NEUROLOGIC DIAGNOSTIC PROCEDURES

Ralph F. Józefowicz, MD

Lumbar Puncture

Sampling of cerebrospinal fluid (CSF) via lumbar puncture is crucial for accurate diagnosis of meningeal infections and carcinomatosis. CSF analysis is also helpful in evaluating patients with central or peripheral nervous system demyelinating disorders and with intracranial hemorrhage, particularly when imaging studies are inconclusive.

The CSF formula often provides an important clue as to the pathologic process involved. An elevated WBC count is seen with infections and other inflammatory diseases, as well as carcinomatosis. The WBC differential may point to a specific class of pathogen: polymorphonuclear leukocytes suggest a bacterial process, while mononuclear cells suggest a viral, fungal or immunologic cause. The CSF glucose concentration is typically reduced in bacterial and fungal infections, as well as with certain viral infections (Mumps virus) and with sarcoidosis. The CSF protein concentration is elevated in a variety of disorders, including most infections and demyelinating neuropathies. Table 1 lists characteristic CSF formulae for several neurological conditions.

A lumbar puncture should not be performed in patients who have obstructive, non-communicating hydrocephalus or a focal CNS mass lesion causing raised intracranial pressure, since reducing the CSF pressure acutely in these settings via lumbar puncture may result in cerebral or cerebellar herniation. Lumbar puncture may be safely performed in patients with a communicating hydrocephalus, such as with idiopathic intracranial hypertension (pseudotumor cerebri), and may be an effective treatment for selected patients with this condition.
<table>
<thead>
<tr>
<th></th>
<th>Color Turbidity</th>
<th>Opening pressure</th>
<th>WBC</th>
<th>Differential</th>
<th>RBC</th>
<th>Protein</th>
<th>Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal</strong></td>
<td>Clear colorless</td>
<td>70-180 mm H₂O</td>
<td>0-5</td>
<td>Mononuclear</td>
<td>0</td>
<td>&lt;60 mg/dl</td>
<td>&gt;2/3 serum</td>
</tr>
<tr>
<td><strong>Bacterial meningitis</strong></td>
<td>Cloudy Straw-colored</td>
<td>↑</td>
<td>↑↑</td>
<td>PMNs</td>
<td>0</td>
<td>↑↑</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Viral meningitis</strong></td>
<td>Cloudy Colorless</td>
<td>↑</td>
<td>↑</td>
<td>Lymphs</td>
<td>0</td>
<td>↑</td>
<td>NI</td>
</tr>
<tr>
<td><strong>Fungal and TB meningitis</strong></td>
<td>Cloudy Straw-colored</td>
<td>↑</td>
<td>↑</td>
<td>Lymphs</td>
<td>0</td>
<td>↑↑</td>
<td>↓↓</td>
</tr>
<tr>
<td><strong>Viral encephalitis</strong></td>
<td>Cloudy Straw-colored</td>
<td>NI - ↑</td>
<td>↑</td>
<td>Lymphs</td>
<td>0</td>
<td>NI (Herpes ↑)</td>
<td>NI</td>
</tr>
<tr>
<td><strong>Brain abscess</strong></td>
<td>Cloudy Straw-colored</td>
<td>↑</td>
<td>↑</td>
<td>Lymphs</td>
<td>0</td>
<td>↑</td>
<td>NI</td>
</tr>
<tr>
<td><strong>Subarachnoid hemorrhage</strong></td>
<td>Cloudy Pink</td>
<td>↑</td>
<td>↑</td>
<td>PMNs and Lymphs</td>
<td>↑↑</td>
<td>↑</td>
<td>NI</td>
</tr>
<tr>
<td><strong>Guillain-Barré Syndrome</strong></td>
<td>Clear Yellow</td>
<td>NI - ↑</td>
<td>0-5</td>
<td>Mononuclear</td>
<td>0</td>
<td>↑</td>
<td>NI</td>
</tr>
</tbody>
</table>
Electroencephalography (EEG)

Electroencephalography is the recording and measurement of scalp potentials in order to evaluate baseline brain functioning as well as paroxysmal brain electrical activity suggestive of a seizure disorder.

An EEG is performed by securing 20 electrodes to the scalp at predetermined locations, based on an international system that uses standardized percentages of the head circumference, the "10-20 system". Each electrode is labeled using a letter and a number, the letter identifying the skull region (Fp=frontopolar, F=frontal, P=parietal, T=temporal, O=occipital, V=vertex) and the number the specific location, with odd numbers representing the left sided electrodes, and even numbers the right sided electrodes. These electrodes are then connected in various combinations of pairs to generate voltage potential differences, and the potentials are recorded on a chart recorder.

In order to delineate the spatial distribution of the changing electric field for an EEG, orderly arrangement of electrode pairs are used, and each specific arrangement is known as a montage. Montages are generally of two types: referential, in which each electrode is connected to a single reference electrode such as the ear; and bipolar, in which electrodes are connected sequentially to one another, forming a chain. A standard EEG generally records about 30 minutes of brain activity, both in the awake state and in the first two stages of sleep. Various activating procedures are used during the recording of an EEG, including hyperventilation and photic stimulation. These activating procedures may precipitate seizure discharges in some patients with seizure disorders, increasing the sensitivity of the test.

The amplitudes of scalp electrical potentials are quite low, averaging 30-100 μV, and represent a summation of excitatory post synaptic potentials (EPSP’s) and inhibitory post synaptic potentials (IPSP’s) generated, to a large extent, by the pyramidal cells in layer 4 of the cerebral cortex which behave as electric dipoles. Action potentials are of too brief a duration to have an effect on the EEG.

The EEG is analyzed with respect to symmetry between each hemisphere, wave frequency and amplitude, and the presence of spikes (20-70 msec) and sharp waves (70-200 msec) that may indicate a seizure focus. EEG frequencies are divided into four categories as follows:

- Delta < 4 Hz
- Theta 4-7 Hz
- Alpha 8-13 Hz
- Beta > 13 Hz

The normal waking EEG in a patient with eyes closed contains rhythms of alpha frequency in the occipital leads and of beta frequency in the frontal leads. Normal sleep causes a generalized slowing of the EEG frequencies and an increase in amplitude in each stage of sleep, such that stage 4 sleep contains > 50% large amplitude delta rhythm.
EEG abnormalities are of two types: abnormalities in background rhythm and abnormalities of a paroxysmal nature. Some of the more common EEG abnormalities are noted in Table 2.

### Table 2: EEG abnormalities

<table>
<thead>
<tr>
<th>EEG Abnormality</th>
<th>Clinical correlate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Background rhythm abnormalities</strong></td>
<td></td>
</tr>
<tr>
<td>Generalized slowing</td>
<td>Hypoxic and metabolic encephalopathies</td>
</tr>
<tr>
<td>Focal slowing</td>
<td>Large mass lesions (tumor, large stroke)</td>
</tr>
<tr>
<td>Triphasic waves</td>
<td>Hepatic and renal encephalopathies</td>
</tr>
<tr>
<td>Electro-cerebral inactivity with lack of response to</td>
<td>Brain death</td>
</tr>
<tr>
<td>all stimuli</td>
<td></td>
</tr>
<tr>
<td><strong>Paroxysmal abnormalities</strong></td>
<td></td>
</tr>
<tr>
<td>3 Hz spike and wave, augmented by hyperventilation</td>
<td>Absence epilepsy</td>
</tr>
<tr>
<td>3-4 Hz spike and wave in light sleep or with photic</td>
<td>Primary generalized epilepsy</td>
</tr>
<tr>
<td>stimulation</td>
<td></td>
</tr>
<tr>
<td>Centro-mid temporal spikes</td>
<td>Benign Rolandoic epilepsy</td>
</tr>
<tr>
<td>Anterior temporal spikes or sharp waves</td>
<td>Simple or complex partial seizures of mesial temporal</td>
</tr>
<tr>
<td></td>
<td>origin</td>
</tr>
<tr>
<td>Hypsarrhythmia (high voltage chaotic slowing with</td>
<td>Infantile spasms (West syndrome)</td>
</tr>
<tr>
<td>multifocal spikes)</td>
<td></td>
</tr>
<tr>
<td>Burst suppression</td>
<td>Severe anoxic brain injury, Barbiturate coma</td>
</tr>
</tbody>
</table>

The major usefulness of an EEG is to diagnose and categorize a seizure disorder. It is important to realize that EEG’s are neither highly sensitive nor completely specific for diagnosing seizures. Since seizures are paroxysmal events, it is not unusual for an EEG to be normal, or only minimally abnormal in a patient with epilepsy if it is recorded during an interictal phase (the time period between seizures). In fact, only about 50% of patients with seizures will have epileptiform activity on their first EEG. Repeating the EEG with provocative maneuvers, such as sleep deprivation, hyperventilation and photic stimulation, may increase this percentage to 90%. Conversely, about 1% of adults and 3.5% of children who are neurologically normal and who never had a seizure, will have epileptiform activity on an EEG.
The EEG may provide clues in the diagnosis of certain neurologic conditions, including viral encephalitis, slow virus infections, and some forms of coma. In each of these situations, the EEG can have specific patterns that suggest a specific neurologic diagnosis. In herpes simplex encephalitis, periodic lateralizing epileptiform discharges (PLEDs) emanating from the temporal lobes are frequently present. Triphasic slow waves are the hallmark of hepatic encephalopathy. Creutzfeldt-Jacob disease is characterized by the presence of bilateral synchronous repetitive sharp waves. The EEG is also helpful in confirming brain death when an apnea test cannot be performed due to cardiac instability.

In the past, the EEG was often used for localizing neurological lesions such as stroke, brain tumor, or abscess. With the advent of neuroimaging, EEG is almost never used for these purposes.

**Nerve Conduction Study (NCS)**

A nerve conduction study is the recording and measurement of the compound nerve and muscle action potentials elicited in response to an electrical stimulus.

To perform a motor NCS, a surface (active) electrode is placed over the belly of a distal muscle that is innervated by the nerve in question. A reference electrode is placed distally over a joint. The nerve is then supramaximally stimulated at a predetermined distance proximal to the active electrode and the resultant compound motor action potential (CMAP) is recorded. The terminal latency, amplitude and duration of the evoked potential are measured directly, and the conduction velocity is calculated from the latencies of the evoked potentials with stimulation at two different points: the distance between the two points (conduction distance) is divided by the difference between the corresponding latencies (conduction time), resulting in a calculated velocity (conduction velocity = distance/time).

To perform a sensory NCS, the active electrode is placed over that portion of the skin innervated by the nerve in question and a sensory nerve action potential (SNAP) is recorded following electrical stimulation of the nerve, similar to that noted for a motor NCS.

NCS abnormalities include reduced amplitudes, prolonged terminal latencies, conduction block and slowed conduction velocities. The clinical significance of these abnormalities is noted in table 3.
Table 3 – NCS Abnormalities

<table>
<thead>
<tr>
<th>NCS Abnormality</th>
<th>Clinical correlate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced amplitude</td>
<td>Axonal neuropathy</td>
</tr>
</tbody>
</table>
| Prolonged terminal latency | Demyelinating neuropathy  
                          | Distal compressive neuropathy                          |
| Conduction block         | Severe focal compressive neuropathy  
                          | Severe demyelinating neuropathy                        |
| Slowed conduction velocity | Demyelinating neuropathy                               |

A NCS is helpful in documenting that a neuropathy exists, quantitating the severity, and noting the distribution of the neuropathy, i.e. whether it is distal, proximal or diffuse. In addition, the NCS can provide information on the modality involved, i.e. motor versus sensory, and can also give clues as to the underlying pathology, whether axonal or demyelinating. A NCS is also helpful in diagnosing compressive neuropathies, such as carpal tunnel syndrome, tardy ulnar palsy, peroneal nerve palsy, and tarsal tunnel syndrome.

**F Wave and H Reflex**

The F wave and H reflex are ways at looking at the conduction characteristics for proximal portions of nerves, including the nerve roots.

The F wave is a late CMAP evoked intermittently from a muscle by a supramaximal electrical stimulus to the nerve, and is due to antidromic activation (backfiring) of α motor neurons. F waves can be elicited from practically all distal motor nerves.

The H reflex is a late CMAP that is evoked regularly from a muscle by a submaximal stimulus to a nerve, and is due to stimulation of Ia afferent fibers (a spinal reflex). The H reflex can only routinely be obtained from calf muscles with stimulation of the tibial nerve in the popliteal fossa.

F waves are helpful in diagnosing Guillain-Barré syndrome, in which demyelination is often confined to proximal portions of nerves early in the course of the disease. The H reflex is often absent in patients with an acute S1 radiculopathy.

**Repetitive stimulation study (RSS)**

The repetitive stimulation study is a method of measuring electrical conduction properties at the neuromuscular junction. To perform a RSS, a surface recording electrode is placed over a muscle belly and the nerve innervating that muscle is electrically stimulated with a supramaximal stimulus at a certain frequency. A series of electrical potentials is then recorded whose amplitude is roughly proportional to the number of muscle fibers that are being activated.
The RSS is helpful in diagnosing neuromuscular junction disorders, such as myasthenia gravis and the myasthenic syndrome (Lambert-Eaton syndrome). In myasthenia gravis, the amplitudes of the evoked potentials will become progressively smaller with repetitive stimulation in clinically involved muscles. Clinically uninvolved muscles often do not demonstrate this decrement. In the myasthenic syndrome, one sees an increment in the amplitudes of the evoked potentials with repetitive electrical stimulation.

**Electromyography (EMG)**

Electromyography is the recording and study of insertional, spontaneous, and voluntary electrical activity of muscle. This test allows one to physiologically evaluate the motor unit, including the anterior horn cell, peripheral nerve, and muscle.

An EMG is performed by inserting a needle electrode into the muscle in question, and evaluating the compound motor action potentials both visually (on the oscilloscope screen) and aurally (over the loud speaker). Muscles are typically studied at rest and when voluntarily contracted.

When performing an EMG the electrical activity of muscle is studied in four settings: (1) **insertional activity** (occurring within the first second of needle insertion); (2) **spontaneous activity** (electrical activity at rest); (3) **voluntary activity** (electrical activity with muscle contraction); and (4) the **recruitment pattern** (change in electrical activity with maximal contraction). Table 4 lists the clinical significance of EMG abnormalities in these four settings.
Table 4 – EMG Abnormalities

<table>
<thead>
<tr>
<th>EMG Abnormality</th>
<th>Clinical correlate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insertional activity</strong></td>
<td></td>
</tr>
<tr>
<td>Prolonged</td>
<td>Acute denervation</td>
</tr>
<tr>
<td></td>
<td>Active (inflammatory) myopathy</td>
</tr>
<tr>
<td><strong>Spontaneous activity</strong></td>
<td></td>
</tr>
<tr>
<td>Fibrillations and positive waves</td>
<td>Acute denervation</td>
</tr>
<tr>
<td></td>
<td>Active (inflammatory) myopathy</td>
</tr>
<tr>
<td>Fasciculations</td>
<td>Chronic neuropathies</td>
</tr>
<tr>
<td></td>
<td>Motor neuron disease</td>
</tr>
<tr>
<td></td>
<td>(rare fasciculations may be normal)</td>
</tr>
<tr>
<td>Myotonic discharges</td>
<td>Myotonic disorders (myotonic dystrophy)</td>
</tr>
<tr>
<td><strong>Voluntary activity</strong></td>
<td></td>
</tr>
<tr>
<td>Neuropathic potentials:</td>
<td>Chronic neuropathies</td>
</tr>
<tr>
<td>(large amplitude, long duration,</td>
<td></td>
</tr>
<tr>
<td>polyphasic potentials)</td>
<td></td>
</tr>
<tr>
<td>Myopathic potentials:</td>
<td>Chronic myopathies</td>
</tr>
<tr>
<td>(small amplitude, short duration,</td>
<td></td>
</tr>
<tr>
<td>polyphasic potentials)</td>
<td></td>
</tr>
<tr>
<td><strong>Recruitment</strong></td>
<td></td>
</tr>
<tr>
<td>Reduced</td>
<td>Chronic neuropathies</td>
</tr>
<tr>
<td>Rapid</td>
<td>Chronic myopathies</td>
</tr>
</tbody>
</table>

The EMG is helpful when evaluating patients with weakness, in that it can help one determine whether weakness is due to anterior horn cell disease, nerve root disease, peripheral neuropathy, or an intrinsic disease of muscle itself (myopathy).

