Neurological Disease

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1. Coma
    a. Coma is defined as "a state of extreme unresponsiveness, in which an individual exhibits no voluntary movement or behavior" (1).
        i. Alternatively, coma is a state of *unarousable unresponsiveness* in which the patient lies with the eye closed and has no awareness of self and surroundings (2).
    b. Coma lies on a spectrum with other alterations in consciousness – from confusion to delirium to obtundation to stupor to coma and, ultimately, brain death (2).
    c. To be clearly distinguished from syncope, concussion, or other states of transient unconsciousness coma must persist for at least one hour (2).
    d. There are 2 important characteristics of the conscious state (3)
        i. The level of consciousness – "arousal or wakefulness"
            1. Regulated by physiological functioning and consists of more primitive responsiveness to the world such as predictable involuntary reflex responses to stimuli.
            2. Arousal is maintained by the reticular activating system (RAS) - a network of structures (including the brainstem, the medulla, and the thalamus)
        ii. The content of consciousness – "awareness"
            1. Regulated by cortical areas within the cerebral hemispheres,
    e. There are two main causes for coma:
        i. Bihemispheric diffuse cortical or white matter damage or
        ii. Brainstem lesions bilaterally affecting the subcortical reticular activating systems.
    f. A huge number of conditions can result in coma. One way to categorize these conditions is to divide them into the anatomic and the metabolic causes of coma.
        i. Anatomic causes of coma are those conditions that disrupt the normal physical architecture and anatomy, either at the level of the cerebral cortex or the brainstem
        ii. Metabolic causes of coma consist of those conditions that change the chemical environment of the brain.
        iii. The main causes are divided into:
            1. Metabolic – Electrolyte abnormalities (hypo- or hyper-natremia, hypo- or hyper-calcemia), hypoglycemia, DKA, nonketotic hyperosmolar coma, hypothyroidism, uremia, hepatic encephalopathy, hypo- or hyper-thermia, hypercarbia, hypoxia/anoxia
            2. Intoxications – Barbiturates, opiates, alcohol, benzodiazepines, other drugs of abuse, salicylates
            3. Toxins – Carbon monoxide
            4. Infections, both CNS and non-CNS – Meningitis, cerebritis, encephalitis, sepsis
            5. Seizures – nonconvulsive status epilepticus, post-ictal states
            6. Intracranial processes
                a. Cortical - TBI, SAH, cerebral edema
                b. Brain stem – high-grade SAH, severe TBI, posterior fossa hemorrhage
                c. Herniation syndromes from any of the above or local effects from tumors and other mass lesions
    g. Diagnosis of unexplained coma is clinical, but the work up for etiology can be complex and should include the following as clinically indicated:
        i. History (ie drug ingestion, trauma, anoxia)
        ii. Physical examination to evaluate brain stem involvement (pupillary response, etc.) and possible etiologies such as trauma
        iii. Standard laboratory testing to evaluate electrolyte abnormalities
        iv. Toxicology screen
        v. ABG to evaluate for hypoxia or hypercarbia and for metabolic acidosis that may be associated with certain ingestions
        vi. Head CT to look for intracranial hemorrhage, cerebral edema, etc
        vii. EEG to R/O seizures
        viii. Lumbar puncture
        ix. MRI can be considered when other tests fail to demonstrate cause
    h. Treatment of coma is largely supportive.

i. Initial resuscitation will frequently include intubation either due to a failure to protect the airway or ventilator failure.
ii. Administration of dextrose and naloxone (0.2-0.4 mg) for patients with unclear etiology and acute development of coma
iii. Treatment of coma obviously is dictated by the underlying cause

2. Brain Death
   a. In the setting of very severe neurological injury, brain death often occurs following coma.
      i. The cycle of neuronal injury leading to neuronal swelling leading to increased intracranial pressure leading to decreased intracranial blood flow causing further neuronal injury leads to a situation where the intracranial pressure exceeds the systemic blood pressure resulting in brain death.
   b. The leading causes of brain death in adults are traumatic brain injury and subarachnoid hemorrhage (4). Hypoxic-ischemic insults and fulminant hepatic failure are also common causes.
   c. Brain death is defined legally by the Uniform Determination of Death Act (UDDA) from The President's Commission report on "guidelines for the determination of death"http://www.neurology.org/content/74/23/1911.full - ref-1 (5).

      i. "An individual who has sustained either (6)
         1. Irreversible cessation of circulatory and respiratory functions, or
         2. Irreversible cessation of all functions of the entire brain, including the brain stem, is dead.
         3. A determination of death must be made with accepted medical standards."
   d. The American Academy of Neurology (AAN) published a practice parameter in 1995 to delineate the medical standards for the determination of brain death (7).
      i. There are several important principles
         1. Brain death is a clinical diagnosis
         2. To determine brain death, there must be *absence of function* of the entire brain, including the brain stem and *irreversibility*.
         3. 3 clinical findings necessary to confirm irreversible cessation of all functions of the entire brain, including the brain stem: coma, absence of brainstem reflexes, and apnea.
      ii. The following is taken directly from those practice parameters (7) as well as a recent update to the 1995 practice parameters which clarified a few salient points about brain death determination (8):
         1. Prerequisites. Brain death is the absence of clinical brain function when the proximate cause is known and demonstrably irreversible.
            i. Establish irreversible and proximate cause of coma.
            ii. Clinical or neuroimaging evidence of an acute CNS catastrophe that is compatible with the clinical diagnosis of brain death
            iii. Exclusion of complicating medical conditions that may confound clinical assessment (no severe electrolyte, acid-base, or endocrine disturbance).
            iv. No drug intoxication or poisoning
            v. Normal or near-normal temperature (>36°C).
            vi. Normotension - Neurologic examination is usually reliable with a systolic blood pressure ≥100 mm Hg
         b. The three cardinal findings in brain death are coma or unresponsiveness, absence of brainstem reflexes, and apnea.
            i. Coma or unresponsiveness--no cerebral motor response to pain in all extremities or face
            ii. Absence of brainstem reflexes including absence of pupillary response, corneal reflex, ocular-vestibular or oculo-cephalic reflex, pharyngeal or tracheal reflexes
            iii. Apnea testing - Absence of a breathing drive.
               1. Absence of a breathing drive is tested with a CO_2 challenge.
               2. Documentation of an increase in $Paco_2$ above normal levels (> 60 mmHg or rise of > 20 mm Hg typically)
               3. Prerequisites: 1) normotension, 2) normothermia, 3) euvolemia, 4) eucapnia ($Paco_2$ 35–45 mm Hg), 5) absence of hypoxia, and 6) no prior evidence of CO_2 retention (i.e., chronic obstructive pulmonary disease, severe obesity).

