24 mo or received no treatment (*53*). The three treatment groups did not overall differ in the risk of seizures, but there was a nonsignificant 10% reduction of seizures in the two groups that received antiepileptic medications. Meningiomas had the highest risk for seizures (75% by 4 yr) and pituitary tumors the lowest (21% by 4 yr). Longer operations, those associated with dissection of the lesion away from the surface of the brain and left-sided or bilateral lesions, also

carried a higher risk. Early seizures (within 1 wk) after craniotomy did not increase the likelihood of late epilepsy.

Adding to the debate are the results of a more recent prospective, stratified, randomized, double-blind Dutch study that compared outcomes for 300 mg phenytoin/d to 1500 mg valproate/d given for 1 yr to 100 postcraniotomy patients. Fourteen patients had postoperative seizures, but there was no difference in seizure incidence between the two groups *(54)*. Finally, a meta-analysis of six controlled studies addressing the issue showed a tendency of prophylactic antiepileptics to prevent postoperative convulsions in patients without pre-existing seizures, but this effect did not reach statistical significance ($p = 0.1$, one tailed) *(55)*.

Several studies have examined the need for antiepileptic use, either prophylactically or after surgery, usually in mixed primary or metastatic brain tumor populations. In a double-blind, randomized study of PHT (100 mg three times a day) vs placebo in 281 postcraniotomy patients, the PHT group had significantly fewer seizures (12.9 vs 18.4%), and highest protection was present between days 7 and 72. Routine prophylaxis with PHT (in a dosage of 5–6 mg/kg/d) was recommended by the authors in high-risk patients postcraniotomy. Preferably treatment should be started 1 wk preoperatively, and therapeutic levels of phenytoin should be maintained *(20)*. However, the subgroup analysis of 81 patients with brain tumors and craniotomy showed that 21% of patients treated with PHT had seizures vs only 13% of the nontreated patients (OR 1.8, 95% CI 0.6–6.1). Only the meningioma subgroup in this study had slightly lower risk for seizures in treated vs placebo patients. Therefore, based on these results, the recommendations for PHT prophylaxis should not apply to brain tumors.

In a subsequent Italian study, 65 of 128 (51%) patients with supratentorial brain tumors had preoperative seizures and were treated with AEDs. Those without preoperative seizures were randomized to receive phenobarbital (PB) or PHT as prophylactic treatment, or received no treatment. No significant difference in seizure incidence was found between patients treated (7%) and those not treated (18%). The authors suggested short-term preventive antiepileptic treatment after surgery in patients without preoperative seizures and continuation of postoperative treatment in patients with preoperative epilepsy *(56)*.

More recently, Glantz et al. conducted a well-designed randomized, double-blind, placebo-controlled study comparing the incidence of first seizures in 74 valproate (VPA)- and placebo-treated patients with newly diagnosed supratentorial brain tumors. The drug and placebo groups did not differ significantly in the incidence of seizures: 35% in the VPA and, surprisingly, 24% in the placebo-treated group (OR 1.7, 95% CI 0.6–4.6, $p = 0.3$). Based on these results, no prophylactic treatment with VPA could be recommended *(50)*.

Finally, a prospective, randomized, unblinded study from Canada examined the effect of prophylactic PHT administration in newly diagnosed patients with primary and metastatic brain tumors without prior seizures. Seizures occurred in 26

(26%) of all patients, 11 (24%) in the treated, and 15 (28%) in the nontreated group (OR 0.82, 95% CI 0.3–2) *(57)*.

Similarly, reports on patients exclusively with metastatic brain tumors do not support the use of prophylactic anticonvulsants *(6,58)*. In a large retrospective analysis of 195 patients with metastatic brain tumors, Cohen et al. reported that 18% of patients presented with seizures. Of the remaining seizure-free patients, 40% were treated prophylactically with antiepileptics (PHT in >90%). In a follow-up period of up to 59 wk, 10% of patients developed late seizures. The incidence of seizures did not differ between the treated (13.1%) and untreated (11.1%) groups. This study is flawed, however, because two-thirds of the patients with seizures had subtherapeutic antiepileptic levels. The authors did not advocate the use of antiepileptic medications, unless the patient has the first seizure *(6)*.

Summarizing the foregoing information, the Quality Standards Subcommittee of the American Academy of Neurology published a meta-analysis of 12 studies, which had addressed the issue of prophylactic antiepileptic treatment for newly diagnosed brain tumor patients. Four were randomized and eight were cohorts. Only one study showed significant difference between treated and untreated groups and actually favored the untreated. The overall OR from the randomized trials was 1.09; the 95% CI was 0.63–1.89 ($p = 0.8$) for seizure incidence and 0.74–1.44 (OR 1.03, $p = 0.9$) for seizure-free survival. Therefore, the subcommittee recommended no prophylactic use of antiepileptics on patients with newly diagnosed brain tumors. Tapering and discontinuing the antiepileptics was appropriate after the first postoperative week in patients without a seizure (who were nevertheless treated). Although not excluding the possibility that some subgroups of brain tumor patients (i.e., those with melanoma, hemorrhagic or multiple metastatic lesions, tumors located near the rolandic fissure, slow-growing primary CNS tumors) may be at a higher risk for seizures, the subcommittee did not find any reason for prophylaxis in patients *(47)*.

Treatment of Seizures in the ICU

Treatment of seizures or SE in patients with brain tumors follows the general guidelines that are presented in Chapter 14. However, there are several important details regarding these complex patients that the intensivist should master.

Interactions between the various medications pose the most important problem and can lead to unforeseen complications. Antiepileptics, especially those affecting the cytochrome P450 system, may affect the metabolism of chemotherapeutic agents used for the treatment of metastatic or primary CNS tumors. These agents have a narrow therapeutic window and real potential for toxicity or lethal side effects if their activity is increased by an additional agent; if their activity is decreased they may lose their anticancer efficacy. Usually, the addition of PHT, carbamazepine (CBZ), PB, and other inducers of the cytochrome P450 system, reduces the levels or efficacy of cyclophosphamide, methotrexate, Adriamycin, nitrosoureas, paclitaxel, etoposide, topotecan, irinotecan, thiotepa, and corticosteroids *(47,59)*. In addition, competition for binding to plasma proteins may be impor-

tant with several of those medications, especially in states of hypoalbuminemia, not uncommon in the ICU or during chemotherapy. Measuring the free levels of drugs and adjusting the dose can be useful to avoid toxicity or subtherapeutic levels.

Regarding the steroids, either their dose should be increased or the patient should be switched to one of the newer, noninducing antiepileptic agents (lamotrigine, tiagabine, leviracetam, zonisamide, vigabatrin, and gabapentin). The same may be true for several other antitumor agents, but the intensivist should be cautious because no data from large studies are available reporting their interaction with the newer antiepileptics *(59)*. On the other hand, chemotherapeutic agents or corticosteroids can affect the metabolism of several antiepileptics, increasing or decreasing their levels *(60–62)*. This may explain the subtherapeutic levels of these drugs in the studies that evaluated their prophylactic use *(6,50,56,57)*. In addition, several chemotherapeutic agents may have proconvulsant activity on their own *(43,46)* (*see* Chapter 12), and the intensivist should be aware that the aforementioned studies of prophylactic antiepileptic treatment did not control for the presence of specific chemotherapeutic agents.

An interesting aspect of the use of AEDs in patients with cancer is the potential of these agents for antineoplastic or immunosuppressive effect *(63–66)*. VPA is probably exhibiting in vitro favorable proapoptotic action and PBT immunosuppression, but clinical studies are not available. Neutropenia secondary to myelosuppressive chemotherapy may worsen with CBZ, an adverse effect that should be monitored very carefully *(67)*. Gabapentin may also ameliorate the nausea induced by chemotherapy, and this may be of additional benefit in patients with seizures and breast cancer *(68)*.

Interaction between antiepileptics and irradiation treatment offered to the brain or spine may lead to dermatologic complications. Skin rash in patients treated with PHT and brain irradiation may herald Stevens–Johnson syndrome *(49,69)*, and VPA has been implicated in Rowell's syndrome (lupus erythematosus associated with erythema multiforme–like lesions) *(70)*. However, one retrospective study of 289 patients with brain tumors treated with antiepileptics and radiation found only one (0.3%) patient developed erythema multiforme. Phenytoin was associated with milder rashes in 22% of patients, a higher incidence than the usual 5–10%. These rashes did not appear to be related to radiation because they usually occurred before its initiation *(71)*.

Individualizing the treatment in the ICU and afterward is probably best. Factors that should be considered before one decides if and when to treat the patient and which medications to use include the histopathology of the tumor, the location of the mass, the presence of pre-existing epilepsy, the extent of additional injury incurred by craniotomy, the involvement of other important organs metabolizing the drugs, the nutritional state of the patient, the pharmacological interactions between the agents, and the ability of the patient to tolerate side effects of the treatment.

OUTCOME

Although not pertinent to the ICU management, certain data in fact support a better outcome in patients with brain tumors and seizures *(14)*. In a retrospective analysis of 560 patients with primary supratentorial tumors, the median survival of the 164 (29%) patients presenting with epilepsy was 37 mo compared with 6 mo of those presenting with other symptoms ($p < 0.0001$) *(72)*. In the study by Whittle and Beaumont of 34 supratentorial oligodendrogliomas, 17% of patients who presented with seizures and 67% of those who presented with other symptoms had died in the follow-up. However, in a multivariate model, young age and not epilepsy was a favorable independent predictor *(10)*. This information can be of some help in the discussions the intensivist may have with the patients or relatives in the ICU.

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Global Hypoxia–Ischemia and Critical Care Seizures

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SUMMARY

Seizures after cardiopulmonary arrest are a common problem in the intensive care unit, occurring in as many as one-third of these patients during their hospitalization. The etiology, treatment, and prognostic importance of seizures in this setting have not been well-delineated in the literature. Whether seizures exacerbate global hypoxic–ischemic brain injury in humans remains unclear, which raises uncertainty about how aggressively they should be treated. Some pathological data suggest that anoxic brain injury is worsened by generalized tonic–clonic (GTC) status epilepticus (SE). Especially when the prognosis remains uncertain, GTC SE should be treated in the conventional manner. Partial seizures and simple myoclonus are unlikely to exacerbate neuronal damage, and treatment probably should be reserved for seizures that are traumatic to family members or interfere with mechanical ventilation. Status myoclonus (SM) in hypoxic–ischemic coma is particularly troublesome because it can be highly refractory to conventional anticonvulsants and appears to portend an extremely poor prognosis, regardless of its management. Case series that report 100% mortality or vegetative state from this condition have involved only highly selected patient populations. Several cases have been reported of patients with good neurological outcomes despite SM in postanoxic coma. The most prudent course of action is to continue intensive management of patients with SM—including anticonvulsant therapy—and to rely on more precise means of prognostication (clinical exam, electroencephalography, and somatosensory evoked potential) to inform the decision to withdraw supportive care. The decision to use anesthetic agents and paralytics in this setting must be individualized.

Key Words: Hypoxic–ischemic encephalopathy; seizures; status epilepticus; postanoxic myoclonus.

INTRODUCTION

The increasing success of cardiopulmonary resuscitation (CPR) in reviving individuals from cardiac and respiratory arrest has generated a dramatic upsurge in hospital admissions for patients in postresuscitative coma. This paradox is largely a result of the absence of primary brain-directed therapies for global hypoxia–ischemia. As many as one-third of comatose CPR survivors will experience seizure activity at some time during their hospital course, most commonly within the first 24 h *(1–3)*. The immediate postresuscitation period is also marked by the highest risk of hemodynamic instability, recurrent arrest, and prognostic uncertainty. Cardiac intensive care units (ICUs) in the United States have become accustomed to facing the challenge of managing seizures and myoclonus in the setting of hypoxic–ischemic coma. Despite the common occurrence of this problem, clinical and basic science research in the area has been sparse, and several important questions remain unanswered. Do seizures exacerbate brain damage in hypoxic–ischemic coma? How aggressively should they be treated, and with which agents? Can some seizure types offer prognostic information that affects the decision to withdraw care? This chapter provides a comprehensive presentation of existing literature related to this problem.

EPIDEMIOLOGY

Community-based population data on critical care seizures are not currently available. The epidemiologic information related to this problem is primarily based on reports from highly selected patient populations. Several small studies describe the epidemiology of various seizure types in the setting of hypoxic–ischemic insults. In a referral population of 114 patients who survived CPR for over 24 h, Krumholz et al. *(1)* described seizures in 44%. Thirty-five percent of patients had myoclonus alone or in association with other seizure types. Status epilepticus (SE) was found in 32%, the majority of which was either status myoclonus (SM) alone or a combination of SM and generalized tonic–clonic (GTC) SE, which the authors termed myoclonic status epilepticus. In prospective *(2)* and retrospective *(3)* studies of all comatose patients admitted after CPR, Snyder et al. found that one-third of patients experienced seizures, the majority of which had more than one seizure type. Myoclonic seizures were described in 19%, partial seizures in 19%, and GTC seizures in 6% of the total population. The incidence of myoclonic seizures was bimodal, with the majority beginning within 12 h after CPR and the remainder delayed by several days *(2)*. In the classic outcome study by Levy et al. *(4)*, 15% of patients in hypoxic–ischemic coma experienced generalized convulsions, whereas 10% had isolated myoclonus. The posthypoxic syndrome of action myoclonus described by Lance and Adams *(5)* can occur within a few days of cardiac arrest, but the incidence rate among survivors has never been studied.

PATHOPHYSIOLOGY

Pathological and Chemical Changes in Hypoxic–Ischemic Injury and Seizures

Experimental animal studies have provided insights into the mechanism of epileptogenesis in hypoxic–ischemic coma. Adenosine triphosphate (ATP)-sensitive potassium channels (K_{ATP}) are activated by hypoxic stress, resulting in protective cellular hyperpolarization by inward rectifying potassium currents *(6)*. K_{ATP} knockout mice subjected to brief episodes of hypoxia are more susceptible to generalized seizures *(6)*. The highest concentration of K_{ATP} channels is located within the substantia nigra–pars reticulata (SN_{PR}), which acts as a central gating system for the propagation of generalized seizures *(6)*. In prolonged hypoxia–ischemia, SN_{PR} may be damaged and the gating function of the K_{ATP} receptors may be lost. Alternatively, hypoxic depletion of ATP could result in loss of the inward rectifying potassium current and failure to block seizure propagation at the SN_{PR} *(6)*.

Prolonged generalized seizures induce permanent neuronal injury that shares some characteristics with global hypoxia. Excess glutamate release activates the receptors of *N*-methyl-D-aspartate (NMDA), resulting in intracellular accumulation of calcium and early apoptosis *(7)*. When mitochondrial energy stores are depleted during hypoxic and ischemic states, the cytotoxicity of NMDA receptor activation is markedly potentiated *(8)*. Experimental blockade of the NMDA receptor inhibits neuronal toxicity even though it does not shorten the duration of the seizure *(9)*.

Pathological studies of uncomplicated seizures in humans report either no neuronal injury or ischemic cell changes limited to the hippocampus, particularly the Sommer sector (H1) *(10)*. After prolonged SE, the cortex may show laminar ischemic changes similar to hypoxic–ischemic encephalopathy with or without involvement of the cerebellar Purkinje cells *(10)*. Experimental data from well-oxygenated baboons with chemically induced SE showed cortical damage but limited cerebellar pathology *(11)*. In mechanically ventilated rats, prolonged seizures produced cellular changes limited to the SN_{PR}, hypothalamus, and globus pallidus *(12,13)*. Damage to the white matter and deep gray matter structures other than the hippocampus is not typically demonstrated in adult humans in the absence of concomitant hypoxia or ischemia *(10)*. On the other hand, pathological changes demonstrated in global hypoxia–ischemia involve all neuronal layers of the cortex, subcortical gray matter structures, cerebellum, and spinal cord, as determined from human autopsy series *(14)*.

Animal data have been important in studying whether seizures exacerbate hypoxic–ischemic neuronal injury. Young et al. studied extracellular inhibitory and excitatory amino acid concentrations in juvenile rabbits with hypoxia alone, seizures alone, and seizures after hypoxia *(15)*. They found no increase in glutamate or γ-aminobutyric acid (GABA) with hypoxia or seizures. When seizures were preceded by a period of hypoxia, however, there was a dramatic increase in both

glutamate and GABA *(15)*. Concomitant hypoxia and seizures potentiate neuronal excitotoxicity, and excess glutamate release may lower the seizure threshold. In neonatal rats subjected to 3 h of unilateral stagnant hypoxia, concentrations of glutamate and GABA in the cerebrospinal fluid (CSF) were elevated *(16)*. When these rats were subjected to prolonged SE, the concentration of GABA increased further but glutamate did not *(16)*. These findings suggest that glutamate neurotoxicity in the setting of hypoxia–ischemia was not enhanced by seizures. Several pathological studies of global hypoxic–ischemic insults in neonatal rats found no further increase in lesion size after SE *(16–18)*. In newborn rats with limited hypoxic–ischemic lesions from unilateral carotid ligation, however, SE resulted in heightened neuronal injury *(19)*. It is believed that prolonged global hypoxia–ischemia results in such devastating neurological injury that the additional damage caused by seizures, if present, may be pathologically undetectable *(19)*.

Myoclonus in Hypoxic–Ischemic Coma

Many clinicians ascribe SM in the hypoxic–ischemic coma setting to agonal neuronal firing that is a fragment of GTC SE *(20–22)*. Celesia et al. *(22)* speculated that hypoxic–ischemic destruction of the neocortex, cerebellum, and subcortical gray matter disrupts the normal propagation and regulation of tonic–clonic seizure activity, resulting in SM. They note that hypoxic damage to the neocortical laminar and intralaminar nuclei disrupts Jacksonian seizure progression, and destruction of the thalamic relay system prevents generalization to GTC convulsions *(22)*.

Pathological data were provided in several case series of patients with SM in postanoxic coma *(20–22)*. In the series of Young et al. *(20)*, damage was seen in all layers of the cerebral cortex, hippocampus, basal ganglia, cerebellar Purkinje cells, and spinal cord gray matter. These findings are more reflective of severe hypoxic–ischemic injury than neuronal damage from SE *(20)*. In the series of Celesia et al. *(22)*, the only two patients with Ammon's horn sclerosis—reflective of neuronal damage from SE—had GTC SE prior to the development of SM. In the study by Wijdicks et al. *(21)*, postanoxic patients with SM showed involvement of all cortical laminae significantly greater than those who died without SM. The damage in the hippocampus and cerebellum was not significantly different between the two groups. These data were interpreted to reflect the greater anoxic brain injury experienced by patients with SM *(21)*, but the study was not designed to discern whether myoclonic seizures contributed to this injury.

Lance–Adams Syndrome

Although in their classic paper describing the posthypoxic syndrome of action myoclonus, Lance and Adams *(5)* implicated damage to the ventrolateral thalamic nuclei as the causative lesion, subsequent reports have focused on impaired serotonin neurotransmission and lesions in the caudal medulla and cortex. Many patients with Lance–Adams syndrome have low CSF concentrations of serotonin metabo-

lites *(23,24)*. Rat models of posthypoxic myoclonus demonstrate impaired neurotransmission at receptors for two 5-hydroxytryptamines: $5\text{-}HT_{1B}$ and $5\text{-}HT_{2A/2B}$ *(25,26)*. Myoclonus is often attenuated by treatment with 5-hydroxytryptophan (5-HTP), valproic acid, and clonazepam—substances known to enhance serotonergic neurotransmission—in both rat *(27)* and human *(28)*. Excess CSF serotonin metabolites, exacerbation of myoclonus with serotonin agonists, and amelioration with the serotonin antagonist methysergide was reported in a single patient with severe hypercarbic respiratory arrest *(29)*. The exact role of serotonin in Lance–Adams syndrome remains unclear.

CLINICAL PRESENTATION

GTC Seizures

GTC seizures following CPR were reported in 16 of 114 cardiac arrest survivors in the Krumholz prospective series *(1)*. GTC SE occurred in conjunction with myoclonus in 17% of patients, a constellation Krumholz et al. termed "myoclonic status epilepticus." The majority of these seizure episodes began within 5 h (range: 1–12 h) of cardiac arrest and lasted an average of 17.5 h (range: 2–48 h). All patients were profoundly comatose at seizure onset. In the same series, respiratory arrests were more frequently implicated in myoclonic SE than cardiac arrests *(1)*. Snyder et al. *(3)* reported GTC seizures in 4 of their 63 patients in coma after CPR in another prospective series. The majority of these seizure episodes occurred in close proximity to the administration of lidocaine. One of the patients had GTC convulsions and myoclonus simultaneously.

Focal and Complex Partial Seizures

Focal and complex partial seizures following CPR have not been extensively reported in the literature. Krumholz et al. *(1)* mention that 3 of the 114 cardiac arrest survivors studied developed focal motor seizures. Snyder et al. *(3)* reported complex and simple partial seizures in 12 of their 63 patients in hypoxic–ischemic coma. Most patients were profoundly comatose at the onset of seizures. Partial seizures typically began within the first 12 h after arrest but could be delayed 2–4 d *(3)*. The majority of seizure episodes lasted less than 48 h, but a few patients had recurrence of partial seizures after 4–6 d. The majority of patients with partial seizures had seizures of other types as well, including GTC seizures and myoclonus.

Myoclonus

Cortical, reticular, segmental, generalized, reflex, and action myoclonus have all been described as sequelae to hypoxic–ischemic encephalopathy *(1,3,5,20–22,30–37)*. Cortical myoclonus is believed to be a fragment of focal seizures, with myoclonic jerks involving only a small number of adjacent muscle groups *(38)*. It preferentially involves distal appendicular structures, typically affecting agonist and antagonist muscle groups simultaneously, and it may be multifocal *(38)*. Cortical myoclonus occurs spontaneously but may be accentuated by volitional move-

ment (action myoclonus) or somatosensory stimulation (reflex myoclonus) *(38)*. The movements are typically preceded by time-locked electroencephalographic (EEG) discharges at the sensorimotor cortex. Reticular myoclonus is felt to be a fragment of generalized epilepsy, with myoclonic jerks involving the entire body *(38)*. Axial structures and proximal muscle groups are preferentially involved, and the jerks may also be triggered by movement or somatosensory stimuli *(38)*. Reticular myoclonus is believed to result from lesions of the nucleus reticularis gigantocellularis in the caudal medulla *(38)*. EEG spikes are generalized and follow the movement, suggestive of a subcortical discharge referred to the cortex *(38)*. Primary generalized myoclonus involves synchronous jerks of the distal appendicular muscles time-locked to generalized cortical discharges on EEG *(38)*. SM is any form of epileptic myoclonus that persists for more than 30 min. Segmental myoclonus is felt to be a nonepileptic brainstem or spinal cord reflex resulting in isolated, nonrhythmic jerks of axial structures with no EEG correlate.

Snyder et al. *(3)* reported myoclonic seizures in 12 of their 63 CPR survivors. Most patients had synchronous, symmetric jerks involving the face, adductors of the thighs, and flexors of the arms. Others had asynchronous, asymmetric jerks involving the extremities alone. Myoclonus occurred in 30% of CPR survivors in the series of Krumholz et al. *(1)*, the majority of whom (78%) had generalized or multifocal cortical myoclonus with co-occurrence of other seizure types. Segmental myoclonus involving the eyes, palate, and pharynx was noted in several patients. In the series of Young et al. *(20)*, myoclonic jerks were always bilaterally synchronous and involved the face, particularly the eyelids. The extraocular muscles could be involved as well *(20,21)*. Limb jerks occurred variably and simultaneously with facial movements. Myoclonic jerks occasionally involve the diaphragm and interfere with mechanical ventilation *(20)*. Myoclonus typically begins within 12 h of cardiopulmonary arrest, with a mean duration around 24 h *(1,3,21,22)*. A subgroup of patients develop myoclonus only 3–5 d after arrest, and it persists for days to weeks *(3)*. Spontaneous myoclonus typically occurs at a frequency of a jerk every 1–5 s *(22)*. Stimulus sensitivity has been reported in many patients *(3,20–22,31,32,34)*, with increased jerks on tracheal suctioning, touch, painful stimuli, or loud noise. Stereotyped myoclonic jerks have also been reported with episodic hypotension *(21)*. One group reported reticular myoclonus in synchrony to the carotid pulse that was ablated by carotid sinus massage *(37)*.

Lance–Adams Syndrome

Some mention must be made of Lance–Adams syndrome because it may evolve while the patient remains in the ICU *(5,39,40)*. In the original case series of Lance and Adams *(5)*, three of the four patients began experiencing myoclonus during the first few days after resuscitation while they remained in postanoxic coma. "Generalized myoclonus," the authors reported, "was a feature of the early stages of the illness soon after the episode of hypoxia; but after a few days, when consciousness was regained and the patients' condition stabilized, the movements became restricted in site and all tendency to rhythmicity was lost" *(5)*. In one series, 9 of 14

patients first experienced myoclonus within days of the hypoxic event, and—in all but one—myoclonic jerks were first noted during coma *(40)*. After arousal from coma, the patients had normal or near-normal intellect, subtle cerebellar signs, and lability of mood *(5)*. The myoclonic jerks were brief, variable in amplitude, and typically comprised a series of contractions of agonist and antagonist groups. Myoclonus was usually limited to the activated limb, but occasionally spread contralaterally or ipsilaterally. It could be enhanced by emotional states or sensory stimuli such as pinprick, touch, tendon tap, or loud noise. Postanoxic myoclonus can share characteristics of both cortical and reticular myoclonus *(40–45)*. The majority of patients in one series *(40)* had cortical discharges on EEG preceding and time-locked to myoclonic jerks. These jerks were predominantly distal and limited to the part of the body involved in the volitional movement. Myoclonic jerks involved the facial muscles in several patients, interfering with swallowing and speaking. Other patients had stimulus-sensitive myoclonic jerks that were bilateral, synchronous, and predominantly involving axial structures, suggestive of reticular reflex myoclonus *(40)*. One case report *(42)* described a patient who developed both cortical action myoclonus and reticular reflex myoclonus after CPR.

LABORATORY INVESTIGATION

Electroencephalography

EEG has been the mainstay of clinical investigation in postanoxic seizures. In a recent study *(46)* from a single university center, cardiorespiratory arrest was the indication for ordering an EEG in 11% (29 out of 261) of emergent studies. EEG was ordered to rule out SE in 23 patients and seizures in 3 patients. Suspicious clinical activity was reported in 65% and previously witnessed seizures in 10%. Twenty-one patients were already receiving antiepileptic medications when the study was ordered. Generalized slowing was the most common EEG finding (11 cases), followed by convulsive SE (8 cases), epileptiform discharges (4 cases), and nonconvulsive status epilepticus (NCSE) as seen in Fig. 1 (3 cases). In the multivariate analysis, history of cardiopulmonary arrest was the only independent predictor of convulsive or NCSE *(46)*.

Krumholz et al. *(1)* found epileptiform discharges in 58% of survivors with clinical seizures or myoclonus and 88% of those with myoclonic status epilepticus. Epileptiform discharges were rare in CPR survivors without clinical seizures or myoclonus (9%, $p < 0.001$). Burst suppression (Fig. 2) was also seen more frequently (76%, $p < 0.001$) in patients with myoclonic SE *(1)*. EEG characteristics of the various types of seizure after head injury have also been described. Snyder et al. *(3)* commented that the most common finding in patients with partial seizures was diffuse slowing, with spike activity and rhythmic slowing occurring in the minority of patients.

The EEG findings in comatose patients with myoclonus are highly variable. The most frequently reported patterns include burst suppression, diffuse slowing, isoelectric tracing, periodic spikes and polyspike–slow wave complexes, and alpha coma *(1,3,20–22,30–32)*.
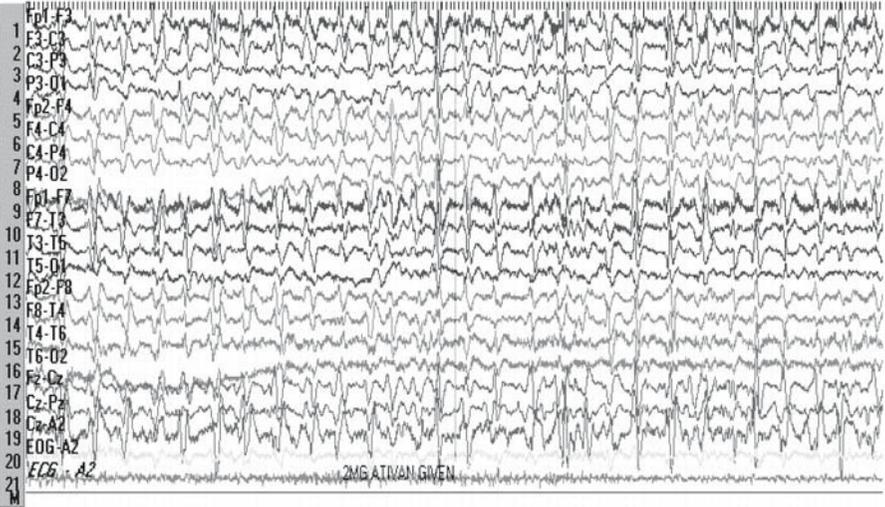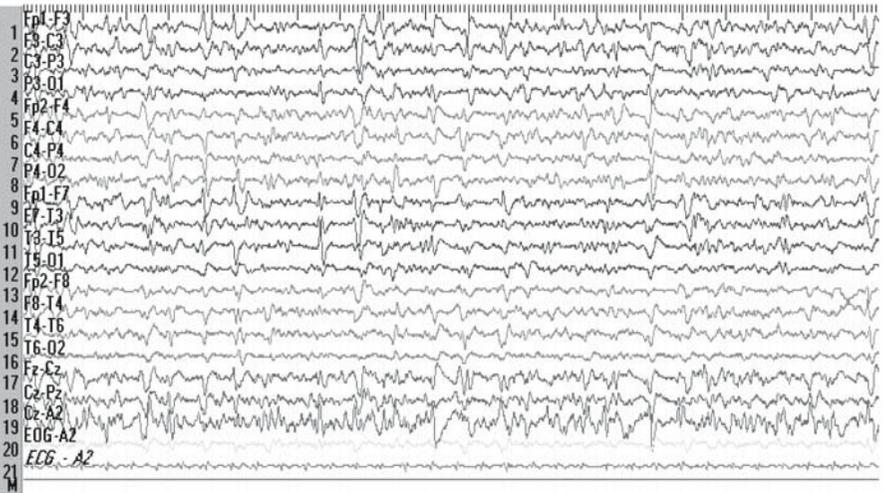
Fig. 1. Nonconvulsive SE. This 75-yr-old woman, involved in a car accident, had an admission Glasgow Coma Scale score of 15. She had a cardiac arrest in the ICU, after which she never regained consciousness; during her protracted stay on the ICU, she developed multiorgan failure. EEG was performed to rule out nonconvulsive SE with the following results: **(A)** continuous bursts of triphasic wave activity at a rate of 1–2 Hz, occasionally intermixed with bursts of spike activity and **(B)** significant decrease of the epileptiform activity after iv administration of 2 mg of lorazepam; the patient did not have any clinical improvement and remained in coma.
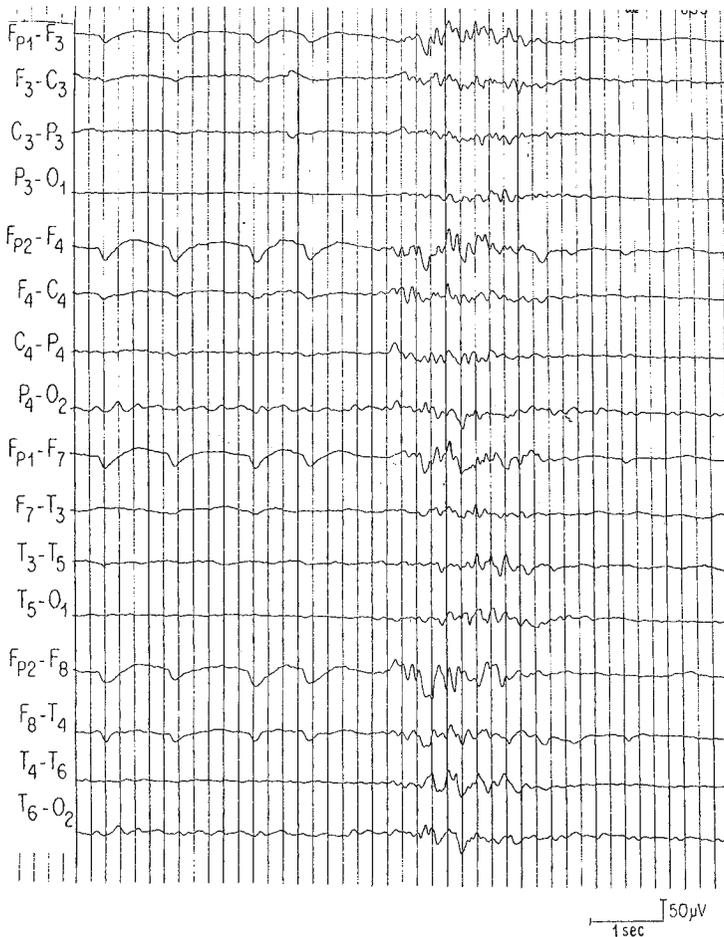
Fig. 2. Burst suppression EEG pattern in a 62-yr-old man with generalized myoclonus, arising from coma after resuscitation from cardiac arrest.

The most common tracing in most series is diffuse slowing with or without periodic spikes or polyspike complexes *(30)*. The interval between complexes is stable for a given patient but ranges from 0.5 to 5 s *(30)*. The complexes may or may not be time-locked to the myoclonic jerks *(20,22)*. In stimulus-sensitive myoclonus, tactile and auditory stimulation elicit bursts of generalized spike–polyspike complexes that precede and are time-locked to clinical myoclonus *(22,32)*.

Burst suppression is the second most frequently reported pattern *(30)*. The bursts typically last 1–10 s and are separated by prolonged periods of suppression ranging from 5 to 25 s *(30)*. One series reported periods of interburst suppression lasting as long as 2–4 min *(32)*. Burst suppression patterns in hypoxic–ischemic coma with-

out myoclonus have typical intervals around 15 s *(47)*, and prolonged suppression in this scenario may reflect more profound brain injury *(32)*.

As described earlier, patients with Lance–Adams syndrome follow three EEG patterns: focal time-locked spikes that precede the myoclonus (cortical myoclonus), generalized non-time-locked spike–slow wave complexes that follow the myoclonus (reticular myoclonus), and no abnormal EEG activity (segmental myoclonus) *(40–45)*. EEG has also been used for prognostic purposes after cardiopulmonary arrest *(48–50)*. In a systematic review of EEG data *(51)*, five out of six studies demonstrated 100% specificity for poor outcome in CPR survivors with burst–suppression or isoelectric patterns within the first week. The odds ratio for poor outcome with these EEG patterns was 9.0, with a 95% confidence interval (CI) of 2.5–33.3 *(51)*.

Electromyography

Electromyography (EMG) may be useful in delineating reticular myoclonus from cortical myoclonus in patients with Lance–Adams syndrome, especially in conjunction with EEG. Patients with cortical myoclonus demonstrate EMG discharges that occur in a rostrocadual distribution, are time-locked to cortical spikes on EEG, and have conduction delays similar to direct cortical stimulation of the motor tract *(5,38)*. Patients with reticular myoclonus involving the cranial nerves demonstrate a caudorostral distribution of EMG discharges originating in the caudal medulla that are not time-locked to cortical EEG spikes and normally precede them *(38,41,43)*.

Somatosensory Evoked Potentials

Somatosensory evoked potentials (SSEP) have prognostic utility in postanoxic coma and have contributed to clinical research in Lance–Adams syndrome. The phenomenon has not been studied in acute postanoxic myoclonus *per se*. Bilateral absence of early cortical SSEP responses portends poor outcome in hypoxic–ischemic coma *(47,52–58)*. In a systematic review of SSEP data *(51)*, bilateral absence of N20 cortical responses measured in the first week of hypoxic–ischemic coma was 100% specific for poor outcome with a pooled 95% CI for a false-positive test of 0–2.0%. It is the most precise means of predicting poor outcomes in these patients, likely related to the minimal influence of medications and metabolic derangement *(51)*. SSEP has also been useful in studying Lance–Adams syndrome. Patients with cortical action myoclonus often demonstrate abnormally large evoked potentials in the sensorimotor cortex, whereas patients with reticular myoclonus do not *(38,40,42,43)*. These data have been used to support the hypothesis that cortical reflex myoclonus results from hyperexcitability of the sensory input to a cortical reflex arc *(38)*.

Brain Imaging

Brain imaging has been extensively studied in patients after cardiopulmonary arrest, but not in the subpopulation with hypoxic–ischemic seizures and myoclonus. Torbey et al. *(59)* demonstrated loss of distinction between the gray and white matter on computed tomography (CT) scan immediately after cardiac arrest. A gray matter/white matter Hounsfield unit ratio below 1.18 at the level of the basal ganglia predicted death in this small retrospective study *(59)*. In one series, brain CT scans done at various times after cardiopulmonary arrest were grossly normal in 77% of all comatose patients with or without subsequent seizures *(21)*. Cerebral edema and hypodensities in the deep cortical white matter, cerebellum, thalamus, and cortical watershed areas occurred more frequently in patients with myoclonus than in those without myoclonus.

Magnetic resonance imaging (MRI) has been used to study the brains of survivors of cardiac arrest and in SE, but not in the subpopulation with both seizures and cardiorespiratory arrest. One small study of CPR survivors *(60)* showed restricted diffusion in the basal ganglia, cerebellum, and cortex on the day of arrest. Diffusion was restricted mostly in the cortical and subcortical gray matter between 24 h and 13 d and in the white matter between 14 and 20 d. After 21 d, diffusion-weighted imaging was normal *(60)*. In the absence of hypoxic or ischemic insults, SE is known to induce T2- and diffusion-weighted hyperintensities and T1-weighted hypointensities, as well as contrast enhancement in the involved cortex, adjacent subcortical white matter, and hippocampus *(61)*. These changes represent cortical cytotoxic edema and subcortical vasogenic edema that typically reverse when seizures are controlled *(61)*. For an illustrative case, *see* Fig. 3.

Brain imaging is poorly studied in CPR survivors with seizures. In one series, brain MRIs and CT images in patients with Lance–Adams syndrome were normal in one-third of patients, showed cortical or cerebellar infarcts in one-third, and showed mild cortical and cerebellar atrophy in the remaining one-third *(40)*.

CSF

CSF has not been studied in the setting of acute hypoxic–ischemic seizures in humans. In Lance–Adams syndrome, conflicting data have been reported regarding concentrations of serotonin metabolites, as described earlier. The majority of patients have depressed serotonin metabolites and often respond clinically and biochemically to serotonin precursors and agonists like 5-HTP, clonazepam, and valproic acid *(24,28)*. Patients with elevated CSF serotonin metabolites tend to respond to serotonin antagonists like methysergide *(29)*.

DIFFERENTIAL DIAGNOSIS

Many conditions that cause cardiopulmonary arrest may also lower the seizure threshold. This understanding is especially important if prolonged seizures are taken as an indication of severe irreversible brain injury that may influence the decision to limit medical care. Patients with a previous diagnosis of epilepsy may present in
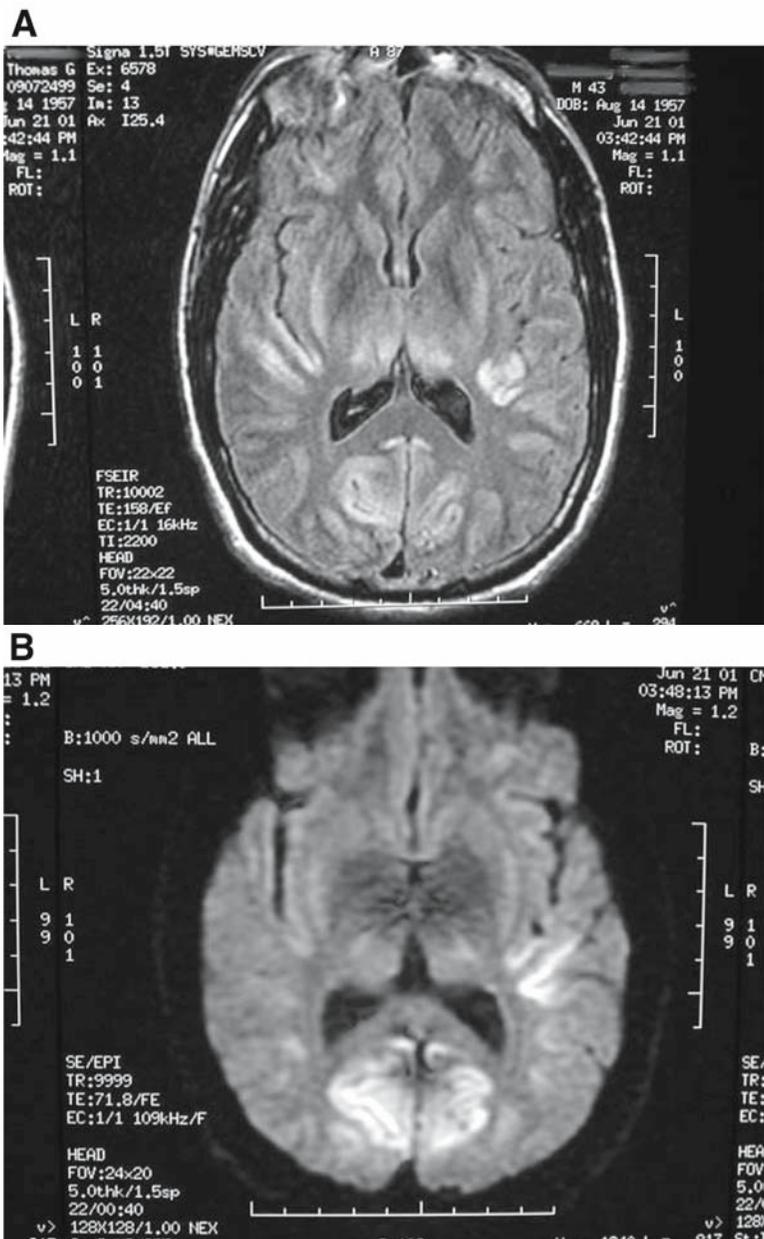
Fig. 3. Nonconvulsive SE in a patient with postanoxic myoclonus: This 43-yr-old white man was admitted after being found in the bottom of a lake, where he had stayed for approx 15 min. He was initially pulseless and without breathing. In the ICU he developed continuous bilateral and synchronous myoclonic jerks in the upper and lower extremities. In addition, the patient had several GTC convulsions, which were suppressed by PHT and VPA.
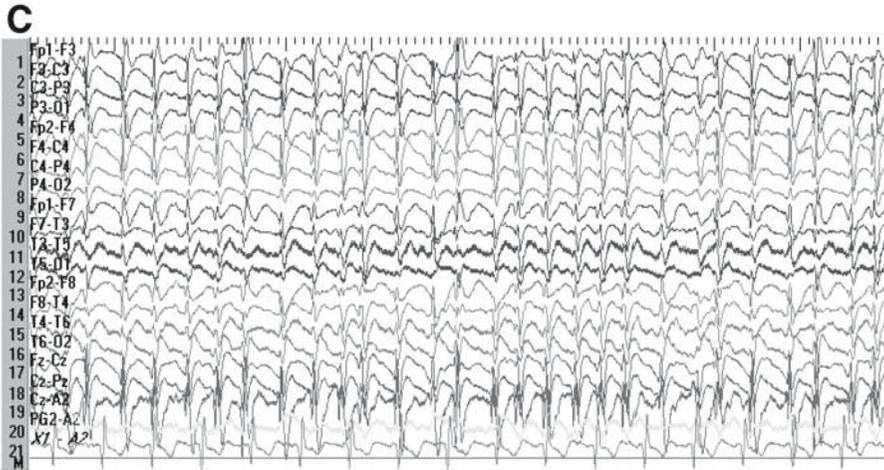
Fig. 3. *continued*

The patient regained only brainstem reflex function and eventually expired in palliative care 12 d after extubation. **(A)** and **(B)** Diffusion-weighted MR images of the brain 29 h later demonstrating diffuse abnormalities, especially in the basal ganglia, thalamus, and insular and occipital cortex. **(C)** Continuous EEG monitoring demonstrating bihemispheric continuous runs of sharp and slow waves, which did not correlate with myoclonic jerking or clinical convulsions

SE after a relatively brief episode of hypoxia. Preexisting epilepsy may not be known at the initial point of care, and baseline antiepileptic drug levels may be helpful in this regard. Drugs given to patients during the resuscitation may trigger or lower seizure threshold. Lidocaine, used as part of the standard Advanced Cardiac Life Support protocol, is well-known to induce seizures at serum levels exceeding 9 µg/mL *(62–64)*.

Propafenone, although rarely used in cardiac arrest, has also been reported to lower the seizure threshold *(65)*. Streptokinase, prourokinase, and tissue-type plasminogen activator given during acute myocardial infarction may also induce seizures *(66)*. Although rarely used in the modern management of asthma, theophylline administered for respiratory arrest secondary to status asthmaticus is epileptogenic *(67)*. Stimulants, tricyclic antidepressants, and cocaine can potentially cause arrhythmic cardiac arrest and seizures *(59,63,68,69)*. Seizures resulting from withdrawal from alcohol, barbiturate, and benzodiazepine (BZD) must be considered in the first few days of admission in alcoholics and sedative users who present with respiratory or cardiac arrest. Penicillins, fluoroquinolones, and other antibiotics may trigger seizures. Rapid withdrawal of anesthetic agents, such as propofol and barbiturates, may also precipitate prolonged seizures. For more details on drug-induced seizures, review Chapter 12.

Metabolic derangements, such as hyponatremia and hypomagnesemia, are common in patients with congestive heart failure, intrinsic renal disease, the syndrome of inappropriate antidiuretic hormone release and diuretic users. If severe, hyponatremia may produce obtundation—with or without focal neurological deficits—and seizures. This topic is discussed in greater detail in Chapter 10. Profound hypoglycemia in insulin users may also precipitate coma and seizures in the setting of cardiopulmonary arrest. Seizures in encephalopathic patients may be difficult to clinically distinguish from shivering, rigors, hyper-ekplexia, and reflex startle responses *(38,42)*. EEG, with or without paralytic medications, may be helpful in this regard. Specific discussion on the role of metabolic and systemic derangement in seizure disorder is provided elsewhere in this book.

TREATMENT

General Considerations

Seizures are most likely to occur during the first day after cardiopulmonary arrest. This is a period of hemodynamic instability, prognostic uncertainty, and high risk of recurrent arrest. Cardiac arrest and profound hypotension often cause hepatic and renal damage, which may alter the metabolism and excretion of resuscitative and anticonvulsant medications. Drugs used to control these often highly refractory seizures may have untoward effects on cardiac rhythm, blood pressure, and level of consciousness.

Intravenous phenytoin (PHT) is well-known to induce hypotension and may trigger arrhythmias such as ventricular fibrillation, complete heart block, bradycardia, and asystole. Divalproex sodium, PHT, and barbiturates can precipitate hepatic injury that may be especially problematic in the setting of shock liver. Divalproex sodium and PHT also have significant interactions with many antiarrhythmic agents, including lidocaine and amiodarone. Intravenous BDZs and barbiturates may also induce hypotension and may interfere with neurological examination such that a falsely poor prognosis is given.

Simple and Complex Partial Seizures

Simple and complex partial seizures have not been demonstrated to cause neuronal injury in most case series and may not require aggressive management in postanoxic coma. In the case series of Snyder et al. *(3)*, few patients had partial seizures in isolation, and most patients had good seizure control with PHT alone, phenobarbital (PB) alone, or both. The decision to treat partial seizures in comatose patients must be individualized, weighing the ease of treatment versus the low risk of exacerbated neuronal injury in this setting.

GTC Seizures

GTC seizures are known to cause progressive neuronal injury after 30 min *(6,9,10)*. They typically begin during the first day after cardiopulmonary arrest, a period in which the ultimate prognosis remains unclear. The pathological data in postanoxic patients with GTC SE are limited, but one series *(22)* did demonstrate

Ammon's horn sclerosis—typical of epileptic neuronal injury—in two such patients. GTC SE should be managed aggressively in these patients, particularly when it occurs early in the hospital course, as detailed in Chapter 14.

Myoclonus

Isolated epileptic myoclonus and segmental myoclonus are not harmful and do not require treatment unless they interfere with mechanical ventilation or have psychologically harmful effects on family members. Whether SM exacerbates the brain damage caused by hypoxic–ischemic encephalopathy remains unclear. Most clinicians argue that SM represents agonal neuronal activity that reflects neurological devastation. A review of the literature for this publication found five patients *(5,22,36,70)* who developed SM in postanoxic coma and had good neurological outcomes. Although several case series *(1,3,20,21,30,35)* report uniform mortality or vegetative state in postanoxic SM, these results may reflect a self-fulfilling prophesy because SM itself may have been used as an argument to withdraw supportive care *(21,35)*. The natural history of this disease with continued intensive management is not clear. Although pathological studies from patients with SM after cardiopulmonary arrest show greater cortical involvement than similar patients without SM *(21)*, it is unclear whether SM is reflective or causative of this injury. SM is often refractory to treatment short of pharmacological coma. Medications employed with varying degrees of success include PHT, PB, levetiracetam, valproic acid, and BDZs *(1,3,20–22,30,32,33,35)*.

Prophylactic Anticonvulsant Use

Prophylactic use of anticonvulsants in postanoxic coma has not been rigorously studied outside of thiopental in the Brain Resuscitation Clinical Trial I Study Group *(71)*. In this study, comatose survivors of cardiac arrest were randomized to standard care with or without a loading dose of thiopental. There was no statistically significant difference in outcome between the groups *(71)*. A subgroup analysis of seizure activity demonstrated a trend toward fewer seizures, lower mortality, and better neurological outcomes in the treatment arm, but the difference failed to reach statistical significance. No description of the seizure activity is given in this study *(71)*.

Lance–Adams Syndrome

Lance–Adams syndrome may develop while the patient remains in the ICU and may interfere with physical rehabilitation, swallowing, and weaning from the ventilator. Various treatment strategies have been employed for the amelioration of action myoclonus in Lance–Adams syndrome *(5,23,24,26,28,29,40,42–45,72–77)*. Clinical improvement has been reported with 5-HTP *(23,24,28,76)*, valproic acid *(73)*, carbamazepine *(74)*, gabapentin *(72)*, clonazepam *(24)*, levodopa *(75)*, monoamine oxidase inhibitors *(24)*, piracetam *(40)*, and methysergide *(29)*. In a recent study of levetiracetam *(77)*, two patients with Lance–Adams syndrome

responded to doses of 750–1500 mg/d. As discussed earlier, many patients with Lance–Adams syndrome have depleted serotonin metabolites in the CSF and respond to serotonin precursors and agonists *(24,28)*. Others have elevated CSF serotonin precursors and improve with methysergide, a serotonin antagonist *(29)*. If clinical response to medications involving serotonergic neurotransmission is unclear, it may be reasonable to use CSF serotonin metabolite concentrations as a guide to therapy—although this approach has not been rigorously studied. Lance–Adams syndrome has been shown to improve several years after the anoxic event *(40)*. In one series *(40)*, 14 patients were followed for 3.7 yr. Three patients were eventually able to discontinue antimyoclonic medications, and five patients were able to ambulate independently. Subtle improvement was the rule in the remaining patients.

Supportive Management

A relatively benign intervention in any seizure type is the optimization of factors that affect systemic function, such as electrolytes, medications, and infections. Correction of hypoglycemia, hyponatremia, hypocalcemia, and hypomagnesemia may reduce the risk of recurrent cardiac events and seizures. As with any severe neurological injury, serum glucose levels should be normalized, using insulin as needed. Acid–base disturbances should be optimized with appropriate adjustments to the mechanical ventilator. Discontinuation of proconvulsant medications should be undertaken if possible.

PROGNOSIS AND OUTCOMES

The prognostic significance of seizures in hypoxic–ischemic coma has been a source of controversy in the literature. Levy's classic study of a general population of patients in hypoxic–ischemic coma failed to demonstrate poorer outcomes in the subpopulation with seizures of any type *(4)*. Although Snyder et al. *(2)* showed 17% survival in hypoxic–ischemic coma patients with myoclonus and 32% survival with seizures vs 43% survival without any seizure activity, the difference failed to reach statistical significance. Likewise, there was only a trend toward higher incidence of excellent outcome in survivors without seizure than in patients who had any form of seizure activity *(2)*. The large study by Krumholz et al. *(1)* showed that seizures or myoclonus *per se* are not significantly related to outcome, but convulsive status epilepticus and myoclonic SE confer poor outcome as judged by survival and recovery of consciousness (*see* Table 1).

The decision to withdraw supportive care in patients with postanoxic SM should be based on more precise predictors of outcome, such as SSEP, EEG, and serial neurological examination *(2,4,48–58,78–83)*. A systematic review *(51)* of all outcome predictors—including seizures and myoclonus—after cardiopulmonary arrest found that only bilaterally absent N20 peak on SSEP within the first week and absent pupillary light reflex or motor response to pain at day 3 had 100% specific-

Table 1
Survival and Consciousness at Discharge of Comatose Patients After Cardiopulmonary Resuscitation

	N	Alive at discharge	Conscious at discharge
All patients	114	30 (26%)	21 (18%)
No seizure or myoclonus	64	21 (33%)	15 (23%)
Any seizure or myoclonus	50	9 (18%)	6 (12%)
All status epilepticus (SE)	36	4 (11%)[a]	1 (3%)[a]
SE without myoclonus	10	1 (10%)	1 (10%)
SE with myoclonus	19	3 (16%)	0[a]
Status myoclonus alone	7	0	0

[a] Significantly different from patients without this condition ($p < 0.01$).
(Modified from ref. *1*.)

ity for poor outcome. If continued supportive management is desired because of family choice or prognostic uncertainty and standard anticonvulsant medications have failed to ameliorate SM, the decision to pursue pharmacological coma or neuromuscular blockade must be individualized. Because most SM abates within 48 h, it may be practical to use anesthetic agents and paralytics for this period of time without prolonged loss of the ability to examine the patient *(1)*.

ACKNOWLEDGMENTS

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6

Seizures in Renal and Hepatic Failure and Endocrine Disease

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SUMMARY

Hepatorenal failure and endocrine disease are associated with seizures. Seizures arise either as a direct result of the organ failure or as a result of a secondary metabolic disturbance, including toxins arising from the disease process or changes in serum electrolytes. Correction of electrolyte abnormalities or medical management of the underlying disease process will often prevent further seizures. Organ failure and endocrine abnormalities are commonly seen in the critically ill population, and these patients are more prone to seizures. Organ failure can influence the treatment of both new-onset and pre-existing seizure disorders by altering the pharmacokinetics of major anticonvulsants. Alternatively, anticonvulsants can precipitate organ failure. Therefore pharmacotherapy of seizures in these settings should be undertaken cautiously.

Key Words: Hepatic failure; renal failure; endocrinopathy; diabetes; dialysis; encephalopathy.

INTRODUCTION

Seizures are a common complication of organ failure and endocrine disease, either as a result of general biochemical and metabolic abnormalities or as a specific syndrome related to the primary disease process. Critically ill patients may be hospitalized as a result of the organ failure or endocrine disease, or these conditions may arise as complications of another disease process. The acuity of onset of these problems may determine the overall response of the organism to the factors that alter seizure threshold. Even acute organ failure typically occurs in progressive stages, each of which may be associated with differing susceptibility to seizures. Endocrine disease is typically more indolent in onset, but the effects are dependent

on the hormone cascade involved and the organism's natural storage of the relevant hormone: hypothyroidism is rarely acute unless there is sudden loss of large amounts of thyroid tissue, whereas Addisonian crisis may develop quickly because of daily requirements for steroid hormone production.

The principles of seizure management in this group of patients follow an algorithm common to seizures complicating other medical conditions. Acute seizures should be controlled, seizure prophylaxis with antiepileptic agents should be instituted, and any causative factors should be corrected, including acute control of biochemical/metabolic abnormalities and treatment of the primary disease process.

This chapter reviews the features of seizures in hepatorenal failure and endocrine disease including their incidence, treatment, and clinical implications for critical care. Seizure medications are metabolized and excreted by the hepatorenal system and, therefore, management of seizures in the setting of renal or hepatic failure must be undertaken cautiously.

ORGAN FAILURE

Hepatic Failure

Hepatic failure is a common indication for admission to an intensive care unit (ICU), and in addition hepatic failure frequently complicates other serious illnesses. More than 2000 cases of acute hepatic failure occur in the United States every year, with an estimated mortality of 80% *(1)*. Acute hepatic failure is most commonly caused by infection, inflammation, acute hypotension, toxin exposure, or fulminant primary liver disease. The biochemical effects of hepatic failure include significant alterations in glucose metabolism, buildup of tissue and serum ammonia, failure to remove metabolites and toxins from the circulation, and changes in the bioavailability of drugs normally cleared by the liver. This combination of events can cause progressive encephalopathy, a spectrum of neurological dysfunction classically divided into four stages. Stage I is euphoria or depression, with mild confusion, slurred speech, and disordered sleep; stage II is lethargy and moderate confusion; stage III is marked confusion, incoherent speech, and somnolence; stage IV is coma with cerebral edema formation and elevated intracranial pressure (ICP).

Seizures can arise in any of the stages of hepatic failure either as a result of the encephalopathic process or secondary to other changes in serum levels of electrolytes, glucose, or other metabolites. The incidence of seizures in hepatic encephalopathy has been reported as varying from 2 to 33% *(2)*. Ellis et al. enrolled 42 patients with stage III and IV hepatic encephalopathy in a controlled trial to evaluate the benefit of prophylactic phenytoin administration *(3)*. Subclinical seizure activity as documented by continuous electroencephalography (EEG) was seen in 3 of 20 patients in the treated group, compared with 10 of 22 in the untreated group. One study has reported the incidence in hepatic encephalopathy of status epilepticus (SE) that was refractory to anticonvulsants but responded to lactulose therapy with a reduction in the serum ammonia levels *(4)*. The pathophysiology of hepatic encephalopathy is unclear, but it has been postulated to arise from a combination of

hyperammonemia, abnormal glutamine metabolism, elevated glutamate levels, enhanced stimulation of γ-aminobutyric acid (GABAergic effects) and the contribution of false neurotransmitters.

Bickford and Butt *(5)* have described three classical phases of EEG changes in hepatic encephalopathy, the incidence of which is directly related to arterial ammonia levels. The first stage involves a diffuse θ pattern, the second stage involves triphasic waveforms with often sharp or spike morphology, and the third stage consists of arrhythmic Δ activity with poor bilateral synchrony. The majority of seizures are reported to occur with the second-stage EEG pattern. Ficker et al. reviewed EEG data from 120 Mayo Clinic patients with hepatic encephalopathy *(6)*. Epileptiform abnormalities were identified in 18 patients (15%). Interictal discharges were observed in 13 patients consisting of focal spike and sharp wave discharges. Ten patients had electrographic seizures, either focal (6 patients) or generalized (5 patients), and 12 patients had clinical seizures (focal in 4 and generalized in 8 patients). Most patients with epileptiform activity died or deteriorated; the authors suggested that the presence of seizures is associated with a poor prognosis. Special care must be taken in patients with asterixis, which can cause a rhythmic artifact on the EEG that could be mistaken for ictal activity.

Special cases of liver failure with associated neurological dysfunction include Wilson's disease, Reye's syndrome, and the hepatic porphyrias. Wilson's disease (hepatolenticular degeneration) is a rare autosomal recessive disease, occurring between the first and third decades and characterized by failure of copper metabolism leading to copper deposits in the liver and brain. The disease has been localized to an abnormal gene (*ATP7B*) on chromosome 13q14.3 that codes for a copper transporting adenosine triphosphatase. The condition usually presents as liver disease and/or neuropsychiatric disease. Seizures occur infrequently, and more commonly movement disorders predominate. Dening et al. reviewed the incidence of seizures in Wilson's disease both in a series of 200 of their own patients and in the literature *(7)*. They found a seizure prevalence of 6.2%, which is 10 times higher than in the general population. Seizures were recorded at any stage of the disease but most commonly after beginning treatment. The authors found that seizures responded well to therapy, with 60% of cases remaining seizure-free at 7 yr. They also concluded that penicillamine-induced pyridoxine deficiency was responsible for seizures in only a few cases and that the most likely etiology of the seizures was copper deposition in the brain.

Reye's syndrome, a disorder almost exclusively of children, is associated with aspirin use in the context of a viral illness (typically influenza A/B or varicella). The disorder is characterized by rapid hepatic failure, encephalopathy presenting as seizures or coma, and fatty infiltration of the viscera. The majority of reported cases occurred in the pediatric population, but adult cases have been also described *(8,9)*. The incidence of Reye's syndrome has declined dramatically since 1986, when the US Food and Drug Administration required that all aspirin products have labels warning about the possible association. The pathophysiology of the condi-

tion is poorly understood, but it is probably related to hepatic mitochondrial dysfunction. There are few data about the absolute prevalence of seizures in Reye's syndrome; however, seizures may relate to progressive cerebral edema, raised ICP, and cerebral hypoperfusion. Some studies have recorded the EEG in Reye's syndrome and reported increased Δ activity with overall EEG suppression and 14-Hz positive burst discharges *(10,11)*. The prognostic significance of seizures in Reye's syndrome is unclear, because some patients with seizures completely recover. However, some patients are left with epilepsy, including West and Lennox–Gastaut syndromes.

The hepatic porphyrias include acute intermittent porphyria, variegate porphyria, and hereditary coproporphyria, resulting from different enzymatic deficiencies in heme synthesis with similar neurologic manifestations. Neurological manifestations include abnormal behavior, confusion, agitation, anxiety, hallucinations, and seizures. It has been estimated that 3.7% of patients with acute intermittent porphyria have seizures, including generalized and focal with secondary generalization *(12)*. In some cases seizures can be related to hyponatremia *(12)*. Porphyria may complicate the treatment of seizures. Acute exacerbations of porphyria can be triggered by a large number of anticonvulsant drugs including phenytoin (PHT), barbiturates, ethosuximide, diazepam (DZ), valproate (VPA), carbamazepine (CBZ), and lamotrigine (LTG). Management of seizures in porphyric patients requires management of the porphyria with hematin infusions, removal of any precipitants including antiepileptic agents, and the use of antiepileptics that will not exacerbate the porphyric state. The effect of newer antiepileptics on cells cultured in chicken embryos and treated with deferoxamine (blocking heme synthesis) was reported by Hahn et al. *(13)*. Antiepileptic drug (AED) concentrations representative of doses used in humans were achieved. Felbamate, LTG, and tiagabine, but not gabapentin or vigabatrin (VGB), increased mRNA levels of aminolevulinic acid synthase, the rate-controlling enzyme for porphyrin synthesis and levels of porphyrins. Therefore, anticonvulsants clinically recommended in this situation include gabapentin and VGB *(13,14)*. Alternatively, isoflurane anesthesia can be used.

