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Head Trauma and Subdural Hematoma

Part I: Emergency Management and Imaging Modalities

Authors: **Danica N. Barron, MD,** Alameda County Medical Center-Highland General Hospital, Department of Emergency Medicine, Oakland, CA; **M. Andrew Levitt, DO,** Associate Clinical Professor, University of California, San Francisco, Department of Medicine; Director of Research, Alameda County Medical Center-Highland General Hospital, Department of Emergency Medicine; **R. Carter Clements, MD,** Assistant Clinical Professor, University of California, San Francisco, Department of Medicine; Assistant Chief, Alameda County Medical Center-Highland General Hospital, Department of Emergency Medicine.

Peer Reviewers: **David Kramer, MD, FACEP,** Program Director, Associate Professor, Department of Emergency Medicine, York Hospital, Penn State University; **David P. Sklar, MD,** Professor and Chair, Department of Emergency Medicine, University of New Mexico School of Medicine, Albuquerque, NM.

Traumatic brain injury (TBI) is a serious public health problem that affects 2 million Americans annually. It is the leading cause of death in people younger than age 45. According to data from the Head Injury Task Force of the National Institute of Neurologic Disorders and Strokes, 500,000 victims are hospitalized annually as a consequence of their injuries. Approximately 100,000 people die, most of whom perish hours after the incident.[1,2] Of the patients who survive, an estimated 70,000-90,000 will suffer from some form of significant, permanent neurological disability, and 2000 exist in a persistent vegetative state.[3] As most victims of TBI are young and previously healthy, the cost to society in terms of disruption of families, lost productivity, and health care expenditures is enormous, exceeding $25 billion per year.[3]

Motor vehicle accidents are the most common cause of TBI (45.5%), followed by falls (15%) and assault (13.7%).[4] Although the proportion of penetrating TBI is difficult to ascertain, a recent review of 16,524 head injuries reveals that 4.6% of the injuries were caused by firearms and 0.4% were related to stab wounds.[4] Suicide is the most common cause of gunshot wounds to the brain in the civilian population.[5] The incidence of TBI is low in those younger than age 10, but dramatically increases during adolescence. Between ages 30 and 70, the incidence declines and then rises again in the elderly, which is largely attributed to increased incidence of falls. Elderly patients tend to have a higher incidence of brain contusions and multiple brain lesions,[6] which is likely caused by greater motion of a smaller brain within the cranium. In children, bicycle accidents are common and account for 7% of all TBI cases.[2] The frequency of assault-related TBI is inversely related to socioeconomic status and in many economically depressed neighborhoods, assault may be the leading cause of TBI.[7] Alcohol use is noticeably linked with TBI, and alcohol intoxication is present in one-fourth to one-half of TBI patients.[8-11] TBI is not an isolated injury, and at least 75% of cases involve serious injuries to other organ systems.[12]

In the past, TBI patients were judged unrecoverable. Few surgical and medical options existed. During "the decade of the brain,"

the 1990s, an enormous amount of new information was published on the pathophysiology of TBI which demonstrated that prompt and intensive management leads to a markedly better prognosis. In particular, early recognition and treatment of comorbid disorders, including hypoperfusion, ischemia, and high intracranial pressure in the injured brain, is crucial to good neurological outcome. The purpose of this article is to summarize the pathophysiology of TBI and its clinical classification, emergency management, and diagnostic imaging. This two-part series will review patterns of posttraumatic injuries and trends in future treatment modalities, with an emphasis on subdural hematoma, will be addressed. Pediatric injuries, a common and important problem in emergency medicine, have recently been addressed in American Health Consultants' Trauma Reports *(Current Concepts in the Emergency Management of Severe Traumatic Brain Injury in Children, 2000;1[1]:16;Current Concepts in the Management of Minor Closed Head Injury in Children, 2001;2[1]:1-12).*

— The Editor

Pathophysiology

Essential to the emergency care of TBI patients is an appreciation of the dynamic changes that occur at the time of impact and during the first hours following the injury. Traditionally, the description of pathophysiology of TBI has been temporally divided into primary injury, occurring at the moment of the injury; and secondary brain injury, resulting from processes that complicate the injury. Primary brain injury is the physical deformation of brain tissue caused by the inciting event. Secondary brain injury is defined as the biochemical and physiological changes that occur following primary brain injury. Secondary brain injury exacerbates the injured brain via hypoxemia, hypotension, edema, infection, and/or increased intracranial pressure.[7,13] The processes that cause secondary brain injury result from damage from free radicals, receptor dysfunction, calcium-mediated damage, and inflammation.[14,15] Exogenous or iatrogenic events, such as inadequate resuscitation of shock, nosocomial infections, and anesthetic agents, also may precipitate secondary injury.[7]

The application of force to the head causes an intricate cascade of mechanical and physiological phenomena. This force may be related to head-contact injuries, leading to local skull bending, volume changes, and propagation of shock waves. Injury that occurs following a penetrating object is chiefly imparted by the kinetic energy of the object, which is the square of the velocity. Velocities of less than 320 m/s induce injury through direct disruption and laceration of tissue. Fracture of the skull may cause penetration of a portion of this bone as a missile in its own right. At velocities greater than 320 m/s, shock waves emanate from the object and may create significant pressure gradients.[16] In addition, centrifugal forces generated by the missile produce a temporary cavity as it passes through the tissue. This cavity, which may be more than 30 times the diameter of that of the object, produces substantial strains in surrounding tissue, disrupting vascular structures and causing severe axonal tears.[17] Higher velocity injuries are seen with military weapons. Civilian shootings may involve hollow-point rounds, which expand their diameter on impact, causing a larger primary wound track and greater tissue destruction. Missiles involving a trajectory crossing the sagittal sinus are particularly devastating, as both cerebral hemispheres are affected. Alternately, a head-motion injury such as rapid acceleration, deceleration, and rotation of the head can create shearing injuries within the cranium. The brain is ill-equipped to handle inertial loading due to its viscoelastic structure. Severe strains or deformations of the brain at the surface may cause cortical contusions and/or a subdural hematoma (SDH) from the rupture of bridging veins between the cortical surface and the dural sinuses; if the injury is deeper within the parenchyma, diffuse axonal injury (DAI) may ensue.[18-20] Reverberating shock waves may precipitate small intracerebral hemorrhages.[21] Note that impact to the head is not necessary for SDH to occur; it is the acceleration of the brain relative to the skull and not the head contact per se that causes

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Editorial Group Head: Valerie Loner
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SDH.[22] SDH and DAI are the most common culprits in fatal head injuries, with DAI almost entirely a consequence of vehicular accidents and most cases of SDH due to falls or assaults.[13]

Two different pathophysiological cascades may occur, resulting in either focal or diffuse brain injuries. Trauma causing focal brain injury, such as contusion or hematoma, may precipitate local mass effects and lead to brain shifts, herniation, and progressive brain stem compression. Adjacent to the localized area of tissue destruction is a concentric zone of ischemia and edema in which cytotoxic and inflammatory mechanisms may be triggered, expanding the area of original injury. In diffuse brain injuries, the original event causes a primary defect in the axonal membrane. Ionic shifts, especially the sudden load of calcium within the axonal interior, may cause the death of cells that were initially capable of surviving the mechanical insult. Most tissue injury does not result from the initial injury forces causing widespread structural degeneration, but via these tissue strains altering cell membrane function, axon neurofilaments, and axolemmal permeability. Thus, emergency physicians are dealing with not destroyed, but dysfunctional (and potentially salvageable) brain tissue.[23]

The changes in cell membrane and function resulting after TBI trigger a cellular response, ultimately producing physiological and supraphysiological concentrations of neurotransmitter and neurochemical mediators of injury. In particular, levels of glutamate and aspartate are increased in the extracellular space after TBI and are key components in a process known as cellular excitotoxicity involving the massive depolarization of brain cells. These neurotransmitters control the movement of sodium and/or calcium into and potassium out of the cell. Critical cellular processes are disrupted by excess intracellular calcium caused by the ionic shifts, such as phosphorylation of proteins and construction of proteases, enzymes, and microtubili. Ultimately, the membrane becomes increasingly permeable, the cytoskeleton dissolves, and the cell dies.[24-26] Another major cause of brain injury aside from the excitotoxic mechanism appears to involve oxygen radicals and lipid peroxidation. During periods of hypoperfusion, hypoxia, and metabolic acidosis, oxidative pathways are activated. The radicals generated from these reactions are highly active and readily oxidize proteins, DNA, and more importantly, membrane fatty acids, leading to cellular dysfunction, cell lysis, and demise. It is believed that pharmacological agents prevent neuropathological changes in the injured brain by scavenging free radicals or decreasing membrane lipid peroxidation.[27,28] Finally, the role of programmed cell death, apoptosis, is a topic of hot debate; it appears to halt this cascade by sacrificing injured cells.[29,30]

Although the complexities of the chemical interactions contributing to TBI have yet to be fully elucidated, the physiological consequences of these cellular changes are better understood and include alterations in cerebral perfusion, edema, and inflammation. Cerebral blood flow (CBF) is tightly controlled by cerebral vascular resistance and is largely unaffected by fluctuations in systemic arterial pressure or intracranial pressure (ICP). This phenomenon, termed cerebral autoregulation, is achieved by constriction and relaxation of arterioles and venules in response to neurotransmitters and local chemicals. Cerebral autoregulation also is intimately associated with the integrity of the blood-brain barrier (BBB), a formation of specialized cerebral vascular cells. In between these cells exist tight junctions that prevent passive diffusion of electrolytes, plasma proteins, and large molecules into the brain extracellular space. Cerebral autoregulation permits a constant flow of blood between a range of mean arterial pressure (MAP) of 50-140 mmHg.[31] CBF is equal to the cerebral perfusion pressure (CPP) divided by cerebral vascular resistance. CPP is calculated as the difference between MAP and ICP. As the CBF is difficult to measure directly, the CPP is used as a guide for estimating cerebral perfusion. In healthy individuals, ICP ranges between 0 and 10 mmHg, and elevated ICP is defined as pressure in excess of 20 mmHg for 5 minutes or more.[32] CPP values normally vary between 70 and 100 mmHg; due to cerebral autoregulation, ischemia in the non-injured brain does not occur until the CPP decreases below 40 mmHg.[31] Following injury to the brain, however, mediators of injury may impair cerebral autoregulation and usually insignificant fluctuations in MAP can have a profound effect on CBF. In addition, as injured endothelial cells fail, the BBB may be compromised, affecting the diffusion of electrolytes, plasma proteins, and other molecules into the brain extracellular space.[31,33]

The brain is housed in a fixed space containing the parenchyma, cerebrospinal fluid (CSF), extracellular fluid, and blood. These tissues are largely incompressible. Following TBI, there is an increase in blood and tissue edema that increases the intracranial volume.[34] Initially, elevations in intracranial volume are accommodated by movement of blood and CSF out of the vault. However, further increases in intracranial volume are met by sharp increases of ICP. Elevated ICP is not harmful unless it increases to a point where CPP falls below a critical value. Further lowering of CPP leads to cerebral ischemia causing neuronal injury and cerebral edema. The ensuing edema can cause further increases in ICP and exacerbate diminished CBF, leading to irreversible neuronal damage.[35] Studies have shown that in patients with TBI, CBF may be reduced to less than one-half of that in normal individuals.[36-38] The presence of blood collections in the tissues from epidural or subdural hematomas can be especially problematic, not only by increasing ICP, but also by releasing iron during decomposition and promoting oxidation.[39] Furthermore, blood in the subarachnoid space can trigger vasospasm, worsening ischemia. Even after CBF is restored, however, damage also may occur during reperfusion of the injured area, via activation of mediators of injury causing edema.