4. If respiratory movements are absent and arterial Pco_2 is ≥60 mm Hg (or 20 mm Hg increase in arterial Pco_2 over a baseline normal arterial Pco_2), the apnea test result is positive (i.e., supports the clinical diagnosis of brain death).

2. Pitfalls in the diagnosis of brain death
    a. The following conditions may interfere with the clinical diagnosis of brain death, so that the diagnosis cannot be made with certainty on clinical grounds alone. In these cases confirmatory tests are recommended.
        i. Severe facial trauma
        ii. Preexisting pupillary abnormalities
        iii. Toxic levels of any sedative drugs, aminoglycosides, tricyclic antidepressants, anticholinergics, antiepileptic drugs, chemotherapeutic agents, or neuromuscular blocking agents
        iv. Sleep apnea or severe pulmonary disease resulting in chronic retention of CO_2
3. Clinical observations compatible with the diagnosis of brain death
    a. These manifestations are occasionally seen and should not be misinterpreted as evidence for brainstem function.
        i. Spontaneous movements of limbs other than pathologic flexion or extension response
        ii. Respiratory-like movements (shoulder elevation and adduction, back arching, intercostal expansion without significant tidal volumes)
        iii. Sweating, blushing, tachycardia
        iv. Normal blood pressure without pharmacologic support or sudden increases in blood pressure
        v. Absence of diabetes insipidus
        vi. Deep tendon reflexes; superficial abdominal reflexes; triple flexion response
        vii. Babinski reflex
4. Confirmatory laboratory tests
    a. In cases where a clinical examination cannot be reliable performed, confirmatory tests are desirable (listed from most sensitive to least sensitive):
        i. Conventional angiography
        ii. Electroencephalography
        iii. Transcranial Doppler ultrasonography
        iv. Technetium-99m hexamethylpropyleneamineoxime brain scan
        v. Somatosensory evoked potentials
5. Documentation
    a. The time of brain death is documented in the medical records.
    b. Time of death is the time the arterial Pco_2 reached the target value or when the ancillary test has been officially interpreted.
    c. Federal and state law requires the physician to contact an organ procurement organization following determination of brain death.

e. Policies surrounding the determination of brain death are typically State or Institution-specific.
    i. Some policies require the clinical examination to be performed by neurologists, neurosurgeons, and/or intensivist.
    ii. Some require an apnea test with each clinical examination, while some only require one.
    iii. If a certain period of time has passed since the onset of the brain insult to exclude the possibility of recovery (usually several hours), 1 neurologic examination should be sufficient to pronounce brain death.
        1. However, some US state statutes require 2 examinations, typically separated by 6 hours for adults.
        2. Some require that 2 different physicians perform the examinations.
    iv. Most policies have different criteria for pediatric patients often requiring extended periods between clinical examinations or require confirmatory testing.
f. Pathophysiological changes at the time of brain death
    i. Cardiovascular effects
        1. Progression of brain death causes rostral to caudal ischemia
        2. Two phases in the process of brain death
            a. As the medulla becomes ischemic, there is an initial sympathetic surge

b. Subsequent spinal cord ischemia results in deactivation of sympathetic nervous system
i. Causes low serum catecholamine levels and loss of cardiac stimulation
3. Brain ischemia induces myocyte necrosis
4. Ultimately results in cardiac dysfunction and vasodilatation
a. Hypotension present in 80% of brain dead donors and is sustained in 20% (9).
b. Compounded by hypovolemia and endocrine dysfunction
5. Arrhythmias are also common

ii. Pulmonary effects
1. With the initial catecholamine storm, at moment of peak vaso-constriction, left-sided heart pressures exceed pulmonary pressures which temporarily halts pulmonary blood flow
a. Severely injures lung tissue
b. Causes interstitial edema and alveolar hemorrhage (neurogenic pulmonary edema)
2. Hypoxia compounded by V/Q mismatch, atelectasis, pneumonia, aspiration, pulmonary contusion, pneumothoraces, etc.

iii. Endocrine abnormalities
1. Lead to rapid disturbances of the hypothalamic-pituitary axis
a. Vasopressin is decreased
b. Suppression of thyroid hormone release
2. Reduced insulin release due to catecholamine or inotrope infusion causing hyperglycemia which is compounded by:
a. Large volume of dextrose solutions to treat DI
b. Stress response – increases in counterregulatory hormones
c. Changes in carbohydrate metabolism
d. Peripheral resistance to insulin
3. Autonomic surge lead to decreased levels of fT3, cortisol and insulin (10,11)
a. Converts aerobic into anaerobic metabolism
b. Depletes myocardial oxygen stores
c. Causes lactate accumulation and organ function deterioration

iv. Hypothermia
1. Caused by hypothalamic failure
2. Causes poikilothermia
3. Heat production is also decreased due to decrease in metabolic activity
4. Increased heat loss due to vasodilatation
5. Contributes to hemodynamic instability
a. Causes myocardial depression
b. Causes vasodilatation
c. Coagulopathy
d. Left shift of the oxyhemoglobin dissociation curve
e. Cold-induced diuresis
f. At very low temperatures, refractory dysrhythmias develop

v. Coagulopathy
1. Results from continuous release of large amounts of tissue thromboplastin and plasminogen from ischemic and necrotic brain
2. Compounded by hypothermia and ongoing hemorrhage and fluid resuscitation worsening the dilutional coagulopathy

vi. Incidence of pathophysiological changes after brain stem death (12)
1. Hypotension - 80%
2. DI - 65%
3. DIC - 30%
4. Cardiac arrhythmias - 30%
5. Pulmonary edema - 20%
6. Acidosis – 10%

