Neurocritical Care

Aaron M. Cook, Pharm.D., BCPS

University of Kentucky Medical Center
Lexington, Kentucky

Gretchen M. Brophy, Pharm.D., FCCP, FCCM, FNCS, BCPS

Virginia Commonwealth University
Medical College of Virginia Campus
Richmond, Virginia

Neurocritical Care

Aaron M. Cook, Pharm.D., BCPS

University of Kentucky Medical Center
Lexington, Kentucky

Gretchen M. Brophy, Pharm.D., FCCP, FCCM, FNCS, BCPS

Virginia Commonwealth University
Medical College of Virginia Campus
Richmond, Virginia

Learning Objectives

1. Identify pertinent pathophysiologic and laboratory changes that acutely occur after neurologic injuries and require therapeutic intervention.
2. Describe monitoring devices commonly used in neurocritical care patients that help with developing and optimizing treatment strategies.
3. Develop an evidence-based treatment strategy for neurocritical care patients that will optimize patient outcomes and reduce the risk of adverse drug effects and drug interactions.
4. Recommend a monitoring plan to assess response to therapeutic regimens and specific therapeutic goals for neurocritical care patients.
5. Reassess and develop new plans of care for neurocritical care patients according to therapeutic and adverse outcomes, and progress toward therapeutic goals.

Abbreviations in This Chapter

ADH	Antidiuretic hormone
AED	Antiepileptic drug
CNS	Central nervous system
CPP	Cerebral perfusion pressure
CSF	Cerebrospinal fluid
CSWS	Cerebral salt-wasting syndrome
DIND	Delayed ischemic neurologic deficit
ED	Emergency department
EEG	Electroencephalogram
GCS	Glasgow Coma Scale
ICH	Intracerebral hemorrhage
ICP	Intracranial pressure
ICU	Intensive care unit
MAP	Mean arterial pressure
PCC	Prothrombin complex concentrate
SAH	Subarachnoid hemorrhage
SCI	Spinal cord injury
SIADH	Syndrome of inappropriate antidiuretic hormone
TBI	Traumatic brain injury
VTE	Venous thromboembolism

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. A 56-year-old woman is hospital day 4 after her acute aneurysmal subarachnoid hemorrhage (SAH). She is oriented and following commands. Laboratory values reveal a serum sodium of 128 mmol/L. Other serum chemistry values include potassium (K) 3.9 mEq/L, chloride 103 mEq/L, bicarbonate (HCO_3) 27 mEq/L, blood urea nitrogen (BUN) 10 mg/dL, and serum creatinine (SCr) 1.0 mg/dL. Her urine output ranges from 1 to 2 mL/kg/hour, and her fluid balance has been +435 during the past 24 hours (currently receiving 0.9% sodium chloride at 125 mL/hour). Which is the best initial therapy for this patient's hyponatremia?
   A. Tolvaptan 20 mg orally daily.
   B. 1.5% sodium chloride infusion at 125 mL/hour.
   C. Water restriction to less than 1.5 L/day.
   D. No treatment indicated right now.

2. A 20-year-old female college student presents to the emergency department (ED) together with her roommates with a 1-day history of fever, neck stiffness, and progressive confusion. She has no significant medical history and no allergies to medications. A lumbar puncture is obtained that reveals a cerebrospinal fluid (CSF) white blood cell count (WBC) of 34 x 10^3 cells/mm^3, red blood cell count (RBC) 1 x 10^3 cells/mm^3, protein 78 mg/dL, and glucose 21 mg/dL. The Gram stain is pending. Other serum laboratory values include sodium (Na) 138, K 4.1 mEq/L, SCr 0.9 mg/dL, glucose 110 mg/dL, and WBC 17.1 x 10^3 cells/mm^3. Which is the most appropriate antimicrobial regimen to initiate for this patient's probable meningitis?
   A. Vancomycin, acyclovir.
   B. Vancomycin, cefepime, ampicillin.
   C. Vancomycin, levofloxacin, ampicillin.
   D. Vancomycin, ceftriaxone.

3. A 25-year-old man is admitted after a two-story fall from a ladder. His initial computed tomography (CT) scan of the brain reveals a large right temporal subdural hematoma, an overlying skull fracture, and a left temporal contusion. His post-resuscitation

Glasgow Coma Scale (GCS) score is E1-M4-V1T. An intracranial pressure (ICP) monitor is placed with an opening pressure of 32 mm Hg and a cerebral perfusion pressure (CPP) of 53 mm Hg. Serum laboratory values include Na 141 mEq/L, K 3.6 mEq/L, BUN 8 mg/dL, SCr 1.1 mg/dL, glucose 178 mg/dL, WBC 14.8 x 10^3 cells/mm^3, pH 7.46, and pCO_2 34. Which supportive care issues are most relevant to the appropriate treatment of a patient with a severe traumatic brain injury (TBI)?

A. Avoid enteral nutrition for the first 5–7 days because of the lack of gastrointestinal (GI) tolerance in severe TBI.
B. Maintain CPP between 50 and 70 mm Hg to optimize perfusion and reduce complications.
C. Provide dextrose 5% or other dextrose-containing intravenous fluids to compensate for the patient's increased metabolic needs.
D. Initiate high-dose methylprednisolone therapy within 8 hours of injury to reduce cerebral edema.

4. A 69-year-old woman presents to the ED with a 30-minute history of difficulty with word finding and left upper extremity weakness. Her NIH Stroke Scale score is 13. A CT scan of the head reveals no acute abnormalities. The patient's home medications include lisinopril, carvedilol, warfarin, and atorvastatin. Her medical history includes hypertension, atrial fibrillation, and transient ischemic attacks (diagnosed 6 months ago). Serum laboratory values include Na 145 mEq/L, K 4.0 mEq/L, BUN 18 mg/dL, SCr 1.2 mg/dL, glucose 132 mg/dL, WBC 8.7 x 10^3 cells/mm^3, hematocrit 38.9%, platelet count 355,000/mm^3, and international normalized ratio (INR) 1.5. Her vital signs include blood pressure 167/98 mm Hg, heart rate 132 beats/minute, Sao_2 98%, and respiratory rate 14 breaths/minute. Which is the most appropriate next step in this patient's care?

