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TACTICS OF FAMILY DOCTORS IN CASE OF SYNCOPAL STATES

STUDY GUIDE

for the students of the specialty "Medicine"

in the program of the educational discipline "General Practice - Family Medicine"

Zaporizhzhia

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M99 Tactics of family doctors in case of syncopal states = Тактика сімейного лікаря при синкопальних станах: study guide for the practical classes and individual work for 6th-years students of international faculty (speciality «General medicine»), discipline «General practice – family medicine» / N. S. Mykhailovska, A. V. Grytsay, I.S. Kachan. – Zaporizhzhia : ZSMU, 2020. – 166 p.

The study guide for practical classes and independent work of students of the 6th year of the international faculty of specialty "Medicine" is made in accordance with the program of the discipline "General Practice - Family Medicine". The aim of the publication is to promote a better understanding of theoretical knowledge and practical skills in the relevant topic. The study guide is also intended for interns, family doctors, physicians and other specialties who wish to supplement their knowledge of this section of medicine.

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CONTENT

PREFACE

In the doctor`s practice, coma presents one of the greatest difficulties for the diagnosis and choice of therapy. The prognosis and fate of the patient in a coma state largely depends on the organization of care at the prehospital and hospital stage. It is important for the doctor to determine the cause of the coma. But before identifying the etiology of a coma, it is necessary to ensure effective maintenance of the vital functions of the patient - respiration and blood circulation, otherwise their serious violations may occur, while the coma itself may be reversible.This textbook includes the educational material for practical classes and individual work of students (Content module 5 «The organization of the emergency on the pre-admission stage in the practice of family doctor»), the tests for initial and final control for academic discipline «General practice – family medicine», recommended literature.

The purpose of this textbook is acquiring of knowledge and practical skills of 6^{th}-years students during preparation for classes and final module control.

The necessity of this textbook is conditioned by absence of such workbooks, which satisfy requirements of basic parts of academic subject «General practice – family medicine».

This textbook can be recommended for students of institutes of higher education (IV accreditation level) in the study of appropriate topic, intern, general practitioner – family doctor, other specialists.

LIST OF ABBREVIATIONS

ABG	arterial blood gas
ACEP	American College of Emergency Physician
AV	Atrioventricular
BNP	B-type natriuretic peptide
BP	blood pressure
BPPV	Benign paroxysmal positional (or positioning) vertigo
CBF	cerebral blood flow
CHF	congestive heart failure
CK	creatine kinase
CNS	central nervous system
CO	Cardiac output
COPD	chronic obstructive pulmonary disease
CPR	cardiopulmonary resuscitation
CSF	cerebrospinal fluid
CT	computed tomogaphy
DIC	disseminated intravascular coagulation
DVT	deep venous thrombosis
ED	emergency department
EEG	Electroencephalography
EF	ejection fraction
EPS	electrophysiologic studies
GABA	gamma-aminobutyric acid
GCSE	generalized convulsive SE
GTCS	generalized tonic-clonic seizure
ICD	implantable cardioverter/defibrillator
ICH	Intracranial hemorrhage
ICP	intracranial pressure

IM	intramuscular
IV	Intravenous
MAP	Mean arterial pressure
MERRF	Myoclonic epilepsy with ragged red fibers
MI	myocardial infarction
MLF	medial longitudinal fasciculus
MRA	magnetic resonance arteriography
MRI	magnetic resonance image
MTLE	Mesial Temporal Lobe Epilepsy Syndrome
NMDA	N-methyl-D-aspartate
NMS	neurally-mediated syncope
NYHA	New York Heart Association
PET	positron emission tomography
PVCs	premature ventricular contractions
RAS	reticular activating system
SCD	sudden cardiac deaths
SE	status epilepticus
SFSR	San Francisco Syncope Rule
SPECT	single photon emission computed tomography
SVR	Systemic vascular resistance
TCA	Tricyclic antidepressant
TED	thromboembolic disease
TIAs	Transient Ischemic Attacks
UTI	urinary tract infection
VF	ventricular fibrillation
VOR	vestibuloocular reflex
VT	ventricular tachycardia

SYNCOPE. DIZZINESS AND VERTIGO. CARDIOVASCULAR COLLAPSE, CARDIAC ARREST, AND SUDDEN CARDIAC DEATH. SEIZURE

I. Theme actuality. First aid for children and adults has great importance for their further treatment and recovering diagnosis at pre-admission stage. And at the same time family doctor always faces a problem: what is better – either to give maximum necessary scope of emergency on the site of the incident or to take the patient to the nearest hospital as soon as possible. According to expert data there is only one decision of this problem. This means give maximum necessary scope of emergency in a short-run and then to admit to specialized hospital. Stabilization of patient's vital functions is the criteria of emergency scope in the place of the incident. Fundamental factors in this process are timeliness of emergency on the site of the incident, vocational training of a specialist and sufficient medical provision.

In this textbook syncope, dizziness and vertigo, cardiovascular collapse, cardiac arrest, and sudden cardiac death and seizure are considered with particular reference to clinical manifestations, differential diagnosis, and treatment [2].

II. Study purposes: to be able to detect the signs of syncope, dizziness and vertigo, cardiovascular collapse, cardiac arrest, and sudden cardiac death, and seizure, to propose a plan of examination and treatment of patients with seizure and loss of consciousness.

III. Concrete purposes of the module: diagnostics and emergency in the case of syncope, dizziness and vertigo, cardiovascular collapse, cardiac arrest, and sudden cardiac death, and seizure.

IV. A student must be able:

- to estimate general state of the patient;

- to acquire skills of clinical examination of the patients with syncope, dizziness and vertigo, cardiovascular collapse, cardiac arrest, and sudden cardiac death, and seizure;

- to diagnose the state of the patient on the basis of patient complaints, medical history, degree of consciousness impairement and data of clinical examination;

- to define a plan for examination of patient;

- to estimate vital functions;

- to integrate data of clinical examination and laboratory data.

V. Tasks for initial independent training

1. The status of patient when his speech and thoughts become slow, his attention is distracted, there is fatigue, drowsiness and lack of perception and evaluation of what is happening:

A. Clear consciousness.

B. Obtundation.

C. Sopor.

D. Coma.

E. Syncope.

2. The status of patient when his mental state is depressed. After repeated appeal to the patient he opens his eyes but there is no contact with him:

A. Clear consciousness.

B. Obtundation.

C. Sopor.

D. Coma.

E. Syncope.

3. The status of patient when a dead faint and non-responsiveness to external irritants are observed:

A. Clear consciousness.

B. Obtundation.

C. Sopor.

D. Coma.

E. Syncope.

4. Short-time loss of consciousness accompanied by loss of postural tone and caused by temporary inadequate blood supply to brain is:

A. Clear consciousness.

B. Obtundation.

C. Sopor.

D. Coma.

E. Unconsciousness (Syncope).

5. Most important criteria of coma severity is:

A. Dead faint.

B. Non-responsiveness to external irritants.

C. Two-sided fixed mydriasis.

D. Areflexia.

E. Reduced muscle tone.

6. Types of syncopes are:

A. Neurogenic.

B. Orthostatic.

C. Cardiogenic.

D. Cerebrovascular.

E. All of mentioned above.

7. The paroxysm which starts with vertigo, loss of consciousness and fall of patient, with further tonoclonic spasms, ends by loss of consciousness with further sleep or psychomotor agitation:

A. Absence.

B. Unconsciousness.

C. Generalized tonic-clonic seizure.

D. Myoclonic seizure.

E. Focal seizure k.

8. The status of patient when there is sudden short-time loss of consciousness with physical inactivity of the patient:

A. Absence.

B. Unconsciousness

C. Atonic seizure.

D. Myoclonic seizure.

E. Focal seizure.

9. Generalized clonic seizure is typical for:

A. Epilepsy.

B. Alcoholic abstinence.

C. Fever, infectious brain diseases.

D. Metabolic disorders.

E. All of mentioned above.

10. Which metabolic disorders lead to coma:

A. Uremia.

B. Diabetis mellitus.

C. Hypoglycemia.

D. Hepatic coma.

E. All of mentioned above.

Anwsers:

1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
B	C	D	E	C	E	C	A	E	E

SYNCOPE

Background. Syncope is defined as a transient, self-limited loss of consciousness with an inability to maintain postural tone that is followed by spontaneous recovery. The term syncope excludes seizures, coma, shock, or other states of altered consciousness. Although most causes of syncope are benign, this symptom presages a life-threatening event in a small subset of patients [1].

Syncope is a prevalent disorder, accounting for 1-3% of emergency department (ED) visits and as many as 6% of hospital admissions each year in the U.S. As much as 50% of the population may experience a syncopal event during their lifetime. Although many etiologies for syncope are recognized, categorization into reflex (neurally mediated), orthostatic, and cardiac (cardiovascular) may be helpful during the initial evaluation. Cardiac syncope is associated with increased mortality, whereas noncardiac syncope is not. Syncope may result in significant morbidity due to falls or accidents that occur as a result. In the U.S. alone, an estimated $2 billion annually is spent on patients hospitalized with syncope.

Although most causes of syncope are benign, this symptom presages a life-threatening event in a small subset of patients. It is unclear whether hospital inpatient admission of asymptomatic patients after syncope affects outcomes. No current criterion standard exists for diagnosing undifferentiated syncope. Many physicians continue to admit patients because of perceived risk. The reviews of the 2001 American College of Emergency Physician (ACEP) clinical policy suggest that evidence-based criteria may decrease admission rates by nearly half by identifying cardiac causes of syncope. Inpatient admission should be reserved for patients in whom identification of specific immediate risk, such as those with structural heart disease or history of ventricular arrhythmia, is needed. Outpatient management can be used for patients who are low risk for a cardiac etiology in order to define a precise cause in order to effect mechanism-specific treatment [2].

Pathophysiology

Syncope occurs due to global cerebral hypoperfusion. Brain parenchyma depends on adequate blood flow to provide a constant supply of glucose, the primary metabolic substrate. Brain tissue cannot store energy in the form of high-energy phosphates found elsewhere in the body; therefore, a cessation of cerebral perfusion lasting only 3-5 seconds can result in syncope [3].

Cerebral perfusion is maintained relatively constant by an intricate and complex feedback system involving cardiac output, systemic vascular resistance, arterial pressure, intravascular volume status, cerebrovascular resistance with intrinsic autoregulation, and metabolic regulation. A clinically significant defect in any one of these or subclinical defects in several of these systems may cause syncope.

Cardiac output (CO) can be diminished secondary to mechanical outflow obstruction, pump failure, hemodynamically significant arrhythmias, or conduction defects. Systemic vascular resistance (SVR) can drop secondary to vasomotor instability, autonomic failure, or vasodepressor/vasovagal response. Mean arterial pressure (MAP) decreases with all causes of hypovolemia. Medications can affect CO, SVR, or MAP[1].

Other conditions can mimic syncope. A CNS event, such as a hemorrhage or an unwitnessed seizure, can present as syncope. Syncope can occur without reduction in cerebral blood flow in patients who have severe metabolic derangements (eg, hypoglycemia, hyponatremia, hypoxemia, hypercarbia).

Frequency

U.S. Framingham data demonstrate a first occurrence rate of 6,2 cases per 1000 patient-years [5, 6]. Syncope reoccurs in 3% of affected individuals, and approximately 10% of affected individuals have a cardiac etiology**. International.** Data from Europe and Japan suggest a similar occurrence rate to the United States, accounting for 1-3,5% of ED visits [1].

Mortality/Morbidity. Data suggest that patients with cardiac syncope are more likely to experience a poor outcome. Patients who have a significant cardiac history and those who seem to have a cardiac syncope (because of associated chest pain, dyspnea, cardiac murmur, signs of congestive heart failure [CHF], or ECG abnormalities) should be considered to be at increased risk. Most published methods of risk stratification take into account cardiac symptoms and risk factors [9].

Morbidity from syncope includes recurrent syncope, which occurs in 20% of patients within one year of the initial episode. Lacerations, extremity fractures, head injuries, and motor vehicle accidents can occur secondary to syncope.

Syncope in a patient with poor baseline cardiac function portends a poor prognosis irrespective of etiology. Middlekauff et al studied 491 patients with New York Heart Association (NYHA) functional class III or IV disease and noted that, regardless of the cause, 45% of those with syncope died within 1 year, whereas 12% of those without syncope died during the same interval [2].

Patients with cardiac syncope appear to do worse than patients with noncardiac syncope [8, 9].

Risk of serious outcome and death in patients with syncope increases with higher peak troponin concentrations, according to a prospective cohort study of 338 patients who had plasma troponin I levels measured 12 hours after syncope, using a sensitive assay [10].

Decision rules may assist in identifying patients who are at risk. A risk stratification system predicts an increased incidence of death at 1 year based on the presence of abnormal ECG findings, a history of ventricular arrhythmia, a history of CHF, and age older than 45 years [11].

A risk of arrhythmia is proportional to the number of cardiac risk factors, including abnormal ECG findings, history of CHF, and age older than 65 years [12].

The presence of abnormal ECG findings, a history of CHF, dyspnea, a hematocrit level of less than 30, and hypotension identifies patients who are at immediate risk for

serious outcomes within 7 days, with a 96% sensitivity [13]. The presence of these findings should prompt serious consideration for hospital admission.

The Risk stratification of Syncope in the Emergency department, or ROSE, criteria suggest that an elevated B-type natriuretic peptide (BNP), Hemoccult positive stool, anemia, low oxygen saturation, and presence of Q waves on ECG predict serious outcomes at 30 days [16]. These rules had a 87% sensitivity and a 98,5% negative predictive value to help risk stratify patients. The isolated finding of BNP greater than 300 pg/mL was a major predictor of serious outcomes and was present in 89% of patients who died within 30 days.

Constantino et al discovered that 6,1% of patients had severe outcomes within 10 days of syncope evaluation [1]. The mortality rate was 0,7%, and 5,4% of patients were readmitted or experienced major therapeutic intervention. Risk factors associated with severe short-term outcomes included abnormal ECG, history of CHF, age older than 65 years, male gender, history of chronic obstructive pulmonary disease (COPD), structural heart disease, presence of trauma, and lack of prodromal symptoms.

Race, sex, and age

No significant differences regarding race are observed with respect to syncope risk. Larger prospective studies fail to show clinically significant differences between men and women.

The syncope occurs in all age groups but is most common in adult populations. Noncardiac causes tend to be more common in young adults, whereas cardiac syncope becomes increasingly more frequent with advancing age.

Syncope is relatively uncommon in pediatric populations. (a prevalence of less than 0,1% in children) [4]. Pediatric syncope warrants prompt detailed evaluation.

Advancing age is an independent risk factor for both syncope and death. Various studies suggest categorizing patients older than 45 years, 65 years, and 80 years as "higher risk." Advancing age correlates with increasing frequency of coronary artery and myocardial disease, arrhythmia, vasomotor instability, autonomic failure, polyneuropathy, and use of polypharmacy.

Syncope Clinical Presentation

History and physical examination are the most specific and sensitive ways to evaluate syncope. The diagnosis is achieved with a thorough history and physical examination in 50-85% of patients. No single laboratory test has greater diagnostic efficacy. The 2007 American College of Emergency Physicians (ACEP) Clinical Policy on Syncope lists history and physical and 12-lead ECG as their only current level A recommendations [1].

A detailed account of the event must be obtained from the patient. The account must include the circumstances surrounding the episode: the precipitant factors, the activity the patient was involved with prior to the event and the patient's position when it occurred.

Precipitant factors can include fatigue, sleep or food deprivation, warm ambient environment, alcohol consumption, pain, and strong emotions such as fear or apprehension.

Activity prior to syncope may give a clue as to the etiology of symptoms. Syncope may occur at rest; with change of posture; on exertion; after exertion; or with specific situations such as shaving, coughing, voiding, or prolonged standing. Syncope occurring within 2 minutes of standing suggests orthostatic hypotension [2].

Assess whether the patient was standing, sitting, or lying when the syncope occurred. Syncope while seated or lying is more likely to be cardiac [8].

The following questions should be answered:

- Was loss of consciousness complete?
- Was loss of consciousness with rapid onset and short duration?
- Was recovery spontaneous, complete, and without sequelae?
- Was postural tone lost?

If the answers to these questions are positive, the episode has a high likelihood of being syncope. If one or more answers are negative, consider other forms of loss of consciousness prior to proceeding with syncope evaluation [2]. The clinician should attempt to gather all information with respect to symptoms preceding the syncope.

Prior faintness, dizziness, or light-headedness occurs in 70% of patients experiencing true syncope. Other symptoms, such as vertigo, weakness, diaphoresis, epigastric discomfort, nausea, blurred or faded vision, pallor, or paresthesias, may also occur in the presyncopal period.

Symptoms of nausea or diaphoresis prior to the event may suggest syncope rather than seizure when the episode was not witnessed, whereas an aura may suggest seizure.

Patients with true syncope do not remember actually falling to the ground. Presyncope involves the same symptoms and pathophysiology but terminates prior to loss of consciousness and can occasionally include loss of postural tone [6].

The duration of symptoms preceding a syncopal episode has been reported to be an average of 2,5 minutes in vasovagal syncope and an average of only 3 seconds in arrhythmia-related cardiac syncope.

Clinicians should specifically inquire as to red flag symptoms, such as exertional onset, chest pain, dyspnea, low back pain, palpitations, severe headache, focal neurologic deficits, diplopia, ataxia, or dysarthria prior to the syncopal event.

Patients should be asked to estimate the duration of their loss of consciousness. Syncope is associated with patient estimates ranging from seconds up to 1 minute in most cases. To discriminate from seizures, patients should also be asked if they remember being confused about their surroundings after the event or whether they have oral trauma, incontinence, or myalgias [7].

A detailed account of the event must also be obtained from any available witnesses. Witnesses can aid the clinician in differentiating among syncope, altered mental status, and seizure.

Convulsive activity, automatisms, or attempts to elicit focality can indicate seizure. Witnesses may be able to estimate the duration of unconsciousness and to assist in ascertaining whether the patient experienced postevent confusion.

Postevent confusion is the most powerful tool for discriminating between syncope and seizure. A postictal phase suggests that a seizure has occurred. Postevent confusion has been described with syncope, but the confusion should not last more than 30

seconds. Seizurelike activity can occur with syncope if the patient is held in an upright posture [2].

A medication history must be obtained in all patients with syncope with special emphasis placed on cardiac and antihypertensive medications. Drugs commonly implicated in syncope include the following:

- Agents that reduce blood pressure (eg, antihypertensive drugs, diuretics, nitrates);
- Agents that affect cardiac output (eg, beta-blockers, digitalis, antiarrhythmics);
- Agents that prolong the cardiac output (QT) interval (eg, tricyclic antidepressants, phenothiazines, quinidine, amiodarone);
- Agents that alter sensorium (including alcohol, cocaine, analgesics with sedative properties);
- Agents that alter serum electrolytes (especially diuretics).

Inquiry must be made into any personal or familial past medical history of cardiac disease. Patients with a history of myocardial infarction (MI), arrhythmia, structural cardiac defects, cardiomyopathies, or CHF have a uniformly worse prognosis than other patient groups.

Remember to consider the broad differential diagnosis of syncope. Assess whether the patient has a history of seizure disorder, diabetes, stroke (CVA), deep venous thrombosis (DVT), or abdominal aortic aneurysm or if pregnancy is a possibility [1].

Physical examination

A complete physical examination is requisite for all patients who present to the Emergency Departement (ED). Special attention must be paid to certain aspects of the physical examination in patients who present with syncope.

Always analyze the vital signs. Fever may point to a precipitant of syncope, such as a urinary tract infection (UTI) or pneumonia. Postural changes in blood pressure (BP) and heart rate may point toward an orthostatic cause of syncope but are generally unreliable. Tachycardia may be an indicator of pulmonary embolism, hypovolemia, tachyarrhythmia, or acute coronary syndrome. Bradycardia may point toward a

vasodepressor cause of syncope, a cardiac conduction defect, or acute coronary syndrome [5].

A glucose level, checked by rapid fingerstick (eg, Accu-Chek), should be evaluated in any patient with syncope. Hypoglycemia can produce a clinical picture identical to syncope, including the prodromal symptoms, absence of memory for the event, and spontaneous resolution.

A detailed cardiopulmonary examination is essential. Irregular rhythms, ectopy, bradyarrhythmias, and tachyarrhythmias should be detected. Auscultation of heart sounds may reveal murmurs indicating high-grade valvular defects. Search for objective evidence of CHF, including jugular venous distension, lung rales, hepatomegaly, and pitting-dependent edema. Examine the abdomen for the presence of a pulsatile abdominal mass [8].

A detailed neurologic examination assists in establishing a baseline as well as defining new or worsening deficits. Patients with syncope should have a normal baseline mental status. Confusion, abnormal behavior, headache, fatigue, and somnolence must not be attributed to syncope; a toxic, metabolic, or CNS cause must be considered. The patient should have a detailed neurologic examination, including evaluation for carotid bruits, cranial nerve deficits, motor deficits, deep tendon reflex lateralization, and sensory deficits. Severe neuropathies may correlate with vasodepressor syncope.

The patient must be examined for signs of trauma. Trauma may be sustained secondary to syncope with resultant head injury, lacerations, and extremity fractures. Tongue trauma is thought to be more specific for seizures. Remember to consider antecedent head trauma resulting in loss of consciousness as opposed to syncope with resultant trauma if the history or findings are unclear.

All patients with syncope require a stool guaiac examination. In one study, all patients with anemia contributing to syncope were guaiac-positive.

A few bedside examinations may help to elucidate the origin of a patient's syncope. The Hallpike maneuver may be performed in patients who describe short,

intermittent prodromes with primarily vertiginous components to assess for benign paroxysmal positional vertigo [1].

Orthostatic changes marked by a decrease in systolic BP by 20 mm Hg, a decrease in diastolic BP by 10 mm Hg, or an increase in heart rate by 20 beats per minute (bpm) with positional changes or systolic BP less than 90 mm Hg with the presence of symptoms may indicate postural hypotension. Bradycardia coinciding with the examination indicates vasodepressor syncope. Be aware that this examination is notoriously insensitive and has limited use.

Carotid sinus massage has been used with some success to diagnose carotid sinus syncope but can prompt prolonged sinus pauses and hypotension [5].

Causes

Cardiac (cardiopulmonary) syncope may be due to vascular disease, cardiomyopathy, arrhythmia, or valvular dysfunction and predicts a worse short-term and long-term prognosis (see Table 1). Obtaining an initial ECG is mandatory if any of these causes are possible for the differential diagnosis.

Low flow states, such as those associated with advanced cardiomyopathy, CHF, and valvular insufficiency, may result in hypotension and cause transient global cerebral hypoperfusion. Often, these patients are on medications that reduce afterload, which may contribute to the cause of syncope.

Ventricular arrhythmias, such as ventricular tachycardia and torsade de pointes, tend to occur in older patients with known cardiac disease. These patients tend to have fewer recurrences and have a more sudden onset with few, if any, presyncopal symptoms. Associated chest pain or dyspnea may be present. This type of syncope is generally unrelated to posture and can occur during lying, sitting, or standing. Often, these arrhythmias are not revealed on the initial ECG but may be captured with prolonged monitoring.

Supraventricular tachyarrhythmias include supraventricular tachycardia and atrial fibrillation with rapid response. These may be associated with palpitations, chest pain, or dyspnea. Patients typically have prodromal symptoms and may have syncope while

attempting to stand or walk because of resultant hypotension. These symptoms may spontaneously resolve prior to evaluation but are often noted during initial triage and assessment. Be sure to scrutinize ECG findings for evidence of Wolff-Parkinson-White syndrome, Brugada syndrome, and long QT syndrome [8].

Bradyarrhythmias include sick sinus syndrome, sinus bradycardia, high-grade atrioventricular blocks, pacemaker malfunction, and adverse medication reactions. Generally, these patients have a history of cardiac problems and are symptomatic. Chest pain, dyspnea, decreased exercise tolerance, and fatigue may all be present. Consider cardiac ischemia and medication side effects as additional causes.

Cardiac outflow obstruction may also result in sudden-onset syncope with little or no prodrome. One critical clue is the exertional nature, and the other is the presence of a cardiac murmur. Young athletes may present with this etiology for syncope. Specific pathology includes aortic stenosis, hypertrophic obstructive cardiomyopathy, mitral stenosis, pulmonary stenosis, pulmonary embolus, left atrial myxoma, and pericardial tamponade [1].

Syncope can also result from an acute MI, acute aortic dissection, and pulmonary embolus. These conditions can have associated chest pain, neck pain, shoulder pain, dyspnea, epigastric pain, hypotension, alteration of mental status and can result in sudden death.

Reflex (neurally mediated) syncope may be due to vasovagal syncope, which is mediated by emotional distress such as fear or physical pain. Situational syncope describes syncope that occurs with a fixed event such as micturition, deglutition, exercise induced, and carotid sinus syncope. These causes tend to be more benign and do not predict poor outcomes.

Vasovagal syncope is the most common type in young adults but can occur at any age. It usually occurs in a standing position and is precipitated by fear, emotional stress, or pain (eg, after a needlestick). Autonomic symptoms are predominant. Classically, nausea, diaphoresis, fading or "graying out" of vision, epigastric discomfort, and light-

headedness precede syncope by a few minutes. Syncope is thought to occur secondary to efferent vasodepressor reflexes by a number of mechanisms, resulting in decreased peripheral vascular resistance. It is not life threatening and occurs sporadically [3].

Situational syncope is essentially a reproducible vasovagal syncope with a known precipitant. Micturition, defecation, deglutition, tussive, and carotid sinus syncope are types of situational syncope. These stimuli result in autonomic reflexes with a vasodepressor response, ultimately leading to transient cerebral hypotension. These are not life-threatening but can cause morbidity. The treatment involves avoidance of the precipitant when possible and the initiation of counter maneuvers when anticipated.

Syncope due to orthostatic hypotension can occur through several mechanisms. Pure autonomic failure can be associated with Parkinson's disease or dementia. Secondary autonomic insufficiency can be due to diabetes, uremia, or spinal injury. Drugs such as alcohol cause orthostatic intolerance and medications such as vasodilators and antidepressants block orthostatic reflexes. Volume depletion due to blood loss, vomiting, diarrhea, poor oral intake, and diuretics also cause orthostatic syncope [7].

Dehydration and decreased intravascular volume contribute to orthostasis. Orthostatic syncope describes a causative relationship between orthostatic hypotension and syncope. Orthostatic hypotension increases in prevalence with age as a blunted baroreceptor response results in failure of compensatory cardioacceleration. In elderly patients, 45% of these cases are related to medications. Limited evidence suggests that polydipsia may reduce recurrences. Orthostasis is a common cause of syncope and tends to be recurrent. Bedside orthostatics cannot exclude this as an etiology; if suspected, patients should be referred to a primary care provider for outpatient tilt-table testing.

Table 1

Causes of Faintness and Disturbances of Consciousness

I. Circulatory (reduced cerebral blood flow)

A. Inadequate vasoconstrictor mechanisms
   1. Vasovagal (vasodepressor)
   2. Postural hypotension
   3. Primary autonomic insufficiency
   4. Sympathectomy (pharmacologic, due to antihypertensive medications such as methyldopa and hydralazine, or surgical)
   5. Diseases of central and peripheral nervous systems, including autonomic nerves
   6. Carotid sinus syncope (see also "Bradyarrhythmias", below)
   7. Hyperbradykininemia

B. Hypovolemia
   1. Blood loss - gastrointestinal hemorrhage
   2. Addison's disease

C. Mechanical reduction of venous return
   1. Valsalva maneuver
   2. Cough
   3. Micturition
   4. Atrial myxoma, ball valve thrombus

D. Reduced cardiac output
   1. Obstruction to left ventricular outflow: aortic stenosis, hypertrophic subaortic stenosis
   2. Obstruction to pulmonary flow: pulmonic stenosis, primary pulmonary hypertension, pulmonary embolism
   3. Myocardial: massive myocardial infarction with pump failure
   4. Pericardial: cardiac tamponade

E. Arrhythmias
   1. Bradyarrhythmias
      a. Atrioventricular (AV) block (second- and third-degree), with Stokes-Adams attacks
      b. Ventricular asystole
      c. Sinus bradycardia, sinoatrial block, sinus arrest, sick-sinus syndrome

d. Carotid sinus syncope (also inadequate vasoconstrictor mechanisms)
e. Glossopharyngeal neuralgia (and other painful states)
2. Tachyarrhythmias
a. Episodic ventricular tachycardia with or without associated bradyarrhythmias
b. Supraventricular tachycardia without AV block

II. Other causes of disturbances of consciousness

A. Altered state of blood to the brain
1. Hypoxia
2. Anemia
3. Diminished carbon dioxide due to hyperventilation (faintness common, syncope seldom occurs)
4. Hypoglycemia (episodic weakness common, faintness occasional, syncope rare)

B. Cerebral
1. Cerebrovascular disturbances (cerebral ischemic attacks)
a. Extracranial vascular insufficiency (vertebral-basilar, carotid)
b. Diffuse spasm of cerebral arterioles (hypertensive encephalopathy)
2. Emotional disturbances, anxiety attacks, and hysterical seizures [3].

Syncope Differential Diagnoses

- **Acute Hemorrhage**, usually within the gastrointestinal tract, is an occasional cause of syncope. In the absence of pain and hematemesis, the cause of the weakness, faintness, or even unconsciousness may remain obscure until the passage of a black stool.
- **Adrenal Insufficiency and Adrenal Crisis**
- **Aneurysm, Abdominal**
- **Anxiety Attacks and the Hyperventilation Syndrome.** Anxiety, such as occurs in panic attacks, is frequently interpreted as a feeling of faintness or dizziness without loss of consciousness. The symptoms are not accompanied by facial pallor and are not relieved by recumbency. The diagnosis is made on the basis of the associated symptoms, and the attack can be reproduced by hyperventilation.

Hyperventilation results in hypocapnia, alkalosis, increased cerebrovascular resistance, and decreased cerebral blood flow. The release of epinephrine in anxiety states also contributes to the symptoms [2].

- **Aortic Stenosis**
- **Asystole**
- **Atrial Fibrillation**
- **Brugada Syndrome**
- **Cardiomyopathy, Restrictive**
- **Cerebral Transient Ischemic Attacks (TIAs)** occur in patients with atherosclerotic narrowing, occlusion, or emboli to the major arteries of the brain. The symptoms are manifold. Sudden drop attacks may mimic syncope. Isolated loss of consciousness is rare[1].
- **Dissection, Aortic**
- **Heart Block, Second Degree**
- **Heart Block, Third Degree**
- **Hypoglycemia**: is usually traceable to a serious disease such as a tumor of the islets of Langerhans; advanced adrenal, pituitary, or hepatic disease; or to excessive administration of insulin; it leads to confusion or loss of consciousness. Mild hypoglycemia, often reactive type and occurring 2 to 5 h after eating, is not usually associated with a disturbance of consciousness [8].
- **Hyponatremia**
- **Hysterical Fainting** is usually unattended by an outward display of anxiety. Lack of change in pulse and blood pressure or color of the skin and mucous membranes distinguishes it from the vasodepressor faint.
- **Long QT Syndrome**
- **Mitral Stenosis**
- **Multifocal Atrial Tachycardia**
- **Myocardial Infarction**
- **Pacemaker and Automatic Internal Cardiac Defibrillator**

- **Pulmonary Embolism**
- **Pulmonic Valvular Stenosis**
- **Sinus Bradycardia**
- **Subarachnoid Hemorrhage**
- **Tetralogy of Fallot**
- **Torsade de Pointes**
- **Toxicity, Amphetamine, Antidepressant,**
- **Toxicity, Antidysrhythmic, Beta-blocker, Calcium Channel Blocker**
- **Toxicity, Cocaine**
- **Toxicity, Cyclic Antidepressants**
- **Wolff-Parkinson-White Syndrome** [1]

Syncope Workup

Laboratory Studies. Currently, no specific testing has sufficient power to be absolutely indicated for evaluation of syncope. Research-based and consensus guideline recommendations are listed below [13].

Serum glucose level. In one study, 2 of 170 patients with syncope tested for serum glucose were found to be hypoglycemic. Despite this low yield, rapid blood glucose assessment is easy, fast, and may be diagnostic, leading to efficient intervention.

CBC count. If performed empirically, a CBC count has an exceedingly low yield in syncope. Some risk stratification protocols use a low hematocrit level as a poor prognostic indicator.

A prospective evaluation of syncope found that 4 of 170 patients had signs and symptoms of GI hemorrhage with a confirmatory CBC count. No occult bleeding was diagnosed based on an empiric CBC count in this study [8].

Anemia has been shown in several studies to suggest poor short-term outcomes.

Serum electrolyte levels with renal function

These tests if performed empirically have an exceedingly low yield in syncope. Some risk stratification protocols use electrolyte level abnormalities and renal insufficiency as poor prognostic indicators.

Sometimes, patients with syncope had electrolytes drawn as part of the routine workup [2]. One patient was unexpectedly found to be hyponatremic secondary to diuretic use.

Serum electrolyte tests are indicated in patients with altered mental status or in patients in whom seizure is being considered. If arrhythmia is noted, evaluation of electrolytes may be useful.