The actual brain damage that occurs at the time of injury cannot be reversed; therefore, optimization of posttraumatic neurological function depends on alleviating factors contributing to secondary injury to the brain. As described above, the traumatized brain is especially vulnerable to ischemia due to metabolic and molecular derangements. Alterations in CBF and ischemia are central to the theme of secondary brain injury and may be caused by factors superimposed on the primary injury or as a consequence of extrinsic changes. These factors include hypotension, hypoxia, infection, hyperthermia, seizures, and electrolyte imbalances. The traumatic coma data show that the two most common secondary insults are hypoxia (paO_2 < 60 mmHg) and hypotension (systolic blood pressure < 90 mmHg), which when present in

Table 1. Important Historical Facts in Head Injury

MECHANISM OF INJURY
Condition of car (drivable, windshield, deployment of airbags, steering column)
Height of fall, landing surface, number of steps
COMORBIDITIES
Past medical history (coagulopathy, chronic alcoholism, hemophilia)
Medication history (warfarin)
Complaints preceding trauma (chest pain, dizziness, headache)
Drug/alcohol ingestion
CONDITION POST INJURY
Seizures
Duration of loss of consciousness
Repetitive questioning
Amnesia to event
Compared to baseline
Other injuries

Adapted from: Biros MH. Head Trauma. In: Rosen P, Barkin R, eds. *Emergency Medicine: Concepts and Clinical Practice.* 4th ed. Mosby-Year Book; 1998.

Table 2. The Glasgow Coma Scale

EYE OPENING		
Spontaneously	4	Reticular activating system is intact; patient may not be aware
To verbal command	3	Opens eyes when told to do so
To pain	2	Opens eyes in response to pain
None	1	Does not open eyes to any stimuli
VERBAL RESPONSE		
Oriented—converses	5	Relatively intact CNS. Aware of self and environment
Disoriented—converses	4	Well articulated, organized, but patient is disoriented
Inappropriate words	3	Random, exclamatory words
Incomprehensible	2	Moaning, no recognizable words
No response	1	No response or intubated
MOTOR RESPONSE		
Obeys verbal commands	6	Readily moves limbs when told to
Localizes to painful stimuli	5	Moves limb in an effort to remove painful stimuli
Flexion withdrawal	4	Pulls away from pain in flexion
Abnormal flexion	3	Decorticate rigidity
Extension	2	Decerebrate rigidity
No response	1	Hypotonia, flaccid: suggests loss of medullary function or concomitant spinal cord injury

Adapted from: Teasdale G, Jennett B. Assessment of coma and impaired consciousness: A practical scale. *Lancet* 1984;2:81-84.

combination may more than double mortality.[40] Apnea is a frequent finding immediately following TBI, and alcohol and other drugs may exacerbate initial respiratory depression. Hemorrhage from internal or orthopedic injuries, decreased cardiac output from cardiac contusion, tamponade or tension pneumothorax, or neurogenic injury from a spinal cord insult may decrease CPP to critical levels. Wilberger and colleagues observed that one episode of hypotension in the prehospital/emergency department period can increase mortality by 50%.[41] Proof of the significance of secondary neuronal injury is shown by the 30-40% of patients who talk or obey commands prior to death, indicating that the primary injury, by itself, was insufficient to cause mortality.[42] Therefore, attenuation of these secondary factors and prevention of cerebral ischemia are important to maximizing neurological recovery.[31]

Emergency Management of TBI

History. Table 1 lists key historical data that should be obtained from the patient and witnesses to the injury. Important comorbid factors include propensity toward coagulopathy (e.g., alcohol, anticoagulant therapy), prior history of TBI, and preexisting seizure disorders. Details regarding the mechanism of injury, including height of fall, landing surface, condition of car, deployment of airbags, use of seatbelt, and associated fatalities or severely injured people should be sought. Information regarding the patient's condition postinjury and the patient's condition upon arrival of first responders also should be determined.[43] Any history of physiological anisocoria should be noted, as it is present in 10% of the general population. Finally, family members and/or acquaintances may be useful for documenting the patient's baseline mental status.[43]

The Acute Neurological Examination. According to Advanced Trauma Life Support (ATLS) guidelines,[44] the first tasks in the acute resuscitation of trauma victims involve airway, breathing, and circulation, and the TBI patient is no exception. A revised version of the ATLS guidelines is expected in July 2002. For this review, we have divided management of TBI according to the clinical spectrum of the disease. The initial resuscitation of patients with blunt and penetrating TBI is identical and specifics regarding airway management and fluid resuscitation are discussed in the section addressing severe head trauma.

A brief neurological examination should be performed early in the management as part "D" (deficit) in the initial "ABCs" of the ATLS primary survey. Accurate and objective assessment of neurological status serves as a basis that can be recorded and used for comparison during the resuscitation and further evaluation of the patient. Terms such as "obtunded," "stuporous," and "lethargic" should be avoided where possible. Stable patients who are awake may undergo a relatively comprehensive neurological examination, whereas critical patients may require a more efficient examination, which includes Glasgow Coma Scale (GCS) score (see Table 2), pupillary function, motor function, and mental status (see Table 3). This abridged version is not a substitute for a comprehensive examination that should be performed when the patient is more stable. The importance of repeated neurological exams cannot be emphasized enough, as the clinical status of TBI patients can change rapidly. An expanding hematoma may cause rapid deterioration of an awake, talking patient within minutes. Likewise, severely inebriated patients

Table 3. Abridged Neurological Examination in the Severe TBI Patient

- Mental status
- Glasgow Coma Scale
- Pupils (size, responsiveness, asymmetry)
- Motor exam (symmetry, abnormal movements, strength, reflexes)
- Cranial nerves (gag reflex, corneal reflex)
- Brainstem function (respiratory rate and pattern, eye movements)

Adapted from: Biros MH. Head Trauma. In: Rosen P, Barkin R, eds. *Emergency Medicine: Concepts and Clinical Practice.* 4th ed. Mosby-Year Book; 1998.

may soon awaken if the coma is related to alcohol rather than severe TBI. While not included in the evaluation of GCS score, assessment of pupillary function may provide important information. Pupillary asymmetry is especially concerning and is thought to result from transtentorial herniation causing mechanical compression of the third cranial nerve and subsequent brainstem compromise. Bilateral, nonreactive pupillary dilation usually is associated with severe TBI and a poor prognosis. The Brain Trauma Foundation recommends a pupillary size of greater than 4 mm as diagnosis for a "blown" pupil.[45] A recent study demonstrated that anisocoria of 1 mm or greater is associated with intracranial lesions in 30% of patients, whereas patients with anisocoria of 3 mm or greater harbored intracranial lesions in 43% of cases. A higher incidence of lesions occurred in older patients injured as a result of something other than being occupants of vehicles involved in accidents.[46] Of note, paralytic agents do not alter pupillary function. In the comatose patient, loss of extraocular eye movements is not uncommon, but eyes may deviate toward the side of an intracranial lesion. Roving eye movements or disconjugate gaze also may be seen in TBI. Identification of seizure in TBI patients can be subtle and noted by small, rhythmic eye movements or persistent nystagmus. Loss of corneal and oculocephalic reflexes in association with TBI suggests severe brainstem dysfunction. In the unconscious patient, an unequal motor exam suggests hematoma or significant damage to the contralateral cerebral hemisphere. The mechanism of injury also is important, as 80% of patients with focal motor findings may require surgery if their mechanism was unrelated to a motor vehicle accident, as compared with 30% of patients who were either occupants, pedestrians, or motorcyclists.[21]

Classification of TBI. Numerous attempts have been made to classify TBI in terms of severity for directing management and assessing prognosis. Although studies have shown changes in levels of biological markers following TBI, there are no easily measured markers to guide the clinician.[47] Brain stem auditory evoked potentials, single photon emission computed tomography (SPECT), and magnetic resonance imaging (MRI) may prove to be useful, but are difficult to perform in the emergent setting. At this point, the GCS score (see Table 2), developed in 1974 by Teasdale and Jennett, enables assessment of the TBI patient with regard to neurological function.[48] In the early 1980s, Rimel and colleagues divided the GCS score into three categories: scores of 8 or less were "severe," 9-12 were "moderate," and 13-15 were "mild."[49] However, data suggest that patients with GCS scores of 13 may have complication rates more consistent with moderately classified injuries.[50-55] Therefore, the term "mild" TBI is generally reserved for patients with GCS scores of 14-15.[56-58]

Imaging in TBI

Computed Tomography Scanning. The advent of computed tomography (CT) scanning in the 1970s revolutionized the work-up of TBI by providing timely anatomic and pathologic information used to identify TBI patients with surgical conditions. Skull radiographs, although still in use in many countries, have been almost completely superseded by head CT scanning in North America. Newer machines have reduced the scanning time to less than two minutes, which allows clinicians not only to determine at-risk patients earlier, but also to scan potentially less stable patients. Although there is little debate regarding the clinical utility of CT scanning, significant controversy exists as to which patients should be scanned. There is little argument that TBI patients with GCS scores of less than 13 need to be scanned and early in its history, the CT scan was a scarce resource that was reserved for such individuals.

As CT scanning became more widely available, studies demonstrated that scanning even minor TBI patients was less expensive than admitting patients for observation.[59] Debate then arose over the need to immediately identify all patients with intracranial lesions vs. emphasis on cutting costs. One group demonstrated that home observation of TBI patients might be unreliable,[60] further emphasizing the need to identify those patients at risk prior to discharge. The indications for performing a head CT scan will be discussed in the section addressing minor head trauma.

