

Coma and Delirium

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Objectives:

- Understand the anatomic and physiologic determinants of consciousness
- Recognize the need for common definitions of behavior in comatose and delirious patients
- Be able to perform a rapid coma examination
- Develop an initial management approach

Key words: coma; death; delirium; obtundation; stupor; vegetative state

Altered mental status belongs in the category of terms that are widely understood but lack a consensual definition. In modern multidisciplinary ICUs, the combination of the diseases being managed and the drugs employed for that management results in a large percentage of patients who develop at least a temporary impairment of awareness or behavior. This area has been obscured by the psychiatric redefinition of delirium into a very broad concept which no longer requires agitation for its diagnosis. Intensivists should be aware of this as they interact with their psychiatric and neurologic colleagues.

Definitions

Definitions are derived from Plum and Posner,¹ except as noted.

Confusion

Confused patients are bewildered, and often have difficulty following commands. Disorientation to place and time is common ("except in rare instances of acute delirium, disorientation to self is confined to psychologic disturbances"¹). Memory is disturbed. Drowsiness is prominent, and may alternate with nighttime agitation.

Delirium

Delirium is "a floridly abnormal mental state characterized by disorientation, fear, irritability,

misperception of sensory stimuli, and, often, visual hallucinations."¹ This definition is diagnostically more specific than that in the Diagnostic and Statistical Manual of Mental Disorders IV² ("The essential feature of a delirium is a disturbance of consciousness that is accompanied by a change in cognition that cannot be better accounted for by a preexisting or evolving dementia. The disturbance develops over a short period of time, usually hours to days, and tends to fluctuate during the course of the day. There is evidence from the history, physical examination, or laboratory tests that the delirium is a direct physiologic consequence of a general medical condition, substance intoxication or withdrawal, use of a medication, or toxin exposure, or a combination of these factors."²). Delirium has also been termed "acute brain failure," which may be a foreign notion to localizationists but is a valuable tool for communication.

Obtundation

Obtundation is mental blunting, associated with slowed psychological responses to stimulation and an increase in drowsiness and in the number of hours slept.

Stupor

Stupor is "a condition of deep sleep or behaviorally similar unresponsiveness in which the patient can be aroused only by vigorous and repeated stimuli."¹ This is not sleep from an EEG perspective.

Coma

Coma is "a state of unarousable psychologic unresponsiveness in which the subjects lie with eyes closed. Subjects in coma show no psychologically understandable response to external stimuli or inner need. They neither utter understandable words nor accurately localize noxious stimuli with discrete defensive movements."¹

Vegetative State

Vegetative state is “the subacute or chronic condition that sometimes emerges after severe brain injury and comprises a return of wakefulness accompanied by an apparent total lack of cognitive function. An operational definition is that the eyes open spontaneously in response to verbal stimuli. Sleep-wake cycles exist. The patients spontaneously maintain normal levels of blood pressure and respiratory control. They show no discrete localizing motor responses and neither offer comprehensible words nor obey any verbal commands. *Persistent or chronic vegetative state* refers to this condition in its permanent form and designates subjects who survive for prolonged periods (sometimes years) following a severe brain injury without ever recovering any outward manifestations of higher mental activity. In most instances the vegetative state follows upon a period of sleeplike coma. ...Nearly all patients in coma begin to awaken within 2 to 4 weeks no matter how severe the brain damage. ...Although many such patients are akinetic and mute, others with apparently similar degrees of brain damage may be restless, noisy, and hypermobile.”¹ Synonyms include coma vigil, apallic syndrome, cerebral death, neocortical death, total dementia, and akinetic mutism. It is important to recognize that persistent vegetative state after trauma, especially in the younger patient, does not carry nearly as dismal a prognosis for recovery as does that following anoxia.³

ICU Psychosis

Considerable debate exists about the existence of a specific disorder of behavior or perception related solely to ICU confinement. Opinions vary (even in the same text) from:

When faced with a patient who is confused and perhaps agitated, the first question must be “Is the patient delirious?” *The clinician should not attribute the change in mental status to an “ICU psychosis.”* The brain’s response to a physiologic (*sic*) insult, whether metabolic, anoxic, toxic, or infectious, is delirium.⁴

to: The incidence of abnormal behavior, perception, or cognition in adult patients admitted to an ICU is somewhat disputed, but every observational study has reported some incidence of such abnormalities with the highest estimates placed at 70 percent. These aberrations typically occur after

5 to 7 days of ICU stay, and risk of their development increases with duration of stay. It is perhaps intuitively clear that life in the ICU is sufficiently stressful to result in overt psychiatric consequences for the patient. Physically, the patient often experiences substantial pain. Sleep is unlikely to even approximate the normal architecture, and sleep deprivation is common. Perception is grossly distorted with loss of day-night cycles, immobilization, technology’s noise, and overwhelming monotony. Emotionally, the patient must contend with the fear of death, the loss of self-control, the total invasion of privacy, and the dependence on staff and machines to perform even basic bodily functions. This physical and emotional crisis occurs most commonly in conjunction with polypharmacy and neurologic consequences of underlying disease.