Cardiac enzymes. These tests are indicated in patients who give a history of chest pain with syncope, dyspnea with syncope, or exertional syncope; those with multiple cardiac risk factors; and those in whom a cardiac origin is highly suspected.

Total creatine kinase (CK). A rise in CK levels may be associated with prolonged seizure activity or muscle damage secondary to a prolonged period of loss of consciousness. BNP level >300 pg/mL is a predictor of serious outcomes at 30 days [1].

Urinalysis/dipstick. In elderly and debilitated patients, UTI is common, easily diagnosed, and treatable and may precipitate syncope. UTIs may occur in the absence of fever, leukocytosis, and symptoms in this population.

Imaging Studies

Chest radiography. In elderly patients and in patients who are debilitated, pneumonia is common, easily diagnosed, and treatable and may precipitate syncope. Pneumonia may occur in the absence of fever, leukocytosis, and symptoms in this population.

Evaluation of a select number of etiologies of syncope may be aided by chest radiography. Pneumonia, CHF, lung mass, effusion, and widened mediastinum can all be seen if present and may guide therapy [5].

Head CT scanning (noncontrast). Head CT scanning is not indicated in a nonfocal patient after a syncopal event. This test has a low diagnostic yield in syncope. Of 134 patients prospectively evaluated for syncope using CT scanning, 39 patients had abnormal findings on scans [2]. Only 1 head CT scan was diagnostic in a patient not expected to have intracranial pathology. Of the remaining scans, 5 showed subdural hematomas thought to be secondary to syncope.

Head CT scanning may be clinically indicated in patients with new neurologic deficits or in patients with head trauma secondary to syncope.

Chest/abdominal CT scanning is indicated only in select cases, such as cases in which aortic dissection, ruptured abdominal aortic aneurysm, or pulmonary embolus is suspected.

Brain MRI/magnetic resonance arteriography (MRA) may be required in select cases to evaluate vertebrobasilar vasculature and are more appropriately performed on an inpatient basis in consultation with a neurologist or a neurosurgeon.

Ventilation-perfusion (V/Q) scanning is appropriate for patients in whom pulmonary embolus is suspected.

Echocardiography. In patients with known heart disease, left ventricular function and ejection fraction have been shown to have an accurate predictive correlation with death.

Echocardiography is the test of choice for evaluating suspected mechanical cardiac causes of syncope [1].

Other Tests

Electrocardiography. Obtain a standard 12-lead ECG in syncope. This is a level A recommendation by 2007 ACEP consensus guidelines for syncope. ECG is used in most every clinical decision rule for risk stratification. Normal ECG findings are a good prognostic sign.

ECG can be diagnostic for acute MI or myocardial ischemia and can provide objective evidence of preexisting cardiac disease or dysrhythmia such as Wolff-Parkinson-White syndrome, Brugada syndrome, atrial flutter, or AV blocks.

Bradycardia, sinus pauses, nonsustained ventricular tachycardia and sustained ventricular tachycardia, and atrioventricular conduction defects occur with increasing frequency with age and are truly diagnostic only when they coincide with symptoms. Holter monitor/loop event recorder. This is an outpatient test. In the past, all patients with syncope were monitored for 24 hours in a hospital. Later, loop recorders and signal-averaged event recorders allowed for monitoring over longer time periods, which increased the yield of detecting an arrhythmia.

Recent studies show that age-matched asymptomatic populations have an equivalent number of arrhythmic events recorded by ambulatory monitoring. Loop recorders have a higher diagnostic yield than Holter monitor evaluation with a marginal cost savings [3].

A one study showed that symptomatic arrhythmias were found in just 0.5% of patients referred for syncope [4]. In fact, patients had symptoms without arrhythmias more often than symptoms with arrhythmias, advancing the notion that ambulatory monitoring has a higher negative than positive diagnostic yield.

Head-up tilt-table test is useful for confirming autonomic dysfunction and can generally be safely arranged on an outpatient basis. The test involves using a tilt table to stand a patient at 70 degrees for 45 minutes. Various modified protocols with concomitant medications, fasting, and maneuvers exist. Normally norepinephrine (NE) levels rise initially and are maintained to hold BP constant. A positive result occurs when NE levels fatigue with time and a falling BP and pulse rate produce symptoms. The head-up tilt-table test is less sensitive than electrophysiologic stress testing, and a negative result does not exclude the diagnosis of neurogenic syncope [5].

Electroencephalography (EEG) can be performed at the discretion of a neurologist if seizure is considered a likely alternative diagnosis.

Stress test/electrophysiologic studies (EPS) have a higher diagnostic yield than the Holter monitor and should be obtained for any patient with a suspected arrhythmia as a cause of syncope.

A cardiac stress test is appropriate for patients in whom cardiac syncope is suspected and in whom have risk factors for coronary atherosclerosis. This test can assist with cardiac risk stratification and can guide future therapy.

Procedures

Carotid sinus massage has been used with some success to diagnose carotid sinus syncope. Patients are placed on a cardiac monitor and beat-to-beat BP monitoring device. Atropine is kept at the bedside.

Longitudinal massage lasting 5 seconds is initiated at the point of greatest carotid pulse intensity at the level of the thyroid cartilage on one side at a time.

The maximal response occurs after approximately 18 seconds, and a positive result is one that produces 3 seconds of asystole or syncope. If the result is negative, the process is repeated on the other carotid sinus. Carotid sinus massage may theoretically precipitate an embolic stroke in persons with preexisting carotid artery disease [1].

Syncope Treatment & Management

Prehospital Care. Prehospital management of syncope covers a wide spectrum of acute care and includes rapid assessment of airway, breathing, circulation, and neurologic status.

Treatment may require the following:

- Intravenous access
- Oxygen administration
- Advanced airway techniques
- Glucose administration
- Pharmacologic circulatory support
- Pharmacologic or mechanical restraints
- Defibrillation or temporary pacing

Advanced triage decisions, such as direct transport to multispecialty tertiary care centers, may be required in select cases [8].

Emergency Department Care. In patients brought to the ED with a presumptive diagnosis of syncope, appropriate initial interventions include intravenous access, oxygen administration, and cardiac monitoring. ECG and rapid blood glucose evaluation should be promptly performed. A study to determine the sensitivity and specificity of the San Francisco Syncope Rule (SFSR) ECG criteria for determining cardiac outcomes found that when used correctly, the criteria can help predict which syncope patients are at risk of cardiac outcomes. ECG criteria predicted 36 of 42 patients with cardiac outcomes, with a sensitivity of 86%, a specificity of 70%, and a negative predictive value of 99% [5].

Syncope may be the manifestation of an acute life-threatening process but is generally not emergent. Clinically ruling out certain processes is important. The treatment choice for syncope depends on the cause or precipitant of the syncope. Patients in whom a cause cannot be ascertained in the ED, especially if they have experienced significant trauma, warrant supportive care and monitoring.

Situational syncope treatment focuses on educating patients about the condition. For example, in carotid sinus syncope, patients should be instructed not to wear tight collars, to use a razor rather than electric shaver, and to maintain good hydration status; they should also be informed of the possibility of pacemaker placement in the future.
Orthostatic syncope treatment also focuses on educating the patient. Inform patients about avoiding postprandial dips in BP, teach them to elevate the head of their bed to prevent rapid BP fluctuations on arising from bed, and emphasize the importance of assuming an upright posture slowly. Additional therapy may include thromboembolic disease (TED) stockings, mineralocorticoids (eg, fludrocortisone for volume expansion), and other drugs such as midodrine (an alpha-1-agonist with vasopressor activity). Patients' medications must be reviewed carefully to eliminate drugs associated with hypotension. Intentional oral fluid consumption is useful in decreasing frequency and severity of symptoms in these patients.

Cardiac arrhythmic syncope is treated with antiarrhythmic drugs or pacemaker placement. Consider cardiologist evaluation or inpatient management since this is more commonly associated with poor outcomes [1]. Trials assessing beta-blockade to prevent syncope have conflicting results, but no clear effect has been demonstrated.

Cardiac mechanical syncope may be treated with beta-blockade to decrease outflow obstruction and myocardial workload. Valvular disease may require surgical correction. This, too, is associated with increased future morbidity and mortality.

Consultations. The etiology of syncope dictates the need, if any, for specialty consultation. Select cases may require consultation with a neurosurgeon, a neurologist, a cardiologist, a vascular surgeon, a cardiothoracic surgeon, an endocrinologist, or a toxicologist [8].

Medication Summary. The goals of pharmacotherapy are to prevent complications and to reduce morbidity.

Anticholinergics. Class Summary. These agents improve conduction through the atrioventricular node by reducing vagal tone via muscarinic receptor blockade. For patients with infranodal block, this therapy is ineffective.

Atropine: Anticholinergic (or parasympatholytic) drug that exerts its action by competitively inhibiting acetylcholine at muscarinic receptors on postganglionic smooth muscle. Can counteract rapidly heightened vagal tone in response to pathologic carotid sinus syndrome. Additionally, can reverse bradycardia and lessen degree of heart block when vagal activity is etiologic factor. Usual doses are used to reduce severe bradycardia and syncope associated with hyperactive carotid sinus reflex [5].

Nutrient Supplements. Class Summary

Parenterally injected dextrose is used in patients unable to sustain adequate oral intake. Its direct oral absorption results in a rapid increase in blood glucose concentrations. Dextrose (D-Glucose)

Nutrient replenisher serves to restore blood glucose levels. Each 100 mL of 5% dextrose contains 5 g of dextrose, whereas each 100 mL of 10% dextrose contains 10 g of dextrose. Should be given only after demonstrated hypoglycemia [1].

Benzodiazepines. Class Summary

CNS agents of the 1,4-benzodiazepine class exert their effects by binding at stereo-specific receptors in the CNS. Their exact mechanism of action has not been clearly elucidated. Benzodiazepines cause a dose-related CNS depression, which varies from mild sedation to hypnosis.

Alprazolam: Indicated for treatment of anxiety and management of panic attacks. Following PO administration, absorbed readily. Peak concentrations in plasma occur 1-2 h following administration.

Vasopressor. Class Summary

Midodrine forms an active metabolite, desglymidodrine, which is an alpha-1-agonist that acts on receptors of the arteriolar and venous vasculature, producing an increase in vascular tone and elevation of BP. This drug has minimal beta effects and diffuses poorly across the blood-brain barrier.

Midodrine HCl. Increases standing, sitting, and supine systolic and diastolic BP in patients with orthostatic hypotension of various etiologies. Standing systolic BP elevated by approximately 15-30 mmHg at 1 h after 10-mg dose, with some effect persisting for 2-3 h has no clinically significant effect on standing or supine pulse rates in patients with autonomic failure [13].

Syncope Follow-up

Further Inpatient Care. The specialized syncope units with protocoled approaches to ruling out cardiac causes of syncope reduce hospital costs and length of stay without compromising quality of care [2].

Transfer. Patients with select etiologies of syncope may require transfer for specialty evaluation or procedures.

Deterrence/Prevention. Education may have a substantial impact on the prevention of recurrence, especially in situational and orthostatic syncope.

Patients may be trained to avoid situations that prompt syncope in situational cases. In orthostatic syncope, patients should drink 500 mL of fluid each morning in addition to their usual routine and should avoid standing up too quickly.

Complications. Patients with recurrent syncope should be cautioned to avoid tall ledges and to refrain from driving. Recurrent falls due to syncope can result in lacerations, orthopedic injuries, and intracranial trauma.

Prognosis

Cardiac syncope has a poorer prognosis than other forms of syncope. The 1-year end point mortality rate has been shown to be as high as 18-33%. Studies evaluating mortality rates within 4 weeks of presentation and 1 year after presentation both report

statistically significant increases in this patient group. Patients with cardiac syncope may be significantly restricted in their daily activities, and the occurrence of syncope may be a symptom of their underlying disease progression.

Syncope of any etiology in a patient with cardiac conditions (to be differentiated from cardiac syncope) has also been shown to imply a poor prognosis. Patients with arrhitmia functional class III or IV who have any type of syncope have mortality rate as high as 25% within 1 year [5].

However, some patients do well after definitive surgical treatment or pacemaker placement. Evaluation by a cardiologist for pacemaker placement should be considered in select patients over 40 years of age with recurrent syncope confirmed to be neurally-mediated syncope (NMS) with a documented period of asystole. Preliminary data suggests that although syncope may recur in this subset of patients there is a reduction in frequency of >50% [2].

Noncardiac syncope seems to have no effect on overall mortality rates and includes syncope due to vasovagal response, autonomic insufficiency, situations, and orthostatic positions.

Vasovagal syncope has a uniformly excellent prognosis. This condition does not increase the mortality rate, and recurrences are infrequent.

Situational syncope and orthostatic syncope also have an excellent prognosis. They do not increase the risk of death; however, recurrences do occur and are sometimes a source of significant morbidity in terms of quality of life and secondary injury. Syncope of unknown etiology generally has a favorable prognosis, with 1-year follow-up data showing a low incidence of sudden death (2%), a 20% chance of recurrent syncope, and a 78% remission rate.

Patient Education. Patients who present to the ED with syncope should be instructed not to drive. Syncope-related injury during driving is rare but has been documented [3].

DIZZINESS AND VERTIGO

Dizziness is a common and often vexing symptom. Patients use the term to encompass a variety of sensations, including those that seem semantically appropriate (e.g., lightheadedness, faintness, spinning, giddiness, etc.) and those that are misleadingly inappropriate, such as mental confusion, blurred vision, headache, tingling, or "walking on cotton". Moreover, some patients with gait disturbances and no abnormal cephalic sensations will describe their problem as "dizziness". A careful history is necessary to determine exactly what a patient who states, "Doctor, I'm dizzy", is experiencing [1].

After eliminating the misleading symptoms such as confusion, "dizziness" usually means either faintness (analogous to the feelings that precede syncope) or vertigo (an illusory or hallucinatory sense of environmental or self-movement). In other instances, neither of these terms accurately describes a patient's symptoms, and the explanation may only become apparent when the neurologic examination reveals spasticity, parkinsonism, or other ambulation disturbances as the cause of the complaint. Operationally, dizziness is classified into four categories:

1) faintness,

2) vertigo,

3) miscellaneous head sensations,

4) gait disturbances.

Faintness (syncope) is a loss of consciousness secondary to cerebral ischemia, more specifically ischemia to the brainstem. Prior to the actual faint, there are often prodromal symptoms (faintness) reflecting ischemia to a degree insufficient to impair consciousness [13].

Vertigo is a hallucination of self- or environmental movement, most commonly a feeling of spinning, usually due to a disturbance in the vestibular system. The end organs of this system, situated in the bony labyrinths of the inner ears, consist of the three semicircular canals and the otolithic apparatus (utricle and saccule) on each side. The canals transduce angular acceleration, while the otoliths transduce linear

acceleration and static gravitational forces, the latter providing a sense of head position in space. The neural output of the end organs is conveyed to the vestibular nuclei in the brainstem via the eighth cranial nerve. The principal projections from the vestibular nuclei are to the nuclei of cranial nerves III, IV, and VI the spinal cord, the cerebral cortex, and the cerebellum. The vestibuloocular reflex (VOR) serves to maintain visual stability during head movement and depends on direct projections from the vestibular nuclei to the VI cranial nerve (abducens) nuclei in the pons and, via the medial longitudinal fasciculus, to the III (oculomotor) and IV (trochlear) cranial nerve nuclei in the midbrain. These connections account for the nystagmus (to-and-fro oscillation of the eyes) that is an almost invariable accompaniment of vestibular dysfunction. The vestibulospinal pathways assist in the maintenance of postural stability. Projections to the cerebral cortex, via the thalamus, provide conscious awareness of head position and movement. The vestibular nerves and nuclei project to areas of the cerebellum (primarily the flocculus and nodulus) that modulate the VOR [1].

The vestibular system is one of three sensory systems subserving spatial orientation and posture; the other two are the visual system (retina to occipital cortex) and the somatosensory system that conveys peripheral information from skin, joint, and muscle receptors. The three stabilizing systems overlap sufficiently to compensate (partially or completely) for each other's deficiencies. Vertigo may represent either physiologic stimulation or pathologic dysfunction in any of the three systems.

Physiologic Vertigo occurs when:

1) the brain is confronted with a mismatch among the three stabilizing sensory systems;

2) the vestibular system is subjected to unfamiliar head movements to which it has never adapted, such as in seasickness;

3) unusual head/neck positions, such as the extreme extension when painting a ceiling [5].

Intersensory mismatch explains carsickness, height vertigo, and the visual vertigo most commonly experienced during motion picture chase scenes; in the latter, the

visual sensation of environmental movement is unaccompanied by concomitant vestibular and somatosensory movement cues. Space sickness, a frequent transient effect of active head movement in the weightless zero-gravity environment, is another example of physiologic vertigo.

Pathologic Vertigo results from lesions of the visual, somatosensory, or vestibular systems. Visual vertigo is caused by new or incorrect spectacles or by the sudden onset of an extraocular muscle paresis with diplopia; in either instance, CNS compensation rapidly counteracts the vertigo. Somatosensory vertigo, rare in isolation, is usually due to a peripheral neuropathy that reduces the sensory input necessary for central compensation when there is dysfunction of the vestibular or visual systems [8].

The most common cause of pathologic vertigo is vestibular dysfunction. The vertigo is frequently accompanied by nausea, jerk nystagmus, postural unsteadiness, and gait ataxia. Since vertigo increases with rapid head movements, patients tend to hold their heads still.

Labyrinthine dysfunction causes severe rotational or linear vertigo. When rotational, the hallucination of movement, whether of environment or self, is directed away from the side of the lesion. The fast phases of nystagmus beat away from the lesion side, and the tendency to fall is toward the side of the lesion.

When the head is straight and immobile, the vestibular end organs generate a tonic resting firing frequency that is equal from the two sides. With any rotational acceleration, the anatomic positions of the semicircular canals on each side necessitate an increased firing rate from one and a commensurate decrease from the other. This change in neural activity is ultimately projected to the cerebral cortex, where it is summed with inputs from the visual and somatosensory systems to produce the appropriate conscious sense of rotational movement [13].

The cessation of movement, the firing frequencies of the two end organs reverse: the side with the initially increased rate decreases, and other side increases. A sense of rotation in the opposite direction is experienced; since there is no actual head movement, this hallucinatory sensation is vertigo. Any disease state that changes the

firing frequency of an end organ, producing unequal neural input to the brainstem and ultimately the cerebral cortex, causes vertigo. The symptom can be conceptualized as the cortex inappropriately interpreting the abnormal neural input from the brainstem as indicating actual head rotation. Transient abnormalities produce short-lived symptoms. With a fixed unilateral deficit, central conpensatory mechanisms ultimately diminish the vertigo. Since compensation depends on the plasticity of connections between the vestibular nuclei and the cerebellum, patients with brainstem or cerebellar disease have diminished adaptive capacity, and symptoms may persist indefinitely. Compensation is always inadequate for severe fixed bilateral lesions despite normal cerebellar connections: these patients are permanently symptomatic [14].

Acute unilateral labyrinthine dysfunction is caused by infection, trauma, and ischemia. Often, no specific etiology is uncovered, and the nonspecific terms acute labyrinthitis, acute peripheral vestibulopathy, or vestibular neuritis are used to describe the event. It is impossible to predict whether a patient recovering from the first bout of vertigo will have recurrent episodes.

Acute bilateral labyrinthine dysfunction is usually the result of toxins such as drugs or alcohol. The most common offending drugs are the aminoglycoside antibiotics.

Schwannomas involving the VIII cranial nerve (acoustic neuroma) grow slowly and produce such a gradual reduction of labyrinthine output that central compensatory mechanisms can prevent or minimize the vertigo; auditory symptoms of hearing loss and tinnitus are the most common manifestations. While lesions of the brainstem or cerebellum can cause acute vertigo, associated signs and symptoms usually permit distinction from a labyrinthine etiology (Table 2). However, labyrinthine ischemia may be the sole manifestation of vertebrobasilar insufficiency. Occasionally, an acute lesion of the vestibulocerebellum may present with monosymptomatic vertigo indistinguishable from a labyrinthopathy [3].

Table 2

Differentiation of Peripheral and Central Vertigo

Sign or symptom	Peripheral (Labyrinth)	Central (Brainstem or Cerebellum)
Direction of associated nystagmus	Unidirectional; fast phase opposite lesion*	Bidirectional or unidirectional
Purely horizontal nystagmus without torsional component	Uncommon	Common
Vertical or purely torsional nysagmus	Never present	May be present
Visual fixation	Inhibits nystagmus and vertigo	No inhibition
Severity of vertigo	Marked	Often mild
Direction of spin	Toward fast phase	Variable
Direction of fall	Toward slow phase	Variable
Duration of symptoms	Finite (minutes, days, weeks) but recurrent	May be chronic
Tinnitus and/or deafness	Often present	Usually absent
Associated central abnormalities	None	Extremely common
Common causes	Infection (labyrinthitis), Meniere's, neuronitis, ischemia, trauma, toxin	Vascular, demyelinating, neoplasm

- Direction of associated nystagmus
- Purely horizontal nystagmus without torsional component
- Vertical or purely torsional nysagmus
- Visual fixation
- Severity of vertigo

- Direction of spin
- Direction of fall
- Duration of symptoms
- Tinnitus and/or deafness
- Associated central abnormalities
- Common causes
- Unidirectional; fast phase opposite lesion*
- Uncommon
- Never present
- Inhibits nystagmus and vertigo
- Marked
- Toward fast phase
- Toward slow phase
- Finite (minutes, days, weeks) but recurrent
- Often present
- None
- Infection (labyrinthitis), Meniere's, neuronitis, ischemia, trauma, toxin
- Bidirectional or unidirectional
- Common
- May be present
- No inhibition
- Often mild Variable Variable May be chronic
- Usually absent
- Extremely common
- Vascular, demyelinating, neoplasm

* In Meniere's disease, the direction of the fast phase is variable

Recurrent unilateral labyrinthine dysfunction, in association with signs and symptoms of cochlear disease (progressive hearing loss and tinnitus), is usually due to Meniere's disease. When auditory manifestations are absent, the term vestibular neuronitis denotes recurrent monosymptomatic vertigo. TIAs of the posterior cerebral circulation (vertebrobasilar insufficiency) very infrequently cause recurrent vertigo without concomitant motor, sensory, visual, cranial nerve, or cerebellar signs [5].

Positional vertigo is precipitated by a recumbent head position, either to the right or to the left. Benign paroxysmal positional (or positioning) vertigo (BPPV) is particularly common. Although the condition may be due to head trauma, usually no precipitating factors are identified. It generally abates spontaneously after weeks or months. The vertigo and accompanying nystagmus have a distinct pattern of latency, fatigability, and habituation that differs from the less common central positional vertigo (Table 3) due to lesions in and around the fourth ventricle. Moreover, the pattern of nystagmus in BPPV is distinctive. The lower eye displays a large-amplitude torsional nystagmus, and the upper eye has a lesser degree of torsion combined with upbearing nystagmus. If the eyes are directed to the upper ear, the vertical nystagmus in the upper eye increases in amplitude.

Vestibular epilepsy, vertigo secondary to temporal lobe epileptic activity, is rare and almost always intermixed with other epileptic manifestations [1].

Psychogenic vertigo, usually a concomitant of agoraphobia (fear of large open spaces, crowds, or leaving the safety of home), should be suspected in patients so "incapacitated" by their symptoms that they adopt a prolonged housebound status. Despite their discomfort, most patients with organic vertigo attempt to function. Organic vertigo is accompanied by nystagmus; a psychogenic etiology is almost certain when nystagmus is absent during a vertiginous episode.

Evaluation of patients with pathologic vestibular vertigo depends on whether a central etiology is suspected (Table 2). If so, magnetic resonance imaging of the head is mandatory. Such an examination is rarely helpful in cases of recurrent

monosymptomatic vertigo with a normal neurologic examination. Typical BPPV requires no investigation after the diagnosis is made (Table 3).

Vestibular function tests serve to:

1) demonstrate an abnormality when the distinction between organic and psychogenic is uncertain,

2) establish the side of the abnormality,

3) distinguish between peripheral and central etiologies [8].

The standard test is electronystagmography, where warm and cold water (or air) are applied, in a prescribed fashion, to the tympanic membranes, and the slow-phase velocities of the resultant nystagmus from the right and left ears are compared. A velocity decrease from one side indicates hypofunction ("canal paresis"). An inability to induce nystagmus with ice water denotes a "dead labyrinth". Some institutions have the capability of quantitatively determining various aspects of the vestibuloocular reflex using computer-driven rotational chairs and precise oculographic recording of the eye movements.

Table 3

Benign Paroxysmal Positional Vertigo (BPPV) and Central Positional Vertigo

Features	**BPPV**	**Central**
Latency*	3-40 s	None: immediate vertigo and nystagmus
Fatigability+	Yes	No
Habituation++	Yes	No
Intensity of vertigo	Severe	Mild
Reproducibility§	Variable	Good

* Time between attaining head position and onset of symptoms,

+Disappearance of symptoms with maintenance of offending position,

++Lessening of symptoms with repeated trials.

§ Likelihood of symptom production during any examination session

Treatment

Treatment of acute vertigo consists of bed rest and vestibular suppressant drugs such as:

- antihistaminics (meclizine, dimenhydrinate, promethazine),
- centrally acting anticholinergics (scopolamine),
- tranquilizer with GABA-ergic effects (diazepam).

If the vertigo persists beyond a few days, most authorities advise ambulation in an attempt to induce central compensatory mechanisms, despite the short-term discomfiture to the patient. Chronic vertigo of labyrinthine origin may be treated with a systematized exercise program to facilitate compensation [1].

Prophylactic measures to prevent recurrent vertigo are variably effective. Antihistamines are commonly utilized. Meniere's disease may respond to a very low salt diet (1 g/day). Persisting (beyond 4 to 6 weeks) BPPV responds dramatically to specific exercise programs.

There are a variety of inner ear surgical procedures for all forms of refractory chronic or recurrent vertigo, but these are only rarely necessary [5].

Miscellaneous Head Sensations

This designation is used, primarily for purposes of initial classification, to describe dizziness that is neither faintness nor vertigo. Cephalic ischemia or vestibular dysfunction may be of such low intensity that the usual symptomatology is not clearly identified. For example, a small decrease in blood pressure or a slight vestibular imbalance may cause sensations different from distinct faintness or vertigo but that may be identified properly during provocative testing techniques. Other causes of dizziness in this category are hyperventilation syndrome, hypoglycemia, and the somatic symptoms of a clinical depression; these patients should have normal neurologic examinations and vestibular function tests.

Gait Disturbances. Some individuals with gait disorders complain of dizziness despite the absence of vertigo or other abnormal cephalic sensations. The causes include peripheral neuropathy, myelopathy, spasticity, parkinsonian rigidity, and

cerebellar ataxia. In this context, the term dizziness is being used to describe disturbed mobility. There may be mild associated lightheadedness, particularly with impaired sensation from the feet or poor vision; this is known as multiple-sensory-defect dizziness and occurs in elderly individuals who complain of dizziness only during ambulation. Decreased position sense (secondary to neuropathy or myelopathy) and poor vision (from cataracts or retinal degeneration) create an overreliance on the aging vestibular apparatus. A less precise, but sometimes comforting, designation is benign dysequilibrium of aging [8].

Approach to the Patient

The most important diagnostic tool is a careful history focused on the meaning of "dizziness" to the patient. Is it faintness? Is there a sensation of spinning? If either of these is affirmed and the neurologic examination is normal, appropriate investigations for the multiple etiologies of cephalic ischemia or vestibular dysfunction are undertaken.

When the meaning of "dizziness" is uncertain, provocative tests may be helpful. These office procedures simulate either cephalic ischemia or vestibular dysfunction. Cephalic ischemia is obvious if the dizziness is duplicated during orthostatic hypotension. Further provocation involves the Valsalva maneuver, which decreases cerebral blood flow and should reproduce ischemic symptoms [5].

The simplest provocative test for vestibular dysfunction is rapid rotation and abrupt cessation of movement in a swivel chair. This always induces vertigo that the patients can compare with their symptomatic dizziness. The intense induced vertigo may be unlike the spontaneous symptoms, but shortly thereafter, when the vertigo has all but subsided, lightheadedness supervenes that may be identified as "my dizziness". When this occurs, the dizzy patient, originally classified as suffering from "miscellaneous head sensations", is now properly diagnosed as having mild vertigo secondary to a vestibulopathy.

Patients with symptoms of positional vertigo should be appropriately tested (Table 3); positional testing is more sensitive with special spectacles that preclude visual fixation (Frenzel lenses).

A final provocative test, requiring the use of Frenzel lenses, is vigorous head shaking in the horizontal plane for about 10 s. If nystagmus develops after the shaking stops, even in the absence of vertigo, vestibular dysfunction is demonstrated. The maneuver can then be repeated in the vertical plane. If the provocative tests establish the dizziness as a vestibular symptom, the previously described evaluation of vestibular vertigo is undertaken.

Hyperventilation is the cause of dizziness in many anxious individuals; tingling of the hands and face may be absent. Forced hyperventilation for 1 min is indicated for patients with enigmatic dizziness and normal neurologic examinations. Similarly, depressive symptoms (which patients usually insist are "secondary" to the dizziness) must alert the examiner to a clinical depression as the cause, rather than the effect, of the dizziness [3].

CNS disease can produce dizzy sensations of all types. Consequently, a neurologic examination is always required even if the history or provocative tests suggest a cardiac, peripheral vestibular or psychogenic etiology. Any abnormality on the neurologic examination should prompt appropriate neurodiagnostic studies.

ACUTE CONFUSIONAL STATES AND COMA

Confusionai states and coma are among the most common problems in general medicine. It is estimated that over 5% of admissions to the emergency ward of large municipal hospitals are due to diseases that cause a disorder of consciousness. Because a clouding of consciousness (confusion) cannot easily be separated from a diminished level of consciousness (drowsiness, stupor, and coma) and the two are produced by many of the same medical disorders, these conditions are presented here [3].

Although the interpretation of consciousness is a psychological and philosophical matter, the distinction between level of consciousness, or wakefulness, and content of consciousness, or awareness, has neurologic significance. Wakefulness-alertness is maintained by a system of upper brainstem and thalamic neurons, the reticular activating system (RAS), and its broad connections to the cerebral hemispheres. Therefore, reduced wakefulness results from depression of the neuronal activity in either the cerebral hemispheres or in the RAS. Awareness and thinking are dependent on integrated and organized thoughts, subjective experiences, emotions, and mental processes, each of which resides to some extent in anatomically defined regions of the brain. Self-awareness requires that the organism senses this personal stream of thoughts and emotional experiences. The inability to maintain a coherent sequence of thoughts, accompanied usually by inattention and disorientation, is the best definition of confusion and is a disorder of the content of consciousness [1].

The unnatural condition of reduced alertness and lessened responsiveness is a continuum that in extreme form characterizes the deep sleeplike state from which the patient cannot be aroused, called coma.

Drowsiness is a disorder that simulates light sleep from which the patient can be easily aroused by touch or noise and can maintain alertness for some time.

Stupor defines a state in which the patient can be awakened only by vigorous stimuli, and an effort to avoid uncomfortable or aggravating stimulation is displayed. As already indicated, both drowsiness and stupor are usually attended by some degree

of mental confusion. Verbal responses in these states are therefore incorrect, slow, or absent during periods of arousal [3].

Coma indicates a state from which the patient cannot be aroused by stimulation, and no purposeful attempt is made to avoid painful stimuli.

In clinical practice these terms must be supplemented by a narrative description of the behavioral state of the patient and of responses evoked by various stimuli precisely as they are observed at the bedside. Such descriptions are preferable to ambiguous summary terms such as semicoma or obtundation, the definitions of which differ between observers [5].

The confusion is a behavioral state of reduced mental clarity, coherence, comprehension, and reasoning. Inattention and disorientation are the main early signs; however, as an acute confusional state worsens there is deterioration in memory, perception, comprehension, problem solving, language, praxis, visuo-spatial function, and various aspects of emotional behavior that are each identified with particular regions of the brain. Early in the process it is difficult to know if these complex mental functions are reduced solely as a result of the pervasive defect in attention, but global cortical dysfunction is expected from the metabolic diseases and pharmacologic agents that are the most common sources of the acute confusional state. When there is in addition to confusion an element of drowsiness, the patient is said to have an encephalopathy.

Confusion may be a feature of a dementing illness, in which case the chronicity of the process and often a disproportionate effect on memory distinguish it from acute confusion. The confusional state may also derive from a single cortical deficit in higher mental function such as impaired language comprehension, loss of memory, or lack of appreciation of space, in which case each state is defined by the dominant behavioral change (namely, aphasia, dementia, and agnosia) rather than characterizing the state as confusion [3].

The drowsiness caused by systemic metabolic changes or by brain lesions is typically accompanied by confusion (encephalopathy). In these instances the primary

problem that is causing a diminished level of consciousness should be addressed. A difficult circumstance arises when a process that ultimately leads to drowsiness or stupor begins with confusion or delirium in a fully awake patient.