The EMG can differentiate acute denervation from chronic denervation, and may thus give an indication as to the time course of the lesion causing the neuropathy. In addition, based on which muscles have an abnormal EMG pattern, one can determine whether the neuropathy is due to a lesion of a nerve root (radiculopathy), the brachial or lumbosacral plexus (plexopathy), an individual peripheral nerve (mononeuropathy), or multiple peripheral nerves (polyneuropathy).

The EMG is also helpful in differentiating active (inflammatory) myopathies from chronic myopathies. The active myopathies include dermatomyositis, polymyositis, inclusion body myositis, and some forms of muscular dystrophy such as Duchenne dystrophy.
The chronic myopathies include the other muscular dystrophies, the congenital myopathies, and some metabolic myopathies. Myotonic dystrophy and congenital myotonia produce characteristic myotonic discharges.

It is important to note that it may take several weeks for a muscle to develop EMG signs of acute denervation following nerve transection. For this reason, an EMG performed in the acute setting following nerve injury should be interpreted with caution, and may need to be repeated at a later date.

Evoked Potentials

Evoked potentials are ways of measuring conduction velocities for sensory pathways in the central nervous system by means of computer averaging techniques. Three types of evoked potentials are routinely performed: visual, brain stem auditory, and somatosensory.

Pattern Reversal Visual Evoked Responses (PVER):

The PVER measures conduction velocities for central visual pathways, in particular the optic nerves. To perform this test, EEG electrodes are placed over the occipital regions of the scalp and the patient is asked to look at the center of a black and white checkerboard screen with one eye patched for 3 minutes. The color of the checks alternates about twice per second, a process known as pattern reversal. The scalp potentials elicited by the pattern reversal are then recorded and signal-averaged by a computer. This signal averaging cancels the random EEG activity and differentially amplifies the evoked potential.

A single waveform (P 100) is recorded for each eye, and the amplitude and latency are measured. The normal latency for the P 100 waveform is approximately 100 msec. A prolonged P 100 latency in one eye implies slowed conduction velocity in the optic nerve and suggests demyelination of that nerve.

PVER testing is helpful when multiple sclerosis is suspected clinically and one needs to document the presence of a second demyelinating lesion in the CNS that may not be clinically evident.

Brain Stem Auditory Evoked Responses (BAER):

The BAER measures conduction velocities for central auditory pathways in the brainstem. EEG electrodes are placed over the posterior scalp and a series of clicks at a frequency of 5 Hz are delivered to each ear separately for 3 minutes. The scalp potentials elicited by the clicks are then recorded and signal-averaged by a computer. This signal averaging cancels the random EEG activity and differentially amplifies the evoked potential. A series of five waves is recorded for each ear, and each wave corresponds to a different point in the central auditory pathway as noted in table 5.
Table 5 – BAER Generators

<table>
<thead>
<tr>
<th>Wave</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Auditory nerve</td>
</tr>
<tr>
<td>II</td>
<td>Cochlear nucleus</td>
</tr>
<tr>
<td>III</td>
<td>Superior olivary nucleus</td>
</tr>
<tr>
<td>IV</td>
<td>Lateral lemniscus</td>
</tr>
<tr>
<td>V</td>
<td>Inferior colliculus</td>
</tr>
</tbody>
</table>

The wave latencies for the right and left ears are compared, and a delay in any of the latencies suggests a lesion at that point in the central brain stem auditory pathway. BAER testing is helpful in diagnosing an acoustic schwannoma. In these patients only wave I is present, indicating a lesion in the distal acoustic nerve.

Somatosensory Evoked Responses (SER)

The SER measures conduction velocities for central somatosensory pathways in the posterior columns of the spinal cord, brain stem, thalamus and primary sensory cortex in the parietal lobes. To perform the SER, recording electrodes are placed over Erb’s point (for medial nerve stimulation), popliteal fossa and lumbar spine (for peroneal or tibial nerve stimulation), and over the posterior and lateral regions of the scalp. A series of electrical shocks at a frequency of 5 Hz are delivered to the median nerve (for an upper extremity SER) or to the peroneal or tibial nerves (for a lower extremity SER) for 3 minutes. The scalp potentials elicited by the electrical shocks are then recorded and signal-averaged by a computer. This signal averaging cancels the random EEG activity and differentially amplifies the evoked potential.

A series of waves is recorded for each nerve stimulated, with each wave corresponding to a different point in the somatosensory pathways in the spinal cord, brain stem and cerebral cortex. The wave latencies for the right and left limbs are compared, and a delay in any of the latencies suggests a lesion at that point in the somatosensory pathways.

SER testing, like PVER, is helpful when multiple sclerosis is suspected clinically and one needs to document the presence of a second demyelinating lesion in the CNS that may not be clinically evident. SER is also useful in monitoring spinal cord function intraoperatively in patients undergoing spinal surgery.

Electronystagmography (ENG)

The ENG accurately records eye movements and nystagmus following certain provocative maneuvers. To perform this test, disc electrodes are placed over the bridge of the nose and lateral to each outer canthus, and the electrical leads from these discs are connected to an oscilloscope. Since the cornea is electropositive and the retina is electronegative, these electrodes will accurately record lateral eye movements.

The patient is first observed for spontaneous nystagmus with the eyes open and closed, and then for nystagmus evoked with lateral gaze, for nystagmus induced by hot and cold air instilled in the outer ears (caloric-induced), and for positional nystagmus. The latter is performed by rotating the patient in a specialized chair. Spontaneous nystagmus
suggests vestibular pathology, as does an imbalance in the nystagmus evoked by these maneuvers in the right and left ears.

References


STATUS EPILEPTICUS
Ralph F. Józefowicz, MD

Definition

"Epileptic seizures that are so frequently repeated or so prolonged as to create a fixed and lasting epileptic condition."

Continuous seizures lasting at least 30 minutes even when consciousness is not impaired.

Classification of Status Epilepticus

Generalized Status Epilepticus

• Convulsive
  • Tonic
  • Clonic
  • Myoclonic
• Nonconvulsive
  • Absence

Partial Status Epilepticus

• Simple
  • Somatomotor
  • Aphasic
• Complex
  • Complex partial seizures

Convulsive

• Generalized tonic clonic: the majority of these have a focal onset, usually consisting of adverisive head and eye movements (away from the discharging hemisphere). Active CNS lesions, including tumor, abscess, stroke, intracerebral hemorrhage, head trauma, meningitis or encephalitis, should be ruled out in patients without a previous history of seizures. Focal brain lesions resulting in tonic clonic status epilepticus are usually located in the frontal or temporal lobes.

• Myoclonic: Frequently repeated, generalized, brief muscular contractions without alterations in consciousness. Childhood myoclonic status epilepticus usually results from genetic disorders of brain development. Adult myoclonic status epilepticus is frequently associated with metabolic encephalopathies (renal, hyperglycemic, anoxic).

• Tonic: Usually found in patients with the Lennox-Gastaut syndrome, which is a childhood syndrome of diffuse brain dysfunction associated with significant mental retardation and various seizure types including tonic seizures, atypical absence seizures and drop attacks. Tonic status epilepticus may be enhanced by intravenous diazepam, and should be treated with phenytoin or phenobarbital.
- **Focal (Simple Partial):** This form of status epilepticus arises from a disturbance in a specific area of the cortex. Focal motor status epilepticus is the most common. Consciousness is typically preserved. Jacksonian status epilepticus and epilepsia partialis continua are two forms of focal motor status epilepticus.

**Nonconvulsive**

- **Complex partial (psychomotor) -** A continuous series of repeated complex partial seizures associated with prolonged alterations in consciousness (twilight state). May last for days. Responds to phenytoin and phenobarbital.

- **Absence -** A prolonged state of one absence seizure with altered responsiveness (twilight state). Frequently seen in the elderly. May also last for days. Responds to ethosuximide and valproic acid.

### TABLE 3. Clinical characteristics of prolonged twilight states

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Complex partial status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged state of one attack rather than repeated attacks</td>
<td>Continuous series of repeated attacks</td>
</tr>
<tr>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Phase of responsiveness with confusion, disorientation, speech arrest, amnesia, and automatism</td>
<td>Present</td>
</tr>
<tr>
<td>Absent</td>
<td>Phase of total unresponsiveness with stereotyped automatism</td>
</tr>
<tr>
<td>Continuous or noncontinuous diffuse irregular 1.5–4-Hz multi-spike-wave complexes; no patterns are time-locked with automatism</td>
<td>Phase of total unresponsiveness and stereotyped automatism</td>
</tr>
</tbody>
</table>

From Belafsky et al. (3).

**Incidence of Tonic-clonic Status Epilepticus**

- It is estimated that there are 100,000 admissions per year in the United States for convulsive status epilepticus (0.5% of the population).

- About 1-5% of the epileptic population in the United States has an episode of convulsive status epilepticus per year.
Etiology of Tonic-clonic Status Epilepticus

- **Anticonvulsant Drug Noncompliance** - the most common cause.
- **Alcohol Related** - typically seen with withdrawal in the setting of a fixed seizure disorder.
- **Drug Overdose** - particularly with Lidocaine, Theophylline, INH, Cocaine, and neuroleptic agents.
- **Metabolic Disorders** - particularly hyponatremia, hypocalcemia, hypo or hyperglycemia, hypoxia, hyperosmolarity, and with uremia and hepatic failure.
- **Brain Tumors** - particularly those located in the frontal or temporal lobes.
- **Vascular Diseases** - particularly intracerebral hemorrhage and embolic strokes.
- **CNS Infection** - including cerebral abscess, meningitis and encephalitis.
- **Head Trauma** - particularly frontal.

The following table lists the etiology of status epilepticus in 98 patients who presented to San Francisco General Hospital between 1970 and 1979 with convulsive status epilepticus.

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Patients With Preceding Seizure Disorder</th>
<th>Patients Without Previous Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation or irregularity of anticonvulsant drug regime</td>
<td>27*</td>
<td>0</td>
</tr>
<tr>
<td>Alcohol-related</td>
<td>11†</td>
<td>4</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Drug overdose</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Metabolic disorders</td>
<td>3†</td>
<td>5</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Cerebral tumor</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Cerebral trauma</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abscess</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Meningitis</td>
<td>0</td>
<td>2†</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>11</td>
<td>4</td>
</tr>
</tbody>
</table>

**NOTE:** Some patients have been counted more than once, because the etiology of their status was multifactorial. * Alcohol withdrawal a coexisting factor in five; † other metabolic factors also important in one; ‡ anticonvulsant drug irregularity also implicated in five; § meningitis implicated in one; ‡ alcohol important in one.
Pathophysiology of Status Epilepticus

Certain cells of the telencephalon, including hippocampal bursting cells and cells in the middle layer of the cerebral cortex, are particularly prone towards ischemic and traumatic damage. As a result, various biochemical membrane abnormalities develop in these cells, producing bursting behavior, synchrony of firing and recruitment of normal neurons, resulting in a focal seizure.

The cellular and molecular events that accompany the transformation of a single seizure to status epilepticus have not been investigated. Convulsive status epilepticus causes intracellular calcium and sodium to rise, while free fatty acids and prostaglandins accumulate.

This results in impaired protein synthesis; secondary metabolic complications including lactic acidosis, hypoglycemia, hypoxia, and hyperpyrexia; and significant neuroendocrine imbalance with resultant release of numerous hormones including prolactin, growth hormone, ACTH, cortisol, insulin, glucagon, epinephrine and norepinephrine. As a result of these changes, permanent neuronal cell damage results which produces neurologic sequela. The following figure illustrates this point.

---

**FIG. 2.** Molecular events that lead to cell damage in convulsive status. Various biochemical membrane abnormalities are postulated to produce bursting behavior in hippocampal and cerebral cortical neurons. Synchrony of neuronal aggregates and recruitment of normal neurons are considered essential for the spread of seizures. The cellular and molecular events that accompany the transformation of a single ictal event to status epilepticus have not been investigated. Convulsive status causes intracellular calcium and sodium to rise, while free fatty acids and prostaglandins accumulate. Neuroendocrine imbalance, impaired protein synthesis, and secondary metabolic complications also result (see text).
Sequeleae of Prolonged Status Epilepticus

- The cerebral metabolic rate is increased significantly, with resultant depletion of substrates, particularly oxygen and glucose.

- Respiratory impairment occurs with subsequent hypoxia and hypercarbia. There are three causes for respiratory impairment in status epilepticus: mechanical causes interfering with chest wall motion; inhibition of brain stem respiratory centers of brain stem with respiratory centers by continuous electrical discharges; and massive autonomic activation with subsequent bronchospasm and an increase in pulmonary secretions.

- Cerebral blood flow autoregulation is abolished, and cerebral blood flow then becomes dependent upon systemic blood pressure.

- Numerous metabolic, cardiac, pulmonary, renal and autonomic complications may occur, as listed below:

<table>
<thead>
<tr>
<th>TABLE 1. MEDICAL COMPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic</td>
</tr>
<tr>
<td>Lactic acidosis</td>
</tr>
<tr>
<td>CO₂ narcosis</td>
</tr>
<tr>
<td>Hyperkalemia</td>
</tr>
<tr>
<td>Hypertension, hypoglycemia, shock</td>
</tr>
<tr>
<td>Cardiopulmonary</td>
</tr>
<tr>
<td>Arrhythmias</td>
</tr>
<tr>
<td>High output failure</td>
</tr>
<tr>
<td>Pulmonary edema</td>
</tr>
<tr>
<td>Pneumonia, aspiration</td>
</tr>
<tr>
<td>Renal</td>
</tr>
<tr>
<td>Acute tubular necrosis and</td>
</tr>
<tr>
<td>myoglobinuria secondary to</td>
</tr>
<tr>
<td>rhabdomyolysis</td>
</tr>
<tr>
<td>Autonomic</td>
</tr>
<tr>
<td>Hyperpyrexia</td>
</tr>
<tr>
<td>Vomiting, electrolyte, fluid loss</td>
</tr>
<tr>
<td>Hypersecretions: sweat, salivation,</td>
</tr>
<tr>
<td>tracheo-bronchial</td>
</tr>
</tbody>
</table>

Fever, without an infectious cause, has been noted in 72% of patients with status epilepticus in one series. Peripheral blood leukocytosis has been noted in up to 62% of patients, with white blood counts as high as 29,000. CSF pleocytosis has been noted in 18% of patients (up to 70 cells, usually PMN's), and CSF protein was found to be elevated in 15% of patients. CSF glucose is typically normal.
The mortality rate of status epilepticus is approximately 10-12%. The longer status continues, the more difficult it is to control. After about 60 minutes of status epilepticus neuronal cell death may occur, particularly in the hippocampus, amygdala, cerebellum, thalamus, and cerebral cortex. This occurs even in artificially ventilated animals given glucose, suggesting increased metabolic demands by the continuously firing neurons as the etiology. Hence, status epilepticus should be terminated as quickly as possible.