Treatment of Seizures in Hepatic Failure

Several other aspects of hepatic failure can influence seizure activity *(15)*. In patients with a pre-existing seizure disorder, hepatic failure may alter serum levels of anticonvulsants normally cleared by the liver. Table 1 lists the common antiepileptics, outlines the role of hepatic and renal function in their metabolism and clearance, and lists the known effects of the agents on hepatic and renal function. The degree of hepatic failure can also play a role in the metabolism of drugs. In early hepatitis, there may be increased blood flow to the liver with relatively normal hepatocytes, a situation that may increase hepatic clearance of drugs. In more advanced hepatic failure with liver necrosis, hepatocellular tissue decreases, and, therefore, serum levels of drugs cleared by the liver may rise *(16)*. In addition, hepatic failure is associated with hypoalbuminemia; this state can lead to increased serum-free levels of drugs of the antiepileptics that are highly bound to serum pro-

Table 1
Antiepileptic Medications: Characteristics Related to Hepatic or Renal Failure

Medication	Protein binding	Liver metabolism	Renal clearance	Dialyzable	Adverse hepatic effects	Adverse renal effects
Phenobarbital	20–60	Metabolized—inactive	21% including metabolites	Y	Hepatotoxicity	Nephrotoxicity
Phenytoin	88–93	Metabolized—inactive	2% and inactive metabolites	N	Hepatitis/hepatic necrosis	Interstitial nephritis, nephrotoxicity, renal failure
Clonazepam	86	Metabolized	0.5–1.0% including inactive metabolites	N/A	Transient elevation LFTs	None
Ethosuximide	Minimal	80% Metabolized—inactive	20%—unchanged	Y	None	None
Carbamazepine	75	98% Metabolized—some active	72% including metabolites	Y	Hepatitis, cholangitis, abnormal LFTs, hepatic failure, bile duct injury	Renal failure, tubulointerstitial nephritis (rare) Renal failure (rare)
Valproate	90	Metabolized—some active	70–80% including metabolites	Y	Elevated LFTs (common), hepatic failure, hepatitis, hepatotoxicity (0.02%)	Renal failure (rare)
Lamotrigine	55	Metabolized—inactive	94% including metabolites	Y	Elevated LFTs (rare), acute hepatitis (rare), hepatic failure (rare)	Renal failure (rare)
Gabapentin	< 3	Not metabolized	76–84% unchanged	Y		
Topiramate	9–17	Minimal	55–97% unchanged	Y	1% incidence of elevated LFTs, hepatic failure (rare)	2% incidence of renal calculi
Vigabatrin	None	Small amount	65% unchanged	Y	Hepatic failure (rare)	None

Table 1
Continued

Medication	Protein binding	Liver metabolism	Renal clearance	Dialyzable	Adverse hepatic effects	Adverse renal effects
Levetiracetam	None	Small amount	66% unchanged, 25% inactive metabolites	Y	None	None
Tiagabine	96	Metabolized—inactive	2% unchanged, 25% inactive metabolites	N	None	None
Felbamate	22–25	Unknown	90%, with 40% metabolites of unknown activity	N/A	5% incidence of elevated LFTs, 6 per 75,000 patient-yr incidence of hepatic failure	None
Zonisamide	40–60	Metabolized—inactive	35% unchanged, some metabolites	N/A	None	1.9% incidence of renal calculi, transient increase in blood urea nitrogen (common)

Y, yes; N, no; LFT, liver function test.

tein. Therefore, hypoalbuminemia, a common finding in the ICU even outside the context of hepatic failure, can increase the risk of antiepileptic toxicity *(17)*.

Certain anticonvulsants, such as PHT, barbiturates, topiramate, felbamate, VPA, and LTG, can also have a direct toxic effect on the liver *(18)*. The interested reader should refer to Chapter 14 for more details.

Renal Failure

Introduction

Renal failure represents a decline in the glomerular filtration rate that can occur acutely or chronically. Acute and chronic renal failure influences outcome from critical illness. In the critically ill population such failures usually arise acutely as a result of sepsis, drug toxicity, or hypotension, or as part of multiple organ failure. Chronic renal failure is a gradual and progressive loss of renal function that can ultimately result in end-stage renal disease. ICU admission as a result of chronic renal failure is usually related to secondary complications such as respiratory distress, hyperkalemia, uremic encephalopathy, and postcardiopulmonary resuscitation. Estimates of the incidence of acute renal failure (ARF) in the ICU population are approx 3–4% *(19,20)*. Schwilk et al. examined 3591 ICU admissions and found a 4.3% incidence of ARF, compared with 0.6% of the remaining hospital population *(20)*. The incidence of ARF is proportional to the American Society of Anesthesiologists (ASA) score; ASA 5 patients had an incidence of 20.7% compared with 0.2% in ASA 2 patients. Electrolyte abnormalities, which are common in acute and chronic renal failure, include hyperkalemia, hyponatremia, acidosis secondary to loss of bicarbonate, and secondary hyperparathyroidism.

In one study, seizures were reported in 5 of 13 patients with ARF, typically occurring in the second week of illness *(21)*. Seizures in chronic renal failure are often a late manifestation and occur in approx 10% of patients *(22)*, for example, *see* Fig. 1. Even in patients on chronic hemodialysis with no known evidence of seizures, bilateral spike–wave patterns have been reported on EEG in 8–9% of cases *(23)*. Pediatric renal failure patients are also seizure prone; analysis of 108 children with renal failure revealed a 15% incidence of seizures; all the patients with seizures had received dialysis at some point *(24)*.

Uremic Encephalopathy

Uremic encephalopathy is characterized by a waxing and waning neurological decline that can occur in both acute and chronic renal failure. A more rapid deterioration in renal function leads to a more severe and rapidly progressive encephalopathy. Early symptoms include apathy, fatigue, and decreased attention span. Frontal lobe symptoms follow, with impaired abstract thinking, behavioral changes, and such frontal lobe release signs as paratonia and the palmomental reflex. Seizures occur late after delirium, hallucinations, agitation, and torpor. They are usually a preterminal finding and are typically of the generalized tonic–clonic GTC type *(15)*. The degree of azotemia correlates poorly with neurological dysfunction *(25)*. The pathophysiology of uremic encephalopathy is poorly understood, but some
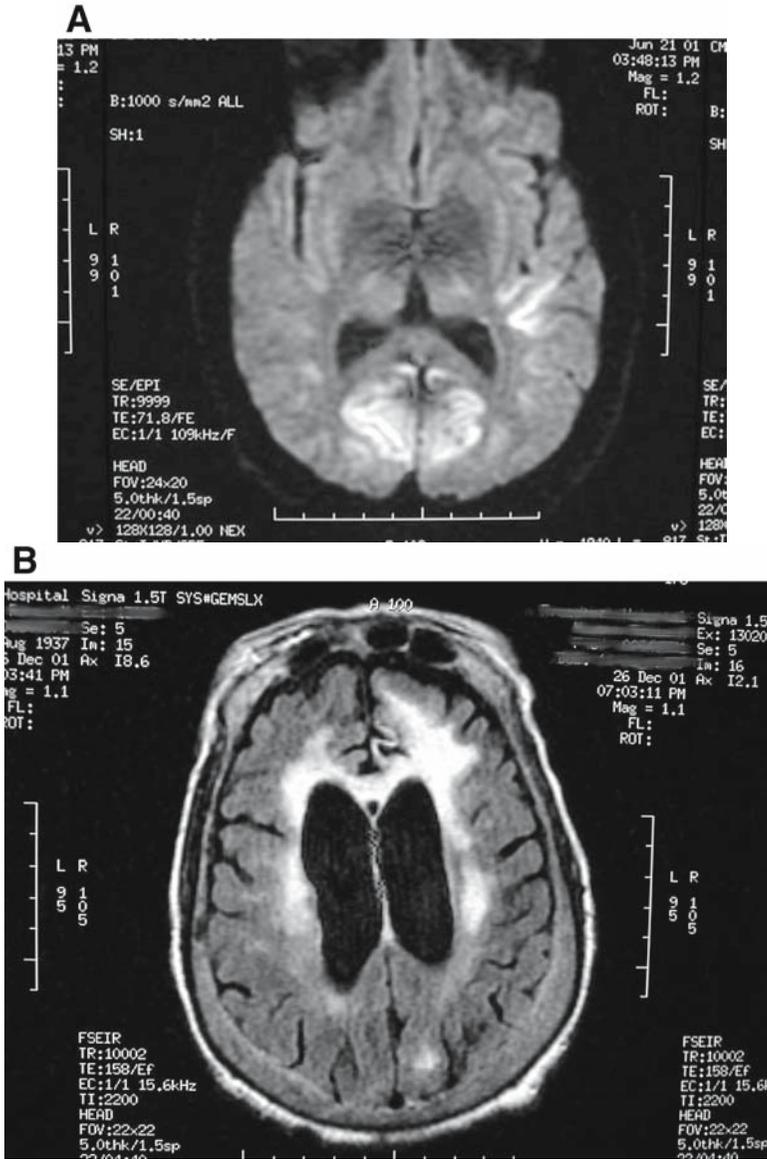
Fig. 1. This 64-yr-old woman with end-stage renal disease and history of strokes, on regular hemodialysis, was found down shaking and unresponsive by her daughter. The patient was admitted to the ICU and was intubated for aspiration pneumonia. **(A,B)** MRIs of the brain with FLAIR sequence showing diffuse periventricular white matter changes. **(C)** EEG, requested to rule out nonconvulsive SE, showing runs of sharp triphasic waves. **(D)** EEG 2 min after the iv administration of 2 mg of lorazepam, demonstrating significant attenuation but no resolution of the triphasic waves. With an additional 2 mg of the drug, the
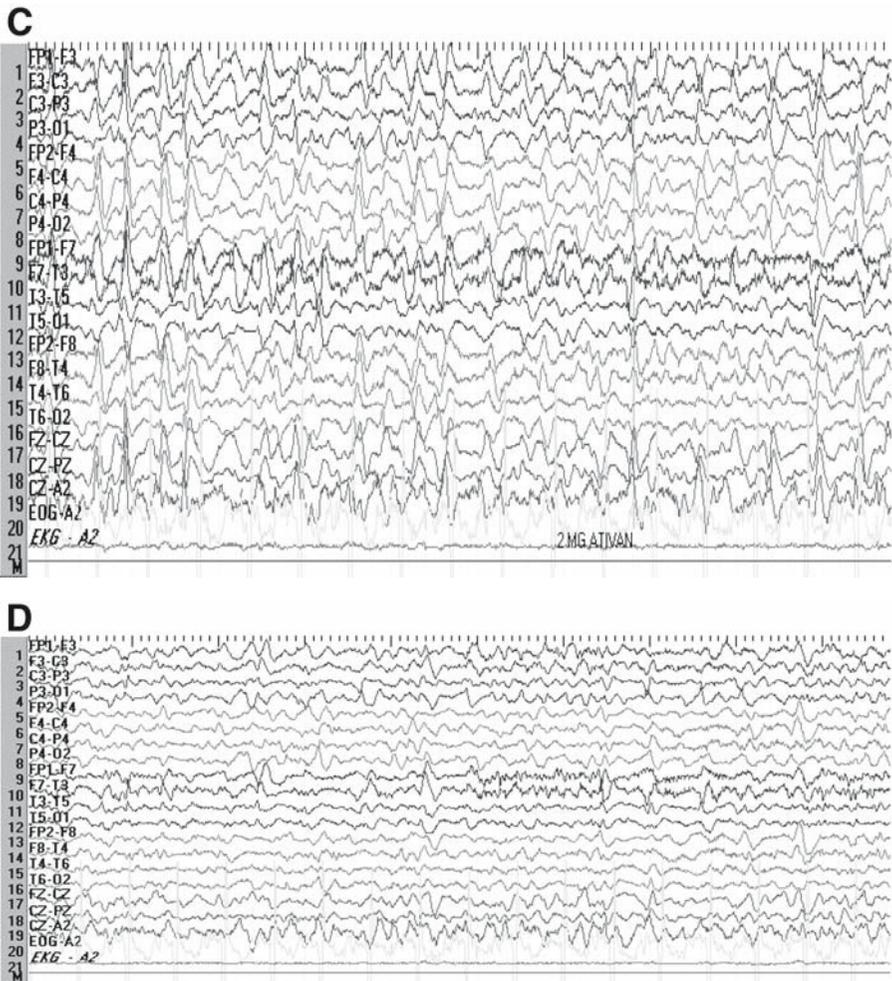
Fig. 1. *continued*

triphasic waves were further suppressed. However, there was no clinical improvement on the patient's mental status, despite these measures and loading with PHT. She was extubated few days later and discharged to palliative care according to her wishes without regaining a full consciousness.

have suggested that disruption in synaptic function, possibly related to a parathormone (PTH)-dependent enhancement of calcium transport, may lead to increased levels of calcium in the cortex *(26)*. In both clinical and experimental studies, EEG abnormalities have been improved by parathyroid resection *(27,28)*. Various organic byproducts of renal failure have been implicated as uremic neurotoxins. In experimental studies, it has been shown that neurotoxic organic acids share a common transport mechanism between the proximal renal tubule and the cerebral vascula-

ture in the form of the transmembrane proteins organic anion transporter (OAT)1 and OAT3 *(29)*. There is evidence of decreased synaptic function and neurotransmission, leading to an overall decrease in the cerebral oxygen consumption and metabolic rate of cerebral tissue. Accumulation of guanidine compounds, like guanidine succinate, that inhibit release of GABA and glycine in animal models of uremia has been implicated *(15)*. The EEG in uremic encephalopathy typically shows nonspecific changes of encephalopathy, with large amounts of predominantly θ and Δ activity. It is important to distinguish this activity from seizures, especially when these waveforms become rhythmic. Tanimu et al. reported a patient with end-stage renal disease undergoing hemodialysis who became confused and was thought to have uremic encephalopathy. The EEG revealed generalized spike–wave discharges at 2–3 Hz that responded to intravenous diazepam with immediate resolution of the confusion *(30)*. Thus, nonconvulsive absence SE must also be considered in acutely encephalopathic hemodialysis patients. EEG abnormalities are seen most often in the acute encephalopathic state within 48 h of the onset of renal failure. Later in the course, when the encephalopathy becomes more chronic, the EEG changes are less prominent. There is a correlation between slow frequencies (<7 Hz) and increases in serum creatinine. In addition, bilateral spike–wave complexes without clinical seizures have been reported in up to 14% of patients with chronic uremic encephalopathy *(15)*.

Dialysis Dysequilibrium Syndrome

Seizures can also occur during hemodialysis as part of the dialysis dysequilibrium syndrome (DDS). First described in the 1960s, the syndrome in its mildest form presents as restlessness, nausea, muscle cramps, and headache. In more severe forms, DDS is characterized by delirium, myoclonus and subsequently generalized seizures, papilledema, and raised ICP. Symptoms typically arise toward the end of hemodialysis and usually resolve within hours to days *(31)*. DDS is seen less commonly at present because of slower dialysis rates and more frequent sessions. It has become a diagnosis of exclusion, and other disorders including intracranial bleeding or infection must be excluded first. The origin of DDS is tentatively attributed to rapid shifts of water into the brain as a result of the presence of idiogenic osmoles in the tissue *(32)* and intracellular acidosis *(33)*. Before dialysis the tissue is protected from osmotic stress by idiogenic osmoles. With dialysis, serum osmoles are removed. Therefore, the tissue becomes hyperosmotic compared with serum, and water entering the tissue causes edema.

Subdural Hematoma

Subdural hematoma (SDH), another possible cause of seizures in uremic patients, should also be considered, especially in the ICU population *(34,35)*. It occurs in 1–3.3% of patients undergoing dialysis and rarely is associated with head trauma. In an autopsy series of chronic dialysis patients who had sudden death, acute SDH was the third most common cause of death, occurring in 8.6% of patients

(36). It can be bilateral in 20% of cases and may clinically present as obtundation, ataxia, and hemiparesis. The absolute incidence of seizures with SDH in the chronic renal failure population is unknown.

Dialysis Dementia

Dialysis dementia was first described by Alfrey et al. in 1972 *(37)*. This disorder is characterized by a progressive decline in cerebral function that can ultimately result in death. Dialysis dementia occurs in 0.6–1.0% of all dialysis patients and occurs at a mean age of 50 yr, with a mean time of onset at 35 mo after the start of dialysis and a mean survival of 6–9 mo after symptom onset *(38)*. Early symptoms are dysarthria, dysphasia, lethargy, and depression. Seizures occur in 60% of patients in the advanced stages, along with psychosis and hallucinations, and these events should be distinguished from myoclonus, which can occur in up to 80% of cases *(39)*. EEG abnormalities may precede symptoms by months, and they include intermittent high-voltage slowing and spike–wave activity, particularly in frontal leads *(40)*. Elevated aluminum levels are reported in the cerebral cortex in dialysis dementia, and therapy with chelating agents such as desferrioxamine can reverse the dementia in up to 70% of cases.

Treatment of Seizures Related to Renal Failure

Treatment of seizures in renal failure focuses on three approaches. First, seizure prophylaxis should be initiated with an anticonvulsant, ideally one that has no renal clearance. Second, reversible epileptogenic electrolyte abnormalities, including hyponatremia and hypercalcemia, should be corrected. Third, the underlying renal condition should be aggressively corrected and renal replacement therapy initiated where appropriate. In the case of uremic encephalopathy, correction of the uremia usually resolves neurological dysfunction including seizures.

Renal failure has important implications for anticonvulsant pharmacokinetics. Changes in the clearance of renally excreted anticonvulsants can affect the dosing requirements both for seizure prophylaxis in patients with pre-existing seizure disorders and for seizure prophylaxis in new-onset seizures associated with renal failure (*see* Table 1 for renal clearance of common antiepileptics). Anticonvulsants with significant renal clearance (e.g., gabapentin, topiramate, and oxcarbazepine [OXC]) must be avoided in renal failure or used in markedly reduced doses. Jones et al. reported that gabapentin dosing in a patient who missed hemodialysis led to ICU admission for desaturation and respiratory failure. Gabapentin normally has a half-life of 5–7 h. In patients with renal failure not undergoing hemodialysis, the half-life can increase to 132 h, but with hemodialysis it may decrease to 3.8 h *(41)*.

Other factors connected to renal failure can influence the pharmacokinetics of anticonvulsants. Edema from renal failure increases the volume of distribution of the bound drug, therefore reducing the effective concentration. Also, drugs that are significantly bound to protein in plasma have higher effective serum concentrations if protein-losing nephropathy causes a reduction in plasma protein concentration. For example, the accepted therapeutic range of phenytoin in patients with

normal renal function is 10–20 mg/L, and this is reduced to 5–10 mg/L in patients with end-stage renal disease *(42)*. Cross-reactivity with fosphenytoin metabolites in critically ill patients with renal insufficiency allows the detection of falsely elevated phenytoin levels by certain immunoassays after fosphenytoin administration *(43)*.

In addition to these issues, dialysis itself can remove quantities of anticonvulsants from the blood, and anticonvulsant dosing may need to be adjusted relatively to the dialysis session. The intensivist should remember that the amount of drug removed during dialysis is typically inversely related to its protein-bound fraction and that the renally excreted drugs are the ones that are more dialyzed. Up to 35% of phenobarbital (PB) is removed during a session of continuous ambulatory peritoneal dialysis *(44)*. Although PHT is not dialyzable and no supplemental dose is required after dialysis, high-flux dialysis can result in up to 48.5% reduction in total body PHT. The intensivist must be aware of this possibility in patients receiving dialysis, especially if a seizure disorder is exacerbated *(45)*. Gabapentin is cleared by renal excretion only, and 35% of the drug is removed during a dialysis session *(46)*. For patients undergoing dialysis on gabapentin, an initial loading dose of 300–400 mg has been recommended. After each dialysis session, an additional dose of 200–300 mg of the drug may be enough to maintain steady-state plasma concentration *(46)*. Table 1 outlines the extent to which common antiepileptics are dialyzable. For more details, *see* Chapter 14.

ENDOCRINE DISEASE

Thyroid Disease

Thyroid disease usually causes reversible neurological change. Marked derangement of thyroid dysfunction, both hyper- and hypothryroidism, can cause seizures *(47,48)*; however, it is more usual for thyroid disease to worsen seizures in a patient with a pre-existing seizure disorder. Several derangements in thyroid hormone can occur in the context of critical illness. Most commonly seen is the sick euthyroid syndrome, characterized by reduced T3 levels, normal or low T4 levels, and decreased levels of thyroid-stimulating hormone (TSH) *(49)*. Critical illness is associated with reduced TSH secretion and pulsatility. In addition, low levels of TSH may be found in patients who received glucocorticoids and dopamine *(50)*. Generalized and focal seizures rarely can be seen in thyrotoxicosis and thyroid storm *(51–53)* and approx 66% of hyperthyroid patients exhibit an abnormal EEG. These abnormalities include generalized slow wave activity, focal spike, or focal slow waves and triphasic waves. These abnormal EEG patterns reverse after treatment of the hyperthyroidism *(54,55)*.

Lin et al. reviewed the literature in 1992 and found only 13 cases of thyrotoxicosis associated with seizures since 1956 *(56)*. Recurrent encephalopathy and generalized seizures associated with relapses of thyrotoxicosis have also been reported *(57)*. The mechanism of hyperthyroidism causing these changes is unknown, but

possibilities include a direct effect of thyroxine on cerebral metabolism, changes in ion channels, and upregulation of catecholamine receptors. In experimental hyperthyroidism, seizure thresholds to epileptogenic drugs have been shown to be reduced *(58)*. Correction of the thyrotoxicosis prevents seizure onset and returns observed EEG abnormalities to normal *(55)*. Another possible etiology is cerebral sinus thrombosis, a state highly associated with seizures. Siegert et al. reported two cases of Graves disease in which patients who presented with seizures and hemiplegia were found to have sagittal sinus thrombosis *(59)*. The conditions were controlled with PHT, oral anticoagulants, and prednisone. The authors attributed the sinus thrombosis to either a thyrotoxicosis-induced hypercoagulable state (with increased factor VIII activity) or venous stasis in the neck resulting from compression of a large goiter.

Seizures are unusual in myxedema *(60)*, although in some cases they may be the presenting sign *(61)*. Psychiatric symptoms, encephalopathy, and coma are more common manifestations. However, it has been reported that up to 20–25% of patients with myxedema coma may experience generalized convulsions or complex partial seizures. The EEG in myxedema typically has nonspecific generalized slowing and impaired photic driving *(62)*. Nonconvulsive seizures or status occasionally must be distinguished from the unusually prolonged postictal state, and an EEG is mandatory in the latter case. Seizures resulting from severe myxedema respond to replacement therapy. The low-voltage slow patterns on the EEG may normalize before the clinical state of the patient improves and can be used as a prognostic index during treatment.

Chronic administration of AEDs is not indicated. Recurrence of seizures is suggestive of inadequate treatment or cessation of treatment, but in such cases the intensivist must rule out other intracranial pathology. Because CBZ increases the metabolism of thyroid hormones, its use in hypothyroid patients has to be carefully followed by additional thyroid replacement therapy to avoid precipitation of a hypothyroid crisis *(63)*. The same is true with other AEDs such as PHT and PB.

Hashimoto's encephalopathy is a complication of Hashimoto's thyroiditis, a steroid-responsive, relapsing thyroid disorder characterized by high titers of thyroid autoantibodies *(64)*. A common feature of Hashimoto's encephalopathy is seizures represented by diffuse EEG abnormalities. The seizures may be generalized *(64,65)* or partial *(65,66)*, and the EEG abnormalities include generalized slowing, rhythmic bifrontal or temporal triphasic waves, and periodic sharp waves *(67)*. Clinically myoclonus may also be seen, and this usually responds to thyroxine replacement therapy. The incidence of seizures is independent of the degree of thyroid dysfunction and may occur in the presence of elevated antibodies alone. When a lumbar puncture is done for diagnostic purposes, the intensivist can expect abnormal results up to 60% of the time when leukocytosis, elevated protein and IgG index, or oligoclonal bands are present *(68)*. The pathophysiology of the disease is autoimmune, but the mechanism underlying the seizures is not clear; autoimmune cerebral vasculitis or direct antineural antibodies have been implicated. Immunosuppressive therapy with steroids improves the clinical picture.

Diabetes Mellitus and Glycemic Homeostasis

Disturbances in glycemic control are commonly seen in critically ill patients, irrespective of a prior history of diabetes. Van den Berghe et al. *(69)* examined 1548 ICU admissions and found that 1155 patients had mildly elevated serum glucose and 182 had moderate glucose elevation. Only 204 had a history of diabetes. In this study, aggressive control of serum glucose was associated with improved outcome.

Seizures have been reported in 7–20% of all diabetic patients. There is a paucity of data to support whether absolute serum levels of glucose or, rather, rapid changes are more important for epileptogenesis. Anticonvulsants used at doses that control seizures in other disorders often seem to be ineffective in treating seizures resulting from hypo- or hyperglycemia *(70)*. Glucose transport across the blood–brain barrier (BBB) is reduced during seizures, and, therefore, it is assumed that tissue hypermetabolism during the ictus is independent of the plasma glucose level *(71)*. It is unclear whether this presumed energy substrate deficiency prolongs the seizures.

Six percent of nonketotic hyperosmolar hyperglycemia (NHH) patients present with focal motor seizures, and 25% of these eventually develop seizures *(72)*. Seizures in NHH occur early in hyperglycemia and when osmolality is only modestly increased, with minimal reduction in sodium levels and usually when consciousness is preserved. Seizures related to NHH may occasionally have strange features. Reflex seizures (after limb movement) have been well-described *(73,74)*. These phenomena may present as speech arrest *(75)*, or there may be a visual component *(76,77)*. Transient subcortical T2 and fluid-attenuated inversion recovery (FLAIR) hypointensity have been described in the setting of SE and nonketotic hyperglycemia and attributed to the accumulation of free radicals and iron deposition *(78)*. There is a lower incidence of seizures in ketotic hyperglycemia than with nonketotic hyperglycemia *(70,73)*. This discrepancy is tentatively attributed to an anticonvulsant effect exerted by ketosis through the production of GABA *(79)*. GABA is thought to increase as a result of intracellular acidosis, which enhances GABA synthesis by glutamic acid decarboxylase. Ketogenic diets in patients with intractable epilepsy are thought to be effective through a similar mechanism.

Symptomatic hypoglycemia can occur in several endocrine disorders including primary hypothalamic–pituitary insufficiency (growth hormone, adrenocorticotropic hormone [ACTH], TSH), primary adrenal insufficiency, primary hypothyroidism, and overtreated diabetes mellitus with either insulin or oral hypoglycemic agents such as sulfonylureas. Salicylates can also induce hypoglycemia by increasing glucose uptake in muscle tissue. Hypoglycemia can also be the result of pancreatic islet cell dysfunction such as islet cell hyperplasia or insulinoma *(80)*. In such cases, the seizures present during the night or early morning and are resistant to conventional antiepileptic treatment. Seizures are the most common presenting neurological symptoms of hypoglycemia at any age. Hypoglycemic seizures usually occur at a serum glucose <40 mg/dL *(81)*. Clinically, patients often but not always

exhibit signs of sympathetic excitation before the seizures occur. Tachycardia, palpitations, sweating, nervousness, hunger, headache, or tremor may be followed by a change in mental status, focal neurological signs, seizures, and coma. These symptoms and signs can be absent in patients with autonomic neuropathy such as chronic diabetics *(82)* or patients taking ß-adrenergic blockers such as propranolol.

Hart and Frier retrospectively analyzed the clinical features of patients admitted to a large teaching hospital with hypoglycemia and found seizures in 20% of all cases *(83)*. EEG changes in hypoglycemia are nonspecific. Bjorges et al. recorded quantitative EEG in 19 diabetic and 17 nondiabetic children exposed to a gradual reduction in serum glucose *(84)*. Early changes in the EEG were increased amounts of Δ and θ activity followed by epileptiform activity. At a specific serum glucose level diabetic children displayed significantly more EEG abnormalities than nondiabetic children. This suggests that seizure thresholds may be lower in diabetic patients and that factors other than absolute serum glucose levels are responsible for the seizures.

Pituitary Hormones

Pituitary dysfunction can result in several secondary endocrinopathies including alterations in thyroid and corticosteroid function. Seizures can arise as a result of any of these secondary endocrinopathies, as detailed elsewhere. Conditions specific to the pituitary gland include diabetes insipidus and the syndrome of inappropriate antidiuretic hormone release (SIADH). SIADH by definition is caused by excess secretion of antidiuretic hormone (ADH) from the posterior pituitary, resulting in excess water retention in the distal renal tubule and collecting duct. SIADH can be caused by neoplasm, trauma, pain, infections, cavernous sinus thrombosis, cerebrovascular accident, multiple sclerosis, hydrocephalus, psychosis, congenital lesions, and drugs (CBZ, neuroleptics, tricyclics antidepressants, selective serotonin reuptake inhibitors) *(85)*. It can also occur postoperatively after transphenoidal surgery or endoscopic third ventriculostomy *(86)* and metabolic abnormalities. Several of these conditions are seen in the critically ill patient population. Water retention results in acute hyponatremia, and this hyponatremia can lead to seizures. In contrast, the lack of ADH is diabetes insipidus (DI), characterized by polyuria, low urine specific gravity, and hypernatremia. Seizures do not typically occur in DI, although seizures can occur in any severe hyperosmolar state. Few studies have examined the absolute incidence of seizures in DI. Transient DI has been extensively reported in pregnancy *(87)*. Combs et al. have reported a primigravida with transient DI, hypertension, and multiple seizures resistant to both magnesium sulfate and DZ *(88)*. These symptoms were successfully treated with PHT.

Sex Hormones

The role of sex hormones in the critically ill population has yet to be defined. The hypothalamic–pituitary axis is clearly disturbed in prolonged illness *(89)*. Although endocrinopathies of the sex hormones *per se* are not associated with sei-

zures in the ICU, sex steroid hormones have been found to have influence on seizure frequency in both experimental and clinical studies. In women, menarche, pregnancy, and the menopause can all influence seizure frequency, although these features are not common *(90)*. The relationship between seizure frequency and the menstrual cycle (catamenial epilepsy) was first suggested by Locock in 1857 *(91)*, and more recent studies have reported perimenstrual exacerbation of seizures in up to 78% of women *(92)*; an increase in the frequency of paroxysmal EEG discharges has also been observed perimenstrually *(93)*.

The origin of menstrual variations in seizures is not clear; however, in animal studies estrogen has been found to be proconvulsant and progesterone anticonvulsant *(94,95)*. Estrogen has also been shown to be proconvulsant in male animals *(96)*. In 1959 Logothetis et al. reported exacerbation of paroxysmal EEG abnormalities and seizures following intravenous estrogen in women with catamenial epilepsy *(97)*. Clomiphene, an antiestrogen at the hypothalamic and pituitary levels, can also reduce seizure frequency *(98)*, although it is not clear whether this is related to clomiphene-induced cycle changes or to a direct effect on the hypothalamus/pituitary. Anovulatory menstrual cycles are characterized by lack of ovulation and a lack of an increase in progesterone in the second half of the cycle. In a prospective study of 132 menstrual cycles from 35 patients, a perimenstrual increase in seizure frequency was seen only in ovulatory cycles *(99)*. It is postulated that the change in seizure frequency relates to progesterone withdrawal immediately prior to the menses. In the perimenopausal period, estrogen/progesterone ratios become higher; thus, it is not surprising that one study demonstrated that 64% of 39 women experienced a worsening of seizures perimenopausally *(100)*. During the menopause there is an absolute reduction of all sex steroids, and it has been reported that 68% of women report a clear reduction in seizure frequency *(100)*.

Parathyroid Hormones

The role of PHT in the critically ill has yet to be clearly defined. Hypocalcemia and hypercalcemia have both been documented in the critically ill population, and hypocalcemia is associated with worse outcomes *(101,102)*. Hypocalcemia has been associated with elevated PTH levels early in nonsurviving surgical ICU patients *(102)*. Lind and Ljunghall examined 83 critically ill patients and found a 32% incidence of hypercalcemia. PTH levels were measured in six of these patients without renal failure and found to be elevated *(101)*. This suggests that a primary PTH dysfunction may cause hypercalcemia in the critically ill.

Seizures secondary to hypocalcemia in hypoparathroidism are common neurological manifestations, especially in children *(62)*. Such seizures occur in 30–70% of patients and may be difficult to control *(103)*. There may be a GTC seizure pattern *(104)*, focal, or, less frequently, atypical absence and akinetic attacks *(62)*. Seizures may be seen in chronic hypoparathyroidism late after thyroidectomy *(105,106)*. Some patients with familial hypoparathyroidism do not experience seizures, even with severe hypocalcemia *(107)*. Some seizures in hypoparathyroidism

are refractory to therapy and are thought to be secondary to calcinosis of the brain. Idiopathic hypoparathyroidism can present with bilateral basal ganglia calcification, a useful imaging clue in a patient with seizures *(108)*.

AEDs, PHT and PB which induce hepatic enzymes, can accelerate conversion of vitamin D and 25-hydroxyvitamin D into their inactive metabolites. These drugs can also impair calcium absorption from the gut and resorption from bone, contributing to hypocalcemia. Thus, the use of these medications for patients with hypoparathyroidism could be questioned. Hyperparathyroidism can also cause seizures *(109)*, events most likely connected to hypercalcemia *(110)*, because hypercalcemia has been shown to cause seizures in other settings *(111)*.

Adrenal Glands

Adrenal dysfunction is well-recognized in the critically ill population. Cortisol and catecholamines have both been shown to be elevated in this group of patients *(112,113)*. The incidence of absolute adrenal insufficiency is low. However, the recently introduced concept of relative adrenal insufficiency postulates that patients may fail to mount a level of corticosteroid response appropriate for the severity of their disease *(114)*.

The adrenal gland is responsible for production of corticosteroid hormones and catecholamines. Alterations in corticosteroid function do not typically cause seizures; however, the secondary metabolic effects of these disorders can be epileptogenic. Adrenal insufficiency, including Addison's disease, may present with hypoglycemic seizures *(115)*. Hypoglycemic seizures and coma resulting from isolated ACTH deficiency have been reported in children but rarely in adults *(116)*. Addison's disease can also cause hyponatremia, another potential cause of seizures. However, the onset of hyponatremia in this setting is relatively gradual and the promotion of seizure occurrence less aggressive.

The relationship between Cushing's syndrome and seizures is unknown. Hypercortisolism may potentially exacerbate seizure disorders. Some adrenocorticosteroids, including cortisol, are glutamatergic and may antagonize $GABA_A$ receptors in the brain, therefore causing a proconvulsant effect. Herzog et al. reported three patients with Cushing's syndrome, seizures, and electromyographically confirmed myopathy. Their elevated serum ACTH and 24-h urinary cortisol concentration normalized after treatment with ketoconazole (200 mg three to four times a day), their seizure frequency decreased dramatically, and their weakness was improved *(117)*. Dysfunction of the catecholamine function of the adrenal gland is typified by pheochromocytoma. Seizures may occur in patients with pheochromocytoma, and they are most commonly generalized. Their incidence appears to correlate with the degree of blood pressure elevation *(118)*. Seizures are sometimes the presenting complaint *(119)*. The occurrence of seizures can be related to either the high catecholamines or hypertensive encephalopathy. Cerebral vasospasm caused by markedly elevated catecholamine levels can induce focal ischemia and seizure foci. Intracerebral hemorrhage during blood pressure elevation as a cause of seizures should be excluded by neuroimaging studies *(119–121)*.

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Seizures in Organ Transplant Recipients

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SUMMARY

Seizures are a nonspecific neurological manifestation of cerebral dysfunction and are not indicative of any particular disease processes or pathology. Thus, the evaluation and treatment of seizures in transplant patients generally follows the same clinical approach used for other patients. A seizure in a transplant patient is commonly unanticipated and entirely unexplained. The effects can be substantial, with aspiration, loss of vascular catheters, and tissue trauma. Patients undergoing organ transplantation are at risk for seizures for multiple reasons, and although much of the neurological and transplantation literature reports on the incidence of seizures according to the particular organ transplanted (Table 1), there are many similarities (e.g., immunosuppression drugs). This chapter concentrates on organ transplantation as a whole.

Key Words: Organ transplant; chemotherapy; seizures.

INCIDENCE OF SEIZURES IN TRANSPLANT PATIENTS

The incidence of neurological complications and seizures in a given transplant population tends to decrease with time, presumably as familiarity and experience with immunosuppression regimens and their complications accumulate. This fact may explain at least part of the wide range of seizure incidence reported in organ transplant (Table 1) *(1)*. Reduction in the incidence of severe immunosuppression toxicity may have reduced the incidence of seizures.

Liver Transplant

The postoperative care of liver transplant patients is well established and primarily focuses on the management of hemodynamic function, pulmonary function, fluid balance, electrolyte status, and careful attention to the transplant-related

Table 1
Incidence of Seizures in Organ Transplant Patients

Transplant organ	Incidence of seizures	Common etiologies (if available)
Liver	3–42%	Immunosuppression drug neurotoxicity
	10%	Infection *(5)*
Bone marrow transplant	3–29%	Immunosuppression drug neurotoxicity
	7%	Acute GVHD *(10)*
Heart	2–43%	New ischemic lesion *(12)*
Kidney	5–20%	Immunosuppression drug neurotoxicity *(16)*
Lung	22–27%	Immunosuppression drug neurotoxicity *(18)*
Pancreas	13%	*See* ref. *20*

GVHD, graft-vs-host disease.

coagulopathy. Review of the liver transplantation literature shows a wide range for the incidence of seizures *(1–7)*. Interestingly, despite the initial suggestion that posttransplant seizures often heralded a poor outcome *(4)*, a subsequent study of 630 orthotopic liver transplant (OLT) patients *(5)* found that only 28 (4%) of patients had generalized tonic–clonic (GTC) seizures, and only in 7 (1%) of the patients did the seizure "herald a catastrophic neurological event" *(5)*. In that study the cause of the seizures varied, but immunosuppression toxicity, defined as toxic blood levels or an increase of 100% or greater, was the most common etiology (cyclosporine in 11 [40%] patients and tacrolimius [FK506] in 6 [21%] patients). In addition to immunosuppressant drug toxicity, causes of seizures included acute uremia (one patient), meningioma (one patient) and unknown in two patients. In the seven patients in whom seizures portended a poor prognosis, the etiology of seizures includes: intracranial hemorrhage (one patient), sepsis (one patient), infection in the central nervous system (CNS) (three patients), anoxic encephalopathy (one patient), and cerebral edema with fulminant hepatic failure (one patient). The study did not attempt to distinguish between partial onset seizures that were secondarily generalized and GTC seizures. Partial seizures that did not generalize were not included.

Bone Marrow Transplant

Bone marrow transplantation (BMT) is rapidly advancing as an effective treatment of lymphopoietic and hematopoietic disorders. The literature describing neurological complications of BMT is limited, but seizures have been reported to occur in as many as 10% of patients *(8)*. However, the incidence of seizures appears to depend on the patient population considered *(1,2)*, with 29% (6 of 21 patients) of sickle cell anemia patients having seizures compared with 3% (5 of 168 patients) for Hodgkin's disease *(9)*. This difference may be caused by pre-existing, or perioperative CNS lesions such as stroke in the patients with sickle cell anemia. In a prospective study from Italy, 115 patients were followed for a median period of

90 d after BMT for leukemia, and 7% (8 of 115 patients) had seizures. Neurotoxicity related to immunosuppression drugs and acute graft-vs-host disease (GVHD) were found to be the most common etiology for seizures in this population *(10)*. A case of nonconvulsive status epilepticus (NCSE) has also been reported in a patient 2 yr after autologous bone marrow stem cell transplantation for diffuse large-cell non-Hodgkin's lymphoma. This patient with recurring episodes of altered mental status was found to have a left temporal lobe lymphoma *(11)*. Other etiologies that may be more frequent in this patient population are strokes associated with thrombocytopenia, cerebral venous sinus thrombosis, and cardioembolic events.

Heart Transplantation

The primary medical concern following heart transplantation is hemodynamic status. The reported range of seizure incidence in heart transplantation patients is varied, ranging between 2 and 43% *(1)*. In a report on consecutive orthotopic heart transplant patients, 15% (12 of 82 consecutive patients) had seizures *(12)*, and the most frequent cause of seizures was a postoperative stroke. This is unique to heart transplantation, supporting a more extensive evaluation of seizures in these patients. In another recent report from Brazil, 69 patients underwent orthoptic heart transplantation. Neurologic complications occurred in 19 (31%) patients, including 11 (17.7%) with seizures. Seizures were seldom recurrent, and no patients received long-term antiepileptic drugs (AEDs). All patients with seizures had normal computed tomography (CT) or magnetic resonance imaging (MRI) of the brain, and the seizures were attributed to metabolic derangements (two patients) and drug toxicity (cyclosporine in eight patients and imipenem in two patients) *(13)*.

Most reports identify a higher seizure incidence in pediatric heart transplant patients than in adults. Whether this increase is secondary to an underlying increased seizure tendency in children, more limited experience with immunosuppression, or another culprit is not known *(1)*. A recent report contrasting the differences in seizure incidence in 6 of 107 children (32%) and 7 of 77 adults (13%) from a single institution supported the difference, although it did not reach statistical significance *(14)*.

Kidney Transplantation

The kidney transplant patient is the least likely to have a prolonged stay in the intensive care unit (ICU). However, infrequently the transplanted kidney is slow to achieve adequate function, and uremia can occur with progressive encephalopathy and seizures in the immediate posttransplant course. The range of seizure incidence in kidney transplantation is reported to be 5–20% *(1)*. In a series of 109 pediatric renal transplant patients, 20 patients (18%) had at least one seizure. The etiology in this series was multifactorial: hypertension (15 patients), fever/infection (4 patients), and acute allograft rejection (6 patients). Only 2 patients had significant intracerebral pathology *(15)*. A large series of 402 kidney transplants reported a significantly lower overall seizure incidence of 5% (20 of 402 patients) *(16)*.

A syndrome of rejection encephalopathy has also been reported in renal transplant patients *(17)*. Fifteen episodes of encephalopathy had occurred in 13 patients during an acute rejection crisis. The severity of the encephalopathy was found to be related to the severity of the rejection crisis and not to other features such as blood pressure, fever, steroid therapy, or plasma electrolytes. The encephalopathy syndrome was associated with headache, papilledema, altered mental status, and GTC seizures in 6% of cases. The electroencephalogram (EEG) showed generalized slowing with focal abnormalities in 25% of cases.

Lung Transplantation

Data are starting to accumulate on the incidence of seizures in lung transplantation. A study of 81 lung transplant patients reported an incidence of 22% (18 of 81 patients) of patients suffering seizures. In this study the occurrence of partial versus GTC seizures was considered, and interestingly the majority of seizures had partial onset in 16 of the 18 patients (89%). Reported etiologies included sustained hypertension (two patients), stroke (four patients), and imipenem toxicity (two patients). Eleven patients had seizures within 10 d after initiation of methylprednisolone treatment for allograft rejection. Eight of the nine patients who underwent MRI had focal areas of T2 signal abnormality consistent with the localization of seizure semiology *(18)*. The reported incidence of seizures in pediatric lung transplantation can reach 27% *(19)*.

Pancreas Transplantation

There are very few data for the neurological complications or seizures in pancreas transplantation. One report of 15 patients cited a 13% incidence of seizures *(20)*.

CLINICAL EVALUATION OF PATIENTS

The evaluation of the organ transplant patient who has had a seizure after the surgery begins with the clinical history. A prior seizure disorder is not a contraindication for organ transplantation; however, patients with pre-existing seizure disorders are presumed to be at increased risk for postoperative seizures because of metabolic/electrolyte abnormalities in the postoperative period. Knowledge of a pre-existing seizure disorder should allow measures to be taken to reduce the risk of perioperative seizures, for example, attention to maintenance of therapeutic AED levels. (Maintenance of AED levels can be challenging in the transplant patient as is discussed in more detail in subsequent sections on the various medications.)

The first step is to establish the correct diagnosis. Simple partial motor seizures and GTC seizures are easily recognized. In an encephalopathic patient, complex partial seizures are less readily identified by ICU personnel. Movement disorders, especially in the encephalopathic patient, can be confused with seizures. Nonepileptic myoclonus and tremor are commonly seen in patients with toxic and

metabolic derangements. Nonepileptic myoclonus, which should not be confused with seizures, is commonly caused by drug toxicity or organ failure (e.g., liver or kidney failure). Persistent epileptic myoclonus is usually more focal (e.g., facial muscle twitching) and is frequently the manifestation of ischemic brain injury, often with associated laminar cortical necrosis. NCSE can be especially difficult to diagnosis and usually requires a high index of suspicion before subtle clinical signs, such as eye movement irregularities, are interpreted as symptomatic. Nonepileptic behavioral spells should also be considered. In these cases, the EEG is very helpful, and recording during the movement or symptom in question generally yields a definitive answer. Similar to the evaluation of other patient populations with seizures, the classification of the seizure type is important, and in particular whether the seizure is of partial onset or generalized. Whether a generalized seizure is secondarily generalized or generalized from onset can have significant prognostic implications. Whereas a new-onset partial seizure can be an ominous sign of a focal CNS lesion, most GTC seizures in the posttransplant period do not portend a poor outcome *(1,5)*. The occurrence of new partial seizures, suggesting a possible structural etiology, may have greater prognostic significance than GTC seizures, but this has never been investigated.

ETIOLOGY OF SEIZURES IN TRANSPLANT PATIENTS

Some common etiologies for seizures in the posttransplant patients are detailed in Table 2. The cause of seizures in the posttransplant population is often multifactorial: for example, metabolic abnormalities coexisting with elevated levels of immunosuppression drugs, as well as antibiotics that can lower the seizure threshold. In transplantation patients, perioperative seizures can result from immunosuppression drug neurotoxicity, metabolic and electrolyte abnormalities (commonly involving calcium, sodium, magnesium, and low serum glucose), CNS infections, or sepsis, or they can be related to CNS lesions, such as neoplasm or acute stroke. The development of a new CNS malignancy (usually a late complication of immunosuppression) or recurrence should be considered (*see* Case Study 1 in the last section of this chapter). The cause of seizures in some cases varies between transplant populations. For example, in a review of cardiac transplant patients Grigg et al. *(12)* found the most frequent cause of seizures was a perioperative stroke. Patients undergoing BMT may have significant thrombocytopenia and associated cerebral hemorrhage, or leukocytosis and cortical venous thrombosis as an etiology for seizures. Liver transplant patients can have a significant coagulopathy with risk of cerebral hemorrhage. It has also been suggested that seizures may be related to steroid regimens if these disrupt the blood–brain barrier (BBB), making the patient more susceptible to the neurotoxic effects of immunosuppression drugs like cyclosporine and FK506 *(18)*.

Although the occurrence of seizures in the posttransplant patient may be the harbinger of an impending neurological catastrophe, which usually initiates an emergency neurological consultation and requires immediate evaluation and man-

Table 2
Possible Etiologies of Seizures in Posttransplant Patients

Immunosuppression neurotoxicity	Cerebrovascular events
FK506 (tacrolimus)	Ischemic and/or hemorrhagic infarcts
Cyclosporin A	Intracranial hematoma
OKT3 (muronmonab-CD3)	Cerebral sinus thrombosis
	Hypoxic–ischemic event
	Subarachnoid hemorrhage
Metabolic derangements	
Hyponatremia	**CNS infection**
Hypocalcemia	Meningitis
Hypomagnesemia	Encephalitis
Hyperglycemia (often hyperosmolar, nonketotic)	Abscess
	Consider fungae: *Aspergillus*, *Nocardia*, *and Listeria*
	Malignancy
	Lymphoma (complication of immunosuppression or recurrence)
	Glioma
	Other metastatic cancer

agement, more often seizures are isolated events resulting from metabolic derangements and immunosuppression drug neurotoxicity. In fact, even the ominous new partial seizure disorder may not have the same implication in transplant patients as in the general population, where new partial seizures often are the first manifestation of a new structural lesion, such as a neoplasm. Partial seizures were the most common seizure type in patients who had received a new lung and, when not secondary to focal structural CNS lesions, they were attributed to focal abnormalities immunosuppression drug neurotoxicity and, therefore, possibly reversible *(18)*.

Immunosuppression Drugs

From an immunological perspective, organ transplantation represents the introduction of a massive quantity of foreign antigenic substrate, which if recognized by the host system will initiate a robust immune response. Without immunosuppression drugs, organ transplantation would not be possible. However, immunosuppression drugs used in organ transplantation have a narrow therapeutic range *(21,22)*, and the myriad neurologic manifestations of neurotoxicity related to these drugs are established *(21)* (Table 3). Neurotoxicity related to immunosuppression drugs should be high on the differential of possibilities for seizures in all posttransplant patients. The clinical profile of such neurotoxicity is nonspecific but often fairly characteristic and readily diagnosed (Table 3). One of the most interest-

Table 3
Neurological and Psychiatric Complications From Immunosuppressive Drug Toxicity (in order of frequency)

Tremors
Psychiatric symptoms: anxiety, panic, maniac behavior, and delusions
Visual hallucinations
Vascular-type headaches
Generalized tonic-clonic seizures
Akinetic mutism
Speech apraxia
Cortical blindness
Cerebellar syndrome
Extrapyramidal syndrome
Coma

(Data from ref. *21*.)

ing neurological complications of immunosuppression agents is a reversible posterior leukoencephalopathy syndrome (PRES) reported with cyclosporine and FK506 *(21,23–26)*. There is a propensity for immunosuppression-related neurotoxicity in the posterior circulation vascular territory, which may be related to BBB differences in the posterior and anterior circulations.

Immunosuppression drugs used in organ transplantation clearly are an important etiology of seizures. In a series of patients undergoing liver transplantation at the Mayo Clinic, 17 of 28 (61%) seizures were related to immunosuppression neurotoxicity *(5)*.

Cyclosporine

The immunosuppression effect of cyclosporine is primarily achieved by inhibiting T-lymphocyte maturation and reducing interleukin-2 production. Cyclosporine-related neurotoxicity most commonly develops within weeks after transplantation and occurs frequently with intravenous loading *(7,21)*. The incidence of cyclosporine-related neurotoxicity depends on the transplanted organ, occurring in approx 10% of liver transplant patients who receive the drug intravenously in the postoperative period *(7)*, but in only approx 5% of BMTs *(27)*. This difference may be indicative of additional metabolic abnormalities seen in liver transplant patients. The risk of cyclosporine neurotoxicity has been reported to be increased by the presence of hypomagnesemia *(28)*, hypocholesterolemia *(29)*, corticosteroids *(18)*, hypertension *(30)*, and high drug concentrations *(23,24)*. Cyclo-sporine is well-known to cause magnesium wasting, and levels must be followed closely.

The range of neurotoxicity-related complications is wide and commonly can include psychiatric manifestations with agitation, manic behavior, bizarre delusions, panic, paranoia, and severe mood changes. The presentation of psychiatric symp-

toms usually resolves with reduction or discontinuation of cyclosporine. However, if these initial symptoms are not recognized, cyclosporine neurotoxicity can lead to actual structural abnormalities on MRI primarily involving the cerebral white matter. Cyclosporine appears to have a propensity to involve the posterior circulation vascular territory, and neurological symptoms of visual hallucinations, cortical blindness, cerebellar syndrome, extrapyramidal syndrome, and coma have been described *(21)*. Thus, cyclosporine is one of the agents causing a posterior reversible leukoencephalopathy syndrome *(21,23–26)*.

Seizures are commonly attributed to cyclosporine neurotoxicity *(5)*. In fact, cyclosporine should be considered first in the differential when one is evaluating new seizures in the posttransplant patient.

Tacrolimus (FK506)

The clinical experience with FK506 is now comparable to that with cyclosporine, and the overall neurotoxicity profile is possibly better, but the incidence of seizures is similar *(31,21)*. Most commonly, FK506 neurotoxicity manifests with postural hand tremor *(6)*, but similar to cyclosporine, cortical blindness and GTC seizures also occur. A posterior leukoencephalopathy syndrome with MRI abnormalities similar to those seen with cyclosporine has also been reported *(32)*.

Muromonab-CD3 (OKT3)

Muronmonab-CD3 (OKT3) achieves immunosuppression by inactivating CD3 lymphocytes, and is most often combined with corticosteroids, azathioprine, and cyclosporine. The most common neurologic symptom of OKT3 is headache but, rarely, neurotoxicity has been reported to produce aseptic meningitis, seizures, cerebral edema, and vision loss *(33–35)*.

Carmustine and Busulfan

Carmustine and busulfan are used in conditioning regimes in anticipation of BMT, and in high doses they can cause seizures in 3–10% of patients *(36,37)*.

DIAGNOSTIC EVALUATION

The clinical evaluation of a new seizure in the posttransplant patient should proceed within the overall clinical context. Generalized seizures are often the manifestation of gross electrolyte abnormalities or immunosuppression drug toxicity, and if such an abnormality is identified, additional studies requiring transport of a critically ill patient to the radiology suite, and performing lumbar punctures and other invasive procedures, may impose unnecessary risks with little potential diagnostic yield.

History and Examination

A detailed list of medications should be obtained. Evidence for a focal abnormality on neurological exam necessitates neuroimaging with MRI technique.

Laboratory Tests

Blood count and coagulation studies are essential. Electrolytes, most importantly sodium, calcium, and magnesium, must be determined, along with glucose, arterial blood gas, if clinically indicated, and AED levels. Immunosuppression drugs (e.g., cyclosporine, FK506) and antibiotic levels (e.g., imipenem) should be ascertained. Blood cultures for bacteria, viruses, and fungi may be clinically indicated.

Imaging

Although the acutely ill patient may be evaluated with CT, the standard of care in the evaluation of new-onset seizures is MRI (*see* Case Study 1, in the last section of the chapter). In patients with focal seizures or focal EEG abnormality, an MRI scan is indicated. The MRI characteristics of severe immunosuppression-related neurotoxicity are well-described *(21,26)*.

Cerebrospinal Fluid (CSF)

If clinically indicated (consider risk of complications associated with coagulopathy or thrombocytopenia), CSF should be withdrawn and tested. The presence of increased intracranial pressure must be ruled out prior to CSF testing. Gram stain, differential cell count, protein, and glucose should be obtained on the CSF screen. When indicated, bacterial, viral, and fungal cultures should also be obtained.

EEG

EEG may be useful to rule out NCSE in the encephalopathic patient. Video-EEG is very useful if there is uncertainty about whether an intermittent paroxysmal movement or spell is a seizure. Continuous video-EEG recording can also be used to assess efficacy of AED therapy. The presence of a focal abnormality on EEG raises the concern of a structural focal lesion.

MANAGEMENT OF SEIZURES

The first step in the management of seizures is to correct any precipitating causes, with close attention to electrolyte and metabolic abnormalities and immunosuppression drug levels. In the case of immunosuppression drug neurotoxicity or electrolyte abnormality and a single brief GTC seizure, discontinuation of the drug for several days and correction of the electrolyte abnormality may be all that is required.

The treatment with AEDs in the organ transplant patient population is often complicated by numerous factors *(21,22,38)*, which can include a critically ill patient, viability of a transplanted organ, potential for drug–drug interactions (e.g., cyclosporine and phenytoin [PHT]), and impairment of the organ system (e.g., liver, kidney) responsible for AED metabolism and clearance. The concern for AED toxicity to the transplanted organ is often raised, but there is little if any clinical evidence to support this. It is well-known that idiosyncratic AED reactions can produce catastrophic organ failure, such as acute liver failure, and bone marrow suppression. However, we are not aware of data to support contentions that the transplant

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┌─────────────────────────────────────────────────────────────┐
│   Single Seizure: Lorazepam 2-4 mg IV ( repeat if needed)    │
│   Status Epilepticus: Lorazepam 0.1 mg/kg at 2 mg/min        │
│ IV Phenytoin 20 mg/kg (additional 10mg/kg if refractory) or  │
│                      Fosphenytoin                            │
└─────────────────────────────────────────────────────────────┘
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Metabolic causes corrected
No drug toxicity
No structural lesion on imaging → If any

Normal No further Rx ← EEG

EEG ↓ Epileptiform Activity → phenytoin maintenance (3-5 mg/kg)

If any ↓ phenytoin maintenance (3-5 mg/kg)

Fig. 1. Managing a single seizure in a transplant patient. The management of refractory seizures in the transplant patient is similar. (Modified with permission from ref. *1*.)

patient is at greater risk of these rare idiosyncratic reactions. Nonetheless, caution is indicated.

An important question to answer is whether long-term treatment with an AED is necessary. In our experience, if a clear provoking etiology (e.g., cyclosporine toxicity or electrolyte abnormality) can be identified and corrected, then long-term treatment of a single convulsion with an AED is not indicated. Treatment with an AED should be initiated in the setting of a metabolic derangement that cannot be corrected, a structural CNS lesion or CNS infection (where the probability of a recurrent seizure is high), or if the patient is critically ill and believed to be unable to tolerate further seizures. A protocol has been developed (Fig. 1) for treatment of seizures in the posttransplant patient. If GTC seizures are refractory, lasting beyond 5–8 min in this patient population, we proceed to a more aggressive protocol for status epilepticus. For GTC seizures that are refractory to lorazepam and PHT, we usually proceed to midazolam (a bolus of 0.1 mg/kg: followed with 0.05–0.4 mg/kg/h) or propofol (5–10 mg/kg/h). Continuous EEG monitoring is indicated in this situation.

Antiepileptic Drugs

The use of intravenous antiepileptic drugs requires close attention to vital signs and continues EKG monitoring.

Phenytoin

The drug of choice for treatment of GTC seizures in the posttransplant patient is PHT. The standard loading dose is 18–20 mg/kg. For patients requiring rapid intra-

venous loading, we use fosphenytoin because it is better tolerated, with less risk of hypotension, and can be safely infused at a faster rate (150 mg/min) than is possible with PHT (50 mg/min). Because many transplant patients have derangements in fluid status and may have hypoalbuminemia with associated decreased protein binding of PHT (and other protein-bound AEDs, e.g., valproic acid [VPA] and carbamazepine [CBZ]), both the free and total PHT levels are used (therapeutic range: total PHT 10–20 µg/mL; free PHT 1–2 µg/mL). The active drug is the unbound free PHT fraction, and it is not uncommon for patients to have toxic side effects if the free PHT level is high, although the total PHT level is subtherapeutic.

Benzodiazepines

Benzodiazepines (BZDs) are a class of drug with proven antiepileptic effect that act on γ-aminobutyric acid receptors (GABAergic). Lorazepam has become a first-line drug for the emergent treatment of seizures because its duration of antiepileptic action is longer than that of other BZDs *(39)*. The recommended lorazepam dose in SE is 0.07–0.1 mg/kg (infused at a rate of 2 mg/min). However, for the acute single seizure that is not prolonged in duration (i.e., not SE), we generally use approx 0.05 mg/kg intravenously to avoid respiratory depression. Midazolam is a short acting BZD commonly used in the protocol for SE *(39)*.

Phenobarbital

An effective older AED that is available in intravenous form, phenobarbital (PB) can be used if the patient is allergic to PHT. PB has been suggested as the best choice *(1)* during the 2–6 wk of bone marrow engraftment because, unlike PHT, VPA, and CBZ, PB has not been reported to cause bone marrow suppression. The intravenous loading dose of PB is 10–20 mg/kg, which can be complicated by hypotension and respiratory depression. Thus, usually a smaller dose of 3 mg/kg can be tried first in patents who are not intubated and not in SE.

Valproic Acid

VPA is available as an intravenous preparation and has been demonstrated to be efficacious in the treatment of SE *(40,41)*. Although data are limited, VPA does not interfere with cyclosporine and FK506 metabolism. Our neurosurgical colleagues have commented on their impression of a coagulopathy associated with VPA, and recent studies show a reduction in fibrinogen concentration, platelet count, and factor VIII complex with this drug. In one often-cited study, 63% of children treated with VPA had a history of bleeding, and 23% had prolonged bleeding times *(42)*. In comparison to a control group, significant differences in coagulation parameters, similar to what is seen in patients with congenital von Willebrand disease, were demonstrated. The decreases in coagulation parameters were not dependent on either VPA dose or time period of administration. For this reason, and not because of potential idiosyncratic reactions, caution is recommended in the prescribing of VPA acute transplant patient who may already have a coagulopathy.

AED Interaction With Immunosuppression

It is important to recognize that PHT, CBZ, and PB decrease serum cyclosporine *(43)* and FK506 *(38)* levels, and if appropriate dosing changes are not made, discontinuation of these AEDs can lead to toxic immunosuppression drug concentrations. There is no known interaction with VPA or gabapentin. Interaction between immunosuppression drugs and the newer AEDs such as levatracitam, lamotrigine, and topiramate have not been studied, and these medications likely will provide useful alternatives. At this time they cannot be recommended as first-line drugs except for patients with known multidrug allergies.

CASE STUDIES

Case Study 1

A 59-yr-old right-handed man with a history of non-Hodgkin's lymphoma was treated with BMT. The course was complicated by an acute reactivation of hepatitis B requiring antiviral treatment. Six months after transplantation, he complained of malaise and fatigue and had a low-grade fever. The following day, he had a GTC seizure. Within 15 min he had a second, and then a third GTC seizure before recovering awareness. On arrival at Saint Marys Emergency Department, he had a Glasgow Coma Scale (GCS) score of 9, was not verbalizing, and could not follow commands, but there was withdrawal to pain symmetrically. The patient was loaded with intravenous PHT and admitted to the medical ICU. Detailed laboratory studies were unremarkable. The CT image of the head was unremarkable. The EEG (Fig. 2) showed left frontal quasiperiodic lateralized epileptiform discharges (PLEDs), raising the possibility of herpes encephalitis, although the distribution of the interictal discharges would have been unusual for this diagnosis. The patient was covered with acyclovir as well as antibiotics. The CSF examination was normal with only 1 nucleated cell, a protein of 44, glucose of 84, and negative herpes polymerase chain reaction.

The presence of a focal onset seizure, or focal EEG (left frontal PLEDs), is concerning for a structural lesion involving the left frontal head region. The patient had an MRI exam the following morning that was assessed to be normal. However, the MRI (Fig. 3A) quality was marginal because of movement artifact. By the following day the patient had a GCS 15 and was showing rapid improvement. A follow-up EEG 1 mo later (not shown) continued to show the left frontal PLEDs, albeit in a more quasiperiodic pattern. Because of the persistence of the focal EEG abnormality, MRI was repeated, with attention to the left frontal region. The MRI, 1 mo after presentation with new seizures, demonstrated a clear region of focal enhancement later determined to be lymphoma (Fig. 3B). The patient underwent brain radiation, but the lymphoma did not respond and he died 2 mo later. The important point demonstrated by this case is that a focal onset seizure, or focal EEG abnormality, can be an ominous sign, the etiology of which must be pursued vigorously.
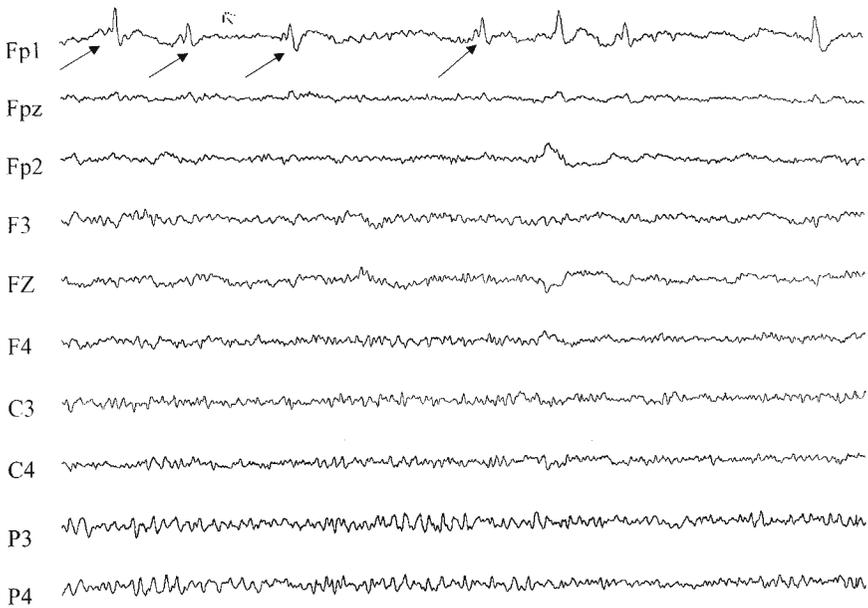
Fig. 2. EEG (Laplacian montage) for case study 1 showing quasiperiodic lateralized epileptiform discharges over the left frontal head region.
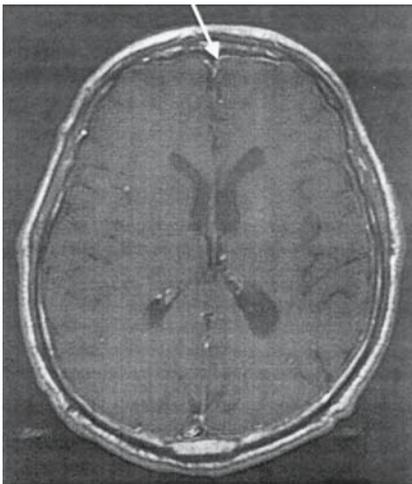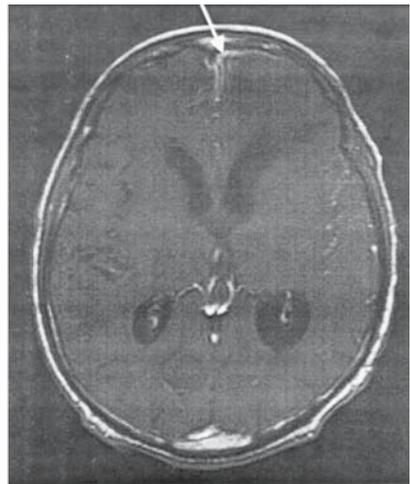
6/23/00   7/19/00

Fig. 3. MRI with contrast for case study 1: **(A)** possible subtle area of left frontal meningeal enhancement on 6/23/00 and **(B)** follow-up scan 1 mo later.