TBI patients can deteriorate suddenly; therefore, adequate resuscitation is important to avoid further cerebrovascular compromise while the patient is in the relatively inaccessible environment of the CT scanner. Prevention of deterioration in TBI patients who initially appear to be at low risk appears to cause the greatest reduction of morbidity and mortality in head traumatized patients.[61] Rapid CT scan may be performed in patients who respond to resuscitation, regardless of initial hypotension and subsequent need for surgery.[62] In cases of massive hemorrhage that is unresponsive to fluid administration, however, correction of homeostasis is priority. Severely injured (GCS score < 9) or combative patients may require adequate sedation, paralysis, and intubation prior to CT to eliminate motion artifact and protect the patient's airway. Conscious sedation with parenteral benzodiazepines may suffice for less severe TBI patients (GCS scores 9-13).

The CT scan has revolutionized the management of TBI; however, it is a low contrast study. Specifically, the CT scan is excellent for demonstrating intracranial hemorrhages but is poor at defining non-hemorrhagic injured areas. Therefore, TBI patients with severe DAI and a low presenting GCS score may have a relatively normal-appearing initial head CT scan. As a consequence, the initial head CT scan reading poorly correlates with the eventual neurologic outcome of the TBI patient.[63] Furthermore, the CT scan provides infor-

mation on neither the functional nor the metabolic status of the brain or CBF. Notwithstanding, the CT scan is rapid, readily available, and fortunately identifies most surgically amenable lesions.

Magnetic Resonance Imaging. Almost all studies have used the head CT scan as the gold standard for identifying intracranial pathology. However, MRI is superior to the head CT scan for identifying hemorrhages in brain parenchyma, defining nonhemorrhagic areas (DAI, cortical contusions, subcortical gray matter injury) and brainstem lesions, and permitting better approximation of the total degree of injury.[18,64] Similar to CT scanning, though, studies have shown that MR scan findings do not accurately predict eventual neurological outcome. However, data suggest that the presence of hemorrhage in DAI-type lesions and traumatic space-occupying lesions have a poorer prognosis.[65] MRI does take markedly longer to perform than head CT scan; one study found an average time of 2-5 minutes for head CT scan and 45 minutes for head MRI.[66] Therefore, it is not feasible in the initial management of the TBI patient. As technology improves, the enhanced detail provided by MRI may become important in the future management of early TBI.

Angiography. Penetrating TBI frequently causes vascular lesions, such as carotid-cavernous or arteriovenous fistula, arterial occlusion, arterial transection, or traumatic aneurysm. Traumatic aneurysms are particularly prone to rupture, producing delayed traumatic intracerebral hematoma and/or subarachnoid hemorrhage.[67,68] The incidence of traumatic aneurysms ranges from 3% to 33% of the penetrating TBI population.[67,69-70] Patients with penetrating or perforating TBI involving the sphenoid bone, temporal bone, or posterior fossa may have injuries to the carotid and/or vertebral arteries, or major venous sinuses. These individuals should undergo cerebral angiography to exclude vascular occlusion, traumatic dissection, or false aneurysm. Angiography also may be considered in the presence of delayed intracerebral hemorrhage or otherwise unexplained subarachnoid hemorrhage, particularly in association with a deteriorating neurological examination.[71]

References

1. Bennett BR, Jacobs LM, Schwarz RJ. Incidence, cost and DRG-based reimbursement for traumatic brain injured patients: A 3-year experience. *J Trauma* 1989;29:566-565.
2. Jennett B, Frankowski RF. The epidemiology of brain injury. In: Braakman R, ed. *Handbook of Clinical Neurology.* St. Louis, MO: Elsevier Science; 1990.
3. Borzuck P. Neurologic emergencies: Mild head trauma. *Emerg Med Clin North Am* 1997;15:563-577.
4. Gennarelli TA, Champion HR, Sacco WJ, et al. Mortality of patients with head injuries and extracranial injury treated in trauma centers. *J Trauma* 1989;29:1193-1201.
5. No authors listed. Part 2: Prognosis in penetrating brain injury. *J Trauma* 2001;51:S44-S86.
6. Pennings JL, Bachulis BL, Simons CT, et al. Survival after severe brain injury in the aged. *Arch Surg* 1993;128:787-793.
7. Zink BJ. Critical resuscitations: Traumatic brain injury. *Emerg Med Clin North Am* 1996;14:116-150.
8. Dikmen SS, Machamer JE, Donovan DM, et al. Alcohol use before and after traumatic head injury. *Ann Emerg Med* 1995;26:167-176.
9. Kraus JF, Morgenstern H, Fife D, et al. Blood alcohol tests, prevalence of involvement, and outcomes following brain injury. *Am J Public Health* 1989;79:294-299.
10. Jagger J, Fife D, Vernberg K, et al. Effect of alcohol intoxication on the diagnosis and apparent severity of brain injury. *Neurosurgery* 1984;15:303-306.
11. Brismar B, Engstrom A, Rydberg U. Head injury and intoxication: A diagnostic and therapeutic dilemma. *Acta Chir Scand* 1983;149:11-14.
12. Miller JD. Changing patterns in acute management of head injury. *J Neurol Sci* 1991;103:S33-S37.
13. Pearl GS. Forensic pathology, part 1: Traumatic neuropathology. *Clin Lab Med* 1998;18:39-64.
14. Graham DI, Adams JH, Nicoll JAR, et al. The nature, distribution and causes of traumatic brain injury. *Brain Pathol* 1995;5:397-406.
15. Miller JD. Head injury. *J Neurol Neurosurg Psychiatry* 1993;56: 440-447.
16. Hopkinson DAW, Marshall TK. Firearm injuries. *Br J Surg* 1967; 54:344-353.
17. Rosenwasser RH, Andrews DW, Jiminez DF. Penetrating craniocerebral trauma. *Surg Clin North Am* 1991;71:305-317.
18. Gentry LR. Imaging of closed head injury. *Radiology* 1994;191:1-17.
19. Povlishock JT. Pathobiology of traumatically induced axonal injury in animals and man. *Ann Emerg Med* 1993;22:280-286.
20. Povlishock JT. Traumatically induced axonal injury: Pathogenesis and pathobiological implications. *Brain Pathol* 1992;1:1-12.
21. Gennarelli TA. Mechanisms of brain injury. *J Emerg Med* 1993;11: 5-11.
22. Gennarelli TA, Thibault LE. Biomechanics of acute subdural hematoma. *J Trauma* 1982;22:680-686.
23. Zink BJ. State of the art: Traumatic brain injury outcome: Concepts for emergency care. *Ann Emerg Med* 2001;37:318-332.
24. Bullock R, Kuroda Y, Teasdale GM, et al. Prevention of post-traumatic excitotoxic brain damage with NMDA antagonist drugs: A new strategy for the nineties. *Acta Neurochir* 1992;55:49-55.
25. Hayes RL, Dixon CE. Neurochemical changes in mild head injury. *Semin Neurol* 1994;14:25-31.
26. Siesjo BK. Basic Mechanisms of traumatic brain damage. *Ann Emerg Med* 1993;22:959-969.
27. Braughler JM, Hall ED. Central nervous system trauma and stroke I: Biochemical considerations of oxygen radical formation and lipid peroxidation. *Free Radic Biol Med* 1989;6:289-301.
28. Hall ED, Braughler JM. Central nervous system trauma and stroke II. Physiological and pharmacological evidence for involvement of oxygen radicals and lipid peroxidation. *Free Radic Biol Med* 1989; 6:303-313.
29. White BC, Sullivan JM. Apoptosis. *Acad Emerg Med* 1998;5:1019-1031.
30. Cairns CB. Apoptosis: only the good die young. *Acad Emerg Med* 1998;5:948-950.
31. Marik P, Chen K, Varon J, et al. Management of increased intracranial pressure: A review for clinicians. *J Emerg Med* 1999;17:711-719.
32. Miller JD, Butterworth JF, Gudeman SK, et al. Further experience in the management of severe head injury. *J Neurosurg* 1981;75:685-693.
33. Fessler RD, Diaz FG. The management of cerebral perfusion pressure and intracranial pressure after severe head injury. *Ann Emerg Med* 1993;22:998-1003.