Complex partial status epilepticus can lead to memory deficits, both immediate and chronic, due to hippocampal damage. Prolonged complex partial status epilepticus may occasionally lead to the Kleuver-Bucy syndrome, consisting of memory impairment, hyperphagia and hypersexuality due to bitemporal dysfunction.

**Diagnosis of Status Epilepticus**

- **Observe the seizure** and determine seizure type.
- **Blood Studies**, including blood counts, electrolytes, glucose, urea nitrogen, liver function tests, blood gases, anticonvulsant drug levels and alcohol level.
- **Urine Toxicology Screen**.
- **Head CT Scan**, particularly for status occurring in a patient without a previous history of seizures.
- **Lumbar Puncture** if evidence for meningitis or encephalitis is present.
- **EEG**, particularly if pseudoseizures are a diagnostic possibility. The EEG is also very useful in evaluating twilight states, including complex partial status epilepticus and absence status epilepticus.

**Treatment of Status Epilepticus**

- Established **Airway** insure adequate **Breathing** maintain **Circulation**.
- **Oxygen** should be administered.
- **Establish IV with normal saline**. Venous bloods for analysis could be obtained at the same time. Do not use hypotonic dextrose containing solutions, as phenytoin and benzodiazepines precipitate in hypotonic solutions.
- **Intravenous glucose** (25 g) and **Thiamine** (100 mg) should be administered if hypoglycemia is documented.
- **Lorazepam** (2-8 mg IV) or Diazepam (5-20 mg IV) should be administered to terminate status.
• Phenytoin (18 mg per kg, up to 1,000 mg IV, no faster than 30 mg per minute) or Phosphonytoin should be administered to prevent recurrence of seizures. If hypotension develops slow infusion rate.

• Phenobarbital (up to 20 mg per kg IV, no faster than 100 mg per minute) may be administered if lorazepam and phenytoin are ineffective in terminating status. The patient needs to be intubated at this point, as lorazepam and phenobarbital in combination may lead to respiratory depression and arrest.

• Barbiturate Coma with Pentobarbital may be effective for status epilepticus lasting more than one hour and refractory to all other forms of treatment. This treatment modality has potential serious side effects, including hypotension, and should only be carried out in an intensive care unit with continuous EEG monitoring and intra-arterial pressure monitoring. The following table details a protocol for pentobarbital coma.

Table 2. Barbiturate anesthesia: Protocol for refractory status epilepticus

1. Intubation and ventilation, ICU admission, arterial line (central venous pressure line and/or Swan-Ganz if pre-existing cardiopulmonary disease).

2. EEG for monitoring control of seizures and level of anesthesia (check q 15-30 minutes during induction, then q 1-2 hours once burst-suppression pattern attained).

3. Pentobarbital-loading dose of 15 mg/kg over 1 hour, maintenance infusion of 1-2 mg/kg/hr, additional loading doses (5 mg/kg to maximum of 30 mg/kg in first 12 hours) as needed to control seizures or attain burst-suppression.*

4. Low-dose dopamine (followed by dobutamine, if necessary) for hypotension.

5. Continue maintenance phentoytin and phenobarbital with monitoring of blood levels.

6. Stop pentobarbital at 12 hours and observe. If seizures recur, reinstate infusion and continue for 24 hours before withdrawal. Repeat as needed.

*NB The initial maintenance infusion we now recommend is 0.5 mg/kg/hr, with adjustment to higher doses based upon clinical and EEG responses. See text for further details.
Major Anticonvulsant Drug Toxicities

- **Benzodiazepines** (diazepam, lorazepam) - Drowsiness, ataxia, confusion, respiratory depression, hypotension, paradoxical excitement.

- **Phenytoin** - Hypotension, cardiac conduction disturbances, nystagmus, ataxia, dysarthria.

- **Barbiturates** - Sedation, respiratory depression, hypotension, nystagmus, ataxia.

The following two tables list some properties and clinical parameters of the drugs useful in treating status epilepticus.

### TABLE 2. Properties of drugs of importance in treating status epilepticus

<table>
<thead>
<tr>
<th>Property</th>
<th>Diazepam</th>
<th>Phenytoin</th>
<th>Phenobarbital</th>
<th>Paraldehyde</th>
<th>Valproate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of administration</td>
<td>i.v.</td>
<td>i.v.</td>
<td>i.v.</td>
<td>i.v., rectal</td>
<td></td>
</tr>
<tr>
<td>Time to enter brain</td>
<td>10 sec</td>
<td>1 min</td>
<td>20 min</td>
<td>&lt;2 min</td>
<td>1 min</td>
</tr>
<tr>
<td>Time to enter peak brain</td>
<td>15–30 min</td>
<td>30 min</td>
<td>20 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>concentration</td>
<td>0.2–0.8</td>
<td>25</td>
<td>45</td>
<td>150–120</td>
<td>50</td>
</tr>
<tr>
<td>Effective serum concentration</td>
<td>1 min</td>
<td>1–2 liter/kg</td>
<td>0.5–0.8 liter/kg</td>
<td>0.7 liter/kg</td>
<td>0.9 liter/kg</td>
</tr>
<tr>
<td>in status epilepticus (µg/ml)</td>
<td>20 min</td>
<td>22+</td>
<td>50–120</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Effective half-life (hr)</td>
<td>0.25</td>
<td>0.6–1.4</td>
<td>0.6–0.9</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>Brain/plasma ratio</td>
<td>3.4</td>
<td>8.3</td>
<td>7.41</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>pKa</td>
<td>395.1</td>
<td>26.3</td>
<td>32.6</td>
<td>1.36</td>
<td></td>
</tr>
<tr>
<td>Partition coefficient*</td>
<td>96%</td>
<td>87–93%</td>
<td>45–50%</td>
<td>80–94%</td>
<td></td>
</tr>
<tr>
<td>Protein binding</td>
<td>0.25 mg/kg up to 20 mg</td>
<td>50 mg/min</td>
<td>100 mg/min</td>
<td>&gt;0.5 g</td>
<td>0.1 ml/kg</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>1–2 liter/kg</td>
<td>0.5–0.8 liter/kg</td>
<td>0.7 liter/kg</td>
<td>0.9 liter/kg</td>
<td>0.13–0.16 liter/kg</td>
</tr>
</tbody>
</table>

*Octanol/water, pH 7.5 (data from Cornford and W.H. Oldendorf, personal communication).
Adapted from Treiman and Delgado-Escueta (34).

### TABLE 3. Drugs of importance in treating status epilepticus: clinical parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Diazepam</th>
<th>Phenytoin</th>
<th>Phenobarbital</th>
<th>Paraldehyde</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indications</td>
<td>Most forms of status</td>
<td>Phenytoin withdrawal, intracranial bleed</td>
<td>Phenobarbital withdrawal</td>
<td>Ethanol withdrawal</td>
</tr>
<tr>
<td>Loading dose</td>
<td>0.25 mg/kg up to 20 mg</td>
<td>18 mg/kg</td>
<td>20 mg/kg</td>
<td>0.1 ml/kg</td>
</tr>
<tr>
<td>Rate of administration</td>
<td>2 mg/min</td>
<td>50 mg/min</td>
<td>100 mg/min</td>
<td></td>
</tr>
<tr>
<td>Potential side effects</td>
<td>10–30 min</td>
<td>None</td>
<td>&gt;0.5 g</td>
<td></td>
</tr>
<tr>
<td>Depression of consciousness</td>
<td>0.5–1 min</td>
<td>None</td>
<td>&gt;0.5 g</td>
<td></td>
</tr>
<tr>
<td>Respiratory arrest</td>
<td>Occasional</td>
<td>50% of patients</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Rare</td>
<td>None</td>
<td>None</td>
<td>&gt;2 g</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>Rare</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Treiman and Delgado-Escueta (34).
COMA AND RAISED INTRACRANIAL PRESSURE
Ralph F. Jozefowicz, MD

COMA

Pathophysiology

Consciousness: The cerebral hemispheres and the brain stem reticular activating system are both integrally involved in maintenance of consciousness. The content of consciousness resides in the cerebral hemispheres; the role of the brain stem reticular activating system is to "awaken" the cortex.

Only one cerebral hemisphere and an intact reticular activating system are needed to maintain consciousness. Hence, unilateral hemispheric strokes do not routinely cause coma. Coma therefore implies failure of both cerebral hemispheres or the brain stem reticular activating system.

Causes of Coma: From a pathophysiological standpoint, there are four causes of coma:

- **Supratentorial mass lesions**, including epidural hematoma, subdural hematoma, intracranial hemorrhage, tumor, cerebral abscess, or massive stroke with edema. These lesions produce coma by pressure on the opposite cerebral hemisphere or brain stem, and produce "hemispheric" signs on examination.

- **Infratentorial mass lesions**, including brain stem or cerebellar infarcts, hemorrhages or tumors. These lesions compress the reticular activating system and produce "brain stem" signs on examination.

- **Metabolic encephalopathy**, including hypo or hyperglycemia, hypo or hypernatremia, hypercalcaemia, acid-base disorders, cerebral anoxia, meningitis, subarachnoid hemorrhage, drug overdose, hepatic failure, renal failure, or the post-ictal state following seizures. These lesions produce diffuse, non-focal cortical dysfunction and, in most cases, brain stem function remains intact.

- **Psychogenic coma**, in which the patient is physiologically awake but appears comatose by not responding to his environment.

Evaluation of patients in coma

- **History**, particularly details concerning the onset of coma, recent complaints, recent injury, previous medical illnesses, previous psychiatric history and access to drugs.

- **General physical examination**, including vital signs, evidence of trauma, evidence of systemic illness, and examination for meningismus.
- **Neurologic examination**

  - **Level of consciousness**, in which the highest response to stimuli, verbal or noxious, is recorded. It is preferable to describe exactly the response of the patient to stimuli, rather than to attach vague labels such as "lethargic", "stuporous", or "comatose".

  - **Spontaneous respirations**: Various abnormal patterns of respiration can be seen with lesions at various levels of the diencephalon or brain stem (See figure below).

![Diagram of abnormal respiratory patterns](image)

**Figure 6.** Abnormal respiratory patterns associated with pathologic lesions (shaded areas) at various levels of the brain. Tracings by chest-abdomen pneumograph, inspiration reads up. **a**, Cheyne-Stokes respiration. **b**, Central neurogenic hyperventilation. **c**, Apneusis. **d**, Cluster breathing. **e**, Ataxic breathing.
- **Pupils:** Pupillary size depends on the balance between the parasympathetic nervous system causing constriction via cranial nerve III; and the sympathetic nervous system causing dilatation via the sympathetic pathway which originates in the hypothalamus, traverses the brain stem and cervical and upper thoracic spinal cord, and forms the peripheral sympathetic nervous system that courses through the superior cervical sympathetic ganglion, and travels along the external carotid artery and with the ophthalmic division of the trigeminal nerve (See Figure below). The pupillary abnormalities seen in the various types of coma are shown in the accompanying figure.

![Diagram of the pupillary pathways](image)

**Figure 7.** A, The parasympathetic pupilloconstrictor pathway. B, The sympathetic pupillodilator pathway.
- **Eye movements**: Voluntary and reflex eye movements are coordinated by the cortical connections (frontal eye fields and occipital cortex), vestibular apparatus, medial longitudinal fasciculus, and cranial nerves III, IV, and VI. In a comatose individual, eye movements can be evaluated by means of the oculocephalic (doll's eyes) reflex and caloric testing. The figure below details the eye movement abnormalities seen in the various forms of coma.
**CONDITION:** OCULAR REFLEXES IN UNCONSCIOUS PATIENTS

<table>
<thead>
<tr>
<th>Brainstem Intact</th>
<th>Cold H₂O</th>
<th>Cold H₂O</th>
<th>Cold H₂O</th>
<th>Hot H₂O</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLF (bilateral)</td>
<td>Cold H₂O</td>
<td>Cold H₂O</td>
<td>Cold H₂O</td>
<td>Hot H₂O</td>
</tr>
<tr>
<td>Low Brainstem Lesion</td>
<td>Cold H₂O</td>
<td>Cold H₂O</td>
<td>Cold H₂O</td>
<td>Hot H₂O</td>
</tr>
</tbody>
</table>

Figure 12. Ocular reflexes in unconscious patients. The upper section illustrates the oculocerebellar (above) and oculovestibular (below) reflexes in an unconscious patient whose brainstem oculomotor pathways (see Fig. 11) are intact. Horizontal eye movements are illustrated on the left and vertical eye movements on the right: lateral conjugate eye movements (upper left) to head turning are full and opposite in direction to the movement of the face. A stronger stimulus to lateral deviation is achieved by douching cold water against the tympanic membrane(s). There is tonic conjugate deviation of both eyes toward the stimulus; the eyes usually remain tonically deviated for 1 or more minutes before slowly returning to the midline. Because the patient is unconscious, there is no nystagmus. Extension of the neck in a patient with an intact brainstem produces conjugate deviation of the eyes in the downward direction, and flexion of the neck produces deviation of the eyes upward. Bilateral cold water against the tympanic membrane likewise produces conjugate downward deviation of the eyes, whereas hot water (no warmer than 44°C) causes conjugate upward deviation of the eyes.

In the middle portion of the drawing, the effects of bilateral medial longitudinal fasciculus lesions on ocul-cephalic and oculovestibular reflexes are shown. The left portion of the drawing illustrates that oculocerebellar and oculovestibular stimulation deviates the appropriate eye laterally and brings the eye, which would normally deviate medially, only to the midline, since the medial longitudinal fasciculus, with its connections between the abducens and oculomotor nuclei, is interrupted. Vertical eye movements often remain intact. The lower portion of the drawing illustrates the effects of a low brainstem lesion. On the left, neither oculocerebellar nor oculovestibular movements cause lateral deviation of the eyes because the pathways are interrupted between the vestibular nucleus and the abducens area. Likewise, in the right portion of the drawing, neither oculocerebellar nor oculovestibular stimulation causes vertical deviation of the eyes. On rare occasions, particularly with low lateral brainstem lesions, oculocepalic responses may be intact even when oculovestibular reflexes are abolished (see Patient 1-3).
- **Motor response**: In patients with altered mental status, motor responses to stimuli may vary from removal of the stimulus, withdrawal from the stimulus, decorticate posturing (upper extremity flexion and lower extremity extension), decerebrate posturing (extension of all four limbs), to no response to stimulation. Note that flexion of any limb generally implies a higher level of brain functioning than extension. The figure below describes the various motor responses to noxious stimulation in patients with coma.

**Figure 13.** Motor responses to noxious stimulation in patients with acute cerebral dysfunction. Noxious stimuli can be delivered with minimal trauma to the supraorbital ridge, the nail bed, or the sternum as illustrated at top. Levels of associated brain dysfunction are roughly indicated at left. The text provides details.
• **Glasgow coma scale.** The Glasgow coma scale is widely used to evaluate nervous system functioning in patients with coma. This scale is easily applied and is a reproducible measure of brain functioning in most forms of altered responsiveness. Verbal response, eye opening and motor response are each assessed and a score is assigned for each category. These individual scores are added to give a composite score. Severe coma is defined as a score of eight or less, moderate 9 to 12 and mild 12 to 15.