A. Initiate aspirin 324 mg orally x 1.
B. Initiate alteplase 0.9 mg/kg intravenously (10% bolus dose, 90% infusion up to 90 mg maximum).
C. Initiate nicardipine to reduce blood pressure to systolic blood pressure (SBP) less than 140 mm Hg, followed by alteplase 0.9 mg/kg intravenously (10% bolus dose, 90% infusion up to 90 mg maximum).
D. Initiate vitamin K 10 mg intravenously x 1.

5. An 18-year-old man is admitted to the intensive care unit (ICU) after falling from a tree. Initial trauma screening reveals a C3–C4 fracture and dislocation with an incomplete spinal cord injury (SCI) at the corresponding levels (he has some sensory function bilaterally). The fracture has been reduced, and he arrives in the ICU 6 hours after injury. Which is the most appropriate statement related to initiating high-dose methylprednisolone therapy for this patient's SCI?

A. High-dose methylprednisolone therapy may be used because he has an incomplete injury with some sensory function.
B. High-dose methylprednisolone therapy should be used because it will augment spinal perfusion.
C. High-dose methylprednisolone therapy should not be used because of the potential for adverse effects and questionable benefit.
D. High-dose methylprednisolone therapy should not be used because the patient is outside the treatment window.

6. A 27-year-old woman presents with fever, agitation, hypertension, and muscle rigidity. Her drugs-of-abuse screen is negative, and serotonin syndrome is a possible diagnosis. Which home medication is most likely to be a causative agent for serotonin syndrome?

A. Buspirone.
B. Levetiracetam.
C. Cyproheptadine.
D. Bupropion.

7. A 58-year-old woman with a Hunt and Hess grade 4 SAH resides in your ICU. She is day 6 after her SAH. Her current medications include 0.9% normal saline at 100 mL/hour, nimodipine 60 mg per tube every 4 hours, norepinephrine 0.05 mcg/kg/minute (5 mcg/minute), famotidine 20 mg intravenously every 12 hours, docusate 250 mg per tube every

12 hours, and morphine as needed for headache. Current laboratory values include Na 144 mEq/L, K 4.1 mEq/L, SCr 0.6 mg/dL, serum osmolality 322 mOsm/L, and hematocrit 32.3%. Her blood pressure is 167/99 mm Hg, heart rate 133 beats/minute, respiratory rate 18 breaths/minute, Sao_2 99%, and central venous pressure 5 mm Hg. Her most recent transcranial Doppler velocities are mean middle cerebral artery 125/135 (right/left), with a corresponding Lindegaard ratio of 3.5/3.7 (right/left). Her ICP is currently 24 mm Hg. She has a Licox monitor placed in the hemisphere ipsilateral to her aneurysm, which currently shows a partial pressure of brain tissue oxygen ($PbtO_2$) of 14%. She is intubated and on the ventilator. Which treatment would be most appropriate for this patient?

A. Verapamil 2.5 mg intra-arterially x 1.
B. 3% sodium chloride 2.5 mL/kg intravenously x 1.
C. 20% mannitol 0.25 g/kg intravenously x 1.
D. 1 unit of packed RBCs.

8. Which sedative is most desirable for a patient diagnosed with a SAH and currently having vasospasm?

A. Lorazepam 1 mg/hour.
B. Midazolam 4 mg/hour.
C. Morphine 2 mg/hour.
D. Propofol 25 mcg/kg/minute.

I. HYPONATREMIA

A. Epidemiology
1. Hyponatremia (Na less than 135 mEq/L) is common in patients with neurologic injury.
2. SAH 12%–43%
3. TBI 20%

B. Diagnosis/Pathophysiology
1. Laboratory tests (serum sodium) are needed to diagnose hyponatremia.
2. Urine sodium, urine osmolality, serum osmolality, and measurement of intravascular volume may also be helpful in determining the specific pathogenesis for hyponatremia.

C. Causes
1. Consideration of iatrogenic hyponatremia
2. Typically caused by an increase in salt-free water or loss of serum sodium

D. Differentiation Between Syndrome of Inappropriate Antidiuretic Hormone (SIADH) and Cerebral Salt-Wasting Syndrome (CSWS) – Typically by intravascular volume
1. Measure intravascular volume using a central venous pressure catheter or similar invasive monitoring.
2. Monitor fluid balance, weights, skin turgor
3. Echocardiogram to estimate ventricular filling pressures

Table 1. Differential Diagnosis for SIADH and CSWS[a]

	Serum Sodium (mEq/L)	Serum Osmolality (mOsm/L)	Urine Sodium (mEq/L)	Urine Osmolality (mOsm/L)	Intravascular Volume Status
SIADH	< 135	< 285	> 25	> 200	Euvolemia
CSWS	< 135	< 285	> 25	> 200	Hypovolemia

[a]Note: Medications, particularly diuretics, may alter serum or urine measurements of osmolality or Na concentration.
CSWS = cerebral salt-wasting syndrome; SIADH = syndrome of inappropriate antidiuretic hormone.

E. Clinical Impact
1. Hyponatremia may result in increased brain edema and elevated ICP.
2. May cause neurologic symptoms such as delirium, agitation, tremor, seizure, or coma

F. SIADH: Increased secretion of antidiuretic hormone ([ADH] or vasopressin) results in increased water retention at the renal distal tubules.