Some authors have objected to the use of the term “ICU psychosis,” largely because it is a convenient catchall obscuring the identification of specific disorders. Nonetheless, it is our observation that when all organic causes of abnormal mentation described above have been excluded, many patients are encountered with persisting difficulties that do respond to modification of the ICU experience. *We emphasize, however, that this is a diagnosis of exclusion and that other possibilities must be rigorously considered and sought.*⁵

Death

Rather than using terms like brain death, I find it more useful to think of death as death, and as a consequence of either complete cardiopulmonary or complete brain failure. This helps counteract the notion that “brain death” is somehow less a form of death than cardiopulmonary death. The old distinction of “death” and “brain death” is a major stumbling block in the pursuit of organ donation, and to a lesser extent, in the withdrawal of support from dead patients whose bodies are being ventilated and kept perfused with vasopressors.

Diagnosing Death by Brain Criteria

Diagnosing death by brain criteria requires a permissive diagnosis and the absence of brainstem reflexes. In certain circumstances, additional testing is needed.

Permissive diagnosis is a reason sufficient to explain death; failure to meet this criterion explains

almost all cases of recovery after the diagnosis of "brain death." Hypothermia and drug intoxication must be excluded or corrected before proceeding, and intact neuromuscular transmission should be demonstrated (spinal reflexes are adequate; in case of question, train-of-four stimulation may be used).

Absence of brainstem reflexes usually include (1) cervico-ocular reflex; (2) vestibulo-ocular reflex; (3) cough reflex; (4) gag reflex; (5) corneal reflex; (6) pupillary reflexes; and (7) absence of response to noxious stimuli applied to the face. (8) *Apnea testing* should be included here but is often listed as a separate criterion. The patient should not breathe when the P_{aCO_2} is allowed to rise from 40 torr to 60 torr (the British use 50 torr as the target). The patient must be adequately preoxygenated and should receive supplemental oxygen during the test (either 10 cm H_2O of continuous positive airway pressure or a tracheal catheter supplying a 10-L/min flow).

Confirmatory tests are not required in most circumstances. The exceptions to this are primarily in circumstances where the examinations above cannot be completed (eg, patients who do not tolerate the apnea test from a cardiovascular standpoint, or whose faces are too swollen to examine their eye movements).

- The most useful confirmatory test is a nuclide angiogram.
- Contrast angiography may also be used.
- EEG is not required and is of limited utility; the conditions that render the physical examination unreliable (eg, hypothermia, hypnosedative drug intoxication) also may make the EEG appear to show cerebral electrical silence.

Unconsciousness

Unconsciousness is produced in one of three ways: diffuse bilateral involvement of the cerebral hemispheres, injury to the brainstem reticular activating system (RAS), or a combination of focal injuries to the cortex and brainstem. Herniation is a special case of RAS insult, caused by a cerebral space-occupying lesion that produces a mechanical shift of brainstem structures.

Consciousness has two necessary components: arousal and content. Specific structures in the CNS modulate arousal; lesions in these areas render the patient unable to respond in spite of intact sensory afferents. Unconsciousness is the condition in which the patient makes no appropriate responses

to stimuli, either external (eg, pain) or internal (eg, thirst). This state does not exclude posturing and other reflex movements.

Causes of Unconsciousness

There are a large number of causes of coma, and it is convenient to classify them as those producing diffuse bihemispheric dysfunction vs those with structural lesions producing mass effect. Some of the major causes are shown in shown in Table 1. Nonconvulsive status epilepticus may present as unresponsiveness. Subtle signs, such as eyelid fluttering, mild facial twitching, or nystagmus may