3. CNS Infections
a. Bacterial meningitis
i. Approximately 80% of bacterial meningitis cases are caused by the *Streptococcus pneumonia* and *Neisseria meningitides*, with Neisseria predominating in adults under the age of 45 (13).
1. E coli and Staph species are frequently causative in hospitalized patients

ii. Over the past few decades, Pneumococcal and Haemophilus vaccinations have modified the incidence of bacterial meningitis significantly.
iii. Usually caused by encapsulated organisms in immonuocompetant hosts, organisms typically enter the CNS via the bloodstream.
    1. Direct inoculation of the CNS can occur in the setting of trauma, surgery, monitoring devices, or seeding through parameningeal structures
iv. The clinical presentation of patients with meningitis include rapid onset of fever, headache, photophobia, nuchal rigidity, lethargy, malaise, altered mentation, seizure, or vomiting (14,15)
    1. The "classic triad" of fever, neck stiffness, and altered mental status may be present in up to 2/3rds of patients, with fever being the most common (16).
    2. Immunocompromised may mount none of the classic symptoms and therefore meningitis should be in the differential diagnosis of any immunocompromised patient with altered mental status.
    3. Physical examination findings classically include:
        a. Focal deficits and increased intracranial pressure (ICP)
        b. Nuchal rigidity
        c. Meningeal irritation (Brudzinski's and Kernig's sign)
        d. Purpura or petechia of the skin in meningococcemia
    4. Diagnosis with lumbar puncture (LP) can make the diagnosis and speciate organisms to guide antibiotic choice.
        a. LP can generally be safely performed without first obtaining a CT, although this is controversial. If concern about increased ICP or mass lesion exists, empiric antibiotics should be administered immediately so that head CT can be obtained prior to LP and not delay antibiotic administration.
        b. Four tubes of CSF should be obtained and sent for cell count with differential, protein, glucose, Gram stain and culture.
        c. CSF analysis in bacterial meningitis includes classically:
            i. High opening pressure
            ii. High WBCs with a predominance of PMNs
            iii. Low glucose (<40)
            iv. High protein
v. Treatment is rapid administration of a bactericidal antibiotic with good CNS penetration and the use of anti-inflammatory agents
    1. Initial antibiotic choice should have broad-spectrum coverage of the most common pathogens
    2. Ceftriaxone or cefotaxime, and vancomycin is often recommended as first line therapy
    3. In the very young, very old, and immunocompromised patients, empiric coverage for Listeria should be given with ampicillin
    4. Delay in administration of antibiotics has been associated with markedly worse clinical outcomes (17)
    5. Current recommendations in adults include the use of dexamethasone to prevent the sequelae of bacterial lysis,
        a. The initial dose should be given just before or at the same time as antibiotics and continue for 4 days (18)
vi. Mortality rates range from 20-25% with higher rates in the elderly and those with major comorbidities.
    1. Neurological sequelae persist in 20-30% of survivors with pneumococcal meningitis (14)

b. Viral Meningitis
    i. Viral meningitis is important because although typically self-limited, early or partially treated bacterial meningitis can mimic viral meningitis.
    ii. The most common causative viruses are enteroviruses, arbovirus, herpes simplex, cytomegalovirus, adenovirus, and HIV (19).
    iii. The clinical course of most of types of viral meningitis is benign and self-limited with the exception of HSV.
c. Viral encephalitis
    i. Causative agents include arboviruses, HSV, herpes zoster virus (HZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), and rabies.
        1. During epidemics, the arboviruses can account for 50%
        2. Epidemics are often seasonal from June to September
        3. In immunocompromised host, CMV and HZV are frequently seen
    ii. Clinical manifestations include:

1. Rapid development of fever
2. Headache
3. Confusion
4. Localizing neurological signs
5. New-onset seizures
6. Meningeal irritation causing headache, photophobia, nuchal rigidity

iii. Diagnostic evaluation includes ruling out bacterial meningitis and subarachnoid hemorrhage
1. LP often appears "aseptic"
a. PCR and specific encephalitis serologies should be done on CSF to identify specific causative agents
2. CT and MRI may demonstrated abnormalities
3. EEG is helpful for certain diseases such as HSV encephalitis
4. Open brain biopsies may be indicated for selected patients with atypical presentations, clinical deterioration despite treatment, or nondiagnostic PCR results

iv. Treatment is largely supportive
1. Empiric treatment with acyclovir while awaiting PCR results
2. HSV is treated with acyclovir (10 mg/kg q8h x 10-14 days). Must be renal-dose adjusted
3. Ganciclovir +/- foscarnet for CMV encephalitis

v. Prognosis is dependent on the causative organism with excellent prognosis for EBV and Colorado tick fever, for example, and over 50-70% mortality for Eastern Equine Virus (EEE) and near 100% mortality for rabies.

d. Brain abscess
i. Traditional causes of brain abscess include otitis media and sinusitis.
1. With improvements in treatment for these common conditions, tooth abscesses, endocarditis, and pulmonary infections are becoming more common causes
2. Multiple abscesses usually suggest hematogenous spread (20)

ii. Classic symptoms include headache, focal neurological deficit, and change in mental status
1. Also may have nonspecific indolent courses
2. Papilledema may occur which is rare with other CNS diseases
3. Focal symptoms depend on location of lesion

iii. Diagnosis is typically made with CT
1. CT with IV contrast demonstrates hypodense lesions with contrast-enhancing rings
2. MRI is highly sensitive

iv. Treatment (21)
1. Antibiotics – empiric coverage with Nafcillin or a third-generation cephalosporin and Flagyl
a. In immunosuppressed patients, antifungals, anti-TB, antiparasitic, and atypical bacteria should also be instituted
2. Surgical drainage for large (>3 cm), superficial, or cerebellar abscesses.
3. Surgical drainage is also indicated for patients who are immunosuppressed, in coma, or have rapid clinical deterioration.
4. Medical management, at least initially, is advocated for patients with brainstem, multiple, or deep-seated lesions <3 cm