8 May 2002   17 May 2002
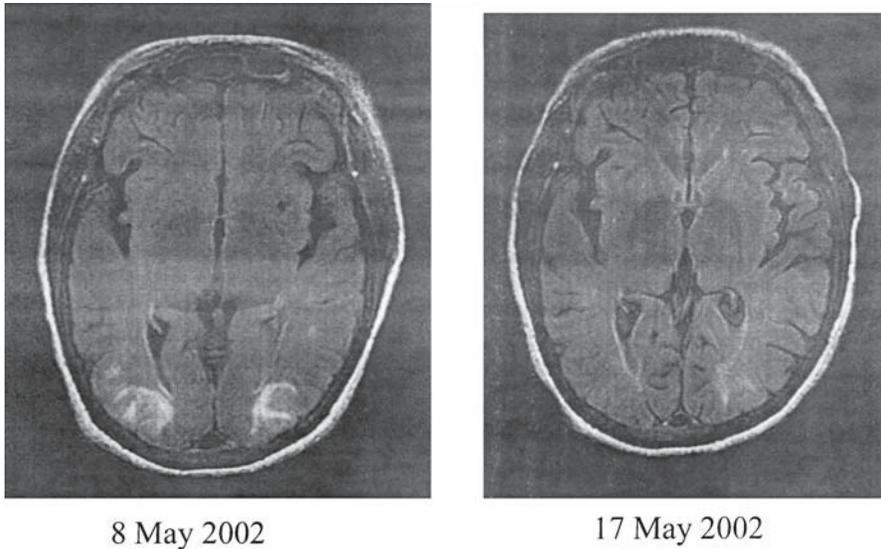
Fig. 4. Reversible posterior leukoencephalophy syndrome in renal transplant patient treated with FK506 (case 2): **(A)** MRI before FK506 was withdrawn and **(B)** MRI after discontinuation of the drug (9 d later).

Case Study 2

A 36-yr-old African-American female with history of sickle cell disease and renal transplant presented with complaint of fatigue, dyspnea, and productive cough. The patient's immunosuppression regimen includes FK506 and prednisone. The workup demonstrated hemoglobin of 3.8, white cell count of 10,800, stippling, teardrop, and fragmented red blood cells, and serum creatinine of 4.4. The patient was admitted to the hospital and received a blood transfusion. Later that evening she complained of confusion and blurred vision and subsequently had two GTC seizures, which led to an ICU admission. Her FK506 level was 10.2 (3.0–20.0). The EEG showed generalized slowing that was maximal over the posterior head region, but no epileptiform activity was appreciated. The MRI demonstrated bilateral subcortical T2 signal abnormalities in the occipital regions, suggestive of the posterior reversible leukoencephalopathy syndrome (Fig. 4A). Contrast and diffusion weighted images are not shown, but were unremarkable. She was loaded with intravenous fosphenytoin.

Later she had a renal biopsy, the results of which suggested FK506 toxicity, and her immunosuppression regimen was changed to sirolimus and her prednisone dose increased. Shortly after discontinuation of FK506, a repeat MRI exam showed significant improvement (Fig. 4B). This case is an example of posterior reversible leukoencephalopathy syndrome caused by FK506 neurotoxicity *(21)*.

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Extreme Hypertension, Eclampsia, and Critical Care Seizures

Errol Gordon and Michel T. Torbey

SUMMARY

The association between seizures and blood pressure elevation remains a common medical emergency encountered in the setting of an intensive care unit. Syndromes such as preeclampsia or eclampsia, hypertensive encephalopathy, and posterior leukoencephalopathy commonly present with seizures. The primary treatment goal is to reduce the arterial blood pressure. In most cases, seizure control is thus achieved, but unique medications, such as magnesium sulfate, may be needed. Fortunately the pathophysiologic mechanism leading to seizures is reversible in most cases that are treated immediately and aggressively. Delayed treatment may result in irreversible brain injury or increased mother or fetus mortality.

Key Words: Seizures; eclampsia; hypertensive encephalopathy; leukoencephalopathy; magnesium.

INTRODUCTION

Most physicians are familiar with the syndrome of a sudden elevation of blood pressure, preceded by a severe headache, and followed by convulsions, coma, or a variety of transitory cerebral phenomena. The pediatrician faces the problem with acute nephritis, the obstetrician with toxemia of pregnancy, and the internist with hypertensive vascular disease. *(1)*

Seizures have been reported in both chronic and acute hypertension *(2)*. The association between hypertension and seizure occurrence is unclear. In chronic hypertension, seizures may be secondary to the effect of blood pressure (BP) elevation on the cerebral blood vessels and its association with higher risk of stroke. In acute hypertension, seizures may be secondary to disruption of the blood–brain barrier (BBB) and secondary cerebral edema. In a population-based study from

Rochester, Minnesota, 195 patients aged 55 yr or older with first unprovoked seizures were matched on age, gender, and duration of follow-up with patients without seizures *(3)*. The BP of the seizure patients had been obtained in before the first seizure occurrence. Overall, hypertension did not increase the risk of seizures, but the study found that a subgroup with left ventricular hypertrophy (LVH)—a marker of severe, long-standing hypertension—without diuretic treatment had an 11-fold increased risk of unprovoked seizures. Interestingly, patients with LVH who were treated with diuretics did not have an increased risk. This chapter reviews the different acute hypertensive syndromes encountered in the intensive care unit (ICU) and emphasizes the specific management of seizures associated with these disorders.

HYPERTENSION AND PREGNANCY

Hypertensive disorders of pregnancy are common, affecting 7–15% of pregnant women *(4)*. In the United Kingdom, 18.6 % of maternal deaths are caused by hypertensive diseases *(5)*. Five hypertensive disorders are commonly reported in pregnant women: gestational hypertension, preeclampsia, eclampsia, preeclampsia with superimposed chronic hypertension, and chronic hypertension *(6)*. Only preeclampsia and eclampsia are associated with seizures.

Preeclampsia and Eclampsia

As early as the fourth century B.C., Hippocrates was among the first to recognize fits occurring in pregnant women *(7)*. This condition was coined eclampsia, a Greek word meaning "shine forth," thus implying a sudden development *(8)*. Preeclampsia and eclampsia are among the most common causes of maternal and fetal morbidity and mortality. In a retrospective review of 4024 pregnancy-related deaths, 19.6% were related to preeclampsia-eclampsia *(9)*.

Preeclampsia is hypertension in pregnancy diagnosed after 20 wk with associated proteinurea *(9)*. Eclampsia is defined as seizures occurring before, during, or after delivery. Although eclampsia is usually preceded by preeclampsia, in up to 38% of cases it can occur without symptoms or signs of preeclampsia *(8)*. Table 1 summarizes the definitions of preeclampsia and eclampsia.

Epidemiology

Preeclampsia affects up to 7% of pregnancies, and less than 1 % of these women develop eclampsia *(10)*. Every year, approx 1 in 50 women experiencing eclamptic seizures die from complications *(11)*. In a prospective survey of eclampsia in the United Kingdom, the incidence of eclampsia was 4.9 in 1000 *(12)*. The leading cause of death with preeclampsia-eclampsia patients is cerebrovascular accidents (CVAs) particularly intracerebral hemorrhages (ICHs). The mortality rate ranges from 2 to 24%. Table 2 summarizes the specific causes of death associated with eclampsia and preeclampsia. The case fatality in women with eclampsia is 71 per 10,000 *(9)*. Although the incidence of preeclampsia has not changed significantly

Table 1
Definitions of Preeclampsia and Eclampsia

Preeclampsia
  Newly diagnosed hypertension after 20 wk gestation
  Relative increase of 15 mmHg diastolic or 30 mmHg systolic or absolute above >140/
    90 mmHg
  Either or
  Proteinuria (>300 mg/24 h or 1+ in dipstick testing)
  Generalized edema (particularly in nondependent areas like hands and face)
Severe Preeclampsia
  BP >160/110 mmHg
  Proteinuria 2 or 3+
  Serum creatinine >1.2 mg/dL
  Oliguria <500 mL/24 h
  Headache with or without visual symptoms, epigastric pain, pulmonary edema, throm-
    bocytopenia <100,000/μL or increased aspartate or alanine transaminase.
Eclampsia
  Presence of seizures

Table 2
Specific Causes of Death Among Patients With
Preeclampsia and Eclampsia

Cause of death	Deaths (%)	
	Preeclamsia	Eclampsia
Intracerebral hemorrhage	15.8	18.8
Cerebral edema	1.1	1.8
Cerebral embolism	0.4	0.8
Renal or hepatic failure	7.2	5.4
HELLP syndrome	4.8	2.3
Other	13.9	11.8

(Adapted from ref. *9*.)

over the past six decades, the rate of major complications from the disease has been on a marked decline *(13)*.

Several risk factors for eclampsia have been identified. Those include prima gravidity, lack of prenatal care, urinary tract infections, family history, diabetes mellitus, multiple gestation, extremes of age, obesity, black ethnicity, preexisting hypertension, vascular renal disease, prolonged labor, and hydatidiform moles *(10,14)*.

Pathophysiology

The underlying pathophysiology of eclampsia remains to be fully elucidated, but vascular endothelial damage or dysfunction appears to be the common patho-logical feature in the placenta, kidneys and brain *(15)*. In 2001 Odent *(16)* proposed

that preeclampsia could be the result of maternal–fetal conflict. The developing fetal brain requires eicosapentaenoic acid (EPA), a long-chain *n*-3 polyunsaturated fatty acid. The theory suggests that the fetal need for EPA overrides the maternal need. A decrease in maternal EPA in preeclampsia and eclampsia women in comparison to their normotensive counterparts appears to play a role in the development of this condition *(16)*. Other mechanisms suggested for eclamptic convulsions include cerebral vasospasm, hemorrhage or edema, and metabolic or hypertensive encephalopathy *(17)*.

Clinical Presentation

By definition, eclampsia is characterized by the presence of seizures. They can occur before, during, or after labor *(18)*. Antepartum eclampsia refers to the onset of seizures before the start of labor. Intrapartum eclampsia refers to seizures that occur during labor, and postpartum eclampsia is the occurrence of seizures within 7 d of delivery of the fetus and placenta. In 2% of women, eclampsia occurs more than 7 d past delivery *(19)*. In some women, seizures occur as late as 11 d *(20)*. In the United States, 53% of women had antepartum seizures, 36% intrapartum seizures, and 11% postpartum seizures *(19)*. In the United Kingdom 38% had antepartum seizures, 18% intrapartum seizures, and 44% postpartum eclampsia *(12)*.

The syndrome may also be associated with headaches, visual complaints, epigastric pain, oliguria, depression of consciousness, thrombocytopenia, fetal growth retardation, and elevated liver enzymes.

Electrographic and Radiographic Features

Abnormal electroencephalograms (EEGs) are reported with preeclampsia *(21)*. Diffuse slow activity (θ or Δ waves), sometimes with focal slow activity, are usually found on EEG *(21)*. Paroxismal spike activity has been reported, but this is not pathognomonic of preeclampsia because similar patterns are found in other conditions *(21)*. No correlation was found between EEG abnormalities and the degree of maternal arterial pressure *(21)*.

The radiological features found in patients with eclampsia are certainly not unique. Diffuse cerebral edema *(22)*, hemorrhages *(23)*, and infarcts *(24)* have been demonstrated in patients with eclampsia by means of computed tomography (CT) scan. Magnetic resonance imaging (MRI) studies of brains of patients with eclampsia revealed focal changes characteristic of ischemia *(25)*. MRI features consistent with reversible posterior leukoencephalopathy have also been reported *(26)*.

Management

Early detection remains the mainstay of treatment in patients with eclampsia. The best treatment for preeclampsia and eclampsia is delivery. If delivery is not possible, then management of the patient should include hospitalization, close observation, and seizure prophylaxis until delivery can be performed. In a review of obstetric patients admitted to a medical–surgical ICU in a large tertiary referral center over a 5-yr period, preeclampsia was the single most common diagnosis, representing 22% of all patients *(27)*.

Over the last two decades magnesium has emerged as the drug of choice for preventing eclampsia. Large randomized trials and systematic reviews have shown the usefulness of magnesium sulfate in treating recurrent eclamptic seizures and in the prophylaxis of eclampsia *(28–31)*.

In 1995 the Eclampsia Trial Collaborative Group showed unequivocally that magnesium given intramuscularly or intravenously is superior to phenytoin (PHT) or diazepam (DZ) in reducing recurrent eclamptic seizures *(26)*. This international multicenter randomized study included 1687 women with eclampsia. The women allocated to magnesium sulfate therapy had a 52% reduction in incidence of recurrent seizures (95% confidence interval [CI] 37–64%) over those given DZ (13.2% vs 27.9%). Maternal and perinatal morbidity were comparable between the two groups. In a second comparison between magnesium sulfate and PHT, the women randomized to receive magnesium sulfate had a 67% (95% CI 47–79%) reduced incidence of recurrent seizures (5.7% vs 17.1%). Maternal mortality was nonsignificantly lower in the magnesium group than in the PHT group *(26)*. Women who received magnesium were also less likely to be ventilated than those on PHT (14.9% vs 22.5%). Women in the magnesium group were also less likely to develop pneumonia (3.9% vs 8.8%) and were less likely to be admitted to the ICU (16.7% vs 25.1%) in comparison to the PHT group.

The so-called Magpie study, another randomized placebo-controlled trial, was designed to assess the value of magnesium for prophylaxis in eclampsia *(30)*. The study included approx 10,000 women with preeclampsia who were randomized to receive magnesium sulfate before or during labor or after giving birth *(30)*. Magnesium was effective in reducing seizures 58% (95% CI 40–71%). Treatment was also safe for the neonate in this setting, and there was no excess of serious maternal morbidity or mortality. Of the 5055 women who were randomized in each group, 46 (0.9%) had respiratory depression and 5 (0.1%) had respiratory arrest in the magnesium compared with 27 (0.5%) and 2 (0.04%) in the placebo group. Respiratory arrest was responsible for one death in each group *(30)*.

Another multicenter, randomized unblinded study compared magnesium with the calcium channel blocker nimodipine, a cerebral vasodilator, for ability to prevent eclampsia *(31)*. Preeclampsia women who received nimodipine were more likely to have a seizure than those who received magnesium sulfate (2.6% vs 0.8%, $p = 0.01$). The antepartum risk for eclampsia did not differ between the two treatment arms, but the nimodipine arm had a higher risk of postpartum seizures (1.1% vs 0%, $p = 0.01$). Neonatal outcomes did not differ between the two groups *(31)*.

Similar results were reported in a Cochrane Database review analysis that included published randomized studies between magnesium and placebo or antiepileptics *(29)*. The authors concluded after reviewing six studies that magnesium sulfate more than halves the risk of eclampsia, and probably reduces the risk of maternal death. A quarter of women had side effects, particularly flushing. The relative risk (RR) of placental abruption was reduced for women allocated to magnesium sulfate (RR 0.64, 95% CI 0.5–0.8). Women allocated to magnesium sulfate

Table 3
Effect of Magnesium on Risk of Eclampsia

Treatment compared with magnesium sulfate	Relative risk (95% CI)	Ref.
Placebo	0.41 (0.29–0.59)	*30*
Phenytoin	0.05 (0–0.84)	*26*
Nimodipine	0.33 (0.14–0.77)	*31*

had a small, nonsignificant, increase (5%) in the risk of Cesarean section. Magnesium sulfate was better than PHT and nimodipine in reducing the risk of eclampsia, but there was an increased risk of Cesarean section (RR I .2, 95% CI 1.05–1.4). The result from the Cochrane review are summarized in Table 3.

The most commonly used magnesium protocol in eclampsia is a 4- to 6-g iv bolus over 5 min, followed by a 1- to 2-g/h iv infusion for at least 48 h postpartum. If the treatment is used prophylactically in preeclampsia, it can be stopped after 24 h *(10)*. Half this dose should be used in patients with serum creatinine more than 1.3 mg/dL *(10)*.

Patients should be admitted to the neurointensive care unit (NICU) and monitored closely, particularly the respirations, patellar reflexes, and urine output. Magnesium is known to affect the neuromuscular junction, but it should not have any deleterious effect on a patient's mental status. If patellar reflexes are lost, the next magnesium should be held and its level should be checked. It may be restarted at a lower dose when the reflexes return if still desired. If the urine output falls below 25 cc/h, the rate of infusion of magnesium or the intramuscular dose should be cut in half. In case of respiratory depression or arrest, the patient airway must be first secured (by endotracheal intubation if needed) and 1 g of calcium gluconate (10% solution) should be administered intravenously.

Several anticonvulsant regimens can be used for patients with refractory seizures. An additional dose of magnesium sulfate (1–2 g iv) can be given or a loading dose of PHT (18 mg/kg iv at a maximum rate of 50 mg/min) can be tried. A dark room with low noise, padded bed rails, and continuous fetal monitoring are additional measures.

HELLP Syndrome

Pritchard et al. first described the association between coagulation and liver enzymes abnormalities with preeclampsia in 1954 *(32)*. In 1982 Weinstein coined the term HELLP for this syndrome of Hemolysis (anemia, increased bilirubin schistocytes in blood smear), Elevated Liver enzymes, and a Low Platelet count (<100,000/mm³) *(33)*. HELLP can usually complicate the course of up to 10% of eclamptic patients *(17,34)*. Mortality resulting from HELLP syndrome ranges from 2 to 24% of cases *(9)*.

Management of seizures in patients with HELLP syndrome is similar to that for patients with eclampsia. Magnesium should be initiated at seizure onset. Although no specific data exist regarding seizures, antepartum administration of corticoster-

oids (10 mg of dexamethasone every 12 h until delivery) has been shown in randomized trials to stabilize and improve the laboratory values and clinical status of the mother and potentially the fetus *(35,36)*. The increase in liver enzymes may limit the use of some anticonvulsants such as PHT, carbamazepine, and/or valproic acid. Levetiracetam may be used as a second-line agent or as a second agent if magnesium fails to stop the seizures. The drug can be started orally at 500 mg every 12 h and increased to a maximum dose of 3000 mg/d. If patients develop status epilepticus (SE), phenobarbital or pentobarbital can be used as a therapeutic option. More details regarding treatment of seizures in patients with liver dysfunction can be found in Chapter 6.

HYPERTENSIVE ENCEPHALOPATHY

Hypertensive encephalopathy (HE) is a complex cerebral disorder associated with a variety of conditions in which systemic BP rises acutely. The term was coined by Oppenheimer and Fishberg in 1928 *(37)* and is defined as generalized or focal cerebral dysfunction that either partially or completely reverses with antihypertensive treatment *(38)*.

Epidemiology

Hypertension is a prevalent disorder involving 20–30% of adults in developed countries *(39)*. The definition of hypertension remains controversial. In the United Kingdom, hypertension is defined as BP exceeding 160/100 mmHg on two or more clinic readings, whereas in the United States the cutoff is 140/90 mmHg. Although, improved treatment of chronic hypertension has led to a reduction in the incidence of hypertensive emergencies *(40)*, recognition and treatment of hypertension in the general population are still not adequate *(41)*.

Clinical Features

HE is characterized by acute or subacute onset of lethargy, confusion, visual disturbances, and seizures *(2)*. Other symptoms may include headache, stroke, and/or papilledema *(38)*. Symptoms may or may not be associated with proteinurea or hypertensive retinopathy *(2)*. Seizures are often the initial presentation, and they may be focal, generalized, or focal with secondary generalization *(2)*. Initially, it was thought that the cerebral dysfunction associated with elevated BP was related to the uremia from kidney disease *(42)*. Table 4 gives frequency data for each of the presenting symptoms.

Pathophysiology

The endothelium plays an active role in controlling BP by regulating the release of nitric oxide (NO) and other vasodilator molecules *(2,43)*. Although the pathophysiology of HE is not fully understood, an initial abrupt rise in vascular resistance seems to be a necessary initiating step *(2)*. The sheer stress on the endothelial wall results in an initial burst of NO followed by steady-state release of NO, pro-

Table 4
Presenting Symptoms of Patients
Admitted With Malignant
Hypertension

Symptoms	No. of patients
Headache	10 (30%)
Stroke	9 (27%)
Cardiorespiratory	7 (21%)
Altered mental status	4 (13%)
Blurred vision	3 (9%)
Seizures	3 (9%)
Loss of consciousness	3 (9%)
Dizziness	1 (3%)
Asymptomatic	1 (3%)

(Adapted from ref. *38.*)

moting vasodilatation *(2,44)*. If the BP remains elevated, the compensatory mechanism may fail, causing more elevation in BP and endothelial damage. A cascade follows that increases endothelial cell expression of adhesion molecules and makes the endothelium more permeable *(2)*. Ultimately, the endothelial fibrinolytic activity may be inhibited and the coagulation cascade activated.

Cerebral blood flow (CBF) is regulated through a homeostatic mechanism referred to as autoregulation. Normotensive individuals maintain persistent CBF when their mean arterial pressure (MAP) stays in a range of 60–120 mmHg *(2)*. Hyperperfusion of the cerebral vasculature is blunted by a compensatory vasoconstriction of the blood vessels. This compensatory mechanism is overwhelmed at MAP of 180 mmHg, whereupon cerebral autoregulation breaks down and vasodilatation occurs. This results in breakdown of the BBB, which causes edema and possible microinfarcts. Previously normotensive patients can develop signs of HE at BPs as low as 160/100 mmHg, whereas individuals with chronic hypertension will tolerate pressure as high as 220/110 mmHg before signs of HE ensues.

Electrographic and Radiographic Features

There is no known characteristic EEG feature of HE. Loss of posterior dominant α-rhythm, generalized slowing, and posterior epileptiform discharges are seen on EEG. These findings usually resolve following clinical improvement *(45,46)*. Imaging of the brain in a hypertensive, confused, lethargic patient who develops seizures in the ICU is crucial. Although the clinical presentation of HE is characteristic, the intensivist must, especially if there are focal neurological signs present, exclude the presence of intracranial hemorrhage or other mass, which induces the elevation of systemic BP as a compensatory mechanism for cerebral perfusion. This is indeed a very common situation with ischemic or hemorrhage strokes, and many

times it is unclear whether it is the cause or the effect. As a general statement, if the volume of intraparenchymal blood is small, or if because of coexisting brain atrophy there is enough room inside the cranial cavity, the hemorrhage is probably the result of hypertension, with additional effect from a probably abnormal underlying vasculature.

In uncomplicated cases, cerebral imaging of individuals with HE shows edema in the cortex and subcortical white matter in the posterior areas of the brain (i.e., occipital, posterior parietal, and temporal lobes) *(47)*. The predilection for involvement of the posterior circulation may be caused by paucity of sympathetic neural control in the posterior cerebral artery territory in comparison to the carotid artery territory (48). Findings by Schwartz et al. of increased apparent diffusion coefficient (ADC) values and lack of high signal on the diffusion-weighted images (DWIs) support the theory that the edema associated with HE is vasogenic *(47)*.

Management

Patients should be admitted to the NICU for treatment and monitoring. An arterial line for continuous pressure monitoring should be placed immediately. If cerebral edema was present on the initial head CT image and the patient has a Glasgow Coma Scale score of 8 or less, an intracranial pressure (ICP) monitoring device should be placed. It is important to obtain a thorough past medical history for previous CVAs and renal disease. One should also inquire about antihypertensive medications and compliance. It is also paramount to ask for of over-the-counter medication use (i.e., sympathomimetics) and illicit drug use, such as cocaine.

The goal of therapy in HE is to gradually decrease the MAP by approx 25% or to reduce the diastolic BP to about 100 mmHg over a period of several minutes to hours. Precipitous reduction in BP to normotensive or hypotensive level should be avoided because it might provoke cerebral hypoperfusion and ischemia. Sodium nitroprusside is the drug of choice for the initial treatment of HE. Because of the effect of nitroprusside on ICP, other agents such as β-blockers or angiotensin-converting enzyme inhibitors should be used after the initial control of BP. Hydralazine appears to be less effective in treating HE. Clonidine should be avoided because of its potential for CNS depression *(47)*. Bed rest, sedation, and analgesia may further help BP control. Table 5 lists the most common antihypertensives used and their side effects. Treatment of HE-induced seizures is not different from the general treatment of ICU seizures, which are outlined in Chapter 14.

POSTERIOR LEUKOENCEPHALOPATHY SYNDROME

Posterior leukoencephalopathy (PLE) is a recently recognized neurological disorder. It is characterized by white matter edema in the posterior parietal and occipital lobes of the brain *(49)*. The term was first used by Hinchey et al. to describe 15 patients admitted with a wide variety of medical illnesses *(49)*. Of these, 7 were receiving immunosuppressive therapy, 4 had HE, and 3 were not hypertensive at all. In all patients, the neurological abnormalities resolved within 2 wk. This syn-

Table 5
Commonly Used Parenteral Antihypertensive Drugs

Medication	Mechanism of action	Bolus dose	Infusion rate	Pros	Cons
Sodium nitroprusside	Vasodilator	No bolus dose	0.25–10.0 µg/kg/min	Short duration of action	↑ CBF, ↑↑↑ ICP
				Immediate onset of action	Cyanide toxicity
Nitroglycerin	Vasodilator	50 µg iv	5–100 µg/kg/min	Short duration of action	↑ CBF, ↑↑ ICP
				Rapid onset of action	Methemoglobin production
Hydralazine	Vasodilator	2.5–10 mg iv every 20–30 min; max 40 mg	No drip	Good antihypertensive effect	Longer duration of action
					↑ CBF, ↑ ICP Glomerulonephritis, lupuslike syndrome, hemolytic anemia
Clonidine	α_2-Agonist	0.1–0.2 mg po	No drip	Might be helpful in alcohol withdrawal	↓ CBF
Labetalol	$\alpha_1, \beta_1, \beta_2$ Receptor antagonist	5–20 mg iv every 15 min: total of 340 mg	0.5–2 mg/min	Rapid onset of action; no effect on ICP	CHF Bronchospasm Bradycardia
Esmolol	β_1-Selective	500 µg/Kg over 1 min	50–200 µg/kg/min	Rapid onset of action; no effect on ICP	Bradycardia
Enalaprilat	ACE inhibitor	0.625–5 mg iv every 6 h	No drip	No effect on ICP or CBF	Could cause abrupt decrease in BP Potential ↑ ICP in patients with poor compliance Renal dysfunction

CBF, cerebral blood flow; ICP, intracranial pressure; CHF, congestive heart failure; ACE, angiotension-converting enzyme.

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drome has also been reported with uremia, hemolytic uremic syndrome, thrombotic thrombocytopenia purpura, cyclosporine A, cisplatin, interferon-α, intrathecal methotrexate, severe hypercalcemia, and indinavir *(50–52)*. For those patients who do not exhibit hypertension (children or adults), the syndrome of posterior reversible leukoencephalopathy has been coined *(49)*, although some believe that a term such as reversible occipital–parietal encephalopathy is more appropriate, because both gray and white matter are involved *(53)*.

Clinical Features

The most common presenting signs and symptoms of PLE syndrome include lethargy, confusion and somnolence, paucity of speech, headaches, and visual complaints. Lethargy and somnolence are often the first signs noted. Memory difficulties are not uncommon. Visual disturbances range from blurred vision to hemianopsia *(49)*.

Seizures are common at onset: 11 out of 15 (73%) of the originally reported patients had one or more seizures. They are usually generalized tonic–clonic but can also have a focal onset. Multiple seizures are more common than single seizures. SE has also been reported *(49)*. Seizures generally precede the other manifestations of the syndrome. Visual auras or visual hallucinations also precede the tonic–clonic or occipital seizures. Following a seizure, patients usually have a prolonged mental status change and a few end up in stupor or coma *(54)*.

Pathophysiology

The PLE syndrome shares similar pathophysiological mechanisms with HE and eclampsia. Two pathophysiological mechanisms have been proposed *(55)*. The first evokes cerebral vasospasm and cerebral ischemia as a cause of the changes seen on neuroimaging *(56)*. The second suggests a breakdown in cerebrovascular autoregulation with secondary vasogenic edema. Recent MRI findings support the autoregulation hypothesis *(57)*. The pathological process is characterized by cerebral edema and petechial hemorrhages, especially in the parieto-occipital and occipital lobes. Microscopically, these petechiae are ring hemorrhages around capillaries and precapillaries that are occluded by fibrinoid material *(58)*.

Radiological Features

The most common neuroimaging abnormality on both MRI and CT is white matter edema in the posterior areas of the cerebral hemispheres of patients with PLE syndrome. These changes are predominantly symmetrical and involve specifically the occipital, parietal, and posterior temporal lobes *(49)*. Other lesions are reported in the pons, thalamus, and cerebellum. The gray matter is involved in some patients and hence the term "Leukoencephalopathy" may not be the most appropriate *(57)*. Individuals with predominantly gray matter disease have a better course than those with predominantly white matter lesions. Brainstem lesions are found in 56% of patients *(57)*. On MRI, the high signal on DWI without the typical ADC

dropout suggests vasogenic edema *(47)*. This is referred to as pseudonormalization. Some patients with pseudonormalization can progress to having an infarct.

Management

Patients may need to be monitored in the NICU. Indications for transfer to the NICU include cerebral edema with midline shift and seizures. If the cause of PLE is found to be acute hypertension, then aggressive BP management should be initiated. Treatment paradigms are similar to those for HE. If a particular drug was thought to be the inciting agent, discontinuing the drug should be seriously considered. For seizures, BZDs are indicated as the agents of first choice. If seizures are refractory or recurrent, an additional anticonvulsant is indicated. The choice of anticonvulsant will depend on patient's general clinical condition and associated renal or liver abnormalities. For more details regarding treatment of ICU seizures, see Chapter 14.

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Infection or Inflammation and ICU Seizures

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SUMMARY

Effective treatment of seizures associated with central nervous system (CNS) infection and inflammation depends on rapid diagnosis and early attainment of bactericidal activity in the cerebrospinal fluid with appropriate antimicrobial agents, or appropriate management of vasculitis-induced cerebral complications. Despite the rarity of these disorders, there is nothing specific regarding the management in the intensive care unit of seizures in these situations, except for a high suspicion by the medical staff. Improvement in long-term neurologic outcome depends on both therapy of the infectious/inflammatory process and the intensive care multisystem monitoring commonly warranted in this patient population. The primary goal of preserving CNS function is shared by the neurologist and the intensivist, making a multidisciplinary approach essential.

Key Words: Central nervous system; infection; inflammation; intensive care unit; seizures.

INTRODUCTION

Seizures in critically ill patients are potential markers or contributors of significant morbidity and mortality. Seizures are a relatively common neurologic manifestation in patients admitted to an intensive care unit (ICU) and are not uncommonly associated with infection. Of 217 patients admitted to a general medical/coronary ICU with neurologic complications of a nonneurologic primary diagnosis, 28% of neurologic complications were seizures, second only to metabolic encephalopathy *(1)*. Sepsis was the second most common cause of seizures after vascular lesions. In any patient presenting with fever and seizures, central nervous system (CNS) infection and inflammation need to be considered in the differential diagnosis. CNS infections are markedly different from systemic infections because of the closed anatomic space of the CNS, its immunological isolation from the rest

of the body, and the often nonspecific nature of the key manifestations. Early recognition of seizure activity and aggressive management are essential to patient recovery and prevention of long-term neurologic sequelae. This chapter focuses on the significance of seizures in both systemic and CNS infection and inflammatory conditions.

The spectrum of clinical manifestations of CNS infection and inflammation is vast. Seizures complicate many nervous system infections, some commonly, such as meningitis, herpes simplex encephalitis, and cerebral malaria. The patient may present in a life-threatening state, as seen in full-blown meningoencephalitis, or in an asymptomatic state, as seen in the dormant stages of spirochete infections. Common CNS infections that may require critical care are meningitis, ventriculitis, encephalitis, and brain abscess.

CNS INFECTIOUS DISORDERS

Meningitis

Meningitis is the inflammation of the pia and arachnoid membranes (leptomeninges) that surround the brain and spinal cord *(2)*. The classification of meningitis includes acute, aseptic, and septic syndromes (<4 wk duration), recurrent meningitis (multiple acute episodes of <4 wk each), and chronic meningitis (>4 wk duration).

Acute aseptic meningitis, defined by negative routine screening cultures and stains of cerebrospinal fluid (CSF), is the most common form of meningitis *(3)*. This usually starts with high-grade fever and severe headache. Associated problems such as nausea, vomiting, pharyngitis, diarrhea, neck stiffness, and photophobia may occur. Seizures are not a common manifestation. Rapid and complete recovery is the usual course. Viral infection is commonly the cause of aseptic meningitis. Between 55 and 70% of cases are caused by enteroviruses (echovirus, Coxsackie A and B, poliovirus, and the numbered enteroviruses) *(3,4)*.

Other causes of aseptic meningitis include human immunodeficiency virus (HIV), parasites, rickettsiae and mycoplasma, and autoimmune diseases such as Behçet's disease, Kawasaki disease, and Vogt–Koyanagi–Harada disease *(2)*. Malignancies and drug reactions have also been implicated. In a population-based study, the 20-yr risk for unprovoked seizures was 2.1% after aseptic meningitis, not increased over the general population risk for unprovoked seizures *(5)*.

Acute septic meningitis is the bacterial infection of the meninges. It is a neurologic emergency with mortality and morbidity rates as high as 25 and 60%, respectively *(6)*. The classical presentation of septic meningitis includes fever, headache, reduced alertness, and meningeal irritation. Seizures have been reported to occur in 5–28% of cases *(7–10)*. One retrospective review of 103 episodes of acute bacterial meningitis in adults found documentation of seizures in 29 cases (28%) *(10)*. The relatively high incidence may reflect a large number of *Listeria monocytogenes* cases, which are more commonly associated with seizures. Seizures were usually observed within 24 h of presentation (76%). Seizure activity was an independent

predictor of mortality in this series (34% mortality in patients with seizures vs 7% without seizures; odds ratio [OR] 17.6, *p* < 0.001). Decreased level of consciousness on presentation was also predictive of death (26% vs 2%). Coma can be a consequence of fulminant bacterial meningitis with diffuse cerebral edema leading to cerebral herniation. Multiple cerebral infarcts secondary to vasculitis have also been described *(11)*. Systemic complications can occur in 22% of patients *(8)*, with septic shock in 12%, pneumonia in 8%, and disseminated intravascular coagulation in 8%.

In a univariate analysis, patients with bacterial meningitis had a poorer prognosis if the following were present: age greater than 60 yr and coma at onset or focal seizures within the first 24 h of admission (72% vs 18% mortality among those without early-onset seizures; *p* < 0.001) *(7)*. This large retrospective study from the Massachusetts General Hospital evaluated 445 patients with acute bacterial meningitis between 1962 and 1988 *(7)*. Seizures occurred in 23% of 493 episodes of meningitis. They were focal in 7%, generalized in 13%, and not characterized in 3%. In two-thirds of cases, seizures occurred within 24 h of admission, and more than one-third of early seizure patients had a history of alcoholism. *Streptococcus pneumoniae* was more frequently found in patients who developed seizures (58% vs 30% in patients without seizures; *p* < 0.001), but alcoholism was a confounding factor.

Seizures in a patient with meningitis warrant a neuroimaging study (ideally a contrast-enhanced computed tomography [CT] scan or magnetic resonance imaging [MRI]). Seizure is a manifestation of cortical irritation, and its occurrence may indicate a cortically based complication (empyema, stroke, venous thrombosis). Cortical venous thrombosis usually presents with seizures and focal neurological signs. However, it is an uncommon event during bacterial meningitis: in a large series, only 5.1% of autopsies of patients who died from meningitis revealed septic cortical vein thrombosis *(12)*. Occurrence of seizures requires rapid treatment with anticonvulsants. Prophylactic anticonvulsants have no established benefit. Patients with persistent alteration in mental status or coma should undergo electroencephalography (EEG) to rule out subclinical seizures. Continuous EEG monitoring (CEEGM) may be a better option in these cases. Jordan used CEEGM to evaluate 200 patients admitted to a neurological intensive care unit (NICU). The study had decisive or contributing impact on clinical decision making in 12 of 13 patients with intracranial infection *(13)*.

Recurrent meningitis can be caused by infectious and noninfectious causes. Viruses are the most likely infectious agents. The clinical presentation may resemble aseptic meningitis. Mollaret's meningitis is a type of recurrent aseptic meningitis associated with Epstein–Barr virus (EBV) and herpes simplex virus (HSV) type I *(14,15)*. Epileptic seizures are part of the clinical presentation of Mollaret's meningitis *(16)*.

Chronic meningitis has a nonspecific presentation, with variable fever, headache, neck rigidity, and signs of parenchymal involvement, such as altered mental

status, seizures, or focal neurologic deficits *(2)*. Infectious causes are commonly CNS tuberculosis and cryptococci. Noninfectious causes include neoplasms, neurosarcoidosis, and CNS vasculitis *(2)*.

Empiric antibiotic therapy for a suspected bacterial CNS infection should be given in consideration with the patient's age, competence of the immune system, and associated morbidities. An immune-competent adult should be started on a third-generation cephalosporin (4 g/d ceftriaxone or 8–12 g/d cefotaxime) with the addition of ampicillin (12 g/d) for patients over age 50 yr who are more susceptible to *Streptococcus agalactiae* and *L. monocytogenes*. Immune-compromised adults, including patients with lymphoreticular tumors and those receiving cytotoxic chemotherapy or high-dose corticosteroid treatment, should be treated with ampicillin and a broad-spectrum cephalosporin such as ceftazidime (6 g/d), which has more activity against Gram-negative organisms *(5)*.

Neurosurgical patients, including those with CSF shunts, and head trauma patients require both Gram-positive and Gram-negative coverage with a recommended combination of vancomycin (2–3 g/d) and ceftazidime (6 g/d) *(5)*. In areas with known high penicillin-resistant *S. pneumoniae* isolates, empiric therapy should also begin with vancomycin and a third-generation cephalosporin. Clinically significant *S. pneumoniae* resistance to vancomycin has not been documented *(17)*. Seizure treatment in the context of acute or chronic meningitis is not different from the treatment offered for seizures from other causes, and details can be found in Chapter 14.

Encephalitis

Encephalitis is an acute infection of brain parenchyma and should be suspected in a febrile patient who presents with altered mental status and signs of diffuse cerebral dysfunction. Encephalitis is usually caused by viral infection, most commonly HSV (15% of cases), varicella zoster virus (VZV), EBV, mumps, enteroviruses, lymphocytic choriomeningitis virus (LCM), and togaviruses *(18)*. The route of invasion is varied and can be the bloodstream, the skin through an insect bite, or the respiratory or digestive system. Specific viruses can have characteristic presentations, such as parotitis associated with mumps and herpetic rash with herpes simplex encephalitis (HSE). Diplopia, dysarthria, and ataxia can be seen in immunocompromised patients with brainstem HSE *(19,20)*. Clinical presentation often includes a prodrome with fever, headache, and myalgia and mild respiratory infection. Changes in level of consciousness, with focal neurological deficits, may follow.

Seizures, both focal and generalized, are a common manifestation of the encephalitides. They can occur in the acute infection stage, when the patient is admitted to an ICU, or later in life. They can be easily controlled with antiepileptic medications, but many times they become intractable. Epilepsy surgery may be a better option if there is a clearly localized focus. In a series of 38 patients who developed medically intractable partial seizures, Marks et al. found that 16 of the

patients had a history of meningitis and 22 had encephalitis. Meningitis was pathologically associated with mesial temporal sclerosis and encephalitis with neocortical foci. However, in patients with encephalitis at less than age 4 yr, seizures were also associated with mesial temporal sclerosis *(21)*. In another population-based study, Annegers et al. found that the risk of developing unprovoked seizures within 20 yr was 22% in patients with viral encephalitis and early seizures, 10% for those with viral encephalitis without early seizures, 13% in patients with bacterial meningitis and early seizures, and only 2.4% in patients with bacterial meningitis without early seizures *(5)*.

Japanese Encephalitis

Japanese encephalitis (JE) is the most important epidemic viral encephalitis in the world, causing an estimated 50,000 cases annually *(22)*. Mortality is 30%, and half the survivors are left with severe neurologic sequelae *(23,24)*. Although JE virus is confined mainly to Asia, related neurotropic flaviviruses include West Nile virus, Murray Valley encephalitis virus, and tick-borne encephalitis virus, which cause similar diseases in other geographical locations *(25–27)*. JE virus is neurotropic and replicates rapidly in neurons, causing a perivascular inflammatory reaction that results in infection, neuronal dysfunction, and death *(28)*.

Solomon prospectively studied 144 patients infected with JE virus (134 children and 10 adults) *(29)*. JE virus was diagnosed by means of antibody detection, culture of serum and CSF, and immunohistochemistry of autopsy material. Forty patients (28%) had a witnessed seizure during the admission; of these, the majority (24 of 40; 62%) died or had a poor outcome compared with 26 of 104 (14%) in the group with no witnessed seizure (OR 4.5; 95% confidence interval [CI] 1.94–10.52). Patients with more than one witnessed seizure (29 of 40) were more likely to have a poor outcome (21 of 29; 72% died or had severe sequelae) compared with patients with a single seizure (4 of 11; 33% poor outcome; OR 5.25; 95% CI 1.02–29.4). Ten of 18 patients who had generalized tonic–clonic (GTC) seizures and all 15 patients with subtle clinical manifestations of seizures (twitching of a digit, eyebrow, nostrils, excess salivation, irregular breathing, eye deviation with or without nystagmus) were in status epilepticus (SE). These patients had a higher mortality than those without development of SE (44% [11 of 25] vs 0% of 15).

The acute background EEG patterns were also associated with outcome in this study. Of 234 EEGs performed on 55 patients, poor outcome was associated with acute EEG findings of slow nonreactive, low-amplitude, burst suppression, or isoelectric patterns in 16 of 19 patients (84%) compared with poor outcome in 14 of 36 patients (39%), with findings of slow reactive or normal EEG patterns (OR 8.4; 95% CI 1.8–44.5). Independent predictors of poor outcome by logistic regression in this patient cohort were comatose state, more than one witnessed seizure, herniation syndrome, and illness for 7 d or more. Patients with seizures were more likely to have elevated opening pressure on lumbar puncture ($p = 0.03$) and to develop brainstem signs consistent with a herniation syndrome ($p < 0.0001$). It is possible that these events are related.

Seizures increase cerebral blood flow and, therefore, intracranial volume, resulting in increased intracranial pressure (ICP) *(30)*. If seizures are prolonged, cerebral edema may occur secondary to numerous metabolic consequences including hypoxemia, hypoglycemia, increased lactate production, low CSF glucose, high CSF lactate, metabolic acidosis, and carbon dioxide retention if airway management is suboptimal *(31,32)*. Cerebral edema causes further increase in ICP and may predispose an already inflamed brain to life-threatening compartmental shifts through the tentorium and foramen magnum, resulting in herniation syndromes. Although it is not possible from this study to determine whether seizures are a cause or a marker of severe disease, anticonvulsant prophylaxis in this patient population and aggressive surveillance for and management of seizures may improve outcome. Over 30% of patients with seizures had subtle manifestations that might have been missed without EEG recording.

Herpes Simplex Encephalitis

HSE, usually caused by HSV-1, is the most important form of treatable encephalitis. HSE is a medical emergency; prognosis depends on the patient's condition once treatment is started *(33)*. HSE has a mortality rate of 50–70% with significant long-term morbidity in survivors, including seizures and cognitive and behavioral disorders *(34)*. In a retrospective study from New Zealand, patients with HSE presented with acute-stage seizures in 50% of cases, and seizures constituted the fourth most common presenting symptom after headache, confusion, and nausea/vomiting. Thirty-four of 49 initial patients were followed for an average of 2–6 yr; 24% of them had developed epilepsy. In this series, the frequency of seizures was not different between patients with good and poor outcomes. However, the presence of bilateral epileptiform abnormalities was more common among those with poor outcome (0 of 18 with good outcome vs 5 of 10 with poor outcome; *p* < 0.01) *(35)*.

HSE has a predilection for the temporal and orbitofrontal lobes, resulting in a clinical picture of altered consciousness, memory loss, personality change, and confusion or olfactory hallucinations, following a prodrome of headache and fever *(33)*. MRI shows typical asymmetrical changes in the anterior and medial temporal lobe, inferior frontal lobe, insular cortex, and splenium of the corpus callosum on fluid-attenuated inversion recovery (FLAIR) sequences as early as day 2 *(34)*. Diagnosis of HSE is highly sensitive and specific, and CSF polymerase chain reaction (PCR) is used to amplify viral DNA and MRI findings.

EEG should be performed when encephalitis is suspected, to distinguish focal encephalitis from generalized encephalopathy and to look for abnormal findings of HSE. Diffuse, bihemispheric slow waves and triphasic waves as in hepatic failure may suggest encephalopathy. Although no specific EEG patterns are pathognomonic of HSE, focal or lateralized EEG abnormalities in the presence of encephalitis are highly suspicious *(36)*. Early changes in HSE may be nonspecific spike–slow wave activity, Δ waves, or triphasic waves that evolve into the typical 2- to 3-Hz unilateral periodic lateralized epileptiform discharges (PLEDs), originating from the temporal lobes, seen in 84% of typical patients with HSE *(37)*. Periodic dis-

charges tend to occur only during the acute stage and may disappear on the side of initial involvement before appearing on the newly involved side. When present bilaterally, they often occur in a time-locked relationship with each other *(37)*. Their appearance later in the disease course may indicate a recurrence *(36)*. EEG findings in either the acute stage or on long-term follow-up have not been shown to predict survival or severity of neurologic disability *(36)*. In addition, the relationship between epileptiform abnormalities and occurrence of seizures has been reported as inconsistent *(36)*. Lai and Gragasin found that among nine patients who had seizures in the acute stage of HSE, only four had epileptiform abnormalities on EEG; another four patients with no evidence of clinical seizure activity had nonperiodic epileptiform discharges on EEG *(36)*.

Specific treatment with acyclovir is indicated in HSE, at a dosage of 10 mg/kg every 8 h for 10–14 d. Supportive therapy also includes aggressive management of elevated ICP and treatment of seizures, usually with intravenous phenytoin (PHT). In patients with proven HSE, treatment with acyclovir significantly increases likelihood of survival to 65–100% if disease is present for 4 d or less *(38)*. Other studies still predict 25% mortality, even if acyclovir is started within 5 d of symptom onset *(39)*. Cerebral edema, persistent vegetative state, and systemic infection are the usual predictors of a fatal outcome. Other risk factors for poor prognosis include MRI abnormalities, bilateral EEG abnormalities, and focal hyperperfusion on single-photon emission computed tomography (SPECT) *(40,41)*. Only half of patients return to their previous or similar level of productivity *(42)*. Although there are no randomized studies in humans, seizure prophylaxis should be instituted, in our opinion, in every patient with proven HSE. In a rabbit model prophylactic administration of phenobarbital (PB) daily reduced mortality significantly *(43)*. If treatment is started, it should be continued for at least 1 yr (if there were acute-stage seizures present). Discontinuing the treatment may be decided on the basis of late seizures or EEG findings. Pathologically proven chronic HSV-1 encephalitis has been reported in patients with medically intractable seizures many years after the clinical acute encephalitis syndrome *(44)*.

Brain Abscess

A brain abscess is a purulent infection of brain parenchyma. It occurs most commonly in children age 4–7 yr and in the third decade in adults *(18)*. It commonly presents with site-specific focal neurological deficits such as aphasia and weakness. However, a focal exam may be absent, and many patients present with signs of increased ICP. General manifestations of increased ICP include headache, change in mental status, and nausea and vomiting *(45)*. Fever is less common. Neck rigidity may be present in 25% of cases and may indicate associated meningitis *(46)*. Seizures, often of the GTC type, can occur in up to 40% of cases *(47)*.

The route of transmission is usually contiguous spread from a local primary focus such as paranasal sinusitis, otitis media, mastoiditis, or penetrating head trauma. Ten percent of cases spread hematogenously, usually from a pulmonary

source such as bronchiectasis or lung abscess, but also from heart valves (infective endocarditis) or conditions causing a right-to-left shunt such as cyanotic heart disease in children, Weber–Osler–Rendu syndrome, and patent foramen ovale in adults *(46)*. A single abscess is usual with contiguous spread, but multiple abscesses are seen in 20% of cases of hematogenous seeding *(47)*. Blood cultures in the presence of an intracranial abscess are usually negative. The cause of cerebral abscesses is polymicrobial in 30–60% of cases, and anaerobic organisms are identified in about 30% of all isolates *(47)*. The most common infectious agents are streptococcal species, especially *Streptococcus milleri*. Other organisms include *Bacteroides* species, the Enterobacteriaceae family and *Staphylococcus aureus (18)*. *L. monocytogenes*, as well as mycobacterial, fungal, and parasitic agents, may be causative in immunosuppressed patients. Brain abscesses with *Mycobacteria* and *Nocardia* often have associated pulmonary involvement *(18)*.

The incidence of postoperative epilepsy in 56 patients with a supratentorial abscess was 38% in one study, of which 6 (11%) had seizures before operation *(48)*. Although the first seizure occurred in 70% during the first year, the occurrence of late seizures was not uncommon. Preoperative epilepsy was not a risk for postoperative seizures *(48)*. Parietal lobe location of abscess had the highest incidence of epilepsy (100%). In a population-based study from Olmstead County, Minnesota, epilepsy was found in 5 of 18 (28%) surviving patients with brain abscess *(49)*.

Treatment of brain abscess requires antibiotic therapy, prophylactic anticonvulsants, and often surgical intervention. Empiric antibiotic coverage with a third-generation cephalosporin and metronidazole is acceptable, but metronidazole should be replaced by oxacillin or vancomycin for staphylococcal species or with a history of trauma or a recent neurosurgical procedure *(47)*. *Pseudomonas aeruginosa* should be treated with ceftazidime. Oral antibiotics for up to 3 mo usually follow a 4- to 8-wk course of intravenous antibiotics *(18)*. Glucocorticoid therapy is recommended if cerebral edema is significant, especially with early signs of cerebral herniation *(18)*.

Definitive therapy with surgical excision and debridement of the abscess is recommended for posterior fossa lesions. The presence of a thick fibrotic capsule and impending rupture into the ventricles *(50)* implies a higher risk of residual neurologic deficits with this surgical approach, making aspiration a safer procedure; nevertheless, repeat operations may be required, including excision. Medical therapy alone may also be a reasonable option for patients who are high surgical risk, for multiple small abscesses, or when there is high suspicion of *Toxoplasma* infection. Treatment of seizures resulting from a brain abscess is not different from the treatment of seizures resulting from other causes. More information is available in Chapter 14.

Prophylactic treatment is controversial, and no randomized studies exist. Location of the abscess (parietal lobe), extension to the cortex, concurrent meningitis, or surgical treatment (craniotomy) would make us strongly consider starting the ICU patient on prophylactic antiepileptic treatment. The duration of the treatment, either

after a seizure or prophylactically, is also unknown, but we would recommend treating for at least the duration of the antimicrobial treatment (usually 3–6 mo).

Intracranial Extra-Axial Pyogenic Infections

Epidural abscesses and subdural empyemas are bacterial infections within the extracerebral spaces. Epidural abscesses, which usually occur in the frontal region, can present with headache, fever, and nausea, although neurological symptoms and complications are quite rare because of the protective effect of the tight adherence of dura to overlying skull. A subdural empyema, which is most commonly situated over the cerebral convexity, can cause altered level of consciousness, focal neurologic deficits, and seizures. The spread of infection through the subdural space can cause inflammation of the brain parenchyma and result in edema, elevated ICP, septic thrombophlebitis, venous infarction, or mass effect *(18,51)*. These extra-axial infections may result as a complication of trauma, neurosurgical procedures, meningitis, sinusitis, and other extracranial sources of infection. Otorhinogenic spread occurs mostly via the valveless emissary veins, allowing superficial infections to drain into the dural sinuses, causing thrombophlebitis with infection of the subdural or epidural space *(18)*. Subdural empyemas and epidural abscesses are commonly caused by staphylococcal species. Forty percent of cases can be polymicrobial *(18)*. Streptococci, followed by staphylococcal organisms and anaerobes such as *Propionebacterium* and *Peptostreptococcus*, are the most common causes *(18)*. Seizures are uncommon with epidural abscess and relatively common with subdural empyema. In a period of 14 yr, 25 patients were retrospectively identified in a Taiwanese hospital: 15 with subdural empyema and 9 with epidural abscess. Seizures were found in 54% of patients: in only 1 patient with epidural abscess and in 12 of 15 (80%) patients with subdural empyema *(52)*. The same pattern of rarity of seizures with epidural abscess and relative frequency with subdural empyema is also encountered in children *(53)*.

A study of 89 patients with subdural empyema was conducted to assess the incidence of late seizures *(54)*. Mortality was 24 of 89 (27%). The incidence of early seizures was similar in those who died (62.5%) and those who survived (63%). All patients received anticonvulsant prophylaxis, which was continued for 12–18 mo. Early seizures were more common when paranasal sinusitis was present but did not correlate with occurrence of late epilepsy. Of patients with follow-up, 29% who had early seizures had further attacks; of patients with no early seizures, 42% developed epilepsy during the follow-up period, most within the first 2 yr *(54)*. No factors were identified that predicted the occurrence of late seizures.

Subdural empyema can be treated with intravenous antibiotic therapy, with either a third-generation cephalosporin and metronidazole, or piperacillin with tazobactam, followed by early surgical evacuation *(47)*. A prophylactic anticonvulsant is recommended. Craniotomy is generally preferred to multiple burr holes (54). Antibiotics should be continued for 2–6 wk and may be considered to be the only therapy for fluid collections less than 1 cm in diameter with rapid clinical improvement *(55)*.

Ventriculitis

Ventriculitis is a pyogenic infection of the ventricular cavity. Arbitrary criteria for diagnosis include a CSF white blood count greater than 200/mm^3, or positive culture of the ventricular fluid *(56)*. The ventricles may act as a reservoir for persistent inflammation, which may block the CSF outflow tracts and act as a brain abscess *(56)*. The most common infecting organisms are staphylococcal species. Thirty percent of all meningitides may be associated with ventriculitis, and over 90% of neonatal meningitis is complicated by ventriculitis *(51,57)*. This infection should be considered in patients with meningitis who do not quickly respond to antibiotics. Ventriculitis is frequently associated with CSF shunts. Intracranial devices, intrathecal chemotherapy, and rupture of a periventricular abscess through the ependyma can also increase the risk for ventriculitis. The incidence of seizures in ventriculitis is not known, although it is probably similar to meningitis, given the frequent co-occurrence of the two conditions.

A common cause of ventriculitis is shunt placement. Seizures are more frequent after shunt placement. In an older study, 18.2% of 99 patients with ventriculitis who were not shunted developed seizures vs 65.4% of those receiving a shunt for hydrocephalus. EEG abnormalities were also more common in the shunted group (95%) than in the nonshunted group (47%) *(58)*. In another study 15.2% of children younger than age 1 yr with ventricular shunts developed postshunt epilepsy, in contrast with only 6.9% of patients older than 50 yr *(59)*. Most studies evaluating seizures and hydrocephalus are in children.

Patients with CNS malformations and mental retardation have the highest risk of postshunt seizures *(60)*. A large retrospective study of children and adults from Oregon reported an increase in incidence of epilepsy (based on long-term administration of antiepileptic drugs [AEDs]) from 12% before shunt insertion to 33% 10 yr later. The hazard rate was 2%/yr. The cause of hydrocephalus was a strong determinant of epilepsy (patients with posthemorrhagic hydrocephalus had the highest risk, and those with myelomeningocele had the lowest). Interestingly, CSF shunt infection was not associated in this series with increased risk for epilepsy *(61)*. This finding was not confirmed in a later study in children shunted for hydrocephalus: children with shunt malformation, infection, or a combination of these had higher incidence of epilepsy *(62)*. Thus, shunt-related ventriculitis may or may not increase the incidence of seizures; the independent effect of infection has not been compared with purely ventricular catheter or shunt placement (which is generally agreed to increase incidence of seizures).

Treatment of ventriculitis requires externalization or removal and replacement of the infected intraventricular device. Vancomycin is preferred in acute Gram-positive ventriculitis because of the increasing resistance patterns to β-lactam antibiotics *(63)*. Although vancomycin adequately penetrates the blood–brain barrier when the meninges are inflamed, CSF drug concentrations may be compromised in the case of ventriculitis or an improving bacterial meningitis, where the meningeal inflammatory response may be less extensive *(64)*. CSF penetration of vancomycin

may be negligible under these conditions, and intraventricular instillation of antibiotic may achieve adequate concentrations and be necessary for successful eradication *(65)*. Treatment of Gram-negative ventriculitis is more controversial: most studies show no significant clinical benefit with intrathecal administration of gentamicin or amikacin *(66,67)*. The intrathecal or intraventricular instillation of antimicrobials may be a risk factor for seizures. One should consider the prophylactic use of AEDs in such cases, especially if there is cortical irritation by periventricular drain catheter hematoma.

HIV Infection and Seizures

New-onset seizures (NOS) are not uncommon in HIV patients, occurring in 3% of patients in a prospective study and between 11 and 17% of HIV patients in retrospective studies *(68–73)*. Seizures are usually seen in the advanced stages of the disease, although they may occur early or as the presenting symptom of HIV infection *(74)*. Von Paesschen found that out of 68 selected patients with seizures, 62 had acquired immunodeficiency syndrome (AIDS) and only 6 patients had AIDS-related complex or just HIV seropositivity *(74)*. Although most patients have generalized seizures, partial seizures, both simple and complex partial, may be seen in patients with diffuse brain disease such as HIV encephalopathy or meningitis *(74)*. The reported incidence of convulsive SE is 8–18% and is often associated with poor prognosis *(68,70,71)*. The most common EEG finding is nonspecific diffuse slowing; focal slowing with epileptiform activity is infrequent *(68,70)*.

The pathophysiology of generalized seizures and SE in HIV-infected patients may be related to lowered threshold for cortical excitability and impaired inhibitory mechanisms for terminating seizures once started *(75)*. In the majority of patients, seizures are associated with an underlying intracranial mass lesion, infection, or metabolic disturbance (Table 1). Intracranial mass lesions, including opportunistic infections, neoplasms, and cerebrovascular disease, make up almost half of neurological disorders in AIDS patients *(70)*. These are all commonly associated with seizures. Wong et al. *(70)* reported on 70 of 630 (11%) HIV-positive patients who presented with NOS. Generalized seizures occurred in 94% of patients, partial in 26%, and SE in 14%. An associated space-occupying lesion (SOL) or CNS infection was found in 38 patients (54%) with the following diagnoses: cerebral toxoplasmosis (11 patients), CNS lymphoma (8 patients), metabolic derangements (8 patients), cryptococcal meningitis (7 patients), and vascular infarction (4 patients). In this series, PHT was associated with adverse drug reactions in 16 of 62 (26%) of patients who received it.

Toxoplasmosis, the most common cause of intracranial mass lesion in AIDS, presents with seizures as an early manifestation 15–40% of the time *(68)*. The incidence of diagnosing toxoplasmosis in HIV-infected patients with NOS ranges from 12 to 28% *(68,74,76)*. Timely identification and treatment of toxoplasmosis with sulfadiazine and pyrimethamine is important for clinical improvement.

The second most common intracranial mass lesion producing seizures in AIDS patients is CNS lymphoma. Other focal CNS lesions include brain abscess (tuber-

Table 1
Common Causes of Seizures in HIV-Infected Patients

Intracranial space occupying lesions
    CNS lymphoma
    Brain abscess (*Tuberculoma, Cryptococcus, Nocardia*)
Opportunistic infection
    Cerebral toxoplasmosis
    Cryptococcal meningitis, tuberculous meningitis
    Cytomegalovirus encephalitis
    Cysticercosis
    Progressive multifocal leukoencephalopathy
Metabolic derangements
    End-stage renal disease
Drugs
    Foscarnet
    Perinatal exposure to nucleoside analogs (febrile seizures)
Other
    Vascular infarction
    HIV-associated dementia

culous, cryptococcal, nocardial), tuberculomas, syphilitic gummas, and cerebrovascular diseases. Progressive multifocal leukoencephalopathy (PML), although a white matter disease without significant mass effect, can produce seizures, either partial or generalized *(77)*. The mechanism may involve lesions adjacent to cerebral cortex, axonal conduction abnormalities, or disturbance of the neuron–glia balance *(75)*. Meningitis and encephalitis as a cause of NOS in HIV-infected patients ranges from 12 to 16%, with cryptococcal meningitis being the most frequent meningoencephalitis-producing seizures *(68,70,71,75,76)*. Subacute sclerosing panencephalitis has emerged in HIV-infected children in developed countries and often presents with seizures and encephalopathy *(75)*. Other less common infectious causes of seizures in AIDS patients include aseptic meningitis, neurosyphilis, herpes zoster leukoencephalitis, and cytomegalovirus encephalitis *(76)*.

In 6–46% of reported HIV patients with NOS, no identifiable cause is found, and the etiology of seizures is attributed to the HIV infection itself *(68–73)*. In one study, HIV encephalopathy was responsible for seizures in 24% of patients *(68)*. In another series, 41% of patients had cerebral atrophy identified as the only lesion on CT scan *(71)*. Dore et al. found that 18% of patients with NOS of no identifiable etiology were taking foscarnet, which was postulated as potentially epileptogenic *(76)*. Modi et al. *(73)* studied 15 HIV-infected heterosexual patients from South Africa who presented with NOS as the sole neurologic manifestation and were taking no medications. The patients were predominantly female, with mean age 31 yr, and mean latency of 1.6 mo between discovery of HIV positivity and seizure onset. Sixty percent had AIDS-defining CD4^{+} T-lymphocyte counts, and there was a high

prevalence of pulmonary tuberculosis and multiple nonneurologic illnesses. Thirteen patients had generalized seizures and 2 presented with SE. Their EEG findings were normal in one-third, and 40% showed a generalized epileptic disturbance (GED). Despite normal neurologic exam excluding dementia, normal CSF analysis (apart from presence of HIV), and normal CT/MRI scans of the brain, SPECT scans of the brain showed abnormal left or right temporal lobe perfusion deficits. The restricted temporal lobe hypoperfusion may represent a focal metabolic abnormality or encephalopathy induced by the HIV virus that is postulated to manifest as seizures. SPECT scan showing multiple or focal uptake defects is also reported as very sensitive in detecting the early stages of AIDS dementia *(78)*. Postmortem neuropathological examination of the brain in 17 patients who had experienced NOS without identifiable cause showed microglial nodules or multinucleated cells or both in 6 patients, suggesting that the HIV infection was the likely cause of the seizures *(70)*.

The likely pathophysiology of seizures in HIV-infected patients without identifiable etiology relates to the role of HIV infection in the brain. Specifically, HIV- or immune-related toxins produced by interactions between macrophages, microglia, monocytes, and astrocytes may injure or kill neurons *(75)*. Neurotoxic substances, including eicosanoids, platelet-activating factor, quinolate, cysteine, cytokines, and free radicals, increase glutamate release, activate voltage-dependent calcium channels and channels operated by *N*-methyl-D-aspartate (NMDA) receptors, leading to calcium influx and neuronal death. Neurotransmitter imbalances may also predispose to seizures.

Seizures are generally a poor prognostic indicator in HIV-infected patients and will likely recur. Therefore, treatment is recommended for patients experiencing a first seizure without a reversible cause. In view of potential drug–drug interactions as a result of hepatic enzyme induction, and drug–disease interactions caused by reduced concentrations of protease inhibitors and therefore antiviral efficacy *(79)*, the anticonvulsant of choice is ideally one that has no effect on viral replication, has limited protein binding, and does not have effects on the cytochrome P450 system *(80)*. Candidates include gabapentin, topiramate, and tiagabine. Most nucleoside reverse transcriptase inhibitors are renally metabolized through glucuronidation by enzyme systems other than cytochrome P450 and thus do not affect the hepatically metabolized AEDs. On the other hand, the nonnucleoside reverse transcriptase inhibitors (like nerivapine, delaviradine, and efivanenz) use the cytochrome P450 system and may lead to either induction (efivarenz) or inhibition (nevirapine and delaviradine), affecting the antiepileptics that use these systems (Table 2) *(81)*.