34. Bouma GJ, Muizelaar JP, Fatouros P. Pathogenesis of traumatic brain swelling: Role of cerebral blood volume. *Acta Neurochir Suppl* (Wien) 1998;71:272-275.
35. Shapiro HM. Intracranial hypertension: Therapeutic and anesthetic considerations. *Anesthesiology* 1975;43:445-471.
36. Bouma GJ, Muizelaar JP, Choi SC. Cerebral circulation and metabolism after severe traumatic brain injury: The elusive role of ischemia. *J Neurosurg* 1991;75:685-693.
37. Jaggi JL, Obrist WD, Gennarelli TA. Relationship of early cerebral blood flow and metabolism to outcome in acute head injury. *J Neurosurg* 1990;72:176-182.
38. Raichle ME, Plum F. Hyperventilation and cerebral blood flow. *Stroke* 1972;3:566-575.
39. Gutteridge JMC, Rowley DA, Holliwell B. Superoxide-dependent formation of hydroxyl radicals in the presence of iron salts. Detection of free iron in biological systems by using bleomycin-dependent degradation of DNA. *Biochem J* 1981;199:263-165.
40. Chestnut RM, Marshall LF, Klauber MR, et al. The role of secondary brain injury in determining outcome from severe head injury. *J Trauma* 1993;34:216-222.
41. Wilberger JE. Contemporary treatment paradigms in head injury. *Clin Neurosurg* 2000;46:143-152.
42. Menon DK. Cerebral protection in severe head injury: Physiological determinants of outcome and their optimization. *Brit Med Bull* 1999;55:226-258.
43. Biros MH. Head Trauma. In: Rosen P, Barkin R, eds. *Emergency Medicine: Concepts and Clinical Practice.* 4th ed. St. Louis, MO: Mosby-Year Book; 1998.
44. American College of Surgeons Committee on Trauma. Advanced Trauma Life Support for Doctors. 6th ed. American College of Surgeons: Chicago, IL; 1997.
45. Anonymous. The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care. Pupillary diameter and light reflex. *J Neurotrauma* 2000;17:583-590.
46. Chestnut RM, Gautille T, Blunt BA, et al. The localizing value of asymmetry in pupillary size in severe head injury: Relation to lesion type and location. *Neurosurgery* 1994;34:840-846.
47. Romner B, Ingebrigsten T, Kongstad P, et al. Traumatic brain damage: Serum S-100 protein measurements related to neuroradiological findings. *J Neurotrauma* 2000;17:641-647.
48. Teasdale G. Jennett B. Assessment of coma and impaired consciousness: A practical scale. *Lancet* 1984;2:81-84.
49. Rimel RW, Giordani B, Barth JT, et al. Disability caused by minor head injury. *Neurosurgery* 1981;9:221-228.
50. Hsiang JNK, Yeung T, Yu ALM, et al. High-risk mild head injury. *J Neurosurg* 1997;87:234-238.
51. Borczuk P. Predictors of intracranial injury in patients with mild head trauma. *Ann Emerg Med* 1995;25:731-736.
52. Gomez PA, Lobato RD, Ortega JM. Mild injury: Difference in prognosis among patients with a Glasgow Coma Scale score of 13 to 15 and analysis of factors associated with abnormal CT findings. *Br J Neurosurg* 1996;10:453-460.
53. Culotta VP, Sementilli ME, Gerold K, et al. Clinicopathological heterogeneity in the classification of mild head injury. *Neurosurgery* 1996;38:245-250.
54. Tellier A, Della Malva LC, Cwinn A, et al. Mild head injury: A misnomer. *Brain Inj* 1999;13:463-475.
55. Wang MY, Griffith P, Sterling J, et al. A prospective population-based study of pediatric trauma patients with mild alterations in consciousness (Glasgow Coma Scale score 13-14). *Neurosurgery* 2000;46:1093-1099.
56. Narayan RK, Greenberg RP, Miller JD, et al. Improved confidence of outcome prediction in severe head injury. A comparative analysis of the clinical examination, multimodality evoked potentials, CT scanning, and intracranial pressure. *J Neurosurg* 1981;54: 751-762.
57. Stein SC, Ross SE. Mild head injury: Plea for routine early CT scanning. *J Trauma* 1992;33:11-33.
58. Stein SC, Ross SE. Minor head injury: A proposed strategy for emergency management. *Ann Emerg Med* 1993;22:1193-1196.
59. Stein SC, O'Malley KF, Ross SE. Is routine computed tomography scanning too expensive for mild head injury? *Ann Emerg Med* 1991;20:1286-1289.
60. Saunders CE, Cota R, Barton CA. Reliability of home observation for victims of mild closed-head injury. *Ann Emerg Med* 1986;15:160-163.
61. Klauber MR, Marshall LF, Luerssen TG, et al. Determinants of head injury mortality: Importance of the low risk patient. *Neurosurgery* 1989;24:31-36.
62. Winchell RJ, Hoyt DB, Simons RK. Use of computed tomography of the head in the hypotensive blunt-trauma patient. *Ann Emerg Med* 1995;25:737-742.
63. Cheung DS. Evidence based emergency medicine: Evaluation and diagnostic testing. Evaluation of the patient with closed head trauma: An evidence based approach. *Emerg Med Clin North Am* 1999;17:9-23.
64. Sklar EM, Quencer RM, Bowen BC, et al. Magnetic resonance applications in cerebral injury. *Radiol Clin North Am* 1992;30:353-366.
65. Paterakis K, Karantanas AH, Komnos A, et al. Outcome of patients with diffuse axonal injury: The significance and prognostic value of MRI in the acute phase. *J Trauma* 2000;49:1071-1075.
66. Ogawa T, Sekino H, Uzura M, et al. Comparative study of magnetic resonance and CT scan imaging of cases of severe head injury. *Acta Neurochir Suppl* (Wien) 1992;55:8-10.
67. Aarabi B. Traumatic aneurysms of brain due to high velocity missile head wounds. *Neurosurgery* 1988;22:1056-1063.
68. Haddad FS, Haddad GF, Taha J. Traumatic intracranial aneurysms caused by missiles: Their presentation and management. *Neurosurgery* 1997;28:1-7.
69. Amirjamshidi A, Rahmat H, Abbassioun K. Traumatic aneurysms and arteriovenous fistulas of intracranial vessels associated with penetrating head injuries occurring during the war: Principles and pitfalls in diagnosis and management—a survey of 31 cases and review of the literature. *J Neurosurg* 1996;84:769-780.
70. Jinkins JR, Dadsetan MR, Sener RN, et al. Value of acute-phase angiography in the detection of vascular injuries caused by gunshot wounds to the head: Analysis of 12 cases. *Neurosurgery* 1991;29: 67-72.
71. Pruitt BA, Jr, ed. Vascular complications of penetrating brain injury. *J Trauma* 2001;51:S26-S28.

Physician CME Questions

89. Which of the following is the most common cause of traumatic brain injury (TBI)?
    A. Falls
    B. Gunshot wounds
    C. Motor vehicle accidents
    D. Recreational injuries

90. Which of the following statements about TBI is correct?
    A. The incidence of TBI is high in those younger than age 10.
    B. The incidence of TBI dramatically decreases during adolescence.
    C. Elderly patients tend to have a higher incidence of brain contusions and multiple brain lesions.
    D. Bicycle accidents in children account for 50% of all TBI cases.

91. In the traditional description of the pathophysiology of TBI, secondary brain injury refers to which of the following?
    A. Resulting from processes that complicate the injury
    B. Occurring at the moment of the injury
    C. Physical deformation of brain tissue caused by the inciting event
    D. All of the above

92. Impact to the head is *not* necessary for subdural hematoma to occur.
    A. True
    B. False

93. Optimization of posttraumatic neurological function and avoidance of secondary brain injury depends on alleviating which of the following?
    A. Hypoxia
    B. Hypotension
    C. Infection
    D. Seizures
    E. All of the above

94. A brief neurological examination for critically injured patients includes all of the following *except*:
    A. Glasgow Coma Scale (GCS).
    B. pupillary function.
    C. motor exam.
    D. mental status evaluation.
    E. cerebellar exam.

95. Which of the following medications is an important historical fact in patients with head injury?
    A. Zolpidem
    B. Acetaminophen with codeine
    C. Albuterol
    D. Warfarin
    E. Amoxicillin

96. A head computerized tomography (CT) scan is excellent for identifying all of the following *except*:
    A. subarachnoid hemorrhage.
    B. diffuse axonal injury.
    C. subdural hematoma.
    D. epidural hematoma.

Emergency Medicine Reports CME Objectives

To help physicians:

- quickly recognize or increase index of suspicion for specific conditions;
- understand the epidemiology, etiology, pathophysiology, and clinical features of the entity discussed;
- be educated about how to correctly perform necessary diagnostic tests;
- take a meaningful patient history that will reveal the most important details about the particular medical problem discussed;
- apply state-of-the-art therapeutic techniques (including the implications of pharmaceutical therapy discussed) to patients with the particular medical problems discussed;
- understand the differential diagnosis of the entity discussed; understand both likely and rare complications that may occur; and
- provide patients with any necessary discharge instructions.

In Future Issues: Head Trauma/Subdural Hematoma: Part II

Emergency Medicine Reports
The Practical Journal for Emergency Physicians

Head Trauma/ Subdural Hematoma: Part I

Important Historical Facts in Head Injury

MECHANISM OF INJURY

- Condition of car (drivable, windshield, deployment of airbags, steering column)
- Height of fall, landing surface, number of steps

COMORBIDITIES

- Past medical history (coagulopathy, chronic alcoholism, hemophilia)
- Medication history (warfarin)
- Complaints preceding trauma (chest pain, dizziness, headache)
- Drug/alcohol ingestion

CONDITION POST INJURY

- Seizures
- Duration of loss of consciousness
- Repetitive questioning
- Amnesia to event
- Compared to baseline
- Other injuries

Adapted from: Biros MH. Head Trauma. In: Rosen P, Barkin R, eds. *Emergency Medicine: Concepts and Clinical Practice.* 4th ed. Mosby-Year Book; 1998.

Abridged Neurological Examination in the Severe TBI Patient

- Mental status
- Glasgow Coma Scale
- Pupils (size, responsiveness, asymmetry)
- Motor exam (symmetry, abnormal movements, strength, reflexes)
- Cranial nerves (gag reflex, corneal reflex)
- Brainstem function (respiratory rate and pattern, eye movements)

Adapted from: Biros MH. Head Trauma. In: Rosen P, Barkin R, eds. *Emergency Medicine: Concepts and Clinical Practice.* 4th ed. Mosby-Year Book; 1998.

The Glasgow Coma Scale

EYE OPENING		
Spontaneously	4	Reticular activating system is intact; patient may not be aware
To verbal command	3	Opens eyes when told to do so
To pain	2	Opens eyes in response to pain
None	1	Does not open eyes to any stimuli
VERBAL RESPONSE		
Oriented—converses	5	Relatively intact CNS. Aware of self and environment
Disoriented—converses	4	Well articulated, organized, but patient is disoriented
Inappropriate words	3	Random, exclamatory words
Incomprehensible	2	Moaning, no recognizable words
No response	1	No response or intubated
MOTOR RESPONSE		
Obeys verbal commands	6	Readily moves limbs when told to
Localizes to painful stimuli	5	Moves limb in an effort to remove painful stimuli
Flexion withdrawal	4	Pulls away from pain in flexion
Abnormal flexion	3	Decorticate rigidity
Extension	2	Decerebrate rigidity
No response	1	Hypotonia, flaccid: suggests loss of medullary function or concomitant spinal cord injury

Adapted from: Teasdale G, Jennett B. Assessment of coma and impaired consciousness: A practical scale. *Lancet* 1984;2:81-84.

Supplement to *Emergency Medicine Reports*, December 3, 2001: "Head Trauma and Subdural Hematoma. Part I: Emergency Management and Imaging Modalities." *Authors:* **Danica N. Barron, MD,** Alameda County Medical Center-Highland General Hospital, Department of Emergency Medicine, Oakland, CA; **M. Andrew Levitt, DO,** Associate Clinical Professor, University of California, San Francisco, Department of Medicine; Director of Research, Alameda County Medical Center-Highland General Hospital, Dempartment of Emergency Medicine; **R. Carter Clements, MD,** Assistant Clinical Professor, University of California, San Francisco, Department of Medicine; Assistant Chief, Alameda County Medical Center-Highland General Hospital, Department of Emergency Medicine.

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Supplement 514A **December 3, 2001**

The annual flu season places dramatically increased demands on emergency department and urgent care facilities. Public health programs and staff physicians have long focused on the diagnosis and treatment of influenza in high-risk adults. While no one questions the efficacy of annual targeted immunization efforts and treatment of compromised adults, it has become increasingly evident that current programs miss important opportunities to reduce community exposure and control morbidity by not focusing on children. Recent advances in epidemiology, immunization, treatment, and chemoprophylaxis force clinicians to focus their attention on children as important adjuncts to influenza control.