**Glasgow Coma Scale**

<table>
<thead>
<tr>
<th>Level of Response</th>
<th>Scale Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Verbal Response</strong></td>
<td></td>
</tr>
<tr>
<td>Oriented</td>
<td>5</td>
</tr>
<tr>
<td>Confused</td>
<td>4</td>
</tr>
<tr>
<td>Inappropriate words</td>
<td>3</td>
</tr>
<tr>
<td>Incomprehensible</td>
<td>2</td>
</tr>
<tr>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td><strong>Eye Opening</strong></td>
<td></td>
</tr>
<tr>
<td>Spontaneously</td>
<td>4</td>
</tr>
<tr>
<td>To speech</td>
<td>3</td>
</tr>
<tr>
<td>To pain</td>
<td>2</td>
</tr>
<tr>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td><strong>Motor Response</strong></td>
<td></td>
</tr>
<tr>
<td>Obeys commands</td>
<td>6</td>
</tr>
<tr>
<td>Localizes pain</td>
<td>5</td>
</tr>
<tr>
<td>Withdraws</td>
<td>4</td>
</tr>
<tr>
<td>Abnormal flexion</td>
<td>3</td>
</tr>
<tr>
<td>Abnormal extension</td>
<td>2</td>
</tr>
<tr>
<td>None</td>
<td>1</td>
</tr>
</tbody>
</table>

**Laboratory studies**

• **Blood studies:** Complete blood count, electrolytes, calcium, glucose, urea nitrogen, liver functions, and blood gases. Ammonia, thyroid functions and cortisol level should be obtained if indicated.

• Urine toxicology screen.

• Head CT scan.

• Lumbar puncture.

• EEG.
Treatment

- Establish airway, control breathing, maintain circulation.

- **Naloxone (Narcan):** Naloxone should be administered to all patients in whom the etiology of coma is uncertain, since it is non-toxic and works rapidly if coma is due to narcotic overdose.

- **Glucose and Thiamine:** Serum glucose levels should be determined rapidly with BG chemstrips, and glucose (50 grams IV) administered to patients who are hypoglycemic. Thiamine (100 mg IV) should be given to all individuals who require glucose since administration will prevent Wernicke encephalopathy, and it is non-toxic in this dose.

- **Treat specific causes:** Seizures, raised intracranial pressure, CNS or systemic infection, drug overdose, and electrolyte or acid-base imbalance all may cause coma and appropriate therapies should be employed.
RAISED INTRACRANIAL PRESSURE
Ralph F. Jozefowicz, MD

Pathophysiology

The cranium is a rigid structure divided into compartments by portions of dura mater, notably the falx cerebri and the tentorium cerebelli. The foramen magnum is the only access to the cranium. Within the cranial cavity lie three "fluid" structures, notably the brain, blood and cerebrospinal fluid. Increases in one of the fluid contents causes a decrease in the other two within the cranial cavity.

The deleterious effects of raised intracranial pressure are due to alteration of cerebral perfusion pressure and cerebral herniation.

Cerebral perfusion pressure (CPP) is equal to the difference between mean arterial pressure (MAP) and intracranial pressure (ICP).

\[
\text{CPP} = \text{MAP} - \text{ICP}
\]

Cerebral perfusion pressure is normally 60 Torr or greater, and a CPP less than 40 Torr (as can be seen with markedly reduced MAP or raised ICP), results in inadequate cerebral blood flow with resultant neuronal cell death.

Raised intracranial pressure may be diffuse due to encephalopathy or meningitis, or may be focal, due to tumor, abscess, hemorrhage or stroke with localized edema.

When local pressure gradients from focal brain lesions shift the rather fluid brain substance in relation to the rigid faix, tentorium or foramen magnum, cerebral herniation results. Several different herniation syndromes occur, depending upon the location of the expanding mass lesion, as follows:

Supratentorial mass lesions

- **Uncal herniation**, causing ipsilateral third cranial nerve palsy and contralateral hemiparesis (due to pressure on the cerebral peduncle).

- **Central (transtentorial) herniation**, causing progressive rostral-caudal loss of brain stem function due to pressure on the entire brain stem.

- **Trans-faix (subfalcial) herniation**, occasionally causing infarction of the anterior cerebral artery that lies in the interhemispheric fissure.

Infratentorial mass lesions

- **Cerebellar tonsillar herniation**, causing compression of the medulla by the cerebellar tonsils.

- **Upward herniation** of the brain stem through the tentorium, resulting in caudal-rostral loss of brain stem function.
Diagnosis of raised intracranial pressure

- **History:** The clinical signs and symptoms of raised intracranial pressure are variable, dependent upon the cause and the location of any focal lesions. Most patients with raised intracranial pressure will have an altered mental status and may complain of headache. Papilledema is the hallmark of diagnosis, but is a relatively late finding and may never develop in a small number of patients. The Cushing reflex (elevated systemic blood pressure and bradycardia) may be seen when pressure is transmitted to the medullary autonomic centers.

- **Physical examination:** The cranial nerves should be carefully evaluated in patients with suspected raised intracranial pressure. Third nerve palsies are strongly suggestive of uncal herniation, and sixth nerve palsies may be seen as a false localizing sign in many patients with diffusely elevated intracranial pressure.

Recall that the sixth cranial nerve has the longest course of any cranial nerve within the skull from where it exits the brain stem to where it exits the skull. Hence, any brain lesion that causes raised intracranial pressure will preferentially stretch this nerve and cause paralysis of lateral gaze.

Abnormal respiratory patterns and motor responses should be noted since these may indicate incipient brain stem herniation.

- **Laboratory studies:** The head CT scan is the single most important laboratory study for the evaluation of raised intracranial pressure, and should be obtained in all patients once they are neurologically stable.
Treatment of raised intracranial pressure

Raised intracranial pressure, once diagnosed, should be immediately treated to prevent subsequent brain damage. All patients should have their head and neck elevated 30 degrees to facilitate venous drainage.

The following list identifies several methods for rapidly reducing intracranial pressure:

- **Hyperventilation**: Tracheal intubation with hyperventilation to lower the pCO₂ to 25 to 30 Torr will rapidly reduce intracranial pressure by causing vasoconstriction of cerebral blood vessels. This method acts within minutes, but the beneficial effect lasts only about eight hours since the pH level of brain extracellular fluid is restored to normal by active transport processes after several hours of hyperventilation.

- **Mannitol**: Mannitol is an osmotic diuretic that decreases brain water and total body water. The usual dose is 1/2 to 1 gm/kg IV, and this could be repeated every four to six hours as necessary. A serum osmolality of approximately 325 mOsm should not be exceeded because excessive hyperosmolarity may damage neurons. Mannitol usually acts within minutes.

- **Dexamethasone**: This corticosteroid stabilizes vascular membranes and thereby prevents vasogenic brain edema. The usual dose is 10 mg IV initially, then 4 mg every six hours. Dexamethasone acts within 24 hours and is most helpful when brain edema is due to an expanding mass lesion, such as a tumor or abscess. It is not helpful with cytotoxic brain edema as can occur with diffuse or focal brain ischemia or following head trauma.

- **Barbiturate Coma**: High dose pentobarbital therapy (325 mg/kg) may reduce cerebral blood flow and intracranial pressure by decreasing the cerebral metabolic rate. This treatment is controversial and has potentially significant side effects, and hence should be reserved for neurologic or neurosurgical centers that routinely employ its use.

- **Neurosurgical Intervention**: CSF drainage via a ventriculostomy, drainage of hematomas, and excision of expanding mass lesions are all life saving measures that rapidly reduce intracranial pressure under the proper circumstances. Urgent evacuation of hematomas in the posterior fossa is particularly important since brain compliance in the posterior fossa is limited and relatively small increases in hematoma volume in this compartment may lead to fatal brain stem compression.
CEREBRAL VASCULAR ACCIDENTS
Ralph F. Józefowicz, MD

Definitions

- **Stroke**: A fixed neurologic deficit of sudden onset, usually due to pathologic processes in blood vessels.

- **TIA (Transient Ischemic Attack)**: A neurologic deficit of sudden onset that resolves completely with 24 hours (usually within one hour in most circumstances).

Types of Stroke

1. **Thrombotic**: A stroke caused by thrombosis of large intracranial vessels, usually at points of bifurcation. Thrombotic strokes usually have a stuttering onset, or occur while the patient is asleep, with the neurologic deficit being noted upon awakening. The neurologic findings seen with thrombotic strokes are determined by the vessel occluded, as follows:

   - **Anterior Cerebral Artery**: Leg greater than arm weakness, due to infarction of the medial motor strip.

   - **Middle Cerebral Artery**: Arm and leg affected equally, due to involvement of internal capsule. Visual field cut and higher cortical deficits (aphasia, apraxia, agnosia) are also seen.

   - **Posterior Cerebral Artery**: Visual field cut commonly seen.

   - **Vertebro-Basilar System**: Numerous brain stem findings, including ophthalmoplegia, pupillary abnormalities, facial weakness and numbness, difficulty with swallowing and speech, long tract signs, vertigo, ataxia, and occasionally syncope.

     The lateral medullary syndrome is a common brain stem syndrome due to infarction of the vertebral artery, and presents with nausea, vomiting, cardiac arrhythmias, ipsilateral facial numbness and contralateral body numbness, ipsilateral ataxia, hoarseness, dysphagia, and ipsilateral Horner's syndrome.

2. **Embolic**: A stroke due to occlusion of small, distal cortical vessels from an embolus. These strokes are usually of abrupt onset and occur during the day. The deficit is maximal at the start with gradual resolution. There are two sources of emboli:

   - **Atherosclerotic plaques** involving the ascending aorta, internal carotid arteries and their branches, as well as the vertebro-basilar system.

   - **Cardiac sources**, primarily in the setting of recent myocardial infarction with mural thrombus, atrial fibrillation, low-output state, and valvular heart disease.
3. **Hemorrhagic:** A stroke due to cerebral hemorrhage of sudden onset. Four major types can be seen:

- **Hypertensive intracerebral hemorrhage:** Due to rupture of small, penetrating blood vessels from chronic hypertension. Most common locations include the pons, cerebellum, thalamus and putamen.

- **Arterio-venous malformation,** which can be located anywhere within the cerebrum, cerebellum, or brain stem.

- **Ruptured aneurysm,** particularly if the jet of blood from the dome of the aneurysm points towards the brain parenchyma.

- **Amyloid angiopathy (congophilic angiopathy):** A significant cause of lobar hemorrhage in elderly patients, particularly in those without a history of hypertension. The amyloid protein is deposited in the walls of cerebral blood vessels and weakens them, making them prone to spontaneous hemorrhage. This amyloid is identical to the 8 amyloid that is deposited in the brains of patients with Alzheimer's disease.

4. **Lacunar:** A stroke due to infarction of small, deep, penetrating blood vessels, usually in the setting of chronic hypertension. The most common locations include the internal capsule, thalamus and pons. Four clinical syndromes have been described:

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure motor</td>
<td>internal capsule or pons</td>
</tr>
<tr>
<td>Pure sensory</td>
<td>thalamus</td>
</tr>
<tr>
<td>Clumsy hand, dysarthria</td>
<td>pons</td>
</tr>
<tr>
<td>Leg paresis, ataxia</td>
<td>internal capsule or pons</td>
</tr>
</tbody>
</table>

**Complications**

Both early and late complications of stroke are frequently encountered. The six more common complications include:

- **Surrounding edema,** usually most prominent at 72 to 96 hours following the stroke. Usually seen with large, thrombotic occlusions. The patient is usually lethargic.

- **Cerebral herniation,** often seen with a massive thrombotic occlusion with resultant cerebral edema. Large cerebellar infarcts with edema may cause pontine compression and death.

- **Stroke in evolution,** due to progressive occlusion of a large vessel from ongoing atherosclerosis. Clinical findings include worsening neurologic deficits in the same vascular distribution.

- **Locked-in syndrome:** A stroke syndrome of preserved consciousness and sensation (visual, auditory and tactile) with practically absent motor output, (eye
blinking and vertical eye movements usually preserved) due to infarction of branches of the basilar artery supplying the ventral portions of the brain stem.

- **Seizure**: Seizures are an early complication of embolic strokes, since these usually lodge in the periphery. Seizures can be a late (9 months or later) complication of thrombotic strokes, and are particularly seen in the elderly with concomitant metabolic derangements.

- **Hemorrhagic transformation**, of embolic, and occasionally of large thrombotic infarcts, usually within 24 hours of stroke onset. Anticoagulation and severe hypertension may increase the incidence of this complication.

**Evaluation of the Stroke Patient**

**History**

In addition to obtaining a complete account of the presenting illness, the following points should be kept in mind:

- **Onset of deficit**: Was it abrupt (embolic or hemorrhagic) or stuttering (thrombotic or lacunar)? Was it preceded by TIA’s in the same vascular distribution (thrombotic)? Was the deficit present upon awakening (thrombotic) or did it come on during the day (embolic or hemorrhagic)?

- **Associated neurologic symptoms**: Specifically ask for visual symptoms (field cut suggests posterior or middle cerebral artery distribution), brain stem symptoms (diplopia, dysarthria, dysphagia, vertigo, ataxia, nausea or vomiting), language disturbances (aphasia suggests cortical localization).

- **Risk factors**: Especially hypertension, diabetes mellitus, cigarette smoking and heart disease, including recent myocardial infarction, valvular heart disease and cardiac arrhythmias, particularly atrial fibrillation.

- **Strokes in young individuals**: Ask about birth controls pills, hematologic disorders (sickle cell disease, polycythemia), collagen vascular disorders (systemic lupus erythematosus).

**Physical Examination**

The following aspects of the physical examination are most important in evaluating stroke:

- **Blood pressure**, including both right and left arms (to look for subclavian stenosis, which may suggest concomitant vertebro-basilar disease).

- **Palpation of cranial and carotid pulses**, and auscultation for cranial, carotid and subclavian bruits.

- **Neck range of motion** (the vertebral arteries pass through the transverse spinal canals, which may be narrowed in the setting of significant osteoarthritis).
• **Cardiac examination**, including rhythm and murmurs.

• **Careful neurologic examination**, including mental status testing, aphasia testing, visual fields, funduscopic exam, pupils and ocular motions.

**Laboratory Studies**

Judicious use of the laboratory may help in accurately diagnosing the etiology of stroke. The following tests may be of benefit:

• **Routine blood work**, including blood count (to look for hematologic disorders), coagulation studies, and screening chemistries.

• **Sedimentation rate**, to look for temporal arteritis and other collagen vascular disorders.

• **EKG**, to rule out recent myocardial infarction and atrial fibrillation.

• **Head CT scan**, to look for evidence of hemorrhage in the acute setting. "Bland", ischemic infarcts require 48 to 72 hours following their onset to become visible on head CT scans.

• **Cardiac echo examination**, to look for valvular heart disease and intracardiac emboli.

• **Carotid ultrasound**, to look for stenotic lesions and ulcerated plaques.

• **MRI and MRA**: Diffusion-weighted imaging (DWI) is a new MR pulse sequence that can detect cerebral ischemia within minutes of its onset. It is thus very helpful in determining if acute infarction has occurred. MR angiography (MRA) is another new pulse MR sequence that allows one to visualize blood vessels. It is non-invasive and does not require administration of contrast. It tends to overestimate the degree of stenosis, when compared with conventional angiography.