4. Cerebral edema
a. There are numerous causes of cerebral edema or elevated intracranial pressure
b. Some of the most common are:
i. Traumatic brain injury (TBI)
ii. Ischemic strokes
iii. Non traumatic intracranial hemorrhage
iv. Infections such as meningitis or encephalitis
v. Tumors
vi. Fulminant hepatic failure
vii. Hypoxia/anoxia

c. Placement of intracranial monitoring devices to monitor intracranial pressure (ICP) and trend therapy is indicated for the following conditions
i. TBI (22)
1. "Salvageable patients" with a GCS 3-8 after resuscitation and an abnormal CT
2. Severe TBI with a normal CT scan with 2 or more of the following
a. Age >40

b. Unilateral or bilateral posturing
c. SBP <90

ii. Non-traumatic intracranial hemorrhage (23)
1. Lobar or gangionic hemorrhage with motor GCS ≤4 or midline shift on CT

iii. Ischemic stroke (21)
1. MCA infarct - Edema with midline shift on CT
2. Cerebrallar infarct - Acute hydrocephalus

iv. HSV encephalitis (21)
1. Motor GCS ≤4
2. Necrotic mass

v. Aneurysmal subarachnoid hemorrhage (SAH) (21)
1. Acute hydrocephalus

d. Key concepts of management of cerebral edema
i. Monroe-Kellie Doctrine
1. The intracranial contents are brain tissue, blood, and cerebrospinal fluid (CSF)
2. The total volume of the contents of the intracranial vault must remain constant because the skull is rigid and incompressible
3. If there is an increase in volume in any of the 3 components, it must occur at the expense of the other 2 or herniation will occur
4. An easy way to remember what treatments are helpful in the management of cerebral edema is to think of which of the 3 compartments (brain tissue, blood, or CSF) a therapy targets

ii. Cerebral perfusion pressure
1. Management of cerebral edema is not just about management of ICP, but also cerebral perfusion pressure (CPP)
a. CPP = MAP – ICP
2. CPP should be maintained to maximize perfusion but minimize the risks of systemic hypertension
3. The optimal CPP is a matter of some debate, but clearly CPP <50 should be avoided (22)
4. Aggressive attempts to raise CPP >70 with fluids and vasoactives have been associated with an increased risk for ARDS (23)
5. The optimal CPP for patients with TBI is thought to be between 50 – 70 mm Hg

iii. Autoregulation
1. The intact cerebrovascular system normally maintains cerebral blood flow (CBF) at CPP from 50 to 150 mm Hg or MAP of 60 to 160 mm Hg via autoregulation via reflexive vasodilatation and vasoconstriction in response to alterations in cerebral perfusion.
2. Similarly, in the normal brain, there is pCO2 responsiveness (and to a much lesser degree pO2 reactivity) whereby elevated pCO2 causes vasodilatation and lower pCO2 induces vasoconstriction.
3. In the setting of intracranial insults, autoregulation may be lost and responses to alterations in systemic pressure (or alterations in PCO2) may be markedly abnormal in the injured brain
a. Loss of autoregulation causes a linear increase between CBF and CPP

e. Management of cerebral edema
i. In TBI, outcomes have been shown to be better when ICP and CPP are managed via an algorithmic evidence-based approach based on the Brain Trauma Foundation Guidelines (24).
ii. As a general rule, ICP should be kept lower than 20 mm Hg (22)
iii. General measures for all patients at risk of cerebral edema
1. Maintain adequate oxygenation and ventilation
2. Mechanical ventilation for all patients who are at risk of loss of ability to protect the airway
3. Prevent hypotension. Keep SBP >90 mm Hg (22)
4. Maintain normothermia as fever causes an increase in CBF via an increase cerebral metabolic rate
5. Semi-upright head position at 30◦
6. Adequate analgesia and sedation to minimize agitation and pain
7. Maintain euvolemia
8. Provide seizure prophylaxis when appropriate (essentially all CT verified TBI except isolated SAH or IVH)

9. Avoid noxious stimuli

iv. Management of elevated ICP targets the "3 compartments"
    1. CSF compartment
        a. Drainage of CSF via intraventricular catheters (IVC) or external ventricular drains (EVD)
        b. Lumbar drains should be avoided except in rare cases due to the risk of induced herniation syndromes
    2. Blood compartment
        a. Sedation
            i. Adequate sedation should be provided to not only prevent systemic and intracranial responses to stimuli, but also to lower CBF via decreasing cerebral metabolic rate
            ii. Sedatives should preferably be short acting
            iii. Propofol is recommending for acute ICP management, but has not been shown to improve outcome (22)
            iv. Benzodiazepines are frequently used in many institutions
            v. Barbiturates
                1. Are effective therapy in managing severe cerebral edema
                2. Act by markedly reducing CBF via reduction of cerebral metabolic rate
                3. Should not be used prophylactically
                4. Are indicated for management of intracranial hypertension that is "refractory to maximum standard medical and surgical treatment" (22).
                5. Hemodynamic stability is essential prior to use due to the profound systemic effects of barbiturate administration
                6. Therapy should be targeted to burst suppression on EEG
        b. Hyperventilation (22)
            i. Controversial because although highly effective at lowering ICP due reflexive vasoconstriction and a reduction in CBF, this reduction in CBF may cause ischemia, especially within the first 24 hours after injury.
            ii. Prophylactic hyperventilation $pCO2 < 25$ mm Hg is not recommended
            iii. Hyperventilation should be avoided in the first 24 hours after injury
            iv. Hyperventilation should be used as a temporizing measure to reduce ICP
            v. Low-normal pCO2 (35-38 mm Hg) should be targeted
            vi. Hypercarbia should be avoided to minimize the risk of vasodilatation and hyperemia
            vii. If therapeutic hyperventilation is going to be used, ancillary measures of cerebral perfusion (PbrO2 or SjO2) should be used
    3. Brain tissue
        a. Surgical evacuation
            i. As a general rule, mass lesions causing midline shift and/or significant local compressive effects should be surgically evacuated in a patient who is neurologically compromised
            ii. For intraparenchymal lesions, location of a lesion may determine whether surgical evacuation is appropriate
        b. Osmolar therapies
            i. Both mannitol and hypertonic saline are effective at lowering intracranial pressure by decreasing brain tissue water content
            ii. Mannitol
                1. Immediate plasma expanding effect that decreases Hct, decreases blood viscosity, increases CBF, increases cerebral oxygen delivery
                2. Autoregulatory vasoconstriction then may decrease CBV and ICP
                3. "Brain shrinkage" effect from extraction of water from the extracellular space to the intravascular compartment
                    a. May take up to 30 minutes
                4. Rebound phenomenon can occur