Box 1. Typical Causes of SIADH

Traumatic brain injury	Pneumonia/tuberculosis	Oxcarbazepine
Brain tumor	Lung cancer	Chlorpropamide
Stroke	Medications	Nicotine
Brain infection	Selective serotonin reuptake inhibitors	Opioids
Subarachnoid hemorrhage	Tricyclic antidepressants	Antipsychotic medications
Intracerebral hemorrhage	Carbamazepine	Nonsteroidal anti-inflammatory drugs

G. Treatment – New guidelines for the diagnosis and management of hyponatremia are available. (Intensive Care Med 2014;40:320-331)

Table 2. Treatment Strategies for SIADH

	Fluid Restriction	**Oral Na**	**Intravenous Na**	**Demeclocycline**	**Vasopressin (V)-Antagonists**
Mechanism of action	Restriction of free water results in increased impact of insensible losses, permitting Na concentration to rise	Supplementation of Na	Supplementation of Na	Inhibition of renal V1 vasopressin receptors	Inhibition of renal V1 vasopressin receptors (conivaptan V1 + V2 receptors; tolvaptan V1 only)
Dose	< 1500 mL/day	4–16 g/day (1 g = 17 mEq Na)	0.9%–3% at 0.5–1.5 mL/kg/hr	300 mg every 12 hr up to 1200 mg/day	Conivaptan: 20–40 mg intravenously daily Tolvaptan: 15–60(Intensive Care Med 2014; 40: 320-331) mg PO daily
Efficacy	Modest, delayed (over 2+ days)	Modest, more effective for CSWS (over 2+ days)	Modest, more effective for CSWS (over 2+ days)	Modest, delayed (over 1 wk)	Modest, prompt over the first 24 hr
Common adverse effects	Thirst	Thirst, diarrhea	Fluid overload	GI upset, hepatotoxicity, photosensitivity	Conivaptan: infusion pain
Common considerations	Difficult to ensure adherence; caution for permitting hypovolemia in patients with cerebral perfusion needs such as SAH, TBI		≤ 2% sodium chloride may be given through peripheral intravenously	Chelation occurs with coadministered cations	Cost; drug-drug interactions are common

PO = orally; wk = week.

1. Treatment of SIADH can be challenging in many neurocritical care patients such as those with SAH and TBI.
2. Treatment of choice is fluid restriction, which is typically not feasible in patients with SAH or TBI.
3. Priority on maintaining euvolemia to optimize CPP, particularly when treating elevated ICP or cerebral vasospasm

H. Cerebral Salt Wasting Syndrome
   1. Etiology is largely unknown, but speculation is typically focused on the increased secretion of natriuretic peptides, causing loss of Na at the renal distal tubules.
   2. Typical causes include TBI, SAH, and brain tumor.
   3. Fludrocortisone 0.1–0.4 mg/day may be helpful in reducing Na loss in CSWS. (Arch Intern Med 2008; 168:325-326)

I. Considerations for Rapid Correction of Hyponatremia
   1. Recommended increase in serum sodium concentration is 0.5 mEq/L/hour.
   2. Patients with chronic hyponatremia may need to be corrected more slowly because of the equilibration of brain electrolytes with chronic hyponatremic state. (New England Journal of Medicine 2000; 342:1581-1589)
   3. Patients with acute hyponatremia may tolerate quicker correction.

Na requirement (mmol) = total body water (0.6 x kg)[a] x (desired Na – current Na)

Infusion rate (mL/hr) = (Na requirement x 1000)/(infusion Na concentration x time)

Figure 1. Common equations used for Na correction in hyponatremia. (New England Journal of Medicine 2000; 342:1581-1589)

[a]0.6 for men, 0.5 for women; infusion Na concentration in millimoles per liter and time in hours.

   4. Quicker correction in patients with severe symptoms (coma, seizures) may be prudent – Up to 1–2 mEq/L/hour
   5. Too rapid correction of serum sodium may result in central pontine myelinolysis; a routine approach should be to limit Na increase to 12 mEq/L in the first 24 hours. (Intensive Care Med 2014;40:320-331)

II. HYPERNATREMIA

A. Epidemiology
   1. Hypernatremia (Na greater than 150 mEq/L) is also common in patients with neurologic injury.
   2. SAH up to 22%
   3. TBI up to 21%

B. Diagnosis/Pathophysiology: Laboratory tests (serum sodium) are needed to diagnose hypernatremia. Urine sodium, urine osmolality, urine volume, and serum osmolality may also be helpful in determining the specific pathogenesis.

C. Typical Causes

D. Consideration of Iatrogenic Hypernatremia

E. Diabetes Insipidus
   1. Decreased secretion of ADH or vasopressin results in decreased retention of water at the renal distal tubules.
   2. Characterized by voluminous (greater than 250 mL/hour), dilute urine output

F. Treatment
   1. Hypotonic solutions for free-water replacement
      a. Dextrose 5%–water
      b. 0.45% sodium chloride
      c. Water supplementation orally or per tube
   2. Vasopressin analogs
      a. Supplementation of ADH to normal functional levels
      b. Titrate therapy to normalized urine output, serum sodium correction, and urine-specific gravity.
      c. Desmopressin
         i. Intravenously or subcutaneously: 0.5–4 mcg every 8–12 hours (usual starting dose 1–2 mcg)
         ii. Intranasally: 10–40 mcg/day divided into two or three doses (usual starting dose 10 mcg)
         iii. Orally: 50–800 mcg divided into two doses (usual starting dose 50 mcg)
         iv. May be dosed as needed depending on laboratory values initially
      d. Patients after pituitary removal may more commonly require long-term therapy.
   3. Arginine vasopressin – Continuous infusion 1–15 units/hour (usual starting dose 1 unit/hour; titrate to urine output)
   4. Considerations for rapid correction of hypernatremia
      a. Recommended decrease in serum sodium concentration is around 0.5 mEq/L/hour.
      b. Too rapid correction of serum sodium may result in cerebral edema.
      c. In general, neurocritical care patients should receive minimal amounts of dextrose or free water–containing fluids to avoid the risk of cerebral edema.

III. STATUS EPILEPTICUS

A. Epidemiology – Accounts for 150,000 admissions in the United States annually

B. Status Epilepticus – Continuous seizures for 5 minutes or more OR intermittent seizures with no regaining of consciousness in between for more than 5 minutes (New England Journal of Medicine 1990;323:497-502)

C. Refractory Status Epilepticus – Status epilepticus that persists after standard treatment (e.g., a benzodiazepine followed by another antiepileptic drug [AED])

D. Diagnosis/Pathophysiology – Diagnostic tests
   1. Laboratory tests often show electrolyte abnormalities (particularly Na, magnesium, and phosphorus).
   2. Electroencephalogram (EEG) monitoring is necessary to identify and characterize seizures.
      a. Continuous monitoring is preferred in status epilepticus patients to capture intermittent or fluctuating seizure patterns. (Neurocrit Care 2012;17:3-23)
      b. Typical recommended duration is at least 48 hours, and monitoring should be initiated as soon as possible after suggestion or diagnosis of seizure.