The confused patient is usually subdued, not inclined to speak, and is inactive physically. In certain cases confusion is accompanied by illusions (misperceptions of environmental sight, sound, or touch) or hallucinations (spontaneous endogenous perceptions). While psychiatrists use the term delirium interchangeably with confusion, neurologists prefer to reserve it as a description for an agitated, hypersympathotonic, hallucinatory state most often due to alcohol or drug withdrawal or to hallucinogenic drugs [1].

Coma-like syndromes and related states

Coma is characterized by complete unarousability. Several other syndromes render patients apparently unresponsive or insensate but are considered separately because of their special significance.

▪The vegetative state, an unfortunate term, describes patients who were earlier comatose but whose eyelids have after a time opened, giving the appearance of wakefulness. There may be yawning, grunting, and random limb and head movements, but there is an absolute absence of response to commands and an inability to communicate, in essence, an "awake coma". There are accompanying signs of extensive damage to both cerebral hemispheres, i.e., Babinski signs, decerebrate or decorticate limb posturing, and absent response to visual stimuli. Autonomic nervous system functions such as cardiovascular, thermoregulatory, and neuroendocrine control are preserved and may be subject to periods of overactivity. The vegetative state results from global damage to the cerebral cortex, most often from cardiac arrest or head injury [1].

▪Akinetic mutism, refers to a partially or fully awake patient who when unstimulated remains immobile and silent. The state may result from hydrocephalus, from masses in the region of the III ventricle, or from large bilateral lesions in the

cingulate gyrus or other portions of both frontal lobes. Lesions in the periaqueductal or low diencephalic regions may cause a similar state.

▪Abulia can be viewed as a mild form of akinetic mutism with the same anatomic origins. The abulic patient is hypokinetic and slow to respond but generally gives correct answers. It is typical to halt while reciting numbers or sequential calculations and, with a delay, to resume correctly.

▪The locked-in state describes a pseudocoma, in which patients are awake but de-efferented, i.e., have no means of producing speech or limb, face, or pharyngeal movements. Infarction or hemorrhage of the ventral pons, which transects all descending corticospinal and corticobulbar pathways are the usual causes. The RAS arousal system, vertical eye movements, and lid elevation remain unimpaired. Such eye movements can be used by the patient to signal to the examiner. A similar awake state simulating unresponsiveness may occur as a result of total paralysis of limb, ocular, and oropharyngeal musculature in severe cases of acute Guillain-Barre syndrome (a peripheral nerve disease). Unlike brainstem stroke, vertical eye movements are not selectively spared [5].

Certain psychiatric states can mimic coma by producing an apparent unresponsiveness.

▪Catatonia is a peculiar hypomobile syndrome associated with major psychosis. In the typical form patients appear awake with eyes open but make no voluntary or responsive movements, although they blink spontaneously and may not appear distressed. It is characteristic but not invariable to have a "waxy flexibility", in which limbs maintain their posture when lifted by the examiner. Upon recovery, such patients have some memory of events that occurred during their catatonic stupor. Patients with hysterical or conversion pseudocoma show signs that indicate voluntary attempts to appear comatose, though it may take some ingenuity on the part of the examiner to demonstrate these. Eyelid elevation is actively resisted; blinking occurs to a visual threat when the lids are held open, and the eyes move concomitantly with head rotation, all signs belying brain damage [8].

Anatomic correlates of consciousness

A normal level of consciousness (wakefulness) depends upon activation of the cerebral hemispheres by neurons located in the brainstem RAS. Both of these components and the connections between them must be preserved for normal consciousness to be maintained. The principal causes of coma are therefore:

1) widespread damage in both hemispheres from ischemia, trauma, or other less common brain diseases;

2) suppression of cerebral function by extrinsic drugs, toxins, or hypoxia or by internal metabolic derangements such as hypoglycemia, azotemia, hepatic failure, or hypercalcemia;

3) brainstem lesions that cause proximate damage to the RAS [1].

The RAS is a physiologic system contained within the rostral portion of the reticular formation; it consists of neurons located bilaterally in the medial tegmental gray matter of the brainstem that extends from the medulla to the diencephalon. Animal experiments and human clinicopathologic observations have established that the region of the reticular formation that is of critical importance for maintaining wakefulness extends from the rostral pons to the caudal diencephalon. A practical consideration follows: Destructive lesions that produce coma also affect adjacent brainstem structures of the upper pons, midbrain, and diencephalon that are concerned with pupillary function and eye movements. Abnormalities in these systems provide convenient, albeit indirect evidence of direct brainstem damage as the source of coma. Lesions confined to the cerebral hemispheres do not immediately affect the brainstem RAS, although secondary dysfunction of the upper brainstem often results from compression by a mass in a cerebral hemisphere (transtentorial herniation) [3].

Brainstem RAS neurons project rostrally to the cortex, primarily via thalamic relay nuclei that exert a tonic influence on the activity of the cerebral cortex. Experimental work in primates suggests that the brainstem RAS affects the level of consciousness by suppressing the activity of the nonspecific nuclei that, in turn, have a predominantly inhibitory effect on the cortex, but this is an oversimplification. It is

believed that high-frequency (30 to 40 Hz) rhythms synchronize cortical and thalamic neurons during wakefulness. The basis of behavioral arousal by environmental stimuli (somesthetic, auditory, and visual) is related to the rich innervation that the RAS receives from these sensory systems [8].

The relays between the RAS and the thalamic and cortical areas are accomplished by neurotransmitters. Of these, the influences on arousal of acetylcholine and biogenic amines have been studied most extensively. Cholinergic fibers connect the midbrain to other areas of the upper brainstem, thalamus, and cortex. Serotonin and norepinephrine also subserve important functions in the regulation of the sleep-wake cycle. Their roles in arousal and coma have not been clearly established, although the alerting effects of amphetamines are likely to be mediated by catecholamine release.

A reduction in alertness is related in a semiquantitative way to the total mass of damaged cortex or RAS and is not focally represented in any region of the hemispheres, with the exception that large, acute, and purely unilateral hemispheral lesions, particularly on the left, may cause transient drowsiness even in the absence of damage to the opposite hemisphere or RAS. Hemispheral lesions in most instances cause coma indirectly when a large mass in one or both hemispheres secondarily compresses the upper brainstem and diencephalic RAS. This is most typical of cerebral hemorrhages and rapidly expanding tumors. The magnitude of decrease in alertness is also related to the rapidity of onset of the cortical dysfunction or RAS compression [13].

This secondary compressive effect has led to a concept of transtentorial herniation with progressive brainstem dysfunction to explain the neurologic signs that accompany coma from supratentorial mass lesions. Herniation refers to displacement of brain tissue away from a mass, past a less mobile structure such as the dura, and into a space that it normally does not occupy. The common herniations seen at postmortem examinations are transfalcial (displacement of the cingulate gyrus under the falx in the anterior midline), transtentorial (medial temporal lobe displacement into the tentorial opening), and foraminal (the cerebellar tonsils forced into the foramen magnum). Uncal transtentorial herniation, or impaction of the anterior medial temporal gyrus into the

anterior portion of the tentorial opening, causes compression of the III nerve with pupillary dilation. Subsequent coma may be due to midbrain compression by the parahippocampal gyrus. Central transtentorial herniation denotes symmetric downward movement of the upper diencephalon (thalamic region) through the tentorial opening in the midline and is heralded by miotic pupils and drowsiness. These shifts in brain are thought to cause a progression of rostral to caudal brainstem compression of first the midbrain, then the pons, and finally the medulla, leading to the sequential appearance of neurologic signs corresponding to the level damaged and to progressively diminished alertness. However, many patients with supratentorial masses do not follow these stereotypic patterns; for example, an orderly progression of signs from midbrain to medulla is often bypassed in catastrophic lesions where all brainstem functions are lost almost simultaneously, furthermore, drowsiness and stupor typically occur with moderate lateral shifts at the level of the diencephalon when there is only minimal vertical displacement of structures near the tentorial opening and well before downward herniation is evident on computed tomogaphy (CT) scan or magnetic resonance imaging (MRI) [5].

Pathophysiology of coma and confusion

Coma of metabolic origin is produced by interruption of energy substrate delivery (hypoxia, ischemia, and hypoglycemia) or by alteration of the neurophysiology responses of neuronal membranes (drug or alcohol intoxication, toxic endogenous metabolites, anesthesia, or epilepsy). These same metabolic abnormalites can cause widespread neuronal dysfunction in the cortex that reduces all aspects of mentation and results in an acute confusional state. In this way, acute confusion and coma can be viewed as a continuum in metabolic encephalopathy [1].

The neurons of the brain are dependent on cerebral blood flow (CBF), oxygen, and glucose. CBF is approximately 75 mL per 100 g/min in gray matter and 30 mL per 100 g/min in white matter (mean 55 mL per 100 g/min). Oxygen consumption is 3,5 mL per 100 g/min, and glucose consumption is 5 mg per 100 g/min. Brain stores of glucose provide energy for approximately 2 min after blood flow is interrupted, and

consciousness is lost within 8 to 10 s. Hypoxia and ischemia simultaneously exhaust glucose more rapidly. The EEG becomes diffusely slowed (typical of metabolic encephalopathies) when mean CBF is below 25 mL per 100 g/min; at 15 mL per 100 g/min, all recordable brain electrical activity ceases. If all other conditions such as temperature and arterial oxygenation remain normal, CBF less than 10 mL per 100 g/min causes irreversible brain damage. The rapidity of the development of ischemia and its duration are also important determinants of irreversible damage [13].

Confusion and coma due to hyponatremia, hyperosmolarity, hypercapnia, hypercalcemia, and the encephalopathies of hepatic and renal failure are associated with a variety of metabolic derangements of neurons and astrocytes. The reversible toxic effects of these conditions on the brain are not understood but may, in different cases, impair energy supplies, change ion fluxes across neuronal membranes, and cause neurotransmitter abnormalities. In some instances there are specific morphologic changes of nerve cells. For example, the high brain ammonia concentration associated with hepatic coma interferes with cerebral energy metabolism and the Na^+, K^+-ATPase pump, increases the number and size of astrocytes, causes increased concentrations of potentially toxic products of ammonia metabolism, and results in abnormalities of neurotransmitters, including possible "false" neurotransmitters, which may act competitively at receptor sites. Ammonia or other metabolites also may bind to benzodiazepine - gamma-aminobutyric acid receptors to cause central nervous system (CNS) depression by an endogenous mechanism. Furthermore, these changes are not mutually exclusive [11].

The mechanism of the encephalopathy of renal failure is also poorly understood. Unlike ammonia, urea itself does not produce CNS toxicity. A multifactorial cause has been proposed including an increased permeability of the blood-brain barrier to toxic substances such as organic acids and an increase in brain calcium or cerebrospinal fluid (CSF) phosphate content.

Abnormalities of osmolarity are involved in the coma and seizures caused by several systemic medical disorders, including diabetic ketoacidosis, the nonketotic

hyperosmolar state, and hyponatremia. Brain water volume correlates best with level of consciousness in hyponatremic-hypoosmolar states, but other factors probably also play a role. Sodium levels below 125 mmol/L cause acute or subacute confusion and below 115 mmol/L are associated with coma and convulsions, depending on the rapidity with which the hyponatremia develops. Serum osmolarity is generally above 350 mosmol/L in hyperosmolar coma [1].

The large group of drugs that depress the CNS, anesthetics, and some endogenous toxins appear to produce coma by suppression of both the RAS and the cerebral cortex. For this reason, combinations of cortical and brainstem signs occur in drug overdose and some other metabolic comas, which may lead to a specious diagnosis of structural brainstem damage.

Although all metabolic derangements alter neuronal electrophysiology, the only primary disturbance of brain electrical activity encountered in clinical practice is epilepsy. Continuous, generalized electrical discharges of the cortex (seizures) are associated with coma even in the absence of epileptic motor activity (convulsions). Coma following seizures, termed the postictal state, may be due to exhaustion of energy metabolites or be secondary to locally toxic molecules produced during the seizures. Recovery from postictal unresponsiveness occurs when neuronal metabolic balance is restored. The postictal state produces a pattern of continuous, generalized slowing of the background EEG activity similar to that of metabolic encephalopathy [3].

Approach to the Patient

In Coma: The diagnosis and acute management of coma depend on knowledge of its main causes in clinical practice, an interpretation of certain clinical signs, notably the brainstem reflexes, and the efficient use of diagnostic tests. It is common knowledge that acute respiratory and cardiovascular problems should be attended to prior to neurologic diagnosis. A complete medical evaluation, except for the vital signs, funduscopy, and examination for nuchal rigidity, may be deferred until the neurologic evaluation has established the severity and nature of coma [8].

History. In many cases, the cause of coma is immediately evident (e.g., trauma, cardiac arrest, or known drug ingestion). In the remainder, historical information about the onset of coma is often sparse. The most useful historical points are:

1) the circumstances and temporal profile of the onset of neurologic symptoms;

2) the precise details of preceding neurologic symptoms (confusion, weakness, headache, seizures, dizziness, diplopia, or vomiting);

3) the use of medications, illicit drugs, or alcohol;

4) a history of liver, kidney, lung, heart, or other medical disease.

Telephone calls to family and observers on the scene are an important part of the initial evaluation. Ambulance attendants often provide the best information in an enigmatic case [5].

Physical examination and general observations. The temperature, pulse, respiratory rate and pattern, and blood pressure should be measured. Fever suggests systemic infection, bacterial meningitis, encephalitis, or a brain lesion that has disturbed the temperature-regulating centers. High body temperature, 42° to 44°C, associated with dry skin should arouse the suspicion of heat stroke or anticholinergic drug intoxication. Hypothermia is observed with bodily exposure to lowered environmental temperature; alcoholic, barbiturate, sedative, or phenothiazine intoxication; hypoglycemia; peripheral circulatory failure; or hypothyroidism. Hypothermia itself causes coma only when the temperature is below 31°C. Aberrant respiratory patterns that may reflect brainstem disorders are discussed below. A change of pulse rate combined with hyperventilation and hypertension may signal an increase in intracranial pressure [1]. Marked hypertension is a very helpful signature of hypertensive encephalopathy, cerebral hemorrhage, or hydrocephalus and occurs acutely, but to lesser degree, after head trauma. Hypotension is characteristic of coma from alcohol or barbiturate intoxication, internal hemorrhage, myocardial infarction, septicemia, and Addisonian crisis. The funduscopic examination is used to detect subarachnoid hemorrhage (subhyaloid hemorrhages), hypertensive encephalopathy (exudates, hemorrhages, vessel-crossing changes), and increased intracranial pressure

(papilledema). Generalized cutaneous petechiae suggest thrombotic thrombocytopenic purpura or a' bleeding diathesis associated with intracerebral hemorrhage [2].

General neurologic assessment. An exact description of spontaneous and elicited movements is of great value in establishing the level of neurologic dysfunction. The patient's state should be observed first without examiner intervention. The nature of respirations and spontaneous movements are noted. Patients who toss about, reach up toward the face, cross their legs, yawn, swallow, cough, or moan are closest to being awake. The only sign of seizures may be small excursion twitching of a foot, finger, or facial muscle. An outturned leg at rest or lack of restless movements on one side suggests a hemiparesis.

The terms decorticate and decerebrate rigidity, or "posturing", describe stereotyped arm and leg movements occurring spontaneously or elicited by sensory stimulation. Flexion of the elbows and wrists and arm supination (decortication) suggest severe bilateral damage in the hemispheres above the midbrain, whereas extension of the elbows and wrists with pronation (decerebration) suggests damage to the corticospinal tracts in the midbrain or caudal diencephalon. Arm extension with minimal leg flexion or flaccid legs has been associated with lesions in the low pons. These terms, however, have been adapted from animal work and cannot be applied with the same precision to coma in humans. Acute lesions of any type frequently cause limb extension regardless of location, and almost all extensor posturing becomes flexion as time passes, so posturing alone cannot be utilized to make an anatomic localization. Metabolic coma, especially after acute hypoxia, also may produce vigorous spontaneous extensor (decerebrate) rigidity. Posturing may coexist with purposeful limb movements, usually reflecting subtotal damage to the motor system. Multifocal myoclonus is almost always an indication of a metabolic disorder, particularly azotemia, anoxia, or drug ingestion. In a drowsy and confused patient bilateral asterixis is a certain sign of metabolic encephalopathy or drug ingestion [11].

Elicited movements and level of arousal. If the patient is not aroused by conversational voice, a sequence of increasingly intense stimuli is used to determine

the patient's best level of arousal and the optimal motor response of each limb. It should be recognized that the results of this testing may vary from minute to minute and that serial examinations are most useful. Nasal tickle with a cotton wisp is a strong arousal stimulus. Pressure on the knuckles or bony prominences is the preferred and humane form of noxious stimulus. Pinching the skin over the face, chest, or limbs which caused unsightly ecchymoses is not necessary [8].

Responses to noxious stimuli should be appraised critically. Abduction avoidance movement of a limb is usually purposeful and denotes an intact corticospinal system to that limb. Stereotyped posturing following stimulation of a limb indicates severe dysfunction of the corticospinal system. Adduction and flexion of the stimulated limbs may be reflex movements and imply corticospinal system damage. Brief clonic or twitching limb movements occur at the end of extensor posturing excursions and should not be mistaken for convulsions [2].

Brainstem reflexes are a key to localization of the lesion in coma. As a rule, coma associated with normal brainstem function indicates widespread and bilateral hemispheral disease or dysfunction. The brainstem reflexes that allow convenient examination are pupillary light responses, eye movements, both spontaneous and elicited, and respiratory pattern.

Pupillary reaction is examined with a bright, diffuse light and, if the response is absent, confirmed with a magnifying lens. Light reaction in pupils smaller than 2 mm is often difficult to appreciate, and excessive room lighting mutes pupillary reactivity. Symmetrically reactive round pupils (2,5 to 5 mm in diameter) usually exclude midbrain damage as the cause of coma. One enlarged (greater than 5 mm) and unreactive or poorly reactive pupil results either from an intrinsic midbrain lesion (on the same side) or, far more commonly, is secondary to compression or stretching of the III nerve by the secondary effects of a mass. Unilateral pupillary enlargement usually denotes an ipsilateral mass, but this sign occasionally occurs contralateral possibly by compression of the midbrain or III nerve against the opposite tentorial margin. Oval and slightly eccentric pupils accompany early midbrain - III nerve

compression. Bilaterally dilated and unreactive pupils indicate severe midbrain damage, usually from secondary compression by transtentorial herniation or from ingestion of drugs with anticholinergic activity [1]. The use of mydriatic eye drop by a previous examiner, self-administration by the patient, or direct ocular trauma may cause misleading pupillary enlargement. Reactive and bilaterally small but not pinpoint pupils (1 to 2,5 mm) are most commonly seen in metabolic encephalopathy or after deep bilateral hemispheral lesions such as hydrocephalus or thalamic hemorrhage. This has been attributed to dysfunction of sympathetic nervous system efferents emerging from the posterior hypothalamus. Very small but reactive pupils (less than 1 mm) characterize narcotic or barbiturate overdose but also occur with acute, extensive bilateral pontine damage, usually from hemorrhage. The response to naloxone and the presence of reflex eye movements distinguish these. The unilaterally small pupil of a Horner's syndrome is detected by failure of the pupil to enlarge in the dark. It is rare in coma but may occur ipsilateral to a large cerebral hemorrhage that affects the thalamus. Lid tone, tested by lifting the eyelids, palpating resistance to opening, and speed of closure, is reduced progressively as coma deepens [5].

Eye movements are the second foundation of physical diagnosis in coma because their examination permits an analysis of a large portion of the brainstem. The eyes are first observed by elevating the lids and noting the resting position and spontaneous movements of the globes. Horizontal divergence of the eyes at rest is normally observed in drowsiness. As patients either awaken or coma deepens, the ocular axes become parallel again. An adducted eye at rest indicates lateral rectus paresis (weakness) due to a VI nerve lesion, and when bilateral, it is often a sign of increased intracranial pressure. An abducted eye at rest, often accompanied by ipsilateral pupillary enlargement, indicates medial rectus paresis due to III nerve dysfunction. With few exceptions, vertical separation of the ocular axes, or skew deviation, results from pontine or cerebellar lesions.

Spontaneous eye movements in coma generally take the form of conjugate horizontal roving. This motion exonerates the midbrain and pons and has the same

meaning as normal reflex eye movements. Cyclic vertical downward movements are seen in specific circumstances. "Ocular bobbing" describes a brisk downward and slow upward movement of the globes associated with loss of horizontal eye movements and is diagnostic of bilateral pontine damage. "Ocular dipping" is a slower, arrhythmic downward movement followed by a faster upward movement in patients with normal reflex horizontal gaze and denotes diffuse anoxic damage to the cerebral cortex. The eyes may turn down and inward in thalamic and upper midbrain lesions [8].

"Doll's-eye," or oculocephalic, responses are reflex movements tested by moving the head from side to side or vertically, first slowly then briskly; eye movements are evoked in the opposite direction to head movement. These responses are generated by brainstem mechanisms originating in the labyrinths and cervical proprioceptors. They are normally suppressed by visual fixation mediated by the cerebral hemispheres in awake patients but appear as the hemispheres become suppressed or inactive. The neuronal pathways for reflex horizontal eye movements require integrity of the region surrounding the VI nerve nucleus and are yoked to the contralateral III nerve via the medial longitudinal fasciculus (MLF). Two disparate pieces of information are obtained from the reflex eye movements. First, in coma resulting from bihemispheral disease or metabolic or drug depression, the eyes move easily or "loosely" from side to side in a direction opposite to the direction of head turning. The ease with which the globes move toward the opposite side is a reflection of disinhibition of brainstem reflexes by damaged cerebral hemispheres. Second, conjugate oculocephalic movements demonstrate the integrity of brainstem pathways extending from the high cervical spinal cord and medulla, where vestibular and proprioceptive input from head turning originates, to the midbrain, at the level of the III nerve. Thus full and conjugate eye movements that are induced by the oculocephalic maneuver demonstrate the intactness of a large segment of brainstem and virtually exclude a primary lesion of the brainstem as the cause of coma [3].

Incomplete ocular adduction indicates an ipsilateral midbrain (III nerve) lesion or damage to the pathways mediating reflex eye movements in the MLF (i.e., internuclear

ophthalmoplegia). III nerve damage is usually associated with an enlarged pupil and horizontal ocular divergence at rest, whereas MLF lesions are unrelated to pupillary function and leave the globe in the primary position. Adduction of the globes is by nature more difficult to obtain than abduction, and subtle abnormalities in the doll's-eye maneuver should be interpreted with caution [2].

Caloric stimulation of the vestibular apparatus (oculovestibular response) is an adjunct to the oculocephalic test, acting as a stronger stimulus to reflex eye movements but giving fundamentally the same information. Irrigation of the external auditory canal with cool water causes convection currents in the endolymph of the labyrinths of the inner ear. An intact brainstem pathway from the labyrinths to the oculomotor nuclei of the midbrain is indicated, with brief latency, by tonic deviation of both eyes (lasting 30 to 120 s) to the side of cool-water irrigation. Bilateral conjugate eye movements therefore have similar significance as full oculocephalic responses. If the cerebral hemispheres are functioning properly, as in hysterical coma, an obligate rapid corrective movement is generated away from the side of tonic deviation. The absence of this nystagmus-like quick phase signifies that the cerebral hemispheres are damaged or suppressed [1].

Conjugate horizontal ocular deviation at rest or incomplete conjugate eye movements with head turning indicate damage in the pons on the side of the gaze paresis or frontal lobe damage on the opposite side. This phenomenon may be summarized by the following aphorism: The eyes look toward a hemispheral lesion and away from a brainstem lesion. It is usually possible to overcome the ocular deviation associated with frontal lobe damage by oculocephalic testing. Seizures also may cause aversive (opposite) eye deviation with rhythmic, jerky movements to the side of gaze. On rare occasions, the eyes may turn paradoxically away from the side of a deep hemispheral lesion ("wrong-way eyes"). In hydrocephalus with dilatation of the III ventricle, the globes frequently rest below the horizontal meridian. Two types of rapid rhythmic eye movements may occur in stupor or coma. Ocular myoclonus is a rapid horizontal oscillatory nystagmus usually associated with a similar movement of the

palate and due to damage to the central tegmental fasciculus, a longitudinal tract in the brainstem. Opsoclonus is an irregular, jerky, saccadic movement varying in direction those results from cerebellar lesions [5].

A major pitfall in coma diagnosis may occur when reflex eye movements are suppressed by drugs. The eyes then move with the head as it is turned as if the globes locked in place, thus spuriously suggesting brainstem damage. Overdoses of phenytoin, tricyclic antidepressants, and barbiturates are commonly implicated as well as, on occasion, alcohol, phenothiazines, diazepam, and neuromuscular blockers such as pancuronium. The presence of normal pupillary size and light reaction will distinguish most drug-induced comas from brainstem damage. Small to midposition, 1- to 3-mm nonreactive pupils may occur with very high serum levels of barbiturates or secondary to hydrocephalus [8].

Although the corneal reflexes are rarely useful alone, they may corroborate eye movement abnormalities because they also depend on the integrity of pontine pathways. By touching the cornea with a wisp of cotton, a response consisting of brief bilateral lid closure may be observed. The corneal response may be lost if the reflex connections between the V and VII cranial nerves within the pons are damaged. The normal efferent response is bilateral, with closure of both eyelids. CNS depressant drugs diminish or eliminate the corneal responses soon after the reflex eye movements become paralyzed but before the pupils become unreactive to light [1].

Respiration. Respiratory patterns have received much attention in coma diagnosis but are of inconsistent localizing value. Shallow, slow, but well-timed regular breathing suggests metabolic or drug depression. Rapid, deep (Kussmaul) breathing usually implies metabolic acidosis but also may occur with pontomesencephalic lesions. Cheyne-Stokes respiration in its classic cyclic form, ending with a brief apneic period, signifies mild bihemispheral damage or metabolic suppression and commonly accompanies light coma. Agonal gasps reflect bilateral lower brainstem damage and are well known as the terminal respiratory pattern of severe brain damage. In brain-dead patients, shallow respiratory-like movements with irregular, nonrepetitive back arching

may be produced by hypoxia and are probably generated by the surviving cervical spinal cord and lower medulla. Other cyclic breathing variations are not usually diagnostic of specific local lesions [5].

Acute Confusion is characterized by difficulty in maintaining a coherent stream of thinking and mental perfomance. This is manifested most obviously by inattention and disorietation, which in turn may generate difficulty with memory and all mental activities. Attention may be gauged by the clarity of and speed of response while the history is being taken but should also be examined by having the patient repeat strings of numbers (most adults easily retain 7 digits forward and 4 backward) or perform serial calculations that require holding the result of one calculation in a working memory in order to pursue the next step - the serial 3-from-30 subtraction test is the usual paradigm. Orientation and memory are tested by asking the patient in a forthright manner the date, inclusive of month, day, year, and day of week; the precise place; and some items of generally acknowledged and universally known information (the name of the President, a recent national catastrophe, the state capital). Further probing may be necessary to reveal a defect - why is the patient in the hospital; what is his or her address, zip code, telephone number, social security number? Problems of increasing complexity may be pursued but they give little more practical information once a confusional state has been established [13].

Evidence of drug ingestion should be sought on general physical examination. Other salient neurologic findings are the level of alertness, which typically fluctuates in acute cases; indications of focal damage of the cerebrum such as hemiparesis, hemianopia, and particularly aphasia; adventitious movements of myoclonus; or convulsions. The most pertinent sign of a metabolic encephalopathy is asterixis, which is an arrhythmic flapping tremor that is typically elicited by asking the patient to hold the arm out straight with the wrist fully extended. After a few seconds, a large jerking lapse in the posture of the hand occurs and then a rapid return to the original position. The same can be appreciated in any tonically held posture, even of the tongue, and in extreme form the movements may intrude on voluntary limb motion. Bilateral asterixis

always signifies a metabolic encephalopathy, for example, from hepatic failure or from drug ingestion, especially with anticonvulsants. Myoclonic jerking and tremor in an awake patient are typical of uremic encephalopathy or antipsychotic (butyrophone) drug ingestion.

The language of the confused patient may be disorganized and rambling, even to the extent of incorporating paraphasic words. These features, along with impaired comprehension that is due to inattention, may be mistaken for aphasia [3].

Distinguishing dementia from confusion is a great problem. The memory loss of dementia necessarily engenders a confusional state that varies in severity from hour to hour and day to day. Poor mental performance is derived mainly from incomplete recollection, inadequate access to names and ideas, and on the inability to retain new information, thus affecting orientation and factual knowledge; attention is preserved in the early stages of the process. Depending upon the nature of the dementing disease, there may be added specific deficits of language, praxis, visual-spatial performance, or a slowed frontal lobe state. Eventually dementia produces a chronic confusion with breakdown of all types of mental performance, and the distinction from confusion depends simply on the chronic nature of the condition [5].

Laboratory examination for acute confusion and coma

Four laboratory tests are used most frequently in the diagnosis of confusion and coma: chemical-toxicologic analysis of blood and urine, CT or MRI, EEG, and CSF examination.

▪Chemical blood determinations are made routinely to investigate metabolic, toxic, or drug-induced encephalopathies. The major metabolic aberrations encountered in clinical practice are those of electrolytes, calcium, blood urea nitrogen (BUN), glucose, plasma osmolarity, and hepatic dysfunction (NH_3). Toxicologic analysis is of great value in any case of coma where the diagnosis is not immediately clear. However, the presence of exogenous drugs or toxins, especially alcohol, does not ensure that other factors, particularly head trauma, may not also contribute to the clinical state. Ethanol levels in nonhabituated patients of 200 mg/dL generally cause confusion and impaired

mental activity and above 300 mg/dL are associated with stupor. The development of tolerance may allow the chronic alcoholic to remain awake at levels over 400 mg/dL.

▪The increased availability of CT and MRI has focused attention on causes of coma that are radiologically detectable (e.g., hemorrhages, tumors, or hydrocephalus). This approach, although at times expedient is imprudent because most cases of confusion and coma are metabolic or toxic in origin. The notion that a normal CT scan excludes anatomic lesions as the cause of coma is also erroneous. Early bilateral hemisphere infarction, small brainstem lesions, encephalitis, meningitis, mechanical shearing of axons as a result of closed head trauma, absent cerebral perfusion associated with brain death, sagittal sinus thrombosis, and subdural hematomas that are isodense to adjacent brain are some of the lesions that may be overlooked by CT. Even MRI may fail to demonstrate these processes early in their evolution. Nevertheless, in coma of unknown etiology, a CT or MRI scan should be obtained. In those cases in which the etiology is clinically apparent, these provide verification and define the extent of the lesion [1].

With acute mass lesions, 3 to 5 mm of horizontal displacement of the pineal body from the midline generally corresponds to drowsiness 5 to 8 mm corresponds to, stupor, and greater than 8 mm corresponds to coma. As a supratentorial mass enlarges, the opposite perimesencephalic cistern is first compressed from lateral movement of the brainstem, the ipsilateral cistern is widened, and finally, both are compressed from the lateral mass effect. The lateralventricle opposite the mass becomes enlarged as the III ventricle is compressed. These radiologic features of tissue shifts near the tentorial opening are helpful in correlating the clinical state with the progress of a mass lesion on scans. For technical reasons, MRI is difficult to perform in comatose patients, and it also does not demonstrate hemorrhages as well as CT [5].

▪The EEG is useful in metabolic or drug-induced confusional states but is rarely diagnostic in coma, with the exception of comas due to clinically unrecognized seizures, herpes virus encephalitis, and Creutzfeldt-Jakob disease. The amount of background slowing of the EEG is a useful gauge of the severity of any diffuse

encephalopathy. Predominant high-voltage slowing (delta-waves) in the frontal regions is typical of metabolic coma, as from hepatic failure and widespread fast (beta) activity implicates the effects of sedative drugs. A pattern of "alpha coma" is defined by widespread, invariant 8- to 12-Hz activity superficially resembling the normal alpha rhythm of waking but unresponsive to environmental stimuli. Alpha coma results from either high pontine or diffuse cortical damage and is associated with a poor prognosis. Coma due to persistent epileptic discharges that are not clinically manifested may be revealed by EEG recordings. Normal alpha activity on the EEG also may alert the clinician to the locked-in syndrome or a hysterical case. Computed on-line EEG analysis and evoked potential recordings (auditory and somatosensory) are useful additional methods for coma diagnosis and monitoring [1].

▪Lumbar puncture is now used more judiciously in cases of coma or confusion because the CT scan excludes intracerebral hemorrhages and most subarachnoid hemorrhages. The use of lumbar puncture in coma is limited to diagnosis of meningitis or encephalitis and instances of suspected subarachnoid hemorrhage in which the CT is normal. Lumbar puncture should not be deferred if meningitis is a strong clinical possibility. Xanthochromia is documented by spinning the CSF in a large tube and comparing the supernatant to water. This yellow coloration indicates preexisting blood in the CSF (or very high protein levels) and permits exclusion of a traumatic puncture. In addition, initial and final tubes should be inspected for a decrement in the number of erythrocytes, indicating traumatic puncture. Knowing the pressure within the subarachnoid space is of further help in interpreting abnormalities of the cell count and protein content of the CSF [13].