Table 1. Causes of Coma

Presentation as Diffuse Bihemispheric Process (Usually Symmetric, Often With Intact Brainstem Reflexes)
<i>Drug intoxication</i>
Barbiturates
Opiates
Alcohol
Antidepressants
Benzodiazepines
Sedatives/tranquilizers
Drugs of abuse
Antipsychotic agents
Anticholinergics
Salicylates
<i>Metabolic</i>
Hypo- or hypernatremia
Hypoglycemia
Nonketotic hyperosmolar coma
Diabetic ketoacidosis
Hypo- or hypercalcemia
Hypothyroidism
Uremia
Hepatic encephalopathy
Hypo- or hyperthermia
Hypercarbia
Hypoxia
<i>Other Causes</i>
Diffuse presentations
Toxins, especially carbon monoxide, methanol
Meningitis/encephalitis: viral or bacterial
Sepsis
Hypertensive encephalopathy
Subarachnoid hemorrhage (low grade)
Head trauma, mild
Seizures/postictal
Presentation as brainstem process (often asymmetric, impaired brainstem function)
Brainstem infarction/hemorrhage
Posterior fossa tumor
Herniation: from any cerebral space-occupying lesion (tumor, stroke, hemorrhage)
Subarachnoid hemorrhage (higher grades)
Trauma, severe

be the only evidence that the patient is seizing. Similarly, a postictal state may show prolonged unresponsiveness, and include focal signs of hemiparesis (Todd's paralysis) or posturing.

Psychiatric conditions mimicking coma include catatonia, conversion reactions, and feigned coma. In these conditions, pupillary responses will be normal, as will ocular movements. The motor examination may demonstrate normal tone in supposedly paretic limbs, and when asleep, the patient will have normal movements.

The Anatomy of Consciousness

Two major neuroanatomic structures are necessary for consciousness: the RAS and the cerebral hemispheres. The RAS is primarily responsible for arousal mechanisms, and the hemispheres influence the content of consciousness.

The RAS receives input from all major afferent tracts, and projects widely to the thalamus, basal forebrain, and the cerebral hemispheres. The crucial segment of the RAS for arousal is between the rostral midbrain and the midpons. Isolated lesions in this portion of the RAS produce coma, whereas lower lesions do not. Damage to the thalamus or hypothalamus can also alter consciousness, which is understandable given the large interconnection between these structures and the RAS, but bilateral involvement is usually required.

Focal lesions in the cerebral cortex tend not to alter arousal but instead affect the content of consciousness. To affect arousal, large areas of both hemispheres need to be involved, either on a structural or metabolic basis. Large focal processes such as tumor or infarction may alter the contralateral hemisphere by pressure effects, or by disrupting circulation or metabolism. Dominant-hemisphere lesions may be more significant in affecting arousal than ones in the nondominant hemisphere.

Herniation

Herniation is caused when pressure of a mass lesion forces brain tissue to shift from one intracerebral compartment to another, and it can cause unconsciousness when pressure on the brainstem disrupts the RAS.⁶ The total volume contained in the cranial vault is limited and a mass lesion must cause some shift of the intracerebral contents. Initially, a mass lesion displaces cerebrospinal fluid, but eventually a limit is reached and intracranial

pressure (ICP) increases. Brain tissue is highly inelastic so this pressure causes herniation.

Central herniation is presumed to be from a pressure cone forcing the brain out towards its only exit, the foramen magnum. Uncal herniation occurs when the medial temporal lobe is forced over the tentorial edge into the space beside the lateral midbrain. This compresses the third cranial nerve and particularly the parasympathetic fibers to the pupil traveling around the outside of the nerve, causing unilateral dilation of the pupil on the side of the lesion, the "blown pupil."

Ropper⁷ has ascribed many of the signs of herniation to horizontal displacement of the brainstem. Acute pupillary dilation often corrects within minutes of initiating therapy for increased ICP, which is more consistent with lateral displacement than with irreversible uncal herniation.

Downward herniation can distract the basilar artery, which is tethered to the skull base, away from the brainstem and cause hemorrhage or infarction. Eventually, the downward movement increases subtentorial pressure and forces the cerebellar tonsils out the foramen magnum. Tonsillar herniation can also occur if a lumbar puncture is performed on a patient with elevated ICP, generating a large transforaminal pressure gradient. This is often catastrophic, as acute pressure on the medulla causes sudden respiratory arrest. Upward herniation of brainstem structures through the tentorium is possible in the setting of large posterior fossa masses that increase subtentorial pressure.

Evaluation of Unconsciousness

Evaluation must be rapid because morbidity is often related to how quickly therapy is begun. Many of the diffuse metabolic or toxic causes of coma resolve without long-term CNS damage, where as acute structural disease, especially if causing herniation, may be rapidly fatal.

A key tenet of the care of the comatose patient is that initial treatment must proceed simultaneously with diagnosis. Acute (over seconds to minutes) coma suggests cerebrovascular disease, either hemorrhagic or ischemic, or cardiac arrest. A recent history of head injury may indicate a subdural or epidural hematoma. A subacute course (many minutes to hours), may suggest intoxication or infection, while a more prolonged period of altered mental status might occur from a CNS tumor or a systemic metabolic disturbance. Weakness or falling to one

side suggests a focal lesion. A history of epilepsy may point to a postictal state. Witnesses should be carefully questioned about possible toxic ingestion.