• **Cerebral angiography**: This study is the "gold standard" to evaluate carotid stenosis, and to look for ulcerated, atherosclerotic plaques involving the anterior and posterior circulation. The study should only be obtained if the patient is a candidate for carotid endarterectomy. In general, angiography should be postponed for 2 weeks following an acute stroke to minimize possible complications.

• **24 hour cardiac Holter monitoring**, particularly to look for intermittent atrial fibrillation as a source of emboli.

**Therapy**

The optimal therapy of stroke remains controversial. What follows is one neurologist's reasonable approach:
Routine measures

- **Admit to hospital.** Unless overwhelming evidence dictates otherwise, all acute stokes should be admitted for initial workup.

- **IV-Normal saline at 50 cc/hr.** Avoid hypotonic solutions, since ischemic brain tissue readily absorbs free water, worsening cerebral edema. In addition, all patients with stroke are at risk for developing SIADH with resultant hyponatremia. Avoid glucose containing solutions, since hyperglycemia can promote focal seizure activity in the setting of acute stroke.

- **Blood pressure control:** "Don't just do something, stand there!" Slight hypertension following acute stroke is a normal, adaptive physiologic mechanism to maintain cerebral perfusion through ischemic, edematous brain tissue. Furthermore, most patients with stroke have hypertension, and a resultant shift of the cerebral blood flow autoregulatory curve towards the right, which means that they require higher perfusion pressures to maintain adequate blood flow. Don't over-treat!" Severe hypertension in the setting of intracerebral hemorrhage is perhaps the only indication where rapid control of elevated blood pressure is warranted. Never reduce mean arterial blood pressure below 120 mm Hg, since cerebral blood flow may be seriously compromised below this level.

- **Treatment of cerebral edema:** The best treatment is prevention, with careful attention to fluid status, i.e. avoiding hypotonic, glucose-containing solutions. Corticosteroids are usually ineffective in reducing the cytotoxic cerebral edema seen with stroke.

Anticoagulation

Anticoagulation in the setting of acute stoke is extremely controversial. In general, completed strokes should not be anticoagulated, since there is no evidence that anticoagulation is beneficial in this setting. There are four relatively non-controversial indications for anticoagulation in acute stroke:

- **Obvious cardiac source of emboli,** including recent myocardial infarction, low output state, valvular heart disease and atrial fibrillation. Anticoagulation is continued as long as the risk of embolization remains high (6 months for recent MI, indefinitely for all other cardiac sources).

- **Progressive vertebro-basilar stroke,** since this can evolve into the "locked in" syndrome.

- **Crescendo TIAs,** since this usually implies crucial carotid stenosis that can lead to complete carotid occlusion.

- **Stroke in evolution,** which means a stroke that is progressing in the same vascular distribution due to evolving thrombosis. Do not confuse this somewhat rare situation with clinical worsening of the stroke patient due to edema. In most cases, strokes
evolve while the patient is at home or en route to hospital, and are usually completed by the time they reach the emergency room.

Heparin is the anticoagulant of choice, and is usually started without a bolus, within hours of stroke onset if the infarct is small in size. With large infarcts, anticoagulation should be delayed for several days to prevent "hemorrhagic transformation".

Anti-platelet agents

- Aspirin, 325-1300 mg daily, is recommended for prevention of thrombotic strokes, and should be given to all patients unless contraindications exist.

- Clopidogrel, a platelet anti-aggregant, has been shown to be slightly more effective than aspirin for the prevention of stroke. It has few side effects and is tolerated well, but is quite expensive. At present, clopidogrel should be reserved for patients who are intolerant of aspirin or who have failed aspirin.

- Dipyridamole is another anti-platelet agent that, when combined with aspirin in a long-acting preparation (Aggrenox), has been found to be slightly more effective than aspirin alone. It is also expensive. Dipyridamole causes headaches in many patients and this limits its usefulness.

- Ticlopidine, a platelet anti-aggregant, has significant toxicity and may cause severe neutropenia, diarrhea and rash in a small number of patients. It is rarely prescribed at present because of this.

Thrombolytic therapy

Recombinant tissue plasminogen activator (TPA), if administered intravenously within three hours of onset of stroke symptoms, has been found to be beneficial in reducing stroke morbidity in patients presenting with ischemic stroke. A head CT scan must be obtained prior to instituting TPA, and within the three-hour window, to rule out intracerebral hemorrhage. Administering TPA more than three hours after stroke onset has been associated with a high incidence of fatal intracerebral hemorrhage.

Surgery

Carotid endarterectomy and evacuation of intracerebral hematomas have a limited role in the treatment of stroke.

- Carotid endarterectomy: This procedure has been found to reduce the incidence of subsequent stroke or death in patients who have had a recent hemispheric TIA or a mild, non-disabling stroke and who have a high-grade stenosis (70 - 99%) in the ipsilateral internal carotid artery. The benefits of surgery in patients with moderate (50 - 69%) stenosis are modest and must be weighed against surgical risks and co-morbidities. There is no benefit of surgery in patients with stenosis less than 50%.
Recent evidence has shown that endarterectomy may reduce the incidence of subsequent stroke in patients with asymptomatic high-grade carotid stenosis.

- **Surgical evacuation of hematoma due to intracranial hemorrhage:** This procedure is lifesaving with posterior fossa hemorrhages, since the massive resultant edema may result in fatal brain stem compression. The role of this procedure in hemispheric hemorrhages is less certain, and is usually reserved for patients that are worsening clinically, and have a cortical hemorrhage that can be easily evacuated.

**Physiotherapy**

*Physical therapy* (gait training), *occupational therapy* (hand function, activities of daily living), *speech therapy* (speech and swallowing), and *rehabilitative medicine* should be consulted early for all patients who may benefit from these services.
SUBARACHNOID HEMORRHAGE
Ralph F. Jozefowicz, M.D.

Definition
A hemorrhage into the subarachnoid space, usually due to rupture of an intracranial aneurysm.

Epidemiology
The incidence of aneurysmal subarachnoid hemorrhage is about 10 cases for every 100,000 people worldwide. About 26,000 individuals in the United States are affected yearly. Sixty-five percent of patients with this disorder die or are severely disabled.

Pathophysiology
Sources of subarachnoid hemorrhage
1. Rupture of an intracranial aneurysm.

- **Congenital (berry or saccular) aneurysms:** These aneurysms are felt to develop at the time of birth due to defects in the blood vessel media at the circle of Willis. The aneurysms enlarge as a result of systolic blood pressure waves, and may ultimately rupture and result in a subarachnoid hemorrhage. In general, saccular aneurysms less than 3 mm in diameter do not bleed; those greater than 10 mm in diameter are more likely to bleed than smaller aneurysms. Some aneurysms never bleed, and the incidence of asymptomatic saccular aneurysms from various general autopsy series has ranged from 0.2% to 9%. Although aneurysms can be present anywhere near the circle of Willis, several locations are more frequent, as follows:
  - Anterior communicating artery - 30%
  - Posterior communicating artery - 24%
  - Middle cerebral artery - 13%
  - Multiple locations - 20%

- **Mycotic (infectious) aneurysms:** These aneurysms arise as a result of septic emboli from a cardiac source lodging in distal cerebral blood vessels and producing a local vascular infection with resultant weakening of the media and aneurysmal dilatation. Rupture of these aneurysms frequently produces an intracerebral hemorrhage but subarachnoid hemorrhage can also result if cortical blood vessels are involved.

- **Atherosclerotic (fusiform) aneurysms:** These aneurysms typically involve larger blood vessels at the base of the brain and typically do not rupture.
2. **Arterio-venous malformations (AVM):** The incidence of hemorrhage from large AVMs is approximately 1% to 2% per year. Deep AVMs result in intraparenchymal or intraventricular hemorrhage and cortical AVMs may result in subarachnoid bleeding.

3. **Head trauma:** Severe head trauma may result in cerebral contusion with hemorrhage, which may be epidural, subdural, subarachnoid or intraparenchymal. Frequently, hemorrhage may occur in several brain compartments.

4. **Intracerebral hemorrhage with extravasation of blood into the subarachnoid space:** The subarachnoid blood in this setting is secondary to the primary hemorrhage, and the overall prognosis depends upon the severity of the primary intracerebral hemorrhage.

**Complications of subarachnoid hemorrhage**

- **Rebleeding:** The peak incidence of rebleeding occurs in the first 24 hours after the initial event. The cumulative risk of rebleeding during the next two weeks is about 20%. Rebleeding of a recently ruptured aneurysm results in death in approximately 65% of patients.

- **Delayed cerebral ischemia:** This complication is often associated with cerebral vasospasm, and is usually encountered between the 4th and 14th days after subarachnoid hemorrhage, with a peak incidence on the 7th day. The frequency of this complication ranges from 25 to 36%. The majority of patients with this complication develop complete cerebral infarction or die. Recent evidence suggests that the "vasospasm" associated with cerebral ischemia is secondary to structural changes of the cerebral blood vessels and not to muscular spasm of the vessel walls. Hence, attempts to relax "vasospasm" by vasoactive agents have frequently been unsuccessful.

- **Hydrocephalus:** This complication is not uncommon, with an estimated frequency of between 3% and 20%. Mechanisms include obstruction of CSF drainage from intraventricular reflux of blood, to interference with CSF absorption through the arachnoid granulations.

- **Hyponatremia:** This complication occurs frequently, either due to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) associated with an expanded blood volume, or a central salt wasting syndrome associated with reduced blood volume.

- **Arrhythmias:** Life-threatening cardiac arrhythmias, EKG changes, and morphologic changes in the heart can occur as a result of the massive sympathetic discharge that often accompanies SAH.
Diagnosis

History

Most patients with subarachnoid hemorrhage present with "the worst headache of my life". Nausea and vomiting, and brief loss of consciousness are other presenting symptoms. The following table lists other presenting symptoms in a series of 41 patients with subarachnoid hemorrhage:

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>35</td>
</tr>
<tr>
<td>Nausea</td>
<td>18</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14</td>
</tr>
<tr>
<td>Brief loss of consciousness</td>
<td>13</td>
</tr>
<tr>
<td>Neck stiffness or pain</td>
<td>6</td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>6</td>
</tr>
<tr>
<td>Vertigo</td>
<td>6</td>
</tr>
<tr>
<td>Faintness</td>
<td>5</td>
</tr>
<tr>
<td>Confusion</td>
<td>5</td>
</tr>
<tr>
<td>Convulsions</td>
<td>3</td>
</tr>
<tr>
<td>Coma</td>
<td>3</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>3</td>
</tr>
<tr>
<td>Visual loss</td>
<td>2</td>
</tr>
<tr>
<td>Diplopia</td>
<td>2</td>
</tr>
<tr>
<td>Malaise and diffuse aches</td>
<td>2</td>
</tr>
<tr>
<td>Photophobia, back pain, leg pain, ataxia, speech disturbance, chest pain, paraparesis</td>
<td>1 each</td>
</tr>
</tbody>
</table>

Physical Examination

Blood in the subarachnoid space almost always produces meningismus, photophobia and pain with attempted lateral gaze. Subarachnoid hemorrhages can sometimes be seen on funduscopic examination. Focal neurologic findings suggest intraparenchymal bleeding or cerebral ischemia.
Grading system for patients after subarachnoid hemorrhage

The Hunt-Hess scale is frequently used to grade patients with subarachnoid hemorrhage. In general, patients with a grade of I, II, or III have a good to excellent outcome following aneurysmal surgery and patients with a grade of IV or V have a poor prognosis.

Grading system for Patients after Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>Grade</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Normal neurologic status, minimal headache, and slightly stiff neck</td>
</tr>
<tr>
<td>II</td>
<td>Moderate to severe headache, meningismus, no confusion or neurologic deficit except related to a cranial nerve</td>
</tr>
<tr>
<td>III</td>
<td>Patient is persistently confused or has focal neurologic deficit</td>
</tr>
<tr>
<td>IV</td>
<td>Patient is persistently stuporous to semicomatose</td>
</tr>
<tr>
<td>V</td>
<td>Deep coma; vegetative disturbances</td>
</tr>
</tbody>
</table>

Laboratory studies

- **Head CT scan:** The head CT scan is positive in approximately 85% of patients with subarachnoid hemorrhage and should be the first test obtained to screen for this disorder.

- **Lumbar puncture:** This should be performed if the CT scan is negative and the subarachnoid hemorrhage is clinically suspect. If the tap is bloody, the fluid should be spun down to look for xanthochromia, which is due to lysis of blood cells, and indicates a hemorrhage of at least 8 to 10 hours duration. Traumatic taps have a clear supernatant and show a significant disparity in the number of red cells between tubes 1 and 4.

- **Cerebral angiography:** This test is the "gold standard" for demonstrating aneurysms. Complete four vessel cerebral angiography should be performed, as aneurysms are frequently multiple. An initially negative angiogram could be due to vasospasm, and angiography should be repeated in approximately two weeks.

- **MRI and MRA:** These new imaging techniques can demonstrate aneurysms well in many cases, but cerebral angiography still remains the gold standard for visualizing aneurysms.

Treatment

Medical management

- **Strict bed rest** in a quiet and darkened room.
• The **head of the bed is elevated** to 30° to promote venous drainage and reduce the potential for cerebral edema.

• **Normal saline** is administered to reduce the potential for vasospasm and prevent hyponatremia.

• **Blood pressure control.** Hypertension can result from cerebral edema or sympathetic discharge, and increases the risk for rebleeding. Hypotension, on the other hand, increases the risk for cerebral ischemia. In general, only severe and elevated blood pressures should be treated, and the mean arterial pressure should not be lowered below 120 mm Hg. Nitroprusside is the preferred therapy, since it provides minute-to-minute control. Labetalol and nifedipine are other alternatives.

• **Stool softeners** should be administered to prevent straining at stools that may increase intracranial pressure.

• **Analgesia,** with codeine phosphate orally (30 mg q 4-6 hrs.), or morphine IV (5-10 mg q 3-4 hrs.).

• **Anxiolytics,** including diazepam or phenobarbital. The latter may be preferred because of its antiepileptic properties.

• **Anticonvulsants.** Approximately 10% to 26% of patients with aneurysmal subarachnoid hemorrhage may experience seizures, and prophylactic anticonvulsant therapy, although controversial, may be helpful in preventing sudden increases in blood pressure associated with seizure activity.

**Delayed cerebral ischemia:**

• **Volume expansion therapy:** The combination of fluid intake greater than 3 liters per day and the avoidance of antihypertensives was found effective in reducing the incidence of cerebral ischemia in one recent study. Normal saline is the fluid of choice because of the high incidence of hyponatremia due to SIADH or central salt wasting.

• **Nimodipine:** This calcium channel blocker was found effective in reducing the occurrence of severe neurologic deficits due to cerebral arterial spasm in a study of 125 patients with aneurysmal subarachnoid hemorrhage in one recent study. Nimodipine seems to dilate the intraparenchymal arterioles of the brain and promotes leptomeningeal collateral circulation. It may also improve red blood cell deformability and exert an antiplatelet aggregating effect. It does not reverse large vessel spasm. A dosage of 60 mg po q 4 h for 21 days is recommended. Side effects are minimal.

**Raised intracranial pressure**

• Conventional measures, including intubation with hyperventilation, and mannitol should be employed for symptomatic raised intracranial pressure. Dexamethasone is controversial in this setting, but may help reduce meningeal inflammation and the
headache associated with subarachnoid hemorrhage. Ventriculostomy should be
considered for treatment of hydrocephalus, but care should be exercised in
performing this procedure in the setting of unilateral hemispheric edema, since this
procedure may result in subfalcial herniation.