E. Causes

Table 3. Typical Etiologies of Status Epilepticus

Cause of Status Epilepticus	Approximate % of Patients
Epilepsy	33–55
Miscellaneous	12–24
Stroke	14–22
AED nonadherence	20
Drug withdrawal	10–14
Brain tumor	10
Metabolic	10
Traumatic brain injury	7
Drug toxicity	5
CNS infection	3

AED = antiepileptic drug; CNS = central nervous system.

F. Clinical Impact
   1. Mortality rate ranges from 9% (primarily in patients with preexisting epilepsy/AED nonadherence) to 30% (in patients with a concomitant pathology such as TBI or stroke).
      a. Mortality in non-convulsive status epilepticus is about double that in seizures that are more overt.
      b. Elderly individuals have a higher mortality rate.
   2. Discharge disposition: 14%–18% of patients presenting to the ED in status epilepticus ultimately have a neurologic deficit.

G. Agent Selection (Neurocrit Care 2012;17:3-23)
   1. Emergent therapy
      a. Benzodiazepine therapy preferred
      b. Lorazepam 0.1 mg/kg intravenously (max 4 mg/dose) OR
      c. Midazolam 5–10 mg intramuscularly
   2. Urgent therapy
      a. Typically, initiate an AED after benzodiazepine therapy if seizures persist or if a maintenance therapy needs to be started to prevent future seizures.
      b. Valproate 20–40 mg/kg intravenously
      c. (Fos)Phenytoin 18–20 mg/kg intravenously
      d. Phenobarbital 20 mg/kg intravenously
      e. Levetiracetam 1–3 g intravenously
   3. Refractory therapy
      a. If seizures persist after after emergent and urgent therapy, refractory status epilepticus should be treated aggressively and in a timely manner.
      b. Several AEDs are options for refractory status epilepticus, though limited data exist supporting any one agent or approach over another.
      c. Midazolam high-dose infusion 0.5–2 mg/kg/hour (target burst suppression)
      d. Pentobarbital infusion (loading dose about 25 mg/kg total, continuous infusion 1–5 mg/kg/hr [target burst suppression])
      e. Propofol infusion 20 mcg/kg/minute (target burst suppression)
      f. Valproate 20–40 mg/kg intravenously (if not already given)
      g. Lacosamide 200–400 mg intravenously
      h. Topiramate 200–400 mg orally/nasogastrically
      i. Other AEDs listed earlier if not already given

H. Monitoring
   1. Continuous EEG monitoring is necessary.
   2. Proactive monitoring of serum concentrations typically necessary for agents such as phenytoin and valproic acid to ensure adequate concentrations and mitigate risk of toxicity.

Table 4. Characteristics of Agents for Status Epilepticus

AED	Dosing	Common Adverse Effects	Considerations
Lorazepam	0.1 mg/kg intravenously (slow intravenous push); typically up to 8 mg total (max 4 mg/dose)	Sedation, hypotension	Intravenous formulation contains propylene glycol
Midazolam intermittent	5–10 mg IM	Sedation, hypotension	Short duration with intravenous bolus
Diazepam	0.15 mg/kg intravenously (slow intravenous push); typically up to 10 mg total	Sedation, hypotension	Intravenous formulation contains propylene glycol
Fosphenytoin	18–20 mg PE/kg intravenously (not to exceed 150 mg PE/min); may also give IM (if routine dosing)	Hypotension, arrhythmia	Several drug-drug interactions
Phenytoin	18–20 mg/kg intravenously (not to exceed 50 mg/min)	Hypotension, arrhythmia, phlebitis, purple glove syndrome	Several drug-drug interactions, intravenous formulation contains propylene glycol and ethanol
Valproic acid	20–40 mg/kg intravenously (not to exceed 6 mg/kg/min)	Hyperammonemia	Many drug-drug interactions, avoid in patients with TBI
Levetiracetam	1–3 g intravenously (not to exceed 5 mg/kg/min)	Sedation/paradoxical excitation, irritability	Renally eliminated, limited drug-drug interactions
Lacosamide	200–400 mg intravenously (typically over 15–30 min)	Dizziness, bradyarrhythmia	Limited drug-drug interactions
Topiramate	Oral/enteral loading dose of 500 mg BID x 2 days, tapering to 200 mg BID by 200 mg/day every 2 days	Metabolic acidosis	No intravenously formulation available
Phenobarbital	20 mg/kg (not to exceed 100 mg/min)	Sedation, hypotension, respiratory depression	Intravenous formulation contains propylene glycol
Pentobarbital	10 mg/kg (typically over 15–30 min, depending on blood pressure); typically need additional 5- to 10-mg/kg boluses to full loading dose of 25–30 mg/kg; 1- to 3-mg/kg/hr infusion	Sedation, hypotension, respiratory depression, constipation, cardiac depression, immunosuppression	Intravenous formulation contains propylene glycol; target is burst suppression; several drug-drug interactions

Table 4. Characteristics of Agents for Status Epilepticus *(continued)*

AED	Dosing	Common Adverse Effects	Considerations
Midazolam high-dose infusion	0.05–2 mg/kg/hr	Sedation, hypotension, respiratory depression	Potential tachyphylaxis, target is burst suppression
Propofol	20–200 mcg/kg/min, titrate by 5 mcg/kg/min	Sedation, hypotension, respiratory depression, propofol infusion syndrome	Target is burst suppression; provides 1.1 kcal/mL
Ketamine	0.5–7 mg/kg/hr	Excitation, hypertension, possible neurotoxicity, hallucinations	

AED = antiepileptic drug; BID = twice daily; hr = hour(s); IM = intramuscular(ly); min = minute(s); PE = phenytoin equivalents.