The intensivist should also remember that the HIV-protease inhibitors are substrates for and inhibitors of the hepatic CYP3A enzyme system and can affect AED concentrations. Carbamazepine (CBZ) at a dose of 200 mg/d for post-zoster meralgia reached antiepileptic therapeutic levels in an HIV patient receiving triple antiretroviral therapy (indinavir, zidovudine, and lamivudine). On the other hand,

Table 2
Antiepileptic and HIV–Protease Inhibitor (PI) Interactions

Antiepileptic	Protease inhibitor	Interaction
Phenytoin	RI, SA, IN, NE	Increase PHT levels; decreased PI efficacy
Phenobarbital	RI, SA, IN, NE	Decreased PI efficacy
Valproic acid	RI	Decreased valproate efficacy
Diazepam	RI, SA, IN, NE	Increased diazepam toxicity; contraindicated
Clonazepam	RI, SA, IN, NE	Increased clonazepam toxicity; substitute clonazepam
Lamotrigine	RI	Decreased lamotrigine efficacy
Topiramate	RI	? Increased topiramate toxicity
Tiagabine	RI, SA, IN, NE	Increased tiagabine toxicity
Felbamate	RI, SA, IN, NE	Decreased PI efficacy
Ethosuximide	RI	Increased ethosuximide toxicity; substitute or decrease dose
Gabapentin	—	—
Vigabatrin	—	—

RI, ritonavir; SA, saquinavir; IN, indinavir; NE, nelfinavir.
(Adapted from ref. *82*.)

indinavir plasma concentrations decreased significantly and HIV-RNA became detectable during the period of CBZ treatment *(82)*.

In addition to drug–drug metabolic interactions, the intensivist should consider hypoalbuminemia, a common situation in the ICU and in HIV-seropositive patients. Highly protein-bound AEDs (PHT, valproic acid [VPA], CBZ, clonazepam, diazepam) may displace highly protein-bound antiretroviral drugs (delaviradine, efivanez, saquinavir vitonavir, nelfinavir, lopinavir, and ampenavir) or vice versa, leading to toxic free concentrations of either drug *(83)*. The HIV-induced hypergammaglobulinemia may also predispose patients to hypersensitivity reactions from antiepileptics, especially PHT *(84)*.

PHT remains the most widely prescribed anticonvulsant for these patients, although side effects, including skin rashes, leukopenia, thrombocytopenia, and hepatic dysfunction, are common *(70,75)*. VPA should be avoided if possible, because it has been shown to stimulate HIV replication in vitro *(80,85,86)*. However, in a retrospective study of manic HIV-positive patients who were taking divalproex sodium and antiretrovirals, the HIV-1 viral load did not increase. One patient who was not taking antiretrovirals had a 0.17 log viral load increase *(87)*.

VASCULITIDES

Vasculitides comprise a heterogeneous group of multisystem disorders characterized by inflammation and necrosis of blood vessel walls, resulting in various sequelae including aneurysms, vessel wall rupture and hemorrhage, and occlusion and infarction *(88,89)*. Vasculitis affecting the CNS is both extremely variable and

challenging because of a lack of specific signs and symptoms and lack of non-invasive diagnostic tests. Vasculitis isolated to the CNS is referred to as primary CNS angiitis; secondary vasculitis is associated with numerous conditions, including infections, lymphoproliferative disease (lymphoma), drug abuse (amphetamines), connective tissue disease, and other forms of systemic vasculitis *(88)*. In most cases, the diagnosis is based on clinical presentation, presence of specific serum markers, and biopsy of lesions. A new era in neuroimaging diagnosis is also foreseen. Goerres et al. report a patient with refractory epilepsy evaluated with positron emission tomography (PET) using [^{11}C]CR-PK11195, a specific ligand for the peripheral benzodiazepine (BDZ) binding site, abundant on cells of mononuclear phagocytic lineage. No gadolinium enhancement was found. PET showed several areas in the occipital and temporal lobes of abnormal PK11195 binding and a biopsy confirmed chronic vasculitis *(90)*.

Necrotizing Vasculitides

The nectotizing vasculitides include classic polyarteritis nodosa (PAN), Wegner's granulomatosis (WG), allergic angiitis and granulomatosis (Churg-Strauss [CS]), necrotizing systemic vasculitis overlap syndrome, and lymphomatoid granulomatosis *(88)*.

Wegner's Granulomatosis

WG is a necrotizing granulomatous vasculitis involving upper and lower respiratory tracts; three-quarters of patients develop glomerulonephritis. Neurologic abnormalities are common and include cranial neuropathies resulting from contiguous extension of granulomas from the nasopharynx, encephalopathy, seizures, pituitary abnormalities, and focal motor and sensory deficits caused by small-vessel vasculitis *(88)*. Peripheral neuropathies are also common. Seizures are usually a late complication.

Polyarteritis Nodosa

CNS involvement in PAN ranges from 4 to 41% and is usually a late manifestation *(89)*. Peripheral nervous system damage is much more common (50–75% of cases). CNS lesions include focal lesions causing transient ischemic attacks, stroke (ischemic or hemorrhagic), seizures and, more commonly, diffuse lesions causing multifocal neurologic findings and encephalopathy *(89,91)*. Generalized or partial seizures have been described in 25–50% of patients with CNS complications and often occur together with acute disease such as headache, acute confusional state, and focal neurologic deficits *(92)*. Seizures in PAN do not usually require long-term management.

CNS disease is usually associated with systemic features such as fevers, cutaneous involvement, and renal complications *(93)*. Elevated erythrocyte sedimentation rate (ESR), leukocytosis, anemia, thrombocytosis, hematuria, proteinuria, and circulating immune complexes may be found. Hepatitis B antigenemia is present in up to 30% of patients, and their treatment and outcome may be different from those

with idiopathic PAN *(88,93)*. Angiography may demonstrate vasculitis, because medium-sized vessels are involved. The presence of neurologic complications does not influence survival, which is significantly increased with treatment with corticosteroids and cytotoxic agents. Recommended treatment of seizures includes anticonvulsants as adjuncts to immunosuppressive therapy.

CS Syndrome

CS syndrome can involve multiple organs, particularly pulmonary vessels, causing asthma and pulmonary infiltrates along with eosinophilia *(88)*. Neurologic abnormalities are similar to those of PAN, and early encephalopathy being frequent because of small-vessel involvement. The CNS was involved in 62% of 47 cases from the Mayo Clinic. In this series, no patients had seizures *(94)*.

Vasculitides Associated With Connective Tissue Disease

Systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), scleroderma, Sjøgren's syndrome (SS), and mixed connective tissue disease (MCTD) are vasculitides associated with connective tissue disease. Although CNS involvement is common in SLE and MCTD, occurring in 20–50% of patients, it is rare in scleroderma and RA *(89)*.

Systemic Lupus Erythematosus

SLE is characterized by immunologic mediated damage to multiple organs, particularly skin, kidneys, and joints, secondary to generation of autoantibodies and immune complexes *(88)*. Seizures unrelated to renal failure, hypertension, or medications occur in approx 14–17% of patients with SLE, usually in the early phases of illness, and most are nonrecurrent *(93)*. One large series reported 6 of 17 patients with a single seizure, and only 3 patients who continued to have seizures after 3 mo *(95)*. Seizures are the first and only manifestation of SLE in approx 3% of patients *(93)*. These patients have frequent laboratory abnormalities including antinuclear antibodies (92%), leukoerythrogenic cells (76%), and hypocomplementemia (57%) *(95)*. The presence of seizures does not alter mortality risk. However, during the terminal phases of disease, seizures may occur with increased frequency.

Seizures commonly occur together with neuropsychiatric (NP) findings, thrombocytopenia, and cutaneous signs of vasculitis *(93)*. NP disturbances are common in SLE. They often occur in the first year of disease but are rarely the presenting symptom *(96)*. One study of NP findings in a large cohort of southern Chinese patients with SLE who were followed for 16 yr reported that seizure disorder was the most common event (occurring in 28% of patients), followed by cerebrovascular disease (19%), acute confusional state (14%), and psychosis (11%) *(97)*. Seizures were mostly of the GTC type. Serological and other clinical associations with NP syndromes in SLE patients include vasculitis, antiphospholipid antibodies and hematological complications (thrombocytopenia, leukopenia) *(97,98)*, higher risk of renal failure *(99)*, and history of cyclophosphamide treatment *(97)*.

The pathogenesis of seizures and other NP syndromes in SLE is not well-understood. Antiphospholipid antibodies are more frequently found in patients with SLE and seizures than in patients with SLE without seizures. In a study of 221 unselected patients with SLE, 43.8% of patients with epilepsy had detectable lupus anticoagulant vs 20.8% of patients without (p = 0.057). A significant association was found between moderate to high titers of IgG anticardiolipin antibodies and the presence of seizures (p = 0.02) *(100)*. One important mechanism is likely an occlusive vasculopathy, suggested by the strong association between antiphospholipid antibodies and NP symptoms *(97,98)*. In a prospective study of 76 Indian women with SLE, a strong association was found between seizures and anticardiolipin and anti-β-2 glycoprotein I antibodies *(101)*. Circulating anticardiolipin antibodies from SLE patients with seizures decreased responses mediated by γ-aminobutyric acid in snail neurons in vitro *(102)*. Pathologic studies of SLE patients with seizures have shown cerebral microinfarcts and subarachnoid hemorrhage *(103)*. True vasculitis is actually rare in SLE, and frequent findings include hyalinization, perivascular inflammation, and endothelial proliferation *(88,103)*. The most common pathological finding at autopsy is a noninflammatory small-vessel vasculopathy *(104)*. In vitro and in vivo studies suggest that antiphospholipid antibodies may activate vascular endothelial cells, leading to expression of leukocyte adhesion molecules and generating a prothrombotic state on the endothelial cell surface *(105,106)*. Evidence of disordered immune regulation is also present in the CNS in the form of immune complexes in CSF *(107)* and choroid plexus *(108)*, elevated IgG CSF–serum index, oligoclonal CSF IgG *(109)*, and lymphocytotoxic antibodies that cross-react with brain *(110)*.

In patients with SLE who present with seizures, it is important to consider several neurologic conditions including infarction (cardioembolism from Libman–Sacks endocarditis, a mural thrombus, antibody-raised homocysteine levels, carotid dissection, and hypertensive small-vessel disease), cerebral venous sinus thrombosis, encephalitis, and cerebral vasculitis. In patients on immunosuppressants, it is crucial to rule out infections, including intracranial abscess and cryptococcal meningitis. Widespread vascular abnormalities on angiography should suggest a cause other than SLE for seizures caused by lack of large-vessel involvement by this disease *(93)*.

EEG abnormalities are frequent, but nonspecific, findings *(111)*. One small study of brain pathology in SLE patients reported the strongest association between presence of cerebral microinfarcts and seizures (4 of 5 patients) *(112)*. Patients with SLE (as well as WG and PAN) who are being treated with cytotoxic therapy have also been reported to develop reversible posterior leukoencephalopathy syndrome (RPLS) with resulting seizures and other typical clinical and radiological manifestations *(113)*. The etiology of RPLS in this context is believed to be dysfunction of the vascular endothelium secondary to several factors including hypertension, renal failure with fluid retention, and cytotoxic drugs. The condition is reversible with prompt administration of antihypertensive and anticonvulsant medications and correction of fluid overload management *(113)*.

Treatment of seizures during a disease flare depends on frequency of attacks and etiology. Most CNS complications occur in untreated patients or those on low-dose corticosteroids *(93)*. Single seizures occurring during disease flares may respond to corticosteroids alone, but recurrent attacks should be treated with anticonvulsants *(93)*. It is rare for the disease to worsen because use of hydantoins, ethosuxamide, and trimethadione has caused drug-induced SLE, and this small risk should not prevent the use of appropriate anticonvulsants *(93)*. The intensivist is frequently perplexed when a patient on antiepileptics develops a rash. Possibilities include allergic reaction, unmasking of SLE by the drug, or anticonvulsant hypersensitivity syndrome. The latter is characterized by the triad of fever, rash, and internal organ involvement, with incidence of 1:1000 to 1:10,000 exposures. Aromatic antiepileptics (PHT, PB, CBZ) and also lamotrigine, VPA, felbamate, primidone, and trimethadione have been implicated *(114–117)*. The reaction usually develops 1–12 wk after initiation of therapy and is thought to be caused by insufficient detoxification of arene oxides (metabolites of aromatic antiepileptics). Lymphadenopathy, hypothyroidism (even 2 mo later) and multiorgan involvement (skin, liver, kidney, lungs, CNS) can lead to fatal complications. Cross-reactivity among aromatic antiepileptics occurs in 75% of cases. Immediate discontinuation of the drug, hydration, antihistamines, and topical and systemic corticosteroids can be used. Because of genetic predisposition, siblings of patients may be at increased risk.

Drug-induced SLE is much more frequent, with distinct clinical and laboratory abnormalities. Drugs such as PHT, CBZ, ethosuxamide, trimethadione, primidone and VPA have been implicated, but PB and BZDs are rarely implicated *(117)*. The clinical presentation of drug-induced SLE is frequently abrupt onset of malaise and fever. Overall, however, the disease is milder than idiopathic SLE and renal or neurological involvement is rare, with pleuropulmonary and pericardial manifestations more common. The main difference between drug-induced SLE and hypersensitivity syndrome is the presence of autoantibodies in the former, including antihistone, antinuclear antibodies, that may persist for months or years after discontinuation of the drug, as opposed to the symptoms that promptly remit.

Rheumatoid Arthritis

CNS involvement causing seizures in RA is uncommon (20% of patients with CNS involvement have seizures) *(118)*, but it can include isolated CNS vasculitis involving small and intermediate sized vessels, blood hyperviscosity, meningeal infiltration with inflammatory cells, rheumatoid nodules and plaques, and choroid plexus infiltration *(119–122)*. One reported case of RA of the CNS presenting with focal seizures was attributed to a focal meningeal vasculitis *(122)*. The patient responded to etanercept, cochicine, and anticonvulsant therapy.

Scleroderma

NP symptoms have been reported in 5 of 32 (16%) patients with systemic sclerosis, and secondary generalized or focal motor seizures were noticed among them. EEG was normal in this series, and primary CNS involvement could not be con-

firmed *(123)*. Simple partial motor seizures associated with fibrosis of cerebral arterioles and arteritis involving middle cerebral artery branches and vasa vasorum of the carotid artery have been reported in scleroderma patients *(124)*. These are thought to be the result of hypertension *(88)*.

Sjøgren's Syndrome

SS, characterized by xerophthalmia and xerostomia, may also present with CNS involvement, either focal or diffuse in 25% of cases *(89)*. CNS manifestations include seizures as well as focal motor, sensory, and language deficits, movement disorders, brain-stem syndromes, encephalopathy, dementia, and recurrent aseptic meningitis *(89,125)*. Complex partial and simple partial motor seizures have been described. Cerebral findings are associated with antineuronal antibodies, or an autoimmune inflammatory cerebral vasculopathy affecting predominantly small vessels, and multiple areas of increased signal intensity on MRI with T2 and proton-density weighing *(89,126)*. Other common findings are peripheral neuropathy, elevated ESR, cutaneous vasculitis, and renal tubular acidosis *(125)*.

Mixed Connective Tissue Disease

Generalized motor seizures have been reported in association with ataxia, hemiparesis, meningeal signs, and psychiatric disturbances *(127)*. The neuropathology of these findings is not well understood. Intractable temporal lobe seizures have been reported in patients with ulcerative colitis. Steroid tapering and abdominal surgery led to SE *(128)*.

Vasculitis Associated With Other Systemic Diseases

Behçet's disease, ulcerative colitis, sarcoidosis, relapsing polychondritis, and Kolmeier–Degos disease are vasculitides associated with another set of systemic diseases.

Behçet Disease

Behçet syndrome is a multisystem inflammatory disease of unknown cause that involves the CNS in approx 5% of patients *(129)*. Criteria for diagnosis (International Study Group for Behçet's Syndrome) are recurrent oral ulceration plus two of the following conditions: recurrent genital ulceration, eye lesions, skin lesions, or positive pathergy test (hypersensitivity of the skin to nonspecific physiological insult) *(130)*. Neurological involvement in Behçet syndrome usually manifests as a subacute brainstem meningoencephalitis, occasionally with hemispheric or spinal cord involvement, and MRI lesions in about 75% of cases *(131)*. Seizures are observed independently, but are an important indication of CNS involvement; alternately, seizures can accompany cerebral venous sinus thrombosis or may be related to interferon-α treatment *(132–135)*. In one review of 223 patients with neurologic Behçet disease, seizures were observed in 10 (4.5%) cases *(132)*. Seizures occurred during neurologic exacerbation in only five patients, giving a prevalence 2.2% to seizures resulting from the disease. In the other five patients, seizures

were not related to neurologic Behçet disease attacks. The most common seizure type was GTC seizures with focal motor seizures, which were controllable in most cases. Seizures were associated with abnormal CSF findings (high protein, pleocytosis) in most cases, a poor prognostic factor in neuro-Behçet disease, indicating parenchymal involvement *(129)*. It was postulated that seizure occurrence may indicate dissemination of the inflammatory process to involve cortex. Seizures may also be associated with cerebral hypoperfusion; in a study of Behçet's disease evaluated by SPECT, three of seven patients had seizures and hypoperfusion in the temporal lobe, including the mesial portion *(136)*. The occurrence of seizures also seemed to be associated with a high mortality rate, although it remains an unusual neurologic complication for this disease. Seizures are usually controlled with monotherapy with CBZ or PHT, but PB and oxcarbazepine have also been used successfully *(132)*. Immunosuppressive therapy with intravenous steroids and cyclophosphamide or chlorambucil may also help to control seizures *(137)*.

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Electrolyte Disturbance
and Critical Care Seizures

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SUMMARY

Electrolyte disturbances in the ICU are extremely common. The electrolyte disorder most commonly associated with seizure is hyponatremia, although extremely low Mg^{2+}, phosphate, and both very low and very high Ca^{2+} values can cause seizures. Critical care physicians must be vigilant to suspect and identify electrolyte disturbances in their patients, because a growing amount of information suggests that they are a marker, and potentially a cause, of poor prognosis. Electrolyte disturbance should never be accepted as the etiology of a seizure until a thorough investigation has been undertaken.

Key Words: Electrolyte imbalance; seizure; hyponatremia; hypernatremia; hypocalcemia; hypercalcemia; hypophosphatemia.

INTRODUCTION

Electrolyte imbalances are very common in the intensive care unit (ICU). As will be reviewed, in some cases electrolyte disturbances may be associated with increased mortality in ICU patients. In patients with neurologic and neurosurgical disease, the added potential for disruption of the blood–brain barrier (BBB) exists, and mechanisms for electrolyte homeostasis may break down.

As common as electrolyte disturbances are, they are still a relatively uncommon cause of seizure. A thorough search should be undertaken to identify other seizure etiologies before a seizure is ascribed entirely to an electrolyte disturbance. As will be discussed further, both the seizure and the electrolyte disturbance may result from the same underlying cause; for example, encephalitis may cause both hyponatremia and seizure. A complete discussion of ion regulation in the brain and

the pathogenesis of electrolyte induced seizures is beyond the scope of this chapter and has been covered well elsewhere *(1)*. This chapter reviews some major concepts in seizure pathogenesis and electrolytes.

MECHANISMS FOR ION REGULATION AND EFFECTS OF CONCENTRATION CHANGES

Ion concentrations in the cerebrospinal fluid (CSF) and the interstitial fluid of the brain differ from their concentrations in plasma: potassium (K^+), calcium (Ca^{2+}), and bicarbonate (HCO_3^-) concentrations are lower than in plasma, whereas magnesium (Mg^{2+}), sodium (Na^+), chloride (Cl^-), and hydrogen (H^+) concentrations are higher *(1)*. The gradient between the brain and the plasma is maintained by active transport processes. The endothelial cells that form the BBB have a $3Na^+$(sodium), $2K^+$-ATPase pump that transports K^+ out of the brain against its gradient. Disease states that disrupt the BBB can cause failure of active transport mechanisms if the disruption is severe. We briefly review the effects on neuronal excitability of changes on K^+ concentration, acid–base status, and osmolality.

Potassium

Raising the concentration of extracellular K^+ depolarizes the neuronal membrane. If the increase is mild, the membrane potential moves closer to firing threshold and the effect on transmission is excitatory. As the concentration of extracellular K^+ continues to rise, however, there is partial inactivation of Na^+ and Ca^{2+} currents in the presynaptic axon, leading to reduced action potential amplitude and decreased excitability, so that the firing threshold forms a U-shaped curve with increasing K^+ concentrations. At the normal physiologic level of 2.7–3.5 m*M*, the low K^+ level provides a brake on neuronal excitation. Many in vitro experiments using slices of rat hippocampal cortex and baths containing various concentrations of K^+ have demonstrated this effect. When K^+ concentration is raised to 5.0–6.25 m*M*, synaptic transmission is increased; at higher levels synaptic transmission eventually becomes depressed. On the other hand, CA3 neurons in the hippocampus become spontaneously active when K^+ concentrations reach a level of 6.5–7 m*M*. If the concentration continues to increase, spreading depression occurs. The ongoing discussion of mechanisms involved in spreading depression was reviewed in 2001 *(2)*.

Acid–Base Status

Alkalosis increases the excitability of the cortex, whereas acidosis decreases excitability *(1)*. Clinically, severe alkalosis can induce tetany resembling the tetany seen with hypocalcemia. This was once thought to occur because of an increase in the bound fraction of Ca^{2+}; however, the actual decrease in H^+ ion seems to be the major mechanism. H^+ inhibits voltage-gated channels, but in most brain tissue increased H^+ concentration inhibits Ca^{2+} channels and Na^+ channels to a greater extent than K^+ channels. Therefore, alkalosis (decreased H^+ concentration) increases the inward Ca^{2+} and Na^+ currents more than it increases the outward K^+

current. The increased Ca^{2+} current results in increased neurotransmitter release and increased synaptic transmission.

An important factor to consider in management of acid–base disturbances is that carbon dioxide (CO_2) passes freely across the BBB, but H^+ does not; therefore, if an acute metabolic acidosis with increased H^+ results in respiratory compensation with a lowered partial arterial pressure of CO_2 (Pa_{CO_2}), the brain may "see" just the lowered Pa_{CO_2} and a central alkalosis will result. Patients with acute metabolic acidosis may have an increase in their central acidosis when treated with bicarbonate solutions by similar mechanisms.

Osmotic Effects

Although little is known about the regulation of water transport across the BBB, it appears that water moves easily across this barrier. Ions do not move freely and need to be passed through channels in the capillary endothelium membrane, as discussed earlier *(1)*. When osmolality of plasma acutely drops compared with the osmolality of cerebral interstitial fluid (as in water intoxication), then water will move into the brain and cell and brain volumes will increase. Compensatory mechanisms are significantly effective at restoring cell and brain volumes within 48 h.

An acute increase in plasma osmolality draws water from the brain, principally from the CSF and the interstitial fluid compartments. The most usual reasons for large changes in plasma osmolality are changes in Na^+ concentration or addition of other osmolar substances, such as ketoacids in diabetic ketoacidosis. The issues involved in the treatment of hypo- and hypernatremia are discussed in the next section.

Osmotic stresses have direct effects on synaptic transmission. Synaptic transmission in rat cortical slices is enhanced by lowering the osmolality of the surrounding bath *(3)*. Increasing osmolality decreases synaptic transmission. A decrease in the osmolality of the bathing fluid results in increased inward Ca^{2+} currents in the presynaptic neuron *(4)*. This mechanism may explain the observed changes in synaptic transmission. For reasons that are not understood, if the osmolality of the fluid bath is kept equivalent with mannitol while the Na^+ is decreased, an increase in Ca^{2+} currents still occurs *(4)*.

The physiology of Mg^{2+}, Ca^{2+}, and phosphorus and their effects on neuronal excitability is reviewed later.

SODIUM IMBALANCE

Hyponatremia

Hyponatremia is a frequent and underrecognized cause of encephalopathy and seizures in the ICU. In one series of 55 patients from the Mayo Clinic with new-onset seizures in the medical and surgical ICUs, hyponatremia of less than 125 meq/L was present in 18.2% of the patients *(5)*. Seizures associated with hyponatremia are treated similarly to other seizures, but with the added need to determine and correct the source of the hyponatremia. The differential diagnosis of hyponatremia

Table 1
Etiology of Hyponatremia in Patients With Low Plasma Osmolality

Altered renal excretion of water
    Decreased extracellular volume
        Renal sodium loss: diuretics, adrenal insufficiency, SAH
        Extrarenal sodium loss: diarrhea, vomiting, fluid sequestration ("third spacing")
    Normal extracellular volume
        SIADH, hypothyroidism, adrenal insufficiency, neoplasms, drugs, postoperative
            state, pain, acute respiratory failure, SAH, ischemic stroke, TBI
    Increased extracellular volume
        CHF, cirrhosis, renal failure
Excessive water intake
    Psychogenic polydipsia
    Hypo-osmolar irrigant solutions (such as those used during transurethral resection
        of the prostate)

SIADH, syndrome of inappropriate secretion of ADH; ADH, antidiuretic hormone; SAH, sub-arachnoid hemorrhage; TBI, traumatic brain injury; CHF, congestive heart failure.

is broad, and a complete discussion is beyond the scope of this chapter (*see* Tables 1 and 2). The essential distinction that must be made is whether the hyponatremia is acute or chronic. This will determine the risk of cerebral edema, as well as how fast sodium may safely be corrected. Either acute or chronic hyponatremia can cause seizures, although seizures occur most often in the acute setting. Hyponatremia is considered to be acute if it develops over less than 48 h, because brain adaptation to reduced osmolarity occurs rapidly *(6)*. Seizures, encephalopathy, and other major neurologic manifestations can occur with even mild hyponatremia if the onset is rapid. Seizures may have focal or generalized onset. Reported electro-encephalography (EEG) findings in hyponatremia are nonspecific, and frequently no changes are seen *(7)*.

Acute, severe hyponatremia should be rapidly corrected; if left untreated, it is associated with significant rate of death or morbidity caused by cerebral edema. Animal experiments have shown that following induced hyponatremia there is an initial phase of rapid ion transfers out of the cell (K^+, Na^+, Cl^-), followed by a slow phase during which the intracellular concentrations of organic osmolytes decrease. Until the slow phase is complete, cellular edema exists. The mechanism by which hyponatremia produces seizures appears to have several components: low osmolarity and decreased Na^+ concentration have both been shown in vitro to increase neuronal excitability *(4,8)*. Additionally, if onset of hyponatremia is acute, then cell and brain swelling can cause a decrease in cerebral perfusion pressure.

Clinically, acute hyponatremia poses the greatest danger when the rate of serum Na^+ decrease is greater than 0.5 meq/L/h with a serum Na^+ concentration of less than 120 meq/L *(9)*. Some recommend that in the setting of acute, symptomatic hyponatremia serum Na^+ can be corrected by using 3% saline solution as rapidly as 2.4 meq/L/h until the range of mild hyponatremia is reached, when correction

Table 2
Drugs and Other Substances Reported to Cause Hyponatremia[a]

SIADH induction	*Trazodone*
Thiazides	Direct ADH-like effect
Furosemide	*Desmopressin*
Cyclophosphamide	Oxytocin
Vincristine	Increased Sensitivity to ADH
Cisplatin	Chloropropamide
Barbiturates	Tolbutamide
Morphine	Indomethacin
Clofibrate	Mechanism uncertain
Lisinopril	*Neuroleptic drugs*
"Ecstasy" (3,4-methylenedioxymetham-	Monoamine oxidase inhibitors
phetamine)	*Hyperglycinemia following transure-*
Carbamazepine	*thral prostate resection*
Oxcarbazepine	*Laxatives containing polyethylene*
Lamotrigine	*glycol*
Tricyclic antidepressants	*Visicol use during colonoscopy*
Serotonin-reuptake inhibitors	
(fluoxetine, sertraline)	

ADH, antidiuretic hormone; SIADH, syndrome of inappropriate secretion of ADH.
[a]Italic type indicates drug reported to cause seizures.
(Data from refs. *34–37*, *86–101*.)

should be stopped for 24 h *(10,11)*. Other authors believe that so rapid a correction represents an unnecessary risk and recommend initial correction at a rate of 1–2 meq/L/h, to be stopped as soon as neurologic symptoms improve *(12)*. Particularly if the exact duration of the hyponatremia is in doubt, caution should be used.

Patients with chronic hyponatremia frequently have mild symptoms, and the urgency of correction is less. One series of hyponatremic patients from New York City and Oxford, England, with serum Na^+ levels less than 120 meq/L found that 76% had associated confusion, and 6% had long tract signs, but only 3.3% developed seizures *(13)*. Correction of chronic hyponatremia is generally recommended to be at the rate of less than 10 meq/L/24 h to avoid central pontine myelinolysis (CPM), a deservedly famous complication of rapid Na^+ correction. Postcorrection seizures can also occur, as in the aforementioned study, where the incidence was 1% *(13)*. Even with slow correction, however, CPM has been reported to occur, and patients with coexisting thiamine deficiency and multiple electrolyte abnormalities may be at increased risk *(14)*. Liver failure and hypokalemia also are associated risk factors for CPM. A recent report suggests that uremia may protect against CPM, perhaps by resisting the movement of water out of the brain *(15)*. The pathogenesis of CPM is still under investigation. An animal model of CPM has shown magnetic resonance imaging (MRI) evidence of BBB disruption and complement deposition following rapid Na^+ sodium correction *(16)*.

The exact rate of correction that can be tolerated by a patient with chronic hyponatremia is the subject of debate. Sterns et al. and other investigators reported patients who developed CPM following corrections of serum sodium of greater than 0.5 meq/L/h *(17,18)*. This number has become the accepted rate limit for safe correction, although critics have pointed out that many of the patients reported had multiple risk factors for CPM. Animal data show that in rats with chronic hyponatremia of less than 120 meq/L, lesions appear when the change in serum Na^+ is greater than 25 meq/L/24 h. The first lesions are noted at the level of 14–16 meq/L/24 h *(19)*. These animal data are nevertheless supportive of the clinical observations in humans. From the same data, a high initial rate of correction was tolerated without resulting CPM as long as the total daily limit of Na^+ correction was respected.

In 1999 a patient was reported who tolerated rapid reinduction of hyponatremia with hypotonic saline following a rise in serum Na^+ by 21 meq/L over 24 h. Neurologic deterioration followed the overly rapid correction but improved when the patient was given hypotonic saline *(20)*. Earlier the authors of this report had published animal data suggesting that a window of 2–4 h exists following onset of neurologic symptoms before irreversible CPM occurs, and a rescue therapy of hypotonic saline can be given during this period *(21)*.

Other treatment modalities for hyponatremia have been explored. For instance, antagonists to the antidiuretic hormone (ADH) vasopressin are in stages of clinical testing for hyponatremia involving the syndrome of inappropriate secretion of ADH (SIADH) *(10)*. A suggested treatment algorithm for hyponatremia is shown in Fig. 1.

Acute Hyponatremia in the ICU

Common ICU settings for acute hyponatremia to occur include the postoperative state and SIADH secondary to medications or other substances (*see* Table 2); SIADH or cerebral salt wasting from intracerebral processes such as meningitis, encephalitis, and subarachnoid hemorrhage (SAH); adrenal insufficiency; and potomania or psychogenic polydipsia. Some of these are discussed in detail in this chapter.

Postoperative patients have a risk of developing hyponatremia that is frequently overlooked. One prospective study found that 4.4% of all postoperative patients develop hyponatremia of less than 130 meq/L. The authors ascribed this mainly to hypotonic fluid administration and elevated serum ADH levels in their patients *(22)*. However, in the ICU setting the incidence may be higher. Of the 55 ICU patients with new-onset seizure reported by Wijdicks and Sharbrough, 8 of the 10 hyponatremic patients had undergone postoperative fluid loading *(5)*. Hyponatremic encephalopathy resulting in death or persistent vegetative state following surgery in otherwise healthy patients has been reported *(23)*. There are probably multiple mechanisms for postoperative hyponatremia, including iatrogenic free water loading and increased ADH levels secondary to volume loss, hypotension, and possibly other factors. A study of ADH levels in 16 patients undergoing uncomplicated cholecystectomy found that ADH levels increased on average 8.8 times their baseline levels during surgery and remained high for an additional 2 d despite estimated blood losses of only 80–300 mL *(24)*.

Fig. 1. Algorithm for treatment of sodium imbalance. CSW, cerebral salt wasting syndrome; N, normal. (From: Diaz JL, Granados M, Suarez JI. Management of Medical Complications in the Neurosciences Critical Care Unit. In: Suarez JI, ed. Critical Care Neurology and Neurosurgery. Totowa, NJ: Humana; 2004.)

Patients with intracranial disease have a well-recognized risk of developing hyponatremia. Originally this was described as a salt-wasting syndrome caused by inability of the renal tubule to reabsorb sodium secondary to the cerebral lesion *(25)*. The syndrome is characterized by hyponatremia, natriuresis, and a decrease in the extracellular fluid volume. A natriuretic factor was hypothesized but not found. Subsequently, SIADH was described, and most patients with hyponatremia following SAH were diagnosed clinically as having SIADH *(26)*. These patients had clinical diagnoses made on the basis of hyponatremia without dehydration (euvolemic or hypervolemic state), inappropriately elevated urine Na^+, and urine osmolality higher than the serum osmolality. Fluid restriction was frequently used as a treatment for hyponatremia. A retrospective report of 134 patients with SAH found that one-third of them had hyponatremia ($[Na^+]$ <135 mEq/L) during their hospital course, with 18% fulfilling criteria for SIADH. Of the patients with hyponatremia who were treated by fluid restriction, 21 of 26 developed cerebral infarctions *(27)*. Subsequently, the same author reported that plasma volume decreased by greater than 10% during the first week after SAH in 11 of 21 patients studied. Additionally, serum vasopressin levels were elevated at admission in 14 of 21 patients and fell during the first week in all patients *(28)*. Other investigators have since reported that atrial natriuretic peptide (ANP) levels are elevated in patients with aneurysmal SAH and could account for natriuresis *(29,30)*. Most recently, a prospective observational study of 10 ICU patients with aneurysmal SAH who underwent clipping and a control group of patients who underwent craniotomy for resection of cerebral tumors had serum and urine electrolytes and plasma concentrations of brain natriuretic peptide (BNP), aldosterone, cortisol, ADH, and renin measured daily for 7 d postoperatively. None of the patients in either group developed hyponatremia, but all the patients with SAH developed increased urine output, increased urinary excretion of Na^+, and increased fractional sodium filtration with elevated BNP and low aldosterone levels. None of the patients in the craniotomy group developed these findings. The authors suggested that their patients had salt-wasting syndrome associated with increased secretion of BNP and subsequent suppression of aldosterone synthesis *(31)*. BNP in humans is mainly of cardiac origin, but it is secreted by the hypothalamus as well. Further work remains to be done to define this syndrome.

Currently, most hyponatremia episodes in SAH are considered to be associated with hypovolemia and are treated with volume expansion and mineral-corticoid supplementation when needed. If a patient is in symptomatic vasospasm, 3% NaCl may be given *(32)*. A recent prospective study of patients with SAH did not find that hyponatremia was independently associated with poor outcome *(33)*. Acute hyponatremia is also commonly observed following transurethral resection of the prostate or endometrial resection when the operative field is irrigated with hypotonic glycine solutions *(34–37)*. Neurological abnormalities include visual disturbances, seizures, confusion, and cerebral edema (on computed tomography [CT] or MRI of the brain). In this instance the administration of different irrigating solu-

tions (i.e., sorbitol–mannitol), diuretics, and sodium reloading are measures that should be undertaken to prevent or treat seizures. However, no randomized studies have been carried out, and the role of anticonvulsant medications is uncertain.

Psychogenic polydipsia is a not uncommon cause of severe, acute hyponatremia that deserves mention. Patients with polydipsia usually are considered able to tolerate large, rapid increases in Na^+ concentration and are at high risk of dying if left untreated *(38)*. In a retrospective review of 10 yr of institutional experience, one author reported 5 episodes of rapid Na^+ correction in this setting that resulted in neurologic complications out of 24 episodes of psychogenic polydipsia leading to hyponatremia. The complications included mild symptoms that resolved in two patients and clinical CPM in three patients. In two of these patients, hyponatremia was likely of subacute onset, and a third patient was chronically malnourished and abused alcohol *(39)*. If the exact onset of the hyponatremia is in doubt, caution should be used.

In summary, hyponatremic patients with seizures should be treated with standard antiepileptic drugs, and the duration and underlying cause of their hyponatremia should be assessed to determine the appropriate rate of correction. Frequently patients will have a single seizure without recurrence, and the full differential diagnosis should be considered before the seizure is ascribed to hyponatremia.

Hypernatremia

Although hypernatremia is an extremely common problem in the ICU, especially in the elderly, associated seizures are rare. Other causes of seizures, such as meningitis, mass lesion, cortical vein or sinus thrombosis, subdural hemorrhage, or nonketotic hyperglycinemia should be considered before a particular seizure is ascribed to hypernatremia. In a neurologic patient, the possibility of neurogenic diabetes insipidus should be considered. This syndrome can occur after SAH, head trauma, intracranial tumors (i.e., transphenoidal pituitary tumor resection), or inflammation. Another common cause of hypernatremia in ICU patients is administration of osmotic diuretics such as mannitol for treatment of increased intracranial pressure. Finally, decreased response to thirst, in the presence of obtundation or lethargy, without adequate water access can be another cause of hypernatremia in hospitalized patients.

The acuity of the hypernatremia is important in deciding how fast to treat. Excessively fast rehydration can lead to cerebral edema, increased encephalopathy, and seizures *(40,41)*. Although again, seizures are rare, hypernatremia portends a poor prognosis: mortality ranges between 40 and 60% in hospitalized patients with hypernatremia *(42)*. In a recent prospective, observational study of 298 patients with SAH, the incidence of hypernatremia was 19%, and it was an independent predictor of poor prognosis (odds ratio [OR] 2.7, 95% confidence intervals [CI] 1.2–6.1) *(33)*. A different, retrospective study of 389 ICU patients showed the incidence of hypernatremia greater than 150 mmol/L at admission to be 8.9%, with 5.7% of patients subsequently developing hypernatremia during the admission. The

mortality rate for the patients with hypernatremia at admission was 20.3% compared with 32% in patients who developed hospital-acquired hypernatremia ($p < 0.001$) *(43)*.

HYPOMAGNESEMIA

Mg^{2+} deficiency is the most common electrolyte disturbance in hospitalized patients, and in the ICU its incidence has been found to be 20–65% *(44,45)*. As an isolated cause of seizure, it occurs rarely, but its clinical importance is large in the critically ill patient population. Multiple studies have shown that low Mg^{2+} is a risk factor for poor prognosis. A prospective, observational study of 381 patients admitted to the regular floor and to the ICU showed that the mortality rates of patients with admission Mg^{2+} levels of less than 1.5 were twice the rates of nonhypomagnesemic patients who were similar with respect to other variables *(46)*. Other studies failed to find an association between admission Mg^{2+} and mortality *(47)*. In a prospective, observational study from Brussels, Belgium, of 446 consecutive ICU patients, ionized and un-ionized Mg^{2+} levels were measured. The results demonstrated an ionized hypomagnesemia (normal values 0.42–0.59 mmol/L) at admission in 18% of patients and showed that there was no correlation with outcome. Ionized hypomagnesemia that developed during ICU admission was correlated with increased length of ICU stay, higher admission severity of illness (as determined by the APACHE II [Acute Physiology and Chronic Health Evaluation II] score), higher prevalence of sepsis, and higher mortality rate *(48)*. Although the relative merits of measuring ionized or total serum Mg^{2+} levels remains under discussion, Mg^{2+} levels clearly are of significance.

Mg^{2+} is required for normal endocrine function, protein synthesis, and enzymatic reactions. The average adult human body has approx 24 g of Mg^{2+}, of which roughly two-thirds is stored in the bone and one-third in the cardiac muscle, skeletal muscle, and liver. Normal Mg^{2+} homeostasis is entirely dependent on dietary intake. In normal circumstances, an adult ingests 200–300 mg of Mg^{2+} daily and absorbs about half this amount. Mg^{2+} is filtered by the kidney; around 2.5 g of Mg^{2+} a day enters the tubules, and roughly 95% is reabsorbed in the proximal convoluted tubule and the loop of Henle. Mg^{2+} is almost entirely intracellular, but acidosis and ischemia promote release of magnesium from the cell. Among the activities Mg^{2+} is believed to support are the cell membrane Na^+,K^+-ATPase pump, proper selectivity of ion channels, and Ca^{2+} channel blockade. In a low Mg^{2+} state, intracellular Ca^{2+} concentrations rise, and this may be the reason for the increased vasoconstriction seen with low Mg^{2+} *(49)*.

The situations in which Mg^{2+} deficiency arises are decreased nutritional intake, stress-induced catecholamine release, gastrointestinal malabsorption, and failure of the kidney to reabsorb the filtered ion, as part of an endocrine disorder: acute shifts into the cell from the serum also increase this deficiency (Table 3) *(50)*. All these situations arise most frequently in the ICU *(44)*. The clinical effects of Mg^{2+}

Table 3
Causes of Clinical Hypomagnesemia

Malnutrition and gastrointestinal factors	Hereditary renal magnesium wasting
Alcoholism	(Bartter's and Gitelman's
Protein-calorie malnutrition	syndromes)
Total parenteral nutrition without mag-	Aldosteronism
nesium replacement	Alcohol
Nasogastric suction	Endocrine
Intestinal bypass surgery	Diabetic ketoacidosis
Short-bowel syndrome	Hyperparathyroidism
Diarrhea	Hyperthyroidism
Laxative abuse	Hyperaldosteronism
Colonic neoplasm	Acute intracellular shifts
Bulimia	Refeeding syndrome
Pancreatitis	Glucose infusions
Renal wasting	Amino acid infusions
Diuretics	Insulin
Antibiotics (aminoglycosides,	Catecholamines
foscarnet)	β_2 agonists
Cisplatin	Metabolic acidosis
Cyclosporine	Other
Hypercalcemic states	Exchange transfusion
Postobstructive diuresis	Acute intermittent porphyria
Acute tubular necrosis (diuretic	Citrated blood products
phase)	Phosphorus depletion

depletion include the generation of cardiac arrhythmias (supraventricular tachycardias, atrial fibrillation, ventricular tachycardias), electrocardiographic changes (long QT interval, long PR interval, wide QRS, peaked T waves, ST segment depression), vasospasm and bronchospasm resulting from smooth muscle constriction, hypertension, endocrine and electrolyte effects (parathormone [PTH] stimulation or suppression, insulin resistance, refractory hypokalemia, hypocalcemia, and hypophosphatemia), and neurologic manifestations. Patients usually do not have neurologic manifestations until total serum levels drop below 1.0 mg/dL. The primary patient complaint may be tremor, fasciculations, spontaneous carpopedal spasm, or generalized muscle weakness. On exam, Chvostek's and Trousseau's signs may be elicited. Seizures, when they occur, are usually generalized. Because seizures also release catecholamines, thus lowering the Mg^{2+} levels, low postseizure concentrations may be the effect rather than the cause *(51)*. There is some controversy about whether tetany ever occurs without coexisting severe hypocalcemia; reports exist, but in a prospective study of hypomagnesemic patients no tetany was observed, and tremor and fasciculations were seen only in patients who were also hypocalcemic *(52,53)*.

Mg^{2+} deficiency is a rare cause of intractable seizures in humans *(54)*. In infants, these seizures occur with the rare condition of primary familial hypomagnesemia *(55)*. Such infants are supplemented for life with oral Mg^{2+}, and this improves outcome *(56)*. In adult patients, the exact threshold level of Mg^{2+} necessary to cause intractable seizures is not well-understood. The mechanism by which low Mg^{2+} causes seizures is under investigation. Mg^{2+} acts as a membrane stabilizer by screening the surface charge of the cell membrane, a property it shares with Ca^{2+}. In contrast, at all synapses Mg^{2+} and Ca^{2+} antagonize each other; Mg^{2+} inhibits neurotransmitter release, while Ca^{2+} promotes it *(1)*. Mg^{2+} present at normal levels antagonizes *N*-methyl-D-aspartate (NMDA) receptor activation by undetermined mechanisms, helping to modulate the influx of Ca^{2+} into the cell. In rats a neuroprotective effect of Mg^{2+} has been seen to NMDA-induced seizures *(57)*. This may be one mechanism by which low Mg^{2+} facilitates seizures, but it does not appear to be the primary mechanism. In vitro, rat hippocampal slices suspended in an Mg^{2+}-free bath develop seizurelike discharges that evolve to late recurrent discharges approx 2 h later and are not blocked by anticonvulsants *(58)*. NMDA receptor blockade with antagonists aborts epileptiform discharges as a result of low Mg^{2+}, suggesting a role of NMDA receptor activation for the generation of hypomagnesemic seizures *(59)*. One investigator has found that seizurelike discharges induced in this manner are associated with an increase in the ratio of reduced nicotinamide adenine dinucleotide (NAD) to NAD, unlike discharges elicited with 4-aminopurine, suggesting that failure of energy metabolism could be involved in the evolution of recurrent discharges in this model *(60)*. An interesting feature in experimentally induced hypomagnesemia seizures is that these events can be provoked by noise in several rat strains. By changing the intensity of the noise stimulus, one can change the susceptibility of the audiogenic seizures. This characteristic has been used to test the antiepileptic effect of drugs such as PHT, carbamazepine, phenobarbital, ethosuximide, and diazepam *(61,62)*.

Any seizing patient with the right clinical risks for hypomagnesemia must have his or her Mg^{2+} level determined, as well as levels of the other electrolytes that are commonly low in the presence of hypomagnesemia (K^+, Ca^{2+}, phosphorus). In the absence of renal failure and when clinical suspicion is strong, therapy may be started while information on Mg^{2+} levels is still pending. No clinical trial has demonstrated that Mg^{2+} infusion is adequate therapy for seizures arising in the context of low Mg^{2+} levels, and standard anticonvulsants are used. PHT may be preferred to valproate because of the lack of animal data to suggest that it may have more sustained efficacy *(62,63)*. Mg^{2+} can be dosed at 4–6 g of magnesium sulfate intravenously and given rapidly at a rate not faster than 1 g/min. This dose can be repeated every 6 h until loss of patellar reflexes is seen (an early sign of Mg^{2+} intoxication).

Table 4
Causes of Hypocalcemia

Postthyroidectomy
Postparathyroidectomy or autoimmune hypoparathyroidism
Pseudohypoparathyroidism
Repeated transfusions
Critical illness
Plasmapheresis
Sepsis
Acute pancreatitis
Fat embolism
Crush injury
Rhabdomyolysis
Hypomagnesemia
Primary hypomagnesemia with secondary hypocalcemia
Vitamin D deficiency
Heparin
Other drugs (foscarnet, pentamidine)
Chronic renal failure
Acute renal failure

DISORDERS OF CA^{2+} HOMEOSTASIS

Hypocalcemia

The classic setting for hypocalcemic seizures is in the newborn period. In the past many newborns had hypocalcemic, hypomagnesemic seizures with onset at 4–14 d of life caused by the high phosphate content in formulas based on cow milk *(64)*. With improvement in formula composition, the most common time for neonatal hypocalcemic, hypomagnesemic seizures is now from birth to age 3. By one recent retrospective series, these seizures occurred most frequently in infants with congenital heart disease (7 out of 15 patients) and only one had a mother with hyperparathyroidism. The author suggested that the heart defects could be associated with an incomplete form of DiGeorge's syndrome, but no further information was available to support this. Prognosis depended on the severity of the associated medical conditions *(65)*.

In adult patients hypocalcemia usually presents with manifestations of neuromuscular irritability such as tetany, carpopedal spasms, and perioral and limb paraesthesias *(66)*. With very low Ca^{2+} levels such as occur following complete parathyroidectomy, papilledema, confusion, and seizures can occur. Generalized convulsions and status epilepticus usually follow a generalized tetanic episode. Seizures secondary to alendronate-induced hypocalcemia were reported in 2002 *(67)*. Although seizures resulting purely from hypocalcemia are rare, neurologists should be familiar with the many causes of hypocalcemia that occur in the ICU (*see* Table 4).

The mechanism of hypocalcemic seizures in rat hippocampal models appears to involve epileptiform discharges predominantly from area CA1 of the hippocampus. Because the epileptiform discharges could not be abolished by blockade of NMDA and non-NMDA receptors, it was suggested that ephaptic transmission occurs in very low Ca^{2+} states (<0.3 meq/L) *(68)*.

Treatment of hypocalcemic seizures includes intravenous Ca^{2+} and an anti-epileptic medication. The usual dose is 2 ampules of Ca^{2+} gluconate (a 10-cc ampule contains 4.6 meq of elemental Ca^{2+}) or 1 ampule of Ca^{2+} chloride (a 10 cc ampule contains 13.6 meq of elemental Ca^{2+}) intravenously slowly (over 10–20 min). Additional continuous infusion can be started at a rate of 1–1.5 ampules of Ca^{2+} gluconate over 6–8 h with serum Ca^{2+} level measurement every 4–6 h to maintain serum Ca^{2+} levels near 8 mg/dL. The patient should have Mg^{2+} replaced as well. Hyperphosphatemia should be treated, if present. Cardiac monitoring is usual because Ca^{2+} can occasionally cause bradyarrhythmias and first-degree heart block, particularly if the patient is already taking digoxin.

Hypercalcemia

Severe hypercalcemia (>13.5 meq/L) such as occurs in primary hyperparathyroidism has been reported to cause seizures in the setting of confusion and encephalopathy, although this is uncommon *(69,70)*. This presentation with generalized or focal seizures and coma is sometimes referred to as parathyroid storm. Hypercalcemia as the result of a neoplasm, either by direct invasion of bone or as a result of PTH-related protein (PTHrP) release, also can cause this presentation and is an oncologic emergency *(71)*. Among drugs, lithium can cause hypercalcemia through PTH secretion *(72)*.

Multiple patients with severe hypercalcemia and a posterior leukoencephalopathy with visual loss, confusion, drowsiness, and seizures have been reported *(73,74)*. These patients had multiple areas of subcortical ischemia by neuroimaging, predominantly in the parieto-occipital regions. Cytotoxic edema is suggested by the presence of diffusion-weighted imaging abnormalities on MRI *(73)*. EEG has revealed either occipital intermittent rhythmic Δ activity *(73)* or periodic lateralizing epileptiform discharges (PLEDs) *(74)*. Symptoms resolved with treatment of the serum Ca^{2+}. One author suggests partly reversible vasospasm of the cerebral vessels as an explanation *(74)*.

The pathophysiology of hypercalcemia-induced seizures is still unclear, in as much as in rat hippocampus the tendency for neurons to produce multiple spikes is reduced *(75)*. EEG findings in hypocalcemia include bursts of high-voltage slow waves with sharp and spike waves and without triphasic waves *(76)*. In hypercalcemia bursts of high-voltage slow waves and triphasic waves have been reported, but PLEDs may be seen *(74,76)*.

The treatment of hypercalcemia requires vigorous intravenous hydration (6–10 L/d) to replete volume and avoid renal failure, and limitation of oral Ca^{2+} intake to 0.5–1.0 mg/d. Following this, intravenous furosemide can be given to encourage

Table 5
Causes of Hypophosphatemia

Decreased intake/absorption
    Starvation
    Total parenteral nutrition formula without phosphorus
    Alcoholism
Intracellular redistribution
    Refeeding syndrome
    Acute asthma
    Chronic obstructive pulmonary disease
    Respiratory alkalosis
    Sepsis
Increased renal loss
    Fanconi's syndrome
    Cystinosis
    Amyloidosis
    Myeloma
    Wilson's disease nephrosis
    Cadmium toxicity
    Acute lead toxicity
    Acetaminophen toxicity
    Hyperparathyroidism
    Vitamin D-resistant rickets
    Medications (acetazolamide, theophylline, steroids, dopamine, estrogen,
        cisplatin)

calciuresis. In the case of chronic hypercalcemia or when hydration and furosemide fails to normalize serum Ca^{2+}, agents such as intravenous mithramycin, pamidronate, and etidronate are used. Calcitonin can also be used, but tachyphylaxis reduces its utility for long-term treatment.

HYPOPHOSPHATEMIA

Low phosphate levels frequently accompany deficiencies in other electrolytes. The majority of serious complications occur with severe hypophosphatemia, defined as serum concentrations less than 1 mg/dL (<0.32 mmol/L). Moderate hypophosphatemia is considered to be 1.0–2.0 mg/dL (0.3–0.7 mmol/L). The reported incidence of hypophosphatemia in a general population of hospitalized patients is 2.5–3.1% *(77)*. In the ICU setting, an incidence at admission of 17–45% has been reported *(77,78)*. A higher incidence among some neurologic patients may be present. In a report of 18 ICU patients with severe head injury, 61% had hypophosphatemia at admission, along with other electrolyte abnormalities. There may be a yet undefined mechanism in cerebral injury causing phosphate wasting. However, a caveat is that some of the patients had received a dose of mannitol prior to electrolyte measurements *(79)*. Hypophosphatemia can arise because of insufficient intake

or absorption, intracellular redistribution, or renal losses (*see* Table 5). The refeeding syndrome, a famous cause of hypophosphatemia in the ICU, can occur after starvation of duration as short as 48 h *(80)*.

Phosphorus is a vital component of normal metabolism. Phosphorus is required for adenosine triphosphate (ATP) synthesis, and the neurologic symptoms are believed to arise from ATP deficiency. Phosphorus is also required for 2,3-diphosphoglycerate production, and hypophosphatemia therefore increases the affinity of the red blood cells for oxygen, decreasing peripheral oxygenation. Hemolytic anemia may occur in severe hypophosphatemia secondary to increased rigidity of the red blood cells, which require ATP to remain deformable. Leukocyte and platelet function is decreased. Cardiac and respiratory failure may occur.

Normal daily dietary intake of phosphorus is approx 1.0–1.5 g. Phosphorus is absorbed in the jejunum of the small intestine and is in the serum as a free ion. Phosphorus is freely filtered by the kidney, and 80–90% is reabsorbed in the proximal tubules. Of the daily phosphorus intake, approximately two-thirds is excreted in the urine with normal renal function. PTH and 1,25-dihydroxyvitamin D_3 decrease phosphate reabsorption. Roughly 80% of total body phosphorus is in the bone. Of the remaining 20%, almost all is in the intracellular space *(81)*.

Classic neurologic findings of hypophosphatemia are muscle weakness, either symptomatic or asymptomatic. A painful myopathy may develop, which can progress to rhabdomyolysis *(82)*. Paresthesias, tremors, and neuropathy have been reported. Acute hypophosphatemia has been reported to cause coma or seizures *(83)*.

Replacement of phosphorus has been associated with diarrhea, hypotension, cardiac arrhythmia, confusion, paresthesia, metastatic calcification, hyperkalemia or hypernatremia from the salt used to bind the phosphorus, hypocalcemia, and hypomagnesemia *(81)*. Traditionally, the dosage used to treat severe hypophosphatemia has been 0.125 mmol/kg/h over a 4-h infusion (35 mmol in a 70-kg person), and a dose used to treat moderate hypophosphatemia is 0.0125 mmol/kg/h over 6 h (5.25 mmol in a 70-kg person) *(84)*. A prospective study of 11 ICU patients with moderate hypophosphatemia and initial serum phosphorus levels of 1.6–1.9 mg/dL (0.51–0.61 mmol/L) used 15 mmol of sodium phosphate intravenously over 2 h, to be repeated every 6 h as needed. The protocol was well-tolerated *(85)*.

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11

Alcohol-Related Seizures in the ICU

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SUMMARY

Alcohol abuse is a common cause of seizures resulting in admission to the intensive care unit. The cause of the alcohol-related seizures (ARS) is usually abstinence in a chronic alcoholic, although some patients may still have detectable levels of alcohol in their blood. ARS generally occur between 7 and 48 h after abstinence. Approximately half of patients presenting with ARS will have recurrent seizures (usually two to four) within a vulnerable 6-h period following the initial ARS. Although patients with ARS rarely enter status epilepticus (SE), alcohol withdrawal is a common contributing factor in many cases of SE. Evaluation involves searching for a focal cause of the seizure as well as looking for comorbid conditions, including delirium tremens, that may complicate the management of chronic alcohol abusers. Treatment of ARS is similar to general management of alcohol withdrawal, with benzodiazepines being the mainstay of treatment. Treatment of alcohol-related SE is similar to that of other causes of SE. Phenytoin is not indicated for treatment of ARS unless the patient enters SE.

Key Words: Seizure; withdrawal; alcohol; status epilepticus; intensive care; ICU; delirium tremens; antiepileptic; phenytoin.

INTRODUCTION

Alcohol-related seizures (ARS) are a common cause of adult-onset seizures *(1)*. Management of these patients involves careful evaluation to assess for life-threatening illness as well as causes of seizures other than alcohol. The hospital course may be complicated by status epilepticus (SE), polysubstance abuse, intracranial pathology, delirium tremens, and other comorbid conditions.

ALCOHOL WITHDRAWAL SYNDROME

The alcohol withdrawal syndrome is a spectrum of signs and symptoms following cessation or reduction in the intake of alcohol. In general, mild symptoms occur early and the more serious symptoms, such as seizures and delirium tremens, occur later in the course of withdrawal.

Minor Alcohol Withdrawal

Symptoms of minor alcohol withdrawal may begin within hours of the last drink, peak within 1–2 d, and generally disappear in 5–7 d *(2–4)*. Symptoms can occur before the blood alcohol levels have reached zero *(4)*. The patient may develop anxiety, tremor, malaise, weakness, irritability, insomnia, vivid dreams, headache, and autonomic disturbances such as tachycardia, hypertension, diaphoresis, orthostatic hypotension, and nausea. The tremor in alcohol withdrawal is a tremor of the hand and tongue and is worse when outstretched. The tremor lasts a few days; the inner shakiness and uneasiness may remain 10–14 d. After this, the patient is able to sleep throughout the night without sedation *(5)*. Symptom severity generally relates to the duration and intensity of the alcohol intake *(4)*.

Alcohol Hallucinosis

Alcohol hallucinosis is a condition that occurs in about 25% of long-term heavy drinkers *(6)*. The patient experiences visual, auditory, tactile, or olfactory hallucinations *(7)*. The bizarre perceptions usually begin within 12–24 h after the last drink and stop in another 24–48 h *(6)*, although there are reports of patients developing a chronic paranoid delusional state *(2)*. The electroencephalogram (EEG) is generally normal *(7)*, and the presence of a grossly normal sensorium helps distinguish hallucinosis from delirium tremens *(6)*.

Delirium Tremens

Delirium tremens is the most severe form of alcohol withdrawal. It occurs in less than 5% of patients hospitalized for alcohol withdrawal and is characterized by delirium, vivid hallucinations, and autonomic hyperactivity such as systolic hypertension, tachycardia, diaphoresis, mild hyperthermia ($\leq$100.5°F), and dilated but reactive pupils *(2,6–8)*. Although the range of onset may be large *(6)*, the syndrome usually begins on the second or third day of abstinence and in most cases resolves within 5 d *(5)*. If seizures occur in the course of alcohol withdrawal, they nearly always occur before the onset of delirium tremens. If they occur after the onset of delirium tremens, an organic cause is likely *(2)*. The transient EEG changes that may be seen during the peak incidence of alcohol withdrawal seizures resolve before the onset of delirium tremens *(9,10)*. The EEG during delirium tremens is generally normal, or there is an increase in fast frequencies. This fact may help in differentiating delirium tremens from other causes of altered sensorium.

Patients at risk for delirium tremens are generally older than age 30 yr and have a long-standing history of alcoholism *(6)*. The risk for delirium tremens begins at a daily consumption rate of 80 g of ethanol but becomes appreciable only at 120 g/d and up (i.e., half a 750-mL bottle per day) *(8)*. Only about 1–10% of patients with minor withdrawal symptoms will go on to develop delirium tremens *(2)*. Medical illness or a history of major withdrawal also increases the risk of withdrawal delirium *(2,7)*.

Concurrent medical conditions are often seen and may mask delirium tremens. Therefore, one must be aware that unexplained hypertension, tachycardia, fever, or sweating may be signs of delirium tremens in a patient who is not exhibiting the usual signs and symptoms *(6)*. Before assigning a diagnosis of delirium tremens, other causes of delirium in the alcoholic should be considered, such as pneumonia, sepsis, meningitis, hypoxia, hypercapnia, electrolyte disorders, cardiac ischemia or arrhythmia, hypertension or hypotension, hypoglycemia, hepatic disease, renal disease, thiamine deficiency, the postictal state, dehydration, medications or illicit drugs, ketoacidosis, trauma, subdural hemorrhage, intracerebral bleeding, subarachnoid hemorrhage (SAH), and acute ischemic stroke *(6,11–13)*.

With improved understanding and treatment, death rates have dropped in the last 40 yr from about 20% to just about 1% more recently *(2)*. Death is usually the result of complications of medical illness such as pneumonia, sepsis, and arrhythmia.

ALCOHOL-RELATED SEIZURES

ARS are a common cause of new-onset seizures in adults *(1,9,12)*. One study detected alcohol intoxication in the immediate histories of half the patients seen in the emergency room (ER) for seizures *(12)*. ARS can generally be thought of as a withdrawal phenomenon, occurring after several hours of abstinence. In some cases, however, the patient may still be intoxicated or have detectable levels of alcohol when the seizure occurs *(9,12,14,15)*.

The seizures generally occur between 7 and 48 h after cessation of alcohol *(9)*. Seizures occurring after 72 h are likely to be associated with concurrent drug abuse or intracranial pathology *(16)*. About half the patients presenting with an ARS will have recurrent seizures (usually 2–4) within a vulnerable 6-h period following the initial ARS *(9)*. Because an ARS almost never occurs during delirium tremens, seizures occurring after onset of delirium are likely to have an organic cause, even if the patient has a history of ARS *(2)*.

During the peak incidence of ARS, the EEG is often abnormal, showing sharp waves, spikes, paroxysmal changes, and a photomyoclonic response *(9,10)*. This phase is very transient and usually quickly returns to normal. If the EEG is obtained after peak incidence of ARS but within the first few days of the ARS, the EEG may show increased β activity, reduced α activity, or a low-voltage EEG pattern *(17)*.

Although binge drinking has been shown to cause ARS *(12)*, the risk of having an ARS is greatest in alcoholics with a history of detoxification, many years of alcohol abuse, prior ARS, and a score greater than 15 on the Clinical Institute With-

drawal Assessment for Alcohol (CIWA-A) scale, a validated scale for the assessment of alcohol withdrawal severity *(18–21)*. The typical patient is male, between the age of 30 and 60 yr, and is experiencing a period of abstinence following a period of chronic intoxication *(9)*.

In patients with a predisposition to seizures, such as idiopathic and posttraumatic epilepsy, much shorter periods of intoxication are required to trigger ARS. In some cases, even a single evening of drinking is sufficient. These seizures are similar to ARS in patients without epilepsy in that they generally occur after a discrete period of abstinence, not during the period of intoxication *(9)*.

Although ARS are usually generalized, focal seizures may occur as well. In their study of 472 adults, Earnest and Yarnell *(1)* found that focal seizures occurred in 24% of ARS. In this series, a focal lesion was found in only 15% of patients, in comparison to 47% of nonalcoholic focal seizures. Other authors have also reported a low prevalence of focal lesions in patients with focal ARS *(22)*. These studies were performed during the era before computed tomography (CT) scans were routinely available and, therefore, may have underestimated the frequency of focal lesions, especially traumatic lesions *(12)*.

It is very difficult to predict which patients will have recurrent seizures (i.e., seizures within one alcohol withdrawal episode) during the vulnerable 6-h period following an ARS. Rathlev et al. *(23)* conducted a retrospective analysis of the placebo arms of two prospective randomized trials of drug treatments for the prevention of recurrent ARS. They found that the following clinical characteristics were not predictors of recurrent seizures within 6 h following an ARS: age, gender, systolic blood pressure (BP), diastolic BP, temperature, respiratory rate, heart rate, history of ARS, history of nonalcohol-related seizures, daily ethanol intake, and duration of alcohol abuse. They did find that patients with an initial alcohol level greater than 100 mg/dL had a significantly lower risk (0%) for recurrent ARS within the study period than patients with blood alcohol concentration less than 100 mg/dL (36%, $p < 0.01$). The reason for this unexpected finding is a matter of speculation, and it is possible that recurrent seizures would have been observed in some of these patients if the study period had been extended beyond 6 h. Data from a 48-h follow-up period, available from only one of the two studies, showed that 14% of patients developed recurrent seizures after discharge from the hospital, and all but one of these patients had a serum alcohol level of zero on the first visit. The exception had a level of 22 mg/dL.