a. May "open" the BBB leading to accumulation in the brain and a reverse osmotic shift
b. Leads to "paradoxical" elevation of ICP
5. Most marked after repeated boluses or continuous infusion
6. Typical doses is 0.25 -1.0 gm/kg
7. Cares should be taken to avoid systemic hypotension due to osmotic effects and risk of hypovolemia
8. Should be used only in patients without ICP monitors with evidence of impending herniation or significant neurological deterioration (22)

iii. Hypertonic saline
1. Similar to mannitol, HTS reduces ICP primarily through an immediate hemodynamic effect and a delayed osmotic effect.
2. Bolus administration expands plasma volume and causes hemodilution and an increase in CO and MAP
3. Compensatory vasoconstriction may then result in reduced CBV and ICP
4. Like mannitol, HTS creates a driving force for extraction of water from the cerebral extracellular space into the intravascular compartment which reduces brain water content
5. HTS is less likely to cross the BBB than mannitol and therefore less likely to cause rebound cerebral edema
6. Other potentially beneficial effects of HTS include
a. improvements in pulmonary gas exchange
b. decreased leucocyte adhesion
c. modulation of the inflammatory response
d. widespread depolarization→ $\downarrow Na^+$ and $\uparrow Ca^+$ allowing glutamate to leak out resulting in further depolarization that can end in cell death by hyper stimulation
i. HTS may interrupt this feedback loop and help restore normal glutamate levels
7. Comes in a variety of concentrations (3%, 7.5%, 23.4% are the most frequently used)
8. Both bolus dosing and continuous infusions are effective at lowering ICP

v. Other therapies
1. Decompressive craniectomy
a. Commonly used in the management of TBI and increasing in the management of severe cerebral edema in patients with territorial infarction, decompressive craniectomy allows for the intracranial contents to herniate out of a surgical defect and relieve intracranial pressure
b. Indications are typically institution-specific, but generally this procedure is reserved for patients who have intracranial hypertension refractory to conventional medical therapy
c. The recently published DECRA trial demonstrated more unfavorable neurological outcomes in patients with severe TBI treated with early bifrontotemporoparietal decompressive craniectomy (25)
i. Differences in baseline criteria between the 2 groups in this study as well as concerns about patient selection and timing of decompression in the study protocol has resulted in failure of many trauma centers to abandon decompressive craniectomy.
ii. Other studies are currently ongoing
2. Therapeutic hypothermia
a. Therapeutic hypothermia has been extensively investigated as a possible neuroprotective strategy for the prevention or reduction of brain injury due to several causes.
b. The exact mechanism by which therapeutic hypothermia reduces the deleterious effects of brain injury is not entirely known

c. Possible mechanisms include (26)
    i. Reductions in cerebral metabolic rate
    ii. Effects on the "opening of the blood-brain barrier".
    iii. Inhibition of the inflammatory response and release of glutamate, nitric oxide, and free radicals
d. Currently prophylactic hypothermia as a therapeutic adjunct to management of intracranial hypertension is not recommended to reduce mortality following TBI (24) and therapeutic hypothermia is currently not considered standard of care
e. Numerous studies are ongoing, however

5. Seizures
    a. Complicate up to 3% of admissions to the ICU
    b. Status epilepticus is defined as "more than 30 minutes of continuous seizure activity or two or more sequential seizures without full recovery of consciousness between seizures" (27). Classified as
        i. Generalized
            1. Convulsive (tonic-clonic, myoclonic, etc.) (GCSE)
            2. Nonconvulsive (absence, atypical, atonic) (NCSE)
        ii. Partial
            1. Simple
            2. Complex
    c. Convulsive seizures can lead to significant metabolic effects including rhabdomyolysis, acute respiratory failure, lactic acidosis, hyperglycemia, renal failure, etc.
    d. NCSE can cause significant neuronal injury if left untreated
    e. Diagnosis
        i. Pitfalls
            1. Many common ICU condition scan mimic seizure activity (clonus, rigors, atonic movements, posturing, etc.)
            2. Seizures may occur in patients receiving neuromuscular blockade
            3. Partial treatment of GCSE may lead to nonconvulsive, but persistent, SE
        ii. The diagnosis of seizure is made with EEG
            1. Ideally the EEG should be performed without benzodiazepines or antiepileptics to better identify a seizure focus
            2. Can diagnose both partial seizure via identification of an abnormal seizure focus in the cortex and generalized seizures by identification of diffuse cortical activity or postictal slowing and/or depressed amplitude
            3. Mandatory in any patient with an abnormal mental status after a generalized convulsive seizure to R/O partial treatment and NCSE
        iii. Workup for cause of seizure should include
            1. CT and MRI
            2. Evaluation for metabolic disorders such as hypoglycemia or nonketotic hyperglycemia
            3. CSF analysis
    f. Treatment
        i. As a general rule, a single or few self-limited seizures in an ICU patient do not warrant specific treatment.
            1. Remove any potential offending agents, such as medications
            2. Look cause potential causes and treat underlying cause
        ii. The treatment of SE
            1. Airway protection
            2. IV hydration if fever or concern for rhabdomyolysis from extended convulsions
            3. Benzodiazepines – typically lorazepam 0.1 mg/kg
            4. Antiepileptic (AED) administration - no specifically preferred agent (phenytoin, fosphenytoin, levetiracetam)
            5. If SE persists, subspecialty consultation should usually be requested
            6. If SE is refractory and the following can be administered:
                a. High-dose benzodiazepines (midazolam or lorazepam)
                b. Propofol
                c. Phenobarbital