Laboratory Studies

Laboratory studies may not aid in acute management, but frequently help with assessment later in the patient's course. Serum biochemistry will identify major metabolic derangements, including hypoglycemia, nonketotic hyperglycemia, and diabetic ketoacidosis.⁸ A complete blood count should be obtained, as either CNS or systemic infections can cause coma. Urinalysis should be routine, as urosepsis may present first as altered mental status, and often occurs without fever in the elderly. Hypothyroidism can cause coma of unknown etiology, so the thyroid-stimulating hormone level needs to be measured.

A urine toxicologic screen for drugs of abuse is almost always needed because drug overdose is one of the most common causes of coma of unknown etiology (Plum and Posner, 1980). Drug abuse is frequently implicated in cases of trauma. Mixed intoxication with combinations of alcohol, barbiturates, opiates, and benzodiazepines may be seen, and these agents should be screened for routinely. Finally, unconsciousness with focal signs can be caused by cocaine intoxication, which can cause cerebral vasculitis and stroke.

Blood gas analysis is necessary to assess hypoxia, hypercarbia, or abnormal pH. Hypoxia may be caused by drug intoxication. Particular acid-base abnormalities are often helpful in diagnosing metabolic encephalopathies. Respiratory acidosis, with hypoxia, occurs with hypoventilation from respiratory depressants. Metabolic acidosis may suggest particular toxic ingestions (eg, salicylates or alcohols), diabetic ketoacidosis, uremia, sepsis, or lactic acidosis. Compensatory respiratory alkalosis can be seen with many of the metabolic acidoses. Pure respiratory alkalosis, with hyperventilation, may suggest psychogenic coma.

Examination

The neurologic examination is directed at assessing the etiology of unconsciousness, the goal being to determine whether there is a bihemispheric process vs an RAS problem, looking particularly for signs of herniation. One neurologic cause of pseudocoma needs to be excluded immediately,

the "locked-in" state.⁹ In this condition, usually due to pontine infarction or hemorrhage, all cortical control except of vertical gaze is disconnected. Often the patient is only able to look upward, but may not even be capable of opening his eyelids. If the patient can, when his eyelids have been opened, follow the command to look up, the patient is not comatose but locked in, and needs studies directed towards identifying a pontine lesion.

Pupillary Responses

The pupils should be examined, preferably with a bright light and with the room darkened. The pupillary light reflex requires both intact sympathetic and parasympathetic systems to dilate and constrict, respectively. The key paradigm to remember is that damage to the midbrain affects the RAS, but also pupil reactivity, whereas metabolic disease produces coma, but usually leaves the light reflex intact.

Specific structural lesions produce particular pupillary patterns: *hypothalamic lesions*, either by direct involvement or secondary to increased pressure from above, interrupt the efferent sympathetic pathways, producing small, reactive pupils. *Unilateral diencephalic dysfunction* may cause a Horner's syndrome of unilateral pupillary constriction and ptosis, which may be an early sign of herniation. *Dorsal midbrain damage* interrupts the parasympathetic efferents, and the pupils become slightly large and unreactive, but may spontaneously fluctuate in size (hippus). *Central midbrain lesions* damage both sympathetic and parasympathetic tracts, producing fixed, often irregular, midposition pupils. This is most frequently seen in the setting of true transtentorial herniation and generally implies a poor outcome. *Pontine lesions*, usually hemorrhagic, interrupt the descending sympathetic fibers and irritate the parasympathetic fibers, producing pinpoint pupils. More *caudal lesions* affect only the sympathetic system, again causing a Horner's syndrome. Finally, a unilateral fixed, dilated pupil suggests *third nerve dysfunction*.

Small, reactive pupils are the hallmark of drug intoxication (particularly opiate) and metabolic disease, but there are a few exceptions. The light reflex is usually resistant to metabolic disease, but it may be suppressed in the setting of severe drug overdose, especially from barbiturates. Severe opiate intoxication may mimic the pinpoint

pupils of pontine hemorrhage. Anticholinergics may produce large, unreactive pupils associated with altered mental status, as can glutethimide intoxication. Anoxia may cause fixed dilated pupils, which become reactive if cerebral oxygen delivery is restored in time.