— The Editor

Influenza Update: Focus on Children

Author: **Stephen R. Luber, MD, FAAP,** Pediatrician, Rockwood Clinic, Spokane, WA.

Peer Reviewer: **Theodore C. Chan, MD, FACEP,** Associate Professor of Clinical Medicine, Emergency Medicine, University of California, San Diego.

Epidemiology

Children account for nearly two-thirds of diagnosed cases of influenza during a typical season.[1] More than 30% of children living in communities will be affected.[1] The first sign of a typical flu season is increased school absenteeism;[1] only later does the increased hospitalization of the vulnerable elderly occur. Adults contract the illness from children, and infection rates dramatically increase in households with school-age children.

Two recent, population-based studies highlighted the direct effect of influenza on children. Evaluation of hospitalization rates in Group Health Seattle and Kaiser Northern California indicated dramatically increased rates of hospitalization in healthy children younger than age 2.[2] Analysis of Tennessee Medicaid patients indicated hospitalization rates of children younger than age 2 that were similar to high-risk adults with substantive excess use of antibiotics.[3] An accompanying editorial in the *New England Journal of Medicine* suggested strong consideration and further study of universal childhood immunization.[4]

Influenza strikes hard in Japan. The population is long-lived and many elderly live in homes with schoolchildren present. From 1962 to 1987, most Japanese schoolchildren were vaccinated against influenza. The vulnerable elderly were considered secondary targets for immunization. Excess influenza and pneumonia deaths dropped 40%, with between 37,000 and 49,000 excess deaths per year averted. The laws mandating this effort were relaxed in 1987 and repealed in 1994. Subsequent vaccination rates dropped to low levels, leading to a sharply rising number of deaths.[5]

Similar findings are emerging from a study of immunizing school children with attenuated live vaccine in a Texas community. Immunization rates of 50% have demonstrated the ability to prevent community epidemics and dramatically reduce excess mortality in the elderly. Immunization of school children was shown to be cost effective when considering indirect costs

of illness.[6] In another, less recent study by Monto and colleagues in Tecumseh, MI, school-age immunization reached 85% and the incidence of influenza-like illness was one-third that of neighboring communities.[7]

Immunization

The Centers for Disease Control and Prevention (CDC) recommendations for annual flu vaccination target high-risk patients, health care personnel, and the elderly. The program is not designed to control epidemics of influenza but to reduce the affect of the illness on vulnerable populations.[8] *(See Table 1.)* A trivalent, inactivated virus vaccine confers protection from disease of nearly 80% to those younger than 65 years and declines with age.[8] Although of declining efficacy in preventing illness in the frail elderly, vaccinations maintain effectiveness for the prevention of complications, hospitalizations, and death in nursing home populations. Production of vaccine was limited and delayed in flu season 2000-2001. The vaccine often went to mass distribution centers and was unavailable to physicians and clinics seeing targeted, high-risk populations. While the vaccine supply appears better this year, there are only three manufacturers and delayed deliveries are expected. Significant efforts to distribute vaccine to targeted, high-risk groups have been cited but lack of formal controls will cause physicians, once again, to be unable to acquire needed vaccines.

A live attenuated, cold-adapted, trivalent, intranasal virus vaccine has undergone successful trials with efficacy as good or greater than traditional inactivated vaccines.[9,10] No adverse events were reported. Developed by Aviron, the live virus vaccine stimulates cellular immunity in addition to humeral immunity, leading to a robust flexible immunity. The intranasal delivery is particularly attractive for the pediatric population. The vaccine targets healthy recipients. Acceptance of this vaccine, combined with increased childhood immunizations, may have a significant effect on propagation of annual epidemics. The new vaccine complements, rather than replaces, the use of inactivated vaccines for high-risk patients. Approval had been sought for the coming 2001-2002 flu season but on July 27, the Food and Drug Administration (FDA) held off on approval; it recognized efficacy but cited the need for more safety data.

Clinical Picture and Diagnosis

The clinical picture of influenza in young children often is subtle, with signs and symptoms mimicking other common childhood diseases. The clear and distinctive clinical picture of adult influenza often is muddied by the subjective nature of the pediatric history and its interpretation by concerned parents. The child's ability to describe the myalgias, headache, and malaise of influenza is limited. Gastrointestinal symptoms of vomiting and diarrhea occur in up to one-third of children. The infection may present as acute laryngotracheitis/croup or classic bronchiolitis. Infants may present with severe bronchiolitis progressing to respiratory failure. Differentiation from parainfluenza or respiratory syncytial virus (RSV) infections requires culture or immunoassay. The very young infant/neonate may appear moribund and require a septic workup. Febrile seizures are not uncommon in the infant. Physicians must have a strong index of suspicion or diagnostic curiosity to make the correct diagnosis.[11,12]

Influenza arrives during months in which annual RSV epidemics traditionally have received the primary attention of the pediatrician, and overlap with parainfluenza I croup seasons often direct the physician's attention away from the primary pathogen. Atypical presentations of croup or RSV-negative bronchiolitis merit diagnostic consideration.

Although some viral pathogens produce a clinical picture so compelling as to permit specific diagnosis, the protean nature of viral respiratory infections has long led to the diagnosis of exclusion: viral syndrome. Pediatricians have long ignored pre-

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Table 1. Influenza Vaccine* Dosage By Age Group-United States, 2001-2002 Season

AGE GROUP	PRODUCT†	DOSE	NUMBER OF DOSES	ROUTE §
6-35 mos	Split virus only	0.25 mL	1 or 2¶	Intramuscular
3-8 yrs	Split virus only	0.50 mL	1 or 2¶	Intramuscular
9-12 yrs	Split virus only	0.50 mL	1	Intramuscular
> 12 yrs	Whole or split virus **	0.50 mL	1	Intramuscular

* Contains 15 mg each of A/New Caledonia/20/99 (H1N1)-like, A/Moscow/10/99 (H3N2)-like, and B/Sichuan/379/99-like strains. For the A/Moscow/10/99 (HeN2)-like antigen, manufacturers will use the antigenically equivalent A/Panama/2007/99 (H3N2) virus. For the B/Sichuan/379/99-like antigen, manufacturers will use one of the antigenically equivalent viruses B/Johannesburg/5/99, B/Victoria/504/2000, or B/Guangdong/120/2000.

† Because of their decreased potential for causing febrile reactions, only split-virus vaccines should be used for children. The vaccines might be labeled as "split," or "subvirion," or purified-surface-antigen" vaccine. Immunogenicity and side effects of split- and whole-virus vaccines are similar among adults when vaccines are administered at the recommended dosage.

§ For adults and older children, the recommended site of vaccination is the deltoid muscle. The preferred site for infants and young children is the anterolateral aspect of the thigh.

¶ Two doses administered ≥ 1 month apart are recommended for children ages < 9 years who are receiving influenza vaccine for the first time.

** No whole virus vaccine will be distributed in the U.S. during the 2001-2002 influenza season.

Source: Bridges CB, Fukuda K, Cox NJ, et al. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2001;50(RR-4):1-44.

cise identification of the respiratory pathogens affecting their patients. The lack of effective treatment, coupled with delayed laboratory confirmation, limited the necessity of specific diagnosis. The viral diagnosis paradigm was simply an exclusion of treatable bacterial illness in the differential diagnosis. The emergence of effective diagnostic techniques and effective therapy dictates rethinking the clinical approach to the respiratory viral syndrome.

The availability of CLIA (Clinical Laboratories Improvement Act) made rapid diagnostic kits for influenza available for diagnosis and timely intervention. Sensitivity approaches 80% in hospitalized sick children. The use of nasopharyngeal (NP) swabs as opposed to throat swabs also can increase outpatient sensitivity from 60% to 80%. *(See Table 2.)* Each patient is not necessarily tested. Rather, selective utilization serves to calibrate the clinician's clinical acumen and to provide office confirmation of local disease presence. The clinician may be more comfortable with a confirmed viral diagnosis and more easily use effective antiviral treatment, while reassuring concerned parents of the lack of indication for antibiotics. Use of diagnostic tests in a children's hospital emergency department has led to a significant decrease in antibiotic use, while increasing the use of appropriate antiviral medications.[13] Reimbursement has been forthcoming, making the tests cost-effective in private and clinic practice.

The classic diagnostic tradition of history and physical exam can be remarkably accurate in school-age children. When influenza virus is confirmed in a region or community by local or state health departments or by the CDC, persons with fever, muscle aches, and cough most likely have influenza.[14] Several studies have shown clinical accuracy of 85% in adults during confirmed outbreaks. During the clinical trials of zanamivir (Relenza), it was found that experienced physicians using key factors in the patient history were as accurate in their diagnoses as they were when they used rapid immunoassay kits.[15]

Treatment

The opportunity to effectively intervene in viral illness is a new and sometimes uncomfortable concept for physicians, patients, and their parents. Physicians have not had effective agents for a great length of time and may be uncomfortable with new forms of therapy. The need to begin antiviral therapy early contradicts the long-held advice to see the physician only if several days pass without resolution of presenting symptoms. Parents hesitate to seek professional help for potentially mild, self-limited conditions. While this strategy remains effective for dealing with common winter upper respiratory infections, it leaves the physician without the ability to intervene in potentially serious infections. Increasingly broad arrays of antiviral agents recently have been marketed and more are in the drug pipeline. Practitioners need to rethink their service patterns to take advantage of new therapies to relieve significant morbidity and avoid mortality from viral agents.

The treatment of influenza may serve as a model for emerging antiviral therapy. Specific antiviral therapy of influenza began with the introduction of amantadine (Symmetrel) 30 years ago. The drug targets the M2 membrane protein of influenza A and is effective for reducing the duration of symptoms of established illnesses. It also is effective as a prophylactic agent during epidemics in both adults and children.[16] A rapid emergence of resistance and lack of activity against influenza type B reduces its usefulness. Neurologic side effects are significant in very young and elderly patients. Resistance has been documented within single households, with treated index cases transmitting resistant virus to other family members.[17] Rimantadine (Flumadine) addressed the neurologic toxicity but, like amantadine, it is subject to rapid emergence of resistance, lacks efficacy against type B, and is not FDA-indicated for acute therapy in children. Many experts do support its use in children.