d. Ketamine

6. Ischemic Stroke
    a. The most common neurological cause of admission to the hospital in the US
    b. Account for about 80% of all strokes
    c. Source is typically thrombotic from carotid disease or embolic from cardiac sources
    d. For patients presenting to the hospital with acute signs and symptoms of stroke, clear evidence-based guidelines are available
        i. These guidelines are also applicable to hospitalized patients who develop acute signs and symptoms of stroke
        ii. The following evaluation and treatment recommendations are taken directly from the American Heart Association's Guidelines for the Early Management of Adults With Ischemic Stroke (28).
            1. Evaluation
                a. An organized protocol for the emergency evaluation of patients with suspected stroke is recommended
                b. The goal is to complete an evaluation and to decide treatment within 60 minutes of the patient's arrival in an ED.
                c. Designation of an acute stroke team that includes physicians, nurses, and laboratory/radiology personnel is encouraged.
            2. Initial Management
                a. Airway support and ventilatory assistance are recommended for patients who have decreased consciousness or who have bulbar dysfunction causing compromise of the airway
                b. Supplemental O2 should be administered to all patients with any degree of hypoxia
                c. Fever should be aggressively treated
                d. Hyperglycemia should be aggressively treated
                e. Hypertension
                    i. There is conflicting data on management of hypertension for ischemia stroke. A "cautious approach" to the treatment of arterial hypertension should be recommended
                    ii. If the patient is a candidate for rTPA, they should have their blood pressure lowered to systolic blood pressure is ≤185 mm Hg and diastolic blood pressure is ≤110 mm Hg. The blood pressure should be stabilized and maintained below 180/105 mm Hg for at least the first 24 hours after intravenous rtPA treatment.
                    iii. Patients with markedly elevated blood pressure may have their blood pressure lowered.
                        1. Suggested algorithm is to lower blood pressure by ~15% during the first 24 hours after onset of stroke.
                    iv. If the patient is not a candidate for thrombolytics, antihypertensive medications should be withheld unless the systolic blood pressure is >220 mm Hg or the diastolic blood pressure is >120 mm
                    v. Labetalol and Nicardipine are recommended agents based on expert consensus
            3. Imaging
                a. CT scanning of the brain is recommended before initiating any specific therapy to treat acute ischemic stroke
                b. Multimodal CT and MRI may provide additional information that will improve diagnosis of ischemic stroke
                c. Other than hemorrhage, there are no specific CT findings that should preclude treatment with rtPA within 3 hours of onset of stroke
                d. Emergency treatment of stroke should not be delayed in order to obtain multimodal imaging studies however
            4. Treatment
                a. Thrombolytics

i. Intravenous rtPA (0.9 mg/kg, maximum dose 90 mg) is recommended for selected patients present within 3 hours of onset of ischemic stroke. Blood pressure must be controlled prior to administration.
ii. Intra-arterial thrombolysis is an option for treatment of selected patients who have major stroke of <6 hours' duration due to occlusions of the MCA and who are not otherwise candidates for intravenous rtPA.
1. Intra-arterial thrombolysis is reasonable in patients who have contraindications to use of intravenous thrombolysis, such as recent surgery

b. Anticoagulation
i. Urgent anticoagulation is not recommended for patients with moderate to severe strokes because of an increased risk of serious intracranial hemorrhagic complications

c. Antiplatelet agents
i. Aspirin (initial dose is 325 mg) within 24 to 48 hours after stroke onset is recommended

d. Reperfusion devices (such as MERCI) are not recommended at this time

5. Management of complications
a. Patients with major infarctions affecting the cerebral hemisphere or cerebellum are at high risk for increased intracranial pressure.
b. Aggressive treatment of edema and close monitoring of the patient for signs of neurological worsening during the first days after stroke are recommended
c. Patients with acute hydrocephalus secondary to an ischemic stroke should be treated with placement of a ventricular drain
d. Decompressive surgical evacuation of a space-occupying cerebellar infarction is a potentially life-saving measure, and clinical recovery may be very good
e. Recurrent seizures after stroke should be treated
f. Osmotherapy, has been recommended for treatment of deteriorating patients with malignant brain edema after large cerebral infarction, with the recognition that these measures are unproven
g. Hyperventilation should be used as a short-term intervention.
h. Decompressive surgery for malignant edema of the cerebral hemisphere may be life-saving, but the impact of morbidity is unknown.
i. Both the age of the patient and the side of the infarction (dominant versus nondominant hemisphere) may affect decisions about surgery.
ii. Although the surgery may be recommended for treatment of seriously affected patients, the physician should advise the patient's family about the potential outcomes, including survival with severe disability
i. Corticosteroids are not recommended
j. Prophylactic administration of anticonvulsants is not indicated

iii. Evidence-based secondary prevention includes:
1. Control of hypertension
2. Control of diabetes
3. Lipid lowering agents and life-style modifications
4. Cessation of smoking
5. Weight reduction
6. Reduction in alcohol consumption
7. Treatment of carotid stenosis
a. For patients with recent TIA or ischemic stroke within the last 6 months and ipsilateral severe (70% to 99%) carotid artery stenosis, carotid end-arterectomy (CEA) is recommended.
b. For patients with recent TIA or ischemic stroke and ipsilateral moderate (50% to 69%) carotid stenosis, CEA is recommended, depending on patient-specific factors
c. When CEA is indicated for patients with TIA or stroke, surgery within 2 weeks is suggested

d. Among patients with symptomatic severe stenosis (>70%) in whom the stenosis is difficult to access surgically, severe medical conditions, or other circumstances exist such as radiation-induced stenosis, carotid artery stenting (CAS) may be considered