Eye Movements

If purposeful movements, such as visual tracking movements looking toward a loud noise, are absent, check for spontaneous roving eye movements. Roving movements are often seen with metabolic encephalopathies. All of these findings imply intact cortical control of the brainstem. A fixed deviation of eyes usually means there is a hemispherical lesion on the side toward which the eyes deviate, often associated with a contralateral hemiparesis. Isolated pontine lesions can cause eye deviation toward the damaged side, associated with an ipsilateral (*ie*, contralateral to the pontine lesion). A fixed downward gaze is seen with midbrain compression from above. Inability of one eye to move medially is seen with upper brainstem lesions to the medial longitudinal fasciculus, on the side of the abnormal eye, and is called an internuclear ophthalmoplegia.

If no spontaneous movement is found, the cervico-ocular reflex should be tested (doll's eyes maneuver); an important caveat is to be sure that there is no possibility of a cervical cord or spine lesion prior to testing. The reflex is tested by rapidly turning the head from midline to one side and observing the eye movements. In the intact brainstem, this produces a contralateral conjugate eye movement, the net effect of which is to keep the eyes seemingly fixed on a point in space. After a few moments the eyes should return to mid-position. The head should then be turned in the opposite direction to check for symmetry of the response. Failure of the reflex in either direction implies brainstem dysfunction. The reflex also works in the vertical plane, and should be tested in a similar fashion. If this maneuver fails, or is untestable because of neck injury, the vestibular-ocular reflex may be assessed by caloric testing. This is done by elevating the patient's head to 30 degrees if possible, and rapidly instilling about 50 mL of iced water in the ear canal with a syringe. It is important to first check that the ear canal is clear and that the tympanic membrane is not damaged, a relative contraindication to the test. Cold water instilled against the tympanic membrane produces cooling of

the adjacent semicircular canal, increasing the local density of the endolymph and creating a net flow towards the cooler side. This direction of flow mimics head turning away from the stimulated side, and therefore causes reflex slow eye movement towards the stimulus. In an intact brain, the frontal eye fields attempt to override this brainstem-driven tonic eye deviation, producing rapid saccades away from the stimulus (nystagmus), but with cortical damage, the eyes will maintain a fixed deviation. Cold caloric testing is a potent stimulus to the brainstem and may produce gaze deviation even when head turning fails to do so. The key observation is that whenever conjugate gaze occurs, regardless of the stimulus, it implies an intact brainstem in the region of the RAS. Eye deviation from hemispherical lesions can usually be overcome by these maneuvers, whereas with pontine lesions, the eyes will not cross midline. Total lack of response can be seen with severe brainstem dysfunction, drug ingestion (especially barbiturates, narcotics, and phenytoin), neuromuscular blockade, or bilateral vestibular lesions.

Motor Responses

The patient is observed for spontaneous movement or, if none is present, response to stimulus. The type of motor response and its symmetry provides important clues in assessing the location and severity of focal deficits. Any asymmetry of the motor patterns suggests a contralateral focal cerebral lesion. Comatose patients may not show purposeful movements, such as reaching for their endotracheal tube or localizing painful stimuli, which require an intact sensory system, efferent motor system, and cortical processing. Patients who cannot localize pain may withdraw from focal stimuli, again requiring functioning afferent and efferent tracts.

Abnormal motor responses include decorticate and decerebrate posturing. Decorticate posturing consists of flexion of the arms and extension of the legs, while in decerebrate posturing both the arms and the legs extend. The important principle of localization is that both forms of abnormal posture can occur with hemispherical as well as brainstem lesions. Prognostically, decerebrate is worse than decorticate posturing. Any comatose patient who develops either form of abnormal posturing needs intervention for acute worsening.

Extension of the arms with weak flexion of the legs or absent leg movement implies severe

structural damage of the pontine tegmentum. This finding indicates severe brainstem dysfunction and carries a grave prognosis.¹⁰ Total loss of tone does not necessarily mean upper brainstem damage and can be associated with spinal cord or medullary transection (spinal shock), peripheral nerve injury, or disease or neuromuscular blockade.

Finally, one must be careful not to confuse reflex activity with other responses. In particular, triple flexion of the lower extremity is a reflex signaling upper motor neuron dysfunction. It may look like spontaneous movement of the leg away from painful stimuli, but it is a reflex; the important finding is that the reflex response is very rapid and stereotyped.