Differential Diagnosis

There are many causes for seizures in the intensive care unit (ICU) *(24)*. One must not immediately assume that alcohol is the only cause of seizure in the alcohol-dependent patient. With the help of CT or magnetic resonance imaging (MRI) scans in many of their patients, Rathlev et al. *(25)* conducted a chart review of ER patients who presented with ARS and found that 54% had identifiable etiologic factors other than alcohol. In decreasing order of frequency these were past head trauma (26%), idiopathic epilepsy (16%), cerebrovascular accident (CVA) (6%),

Table 1
Differential Diagnosis of Alcohol-Related Seizures

Alcohol or sedative drug withdrawal
Noncompliance or inconsistent use of antiepileptic medications
Head trauma (acute or remote)
Idiopathic or cryptogenic epilepsy
Illicit drug toxicity (cocaine, amphetamines, opioids, phencyclidine, MDMA, etc.)
Medication toxicity (antidepressants, antipsychotics, anticholinergics, antimicrobials, isoniazid, propranolol, opioids, theophylline, lithium, lindane, etc.)
Cerebrovascular disease
Intracranial neoplasm
CNS infection (meningitis, encephalitis, abscess, HIV, neurosyphilis)
Metabolic disorders (hypoglycemia, electrolyte disturbances)

nontraumatic intracranial lesions (4%), and toxic/metabolic causes (3%). Hillbom reported similar findings in an older study from Finland *(12)*. Table 1 provides a list of differential diagnoses to consider in ARS.

Pre-existing epilepsy may be exacerbated by alcohol abuse. Chronic alcoholism results in enhanced clearance of antiepileptic medications as well as erratic compliance and a lowering of seizure threshold during periods of partial or complete abstinence. Repeated episodes of alcohol withdrawal may lead to kindling of seizures *(26,27)*. Alcohol abusers have an increased risk for epilepsy. However, epileptic patients overall have a lower prevalence of alcohol abuse, possibly because of warnings from doctors and pharmacists about the increased risk for seizures and medication toxicity *(28)*.

Noncompliance or irregular use of antiepileptic medications has been shown to be a common cause of seizures, including SE in alcohol abusers *(22,29)*. It is therefore good practice in most cases not to prescribe antiepileptic drugs (AEDs) for long-term use in alcoholics, even if there is a known seizure focus. This is discussed in more detail later.

Recreational drug use, as well as the use of certain medications, also has been associated with seizures and should be considered in the differential diagnosis in ARS. Alldredge et al. *(30)* identified 49 seizures induced by illicit drugs in 47 patients from 1975 to 1987. Cocaine was the most commonly implicated drug (32 cases), followed by amphetamine (11 cases), heroin (7 cases), and phencyclidine (4 cases). Most often, there was a single generalized tonic–clonic (GTC) seizure during acute intoxication, but seven patients had multiple seizures and two entered SE. In more recent years, 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"), γ-hydroxy-butyrate (GHB), GHB prodrugs, and ketamine have become popular drugs of abuse, particularly at "rave" parties. MDMA and ketamine can cause seizures, whereas it is debated whether GHB and its prodrugs cause true seizures in humans *(31)*. *See* Chapter 13 for further information about recreational drug use and seizures.

Iatrogenic seizures from prescribed medication use should also be considered in alcoholics. An exhaustive list of medications that potentially may cause seizures is

outside the scope of this chapter, because more complete lists may be found elsewhere (*see* Chapter 13) *(32)*. Some of the medications that should be considered in the differential diagnosis of seizures in the alcohol abuser are listed in Table 1. Too rapid of weaning of narcotics and sedative-hypnotics from patients with long-term (>7 d) ICU care can also result in withdrawal seizures *(11,33)*.

Alcohol abusers are at risk for cerebrovascular structural abnormalities that may result in epilepsy such as SAH *(34)*, intracerebral hemorrhage *(35)*, and ischemic stroke *(36)*. Although there are no randomized, controlled trials of alcohol consumption and stroke, Reynolds et al. *(37)* recently conducted a meta-analysis of observational studies addressing this topic. They found that moderate alcohol consumption resulted in a reduced risk of ischemic stroke but heavy intake was associated with an elevated risk of ischemic and hemorrhagic (intracerebral and subarachnoid) stroke. They looked at habitual but not binge drinking. Other studies addressing the risk of binge drinking have also found an increased incidence of ischemic and hemorrhagic stroke *(34–36)*. Several pathophysiologic mechanisms may contribute to alcohol-related CVAs. Alcohol-induced cerebral vasospasm and hypertension, erythrocyte and platelet aggregation, as well as changes in fibrinolytic activity, coagulation, and bleeding time have been implicated *(37–39)*.

Head injury, whether remote or acute, is a common cofactor causing seizures in the alcoholic patient. In addition, alcohol withdrawal symptoms may mask symptoms of head trauma *(9,12)*. Cerebral atrophy frequently seen in chronic alcoholics predisposes them to intracranial hemorrhage *(40)*. Therefore, one must evaluate the patient with ARS for signs of cranial trauma.

Alcohol-dependent patients may also be at increased risk for seizures resulting from concomitant central nervous system (CNS) infections such as meningitis, abscesses, human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS), and neurosyphilis *(3,41)*. Seizures, including SE are common in patients with HIV. This risk is caused by a direct effect of the virus on the CNS or by focal lesions such as toxoplasmosis, lymphoma, cryptococcal meningitis, or infarction *(42)*. Metabolic derangements, such as hypomagnesemia and renal dysfunction, seem to increase the risk of SE in HIV-infected patients *(43)*.

Although metabolic alterations are not common causes of seizures in the alcohol-dependent patient, they should be considered and treated. Hypoglycemia may cause seizures. However, alcohol-associated hypoglycemia is rarely reported in alcoholics *(44)*. Causes of hypoglycemia in the alcoholic patient include poor nutrition, hypothermia, inhibition of gluconeogenesis, and reduced cortisol levels *(3)*. Hypomagnesemia can cause seizures but usually only at levels less than 0.8 meq/L *(32)*. Although chronic alcoholism is a common cause of hypomagnesemia *(45)*, a randomized, controlled trial of parenteral magnesium showed no significant difference in withdrawal symptoms, including ARS *(46)*. Profound hypophosphatemia may also accompany alcohol withdrawal and at levels less than 1 mg/dL may result in antiepileptic-resistant generalized seizures *(32)*. Hyponatremia may accompany alcoholism and should be corrected to levels greater than 120 meq/L *(32)*. Hyper-

ventilation with associated respiratory alkalosis may also lower seizure threshold in alcoholics *(47)*. Wernicke's disease and the Korsakoff amnestic state, which are encountered almost exclusively in alcoholics in western countries, do not include seizures in the clinical presentation. However, these conditions may be associated with autonomic neuropathy and syncopal episodes that may be confused with seizures. In addition, the confusional state that ensues must be differentiated from postictal confusional states.

Sample Case

A 60-yr-old widow was brought to the ER after being found unresponsive by her daughter. En route to the ER she had three GTC seizures, each lasting about 30 s. In the ER, she received intravenous lorazepam and a loading dose of fosphenytoin before being admitted to the ICU. Phenytoin (PHT) was continued, and lorazepam was used as needed for withdrawal symptoms.

The patient's daughter revealed that the older woman had an extensive history of alcohol abuse, including prior admissions for ARS. The patient would spend what little money she had on alcohol and cigarettes. It was estimated that the patient stopped drinking 2–3 d prior to onset of her seizures because she had run out of funds for buying alcohol. She also had a known arteriovenous malformation (AVM) in the left frontal operculum and had been prescribed PHT for prior ARS but proved to be poorly compliant with her medications.

General examination was normal except for sinus tachycardia of 136 beats/min. Neurologic examination found the patient to be unresponsive to voice and pain but without focal deficits on coma examination. Data from a complete blood count, blood chemistries, hepatic panel, arterial blood gas, and urinalysis were obtained and were significant for an elevated mean corpuscular volume (MCV) (106), hypokalemia (2.7), hypomagnesemia (1.4), and a urinary tract infection.

The patient had no more seizures during her hospital stay but on the second day of admission developed intermittent myoclonic jerking of the right upper and lower extremities. An urgent EEG was obtained and showed no electroencephalographic correlation to the movements. The EEG did show an absence of α rhythm and the presence of low-amplitude fast activity throughout the recording (Fig. 1). The myoclonic activity was attributed to alcohol withdrawal and urinary tract infection and responded to valproic acid (VPA) and low-dose clonazepam, as well as treatment of the infection. An MRI of the brain showed no change in the patient's AVM. She had a slow return of her normal mental status over the following few days, with waxing and waning of confusion and disorientation. Neuropsychological evaluation determined that the patient was nondecisional, and she was discharged in the care of her daughter.

Alcohol-Related Status Epilepticus

Although patients with ARS rarely enter SE *(7,12)*, alcohol withdrawal is a common contributing factor in many cases of SE *(22,29,48)*. From 11 to 28% of cases of SE involve alcohol abuse *(22,29,48,49)*. Indeed, in adult patients with no history
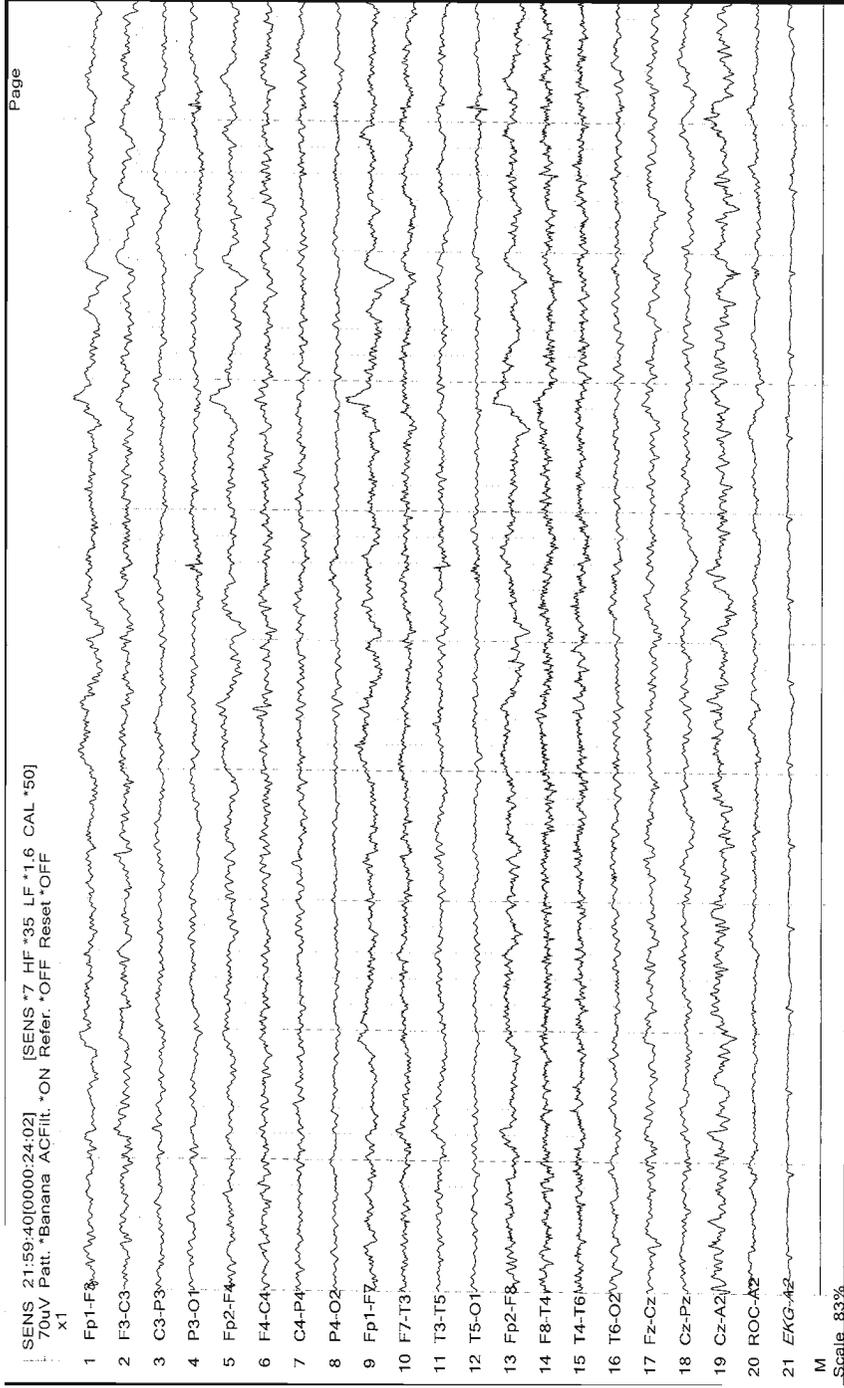
Fig. 1. EEG of a 60-yr-old female alcoholic 1 d after a flurry of ARS and 3–4 d after her last drink. Note the absence of alpha rhythm and presence of low-amplitude fast activity. The patient had a left frontal AVM, but the EEG does not show evidence for this.

of seizures, alcohol abuse was the single most common cause of SE in a study by Lowenstein and Alldredge *(49)*. Alcohol is also occasionally implicated in nonconvulsive status epilepticus (NCSE) *(50)*. Because about half the cases of alcohol-related SE are multifactorial, a search for comorbid etiologies is necessary *(22,29)*. The comorbid conditions to consider in the differential diagnosis of SE in the chronic alcohol abuser are the same as those for ARS without SE (Table 1). Among all cases of SE in adults, discontinuation or irregular use of antiepileptics appears to be the most common etiologic factor *(22,49)*. Because alcoholics usually have erratic compliance with prescribed medications, antiepileptic withdrawal is a common comorbid factor in alcohol-related SE *(29)*. Therefore, prescribing antiepileptic medications for chronic use in alcoholics may be undesirable, even if there is a seizure focus, unless the patient has proven himself to be compliant *(51)*.

Alldredge and Lowenstein *(48)* found that the alcohol abuse history of patients with alcohol-related SE did not differ from the histories of patients experiencing ARS without SE. The typical patient in each group was male, over age 30 yr, with many years of heavy drinking (>300 g of ethanol daily). The SE group tended to be older and had fewer previous ARS. The authors also noted that alcohol-related SE was often the first presentation of ARS, occurring *de novo* in 44% of cases. Focal signs were noticed in 40% of alcohol-related SE cases, but they were not associated with focal CT scan or EEG findings. A lack of structural abnormalities in many cases of focal ARS has been reported by other authors *(1,22)*.

Treatment of alcohol-related SE is similar to that of other causes of SE. Detailed treatment of SE is covered elsewhere in this volume (*see* Chapter 14). Although PHT has been shown to be ineffective in preventing recurrent seizures within the vulnerable 6-h window following a common ARS without SE *(52),* it has been shown to be quite effective in treating ARS with SE. Alldredge and Lowenstein *(48)* controlled alcohol-related SE in about 67% of patients by using PHT, with or without diazepam (DZ). This was similar to their 60% response rate using PHT with or without DZ to treat SE caused by other etiologies *(49)*. Therefore, PHT and benzodiazepines (BZDs) are part of the standard algorithm for treatment of alcohol-related SE *(51,53)*.

Some alcoholics may be taking isoniazid for tuberculosis prophylaxis or treatment. Isoniazid toxicity may cause seizures and status epilepticus by indirectly depleting γ-aminobutyric acid (GABA). Isoniazid binds with pyridoxine, which is needed in the synthesis of GABA. Seizures caused by isoniazid toxicity are resistant to PHT. If an alcohol-dependent patient who is known to also be taking isoniazid is experiencing refractory seizures, intravenous pyridoxine at a dose equivalent to the ingested isoniazid is given. If the dose of isoniazid is unknown, 5 g of pyridoxine is given *(54,55)*.

The prognosis in alcohol-related SE is generally favorable in comparison to other causes of SE such as acute structural problems or metabolic disorders *(49,56)*. In one study *(49)*, 90% of patients with alcohol-related SE had mild or no new neurologic deficits on discharge. However, these patients tend to return to baseline more

slowly than nonalcoholics, regardless of whether sedating medications were used, especially if there are abnormalities on CT scan. About 89% of patients in one study had not returned to baseline consciousness 12 h after termination of alcohol-related SE *(48)*. In general, a longer duration of SE results in a worse neurologic outcome *(49)*.

PATHOPHYSIOLOGY OF ARS

The precise pathophysiology of ARS has not been fully elucidated. It is generally accepted that abstinence or a partial reduction in alcohol intake is a key factor in the pathogenesis of ARS. Two separate research groups report that about one-third of visits to the ER for ARS are on Monday. This pattern was not seen in patients who seize for reasons unrelated to alcohol. These observations support the assertion that ARS are caused by withdrawal from alcohol, seizures being more frequent on Monday because of the relative reduced availability and consumption on Sundays *(12,25)*. Although seizures may occur during intoxication and before alcohol levels reach zero *(9,12,14,15)*, most authors agree that ARS are primarily a withdrawal phenomenon *(1,9,12,22,25,29,48,49)*.

Although there is no known receptor for alcohol, it acts as a CNS depressant by affecting lipids and proteins in the neural membranes. Alcohol potentiates the postsynaptic effects on the $GABA_A$ receptors in the brain, allowing chloride ion influx, and resulting in a hyperpolarization of the membrane. This reduces the firing rate of the neuron, resulting in CNS sedation. The action on the excitatory *N*-methyl-D-aspartate (NMDA) receptor is just the opposite, causing an inhibitory effect on this receptor, further sedating the CNS *(57)*. Ethanol also acts on non-NMDA calcium-involved systems as well as on serotonergic, dopaminergic, noradrenergic, opioid, and adenosinergic neural pathways *(58,59)*.

Chronic exposure to alcohol results in downregulation of the $GABA_A$ receptors, causing tolerance to alcohol-induced chloride ion influx *(57)*. On the other hand, the NMDA receptor undergoes upregulation upon chronic exposure to alcohol *(60)*. Certain areas of the brain appear to be more sensitive to the effects of chronic alcoholism *(57)*. The increase in NMDA binding sites has been shown to occur experimentally in the hippocampus of rats *(61)*. These changes presumably act as a compensatory mechanism for alcohol's sedating effect on the CNS. The relative excess of NMDA receptors and deficiency of GABA receptors in chronic alcoholism may result in enhanced neuroexcitation and reduced neuroinhibition. When the sedating influence of alcohol is lifted during abstinence, the result may be the onset of signs and symptoms of alcohol withdrawal, including ARS *(60)*. Because benzodiazepines and barbiturates are also potentiating to the $GABA_A$ receptor effects, they have cross-tolerance to alcohol and may alleviate the alcohol withdrawal signs and symptoms. The hypomagnesemia and zinc deficiency associated with chronic alcoholism may exacerbate the neurotoxicity that is mediated by NMDA receptor because both magnesium and zinc are negative modulators of NMDA receptor function *(60)*. However, magnesium supplementation does not reduce withdrawal sever-

ity or the likelihood of seizures or delirium *(46)*. The clinical relevance of the deranged zinc metabolism is uncertain *(62)*.

It is also hypothesized that ethanol withdrawal leads to permanent changes in the neurons, resulting in a process of kindling in which seizures become more frequent and severe with each subsequent episode of withdrawal *(26,27)*.

Elevated homocysteine levels have been reported in alcoholics and may also play a role in alcohol withdrawal symptoms *(63)*. Homocysteine may be metabolized into excitatory amino acids. These amino acids, as well as homocysteine itself, can act as agonists at the NMDA receptor, resulting in increased excitatory postsynaptic potentials *(64,65)*. Therefore, the hyperhomocysteinemia may lead to a relative excess of excitatory neurotransmitters in comparison to neuroinhibitory transmitters in the hippocampus *(66)*, resulting in homocysteine-induced ARS.

COMORBID MEDICAL CONDITIONS

It is not the goal of this chapter to provide a comprehensive discussion of the many complicating medical problems that may occur in a patient during alcohol withdrawal. However, it is useful to mention some of the more common as well as dangerous conditions seen in these patients in the ICU. An estimated 71% of detoxifying patients have physical morbidity, primarily hepatic abnormalities, trauma, and infections *(4)*. Gastrointestinal (GI) disease, anemia, and malnutrition are also well-known complications *(67)*. Additional drug use is common in alcohol abusers, particularly BZDs. In one study, more than 41% of alcohol-dependent patients were abusing other drugs *(16)*. As mentioned earlier in this chapter, polysubstance abuse may delay the onset of ARS. Trauma is also common in alcoholism. An estimated 50–60% of trauma patients are chronic alcoholics, and withdrawal may cause significant morbidity following trauma or surgery *(68)*. Thiamine deficiency is relatively common, occurring in 30% of chronic alcoholics, although the Wernicke–Korsakoff syndrome occurs in only 3–10% *(7)*. Fluid and electrolyte abnormalities as well as hypoglycemia may also occur in the alcoholic and are discussed elsewhere in this chapter. Coma in the alcohol-dependent ICU patient may be caused by several conditions, including acute alcohol poisoning, concomitant drug overdose, head trauma, hepatic failure, ICH, hypoxic encephalopathy, hypoglycemia, meningitis, hypothermia, alcoholic ketoacidosis, NCSE, and methanol or ethylene glycol poisoning *(6,50)*.

EVALUATION

When evaluating an alcohol-dependent patient who presents with a seizure, the physician should search for causes other than alcohol that may have resulted in seizure activity. In particular, one must be careful not to overlook life-threatening conditions such as ICH, hypoglycemia, CNS infection, and metabolic derangements. Differential diagnoses to consider are listed in Table 1. The management of new-onset ARS consists of history, repeated physical examinations, CT scan or MRI, laboratory testing, and EEG.

Table 2
Comorbid Medical Conditions in the Alcohol-Dependent Patient

Cardiovascular
    Hypertension, hypotension, dilated cardiomyopathy, atrial and ventricular arrhythmias
Gastrointestinal
    Pancreatitis, gastritis, esophageal varices, GI bleeding, alcoholic hepatitis, cirrhosis,
       liver failure
Neurologic
    Wernicke–Korsakoff syndrome, epilepsy, meningitis, head trauma, ischemic or hemor-
       rhagic stroke, peripheral neuropathy, cerebellar degeneration
Hematologic
    Anemia, leukopenia, thrombocytopenia, coagulopathy
Infectious
    Meningitis, pneumonia, cellulitis, spontaneous bacterial peritonitis, HIV
Metabolic
    Hypoglycemia, electrolyte disturbances, concurrent drug ingestion or withdrawal,
       nutritional deficiencies, alcoholic ketoacidosis, acute alcohol poisoning, methanol
       or ethylene glycol poisoning
Miscellaneous
    Rhabdomyolysis (resulting from alcohol toxicity, hypokalemia, hypophosphatemia),
       trauma, hypothermia, poor wound healing, cancer

(Adapted from refs. *6*, *13*, and *69*.)

If possible, a history should be obtained from the patient, family, friends, or emergency personnel. Details should include past medical history, any history of seizures, drinking history including any episodes of delirium tremens, when and why drinking was stopped, recent or remote serious head trama, medications, and any medication compliance problems.

Physical examination should include a careful assessment for focal signs, level of consciousness, head trauma, signs of intracranial hypertension or herniation, and signs of delirium tremens, as well as a general physical examination to evaluate for hepatic failure, coagulopathy, needle tracks, and other comorbid conditions (Table 2). Repeated neurologic examinations may help reveal declining mental status or the development of focal signs that would necessitate an urgent CT scan.

The selection of laboratory tests depends on individual indications. The intensivist should consider obtaining a complete blood count, as well as glucose, electrolytes, blood urea nitrogen, creatinine, prothrombin time, anticonvulsant levels, calcium, magnesium, phosphorus, serum or urine toxicology, alcohol level, and blood gas *(3)*. Cervical spine precautions (Aspen or Philadelphia collars) and films should be considered if there is suspicion of a fall or head injury. A chest X-ray should be ordered in the patient with fever or pulmonary symptoms or signs. A lumbar puncture (LP) should be performed after the CT scan if there is any suspicion of meningitis. Evaluation for other comorbid conditions seen in the alcoholic should also be considered, depending on the clinical scenario (Table 2).

All new-onset ARS patients require an emergent noncontrasted CT scan, regardless of whether the seizure was focal or generalized. ARS may be focal or generalized, and the focal seizures may or may not be related to underlying focal pathology *(1,12)*. Earnest et al. *(70)* found that in patients with a first-time ARS but no other signs of major intracranial pathology, the CT scan disclosed a clinically significant intracranial process in 6.2% of patients. Of these CT-positive patients, 44% were alert, had no focal signs, and no signs of trauma. These authors concluded that history or signs of minor head trauma, headache, level of consciousness, or minor focal neurologic signs were not significantly associated with intracranial lesions (positive CT) when tested statistically. In slight contrast, Feussner et al. *(71)* studied the value of CT scan in ARS and concluded that a careful neurologic examination adequately determines which patients need a prompt CT scan. An emergent CT scan is not necessary in the patient with a documented history of focal ARS, provided the prior workup included brain imaging, the seizure had identical presentation, there are no new focal neurologic findings, there is no indication of recent head injury, and there is prompt return to baseline *(51)*.

An EEG should also be obtained on all patients with new-onset ARS. It may be ordered nonurgently, perhaps at follow-up. The aim is to identify patients with an underlying seizure focus, which may necessitate, for individuals who can be relied on to be compliant, long-term treatment with antiepileptic medications. An abnormal interictal EEG suggests underlying epilepsy or a symptomatic focus unrelated to ARS *(17)*. For the patient admitted to the ICU, an EEG may be necessary in the management of convulsive SE or NCSE, or to help differentiate delirium tremens from other causes of clouded sensorium *(6,9)*.

TREATMENT

The treatment of single or recurrent ARS is essentially the same as treatment of the alcohol withdrawal syndrome itself *(72)*. The pharmaceutical management of alcohol withdrawal requires the use of BZDs, often with the addition of other classes of medications. Although most of these adjunctive medications neither prevent nor treat seizures, they help relieve many of the other manifestations of the syndrome. This combined approach allows lower overall doses of individual medications. The physician must also keep in mind that alcohol ingestion alters the clearance of hepatically metabolized medications, including certain antiepileptic medications. Short-term ingestion causes a reduction in clearance of many drugs while alcohol is in the body, whereas there is increased clearance of drugs when alcohol is eliminated from the body in a chronic alcoholic. This potential effect on drug metabolism is important in drugs with a narrow therapeutic range such as PHT, and less important in medications with a wide therapeutic range, such as DZ *(7)*. Comorbid medical conditions are not infrequent in the alcohol-dependent patient and should also be considered (Table 2). The decision to admit a patient to the hospital for an ARS depends on several factors (Table 3). For first-time ARS, the patient should be

Table 3
Criteria for Hospital Admission

New-onset seizure in the chronic alcohol abuser
Recurrent seizures[a]
Moderate to severe alcohol withdrawal[a]
Comorbid illness requiring treatment (infection, arrhythmia, liver failure, dehydra-
   tion, etc.)[a]
History of severe alcohol withdrawal
Fever higher than 38.5°C
Wernicke's encephalopathy
Recent head injury with loss of consciousness[a]
Concurrent sedative ingestion[a]

[a]Relative reasons for ICU admission.
(Adapted from refs. *51*, *72*, and *73*.)

admitted to facilitate the workup of new-onset seizures. Alcohol-dependent patients often fail to comply with outpatient follow-up.

Supportive Care

Management of the seizing alcohol-dependent patient involves stabilizing the patient with attention to airway, breathing, and circulation. A quiet, nonstimulating environment is ideal, and the use of physical restraint should be kept to a minimum to help prevent worsening agitation. It may be necessary to intubate the patient in the ICU and monitor with continuous electrocardiograms (EKGs) and pulse oximetry. An intravenous line should be established and the patient given 100 mg of thiamine to reverse or prevent the Wernicke syndrome. This should be given prior to any therapy that involves glucose to prevent further depletion of thiamine with resultant precipitation of the Wernicke syndrome. Duration of thiamine therapy is controversial, but some clinicians continue this dose for 3 d *(2)*. Finger-stick glucose levels should be determined and glucose given intravenously if necessary. However, one should avoid excess glucose unnecessarily, as hyperglycemia may worsen neurologic injury in cerebral ischemia *(74,75)*. Intravenous glucose therapy may also cause substantial falls in serum potassium and phosphate levels *(62)*.

The role of magnesium in seizures is controversial *(45)*. It is common practice to replace the magnesium deficit in chronic alcoholic patients. Magnesium sulfate given in an intramuscular or intravenous dose of 1 g every 6–12 h for 48 h is one protocol. Alternatively, magnesium oxide may be given orally in a dose of 250–500 mg four times daily for 48 h, although diarrhea may occur *(6)*. Hypocalcemia, hypokalemia, and hypophosphatemia may be associated with hypomagnesemia; correction of the magnesium deficit helps in their resolution *(45,62)*. However, as discussed earlier, magnesium supplementation does not appear to alter withdrawal symptoms *(46)*. Magnesium administration in patients with renal failure should be undertaken cautiously.

Hypokalemia in the alcoholic may be a result of inadequate intake, diarrhea, vomiting, secondary hyperaldosteronism, magnesium depletion, or shifting of the potassium into the cells as a result of alkalosis or intravenous glucose therapy. The serum potassium concentration corresponds poorly to total potassium balance, and potassium requirements may be massive *(62)*. Hypokalemia has been suggested as a factor in the genesis of delirium tremens. However, potassium supplementation alone will not reverse delirium *(6)*.

Patients experiencing alcohol withdrawal may also have hyponatremia as well as overhydration or dehydration. Each should be gently corrected. The patient's need for fluid and electrolytes depends on losses. Without significant GI fluid losses, one should not assume that the withdrawing patient is dehydrated. However, patients in severe withdrawal may have extensive fluid replacement needs as a result of hyperthermia, diaphoresis, and vomiting. If renal function is normal, a urine specific gravity of 1.025 and a urine sodium concentration of less than 10 meq/L comprise an indication of volume depletion. Daily weights, and orthostatic BP and pulse, can also help determine fluid status. If serum sodium is normal, volume deficits are best corrected with 5% dextrose in normal saline. Hyponatremia may result from overhydration from excessive secretion of antidiuretic hormone or from volume contraction from fluid losses, and replacement fluid type should be selected accordingly. In most cases, normal saline is appropriate treatment instead of fluid restriction because these patients tend to have volume contraction. Sodium level should be corrected at least to 120 meq/L, but the rate of correction is controversial. Central pontine myelinolysis has been reported with rapid correction *(2,4,6,7,32,76)*.

As mentioned earlier, hypophosphatemia may occur in alcohol abusers and is a possible cause for seizures *(32)*. Other problems that may occur with very low levels include bone pain, stiffness, weakness, loss of appetite, intention tremors, rhabdomyolysis, acute hemolysis, acute respiratory failure, and cardiac failure *(2,6)*. Therapy should be initiated if the serum phosphate concentration is less than 2.5 mg/dL. Supplementation may be by mouth or intravenously, starting at 20–40 mmol of sodium or potassium phosphate. Caution must be exercised in renal failure, and phosphate should not be given if renal failure is attributable to rhabdomyolysis because the damaged muscle will release phosphorus. Other contraindications to phosphate use are hypercalcemia and hypoparathyroidism *(62)*.

Hypocalcemia in the alcoholic is usually the result of a metabolic disturbance such as hyperphosphatemia, hypomagnesemia, or some other cause of functional hypoparathyroidism. Calcium replacement is not recommended except in the treatment of hyperkalemic or hypocalcemic arrhythmias, tetany, hypocalcemic convulsions, or magnesium therapy overdose *(45,62)*. The metabolic disturbance causing the hypocalcemia must be treated *(62)*.

The alcoholic in withdrawal should be evaluated for acid–base derangements and managed appropriately. Acute alcohol ingestion produces a rise in urinary excretion of ammonium and titratable acid, but the immediate effects are clinically

inconsequential. Chronic alcohol abuse produces various acid–base abnormalities that are secondary effects of alcohol and not directly caused by the alcohol itself. Respiratory acidosis may result from the respiratory depressant effects of alcohol. Metabolic acidosis in the alcoholic may be present because of alcoholic ketoacidosis or methanol or ethylene glycol poisoning. It may also be the result of bicarbonate loss in the stool owing to lactulose use. Type 1, type 2, or a mixed form of renal tubular acidosis may also occur if there are protein or phosphate deficiencies or if cirrhosis develops. Patients often hyperventilate during alcohol withdrawal. This leads to respiratory alkalosis, hypokalemia, hypomagnesemia, hypophosphatemia, and compensatory secondary hyperchloremic acidosis. Emesis may lead to metabolic alkalosis *(6,62)*.

If meningitis is suspected, blood cultures should be obtained and empiric antibiotics given without delay. If an LP is performed within 1–2 h after the antibiotics were given, the CSF cultures will remain positive in the majority of patients *(77)*.

Benzodiazepines

The mainstay of treatment of alcohol withdrawal and ARS is the use of BZDs. Because it is not possible to predict which patients will have recurrent seizures, BZDs should be administered to all patients presenting with ARS *(23,25)*. These agents have largely replaced other sedative medications such as chloral hydrate, paraldehyde, and barbiturates. BZDs act on the GABA receptors and are cross-tolerant to alcohol, effectively relieving the signs and symptoms of alcohol withdrawal. They have fewer respiratory and cardiac depressant effects than other CNS depressants *(51)*. They are widely used in the neurological ICU for their anxiolytic, amnestic, and anticonvulsive properties and have the potential advantage of decreasing cerebral metabolism and ICP *(78)*. Several types of BZDs have been used successfully in alcohol withdrawal. All are effective in controlling signs and symptoms of alcohol withdrawal, but the longer-acting ones appear to be better at controlling seizures *(80)*. Although there does not appear to be one BZD with clear superiority in the treatment of alcohol withdrawal, lorazepam has some advantages in that it has an intermediate half-life and hepatic metabolism with nonactive metabolites; moreover, it can be administered by mouth, intramuscularly, or intravenously *(51)*. The low lipophilic properties of lorazepam allow it to remain in the serum longer, providing an anticonvulsant effect of 6–12 h, making it an ideal medication in the treatment of ARS *(79)*.

The goal of using BZDs is to give enough to keep the patient calm but awake. One protocol is to use lorazepam in an intravenous dose of 0.5–4.0 mg, depending on the severity of withdrawal. The dose can be repeated at 15- to 30-min intervals for patients in severe withdrawal, who should be observed in the ICU *(2,51)*. For moderate withdrawal, an oral dosing schedule may be used, giving 6–7 mg of lorazepam a day in three divided doses, tapering to 1–2 mg/d over 4 d *(51)*. Another approach is to give 5 mg of DZ intravenously every 5 min until the patient is calm *(6)*. Short-acting midazolam at an infusion rate of 20–75 mg/h has also been used and may be considered for critically ill patients *(51,81,82)*. Abrupt discontinuation of BZDs should be avoided to prevent BZD withdrawal seizures.

Although fixed-schedule dosing of BZDs is safe and effective in the treatment of alcohol withdrawal, symptom-triggered therapy has been shown to be as effective, with lower requirements for medication and shorter hospital stays *(80)*. This calls for the use of a structural assessment scale, such as the revised CIWA-A scale for monitoring of signs and symptoms. Although symptom-triggered therapy alone may be adequate to prevent ARS *(80)*, it is still recommended to treat all patients presenting with an ARS with BZDs as soon as possible to prevent recurrence *(73)*.

If the patient enters delirium tremens, massive amounts of BZDs may be required in the ICU. Administration of as much DZ as 2640 mg in the first 48 h of treatment has been reported *(83)*. Trauma patients experiencing withdrawal often require much larger doses than nontrauma patients to control signs and symptoms of withdrawal *(68)*. When very large doses of BZDs are used, the patient must be watched closely for respiratory depression. Likewise, if the patient has high levels of serum alcohol, the addition of a BZD may result in respiratory depression *(73)*.

Antiepileptic Medications

Carbamazepine (CBZ) has been used successfully to treat mild to moderate alcohol withdrawal symptoms and has been used widely in Europe for this purpose *(80,84)*. Gabapentin may also show some benefit in mild to moderate withdrawal *(85)*. There are fewer data supporting the use of antiepileptic medications in the treatment of ARS or delirium *(80)*. A placebo-controlled, double-blinded study by Hillbom et al. did not find CBZ or VPA to be useful in treating alcohol withdrawal seizures *(86)*.

Prophylactic antiepileptic treatment with PHT has not been effective in reducing primary ARS. In a randomized study of 831 patients who were admitted to a detoxification unit, PHT-treated patients had more seizures (3%) than clorazepate-treated patients (0.7%) and fewer than placebo-treated patients (6.2%) during the first 96-h period *(87)*. Although PHT has been shown to be effective in alcohol-related SE *(48)*, it has been shown to be ineffective at preventing recurrent ARS within the vulnerable 6-h period following the initial ARS *(88–90)*. In addition, intravenous PHT administration carries the risk of hypotension, arrhythmia, and cardiac arrest, and chronic oral PHT has several long-term consequences *(91)*. Prescribing antiepileptic medications for chronic use in an alcoholic may have adverse consequences. Poor compliance, with erratic use of antiepileptic medication, results in an increase in seizure frequency caused by withdrawal and possibly a kindling effect *(92)*. In addition, antiepileptic withdrawal is a common cause of SE *(22,49)*. Therefore, prescribing PHT to a patient with a known seizure focus but erratic compliance should be discouraged *(51)*.

On the other hand, PHT may be used in ARS if a patient with a known seizure focus is normally compliant and has presented with a subtherapeutic level. A loading dose of PHT may be administered intravenously in such cases. An oral loading dose of PHT can be given but would not reach a therapeutic level until the vulnerable 6-h period had passed, so intravenous loading is preferred *(51)*. For epilepsy

patients who are on antiepileptic medication and abuse alcohol, abstinence or tapering of alcohol intake may result in an increased risk of seizures because of increased AED metabolism owing to a relative lack of competing substrate *(28)*. Therefore, AED levels must be monitored when the patient stops drinking.

PHT may also be used to treat suspected trauma-induced seizures in a patient who is intoxicated or experiencing alcohol withdrawal during the acute phase of injury *(51)*. Temkin et al. demonstrated that PHT significantly reduced seizures during the first week following head injury but did not reduce late seizures *(93)*.

Finally, PHT is indicated in alcohol-related SE, as discussed earlier *(48)*. Fosphenytoin, the intravenous water-soluble phosphate ester of PHT, is safer and can be used in place of intravenous PHT. Unlike PHT, fosphenytoin may also be given intramuscularly *(91)*.

Antihypertensive Agents

Antihypertensive medications can be used to treat the hyperadrenergic manifestations of alcohol withdrawal such as hypertension, tachycardia, and tremors. Clonidine has been shown to be effective in treating mild alcohol withdrawal signs and symptoms but not ARS *(80,94)*. Clonidine may also alleviate anxiety, diaphoresis, and insomnia associated with withdrawal *(7,94)*. β-Adrenergic blockers such as propranolol and atenolol may also be considered as adjunctive medications in alcohol withdrawal, but their role in ARS is limited because, as with clonidine, they cannot be expected to treat or prevent seizures. Furthermore, β-adrenergic blockers may cause delirium or mask the diagnosis of delirium tremens and have other contraindications such as hypotension, congestive heart failure, insulin-dependent diabetes, and asthma or bronchospasm *(51,95)*.

Haloperidol

Haloperidol, which can be given intravenously, intramuscularly, and orally, is a useful adjunct in patients requiring large doses of BDZs for the treatment of major alcohol withdrawal or delirium tremens in the ICU. The following very high doses have been used safely in patients with serious underlying disease: 240 mg of haloperidol and 480 mg of lorazepam in 24 h *(96)*. Haloperidol, unlike the phenothiazines, does not appear to cause seizures in humans *(51,80)*. No randomized studies of its use in ARS are available. Its use should be limited to an ICU setting because of the risk for respiratory depression and hypotension. Patients treated with high intravenous doses of haloperidol need daily EKGs in an ICU to avoid widening of the QRS complex and the risk of torsades. Magnesium level should be monitored and kept at the high normal range.

Propofol

Propofol interacts at the GABA-mediated receptor but not through the BZD site *(97)*. It has been used to control refractory delirium tremens *(98)* as well as refractory SE *(53)*. It has been reported to cause seizures in high doses, but instances are rare and the mechanism is unknown *(98)*.

Barbiturates

PB is cross-tolerant with alcohol, is an extremely effective anticonvulsant, and is effective in controlling alcohol withdrawal. However, disadvantages such as hepatic enzyme induction and risk of respiratory suppression make its use in the United States uncommon *(13)*. However, in an ICU setting, PB can be a useful adjunct to refractory seizures or SE.

Intravenous Alcohol

There are no controlled trials evaluating the use of ethanol in alcohol withdrawal. It is expensive to prepare, requires frequent monitoring, has a narrow therapeutic index, and has multiple medical side effects. Routine use cannot be recommended *(7,13)*.

Alcohol-Related SE

Although PHT is not useful in preventing recurrent ARS, it has been shown to be useful in treating alcohol-related SE *(48)*. Alcohol-related SE is treated like other forms of SE (BZDs, PHT, etc.) and generally responds well to standard treatments *(48,49,72,99)*. *See* section on alcohol-related status epilepticus for further discussion, and Chapter 14.

Outpatient Treatment

Outpatient treatment of ARS may be considered if the patient meets several criteria. The patient must have a known history of ARS and after a 6-h observation period must be fully awake and ambulatory, without recurrent seizures or signs of moderate to severe withdrawal; vital signs and laboratory values must be normal *(73)*. Other causes of seizure must be ruled out by history, physical examination, and/or diagnostic tests. Patients with concomitant sedative abuse should be considered for admission, because withdrawal seizures are delayed in these individuals *(72)*. Further criteria precluding outpatient treatment are listed in Table 3. During the observation period, a test dose of 1–2 mg of lorazepam, 10–20 mg of DZ, or 50–100 mg of chlordiazepoxide can be given orally. The outpatient dosing schedule depends on the severity of symptoms. One outpatient protocol consists of 1–2 mg of lorazepam three times a day, tapering over 3–6 d. This is just a guideline, and the treatment should be individualized *(51)*. Close follow-up should be arranged. Ideally the patient will be discharged home with a close family member or nonalcoholic friend to help the patient abstain, take the medications properly, eat properly, and attend follow-up appointments. Admission to a detoxification or rehabilitation unit should be considered if a safe disposition is not otherwise possible.

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12

Seizure-Inducing Drugs Used for the Critically Ill

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SUMMARY

Critically ill patients are subjected to numerous medication effects during their stay in the intensive care unit (ICU). Some of them have epileptogenic potentials. The most common pathophysiologic mechanism is through blockade of the γ-aminobutyric acid (GABA) receptor, and the most commonly used family of ICU drugs, reducing the seizure threshold, is the antibiotics. The exact role of these medications in inducing a clinical or subclinical seizure, in the context of cerebral injury or other multiorgan failure, is in many cases unclear. Fortunately, the ability to prevent seizures in critically ill patients is within our grasp. However, the intensivist should always seek a medication as the cause of the witnessed seizure and should consider replacing it with another having less epileptogenic potential.

To minimize seizures, the same cautious measures used to minimize or eliminate any unwanted drug side effect should be followed. Always attempt to start and keep the patient on the lowest dose of the medication necessary to exert the desired therapeutic effect. When upward titration in dosage is necessary, increase slowly, keeping a watchful eye on all laboratory and clinical indicators of success or failure. Free levels of antiepileptic or other medications must be considered in the critically ill because of the numerous factors affecting their final action on the target in the central nervous system. A GABAergic receptor agonist antiepileptic drug should be used as first-line antidote in most of the cases.

Key Words: Medication; antiepileptics; antibiotics; seizures.

INTRODUCTION

Seizures occurring in the critically ill patient can be a devastating occurrence. Our role as clinicians is to differentiate among seizures caused by organic disease, by the consequences of the offending sickness itself, and by the medication used to treat the disease or sickness.

Medications, although intended to assist the patient in fighting a particular illness or disease state, may themselves complicate the clinical picture by creating hazards of their own. A meta-analysis performed by Lazarou and colleagues found the incidence of severe adverse drug reactions (ADRs) in hospitalized patients to be 6.7% between 1966 and 1996 *(1)*. Furthermore, they found ADRs to be the sixth leading cause of death in 1994, ranking ahead of diabetes and pneumonia *(1)*. Although seizures caused by medications will not always lead to death, they should be classified as a major ADR, or a "noxious, unintended, and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy" *(2)*. This definition does not include instances in which overdoses, either intentional or accidental, cause the untoward effect. Obviously the risk of medications causing an adverse event in overdose situations is extremely elevated, with a hazard risk exceeding the previously stated 6.7%, and must be avoided at all costs.

The actual rate of occurrence of medication-induced seizures has been difficult to calculate largely because of the lack of clinical studies involving the subject. Largely, associations between medications and seizure risk have been based on clinical assumption and case reports. The Boston Collaborative Drug Surveillance Program noted that the incidence of drug-induced seizures approximates 0.08% (26 of 32,812 patients) *(3)*. Many medications have been implicated, but the San Francisco General Hospital review listed the drugs most commonly reported to cause seizures (as a percent of medication induced witnessed seizures) as follows: psychotropics (35%), isoniazid (20%), bronchodilators (10%), stimulants (10%), and insulin (10%) *(4)*. Over 75 drugs have been associated with seizure induction, and that list will continue to grow as more medications are discovered, tested, and released *(5,6)*.

The overall incidence of first seizures occurring in the general population approximates 0.073–0.086%. Therefore, for a drug to be implicated as the cause of the seizure, the rate of seizures associated with the administration of that drug must exceed approx 0.08% *(7)*. Note that this percentage is very close to the incidence linked to medication administration as reported by the Boston Collaborative group *(3)*. The dilemma is clear.

The incidence of drug-induced seizures occurring in critical care patients may be even more difficult to elucidate. Patients in this special subpopulation may be challenging to assess secondary to an overall depressed state of consciousness or drug-induced paralysis. Subclinical seizures, which are not visible to the outward observer and can be referred to as nonconvulsive seizures or status epilepticus (SE) (if of prolonged duration), may be occurring in these patients.

Table 1
Patient-Specific Predisposing Factors

Pre-existing neurologic disorder (including, but not limited to, epilepsy)
Brain trauma
Strong family history of seizure disorder
Organ dysfunction
Acetylator status

(Adapted from ref. *7*.)

Most medication-induced seizures occur in patients already possessing a predisposition to seizure (Table 1). A patient may have a history of seizure or epilepsy that is not properly communicated to the health care team. He or she may have a family history of seizure that was unknown not only to the health care team but to the patient as well.

Patients are not solely responsible for all the risk for medication-induced seizures. Medications themselves carry certain risks that must be considered before they are used to treat any particular patient (Table 2). There is always a challenge to evaluate the risk for seizures attributed to drugs and the relative risk among a class of drugs. Data are derived from various sources, including in vitro techniques on tissue samples (with intra- and extracellular potential recordings), animal models of epileptogenicity (seizures induced electrically or through other local or systemic chemical administration), and small observational human studies (case reports or case-control studies) *(8)*. The amount of relevance that the prehuman study results have for the human drug experience is always an issue to be addressed late in this process.

Some medications possess an intrinsic epileptogenicity that could cause seizure in virtually all patients if given fast enough and in large enough doses. Unfortunately, complete awareness of medications utilized is not always awarded to the health care team. Prior to hospital admission, the patient may have been medicated, legally or illegally, with substances that by themselves, or through their withdrawal, could predispose to neurologic insult.

Through interactions in drug metabolism, an effective overdose of a medication may be seen at an apparent low or commonly used therapeutic dose. For example, two widely used antidepressant medications belonging to the selective serotonin reuptake inhibitor (SSRI) class, fluoxetine and paroxetine, inhibit the liver isoenzyme CYP2D6. This enzyme is responsible for the elimination of another class of antidepressant medications, the tricyclic antidepressants (TCAs). Inhibition of this metabolism can result in an effective and insidious TCA overdose resulting from a previously stable and nontoxic dosage of the TCA *(8)*.

Patient Risk Factors Specific to Critical Care

Many patient-related risk factors are particularly encountered in the critical care setting and are not commonly seen in other areas of medical practice. Acute-onset

Table 2
Medication-Related Predisposing Factors

Intrinsic epileptogenicity
Metabolic pathway
Ability to permeate blood–brain barrier (lipophilicity, molecular weight, protein binding affinity, ionization)
Route of administration
Dose needed for intended efficacy
Intrinsic hepatic induction/inhibition

(Adapted from ref. *7*.)

seizures in the context of traumatic brain injury, meningitis, anoxic injury, vasculitis, or other neurologic diseases, although not necessarily common, complicate not only the issue of seizure identification but appropriate medication selection as well.

Other systemic derangements also complicate seizure occurrence and presentation in critical care. Issues such as multisystem organ dysfunction, sepsis, and alterations of typical volume of distribution resulting from postoperative fluid shifts or dialysis/continuous venovenous hemofiltration (CVVH) further complicate medication choice in this unique setting.

Table 3 classifies medications commonly used in the intensive care setting according to how much risk of seizures they pose in the critical care patient. Although not a comprehensive list of all medications known to cause seizures because medicine continues to encounter and report new adverse drug events every day, it may be a useful tool for the health care providers in the intensive care unit (ICU).

ELECTROLYTE MANAGEMENT

Seizures do not necessarily occur as a result of direct neural tissue receptor binding or modification induced by a specific medication. Therefore, one must consider the changes any given medication can make not only to the nervous system itself but to the body as a whole. Derangements in overall chemical, nutritional, and fluid homeostasis may increase the epileptogenicity of a specific medication. Many medications used in everyday medical practice have the potential of inducing a wide range of electrolyte shifts, although such a discussion is beyond the scope of this chapter (*see* Chapter 10).

ENDOCRINE MANAGEMENT

Levothyroxine

Exogenously administered thyroid hormone has been shown to cause increased seizure frequency in animals and humans *(5,10)*. This mechanism of induction is currently not well understood. An in vivo imbalance in thyroid hormone has also been known to cause seizures. The mechanism by which thyrotoxicosis induces seizures is also yet to be fully understood *(5)*. Chapter 6 offers further discussion of this topic.

Table 3
Incidence of Seizures Caused by Medications Used in Therapeutic Doses for Appropriate Indications

Common	Occasional	Rare to never
Meperidine	General anesthetics	Antidepressants
Phenothiazine antipsychotics	β-Lactam antibiotics	Anticonvulsants
Clozapine	Isoniazid	Lidocaine
Flumazenil[a]	Theophylline	Narcotics (except
	Alkylating agents	meperidine)
	Butyrophenone antipsychotics	Quinolone antibiotics
		Antivirals
		Cardiac medications

[a]Only when administered to patients using benzodiazepines or a mixed overdose.
(Adapted from ref. *9*.)

TOPICAL ANESTHETICS

Cocaine

Although often thought of as strictly a drug of abuse, cocaine has long been approved by the US Food and Drug Administration for medical use as a topical anesthetic. Seizures have been reported in conjunction with this legal use *(11)*. Toxic effects of the drug are produced through cocaine's blockage of sodium channels *(12)*. When cocaine is utilized in supratherapeutic doses, such as those seen in illegal use, the sleep deprivation induced by its stimulant properties may further exacerbate the epileptogenicity of the drug *(12)*.

Treatment of the cocaine-induced seizure with antiepileptic drugs (AEDs), which also have therapeutic action via sodium channel blockade, may actually worsen the toxic effects of cocaine *(12,13)*. Such antiepileptics, which should be avoided, include carbamazepine (CBZ), lamotrigine (LTG), and phenytoin (PHT) *(13)*. Benzodiazepines (BDZs), the drugs of choice for treating cocaine-induced seizures, improve survival in animal models *(13,14)*. In addition, proper education of the appropriate dosage and usage of cocaine is necessary to help prevent the unintended incidence of adverse drug events.

Lidocaine

Although lidocaine-induced seizures are usually associated with doses utilized for cardiac resuscitation and stabilization, toxic side effects of lidocaine have been reported when the anesthetic is used for local effects, in which the drug is accidentally injected intravenously. Lidocaine is metabolized in the liver, not through the cytochrome P450 (CYP450) system common to many drug metabolic pathways but instead through *N*-demethylation to monoethylglycinexilide (MEGX), which is believed to lower the seizure threshold *(15)*. The definitive role of these metabolites with respect to seizure induction remains unclear.

Serum concentrations of this drug are extremely useful in delineating the proconvulsant risk apparent in any given patient. Serum concentrations between 0.5 and 5 µg/mL have been shown, in experimental models, to decrease epileptiform discharges and secondarily generalized seizures *(15)*. Lidocaine may possess anticonvulsant properties at blood levels less than 5 mg/dL, because serum concentrations below this level have been observed to abolish cortically induced facilitation of motorneurons *(9,15)*. These lower doses of lidocaine have in fact been used to suppress SE in the clinical setting *(4)*. Lidocaine levels greater than 8–9 mg/dL have been repeatedly associated with an increased incidence of seizures *(15)*.

The mechanism by which lidocaine causes seizures is not completely understood, as is the case with most medications. However, it is thought that increased lidocaine levels selectively block the body's own inhibitory mechanisms through selective blockade of inhibitory cortical synapses and neurons. An overall increase in relative cortical excitability, culminating in convulsive activity, has been observed *(15)*.

The lidocaine-induced seizures in experimental animal studies typically start from the amygdala. Thus, a higher incidence of partial seizures should be expected with the use of lidocaine in patients predisposed to having partial seizures; however, this is not true. Seizures are typically short-lived and generalized, ranging, on average, from a few seconds to 1–2 min *(15)*. Early clinical indicators of impending lidocaine toxicity include confusion, slurred speech, nystagmus, and muscle tremors *(15)*. Not all patients have the same risk for developing lidocaine-induced seizures. Patients with a history of renal or hepatic failure, old age, congestive heart failure, and/or shock appear to be at the highest risk *(9)*. Lidocaine must be used very cautiously, and serum concentrations must be monitored in these patient populations. As with cocaine, the treatment of seizures induced by local anesthetics includes BDZs, barbiturates, and/or propofol *(16)*.

Bupivacaine

Bupivacaine, another local anesthetic, is similar to lidocaine not only in therapeutic action, but in epileptogenic activity as well. This drug is more potent than lidocaine, with possible toxicity at doses as low as 2–3 mg/kg (a lidocaine dose of 5–7 mg/kg would place the patient at a similar level of risk). Although the medication remains relatively safe when used as anything other than a high dose infusion, caution for drug selection and monitoring parameters mirror those suggested for lidocaine *(17,18)*.

PSYCHOTROPICS AND NEUROLEPTICS

Antidepressants and antipsychotics have long been implicated in the induction of seizures. The San Francisco General study noted that of all witnessed drug-induced seizures occurring in that hospital, psychotropic medications accounted for 35% *(4)*. The very nature of the medications disposes them to this type of adverse effect. In fact, the potential exists in these medications for lowering seizure thresh-

old through their pharmacologic activity on the brain itself and through pharmacokinetic interactions with other medications, namely AEDs, via common hepatic metabolic pathways *(8)*. Thus, there is a concern for inducing seizures, either when patients take an overdose of those medications or when epileptic patients, who frequently are also depressed or psychotic, seek help for their mental illness. However, there are no convincing data that all these medications can lower the seizure threshold in either the epileptic or nonepileptic brain. Some medications are more proconvulsant than others, and if the intention is to use them at high doses, they should be replaced with other more benign drugs.

If a seizure should occur during appropriate therapy with a psychoactive medication, initial management should be to decrease the dose of medication or switch to a less epileptogenic alternative, if possible. For seizures occurring in the setting of an overdose, one must immediately seek to lower the serum concentration of the offending medication through general measures such as gastric lavage or dialysis. During this immediate, emergent period, treatment with traditional antiepileptic medications should be instituted. In the event of the suspicion of a future repeat occurrence, therapy should once again be altered to accommodate another medication with more benign consequences of supratherapeutic serum levels.

Drug Interactions

It is reemphasized that medications themselves may not be directly responsible for proconvulsant activity. Rather, the indirect actions that drugs exert on the metabolism of other medications, increasing or decreasing serum levels, could be the trigger for an epileptic event. Many psychotropic medications utilize the hepatic CYP450 enzymatic system for elimination from the body. The inhibition of this enzyme system, as caused by many of the antidepressant medications, can inadvertently increase AED levels, causing toxic AED serum concentrations *(8)*. The main inhibitors of the enzyme system appear to be the SSRI antidepressants *(8)*. Blood levels of AEDs should be carefully monitored when concomitant therapy with an SSRI is undertaken.

Antidepressants

Mood disturbances are not uncommon in patients with epilepsy, especially depression. Thus, many studies have been conducted in this patient population, which led to the discovery that some AEDs (valproic acid [VPA], CBZ, etc.) have antidepressant effect. However, not all depressed epileptic patients can be treated for both coexisting conditions with a single drug. In such cases, other traditional antidepressants have been tried, and this contributed vastly to the existing information we have regarding the epileptogenic potential of these drugs. Nevertheless, the intensivist must be very careful to extrapolate these data from the epileptic population to the nonepileptic ICU patients when trying to make decisions regarding starting or continuing a psychotropic medication after, for example, a witnessed seizure.

Table 4
Epileptogenic Risk Stratification of Antidepressants

High risk	Intermediate risk	Low risk
Bupropion[a]	Bupropion	Nefazodone
Maprotoline[a]	Maprotoline	SSRI class
	Clomipramine	Mirtazapine
		MAO-I class

[a]High dose.
(Adapted from refs. *7* and *19*.)

Table 4 presents a synopsis of the proconvulsants potentials of the various antidepressant drug families.

Tricyclic Antidepressants

Overall, seizures induced by psychotropic drugs are a dose-related phenomenon *(8)*. For example, in a meta-analysis of 98 studies in 5476 patients conducted by Peck et al., it was found that seizures occurred in 0.1% patients taking 200 mg/d or less of imipramine and in 0.63% patients taking more than 200 mg/d *(20)*. The overall incidence of seizure related to TCA overdose is 8.4% *(2,21)*. Seizures in such a setting generally occur within an average of 3–6 h postingestion and are uncommon after 24 h *(22,23)*. There is yet to be a consensus on whether serum TCA levels elevated above the therapeutic window are predictive for seizures *(8)*. The incidence of seizures in patients treated with "low-dose" TCAs does not differ significantly from that of the general population, implying that it is not the medication *per se*, but, rather, the brain that is causing the insult *(8)*.

Bupropion

Seizures associated with the use of bupropion also appear to be dose related: an incidence ranging from 1 to 5.4% has been reported for therapies in which the patient takes more than 450 mg/d; however, the incidence drops to 0.44% if the patient is taking 450 mg/d or less *(8,24)*. Seizure induction is thought to be secondary to the pharmacologic effect of bupropion, namely, the inhibition of dopamine reuptake *(25)*. In general, it is felt that seizure risk with bupropion is much higher than with other forms of antidepressant drug therapy. One article estimates the risk to be four times greater than treatment with other classes of antidepressants *(26)*. No direct comparisons regarding seizure occurrence between this agent and other specific antidepressants have been made *(8)*.

Selective Serotonin Reuptake Inhibitors

Overdoses of the SSRI antidepressants fluoxetine, sertraline, fluvoxamine, and venlafaxine have also been implicated in the occurrence of seizures *(8,9)*. Based on analysis of sheer volume of case reports, one could conclude that SSRIs are much less likely to cause seizures than other antidepressant classes, such as the TCAs. However, one must consider how long medications have been in clinical practice

and the associated number of case reports that any given drug may have been generated.

Although SSRIs are inhibitors of the CYP450 system, they are also substrates, and thus susceptible to serum level changes as induced by other medications. As with any other medications, a careful review of drug interactions, especially regarding routes of elimination, should be examined before such agents are initiated or withdrawn, especially in the medically complex ICU patient.

Monoamine Oxidase Inhibitors

Seizures related to the use of monoamine oxidase inhibitors (MAOIs) develop in the setting of overdose in the context of hypertensive crises *(9)*. Seizures also occur in the setting of tyramine ingestion, which can also increase the blood pressure of patients and thereby increase the possibility of seizure induction *(9)*. In general, when medications belonging to this class are taken in doses within the recommended range and without external influences, MAOIs remain relatively safe from a proconvulsant point of view.

Serotonin Syndrome

When taken with other medications that can increase the levels of serotonin in the brain, such as MAOIs, which inhibit the metabolism of serotonin, SSRIs can induce a potentially lethal "serotonin syndrome" in which the endogenous substance builds to a toxic level. Seizures may manifest as part of this syndrome, whereas other signs such as myoclonus (which can occasionally be misinterpreted as seizure activity), delirium, and/or autonomic instability may aid in the differentiation and proper diagnosis *(27)*. Although the side effect is relatively rare when one considers that millions of patients take SSRI antidepressants every day, this possibility should be borne in mind whenever medications that could potentiate such an adverse reaction are initiated or added to the regimen.

Antipsychotics

The site of action of antipsychotic medications supported the postulation that all of them potentially induce seizures. Proconvulsant activity, like that of many medications thought to induce seizures, can be related to the affinity for the receptor of γ-aminobutyric acid (GABA) *(28)*. Overall, however, these medications are safer than TCAs regarding potential of seizure induction following an overdose.

Phenothiazines

The phenothiazine class of antipsychotics has the highest potential of causing seizures *(8)*. They are not commonly used in the ICU for sedation or control of potentially harmful behavior, but they are occasionally administered for control of hiccups or for patients already on this regimen before admission to the ICU. This antipsychotic class causes seizures in up to 3% of patients following overdose *(29)*. The percentage is lower when these drugs are given within the therapeutic dose range. In the 1960s, observational studies in nonepileptic psychiatric inpatients

found a 1.2% seizure incidence in phenothiazine-treated patients vs no seizures in patients not receiving the drug *(30)*. The aliphatic phenothiazines (e.g., chlorpromazine) have been found to induce the highest frequency of seizures in the class, followed by the piperazine derivatives (e.g., fluphenazine) and the piperidine derivatives (e.g., thioridazine) *(9)*. However, these tendencies toward epileptogenicity must be regarded with some skepticism, inasmuch as chlorpromazine has been used much more frequently than medications in the other subclasses of phenothiazines, potentially inflating the reported seizure incidence *(9)*. Patients on phenothiazine antipsychotics appear to be particularly susceptible to convulsion within the first few days of therapy or after sudden dosage increases *(30,31)*. Further intensifying the seizure potential for the phenothiazine class of medications is the ability of these medications to actually reduce the circulating levels of phenytoin and phenobarbital, placing epileptic patients treated with these AEDs at further risk *(9)*.

Butyrophenones

Medications belonging to the butyrophenone class, such as haloperidol, are felt to be less likely to cause seizures than those in the phenothiazine class of medications *(8,9,32)*. Where chlorpromazine could be considered to be "high risk," especially in patients with epilepsy or brain injuries, haloperidol has only rarely been reported to cause seizures following its administration *(8,9,19)*. However, controlled or comparative studies are lacking.

Lithium

A long-used drug for bipolar disorder, lithium has been shown to induce EEG changes and clinical seizures at both therapeutic and toxic serum levels, as well as on drug withdrawal *(32,33)*. EEG changes induced by lithium therapy typically develop early (within 1–2 wk of the onset of therapy) and are reversible with the elimination of doses *(32)*. Because seizures may occur at therapeutic serum lithium concentrations, it is imperative that the ICU team treat the clinical presentation in these patients and not carry false confidence in "normal" lab values.

Because lithium may decrease the seizure threshold, a relative risk factor for the appearance of seizures during lithium therapy is a pre-existing EEG abnormality or seizure history (including childhood febrile seizures) *(32)*. Thorough knowledge of a patient's medical history once again may prevent an untoward epileptic event. In addition, because the combination of lithium and CBZ has been implemented in acute neurotoxicity (lethargy, ataxia, tremor, hyperreflexia), despite therapeutic concentrations of both drugs, the intensivist should be alerted and should use an alternative antiepileptic or mood stabilizing agent when these symptoms emerge *(34,35)*.