8. Prevention of cardioembolic stroke
    a. For patients with ischemic stroke or TIA with persistent or paroxysmal atrial fibrillation, anticoagulation with adjusted-dose warfarin (range, 2.0 to 3.0) is recommended
    b. For patients who are not candidates for anticoagulation, aspirin is recommended
9. Prevention of noncardioembolic stroke
    a. Antiplatelet agents rather than oral anticoagulation are recommended to reduce the risk of recurrent stroke and other cardiovascular events
        i. The combination of aspirin and extended-release dipyridamole, and clopidogrel are all acceptable options for initial therapy
    b. The combination of aspirin and extended-release dipyridamole is suggested instead of aspirin alone, but clopidogrel may be considered instead of aspirin
    c. The addition of aspirin to clopidogrel increases the risk of hemorrhage and is not routinely recommended

7. Hemorrhagic stroke – Intracranial hemorrhage (ICH)
    a. Is the least treatable and most morbid form of stroke
    b. Rapid diagnosis of patients with ICH is crucial because early deterioration is common and associated with a worse prognosis
    c. The following evaluation and treatment recommendations are taken directly from the American Heart Association's Guidelines for the Management of Spontaneous Intracerebral Hemorrhage (29).
    d. Initial Management
        i. Initial management of airway, oxygenation, etc. is the same as for any patient with a neurological emergency
        ii. Corticosteroids are not recommended
        iii. Normoglycemia should be maintained
        iv. Blood pressure control is first line therapy for these patients and based on Class C recommendations:
            1. If SBP is >200 mm Hg or MAP is >150 mm Hg, then consider aggressive reduction of BP with continuous intravenous infusion, with frequent BP monitoring every 5 min.
            2. If SBP is >180 mm Hg or MAP is >130 mm Hg and there is the possibility of elevated ICP, then consider monitoring ICP and reducing BP using intermittent or continuous intravenous medications while maintaining a cerebral perfusion pressure ≥60 mm Hg.
            3. If SBP is >180 mm Hg or MAP is >130 mm Hg and there is no evidence of elevated ICP, then consider a modest reduction of BP (eg, MAP of 110 mm Hg or target BP of 160/90 mm Hg) using intermittent or continuous intravenous medications to control BP and clinically reexamine the patient every 15 min
        v. Rapid correction of coagulaopathy is essential
            1. Patients with a severe coagulation factor deficiency or severe thrombocytopenia should receive appropriate factor replacement therapy or platelets
            2. Patients with ICH whose INR is elevated due to warfarin should have their warfarin withheld, receive therapy to replace vitamin K–dependent factors and correct the INR, and receive intravenous vitamin K
            3. PCCs have not shown improved outcome compared with FFP but may have fewer complications. They are reasonable alternatives to FFP
            4. rFVIIa is not recommended as a sole agent for oral anticoagulant reversal in ICH
    e. Imaging
        i. CT scan or MRI is essential in the management of these patients to differentiate ischemic from hemorrhagic stroke
        ii. CT angiography and contrast-enhanced CT may help to identify patients at risk for hematoma expansion
        iii. CT angiography, CT venography, contrast-enhanced CT, contrast-enhanced MRI, magnetic resonance angiography, and magnetic resonance venography can be useful to evaluate for underlying structural lesions, including vascular malformations and tumors

f. Treatment
    i. Intraventricular administration of recombinant tissue-type plasminogen activator is considered investigational, but appears to have a good safety profile
    ii. Surgical intervention
        1. Patients with cerebellar hemorrhage who are deteriorating neurologically or who have brainstem compression and/or hydrocephalus from ventricular obstruction should undergo surgical removal of the hemorrhage as soon as possible
        2. For patients with lobar clots >30 mL and within 1 cm of the surface, evacuation of supratentorial ICH by standard craniotomy should be considered
g. Management of complications
    i. Seizures
        1. Clinical seizures should be treated
        2. Continuous EEG monitoring is indicated in ICH patients with depressed mental status out of proportion to the degree of brain injury
        3. Patients with a change in mental status who are found to have seizures on EEG should be treated with antiepileptic drugs
        4. Prophylactic anticonvulsant medication should not be used
    ii. Cerebral edema
        1. Patients with a GCS score of ≤8, those with evidence of transtentorial herniation, or those with significant IVH or hydrocephalus might be considered for ICP monitoring and treatment.
        2. A CPP of 50 to 70 mm Hg may be reasonable depending on the status of cerebral autoregulation
        3. Ventricular drainage as treatment for hydrocephalus is reasonable in patients with decreased level of consciousness

8. Aneurysmal Subarachnoid Hemorrhage (aSAH)
    a. aSAH is a medical emergency that is frequently misdiagnosed.
    b. More common in women, blacks, and those with a family history.
    c. A high level of suspicion for aSAH should exist in patients with acute onset of severe headache, the so-called "worst headache of my life."
        i. Other symptoms may include localizing neurological findings which may indicate the location of aneurysm , neck stiffness, 3rd nerve palsy (PCOM aneurysm)and generalized tonic-clonic seizures
        ii. Neck stiffness
    d. Common grading systems include:
        i. World Federation of Neurological Surgeons (WFNS) which is based on GCS and motor deficit on admission
        ii. Hunt and Hess which is based on degree of neurological symptomatology (from asymptomatic or minimal headache to deep coma)
        iii. Fisher Grade based on CT findings
    e. The following evaluation and treatment recommendations are taken directly from the American Heart Association's Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage (30).
    f. Initial Management
        i. Initial management of airway, oxygenation, etc. is the same as for any patient with a neurological emergency
        ii. Fever should be aggressively managed
        iii. Hyponatremia should be avoided and treated
        iv. In patients with unsecured aneurysms, BP control is one of the mainstays of therapy
            1. Blood pressure should be controlled with a titratable agent to balance the risk of stroke, hypertension-related rebleeding, and maintenance of cerebral perfusion pressure
            2. Current recommendations are to maintain a SBP < 160mm Hg to reduce the risk of rebleeding
    g. Imaging
        i. Diagnostic workup should include noncontrast head CT, which, if nondiagnostic, should be followed by lumbar puncture
        ii. CTA may be helpful, but if inconclusive, angiography is still recommended
        iii. DSA with 3-dimensional rotational angiography is indicated for detection of aneurysm in patients with aSAH and for planning treatment to determine whether an aneurysm is amenable to coiling
    h. Treatment