The two prominent surface proteins, hemagglutinin and neuraminidase, have been extensively investigated in the ongoing effort to develop more effective antiviral agents. Hemagglutinin attaches the virus to the epithelial cell membrane and promotes penetration into the cytoplasm; neuraminidase functions in

Table 2. Rapid Diagnostic Tests

CLIA Certified Office-Based Tests*				Detect Viral Antigen		
NAME	COST (DOLLARS)	TIME (MIN.)	STEPS	SENSITIVITY‡	SPECIFICITY‡	COMMENT
Directigen Flu A	19.00	15	11	88%	92%	Flu A only
Flu OIA	16.50	15	5	95%	64%	
QuickVue	20.00	10	3	73%	95%	
ZstatFlu	18.00	20	4	62%	98%	Pharyngeal swab
Influenza Rapid Test	NA	10	4	85%	81%	

* = Average reimbursement $35

‡ = Nasopharyngeal swab

Source: Luber S. Influenza year 2000 update: Epidemiology, diagnosis, and outcome-effectice guidelines for neuraminidase inhibitor therapy. *Emergency Medicine Reports* 2000;21:245-256.

multiple reproductive steps. It degrades the receptor, permitting entry into the cell. After viral replication, it cleaves mucous facilitating, newly formed virions to escape infected cells, separate, and migrate through mucus to infect other epithelial cells. Inhibition of neuraminidase prevents spread of virus within the host and aborts the infection.[18]

The first active drug developed was zanamivir. Clinical studies in experimental and natural infection demonstrated decreased length of viral shedding, symptoms, and severity in both types A and B influenza diseases.[19,20] Ongoing studies of the neuraminidase inhibitors have shown efficacy in childhood. A double-blind, placebo-controlled study of zanamivir in the 1998-1999 Northern Hemisphere flu season recruited 471 children with flu-like symptoms. Three hundred forty-six had culture-proven influenza, and inhaled diskhaler therapy significantly shortened time to alleviation of symptoms and time to resumption of normal activity. The treatment group also used less relief medication. Complications and associated antibiotic use were deceased by 16% and 12%, respectively.[21]

Questions were raised regarding respiratory function deterioration in patients with existing chronic obstructive pulmonary disease (COPD) and asthma. Bronchospasm has occurred in patients with asthma.[20,22] The package insert contains important precautionary information regarding the use of zanamivir with underlying airway disease. The drug is taken as a five-day course using a proven diskhaler design. It is indicated for patients ages 7 and older who have signs and symptoms of influenza A and B of fewer than 48 hours duration.

The desire for an orally active drug led to the development of oseltamivir (Tamiflu). Oseltamivir also has been studied in pediatric populations. A study of 695 patients ages 1-12 years showed a 36-hour or 26% reduction in duration of influenza. The incidence of otitis media was reduced by 44%.[23] Specific efficacy was demonstrated with influenza B infection in other studies, with a decrease of symptom duration by 25%.[22,24] Oseltamivir was well tolerated in clinical trials, with no safety issues raised. In adult, adolescent, and child studies, nausea was reported, with excess emesis over placebo of 5.8%. The recipients described the gastrointestinal symptoms as transient and mild.[25,26] Discontinuance of medication due to adverse events was 1.8% in the oseltamivir group vs. 1.1% with placebo.[23] Prior studies with adolescents and adults indicate significant reduction of gastrointestinal symptoms with concomitant consumption of food.[25] Resistant strains were uncommon and represented viruses with limited infectivity in humans. Adult and adolescent dosage is 75 mg twice a day for five days. It is approved for children ages 1 and older, and dosing is based on weight; it has a fruit-flavored suspension. Current dosage guidelines and indications are seen in Table 3.

Prophylaxis. The neuroaminidase inhibitors have been shown effective for prevention of influenza infection. Zanamivir once a day was 79% effective for the prevention of influenza transmission within families with a confirmed index case.[27] Orally administered oseltamivir 75 mg once a day protected close family contacts against influenza by 92% and interrupted transmission within households by 89%.[28,29] Post exposure, the placebo group had a 12% incidence of influenza, compared with a 1% incidence in the prophylaxis group. The FDA has indicated oseltamivir for prophylaxis in adolescents and adults ages 13 and older.

It has been suggested that use of family prophylaxis after treatment of the index case may be the most effective use of the medication. It not only protects familial contacts but also can serve to reduce community exposure. Family physicians are in a unique position to treat the whole family when an index case is identified. Pediatricians will need to form effective alliances with internists and family physicians to effectively reach the parents of children with influenza.

Reducing Complications and Antibiotic Use. The serious complications of influenza with bacterial pneumonias, Reye syndrome, and prolonged recovery of high-risk patients are well known. The increased frequency of otitis media and other respiratory infections in children with influenza is under appreciated. Antibiotic usage increases with treatment of the otitis media and for the numerous and gratuitous clinical diagnoses of bronchitis, sinusitis, and pneumonia during the flu season. With proper antiviral treatment of influenza, a substantive reduction of antibiotic usage has been demonstrated. This reflects a real decrease in otitis media occurrence, as well as the desired reduction in the overuse of antibiotics for primary viral infection.

In the oseltamivir trials in children ages 1-12 years, 21% of placebo recipients and only 12% of treated subjects had documented otitis media.[22] The 44% reduction in clinical diagnosis was paralleled by a 40% reduction in antibiotic usage.[23] The zanamivir trials of children ages 5-12 years showed a 30% reduction in bacterial complications, with a 20% reduction in

Table 3. Antiviral Agents for Influenza

Generic Name	Trade Name	Indications	Dosage	Wholesale Cost - Treatment	Comments
M2 INHIBITORS - INFLUENZA A					
Amantadine	Symmetrel	Treatment > age 1 Prophylaxis > age 1	100 mg bid × 7 days 100 mg qd	$6.45 (generic) $14.38 (branded)	CNS side effects > age 65 — dose decreased to 100 mg qd If CrCl < 80 mL/min — decrease dose
Rimantadine	Flumadine	Treatment > age 14 Prophylaxis > age 1	100 mg bid × 7 days 100 mg qd	$32.60	If CrCl < 20 mL/min — decrease dose
NEURAMINIDASE INHIBITORS - INFLUENZA A AND B					
Zanamivir	Relenza	Treatment > age 7	2 blisters bid × 5 days	$46.18	Dischaler inhalation device Pending indication: Prophylaxis > age 7 Caution with history of bronchospasm
Oseltamivir	Tamiflu	Treatment > age 18	75 mg bid × 5 days	$59.54	Pending indications: treatment > age 1; prophylaxis > age 1 Mild GI side effects

Source: Luber S. Influenza year 2000 update: Epidemiology, diagnosis, and outcome-effectice guidelines for neuraminidase inhibitor therapy. *Emergency Medicine Reports* 2000;21:245-256.

antibiotic use.[21] Effective treatment of primary viral infections can reduce otitis morbidity and antibiotic usage.

In pivotal clinical trials, the neuraminidase inhibitors showed efficacy with one- to two-day decreases in time to alleviation of all significant symptoms of influenza. Early FDA examination and subsequent professional commentary questioned this apparent marginal benefit from therapy. Health maintenance organizations and other third-party payers also questioned utility, and frequently excluded the medications from their panels. This marginality of efficacy contrasted strongly with clinical observations of patients, physicians, and investigators using the medications. In an effort to reconcile clinical impressions in practice with clinical trial data, investigators followed 1408 patients using prescribed zanamivir in Australia during the 1999 flu season.

Symptom relief was reported by more than 50% of patients within 24 hours and by 77% within 48 hours.[30] Of the 400 elderly patients, 78% were satisfied with their treatment, with 59% experiencing symptom relief within 24 hours.[31] The survey concluded that zanamivir was associated early return to normal activities. They noted the prolonged nature of residual cough in treated influenza after systemic symptoms of fever, headache, myalgia, and malaise had resolved. Investigators speculated that residual cough prolonged the end point in the clinical studies and, thus, caused an underestimation of the clinical effect of treatment.

The identification and treatment of primary viral infections remains a significant challenge to pediatric medicine. It also represents a significant opportunity to reduce an ongoing burden of illness. The technology for effectively preventing, diagnosing, and treating influenza has been demonstrated. Outpatient clinics, emergency rooms, and urgent care centers, as well as private physician offices, need to organize specifically to meet the challenge of early intervention in influenza epidemics. Telephone triage systems need to efficiently screen those with classic symptoms of influenza and promptly direct them to where they can be evaluated and treated with minimal delay.[6] Specific time slots dedicated to prompt evaluation and treatment of infectious disease must be set aside during anticipated flu seasons.

The widespread implementation of influenza prevention and treatment in pediatric populations would provide benefit not only to the index cases but also to household contacts and vulnerable fragile elderly in the community. The antiviral treatment and chemoprophylaxis of contacts of influenza victims will serve as a model for treatment of other specific viral illness as newer antiviral agents that are readily visible in the drug pipeline become available to the practitioner. It will help redefine the meaning of antimicrobial therapy from strictly antibacterial to truly broadly antimicrobial.

Post-September 11 Considerations

The advent of biologic terrorism places new strains on the medical delivery systems as we approach the 2001-2002 influenza season. The scattered but real advent of confirmed inhalation anthrax makes the precise identification and treatment of respira-

tory illness a prime concern for any acute care physician. Unfortunately, the very protean nature of respiratory symptoms makes precise identification unlikely on purely clinical grounds. A detailed history of possible exposure to terrorist agents is a mandatory part of the post-September 11 medical interview. This includes consideration of inhalation toxic agents, as well as communicable disease. Thinking outside the constraints of conventional epidemiology is now mandatory.

The use of real-time influenza reporting systems enables one to either include or exclude the possibility of influenza through community epidemiology. The use of quick diagnostic kits makes a positive diagnosis of the viral infection possible, and increased usage may prevent many needless exposures to unnecessary antibiotics.

The increasing numbers of potentially exposed workers on long courses of broad-spectrum antibiotics also paves the way for proper appreciation of viral respiratory tract infection. While it is certainly possible to contract bacterial illness while on the current recommended regimens for anthrax prophylaxis, a patient with fever, cough, and myalgias while on an established antibiotic course most assuredly will have a viral illness. With proper local epidemiologic surveillance and available laboratory tests, more precise diagnosis will be facilitated, and enhanced use of antiviral agents promoted. More than ever, precision in defining the etiologic agents is not only desirable but also necessary.