Newer Antipsychotics

Newer classes of antipsychotics are not void of their own seizure reports. Clozapine, the first of the new generation of antipsychotics, has been associated

Table 5
Epileptogenic Risk Stratification of Antipsychotics

High risk	Intermediate risk	Low risk
Chlorpromazine[a]	Chlorpromazine[b,c]	Fluphenazine
Clozapine[a,b]	Clozapine[c]	Haloperidol
	Olanzapine	Molindone
	Quetiapine	Pimozide
	Thioridazine	Risperidone
		Trifluoperazine

[a]High dose.
[b]Medium dose.
[c]Low dose.
(Adapted from refs. *7* and *19*).

with an overall incidence of seizures approaching 2.9% *(36)*. However, this incidence does appear to be dose-dependent with the rate of occurrence increasing to approx 4.5% when doses approach 600–900 mg/d, but decreasing to approx 1% with doses less than 300 mg/d *(8)*. Currently, it appears that the newest antipsychotics, such as olanzapine, could be considered safe, but the relative lack of clinical experience with these compounds could prove this assumption false in the years to come *(8,19)*. Table 5 sets forth the relative epileptogenic risk of common antipsychotics.

Treatment

Therapeutic AED treatment, if deemed necessary in the course of antipsychotic therapy, should be tailored to the patient, as already mentioned. It may be beneficial to select an AED with known mood-stabilizing effects, such as CBZ or VPA, to achieve greater therapeutic efficacy *(28,37)*.

In summary, current data are insufficient to permit definitive stratification of any psychotropic medications based on seizure risk other than the highest risk (clozapine) and the apparent lowest risk (MAOIs) *(8)*. The psychotropic medications will likely alternate locations in Tables 3–6 as more clinical experience with the individual agents is gained. Until then, the intensivist concerned about the seizure potential should maintain a conservative approach, balancing risk and benefit in the individual ICU patient.

ANTIEPILEPTIC AGENTS

Paradoxical Epileptogenicity

The concept of AEDs inducing seizures remains controversial. The difficulty in assigning culpability to the medications lies in the disease system they are meant to treat. Seizure disorders are, in and of themselves, usually infrequent and unpredictable, with wild swings between periods of relative seizure control success and fail-

ure. However, there is mounting evidence that toxic levels of the AEDs may precipitate seizures *(31)*.

Confounding situations may occur when the AED prescribed is incorrect for the presenting seizure disorder *(31)*. For example, PHT and CBZ may increase the frequency of primary generalized seizures, and especially absence seizures, when incorrectly prescribed for patients with that particular seizure disorder *(9,38)*. Second, the application of an antiepileptic medication to treat the most obvious, outward seizure may unmask a second epilepsy syndrome, thus creating an apparent increase in seizures when in fact the second seizure had been present all along *(31)*. Third, with AED overdose, a neurotoxicity syndrome has been described, including seizure exacerbation, coma, and encephalopathy. This has been well defined with PHT, CBZ, and VPA *(39)*. With all the foregoing controversy taken in context, the following AEDs are the most frequently reported paradoxical inducers of seizures.

Benzodiazepines

In patients suffering from the uncommon but devastating Lennox–Gaestaut syndrome, rare induction of tonic seizures, occasionally climaxing in tonic status, has been reported from the use of BDZs to quell the primary seizures. The future use of BDZs in these patients should be avoided *(40)*. Nevertheless, BDZs are extremely effective antiepileptics, exerting pharmacologic action through binding at the BDZ receptor site located on the GABA receptor, and achieving a seizure termination rate in up to 90% of patients with generalized seizures *(40)*. In addition, these are a very efficient medication class for use against most drug-induced seizures seen in the ICU.

Phenytoin

PHT is the AED implicated most often as a cause of AED-induced seizures, especially when present in supratherapeutic serum concentrations. The most common reasons for iatrogenic PHT intoxication, according to one retrospective study, were increases in daily PHT dosage and intravenous PHT loading for patients with subtherapeutic PHT concentrations *(31)*.

The unique pharmacokinetic properties of PHT must be blamed for the relatively high number of case reports of seizures occurring with this medication. PHT does not maintain typical linear kinetics; that is, a dose increase of 50% will not achieve a 50% increase in the drug serum concentration. Instead, as the dose of PHT is increased, the metabolic pathway becomes saturated and unable to achieve a rate of removal equal to that achieved at the lower dose, resulting in an exponential increase in the drug's serum concentrations relative to the dose increase (zero-order kinetics). For this reason, therapeutic drug levels must be carefully monitored when a patient is initiated on PHT therapy, when any dose adjustments are made, or when any medications are added to the patient's drug regimen that could potentially interfere with metabolic pathway of the PHT.

Table 6
Effect on Present AED Plasma Levels With Addition of New AEDs

Added AED	Present AED						
	PHT	PB	CBZ	VPA	LVT	BDZs	LTG
Phenytoin (PHT)	—	↔	↓	↓	↔	↔	↓
Phenobarbital (PB)	↑ then ↓	—	↔	↓	↔	↓	↓
Carbamazepine (CBZ)	↔	↔	—	↓	↔	↓	↓
Valproic acid (VPA)	↓/[a]	↑	↔/[b]	—	↔	↑	↑
Levitiracetam (LVT)	↔	↔	↔	↔	—	↔	↔
Benzodiazepines (BDZs)	↓	↔	↔	↔	↔	—	↔
Lamotrigine (LTG)	↔	↔	[b]	↔	↔	↔	—

[a] Increases free PHT levels.
[b] Increases active epoxide metabolite.
(Adapted from refs. *7*, *41*, and *42*.)

Withdrawal or Addition of AEDs

An increase in seizures associated with withdrawal of an AED is expected by the decrease of seizure control resulting from the falling AED serum level. One must be watchful not only for the obvious actual removal of the medication but also for the more insidious effective removal of the AED through the addition or withdrawal of an interacting medication. It appears that the rate of withdrawal of the AED influences the patient's susceptibility to the subsequent onset of seizures. When the drug is quickly discontinued, patients appear to exhibit an increase in postwithdrawal seizures in comparison to the cohort of patients for whom a gradual decrease in AED dose, leading to eventual discontinuation, was employed *(31)*.

Just as the addition or deletion of medications must be carefully monitored to prevent AED toxicity, vigilance must also be maintained with respect to lowering therapeutic AED levels by new pharmacologic therapies, a very common situation in the ICU. The addition of an enzyme-inducing medication may speed the catabolism of an AED, causing an effective AED withdrawal when, in fact, the AED dose has remained constant. The addition of a second or third AED may have this property and can cause this effect on the first AED's level. Table 6 presents common interactions among AEDs.

Finally, one must consider the protein binding of several ICU drugs. Many AEDs are heavily protein-bound, and free serum drug is the active moiety. Not uncommonly, ICU patients have low serum albumin and protein levels, leading to higher or even toxic levels of free AED; this may pass unnoticed if no specific check is made. In addition, competition for protein binding between the various highly bound ICU medications (AEDs or others) may lead to higher than expected active free levels of individual drugs accounting for signs of toxicity. Therefore, it is

Table 7
Relative Protein-Binding Affinities for Commonly Used ICU Drugs and AEDs

Drug	Amount bound (%)
ICU drugs	
Amiodarone	96
Digoxin	20–30
Nitroglycerin	60
Atracurium	82
Vecuronium	60–90
Propofol	>95
AEDs	
Phenytoin	95
Valproic acid	90
Carbamazepine	75–90
Phenobarbital	20–45
Lamotrigine	55
Felbamate	25
Oxcarbazepine (MHD)	38
Topiramate	15
Zonisamide	40
Tiagabine	95
Levitiracetam	<10
Vigabatrin	—
Gabapentin	—

(Adapted from refs. *17* and *43*.)

imperative in critical care that the clinician or pharmacist measure both total and free levels of drugs whenever possible. Table 7 illustrates the wide variety of protein binding that may occur with several common medications and emphasizes the need to look at more discrete pharmacologic interactions in these medically complex patients.

CENTRAL NERVOUS SYSTEM STIMULANTS

Psychostimulants such as caffeine, amphetamines, methylphenidate, and modafinil are gaining increasing popularity in the treatment of diseases such as attention deficit–hyperactivity disorder (ADHD), narcolepsy, and obesity *(44)*.

Because of their diffuse action within the central nervous system (CNS), one would imagine the risk for seizures induced by this class of medications to be high. However, studies have shown that the relative epileptogenicity of these medications is quite low *(45)*. There are no data available regarding the seizure risk with their anecdotal use in ICU comatose patients.

Although caffeine is certainly the most widely used medication in this class, methylphenidate remains the most widely prescribed for the aforementioned disease states. Overall, this stimulant has proven to be quite safe regarding seizure

induction. In fact, methylphenidate has actually been shown to decrease the incidence of seizure in patients with acute brain trauma *(46)*. When this stimulant is used in epileptic patients well controlled on AEDs, there is very minimal risk of seizure exacerbation or prolongation *(47)*. This is supported by the interaction occurring where the addition of methylphenidate may increase the serum concentrations of some AEDs, including PB and primidone *(45)*. Again, the importance of careful monitoring of serum concentrations of medications with the addition or removal of any medical therapy cannot be understated.

For patients without a history of seizures, if the luxury of a pretreatment electroencephalogram (EEG) is available, it may prove beneficial in determining a patient's potential risk for developing seizures while on stimulant therapy. In one study of pediatric patients started on stimulants for ADHD, the risk for seizure in patients with a normal EEG prior to therapy was 0.6%, whereas for patients presenting with epileptiform abnormalities on the EEG prior to the beginning of therapy the risk was 10% ($p < 0.003$). In both groups, the seizures occurred during treatment with methylphenidate, except for one patient with history of seizures, who had one event after discontinuing the drug *(47)*.

Modafinil is an alerting agent approved for the treatment of narcolepsy in adults. It has been also used in children with excessive daytime somnolence. In a small case series of children with these disorders, exacerbation of seizures and psychotic symptoms was reported with modafinil therapy in 2 of 13 children *(48)*.

ANTIASTHMATIC MEDICATIONS

Theophylline/Aminophylline

Theophylline and its intravenously injectable prodrug aminophylline have been frequently implicated as a cause of seizures in the ICU. A patient's seizure history is a very important factor when one is assessing the proconvulsant risk in patients treated with this drug because the majority of patients having seizures with theophylline have had a history of seizure *(31)*. Generalized seizures are noted as occurring in 33% and secondarily generalized in 30% of treated patients. Almost half of patients have three or more seizures, and SE occurs in 29%, usually without permanent neurologic sequelae *(31)*. The mechanism by which theophylline causes seizure is not completely understood, but it is thought to involve adenosine receptors and the inhibition of phosphodiesterase *(8,9,31)*.

Measuring serum levels of theophylline in the setting of drug-induced seizure is useful but appears to have most value in the setting of an acute overdose *(8)*. Serum levels greater than 21 mg/dL are commonly associated with drug-induced seizures, and in one study seizures were seen in two out of three of the patients reaching this serum level *(31)*. However, the usefulness of level measurement in the setting of a chronic overdosage has been questioned *(8)*. Furthermore, although theophylline blood levels may tell the intensivist the likelihood that a patient will have a first seizure, they tend not to correlate with the number of seizures a patient may develop *(4)*.

Concomitant use of fluroquinolone antibiotics such as ciprofloxacin, gatifloxacin, and moxifloxacin has been associated with an increased risk of seizures over that associated with each medication individually. The addition of the quinolone can cause an increase in theophylline serum concentrations, through inhibition of theophylline catabolism, leading to theophylline-associated seizures *(6,49)*. The interaction between these two medications does not end here: theophylline has also been shown to increase the antagonism of the GABA$_A$ receptor achieved by the fluroquinolones, thus increasing the epileptogenicity of the antibiotic *(49)*.

Another characteristic of theophylline-induced seizures is their resistance to conventional antiepileptic treatment, leading to a life-threatening situation. AEDs typically used in the treatment of seizures are rarely effective in controlling theophylline-induced seizures *(9)*. Dialysis therapy is often necessary to help the body clear the drug and thus end the seizure. Hemodialysis is commonly employed for detoxification in chronic toxicity where levels reach 60 µg/mL or in acute ingestions where levels may reach 100 µg/mL *(9)*. Midazolam has also been reported to be effective against refractory seizures caused by theophylline toxicity *(50)*.

ANALGESICS

Meperidine

Although meperidine itself is not known to cause seizures, the toxic metabolite of the analgesic, normeperidine is a well-known proconvulsant. Normeperidine is formed through the metabolism of meperidine via *N*-demethylation in the liver *(51)*. With an elimination half-life nearly five times as long as that of the parent compound (15–40 h vs 3–6 h), the toxic metabolite can quickly accumulate to high levels *(51,52)*. This accumulation theoretically occurs most quickly in patients taking oral meperidine, because extensive first-pass metabolism converts the drug to its metabolites before a therapeutic effect is established, thus creating the need for a larger dose of the parent compound to reach the same level of analgesia, and thereby an increase in normeperidine *(9,51)*. A similar risk occurs in patients requiring rapidly escalating doses because of tolerance, as seen in patients with acute pain syndromes such as pain from malignancy or sickle cell disease *(51)*. Accumulation also occurs promptly in patients with renal failure, because normeperidine is eliminated through the kidneys *(51)*.

Normeperidine-induced seizures often begin after the onset of other clinical markers heralding the impending neurologic sequelae. Overexcitability or delirium, tremors, and myoclonus often arise prior to the onset of the, usually generalized tonic–clonic (GTC) seizures *(51)*.

Treatment of this type of seizure should include supportive measures and, of course, the withdrawal of meperidine therapy. Naloxone should be avoided in these patients if at all possible, because its use will not only reverse any analgesia the patient received from the parent compound but may also exacerbate the seizures by

negating any possible antiepileptic activity the parent drug, meperidine, may be exerting *(9,51)*. Furthermore, treatment with traditional AEDs should be avoided because they have been shown to accelerate the conversion of meperidine to normeperidine, potentially worsening the seizures *(52)*.

Return of baseline neurologic function should not be anticipated until a few days after the cessation of meperidine therapy, because the removal of the compound is essential for recovery. Given that the normeperidine elimination half-life ranges from 15 to 40 h, improvement could be expected in 3–5 d but may take longer depending on the level of the assaulting metabolite *(51)*.

Fentanyl

Although fentanyl is considered a generally safe analgesic medication that is frequently used in the ICU, this injectable opioid has been noted to induce seizures in patients when a high dose are used. Doses ranging from 17.7 to 35.7 µg/kg were documented to produce epileptiform EEG patterns on the nonepileptic hemisphere of patients with complex partial epilepsy *(53)*.

Tramadol

Tramadol, a relatively new analgesic agent possessing pharmacologic action at the µ-opioid receptor, as well as reuptake inhibition of neurotransmitters such as serotonin and norepinephrine, has been linked to increased risk of seizure activity. Case reports of seizure activity seem to be linked to supratherapeutic doses of the medication, and recent studies out of the United Kingdom refute the notion that recommended doses of tramadol used in the general population places an unnecessary seizure burden on patients *(54–56)*. However, the risk for seizures may be elevated in patients taking certain classes of antidepressants (TCAs or SSRIs), because of extensive inhibition of neurotransmitter systems, and careful monitoring of these patients is often necessary.

Opioid Withdrawal

One-third of ICU patients in a study by Wijdicks and Sharbrough had seizures attributable to opioid withdrawal *(27,57)*. Seizures in this population of patients appear to occur, on average, 2–4 d after a sudden withdrawal *(8,27)*. Gradual tapering of narcotics is recommended as a way to avoid this unwanted consequence.

ANTIBIOTIC AGENTS

Antibiotic-induced seizures are seen most frequently in the critical care area of medical practice, as the result of overdose, coadministered medications, or specific patient characteristics. The ICU patients also tend to have the most difficult-to-treat infections, requiring the most frequent or high dosing of antibiotics as a means to eliminate increasingly resistant organisms. In addition, when a seizure occurs in an infected or septic patient, additional workup must be ordered to exclude CNS infection before the convulsions can be definitively attributed to medications, because

Table 8
Antibiotic-Induced Seizures

Patient characteristics increasing overall risk of antibiotic-induced seizures	Pharmacologic attributes increasing overall risk of antibiotic-induced seizures
Age <7 mo or >70 yr	Route of administration
Renal insufficiency	Class of antibiotic chosen
Pre-existing CNS disease, including but not limited to seizure disorders	High dose
Cardiopulmonary bypass	Coadministered drugs: theophylline, other antibiotics, probenecid, cilastatin, and nonsteroidal anti-inflammatory analgesics
Sepsis	
Endocarditis	
CNS infection to be treated with antibiotic	

(Adapted from ref. *49*.)

medications usually remain low in the differential diagnosis for most ICU physicians. Table 8 lists the characteristics of patients and antibiotics that create a high-risk environment for the development of antibiotic-induced seizures.

β-*Lactams*

Many of the β-lactam antibiotic derivatives are known to cause seizures. Table 9 expresses the potential for seizure attributable to antibiotics commonly used in the ICU.

Penicillins

β-Lactams, and particularly the penicillins, have been the most frequently implicated antibiotics in the induction of seizures. One of the best-known chemical inducers of seizure, penicillin has been used as means to produce seizures in animal models. Its intrinsic epileptogenicity is such that if given intravenously in high enough doses, or if applied directly to the brain surface, it can virtually always produce a seizure *(59,60)*. Obviously not all patients receiving penicillin, even in high doses, will have seizures, but certain factors can dramatically increase their risk (Table 10).

Penicillin is known to induce seizures through antagonism of GABA activity, which leads to an overall increase in the excitability of the cortex. Specific mechanisms include an apparent prevention of the binding of GABA to the $GABA_A$ receptor, as well as prevention of the opening of chloride channels associated with $GABA_A$ leading to decreased hyperpolarization of the cell membrane *(9,60,61)*. Most seizures related to the administration of penicillin occur within 12–72 h of initiation of therapy *(49,60,62)*. Seizures tend to be of the GTC type and are often associated with myoclonus, encephalopathy, or coma *(49,60,63)*.

In a series of 46 patients with penicillin-induced neurotoxicity, 31 patients had myoclonic seizures (ocular twitching, jerks in all muscle groups), 26 had GTC sei-

Table 9
Potency of Antibiotics to Induce Seizure After Instillation of 0.1 μmol into the Ventricles of the Rat Brain

Antibiotic	Risk for seizures
Imipenem–Cilastatin	Seizures common
Cefazolin	
Benzylpenicillin	
Ceftezole	
Aztreonam	
Cefamandole	
Azlocillin	
Cefuroxime	
Piperacillin	
Cefonicid	Seizures uncommon

(Adapted from refs. *49* and *58*.)

zures, and 18 patients became comatose. Eleven patients died during the acute neurotoxic phase, and four patients expired later in the course. Among survivors who underwent cessation or reduction of the therapeutic dose, improvement was documented within 12–72 h *(63)*.

The instigating effect of the penicillin brain toxicity is also attributable to a decrease in active transport out of the CNS when coadministered with some anesthetics, thiopental included. This could lead to an accumulation in the CNS at a higher concentration than in the blood *(49)*. The decreased departure of the drug from the CNS is achieved in much the same way penicillin excretion of the kidney is inhibited with coadministration of probenecid, which could also inadvertently lead to seizures through an increase in serum concentration and thus an elevation in the CNS concentration *(49)*.

Neurotoxicity has not been shown to correlate to cerebrospinal fluid (CSF) or serum concentrations of the antibiotic. Brain tissue concentration may be a better indicator *(49)*. Patients with an impaired blood–brain barrier, such as those with CNS infectious disease processes, may also be at increased risk secondary to subsequently elevated brain concentrations of penicillin *(49)*. This mechanism has been postulated in two ICU patient populations treated with high-dose penicillins: those who undergo cardiac bypass (with microembolization of the brain with clots, air, or fat during the procedure) and those with bacterial endocarditis or septicemia. However, convulsions in the latter population have been observed only if there is coexisting renal failure. Interestingly, the incidence of seizures has not been found to correlate with the administered dose of penicillin in patients with meningitis, and in an animal model, benzylpenicillin neurotoxicity was not increased with *Escherichia coli* meningitis *(64,65)*.

Table 10
Patient Risk Factors for Seizure Secondary to Penicillin Administration

Intrathecal administration > intravenous > po

Renal failure: most important patient-related risk factor (allows for quick accumulation of penicillin by impaired glomerular filtration rate and decreased clearance of the drug; increased brain penetration resulting from the lower plasma protein associated with uremia may also contribute to increased toxicity)

Low-protein state: decreases the available plasma protein binding pool for penicillin

Neonates: low protein state reduces penicillin protein binding pool, and underdeveloped glomerular filtration may lead to decreased elimination of penicillin

Elderly: low plasma protein binding pool and decreased glomerular filtration

(Adapted from refs. *6* and *49*.)

Cephalosporins

Seizures associated with cephalosporin antibiotics, another class of the β-lactam antibiotics, resemble seizures associated with penicillin administration *(9)*. In animal models, seizures occur with relative frequency when high-dose cephalosporins are administered, but this has not been reproduced in clinical practice *(9)*. In large daily doses, cefazolin, one of the first-generation cephalosporins, appears to be the most epileptogenic of the class. This is relative, of course; the following doses have been reported as necessary to induce seizure: 50 mg of intraventricular cefazolin or 20 g of intravenous cefazolin per 24 h, yet these amounts are much larger than the typically utilized dose in the ICU *(49)*. Renal failure remains a major patient-related risk factor; doses of cefazolin must be adjusted downward, based on the patient's estimated creatinine clearance *(49)*.

Carbapenems

Yet another subclass of β-lactam antibiotics known to cause seizures is the carbapenems. The postulated mechanism of seizure induction is once again via binding to the $GABA_A$ receptor. Binding affinity for this receptor increases as the antibiotic side chain becomes more basic *(60,66)*. Imipenem and panipenem are very basic; meropenem is much less basic, creating less concern for seizure induction with its use *(66)*.

Because imipenem is used in the United States solely as a combination product with cilastatin, one must consider whether the epileptogenicity of imipenem is magnified by the presence of a second seizure-inducing medication. Cilastatin by itself does not appear to be neurotoxic *(66)*. In fact, neither is the metabolite of the carbapenem antibiotics; rather, it is the parent drug itself that is proconvulsant. Therefore, cilastatin would increase the seizure risk only in the same manner that probenecid could increase the risk of seizures in a patient receiving penicillin. Its objective is the same: to increase the serum concentrations of the parent imipenem molecule by decreasing the drug's excretion by the kidney. Cilastatin may also decrease the clearance of imipenem from the CSF, thus leading to drug concentra-

tions in the CSF exceeding those in the blood *(4)*. Drug accumulation is obviously accelerated in patients with renal impairment or in those receiving high-dose regimens with a short dosing interval.

Except for renal insufficiency, other ICU patient populations at risk are those with pre-existing stroke, epilepsy, brain abscess, and bacterial meningitis *(67,68)*. Overall, the imipenem–cilastatin risk for seizures ranges between 0.2 and 6% *(66)*. Clinically, these seizures can be generalized or focal, and they occur within 3–7 d of the initiation of treatment, although they can occur as early as 36 h. The average daily dose of imipenem–cilastatin in patients who experienced seizures ranged between 13 mg/kg and 4 g of imipenem *(68,69)*.

Patients whose medical course is complicated by hydrocephalus show a marked decrease in the elimination rate of meropenem from the CSF in comparison to that from the serum *(66)*. Therefore, it appears that there may be an accumulation of the drug in the CSF, which would predispose them to an increased risk of seizure.

Treatment of β-lactam-induced seizures includes discontinuation of the antibiotic and administration of an AED that enhances GABA-ergic activity, such as BDZs or barbiturates. PHT and other sodium channel blockers probably should be avoided *(70)*.

Fluroquinolones

The fluroquinolone antibiotics induce seizure through a mechanism similar to that of the β-lactams, that is, through direct antagonism of the GABA molecule binding to the $GABA_A$ receptor *(60,71)*. Receptor binding affinity is likely secondary to the similarities between the chemical structures of GABA and the antibiotics *(60,72)*. Overall incidence of seizure is rare except in cases of overdose or in patients predisposed to seizures. The estimated incidence of this antibiotic-induced seizures is 1%, at most. Typically, these seizures occur later than with penicillins (generally after more than 7 d of therapy) and consist of tonic–clonic spasms, easily controlled with the same AEDs used for the β-lactams *(49,60)*.

Concomitant dosing with other medications can also dramatically increase the proconvulsant activity of the antibiotics. Coadministration of fluroquinolones and nonsteroidal anti-inflammatory drugs (NSAIDs) may elevate the risk of seizure over that seen when the antibiotic is used alone *(60)*. Enoxacin (a fluroquinolone) in combination with fenbufen (a propionic acid derivative) has led to several reported seizure cases in Japan. GABAergic antagonism was potentiated by biphenyl acetic acid (BPAA), an active metabolite of fenbufen *(73)*.

Fluroquinolones can also cause drug interactions, increasing the toxicity of other medications and thus manifesting seizures as a side effect of the latter, as noted earlier in the discussion of theophylline-induced seizures.

Isoniazid

Isoniazid (INH), although not a common antibiotic in the ICU, remains one of the most common causes of drug-induced seizures; the risk for seizures is estimated at 1–3% of treated patients. Almost all seizures emerging as a result of

therapy with INH occur secondary to drug overdose, be it intentional or accidental *(60)*. However, one must remember that because of recent years' resurgence of tuberculosis, more patients are treated with the drug. Some populations, specifically Native Americans, may be at higher risk because of concomitant higher rates of suicide attempts and tuberculosis.

Proconvulsant activity is mediated by the competition between INH and pyridoxine for the enzyme pyridoxine kinase, which mediates the transformation of pyridoxine to pyridoxal phosphate. Pyridoxal phosphate is an essential cofactor in the production of GABA. Therefore, INH therapy results in an inhibition of GABA synthesis and thereby a decrease of the cortical circuit's inhibitory mechanisms *(8,49,60)*. Also, INH directly inhibits glutamic acid decarboxylase to further decrease GABA synthesis *(49)*. Renal failure and a patient's own, intrinsic "slow-acetylator status" may predispose a patient to INH toxicity, although acetylator status has not been fully elucidated as a potential hazard *(49,60,74)*. The onset of seizures, in the presence of an INH overdose, usually begins within hours of ingestion. SE is relatively common and is frequently refractory to standard AED treatment *(60)*.

INH remains less likely than other antibiotics to cause seizures in the hospital or the ICU: most cases of INH-induced seizure result from acute, accidental, or intentional overdose *(49)*. Damaging neurologic sequelae have resulted from exposures as low as 20 mg/kg *(49)*. This is striking because the recommended dosage for children requiring therapy runs from 10 to 15 mg/kg *(49)*. Clear understanding of dosage regimens must be carefully communicated, not only to the health care team, but also to patients or parents of patients on INH.

Signs heralding neurotoxicity include nausea and vomiting, slurred speech, dizziness, and encephalopathy. Neurotoxicity itself may originate as hyper- or hyporeflexia, leading to focal or GTC seizures *(49)*. These seizures usually begin within 1–3 h of the overdose ingestion *(9)*. Elevated anion gap metabolic acidosis with a high serum lactate level does not help identify the problem in the differential diagnosis if it is found after a prolonged seizure. Without a seizure, or after a brief one, a significant anion gap should alert the intensivist to such a possibility. INH levels have been shown to correlate with the likelihood of impending neurotoxicity, although turnaround time for laboratory reporting may hinder the practical application of these levels to guide treatment *(49)*. Again, the best defense against ISH-induced neurotoxicity is a thorough medical history.

Although INH may not be seen exceedingly often in the ICU, patients who have overdosed on INH should be immediately admitted to an ICU because of the high mortality: 8.3–20% of patients may die of the overdose if not emergently treated. Thus, the intensivist must be familiar with the specific management of these seizures *(75)*.

INH-induced seizures are unlikely to respond to the typical AEDs used to curtail seizures *(9)*. Instead, patients should be immediately treated with intravenous pyridoxine to overcome the therapeutic effect of INH and thereby protect against seizure development. The dose of pyridoxine given depends on the amount of INH

ingested: one gram of pyridoxine for every gram of INH taken *(8,49)*. When the exact offending dose of INH cannot be determined, treatment should begin with 5 g of intravenous pyridoxine *(8,49)*. This dose may be repeated at 5- to 20-min intervals until control of seizures has been obtained *(9,49)*.

Metronidazole

The mechanism of action by which metronidazole induces epileptogenicity is largely unknown *(49)*. It is known that seizures seem to develop approx 7–10 d after the initiation of high-dose therapy (5–6 g/d) in susceptible patients *(49)*. Patients witnessed to have seizures on metronidazole therapy were also afflicted with, mainly, metastatic cancers (metronidazole was used a radiation sensitizer) and were also treated with other medications with known proconvulsant actions (e.g., phenothiazines, cefamandole, ciprofloxacin, theophylline) *(49)*. Based on these rare human reports and some limited evidence from animal experiments, metronidazole use should be considered to be safe if not used in high doses or in combination with other epileptogenic drugs.

Overview of Therapy

As a general statement, with the exception of INH, the effective treatment of antibiotic-induced seizures is best achieved by the administration of barbiturates, BDZs, or propofol. The mechanism of seizure abatement by these AEDs most closely counteracts the mechanism of seizure induction by the antibiotics *(49)*. PHT has not shown the same success, in clinical experience or animal seizure models, as the AEDs just mentioned because it does not possess pharmacologic action at the GABA receptor site *(49)*. Chapter 14 provides further details.

ANTIVIRALS

Foscarnet

Foscarnet is used as a first-line treatment of patients with cytomegalovirus (CMV). Because of its frequent use in immunocompromised patients, however, the epileptogenicity of the medication may appear to be elevated. Nevertheless, convincing studies of this adverse event are lacking. Risk factors for foscarnet-related seizures include the presence of toxoplasmosis with CNS involvement and a decrease in creatinine clearance *(76)*. Without the presence of these risk factors and in the absence of any electrolyte abnormalities, there have been no reported seizures in the foscarnet-treated population *(76)*.

Acyclovir

Neurologic sequelae (vomiting, hallucinations, and confusion or coma) as a result of acyclovir dosing have been reported in the literature, although mostly through case reports. Seizures are rare *(77–79)*.

Often, this comes as a consequence of intravenous administration, but it has also been found to occur in patients receiving oral therapy. Although patients with pre-

existing renal dysfunction, the elderly, or patients with overdose may be most susceptible to adverse neurological events *(78)*, seizures cannot be entirely attributed to the drug, but instead to the primary CNS insult by herpes simplex virus or varicella zoster virus. Nevertheless, acyclovir neurotoxicity is distinguished from viral encephalitis by its sudden onset, absence of fever or headache, lack of focal neurologic findings, and normal CSF *(79)*. Discontinuation of the drug and hemodialysis should be considered if neurotoxicity leading to seizures from this drug is suspected.

Gancyclovir

Gancyclovir is also a drug used in the treatment of CMV infection. In one case report of a patient diagnosed with AIDS, gancyclovir administration was associated with seizures after the first month of administration, which worsened with increasing dosing; the seizures did not respond to PHT administration and stopped when gancyclovir was discontinued *(81,82)*.

Antiretrovirals

The incidence of seizures occurring in patients infected with HIV and AIDS is higher than in the general population *(83,84)*. The question yet to be definitively answered is whether this elevated seizure risk is secondary to the disease progression itself, complicated by the many medications required to prolong life, especially in advanced disease, or is it a manifestation of the antiviral medications required for the prevention of this progression?

One Spanish study attempting to answer this question followed 550 patients for 1 yr and monitored their seizure incidence. Seventeen patients, or 3% of the study population, had new-onset seizures over the study year, and only one patient (0.018%) had a seizure attributed to the toxic effects of an antiretroviral agent (zidovudine) when taken in overdose with sulfonamides *(83)*. Eight patients (1.4%) had seizures attributable to medications mentioned earlier in this chapter (foscarnet, cephalosporins, imipenem, cocaine, heroin, Medazepam withdrawal, and oral sulfanamides). Although the epileptogenic effects of zidovudine are well-accepted, one must look at the entire therapeutic picture before assigning neurotoxicity to a particular drug *(83)*. Because of the inherent difficulty of assigning cause and effect to these seizures, it is prudent to begin AED therapy in HIV/AIDS patients after the initial seizure *(84)*.

Selection of AED agent is crucial in this population because there are many drug interactions and disease interactions. VPA, for example, can increase viral reproduction of both the HIV virus in addition to CMV, whereas PHT, CBZ, and PB may increase the metabolism of protease inhibitors via the CYP450 system *(84)*. More information on these interactions can be found in Chapter 9.

IMMUNOMODULATORS

Seizure etiology in the posttransplant patient population may be the most difficult to assess, given the level of medical complexity of these patients. Metabolic abnormalities, including nonketotic hyperosmolar hyperglycemia, weakened immune systems, polypharmacy, and potential coagulopathies all pose as possible instigators of neurologic toxicity. Before the intensivist attributes seizures to a metabolic or drug cause, an extensive workup to exclude infectious agents invading the CNS should be completed.

Cyclosporine

Seizures induced by cyclosporine (CSA) have been reported in liver and, less commonly, renal transplant patients. Patients with the highest risk for seizure during CSA therapy include those on simultaneous high-dose steroids and those with hypertension, hypomagnesemia, and/or hypoalbuminemia *(85)*. Aluminum overload may be another predisposing factor for CSA-treated renal transplant patients *(86)*. A postulated cause of CSA toxicity is the medication-induced capillary leak syndrome, which occurs as a direct insult of the drug on endothelial cells *(60,85)*.

Seizures most often occur when CSA is started within the first postoperative week or when doses are aggressively increased *(31)*. In a study of 630 liver transplant patients, Wijdicks et al. reported 28 (4%) patients developing seizures. CSA was implicated in 11 and tacrolimus (FK506) in 6 of them. All patients were initially treated with AEDs *(87)*.

Negative neurologic sequelae, including seizures, have especially been noted when CSA therapy is combined with high-dose methylprednisolone in liver transplant patients *(60,86)*. Of all age groups, children seem to be at the highest risk for CSA toxicity, and levels of the drug should be monitored most vigilantly *(60,85)*. Other immunosuppressing agents used after organ transplantation and increasing the risk for seizures include FK506 and muromonab-CD3 (OKT3). In renal transplant patients, OKT3 caused seizures in 6% (8 of 122) of cases, all with nonfunctioning grafts resulting from tubular necrosis *(88)*.

Effects of AEDs on Immunomodulation

PHT and PB induce the hepatic enzymes responsible for the metabolism of glucocorticoids. For that reason, it is recommended that the dose of the steroid be empirically increased 25–30% in patients who require concomitant therapy *(60,85)*. Similar effects occur with the induction of CSA's metabolic pathway by phenytoin, phenobarbital, and carbamazepine *(60,85)*. Careful monitoring of CSA blood levels is imperative in the patient who must be maintained on one of these AEDs. VPA is one AED that has failed to show any impact on the metabolism of CSA *(60,85)*. For that reason, it may be recommended as a possible therapeutic option, although its use should be avoided in patients younger than age 2 yr who have undergone liver transplantation because it has had reported deleterious effects on the liver

itself *(60,85)*. Newer AEDs, which are nonhepatic enzyme inducers, like gabapentin, oxcarbazepine, or levetiracetam may also be considered to control seizures. Chapter 7 provides more information.

CHEMOTHERAPEUTIC AGENTS

Alkylating agents, such as chlorambucil and busulfan, are known to be epileptogenic *(9)*. Overmedication with these agents appears to increase the risk; thus, conservative dosing in patients with a predisposition to seizures is warranted *(9)*. It appears that children are more susceptible to the neurotoxic effects of chlorambucil than adults, putting them at higher risk of seizures *(9)*. In one study, seizures occurred in 15% of patients within 2–4 d of receiving high-dose busulfan treatment for nonleukemic malignancies. Pretreatment with intravenous clonazepam may prevent seizures in high-risk patients *(89)*. L-Asparaginase is another such alkylating agent. Its use has been associated with cerebral hemorrhage and infarction, predisposing patients to seizures *(87)*.

OTHER COMMON ICU DRUGS

Flumazenil also presents as a seizure-inducing agent, in part secondary to its pharmaceutical action as a BDZ antagonist that binds directly to the GABA-associated BDZ receptors *(60)*. Neurotoxic effects are not necessarily related to an epileptogenic potential of flumazenil itself; instead the cause may be the acute BDZ withdrawal it induces *(9)*. Risk factors for seizure precipitations include chronic parenteral BDZ use and a mixed overdose with other drugs, especially TCAs *(9)*.

Baclofen is a common agent used to treat spasticity of spinal or cerebral origin in neurology ICU patients. It is administered either orally or intrathecally (through a pump). Baclofen is a $GABA_B$ receptor agonist (a metabotropic receptor, acting through G protein coupling). These receptors are located in both the pre- and postsynaptic membranes of either excitatory or inhibitory neurons. Both tissue and animal studies have shown that baclofen can promote epileptogenesis through inhibition of either presynaptic or postsynaptic inhibitory neurons *(90)*.

Clinical studies support seizure or even induction of SE from overdosing or acute withdrawal from baclofen therapy, administered either orally or intrathecally *(91–93)*. In a recent retrospective study of children with cerebral palsy treated with baclofen, no child older than 10 yr developed seizures. In the group younger than 10 yr, 14% of children without a history of epilepsy developed new-onset seizures 1–2.5 mo after the initiation of therapy with oral baclofen or increase in the dose *(94)*.

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13

Critical Care Seizures Related to Illicit Drugs and Toxins

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SUMMARY

Seizures caused by ingestion of drugs and toxins require specific treatment aiming to terminate epileptiform activity and to eliminate the toxin. Withdrawal from regularly ingested drugs can also be accompanied by seizures requiring admission to an intensive care unit. This chapter discusses diagnostic and therapeutic particulars of seizures induced by illicit drugs of abuse, environmental toxins, and heavy metals.

Key Words: Illicit drugs; opiates; sedatives; stimulants; solvents; toxins; heavy metals; lead; mercury; tin; seizures.

INTRODUCTION

A variety of drugs and toxins cause seizures and status epilepticus (SE) requiring admission to the intensive care unit (ICU). If intoxication is suspected, identification of the causative agent is mandatory because specific therapies aimed at toxin elimination need to be initiated in parallel with anticonvulsant treatment and supportive measures. Seizures may also occur as a result of withdrawal of recreational drugs while a patient is in the ICU for other reasons. Seizures then complicate the course of illness and may interfere with treatment of the primary disease. Timely identification of the seizure's origin and of the drug or the toxin involved is mandatory. Companion symptoms (e.g., delirium), the patient's history, and drug screens in blood and urine must be taken into consideration.

ILLICIT DRUGS

Chronic use, overdose (intoxication), and withdrawal are potential causes of seizures in illicit drugs users. A retrospective analysis identified 49 cases of recreational drug-induced seizures admitted to the San Francisco General Hospital between 1975 and 1987. Whereas the great majority had a single focal or generalized seizure, seven patients had multiple convulsions and two developed SE requiring ICU admission *(1)*. Identified drugs were cocaine (32 cases), amphetamine (11 cases), heroin (7 cases), and phencyclidine (4 cases). All except one patient had complete recovery. This analysis demonstrates that ICU admission for recreational-drug-induced seizures is infrequent. Routine screening for recreational drugs in patients admitted to the hospital because of a seizure has a low yield and should be considered only if a patient's history raises suspicion for drug abuse *(2)*. However, if illicit drugs are suspected and seizure activity is prolonged, ICU care is necessary because management of drug-related seizures may be extremely difficult (especially in cases of cocaine abuse).

Opiates

Opiates act on regions of the brain called opiate receptors, which are able to bind morphine. They include synthetic compounds (e.g., fentanyl) as well as natural substances, both endogenous (e.g., endorphin) and exogenous (e.g., morphine, a constituent of the milky extract of opium poppy, *Papaver somniferum*) or synthetic compounds. Opiates produce psychological and physical dependence. Heroin (diacetylmorphine, a lipophilic morphine analog with faster passage through the blood–brain barrier) is the most commonly used recreational opiate leading to abuse and addiction. Intoxication, usually caused by intravenous administration of an overdose, presents with coma, respiratory depression, pinpoint but reactive pupils, and vomiting. Seizures are expectedly uncommon, owing to the inhibitory actions of opiates on the brain: opiate receptors (μ, δ, κ) inhibit the adenylate cyclase and close Ca^{2+} channels via G protein-mediated pathways and thereby reduce neuronal excitability. Nevertheless, seizures have been reported in 2% of heroin-overdosed patients *(3)* and may be attributed to heroin itself *(4)* or to adulterants. Inadvertent intrathecal application of morphine led to seizure in one reported case *(5)*.

Because seizures related to opiates themselves are uncommon, other causes should be explored. These can be direct toxic effects of adulterant drugs or the result of diseases frequently observed in the addicted population (stroke, infection, neoplasms, metabolic derangement). Adulterant drugs should be sought in laboratory analysis *(6)*. Acute opiate intoxication can be treated with the antagonist naloxone (2 mg intravenously, repeated as needed up to 20 mg). No specific recommendations exist for the use of anticonvulsants.

In contrast to acute overdose, chronic heroin abuse is an independent risk factor for seizures with an adjusted odds ratio of 2.8 ($p < 0.05$) that was increased to 3.6 when concomitant brain pathology was present *(7)*. Seizures sometimes accom-

pany opiate withdrawal, which in adults typically presents with flulike symptoms. A study by Wijdicks and Sharbrough evaluating patients with new-onset seizures admitted to the medical or surgical ICU at the Mayo Clinic identified sudden withdrawal of narcotics as a cause of tonic–clonic seizures (quoted in ref. *8*). Among all admissions with first-ever seizure of identifiable cause, patients in opioid withdrawal constituted the largest group. However, they represented only a small fraction of all ICU admissions during the 10-yr study period (0.066%). Therefore, opioid withdrawal seizure remains a rare cause of ICU admission. General withdrawal symptoms are usually well-handled with methadone (20 mg once or twice daily). Withdrawal in the neonate who was exposed to opiates taken by the mother is more severe and more frequently associated with seizures. The treatment of this condition, the so-called neonatal abstinence syndrome, should be based on substitution of opiates. If sedatives are required, phenobarbital should be preferred to diazepam (DZ) *(9)*.

Sedatives and Hypnotics

Benzodiazepines (BDZs), barbiturates, and other sedative agents (e.g., glutethimide, methaqualone) are used for recreational purposes. Especially barbiturates have an addictive potential of psychological and physical dependence between that of stimulants (*see* next section) and opiates. BDZs with a lower abusive potential than barbituates may also lead to withdrawal symptoms. However, seizures, are not as common as with barbiturates. In a study in which patients were withdrawn from therapeutic doses of BDZs taken for several months, withdrawal seizures were not reported *(10)*. Because BDZs and barbiturates are powerful antiepileptics, seizures have not been observed with overdose—mostly administered for suicidal purpose. However, flumazenil used as a BDZ antidote has reportedly led to partial seizures *(11)* and fatal SE *(12)*.

Withdrawal from BDZs and barbiturates may be complicated by seizures along with delirium tremens (in many aspects similar to alcohol withdrawal) and often requires ICU care. Seizure susceptibility is explained in part by the downregulation of γ-aminobutyric acid (GABA) receptors by long-term use of these sedatives *(13,14)*. Additionally, a role of the glutamatergic system is suspected because reduced seizure susceptibility was observed after BDZ-dependent mice were treated with an *N*-methyl-D-aspartate (NMDA) antagonist *(15)*.

Seizures are observed in 3% of patients going through BDZ withdrawal *(16)*. They typically occur within 1–10 d of stopping the drug, depending on the specific agent's half-life and the dose ingested *(17)*. For example, with short-acting barbiturates like secobarbital, pentobarbital, or amobarbital, seizures are expected within the first 2–3 d after abrupt withdrawal of the drug and, as with alcohol, are followed occasionally by delirium tremens. Withdrawal from long-term use of pentobarbital is associated with seizures in 10% of subjects taking 600 mg/d and in 75% taking 900 mg. With lower daily doses of 400 mg, electroencephalographic (EEG) changes consistent with epileptiform discharges can be found in up to one-third of patients

(18). Sedative withdrawal seizures should be treated with titrated doses of BDZ or barbiturate (determination of a "stabilization dose," usually 200 mg of pentobarbital every 6 h, followed by gradual tapering over 2–3 wk). Most other anticonvulsants are ineffective.

Other sedatives, such as chloral hydrate and meprobamate, can also cause seizures during withdrawal. In contrast, glutethimide (19) and pentazocine/tripelennamine (Ts and blues) can produce seizures on ingestion (20).

Stimulants

Psychostimulants are amphetamines, ephedrine, 4-methylaminorex and methylphenidate (Ritalin). These agents release monoamines at the synaptic nerve terminals. Clinical use of amphetamines is established for treatment of narcolepsy, hyperactivity in children, and the control of obesity. Amphetamines are widely used and thus easy to procure. After cannabis, amphetamines are therefore the most common drugs of abuse. Use of methylenedioxymethamphetamine (MDMA, "ecstasy"), an amphetamine with stimulant and hallucinogenic properties, has quadrupled over the past decade (21). Another psychostimulant with properties similar to those of MDMA is cocaine. In contrast to amphetamines, cocaine blocks the reuptake of monoamines at synaptic nerve endings.

Seizures can occur with psychostimulant overdose and also after intentional administration of high doses. Reported frequencies of cocaine-induced seizures vary between 1 and 40% (22). In one study women were more likely to present with seizures than men (18% vs 6%) (23). Seizures occur with amphetamines, especially MDMA, even at intentional doses (24), but are less frequent than with cocaine (1). Frequent acute adverse reactions of MDMA are hypothermia and hyponatremia (25). An association exists between the use of MDMA or cocaine and acute catastrophic neurovascular events, such as subarachnoid hemorrhage and stroke. These events can produce seizures on their own (26,27). These seizures are commonly focal, whereas the typical cocaine-induced seizure is generalized. Therefore, brain imaging studies should be considered in stimulant users with focal seizures. Convulsions induced by cocaine are usually of short duration and occur immediately or within a few hours. MDMA produces a secondary clonic phase after the initial ictal event (28). Rarely SE develops, requiring ICU care. Complex partial SE (i.e., nonconvulsive SE) has been reported with alkaloid "crack" cocaine abuse (smoked) in a patient who presented with bizarre behavior thought to be "cocaine psychosis" (8). Seizures during stimulant withdrawal have not been reported.

Responsiveness to treatment depends on the drug: methamphetamine seizures respond to DZ and valproate but are refractory to phenytoin (PHT). PHT is more effective for cocaine-induced seizures. However, rare SE after cocaine but also after MDMA is notoriously refractory to conventional treatment and requires ICU management (23,29–31). 4-Methylaminorex-related seizures can be treated with the calcium channel blocker flunarizine (28).

Solvents

Solvents include hydrocarbons, ketones, esters, and ethers and are commonly ingested by inhalation of glues, cleaning fluids, paint thinners, or anesthetics. Addictive effects resemble those of ethanol. Chronic abuse can lead to focal neurological deficits (e.g., cranial nerve palsies, internuclear ophthalmoplegia, peripheral neuropathy) *(32)* and demyelination in the central nervous system (CNS) *(33)*. Severe intoxication or oral administration can be accompanied by seizures *(34,35)*. Seizures may be partial or generalized *(36,37)*. Chronic solvent exposure may also lead to temporal lobe epilepsy, as demonstrated by a case of occupational intoxication *(38)*. In this case seizures were fully controlled after exposure to cyclohexanone and isopropanol was stopped.

Hallucinogens

Marijuana is the illicit drug most frequently used for recreational purposes. It is derived from the hemp plant *Cannabis sativa*. Its major hallucinogenic ingredient is Δ9-tetrahydrocannabinol (THC). THC acts via a specific receptor (CB1) expressed widely throughout the brain; certain brain lipids (anandamides) are endogenous activators of CB1 and operate as retrograde synaptic transmitters *(39)*. Cannabinoids have anticonvulsant properties *(7,40)*, which are described as being similar to those of PHT *(41)* despite different mechanisms of action *(42)*. Proconvulsant activity was also reported for THC in a rat model *(43)*; this discrepancy is likely related to species and the model of seizure induction. Cannabis withdrawal can produce a mild withdrawal syndrome consisting of anxiety, nausea, increased body temperature, and tremors. Seizures are not part of this syndrome.

Other natural (mescaline, psilocybin) and synthetic hallucinogens (lysergic acid diethylamide [LSD]) are not considered to be epileptogenic. However, one case of grand mal seizure after an LSD overdose has been reported *(44)*.

Phencyclidine ("angel dust"), a hallucinogenic anesthetic, has anticonvulsant properties *(45)*. However, intoxication can lead to a severe clinical syndrome characterized by agitation, violence, psychosis, and catatonia, which can be complicated by rhabdomyolysis, hyperthermia, and seizures *(46)*. Fatal SE has been reported in this setting *(47)*.

EPILEPTOGENIC ENVIRONMENTAL TOXINS

Marine Toxins

Among various toxins produced by marine animals or plants, domoic acid (DA) and ciguatera toxins are most relevant in view of epileptogenicity. DA is a potent excitotoxin that is produced by algae (e.g., *Nitzschia pungens*). Humans are intoxicated via the food chain by eating mussels containing the poison. DA is an analog of kainic acid and activates NMDA glutamate receptors *(48)*. Administered to rats, DA produces seizures resulting from unspecific neuronal activation throughout

many brain areas. Excitotoxic brain damage ensues within certain brain regions, with the hippocampus and cerebellum being more vulnerable than others *(49)*.

An epidemic DA intoxication was first identified in Canada in late 1987 *(50)*. After eating poisoned mussels, 107 patients developed acute gastrointestinal (GI) symptoms (76%), incapacitating headache (43%), and loss of short-term memory (25%). Twelve patients (11%) required intensive care because of seizures, coma, and respiratory or circulatory problems. One-fourth of those patients died. Hippocampal and amygdaloid damage was the leading neuropathological finding *(51)*. Hippocampal damage, also demonstrated in survivors by reduced glucose uptake in positron emission tomography (PET) imaging *(51)*, is likely responsible for persisting seizure activity until 4 mo after intoxication and for delayed-onset temporal lobe epilepsy after one year *(52)*. Acute DA-induced seizure activity was resistant to PHT but controlled by DZ and phenobarbital *(51)*.

Although less epileptogenic, ciguatera fish intoxication is the most common nonbacterial marine food poisoning syndrome in humans. Ciguatoxins are heat-stable polyether toxins that act by increasing the permeability of excitable membranes to sodium ions *(53)*. Produced by the benthic (bottom-dwelling) dinoflagellate *Gambierdiscus toxicus*, they enter the food chain to humans via carnivore fish (mackerel, barracuda). Ciguatera is endemic in tropical countries but has been observed in North America and Europe, where the diagnosis is often missed or the condition is wrongly diagnosed as multiple sclerosis *(54)*. This confusion stems from the typical ciguatera symptomatology, namely paraesthesias, especially of thermo- and nociception with hot–cold inversion, occurring several hours after ingestion. Paraesthesias usually begin periorally and then spread centrifugally. Mild cerebellar signs may be present. Complete restitution is common *(55)* but can take as long as several months, and in some cases symptoms persist. Severe intoxication can lead to coma, flaccid paralysis, respiratory paralysis, and generalized tonic–clonic (GTC) seizures *(53,56,57)*. Deaths have been reported *(58)*. Confirmation of diagnosis can be achieved by detecting the toxin in human blood from available bioassays *(55,59)*. Treatment with iv mannitol (10 mL/kg of 20% solution infused slowly over 30–45 min) after initial fluid replacement reduces Schwann cell edema and was reported to completely reverse symptoms in up to 60% of patients *(53,60)*. However, in a double-blind randomized study of mannitol vs normal saline treatment over 24 h, mannitol was not found to be superior and had more side effects *(10)*. Additional supportive therapy may be necessary.

Mushroom and Plant Toxins

The most poisonous mushrooms, those of the *Amanita* species, produce a variety of toxins (amatoxins) *(61)*. *Amanita phalloides* contains the cytotoxic amanitin, which can lead to acute hepatic and renal failure within days of ingestion *(62)*. Seizures can occur as part of fulminant hepatic failure (FHF) and are likely related to ammonia toxicity, which increases synaptic glutamate release *(63)*. Besides anticonvulsant and supportive therapy, specific treatments for *A. phalloides* poisoning

include gastric decontamination, oral-activated charcoal and lactulose, high doses of penicillin, ceftazidime, thioctic acid, or silibinin, and combined hemodialysis and hemoperfusion *(64,65)*. Positive effects of acetylcysteine were also reported *(66)*. BDZs, as the first line drug for agitation and seizures, have been used in the past.

Other *Amanita* species, especially, *A. pantherina* and *A. muscaria*, as well as *Psilocybe*, *Inocybe*, and *Clitocybe* produce neurotoxins *(67)*. Examples of these toxins are ibotenic acid, stizolobic acid, and muscimol. Intoxication occurs most commonly in children (unintentional ingestion) and produces a distinctive syndrome consisting of alternating phases of drowsiness, agitation plus hallucinations, and seizures occurring within 2–3 h of ingestion *(68)*. In a study of nine cases of *A. pantherina* or *A. muscarina* poisoning, seizures were observed in four patients *(69)*. All seizures were controlled by standard anticonvulsant agents. In contrast to *A. phalloides* poisoning, intoxication from neurotoxic *Amanita* species is usually time limited and followed by complete recovery. However, mushroom identification should be sought, because syndromes differ in their course and treatment. Identification may be achieved from the remains of a meal *(70)*.

Besides mushrooms, ingestion of certain plants can induce seizures. Water hemlock or other members of the *Cicuta* genus and their toxin, cicutoxin, are mostly involved. Water hemlock grows along rivers in North America. Intoxication conveys an overall mortality rate of 70% *(71)*. Typical symptomatology includes nausea followed by loss of consciousness and generalized seizures. In one report a patient was successfully treated with hemodialysis and hemoperfusion, forced diuresis, and artificial ventilation *(72)*. Other toxic plants that can sometimes induce seizures (with severe intoxication) include members of the belladonna alkaloid family (jimsonweed, nightshade), azalea, and Christmas rose *(73)*.

Besides direct toxicity, plant ingestion can lead to intoxication by insecticides or herbicides. Amitraz is a widely used insecticide that often leads to intoxication in children. Symptoms, which include loss of consciousness, vomiting, hypotension, hypothermia, and generalized seizures, evolve within 2 h of ingestion *(74,75)*. BDZ treatment is effective against convulsions *(74)*. The outcome is usually good.

Carbon Monoxide

Carbon monoxide (CO) is a colorless, odorless gas that is contained in exhaust fumes of motor vehicles, smoke from fires, and fumes of faulty heating systems. Intoxication results from acute inhalation or from chronic exposure to low concentrations. Seizures can occur with either acute or chronic poisoning. CO has a higher affinity for hemoglobin (forming carboxyhemoglobin [COHb]) than oxygen. It therefore competitively removes oxygen from hemoglobin, thereby producing tissue hypoxia. The brain is the organ most vulnerable to hypoxia, which leads to neurological symptoms ranging from dizziness to coma. CO intoxication is more common during the winter when heating systems are being used. Because initial symptoms are nonspecific, the diagnosis is often missed unless direct spectroscopic

measurement of the whole-blood COHb level is performed. In a prospective study, COHb levels were measured in 753 unselected patients admitted to a hospital's emergency department. Those with clinically suspected diagnosis of CO intoxication were excluded. Two patients from the entire cohort (0.3%) and 1 of 20 (5%) admitted with seizures had COHb levels of greater than 10% *(76)*. In several case reports, mild (10–20% COHb) to moderate (20–40% COHb) CO poisoning presented as an isolated focal or generalized seizure *(77–79)*. Other symptoms of mild to moderate poisoning included headache (90%), dizziness (82%), visual disturbances, and fatigue *(80)*. The classic cherry-red discoloration of the skin (color of COHb) is mostly seen with severe intoxication (40–60% COHb), which also leads to coma, generalized convulsions, and respiratory impairment. Global brain swelling and signs of hypoxia (hypodensities in white matter or basal ganglia) are seen on computed tomography. In one report the EEG was characterized by lateralized sharp waves and a focal electrographic seizure discharge within hours of the CO exposure associated with coma and focal motor seizures *(81)*. Long-term sequelae of severe intoxication range from memory deficits or extrapyramidal disorders to persistent vegetative state *(82)*.

The therapy of choice for acute CO intoxication is hyperbaric oxygen therapy *(83)*, which significantly reduces late sequelae *(84)*. Oxygen itself has neurotoxic properties; especially, when applied under high pressure, oxygen can induce seizures. In one study, seizures occurred in 0.3% of cases at 2.45 atm abs and in 2% at 2.80 atm abs *(85)*. Mortality remains at the 30% level if the patient is not treated with hyperbaric oxygen, but drops to less than 10% if this treatment is offered early *(73,83)*.

Heavy Metals

Heavy metal poisoning stems from environmental pollution (e.g., herbicides, pesticides), occupational exposure (e.g., in mining), iatrogenic ingestion (e.g., as antimicrobials), or intentional ingestion of recreational drugs (e.g., gasoline sniffing). Heavy metals can bind to various reactive groups (ligands) to inhibit their physiological function. Drugs designed to limit the toxic effects of heavy metals (chelators) compete with these endogenous ligands for heavy metal binding. Chelators have a greater affinity for heavy metals and form complexes that are easily eliminated from the body. Most heavy metal poisoning is secondary to chronic exposure.

Lead

Lead intoxication has been common since ancient Roman times, when lead was ingested via water delivered through lead pipe systems. Today, most cases of lead poisoning are the result of occupational exposure. Large-scale prevention programs have been introduced to eliminate this health hazard *(86)*. Lead intoxication also occurs in children who accidentally ingest lead-containing paint or soil. Chronic lead poisoning is therefore more common in adults, whereas acute intoxication more often occurs in children. The symptoms differ: chronic exposure leads to GI, hema-

tological, and renal symptoms. CNS and neuromuscular symptoms predominate with acute intoxication. The neurological syndrome of lead poisoning includes vertigo, clumsiness, ataxia, headache, insomnia, restlessness, and convulsions *(87,88)*. Seizures are often repetitive and tonic–clonic and are followed by somnolence with visual disturbances or coma *(89,90)*. Lead binding to GABA, thereby reducing inhibition in cortical circuits, has been suggested as a possible pathophysiological mechanism for lead-induced seizures *(91)*. Anticonvulsants that increase GABA-mediated inhibition (sodium valproate, barbiturates, and benzodiazepines) are therefore preferred in lead-induced seizures *(91)*. Chronic lead exposure can also produce thiamine deficiency, which lowers seizure thresholds *(92)*. In these cases thiamine should be substituted.

Other treatments for lead intoxication include chelating agents such as edetate calcium disodium (CaNa^{2+} EDTA), dimercaprol, D-penicillamine, or succimer (2,3-dimercaptosuccinic acid). Anemia with basophilic stippling of red cells and lead lines at the metaphyses of long bones are other diagnostic findings. Blood zinc protoporphyrin levels can be used to assess lead exposure over the prior 3 mo *(93)*. Excretion of lead in the urine should be assessed before and after initiation of therapy with chelating agents. Asymptomatic patients with blood lead levels greater than 80 µg/dL or symptomatic patients with blood lead concentration greater than 50 µg/dL should be treated with sodium CaNa^{2+} EDTA intravenously followed by oral administration of succimer for 19 d. Asymptomatic patients with blood lead concentration greater than 50 µg/dL can be treated with succimer alone. CaNa^{2+} EDTA should be combined with dimercaprol in cases with CNS symptoms *(93)*. Dexamethasone and mannitol should be considered in cases of cerebral edema.

Mercury

Mercury poisoning used to be a common side effect of various drugs such as antimicrobials, laxatives, and antiseptics. Whereas these drugs have been replaced with nontoxic and more effective agents, chronic mercury exposure from cosmetics (e.g., skin-whitening cream) distributed in developing countries *(94)* still occurs. Other sources of mercury are occupational exposure *(95)* and environmental pollution, especially to fish containing organic mercury compounds. Therefore, the US Food and Drug Administration recommends that pregnant women, women of child-bearing age, and young children avoid consumption of shark, swordfish, mackerel, and tilefish *(96)*. Mercury intoxication causes a variety of symptoms, including GI, renal, pulmonary, hepatic, and neurological. Neurotoxicity may result from excitotoxic neuronal damage caused by defective glutamate reuptake by astrocytes *(97)*.

The symptomatology of mercury intoxication depends on the route of ingestion and on whether the exposure was acute or chronic. Acute inhalation of vapors containing high doses of elementary mercury is the most hazardous form of intoxication. Clinical signs occur within hours, consisting of GI and respiratory symptoms and GTC seizures *(98)*. Intensive care is mandatory, because respiratory, renal, and hepatic failure may be fatal. In contrast, iv injection of doses of metallic mercury as

high as 8 g are not life threatening: in a case of suicidal injection, gastroenteritis, stomatitis mercuralis, neuropsychological symptoms, and tremor mercuralis occurred without respiratory, hepatic, or renal abnormalities (99). The patient was successfully treated with 2,3-dimercaptopropane-1-sulfonate (DMPS), a chelating agent, and surgical removal of mercury deposits. Chronic exposure to mercury, in metallic or organic form (methylmercury), causes a neuropsychological syndrome (erethism) characterized by irritability, personality change, depression, delirium, insomnia, apathy, memory disturbances, headaches, general pain, and tremors. Hypertension, renal disturbances, allergies, and immunological conditions occur (95). Recurrent seizures and EEG abnormalities may also be present (100). Standard anticonvulsant therapy can be used for mercury-related seizures and epilepsy. The chelating agent DMPS should be given repetitively to remove approx 1 mg of mercury per day of treatment (99).

Tin

Tin has neurotoxic properties as an organic compound (triethyltin, trimethyltin). These organotins are used as preservatives for textiles or wood and in the production of silicone rubber. Intoxication often occurs during occupational exposure. Symptoms include hearing loss, confusion, memory deficits, ataxia, sensory neuropathy, aggressiveness, disturbed sexual behavior, and complex partial and tonic–clonic seizures. Long-term effects include epilepsy, likely because trimethyltin intoxication produces damage in amygdala, piriform cortex, and hippocampus, requiring antiepileptic treatment.

CONCLUSION

Overall, illicit drugs and toxins are a rare cause of seizures requiring ICU admission. But most intoxications can be well managed with specific therapies in addition to anticonvulsant medication. Therefore, careful history taking with explicitly addressing the possibility for toxin exposure is mandatory in every patient admitted to an ICU for intractable seizure or SE.

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Management of Status Epilepticus and Critical Care Seizures

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SUMMARY

There are multiple approaches to the treatment of seizures and status epilepticus (SE) in the intensive care unit (ICU). With only one seizure, the focus should be more on defining the etiology than on treating the patient with antiepileptics; but with more prolonged or recurrent seizures, both approaches should be pursued in parallel. If delayed or untreated, SE carries a grave prognosis, and every ICU should have a protocol for rapid response to this neurological emergency. Continuous electroencephalographic monitoring should become mandatory in the treatment of SE because of the late dissociation between clinical convulsions and electrographic seizures and the inability to use the clinical examination as guide to the treatment. Focal and nonconvulsive SE have etiology and prognosis different from those of generalized convulsive SE and the treatment also differs. Several medications are available for treating seizures, but only few are available for parenteral, fast administration in the treatment of SE. Therefore, the experience from using the newer antiepileptics in the case of resistant SE is limited. Interactions between antiepileptics and common ICU medications may be significant, and concurrent multiorgan failure may alter their metabolism.

Key Words: Status epilepticus; nonconvulsive status epilepticus; anticonvulsant medication; seizures; ICU.

INTRODUCTION

Status epilepticus (SE) is a true medical emergency that requires aggressive and prompt therapeutic intervention preferably in an intensive care unit (ICU). The physician may encounter a patient with SE in the ICU, either because the patient was admitted for management of the SE or because the patient developed SE during the

course of admission for another medical reason. In our neurological ICU (NICU), some patients who are admitted for continuous electroencephalogram (EEG) monitoring after intracranial electrode placement may rarely develop SE (after the antiepileptic medications are withdrawn) and constitute a third category of "semi-intentional" iatrogenic SE.