Patient Case

1. A 37-year-old man is admitted to the ICU after sustaining a traumatic subdural hematoma. On hospital day 2, his GCS score falls from E3-M6-V1T to E1-M5-V1T over 10 minutes, and his nurse notices facial twitching. An EEG is ordered. Current medications include fosphenytoin 200 mgPE intravenously every 12 hours (6 mgPE/kg/day), famotidine 20 mg intravenously every 12 hours, heparin 5000 units subcutaneously every 8 hours, docusate 250 mg nasogastrically twice daily, and a supplemental vitamin infusion for potential alcohol withdrawal. Which is the best acute therapy to treat this patient's suspected seizure activity?

   A. Fosphenytoin 20 mgPE/kg intravenously x 1.
   B. Valproic acid 20 mg/kg intravenously x 1.
   C. Lorazepam 4 mg intravenously x 1.
   D. Levetiracetam 1 g intravenously x 1.

IV. MENINGITIS

A. Epidemiology
   1. Estimated 4100 cases from bacterial meningitis annually in the United States
   2. Mortality ranges from 12% to 15% of cases

B. Diagnosis/Pathophysiology
   1. Clinical signs and symptoms typically include:
      a. Headache (87%)
      b. Neck stiffness (83%)
      c. Nausea (74%)
      d. Fever (77%)
      e. Mental status changes (69%)
      f. Focal neurologic deficits (33%)
      g. Rash (26%) – Typically, *Neisseria meningitidis*
      h. Seizure (15%–23%)
      i. Coma (14%)
   2. Evaluation of CSF is typically necessary.
      a. Obtained by lumbar puncture
      b. CSF WBC and protein typically elevated
      c. Neutrophilia is most common with bacterial infection.

d. CSF glucose typically diminished (CSF/blood glucose ratio less than 0.4)
e. CSF Gram stain and culture
f. Around 85% of cultures are positive in bacterial meningitis in patients who have not received previous antimicrobials.
g. Latex agglutination
h. Commercially available antisera or antibodies directed against common pathogens that yields prompt identification of pathogens in serum, urine, or CSF
i. Polymerase chain reaction
j. Detects the presence of DNA from common pathogens in CSF

3. CSF indices

Table 5. Typical Values for CSF Indices Used for Evaluating Bacterial Meningitis

CSF Indices	Normal Values	Bacterial Meningitis
CSF WBC (cells/mm^3)	0–5	10–10,000
CSF RBC (cells/mm^3)	0–5	0–5
CSF protein (mg/dL)	15–45	100–500
CSF glucose (CSF/serum ration)	> 0.6	< 0.4
CSF lactate (mmol/L)	< 0.4	> 4

Table 6. Sensitivity of Various Diagnostic Tests for Bacterial Meningitis

Pathogen	Blood Culture (%)	CSF Gram Stain (%)	Latex Agglutination (%)	PCR (%)
Haemophilus influenzae	25–90	25–65	78–100	72–92
Streptococcus pneumoniae	60–90	69–93	59–100	61–100
N. meningitidis	40–60	30–89	22–93	88–94
Listeria monocytogenes	10–75	10–35	N/A	N/A
Streptococcus agalactiae	80–85	80–90	N/A	N/A

N/A = not applicable; PCR = polymerase chain reaction.

4. Serum testing
   a. Procalcitonin may be helpful in identifying bacterial infection.
   b. C-reactive protein and erythrocyte sedimentation rate are less specific, but often elevated.
   c. Blood cultures are positive in 66% of patients with meningitis.

C. Common Pathogens and Treatment Recommendations

Table 7. Typical Pathogens and Recommended Antimicrobial Regimens in Bacterial Meningitis

Pathogen	% of Cases	Typical Age Groups	Recommended Therapy	Alternative Therapies
H. influenzae	7%	1 mo to > 50 yo	Third-generation cephalosporin (e.g., ceftriaxone 2 g intravenously every 12 hr)	Cefepime, meropenem, fluoroquinolone, chloramphenicol
S. pneumoniae	47%	1 mo to > 50 yo	Vancomycin + third-generation cephalosporin (e.g., ceftriaxone 2 g intravenously every 12 hr)	Meropenem, fluoroquinolone
N. meningitidis	25%	1 mo to > 50 yo	Third-generation cephalosporin (e.g., ceftriaxone 2 g intravenously every 12 hr)	Penicillin G, ampicillin, fluoroquinolone, aztreonam, chloramphenicol
L. monocytogenes	8%	< 1 mo or > 50 yo	Ampicillin	Penicillin G, SMX/TMP, meropenem
S. agalactiae	12%	< 1 mo	Ampicillin	Penicillin G, third-generation cephalosporin
Escherichia coli	Unknown	< 23 mo or > 50 yo	Third-generation cephalosporin (e.g., ceftriaxone 2 g intravenously every 12 hr)	Cefepime, meropenem, aztreonam, fluoroquinolone, SMX/TMP
Staphylococci	Around 80%	Ventriculitis or shunt infection, penetrating injury	Vancomycin	Nafcillin (MSSA only), linezolid, SMX/TMP

mo = month(s); MSSA = methicillin-susceptible *S. aureus*; SMX/TMP = sulfamethoxazole/trimethoprim; yo = years old.
Clinical Infectious Diseases 2004;39:1267-1284

D. Pharmacokinetic Considerations
   1. The blood-brain barrier typically excludes most hydrophilic substances (many of the commonly used antimicrobials).
   2. The inflammation of the meninges in meningitis permits an increased penetration of substances into the brain.
   3. Antimicrobial penetration is greater.
   4. Central nervous system (CNS) is a difficult compartment to penetrate for many antimicrobials (even considering increased blood-brain barrier permeability in the setting of inflamed meninges).
   5. Need for dose maximization, whenever possible