i. Definitive treatment of aSAH is surgical clipping or endovascular coiling. Which procedure is used is largely dependent on the anatomy of the aneurysm
ii. Surgical clipping or endovascular coiling of the ruptured aneurysm should be performed as early as feasible in the majority of patients to reduce the rate of rebleeding after aSAH with complete obliteration of the aneurysm when possible
iii. For patients with ruptured aneurysms judged to be technically amenable to both endovascular coiling and neurosurgical clipping, endovascular coiling should be considered
iv. Repeat imaging following aneurysm clipping or coiling should be done to evaluate for completeness of obliteration

i. Management of complications
  i. Rebleeding
    1. Strict BP management and repeat intervention for aneurysm obliteration are indicated for patients with rebleed
  ii. Vasospasm/Delayed cerebral ischemia (DCI)
    1. Vasospasm and subsequent cerebral ischemia are one of the leading complications following aSAH
    2. Oral nimodipine should be administered to all patients with aSAH
    3. Maintenance of euvolemia and normal circulating blood volume is recommended to prevent vasospasm
    4. Daily monitoring for arterial vasospasm with transcranial doppler is "reasonable"
    5. Perfusion imaging with CT or MRI can be useful to identify regions of potential ischemia
    6. When vasospasm occurs:
      a. Induction of hypertension is recommended for patients with DCI unless blood pressure is elevated at baseline or cardiac status precludes it
      b. Cerebral angioplasty and/or selective intra-arterial vasodilator therapy is reasonable in patients with symptomatic cerebral vasospasm, particularly those who are not rapidly responding to hypertensive therapy
  iii. Hydrocephalus
    1. Generally, aSAH-associated acute symptomatic hydrocephalus should be managed by cerebrospinal fluid diversion with IVC/EVD or lumbar drain
    2. Seizures
      a. The use of prophylactic anticonvulsants should be used in the immediate posthemorrhagic period, but routine long-term use of anticonvulsants is not recommended except for patients with known risk factors, such as prior seizure, intracerebral hematoma, intractable hypertension, infarction, or aneurysm at the middle cerebral
  iv. Medical complications are known to occur frequently in patients with aSAH
    1. Cerebral salt wasting
    2. Seizures
    3. Arrhythmias
    4. ECG changes resembling acute MI
    5. Pulmonary edema
    6. Infections
    7. DVT/PE

9. Neuromuscular disorders
  a. Myasthenia Gravis (MG)
    i. Myasthenia gravis is an autoimmune disease whereby antibodies destroy the neuromuscular function
    ii. Defective neurotransmission leads to fatigable muscle weakness
    iii. Most patients have thymic hyperplasia or thymomas
    iv. Diagnosis
      1. Anti-AchR antibodies
      2. Edrophonium test
        a. Distinguishes myasthenic crisis from cholinergic crisis (too much anticholinesterase)
        b. Dangerous in cholinergic crisis though
      3. EMG with repetitive stimulation
      4. CT to R/O thymoma

v. Treatment
    1. Respiratory failure
        a. Follow VC, NIF, PImax
        b. Hypercapnea is late sign
        c. Intubation is indicated if VC <12 or significant bulbar dysfunction
    2. Anticholinesterases (pyridostigmine)
    3. Immunosupressives (e.g. steroids)
    4. Thymectomy
    5. Plasma exchange
    6. IV Ig
    7. Avoid drugs that exacerbate condition such as aminoglycosides, macrolides, lidocaine, oral contraceptives, phenytoin, and propranolol among others

b. Guillain-Barre syndrome (GBS)
    i. An acute self-limited inflammatory, demyelinating polyneuropathy
    ii. Commonly precipitated by an infection, commonly CMV, EBV, or *Campylobacter jejuni*
    iii. Limb paresthesias are typically the presenting signs with flaccid paralysis that can remain localized or spread to entire body
    iv. Ptosis and bulbar dysfunction are ominous signs for severity of the disease and need for intubation
    v. Diagnosis
        1. Must R/O other causes of flaccid paralysis such as spinal cord injury
        2. MRI is typically nonspecific
        3. EMG is the most sensitive test with motor neuron conduction block being most typical
        4. CSF analysis is nonspecific
        5. Ganglioside antibodies are frequently detected
    vi. Treatment
        1. Initial steps depend on clinical presentation including, severity of weakness, rapidity of progression, respiratory muscle weakness, dysautonomia, systemic complications, and comorbid disease (23).
        2. Intubation is indicated if VC ≤20 mL/kg and PImax ≤-30 mm Hg (23)
        3. IV Ig 0.4 g/kg for 5 days
        4. Plasma exchange for patients who cannot tolerate IV Ig

c. Critical Illness Polyneuropathy
    i. Relatively recently describe phenomena that is classically described as
        1. Presence of sepsis, multi-organ failure, respiratory failure, or septic inflammatory response syndrome (SIRS).
        2. Difficulty weaning from ventilator
        3. Limb weakness
    ii. Part of a spectrum of disease that has been found in 25-85% of critically ill patients (31)
        1. Other types include acute myopathy of intensive care and combinations of myopathy and neuropathy
        2. 46% of patients admitted with sepsis, multi-organ failure or on prolonged mechanical ventilation go on to develop acquired neuromuscular disorders (32)
    iii. Diagnosis
        1. Causes a flaccid paralysis, often predominantly distal
        2. Failure to wean from mechanical ventilation is a hallmark
        3. Cranial nerves are typically spared
        4. EMG studies are diagnostic and demonstrate axonal neuropathy
    iv. Treatment is supportive
        1. No specific therapy
        2. Aggressive rehabilitation
        3. Prevention of SIRS
    v. Prognosis
        1. Recovery is weeks to months
        2. No medication therapy, only conservative
        3. 50% have complete recovery

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