Persistent convulsive activity not responding to the usual first-line treatment requires admission to an ICU. This condition carries a significant mortality and morbidity and needs immediate and proper intervention. The indication for admission becomes more obscure in patients with nonconvulsive SE (NCSE). This condition has a still evolving definition, unclear pathophysiology, and, most importantly, controversial prognosis. Aggressive treatment of NCSE, especially with intravenous administration of antiepileptic medications, could be justified only if such intervention could clearly alter the prognosis for the better *(1)*. Because there is not enough evidence that such treatment improves the prognosis in NCSE and may actually cause complications (mainly hypotension and respiratory depression), the physician should individualize the admission and management in an ICU setting based on other comorbidities.

There are not many studies specifically reporting on admission of SE patients in an ICU. An older survey of members of the Intensive Care Society in the United Kingdom who were questioned about SE resistant to initial therapy with intravenous diazepam (DZ) and phenytoin (PHT), revealed that only 12% of the 408 respondents were aware of a protocol for SE in their ICUs. At that time, the authors concluded that the therapeutic and monitoring strategies used in the management of refractory SE in their country were insufficient and needed re-evaluation *(2)*. The same group published their experience with 26 patients admitted to an NICU with a diagnosis of SE. On transfer to the NICU only 14 (54%) were in SE; 6 were in drug-induced coma or were encephalopathic, and 6 had pseudo-SE, of whom 4 had been intubated. Prior to transfer, most patients were treated with benzodiazepines (BDZs), chlomethiazole, and PHT; the PHT load was adequate in at least 7 of 16 cases. All those in SE on transfer had their seizures successfully controlled, but 10 patients required general anesthesia with thiopentone, propofol, ketamine, or midazolam *(3)*. In a recent study from San Francisco, patients treated with out-of-hospital BDZs and were still in SE on arrival at the emergency department, were more likely to be admitted to the ICU than those whose seizures were terminated before the arrival at the hospital (73% vs 32%, likelihood ratio $\chi^2 < 0.001$). When these groups were compared based on the cause of SE, no difference was found, suggesting that individual patients had been admitted to the ICU because of the very fact of the ongoing seizure activity, not the underlying etiology *(4)*.

DEFINITION

Over the last decades, the definition of SE has evolved, especially as new data regarding prognosis emerge. The International Classification of Epileptic seizures

has defined SE as any seizure lasting 30 min or more or intermittent seizures lasting longer than 30 min without recovery of consciousness interictally *(5,6)*.

In 1991 Bleck proposed that seizures persisting for 20 min should be defined as SE *(7)*, and in 1993 Ramsay suggested that a better definition should include any seizure that persists for more than twice its normal duration, even though most seizures normally last less than 5 min *(8)*.

In 1998 Treiman et al. defined as SE the presence of two or more discrete seizures with incomplete recovery of consciousness between the seizures or continuous convulsive activity for more than 10 min *(9)*.

More recently, Lowenstein proposed a new operational definition according to which SE refers to at least 5 min of (a) continuous seizures or (b) two or more discrete seizures between which there is incomplete recovery of consciousness. In the clinical setting, the need to treat continuous seizure activity promptly has been recognized, and many practitioners intervene before 20 min have elapsed *(10)*.

More controversial is the definition of NCSE. This is a condition that necessitates confirmation by electroencephalogram (EEG), and different criteria have been proposed by several experts. Most agree on the presence of altered consciousness or behavior for 30 min or more, the absence of overt clinical signs of convulsive activity during that period, and the EEG presence of unequivocal seizure activity, periodic epileptiform discharges or rhythmic discharges with subtle clinical seizure activity, or rhythmic slow discharges with either clinical or EEG response to treatment *(11–14)*.

CLASSIFICATION

Depending on whether convulsive activity is present, SE can be further defined as follows: overt SE with recurrent convulsions manifested as generalized motor activity (generalized convulsive SE [CSE]) or focal motor activity (partial convulsive SE), or nonconvulsive SE. NCSE can be subdivided into four categories: (1) generalized NCSE (absence NCSE) with altered consciousness associated with generalized spike–wave activity on EEG; (2) complex partial NCSE, with either discrete complex partial seizures and no return of normal consciousness or a continuous state of impaired consciousness; (3) myoclonic SE or generalized status myoclonicus (SM), with more overt myoclonic activity (shocklike irregular jerks), easily distinguished from tonic–clonic convulsions (usually after global anoxic or ischemic insult or associated with myoclonic encephalopathies) lasting for at least 30 min *(15)*; and (4) subtle generalized SE (or electrographic SE or SE in comatose patients), characterized by subtle, often unnoticed motor activity (rhythmic twitching of the arms, legs, trunk, or facial muscles, tonic eye deviation, or nystagmoid eye jerking) associated with generalized epileptiform activity on the EEG *(16)*. Diagnosis of NCSE still represents a difficult diagnosis that requires high index of clinical suspicion.

Thus, accurate diagnosis of SE is made based on electroclinical features (Table 1).

Table 1
Classification of SE

	Convulsive SE	Nonconvulsive SE
Primary generalized SE	Tonic–clonic	Absence attacks
	Tonic	Atypical absence
	Myoclonic	Atonic seizures
Partial SE	Partial motor seizures (epilepsia partialis continua)	Aphasic
		Simple partial nonmotor
		Complex partial
Secondary generalized SE	Partial seizure with secondary generalization	Subtle or in coma

INCIDENCE AND CLINICAL PRESENTATION

Numerous studies confirm that SE is a common condition. It accounts for 3–5% of all admissions to the emergency department for seizure disorders and occurs in 2–16% of all epilepsy patients *(17,18)*. De Lorenzo and his colleagues in a prospective population-based epidemiological study in Richmond, Virginia, found that the annual incidence of SE was 41–61 per 100,000 patients. Upon projecting the Richmond data to the US population, it was determined that 125,000–195,000 cases of SE occur every year. The highest incidence of SE occurs during the first year of life and during the decades after the age of 60 yr. Approximately 13% of patients have recurrence of SE and thus, the expected prevalence in the United States is higher. In this important study, partial SE of various types occurred in 25% of cases and NCSE represented about 4% of SE *(19)*.

The most common type of SE encountered in ICU setting is the one presenting with generalized tonic–clonic (GTC) convulsions (including secondary generalization), and identifying the condition and is rarely a diagnostic dilemma *(20)*. Not all patients admitted for SE have a history of epilepsy; indeed, 44% of them do not have such history *(21)*. A new insult to an epileptic brain increases the risk for SE: if there is history of epilepsy and a new acute brain insult, up to 25% of patients may develop SE *(22)*.

The incidence of NCSE is not identified. Overall, NCSE may account from 4% *(19)* to up 25% of all SE cases, depending on whether the study was population or hospital based *(23,24)*. Among patients with NCSE, the incidence for complex partial SE (3.5 of 100,000/yr) is lower than other types of NCSE (15 of 100,000/yr) *(18)*. In a large study from Richmond, Virginia, 164 patients were prospectively evaluated with continuous EEG monitoring (CEEGM) for a minimum of 24 h after clinical control of CSE. After CSE was controlled, CEEGM demonstrated that 52% of the patients did not have after-SE ictal discharges. The remaining 48% demonstrated persistent electrographic seizures, and more than 14% of them manifested

NCSE, predominantly of the complex partial seizure type. Because of absence of overt clinical signs of convulsive activity, the clinical detection of NCSE in these patients would not have been possible with routine neurological evaluations without the use of EEG monitoring *(25)*.

Other hospital-based studies examined the incidence of NCSE. A group from Cincinnati, Ohio, prospectively evaluated hospitalized patients (emergency department, wards, and ICUs) with mental status changes but no clinical convulsions for the presence of NCSE. Out of 198 cases with altered consciousness, 74 (37%) showed EEG and clinical evidence of definite or probable non-tonic–clonic SE. Of those, 42 episodes (57%) were probable or definite complex partial SE, 29 (39%) were probable or definite subtle generalized SE, and 3 (4%) were myoclonic SE. In 23 patients with SE, altered consciousness was the only clinical sign at the time of diagnosis and in 36 cases subtle motor activity was present. Neither clinical signs nor prior history predicted which patients would show SE on EEG. Non-tonic–clonic SE was associated with previous seizures in 18 cases and followed a cerebral infarction in 16 cases. Contrary to other reports, the authors did not find any relationship between duration of SE and EEG pattern. Thus, this study demonstrated that non-tonic–clonic SE is a common finding in patients with unexplained altered consciousness in the hospital, and EEG is a necessary tool in the evaluation of these patients *(16,26)*.

There are scanty data regarding SE incidence in the ICU. Bleck et al. prospectively evaluated 1850 patients admitted to a general medical ICU. Four patients were admitted with primary refractory SE (4.3% of primary NICU admissions). Of 217 patients with nonneurological admissions who developed neurological complications, 61 (28.1%) had seizures. Six of these patients were in SE and required at least two antiepileptic agents to terminate it. Thus, 10 (0.5%) of medical ICU admissions were primary or secondary SE *(20)*.

In another retrospective study from the Mayo Clinic, Wijdicks and Sharbrough reported 55 patients with new-onset seizures among 27,723 patients admitted in the medical or surgical ICU (0.8%). Only four (7.3%) patients with new-onset seizures in these series developed SE *(27)*.

In another study, conducted in the ICU, 236 patients (children and adults) with coma and no overt clinical seizure activity were monitored with at least 30 min continuous EEG as part of their coma evaluation. Only patients who were found to have no clinical signs of SE were included. EEG demonstrated that 19 patients (8%) met the criteria for the diagnosis of NCSE. The most common etiology was hypoxia–anoxia (42% of patients with NCSE); stroke was the second most common (22%). This large-scale EEG evaluation of comatose patients without clinical signs of seizure activity found that NCSE is an underrecognized cause of coma and concluded that EEG should be included in the routine evaluation of comatose ICU patients, even if clinical seizure activity is not apparent *(28)*.

Because of the type of patient population admitted, increasing availability of CEEGM, and familiarity of the NICU staff with NCSE, its reported incidence in

Table 2
Common Clinical Presentations of Seizures in the ICU

Seizure type	Clinical expression
Focal motor	Face or limb motor seizure, may propagate from distal to proximal; no alteration of sensorium
Generalized tonic–clonic	Loss of consciousness, generalized convulsions with tonic phase followed by clonic phase and postictal altered sensorium; urinary loss and tongue biting common
Complex partial	Disturbed sensorium (aura), can be followed by generalized tonic–clonic seizure
Nonconvulsive status	Disturbed sensorium or loss of consciousness; minimal face or distal limb twitches

the NICU is higher. Jordan, who used CEEGM in 124 NICU patients, reported 34% incidence of nonconvulsive seizures. Thirty-three patients (27%) were in NCSE *(29)*.

Table 2 presents common clinical presentations of SE in the ICU.

ETIOLOGY

The largest single identifiable risk factor for generalized CSE is epilepsy associated with low levels of antiepileptic drugs (AEDs): 42% in the Richmond study had epilepsy, and 34% of adults had low AED levels *(19)*. Approximately 15–20% of patients with epilepsy have a history of at least one episode of SE and 12% present with SE *(30)*. However, cerebrovascular accidents, especially in the elderly, represent the most common etiology for SE *(31)*. Cerebrovascular disease and discontinuation of antiepileptic medications were the most prominent causes of SE, in another study from Richmond, Virginia, each accounting for about 22% of all patients in the series. The other principal etiologies were alcohol withdrawal, idiopathic, anoxia, metabolic disorders, hemorrhage, infection, tumor, drug overdose, and trauma *(32)*.

Data from population-based or even hospital-based studies regarding the etiology of SE cannot be projected to the ICU. The same causes of seizures in the ICU are also responsible for SE *(see* Chapter 1). In a retrospective study from a tertiary referral center in London, England, the etiology of 19 patients who were admitted to the NICU in SE was unknown in 6, and SE was attributed to drug reduction or withdrawal in 5. Other causes included encephalitis, neurosarcoidosis, theophylline toxicity, neurocytoma, progressive myoclonic epilepsy, excess alcohol, lymphoma, and cortical dysplasia *(3)*.

The same cerebral or systemic processes leading to CSE can also induce NCSE. In addition, prolonged CSE may evolve to NCSE *(see* below) and use of CEEGM is critical for the diagnosis. Among ICUs, utilization and familiarity with the test and patient population lead to significant differences in the etiologies assigned to NCSE.

In 124 NICU patients monitored with continuous EEG, the highest percentage of nonconvulsive seizures was found in patients with metabolic coma (60%), followed by those with epilepsy (56%), brain tumor (54%), intracranial infection (33%), head trauma (28%), cerebral ischemia (26%), and intracranial hemorrhage (22%) *(33)*. In comatose ICU patients the most common cause of NCSE was anoxia–hypoxia (42%), followed by stroke (22%), infection (5%), head trauma (5%), metabolic disorders (5%), withdrawal from alcohol or AEDs (5%), and tumor (5%) *(28)*. In a recent retrospective study of 100 inpatients with NCSE, most of the etiology was accounted for by acute medical problems (52%), common in the ICU setting, and epilepsy (31%); the remainder (17%) was said to be cryptogenic *(34)*. The cryptogenic category includes *de novo* generalized NCSE, which has been predominantly described in older women who were intoxicated with psychotropic medications or undergoing drug withdrawal *(35)*.

Pathophysiology

Most seizures are self-terminating phenomena lasting from few seconds to few minutes. A single seizure is followed by refractory period characterized by higher seizure threshold that prevents seizure recurrence. However, under certain conditions the mechanisms responsible for seizure termination fail and seizures recur; that is, SE ensues. This may lead to damage to the central nervous system (CNS) either directly or indirectly and further seizures.

Direct mechanisms include abnormal release of excitatory amino acids and decreased release of inhibitory amino acids at the synapse. There is increased glutamate release with repetitive presynaptic activation (called facilitation) eventually leading to excitotoxic damage through Ca^{2+} influx to the neurons via receptors for *N*-methyl-D-aspartate (NMDA) or α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA). At the same time, release of γ-aminobutyric acid (GABA) from the presynaptic storage sites is decreased when the presynaptic neuron is activated repetitively (referred to as fading of inhibition) *(36)*. Except for the transient synaptic effects, there are additional longer lasting ones affecting the expression of genes and leading to apoptosis of more vulnerable classes of cells, especially in the hippocampus. In addition, local epileptogenic processes, if repeated, can lead to dissemination of seizure propensity to other regions of the brain, a process named secondary epileptogenesis.

Indirect CNS damage from SE is the result of systemic derangements that follow. The seminal animal studies by Meldrum have shed light on this issue. After prolonged bicuculine-induced CSE in baboons, neuronal damage and cell loss was evident in the neocortex, cerebellum, and hippocampus. When systemic factors were kept within normal physiological limits (paralyzed and artificially ventilated animals with adequate serum glucose levels), there was decreased but still present neocortical and hippocampal cell damage, but absent cerebellar cell injury *(37,38)*. These experiments suggest that the seizure activity *per se* is responsible for the neuronal damage, and the systemic derangements play an additional role.

Table 3
Systemic Physiologic Changes Induced by Prolonged Generalized Convulsions or Generalized Convulsive SE

CNS	Pulmonary hypertension and edema
Tissue hypoxia (decreased O_2 delivery and increased demand)	Pulmonary embolus
	Metabolic
Cerebral edema (angiogenic and cytotoxic)	Acidosis (both metabolic and respiratory)
Increased CBF and cerebral metabolic rate of oxygen consumption	Dehydration
	Electrolyte changes (hyponatremia, hyperkalemia)
Increased intracranial pressure	Hypoglycemia
CSF pleocytosis	Hyperthermia
Hemorrhage	Skeletomuscular
Cerebral venous thrombosis	Rhabdomyolysis
Cardiovascular	Dislocations
Hypertension followed by hypotension	Fractures (bilateral humeral head, compression of the first four lumbar bodies)
Tachycardia	Renal
Myocardial ischemia	Acute tubular necrosis
Arrhythmias	Gastrointestinal
Cardiac arrest	Hepatic failure
Respiratory	Hematologic
Hypopnea/apnea	Peripheral leukocytosis
Hypoventilation	Disseminated intravascular coagulopathy
Aspiration	

(Adapted from refs. *64* and *91*.)

These derangements are especially important for the ICU patient who is in SE because they are amenable to ICU treatment. Table 3 presents the most common changes by system involved. Lothman divided the systemic changes after CSE into two phases *(36)*. During phase 1 (or early phase, within the first 30 min) the initial consequences of a prolonged seizure or SE are an increase in the cerebral blood flow (CBF) and a massive increase of plasma catecholamines, leading to increased blood pressure (BP), heart rate, serum glucose, sweating, and body temperature. Cardiac arrhythmias are common. Acidosis is the result of increased serum lactate and carbon dioxide (CO_2) retention. Minute ventilation may be increased in this phase, but later, periods of hypopnea predominate and can be exacerbated with respiratory-depressant antiepileptics, such as barbiturates and BDZs. In a clinical study, the pH ranged between 6.28 and 7.5 in 70 spontaneously ventilating patients with SE: it was less than 7.35 in 59 and less than 7.0 in 23 patients. Thirteen patients had partial pressure of arterial CO_2 (Pa_{CO_2}) greater than 60 mmHg, and overall 30 patients had a respiratory component to the acidosis *(39)*. Acidosis is markedly attenuated with neuromuscular blockade, indicating anaerobic muscle metabolism as a major source of lactate *(38)*. On the other hand, hypoxia is usually modest. In primate models of SE, the mean Pa_{O_2} was 58–68 mmHg and alone did not seem to induce cerebral injury *(37,40)*. After approx 30 min of seizing, the patient enters the second phase (or late phase) of SE. The systemic and cerebral protective mecha-

Table 4
Clinical and EEG Seizure Correlation During Generalized SE

Time	Clinical activity	EEG activity
Onset	Discrete convulsions	Discrete seizure activity
	Continuous convulsions	Merging seizure activity
Minutes	Continuous convulsions	Continuous seizure activity
	Minimal twitching in face or distal extremities	Intermittent suppression between bursts of seizure activity
Hours	No muscular activity	Periodic epileptiform discharges on a flat background

(Adapted from refs. *42*, *47*, and *91*.)

nisms progressively fail, leading to multiorgan compromise: hypotension, cardiac failure with increased pulmonary capillary leaking (leading to neurogenic pulmonary edema), loss of cerebral autoregulation (resulting in a systemic-pressure-dependent CBF, which together with the increased intracranial pressure (ICP) exacerbates the cerebral hypoperfusion), renal failure secondary to rhabdomyolysis or acute tubular necrosis, hypoglycemia and hepatic failure, severe electrolyte abnormalities (hyperkalemia that may reach life-threatening levels), and a disseminated coagulopathy. Cardiac arrhythmias are life threatening in up to 60% of patients with prolonged SE *(41)*. Sinus tachycardia or supraventricular tachycardia are most common and can be complicated by the rapid infusion of antiepileptics such as PHT.

Temperature elevation of 40° in seizing primates can be reached within 60–90 min after SE onset and, if persisting for more than 3 h, leads to neuropathic changes greater than those predicted from the seizure duration alone. When the baboons were paralyzed, the mean temperature increase was only 2.05°C over a 7-h observation. A similar dangerous temperature elevation has been observed in humans. Of 90 patients with SE, 70 had hyperthermia, with maximum temperature reaching 107°F. The duration of hyperthermia outlasted the duration of SE, with most patients remaining febrile at 12 h after the cessation of the convulsions, but only 3 of 27 were febrile at 48 h *(39)*.

Another important characteristic of late-phase SE is an electromechanical dissociation that occurs and may lead to misinterpretation of the clinical situation: convulsions may decrease or evolve to minor twitching, although electrical cerebral seizure activity continues as NCSE *(25)*. Table 4 presents a scheme of these evolving stages. It is interesting to note that SE is a dynamic state, with different characteristics, depending on when the patient is examined *(42)*. Thus, depending on the time of observation in the ICU, the patient may have obvious grand mal convulsions or only subtle twitching of the fingers, abdomen, or face; nystagmoid jerks of the eyes may be noted, or no clinical activity at all, but the patient will be in deep coma state. Although the chances in the ICU are that the intensivist will be notified early, because of vital sign monitoring and frequent examinations by the ICU staff, this may not be the case with a patient who was just admitted for ongoing SE. This

Table 5
Differential Diagnosis of ICU Seizures or SE

Myoclonus	Posturing
Toxic/metabolic	Hydrocephalic opisthotonus
Infectious/inflammatory/autoimmune	Shivering/rigors
Spinal cord disease	Hiccoughs
Brainstem/subcortical	Psychogenic SE after anesthesia
Cortical	Narcolepsy–cataplexy
Epileptic	Syncope
Tics	Transient ischemic attacks
Tremor	Transient global amnesia
Asterixis	Voluntary movement
Clonus	Psychogenic seizures

possibility must be kept in mind, and all previously seizing patients who do not regain consciousness soon should be monitored with a continuous EEG to exclude ongoing NCSE.

DIFFERENTIAL DIAGNOSIS

Although GTC convulsions associated with tongue biting, irregular respirations, froth in the mouth, urine incontinence, and postictal diminished responsiveness are quite characteristic, this is not the case with several other repetitive abnormal movements or postures that may be witnessed in the ICU. Usually, there is a false-positive interpretation of various nonepileptic phenomena as seizures or, if continuous, as SE, and several unnecessary tests are ordered. A differential diagnosis of CSE should include among others continuous or multifocal subcortical myoclonus (postanoxic syndromes, Creutzfeldt–Jacob disease, metabolic encephalopathies), asterixis, tics, hemifacial spasm or myokymia, fasciculations (spontaneous or after depolarizing paralytic drug administration), rigors resulting from sepsis, intermittent decorticate or decerebrate posturing, and psychogenic SE following anesthesia (Table 5) *(43,44)*. A careful clinical history, an interview of the staff who witnessed the abnormal movements and a review of ICU medications, as well as of the most recent appropriate laboratory tests, would be enough to permit a sound diagnosis. It is imperative that the ICU nursing and medical staff become familiar with seizures and SE and know not only what to do but also what to look for and document. However, many times there is no history of seizures, the onset of movements was not witnessed, or the clinical presentation is atypical. In these situations of doubt, three major diagnostic steps should be taken, in parallel with the emergent treatment that should be administered to stop the seizures.

First, if there is no known cerebral pathology, a computerized tomographic (CT) scan of the head should be ordered. Not every patient who has a seizure needs a CT (e.g., children with febrile seizures), but the very presence of the patient in the ICU is a proof of complex organ dysfunctions, which may lead to the development of cerebral pathology. Second, a number of biochemical and hematologic tests should

be ordered, which are the same as those included in the treatment of SE algorithm, because such tests have a dual diagnostic and therapeutic significance. Third, an EEG, preferably continuous and with video recording, should be ordered (*see* next section). The sensitivity of the test may be compromised by the treatment already administered, but still it remains the cornerstone of the differential diagnosis.

There are not many data regarding the usefulness of emergent EEG, but in a mixed ICU–ward population of 261 patients, Varelas et al. found that the presence of any epileptic activity on the emergent EEG was independently predicted by a history of cardiorespiratory arrest (odds ratio [OR] 2.6, 95% confidence interval [CI] 1.12–6.25) or witnessed seizures before the test was performed (OR 2.2, 95% CI 1.2–4.1). A history of stroke on admission and a first-ever ordered EEG were negative predictors for epileptic activity on the test (OR 0.2, 95% CI 0.006–0.65 and OR 0.38, 95% CI 0.16–0.88, respectively) *(45)*. In the next sections we examine the data available regarding the indications and timing for ordering the test and the results of the test.

ELECTROENCEPHALOGRAPHY

Indications and Timing

Almost all experts agree that EEG is a valuable test in the management of SE. The issue of when it should be ordered is more controversial. During the first 15 min, the majority of experts do not find a reason to spend valuable time and resources initiating the test *(6,8)*. However, others argue that EEG must be started immediately *(46)* or when there is no improvement in the level of consciousness during the first 15 *(20)* or 30 min *(26)* after the initiation of treatment. The timing of the real onset of SE, when it is not known, may be another reason to order the test, because the presence of a specific phase according to the classification of Treiman et al. *(47)* in the recording may have a diagnostic and prognostic value *(48)*. During the late phase (30–60 min after the "time zero"), an emergent EEG has a more clear indication, if the neurological examination of the patient is compromised by the treatment (sedatives, paralytics) *(26)* or when the depth of barbiturate coma needs to be monitored. A prolonged emergent EEG in this setting may be more useful *(26,45,46,48)*. There is another reason to order this test during the late phase: if appropriate treatment has resulted in the cessation of tonic–clonic activity, yet the patient is slow to return to the baseline status, NCSE must be excluded, as in any case of unexplained altered or fluctuating level of consciousness *(16,29,49)*. Finally, an emergent EEG could be considered if for any reason there is suspicion for pseudo-SE *(50)* or to differentiate myoclonic SE from nonepileptic myoclonus *(48)*.

EEG Findings in SE

Generalized CSE

The grand mal attack is initiated by an abrupt loss of voltage of a few seconds duration (desynchronization, electrodecremental period followed by very fast activity [20–40/s]) in a generalized distribution that corresponds to the tonic phase.

Muscle activity usually obscures the recording, but if there is any doubt and the ICU patient is intubated and mechanically ventilated, one should consider paralytic agents to remove it. In patients who are curarized, rhythmical activity at about 10/s with rapidly increasing amplitude follows the phase of desynchronization. Approximately 10 s after the onset of a seizure, slower frequencies are seen in the theta and delta range. This phase is followed by repetitive bursts of polyspike–wave complexes that correspond to the clonic phase of the seizure. The last clonic contraction is followed by postictal flatness of several seconds. In an ongoing SE, EEG shows slowing and disorganization in the interval until fast low-voltage spiking with focal onset or primary generalization indicate the onset of a new attack. It is very characteristic that the postictal suppression of brain activity that occurs after a single GTC seizure is not usually seen in SE *(51)*. The default of postictal flattening may indicate failure of active inhibition in the postictal stage. A reasonable hypothesis indicates that this type of inhibition that stems from cerebellar structures is weakened by hypoxia.

In the aforementioned study from the group in Richmond, Virginia, after CSE was controlled, CEEGM demonstrated that 52% of patients had no after-SE ictal discharges and manifested EEG patterns of generalized slowing, attenuation, periodic lateralizing epileptiform discharges (PLEDs), focal slowing, and/or burst suppression. The remaining 48% demonstrated persistent electrographic seizures. These results suggested that EEG monitoring after treatment of CSE is essential to recognition of persistent electrographic seizures and NCSE unresponsive to routine therapeutic management of CSE although clinically the patient may seem to be responding (no convulsions) *(25,31)*.

Generalized NCSE or Absence SE

The EEG findings in the ictal episode consist of classical continuous spike–wave activity in 41% of the cases. There is usually a history of absence seizures in childhood with typical 3-Hz spike–wave discharges or a history of mental retardation, diffuse brain dysfunction, and Lennox–Gastaut syndrome with slower (<2.5 Hz) spike–wave discharges *(35)*. Fragmented spike–wave discharges occurring in repetitive bursts are also quite common (28%). Spike–wave activity shows the typical frontal midline maximum. Rhythmical slow activity in the δ or θ range of either frontal or occipital predominance was found in 15.6% of patients studied *(51)*.

Complex Partial SE

In complex partial SE, EEG findings consist of focal onset of electrographic seizures (usually in a temporal or extratemporal distribution) on a slow and disorganized background, intermixed with single or multiple spike–wave complexes interictally, in the context of a confusional state. However, rapid generalization can occur, and the initial focus may be obscured until treatment is given *(14)*.

Focal Motor SE

Epilepsia partialis continua (EPC, or Kojewnikoff's epilepsy) may be associated with a completely normal EEG (*see* the section on Management of Focal SE in this

chapter). In other cases rolandic spiking can be seen in conjunction with contralateral twitching.

Tonic SE

Tonic SE is associated with runs of rapid spikes or very fast polyspikes in generalized synchrony with frontal maximum.

Status Myoclonus

A variety of EEG patterns accompany SM. The most common pattern consists of generalized periodic complexes (spikes, polyspikes, or sharp waves) with attenuation of activity between complexes. The second most common pattern presents with burst suppression *(52)*.

NCSE vs Metabolic Encephalopathy

A number of patients thought to be in NCSE display EEG characteristics of encephalopathy *(13)*. In a study by Granner and Lee, the EEG patterns in patients with NCSE were not uniform: 26% of the 85 patients examined had rhythmic slow waves in the delta range with intermittent spikes *(53)*. It is not clear whether these rhythmic waves are the result of the underlying cerebral injury or a primary expression of NCSE. Triphasic waves (TWs) have typically a small negative (upward) deflection, followed by a large positive wave, which is followed by another low-amplitude, longer negative slow wave. They have a generalized distribution, recur at 0.5–2 Hz, and are not considered to be epileptic in origin. TWs with epileptiform characteristics (spike morphology; waxing and waning) must be differentiated from TWs caused by a metabolic encephalopathy, and this is not always easy in the ICU, where both conditions can coexist. However, the inclusion in the NCSE definition of a response to BDZs is not enough, because even metabolic TWs (e.g., associated with hyperammonemia) can respond to intravenous DZ. Fountain and Waldman retrospectively examined the EEG response to BDZs in 10 patients with definitively diagnosed metabolic encephalopathy. TWs resolved persistently in four patients and intermittently in six patients. Background activity slowed in five patients and was attenuated in five patients. Unresponsive patients did not arouse, and three of five drowsy patients became less responsive after the drug was given *(54)*. If administration of BDZs results in resolution of the EEG abnormality and clinical improvement, the diagnosis of NCSE is straightforward. Sometimes, however, the clinical response in NCSE is delayed *(55)* (and mistakenly not associated with the drug given hours or days before) or absent: in a recent study of 100 cases with NCSE, 25 of 64 (39%) did not have a clinical response and 10 of 64 (16%) had not even an EEG response to BDZs *(34)*.

OUTCOME

Many studies have documented the high morbidity and mortality of CSE and have emphasized the importance of prompt intervention to improve outcomes *(6,32)*. Mortality in CSE ranges from 15 to 22% in adults, but may be lower (3%) in

children *(17,19,39,56)*. In the Richmond population study, it was estimated that 22,200 to 42,000 deaths per year from SE occur in the United States *(19)*. Morbidity and mortality in generalized CSE is attributed to three factors: brain injury caused by an acute insult that induces SE, systemic metabolic and physiologic effects of CSE, and neuronal damage from the abnormal electrical activity of SE. The main factors that influence mortality in CSE are the underlying cause (regarded by most authorities as the most important variable), the duration of SE (mortality 32% if persistent for more than 1 h vs 2.7% if less than 1 h), the treatment, and the age of the patient (children have better outcomes than adults) *(12,32,57)*.

The etiology of SE plays the most important role in mortality. In the large study of 253 adults from Richmond, Virginia, Towne et al. found that SE associated with anoxia (60%), tumors (36%), metabolic etiologies (31%), infection (31%), and CNS hemorrhage (38.5%) had higher mortality. Withdrawal from ethanol and antiepileptic medication was associated with decreased mortality. The mortality rate is 20% when the cause cannot be determined. In the multivariate analysis, duration longer than 1 h, anoxia, and age were independent risk factors for mortality after SE. The mortality rates of focal (30%) and generalized (21%) SE were not significantly different in this study. Neither race nor sex affected mortality significantly *(32)*.

Seizure duration is also predictive of both treatment success rate and mortality. As time passes, SE becomes more refractory to treatment *(21)*. Seizures lasting longer than 60 min are associated with higher mortality rate than SE lasting 30 to 59 min *(32)*. However, seizures of 10–29 min duration have a mortality rate of 4.4% *(58)*. In another retrospective analysis from Columbia Presbyterian Hospital in New York, Mayer et al. did not find a difference in mortality between patients with refractory SE (23%) and those with nonrefractory SE (13%), but this may result from the small number of patients. However, it was clear that patients with refractory SE stayed longer in both NICU and hospital (7.5 d vs 1 d, $p < 0.001$ and 32.5 d vs 11 d, $p < 0.001$) and had reduced Glasgow Outcome Scale score at discharge compared with admission ($p = 0.02$) *(59)*.

In NCSE outcome is less well documented. Patients with absence SE do not have permanent neurologic deficits and do not die from their status. In contrast, complex partial SE can be accompanied by considerable morbidity and mortality. Like generalized CSE, complex partial SE can be precipitated by acute lesions such as stroke or encephalitis, which are responsible for subsequent morbidity. Aggressive and early antiepileptic treatment may not alter the poor outcome in patients who present in coma. There may also be resistance to the drug treatment: in the aforementioned study, Mayer et al. found that NCSE was an independent risk factor for refractoriness to treatment *(59)*. In the large, double-blinded study by Treiman et al. 134 patients with subtle generalized SE were randomized to receive four different intravenous regimens *(9)*. No difference in the success rate between the regimens was found. However, outcomes for subtle SE were significantly worse at 30 d (50.1% of patients with overt SE were discharged from the hospitals vs only

8.8% of those with subtle SE, $p < 0.001$). Similarly, hypotension requiring treatment occurred more often in patients with subtle SE ($p < 0.001$). During the first 12 h after the end of the infusions, no patient with subtle SE regained consciousness, compared with 17% of patients with overt SE (but with no significant difference among the four treatment groups).

A recently published retrospective analysis from the University of Virginia identified 100 consecutive patients with NCSE from an EEG database. Patients were divided into three groups based on etiology: acute medical, epilepsy, and cryptogenic. Overall mortality was 18%. Subgroup analysis showed that mortality was 27% (14 of 52) in the acute medical group, 3% (1 of 31) in the epilepsy group, and 18% (3 of 17) in the cryptogenic group ($p < 0.02$). Mortality was also different between patients with severe mental status impairment (39%) and those with mild impairment (7%, $p < 0.001$), and between patients with acute complications (36%) compared with those without complications (7%, $p < 0.0002$). Two additional, interesting observations from this study were as follows: the absence of correlation between generalized spike–wave discharges on EEG and mortality and the independent association of mental status impairment and etiology with mortality ($p < 0.001$) *(34)*. Thus, although not universally accepted, some authorities believe that it is appropriate to diagnose and treat NCSE early, because duration from 36 to 72 h may lead to serious morbidity and mortality *(60)*.

GOALS OF ICU MANAGEMENT OF SEIZURES AND SE

Management of ICU seizures and SE should include emergent medical management, termination of seizures, prevention of recurrence of seizures, and prevention or treatment of complications. To what extent these goals are met in clinical practice is unclear. In the aforementioned survey of 408 intensivists from the United Kingdom, it was shown that following failure of initial management of resistant SE, the preferred second-line treatment was BDZ infusion (35%) or anesthetic induction agent (32%). The majority of respondents (57%) gave anesthetic induction agents within 60 min of the start of SE. Thiopentone was administered in 82% of these cases. Clinical assessment was used to monitor the response to the treatment in almost half the cases. However, in more specialized ICUs, such as pediatric or neurological or neurosurgical units, the majority of responders used a cerebral function monitor in addition to the clinical examination, emphasizing the greater experience these physicians had *(2)*.

Emergent Medical Management

Basic life support with maintenance of airway, breathing, and circulation (ABC) should be provided as soon as the diagnosis of a seizure or SE is established. Tracheal intubation is important in maintaining adequate oxygenation and preventing aspiration pneumonia. However, few patients with one or more seizures, but almost all patients with SE (especially refractory) need intubation. Adequate oxygen supply with a nonrebreather facial mask and airway patency with oral or nasopharyn-

geal devices may suffice for a patient who has had one or more seizures, but has stopped having convulsions. On the other hand, most ICU physicians would intubate a patient in SE for airway protection and for anticipation of administration of respiratory depressant AEDs. The goal after intubation is adequate oxygenation (initially 100% of the fractional concentration of inspired oxygen) and ventilation with a goal of normal pH: initial hyperventilation in a paralyzed patient with metabolic acidosis is acceptable, but arterial blood gases must be tested frequently to avoid subsequent respiratory alkalosis, which may further decrease seizure threshold. Paralytics are almost always used for the intubation of a seizing patient, but short-acting agents, such as intravenous rocuronium (0.6–1.2 mg/kg) or vecuronium (0.1 mg/kg), are preferable to succinylcholine, which can induce severe hyperkalemia in neurological patients. As for sedation, thiopental, a drug that can also help in seizure control, can be used at 3–5 mg/kg. At least two large intravenous catheters should be inserted and carefully secured for fluid, drug administration, and withdrawal of blood samples. This is not easy in a convulsing patient: an alternative site, such as external jugular catheterization or an alternative route such as intramuscular or rectal administration should be sought. Continuous electrocardiogram, pulse oximetry, and temperature monitoring should be initiated. Noninvasive BP measurements should be started, but the physician should be reluctant to treat elevated pressure during the convulsion phase unless it is extreme (e.g., >230 mmHg systolic) or there is suspicion it is the primary cause of the seizures (*see* Chapter 8). Usually, control of the seizures with the first-line AEDs would be enough to reduce the BP. Continuous invasive monitoring of BP should be reserved for patients in SE given who are given AEDs with strong hypotensive effect, such as barbiturates.

Routine or continuous EEG recording should be used to assess the presence or absence of ongoing seizure activity and to direct effective and rationale treatment, but this should not delay or distract the rest of the urgent management as just discussed.

Blood samples should be obtained for blood count, glucose, electrolytes, liver enzymes, creatinine kinase, toxicology screen, arterial blood gases, and AED levels if appropriate. If hypoglycemia is confirmed, then 50 mL of glucose 50% solution should be given. Because hyperglycemia may exacerbate neuronal damage caused by SE, glucose should be administered only when lab results confirm hypoglycemia *(61,62)*. However, the glucose measurement can be done at the bedside rapidly, and this is preferable. If this option is not available, if the history of the patient is unknown, or if there is a strong suspicion of hypoglycemia and the glucose measurement will take several minutes to be completed, then we recommend giving 1 ampule of D/W 50%, and waiting for the results. In case of history of alcoholism, 100 mg of intravenous thiamine is given first, along with glucose, to avoid precipitating Wernicke's encephalopathy. If the history of the patient is unknown, thiamine should be administered at the same dose. Lumbar puncture is indicated if there are no signs of increased ICP and an infectious process causing

Table 6
Management of Brief Single ICU Seizure (<60 s)

Observe. Eliminate etiology.

Consider chronic therapy: PHT (15–20 mg/kg) or fosphenytoin (15–20 mg/kg PHT equivalents [PE]) loading dose and 300–400 mg/d. Goal serum level of 10–20 µg/mL or free level 1–2 µg/mL.

PHT intolerant patients: intravenous/oral VPA (15–20 mg/kg load, maintenance 600–3000 mg/d) or oral CBZ (600–1200 mg/d).

Seizure precautions: padded bed rails, increased observation.

(Adapted from ref. *218*.)

SE is highly suspected (which is uncommon). Twenty percent of patients with SE may have "benign postictal pleocytosis" ($\leq$70 white blood cells/mm^3) *(63)*. Eight out of 54 (15%) patients with SE may have CSF protein elevation (>50 mg/100 mL), and in only 1 case the value exceeded 75 mg/100 mL *(39)*.

Termination of Seizures and Prevention of Recurrence of Seizures

As a general rule, one brief GTC seizure in the ICU is not an indication for AED administration. By the time the drugs are available at the bedside, the seizure is usually over. Close monitoring of the patient's vital signs, bed padding, and the initiation of a workup for identifying the cause are usually adequate measures (Table 6). Sometimes the etiology is obvious, for example, severe hyponatremia, and management should be focused on correcting the abnormality rather than treating the seizure. In other situations, however, where the presence of an intracranial pathology is already known (e.g., stroke or extra-axial hematoma), and the patient had never been loaded with antiepileptic medications, the balance shifts toward covering the patient with an AED in anticipation of new seizures (as an expression of enhanced cerebral irritability from the lesion). Most often in the ICU, because of routine venous accessibility, this is accomplished through an intravenous load, but per os loading is an acceptable alternative depending on the circumstances. Because of the complexity of ICU patients, the intensivist should individualize the extent of the evaluation, but in most cases the minimal nonmetabolic workup that should be ordered consists of a CT image of the head to exclude new intracranial pathology and an EEG to confirm epileptic discharges.

If the seizure is prolonged enough or recurs after a few minutes, there is enough time to have the proper medications at the bedside. In this situation most intensivists would try to break the convulsion by administering benzodiazepines intravenously for the short-term control of the seizing patient and loading the patient with an intravenous antiepileptic, such as PHT or valproate (VPA) for the long-term control (Table 7). Because at this point it may not be clear if the flurry of seizures heralds the entry of SE, some intensivists will also consider intubating the patient in anticipation of more seizures and the need for airway control during the workup. However, this may not be necessary in most cases, unless the patient is obstructing the upper airway or is vomiting or the second-line drugs fail to control the seizures.

Table 7
Management of a Prolonged Seizure or More Than One Seizure in the ICU

Check oxygen saturation, vital signs. Consider intubation, if risk of aspiration.

Intravenous BDZ, e.g., lorazepam (1–2 mg), DZ (10–20 mg), or midazolam (2–5 mg)
   with concurrent loading dose of PHT or fosphenytoin (PE) of 15–20 mg/kg and main-
   tenance of 300–400 mg/d.

PHT-intolerant patients: VPA (intravenous load 15–20 mg/kg), with maintenance at 400–
   600 mg every 6 h.

Seizure precautions: padded bed rails, increased observation.

(Adapted from ref. *218*.)

If the seizures continue and the patient meets the criteria for SE, then a treatment algorithm should be initiated without delay (Table 8). The earlier the treatment is initiated, the easier the termination of seizures: 80% of patients had termination of SE when treated within 30 min of onset and <40% when treated after the first 2 h from onset *(21)*. If the seizures persist despite two or three first- or second-line intravenous antiepileptics, SE is considered to be refractory and special measures are taken in the ICU. The following sections that follow review the available medication options and the rationale for their use.

Rationale for Using Specific Antiepileptic Medications

Treatment of recurrent seizures and SE requires fast drug absorption, and, therefore, parenteral administration is essential. Among the currently available standard antiepileptics, only PHT, phenobarbital (PB), and VPA are available in injectable preparations. In addition, antianxiety drugs (such as DZ and lorazepam) and anesthetics (such as amorbabital, pentobarbital, thiopental, midazolam, and propofol) are available in parenteral forms. To be able to act rapidly, the drugs need to cross the BBB readily. This is the case with most drugs that are effective in acute seizure management: these highly lipid-soluble compounds cross in seconds to minutes. High lipid solubility also leads to redistribution from the central compartment (blood and extracellular fluid) to peripheral compartments (fat and organs). The redistribution leads to a drop in plasma concentrations. Therefore, repeat infusions are necessary to maintain adequate plasma levels. Continuous administration increases the concentration of the drug in the central compartment and leads to saturation of the peripheral compartment to the degree that the drug no longer redistributes. If drug administration ceases, plasma levels will be maintained by diffusion from the peripheral to the central compartment, which may result in unfavorable side effects, such as prolonged obtundation or cardiorespiratory collapse. These effects are dangerous and account for some of the morbidity and mortality associated with SE *(64)*.

The rationale for using BDZs as first-line drug was until recently based on small uncontrolled studies. The first randomized, double-blind study was conducted by

Table 8
Treatment of ICU Recurrent or Refractory Seizures Over 5 min or More Than Two Discrete Seizures Without Recovery of Consciousness

Consider as SE.

ABC: preserve airway and oxygenation by intubation.

Measure blood glucose at bedside. Give 100 mg iv thiamine and glucose, only if <40–60 mg/100 dL or unable to have a fast result. At the same time draw blood for blood count, electrolytes, liver enzymes, creatinine kinase, toxicology screen, arterial blood gases, and AED levels.

Immediate intravenous BDZs: lorazepam (5–10 mg), DZ (20–40 mg), or midazolam (5–20 mg) over 5 min.

PHT loading dose of 20 mg/kg at 50 mg/min or fosphenytoin, 20 mg/kg PE at 150 mg/min. Consider VPA intravenous load of 15–20 mg/kg, maintenance 400–600 mg every 6 h in PHT-intolerant patients.

Continuous EEG, if available.

If seizures continue, PHT or fosphenytoin (additional 5–10 mg/kg or 5–10 mg/kg PE). Consider VPA intravenous load of 15–20 mg/kg, maintenance 400–600 mg every 6 h.

If seizures continue for more than 60 min: diagnose Refractory Status and institute pharmacological EEG seizure suppression, 10- to 20-s burst suppression, if necessary, with propofol (2 mg/kg iv bolus and 100–150 μg/kg/min infusion) or thiopental (3–4 mg/kg iv bolus and 0.3–0.4 mg/kg/min). Hemodynamic support consists of fluids, pressors, and inotropes.

Once EEG suppressed, complete loading of anticonvulsant. Add more BDZ if necessary, and consider weaning infusion agent several hours later (preferably 12–24 h) while optimal serum anticonvulsant levels are documented.

If seizures persist, consider prolonged barbiturate or anesthetic coma with pentobarbital (12 mg/kg at 0.2–0.4 mg/kg/min followed by an infusion of 0.25–2.0 mg/kg/h) for continued EEG suppression.

(Adapted from refs. *1*, *6*, *8*, *10*, *44*, *46*, *67*, *91*, *94*, *128*, and *218*.)

Leppik et al., who compared DZ and lorazepam in patients with SE. Both drugs were highly efficacious at controlling the seizures (*see* below) *(65)*. Another randomized, nonblinded clinical trial compared a combination of DZ and PHT with PB in 36 patients with generalized CSE. The cumulative convulsion time had a strong trend to be shorter for the phenobarbital group than for the DZ/PHT group (median: 5 vs 9 min, $p < 0.06$). The response latency (elapsed time from the initiation of therapy to the end of the last convulsion) also had a tendency to be shorter for the PB group (median: 5.5 vs 15 min, $p < 0.10$). The frequencies of intubation, hypotension, and arrhythmias were similar in the two groups *(66)*. The results of this study, although not reaching statistical significance because of the small number of patients, provided evidence of the safety and efficacy of PB, but did not convince the majority of the medical community, who preferred shorter acting agents with a safer clinical profile.

Ten years later, a landmark study from the Veterans Affairs (VA) Status Epilepticus Cooperative Study Group was published *(9)*. It was a randomized, double-blind, multicenter trial from 16 VA medical centers of four intravenous regimens, either for overt SE or subtle SE: DZ (0.15 mg/kg) followed by PHT (18 mg/kg), lorazepam (0.1 mg/kg), PB (15 mg/kg), and PHT alone (18 mg/kg). Interestingly, lorazepam followed by PHT, the most commonly used combination today, was not included. If the first treatment had failed, an algorithm to follow with a second and third treatment regimen was also available. Treatment was considered to be successful when all motor and EEG seizure activity ceased within 20 min after the beginning of the drug infusion and there was no return of seizure activity during the following 40 min. Five hundred seventy patients were enrolled. Three hundred eighty-four patients had verified overt CSE and 134 subtle SE. In the CSE group, lorazepam was successful in 64.9% of patients, PB in 58.2%, DZ plus PHT in 55.8%, and PHT in 43.6% ($p = 0.02$, but in the intention-to-treat analysis only with a trend). Lorazepam was significantly superior to PHT in a pairwise comparison ($p = 0.002$). In the subtle SE group no significant differences among the treatments were detected (17.9, 24.2, 8.3, and 7.7%, respectively, for the four regimens, $p = 0.18$, in the intention-to-treat analysis $p = 0.91$). There were no differences among the treatment groups with respect to recurrence during the 12-h study period, the incidence of adverse reactions (hypoventilation, hypotension, cardiac arrhythmias), or the outcome at 30 d. Upon comparison of the two types of SE, however, outcomes for subtle SE were significantly worse at 30 d (50.1% of patients with overt SE were discharged from the hospitals vs only 8.8% of those with subtle SE, $p < 0.001$).

Similarly, hypotension requiring treatment occurred more often in patients with subtle SE ($p < 0.001$). During the first 12 h after the end of the infusions, no patient with subtle SE regained consciousness, compared with 17% of patients with overt SE (but with no significant difference among the four treatment groups). At 30 d, the outcome of patients who responded to the first-line drug in both the overt and subtle SE groups was better than those who did not respond. Mortality in the nonresponders was twice as high as that in the responders. Based on these results, Treiman and colleagues concluded that lorazepam was more efficacious than PHT in overt SE treatment and overall easier to use than the other regimens. Also based on these results, various treatment algorithms have been proposed that combine treatment first with lorazepam and then with PHT within the first 30 min after SE onset *(67)*. After these measures fail and if the patient is in the ICU, anesthesia with midazolam or propofol is suggested.

Alternatively, PB is tried first for the next 30 min, before one proceeds to general anesthesia. However, the current notion is to individualize the treatment to the patient rather than follow a strict, inflexible algorithm: for example, selected patients with good response to intravenous lorazepam may benefit from subsequent oral administration of the drug instead of an additional medication *(68)*. When the first-line drugs fail to control SE, the subsequent choices have markedly reduced

efficacy *(9)*, either because of intrinsic refractoriness or delay of treatment with reduced probability for response *(69)*. Until now we did not have a way to predict which patient would not respond to treatment and for whom the intensivist should, for example, skip treatment steps and go directly to general anesthesia.

Mayer et al. examined the issue of predictive factors for refractory SE in a retrospective study of 74 patients with 83 episodes of SE. Refractory SE was defined as seizures occurring for longer than 60 min despite treatment with BDZs and an adequate loading of a second standard intravenous antiepileptic. In 57 (69%) episodes, seizures occurred after BDZ treatment and in 26 (31%) even after a second agent was administered (i.e., fulfilling the criteria for refractory SE). NCSE and focal motor seizures at onset were independent risk factors for refractory SE in the multivariate analysis (OR 11.6, 95% CI 1.3–11.1, $p = 0.03$; and OR 3.1, 95% CI 1.1–9.1, $p = 0.04$, respectively) *(59)*.

However, there is no standardized management of refractory SE even among neurologists specializing in critical care. In a recently published survey among 63 (out of 91 participants who responded) experts in this field from Austria, Germany, and Switzerland, two-thirds would apply another nonanesthetizing drug (such as PB) for both CSE and complex partial SE after the failure of first-line drugs. A general anesthetic was more often used in CSE than in complex partial SE as an alternative (35% vs 16%, $p = 0.02$). All participants would proceed to general anesthesia for ongoing seizures after these measures had failed, in case of CSE and, interestingly, 75% of them in case of NCSE. One-third of participants would not use EEG but would aim only for clinical seizure termination. The vast majority (72%) responded that they would start weaning general anesthesia within 24–48 h *(70)*.

The following sections present the individual drugs used in the treatment of ICU seizures. Some of the most important data regarding pharmacokinetics, adverse effects, and efficacy, based on published studies pertinent to the ICU will be presented to the interested reader. Table 9 presents an overview of these medications. A more in-depth analysis can be found in standard epilepsy and pharmacology textbooks.

Medications Used to Control ICU Seizures and SE (Table 9)

Benzodiazepines

BDZs have maintained a significant role as first-line intravenous treatment for acute seizures or SE because they were shown to be broad spectrum and potent anticonvulsant agents *(71)*. Their effect is at the synaptic level via the BDZ–GABA$_A$ receptor complex. They enhance the inhibitory GABA action by increasing the Cl$^-$ channel openings and hyperpolarizing the postsynaptic neuron *(72,73)*. However, one must keep in mind that first-line anticonvulsants like BDZs and PHT fail to terminate convulsive SE in 31–50% of cases *(10,59)*.

Table 9
Doses, Half-Life, and Elimination Route for Antiepileptic Medications Used in the ICU for Prolonged Seizures or SE

AED	Loading dose (intravenous except as noted)	Maximum rate	Maintenance (by mouth or intravenously)	Half-life	Elimination
Diazepam	0.15–0.25 mg/kg	5 mg/min		24–57 h	Hepatic
Lorazepam	0.05–0.1 mg/kg	2 mg/min		8–25 h	Hepatic
Midazolam	0.1–0.3 mg/kg	4 mg/min	0.08–0.4 mg/kg/h	1.5–4 h	Hepatic
Clonazepam	1 mg (repeat × 4)	2 mg/min	10 mg/d	20–40 h	Hepatic
Clomethiazole	40–100 mL	5–15 mL/min	0.5–20 mL/min	—	—
Phenytoin	15–20 mg/kg	50 mg/min	4–5 mg/kg/d	12–48 h	Hepatic
Fosphenytoin	15–20 mg PE/kg	150 mg PE/min	4–5 mg PE/kg/d	10–15 min	Hepatic, red blood cells, tissues
Lidocaine	1.5–2 mg/kg	50 mg/min	3–4 mg/kg/h	1.8 h	Hepatic
Valproic acid	10–25 mg/kg	1.5–3 mg/kg/min	15–50 mg/kg/d	7–18 h	Hepatic
Thiopental	2–4 mg/kg	250 mg/min	3–5 mg/kg/h	14–34 h	Hepatic
Pentobarbital	6–12 mg/kg	50 mg/min	0.5–2 mg/kg/h	20 h	Hepatic
Phenobarbital	15–20 mg/kg	100 mg/min	1–4 mg/kg/d	75–120 h	Hepatic, renal (25%)
Propofol	1–2 mg/kg	5 min	5–10 mg/kg/h initially, reduced to 1–3 mg/kg/h	0.5–1 h	Hepatic
Paraldehyde	5–10 mL rectally	Glass syringes	Repeated in 15–30 min	3 h	Hepatic, lungs
Isoflurane	0.8–2% inhaled	Anesthetic system	Titrate to burst suppression		Lungs

PE, phenytoin equivalents.
(Adapted from refs. *1, 3, 6, 67, 91, 94,* and *150.*)

DIAZEPAM

DZ is a highly lipid-soluble BDZ that was used extensively during the last decades but recently has lost some popularity to lorazepam. It is recommended that DZ be administered by direct intravenous injection through a needle or a catheter rather than by infusion. Because of its solubility profile, it rapidly enters the brain tissue. However, it redistributes to other parts of the body (fat stores and muscle) in approx 15 to 20 min after it enters the brain. This results in loss of the clinical effect caused by fall in the brain levels. Its distribution half-life is 30–60 min, and its elimination half-life 24–57 h *(74)*. Nonetheless, sedative adverse effects are persistent and cumulative, in particular with repeated administration, because the drug remains in the fat stores. It has been shown that DZ given in a dose of 5–10 mg/min can terminate seizures in 5–10 min in 70–80% of patients. The recommended dose is 10–20 mg (0.15–0.25 mg/kg, at a rate of 5 mg/min or less) *(65)*.

When prolonged intravenous treatment is recommended for longer term management, the use of an alternative drug is advised. The injectable solution contains 5 mg/mL of DZ in a mixture containing 40% propylene glycol and 10% ethanol and can cause local tissue irritation, venous thrombosis or phlebitis, and pain at the site of injection. Careful monitoring of vital signs is recommended to prevent systemic adverse effects such as hypotension, respiratory depression, profound sedation, and coma. Coadministration of other sedatives such as barbiturates can increase the risk of serious systemic side effects *(43,64,75,76)*.

DZ can also be given by rectal administration. Two controlled clinical studies were conducted to demonstrate the effectiveness of rectal DZ in treating seizure clusters. The trials were randomized, double-blind, placebo-controlled with the first dose administered at the onset of an identified episode. Seizure frequency was measured over the course of 12 h. Both trials showed that a significantly greater percentage of DZ-treated patients (55–62%) were seizure free during the observation periods compared with placebo-treated patients. Somnolence was the most commonly reported adverse effect, and in over 500 patients treated with rectal DZ not a single episode of respiratory depression was reported *(77,78)*. Despite this favorable drug profile, rectal DZ administration in the ICU should be considered only in the very few patients without immediate intravenous access (e.g., those who, during their convulsions, lose their intravenous access, continue to seize, and have no obvious veins for cannulation). However, newer BDZs, such as intramuscular midazolam, may be better suited for those problematic administration route cases (*see* section on midazolam below).

LORAZEPAM

Lorazepam is closely related to DZ in terms of efficacy and adverse effects. It has become the drug of choice in the acute management of seizures because it is less lipid soluble than DZ and subject to less rapid redistribution. Its distribution half-life is less than 10 min, and its elimination half-life is 8–25 h *(74)*. A single injection is highly effective, and it has been associated with lower risk of cardiorespiratory depression and hypotension than DZ. The anticonvulsant effect lasts about

6 to 12 h, making it preferable to DZ (15–30 min) and particularly appropriate for the management of withdrawal seizures *(6)*. In a randomized, double-blind trial, lorazepam was compared with DZ in the treatment of 81 episodes of SE. Patients received one or two intravenous doses of 10 mg of DZ or 4 mg of lorazepam. The onset of action did not differ significantly (mean time to end the seizures was 2 min for DZ and 3 min for lorazepam). Seizures were controlled in 89% of the episodes treated with lorazepam and 76% treated with DZ. Adverse effects, such as respiratory depression, occurred in 13% of the lorazepam-treated and in 12% of the DZ-treated patients *(65)*.

This slightly superior clinical profile of the drug was also confirmed in the pediatric population. The two drugs were compared in 102 children in a prospective, open, "odd and even dates" trial. Convulsions were controlled in 76% of patients treated with a single dose of lorazepam and in 51% of those treated with a single dose of DZ. In this study, some patients received lorazepam rectally with 100% efficacy. Significantly fewer patients treated with lorazepam required additional anticonvulsants to terminate the seizures. Respiratory depression occurred in 3% of lorazepam-treated patients and 15% of DZ-treated patients. Interestingly, no patient who received lorazepam required admission to an ICU *(79)*.

Another recent retrospective study compared lorazepam and DZ treatment for efficacy, safety, and cost in 90 episodes of SE. Fewer seizure recurrences followed lorazepam administration (given either as first, second or third dose of BDZ, $p = 0.0006$). There was no difference in adverse effects or cost. The authors recommended that lorazepam be the first line therapy in preference to DZ in adults with CSE *(80)*.

Because of the strong tendency for tolerance following lorazepam treatment, longer term maintenance AEDs must be given in addition. The recommended dose of lorazepam is 0.05–0.1 mg/kg (usually 4 mg), repeated after 10 min if necessary. The rate of injection should not exceed 2 mg/min.

MIDAZOLAM

Midazolam is a unique water-soluble compound whose benzepine ring closes when in contact with serum and converts it into a highly lipophilic structure, rapidly crossing the BBB. Its water solubility leads to rapid absorption by intramuscular injection or by intranasal or buccal administration. Midazolam is 96% protein bound and is metabolized in the liver before renal excretion. It has an ultrashort distribution half-life of less than 5 min and a short elimination half-life of 1.5–4 h (74). Thus, its action is very short, and seizures may recur a few minutes after they have stopped. However, in the ICU the volume of distribution may be expanded and the half-life may be prolonged, especially with liver dysfunction *(81)*. Acidosis can also reduce the lipid solubility of the drug by opening the benzepine ring structure and thus, decrease CNS entrance and seizure control. Despite these deficiencies, midazolam is probably the best BDZs that can be used as a continuous infusion because of its favorable kinetics and the lack of propylene glycol as a vehicle (which can cause cardiac arrhythmias). An intravenous bolus of 0.1–0.3 mg/kg at a rate not

to exceed 4 mg/min can be repeated once after 15 min. The recommended rate for intravenous infusion is 0.08–0.4 mg/kg/h.

Midazolam's high solubility in water and rapid absorption makes it a better agent for intramuscular injection than the other BDZs, when intravenous administration route becomes a problem in the ICU *(82)*. The mean half-life of intramuscular midazolam (2 h) is slightly longer than the intravenous route. When administered intramuscularly, DZ and lorazepam have a relatively slower absorption, induce local discomfort, or can precipitate at the injection site and are not recommended for the treatment of SE *(6)*. However, intramuscular midazolam has been successfully used to stop frequent seizures or SE within 5–10 min in children and adults *(83–87)*. In a prospective, randomized study in the emergency department im midazolam was compared with intravenous DZ for the ability to stop seizures. Eleven patients received DZ (0.3 mg/kg, maximum 10 mg) and 13 midazolam (0.2 mg/kg, maximum 7 mg). Midazolam was administered faster because there was no need to start an iv line (mean time from arrival to administration of the drug was 3.3 vs 7.8 min, $p = 0.001$) and resulted in faster cessation of seizures (mean time from arrival to cessation 7.8 vs 11.2 min, $p = 0.047$) *(85)*. The usual intramuscular dose of midazolam is 5–10 mg (0.2 mg/kg).

Phenytoin and Fosphenytoin

PHT is insoluble in water, and the parenteral formulation contains 40% propylene glycol and 10% alcohol, as well as sodium hydroxide to adjust the pH to 12. This solution is highly caustic to veins and may cause necrosis to the surrounding tissues by extravasation. The rate of administration has been limited to a maximum of 50 mg/min, although in clinical practice it is given more slowly (over 25–45 min in the adult patient) to minimize the pain at the injection site and to reduce the risk of cardiovascular toxicity from the propylene glycol diluent. It should be mixed only with normal saline, and other drug administration through the same line should be avoided. As a lipid-soluble compound, PHT readily enters the brain (it reaches peak levels within 15 min) and its redistribution out of the CNS is slower than the BDZs, providing some evidence for binding of PHT to the brain *(88)*. The drug is 96% protein bound and competes with other highly bound medications. With low albumin levels, one should consider measuring free instead of total PHT levels. Fast infusion of the drug carries the risk for hypotension and QT prolongation, therefore electrocardiogram (EKG) and frequent BP measurements are recommended. Pain, edema, and ischemia distal to the infusion site characterize the "purple-glove" syndrome, which occurred in 9 of 152 (5.9%) patients who received PHT through a peripheral intravenous line *(89)*. There may be a delay of several hours between the infusion and the clinical presentation of the syndrome, which makes the recognition difficult. Nevertheless, PHT is a highly effective drug in treating SE *(90)*.

Fosphenytoin sodium is a phosphate ester prodrug of PHT that was developed as a replacement for parenteral PHT and was approved in the US market in 1996. After administration, PHT is cleaved from the prodrug by phosphatases found in

the liver, red blood cells, and many other tissues. The conversion rate is not affected by age, hepatic status, or the presence of other drugs. Unlike PHT, fosphenytoin is freely soluble in aqueous solutions, including intravenous solutions. It is supplied as a ready-mixed solution of 50 mg/mL in water for injection and is buffered to a pH 8.6–9.0. This relatively lower pH of the vehicle for fosphenytoin is responsible for the lack of local adverse side effects at the injection site, as opposed to the highly alkaline intravenous PHT solution. Fosphenytoin can be administered intravenously or intramuscularly, and it is extensively bound (approx 95%) to plasma albumin. The dosage of the drug is expressed in PHT equivalents (PE). Seventy-five mg of fosphenytoin results in 50 mg of PHT in the serum after the enzymatic conversion; therefore, 75 mg of fosphenytoin is labeled as 50 mg PE equivalent (thus 15 mg PE of fosphenytoin is the same as 15 mg of PHT) *(91)*. The drug is administered intravenously or intramuscularly at doses corresponding to customary PHT sodium loading (15–20 mg PE/kg) and consistently produces therapeutic plasma phenytoin concentrations (total 10–20 µg/mL and free 1–2 µg/mL). A maintenance dose of 4–7 mg PE/kg can be given either intravenously or intramuscularly. Therapeutic PHT concentrations are attained in most patients within 10 min of rapid intravenous fosphenytoin infusion (≤150 mg PE/min) and within 30 min of slower intravenous infusion (<100 mg/min) or intramuscular injection. Maximal total plasma PHT concentration increases with increasing fosphenytoin dose but is less affected by increasing the infusion rate at a given dose level. It is recommended, following fosphenytoin administration, that PHT concentrations not be monitored until complete conversion of fosphenytoin to PHT has been established. Because the conversion half-life is approximately 10–15 min *(92)*, conversion is completed within 1–1.5 h; serum phenytoin peaks at 30 min following the start of intravenous fosphenytoin infusion and at 3 h after intramuscular injection.

Fosphenytoin given intravenously or intramuscularly has fewer local adverse side effects (pain, itching, or burning at the site of injection) than iv PHT. The incidence of the most common CNS side effects, such as nystagmus, somnolence, ataxia, and headache, does not differ between PHT and fosphenytoin *(93)*. Fosphenytoin has been associated with hypotension in 7.7% of patients but rarely leads to an intervention and with higher pruritus than PHT *(94)*. PHT mistakenly administered at fosphenytoin rates can lead to cardiac arrest *(95)*; therefore, intensivists must be very careful when prescribing the drug in the ICU during emergencies.