Respiration

Respiration is controlled by brainstem structures with mediation by cortical influences, and specific respiratory patterns have localizing value. Unfortunately, these patterns are often not noticed in patients receiving mechanical ventilatory support. The most common abnormal respiratory pattern is Cheyne-Stokes respiration, in which there is a sequential waxing and waning of tidal volume, including periods of apnea. It can be seen in noncomatose patients with congestive heart failure, hypoxia, or occasionally during normal sleep, and is associated with bihemispheric dysfunction in unconscious patients. Respiratory centers in the brainstem increase or decrease the respiratory rate in response to elevated or lowered $Paco_2$ levels, respectively. There is, however, frontal lobe control such that even with very low $Paco_2$ levels, respiration does not stop but only slows, with a reduced tidal volume, until the $Paco_2$ normalizes. When bihemispheric dysfunction is present on a structural or metabolic basis, the modulating influence of the cortex is lost and Cheyne-Stokes respiration is seen.

Damage to the upper brainstem reticular formation is reported to cause sustained hyperventilation, called central neurogenic hyperventilation or central reflex hyperpnea. Tachypnea is often seen in comatose patients, but other causes, particularly hypoxia, neurogenic pulmonary edema, or metabolic disarray, are more likely. To diagnose true central neurogenic hyperventilation requires an increased Pao_2 and decreased $Paco_2$, without other metabolic changes or drug intoxication.

Apneustic, cluster, and ataxic breathing are patterns associated with lesions of the mid-lower pons,

upper medulla, and caudal medulla, respectively, and all provide inadequate ventilation so mechanical support is needed. With apneusis, a patient has a prolonged inspiratory pause, or respiration may consist of cycles of quick inhalation / pause / exhalation / pause. Cluster breathing consists of several rapid shallow breaths followed by a pause, while ataxic breathing is irregular brief respirations of small, random tidal volumes. Finally, apnea is of poor localizing value and may be seen secondary to cardiac arrest, multifocal brain lesions, drug overdose, spinal cord transection, or primary pulmonary process.

CT Scanning

Any unconscious patient with focal signs will need a CT scan, as many such patients will have potentially treatable problems. The differential diagnosis of coma with focal signs includes tumor, increased ICP, intracranial hemorrhage, CNS infection, and stroke. Unfortunately, some structural lesions may not produce focal signs but only brainstem dysfunction. Because of this, most comatose patients with coma of unknown etiology will need early CT scanning. Any comatose patient may also have fallen, and be at risk for a traumatic subdural or epidural hematoma, in addition to the primary problem. Traumatic hematomas may appear after the initial CT, so acute worsening of any patient is an indication for repeat scanning.

Lumbar Puncture and Antibiotics

Other than suspected bacterial meningitis, a lumbar puncture is needed in any patient for whom the cause of coma is still unknown after initial evaluation to look for nonbacterial meningitis or encephalitis, especially viral or fungal, or occult subarachnoid hemorrhage.

Initial Management

Resuscitation

Acute care must always start with basic life support: a patent airway, ventilation, and circulation. An easily reversible cause of coma, if treated sufficiently rapidly, is hypoxia secondary to airway obstruction or pulmonary disease. However, CNS lesions can cause abnormal respiratory patterns as well. Quickly observing the patient's respiratory

pattern may help with localization as described above. Comatose patients are frequently intubated for one of two reasons: ventilatory failure or airway protection. Airway-protective reflexes of gagging and coughing may be lost in coma, increasing the risk of aspiration. Also, the tongue and oropharynx relax, increasing the chance of airway obstruction. The aspiration risk is increased if gastric lavage is used for suspected toxic ingestion without a cuffed endotracheal tube in place.

Prior to intubation, the stability of the cervical spine must be assessed, particularly in patients with trauma. Also, patients who lose consciousness acutely may fall and injure their cervical spine. Because patients with altered mental status may be unable to tell the examiner about neck pain, all comatose patients should be treated as if they have a neck injury unless a reliable witness can attest to the lack of a fall or other potential for neck injury.

A patient in a hard cervical collar may be difficult to intubate orally as neck extension cannot and should not be attempted, so nasotracheal intubation may be preferred. The one exception to nasal intubation would be if there is a suspected basilar skull fracture. If raised ICP is at all possible, 100 mg lidocaine or 300 mg thiopental should be administered IV 1 min prior to intubation to blunt the rise in ICP normally associated with intubation.

A key part of the immediate evaluation is the patient's vital signs, which may themselves help decide the cause of unconsciousness. Severe hypotension can be sufficient to cause symptomatic CNS hypoperfusion and should be corrected urgently with fluids and/or vasopressors. Conversely, a severely elevated blood pressure may cause hypertensive encephalopathy, a neurologic emergency requiring rapid treatment.