Differential diagnosis of confusion and coma

In most instances, confusion and coma are part of an obvious medical problem such as known drug ingestion, hypoxia, stroke, trauma, or liver or kidney failure. Attention is then appropriately focused on the primary illness. A complete listing of all diseases that cause confusion and coma would serve little purpose, since it would not aid diagnosis. Some general rules, however, are helpful. Illnesses that cause sudden or

acute coma are due to drug ingestion or to one of the catastrophic brain lesions - hemorrhage, trauma, hypoxia, or, rarely, acute basilar artery occlusion. Coma that appears subacutely is usually related to preceding medical or neurologic problems, including the secondary brain swelling that surrounds a preexisting lesion. Coma diagnosis, therefore, requires familiarity with the common intracerebral catastrophes. These may be summarized as follows:

1) basal ganglia and thalamic hemorrhage (acute but not instantaneous onset, vomiting, headache, hemiplegia, and characteristic eye signs);

2) subarachnoid hemorrhage (instantaneous onset, severe headache, neck stiffness, vomiting, third or sixth nerve lesions, transient loss of consciousness, or sudden coma with vigorous extensor posturing);

3) pontine hemorrhage (sudden onset, pinpoint pupils, loss of reflex eye movements and corneal responses, ocular bobbing, posturing, hyperventilation, and sweating);

4) cerebellar hemorrhage (occipital headache, vomiting, gaze paresis, and inability to stand);

5) basilar artery thrombosis (neurologic prodrome or warning spells, diplopia, dysarthria, vomiting, eye movement and corneal response abnormalities, and asymmetric limb paresis) [3].

The most common stroke, namely, infarction in the territory of the middle cerebral artery, does not cause coma acutely. The syndrome of acute hydrocephalus causing coma may accompany many intracranial catastrophes, particularly subarachnoid hemorrhage. Acute symmetric enlargement of both lateral ventricles causes headache and sometimes vomiting followed by drowsiness that may progress quickly to coma, with extensor posturing of the limbs, bilateral Babinski signs, small nonreactive pupils, and impaired vertical oculocephalic movements.

If the history and examination are not typical for any neurologic diagnosis and metabolic or drug causes are excluded, then information obtained from CT or MRI may be used as outlined in Table 4. The CT scan is useful to focus the differential diagnosis,

and because of its accuracy and general availability, the diagnoses that it facilitates are listed in the table. As mentioned earlier, the majority of medical causes of coma are established without a CT or with the study being normal [8].

Table 4

Approach to the Differential Diagnosis of Coma

NORMAL BRAINSTEM REFLEXES, NO LATERAL1ZING SIGNS

A. Bilateral hemispheral dysfunction without mass lesion (CT or MRI normal; primary test used for diagnosis is indicated in parentheses)

1. Drug-toxin ingestion (toxicologic analysis)
2. Endogenous metabolic encephalopathy (glucose, ammonia, calcium, osmolality, Poj, Pccv urea, sodium)
3. Shock, hypertensive encephalopathy
4. Meningitis (CSF analysis)
5. Nonherpetic viral encephalitis (CSF analysis)
6. Epilepsy (EEG)
7. Reye's syndrome (ammonia, increased intracranial pressure)
8. Fat embolism
9. Subarachnoid hemorrhage with normal CT (CSF analysis)
10. Creutzfeldt-Jakob disease (EEG)
11. Hysterical coma or catatonia

B. Anatomic lesions of hemisphere found by CT or MRI

1. Hydrocephalus
2. Bilateral subdural hematomas
3. Bilateral contusions, edema, or axonal shearing of hemispheres due to closed head trauma
4. Subarachnoid hemorrhage
5. Acute disseminated encephalomyelitis (CSF analysis)

NORMAL BRAINSTEM REFLEXES (WITH/WITHOUT UNILATERAL THIRD NERVE PALSY), LATERALIZING MOTOR SIGNS (CT OR MRI ABNORMAL)

A. Unilateral mass lesion

1. Cerebral hemorrhage (basal ganglia, thalamus)

2. Large infarction with surrounding brain edema
3. Herpes virus encephalitis (temporal lobe lesion)
4. Subdural or epidural hematoma
5. Tumor with edema
6. Brain abscess with edema
7. Vasculitis with multiple infarctions
8. Metabolic encephalopathy superimposed on preexisting focal lesions (i.e., stroke with hyperglycemia, hyponatremia, etc.)
9. Pituitary apoplexy

B. Asymmetric signs accompanied by diffuse hemispheral dysfunction

1. Metabolic encephalopathies with asymmetric signs (blood chemical determinations)
2. Isodense subdural hematoma (MRI, CT with contrast)
3. Thrombotic thrombocytopenic purpura (blood smear, platelet count)
4. Epilepsy with focal seizures or postictal state (EEG)

MULTIPLE BRAINSTEM REFLEX ABNORMALITIES

A. Anatomic lesions in brainstem

1. Pontine, midbrain hemorrhage
2. Cerebellar hemorrhage, tumor, abscess
3. Cerebellar infarction with brainstem compression
4. Mass in hemisphere causing advanced upper brainstem compression
5. Primary brainstem tumor, demyelination, or abscess
6. Traumatic brainstem contusion-hemorrhage

B. Brainstem dysfunction without mass lesion

1. Basilar artery thrombosis causing brainstem infarction (clinical signs, angiogram)
2. Severe drug overdose (toxicologic analysis)
3. Brainstem encephalitis
4. Basilar artery migraine

Coma after head trauma. Concussion is a common form of transient coma that results from torsion of the hemispheres about the midbrain-diencephalic junction with

brief interruption of RAS function. Persistent coma after head trauma presents a more complex and serious problem. The main causes are subdural or epidural hemorrhage, deep cerebral hemorrhage, bilateral frontotemporal contusions, and extensive white matter damage [1].

Coma with ischemic-anoxic brain damage. There are widespread and complex changes in the CNS following cardiac arrest, profound hypotension, or anoxia. Some of these are physiologic and mediated by alterations in electrical and neurotransmitter function, and others may result from endogenously released neurotoxins that ultimately lead to neuronal death. Several clinically recognizable patterns emerge that occur usually in pure form but that may coexist:

1) a deep coma with preserved brainstem function that evolves to the vegetative state or to a dementia, reflecting damage to neurons throughout the cortex - brainstem function may be suppressed in the first hours, thus emulating brain death, and the limbs may be either flaccid or show vigorous extensor posturing or myoclonic jerks;

2) syndromes of proximal bibrachial and paraparetic weakness or of cortical blindness that are due to bilateral infarctions of the watershed regions between major cortical vessel territories from diminished blood flow;

3) a Korsakoff-amnestic state that indicates the selective vulnerability of neurons in the hippocampal cortex;

4) a cerebellar syndrome [2].

Brain Death is a state of total cessation of cerebral blood flow and global infarction of the brain at a time when respiration is preserved by artificial support and the heart continues to function. It is the only type of irrevocable loss of brain function currently recognized as equivalent to death. Many sets of roughly equivalent criteria have been advanced for the diagnosis of brain death, and it is essential to adhere to those endorsed as standard practice by the local medical community. Ideal criteria are simple, conducted at the bedside, and allow no chance of diagnostic error. There are three essential elements:

1) widespread cortical destruction shown by deep coma;

2) global brainstem damage demonstrated by absent pupillary light reaction, and absent oculovestibular and corneal reflexes;

3) medullary destruction indicated by complete apnea [1].

The pulse rate is also invariant and unresponsive to atropine. Most patients have diabetes insipidus, but in some it develops after the clinical signs of brain death. The pupils need not be enlarged but should not be constricted. The absence of deep tendon reflexes is not required because the spinal cord may remain functional.

The possibility of profound drug-induced or hypothermic CNS depression should always be excluded. Some period of observation, usually 6 to 24 h, is desirable during which this state is shown to be sustained. It is often advisable to delay clinical testing for up to 24 h if a cardiac arrest has caused brain death or if the inciting disease is not known [3].

Demonstration of apnea generally requires that the P_{C02} be high enough to stimulate respiration. This can be accomplished safely in most patients by removal of the respirator and use of diffusion oxygenation sustained by a tracheal cannula connected to an oxygen supply. In brain-dead patients, $C0_2$ tension increases approximately 0,3 to 0,4 kPa/min (2 to 3 mmHg/min) during apnea. At the end of an appropriate interval, arterial P_{C02} should be at least above 6,6 to 8,0 kPa (50 to 60 mmHg) for the test to be valid. Large posterior fossa lesions that compress the brainstem, CNS-depressant drugs, and profound hypothermia can simulate brain death, but adherence to recognized protocols for diagnosis will prevent these errors.

An isoelectric EEG is often used as a confirmatory test for total cortical damage, but it is not absolutely necessary. Radionuclide brain scanning, cerebral angiography, or transcranial Doppler measurements may also be used to demonstrate the absence of cerebral blood flow, but with the exception of the latter, they are cumbersome and have not been correlated extensively with pathologic material [8].

There is no explicit reason to make the diagnosis of brain death except when organ transplantation or difficult resource-allocation (intensive care) issues are involved. Although it is commonly accepted that the respirator can be disconnected

from a brain-dead patient, most problems arise because of inadequate explanation and preparation of the family by the physician.

Treatment

The immediate goal in acute coma is the prevention of further nervous system damage. Hypotension, hypoglycemia, hypercalcemia, hypoxia, hypercapnia, and hyperthermia should be corrected rapidly and assiduously.

An oropharyngeal airway is adequate to keep the pharynx open in drowsy patients who are breathing normally. Tracheal intubation is indicated if there is apnea, upper airway obstruction, hypoventilation, or emesis, or if the patient is liable to aspirate. Mechanical ventilation is required if there is hypoventilation or if there is an intracranial mass and induced hypocapnia is necessary [5].

Intravenous access is established, and naloxone and dextrose are administered if narcotic overdose or hypoglycemia are even remote possibilities. Thiamine is administered with glucose in order to avoid eliciting Wernicke's encephalopathy in malnourished patients. The veins of intravenous drug abusers may be difficult to cannulate; in such cases, naloxone can be injected sublingually through a small-guage needle.

In cases of suspected basilar thrombosis with brainstem ischemia, intravenous heparin or a thrombolytic agent is administered after obtaining a CT scan, keeping in mind that cerebellar and pontine hemorrhages resemble the syndrome of basilar artery occlusion [1].

Physostigmine, when used by experienced physicians with careful monitoring, may awaken patients with anticholinergic-type drug overdose but many physicians believe that this is justified only to treat cardiac arrhythmias resulting from these overdoses.

The use of benzodiazepine antagonists is promising for treatment of overdoses and has transient benefit in hepatic encephalopathy.

Intravenous administration of water should be monitored carefully in any serious acute CNS illness because of the potential for exacerbating brain swelling.

Neck injuries must not be overlooked, particularly prior to attempting intubation or eliciting oculocephalic responses [1].

Headache accompanied by fever and meningismus indicates an urgent need for examination of the CSF to diagnose meningitis, and lumbar puncture should not be delayed while awaiting a CTscan.

Enlargement of one pupil usually indicates secondary midbrain compression by a hemispherical mass and demands immediate reduction of intracranial pressure (ICP). Surgical evacuation of the mass may be appropriate. Medical management to reduce intracranial pressure consists of intravenous fluid normal saline (the safest fluid because it is slightly hyperosmolar in most patients). Therapeutic hyperventilation may be used to achieve an arterial P_{C02} of 3,7 to 4,2 kPa (28 to 32 mmHg), but its effects are brief. Hyperosmolar therapy with mannitol or an equivalent is the mainstay of ICP reduction. It may be used simultaneously with hyperventilation in critical cases. A ventricular puncture is necessary to decompress hydrocephalus if medical measures fail to improve alertness [2].

The use of high-dose barbiturates and other neuronal sparing agents soon after cardiac arrest has not been shown in clinical studies to be beneficial and corticosteroids have no proven value except in cases of brain tumor.

Prognosis of coma and the vegetative state

All schemes for prognosis should be taken as only approximate indicators, and medical judgments must be tempered by other factors such as age, underlying disease, and general medical condition. In an attempt to collect prognostic information from large numbers of patients with head injury, the Glasgow Coma Scale was devised; empirically it has predictive value in cases of brain trauma, Major points include a 95% death rate in patients whose pupillary reaction or reflex eye movements are absent 6 h after onset of coma, and a 91% death rate if the pupils are unreactive at 24 h (although roughly 5% make a good recovery) [3].

Prognostication of nontraumatic coma is difficult because of the heterogeneity of contributing diseases. Metabolic coma generally has a more favorable prognosis than anoxic or traumatic coma. Unfavorable signs in the first hours after admission are the absence of any two of pupillary reaction, corneal reflex, or the oculovestibular response. One day after the onset of coma, the preceding signs, in addition to absence of eye opening and muscle tone, predict death or severe disability, and the same signs at 3 days strengthen the prediction of a poor outcome. In many patients, precise combinations of predictive signs do not occur, and coma scales lose their value. The use of evoked potentials aids prognostication in head-injured and post-cardiac arrest patients. Bilateral absence of cortical somatosensory evoked potentials is associated with death or a vegetative state in most cases. Medical practitioners are becoming less reluctant to withdraw support from non- brain-dead but severely neurologically injured patients as predictions become more reliable and resources more limited.

The prognosis for regaining full mental faculties once the vegetative state has supervened is almost nul. Most instances of dramatic recovery, when investigated carefully, yield to the usual rules for prognosis, but it must be acknowledged that rare instances of awakening to a condition of dementia or paralysis after months or years in this state have been documented [8].

CARDIOVASCULAR COLLAPSE, CARDIAC ARREST, AND SUDDEN CARDIAC DEATH

The vast majority of naturally occurring sudden deaths are caused by cardiac disorders. The magnitude of the problem of cardiac causes is highlighted by estimates that more than 300 000 sudden cardiac deaths (SCD) occur each year in the United States, as many as 50% of all cardiac deaths. SCD is a direct consequence of cardiac arrest, which is often reversible if responded to promptly. Since resuscitation techniques and emergency rescue systems are available to save patients who have out-of-hospital cardiac arrest, which was uniformly fatal in the pasf, understanding the SCD problem has practical importance [1].

SCD must be defined carefully. In the context of time, "sudden" is defined, for most clinical and epidemiologic purposes, as 1 h or less between the onset of the terminal clinical event and death. An exception is unwitnessed deaths in which pathologists may expand the definition of time to 24 h after the victim was last seen to be alive and stable.

Because of community-based interventions, victims may remain biologically alive for days or weeks after a cardiac arrest that has resulted in irreversible central nervous system damage. Confusion in terms can be avoided by adhering strictly to definitions of death, cardiac arrest, and cardiovascular collapse, as outlined in Table 5.

Table 5

Distinction Between Death, Cardiac Arrest, and Cardiovascular Collapse

Term	**Definition**	**Qualifiers or Exeptoins**
Death	Irreversible cessation of all biologic functions	None
Cardiac arrest	Abrupt cessation of cardiac pump function which may be reversible by a prompt intervention but will lead to death in its absence	Rare spontaneous reversions; likelihood of successful interventions; relates to mechanism of arrest and clinical setting

Cardiovascular collaps	A sudden loss of effective blood flow due to cardiac and/or peripheral vascular factors which may reverse spontaneously (e.g., neuro- cardiogenic syncope; vasovagal syncope) or only with interventions (e.g., cardiac arrest)	Nonspecific term which includes cardiac arrest and its consequences and also events which characteristically revert spontaneously

Death is biologically, legally, and literally an absolute and irreversible event. Death may be delayed in a survivor of cardiac arrest, but "survival after sudden death" is contradictory. Currently, the accepted 1 definition of SCD is natural death due to cardiac causes, heralded by abrupt loss of consciousness within 1 h of the onset of acute; symptoms, in an individual who may have known preexisting heart 1 disease but in whom the time and mode of death are unexpected. When biologic death of the cardiac arrest victim is delayed because; 2 of interventions, the relevant pathophysiologic event remains the sudden and unexpected cardiac arrest that leads ultimately to death, even though delayed by artificial methods. The language used should reflect the fact that the index event was a cardiac arrest and that death was" due to its delayed consequences [8].

Etiology, initiating events, and clinical epidemiology

Extensive epidemiologic studies have identified populations at high risk for SCD. In addition, a large body of pathologic data provides information on the underlying structural abnormalities in victims of SCD, and clinical/physiologic studies have begun to identify a group I of transient functional factors that may convert a long-standing underlying structural abnormality from a stable to an unstable state (Table 6). This information is developing into an understanding of the causes and mechanisms of SCD.

Cardiac disorders constitute the most common causes of sudden natural death. After an initial peak incidence of sudden death between birth and 6 months of age (the sudden infant death syndrome), the incidence of sudden death declines sharply and remains low through childhood and adolescence. The incidence begins to increase in

young adults, reaching a second peak in the age range of 45 to 75 years. Increasing age in this range is a powerful risk factor for sudden cardiac death, and the proportion of cardiac causes among all sudden natural deaths increases dramatically with advancing years. From 1 to 13 years of age, only one of five sudden natural deaths is due to cardiac causes. Between 14 and 21 years of age, the proportion increases to 30%, and then to 88% in the middle-aged and elderly [13].

Table 6

Cardiac Arrest and Sudden Cardiac Death

STRUCTURAL CAUSES

I. Coronary heart disease
   A. Coronary artery abnormalities
      1. Chronic atherosclerotic lesions
      2. Acute (active) lesions
         (plaque assuring, platelet aggregation, acute thrombosis)
      3. Anomalous coronary artery anatomy
   B. Myocardial infarction
      1. Healed
      2. Acute
II. Myocardial hypertrophy
   A. Secondary
   B. Hypertrophic cardiomyopathy
      1. Obstructive
      2. Nonobstructive
III. Dilated cardiomyopathy - primary muscle disease
IV. Inflammatory and infiltrative disorders
   A. Myocarditis
   B. Noninfectious inflammatory diseases
   C. Infiltrative diseases
V. Valvular heart disease
VI. Electrophysiologic abnormalities, structural
   A. Anomalous pathways in Wolff-Parkinson-White syndrome
   B. Conducting system disease

C. Membrane channel structure (e.g., congenital long QT syndrome)

FUNCTIONAL CONTRIBUTING FACTORS

I. Alterations of coronary blood flow
   A. Transient ischemia
   B. Reperfusion after ischemia

II. Low cardiac output states
   A. Heart failure
      1. Chronic
      2. Acute decompensation
   B. Shock

III. Systemic metabolic abnormalities
   A. Electrolyte imbalance (e.g., hypokalemia)

IV. Neurophysiologic disturbances
   A. Autonomic fluctuations: central, neural, humoral
   B. Receptor function

V. Toxic responses
   A. Proarrhythmic drug effects
   B. Cardiac toxins (e.g., cocaine, digitalis intoxication)
   C. Drug interactions

Young and middle-aged men and women have very different susceptibilities to SCD, but the gender differences decrease with advancing age [1].

The overall male/female ratio is approximately 4:1, but in 45 to 64-year-old age group, the male SCD excess is nearly 7:1. It falls to approximately 2:1 in the 65- to 74-year-old age group. The difference in risk for SCD parallels the risks for other manifestations of coronary heart disease in men and women. As the gap for other manifestations of coronary heart disease closes in the seventh and eighth decades of life, the excess risk of SCD also narrows. Despite the lower incidence in women, the classic coronary risk factors still operate in women (sigarette smoking, diabetes,

hyperlipidemia, and hypertension) and SDC remains an important clinical and epidemiologic problem [5].

Hereditary factors contribute to the risk of SCD, but largely in a nonspecific manner: they represent expressions of the hereditary predisposition to coronary heart disease. Except for a few specific syndromes, such as the genetic hyperlipoproteinemias, congenital long QT interval syndromes, and a number of myopathic and dysplastic syndromes there are no specific hereditary risk factors for SCD.

The major categories of structural causes of, and functional factors contributing to, the SCD syndrome are listed in Table 6. Worldwide, and especially in western cultures, coronary atherosclerotic heart disease is the most common structural abnormality associated with SCD. Up to 80% of all SCDs in the United States are due to the consequences of coronary atherosclerosis. The cardiomyopathies (dilated and hypertrophic, collectively) account for another 10 to 15% of SCDs, and all the remaining diverse etiologies cause only 5 to 10% of these events. Transient ischemia in the previously scarred or hypertrophied heart, hemodynamic and fluid and electrolyte disturbances, fluctuations in autonomic nervous system activity, and transient electrophysiologic changes caused by drugs or other chemicals (e.g., proarrhythmia) have all been implicated as mechanisms responsible for transition from electrophysiologic stability to instability. In addition, spontaneous reperfusion of ischemic myocardium, caused by vasomotor changes in the coronary vasculature and/ or spontaneous thrombolysis, may cause transient electrophysiologic instability and arrhythmias [13].

Pathology. Data from postmortem examinations of SCD victims parallel the clinical observations on the prevalence of coronary heart disease as the major structural etiologic factor. More than 80% of SCD victims have pathologic findings of coronary heart disease. The pathologic description often includes a combination of long-standing, extensive atherosclerosis of the epicardial coronary arteries and acute active coronary lesions, which include a combination of fissured or ruptured plaques, platelet

aggregates, hemorrhage, and thombosis. In one study, chronic coronary atherosclerosis involving two or more major vessels with >75% stenosis was observed in 75% of the victims. In another study, atherosclerotic plaque assuring, platelet aggregates, and/or acute thrombosis were observed in 95 of 100 individuals who had pathologic studies after SCD. Most of these acute changes were superimposed on preexisting chronic lesions [1].

As many as 70 to 75% of males who die suddenly have prior myocardial infarctions (MI), but only 20 to 30% have recent acute MI. A high incidence of left ventricular (LV) hypertrophy coexists with prior MI.

Clinical definition of forms of cardiovascular collapse

Cardiovascular collapse is a general term connoting loss of effective blood flow due to acute dysfunction of the heart and/or peripheral vasculature. Cardiovascular collapse may be caused by vasodepressor syncope (vasovagal syncope, postural hypotension with syncope, neurocardiogenic syncope), a transient severe bradycardia, or cardiac arrest. The latter is distinguished from the transient forms of cardiovascular collapse in that it usually requires an intervention to achieve resuscitation. In contrast, vasodepressor syncope and many primary bradyarrhythmic syncopal events are transient and non-life-threatening, and the patient will regain consciousness spontaneously [8].

The most common electrical mechanism for true cardiac atrest is ventricular fibrillation (VF), which is responsible for 65 to 80% of cardiac arrests. Severe persistent bradyarrhythmias, asystole, and pulseless electrical activity (an organized electrical activity without mechanical response - formerly called electomechanical dissociation) cause another 20 to 30%. Sustained ventricular tachycardia (VT) with hypotension is a less common cause. Acute low cardiac output states, having precipitous onset, also may present clinically as a cardiac arrest. The causes include massive acute pulmonary emboli, internal blood loss from ruptured aortic aneurysm, intense anaphylaxis, cardiac rupture after myocardial infarction, and unexpected fatal arrhythmia due to electrolyte disturbances.

Clinical characteristics of cardiac arrest

Prodrome, onset, arrest, death

SCD may be presaged by days, weeks, or months of increasing angina, dyspnea, palpitations, easy fatigability, and other nonspecific complaints. However, these prodromal complaints are generally predictive of any major cardiac event; they are not specific for predicting SCD [1].

The onset of the terminal event, leading to cardiac arrest, is defined as an acute change in cardiovascular status preceding cardiac arrest by up to 1 h. When the onset is instantaneous or abrupt, the probability that the arrest is cardiac in origin is >95%. Continuous ECG recordings, fortuitously obtained at the onset of a cardiac arrest, commonly demonstrate changes in cardiac electrical activity in the minutes or hours before the event. There is a tendency for the heart rate to increase and for advanced grades of premature ventricular contractions (PVCs) to evolve. Most cardiac arrests that occur by the mechanism of VF begin with a run of sustained or nonsustained VT, which then degenerates into VF [2].

Sudden unexpected loss of effective circulation may be separated into "arrhythmic events" and "circulatory failure". Arrhythmic events are characterized by a high likelihood of patients being awake and active immediately prior to the event, are dominated by VF as the electrical mechanism, and have a short duration of terminal illness (<1 h). In contrast, circulatory failure deaths occur in patients who are inactive or comatose, have a higher incidence of asystole than VF, have a tendency to a longer duration of terminal illness, and are dominated by noncardiac events preceding the terminal illness.

The onset of cardiac arrest may be characterized by typical symptoms of an acute cardiac event, such as prolonged angina or the pain of onset of MI, acute dyspnea or orthopnea, or the sudden onset of palpitations, sustained tachycardia, or light-headedness. However, in many patients, the onset is precipitous, without forewarning.

Cardiac arrest is, by definition, abrupt. Mentation may be impaired in patients with sustained VT during the onset of the terminal event. However, complete loss of

consciousness is a sine qua non in cardiac arrest. Although rare spontaneous reversions occur, it is usual that cardiac arrest progresses to death within minutes (i.e., SCD has occurred) if active interventions are not undertaken promptly [8].

The ability to resuscitate the victim of cardiac arrest is related to the time from onset to institution of resuscitative efforts, the setting in which the event occurs, the mechanism (VF, VT, pulseless electrical activity, asystole), and the clinical status of the patient prior to the cardiac arrest. Those settings in which it is possible to institute prompt cardiopulmonary resuscitation (CPR) provide a better chance of a successful outcome. However, the outcome in intensive care units and other in-hospital environments is heavily influenced by the patient's preceding clinical status. The immediate outcome is good for cardiac arrest occurring in the intensive care unit in the presence of an acute cardiac event or transient metabolic disturbance, but the outcome for patients with far-advanced chronic cardiac disease or advanced noncardiac diseases (e.g., renal failure, pneumonia, sepsis, diabetes, cancer) is no more successful in hospital than in the out-of-hospital setting.

The success rate for initial resuscitation and ultimate survival from an out-of-hospital cardiac arrest depends in part on the mechanism of the event. When the mechanism is VT, the outcome is best (67%); VF is the next most successful (25%), and asystole and pulseless electrical activity generate dismal outcome statistics. Advanced age also influences adversely the chances of successful resuscitation [13].

Progression to biologic death is a function of the mechanism of cardiac arrest and the length of the delay before interventions. VF or asystole, without CPR within the first 4 to 6 min, has a poor outcome, and there are few survivors among patients who had no life-support activities for the first 8 min after onset. Outcome statistics are improved considerably by lay bystander intervention (basic life support) prior to definitive interventions (advanced life support - defibrillation) and by early defibrillation. Death during the hospitalization after a successfully resuscitated cardiac arrest relates closely to the severity of central nervous system injury. Anoxic encephalopathy and infections subsequent to prolonged respirator dependence account for 60% of the deaths. Another

30% occur as a consequence of low cardiac output states that fail to respond to interventions. Paradoxically, recurrent arrhythmias are the least common cause of death, accounting for only 10% of in-hospital deaths [1].

Among patients who have cardiac arrest in the setting of acute MI, it is important to distinguish between primary and secondary cardiac arrests. Primary cardiac arrests refer to those that occur in the absence of hemodynamic instability, and secondary cardiac arrest are those that occur in patients in whom abnormal hemodynamics i dominate the clinical picture before cardiac arrest. The success rate for immediate resuscitation in primary cardiac arrest during acute MP in a monitored setting should approach 100%. In contrast, as many as 70% of patients with secondary cardiac arrest succumb immediately or during the same hospitalization [3].

Identification of patients at risk for sudden cardiac death. Primary prevention of cardiac arrest depends on the ability to identify individual patients at high risk. One must view the problem in the context of the total number of events and the population pools from which they are derived. The inverted triangle demonstrates that the annual incidence of SCD among an unselected adult population is 1-2 per 1000 population, largely reflecting the prevalence of those coronary heart disease patients among whom SCD is the first clinically recognized manifestation (20-25% of first coronary events are SCD). The incidence (percent per year) increases progressively with addition of identified coronary risk factors to populations free of prior coronary events. The most powerful factors are age, elevated blood pressure, LV hypertrophy, cigarette smoking, elevated serum cholesterol level, obesity, and nonspecific electrocardiographic abnormalities. These coronary risk factors are not specific for SCD but rather represent increasing risk for all coronary deaths. The proportion of coronary deaths that are sudden remains at approximately 50% in all risk categories. Despite the marked relative increased risk of SCD with addition of multiple risk factors (from 1 to 2 per 1000 population per year in an unselected population to as much as 50 to 60 per 1000 in subgroups having; multiple risk factors for coronary artery disease), the absolute incidence remains relatively low when viewed as the relationship between the number

of individuals who have a preventive intervention and the number of events that can be prevented. Specifically, a 50% reduction in annual SCD risk would be a huge relative decrease but would require an intervention in up to 200 unselected individuals to prevent one sudden death. These figures highlight the importance of primary prevention of coronary heart disease. Control of coronary risk factors may be the only practical method to prevent SCD in major segments of the population, because of the paradox that the majority of events occur in the large unselected subgroups rather than in the specific high-risk subgroups (compare "Events/Year" with "Percent/Year"). Under most conditions of higher level of risk, particularly those indexed to a recent major cardiovascular event (e.g., MI, recent onset of heart failure, survival after out-of-hospital cardiac arrest), the highest risk of sudden death occurs within the initial 6 to 18 months and then decreases toward baseline risk of the underlying disease. Accordingly, preventive interventions are most likely to be effective when initiated early [8].

For patients with acute or prior clinical manifestations of coronary heart disease, high-risk subgroups having a much higher ratio of SCD risk to population base can be identified. The acute, convalescent, and chronic phases of MI provide large population subsets with more highly focused risk. The potential risk of cardiac arrest from the onset through the first 72 h after acute MI (the acute phase) may be as high as 15 to 20%. The highest risk of SCD in relation to MI is found in the subgroup that has experienced sustained VT or VF during the convalescent phase (3 days to 8 weeks) after MI. Greater than 50% mortality in 6 to 12 months has been observed among these patients, when managed with conservative medical therapy, and at least 50% of the deaths are sudden. Since the development of aggressive intervention techniques, the incidence appears to have fallen dramatically [1].

After the acute phase of MI, long-term risk for total mortality and SCD are predicted by a number of factors. The most important for both SCD and non-SCD is the extent of myocardial damage sustained during the acute event. This is measured by the degree of reduction in the ejection fraction (EF), functional capacity, and/or the occurrence of heart failure. Increasing frequency of postinfarction PVCs, with a plateau

above the range of 10 to 30 PVCs per hour on 24-h ambulatory monitor recordings, also indicates increased risk, but advanced forms (salvos, nonsustained VT) are probably the more powerful predictor. PVCs interact strongly with decreased left ventricular EF. The combination of frequent PVCs, salvos or nonsustained VT, and an EF<30% identifies patients who have an annual risk of 20%. The risk falls off sharply with decreasing PVC frequency and the absence of advanced forms, as well as with higher EF. Despite the risk implications of postinfarction PVCs, improved outcome as a result of PVC suppression has not been demonstrated [2].

The extent of underlying disease due to any cause and/or prior clinical expression of risk of SCD (i.e., survival after out-of-hospital cardiac arrest not associated with acute MI) identify patients at very high risk for subsequent (recurrent) cardiac arrest. Survival after out-of-hospital cardiac arrest predicts up to a 30% 1-year recurrent cardiac arrest rate in the absence of specific interventions.

A general rule is that the risk of SCD is approximately one-half the total cardiovascular mortality rate. Thus, the SCD risk is approximately 20% per year for patients with advanced coronary heart disease or dilated cardiomyopathy severe enough to result in a 40% 1-year total mortality rate. The very high risk subgroups provide more focused population fractions ("Percent/Year") for predicting cardiac arrest or SCD; but the impact on the overall population, indicated by the absolute number of preventable events ("Events/Year"), is considerably smaller. The requirements for achieving a major population impact are effective prevention of the underlying diseases and/or new epidemiologic probes that will allow better resolution of subgroups within large general populations [8].

Treatment. The individual who collapses suddenly is managed in four stages:

1) the initial response and basic life support,

2) advanced life support,

3) postresuscitation care,

4) long-term management.

The initial response and basic life support can be carried out by physicians, nurses, paramedical personnel, and trained lay persons. There is a requirement for increasing skills as the patient moves through the stages of advanced life support, postresuscitation care, and long-term management.

Initial Response and Basic Life Support

The initial response will confirm whether a sudden collapse is indeed due to a cardiac arrest. Observations for respiratory movements, skin color, and the presence or absence of pulses in the carotid or femoral arteries will promptly determine whether a life-threatening cardiac arrest has occurred. As soon as a cardiac arrest is suspected or confirmed, contacting an emergency rescue system (e.g., 911) should be the immediate priority [1].

▪Agonal respiratory movements may persist for a short time after the onset of cardiac arrest, but it is important to observe for severe stridor with a persistent pulse as a clue to aspiration of a foreign body or food. If this is suspected, a prompt Heimlich maneuver may dislodge the obstructing body.

▪A precordial blow, or "thump," delivered firmly by the clenched fist to the junction of the middle and lower third of the sternum may occasionally revert VT or VF, but there is concern about converting VT to VF. Therefore, it has been recommended to use precordial thumps as an advanced life support technique when monitoring and defibrillation are available. This conservative application of the technique remains controversial.