Paresthesias of the lower abdomen, back, head, or neck have been reported with fosphenytoin in particular, when high doses and rapid infusion rate were used. They rapidly resolve without sequelae. A possible explanation is the competitive displacement of derived PHT from plasma protein binding sites by fosphenytoin. Earlier and higher unbound PHT plasma concentrations, and thus an increase in systemic adverse effects, may also occur following intravenous fosphenytoin loading doses in patients with a decreased ability to bind fosphenytoin and PHT (renal or hepatic disease, hypoalbuminaemia, the elderly). Close vital sign monitoring

and reduction in the infusion rate by 25–50% are recommended for these, frequently encountered, ICU patients *(96)*.

An issue of concern with fosphenytoin is its cost (14–18 times as expensive as generic PHT). In a small study comparing the cost in an emergency department, fosphenytoin (given in 39 patients) had lower overall hospital cost than PHT (given in 19 patients), mainly because of complications associated with the latter *(97)*. A subsequent larger, open label, study by Coplin et al. did not replicate the advantage of fosphenytoin *(98)*. Whether these results can be extrapolated to the ICU remains to be seen.

Valproic Acid

Valproate is an AED with broad-spectrum activity against absence seizures *(99)*, GTC seizures *(100)*, focal seizures *(101,102)*, and myoclonic seizures *(103)*. The drug has enjoyed increasing popularity in the ICU, especially after the introduction of the parenteral formulation. Although VPA is safe and generally well-tolerated, there have been early reports of altered hepatic function and of several fatalities in patients taking VPA in combination with other antiepileptics *(104)*. Careful monitoring of hepatic function is required in patients being treated with VPA, but dose reduction alone may be effective in preventing hepatic complications. To provide information on which patients are at risk for VPA-induced hepatotoxicity, Dreifuss et al. conducted a retrospective review of all reports of fatal hepatic dysfunction received by Abbott Laboratories between 1978 and 1984. Patients found to be at the greatest risk for developing fatal hepatotoxicity were children younger than 2 yr treated with multiple antiepileptics who also had other medical conditions, congenital abnormalities, mental retardation, developmental delay, or other neurologic diseases *(105)*. From 1980 to 1986 the number of VPA-related hepatic fatalities had declined from 8 to 1, whereas the number of patients treated had increased nearly sixfold. Nevertheless, VPA is relatively contraindicated in cirrhosis or hepatic failure where it can accumulate and further promote liver damage, as discussed shortly.

Valproate sodium injection (Depacon) is approved for use when clinical factors make oral administration difficult or impossible. The pharmacokinetics of the oral and parenteral forms are similar, but if achieving therapeutic levels rapidly is the goal, as in many ICU situations, the intravenous form has significant advantages. Compared with PHT, it can be delivered at a more physiological pH, does not require organic solvents, and has a wider range of solution compatibility. In addition, it does not cause sedation or respiratory compromise like the barbiturates or BDZs and has a safer hypotension profile than PHT and the barbiturates *(106)*. The drug's elimination half-life, reported as between 7.2 and 17.7 h in studies given to healthy volunteers, may be attributable to its 90–95% plasma protein binding *(107–109)*. Depacon was approved for infusions up to 10–15 mg/kg at 1.5–3 mg/kg/min in the absence of other AEDs and in VPA-naive patients. Injection intramuscularly may produce muscle necrosis and should be avoided.

In a multicenter, open-label trial examining safety of intravenous VPA, 318 patients with previously treated epilepsy were enrolled; a need for parenteral VPA

therapy for various reasons was documented. The median dose of intravenous VPA was 375 mg given over 1 h. Fifty-four (17%) patients experienced transient adverse effects, such as headache (2.4%), local reactions (2.2%), and somnolence and nausea without vomiting (2.2%). The side effects led six patients to withdraw from the study *(109)*. However, these recommended doses generally result in subtherapeutic levels of VPA, and they have been challenged in subsequent studies.

In a small study by Venkataraman and Wheless, 24 infusions of intravenous valproate were carried out electively in 21 patients with epilepsy. The dose ranged from 21 to 28 mg/kg (mean 24.2 mg/kg) and was weight adjusted. Target infusion rates were 3 or 6 mg/kg/min (i.e., over 4–8 min). No significant BP changes or EKG abnormalities were reported. Based on these results, the authors suggested a rate of 6 mg/kg/min *(110)*. Doses up to 40 mg/kg *(111)* have been given without serious side effects such as significant changes in BP, or electrographic abnormalities, or respiratory depression. This is in contrast to other commonly used parenteral antiepileptics, such as lorazepam, PB, DZ, and fosphenytoin, which have been variably associated with hypoventilation, cardiac arrhythmias, or hypotension *(9,112)*.

Intravenous VPA has not been approved for the management of SE. However, the use of intravenous VPA in SE has been reported in the medical literature in both children and adults *(35,113–116)* and recently in a rat model of SE induced by intrahippocampal application of 4-aminopyridine *(117)*. It has been used in both CSE and NCSE. Price evaluated 24 neurosurgical patients with generalized CSE refractory to DZ who were treated with intravenous VPA, either as a bolus of 400 mg followed by infusion of 100 mg/h or a 15-mg/kg load followed by infusion at 6 mg/kg/h. Seizure control was achieved in 6 of 15 (40%) patients within 2 h in the first group and in 7 of 9 (78%) patients within 1 h in the second. Only one patient developed thrombocytopenia, but no clear cause-and-effect relationship was ever established *(118)*.

In one study conducted in Europe, the efficacy of intravenous sodium valproate was evaluated in 23 VPA-naïve adult patients with SE (8 with CSE and 15 with NCSE). A loading dose of 15 mg/kg followed by 1 mg/kg/h infusion led to VPA levels of 68.5 mg/L at 1 h, which was deemed satisfactory. Disappearance of SE in under 20 min was considered to be successful; a disappearance time exceeding 30 min was considered to be a failure. Use of intravenous VPA resulted in the resolution of SE in 19 (83%) patients (7 of 8 with CSE and 12 of 15 with NCSE). All four patients who failed to respond to VPA, as well as to other antiepileptics, had SE secondary to cerebral lesions. There were no relapses of SE within the first 24 h. All patients showed a slight reduction in systolic BP and heart rate, but none required treatment for that. The serum concentrations varied most in four patients older than 80 yr, but VPA was still well tolerated. Despite these promising results, the authors suggested, that intravenous VPA be used cautiously in the elderly *(115)*.

Another study assessed the safety and efficacy of intravenous VPA in 35 patients with SE. Twenty patients had failed treatment with BDZs, and three patients had failed PHT treatment. SE was interrupted in 27 of 35 (77%) patients; the majority

Table 10
Indications for Use of Intravenous Valproic Acid in SE

1. As adjunctive agent, after BDZs and PHT/fosphenytoin have been properly given and while preparations are being made for third-line agents (propofol, midazolam, or barbiturates).
2. Once third-line agents have been given without complete cessation of SE.
3. Instead of third-line agents in patients who do not wish to be mechanically ventilated.
4. Patients allergic to one or more other antiepileptics.
5. Absence SE or myoclonic SE as first- or second-line agent.

(Adapted from ref. *106*.)

of them responded during the bolus infusion. Among the eight patients classified as treatment failures, five were also refractory to other AEDs, two patients responded to an increased dose of VPA, and one patient responded to clonazepam. Two patients developed nausea and allergic skin rash after the VPA in these series *(119)*.

A case report of a 38-yr-old man who presented with NCSE after his carbamazepine (CBZ) level became subtherapeutic has been reported by Chez et al. The patient was loaded with 30 mg/kg intravenous VPA and responded for 6 h. Seizures recurred when the level fell to 32 mg/L, and the patient received a second loading dose with complete success *(113)*.

In another case, reported by Kaplan *(35)*, a 25-yr-old female with history of absence epilepsy in childhood and catamenial exacerbation of eye fluttering and dysphasia was successfully treated with 500 mg of intravenous VPA over 30 min. A similar case of a 28-yr-old woman with history of absence epilepsy in childhood and tonic–clonic seizures as an adolescent, who presented with nonrhythmic whole-body myoclonic jerks while on therapeutic PHT, was reported by Sheth and Gidal. The patient received 500 mg of iv VPA over 30 min with clinical and EEG response *(120)*.

In a small retrospective review of hospital records, 13 patients with SE and hypotension received intravenous VPA therapy. Mean age of patients was 74 yr, and the mean loading dose of VPA was 25 mg/kg (range: 14.7–32.7), at a mean rate of 36.6 mg/min (range: 6.3–100). There were no significant changes in BP, pulse, or use of vasopressors, suggesting that VPA loading at these high rates is well-tolerated, even in patients with cardiovascular instability. Seizures were controlled in four (31%) patients with intravenous VPA, but eventually all patients died as a consequence of their underlying illness (six were postanoxic and three had stroke) *(112)*.

The same group presented their results of using intravenous VPA in 30 patients on a later occasion. Control of seizures was achieved in 5 of 11 (45%) patients with overt CSE, 2 of 6 (33%) patients with subtle SE, 4 of 8 (50%) patients with complex partial SE, and all 4 (100%) patients with simple partial SE. Among patients with overt convulsive SE, the mean duration of SE prior to treatment in patients who responded was 2.6 h vs 36 h in those who did not respond *(121)*.

Based on a review of the available literature until mid-2000, Hodges and Mazur suggested three clinical situations in which VPA could be considered as a third- or

fourth-line agent for the treatment of SE (Table 10). We would also add a use in patients who have a well-documented allergic reaction to PHT or fosphenytoin, but the intensivist should be aware that there are no randomized studies evaluating the efficacy of VPA in this situation.

Barbiturates

Issues With High Barbiturate Dose Use in the ICU

Barbiturates are potent antiepileptic medications and can be used either as additives to the antiepileptic regimen for better seizure control (infrequently as first- or second-line drugs because of several serious adverse effects) or as inducers of general anesthesia in cases of refractory SE. A major problem with these medications is that when administered in high doses, the need for complete and prolonged support of vital organs challenges and exhausts many ICU resources. The neurological examination, an important assessment tool in all cases of an intracranial pathology associated with SE (e.g., hemorrhage, tumor, trauma) is reduced to few brainstem reflexes (the last retained reflex with increasing depth of coma being the pupillary response) or complete disappearance of all indications of brain activity. This reduces our ability to differentiate between brain death, ongoing nonconvulsive epileptic activity, or profound sedation and obviates the need for ancillary bedside tests including an EEG or a transcranial Doppler for the presence of cerebral flow. Respiratory depression with barbiturates obligates endotracheal intubation and mechanical ventilation. Frequent suctioning of the respiratory secretions is necessary because of ciliary immobility and cough suppression.

Cardiovascular adverse events are equally hazardous. Hypotension caused by both vasodilatation and myocardial depression occurs in almost every case. Monitoring of central venous pressure (goal: 6–8 mmHg) or less often pulmonary wedge pressure (goal: 12–14 mmHg), as well as vasopressor and inotrope infusion (dopamine 10–20 µg/kg/min or neosynephrine 1–8 µg/kg/min) with continuous arterial BP monitoring are standard in our ICU with prolonged administration of high-dose pentobarbital or other barbiturates. In a hemodynamic treatment protocol for thiopental infusion published in 2002, the goal of mean arterial pressure was more than 65 mmHg, and all 10 patients had Swan–Ganz catheter placement. Pulmonary capillary wedge pressure was kept above 10 mmHg and if the cardiac index went below 3 L/min, the patient was started on dopamine or dobutamine infusion, otherwise on norepinephrine *(122)*. These measures will also keep adequate renal perfusion and urinary output, which usually decrease with barbiturate coma. With deep coma, poikilothermia ensues, and special care should be taken to keep the temperature to the predefined range. On the other hand, all barbiturates are potent immunosuppressives *(123)*, and special care should be taken to avoid nosocomial infections.

All procedures should be performed under strict sterility; samples of potentially infected fluids (bronchial secretions, urine, blood) should be collected with even low suspicion level; and all infections should be aggressively treated. Enteral nutrition through nasogastric or nasojejunal tubes, although feasible *(124)*, is usually

problematic because of gastric and bowel hypomobility, and in many cases total parenteral nutrition through a dedicated central line port becomes necessary. Immobility leads to skin ulceration and deep venous thromboses, increasing the risk for pulmonary embolism. Frequent repositioning of the patient in bed and the use of special inflatable or rotating mattresses decrease the incidence of the former. Elastic stockings, sequential compression devices, and low molecular weight heparin administration are common measures taken in the ICU to avoid the latter.

DEPTH AND DURATION OF BARBITURATE COMA

Most authorities agree that ICU patients in barbiturate coma should be monitored with EEG, preferably on a continuous basis. However, there is no consensus regarding the depth of the EEG suppression that must be achieved. Some experts recommend a burst suppression pattern of 5–10 s *(122,125)*, whereas others advocate complete suppression or "flat record" *(8)*. In a retrospective study of 35 patients treated with pentobarbital for refractory SE, persistent seizure control was achieved in 6 of 12 (50%) patients reaching a burst suppression level at the greatest depth of EEG suppression and in 17 of 20 (85%) patients reaching a "flat" record ($p = 0.049$). Three patients with neither pattern and just slow EEG had also persistent control. Survival was nonsignificantly better in the more suppressed group (25% vs 60%, $p = 0.08$). Isolated epileptiform discharges during the barbiturate infusion did not correlate with relapse of SE. These results suggest both that patients with deeper suppression appear to have fewer relapses and a better outcome and that it is not necessary to suppress all epileptiform discharges *(126)*. However, the benefits of the deeper suppression level must be balanced against the adverse effects such as more aggressive treatment portends. A recent systematic review evaluated studies describing use of midazolam or propofol or pentobarbital for refractory SE. Compared with seizure suppression, titration of treatment to EEG background suppression level was associated with a lower frequency of breakthrough seizures (4% vs 53%; $p < 0.001$), but also a higher frequency of hypotension (76% vs 29%; $p < 0.001$) *(127)*.

There is also no general agreement regarding the duration of the induced barbiturate coma. Most authorities believe that 12–24 h is enough *(67)*, but some recommend up to 96 h *(128)*. Krishnamurthy and Drislane conducted a retrospective analysis of 40 patients with 44 refractory SE episodes on pentobarbital coma. Patients with more prolonged treatment (>96 h) and those receiving PB at the time of PB taper were less likely to relapse *(129)*. Treatment is gradually tapered, and the patient is closely monitored clinically and electrographically for recurrence of seizures. If seizures return, the process is reversed and the patient reanesthetized for progressively longer periods as needed. Therapeutic levels of additional antiepileptics should be reached (e.g., PHT level of 20–25 μg/mL) before a new weaning trial. A load of PB sometimes is helpful. Mirski et al. described a patient with refractory generalized SE who was treated with barbiturate-induced burst suppression coma for 53 d with good neurologic recovery *(130)*. Initially, pentobarbital was used, with serum pentobarbital levels necessary to control EEG seizure

activity ranging from 40 to 95 mg/L (177–419 µmol/L). After the first 15 d, PB was introduced and kept at levels that reached 220–290 mg/L (947–1249 µmol/L) for seizure control. In addition, PHT with supratherapeutic levels of 25–35 mg/L (99–139 µmol/L; unbound PHT concentration of 2.0–4.0 mg/L [7.9–15.9 µmol/L]) was used. Maintaining these concentrations required 2500–3000 mg/d of PB and 800–1200 mg/d of PHT. Overall, the patient spent 79 d in the ICU. This extreme case reveals the feasibility of an aggressive treatment approach.

Thus, although some general rules are applicable, treatment should be individualized through "trial and error" attempts. The intensivist should always seek other therapeutic options. In our NICU, we had the experience of two patients with persistent failure of weaning from the barbiturate coma who underwent intracranial grid placement, mapping of the epileptogenic focus, and excellent outcome after surgical resection. This approach has been recently reported in a child with complex partial SE or in patients who fail to respond to three courses of cerebral suppressant therapy for at least 2 wk *(131,132)*. Its safety and effectiveness, however, still must be proved in a controlled study.

PHENOBARBITAL

Parenteral PB is available in preparations that are highly alkaline and may irritate the tissues. The entry of this drug into the brain is more gradual than that of more lipid-soluble compounds such as BDZs. Therefore, peak concentrations in the brain may not occur for 15–20 min after the peak blood concentration has been reached. Because of this limitation, PB is not the best choice as a first-line drug. PB is solely eliminated by the liver and has a prolonged half-life of 4 d (75–120 h). This pharmacokinetic property may be advantageous because it is associated with prolonged antiepileptic effect. However, if the dose is excessive, reversal of the effect will be slow. PB can cause severe sedation and even coma, but in children paradoxical hyperkinetic reactions are not uncommon. Elderly persons with cerebral disease may also exhibit confusion and irritability rather than sedation. Sedation subsides with chronic therapy. Respiratory depression and hypotension can occur, especially if PB is given as a second- or third-line drug to a patient previously treated with BDZs or other barbiturates. In most cases, intubation and maintenance of ventilation are essential if PB is administered. Dupuytren contractures and folate-deficient megaloblastic anemia, requiring supplementation, are not uncommon with more chronic use. The recommended loading dose is 10–20 mg/kg at a rate of 100 mg/min (usual adult dose 600–800 mg) followed by a maintenance dose of 1–4 mg/kg/d *(6,67,91)*.

THIOPENTAL

Thiopental is a highly effective anticonvulsant medication with some potential cerebral protective action. It has rapid onset of action and reduces the ICP, CBF, and cerebral metabolism. Thiopental is the preferred drug for barbiturate-induced anesthesia for refractory SE in Europe *(2)*. A recent study from Finland reported the outcomes of 10 patients treated with high-dose thiopental for refractory SE in

an ICU. The median time from seizure onset to burst-suppression EEG was 11.5 h (range: 6–12 h) and from ICU admission to starting thiopental anesthesia 113 min (range: 80–132 min). The median dose of thiopental to achieve burst suppression was 19 mg/kg (range: 13–21 mg/kg), and the median infusion rate to maintain the burst suppression was 7 mg/kg/h (range: 5–8 mg/kg/h). The median duration of ventilation was 8.5 d and the median ICU length of stay 10 d. Eight patients developed atelectasis and nine received antibiotics based on clinical signs of infection *(122)*. This small study is indicative of the difficulties encountered in the ICU with such treatment. Sedation, hypotension, and respiratory depression calling for intubation and mechanical ventilation usually occur. The drug has a strong tendency to accumulate, and a prolonged recovery time of days should be expected after the anesthetic doses used for the treatment of SE. Monitoring of the blood levels of the drug or its active metabolite pentobarbitone is advisable.

Other less common adverse effects include spasm at the site of injection, hepatic dysfunction, pancreatitis, and hypersensitivity reactions. Administration of thiopental requires full cardiorespiratory support with intravenous fluids, pressors, and prolonged EEG monitoring to maintain a burst suppression pattern. Hypotension below 90 mmHg is a sign that thiopental should be lowered. All these adverse effects make the drug less suitable for elderly patients or those with cardiac, hepatic, or renal disease *(1)*. The recommended dose is 2–4 mg/kg iv bolus given over 20 s, followed by an infusion of 3–5 mg/kg/h in 0.9% sodium chloride solution. Thiopental should be slowly withdrawn 12 h after the last seizure has ceased and when optimal levels of AEDs are documented.

PENTOBARBITAL

Pentobarbital is an alternative to PB and thiopental. It has a shorter elimination half-life than PB (approx 24 h; range: 15–60 h) *(125)*. Because of the short action of the drug, withdrawal results in a fairly prompt recovery of consciousness. However, seizures may recur, as with all barbiturates, during the withdrawal period. In the retrospective study by Krishnamurthy and Drislane, 40 patients were treated for refractory SE with pentobarbital coma. Eight of 9 (89%) patients with relapse of seizures after the drug was discontinued died, compared with only 9 of 26 (35%) with persistently controlled seizures ($p < 0.005$). Etiology was the major determinant of relapse and survival, with 19 of 20 (95%) patients with chronic epilepsy, infections, or focal lesions having achieved good control compared with 2 of 9 (22%) with multiple medical problems ($p < 0.001$). In this study treatment delay did not predict a worsened outcome. Hypotension caused dose reduction but never required treatment discontinuation *(129)*.

Sedation, respiratory depression, and hypotension resulting from both vasodilatation and myocardial depression commonly occur. Decerebrate posturing and flaccid paralysis have been reported. Flaccid paresis may persist for weeks after pentobarbital has been withheld. Blood level monitoring is not very helpful, because there is inconsistent relationship between serum level and seizure control. The recommended intravenous dose is 6–15 mg/kg over 1 h followed by infusion of 0.25–2.0 mg/kg/h or higher until burst suppression EEG pattern is evident.

In a literature review until September 2001, Claassen et al. compared the efficacy of midazolam, propofol, and pentobarbital for the treatment of refractory SE *(127)*. No prospective, randomized trial was found. Overall 28 studies, mainly case series, with a total of 193 patients were included. Mortality was not different between the groups. Compared with the other two medications, pentobarbital was associated with a lower frequency of short-term treatment failure (8% vs 23%; $p < 0.01$), breakthrough seizures (12% vs 42%; $p < 0.001$), and changes to a different continuously infused antiepileptic (3% vs 21%; $p < 0.001$). However, a higher frequency of hypotension was reported with pentobarbital (77% vs 34%; $p < 0.001$).

Propofol

Propofol is a potent anticonvulsant nonbarbiturate anesthetic, with barbiturate-like and BDZ-like effects at the $GABA_A$ receptor *(133)*. It has rapid onset of action (within 3 min) and recovery (5–10 min after the drug has been stopped). It is metabolized in the liver and thus is affected by liver disease. Usage for SE management in anesthetic doses always requires assisted ventilation. Neuroexcitatory effects, possibly through subcortical disinhibition, result in muscle rigidity, opisthotonos, or myoclonic jerks *(1)*. These involuntary movements are usually not associated with EEG changes. However, not all experts agree with this thesis *(134)*: propofol has been shown to increase the frequency of spikes during electrocorticography and to activate neocortical foci *(135,136)*. A systematic review of reports on seizure-like phenomena (SLP) associated with propofol was conducted by Walder et al. In 70 patients without epilepsy, SLP happened during induction in 24 (34%), during maintenance in 2 (3%), and during emergence in 28 (40%); SLP were delayed in 16 (23%). Most frequent clinical presentations of SLP were GTC seizures in 30 patients (43%), increased tone with twitching and rhythmic movements not perceived as GTC seizures in 20 (36%), and involuntary movements in 11 (16%). EEG was performed in 24 patients in all after the SLP had stopped. Two patients had generalized spikes and three generalized slowing. Out of 11 patients with epilepsy, 7 (64%) had GTC seizures during emergence. Only two patients had an EEG: there were generalized spikes and slowing in one patient and focal temporal spikes in the other. The time point of the SLP occurrence according to this study suggests that a change in cerebral concentration of propofol may be causative, because it is quite rare to witness these phenomena during the maintenance phase of anesthesia *(134)*.

The recommended dose is a bolus of 2 mg/kg followed by continuous infusion of 5–15 mg/kg/h initially, reducing to 1–3 mg/kg/h. When seizures have been controlled for at least 12 h the drug should be slowly tapered over 12 h. To prevent rebound seizures, a decremental rate of 5% of the maintenance infusion per hour (i.e., over approx 24 h: *see* ref. *1*) or 1 mg/kg or less every 2 h, has been recommended. Propofol infusion may cause hypotension, which can be prevented by adequate use of vasopressors and intravenous fluids. Bradycardia including asystole has also been reported *(137)*. Metabolic acidosis, increased incidence of infec-

tion, rhabdomyolysis *(137)*, and lipidemia may occur after prolonged use, but the use of 2% formulation of propofol has reduced the incidence of the latter.

A propofol infusion syndrome has been described in children and adults *(138,139)*. Cremer et al. reported seven adult cases with head injury in a neurosurgical ICU. Five of them died owing to progressive myocardial failure and arrhythmias, rhabdomyolysis, metabolic acidosis, and hyperkalemia. All patients received propofol at rates greater than 5 mg/kg/h for longer than 58 h. Interestingly, the incidence was higher after the introduction of 2% propofol (5% before vs 17% after), although it did not reach statistical significance. The authors discouraged these high doses of propofol for long periods *(140)*.

A small retrospective study comparing propofol and midazolam for the treatment of refractory SE found that the two agents did not differ in clinical or electrographic seizure control. Propofol-treated patients with Acute Physiology and Chronic Health Evaluation (APACHE) II score of 20 or higher had greater mortality ($p = 0.05$) *(141)*. These preliminary data suggest that midazolam may be tried before propofol, especially if used for several days.

Ketamine

Animal data suggest that during SE there is an initial response to GABA-ergic agonists that is lost later in the course, at about the same time that NMDA-receptor-mediated transmission becomes enhanced *(142)*. NMDA antagonism at this late state, when SE becomes refractory (i.e., not responding to BDZs, propofol, or barbiturates) seems to be a logical next step *(143)*. The NMDA antagonist ketamine has been used in refractory SE in both animal models *(144)* and humans *(145)*. In a recent case report of subtle SE, ketamine controlled the seizures, but 3 mo later findings of diffuse cerebellar and worsened cerebral atrophy raised the possibility of NMDA-antagonist-mediated neurotoxicity *(146)*. Based on this report, we would caution against the use of ketamine until more data are available.

Isoflurane

Isoflurane, which produces electrographic suppression and has no reported organ toxicity is the most commonly used volatile anesthetic for treating refractory SE that fails to respond to intravenous agents *(147)*. It has minimal hepatic or renal metabolism (thus, no toxicity to the organs), and most is exhaled unchanged. Compared with other volatile anesthetics it also has less severe cardiac and BP effects. Its major limitation for more widespread use is the lack of scavenging apparatus in most ICUs.

In addition, experience with the agent has been limited: only small case series of its use have been reported. Kofke et al. have administered isoflurane for 1–55 h in nine patients with 11 episodes of SE. Seizures stopped in all patients, and burst suppression patterns on EEGs were achieved. Hypotension was recorded in all patients. Seizures resumed upon discontinuation of isoflurane on 8 of 11 occasions. Six of the nine patients died, and the three survivors sustained cognitive deficits. This small series suggests that isoflurane is an effective, rapidly titratable anti-

convulsant but does not reverse the underlying process leading to refractory seizures *(148)*. Isoflurane has also been suggested as an antiepileptic agent in patients with acute intermittent porphyria *(94)*. Its dose is titrated for end-tidal concentration of 0.8–2% and burst suppression on the EEG.

Other Less Commonly Used Medications for SE

Lidocaine can be tried as a second-line drug for the treatment of early SE *(149)*. The drug acts to stabilize cell membranes, an effect that reduces ion exchange and depolarization. Its action is not prolonged, and with repeated doses there is significant risk for toxicity and even exacerbation of seizures (*see* Chapter 12). It is administered as an intravenous bolus of 1.5–2 mg/kg over 2 min, which can be repeated only once (total dose ≤200 mg). A continuous intravenous infusion of 3–4 mg/kg/h should not extend for more than 12 h.

Paraldehyde is a foul-smelling cyclic polymer of acetaldehyde that must be administered through a glass syringe (plastic tubing systems or syringes should be avoided). It was used in the past extensively for treating SE, but during the last decades has lost popularity with the advent of newer antiepileptics. It must be taken from fresh preparations kept in dark containers because, if decomposed, it can induce toxicity or thrombosis of veins and microembolism if given intravenously. The preferred route is through the rectum. Paraldehyde is rapidly absorbed and its antiepileptic effect is evident within few minutes and is usually long lasting. Most of the metabolism occurs in the liver, but 20–30% of the dose is exhaled through the lungs. Sedation, cardiorespiratory depression, and metabolic acidosis with increased lactate are the major adverse effects. The drug is diluted by the same volume of water (5–10 mL for adults) and given rectally in a dose of 5–10 g.

Clomethiazole is given as an intravenous bolus followed by a continuous infusion, but its popularity has declined because of the risk for accumulation with prolonged use. However, the drug has rapid onset of action and can be titrated to desired effect. Cardiorespiratory arrest is a real risk with higher infusion rates or prolonged use, and the patient should be continuously monitored. Other adverse effects include sedation, vomiting, phlebitis, fluid overload, and electrolyte disturbances. Paraldehyde is administered as a bolus of 320–800 mg (40–100 mL) at a rate of 5–15 mL/min, followed by an infusion of 1–4 mL/min and titration to response *(150)*.

Newer Antiepileptics in the Treatment of Prolonged Seizures or SE (Table 11)

Several newer AEDs have found their place in the epileptologist's armamentarium *(151–154)*. Their use in the ICU is limited by the paucity of data regarding specific indications for their use in SE and their availability only in parenteral preparations, with slower onset of action. In certain situations, however, the intensivist should seriously consider using one or more of these agents: as adjuncts to the parenteral antiepileptics when there is a failure to control the seizures, for example, or when a specific organ dysfunction or disease prohibits the use of other

Table 11
Newer Antiepileptics: Dose, Half-Life, and Elimination Route

AED	Dose	Half-life	Elimination	Side effects
Gabapentin	900–3600 mg/d	5–9 h	Renal	Drowsiness, ataxia, headache, fatigue
Topiramate	200–600 mg/d	18–23 h	Renal, hepatic (40%)	Weight loss, renal stones, paresthesias
Levetiracetam	1–3 g/d	6–8 h	Renal	Somnolence, infection, headache
Vigabatrine	1–3 g/d	4–7 h	Renal	Peripheral field constriction, depression
Tiagabine	15–45 mg/d	4–5 h	Hepatic	Dizziness, fatigue, SE induction
Zonisamide	100–600 mg/d	27–38[a] h, 63 h	Renal, hepatic	Rash, somnolence, dizziness, anorexia
Felbamate	1200–3600 mg/d	13[a]–30 h	Hepatic, renal (40%)	Aplastic anemia, hepatitis, weight loss
Lamotrigine	200–600 mg/d	15[a]–29[b]–60[c] h	Hepatic	Rash, headache, somnolence, diplopia
Carbamazepine	400–2400 mg/d	5–25 h	Hepatic	SIADH, neutropenia, aplastic anemia, rash
Oxcarbazepine	900–2400 mg/d	8–10 h	Hepatic, renal (MHD)	Rash, ataxia, SIADH

[a]Enzyme-inducing comedication. [b]monotherapy. [c]VPA comedication.
SIADH, syndrome of inappropriate secretion of antidiuretic hormone; MHD, active OXC metabolite.
(Adapted from ref. 76.)

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antiepileptics. The small case series available show that these newer antiepileptics can be used in cases of refractory SE, but they do not address the issue of when one should switch to or add them to the treatment. The question remains: Should one use them only when one has already tried unsuccessfully all the other options and after the patient had been seizing for hours without control, or earlier, when seizures are more amenable to treatment? Because of lack of studies or guidelines, we believe that the intensivist should individualize the use of these drugs based on the etiology of the seizures, the clinical status of the patient, and the potential for adverse effects or interaction with other critical care or antiepileptic medications. In the following sections we present a synopsis of the pharmacological action of each one of them, along with adverse effects and available data regarding their use in SE.

Felbamate

Felbamate (FBM) has been approved as add-on therapy and monotherapy in adults with partial epilepsy with and without generalization and as adjunctive treatment in children with Lennox–Gastaut syndrome since 1993. The mechanism of action is not well known. It is very likely that FBM blocks the NMDA receptors. It is extensively metabolized by the liver, a property that leads to a number of drug–drug interactions. General use is limited because of occurrence of aplastic anemia and hepatic failure in some patients. FBM has not been used in the treatment of SE. However, studies have shown that FBM displays a potent seizure-protective effect in animal models of self-sustaining SE and SE induced by kainic acid. These results suggest that FBM might be useful when standard AEDs fail in the treatment of refractory cases of SE *(155,156).*

Gabapentin

Gabapentin (GBP) has a structural relationship to GABA, the main inhibitory neurotransmitter in the brain. Nonetheless, it has little or no action at the GABA receptor. It is very likely that GBP binds to a calcium channel receptor in the cerebral neocortex and hippocampus. It lacks hepatic metabolism and it is entirely excreted, unchanged, by the kidneys. GBP was approved as add-on therapy for partial and secondarily tonic–clonic seizures. It has a moderate anticonvulsant effect and it is mainly used as analgesic in certain painful neuropathy syndromes. In one case report, a patient on high-dose GBP (8000 mg/d) for back surgery and no history of epilepsy developed CSE following GBP withdrawal *(157).* In another case, a female patient with acute intermittent porphyria was admitted to the ICU with quadriparesis and change of mental status. Later in the course she developed face and arm twitching and was started on 300 mg of GBP three times a day, with increased seizure frequency and eventually CSE. The patient was started on propofol and within few days she left the ICU on a higher dose of GBP (900 mg, three times a day) *(158).*

Lamotrigine

Lamotrigine (LTG) was approved as adjunctive or monotherapy in partial or generalized epilepsy and in Lennox–Gastaut syndrome. In experimental seizure models, LTG has a profile of action similar to that of PHT and CBZ. It seems that it stabilizes the neuronal membranes by blocking voltage-dependent sodium channels. It is extensively metabolized in the liver through glucuronidation. LMG levels are increased by sodium valproate and lowered by PHT, CBZ, and PB. The effect of LMG on the severity of seizures and the seizure-induced neuronal damage was studied in animal models of SE. Treatment with LMG was shown to have only a mild effect on SE-induced neuronal damage in rats *(159)*. Another experimental study compared the effects of LTG and PHT for treatment of SE in rats. Doses of LTG within or higher than the "therapeutic" concentration used for chronic epilepsy failed to prevent the onset of GTC seizures, but PHT was effective *(160)*.

Human reports of LTG use in SE also exist. In one case report, generalized CSE that presented with recurrent tonic seizures was treated with 600 mg of LTG over 4 h through a nasogastric tube (200 mg for three administrations at 2-h intervals). Reduction in seizure frequency was observed 5 h following initial administration of LTG *(161)*.

Interestingly, cases of NCSE and myoclonic SE treated with LTG have also been reported. In a retrospective analysis of three patients who developed NCSE after replacement of VPA with LTG, Trinka et al. reported that the episodes of NCSE presented as an acute confusional state with mild myoclonus. Ictal EEG showed generalized spike–wave or polyspike–wave activity. The clinical symptoms and the EEG responded promptly to intravenous BDZs, and patients remained well controlled, with dose reduction of LTG (in 1 patient) or discontinuation of LTG (in two patients) *(162)*. In another case report, myoclonic SE was developed when LMG was added to clobazam and vigabatrin (VGB) at a dose of 20 mg/kg for treatment of Lennox–Gastaut syndrome in an 8-yr-old girl. Discontinuation of LTG resulted in rapid disappearance of clinical and electrophysiological manifestations of myoclonic SE *(163)*.

Levetiracetam

Levetiracetam (LVT) was approved as add-on therapy for refractory partial onset seizures with or without secondarily generalization. LVT provides potent protection from seizures in a broad range of animal models of epilepsy in a pattern that is unique in comparison to other AEDs. The mechanism of action is poorly understood. The drug may exert its anticonvulsant effect by binding to a specific brain site, but the exact receptor involved is unknown. LVT is metabolized by hydrolysis, and not through the cytochrome P450 system. LVT and its metabolites are excreted renally. Renal elimination is proportional to the renal clearance, and the half-life increases in renal insufficiency. LVT has not been used in the treatment of SE. In an experimental model of spontaneous recurrent seizures, individual response of rats to LVT varied from complete control to no effect at all *(164)*. Whether these

data support the notion that LVT can be effectively used to treat SE remains to be seen.

Zonisamide

Zonisamide (ZNS) is a sulfonamide derivative that has been used in Japan since 1989. It was approved as add-on therapy for refractory partial epilepsy. It exerts its action by blocking sodium and calcium channels. It has hepatic metabolism through the cytochrome P450 system. In a rat model of secondarily generalized SE induced by kainic acid, Takano et al. showed that 40 min following intravenous administration of ZNS, seizure propagation from the primary focus was inhibited, but there was no suppression of the epileptic activity in the focus *(165)*. When ZNS will be clinically available for intravenous use is unknown.

Topiramate

Topiramate is an AED with multiple mechanisms of action. It exhibits voltage-sensitive, use-dependent, sodium channel blockade and elevates brain GABA levels. It also antagonizes excitatory glutamatergic transmission. Both animal and human data suggest that topiramate may have a beneficial effect in SE. Administration of topiramate after experimental SE in rats can attenuate seizure-induced hippocampal neuronal injury *(166)*. Suspension of topiramate was administered via nasogastric tube in six patients in SE with a duration that ranged from 23 h to 38 d. In these case series, topiramate was effective against both generalized CSE and NCSE. In some patients seizure control, achieved by topiramate, averted the need for barbiturate coma, mechanical ventilation, and ICU admission. In three patients, standard treatment with consecutive intravenous antiepileptic medications, consisting of loading doses of lorazepam or DZ, fosphenytoin, PB, pentobarbital, VPA, midazolam, or propofol failed to control seizure activity. Topiramate was administered at a dose ranging from 300 to 1600 mg/d. The time to response to topiramate ranged from several hours to 10 d. The authors concluded that the parenteral formulation, when it becomes available, would allow widespread use of topiramate in SE *(167)*.

In another small series, topiramate was used to treat successfully two patients with refractory generalized SE and one with complex partial SE *(168)*. Another patient with occipital strokes postnephrectomy was treated for refractory complex partial SE with several antiepileptics, including clobazam, CBZ, paraldeyde, and general anesthesia for 38 d, eventually responded to 400 mg of topiramate twice daily via a nasogastric tube *(169)*. Therefore, topiramate may be a useful adjunct to the ICU treatment of refractory SE.

Tiagabine

Tiagabine (TGB) was initially approved as adjunctive therapy or monotherapy in partial or secondarily generalized seizures. TGB is a derivative of the GABA uptake inhibitor nipecotic acid and increases the cerebral GABA concentration. Although it is metabolized by cytochrome P450, it does not affect the concentration of other adjunctive antiepileptics. There are a number of reports of NCSE develop-

ment during TGB treatment in pediatric and adult patients *(170–172)*. The patients presented with acute intermittent or progressive chronic confusion, and the diagnosis was based on the EEG findings. TGB reduction or discontinuation led to clinical and EEG improvement. In one case report, the patient developed CSE after a TGB overdose *(173)*.

In a review article, a panel of experts attempted to determine whether an increased risk of SE and complex partial SE is associated with TGB therapy. They reviewed 13 cases in which EEGs from patients with altered mental status who were taking TGB showed spike–wave discharges. In addition, they reviewed all cases of suspected SE from TGB clinical trials. The panel concluded that the majority of patients had had prior EEGs with similar findings, and there was no overall difference in the frequency of SE or complex partial SE between TGB- and placebo-treated patients from placebo-controlled trials. The major risk factor for the occurrence of SE and complex partial SE in both the TGB- and placebo-treated groups was a prior episode of SE ($p < 0.0001$) *(174)*. Based on these results, we do not recommend TGB as an alternative antiepileptic medication for the treatment for SE in the ICU if there is a history of convulsive or complex partial SE.

Carbamazepine and Oxcarbazepine

CBZ is one of the most commonly used and studied antiepileptics, with a wide range of action against both partial and secondarily generalized seizures, but it has yet to find its role in the ICU. CBZ, although not one of the newer antiepileptics, is mentioned here because of the commercial lack of an intravenous formulation and the recent development of its 10-keto analog oxcarbazepine (OXC), which has a more favorable adverse effects profile. Both AEDs block voltage-sensitive sodium channels and NMDA-receptor-activated sodium and calcium influx, with stabilization of the cell membrane. CBZ is metabolized to 10,11-epoxide in the liver, and it is this metabolite that has antiepileptic action, but it also plays a significant role in the attributed side affects. OXC does not have an epoxide, nor does it show autoinduction; rather, it exerts its actions through its 10-monohydroxy metabolite (MHD). Both can cause skin rashes in up to 5% of patients (with 25% cross-reactivity), but hyponatremia, caused by the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), is more common with OXC (20% of treated patients may have a Na^+ <135 meq/L, usually responding to lowering the dose and fluid restriction).

CBZ can be dissolved in glycofurol (a common vehicle for other antiepileptics) and other compounds and administered intravenously. This injectable CBZ has been used to control seizures in a mice model of CSE, with antiepileptic activity evident as early as 30 s and a peak at 3 min *(175)*. Despite this potential, the intravenous formulation has not been marketed yet. In the management of SE in ICU, rectally administered CBZ at 6 mg/kg does not offer any advantage over the po route (same absorption and time to achieve maximum serum concentration) *(176)*. CBZ can exacerbate the nonconvulsive seizures of the Lennox–Gastaut syndrome in childhood or induce myoclonic, partial *(177)*, or absence SE *(178,179)*, which can be

particularly resistant to treatment with other antiepileptics, can cause increased ICP pressure or transient MRI abnormalities *(178)* and can respond only to withholding the drug *(177)*. SIADH is attributed to the high epoxide and low CBZ levels in patients treated with other drugs that increase the conversion (PHT, PB and, especially, VPA) *(177)*. CBZ intoxication can lead to alpha coma and SE *(180)* that may be resistant to even barbiturates and can be lethal *(181)*. Midazolam infusion was successful in one case of overdose *(181)*.

There are no studies specifically addressing the use of OXC in SE. A single-blind clinical study from Finland examined the antiepileptic effect of replacing CBZ with OXC in 16 profoundly mentally retarded inpatients. Although the anticonvulsive efficacy of the drug was considered better than that of CBZ in half the patients, two of them developed their first episode of SE during the trial *(182)*. Therefore, both CBZ and OXC, despite their excellent antiepileptic properties, lack the fast action needed in the ICU to treat SE and can have potential for seizure exacerbation.

Hypothermia

Hypothermia decreases the oxygen consumption and metabolic rate of the brain. There has been growing evidence of its beneficial effects in stroke and head trauma. Even in earlier studies, hypothermia has been recognized as a useful measure to decrease seizure activity *(183)*. There are animal data showing that hypothermia ameliorates and hyperthermia aggravates brain damage from seizures or SE *(184)*. In a rat model of seizures induced by kainic acid and SE, ictal discharges were decreased by 50% with mild hypothermia (28°C) and nearly abolished when body temperature was further lowered to 23°C. There was no hippocampal cell loss in hypothermic rats, whereas gross cell loss in the hippocampus was observed at normal body temperature. Hyperthermia (42°C), on the other hand, markedly aggravated the seizures and hippocampal damage induced by kainic acid in all rats; all animals died of tonic seizures within 2 h *(185,186)*.

In addition, hypothermia may have a synergistic effect on thiopental-induced burst suppression EEG patterns. Kim et al. compared normothermic to hypothermic (33.3°C) patients undergoing cerebral aneurysm clipping with EEG monitoring after a thiopental bolus had been given: the onset time for suppression was shortened and the duration of suppression and of isoelectric EEG were prolonged in the group with mild hypothermia *(187)*. Moderate hypothermia (30–31°C) in addition to thiopental-induced coma has been used in 3 children with refractory SE. The seizures were controlled, and 48 h to 5 d later the patients were rewarmed at a rate of 1°C every 3–4 h *(188)*. Thus, although there are no randomized clinical studies evaluating the effect of hypothermia on SE, we prefer to keep our ICU patients with SE normothermic or slightly hypothermic.

Prevention and Treatment of Complications

Complications of GTC seizures can be divided into acute systemic complications because of the sympathetic overdrive and the stress of extreme motor activity

and to persistent neurological complications that occur at a later stage *(189)*. Most of these complications have been already presented in the section on the pathophysiology of SE.

One of the most common complications encountered with SE is hyperthermia: it is usually attributable to excessive muscle activity rather than infection *(39)*, but there are few cases of a CNS infection being the cause of SE. Therefore, the intensivist should be vigilant and order the appropriate workup in atypical cases. Hyperthermia can spontaneously resolve following seizure control. However active cooling is recommended if body temperature exceeds 40°C. Because of the aforementioned beneficial results of hypothermia from experimental animal models *(185)*, we believe that more aggressive and earlier treatment of fever should be instituted in the ICU.

Extreme muscle activity also leads to lactic acidosis *(40)*. Catecholamine excess can cause hyperglycemia, which can further exacerbate acidosis through anaerobic metabolism. Acidosis induced by hypercarbic ventilation attenuates neuronal injury in a rat model of SE *(190)*. Hyperglycemia, on the other hand, may have detrimental effects in several types of brain injury (e.g., ischemia), but its effects are less clear in SE. Regional brain glucose utilization during seizures is increased in the brain, especially the hippocampus *(191)*. In a rat model of L-allylglycine-induced SE, Swan et al. studied the lactate and glucose content of hippocampal cells at increasing plasma glucose concentrations. Although brain lactate concentration was elevated in SE and maximal in the high-glucose group, it did not reach ischemia levels thought to induce cell death, nor did it correlate with neuropathologic damage *(192)*. However, the intracellular pH decreased in hyperglycemic rabbits with pentylenetetrazole-induced SE *(62)*.

Therefore, although hyperglycemia should be avoided in the management of several underlying cerebral injurious processes, which may lead to SE, this may not be the case when seizures or SE ensue. Our personal preference is to start all our nonhypoglycemic ICU patients in SE on finger-stick checks every 6 h for the first 24 h and treat glucose readings greater than 180 mg/dL with subcutaneous insulin based on a "nonaggressive" sliding scale.

Another common complication is rhabdomyolysis, which may cause acute tubular necrosis and renal failure if left untreated. Patients should be screened for myoglobinuria, and serum creatinine level should be measured. If myoglobinuria is detected or creatinine levels are highly elevated, serum potassium monitoring, urinary alkalinization, and forced diuresis should be considered. Cardiorespiratory complications include arrhythmias, hypotension, respiratory depression, neurogenic pulmonary edema, central apnea, and pulmonary aspiration (*see* Table 5). Mean arterial pressure is elevated because of elevated total peripheral resistance, which can lead to decreased cardiac output. Patients with atherosclerotic cardiovascular risk factors may have a gradual deterioration in hemodynamic parameters, whereas other patients decline acutely *(41,193–195)*.

MANAGEMENT OF FOCAL SE

Although single or multiple focal involuntary movements are not uncommonly encountered in the ICU, the intensivist should be familiar with the remote possibility that sensory complaints, changes of mental status, or speech or visual disturbances represent seizures.

Focal SE encompasses a wide range of clinical manifestations lasting for longer than 30 min, including EPC, defined as continuous focal jerking of a body part, usually distal limb, over hours, days or years *(196)*, opercular myoclonic SE (OMASE, characterized by fluctuating cortical dysarthria without true aphasia associated with epileptic myoclonus involving bilaterally the glossopharyngeal musculature) *(197)*, sensory SE *(198)*, aphasic SE *(199)*, or occipital lobe SE (presenting as visual loss, mimicking migraine) *(200)*. Because staff are more familiar with the clinical presentation and treatment of GTC SE, these focal seizures generate many questions in the ICU regarding their nature, need for treatment, and outcome. However, until a more diffuse process is excluded (e.g., hypoglycemia), their very presence indicates focal cerebral pathology, which in turn should alert the clinician. Common causes include vascular or traumatic lesions, epilepsy (benign epilepsy of childhood with rolandic spikes), tumors or Russian spring–summer or Rasmussen's encephalitis (*see* Chapter 1, Presentation and Pathophysiology of Seizures in the Critical Care Environment). More diffuse processes are much less common; according to Schomer *(201)*, the most prominent are nonketotic hyperglycemic diabetes mellitus and hyponatremia, mitochondrial encephalopathies (MELAS-MERRF), or the antibiotics penicillin and azlocillin–cefotaxime *(202)*. Rasmussen's encephalitis was the most common cause of EPC in patients younger than 16 yr and cerebrovascular disease in older patients in a British series of 36 cases *(196)*. Acute disease was also found in most of the 41 patients described by Drislane et al. vascular disease being present in over half of them *(203)*.

Focal SE except for the etiologic implications is also important because it may precede or follow generalized clinical seizures or SE *(203)*. An EEG may be ordered when there is suspicion of secondary generalization or when a new focal neurologic deficit cannot be explained by neuroimaging alone. Subdural hematomas in particular are lesions in which it is important to consider the possibility of focal SE as the reason of worsening symptoms or mental status changes *(203)*.

Although EPC is notoriously resistant to AEDs, in up to one-third of cases there may be improvement or complete resolution with treatment *(196)*. Focal SE usually necessitates polypharmacy, which, in our experience as well as that of others, must include PHT or PB, although there are no randomized studies comparing these medications with the newer antiepileptics or placebo. The same guidelines presented in Tables 6–8 can be used, but most physicians would be reluctant to reach general anesthesia to control focal seizures. In nonmotor simple partial SE there is no evidence that secondary brain damage ensues. On the other hand, the outcome of focal SE with motor symptoms is more strongly related to the underlying condition. EPC following Rasmussen's encephalitis has worse prognosis because of the

progressive nature of the disease *(203,204)*. It should be kept in mind that the longer acting antiepileptics appear to be more helpful and that the response to the drugs may be quite delayed in focal SE (up to 48 h in one series) *(203)*. Intravenous nimodipine, a calcium channel blocker, has been used to successfully treat two patients with EPC *(205)*, but no controlled trials exist. All four patients with simple partial SE treated with intravenous VPA (mean loading dose of 22.9 ± 7.9 mg/kg) achieved seizure control with mean levels of 92.2 ± 50.1 mg/L in a recent study *(121)*.

Management of NCSE

Unlike CSE, there are no widely accepted guidelines or treatment protocols for NCSE, and this may be the result of evolving definition of the condition, the inclusion of different clinical syndromes under the same rubric, and the paucity of animal or human data showing significant secondary neuronal damage *(13)*. The extent and aggressiveness of treatment is unknown, but the presumed cause and type of NCSE may be helpful stratifying it: e.g., if NCSE is secondary to epilepsy, treatment with anesthetic antiepileptics and induction of burst suppression may rarely be necessary because of the better response and outcome in these cases. Supplementing low antiepileptic levels in these patients and individualizing the workup for an additional or triggering etiology may suffice. On the other hand, if the NCSE is caused by acute medical causes or is cryptogenic, then more aggressive treatment is warranted *(34)*. Other factors, which may play a role in the decision to treat by the intensivist, are the age of the patient and the potential for adverse drug effects *(13)*. Elderly ICU patients with NCSE treated with intravenous BDZs have increased mortality that may be independent of the severity of the illness *(206)*. Six of 16 treated patients in this small case series required emergent endotracheal intubation, some accompanied by hypotension, after the drug was administered. Finally, in the large, double-blind study by Treiman et al., 134 patients with subtle generalized SE (defined as coma with ictal EEG discharges with or without rhythmic twitching of the arms, legs, trunk, or facial muscles or tonic eye deviation or nystagmoid eye jerking), were randomized to receive four different intravenous regimens *(9)*. No difference in seizure control between lorazepam, PHT alone, DZ and PHT, or PB was found. The success rate ranged between 7.7% (PHT alone) and 24.2% (PB), a disappointing outcome.

Although most authorities believe that absence SE does not induce neuronal damage and thus treatment does not constitute a medical emergency, seizures still must be terminated. The first-line drugs of choice are intravenous BDZs: DZ (0.2–0.3 mg/kg), lorazepam (0.1 mg/kg) or clonazepam (0.5–1 mg). As second-line drugs, intravenous PHT or VPA can be used. In children (age > 2 yr), ethosuximide or VPA is recommended as a maintenance drug for typical absence SE; thereafter, ethosuximide or VPA can be tried in the SE setting. Crouteau et al. have reported an 11-yr-old boy with absence SE after Lennox–Gastaut syndrome had been treated successfully in the pediatric ICU with propofol (bolus of 50 mg followed by infu-

sion of 3.7 mg/kg for 30 min) *(207)*. The patient needed endotracheal intubation after propofol was administered. There was a marked improvement on the EEG, and the patient was extubated in 90 min.

Complex partial SE, on the other hand, may induce neuronal injury in animals *(208)* and humans *(12)*. It can be precipitated by focal lesions such as stroke or encephalitis and seems to add an extra morbidity to these disorders *(60,209)*. Therefore, although treatment may not need to be instituted as urgent or aggressive as in CSE (because it lacks the systemic complications of the latter), it should still aim at termination of the SE within the first few hours, because serious mortality and morbidity have been associated with status duration from 36 h to more than 72 h *(60)*. Diagnosis of the condition may already be delayed—in 10 of 23 patients in the series from the emergency department the diagnosis was delayed by more than 24 h *(49)*—but treatment should be started as soon as the diagnosis is confirmed. Some patients have rapid clinical or EEG improvement, but in many it is more gradual and delayed: 10 of 23 (43%) patients in the series of Kaplan had rapid EEG resolution of SE, but clinical improvement only after one day *(49)*; only 3 of 24 (12.5%) elderly ICU patients with NCSE in the series of Litt et al. responded to treatment within 24 h, and more than half responded after the first 2 d to treatment *(206)*. Thus, although a fast response to the treatment confirms the diagnosis, absence of response does not exclude it *(34,49,55)*. BDZs administered orally are the first-line drugs for treatment of complex partial SE, followed by a longer acting antiepileptic, such as oral PHT or VPA. Oral clobazam (10–20 mg/d over a period of 2–3 d) has also been recommended *(14)*. Intravenous BDZs (lorazepam) followed by intravenous PHT or PB are kept for more persistent cases of complex partial SE. Intravenous VPA (30 mg/kg) has been successfully used to control NCSE in patients with subtherapeutic CBZ levels *(113)* and complex partial SE *(121)*. Topiramate by nasogastric tube has also been used for refractory complex partial SE in small series of patients *(167–169)*. It is unclear whether more aggressive treatment with general anesthetics is warranted as the next step for refractory complex partial SE because there are no studies evaluating outcomes, and most cases are self-terminating *(14)*.

Finally, there is also no uniform approach regarding treatment of comatose patients with NCSE or comatose patients with prolonged subtle movements. If the electrographic seizures follow CSE, the treatment should be as aggressive as with CSE, i.e., following the same protocol. However, if the electrographic seizures follow an anoxic brain event and are associated with subtle movements, there are few data suggesting that aggressive treatment with intravenous antiepileptics and general anesthesia improves outcome. Most experts believe that postanoxic EEG patterns of burst suppression, periodic discharges, or encephalopathic TPW indicate underlying widespread cortical damage and, therefore, represent agonal events *(14)*. Several treatments have been tried, without convincing results. The large, randomized Brain Resuscitation Clinical Trial I, conducted in comatose patients admitted to an ICU after cardiac arrest, did not find any effectiveness or improvement of

outcomes by administering, in addition to the standard treatment, a single intravenous loading dose of thiopental (30 mg/kg of body weight) *(210)*. In the series of Celesia et al., only 1 of 13 patients with cardiorespiratory arrest and generalized status myoclonicus (GSM) responded to 4 mg of intravenous lorazepam and recovered fully. This patient did not have an EEG. Intravenous PHT failed to stop the seizures in 6 of 9 treated patients with GSM and intravenous PB or DZ in all patients treated. Intravenous lorazepam (4–10 mg) successfully controlled the seizures in three of four patients *(211)*. None of the 11 patients with postanoxic myoclonic SE in the series by Young et al. responded to treatment with intravenous PHT, PB, DZ, lorazepam, or clonazepem (via nasogastric tube), and all patients died *(15)*. In the prospective study by Krumholz et al., comatose patients with myoclonic SE postcardiopulmonary resuscitation were treated early and aggressively with BDZ, PHT, and barbiturates: 7 of 19 (37%) of patients received two antiepileptics and 12 of 19 (63%) three or more. Despite therapy, seizures or attacks of myoclonic SE were often difficult to stop and, even after they were controlled, the outcome did not seem to improve significantly *(212)*. However, the authors advocated early and aggressive treatment, because their results suggested that seizures or myoclonic SE may contribute to progressive neurologic injury. Alternative treatments, such as high-dose intravenous magnesium (to elevate the serum levels up to 14.2 meq/L) were not effective in one patient with myoclonic SE *(213)*.

MANAGEMENT OF SEIZURES AND SE WITH ANTIEPILEPTICS IN ICU PATIENTS WITH ORGAN DYSFUNCTION

Hepatic Failure

Because of their renal clearance, low protein binding and metabolism, gabapentin, leviracetam, vigabatrin seem to be excellent choices (Table 11). However, there are not many data regarding these newer AEDs. Vigabatrin may normalize plasma alanine aminotransferase levels, making impossible its use as an index of the hepatic dysfunction *(214)*.

PHT can accumulate, and its plasma protein binding capacity is reduced. Reduction of the dose and frequent determinations of free levels are required to continue using the drug. PB is metabolized in the liver but is also partially excreted unchanged in the urine (20–25% of the dose). Biliary excretion is minimal, and cholestasis is not a reason to adjust the dosage. Therefore, it can be used orally or intravenously, but one should remember that its half-life in hepatic failure may be prolonged up to 130 h. Measuring serum levels of the drug and close monitoring for respiratory depression is recommended. The same is true for the BDZs: oxazepam is a short-acting drug without oxidative metabolism, but is not available in intravenous form. All BDZ dosing, except for oxazepam, should be reduced with liver failure. Lack of active metabolites makes lorazepam a better choice than DZ, which should be avoided. The short-acting barbiturates, such as pentobarbital and thio-

pental, are completely metabolized in the liver and should not be used because of poor elimination. In addition to hepatotoxicity, which is idiosyncratic and mainly encountered in young children, as noted earlier, and pancreatitis, VPA can induce elevations of ammonia. In epileptic patients without hepatic disease, this adverse effect does not require treatment, unless it is symptomatic *(215)*. However, it can lead to confusion when one is treating patients with hepatic dysfunction and baseline hyperammonemia, who may clinically worsen; therefore, VPA is generally contraindicated in hepatic failure. If absolutely necessary to be used, the dosage should be reduced, because the half-life of the drug is increased up to 18 ± 5 h.

Renal Failure

Drugs hepatically metabolized should be used instead of those with renal elimination, but there are several details that are important to remember. PHT has decreased half-life, and the unbound fraction is increased. Free levels should be followed, and doses should be smaller and more frequent (every 8 h). Only the free fraction is dialyzable; therefore, there is usually no need for extra dosing postdialysis. A significant amount of PB, on the other hand, is dialyzable and must be supplemented postdialysis with careful monitoring of the levels. Because of the potential for accumulation, the dosage of the drug should be reduced. VPA is barely affected by renal failure, since it is mainly hepatically metabolized. As with PHT, the decreased protein binding in uremia may lead to elevated free levels, which should be followed. Dialysis does not affect its levels. An increased risk for VPA-induced pancreatitis has been reported in uremic patients *(216)*, and amylase should be measured in case of unexplained abdominal pain. BDZs do not seem to be affected by uremia or dialysis and, generally, their dose does not need adjustment. Because oxazepam and the active metabolite of DZ are renally excreted, caution is advised with their use in severe uremia.

Among the enterally administered AEDs, CBZ is together with VPA a good option, because its levels are barely affected in uremia and there is no need for postdialysis supplementation. However, rare instances of idiosyncratic renal damage have been reported with this drug *(217)*. Tiagabine, a hepatically metabolized antiepileptic, can also be used without any dosage adjustment in uremia, but if the patient is in SE, it should probably be avoided (*see* p. 345). With gabapentin a sliding scale dosage based on creatinine clearance has been recommended:

>60 mL/min, 400 mg three times a day
30–60 mL/min, 300 mg twice a day
15–30 mL/min, 300 mg every day
<15 mL/min, 300 mg every other day

Because the drug is highly dialyzable, an extra dose of 200–300 mg should be also given after each dialysis session.

The following dosing schedule, based on creatinine clearance, is recommended if levetiracetam is used in renal failure.

Table 12
Effects on Plasma Level of Common ICU Medications on Antiepileptics

Added drug	Primary agents		
	Phenytoin	Carbamazepine	Valproate
Salicylates	↑		↑
Ibuprofen	↑		
Erythromycin		↑↑	↑
Chloramphenicol	↑		
Trimethoprim	↑		
Isoniazide	↑	↑	↑
Fluconazole, ketoconazole	↑↑	↑	
Propoxyphene	↑	↑↑	
Amiodarone	↑	↑	
Diltiazem, verapamil		↑	
Cimetidine	↑↑	↑	
Omeprazole	↑		
Chlorpromazine			↑
Ethanol	↓		
Folic acid	↓		
Rifampicin	↓		
Digitoxin	↓		
Cyclosporine	↓		
Warfarin	↓		
Theophylline	↓		
Glucocorticosteroids	↓		

(Adapted from refs. *218–221.*)

>80 mL/min, 500–1000 mg twice a day
50–80 mL/min, 500–1000 mg twice a day
30–50 mL/min, 250–750 twice a day
<30 mL/min, 250–500 mg twice a day

Topiramate and zonisamide induce formation of renal calculi and probably should be avoided in cases of single kidney and history of renal stones, and after kidney transplantation.

Hematopoetic Dysfunction

Immunosuppressed or postchemotherapy ICU patients have special needs regarding the use of AEDs. PHT can lead to megaloblastic anemia, responding to folate supplementation. An idiosyncratic pseudolymphoma syndrome, with diffuse lymphadenopathy, fever, and skin rash, different from the more common hydantoin

Table 13
Effects of Antiepileptics on Common ICU Medications

	Effect of antiepileptic agents on ICU drugs		
	Phenytoin	Carbamazepine	Phenobarbital
ICU medication			
Warfarin	↓	↓↓	↓↓
Theophylline	↓↓	↓↓	↓↓
Corticosteroids	↓↓	↓↓	↓↓
Haloperidol		↓	↓
Lithium		↑	
Tricyclic antidepressants	↓	↓	↓
Cyclosporine	↓↓	↓↓	↓↓
Nimodipine	↓	↓	↓
Nondepolarizing paralytics	↓	↓	

(Adapted from refs. *218–221*.)

Table 14
Interaction Between Antiepileptic Medications

	Effect on plasma level of primary agents								
	PHT	PB	CBZ	OXC	VPA	TGB	LTG	ZNS	BDZ
Added drug									
PHT		~	↓	↓	↓	↓	↓	↓	
PB	↑, then ↓		~	↓	↓	↓	↓		↓
CBZ	~	~	↓	↓	↓	↓	↓	↓	↓
OXC			↑[a]				↓		
VPA	↓[b]	↑	~ or ↑[a]				↑		↑
ZNS			↑[a]						
BDZ	↓	~			~				

PHT, phenytoin; PB, phenobarbital; CBZ, carbamazepine; VPA, valproate; TGB, tiagabine; OXC, oxcarbazepine; ZNS, zonisamide; BDZ, benzodiazepines; ~, variable.
[a]Epoxide.
[b]Free dephenylhydantoin level.
(Adapted from ref. *218*.)

lupus-like rash, can be misdiagnosed as true lymphoma and lead to unnecessary diagnostic workup. Thrombocytopenia is much less common with PHT, but it is a dose-related adverse effect of VPA. Usually only purpura or petechiae occur, and only rarely organ bleeding. However, in the ICU, in pre- or postoperative patients or those with active bleeding or coagulopathy, any drop in the platelet count should lead to a decrease of the dose of the drug or substitution with an alternative agent.

Neutropenia is less common with VPA, but a well-known adverse effect of CBZ (10%, usually during the first few months of use). The drug should be stopped only in case of white cell count greater than 2500 or absolute neutropenia (<1000 polymorphonuclear cells). CBZ can also induce aplastic anemia. PB when chronically administered can induce folate-deficient megaloblastic anemia; but this is rarely a problem in the ICU. The BDZs have no significant hematologic adverse effects.

DRUG INTERACTION IN THE ICU

Several of the interactions between antiepileptics and common medications used in the ICU have been mentioned in the other chapters of this book. The physician treating ICU seizures or SE should be familiar with the most important of them before assuming treatment failure or being surprised by obvious signs of toxicity. Table 12 presents the effects of these drugs on antiepileptic medication levels. Aluminum hydroxide, magnesium hydroxide, and calcium antacids can decrease the absorption of enterally administered PHT, lowering its level. Conversely, antiepileptic medications can affect the metabolism of numerous ICU drugs, and a few of these interactions are presented in Table 13. Finally, antiepileptic medications interact with each other (Table 14), and the intensivist using polypharmacy in the management of epileptic seizures should consider potential changes in the free or total levels of individual medications.

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