References

1. National Institute of Allergy and Infectious Diseases. Fact Sheet: Flu. December 1997.
2. Izurieta HS, Thompson WW, Kramarz P, et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. *N Engl J Med* 2000;342:232-239.
3. Neuzil KM, Mellen BG, Wright PF, et al. The effect of influenza on hospitalization, outpatient visits, and courses of antibiotics in children. *N Engl J Med* 2000;342:225-231.
4. McIntosh K, Lieu T. Is it time to give influenza vaccine to healthy infants? *N Engl J Med* 2000;342:275-276.
5. Reichert TA, Sugaya N, Fedson DS, et al. The Japanese experience with vaccinating schoolchildren against influenza. *N Engl J Med* 2001;344:889-892.
6. White T, Lavoie S, Nettleman MD. Potential cost savings attributable to influenza vaccination of school-aged children. *Pediatrics* 1999;103:e6.
7. Monto AS, Davenport FM, Napier JA, et al. Modification of an outbreak of influenza in Tecumseh, Michigan by vaccination of school children. *J Infect Dis* 1970;122:16-25.
8. Center for Disease Control and Prevention, Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices. (ACIP). *MMWR Morb Mortal Wkly Rep* 1999;48(RR-04):1-28.
9. Belshe RB, Gruber WC, Mendelman PM, et al. Efficacy of vaccination with live attenuated, cold adapted, trivalent intranasal influenza virus vaccine against a variant (A/Sydney) not contained in the vaccine. *J Pediatr* 2000;136:168-175.
10. Belshe RB, Mendelman PM, Treanor J, et al. The efficacy of live attenuated cold-adapted trivalent intranasal virus vaccine in children. *N Engl J Med* 1998;338:1405-1412.
11. Henderson, F. Viral Respiratory Infection. In: Rudolph A, Hoffman J, Rudolph C. *Rudolph's Pediatrics.* 20th ed. Stamford: Appleton & Lange; 1996.
12. Glezen W, Cherry J. Influenza Viruses. In: Feigin RD, Cherry J, eds. *Textbook of Pediatric Infectious Diseases.* 3rd ed. Philadelphia: Saunders; 1992:1688-1704.
13. Noyola D, Demmler GJ. Effect of rapid diagnosis on management of Influenza A infections. *Pediatr Infect Dis J* 2000;19: 303-307.
14. Dolin R. Influenza. In: Fauci A, Braunwald E, Isselbacher K, et al. *Harrison's Principles of Internal Medicine.* 14th ed. New York: McGraw Hill; 1998.
15. Aoki F, Osterhaus A, Rimmelzwan G, et al. Oral GS4104 successfully reduces duration and severity of naturally acquired influenza [abstract] 38th Interscience Conference of Antimicrobial Agents and Chemotherapy. Sept. 24-27, 1998. San Diego, USA.
16. Amantadine: Does It Have a Role in the Prevention and Treatment of Influenza? NIH Consens Statement 1979 Oct 15-16;2: 51-56.
17. Hayden FG, Belshe RB, Clover RD, et al. Emergence and apparent transmission of rimantadine-resistant influenza A virus in families. *N Eng J Med* 1989;321:1696-1702.
18. Gubareva LV, Webster RG. Neuraminidase inhibitors: New candidate drugs for influenza. *Infect Med* 1999;16:345-354.
19. Boivin G, Goyette N Aoki F, et al. Clinical and virological efficacy of zanamivir in the treatment of Influenza A virus infections during the 1997-1998 flu season. Poster Session ICAAC, 1999.
20. Hayden FG, Osterhaus AD, Treanor JJ, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza virus infections. *N Engl J Med* 1997;337:874-880.
21. Hedrick J, Barzilai A, Behre U. Zanamivir for treatment of symptomatic influenza A and B infection in children five to twelve years of age: A randomized controlled trial. *Pediatr Infect Dis J* 2000;19: 410-417.
22. Monto A, Fleming D, Henry D, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza A and B virus infections. *J Infect Dis* 1999;180:254-261.
23. Whitley RJ, Hayden FG, Reisinger KS, et al. Oral oseltamivir treatment of influenza in children. *Pediatr Infect Dis J* 2001;20: 127-133.
24. Hayden F, Robson R, Jennings L, et al. Efficacy of oseltamivir in experimental human influenza B virus infection, Poster 670. ICAAC 2000.
25. Hayden FG, Atmar RL, Schilling M, et al. Safety and efficacy of a selective oral neuraminidase inhibitor (oseltamivir) to prevent influenza. *N Engl J Med* 1999;341:1336-1343.
26. Hayden FG, Treanor JT, Fritz RS, et al. Use of the oral neuraminidase inhibitor oseltamivir in experimental human influenza: Randomized controlled trials for prevention and treatment. *JAMA* 1999;282:1240-1246.

27. Monto A, Robinson D, Herlocher M, et al. Zanamivir in the prevention of influenza among healthy adults: A randomized controlled trial. *JAMA* 1999;282:31-35.
28. Hayden FG, Atmar RL, Schilling M, et al. Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. *N Engl J Med* 1999;341:1336-1343.
29. Oxford J, Jackson H, Ward P. Short term prophylaxis with oseltamivir effectively prevents spread of influenza A and B. Whitechapel, London: Retroscreen Ltd.
30. Silagy C, Watts R. Zanamivir, a new targeted therapy in the treatment of influenza: A patient perspective assessed by questionnaire. *Clin Drug Invest* 2000;19:111-121.
31. Joseph AM, Neal D. Managing cold and flu: A protocol for the nurse and pharmacist. *Federal Practitioner* 1999;Nov:23-51.

Physician CME Questions

To earn CME credit for this supplement to Emergency Medicine Reports, *please refer to the enclosed Scantron form for directions on taking the test and submitting your answers.*

1. Gastrointestinal symptoms of vomiting and diarrhea occur in how many children with influenza?
   A. Up to one-third
   B. More than one-half
   C. Three-fourths
   D. Almost all

2. The findings of a Texas study with a 50% immunization rate for school children demonstrated:
   A. Immunization of school children was shown to be cost effective when considering indirect costs of illness.
   B. Immunization made no difference.
   C. Immunization prevented community epidemics.
   D. Immunization dramatically reduced excess mortality in the elderly.
   E. All but B are correct.

3. Which of the following about the presentation of influenza in children is correct?
   A. The infection only presents as classic bronchiolitis.
   B. Differentiation from parainfluenza or respiratory syncytial virus (RSV) infections may be accomplished without culture or immunoassay.
   C. Febrile seizures are not uncommon in the infant.

4. Influenza arrives during months in which annual RSV epidemics traditionally have received the primary attention of the pediatrician.
   A. True
   B. False

5. Which of the following may be a complication of influenza?
   A. Bacterial pneumonias
   B. Reye's syndrome
   C. Prolonged recovery of high-risk patients
   D. All of the above

6. According to this article, effective treatment of primary viral infections can reduce otitis morbidity and antibiotic usage.
   A. True
   B. False

CME Objectives

To help physicians identify and treat patients with influenza, as well as inform and immunize their patients against this disease to prevent its spread.

BIOTERRORISM WATCH

Preparing for and responding to biological, chemical and nuclear disasters

Flu or anthrax? First inhalational cases yield clues for clinicians to make the critical call

Use case history, blood work, X-rays, rapid tests

There is a postal worker in your emergency department (ED) with flulike symptoms.

That once insignificant observation about occupation and illness now triggers a detailed algorithm created by the Centers for Disease Control and Prevention (CDC) in Atlanta. **(See algorithm, p. 2.)** Is it flu or inhalational anthrax? Whether a realistic question or not, it is what many of your incoming patients may be asking — particularly if another wave of anthrax scares coincides with a nasty influenza season. Many of the initial symptoms are similar, but investigators dealing with the first inhalational anthrax cases have gleaned out key indicators that will help clinicians make the call.

"It is important to take a careful history from the [patients] when they present," says **Julie Gerberding**, MD, acting deputy director of CDC's National Center for Infectious Diseases. "If the [patients are] mail handlers in a professional environment — where they're dealing with large amounts of mail that is not their own — then the index of suspicion should be raised and more testing should be done to be sure there aren't additional clues to suggest that it is not a common viral infection."

Using the first 10 cases of inhalational anthrax as a baseline patient profile, the CDC reports that the median age of the patients was 56 years (range: 43-73 years), and seven were men.[1]

The incubation period from the time of exposure to onset of symptoms when known (seven cases) was seven days (range: five to 11 days).

The initial illness in the patients included fever (nine) and / or sweats / chills (six). Severe fatigue or malaise was present in eight, and minimal or nonproductive cough in nine. One had blood-tinged sputum. Eight patients reported chest discomfort or pleuritic pain. Abdominal pain or nausea or vomiting occurred in five, and five reported chest heaviness. Other symptoms included shortness of breath (seven), headache (five), myalgias (four), and sore throat (two). The mortality rate was 40% for the 10 patients, much lower than historical data indicated. Indeed, one of the critical reasons to recognize inhalational anthrax early is that it is far more treatable than originally thought.