▪The third action during the initial response is to clear the airway. The head is tilted back and chin lifted so that the oropharynx can be explored to clear the airway. Dentures or foreign bodies are removed, and the Heimlich maneuver is performed if there is reason to suspect that a foreign body is lodged in the oropharynx. If respiratory arrest precipitating cardiac arrest is suspected, a second precordial thump is delivered after the airway is cleared [8].

Basic life support, more popularly known as CPR, is intended to maintain organ perfusion until definitive interventions can be instituted. The elements of CPR are the

establishment and maintenance of ventilation of the lungs and compression of the chest. Mouth-to-mouth respiration may be used if no specific rescue equipment is immediately available (e.g., plastic oropharyngeal airways, esophageal obturators, masked Ambu bag). Conventional ventilation techniques during CPR require the lungs to be inflated 10 to 12 times per minute, i.e., once every fifth chest compression when two persons are performing the resuscitation and twice in succession every 15 chest compressions when one person is carrying out both ventilation and chest wall compression [13].

Chest compression is based on the assumption that cardiac compression allows the heart to maintain a pump function by sequential filling and emptying of its chambers, with competent valves maintaining forward direction of flow. The palm of one hand is placed over the lower sternum, with the heel of the other resting on the dorsum of the lower hand. The sternum is depressed, with the arms remaining straight, at a rate of approximately 80 to 100 per minute. Sufficient force is applied to depress the sternum 3 to 5 cm, and relaxation is abrupt.

Advanced Life Support is intended to achieve adequate ventilation, control cardiac arrhythmias, stabilize the hemodynamic status (blood pressure and cardiac output), and restore organ perfusion. The activities carried, out to achieve these goals include:

1) intubation with an endotracheal tube,

2) defibrillation/cardioversion and/or pacing,

3) insertion of an intravenous line [1].

Ventilation with O_2 (room air if O_2 is not immediately available) may promptly reverse hypoxemia and acidosis. The speed with which defibrillation/cardioversion is carried out is an important element for successful resuscitation. When possible, immediate defibrillation should precede intubation and insertion of an intravenous line; CPR should be carried out while the defibrillator is being charged. As soon as a diagnosis of VT or VF is obtained, a 200 J shock should be delivered. Additional shocks at higher energies, up to a maximum of 360 J, are tried if the initial shock does not successfully abolish VT or VF. Epinephrine, 1 mg intravenously, is given after failed

defibrillation, and attempts to defibrillate are repeated. The dose of epinephrine may be repeated after intervals of 3 to 5 min [14].

If the patient is less than fully conscious upon reversion, or if two or three attempts fail, prompt intubation, ventilation, and arterial blood gas analysis should be carried out. Intravenous $NaHCO_3$, which was formerly used in large quantities, is no longer considered routinely necessary and may be dangerous in larger quantities. However, the patient who is persistently acidotic after successful defibrillation and intubation should be given 1 mg/kg $NaHCO_3$ initially and an additional 50% of the dose repeated every 10 to 15 min [1].

After initial unsuccessful defibrillation attempts, or with persistent electrical instability, a bolus of 1 mg/kg lidocaine is given intravenously, and the dose is repeated in 2 min in those patients who have persistent ventricular arrhythmias or remain in VF. This is followed by a continuous infusion at a rate of 1 to 4 mg/min. If lidocaine fails to provide control, intravenous procainamid (loading infusion of 100 mg/min to a total dose of 500 mg, followed by continuous infusion at 2 to 5 mg/min) or bretylium tosylate (loading dose 5 to 10 mg/kg in 5 min; maintenance dose 0,5 to 2 mg/min) may be tried. Intravenous calcium gluconate is no longer considered safe or necessary for routine administration. It is used only in patients in whom acute hyperkalemia is known to be the triggering event for resistant VF, in the presence of know, hypocalcemia, or in patients who have received toxic doses of calcium channel antagonists [5].

Cardiac arrest secondary to bradyarrhythmias or asystole is mail aged differently. Once it is known that this type of rhythm is preseil there is no role for external shock. The patient is promptly intubated CPR is continued, and an attempt is made to control hypoxemia and acidosis. Epinephrine and/or atropine are given intravenously or an intracardiac route. External pacing devices are now available to attempt to establish a regular rhythm, but the prognosis is generally very poor in this form of cardiac arrest. The one exception is bradyrhythmic/asystolic cardiac arrest secondary to airway obstruction. This form of cardiac arrest may respond promptly to removal foreign

bodies by the Heimlich maneuver or, in hospitalized patiens by intubation and suctioning of obstructing secretions in the airway [8].

Postresuscitation Care is demined by the clinical setting of the cardiac arrest. Primary VF in acute MI is generally very responsive to life-support, techniques and easily controlled after the initial event. Patients are maintained on a lidocaine infusion at the rate of 2 to 4 mg/min for 24 to 72 h after the event. In the in-hospital setting, respirator support is usually not necessary or is needed for only a short time and hemodynamics stabilize promptly after defibrillation or cardioversion. In secondary VF in acute MI (those events in which hemodynamic abnormalities predispose to the potentially fatal arrhythmia), resuscitative efforts are less often successful, and in those patients who are successfully resuscitated, the recurrence rate is high. The clinical picture is dominated by hemodynamic instability. In fact, the outcome is determined more by the ability to control hemodynamic dysfunction than by electrophysiologic abnormalities. Bradyarrhythmias, asystole, and pulseless electrical activity are commonly secondary events in hemodynamically unstable patients and are less responsive to interventions.

The outcome after in-hospital cardiac arrest associated with non-cardiac diseases is poor, and in the few successfully resuscitated patients, the postresuscitation course is dominated by the nature of the underlying disease. Patients with cancer, renal failure, acute central nervous system disease, and uncontrolled infections, as a group, have a survival rate of less than 10% after in-hospital cardiac arrest. Some major exceptions are patients with transient airway obstruction, electrolyte disturbances, and proarrhythmic effects of drugs, and severe metabolic abnormalities, most of whom may have an excellent chance of survival if they can be resuscitated promptly and maintained while the transient abnormalities are being corrected [1].

Long-Term Management After Survival of Out-of-Hospital Cardiac Arrest Patients who do not suffer irreversible injury of the central nervous system and who achieve hemodynamic stability should have extensive diagnostic and therapeutic testing to guide long-term management. This aggressive approach is driven by the fact that

statistics from the 1970s indicated survival after out-of-hospital cardiac arrest was followed by a 30% recurrent cardiac arrest rate at 1 year, 45% at 2 years, and a total mortality rate of almost 60% at 2 years. Historical comparisons suggest that these dismal statistics may be significantly improved by newer interventions, but the magnitude of the improvement is unknown because of the lack of concurrently controlled intervention studies [13].

Among those patients in whom an acute transmural MI is the cause of out-of-hospital cardiac arrest, the management is the same as in any other patient who suffers cardiac arrest during the acute phase of a documented MI. For almost all other categories of patients, however, extensive diagnostic studies are carried out to determine etiology, functional impairment, and electrophysiologic instability as guides to future management. In general, patients who have out-of-hospital cardiac arrest due to chronic ischemic heart disease, without an acute MI, are evaluated to determine whether transient ischemia or chronic electrophysiologic instability was the more likely cause of the event. If there is reason to suspect an ischemic mechanism, coronary revascularization or drugs, most commonly beta-blockers, are used to reduce ischemia. Electrophysiologic instability is best identified by the use of programmed electrical stimulation to determine whether sustained VT or VF can be induced. If so, this information can be used as a baseline against which to evaluate drug efficacy for prevention of inducibility or to determine suitability for map-guided antiarrhythmic surgery, or whether an implantable cardioverter/defibrillator (ICD) might be the best strategy. Using this technique in patients with EF of 30% or more, the recurrent cardiac arrest rate is less than 10% during the first year of follow-up when inducibility is suppressed by a drug [1]. The outcome is not as good for patients with EF under 30% but may be still better than the apparent natural history of survival after cardiac arrest. For patients for whom successful drug therapy cannot be identified by this technique, insertion of an ICD, antiarrhythmic surgery (e.g., coronary bypass surgery, aneurysmectomy, cryoablation), or empiric amiodarone therapy can be considered options. Primary surgical success, defined as surviving the procedure and reverting to a

noninducible status without drug therapy, is better than 90% when patients are selecte for ability to be mapped in the operating room. However, only a small fraction of patients meet the criteria. In addition, VT/VF cannot be induced in a number of survivors of cardiac arrest (30 to 50%), and inducible arrhythmias can be suppressed by drugs in no more than 20 to 30% of those whose arrhythmias can be induced. Because of these limitations of drug therapy and surgical approaches, ICD therapy has evolved into the most commonly used strategy for cardiac arrest survivors. ICDs have very good success rates for sensing and reverting life-threatening arrhythmias, but improvement in long-term total survival outcomes remains ill defined [8].

SEIZURES AND EPILEPSY

Overview. A seizure is an episode of neurologic dysfunction caused by abnormal neuronal activity that results in a sudden change in behavior, sensory perception, or motor activity. The International Classification of Seizures divides seizures into 2 categories: partial seizures (ie, focal or localization-related seizures) and generalized seizures.

The term “epilepsy” refers to recurrent, unprovoked seizures from known or unknown causes. The term “ictus” describes the period in which the seizure occurs, and the term “postictal” refers to the period after the seizure has ended but before the patient has returned to his or her baseline mental status [2].

A focal or partial seizure consists of abnormal neuronal firing that is limited to 1 hemisphere or area of the brain and that manifests itself as seizure activity on 1 side of the body or one extremity and may progress to secondarily generalized seizure. These seizures are classified as simple partial if there is no change in mental status or complex partial if there is some degree of impaired consciousness.

Partial seizures can generalize secondarily and result in tonic-clonic activity. Some partial seizures have very rapid generalization, and the partial phase of the seizure may not be readily apparent clinically or even on scalp EEG recordings. Some partial seizures may have an aura, but primary generalized seizures usually do not. However, secondarily generalized partial seizures are not included in the category of generalized seizures, which includes only primary generalized seizures.

If consciousness is fully preserved during the partial seizure, the clinical manifestations are considered relatively simple and the seizure is termed a simple-partial seizure. If consciousness is impaired, the symptomatology is more complex and the seizure is termed a complex-partial seizure. An important additional subgroup comprises those seizures that begin as partial seizures and then spread diffusely throughout the cortex, i.e., partial seizures with secondary generalization [1].

Simple-Partial Seizures cause motor, sensory, autonomic, or psychic symptoms without an obvious alteration in consciousness. For example, a patient having a partial

motor seizure arising from the right primary motor cortex in the vicinity controlling hand movement will note the onset of involuntary movements of the contralateral, left hand. These movements are typically clonic (i.e., repetitive, flexion/extension movements) at a frequency of approximately 2 to 3 Hz; pure tonic posturing may be seen as well. Since the cortical region controlling hand movement is immediately adjacent to the region for facial expression, the seizure may also cause abnormal movements of the face synchronous with the movements of the hand. The EEG recorded with scalp electrodes during the seizure (i.e., an ictal EEG) may show abnormal discharges in a very limited region over the appropriate area of cerebral cortex if the seizure focus involves the cerebral convexity. Seizure activity occurring within deeper brain structures is often not recorded by the standard EEG however, and may require intracranial electrodes for its detection [5].

Three additional features of partial motor seizures are worth noting:

1) in some patients the abnormal motor movements may begin in a very restricted region such as the fingers and gradually progress (over seconds to minutes) to include a larger portion of the extremity. This phenomenon was originally described by Hughlings Jackson and is known as a "Jacksonian march," representing the spread of seizure activity over a progressively larger region of motor cortex;

2) patients may experience a localized paresis (Todd's paralysis) for minutes to many hours in the involved region following the seizure;

3) in rare instances the seizure may continue for hours or days. This condition, which termed epilepsia partialis continua, is often quite refractory to medical therapy.

Other forms of simple-partial seizures include those that cause changes in somatic sensation (e.g., paresthesia), vision (flashing lights or formed hallucinations), equilibrium (sensation of falling or vertigo), or autonomic function (flushing, sweating, piloerection). Simple-partial seizures arising from the temporal or frontal cortex may also cause alterations in hearing, olfaction, or higher cortical function (psychic symptoms). This includes the sensation of unusual, intense odors (e.g., burning rubber or kerosene) or sounds (crude or highly complex sounds), or an epigastric sensation that

rises from the stomach or chest to the head. Some patients describe odd, internal feelings such as fear, a sense of impending change, detachment, depersonalization, déjà vu, or illusions that objects are growing smaller (micropsia) or larger (macropsia). When such symptoms precede a complex-partial or secondarily generalized seizure, these simple-partial seizures serve as a warning, or aura [8]**.**

Complex-Partial Seizures are characterized by focal seizure activity accompanied by a transient impairment of the patient's ability to maintain normal contact with the environment. Operationally this means that the patient is unable to respond to visual or verbal commands during the seizure and has impaired recollection or awareness of the ictal phase. The seizures frequently begin with an aura (i.e., a simple-partial seizure) that is stereotypic for the patient. The start of the ictal phase is often a sudden behavioral arrest or motionless stare, and this marks the onset of the event for which the patient will be amnestic. The behavioral arrest is usually accompanied by automatisms, which are involuntary, automatic behaviors that have a wide range of manifestations. Automatisms may consist of very basic behaviors such as chewing, lip smacking, swallowing, or "picking" movements of the hands, or more elaborate behaviors such as a display of emotion or running. The patient is typically confused following the seizure, and the transition to full recovery of consciousness may range from seconds up to an hour. Careful examination of the patient immediately following the seizure may show an anterograde amnesia or, in cases involving the **dominant** hemisphere, a postictal aphasia [1].

The routine, interictal (i.e., between seizures) EEG in patients with complex-partial seizures is often normal, or may show brief discharges termed epileptiform spikes, or sharp waves. Since complex-partial seizures often arise from the medial temporal lobe or inferior frontal lobe, i.e., regions distant from the scalp, the EEG recorded during the seizure may be non-localizing. However, the seizure focus is often detected using special electrodes such as sphenoidal or surgically-placed intracranial electrodes.

The range of potential clinical behaviors linked to complex-partial seizures is so broad that extreme caution is advised before concluding that stereotypic episodes of bizarre or atypical behavior are not due to seizure activity. In such cases it is imperative to consider more detailed EEG studies in order to determine whether the behaviors are caused by a seizure disorder [3].

Partial Seizures with Secondary Generalization can spread to involve both cerebral hemispheres and produce a generalized seizure, usually of the tonic-clonic variety. Secondary generalization is observed frequently following simple-partial seizures, especially those with a focus in the frontal lobe, but may also be associated with partial seizures occurring elsewhere in the brain. A partial seizure with secondary generalization is often difficult to distinguish from a primarily generalized tonic-clonic seizure, since bystanders tend to emphasize the more dramatic, generalized convulsive phase of the seizure and overlook the more subtle, focal symptoms present at onset. In some cases, the focal onset of the seizure becomes apparent only when a careful history identifies a preceding aura (i.e., simple-partial seizure). Often, however, the focal onset is not clinically evident and may be established only through careful EEG analysis. Nonetheless, distinguishing between these two entities is extremely important, as there may be substantial differences in the evaluation and treatment of partial versus generalized seizure disorders [1].

Primary generalized seizures probably begin in the thalamus and other subcortical structures, but on scalp EEG recordings, they may appear to start simultaneously in both cerebral hemispheres; therefore, they manifest symptoms bilaterally in the body and are always associated with loss of consciousness.

A generalized seizure consists of abnormal electrical activity involving both cerebral hemispheres that causes an alteration in mental status. Traditionally, the patient with 30 minutes of continuous seizure activity or a series of seizures without a return to full consciousness is defined as being in status epilepticus (SE). Newer definitions suggest that SE is defined by duration of 5 continuous minutes of generalized seizure activity or 2 or more separate seizure episodes without return to baseline [13].

However, it is currently impossible to exclude entirely the existence of a focal region of abnormal activity that initiates the seizure prior to rapid secondary generalization. For this reason, generalized seizures may be practically defined as bilateral clinical and electrographic events without any detectable focal onset. Fortunately, a number of the subtypes of generalized seizures have distinctive features that facilitate clinical diagnosis.

Generalized seizures can be classified as atonic, tonic, clonic, tonic-clonic, myoclonic, or absence on the basis of clinical symptoms and EEG abnormalities. Tonic seizure is the rigid contracture of muscles, including respiratory muscles, which is usually brief. The clonic component is the rhythmic shaking that occurs and is longer. Together, a generalized tonic-clonic seizure (GTCS) is also called a grand mal seizure and is one of the most dramatic of all medical conditions [8].

The following epilepsy syndromes have generalized seizures:

- Benign neonatal convulsions
- Benign myoclonic epilepsy of infancy
- Childhood absence epilepsy
- Juvenile absence epilepsy
- Juvenile myoclonic epilepsy
- Generalized tonic-clonic seizures upon awakening

Patients with generalized tonic-clonic seizures and idiopathic generalized epilepsy typically have no evidence of any localized, regional, or diffuse brain abnormality on history, physical, or neurologic examination; clinical laboratory testing; or imaging studies. The awake EEG of patients with generalized tonic-clonic seizure may be normal; however, certain specific interictal EEG patterns can be distinctive of generalized epilepsy syndromes. In generalized seizure patients, the activation of photic stimulation and/or hyperventilation during an EEG may produce spikes or even seizures [1].

Absence Seizures (Petit Mal) are characterized by sudden, brief lapses of consciousness without loss of postural control. The seizure typically lasts for only

seconds, consciousness returns as suddenly as it was lost, and there is no postictal confusion. Although the brief loss of consciousness may be clinically inapparent or the sole manifestation of the seizure discharge, absence seizures are usually accompanied by subtle, bilateral motor signs such as rapid blinking of the eyelids, chewing movements, or small-amplitude, clonic movements of the hands [8].

Absence seizures almost always begin in childhood (ages 4 to 8 y) or early adolescence and are the main seizure type in 15 to 20% of children with epilepsy. The seizures can occur hundreds of times per day, but the child may be unaware of or unable to convey their existence. This can lead to a situation in which the patient is constantly struggling to piece together experiences that have been interrupted by the seizures. Since the clinical signs of the seizures are subtle, especially to new parents, it is not surprising that the first clue to absence epilepsy is often unexplained "daydreaming" and a decline in school performance recognized by a teacher [1].

The electrophysiologic hallmark of typical absence seizures is a generalized, symmetric, 3 Hz spike-and-wave discharge that begins and ends suddenly on a normal EEG background. Periods of spike-and-wave discharges lasting more than a few seconds usually correlate with the clinical signs, but the EEG often shows many more periods of abnormal cortical activity than were suspected clinically. Hyperventilation tends to provoke these electrographic discharges and even the seizures themselves and is routinely used when recording the EEG.

Typical absence seizures are not associated with other neurologic problems and respond well to treatment with specific anticonvulsants. Although estimates vary, approximately 60 to 70% of such patients will have a spontaneous remission during adolescence. Unfortunately, a significant number of the nonremitting patients have associated generalized, tonic-clonic seizures and suffer from the problems of chronic epilepsy [5].

Atypical Absence Seizures have features that deviate from both the clinical and EEG features of typical absence seizures. For example, the lapse of consciousness is usually of longer duration and less abrupt in onset and cessation, and the seizure is

accompanied by more obvious motor signs that may include focal or lateralizing features. The EEG shows a generalized, slow spike-and-wave pattern with a frequency of 2,5 per second or less, as well as other abnormal activity. Atypical absence seizures are usually associated with diffuse or multifocal structural abnormalities of the brain and therefore may accompany other signs of neurologic dysfunction such as mental retardation. Furthermore, the seizures are less responsive to anticonvulsants compared to typical absence seizures [8].

Generalized, Tonic-Clonic Seizures (Grand Mal) primarily generalized, tonic-clonic seizures are the main seizure type in approximately 10% of all persons with epilepsy. They are also the most common seizure type resulting from metabolic derangements and are therefore frequently encountered in many different clinical settings. The seizure usually begins abruptly without warning, although some patients describe vague premonitory symptoms in the hours leading up to the seizure. This prodrome should be distinguished from the stereotypic auras associated with focal seizures that secondarily generalize. The initial phase of the seizure is usually tonic contraction of muscles throughout the body, accounting for a number of the classic features of the event. Tonic contraction of the muscles of expiration and the larynx at the onset will produce a loud moan or cry. Respirations are impaired, secretions pool in the oropharynx, and the patient becomes cyanotic. Contraction of the jaw muscles may cause biting of the tongue. A marked enhancement of sympathetic tone leads to increases in heart rate, blood pressure, and pupillary size. After 10 to 20 s, the tonic phase of the seizure typically evolves into the clonic phase, produced by the superimposition of periods of muscle relaxation on the tonic muscle contraction. The periods of relaxation progressively increase until the end of the ictal phase, which usually lasts no more than 1 min. The postictal phase is characterized by unresponsiveness, muscular flaccidity, and excessive salivation that can cause stridorous breathing and partial airway obstruction. Bladder or bowel incontinence may occur at this point as well. Patients gradually regain consciousness over minutes to hours, and during this transition there is typically a period of postictal confusion.

Patients will subsequently complain of headache, fatigue, and muscle ache that can last for many hours. The duration of impaired consciousness in the postictal phase can be extremely long, i.e., many hours, in patients with prolonged seizures or underlying CNS diseases such as alcoholic cerebral atrophy [13].

The EEG during the tonic phase of the seizure shows a progressive increase in generalized low-voltage fast activity, followed by generalized high-amplitude, polyspike discharges. In the clonic phase, the high-amplitude activity is typically interrupted by slow waves to create a spike-and-wave pattern. The postictal EEG shows diffuse slowing that gradually recovers as the patient awakens [5].

There are many variants of the generalized tonic-clonic seizure, including pure tonic and pure clonic seizures. Brief tonic seizures lasting only a few seconds are especially noteworthy since they are usually associated with known epileptic syndromes having mixed seizure phenotypes, such as the Lennox-Gastaut syndrome.

Atonic Seizures are characterized by sudden loss of postural muscle tone lasting 1 to 2 s. Consciousness is briefly impaired, but there is usually no postictal confusion. A very brief seizure may cause only a quick head drop or nodding movement, while a longer seizure will cause the patient to collapse. This can be quite dramatic and extremely dangerous, since there is a substantial risk of direct head injury with the fall. The EEG shows brief, generalized spike-and-wave discharges followed immediately by diffuse slow waves that correlate with the loss of muscle tone. Similar to pure tonic seizures, atonic seizures are usually seen in association with known epileptic syndromes [8].

Myoclonic Seizure is a sudden and brief muscle contraction that may involve one part of the body or the entire body. A normal, common physiologic form of myoclonus is the sudden jerking movement observed while falling asleep. Pathologic myoclonus is most commonly seen in association with metabolic disorders, degenerative CNS diseases, or anoxic brain injury.

Although the distinction from other forms of myoclonus is imprecise, myoclonic seizures are considered to be true epileptic events since they are caused by cortical

(versus subcortical or spinal) dysfunction. The EEG shows bilaterally synchronous spike-and-wave discharges. Myoclonic seizures usually coexist with other forms of generalized seizure disorders but are the predominant feature of juvenile myoclonic epilepsy [8].

Unclassified seizures. Not all seizure types can be classified as partial or generalized. This appears to be especially true of seizures that occur in neonates (i.e., less than 1 month of age) and infants (younger than 1 year). The distinctive phenotypes of seizures at these early ages likely result, in part, from differences in neuronal function and connectivity in the immature versus mature CNS [1].

Neonatal Seizures are characteristically very subtle (especially to the non-neonatologist) and may consist of brief episodes of apnea, eye deviation, eye blinking, or repetitive movements of the arms and legs. An EEG is critical for diagnosis in such cases. Generalized tonic-clonic seizures, multifocal clonic seizures, and myoclonus can also be observed in some patients, but these are the exception rather than the rule.

Infantile Spasms are usually seen in infants less than 12 months of age and are characterized by abrupt movements of the head, trunk, or limbs that often occur in clusters of 10 to 20 movements per episode. The classic spasm is a sudden flexion of the neck and abdomen with extension of the limbs ("jackknife" seizure), although other combinations of flexion and extension are described. Infantile spasms are often quite subtle and can appear strikingly similar to the signs of discomfort in a baby with colic. The EEG usually shows hypsarrythmia, which consists of high-voltage slowing, multifocal spikes and a variety of other pleomorphic abnormalities. Infantile spasms are often seen in association with other signs of CNS dysfunction, including developmental delay and mental retardation [3].

Epilepsy syndromes

In addition to recognizing the patterns of different types of seizures, it is also useful to be familiar with some of the more common epilepsy syndromes, since this often helps in the determination of therapy and prognosis. Epilepsy syndromes are disorders in which epilepsy is a predominant feature, and there is sufficient evidence

(e.g., through clinical, EEG, radiologic, or genetic observations) to suggest a common underlying mechanism. Some examples are listed below [5].

Idiopathic (primary) epilepsy syndromes

▪**Benign Neonatal Convulsions** is an idiopathic, generalized seizure disorder observed in otherwise normal newborn infants typically between the second to sixth day of life. The seizures are usually tonic or manifest as short apneic spells and spontaneously remit within days to weeks; the infants have no further problems. A subgroup of patients has an inherited form of this syndrome known as benign familial neonatal convulsions. A mutation in chromosome 20 has been shown to be associated with the disease in at least one family [1].

▪**Juvenile Myoclonic Epilepsy** is a generalized seizure disorder of unknown cause that appears in early adolescence and is usually characterized by bilateral myoclonic jerks that may be single or repetitive. The myoclonic seizures are most frequent in the morning after awakening and can be provoked by sleep deprivation. Consciousness is preserved unless the myoclonus is especially severe. Many patients also experience generalized tonic-clonic seizures, and up to one-third have absence seizures. The condition is otherwise benign, and although complete remission is uncommon, the seizures respond well to appropriate anticonvulsant medication. There is often a family history of epilepsy, and genetic linkage studies suggest a polygenic cause.

▪**Benign Childhood Epilepsy with Centrotemporal Spikes** is idiopathic, focal epilepsy that appears in otherwise normal children between ages 3 and 13 and may account for 25% of all epilepsies in childhood. Patients have brief, simple-partial seizures characterized by hemifacial sensory or motor symptoms that can spread to the limbs or become generalized. Most seizures, especially those that generalize, occur during sleep. The interictal EEG shows a distinctive pattern of high-voltage spikes or sharp waves in the centrotemporal region that may shift from one side to the other. The seizures are easily treated with anticonvulsant medications and almost always remit by age 15. The disorder has an autosomal dominant inheritance pattern with variable

penetrance, and many clinically unaffected family members are found to have the EEG abnormality [5].

Symptomatic (secondary) epilepsy syndromes

▪**Lennox-Gastaut Syndrome** occurs in children (ages 1 to 8 y) and is defined by the following triad:

1) multiple seizure types (usually including generalized tonic-clonic, atonic, and atypical absence seizures);

2) an EEG showing slow (<3 Hz) spike-and-wave discharges and a variety of other abnormalities; and

3) impaired cognitive function in most but not all cases.

Lennox-Gastaut syndrome is associated with CNS disease or dysfunction from a variety of causes, including developmental abnormalities, perinatal hypoxia/ischemia, trauma, infection, and other acquired lesions. The multifactorial nature of this syndrome suggests that it is a nonspecific response of the brain to diffuse neural injury. Unfortunately, many patients have a poor prognosis due to the underlying CNS disease and the physical and psychosocial consequences of severe, poorly controlled epilepsy. A similar syndrome in infancy that often evolves into Lennox-Gastaut syndrome is West syndrome, characterized by infantile spasms, other findings of cerebral dysfunction, and a characteristic EEG pattern [8].

▪**Mesial Temporal Lobe Epilepsy Syndrome** (MTLE) is the most common syndrome associated with complex-partial seizures and is an example of symptomatic, partial epilepsy. Distinctive clinical, electroencephalographic, and pathologic features define this syndrome (Table 7).

High-resolution magnetic resonance imaging can detect the characteristic hippocampal sclerosis that appears to be an essential element in the pathophysiology of MTLE for many patients. Recognition of this syndrome is especially important because it tends to be refractory to treatment with anticonvulsants but responds extremely well to surgical intervention. Major advances in the understanding of basic mechanisms of epilepsy have come through studies of experimental models of MTLE [1].

Table 7

Characteristics of the Mesial Temporal Lobe Epilepsy (MTLE) Syndrome

HISTORY	
History of febrile seizures Positive family history of epilepsy Early onset Rare secondarily generalized seizures	Seizures may remit and reappear Seizures often intractable
CLINICAL OBSERVATIONS	
Aura common Behavioral arrest/stare Complex automatisms Unilateral posturing	Postictal disorientation, memory loss, dysphasia (with focus in dominant hemisphere)
LABORATORY STUDIES	
Unilateral or bilateral anterior temporal spikes on EEG Hypometabolism on interictal PET Hypoperfusion on interictal SPECT Material-specific memory deficits on intracranial amobarbital (Wada's) test MRI findings: Small hippocampus with increased signal on T2-weighted sequences Small temporal lobe Enlarged temporal horn Pathologic findings: Highly selective loss of specific cell populations within hippocampus in most cases	

Abbreviations: PET, positron emission tomography; SPECT, single photon emission computed tomography

Epilepsy is defined as a brain disorder characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition.

The new ILAE practical definition of epilepsy may be applied to any of the following conditions:

• At least two unprovoked (or reflex) seizures occurring >24 hours apart;

• One unprovoked (or reflex seizure) and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; and

• Diagnosis of an epilepsy syndrome.

In addition, epilepsy is considered to be "resolved" for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the past 10 years, with no seizure medicines for the past 5 years [91].

The definition of epilepsy has traditionally excluded "provoked seizures", but the new definition includes persons with photosensitive seizures who had previously been semantically excluded from having the diagnosis of epilepsy. In addition, patients who have had a single seizure, but with an underlying lesion such as stroke that is likely to produce further seizures, may receive the diagnosis of epilepsy. And for patients with a single seizure and clinical history and EEG suggestive of an epilepsy syndrome, a second seizure is no longer required to make the diagnosis of epilepsy [1].

Pathophysiology

A seizure results when abnormal neuronal firing manifests clinically by changes in motor control, sensory perception, behavior, or autonomic function.

Seizures also produce a number of physiologic changes. Many of these systemic responses are thought to be a result of the catecholamine surge that accompanies seizures [2]. During a generalized seizure, there can be a period of transient apnea and subsequent hypoxia. In a physiologic effort to maintain appropriate cerebral oxygenation, the patient may become hypertensive.

Additionally, transient hyperthermia may occur in up to 40% of patients and is thought to result from vigorous muscle activity that occurs in a seizure [3]. Hyperglycemia and lactic acidosis occur within minutes of a convulsive episode and usually resolve within 1 hour [5]. Transient leukocytosis may also be seen but is not accompanied by bandemia (unless infection is present).

In the setting of prolonged convulsive seizure activity or status epilepticus, there is pronounced systemic decompensation, including hypoxemia, hypercarbia, hypertension followed by hypotension, hyperthermia, depletion of cerebral glucose and oxygen, cardiac dysrhythmias, and rhabdomyolysis. These changes may even take place despite adequate oxygenation and ventilation. In extremis, pulmonary edema and disseminated intravascular coagulation (DIC) have also been reported [5].

Basic mechanisms. Mechanisms of seizure initiation and propagation

This sudden biochemical imbalance between excitatory neurotransmitters and the N-methyl-D-aspartate (NMDA) receptor and inhibitory forces (eg, gamma-aminobutyric acid [GABA]) at the neuronal cell membrane results in repeated, abnormal electrical discharges that may stay within a certain area of the brain or they may propagate throughout the brain resulting in generalized seizures. For example, in the event that these neuronal discharges are confined to the visual cortex, the seizure manifests itself with visual phenomena [2].

Partial seizure activity can begin in a very discrete region of cortex and then spread to neighboring regions, i.e., there is a seizure initiation phase and a seizure propagation phase. Studies of experimental models of these phases suggest that the initiation phase is characterized by two concurrent events in an aggregate of neurons:

1) high-frequency bursts of action potentials,

2) hypersynchronization.

The bursting activity is caused by a relatively long-lasting depolarization of the neuronal membrane due to influx of extracellular calcium (Ca^{2+}), which leads to the opening of voltage-dependent sodium (Na^{+}) channels; influx of Na^{+}; and generation of repetitive action potentials. This is followed by a hyperpolarizing afterpotential mediated by gamma-aminobutyric acid (GABA) receptors or potassium (K^{+}) channels, depending on the cell type. The synchronized bursts from a sufficient number of neurons result in a so-called spike discharge on the EEG [5].

Normally, the spread of the bursting activity is prevented by intact hyperpolarization and a region of surrounding inhibition created by inhibitory neurons.