E. Role of Steroids
   1. Clinical impact in meningitis
      a. Somewhat controversial topic with conflicting data, though Cochrane review suggests benefit in adult and pediatric patients (Cochrane Database Syst Rev 2007;CD004405)

b. Meta-analysis of studies of early dexamethasone in pediatric patients with meningitis suggested that steroids reduce the incidence of hearing loss caused by meningitis (relative risk [RR] 0.61; 95% confidence interval [CI], 0.44–0.86). Primarily seen in patients with *H. influenzae* type B (incidence of HiB is now dramatically reduced because of routine vaccination). Number needed to treat for benefit = 20.
c. Overall, studies of adults with meningitis who are treated with early dexamethasone also suggest benefit.
d. Meta-analysis of studies in adults showed that dexamethasone reduced the risk of mortality (RR 0.57; 95% CI, 0.40–0.81) and short-term neurologic sequelae (RR 0.42; 95% CI, 0.22–0.87). (Cochrane Database Syst Rev 2007;CD004405)
e. Large clinical trial using dexamethasone in adults with meningitis showed the following outcomes at 8 weeks (N Engl J Med 2002;347:1549-1556):
    i. Reduced unfavorable outcomes (RR 0.59; 95% CI 0.37–0.94). *S. pneumoniae* subgroup (RR 0.50; 95% CI, 0.30–0.83)
    ii. Reduced mortality (RR 0.48; 95% CI, 0.24–0.96). *S. pneumoniae* subgroup (RR 0.41, 95% CI, 0.19–0.86)
    iii. No difference in focal neurologic abnormalities (RR 0.62; 95% CI, 0.36–1.09)
    iv. No difference in hearing loss (RR 0.77; 95% CI, 0.38–1.58)

2. Mechanism
    a. Possible benefit before or with first dose of antimicrobials
    b. Decrease in inflammation associated with burst of bacterial by-products as a result of lysis after initial antimicrobial exposure
3. Dosing
    a. Adult patients: Dexamethasone 10 mg intravenously every 6 hours x 4 days
    b. Pediatric patients: Dexamethasone 0.4–0.6 mg/kg/day x 4 days

F. Intraventricular Antibiotic Administration
1. Case selection
    a. Recommended in adult patients with CSF shunt or ventriculostomy infections for difficult-to-eradicate pathogens or for patients who cannot undergo the surgical component of therapy
    b. Not recommended in neonatal or infant CNS infection cases
2. Appropriate dosing
    a. Intravenous plus intraventricular is probably superior to intravenous or intraventricular alone.
    b. Use preservative-free formulations.
    c. Daily dosing is usually necessary; may need to adjust according to the amount of CSF drainage from external ventricular drain

Table 8. Various Antimicrobials and Doses for Intraventricular Administration

Antimicrobial	Daily Dose/Volume (adults)	Approximate Osmolality (mOsm/kg)	Common Adverse Effects
Vancomycin	10–20 mg /1 mL NS	291	Headache, mental status changes, possible hyponatremia
Gentamicin	4–8 mg/1 mL NS	293	Seizures
Tobramycin	4–8 mg/1 mL NS	283	Seizures
Amikacin	30 mg/1 mL NS	383	Seizures
Polymyxin B	5 mg/1 mL NS	10	Hypotonia, seizures, meningeal inflammation
Colistimethate	10 mg/3 mL NS	367	Meningeal inflammation
Amphotericin B deoxycholate	0.5 mg/3 mL SWI	256 (in dextrose 5%)	Nausea, vomiting

NS = normal saline; SWI = sterile water for injection.

Pharmacotherapy 2009;29:832-845

V. INTRACRANIAL PRESSURE TREATMENT

A. General Concepts
   1. Elevated ICP decreases tissue perfusion and tissue oxygenation and worsens neurologic outcome.
   2. Monro-Kellie doctrine: ICP equals cerebral blood volume (10%) plus CSF (10%) plus brain tissue (80%). Each of the therapies targeted at decreasing ICP acts on one or more of these components.

B. Treatment Thresholds
   1. Recommendations are to treat sustained ICP greater than 20 mm Hg as measured by external ventricular drain, intraparenchymal catheter, or bolt.
   2. Specific threshold may have interpatient variability.

C. Osmotherapy

Table 9. Comparison of Osmotherapy Agents

	Mannitol	Hypertonic Saline
Mechanism of action	Acute increase in cerebral blood flow results in cerebral vasoconstriction (because of autoregulation), leading to decreased cerebral blood volume Increase in serum osmolality creates osmotic gradient to pull extracellular fluid from brain Osmotic diuretic	Acute increase in cerebral blood flow results in cerebral vasoconstriction (because of autoregulation), leading to decreased cerebral blood volume Increase in serum osmolality creates osmotic gradient to pull extracellular fluid from brain
Typical dose	0.25–1 g/kg over 15 min (0.2-micron filter) Up to 1.6 g/kg if acute herniation	3%: 2.5–5 mL/kg over 15 min 7.5%: 1–2 mL/kg over 15 min 23.4%: 30 mL over 15 min

Table 9. Comparison of Osmotherapy Agents *(continued)*

	Mannitol	**Hypertonic Saline**
Monitoring values	Serum: Osmolality, Na, creatinine, K, osmolar gap Urine: Urine output	Serum: Osmolality, Na, creatinine, K
Adverse effects	Hyper/hyponatremia Hypokalemia Renal failure Hypovolemia Rebound cerebral edema (?)	Hypernatremia Hypokalemia Hyperchloremic acidosis Renal failure Central pontine myelinolysis (?)

1. Monitoring osmolar changes with osmotherapy
2. Traditional serum osmolality threshold was 320 mOsm/L when using mannitol.
   a. Theory was that serum osmolality values greater than 320 were associated with renal dysfunction.
   b. Osmolar gap appears to be a more appropriate and accurate method of evaluating renal dysfunction risk with mannitol.
   c. Approximates the mannitol concentration
   d. Goal osmolar gap is less than 20.
   e. Calculation of osmolar gap

Osmolar gap = Estimated osmolality – measured osmolality

Osmolar gap = [(2 x Na) + (BUN/2.8) + (glucose/18)] – measured osmolality

D. Metabolic Suppression
   1. Mechanism of action: Suppression of electrical activity in brain (i.e., "burst suppression") causes a reduction in cerebral metabolic rate of oxygen ($CMRO_2$).
   2. Reduced $CMRO_2$ leads to decreased cerebral blood volume.
   3. Pentobarbital sodium usually used in the United States (thiopental = Europe)
   4. Risks may outweigh benefit, at least for certain conditions such as large hemispheric infarction.
   5. Typical dose
      a. 25–30 mg/kg intravenous loading dose. Usually given as 10 mg/kg x 1 dose, followed by 5 mg/kg every hour x 3 or 4 doses to avoid hypotension with large bolus dose
      b. 1- to 3-mg/kg/hour infusion after loading dose
   6. Titration
      a. Titrated to goal ICP (usually less than 20 mm Hg)
      b. Burst suppression (target usually is 2–5 bursts/minute) is surrogate for need of additional pentobarbital doses.
      c. Bolus dose is required concomitantly with infusion titration because of its long half-life and rapid redistribution.
   7. Monitoring
      a. ICP
      b. EEG and burst occurrence per minute
      c. Serum concentrations do not correlate well with ICP response and should not be used to titrate infusion. May be useful when therapy has been discontinued as part of brain death examination (to rule out continued intoxication from pentobarbital)