Rebleeding:

- **Antifibrinolytics**: Although epsilon aminocaproic acid (EACA, Amicar) and tranexamic acid reduce the incidence of rebleeding in the acute stages after subarachnoid hemorrhage, the incidence of delayed cerebral ischemia, hydrocephalus, deep venous thrombosis, and pulmonary embolism are increased, offsetting the beneficial effect. In a recent study of 672 patients, these drugs failed to improve the mortality rate during the first month after subarachnoid hemorrhage in treated patients as compared with untreated controls.

- **Aneurysmal surgery**: Surgery is the only accepted means to prevent long-term aneurysmal re-rupture. The optimal timing of surgical intervention remains controversial. Although delayed surgery (11-14 days post bleed) is technically easier and less hazardous than early surgery (0-3 days post bleed), many patients die from re-rupture of the aneurysm within the first week following hemorrhage.

In a recent multicenter study involving 3,521 patients, early surgery was found to be neither more hazardous nor more beneficial than delayed surgery, and the postoperative risk following early surgery was equivalent to the risk of rebleeding and vasospasm in patients waiting for delayed surgery.

A reasonable approach, and that employed in many centers, is to operate early on clinical grade I and II patients provided the CT shows no cerebral edema or mass effect, and angiography demonstrates an aneurysm in a favorable anatomic site without vasospasm. Operative treatment is delayed in poorer grade patients, in those with aneurysms in more difficult locations, and in those with angiographic or clinical vasospasm.

**References**


HEAD TRAUMA
Ralph F. Józefowicz, MD

Complications of Head Trauma

- **Cerebral Concussion:** A sequela of blunt head trauma that results in a brief period of unconsciousness, often associated with retrograde and anterograde amnesia for the event. The severity of the concussion correlates directly with the duration of unconsciousness.

  The mechanism by which blunt head trauma results in loss of consciousness is as follows: abrupt acceleration or deceleration of the head produces rotational shear forces which disrupt axons and myelin sheaths, resulting in neuronal damage. If the shear forces are slight, the period of unconsciousness is brief. If the shear forces are of sufficient magnitude, permanent neuronal damage may occur.

  In general, mild cerebral concussions do not produce any gross injury to the brain. On the other hand, severe concussions result in diffuse axonal injury with resultant edema, cerebral herniation and death.

- **Cerebral Contusion:** A "bruise" of the brain that usually follows translational shear forces following abrupt acceleration or deceleration of the head. These shear forces are maximal at the brain surface and typically brain injury occurs at areas in direct contact with the irregular, inner surface of calvarium, including the frontal poles, temporal poles and undersurface of the temporal lobes. Cerebral contusions are usually accompanied by subpial and intracerebral extravasation of blood.

  Symptoms of cerebral contusion vary with the location and severity of the lesion. Contusions may occur directly at the site of the blow to the head (coup contusion), or at a point opposite the impact (contrecoup contusion).

- **Cerebral Laceration:** A "cut" through the brain surface due to a sharp foreign object or the sharp border of the skull. By definition, the pia mater is torn in a cerebral laceration. Subpial and intracerebral hemorrhage may be present as well.

  Symptoms of a cerebral laceration also depend on the location and severity of the lesion.

- **Cavernous Sinus Arteriovenous Malformation:** A traumatic laceration of the internal carotid artery as it passes through the cavernous sinus. This may be seen following a fracture of the sphenoid bone. In many patients, a loud bruit develops as a result of the fistula, and can be heard over the skull or over the internal carotid artery in the neck. Exophthalmos and paralysis of the cranial nerves that pass through the cavernous sinus (III, IV, V₁, VI) may also be seen. Some of these fistulae resolve spontaneously, and others require surgical correction.

- **Hemorrhage:** Four types of hemorrhage may follow head trauma: epidural, subdural, subarachnoid and intracerebral.
1. **Epidural hematoma:** This form of intracranial hemorrhage often follows a fracture of the temporal bone, and results from a laceration to the middle meningeal artery. The blood accumulates rapidly, since it is under arterial pressure. Epidural hematomas have a convex appearance on the head CT scan.

Clinically, patients with epidural hematomas are initially unconscious, due to a cerebral concussion. They then regain consciousness for a short period of time (lucid interval), and then lose consciousness once again as the hematoma expands and intracranial pressure increases.

Epidural hematomas are neurologic emergencies and prompt neurosurgical drainage by means of a burr hole is warranted.

2. **Subdural hematoma:** This form of intracranial hemorrhage can follow significant, as well as mild degrees of head trauma. Subdural hematomas arise from damage to the small cerebral veins that bridge the cortex and superior sagittal sinus, especially in the frontal regions. Older individuals are more prone to this form of intracranial hemorrhage due to the considerable amount of cerebral atrophy that is present in this population. In these patients, oftentimes trivial head trauma may produce enough force to disrupt these bridging veins.

Symptoms of subdural hematoma are non-specific and consist of headache, mental status changes and focal neurologic abnormalities. Treatment of symptomatic subdural hematomas consists of surgical drainage. Asymptomatic subdural hematomas are oftentimes treated by observation alone, since they frequently regress spontaneously.

The appearance of a subdural hematoma on CT scan depends upon how much time has elapsed since the hemorrhage. Acutely, these hematomas are hyperdense and have a crescent shape (concave). As the blood begins to resorb, these hematomas become isodense with brain tissue and this typically occurs about two weeks following the injury. As the hematoma continues to resorb further, the CT appearance changes to that of a hypodense lesion, having a signal characteristic similar to that of cerebrospinal fluid.

3. **Subarachnoid hemorrhage:** Isolated subarachnoid hemorrhage is uncommon following head trauma. Nonetheless, some subarachnoid bleeding can occur in association with intracerebral hemorrhage following a cerebral contusion or laceration. Recall that the most common cause of spontaneous, non-traumatic subarachnoid hemorrhage is rupture of a congenital (saccular) aneurysm.

4. **Intracerebral hemorrhage:** In a significant number of patients with cerebral contusions, intracerebral hemorrhage may be present. Damage to deep penetrating blood vessels is the cause of this form of intracranial bleeding. Treatment is medical or surgical, depending on the size of the lesion and associated mass effect.
Sequelae of Head Trauma

- **Raised Intracranial Pressure:** All forms of head injury, whether direct or indirect, may result in raised intracranial pressure. The magnitude of the pressure change is proportional to the amount of injury. Typically, the pressure peaks at about 2-4 days following the injury. Persistently raised pressure may result in cerebral herniation.

- **Cerebral Herniation:** Cerebral herniation frequently accompanies head injury, depending on the location and severity of the lesion. Five types of herniation syndromes can be seen: subfalcial, transtentorial (uncal), central, upward and cerebellar tonsillar. These are discussed elsewhere.

- **Seizure:** Seizures may be seen acutely or as a delayed consequence of brain injury. In general, the risk of seizures is proportional to the amount of cortical damage. Delayed seizures usually occur several months following head injury, once the cortical scar has developed.

- **Infection:** As one would expect, the incidence of infection is increased greatly in patients with open fractures of the skull. Basilar skull fractures are another source of infection, particularly if the fracture line involves the sinuses or external auditory canals.

- **CSF Otorrhea/Rhinorrhea:** CSF leakage through the external auditory canals or through the nasal cavities occasionally follows basilar skull fractures. As one would expect, the incidence of secondary bacterial meningitis in these settings is significantly increased. One can easily determine if clear fluid draining from the nares or external auditory canal is spinal fluid: CSF is high in glucose and nasal mucus is not. Applying a drop of fluid to a "dextrostick" is one quick way to make this determination.

- **Post-traumatic Syndrome:** Many patients with a closed head injury develop the post-traumatic syndrome, which is a collection of symptoms including headache, dizziness and vertigo, sleep disorders and depression and lassitude. This syndrome can last for weeks to months following head injury, and the severity of the symptoms often parallels the degree of head trauma.

  This syndrome is sometimes difficult to differentiate from malingering, which occurs in other patients, particularly those with pending law suits and those seeking disability.

  Treatment of the post-traumatic syndrome includes supportive therapy, psychotherapy and anti-depressant medications.

Evaluation of Head Trauma

- **History:** The circumstances of the accident should be carefully detailed. In addition, past medical history, medications, and the possibility of drug or alcohol abuse should be noted.
• **General Physical Examination:**

  • **Skull Fracture:** The skull should be palpated for any defects that may indicate an underlying skull fracture.

  • **Battle Sign:** Ecchymosis over the mastoid process, which suggests a temporal bone fracture with concomitant subperiosteal and subcutaneous hemorrhage.

  • **Raccoon Eyes:** Bilateral orbital ecchymoses resulting from a fracture of the base of the skull involving the anterior fossa.

  • **Hemotympanum:** Blood behind the tympanic membranes, suggesting a fracture of the base of the skull involving the middle fossa.

  • **CSF Otorrhea/Rhinorrhea:** The external auditory canals, nacstriis and pharynx should be examined for the presence of CSF, which indicates a basilar skull fracture.

  • **Orbital Bruits:** These suggest the presence of a traumatic carotid-cavernous sinus fistula.

• **Neurologic Examination:** The neurologic examination is tailored to the level of alertness of the patient. The following five parts of the neurologic examination should receive special attention, particularly if the patient has an altered mental status:

  • Level of consciousness
  • Spontaneous respirations
  • Pupils
  • Eye movements
  • Motor response

• **Laboratory Studies:**

  • Blood studies, including a complete blood count and a chemistry profile
  • Blood alcohol level
  • Urine toxicology screen
  • Head CT scan

**Treatment of Head Trauma**

• **Airway/Breathing/Circulation:** The patency of the airway is first assessed. If spontaneous respirations are insufficient, mechanical ventilation is provided. If hypoperfusion is present, blood products, fluids and pressors are administered as needed.
• **Narcan/Glucose/Thiamine:** Narcan (naloxone) is a narcotic antagonist and should be administered IV on the remote chance that the patient may have been taking narcotics prior to the injury.

Glucose and thiamine should also be administered, the latter to prevent Wernicke encephalopathy, which can be precipitated by a high glucose load in a malnourished individual.

• **Treat Raised Intracranial Pressure:** Endotracheal intubation with hyperventilation and intravenous mannitol should be considered if the patient is showing signs of raised intracranial pressure. If intracranial pressure is markedly increased, barbiturate coma should also be considered. There is no evidence that corticosteroids are beneficial in treating raised intracranial pressure following head trauma. Since these agents have other potentially serious side effects, they should not be administered in this setting.

• **Neurosurgical Intervention:**

  • **Intracranial Pressure Monitoring:** This can be performed by means of a ventriculostomy, which has the added advantage of draining cerebrospinal fluid, as well as by means of a Becker bolt (epidural pressure monitor).

  • **Wound debridement**

  • **Evacuation of hematomas,** particularly if easily accessible, or if the patient is showing signs of raised intracranial pressure.
TREATMENT OF ACUTE AND CHRONIC HYPERTENSION
Ralph F. Józefowicz, M.D.

In order to be able to treat acute and chronic hypertension properly, one must have a clear understanding of cerebral blood flow and the many factors that affect it. Profound alterations in cerebral blood flow occur during many neurologic disorders and a familiarity with these alterations in blood flow is necessary to manage effectively the blood pressure elevations that frequently accompany these clinical situations. Only then can a decision be made whether and how to treat hypertension properly.

CEREBRAL HEMODYNAMICS

Cerebral blood flow (CBF) is dependent entirely upon two factors: (1) the pressure difference tending to push blood through the vessel and (2) the impediment to blood flow through the vessel, or vascular resistance. Expressed mathematically:

\[
\text{CBF} = \frac{\text{mean arterial blood pressure}}{\text{cerebrovascular resistance}}
\]

The mean arterial blood pressure (MABP) is defined as the diastolic blood pressure (DBP) + 1/3 x pulse pressure (PP, which is the difference between the systolic and the diastolic blood pressure).

\[
\text{MABP} = \text{DBP} + \frac{1}{3} \times \text{PP}
\]

\[
\text{PP} = \text{SBP} - \text{DBP}
\]

Cerebrovascular resistance is normally dependent upon arteriolar vascular tone. In pathologic states where intracerebral pressure is increased significantly, cerebrovascular resistance may be dependent entirely upon the intracranial pressure.

Cerebral autoregulation of blood flow

Cerebral blood flow is kept relatively constant with moderate blood pressure changes. This phenomenon, termed autoregulation, is mediated by caliber changes in the cerebral arterioles and small arteries. Thus when blood pressure falls, the arterioles dilate preventing a fall in CBF. Conversely, when blood pressure rises, arterioles constrict preventing a rise in CBF. This response is rapid, being initiated within a few seconds and largely completed in 15 - 30 seconds.

Two mechanisms are felt to be involved in this response: (1) a myogenic response affecting small resistance vessels, felt to be the major mechanism, and (2) alpha adrenergic sympathetic vasoconstriction of larger cerebral vessels. This second mechanism plays a limited role.

In normotensive individuals, CBF remains constant between a range of approximately 60 - 120mm Hg mean arterial pressure (MAP). Below 60mm Hg, autoregulatory
vasodilation is inadequate and CBF falls. Similarly, above 120mm Hg, CBF rises with further blood pressure elevation.

In chronic hypertensive individuals, CBF autoregulation is adapted to higher pressures, and the autoregulatory curve is shifted to higher blood pressure levels, with the lower limit set at 120mm Hg and the upper limit at 160mm Hg (Figure).

These changes are felt to be secondary to adaptation of the cerebral arterioles to chronic hypertension with the development of medial hypertrophy. These vessels consequently cannot dilate as effectively as those present in normotensive individuals. In some cases, with long term antihypertensive therapy, the autoregulation curve may readjust towards normal. This occurs less often in the elderly population.

In certain pathologic states, such as stroke, seizures, cerebral trauma or intracerebral hemorrhage, autoregulation of cerebral blood flow is abolished, and CBF becomes pressure dependent.

**NEUROLOGIC COMPLICATIONS OF HYPERTENSION**

Hypertensive encephalopathy and stroke are two neurologic complications of hypertension. The former requires emergent therapy, but treatment of hypertension in the latter situation is more controversial.

**Hypertensive Encephalopathy**

Hypertensive encephalopathy is a syndrome of diffuse cerebral dysfunction associated with sudden or severe elevations of systemic blood pressure. The clinical features of
complaints, papilledema, transient neurologic deficits and seizures. The etiology of this disorder is felt to represent a failure of cerebral autoregulation with "breakthrough" hyperperfusion and subsequent cerebral edema, petechial hemorrhage and arteriolar necrosis. Hypertensive encephalopathy responds promptly to antihypertensive therapy, and response to therapy is the only definitive criterion for the diagnosis of this syndrome.

Hypertension and Stroke

According to the Framingham study, hypertension (systolic or diastolic) was found to be the most important risk factor for stroke. After stroke has occurred, the persistence of hypertension adversely affects prognosis. Significant evidence suggests that elevated blood pressure damages cerebral arteries. Damage to small cerebral vessels results in lacunar infarcts and intracranial hemorrhage. Damage to larger vessels results in thrombotic and thromboembolic phenomena.

Despite the undisputed fact that hypertension is clearly a risk factor for stroke, a dilemma exists whether or not to treat elevations in blood pressure in acute ischemic stroke. Several observations concerning the role of hypertension in the etiology and pathophysiology of acute stroke can be made.