With sufficient activation there is a recruitment of surrounding neurons via a number of mechanisms. Repetitive discharges lead to the following:

1) an increase in extracellular K^+, which blunts the extent of hyperpolarization and depolarizes neighboring neurons;

2) accumulation of Ca^{2+} in presynaptic terminals, leading to enhanced neurotransmitter release;

3) depolarization-induced activation of the NMDA subtype of the excitatory aminoacid receptor, which causes more Ca^{2+} influx and neuronal activation. The recruitment of a sufficient number of neurons leads to a loss of the surrounding inhibition and propagation of seizure activity into contiguous areas via local cortical connections and to more distant areas via long commissural pathways such as the corpus callosum [1].

Many factors control neuronal excitability, and thus there are many potential mechanisms for altering a neuron's propensity to have bursting activity. Examples of mechanisms intrinsic to the neuron include changes in the conductance of ion channels, response characteristics of membrane receptors, cytoplasmic buffering, second-messenger systems, and protein expression as determined by gene transcription, translation, and posttranslational modification. Mechanisms extrinsic to the neuron include changes in the amount or type of neurotransmitters present at the synapse, modulation of receptors by extracellular ions and other molecules, and temporal and spatial properties of both synaptic and nonsynaptic input. Nonneural cells, such as astrocytes and oligodendrocytes, have an important role in many of these mechanisms as well.

Certain known causes of seizures are explained by these mechanisms. For example, accidental ingestion of domoic acid, which is an analogue of glutamate (the principal excitatory neurotransmitter in the brain), causes profound seizures via direct activation of excitatory aminoacid receptors throughout the CNS. Penicillin, which can lower the seizure threshold in humans and is a potent convulsant in experimental models, reduces inhibition by antagonizing the effects of GABA and its receptor. The

basic mechanisms of other precipitating factors of seizures, such as sleep deprivation, fever, alcohol withdrawal, hypoxia, and infection, are not as well understood but presumably involve analogous perturbations in neuronal excitability. Similarly, the endogenous factors that determine an individual's seizure threshold may relate to these properties as well [8].

Knowledge of the mechanisms responsible for the initiation and propagation of most generalized seizures (including tonic-clonic, myoclonic, and atonic types) remains rudimentary and reflects the limited understanding of the connectivity of the brain at a systems level. Much more is understood about the origin of generalized spike- and-wave discharges in absence seizures. These appear to be related to oscillatory rhythms that are normally generated during sleep by circuits connecting the thalamus and cortex. This oscillatory behavior involves an interaction between $GABA_B$ receptors, T-type Ca^{2+} channels, and K^+ channels located within the thalamus. Pharmacologic studies indicate that modulation of these receptors and channels can induce absence seizures, and there is speculation that the genetic forms of absence epilepsy may be associated with mutations of components of this system [13].

Mechanisms of epileptogenesis. Epileptogenesis refers to the transformation of a normal neuronal network into one that is chronically hyperexcitable. For example, there is often a delay of months to years between an initial CNS injury such as trauma, stroke, or infection and the first seizure. The injury appears to initiate a process that gradually lowers the seizure threshold in the affected region until a spontaneous seizure occurs. In many genetic and idiopathic forms of epilepsy, epileptogenesis is presumably determined by developmentally regulated events.

Pathologic studies of the hippocampus from patients with temporal lobe epilepsy have led to the suggestion that some forms of epileptogenesis are related to structural changes in neuronal networks. For example, many patients with MTLE syndrome have a highly selective loss of neurons that has been proposed to contribute to inhibition of the main excitatory neurons within the dentate gyrus. There is also evidence that, in response to the loss of neurons, there is reorganization or “sprouting" of surviving

neurons in a way that affects the excitability of the network. Some of these changes can be seen in experimental models of prolonged electrical seizures or traumatic brain injury. Thus, an initial injury such as head injury may lead to a very focal, confined region of structural change that causes local hyperexcitability. The local hyperexcitability leads to further structural changes that evolve over time until the focal lesion produces clinically evident seizures. Similar models have also provided strong evidence for long-term alterations in intrinsic, biochemical properties of cells within the network, such as chronic changes in glutamate receptor function. Recent studies of a rare childhood epilepsy syndrome (Rasmussen's syndrome) have also raised the possibility that some forms of epileptogenesis may be caused by an immune response in which autoantibodies against glutamate receptors lead to receptor activation, depolarization, seizures, and excitotoxic cell injury [14].

Etiology. For patients with known seizure disorder, the most likely cause is subtherapeutic levels of antiepileptic medications, which usually occur for 1 of the following reasons:

- Medical noncompliance
- Systemic derangement that may disrupt absorption, distribution, and metabolism of medication (infection) [5].

The causes of seizures and epilepsy

Seizures are a result of a shift in the normal balance of excitation and inhibition within the CNS. Given the numerous properties that control neuronal excitability, it is not surprising that there are many different ways to perturb this normal balance, and therefore many different causes of both seizures and epilepsy. Our understanding of the basic mechanisms involved remains very limited, and consequently there is not a rigorous, mechanistic-based framework for organizing all the etiologies. Conceptually, however, three important clinical observations emphasize how a variety of factors determine why certain conditions may cause seizures or epilepsy in a given patient:

1) the normal brain is capable of having a seizure under the appropriate circumstances, and there are differences between individuals in the susceptibility or

threshold for seizures. For example, seizures may be induced by high fevers in children who are otherwise normal and who never develop other neurologic problems, including epilepsy. However, febrile seizures occur only in approximately 3-5% of children. This implies there are various underlying, endogenous factors that influence the threshold for having a seizure. Some of these factors are clearly genetic, as it has been shown that a family history of epilepsy will influence the likelihood of seizures occurring in otherwise normal individuals. Normal development also plays an important role, since the brain appears to have different seizure thresholds at different maturational stages [3].

2) there are a variety of conditions that have an extremely high likelihood of resulting in a chronic seizure disorder. One of the best examples of this is severe, penetrating head trauma, which is associated with up to a 50% risk of leading to epilepsy. The high propensity for severe traumatic brain injury to lead to epilepsy suggests that the injury results in a long-lasting, pathologic change in the CNS that transforms a presumably normal neural network into one that is abnormally hyperexcitable. This process is known as epileptogenesis, and the specific changes that result in a lowered seizure threshold can be considered epileptogenic factors. Other processes associated with epileptogenesis include stroke, infections, and abnormalities of CNS development. Likewise, the genetic abnormalities associated with epilepsy, such as the gene mutations linked to benign familial neonatal convulsions or JME, likely involve processes that trigger the appearance of specific sets of epileptogenic factors [1].

3) seizures are episodic. Patients with epilepsy have seizures intermittently and, depending on the underlying cause, many patients are completely normal for months or even years between seizures. This implies there are important provocative or precipitating factors that induce seizures in patients with epilepsy. Similarly, precipitating factors are responsible for causing the single seizure in someone without epilepsy. Précipitants include those due to intrinsic physiologic processes, such as psychological or physical stress, sleep deprivation, or hormonal changes associated with

the menstrual cycle. They also include exogenous factors such as exposure to toxic substances and certain medications.

These observations emphasize the concept that the many causes of seizures and epilepsy result from a dynamic interplay between endogenous factors, epileptogenic factors, and precipitating factors. The potential role of each factor needs to be carefully considered when determining the appropriate management of a patient with seizures. For example, the identification of predisposing factors (e.g., family history of epilepsy) in a patient with febrile seizures may increase the necessity for closer follow-up and a more aggressive diagnostic evaluation. Finding an epileptogenic lesion may help in the estimation of seizure recurrence and duration of therapy. Finally, removal or modification of a precipitating factor may be an effective and safer method for preventing further seizures than the prophylactic use of anticonvulsant drugs [5].

Causes according to age

In practice, it is useful to consider the etiologies of seizures based on the age of the patient, as age is one of the most important factors determining both the incidence and likely causes of seizures or epilepsy (Table 8). During the neonatal period and early infancy, potential causes include hypoxic-ischemic encephalopathy, trauma, CNS infection, congenital CNS abnormalities, and metabolic disorders. Babies born to mothers using neurotoxic drugs such as cocaine, heroin, or ethanol are susceptible to drug-withdrawal seizures in the first few days after delivery. Hypoglycemia and hypocalcemia, which can occur as secondary complications of perinatal injury, are also causes of seizures early after delivery. Seizures due to inborn errors of metabolism usually present once regular feeding begins, typically 2 to 3 days after birth. Pyridoxine (vitamin B_6) deficiency, an important cause of neonatal seizures, can be effectively treated with pyridoxine replacement. The idiopathic or inherited forms of benign neonatal convulsions are also seen during this time period [3].

The most common seizures arising in late infancy and early childhood are febrile seizures, which are associated with fevers but without evidence of CNS infection or other defined causes. The overall prevalence is 3-5% and even higher in some parts of

the world, such as Asia. Patients often have a family history of febrile seizures or epilepsy. Febrile seizures usually occur between 3 months and 5 years of age and have a peak incidence between 18 and 24 months. The typical scenario is a child who has a generalized tonic-clonic seizure during a febrile illness in the setting of a common childhood infection such as otitis media, respiratory infection, or gastroenteritis. The seizure is likely to occur during the rising phase of the temperature curve (i.e., during the first day) rather than well into the course of the illness. A simple febrile seizure is a single, isolated event, brief, and symmetric in appearance. Complex febrile seizures have repeated seizure activity, last more than 15 minutes, or have focal features. Approximately one-third of patients with febrile seizures will have a recurrence, but fewer than 10% have three or more episodes. Recurrences are much more likely when the febrile seizure occurs in the first year of life. Simple febrile seizures are not associated with an increase in the risk of developing epilepsy, while complex febrile seizures have a risk of 2-5%t; other risk factors include the presence of preexisting neurologic deficits and a family history of nonfebrile seizures [8].

Table 8

The Causes of Seizures

Neonates (<1 month)	Perinatal hypoxia and ischemia Intracranial hemorrhage and trauma Acute CNS infection (bacterial and viral meningitis) Metabolic disturbances (hypoglycemia, hypocalcemia, hypomagnesemia, pyridoxine deficiency) Drug withdrawal Developmental disorders (acquired and genetic) Genetic disorders
Infants and children (>1 mo and <12 years)	Febrile seizures Genetic disorders (metabolic, degenerative, primary epilepsy syndromes) CNS infection Developmental disorders (acquired and genetic) Trauma

	Idiopathic
Adolescents (12-18 years)	Trauma Genetic disorders Infection Brain tumor Illicit drug use Idiopathic
Young adults (18-35 years)	Trauma Alcohol withdrawal Illicit drug use Brain tumor Idiopathic
Older adults (>35 years)	Cerebrovascular disease Brain tumor Alcohol withdrawal Metabolic disorders (uremia, hepatic failure, electrolyte abnormalities, hypoglycemia) Alzheimer's disease and other degenerative CNS diseases Idiopathic

Childhood marks the age at which many of the well-defined epilepsy syndromes present, including typical childhood absence epilepsy and benign childhood epilepsy with centrotemporal spikes. Some children who are otherwise normal develop idiopathic, generalized tonic-clonic seizures without other features that fit into specific syndromes. Temporal lobe epilepsy usually presents in childhood and may be related to mesial temporal lobe sclerosis (as part of the MTLE syndrome) or other focal abnormalities such as cortical dysgenesis. Other types of partial seizures, including those with secondary generalization, may be the relatively late manifestation of a developmental disorder, an acquired lesion such as head trauma, CNS infection (especially viral encephalitis), or very rarely a CNS tumor. This is also the period that Lennox-Gastaut syndrome is identified, almost always in the child who has other neurologic problems such as static encephalopathy [13].

The period of adolescence and early adulthood is one of transition during which the idiopathic or genetically based epilepsy syndromes, including JME and juvenile absence epilepsy, become less common, while epilepsies secondary to acquired CNS lesions begin to predominate. Seizures in patients in this age range can be associated with head trauma, CNS infections (including parasitic infections such as cysticercosis), brain tumors, congenital CNS abnormalities, illicit drug use, or alcohol withdrawal.

Head trauma is a common cause of epilepsy in adolescents and adults. The head injury can be caused by a variety of mechanisms, and the likelihood of developing epilepsy is strongly correlated with the severity of the injury. A patient with a penetrating head wound, depressed skull fracture, intracranial hemorrhage, or prolonged posttraumatic coma or amnesia has a 40-50% risk of developing epilepsy, while a patient with a closed head injury and cerebral contusion has a 5-25% risk. Recurrent seizures usually develop within 1 year after head trauma, although intervals of 10 years or longer are well known. In controlled studies, mild head injury, defined as a concussion with amnesia or loss of consciousness of less than ½ h, was not found to be associated with an increased likelihood of epilepsy. Nonetheless, most epileptologists know of patients who have partial seizures within hours or days of a mild head injury and subsequently develop chronic seizures of the same type; such cases may represent rare examples of chronic epilepsy resulting from mild head injury [5].

The causes of seizures in older adults include cerebrovascular disease, trauma (including subdural hematoma), CNS tumors, and degenerative diseases. Cerebrovascular disease may account for approximately 50% of new cases of epilepsy in patients older than 65. Acute seizures (i.e., occurring at the time of the stroke) are seen more often with embolic rather than hemorrhagic or thrombotic stroke, Chronic seizures typically appear months to years after the initial event and are associated with all forms of stroke [1].

Metabolic disturbances such as electrolyte imbalance, hypo- or hyperglycemia, renal failure, and hepatic failure may cause seizures at any age. Similarly, endocrine disorders, hematologic disorders, vasculitides, and many other systemic diseases may

cause seizures over a broad age range. A wide variety of medications and abused substances are known to precipitate seizures as well (Table 9).

Table 9

Drugs and Other Substances that Can Cause Seizures

Antimicrobials β-lactam and related compounds Quinolones Isoniazid Ganciclovir Anesthetic and antiarrhythmics Beta-adrenergic antagonists Local anesthetics Class IB agents Immunosuppressants Cyclosporin OKT3 (monoclonal antibodies to T cells) Psychotropics Antidepressants Antipsychotics Lithium	Radiographic contrast agents Theophylline Sedative-hypnotic drug withdrawal Alcohol Barbiturates Benzodiazepines Drugs of abuse Amphetamine Cocaine Phencyclidine Methylphenidate

Genetic causes of epilepsy syndromes have recently been discovered.

Myoclonic epilepsy with ragged red fibers (MERRF) syndrome is associated with a mutation of mitochondrial tRNA-lysine. Mutations in the cystatin B gene may cause another form of progressive myoclonus epilepsy (Unverricht-Lundborg type), and a mutation within the gene encoding the β_4 subunit of the acetylcholine receptor appears responsible for a frontal lobe epilepsy syndrome consisting of nocturnal partial seizures A number of other epilepsy syndromes have been mapped to chromosomal locations. Epilepsy has been produced in transgenic mice having a wide range of genetically engineered mutations, suggesting that many potential genetic abnormalities can result in a change in the seizure threshold [1].

Epidemiology. Epilepsy and seizures affect more than 3 million American of all ages. Approximately 200 000 new cases occur each year, of which 40-50% will recur be

classified as epilepsy [5]. Overall, approximately 50 000-150 000 cases will reach status epilepticus.

Incidence is highest in those younger than 2 years and in those older than 65 years. Males are slightly more likely to develop epilepsy than females.

History of head trauma, history of stroke, and family history of epilepsy are all independent risk factors for first seizures in adults.[7] After the first seizure, overall recurrence risk in adults is 30-40% (greatest in the first 6 months). This risk drops to less than 10% in 2 years [3].

Clinical Presentation

Patient history. The history should first determine whether the event was truly a seizure. It is essential to take the time to gather an in-depth history for in many cases the diagnosis of a seizure is based solely on clinical grounds - the examination and laboratory studies are often normal. Keeping in mind the characteristics of different seizure types, questions need to focus precisely on the symptoms before, during, and after the episode in order to discriminate a seizure from other paroxysmal events. Seizures frequently occur out-of-hospital, and the patient may be unaware of the ictal and immediate postictal phases; thus witnesses to the event should be interviewed carefully [8].

A history of epilepsy is often noted (if the patient is unconscious, family, friends, or prehospital personnel can be questioned). Other history findings may include the following:

- Recent noncompliance with medications
- History of central nervous system pathology (stroke, neoplasms, recent surgery)
- History of systemic neoplasms, infections, metabolic disorders, or toxic ingestions
- Recent trauma or fall
- Alcohol abuse
- Recent travel or immigration to the U.S.

- Pregnancy
- Focal symptoms (partial seizure activity) that then progressed to a generalized seizure [13].

Physical examination. When a patient presents shortly after a seizure, the first priorities are attention to vital signs, respiratory and cardiovascular support, and treatment of seizures if they resume. Life-threatening conditions such as CNS infection, metabolic derangement or drug toxicity must be recognized and managed appropriately.

When the patient is not acutely ill, the evaluation will initially focus on whether or not there is a history of earlier seizures. If this is the patient's first seizure, then the emphasis will be to:

1) establish whether the reported episode was a seizure rather than another paroxysmal event,

2) determine the cause of the seizure by identifying risk factors and precipitating events,

3) decide whether anticonvulsant therapy is required in addition to treatment for any underlying illness.

In the patient with prior seizures or a known history of epilepsy, the evaluation is directed toward:

1) identification of the underlying cause and precipitating factors,

2) determination of the adequacy of the patient's current therapy [1].

The history should also focus on risk factors and predisposing events. Clues for a predisposition to seizures include a history of febrile seizures, earlier auras or brief seizures not recognized as such, and a family history of seizures. Epileptogenic factors such as prior head trauma, stroke, tumor, or vascular malformation should be identified. In children, a careful assessment of developmental milestones may provide evidence for underlying CNS disease. Precipitating factors such as sleep deprivation, systemic diseases, electrolyte or metabolic derangements, acute infection, drugs that lower the seizure threshold, or alcohol or illicit drug use should also be identified [5].

The general physical examination includes a search for signs of infection or systemic illness. Careful examination of the skin may reveal signs of tuberous sclerosis (adenoma sebaceum, “ash- leaf” spots), neurofibromatosis (café au lait spots, peripheral neurofibromas), Sturge-Weber syndrome (facial angioma), or chronic liver or renal disease. A finding of organomegaly may indicate a metabolic storage disease, and limb asymmetry may provide a clue for brain injury early in development. Signs of head trauma and use of alcohol or illicit drugs: should be sought. Auscultation of the heart and carotid arteries may identify an abnormality that predisposes to cerebrovascular disease [1].

A generalized seizure is recognizable at the bedside when tonic-clonic activity is present. If the patient is actively seizing, attempt to observe motor activity, as posturing (decerebrate/decorticate) and eye deviation may provide clues to the epileptic focus.

A partial seizure may present as isolated seizure activity with or without loss of consciousness. The workup for partial seizures is more extensive and requires neurologic consultation. Identifying a partial seizure that then generalizes to a full tonic-clonic seizure may be difficult, as this may be missed as the initial presentation of a generalized seizure.

In a generalized tonic-clonic seizure, accurate vital signs are difficult to obtain. Low-grade fever may be present initially, but prolonged fever may be an indication of infectious etiology [8].

Mental status examination is important. As noted, any seizure with loss of consciousness is considered a complex seizure. All patients require a complete neurologic examination, with particular emphasis on eliciting signs of cerebral hemispheric disease. Careful assessment of mental status (including memory, language function, and abstract thinking) may suggest lesions in the anterior frontal, parietal, or temporal lobes. Testing of visual fields will help screen for lesions in the optic pathways and occipital lobes. Screening tests of motor function such as pronator drift, deep tendon reflexes, gait, and coordination may suggest lesions in motor (frontal) cortex,

and cortical sensory testing (e.g., double simultaneous stimulation) may detect lesions in the parietal cortex [1].

Focal deficits on neurologic examination may be evidence of an old lesion, new pathology, or Todd's paralysis (transient, <24 h paralysis that mimics stroke). Hyperreflexia and extensor plantar responses are indicative of a recent seizure but should resolve during the postictal period.

Special concerns in patients with seizures in the emergency departement (ED) include the following:

- Eclampsia
- Trauma
- Intracranial hemorrhage (ICH)
- Alcohol withdrawal or medication withdrawal
- Drug-induced seizures

Seizures in pregnancy are a complication of severe, untreated preeclampsia. In fact, eclampsia can occur up to 4 weeks after delivery [8]. Seizing pregnant patients should be treated just as nonpregnant patients are because the risk of complications from the seizure outweighs the risk of toxicity from the antiepileptics. Fortunately, eclamptic seizures are usually short in duration. Magnesium sulfate is the treatment of choice for eclamptic seizures because it is the most effective medication for prevention of recurrent seizures [8].

In addition, patients with postpartum eclampsia, especially those with late postpartum eclampsia, have a higher incidence of cerebral venous thrombosis, intracranial hemorrhage, and acute ischemic stroke than do eclamptic patients diagnosed prepartum. Although most women with typical eclampsia do not need brain imaging, postpartum eclamptic patients and those with focal neurological deficits, persistent visual disturbances, and symptoms refractory to magnesium and antihypertensive treatment should undergo thorough diagnostic testing, preferably including MRI [13].

Seizures after trauma can be due to a variety of injuries, and intracranial pathology must be ruled out. The risk of posttraumatic seizures with an obvious

underlying injury is directly related to the severity of the injury but is not significantly affected by early use of antiepileptic medications [1].

Stroke related to ICH may predispose the patient to seizures. Deep, small intraparenchymal bleeds are thought to be low risk unless they involve the temporal regions. Larger bleeds that cause mass effects pose a higher risk of seizures. Common practice is to consider a prophylactic loading dose of an antiepileptic medication (typically phenytoin or fosphenytoin).

Alcohol withdrawal can occur anywhere from 6 to 48 hours after cessation of drinking and can occur at any blood alcohol level. Benzodiazepines are the mainstay of therapy, and large doses may be necessary to control the withdrawal and prevent or control seizures [3].

Barbiturate or benzodiazepine withdrawal may cause seizure. With certain agents, symptoms may not develop for days or even weeks after cessation of use.

Tricyclic antidepressant (TCA) overdose and isoniazid (INH) therapy/overdose are 2 of the more common causes of drug-induced seizures. An ECG will show a widened QRS and prominent R wave in lead aVR. Treatment of TCA overdose consists of bicarbonate infusion and supportive care. Pyridoxine is the treatment of choice for known INH ingestion.

Differential Diagnosis. The various disorders that may mimic seizures

Table 10

The Differential Diagnosis of Seizures

1. Syncope Vasovagal syncope Cardiac arrhythmia Valvular heart disease Cardiac failure Orthostatic hypotension	5. Transient ischemic attack (TIA) Basilar artery TIA
2. Psychological disorders Psychogenic seizure Hyperventilation Panic attack	6. Sleep disorders Narcolepsy/cataplexy Benign sleep myoclonus
	7. Movement disorders Tics Nonepileptic myoclonus Paroxysmal choreoathetosis
	8. Special considerations in children

3. Metabolic disturbances Alcoholic blackouts Delirium tremens Hypoglycemia Hypoxia Psychoactive drugs(e.g., hallucinogens)	Breath-holding spells Migraine with recurrent abdominal pain and cyclic vomiting Benign paroxysmal vertigo Apnea Night terrors Sleepwalking
4. Migraine Confusional migraine Basilar migraine	

In most cases seizures can be distingished from these other conditions by meticulous attention to the history and relevant laboratory studies. On occasion, additional studies, such as video-EEG monitoring, sleep studies, tilt table analysis, or cardiac electrophysiology may be required to reach a correct diagnosis. Two of the more common syndromes in the differential diagnosis are detailed below [1].

- Delirium Tremens
- Delirium, Dementia, and Amnesia
- Eclampsia
- Encephalitis
- Epidural and Subdural Infections
- Febrile Seizures
- Heatstroke
- Hyperventilation Syndrome
- Hypoglycemia
- Hyponatremia
- Hypothyroidism and Myxedema Coma
- Meningitis
- Movement Disorders in Individuals with Developmental Disabilities
- Hemorrhagic Stroke
- Ischemic Stroke
- Subarachnoid Hemorrhage

- Syncope
- Anticholinergic Toxicity
- Antidepressant Toxicity
- Antihistamine Toxicity
- Carbon Monoxide Toxicity
- Cardiac Arrhythmias
- Cyclic Antidepressant Toxicity
- Isoniazid Toxicity
- Transient Global Amnesia
- Transient Ischemic Attack
- Withdrawal Syndromes.

Other conditions to be considered include the following:

- Carotid sinus hypersensitivity
- Fugue states
- Heat exhaustion
- Hyperventilation
- Malingering
- Migraine narcolepsy/cataplexy
- Night terrors
- Panic attacks
- Paroxysmal vertigo
- Trauma

The diagnostic dilemma encountered most frequently is the distinction between a generalized seizure and syncope. Observations by the patent and bystanders that can help discriminate between the two are listed in Table 11.

Table 11

Clinical Features of a Generalized Tonic Clonic Seizure Versus Syncope

Features	Seizure	Syncope
Immediate precipitating factors	Usually none	Emotional stress, Valsalva, other specific causes
Premonitory symptoms	None or aura (e.g., odd odor)	Tiredness, nausea, diaphoresis, tunneling of vision
Posture at onset	Variable	Usually erect
Transition to unconsciousness	Often immediate	Gradual over seconds*
Duration of unconsciousness	Minutes	Seconds
Duration of tonic or clonic movements	30-60 s	Never more than 15 s
Facial appearance during event	Cyanosis, frothing at mouth	Pallor
Disorientation and sleepiness after event	Many minutes to hours	<5 min
Aching of muscles after event	Often	Sometimes
Biting of tongue	Sometimes	Rarely
Incontinence	Sometimes	Sometimes

*May be sudden with certain cardiac arrhythmias.

Characteristics of a seizure include the presence of an aura, cyanosis, unconsciousness, motor manifestations lasting more than 30 s, postictal disorientation, muscle soreness, and sleepiness. In contrast, a syncopal episode is more likely if the event was provoked by acute pain or anxiety or occurred immediately after arising from the lying or sitting position. Patients with syncope often describe a stereotyped transition from consciousness to unconsciousness that includes tiredness, sweating, nausea, and tunneling of vision, and they experience a relatively brief loss of consciousness [1]. Headache or incontinence may be observed following either a seizure or syncope and are thus not useful distinguishing features. A brief period (i.e., 1 to 10 s) of convulsive motor activity is frequently seen immediately at the onset of a syncopal episode, especially if the patient remains in an upright posture after fainting (e.g., in a

dentist's chair) and therefore has a sustained decrease in cerebral perfusion. Rarely, a syncopal episode can induce a full tonic-clonic seizure. In such cases the evaluation must focus on both the cause of the syncopal event as well as the possibility that the patient has a propensity for recurrent seizures [8].

Psychogenic Seizures are nonepileptic behaviors that resemble seizures. The behavior is often part of a conversion reaction precipitated by underlying psychological distress. Certain behaviors, such as side-to-side turning of the head, asymmetric and large amplitude shaking movements of the limbs, twitching of all four extremities without loss of consciousness, pelvic thrusting, and screaming or talking during the event, are more commonly associated with psychogenic rather than epileptic seizures. However, the distinction is sometimes difficult on clinical grounds alone, and there are many examples of diagnostic errors made by experienced epileptologists. This is especially true for psychogenic seizures that resemble complex-partial seizures, since the behavioral manifestations of complex-partial seizures (especially of frontal lobe origin) can be extremely unusual, and in both cases the routine surface EEG may be normal. Video-EEG monitoring is often useful when the clinical observations are nondiagnostic. Generalized tonic-clonic seizures always produce marked EEG abnormalities during and after the seizure. For suspected complex-partial seizures of temporal lobe origin, the use of additional electrodes beyond the standard scalp locations (e.g., sphenoidal electrodes) may be required to detect a seizure focus. Measurement of serum prolactin levels may also help to discriminate between organic and psychogenic seizures, since most generalized seizures and many complex-partial seizures are accompanied by rises in serum prolactin (during the immediate 30-min postictal period), whereas psychogenic seizures are not. It is important to note that the diagnosis of psychogenic seizures does not exclude a concurrent diagnosis of epilepsy, since the two often coexist [5].

Laboratory Studies

Clinical information should guide the specific workup of a patient. Studies have shown a low yield for extensive laboratory tests in the evaluation of a patient presenting

with a first-time single seizure. In 1 study, laboratory tests such as blood counts, blood glucose level, and electrolyte panels were abnormal in as many as 15% of individuals[14]; however, most abnormalities were incidental or insignificant.

An American College of Emergency Physicians Clinical Policy recommends the following in adults with new-onset seizure [5]: serum glucose level, serum sodium level, and pregnancy test in women of childbearing age.

For patients with a first-time, generalized tonic-clonic seizure, an electrolyte panel and a urine or serum pregnancy test should be obtained. Other tests can be ordered at the physician's discretion on the basis of the history and symptoms. For patients with known seizure disorder who are currently taking medications, blood levels of antiepileptic medications should be obtained. Levels are often not available for newer agents. For patients with a history of malignancy, serum calcium levels should be obtained.

No evidence suggests that toxicologic testing changes outcomes [1]. Toxicologic testing may be beneficial for help with future medical and psychiatric management.

An arterial blood gas (ABG) measurement has limited clinical utility for the patient in status epilepticus because it will likely reveal metabolic acidosis but should rapidly correct after the patient stops seizing.

Computed Tomography

For patients with new-onset seizures or those in status epilepticus, noncontrast computed tomography (CT) of the head in the ED is the imaging procedure of choice because of its ready availability and ability to identify potential catastrophic pathologies.

For the patient who presents for a first-time, generalized tonic-clonic seizure that has returned to baseline mental status, who has normal results on neurologic examination, and who has no comorbidities, CT may be completed as on outpatient basis, provided that follow-up is ensured. Because of the availability and speed of CT scanning in the ED, routine CT scanning for first-time seizure is strongly recommended.

For any partial seizure or suspected intracranial process (trauma, history of malignancy, immunocompromise, or anticoagulation, new focal neurologic examination, age >40 y), a head CT should be performed on an emergency basis. 41% of adults have abnormal CT after first generalized seizure, but only 6-10% is abnormal if there are no focal deficits [8]. Another study showed that overall, CT scans in the emergency department for adults presenting with seizure resulted in a change of acute management in 9-17% of patients . The yield from scanning increases with age.

Approximately 3-41% of patients with first-time seizures will have abnormal findings on head CT [18] .The timing of CT scanning is still somewhat controversial.

In patients with a known seizure disorder, consider head CT if any of the following are present: new focal deficits, trauma, persistent fever, new character or pattern to the seizures, suspicion of AIDS, infection, or anticoagulation. In general, however, the evidence is inadequate to support or refute the usefulness of emergency CT in persons with chronic seizures [1].

Magnetic Resonance Imaging (MRI) may be a better diagnostic test because of higher yield and ability to identify smaller lesions, but its availability in the ED may be a limiting factor. MRI is time-consuming and may interfere with adequate patient monitoring.

Other Studies

ECG should be considered in certain patients. Seizure activity can be precipitated by cerebral hypoperfusion from an arrhythmia. ECG may identify the following:

- Prolonged QTc
- Widened QRS
- Prominent R in aVR
- Heart block

Electroencephalography (EEG) is not routinely available in the ED. EEG should be part of the full neurodiagnostic workup, as it has substantial yield and ability to predict risk of seizure recurrence. In the ED, EEG should be considered if available and if the patient is paralyzed, is intubated, or is in refractory status epilepticus to ensure

that seizure activity is controlled. The EEG performed within 24 hours after a first seizure detected epileptiform abnormalities in 51% of patients compared with only 34% of those who had a later EEG [8].

Lumbar puncture should be considered for patients with immunocompromise, persistent fever, severe headache, or persistently altered mental status.

Treatment & Management. "Seizures beget seizures" is a generally accepted clinical axiom. The argument follows that earlier treatment is more effective than later treatment in halting status epilepticus (SE) .

In caring for the seizure patient in the ED, 3 basic pitfalls must be avoided.

1) The failure to recognize seizure activity. Nonconvulsive seizure is a rare presentation of altered mental status but should always be on the differential of the comatose patient. EEG is the diagnostic modality of choice for identifying these patients.

2) The failure to control seizure activity aggressively. Neurologic dysfunction is theorized to occur after 20 minutes of continuous seizure activity, even despite adequate oxygenation and ventilation. Therefore, there should be a low threshold for aggressive treatment of any seizure activity that lasts over 5 minutes.

3) The failure to consider the underlying etiology. Although medication noncompliance and subtherapeutic medication levels are among the most common causes of seizure presentations to the ED, patients should also be screened for underlying infectious or metabolic causes of seizure when indicated. In patients with therapeutic medication levels, fever, altered mental status, or other indication, laboratory and imaging studies should be considered, though breakthrough seizures often occur even in compliant patients with therapeutic drug levels [8].

Therapy for a patient with a seizure disorder is almost always multimodal and includes treatment of underlying conditions that cause or contribute to the seizures, avoidance of precipitating factors, and suppression of recurrent seizures by prophylactic therapy with antiepileptic medications or surgery, and addressing a variety of psychological and social issues. Treatment plans must be individualized, given the many different types and causes of seizures as well as the differences in efficacy and toxicity of antiepileptic medications for each patient. In almost all cases a neurologist

with experience in the treatment of epilepsy should design and oversee implementation of the treatment strategy. Furthermore, patients with refractory epilepsy or those who require polypharmacy with antiepileptic drugs should remain under the regular care of a neurologist [3].