8. Adverse effects
    a. Hypotension
        i. Propylene glycol diluent
        ii. Direct vasodilator
        iii. Reduction in sympathetic tone because of metabolic suppression
        iv. Cardiac depressant (particularly with high doses and duration greater than 96 hours)
    b. Decreased GI motility
        i. Difficulty with enteral nutrition
        ii. Caloric needs are usually around 80%–90% of basal energy needs, so a lower flow rate for enteral nutrition is permissible.
        iii. Ideally, would use a low-residual nutrition product because stooling is rare on pentobarbital infusion
    c. Infection (particularly pneumonia)
    d. Immunosuppression
    e. Withdrawal seizures may be possible.

E. Sedation – Mechanism of action: Decreased systemic oxygen delivery needs; reduced coughing, reduced agitation, decreased cerebral metabolic rate of oxygen
    1. Propofol is typically preferred sedative – Quick onset, short acting, less accumulation with prolonged duration
    2. Benzodiazepines
        a. Not preferred because of duration of action
        b. Also associated with delirium and cognitive impairment
        c. Potential for withdrawal effect, seizures
    3. Dexmedetomidine
        a. Little evidence to support use in neurocritical care
        b. Hypotension risk may be deleterious in specific patient types (e.g., aneurysmal SAH/vasospasm, TBI, SCI).
        c. May be particularly helpful in patients with paroxysmal sympathetic hyperactivity

F. Neuromuscular Blockade
    1. Mechanism of action: Decreased systemic oxygen delivery needs; reduced coughing
        a. Neuromuscular blockers have no intrinsic value for reducing ICP, but they may be helpful in select patients with specific issues that exacerbate ICP elevations.
            i. Prevention of cough, ventilator dyssynchrony (both increase ICP)
            ii. Control pCO_2 (increased pCO_2 may also raise ICP)
        b. Prevention of shivering during hypothermia
        c. Reduces intrathoracic pressure
        d. May be essential in patients requiring high positive end-expiratory pressure (increased intrathoracic pressure may increase ICP)
    2. Various agents may be useful.
        a. Depends on patient organ function, prescriber preference
        b. Vecuronium (particularly if normal organ function)
        c. Cisatracurium (particularly if end-organ dysfunction)
        d. Avoid atracurium, if possible, because of hypotension risk.
        e. Monitor by train-of-four (goal 1-2/4 twitches with no clinical evidence of neuromuscular function [e.g., overbreathing the ventilator rate]).

Patient Case

2. A 25-year-old man is admitted after a two-story fall from a ladder. The initial CT scan of his brain reveals a large right temporal subdural hematoma, an overlying skull fracture, and a left temporal contusion. His postresuscitation GCS is E1-M4-V1T. An ICP monitor is placed with an opening pressure of 32 mm Hg; the CPP is 53 mm Hg. Serum laboratory values include Na 141 mEq/L, K 3.6 mEq/L, BUN 8 mg/dL, SCr 1.1 mg/dL, glucose 178 mg/dL, WBC 14.8 x 10^3 cells/mm^3, pH 7.46, and pCO_2 34. Which is the best initial therapy for this patient's elevated ICP?

   A. Mannitol 20% 1 g/kg intravenously x 1.
   B. 23.4% sodium chloride 1 mL/kg intravenously x 1.
   C. Pentobarbital 10 mg/kg intravenously x 1.
   D. Midazolam 10 mg intravenously x 1.

G. TBI Guidelines (Journal of Neurotrauma 2007;24:S1-S95)
   1. Seizure prophylaxis
      a. Recommended as an option for prevention of early posttraumatic seizures (first 7 days after event)
      b. Phenytoin most commonly recommended agent (because of support for use from prospective clinical trials)(New England Journal of Medicine 1990;323:497-502)
      c. Levetiracetam also commonly used, despite paucity of data
      d. Valproic acid is as effective as phenytoin, but it had a trend toward increased mortality in a prospective clinical trial, so it is not a first-line agent. (Journal of Neurosurgery 1999;91:593-600)
      e. Use of AEDs for prevention of late seizures (after 7 days) has not been proven effective (not recommended).
   2. CPP modulation
      a. CPP = mean arterial pressure (MAP) – ICP.
      b. Surrogate for global cerebral perfusion
      c. Recommended goal is 50–70 mm Hg.
      d. Ideal CPP may have interpatient variability because of the patient's medical history and unique characteristics of the TBI.
      e. Patients with a history of poorly treated hypertension may require higher CPP.
   3. Fluid resuscitation with or without vasopressor therapy
      a. Norepinephrine or phenylephrine is the preferred vasopressor for this indication.
      b. Routine targeting of CPP greater than 80 mm Hg is no more effective than targeting of lower CPP and may result in increased complications (acute respiratory distress syndrome) and pulmonary edema.
   4. Supportive care – Venous thromboembolism (VTE) prophylaxis
      a. Patients with TBI have an increased risk of VTE because of:
         i. TBI-related coagulopathy
         ii. Delay in initiation of pharmacologic VTE prophylaxis
         iii. Immobility
         iv. Concomitant injuries (in the case of polytrauma)
      b. Mechanical prophylaxis should be initiated as soon as possible.
      c. Pharmacologic prophylaxis should be initiated after intracranial bleeding is stabilized.
         i. Typically, 24–48 hours after event
         ii. May depend on coagulopathy on admission, extension of bleeding on CT scan, and other factors
      d. Unfractionated heparin or low-molecular-weight heparin (LMWH) may be used for pharmacologic prophylaxis. LMWH may be preferred in patients with polytrauma, particularly long bone or pelvic fractures.