The majority of patients with ischemic stroke have chronic hypertension and, consequently, the autoregulation curve for CBF is shifted towards higher blood pressures. Furthermore, CBF autoregulation during the acute phases of stroke is impaired, and hence CBF in ischemic areas is passively dependent upon arterial pressure. Therefore, lowering blood pressure in patients with cerebral ischemia may adversely reduce CBF. In addition, brain ischemia often leads to cerebral edema that increases intracranial pressure and cerebrovascular resistance. This may result in a fall in CBF if the mean arterial pressure remains constant or falls. However, if the mean arterial pressure is elevated, cerebral edema may worsen due to the passive dependence of CBF on arterial pressure.

In a study of 340 patients with acute stroke, one half of whom had a history of hypertension, Wallace and Levy noted that, although 84 percent of the patients had an elevated blood pressure initially, the blood pressure fell spontaneously an average of 20mm Hg systolic and 10mm Hg diastolic over the next 10 days, suggesting that early elevation of blood pressure in stroke is likely a physiologic response to brain ischemia.

Numerous reports abound of too rapid or too severe blood pressure lowering resulting in permanent neurologic deficits.

Treatment of hypertension in acute stroke

Given the above observations concerning the role of hypertension in the etiology and pathophysiology of stroke, several recommendations can be made:

- **Mild transient elevation** in blood pressure associated with the acute phases of stroke **should not be treated**.
• Cautious lowering of elevated blood pressure in acute stroke patients should be attempted if:
  • Vital organs such as the heart or kidneys are compromised.
  • The patient has hypertensive encephalopathy.
  • The diastolic blood pressure rises above 130mm Hg.

• Blood pressure reduction should be gradual, maintaining CBF within normal limits of autoregulation, and aiming for a mean arterial pressure of 120mm Hg.

• Rapid "normalization" of blood pressure is to be avoided.

• In some clinical circumstances, i.e. hydrocephalus, raised intracranial pressure may be contributing to systemic hypertension; primary treatment of the raised intracranial pressure may result in lowering of the systemic blood pressure.

**HYPERTENSIVE EMERGENCIES AND URGENCIES**

A hypertensive emergency is defined as a severe elevation in blood pressure associated with evolving cerebral, cardiovascular or renal dysfunction. Most hypertensive crises are thought to be due to an abrupt increase in systemic vascular resistance as a result of increases in circulating vasoconstrictors that subsequently produce arteriolar fibrinoid necrosis. This results in endothelial damage, platelet and fibrin deposition, and loss of autoregulatory function with resultant end-organ ischemia. Further vasoactive substances are then released, resulting in further vasoconstriction and myointimal proliferation. In hypertensive emergencies, the mean arterial pressure should be lowered by approximately 25% over a period of several minutes to hours, depending on the clinical situation. Examples of hypertensive emergencies include:

• Hypertensive encephalopathy
• Severe malignant hypertension accompanied by
  • acute left ventricular failure
  • acute myocardial infarction or unstable angina
  • dissecting aortic aneurysm
  • stroke or head trauma
  • progressive renal insufficiency
  • eclampsia

A hypertensive urgency is defined as a severe elevation in blood pressure associated with impending cerebral, cardiovascular or renal dysfunction. In hypertensive urgencies the mean arterial pressure should be lowered by approximately 25% over a period of 24-48 hours, depending on the clinical situation. Examples of hypertensive urgencies include:

• Severe or accelerated hypertension without evidence for end organ dysfunction.
• Perioperative hypertension.

Although, in general, the diastolic blood pressure is greater than 120-130 mm Hg in both hypertensive emergencies and urgencies, the rate of rise of blood pressure as well as
evidence for end-organ damage are more important determinants of severity than the absolute level of blood pressure. In previously normotensive individuals (women with eclampsia or children with acute glomerulonephritis), or in patients with well-controlled hypertension, hypertensive crises can occur with blood pressure levels as low as 160/100.

Numerous antihypertensive agents are available to treat severe elevations of blood pressure (Table I). These agents are primarily of two types—those that directly dilate the resistance vessels (calcium entry blockers and arteriolar vasodilators) and those that interfere with the sympathetic innervation of the cardiovascular system (ganglionic blockers and adrenergic receptor blockers). Only the most effective agents that are applicable for treatment of neurologic emergencies will be discussed. Centrally active agents, such as methyldopa, should not be used in the treatment of neurologic hypertensive emergencies, as these agents frequently produce mental status alterations that can interfere with the clinical assessment of the patient.

**AGENTS USEFUL IN THE TREATMENT OF HYPERTENSIVE EMERGENCIES AND URGENCIES**

- Nitroprusside
- Labetalol
- Diazoxide
- Trimethaphan
- Nifedipine
- Nicardipine
- Hydralazine
- Clonidine

**NITROPRUSSIDE**

Nitroprusside is a highly potent, predictably effective, short acting arteriolar and venous dilator. It is also a cerebral vasodilator. It has an instantaneous onset of action, and its effect wears off within five minutes of stopping the infusion. It must be given by constant infusion in an ICU setting. It is degraded rapidly by light, and hence tubing and containers used for administration should be wrapped in aluminum foil.

Nitroprusside is metabolized to cyanide by red blood cells and tissue and ultimately thiocyanate in the liver, both of which may accumulate with a prolonged duration of infusion (48 - 72 hours) as well as with hepatic or renal failure. Cyanide toxicity results in lactic acidosis. Signs of thiocyanate toxicity include weakness, hyperreflexia, dysarthria, tinnitus, convulsions and mental status changes.

Plasma thiocyanate concentrations can be monitored and treatment should be interrupted when the concentration of thiocyanate is close to 10 mg/dl to minimize the symptoms of thiocyanate toxicity.

Concerns have been raised about the safety of nitroprusside in treating neurologic hypertensive emergencies, since it may potentially raise intracranial pressure due to its
effect on cerebral blood flow (CBF). Although at low doses nitroprusside increases CBF, it appears to have an opposite effect on CBF at high doses. Nitroprusside remains the agent of choice for the treatment of most neurologic hypertensive emergencies.

A nitroprusside infusion should begin at a rate of 10 mcg per minute, and be increased by 10 to 20 mcg increments every five minutes, until the blood pressure is controlled.

LABETALOL

Labetalol is an alpha and beta adrenergic receptor blocker, which reduces systemic vascular resistance and arterial blood pressure without reflex tachycardia or a change in cardiac output. The beta effect predominates (3:1 beta to alpha). Labetalol was found to be safe and effective in treating hypertensive emergencies in a multicenter study of 59 patients.

Labetalol can be given by IV bolus for rapid control of hypertension. The oral formulation is effective for long term management of hypertension. Labetalol's onset of action after IV bolus is within 5 to 10 minutes, and the effect may persist for up to 24 hours.

Labetalol can also be administered as a constant IV infusion, beginning with a rate of 0.5 mg/min and increasing as necessary to 2-4 mg/min. Although this method requires more intensive monitoring, it may cause less hypotension and bradycardia.

Labetalol is contraindicated in patients with obstructive lung disease, congestive heart failure, sinus bradycardia or atrioventricular block greater than first degree. Its side effects are minimal and include nausea, epigastric burning, rhinorrhea and premature ventricular contractions.

Administration of Labetalol for hypertensive emergencies should start with a 20 mg bolus injection, followed by repeated incremental doses of 20 - 80 mg IV every ten minutes until the desired blood pressure is achieved. Once blood pressure has stabilized, oral therapy with Labetalol can be started with an initial dose of 200 mg.

DIAZOXIDE

Diazoxide is a very potent parenteral arteriolar vasodilator. It has no effect on cerebral blood vessels. It can be given by IV bolus, hence ICU monitoring is not always necessary. Its onset of action is rapid, within minutes, and its effect may persist for 12 or more hours.

Diazoxide can cause reflex tachycardia and fluid and salt retention. Hyperglycemia and hyperuricemia can be seen with prolonged usage.

Large boluses (300mg) were formerly recommended for initial therapy of severe hypertension, but this dose can result in a precipitous reduction in blood pressure with resultant cardiac and cerebral ischemia. Presently, it is recommended that diazoxide be administered as a 50 - 100mg bolus, over 30 seconds, which can be repeated every 10 minutes until the desired blood pressure is attained.
TRIMETHAPHAN

Trimethaphan is a ganglionic blocking agent that competitively inhibits acetylcholine at the post ganglionic membrane. This results in vasodilation of the resistance and capacitance vessels, the latter effect resulting in a lowered cardiac output. Trimethaphan, therefore, is the agent of choice for severe hypertension associated with aortic dissection.

Trimethaphan must be given by continuous IV infusion in an ICU setting. Its onset of action is within minutes, and its effect wears off within 15 minutes of stopping the infusion. Because the effect of this drug is mostly orthostatic, elevating the head of the bed will increase its antihypertensive effect.

Trimethaphan has numerous side effects, including constipation, paralytic ileus, urinary retention, mydriasis, and cycloplegia. Tachyphylaxis can occur within 36 - 72 hours after institution of the infusion, due to sensitization of neureceptors to epinephrine and norepinephrine, as well as sodium and water retention.

The infusion rate for trimethaphan varies from 200 mcg per minute to 6 mg per minute, depending on the patient's response.

NIFEDIPINE

Nifedipine is a calcium antagonist that decreases systemic vascular resistance. This agent also produces an increase in cerebral blood flow. Its onset of action is within 30 minutes when given orally, and within 5 - 10 minutes when given sublingually (or by having the patient bite the capsule and swallow the contents). The effect lasts for 4 - 6 hours.

Nifedipine can cause flushing, headache, fluid retention as well as an increase in heart rate.

The recommended dosage for Nifedipine is one 10 mg capsule orally (or sublingually for a more rapid onset of action), with a repeat dose in 30 minutes if necessary.

NICARDIPINE

Nicardipine is a dihydropyridine calcium antagonist that is a potent antihypertensive agent that reduces blood pressure by decreasing systemic vascular resistance. Unlike Nifedipine, it is water soluble and thus available in both an oral and intravenous preparation. Intravenous Nicardipine has been found to be successful in treating severe systemic hypertension in several studies.

An intravenous Nicardipine infusion can begin at a rate of 5mg/hr and this rate can be increased every 15 minutes by 1 - 2.5mg/hr up to a maximum dose of 15mg/hr. Once satisfactory blood pressure control is achieved, oral therapy with Nicardipine can be
started with an initial dose of 40mg tid. Diuretics and/or beta blockers can be added as necessary.

Side effects include headache, flushing, nausea and vomiting, tachycardia, postural hypotension, and local phlebitis with prolonged infusion.

HYDRAZINE

Hydralazine is a direct arterial vasodilator. It causes direct relaxation of smooth muscle in the peripheral vascular bed, with a much greater effect on small arteries and arterioles than on small veins and venules. Hydralazine increases cerebral blood flow.

Hydralazine’s onset of action is within 10 - 20 minutes and its effect has a duration of 2 - 6 hours.

When administering hydralazine for hypertensive urgencies, start with a 10 mg bolus IV, followed by incremental doses of 10 - 40 mg IV every 10 - 20 minutes, until the blood pressure is controlled.

The side effects of hydralazine include reflex tachycardia, increased cardiac contractility, and a rise in plasma renin with concomitant sodium and water retention. Because of this, hydralazine is usually combined with a central alpha agonist or beta blocker to decrease reflex tachycardia, and with a diuretic to decrease intravascular volume.

Hydralazine is frequently used for the treatment of severe blood pressure elevations seen with eclampsia because it tends to increase placental and fetal blood flow.

CLONIDINE

Clonidine is an orally-active central alpha-agonist that stimulates central post-synaptic alpha2 receptors in the vasomotor center of the brain stem. This causes a decrease in sympathetic nervous system outflow to the heart, peripheral vasculature and kidneys, resulting in a decrease in systemic vascular resistance. Absorption is rapid and complete, with an onset of action in 30 - 60 minutes, peak action in 2 - 4 hours and a duration of action of 12 - 16 hours.

Oral Clonidine loading has been found useful in treating hypertensive urgencies. An initial oral dose of 0.1-0.2mg is given followed by hourly oral doses of 0.05-0.1mg until the goal blood pressure is attained, up to a total of 0.8mg. This method was found effective in 93% of 101 patients that have been described in the literature. An average dose of 0.36mg Clonidine was required, and this resulted in an average lowering of mean arterial pressure by 38mm Hg.

Adverse effects include sedation (approximately 37% in one study), dry mouth, dizziness, weakness, headache, bradycardia and constipation.

Clonidine is contraindicated in patients with sick sinus syndrome and atrio-ventricular block. In addition, caution should be exercised in patients with mental status changes due to hypertension, since Clonidine may adversely effect the level of consciousness.
Diuretics, i.e. furosemide and the thiazides, are useful as adjunct agents to counteract the fluid and sodium retaining properties of most antihypertensive agents. However, administration of a potent diuretic as the first drug in the treatment of hypertensive emergencies should not be done, as most hypertensive emergencies are vasoconstrictive states, with normal or reduced plasma volumes. Addition of a second antihypertensive agent in the face of a significantly reduced plasma volume can result in profound hypotension. Hence, diuretics should be added after the antihypertensive effect of the first agent has been achieved.

A few final points should be made concerning the emergent or urgent treatment of hypertension in neurologic emergencies:

- Treat severely elevated blood pressure only if end organ damage is imminent or present.
- If a decision is made to treat, treat gently and gradually. Don't overtreat.
- Be cognizant of the cerebral blood flow autoregulation curve.
- Use agents that can be titrated easily (Nitroprusside, Labetalol, Nifedipine), and start with a small dose.

**CHRONIC HYPERTENSION**

**DEFINITION AND PREVALENCE OF HYPERTENSION**

Approximately 58 million people in the United States have hypertension, defined as blood pressure greater than 140/90. The risk of vascular complications due to hypertension increases continuously with increasing levels of both systolic and diastolic blood pressure. Even mild hypertension carries a significant risk of vascular complications and should be treated.

Hypertension should not be diagnosed on the basis of a single elevated blood pressure measurement. An initial elevated reading should be confirmed on at least two subsequent visits.

**GENERAL PRINCIPLES OF TREATMENT**

Non-pharmacologic measures, including weight reduction, reduction of alcohol intake, restriction of dietary sodium, potassium supplementation, aerobic exercises, and control of other cardiovascular risk factors should be tried initially in the treatment of mild hypertension. These measures may be effective in normalizing blood pressure in up to 18% of patients with mild hypertension. If these measures fail to control blood pressure adequately within 3 - 6 months, pharmacologic therapy should be considered.

The 1993 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure recommends thiazide-type diuretics or β-blockers as first choice agents, since these drugs have been shown to reduce cardiovascular
morbidity and mortality in controlled clinical trials. The alternative drugs, which include calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, \( \alpha_1 \) receptor blockers, and the \( \alpha_1\beta \) blocker labetalol, are equally effective in reducing blood pressure but have not been used in long-term controlled trials to demonstrate their efficacy in reducing mortality and morbidity. They should therefore be reserved for situations in which diuretics and 8-blockers have proven ineffective, or are intolerable due to side effects.

If after a 1 - 3 month trial blood pressure control is inadequate despite compliance with this regimen, and side effects are not apparent, three options should be considered:

- increase dose of the first drug to or toward maximal levels;
- substitute an agent from another class; or
- add a second drug from another class.

If a diuretic is not chosen as the first drug, it should be added as the second drug since fluid retention may be responsible for a sub-optimal blood pressure response to the first agent.