Treatment of Underlying Conditions. If the sole cause of a seizure is a metabolic disturbance such as an abnormality of serum electrolytes or glucose, then treatment is aimed at reversing the metabolic problem and preventing its recurrence. Therapy with antiepileptic drugs is usually unnecessary unless the metabolic disorder cannot be corrected promptly and the patient is at risk of having further seizures. If the apparent cause of a seizure was a medication (e.g., theophylline) or illicit drug use (e.g., cocaine), then appropriate therapy is avoidance of the drug and there is usually no need for antiepileptic medications unless subsequent seizures occur.

Seizures caused by a structural CNS lesion such as a brain tumor, vascular malformation, or brain abscess may not recur after appropriate treatment of the underlying lesion. However, despite removal of the structural lesion, there is a risk that the seizure focus will remain in the surrounding tissue or develop de novo as a result of gliosis and other processes induced by surgery, radiation, or other therapies. Most patients are therefore maintained on an antiepileptic medication for at least 1 year, and an attempt is made to withdraw medications only if the patient has been completely seizure-free. If the seizures are refractory to medication, the patient may benefit from surgical removal of the epileptic brain region [5].

Avoidance of Precipitating Factors. Unfortunately, little is known about the specific factors that determine precisely when a seizure will occur in a patient with epilepsy. Some patients can identify particular situations that appear to lower their seizure threshold these situations should be avoided. For example, a patient who has seizures in the setting of sleep deprivation should be advised to maintain a normal sleep schedule. Many patients note an association between alcohol intake and seizures, and they should be encouraged to modify their drinking habits accordingly. There are also relatively rare cases of patients with seizures that are induced by highly specific stimuli such as a video game monitor, music, or an individual's voice ("reflex epilepsy"). If

there is an association between stress and seizures, stress reduction techniques such as physical exercise meditation, or counseling may be helpful [3].

Prehospital care of the seizure patient is mostly supportive; most seizures are of short duration, especially pediatric simple febrile seizures. The ABCs (A-irway, B-reathing, C-irculation) should be evaluated as necessary, including oxygenation and airway assessment, temperature assessment, blood glucose assessment, and spinal precautions.

Intravenous (IV) access should be obtained for almost all patients (it may be deferred in those with simple febrile seizures). Emergency medical service protocols should include benzodiazepines (IV, intramuscular [IM], or rectal) for prolonged seizures or SE [2].

ED care should be individualized. Sometimes, the most difficult part of the ED evaluation is determining whether the patient has had a seizure. Clues to the diagnosis include a clear history of tonic-clonic movements, urinary or bowel incontinence, postepisode confusion, and tongue biting. However, myoclonic jerking was found in 90% of individuals in which syncope was induced [1]. Attempt to obtain history from emergency medical service providers, family, friends, or observers who may have been present during the episode.

Mechanisms of action of antiepileptic drugs. It is important to understand the mechanisms of action and the pharmacokinetics of antiepileptic drugs so that these agents can be used effectively in clinical practice, especially in multidrug regimens (Figure 1).

Currently available antiepileptic drugs appear to act primarily by blocking the initiation or spread of seizures. Phenytoin, carbamazepine, valproic acid, and lamotrigine inhibit Na^+-dependent action potentials in a frequency-dependent manner, resulting in a preferential blockade of the sustained high-frequency activity that is characteristic of burst-firing neurons in a seizure focus. Phenytoin also appears to suppress seizure spread through inhibition of specific voltage-gated Ca^{2+} channels. Benzodiazepines and barbiturates augment inhibition by distinct interactions with GABA receptors.

Valproic acid elevates the concentration of GABA in the brain, perhaps through interaction with enzymes involved in the synthesis (glutamic acid decarboxylase) and catabolism (GABA transaminase) of GABA [8].

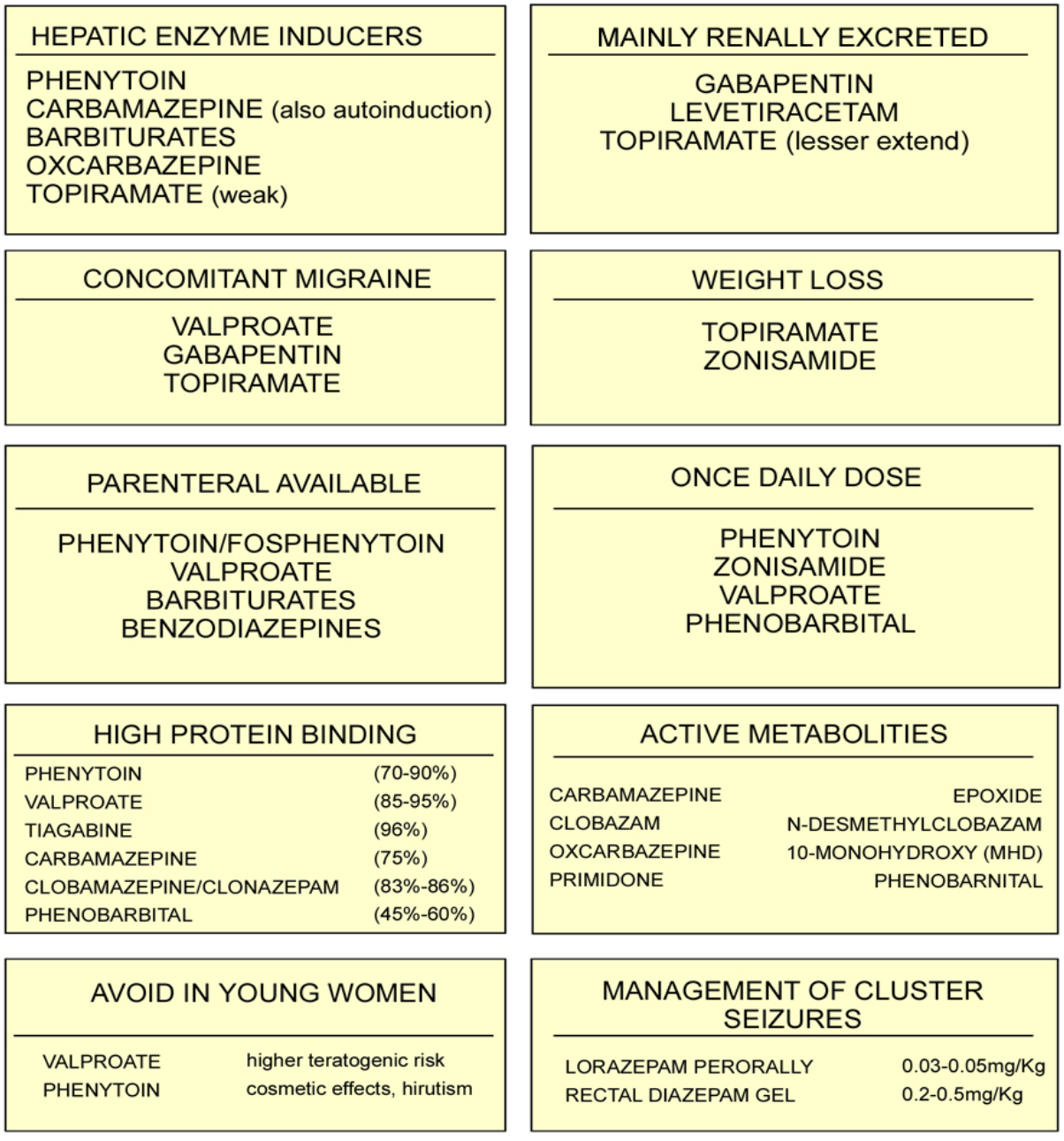

Figure 1. Pearls of antiepileptic drug use and management [8].

Gabapentin, which is a structural analogue of GABA, appears to increase GABA levels by enhancing GABA synthesis and release and may also cause a decrease in glutamate synthesis. The two most effective drugs for absence seizures, ethosuximide

and valproic acid, probably act by inhibiting T-type Ca^{2+} channels in thalamic neurons (Fig. 2, 3).

In contrast to the relatively large number of antiepileptic drugs that can attenuate seizure activity, there are currently no drugs known to prevent the formation of a seizure focus following CNS injury in humans. The eventual development of such "antiepileptogenic" drugs will provide an important means of preventing the emergence of epilepsy following injuries such as head trauma, stroke, and CNS infection.

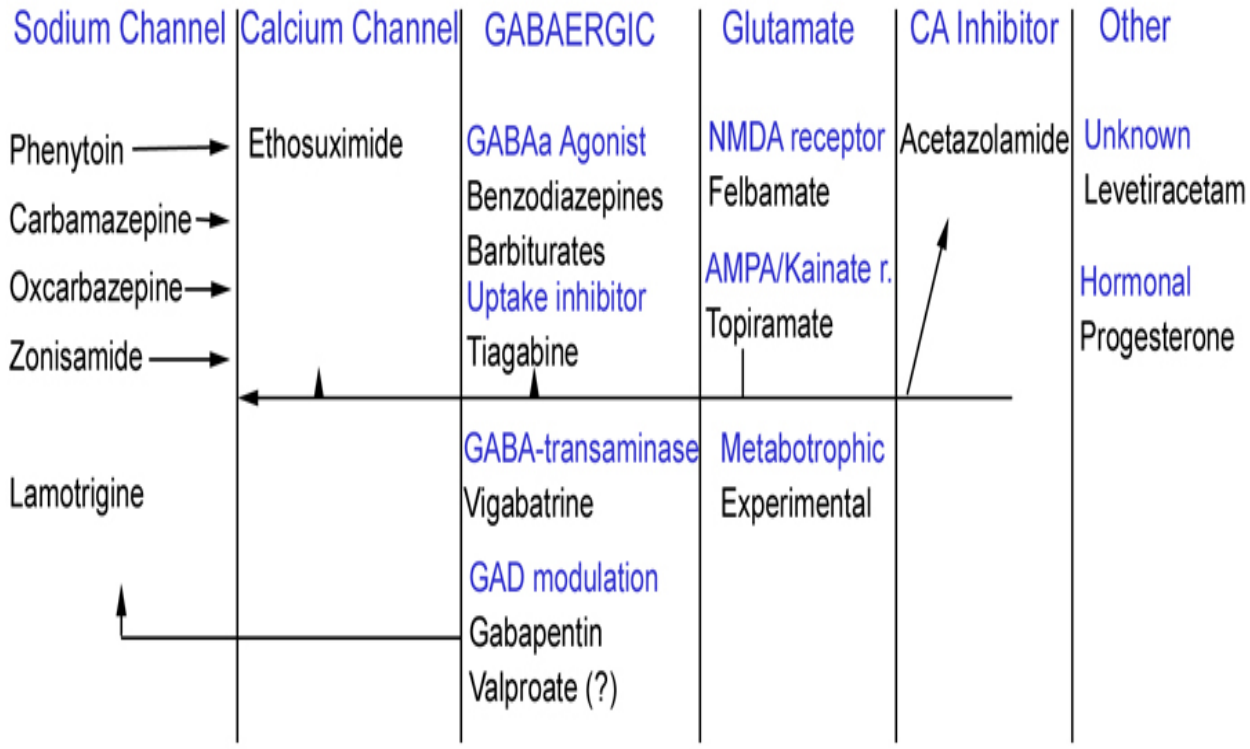

Figure 2. Antiepileptic drugs can be grouped according to their major mechanism of action. Some antiepileptic drugs work by acting on combination of channels or through some unknown mechanism of action [1].

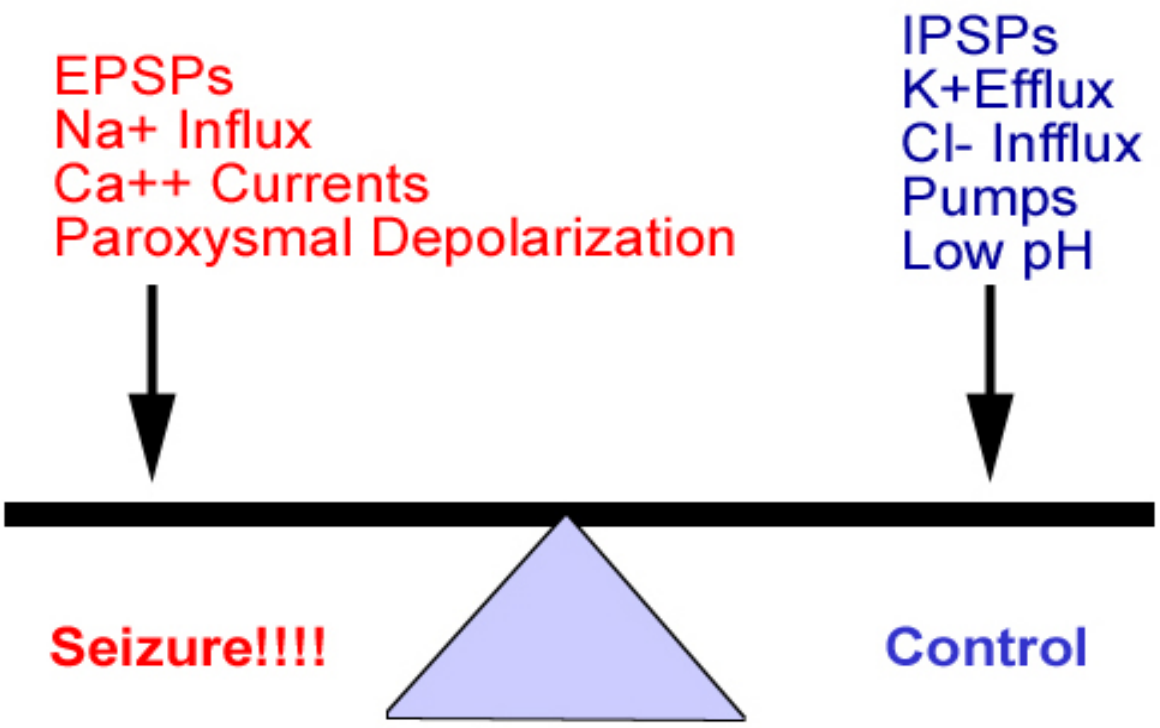

Figure 3**.** Dynamic target of seizure control in management of epilepsy is achieving balance between factors that influence excitatory postsynaptic potential (EPSP) and those that influence inhibitory postsynaptic potential (IPSP) [2].

Medications

Current consensus is that benzodiazepines are the preferred drug class for the initial treatment of SE. Lorazepam, when available, is thought to be the most effective of the benzodiazepines and has a longer seizure half-life than diazepam.

No difference in efficacy was observed between caregiver-administered intranasal midazolam and rectal diazepam for terminating sustained seizures (ie, >5 minutes) in children at home [22]. Caregiver's satisfaction was higher with the inhaled midazolam (easier to administer) and the median time from medication administration to seizure cessation was 1,3 minutes less for inhaled midazolam compared with rectal diazepam.

One new technology being investigated is a benzodiazepine intramuscular pen that can be used in the prehospital setting (including at home) [3].

Phenytoin or fosphenytoin (Cerebyx) is the next drug to be administered when a second drug is needed. Failure to respond to optimal benzodiazepine and phenytoin loading operationally defines refractory SE.

No data clearly support a best third-line drug, controlled trials are lacking, and recommendations vary greatly. The list of third-line drugs includes barbiturates, propofol, valproate, levetiracetam, and lidocaine. A general principle is to maximize benzodiazepine and phenytoin dosages before adding an additional agent. Many of these drugs are classified as category D in pregnancy. However, these drugs may be used in life-threatening situations, such as generalized convulsive SE (GCSE) [1].

Barbiturates may be useful when the condition fails to respond to phenytoin and benzodiazepines. Phenobarbital is the commonly used third-line drug, but midazolam, propofol, and others are increasingly used in preference to this agent, though no rigorous evidence supports the use of one third-line drug over another.

Anesthetics stabilize the neuronal membrane so the neuron is less permeable to ions. This prevents the initiation and transmission of nerve impulses, thereby producing the local anesthetic effects. In SE, lidocaine is indicated during refractory status only and is supported only by anecdotal reports. The consensus seems to be moving toward propofol or midazolam infusions for refractory SE.

Seizure complications are generally uncommon when medications are taken as indicated. Complications include drug side effects, tongue biting, and other minor trauma from falls during seizures. For inpatient treatment, fall precautions should be followed to ensure that patients do not inadvertently injure themselves [1].

Management of patients who have stopped seizing

For those who present with a witnessed seizure who have stopped seizing, supportive care is adequate. If antiepileptic medication levels are found to be low, it is appropriate to give a loading dose in the ED and discharge the patient home, as long as there are no other concerning features to the presentation.

Phenytoin is an extremely common antiepileptic medication and is classically given as “1 g” in the ED; it is sometimes delivered half orally (PO) and half

parenterally. Oral absorption of phenytoin can be erratic, but when the agent is given in the appropriate doses (15-20 mg/kg PO either as a single dose or divided into 400-600 mg per dose every 2 h), it can achieve therapeutic serum levels [5].

Both valproic acid and phenobarbital can also be given parenterally as a 20 mg/kg loading dose [2].

Carbamazepine has proven to be effective for oral loading, but it is associated with a high rate of adverse effects. Therefore, oral loading is not recommended at this time [27].

Newer antiepileptic drugs, such as lamotrigine and levetiracetam, have varying drug profiles and are still being studied. Doses of these medications should be given in consultation with a neurologist.

Initial considerations for patients with ongoing seizure

If the patient's seizure activity has not abated at ED presentation, the ABCs should be addressed as follows.

Administer oxygen. For patients who are in SE or are cyanotic, endotracheal intubation using rapid sequence intubation should be strongly considered. If rapid sequence intubation is employed, short-acting paralytics should be given to ensure that ongoing seizure activity is not masked. Consider EEG monitoring in the ED if the patient has been paralyzed because there is no other method to determine if seizure activity is still present.

Establish large-bore intravenous (IV) access. Initiate rapid glucose determination, and treat appropriately. Consider antibiotics with or without antiviral agents, depending on the clinical situation [1].

The goal of treatment is to control the seizure before neuronal injury occurs (theoretically between 20 min to 1 h). Central nervous system infections and anoxic injury are the leading causes of mortality associated with SE.

Management of patients with active seizure

ED management of active seizures begins with administration of benzodiazepines, which is considered first-line therapy. IV options include lorazepam, diazepam, and midazolam. If IV access cannot be obtained, then IM lorazepam or midazolam, or rectal diazepam can be considered. IV lorazepam was found to be superior to IV diazepam in both seizure cessation and preventing recurrent seizures [8].

A common regimen is 0,1 mg/kg of lorazepam IV given at 2 mg/min or 0,2 mg/kg of diazepam IV given at 5-10 mg/min. Very large doses of benzodiazepines may be needed. There is no specific upper limit to benzodiazepine dose when used for acute seizure control. As with all sedatives, monitor the patient for respiratory or cardiovascular depression.

Phenytoin is usually considered the second-line agent for patients who continue to seize despite aggressive benzodiazepine therapy. The recommended dose is 20 mg/kg IV and can be augmented with another 10 mg/kg IV if the patient is still seizing. Care should be taken with the administration of parenteral phenytoin because the propylene glycol diluent may cause hypotension, cardiac arrhythmias, and death if given too quickly [1].

Fosphenytoin is a phenytoin precursor that is considered to be safer than phenytoin by some authors because it does not contain a propylene glycol diluent [31]. Other authors have disputed the idea that fosphenytoin has a safety advantage, and this agent is much more expensive than phenytoin [2]. Fosphenytoin may be administered IM, and this is an advantage for patients without IV access.

Valproic acid is effective in treating all forms of seizure. The recommended dose acid is 15-20 mg/kg. Valproic acid has an excellent safety profile [33]. It is contraindicated in hepatic dysfunction because of the extremely rare occurrence of fatal idiosyncratic hepatotoxicity [3].

Phenobarbital is similar to lorazepam with respect to efficacy. The recommended dose is 20 mg/kg, but like phenytoin, phenobarbital can be given in doses as high as 30

mg/kg for severe refractory seizures. Phenobarbital may cause hypotension and respiratory depression.

If 2 or more of the initial drug therapies fail to control the seizures, then the next line of treatment includes continuous infusions of antiepileptic medications. The major side effects are hypotension and respiratory depression. The patient should be intubated (if this has not already been done), and preparations should be made to support the patient's cardiovascular status.

Pentobarbital has a shorter duration of action than phenobarbital does but a greater sedating effect. Pentobarbital should be administered in a bolus at 5-15 mg/kg, followed by continuous infusion of 0,5-10 mg/kg/h as tolerated.

Midazolam is administered as a 0,2 mg/kg bolus, followed by continuous infusion of 0,05-2 mg/kg/h. Midazolam is slightly less effective at stopping seizures than either propofol or pentobarbital, but treatment with midazolam has a lower frequency of occurrence of hypotension [5].

Propofol appears to be very effective at terminating seizures, but only limited data are available. Propofol is administered in a bolus at 2-5 mg/kg, followed by continuous infusion of 20-100 µg/kg/min. It is limited by the syndrome of hypotension, metabolic acidosis, and hyperlipidemia seen with prolonged infusions [3].

Currently, there are no randomized controlled trials available to guide the treatment of refractory status epilepticus. New avenues that have been investigated include hypothermia, transcranial stimulation, and deep brain stimulation.

Consultations

Many patients with seizure may be managed without consultation. Consultation should be considered in the following circumstances:

- SE - Consider consulting a neurologist or an intensivist.
- Breakthrough seizure in a compliant patient with therapeutic levels - Consider consulting the physician responsible for long-term management of the patient's seizure disorder. Medication changes may be needed and ideally should be coordinated with a physician providing ongoing care.

Further inpatient care

Disposition is based on the severity and underlying cause of the patient's seizures. Most patients will be admitted to a telemetry floor for close monitoring, further workup, and treatment of their underlying condition. Any patient with SE, severe alcohol withdrawal, or underlying conditions (eg, diabetic ketoacidosis) requiring intensive monitoring and care is best served in an intensive care unit setting.

Further out-patient care. For those with first-time generalized tonic-clonic seizures with no concerning features (eg, failure to return to baseline), a normal ED workup, and not at risk for repeat seizure (eg, alcoholics), the patient can be discharged home once good follow-up is arranged on an urgent basis with the patient's primary care physician or a neurologist [8].

Patients who were found to have subtherapeutic levels of medications may be given loading doses orally or parenterally as indicated and should undergo follow-up with their primary physician or neurologist on an urgent basis.

In/outpatient medications

Inpatient medications are given on the basis of the patient's underlying diagnosis, severity, and pre-existing medications in consultation with a neurologist.

Outpatient medications may include phenytoin, valproic acid, gabapentin, levetiracetam, carbamazepine, phenobarbital, or other medications. Any changes to the medication regimen should be completed in consultation with the patient's neurologist or primary physician. Little evidence suggests the need to start medications out of the ED. In fact, one study showed that antiepileptic drugs started immediately after first unprovoked generalized tonic-clonic seizures or started after seizure recurrence do not affect survival over the succeeding 20 years [3].

Antiepileptic Drug Therapy is the mainstay of treatment for most patients with epilepsy. The overall goal is to completely prevent seizures without causing any untoward side effects, preferably with a single medication and a dosing schedule that is easy for the patient to follow. Seizure classification is an important element in designing the treatment plan, since some antiepileptic drugs have different activities against

various seizure types. However, there is considerable overlap between many antiepileptic drugs, such that the choice of therapy is often determined more by specific needs of the patient, especially the patient's subjective assessment of side effects [1].

When To Initiate Antiepileptic Drug Therapy. Antiepileptic drug therapy should be started in any patient with recurrent seizures of unknown etiology or a known cause that cannot be reversed. Whether to initiate therapy in a patient with a single seizure is controversial. Patients with a single seizure due to an identified lesion such as a CNS tumor, infection, or trauma, in which there is strong evidence that the lesion is epileptogenic, should be treated. The risk of seizure recurrence in a patient with an apparently unprovoked or idiopathic seizure is uncertain, with estimates ranging from 31 to 71% in the first 12 months after the initial seizure. This uncertainty arises from differences in the underlying seizure types and etiologies in various published epidemiologic studies. Generally accepted risk factors associated with recurrent seizures include the following:

1) an abnormal neurologic examination,

2) seizures presenting as status epilepticus,

3) postictal Todd's paralysis,

4) a strong family history of seizures,

5) an abnormal EEG.

Most patients with one or more of these risk factors should be treated. Issues such as employment or driving may influence the decision whether or not to start medications as well. For example, a patient with a single, idiopathic seizure and whose job depends on driving may prefer taking antiepileptic drugs rather than risking a seizure recurrence and the potential loss of driving privileges [8].

Selection Of Antiepileptic Drugs The choices of antiepileptic drugs in the United States for different seizure types are shown in Table 12.

Table 12

Antiepileptic Drugs of Choice

	Generalized Seizures			
Focal-Onset Seizures*	**Generalized Tonic-Clonic**	**Absence**	**Myoclonic**	**Atonic**
FIRST-LINE				
Carbamazepine Phenytoin Valproic acid	Valproic acid Carbamazepine Phenytoin	Ethosuximide Valproic acid	Valproic acid	Valproic acid
ALTERNATI-VES				
Lamotrigine Gabapentin Phénobarbital Primidone	Phénobarbital Primidone	Acetazolamide Clonazepam Phénobarbital	Clonazepam Acetazolamide	Clonazepam

*Simple-partial, complex-partial, and secondarily generalized tonic-clonic seizures.

Older medications such as phenytoin, valproic acid, carbamazepine, and ethosuximide aregenerally used as first-line therapy for most seizure disorders since, overall, they are as effective as recently marketed drugs and significantly less expensive. Experience with newer drugs such as gabapentine and lamotrigine is comparatively limited in the United States, and their use is predominantly as add-on or alternative therapy. Felbamate, introduced in 1993, was found to be associated with a relatively high incidence of irreversible aplastic anemia and hepatic failure and is currently recommended only for medically refractory patients [5].

In addition to efficacy, other factors influencing the specific choice of an initial medication for a patient include the relative convenience of dosing schedule (e.g., once daily versus three or four times daily) and potential side effects. Almost all of the commonly used antiepileptic drugs can cause similar, dose-related side effects such as sedation, ataxia, and diplopia. Close follow-up is required to insure these are promptly recognized and reversed. Most of the drugs may also cause idiosyncratic toxicity such as rash, bone marrow suppression, or hepatotoxicity. Although rare, these side effects need to be carefully considered during drug selection, and patients require laboratory

tests (e.g., complete blood count and liver function tests) prior to the institution of a drug (to establish baseline values) and during initial dosing and titration of the agent.

1. **Antiepileptic drug selection for partial seizures.** Carbamazepine or phenytoin is currently the initial drug of choice for the treatment of partial seizures, including those that secondarily generalize. Overall they have very similar efficacy, but differences in pharmacokinetics and toxicity are the main determinants for use in a given patient. Phenytoin has a relatively long half-life and offers the advantage of once or twice daily dosing compared to two or three times daily dosing for carbamazepine. An advantage of carbamazepine is that its metabolism follows first-order pharmacokinetics, and the relationship between drug dose, serum levels, and toxicity is linear [98]. By contrast, phenytoin shows properties of saturation kinetics, such that small increases in phenytoin doses above a standard maintenance dose can precipitate marked side effects. This is one of the main causes of acute phenytoin toxicity. Long-term use of phenytoin is associated with untoward cosmetic effects (e.g., hirsutism, coarsening of facial features, and gingival hypertrophy), so it is often avoided in young patients who are likely to require the drug for many years. Carbamazepine can cause leukopenia, aplastic anemia, or hepatotoxicity and would therefore be contraindicated in patients with predispositions to these problems [3].

2. **Valproic acid is an effective alternative for some patients with partial seizures**, especially when the seizures secondarily generalize. Gastrointestinal side effects are fewer when using the valproate semisodium formulation. Valproic acid also rarely causes reversible bone marrow suppression and hepatotoxicity, and laboratory testing is required to monitor toxicity. This drug should generally be avoided in patients with preexisting bone marrow or liver disease. Irreversible, fatal hepatic failure appearing as an idiosyncratic rather than dose-related side-effect is a relatively rare complication; its risk is highest in children younger than 2 years old, especially those taking other antiepileptic drugs or with inborn errors of metabolism. Valproic acid therapy should therefore only be used in infants and young children when the benefits clearly exceed this risk [1].

Lamotrigine, gabapentin, and phenobarbital are additional drugs currently used for the treatment of partial seizures with or without secondary generalization. Lamotrigine appears to have an overall efficacy profile similar to the more standard drugs but may cause severe rash or Stevens-Johnson syndrome, particularly in children. Lamotrigine must be started very slowly when used as add-on therapy with valproic acid, since its inhibition of lamotrigine metabolism causes a substantial prolongation of its half-life. Gabapentin is unique among the standard antiepileptic drugs in not having any significant drug interactions. This makes it potentially useful as add-on therapy, especially in patients who are particularly susceptible to side effects of other medications. Gabapentin is also useful in patients with severe liver disease since its clearance is exclusively renal. Until recently, phenobarbital and other barbiturate compounds were commonly used as first-line therapy for many forms of epilepsy. However, the barbiturates frequently cause sedation in adults, hyperactivity in children, and other more subtle cognitive changes; thus, their use should be limited to situations in which no other suitable treatment alternatives exist [8].

3. **Antiepileptic drug selection for generalized seizures.** Valproic acid is currently considered the best initial choice for the treatment of primarily generalized, tonic-clonic seizures, and carbamazepine and phenytoin are suitable alternatives. Valproic acid is also particularly effective in absence, myoclonic, and atonic seizures and is therefore the drug of choice in patients with epilepsy syndromes having mixed seizure types. Ethosuximide remains the preferred drug for the treatment of uncomplicated absence seizures but it is not effective against tonic-clonic or partial seizures. Ethosuxi mide rarely causes bone marrow suppression, so that periodic moni toring of blood cell counts is required. Clonazepam is an alternative for the treatment of myoclonic, atonic, and absence seizures, but it is not indicated for the treatment of most other seizure types. This is especially important since the drug is sometimes abused due to its sedative-hypnotic qualities rather than its antiepileptic effect Although approved for use in partial seizure disorders, lamotrigine is proving to be effective in epilepsy

syndromes with mixed, generalized seizure types such as JME and Lennox-Gastaut syndrome [1].

Initiation And Monitoring Of Therapy. Because the response to any antiepileptic drug is unpredictable, patients should be carefully educated about the approach to therapy. Patients need to understand that the goal is to prevent seizures and minimize the side effects of therapy; determination of the optimal dose is often a matter of trial and error. This process may take months or longer if the baseline seizure frequency is low. Most anticonvulsant drugs need to be introduced relatively slowly to minimize side effects, and patients should expect that minor side effects such as mild sedation slight changes in cognition, or imbalance will typically resolve within a few days. Starting doses are usually the lowest value. Subsequent increases should only be made after achieving a steady state with the previous dose (i.e., after an interval of five or more half-lives) [2].

Monitoring of serum antiepileptic drug levels can be very useful for establishing the initial dosing schedule. However, the published therapeutic ranges of serum drug concentrations are only an approximate guide for determining the proper dose for a given patient. The key determinants are the clinical measures of seizure frequency and presence of side effects, not the laboratory values. Conventional assays of serum drug levels measure the total drug (i.e., both free and protein-bound), yet it is the concentration of free drug that reflects extracellular levels in the brain and correlates best with efficacy. Thus, patients with decreased levels of serum proteins (e.g., decreased serum albumin due to impaired liver or renal function) may have an increased ratio of free to bound drag, yet the concentration of free drug may be adequate for seizure control. These patients may have a "subtherapeutic" drug level, but the dose should be altered only if seizures remain uncontrolled, not just to achieve a "therapeutic" level. In practice, other than during the initiation or modification of therapy, monitoring of antiepileptic drug levels is most useful for documenting compliance [8].

If seizures continue despite gradual increases to the maximum tolerated dose and documented compliance, then it becomes necessary to switch to another antiepileptic

drug. This is usually done by maintaining the patient on the first drug while a second drug is added. The dose of the second drug should be adjusted to decrease seizure frequency without causing toxicity. Once this is achieved, the first drug can be gradually withdrawn (usually over weeks unless there is significant toxicity). The dose of the second drug is then further optimized based on seizure response and side effects.

When To Discontinue Therapy. Overall, about 70% of children and 60% of adults who have their seizures completely controlled with antiepileptic drugs can eventually discontinue therapy. Clinical studies suggest that the following patient profile yields the greatest chance of remaining seizure-free after drug withdrawal:

1) complete medical control of seizures for 1 to 5 years;

2) single seizure type, either partial or generalized;

3) normal neurologic examination, including intelligence;

4) normal EEG.

The appropriate seizure-free interval is unknown and undoubtedly vanes for different forms of epilepsy. However, it seems reasonable to attempt withdrawal of therapy after 2 years in a patient who meets all of the above criteria, is motivated to discontinue the medication, and clearly understands the potential risks and benefits. In most cases it is preferable to reduce the dose of the drug gradually over 2 to 3 months. Most recurrences occur in the first 3 months after discontinuing therapy, and patients should be advised to avoid potentially dangerous situations such as driving or unsupervised swimming during this period [5].