Urgent Corrective Measures

Hypoglycemia can be catastrophic to the CNS, with degree of injury determined by the length of time and level of the low blood glucose.⁸ Finger-stick determinations are potentially unreliable, as the glucometers can be less accurate at low values; a measured serum glucose may in reality be much lower than that estimated by finger-stick methods. A finger-stick glucose reading < 60 mg/dL should prompt urgent replacement of glucose. A dose of 50 mL of D50/W should be given immediately to any patient with coma of unknown etiology. This will

produce no detrimental effect on other causes of coma (except Wernicke's encephalopathy, discussed below). Even in the case of hyperglycemic states producing coma, the marginal increase in total body glucose will not adversely affect treatment or generate CNS damage. In the case of hypoglycemia, glucose replacement may produce rapid reversal of unconsciousness.

Prior to giving glucose, thiamine 1 mg/kg IV must be administered to prevent precipitating acute Wernicke's encephalopathy (confusion, ataxia, and ophthalmoplegia) with associated necrosis of the midline gray structures leading to permanent memory loss. Alcoholics are at particular risk because of poor general nutrition. Although most patients will not be thiamine deficient, the potentially terrible result if missed makes thiamine administration before giving glucose imperative.

Narcotic overdose is a common cause of coma in emergency room patients, as well as in hospitalized and particularly ICU patients. The classic findings in narcotic intoxication are coma, small, reactive pupils, shallow respirations, and hypotension. Unfortunately, not all patients may display these findings. Pupillary responses in particular may be unreliable. Other drug ingestion (eg, anticholinergics) may mask pupil findings. Hypoxia, brainstem lesions, or barbiturates may also blunt the response. Because the physical signs can be unreliable and narcotic overdose is common, any patient with coma of unknown etiology should be given naloxone 0.2 to 0.4 mg by slow IV injection.

Management of Specific Causes¹¹

Elevated ICP

If increased ICP is suspected, treatment needs to be initiated immediately, particularly if herniation is identified. The patient's head should be elevated to between 30 and 45 degrees and, if possible, the neck placed in a neutral position to facilitate venous return. Adequate ventilation and oxygenation are essential as hypoxia or hypercarbia will increase cerebral blood flow and ICP. Hyperventilation to lower the patient's P_{aCO_2} to approximately 25 to 30 mm Hg will acutely reduce cerebral blood volume and ICP, but this effect is transient, and other interventions to control ICP will need to follow.

For severe rises in ICP, mannitol should be administered at a dose of 0.25 to 0.5 g/kg every

4 to 6 h, taking care to correct serum electrolytes, osmolality, and polemic status. The mechanism of action of this agent is uncertain (extracellular space dehydration vs intravascular volume expansion), but its utility is not. Administration of steroids is somewhat controversial, being useful for tumors and abscesses, possibly efficacious in meningitis, and of no benefit in stroke or anoxia. If the cause of coma is unknown, and the patient has evidence of increased ICP, an initial IV dose of 4 to 6 mg dexamethasone may be given empirically while diagnostic studies are undertaken.

Other factors that should be considered in the acute management of ICP include: (1) adequate sedation, with the addition of neuromuscular blockade, if necessary to stop excess muscle activity; (2) low ventilator pressure settings, which allow for good central venous return; and (3) suppression of fever, which accelerates cerebral metabolism and thereby raises oxygen consumption, resulting in increased cerebral blood flow and higher ICP. Fever also accelerates neuronal damage from other causes. Finally, care should be taken not to acutely lower blood pressure (unless hypertension is very severe) to maintain cerebral perfusion pressure.

Investigation of the patient with raised ICP requires a CT scan to exclude a space-occupying lesion and neurosurgical support if one is found. Alternative considerations requiring specific treatment include cerebrovascular accident, subarachnoid hemorrhage, and metabolic encephalopathy.

Drug Intoxication

When drug overdose or toxin ingestion is suspected, activated charcoal at a dose of 50 to 100 mg should be given to prevent system absorption. Gastric lavage may also be useful and is preferred over emesis. Use of both charcoal and lavage require airway protection, and in patients with mental status changes, this usually mandates intubation prior to treatment. For suspected benzodiazepine intoxication, flumazenil given in divided doses up to 1 mg total may produce dramatic arousal, but it is contraindicated in cases where tricyclic antidepressants may also have been consumed, as there is an increased risk of seizures and status epilepticus. Flumazenil is also reported to improve mental function transiently in patients with hepatic coma, probably by reversing the GABAergic effect of accumulating endogenous benzodiazepine receptor ligands.