In patients with mild hypertension that has been satisfactorily controlled with medication for at least one year, antihypertensive drugs may be reduced in a step wise fashion. Successful candidates likely to remain normotensive after stopping antihypertensive medication include young individuals with a normal body weight, low sodium intake, no alcohol consumption, low pre-treatment blood pressure, successful treatment with one drug only, and no or only minimal signs of target organ damage.

Isolated systolic hypertension, defined as systolic blood pressure greater than 160 with diastolic blood pressure less than 90, increases with age and is present in 18% of patients aged 80 years or older. Contrary to previously held views, isolated systolic hypertension is an independent risk factor for cardiovascular disease. In a five year placebo-controlled study of 4,736 persons older than 60 years with isolated systolic hypertension, medical treatment of the hypertension using a stepped-care approach with a diuretic as the first drug reduced the incidence of total stroke by 36%. Hence, isolated systolic hypertension in the elderly should be treated as vigorously as diastolic hypertension.

**DRUGS USEFUL IN THE TREATMENT OF CHRONIC HYPERTENSION**

**DIURETICS**

Three classes of diuretics are frequently used to treat hypertension: thiazide-type diuretics, loop diuretics, and potassium-sparing diuretics. The thiazide-type diuretics cause a prompt diuresis and natriuresis that result in a contraction of extracellular fluid volume. With long term use, these agents can lower peripheral vascular resistance; they have no effect on left ventricular hypertrophy. Although thiazide-type diuretics are effective alone as blood pressure lowering agents, they also enhance the blood pressure-lowering effects of other major classes of antihypertensives.
Thiazide-type diuretics are particularly effective in individuals with salt-sensitive hypertension, volume overload, or a low-renin state. **Black patients and the elderly** are particularly responsive to these agents. Small doses of diuretics are presently recommended for the treatment of hypertension, equivalent to 50mg per day of hydrochlorothiazide. In the older individual, even lower doses are effective, i.e. 12.5-25mg per day.

Thiazide-type diuretics have been found effective in **reducing the risk of hip fractures** in elderly patients by 32% in one study. The calcium-retaining property of this class of agents is felt to be the putative mechanism. The **loop diuretics**, including furosemide and bumetanide, have a shorter duration of action than thiazide-type diuretics. They are generally less effective for the treatment of hypertension, and should be reserved for the hypertensive individual with fluid retention.

**Potassium-sparing diuretics** are primarily used with other diuretics to prevent hypokalemia. In patients with renal insufficiency, particularly diabetics and the elderly, these drugs can cause life-threatening hyperkalemia. **Adverse effects:** Diuretics cause numerous metabolic side effects, including hypokalemia, hypomagnesemia, hyperglycemia and hyperuricemia. These agents also elevate triglycerides and total, LDL and VLDL cholesterol. Diuretics can cause impotence in men.

Although most thiazide-type diuretics are ineffective in patients with renal failure, two new agents, **metolazone and indapamide** may be effective in these patients. In addition, indapamide does not appear to adversely affect lipids or to cause carbohydrate intolerance or severe hypokalemia.

**ALPHA<sub>1</sub> BLOCKERS**

- Prazosin
- Terazosin
- Doxazosin

The alpha<sub>1</sub> blockers act at vascular post-synaptic alpha receptors to produce arterial and venous dilation. This results in a prompt reduction in blood pressure. These agents are cleared primarily by the liver and excreted only minimally by the kidneys. They are effective for the treatment of congestive heart failure, but tolerance to the effect of these drugs develops with time. They cause no change in cerebral blood flow.

Alpha<sub>1</sub> blockers have numerous beneficial effects in the treatment of hypertension. As opposed to most other antihypertensives, these agents **favorably affect lipids**, decreasing the level of triglycerides and total, LDL and VLDL cholesterol, and they increase HDL cholesterol. They have no adverse effects on glucose tolerance and they may improve insulin sensitivity in type 2 diabetics.

Alpha<sub>1</sub> blockers decrease the amount of muscle contraction at the urinary bladder outlet, and have been found effective in treating benign prostatic hypertrophy.

**Adverse effects:** Alpha<sub>1</sub> blockers cause significant orthostatic hypotension, which may be profound after the first dose in patients with low plasma volume. It is recommended
that when these agents are started, a small initial dose be given at bed time. In addition, these agents can cause tachycardia, nausea, fatigue and lethargy.

**BETA BLOCKERS**

**Non-selective Beta Blockers**

Propranolol, Timolol, Nadolol, Pindolol, Penbutolol, Cartelol

**Cardioselective (Beta₁ Blockers)**

Metoprolol, Acebutolol, Atenolol, Betaxolol

**Beta Blockers with Intrinsic Sympathomimetic Activity**

Pindolol, Acebutolol, Penbutolol, Cartelol

**Combined Alpha and Beta Blocker**

Labetalol

These agents block the beta adrenergic receptors, resulting in decreased sympathetic stimulation of the heart and a decrease in the release of renin from the juxtaglomerular cells of the kidney. They lower blood pressure by reducing cardiac output.

The cardioselective beta blockers have a greater effect on cardiac (beta₁) adrenoreceptors than on beta₂-adrenergic receptors of the bronchi and blood vessels. This cardioselectivity occurs only at low doses.

The beta blockers with intrinsic sympathomimetic activity lower blood pressure with less decrease in cardiac output or heart rate at rest. Labetalol has a similar effect.

Beta blockers have been found effective in reducing the incidence of primary or secondary myocardial infarction in patients with coronary artery disease. They also reduce left ventricular hypertrophy.

The beta blockers are particularly effective in the young hypertensive, and may be less effective in black or elderly patients.

**Adverse effects**: Beta blockers can cause bronchospasm, bradycardia and vasoconstriction, and hence are contraindicated in patients with severe obstructive lung disease, heart failure, heart block, or significant peripheral vascular disease. They block the catechol response to insulin-induced hypoglycemia and may also worsen glucose control in diabetics. Impotence, fatigue, depression, sleep disturbances and vivid dreams can all occur. These agents also adversely affect plasma lipids, and cause an elevation of triglycerides and LDL cholesterol, and reduce HDL cholesterol. The beta
blockers with intrinsic sympathomimetic activity have fewer adverse effects on the lipid profile.

**CALCIUM ANTAGONISTS**

- Verapamil
- Diltiazem
- Nifedipine
- Nicardipine
- Isradipine

The calcium antagonists block the transport of calcium across the cell membrane, and thereby reduce the contraction of cardiac and vascular smooth muscle, resulting in a decrease in peripheral vascular resistance and blood pressure. They also affect a slight diuresis and natriuresis; adding a diuretic to enhance the antihypertensive effects of calcium antagonists is therefore not very useful. Sustained release preparations using novel drug delivery systems are available for some of these agents, allowing once daily dosage.

The calcium antagonists are particularly helpful in treating blacks and elderly patients with hypertension. These agents have no adverse effects on lipid profile or glucose metabolism; they effectively reduce left ventricular mass with chronic use. They are not effective in the secondary prevention of myocardial infarction or death in patients with coronary artery disease.

**Adverse effects:** The calcium antagonists all cause headache, flushing, dizziness and peripheral edema. Verapamil and Diltiazem have negative inotropic and chronotropic effects and adversely affect conduction through the AV node. Great caution should be exercised when using these agents concurrently with beta blockers, because severe heart block can result.

**ACE INHIBITORS**

- Captopril
- Enalapril
- Lisinopril
- Benazepril
- Fosinopril
- Ramipril

The angiotensin converting enzyme inhibitors prevent angiotensin II formation and related vasoconstriction, thus reducing total peripheral resistance. They also decrease the secretion of aldosterone.

The ACE inhibitors may improve renal perfusion, particularly in diabetics, and may help prevent the development of diabetic nephropathy and proteinuria. They have no adverse effects on lipid profiles or glucose tolerance. They decrease left ventricular hypertrophy with chronic use, and have proven effective in reducing mortality due to progressive congestive heart failure.
These agents are less effective in older and black patients who typically have low renin, salt sensitive hypertension. Adding a diuretic in this setting will restore the antihypertensive effects of ACE inhibitors.

**Adverse effects:** ACE inhibitors are relatively well tolerated, but can cause headaches and dizziness. Cough has been reported in up to 25% of patients taking these agents. Because ACE inhibitors reduce aldosterone secretion they can cause hyperkalemia, particularly in patients with renal insufficiency, diabetes mellitus, or when combined with potassium-sparing diuretics.

ACE inhibitors can cause profound hypotension in patients who are volume-depleted with high plasma levels of renin. They can also cause reversible renal failure in patients with bilateral renal artery stenosis and should not be used in this setting.

**ANGIOTENSIN RECEPTOR ANTAGONISTS.**

- Losartan (Cozaar)
- Valsartan (Diovan)
- Irbesartan (Avapro)

These new agents block binding of angiotensin II to type 1 angiotensin II receptors in blood vessels and other tissues. These agents offer an advantage over the angiotensin-converting enzyme (ACE) inhibitors, in that they block the angiotensin receptors directly; the ACE inhibitors merely block the conversion of angiotensin I to angiotensin II. Angiotensin II, a vasoconstrictor and simulator of aldosterone secretion, is formed by other enzymes that are not blocked by ACE inhibitors. ACE inhibitors also block the breakdown of bradykinin. Thus, angiotensin receptor antagonists inhibit the renin-angiotensin system more completely and more selectively than ACE inhibitors.

The angiotensin receptor antagonists are less effective in black patients. They tend to raise serum potassium levels and lower serum uric acid levels. There is no evidence that these agents prolong survival in patients with heart failure. Adding a thiazide diuretic may increase the antihypertensive effect.

**Adverse effects:** Angiotensin receptor antagonists are well tolerated and have few side effects. High doses may cause dizziness. Cough, which has been a problem with the ACE inhibitors, is not commonly seen with the angiotensin receptor antagonists, likely due to the fact that these agents do not block the breakdown of bradykinin. Angioedema is a rare complication.

**SPECIAL CONSIDERATIONS**

Blood pressure has numerous hemodynamic determinants, including cardiac output, total peripheral resistance and blood volume. Age, race, obesity and other factors can affect these hemodynamic determinants in different ways. Choosing appropriate antihypertensive therapy based upon an understanding of the hemodynamic effects may lead to a more rational approach to the treatment of hypertension. Table II lists
hemodynamic mechanisms for various groups of patients, and identifies useful drugs in the treatment of hypertension in these groups of patients.

**INTERACTION BETWEEN NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) AND ANTIHYPERTENSIVE AGENTS**

Most NSAIDs produce mild elevations in blood pressure, a 10mm Hg increase in MAP on the average. This blood pressure elevation is most pronounced in patients with low renin hypertension, particularly blacks and elderly patients. The putative mechanism is the ability of NSAIDs to block the cyclo-oxygenase pathway of arachidonic acid metabolism, which blocks the formation of prostaglandins. This results in sodium and water retention, and a deficiency of renal hypotensive factors.

The antihypertensive drug classes most affected by NSAIDs include the thiazide diuretics, beta blockers, alpha blockers and ACE inhibitors. **No interaction has been shown between NSAIDs and calcium antagonists or centrally acting alpha agonists.**
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Onset of Action</th>
<th>Duration of Action</th>
<th>Mechanism of Action</th>
<th>Effect on CBF</th>
<th>Side Effects</th>
<th>Special Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroprusside</td>
<td>Continuous IV infusion begin at 10 mcg/min increase incrementally</td>
<td>Immediate</td>
<td>3-5 minutes</td>
<td>Arteriolar and venous dilator</td>
<td>↑ at low doses and ↓ at high doses</td>
<td>Thiocyanate toxicity (weakness, mental status changes)</td>
<td>Solution is photosensitive, constant monitoring required</td>
</tr>
<tr>
<td>Labetalol</td>
<td>20mg IV bolus followed by incremental 20-80 mg boluses q 10 minutes or constant IV infusion 0.5-4 mg/min</td>
<td>5-10 minutes</td>
<td>Up to 24 hours</td>
<td>α and β adrenergic receptor blocker</td>
<td>?</td>
<td>Nausea, rhinorrhea, PVC's</td>
<td>Oral formulation effective for long term therapy</td>
</tr>
<tr>
<td>Diazoxide</td>
<td>50-100mg bolus IV q 10 minutes</td>
<td>Minutes</td>
<td>12 or more hours</td>
<td>Arteriolar vasodilator</td>
<td>None</td>
<td>Hyperglycemia hyperuricemia reflex tachycardia salt retention</td>
<td>May cause hypotension</td>
</tr>
<tr>
<td>Trimethaphan</td>
<td>Continuous IV infusion-begain at 200 mcg/min and increase incrementally</td>
<td>Minutes</td>
<td>15 minutes</td>
<td>Ganglionic blocking agent</td>
<td>↑</td>
<td>Constipation, ileus, urinary retention, mydriasis, cycloplegia</td>
<td>Rapid tachyphylaxis constant monitoring required, agent of choice for hypertension associated with aortic dissection</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>10 mg po or sl, repeat in 30 minutes prn</td>
<td>30 min po 5-10 min sl</td>
<td>4-6 hours</td>
<td>Calcium entry blocker</td>
<td>↑</td>
<td>Flushing, headache, fluid retention, tachycardia</td>
<td>Puncture capsule if given sl</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>10 mg IV bolus followed by incremental 10-40 mg boluses q 10-20 minutes</td>
<td>10-20 minutes</td>
<td>2-6 hours</td>
<td>Arterial vasodilator</td>
<td>↑</td>
<td>Tachycardia, increased cardiac work</td>
<td>Plasma renin may rise. β blockers and diuretics may be necessary to counteract side effects</td>
</tr>
<tr>
<td>Clonidine</td>
<td>0.1 mg-0.2 mg po followed by 0.05-0.1 mg q one hour up to 0.8 mg</td>
<td>30-60 minutes</td>
<td>8-12 hours</td>
<td>Central α agonist</td>
<td>?</td>
<td>sedation, bradycardia, dry mouth, dizziness</td>
<td></td>
</tr>
<tr>
<td>Nicardipine</td>
<td>Continuous IV infusion begin at 5 mg/hr and increase incrementally</td>
<td>Minutes</td>
<td>8-24 hours</td>
<td>Calcium entry blocker</td>
<td>↑</td>
<td>HA, flushing, local phlebitis, tachycardia</td>
<td></td>
</tr>
</tbody>
</table>
Table 2
Special Considerations for Choosing Antihypertensive Therapy

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Pathophysiologic Mechanism of HTN</th>
<th>Appropriate Drugs</th>
<th>Less Effective Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black Patients</td>
<td>Low renin, ↑ plasma volume, salt sensitive, ↓ CO, ↑ TPR</td>
<td>Ca** antagonists, Diuretics</td>
<td>β Blockers ACE Inhibitors</td>
</tr>
<tr>
<td>Obese Patients</td>
<td>Low renin, ↑ plasma volume, salt sensitive, ↑ CO, ↓ TPR, ↑ SNS activity</td>
<td>Diuretics</td>
<td>β Blockers Ca** antagonists</td>
</tr>
<tr>
<td>Young Patients</td>
<td>↑ CO</td>
<td>β Blockers ACE Inhibitors Ca** antagonists</td>
<td>Diuretics</td>
</tr>
<tr>
<td>Older Patients</td>
<td>Low renin, ↓ plasma volume, ↓ CO, ↑ TPR</td>
<td>Ca** antagonists Diuretics</td>
<td>β Blockers ACE Inhibitors</td>
</tr>
</tbody>
</table>

CO = Cardiac Output; TPR = Total Peripheral Resistance; SNS = Sympathetic Nervous System
BIBLIOGRAPHY