Treatment Of Refractory Epilepsy. Approximately one-third of patients with epilepsy do not respond to treatment with a single antiepileptic drug, and it becomes necessary to try a combination of drugs to control seizures. Patients who have focal epilepsy related to an underlying structural lesion, or those with multiple seizure types and developmental delay are particularly likely to require multiple drugs. There are currently no clear guidelines for rational polypharmacy, but in most cases the initial combination therapy is with two of the three first-line drugs, i.e., carbamazepine, phenytoin, and valproic acid. If these drugs are unsuccessful, then the addition of a

newer drug such as lamotrigine or gabapentin is indicated. Patients with myoclonic seizures resistant to valproic acid may benefit from the addition of clonazepam, and those with absence seizures may respond to a combination of valproic acid and ethosuximide. The same principles concerning the monitoring of therapeutic response, toxicity, and serum levels for monotherapy apply to polypharmacy, and potential drug interactions need to be recognized. If there is no improvement, a third drug can be added while the first two are maintained. If there is a response, the least effective of the first two drugs should be gradually withdrawn [1].

Status epilepticus (SE) is a common, life-threatening neurologic disorder that is essentially an acute, prolonged epileptic crisis. SE can represent an exacerbation of a preexisting seizure disorder, the initial manifestation of a seizure disorder, or an insult other than a seizure disorder. Most seizures terminate spontaneously. The duration of seizure activity sufficient to meet the definition of SE has traditionally been specified as 15 to 30 min. However, a more practical definition is to consider SE as a situation in which the duration of seizures prompts the acute use of anticonvulsant therapy, typically when seizures last beyond 5 min [8].

SE is an emergency, since cardiorespiratory dysfunction, hyperthermia, and metabolic derangements can develop as a consequence of prolonged seizures, and these can lead to irreversible neuronal injury after approximately 2 h. Furthermore, CNS injury can occur even when the patient is paralyzed with neuromuscular blockade but continues to have electrographic seizures. The most common causes of SE are anticonvulsant withdrawal or noncompliance, metabolic disturbances, drug toxicity, CNS infection, CNS tumors, refractory epilepsy, and head trauma [3].

Generalized SE is obvious when the patient is having overt convulsions. However, after 30-45 min of uninterrupted seizures, the signs may become increasingly subtle. Patients may have mild clonic movements of only the fingers, or fine, rapid movements of the eyes. There may be paroxysmal episodes of tachycardia, hypertension, and pupillary dilation. In such cases, the EEG may be the only method of

establishing the diagnosis. Thus, if the patient stops having overt seizures, yet remains comatose, an EEG should be performed to rule out ongoing SE.

Examination for SE includes the following:

- Generalized convulsive SE: Typical rhythmic tonic-clonic activity, impaired consciousness; rarely, may present as persistent tonic seizure
- SE due to the use of illicit, or street, drugs: needle-track marks
- SE due to possible mass lesion or brain infection: Papilledema, lateralized neurologic features
- Subtle or transformed SE: Any patient without improving level of consciousness within 20-30 minutes of cessation of generalized seizure activity
- Associated injuries in patients with seizures: May include tongue lacerations (typically lateral), shoulder dislocations, head trauma, facial trauma

Categorization of SE cases is no simple matter because they often exhibit characteristics of both focal and generalized processes. The Treiman classification is as follows:

- Generalized convulsive status epilepticus
- Subtle status epilepticus
- Nonconvulsive status epilepticus (eg, absence, complex partial)
- Simple partial status epilepticus [5].

Testing. The workup for potential SE is similar to that for any self-limited seizure but is done more expeditiously to confirm the diagnosis and to abort or limit the seizures.

Stat laboratory studies that should be obtained include the following:

- Glucose and electrolyte levels (including calcium, magnesium)
- Complete blood count
- Renal and liver function tests
- Toxicologic screening and anticonvulsant drug levels
- Arterial blood gas results

Other tests that may be appropriate depending on the clinical setting include the following:

- EEG: Criterion standard for diagnosing SE; neurologic consultation is usually required
- Blood cultures
- Urinalysis and/or cerebrospinal fluid analysis

Imaging studies used to evaluate status epilepticus may include the following:

- CT scanning and/or MRI of the brain
- Chest radiography

Aggressive treatment is necessary for SE. Clinicians should not wait for blood level results before administering a loading dose of phenytoin, regardless of whether the patient is already taking phenytoin [3].

Pharmacotherapy

Most patients with SE who are treated aggressively with a benzodiazepine, fosphenytoin, and/or phenobarbital experience complete cessation of their seizures. If SE does not stop, general anesthesia is indicated.

Medications used in the treatment of SE include the following:

- Benzodiazepines (eg, lorazepam, diazepam, midazolam): First-line agents
- Anticonvulsant agents (eg, phenytoin, fosphenytoin)
- Barbiturates (eg, phenobarbital, pentobarbital)
- Anesthetics (eg, propofol)

Supportive care in patients with SE includes the following:

- Maintenance of vital signs
- Airway, breathing, circulation (eg, hemodynamic/cardiac monitoring)
- Respiratory support, with intubation and/or mechanical ventilation if necessary
- Periodic neurologic assessments [5].

Transfer. If a patient is experiencing severe, refractory seizures, has a complicated diagnosis, or has requirements that exceed the resources of the hospital (eg,

a paralyzed seizing patient who requires EEG monitoring that is unavailable in the ED), strong consideration should be given to transferring the patient to a higher level of care.

Treatment algorithms for convulsive status epilepticus (see below) [1].

Deterrence/prevention. To date, there have been no data to indicate that any intervention other than medications effectively prevents seizures or SE. Therefore, medication compliance should always be emphasized to every patient.

Prognosis depends both on the underlying etiology of seizures and on whether seizures can be effectively terminated before irreversible neurologic damage has occurred. The overall mortality rate is about 20% for those who reach SE. The mortality rates are highest for those older than 75 years, reflecting an increased incidence of degenerative, neoplastic, and vascular pathologies.

As many as 50% of patients with epilepsy will have recurrent seizures despite medical therapy [39]. As many as 25% of patients with a first-time generalized seizure will have a recurrence within 2 years [3].

Patient Education. Patients can be counseled to be prepared for seizure activity and to avoid things that would put them at risk for complications. By law, patients are not able to drive unless they have been seizure free on medications for 1 year in most states. Any recreational activity that puts them at increased risk of injury if a seizure were to occur should be performed with at least 1 other person who is knowledgeable of the patient’s condition and able to intervene if necessary.

Patients can also carry rectal diazepam for treatment of breakthrough seizures. Many seizures are preceded by an aura, and patients can be educated to recognize their aura to prepare for a seizure.

Diagnostic work-up flowchart	Treatment flowchart
Check ABCs	▶ Start an IV line, administer a 50-mL bolus of 50% dextrose IV and 100 mg of thiamine, then start the anticonvulsant. In some settings where drug intoxication might be likely, consider also adding naloxone at 0.4-2.0 mg IV to the dextrose bag.
Insert IV	
STAT laboratory studies: ▸ Electrolites, calcium, magnesium ▸ CBC ▸ Liver and renal FX test ▸ Toxicology screen ▸ Anticonvulsant levels ▸ Artierial blood gas	▶ Administer diazepam (0.15 mg/kg) or lorazepam (0.1 mg/kg) IV over 5 minutes, followed preferably by fosphenytoin (15-20 mg phenytoin equivalents PE/kg at a rate not to exceed 150 mg PE/min) or phenytoin (18-20 mg/kg at a rate not to exceed 50 mg/min). Never mix phenytoin with a 5% dextrose solution; put it in a normal saline solution to minimize the risk of crystal precipitation.
Insert urinary catheter	
Urinalysis, urine toxicology	
Cardiac O2 saturation, monitors	▶ Intubate if necessary, and control hyperthermia.
Consider the following during general and neurologic exam: ▸ Trauma ▸ Infection ▸ Stroke ▸ Drug ingestion	▶ If seizures continue after 20 minutes, give additional fosphenytoin (10 mg PE/kg IV) or phenytoin (10 mg/kg IV). Aim for a total serum phenytoin level of about 22-25 µg/mL.
As indicated: ▸ Chest x-ray ▸ CT scan or MRI ▸ Lumbar puncture ▸ Blood culures ▸ Blood toxicology screen	▶ If seizures continue after 20 minutes, give phenobarbital (15 mg/kg IV). ▶ If seizures continue, consider administering general anesthesia.
Treat underlying disorder(s)	
Admit to hospital	

Beyond seizures: other management issues. **Interictal Behavior**

The adverse effects of epilepsy often go beyond the occurrence of clinical seizures, and the extent of these effects depends largely upon the etiology of the seizure disorder, the degree to which the seizures are controlled, and the presence of side effects from antiepileptic therapy. Many patients with epilepsy are completely normal between seizures and able to live highly successful and productive lives. In contrast, patients with seizures secondary to developmental abnormalities or acquired brain injury may have impaired cognitive function and other neurologic deficits. Frequent interictal EEG abnormalities have been shown to be associated with subtle dysfunction of memory and attention. Patients with many seizures, especially those emanating from the temporal lobe, often note an impairment of short-term memory that may progress over time[5].

Patients with epilepsy are at risk of developing a variety of psychiatric problems including depression, anxiety, and psychosis. This risk varies considerably depending on many factors, including the etiology, frequency, and severity of seizures and the patient's age and previous history. Depression occurs in approximately 20% of patients, and the incidence of suicide is higher in epileptic patients than in the general population. Depression should be treated through counseling or antidepressant medication. The selective serotonin reuptake inhibitors typically have no effect on seizures, while the tricyclic antidepressants may lower the seizure threshold. Anxiety can appear as a manifestation of a seizure, and anxious or psychotic behavior can sometimes be observed as part of a postictal delirium. Interictal psychosis is a rare phenomenon that typically occurs after a period of increased seizure frequency. There is usually a brief lucid interval lasting up to a week, followed by days to weeks of agitated, psychotic behavior. The psychosis will usually resolve spontaneously but may require treatment with antipsychotic or anxiolytic medications[8].

There is ongoing controversy as to whether some patients with epilepsy (especially partial-complex epilepsy) have a stereotypical "interictal personality". The predominant view is that the unusual or abnormal personality traits observed in such

patients are, in most cases, not due to epilepsy but result from an underlying structural brain lesion, the effects of antiepileptic drugs, or psychosocial factors.

Psychosocial Issues. There continues to be a cultural stigma about epilepsy, although it is slowly declining in societies with effective health education programs. Because of this stigma, many patients with epilepsy harbor fears, such as the fear of becoming mentally retarded or dying during a seizure. These issues need to be carefully addressed by educating the patient about epilepsy and by ensuring that family members, teachers, fellow employees, and other associates are equally well informed [1].

Employment and Driving. Many patients with epilepsy face difficulty in obtaining or maintaining employment, even when their seizures are well controlled. Federal and state legislation is designed to prevent employers from discriminating against patients with epilepsy, and patients should be encouraged to understand and claim their legal rights. Patients in these circumstances also benefit greatly from the assistance of health providers who act as strong patient advocates.

Loss of driving privileges is one of the most disruptive social consequences of epilepsy. Physicians should be very clear about local regulations concerning driving and epilepsy, since the laws vary considerably among states and countries. In all cases, it is the physician's responsibility to warn patients of the danger imposed on themselves and others while driving if their seizures are uncontrolled (unless the seizures are not associated with impairment of consciousness or motor control). In general, most states allow patients to drive after a seizure- free interval (on or off medications) between 6 months and 2 years [5].

Special issues related to women and epilepsy

Catamenial Epilepsy. Some women experience a marked increase in seizure frequency around the time of menses. This is thought to reflect either the effects of estrogen and progesterone on neuronal excitability or changes in antiepileptic drug levels due to altered protein binding. Acetazolamide (250 to 500 mg/d) has been found effective as adjunctive therapy when started 7 to 10 days prior to the onset of menses and continued until bleeding stops. Some patients may benefit from increases in

antiepileptic drug dosages during this time or from control of the menstrual cycle through the use of oral contraceptives [8].

Pregnancy. Most women with epilepsy who become pregnant will have an uncomplicated gestation and deliver a normal baby. However, epilepsy poses some important risks to a pregnancy. Seizure frequency during pregnancy will remain unchanged in approximately 50% of women, increase in 30%, and decrease in 20%. Changes in seizure frequency are attributed to endocrine effects on the CNS, variations in antiepileptic drug pharmacokinetics (such as acceleration of hepatic drug metabolism or effects on plasma protein binding), and changes in medication compliance. It is therefore useful to see patients at more frequent intervals during pregnancy and monitor serum antiepileptic drug levels. Measurement of the unbound drug concentrations may be useful if there is an increase in seizure frequency or worsening of side effects of antiepileptic drugs [1].

The overall incidence of fetal abnormalities in children born to mothers with epilepsy is 5 to 6%, compared to 2 to 3% in healthy women. Part of the higher incidence is due to teratogenic effects of antiepileptic drugs, and the risk increases with the number of medications used (e.g., 10% risk of malformations with three drugs). A syndrome comprising facial dysmorphism, cleft lip, cleft palate, cardiac defects, digital hypoplasia, and nail dysplasia was originally ascribed to phenytoin therapy, but it is now known to occur with other first-line antiepileptic drugs (i.e., carbamazepine and valproic acid) as well. Also, valproic acid and carbamazepine are associated with a 1 to 2% incidence of neural tube defects compared with a baseline of 0,5 to 1%. Little is currently known about the safety of newer drugs.

Since the potential harm of uncontrolled seizures on the mother and fetus is considered greater than the teratogenic effects of antiepileptic drugs, it is currently recommended that pregnant women be maintained on effective drug therapy. When possible, it seems prudent to have the patient on monotherapy at the lowest effective dose, especially during the first trimester. Patients should also take folate (1-4 mg), since the antifolate effects of anticonvulsants are thought to play a role in the

development of neural tube defects, although the benefits of this treatment remain unproved in this setting [3].

Enzyme-inducing drugs such as phenytoin, phenobarbital, and primidone cause a transient and reversible deficiency of vitamin K-dependent clotting factors in approximately 50% of newborn infants. Although neonatal hemorrhage is uncommon, the mother should be treated with oral vitamin K (20 mg daily) in the last 2 weeks of pregnancy, and the infant should receive an intramuscular injection of vitamin K (1 mg) at birth [8].

Breast Feeding. Antiepileptic medications are excreted into breast milk to a variable degree. The ratio of drug concentration in breast milk relative to serum is approximately 80% for ethosuximide, 40-60% for phenobarbital, 40% for carbamazepine, 15% for phenytoin, and 5% for valproic acid. Given the overall benefits of breast feeding and the lack of evidence for long-term harm to the infant by being exposed to antiepileptic drugs, mothers with epilepsy should not be discouraged from breast feeding. This should be reconsidered, however, if there is any evidence of drug effects on the infant, such as lethargy or poor feeding [13].

TASKS FOR FINAL CONTROL [10-12]

1. Which of the following are not referred to the focal epileptic attacks:

A. Jacksonian sensory.

B. Jacksonian motor.

C. Secondary generalized convulsive attacks with aura.

D. Kojewnikoff's epilepsy.

E. Absences.

2. Which of the following diseases could be taken into account if convulsive attack arose as a result of rise of temperature?

A. Epilepsy

B. Acute inflammatory cerebral diseases.

C. Alcoholism.

D. Acute hypertensive encephalopathy.

E. Brain infarction.

3. First aid in case of generalized tonoclonic seizure is:

A. Prevent further injury risk.

B. Prevent tongue bite.

C. Provide a patency of airways.

D. Diazepam 0,5% - 2 ml (fractionally up to 6 ml) after 10 min until the cessation of convulsions.

E. All of mentioned above.

4. First aid in the case of febrile convulsions:

A. Physical methods of cooling and hyperthermia.

B. Cleansing enema.

C. Antipyretic agents – ibuprofen 5-10mg/kg oral intake (for children older than 3 months), paracetamol 10-15 mg/kg, analgin 50% 0,1 ml per 1 year of life, intramuscularly, but no more than 1 ml.

D. Magnesium sulfate 25% intramuscularly 0,2 ml per 1 year of life but no more than 10 ml, diazepam 0,55 – 0,3 mg per 1 kg.

E. All of mentioned above.

5. While patient was in a stuffy room he felt sick, lazy eyesight, ringing in the ears, paleness and impairment of consciousness during 1 minute. What is working diagnosis?

A. Loss of consciousness.

B. Absence.

C. Torpor.

D. Sopor.

E. Attack without convulsions.

6. Emergency team delivered unconscious patient of 43 years old to admission department. After patient examination it was defined that patient opened his eyes and withdrew his hand in response to painful stimulation, and that his replies were with inappropriate words. Estimate the conscious level by Glasgow coma scale.

A. Clear consciousness.

B. Torpor.

C. Sopor.

D. Coma.

E. Brain death.

7. On the third day of acute respiratory viral infection 20-year-old patient had a headache, vomiting, tonoclonic colvunsions, spoor, oculogyric impairments, hemiparesis; trivial pleocytosis, reduced protein content. What is working diagnosis?

A. Meningitis.

B. Encephalitis.

C. Epilepsy.

D. Cerebral stroke.

E. Migrainous stroke.

8. First aid in the case of hepatic coma is:

A. Glucose 40% - 100 ml, vitamin, glucocorticoids, antidotes.

B. Glucose 40% - 100 ml, morphine hydrochloride, diuretics, barbiturates.

C. Glucocorticoids, antidotes, diuretics, barbiturates.

D. Glucose 40% - 100 ml, vitamin, diuretics, barbiturates.

E. Vitamin, glucocorticoids, antidotes, diuretics.

9. Untidy 50-year-old patient is in a coma. He has miotic pupils, hypersalivation, alcohol odor, muscular hyper tonus of extremities. Body temperature is $35,7^0$C. Blood pressure is 90/60. Define the type of coma:

A. Narcoma.

B. Diabetic coma.

C. Hypoglycemic coma.

D. Uremic coma.

E. Alcoholic coma.

10. 50-year-old patient is unconscious. He does not open eyes to painful stimulation but flexes upper extremities in response to pain. No verbal response. Estimate the level of conscious by Glasgow coma scale:

A. Clear consciousness .

B. Torpor.

C. Sopor.

D. Coma.

E. Brain death.

11. 20-year-old woman suddenly felt unwell while she was taking exercising in sports hall. She felt acute “strike” in her head which was accompanied with severe headache, sickness, multiple vomiting with further impairment of consciousness. The neurological status: somnolentia, tendon reflexes S=D, double-sided pathological Babinskii reflex, Bare test is neganive. Acute symptoms: stiffness of occiput muscles, double-sided Kernig sign, Brudzinski sign. What is working diagnosis?

A. Subarachnoid hemorrhage.

B. Parenchimatous hemorrhage.

C. Cerebellar hemorrhage.

D. Migrainous stroke.

E. Thromboembolic ischemic stroke.

12. 60-year-old patient with malignant course of arterial hypertension and with high blood pressure 210/130 felt diffuse intensive headache, sickness, vomiting, and impairment of consciousness, generalized tonic-clonic seizure. Neurological status: positive meningeal symptoms, no focal neurological symptoms. The eye grounds: double-sided edema of optic nerve disks. After blood pressure correction and brain edema, the described symptoms had been retrogressed after 72 hours. What is working diagnosis?

A. Acute hypertensive encephalopathy.

B. Subarachnoid hemorrhage.

C. Intraventricular hemorrhage.

D. Epilepsy.

E. Cardioembolic ischemic stroke.

13. 55-year-old patient felt sudden headache. He also had vomiting, hyperemia of face and psychomotor agitation. These symptoms arouse on the basis of arterial hypertension and after emotional stress. After 10 minutes there was impairment of consciousness and central superior paraplegia. In 3 hours meningeal symptom arose. What is working diagnosis?

A. Intracerebral bleeding

B. Subarachnoid hemorrhage.

C. Cerebellar hemorrhage.

D. Cardioembolic ischemic stroke.

E. Acute hypertensive encephalopathy.

14. After emotional stress the patient with previous myocardial infarction has coma. There was impairment of vital functions, hemodynamics reduction and respiratory impairment. Primary inspection: miotic pupils, flabby photoreaction, absence of tendon and pathological reflexes. What is working diagnosis?

A. Brainstem hemodynamic stroke.

B. Brainstem cardioembolic stroke.

C. Intracerebral bleeding.

D. Recurrent myocardial infarction.

E. Cardiogenic unconsciousness.

15. After athletic overexertion and alcohol intake 45-year-old patient has coma. Primary inspection: pale skin, hyperhidrosis, mydriasis, blood pressure 100/70 mm Hg, body temperature $36,7^0$C, clonic convulsions, overactive tendon reflexes. Define the type of coma.

A. After epileptic seizure.

B. Diabetic coma.

C. Hypoglycemic coma.

D. Coma as a result of stroke.

E. Alcoholic coma.

16. Emergency team delivered unconscious patient of 18 years old to admission department. Primary inspection: coma, cyanosis of face, injection marks extremities, miosis, Cheyne-Stokes respiration, BP 80/50 mm Hg, heart rate 48 beats per min. Define the type of coma:

A. Narcoma.

B. Diabetic coma.

C. Hypoglycemic coma.

D. Alcoholic coma.

E. Traumatic coma.

17. 50-year old woman was unconscious. Primary inspection: pale face, swelling, dry skin and mucous membranes, urine odor, BP 190/120 mmm Hg, epileptiform activity, meningeal syndrome. Define the type of coma:

A. Hepatic coma.

B. Diabetic coma.

C. Hypoglycemic coma.

D. Uremic coma.

E. Alcoholic coma.

18. 59-year old patient was in coma. Primary inspection: icteric skin and mucous membranes, nosebleed, mydriasis, absence of photoreaction, raw meat odor, periodic clonic convulsions, Cheyne-Stokes respiration, body temperature 38,2^{0}C, BP 80/60 mm Hg, heart rate 120 beats per minute, muffled heart sounds, anuria. Define the type of coma:

A. Hepatic coma.

B. Diabetic coma.

C. Hypoglycemic coma.

D. Uremic coma.

E. Alcoholic coma.

19. 60-year-old woman was unconscious. Primary inspection: dry skin and mucous membranes, cold loose skin, soft eye-bulbs by touch, nosebleed, mydriasis, Kussmaul's respiration, acetone odor, body temperature 36,2^{0}C, BP 70/40 mm Hg, hart rate 120 beats per minute, irregular heart rhythm, muffled heart sounds, thready pulse, abdominal distension, oliguria. Define the type of coma.

A. Hepatic coma.

B. Diabetic coma.

C. Hypoglycemic coma.

D. Uremic coma.

E. Alcoholic coma

20. 40-year old patient suddenly fainted. Primary inspection: unconsciousness, pale skin, generalized tonoclonic convulsion with involuntary urination, cyanosis of face, BP isn’t defined, heart rate 36 beats per minute, ECG: atrioventricular heart block with rare ventricular complexes. What is working diagnosis?

A. Epileptic seizure.

B. Morganya -Adam’s and Stock’s attack.

C. His' bundle peduncles block.

D. Orthostatic syncope.

E. Neurogenic unconsciousness.

21. Among the patients older than 65 years old the causes of convulsive attacks are:

A. Brain-growth.

B. Cerebrovascular accidents.

C. Epilepsy.

D. Metabolic disorders.

E. Infections.

22. 45-year old patient had sudden generalized tonic-clonic convulsion. Patient was in psychic excitement, general trembling. Life history: during 3 days there was alcohol abuse. What is working diagnosis?

A. Epileptic seizure.

B. Abstinent attack.

C. Psychotogenous attack.

D. Unconsciousness.

E. Convulsive attack in case of metabolic disorders.

23. The leading causes of mortality associated with SE are:

A. Central nervous system infections

B. Asphyxia

C. Head trauma

D. Stroke

E. Central nervous system infections and anoxic injury

24. The preferred drug class for the initial treatment of SE is:

A. Phenytoin or fosphenytoin

B. Valproate

C. Lidocaine

D. Benzodiazepines (Lorazepam, diazepam)

E. Barbiturates

25. Seizure complications include:

A. drug side effects, tongue biting, and other minor trauma from falls during seizures

B. drug side effects, drowsiness

C. tongue biting, head trauma

D. trauma from falls during seizures

E. headache

26. Valproic acid is effective in treating all forms of seizure. The recommended dose acid is:

A. 0,1-0,2 mg/kg

B. 15-20 mg/kg.

C. 10 mg/kg IV

D. 1 g PO

E. 30-50 mg/kg

27. If 2 or more of the initial drug therapies fail to control the seizures, then the next line of treatment includes continuous infusions of antiepileptic medications. The major side effects are:

A. drowsiness

B. hypotension and respiratory depression

C. arterial hypertension

D. nausea

E. sleepiness

Answers:

1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
E	B	E	E	A	B	B	A	E	D
11	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
A	A	A	B	E	A	D	A	B	B
21	**22**	**23**	**24**	**25**	**26**	**27**			
B	B	E	D	A	B	B			

BASIC QUESTIONS AFTER A THEME

- Syncope: definition, classification, clinical presentation
- Syncope Differential Diagnoses.
- Algorythm of Syncope Workup,
- Principles of Treatment & Management of syncope.
- Dizziness and vertigo: definition, clinical presentation
- Principles of Treatment of vertigo and dizziness.
- Miscellaneous Head Sensations, Approach to the Patient.
- Acute confusional states and coma: definition, classification, clinical presentation
- Coma-like syndromes and related states: definition, clinical presentation
- Anatomic correlates of consciousness
- Pathophysiology of coma and confusion.
- Approach to the Patient with confusion and coma
- Algorythm of Laboratory examination for acute confusion and coma.
- Differential diagnosis of confusion and coma.
- Treatment, Prognosis of coma and the vegetative state.
- Cardiovascular collapse, cardiac arrest, and sudden cardiac death: Etiology, initiating events
- Clinical definition of forms of cardiovascular collapse. Clinical characteristics of cardiac arrest.
- Long-term management after survival of out-of-hospital cardiac arrest.
- Seizures and Epileptic syndromes: definition, classification
- The causes of seizures and epilepsy, Clinical Presentation
- Algorythm of Laboratory examination in the case of seizure
- Management plan of patients with seizure
- Antiepileptic Drug Therapy: classification, principles.

RECOMMENDED LITERATURE

Main

1. Brignole M., Moya A., Lange F.J. et al. 2018 ESC Guidelines for the diagnosis and management of syncope //Eur. Heart J. – 2018. – V. 39 (21). – P. 1883-1948.

2. Mykhailovska N. S. Syncope. Cardiovascular collapse, cardiac arrest, and sudden cardiac death. Seizure in practice of family doctor: The teaching textbook for the practical classes and individual work for 6th-years students of international faculty (speciality «General medicine») / N. S. Mykhailovska, G. V. Gritsay. – Zaporizhzhia: ZSMU, 2015. – 175 p. – Recommended by MoH of Ukraine, protocol № 4, the 16th of December 2015.

3. Mykhailovska N. S. Emergency in the practice of family doctor. Content module 3. The textbook for the practical classes and individual work for 6th-years students of international faculty (speciality «General medicine») / N. S. Mykhailovska, G. V. Gritsay. – Zaporozhye, 2015. – 164 p. – Recommended by MoH of Ukraine, protocol № 2, the 16.06.2015.

4. Mykhailovska N. S. Principles of family medicine. Content module 1, 2 : The textbook for the practical classes and individual work for 6th-years students of international faculty (speciality «General medicine») / N. S. Mykhailovska, G. V. Gritsay. – Zaporizhzhia: ZSMU, 2015. – 138 p. – Recommended by MoH of Ukraine, protocol № 2, the 16.06.2015.

5. Mykhailovska N. S. The basis of family medicine : E-teaching complex for 6th-years students of international faculty (speciality 222 «Medicine») Discipline: «General practice – family medicine» / N. S. Mykhailovska, G. V. Gritsay. – Zaporizhzhia: ZSMU, 2017.

6. Mykhailovska N. S. The basis of prophylaxis of widespread diseases in the practice of family doctor : The teaching textbook for the practical classes and individual work for 6th-years students of international faculty (speciality «General medicine») / N. S. Mykhailovska, G. V. Gritsay. – Zaporizhzhia: ZSMU, 2016. – 187 p.

7. Mykhailovska N. S. The basis of prevention in the practice of general practitioners : The textbook for the practical classes and individual work for 6th-years students of international faculty (speciality «General medicine») discipline «Generalpractice – family medicine» / N. S. Mykhailovska, G. V. Gritsay. – Zaporizhzhia: ZSMU, 2017. – 224 p.

8. Mykhailovska N. S. The first aid in the case of non-epidemic diseases: study guide for the practical classes and individual work for 6th-years students of international faculty (speciality «General medicine») Discipline «General practice – family medicine» / N. S. Mykhailovska, A. V. Grytsay, L.E. Miniailenko, I.O. Stetsyuk – Zaporizhzhia : ZSMU, 2018. – 106 p.

9. Mykhailovska N. S. Organizational aspects of primary health care system in Ukraine: study guide for the practical classes and individual work for 6th-years students of international faculty (speciality «General medicine») Discipline «General practice – family medicine» / N. S. Mykhailovska, A. V. Grytsay, L.E. Miniailenko – Zaporizhzhia: ZSMU, 2018. – 175 p.

Additional

1. Mykhailovska N.S. The practical workbook. Discipline «General practice – family medicine» for 6-th year students of international faculty. Content module 1,2 / N. S. Mykhailovska, G. V. Gritsay. – Zaporizhzhia: ZSMU, 2017. – 69 p.

2. Mykhailovska N. S. The practical workbook. Discipline «General practice – family medicine»for 6-th year students of international faculty. Content module 3 / N. S. Mykhailovska, G. V. Gritsay. – Zaporizhzhia: ZSMU, 2017. – 75 p.

3. Mykhailovska N. S. Primary role of family medicine in the public health system: compilation of tests for final knowledge control for the practical classes and individual work for 6th-years students of international faculty (speciality «General medicine») Discipline «General practice – family medicine» / N. S. Mykhailovska, A. V. Grytsay, T. V. Oliynik L. E. Miniailenko, I.O. Stetsyuk – Zaporizhzhia : ZSMU, 2018. – 195 p.

4. Reed MJ, Mills NL, Weir CJ. Sensitive troponin assay predicts outcome in syncope. Emerg Med J. Dec 2012;29(12):1001-3. [Medline].

5. Harding A. Head-up Tilt Test Useful for Ruling Out Epilepsy in Patients With Syncope: Study. Medscape Medical News. Available at http://www.medscape.com/viewarticle/822784.. Accessed April 8, 2014.

6. Parry SW, Tan MP. An approach to the evaluation and management of syncope in adults. BMJ. Feb 19 2010;340:c880. [Medline].

7. Rangel I, Freitas J, Correia AS, Sousa A, Lebreiro A, de Sousa C, et al. The usefulness of the head-up tilt test in patients with suspected epilepsy. Seizure. Feb 17 2014;[Medline].

8. Tretter JT, Kavey RE. Distinguishing cardiac syncope from vasovagal syncope in a referral population. J Pediatr. Dec 2013;163(6):1618-1623.e1. [Medline].

9. Silbergleit R, Durkalski V, Lowenstein D, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. N Engl J Med. Feb 16 2012;366(7):591-600. [Medline]. [Full Text].

10. Costantino G, Sun BC, Barbic F et al. Syncope clinical management in the emergency department: a consensus from the first international workshop on syncope risk stratification in the emergency department// Eur Heart J. – 2016. – V.37. – P.1493-1498.

11. D'Ascenzo F., Biondi-Zoccai G., Reed M.J. et al. Incidence, etiology and predictors of adverse outcomes in 43,315 patients presenting to the emergency department with syncope: an international metaanalysis// Int. J. Cardiol. – 2013. – V. 167. – P. 57-62.

12. Deharo JC, Guieu R, Mechulan A et al. Syncope without prodromes in patients with normal heart and normal electrocardiogram: a distinct entity // J Am Coll Cardiol. –2013. –V.62. – P.1075-1080

13. Derose S.F., Gabayan G.Z., Chiu V.Y. et al. Patterns and preexisting risk factors of 30-day mortality after a primary discharge diagnosis of syncope or near syncope //Acad. Emerg. Med. – 2012. – V. 19. – P. 488-496.

14. Drak-Hernandez Y, Toquero-Ramos J, Fernandez JM et al. Effectiveness and safety of remote monitoring of patients with an implantable loop recorder // Rev Esp Cardiol (Engl Ed). – 2013. – V.66. – P. 943-948.

15. Fedorowski A, Melander O. Syndromes of orthostatic intolerance: a hidden danger // J Intern Med. – 2013. – V273. – P. 322-335.

16.Forleo C, Guida P, Iacoviello M, Resta M et al. Head-up tilt testing for diagnosing vasovagal syncope: a meta-analysis // Int J Cardiol. – 2013. – V.168. – P.27-35.

17. Subbiah R., Chia P.L., Gula L.J. et al. Cardiac monitoring in patients with syncope: making that elusive diagnosis // Curr. Cardiol. Rev. – 2013. – V.9. – P.299-307.

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