Seizures

Status epilepticus is another cause of coma requiring emergent action. Clinical generalized convulsive status epilepticus is readily recognized, but nonconvulsive status epilepticus (NCSE) may be difficult to discern. Often the only indication of NCSE may be subtle twitching of individual muscles, particularly the face, rhythmic eye movements, or blinking. Status epilepticus of either type needs rapid treatment both to suppress the seizures and to prevent their recurrence. Lorazepam at 0.1 mg/kg is often effective at terminating seizures. At the same time, 20 mg/kg of phenytoin or fosphenytoin should usually be administered (at a rate no greater than 50 mg/min), with an additional 5 mg/kg to be given if the patient is still seizing. Further therapy may include midazolam, propofol, or high-dose pentobarbital. An emergent EEG is indicated for any patient with suspected NCSE, or a patient being put in drug-induced coma to control seizures.

Meningitis

Emergent antibiotic therapy is indicated for any patient with suspected bacterial meningitis. In this life-threatening illness, treatment should not be delayed to obtain a CT or a lumbar puncture. Lumbar puncture results will not be significantly compromised if obtained immediately after antibiotic administration.

Supportive Care

Fluid therapy and vital organ support must be ongoing. The unconscious patient is totally dependent on nursing care, with particular attention paid to eye, mouth, and pressure area care. Nutritional requirements will usually be provided enterally.

The unconscious patient may be capable of supporting respiration without mechanical ventilation. However, protection of the airway may not be possible after the cessation of respiratory support. For this reason, an early tracheotomy is useful to provide some airway protection from oropharyngeal secretions.

Monitoring Unconsciousness and Prognostication

The Glasgow Coma Scale is a common method for monitoring the progress of coma, producing a score between 15 (normal) and 3 (deep coma) and taking into account eye opening, motor responses, and verbal responses. Frequent assessment with the Glasgow Coma Scale gives an objective measure of progress. Otherwise, the prognosis deteriorates with the duration of coma; patients with postanoxic coma for 3 days rarely survive without severe disability.¹²

Poor prognostic features are listed in Table 2. Outcome from coma is primarily dependent on the cause, assuming that appropriate steps are taken to avoid secondary injury from hypoxia, hypotension, etc. In cases of severe head injury, recent data give an overall mortality of 37%, and good or moderate outcome occurs in 43%.¹³ Coma from anoxia is associated with a poor prognosis, with 90% mortality at 1 year if coma lasts > 6 h. Septic encephalopathy carries a 35 to 53% mortality dependent on severity.¹⁴ Hepatic coma is associated with good recovery in only 27% of patients.¹⁵ Outcome from drug ingestion, if the patient survives until hospitalization, is quite good.

As part of the SUPPORT study, Hamel et al¹⁶ identified day-3 prognostic variables associated with 2-month mortality in a cohort of 596 patients with "nontraumatic coma" (31% cardiac arrest, 36% ischemic stroke or intracerebral hemorrhage, 33% other causes). The variables included abnormal brainstem response (any of absent pupillary response, absent corneal response, or absent or dysconjugate roving eye movements), odds ratio (OR) = 3.2 (95% confidence interval [CI], 1.3 to 8.1); absent verbal response (OR, 4.6; 95% CI, 1.8 to 11.7); absent withdrawal response to pain (OR,

4.3; 95% CI, 1.7 to 10.8); creatinine > 1.5 mg/dL (OR, 4.5; 95% CI, 1.8 to 11.0); and age ≥ 70 years (OR, 5.1; 95% CI, 2.2 to 12.2). Two-month mortality for patients with four or five risk factors was 97%. Brainstem and motor responses best predicted death or severe disability at 2 months; with either an abnormal brainstem response or absent motor response to pain, the rate of death or severe disability at 2 months was 96%.

Somatosensory evoked potentials (SEPs) are useful adjuncts for prognostication.¹⁷ A systematic review showed that the positive likelihood ratio, positive predictive value, and sensitivity were 4.04, 71.2%, and 59.0%, respectively, for normal SEPs (predicting favorable outcome) and 11.41, 98.5%, and 46.2%, respectively, for bilaterally absent SEPs (predicting unfavorable outcome). Twelve of 777 patients were identified with bilaterally absent SEPs who had favorable outcomes. These false positives were typically pediatric patients or patients who had suffered traumatic brain injuries. More exotic techniques hold the promise of greater precision,¹⁸ but as of now no technique is completely correct.

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Table 2. Features Associated With a Poor Prognosis After Cardiorespiratory Arrest

Decerebrate posturing and rigidity for > 24 h in nontrauma patients
Decerebrate posturing and rigidity for > 2 weeks in trauma patients
Absent vestibulo-ocular reflex for > 24 h
Absent pupillary reflexes for > 24 h in postanoxic brain injury
Absent pupillary reflexes for > 3 d in trauma patients

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Notes