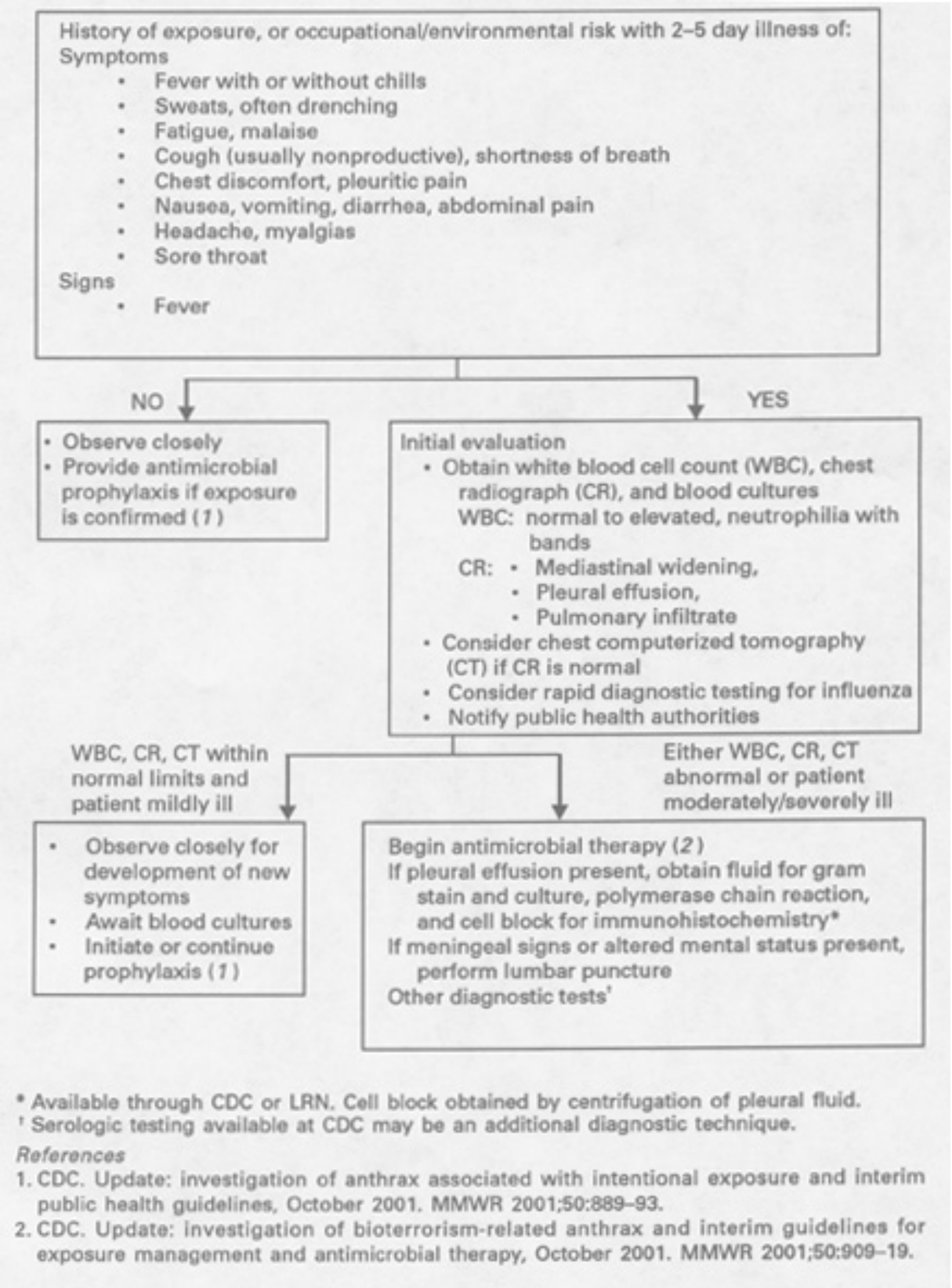
The CDC gathered comparative data on the symptoms and signs of anthrax and influenza, finding, for example, that only 20% of the anthrax patients reported sore throat.[2] Flu sufferers report a sore throat in 64% to 84% of cases. Likewise, 80% of the anthrax cases reported symptoms of nausea and vomiting. That symptom is reported in only 12% of flu cases. Shortness of breath appears to be another key distinguishing symptom, affecting 80% of the anthrax patients but seen in only 6% of flu patients.

"One of the other clues that we are noticing is that the patients with inhalation anthrax actually do not have nasal congestion or a runny nose,"

(Continued on page 3)

This supplement was prepared by Gary Evans, editor of *Hospital Infection Control*. Telephone: (706) 742-2515. E-mail: gary.evans@ahcpub.com.

Clinical Evaluation of People with Possible Inhalational Anthrax



Source: Centers for Disease Control and Prevention. Update: Investigation of bioterrorism-related anthrax and interim guidelines for clinical evaluation of persons with possible anthrax. *MMWR* 2001; 50:945.

Gerberding says. "They don't have the symptoms of an upper-respiratory tract infection. They have a more systemic chest presentation, and that may be another distinguishing characteristic."

Another finding on initial blood work is that none of the inhalational anthrax patients had a low white blood cell count (WBC) or lymphocytosis when initially evaluated. Given that, CDC officials note that future suspect cases with low WBC counts may have viral infections such as influenza. Chest X-rays were abnormal in all patients, but in two an initial reading was interpreted as within normal limits. Mediastinal changes including mediastinal widening were noted in all eight patients who had CT scans. Mediastinal widening may be subtle, and careful review of the chest radiograph by a radiologist may be necessary, the CDC advises.

Complementing the CDC's effort, are the observations of the few clinicians who have actually seen inhalational anthrax cases come into their hospital systems. Two inhalational anthrax cases, both of which survived, were admitted to the Inova Healthcare System in Fairfax, VA (near Washington, DC).

"Clinically, I think the history of the people who presented here is useful," says **Allan J. Morrison Jr.**, MD, MSc, FACP, health care epidemiologist for the Inova system. "They stutter-stepped toward their pulmonary symptoms. That had some mild symptoms and then they were sort of 'meta-stable.' They were not relentlessly progressing. Then they progressed with symptoms more aggressively. Whereas with influenza — in our experience — once you start to get sick, it just keeps on progressing with very high fevers, chills, muscle aches, and pains. As a consequence, we feel there should be a good way to differentiate the two."

Since anthrax is a realistic concern in the Washington, DC, area, what about the aforementioned scenario of symptomatic postal workers in the ED?

"We would take a very aggressive history, not only of occupation but physically where they have been," Morrison says. "If they are symptomatic and have been in or work around a 'hot zone' — a location from which anthrax has either been cultured environmentally or patients have come from there — we will err on the side of being very aggressive about working up anthrax. By that I mean chest X-rays, chemistry profile, [etc.]"

In addition, the hospital system pushed early flu vaccination programs for staff and the surrounding community. "We want to move toward herd immunity," he says. "We are also working with our local hospitals to make sure that they have access to the rapid influenza tests. So for diagnosis — for obvious reasons — it is very helpful to make that distinction early."

One such rapid test is ZstatFlu (ZymeTX Inc., Oklahoma City), which the company claims can yield a diagnosis of influenza A or B some 20 minutes after a throat swab. The test detects neuraminidase, an influenza viral enzyme. However, Gerberding cautions clinicians not to rely solely on such tests. Rather, they should use the results of tests in combination with the patient history and clinical presentation, she says.

"So it is a constellation of history, clinical findings, and laboratory tests," she says. "Hopefully, when we get these all together, we'll be able to at least reduce the anxiety among some people and help clinicians diagnose those patients who really do require the antibiotic treatment. What we don't want to have happen is for everybody coming in with the flu to get an antibiotic because that undermines a whole other set of public health issues relating to antimicrobial resistance and proper management of influenza."

Even the vaccinated can still have flu

Complicating the issue is the fact that the flu vaccine efficacy can vary annually, but is usually 70% to 90% protective, says **Keiji Fukuda**, MD, a medical epidemiologist in the CDC influenza branch. Thus, depending on how well the vaccine matches the circulating strain, a certain portion of flu patients will tell clinicians they have been immunized. But in addition to vaccine breakthrough infections, there is a plethora of other viral and respiratory pathogens that will be creating similar symptoms, he says. In a somewhat sobering reminder — given that at this writing, the total anthrax cases remained in the double digits — Fukuda notes that a typical flu season will send 114,000 people to the hospital and 20,000 to their graves.

"There has been an awful lot of attention on the [anthrax] cases, but the bottom line is that there have been few cases, and these cases generally have occurred in a limited number of communities within a limited number of groups," he says. "And so the epidemiologic message is that anthrax really has not been diagnosed in most parts of the country, whereas we expect to see millions and millions of flu cases all over the place."

If facilities are faced with an onslaught of patients with respiratory illness there are several measures they can take, he notes. Those include:

- Reduce or eliminate elective surgery.
- Relax staff-to-patient ratios within the limits of your licensing agency.
- Emphasize immunizing staff so more staff are available.
- Identify ways to bring in extra staff to help out with the patients.
- Set up walk-in flu clinics to triage the patients.

Reference

1. Centers for Disease Control and Prevention. Update: Investigation of bioterrorism-related anthrax and interim guidelines for clinical evaluation of persons with possible anthrax. *MMWR* 2001; 50:941-948.

2. Centers for Disease Control and Prevention. Consideration for distinguishing influenza-like illness from inhalational anthrax. *MMWR* 2001; 50:984-986. ■

CDC moving quickly on smallpox front

Immunizations, training, vaccine dilution studied

Though officially stating it has no knowledge of any impending use of smallpox as a bioweapon, the Centers for Disease Control and Prevention (CDC) is scrambling with conspicuous speed to be ready for just such an event.

CDC workers from a variety of specialties are not only receiving smallpox vaccinations, they are being trained to give them to others using the old bifurcated needle scarification technique. And, even as creation of a new vaccine is fast-tracked, researchers are trying to determine if the current stockpile of 15.4 million doses can be expanded fivefold by simply diluting the vaccine.

Based on such actions, it is fair to say the agency is at least highly suspicious that the known stocks of smallpox virus are not safely ensconced in their official repositories in Russia and the United States.

"CDC is putting together a number of teams, which will probably total [more than] 100 employees, that could be quickly dispatched in a moment's notice to assist state and local health departments and frontline clinicians investigate suspect cases of smallpox," **Tom Skinner**, a spokesman for the CDC, tells *Bioterrorism Watch.*

"They are Epidemic Intelligence Service (EIS) officers, laboratorians, and others. Part of this includes vaccinating them against smallpox," he explains.

But while confirming that the CDC teams are being trained to administer the vaccine, Skinner would not specify who would be vaccinated following a smallpox bioterror event. "We have a smallpox readiness plan," he says. "Issues around vaccination are covered in that plan. That plan is being finalized. It is considered an operational plan. If we have a case tomorrow, it could be implemented. It covers who should be vaccinated and when."

The general consensus among bioterrorism experts is that those exposed would be vaccinated because the vaccine can prevent infection and possibly death even if given several days out. Likewise, health care workers and their family members would want vaccine if they were expected to care for the infected. Some aspect of quarantine would no doubt come into play because, unlike anthrax, it will be critical to separate the first smallpox cases and their contacts from the susceptible population.

Another aspect of CDC preparations includes the smallpox vaccine dilution study, which is being headed up by **Sharon E. Frey**, MD, associate professor of infectious diseases and immunology at Saint Louis University School of Medicine.

The vaccine, known as Dryvax, is no longer produced, but there are 15.4 million doses left. Frey and colleagues are looking at dilution studies that could maintain vaccine efficacy while increasing the available stock by millions of doses. In a study last year, Frey tried a one to 10 vaccine dilution, which would create a stockpile of more than 150 million doses. However, the resulting vaccine had only a 70% effective rate.

"The undiluted vaccine has about a 95% take rate," she tells *BW*. "It is not perfect, but we would like to be as close to that as we could be."

The new study will include a one to five dilution, which should show greater efficacy while increasing the stockpile to more than 75 million doses.

"We are looking at a 'take' rate for the vaccine, in other words how many people actually develop a typical lesion and whether they have a strong neutralizing antibody response to the vaccine," Frey says. "We know that the vaccine is still good. We actually titered the vaccine and it is very similar to its original titer," she adds. ■