5. Nutrition support
    a. Initiating nutrition support within 48 hours improves immune competence and may improve neurologic outcome. (Critical Care Medicine 1999;27:2525-2531)
    b. Gastric feeding is not well tolerated in patients with TBI, particularly during the first 5–7 days and particularly in those with elevated ICP (causes decreased gastric motility). Postpyloric feeding access should be established as soon as possible.
    c. Metabolic needs are elevated after TBI (typically proportional to the severity of injury).
        i. Patients with TBI typically require 120%–160% of basal metabolic needs.
        ii. Metabolic cart/direct calorimetry can be used to better evaluate caloric needs.
6. Prevention of stress-related mucosal bleeding
    a. Patients with TBI have an increased risk of stress-related mucosal bleeding.
        i. Hypotension associated with TBI or trauma
        ii. Hypersecretion of acid associated with neurologic injury (Cushing ulcers)
        iii. Potential for coagulopathy
        iv. Need for mechanical ventilation
    b. Almost all patients with severe TBI should receive prophylaxis for stress-related mucosal bleeding.
        i. Histamine-2 receptor antagonists (H_2RAs) have traditionally been the preferred agents.
        ii. Proton pump inhibitors (PPIs) also raise gastric pH and permit hemostasis in areas of gastritis.
        iii. Recent meta-analyses have suggested PPIs are superior to H_2RAs, but a well-powered clinical trial has not been completed in the ICU population or in the neuroICU population.
        iv. Which agent to select may depend on:
            (a) Medications taken at home before admission
            (b) Prescriber preference
            (c) Presence of GI bleeding on admission
7. Glycemic control
    a. Hyperglycemia is associated with increased mortality in TBI.
    b. Potential mechanisms
        i. Glucose toxicity in neurons
        ii. Surrogate for severity of injury
        iii. Exacerbation of cerebral edema
    c. Avoid administering dextrose 5% and other hypotonic glucose-containing fluids.
    d. Glycemic goals
        i. Prevent hyperglycemia (greater than 180 mg/dL)
        ii. A range of 140–180 mg/dL seems reasonable.
        iii. Caution should be exercised with glucose values in low-normal range because of risk of hypoglycemia.
        iv. Hypoglycemia is associated with a worse outcome in TBI.
            (a) Glucose obligate substrate for neurons
            (b) Threshold for glucose needs may be altered in TBI.
            (c) May increase seizure risk
8. Steroids
    a. No role for high-dose methylprednisolone in the treatment of inflammation or edema associated with TBI.
    b. Large, prospective, randomized clinical trial showed increased mortality in steroid group compared with placebo (CRASH). (The Lancet 2005;365:1957-1959)

9. Pharmacokinetic alterations
    a. Altered volume of distribution: Patients with TBI have increased volume of distribution due to the following:
        i. Fluid resuscitation
        ii. Transient increased permeability of blood-brain barrier
    b. Hepatic metabolism induction
        i. TBI increases hepatic metabolic capacity (extent to which is likely proportional to severity of injury).
        ii. Results in more effective clearance of hepatically metabolized medications
        iii. Increased dosing requirement for commonly used agents such as phenytoin, midazolam
        iv. Induction subsides over time (usually 1–3 months, but varies by patient).
        v. Hypothermia during TBI may also reduce the induction of hepatic metabolism/cause metabolic rate of medications to be less than baseline.
    c. Augmented renal clearance
        i. Increase in glomerular filtration rate
        ii. Fluid resuscitation
        iii. Increased endogenous catecholamines and glucocorticoid response
        iv. Results in more effective clearance of renally eliminated medications
        v. Increased dosing requirement for commonly used agents such as vancomycin, aminoglycosides, β-lactams
        vi. Augmented renal clearance tends to subside over time (usually after first 7 days, but varies by patient).

VI. PAROXYSMAL SYMPATHETIC ACTIVITY (i.e., "brainstorming")

A. Epidemiology
    1. About 8%–10% incidence in survivors of acquired brain injury
    2. Commonly associated with TBI (specifically diffuse axonal injury), but may occur with other CNS insults
    3. Diagnosis
        a. Typically, four or more symptoms (J Neurotrauma 2014;31:1515-1520)
        b. Fever
        c. Tachycardia
        d. Hypertension
        e. Tachypnea
        f. Dyspnea
        g. Diaphoresis
        h. Muscle rigidity
        i. Common triggers
        j. Pain
        k. Bladder distension
        l. Turning
        m. Tracheal suctioning
        n. Typically unprovoked (hence "paroxysmal")
    4. Pathophysiology largely unknown, but thought to be caused by somatosympathetic activation and heightened activity of brain stem after brain injury

Table 10. Preventive and Abortive Therapies for Paroxysmal Sympathetic Activity

Preventive Therapies	Abortive Therapies
Baclofen IT (titrated according to patient response) Bromocriptine 1.25 mg orally/enterally twice daily (up to 40 mg/day) Clonidine 0.1–0.3 mg orally/enterally three times daily Gabapentin 100–300 mg three times daily (up to 4800 mg/day) Propranolol 20–60 mg orally/enterally every 4–6 hr	Baclofen IT (titrated according to patient response) Clonidine 0.1–0.3 mg orally/enterally three times daily Dantrolene 0.25–2 mg/kg intravenously every 6–12 hr Dexmedetomidine Diazepam 5–10 mg intravenously Fentanyl 25–100 mcg intravenously Morphine 2–8 mg intravenously Propranolol 20–60 mg orally/enterally every 4–6 hr

Curr Treat Options Neurol 2008;10:151-157

VII. ACUTE ISCHEMIC STROKE

A. Epidemiology
   1. Third leading cause of death and No. 1 cause of disability in the United States, with around 750,000 strokes in the United States annually.
   2. 85% of strokes are ischemic in nature.

B. Diagnosis/Pathogenesis
   1. Diagnostic tests
      a. Neurologic examination
      b. Vital signs
      c. NIH Stroke Scale (greater than 25 is severe, range 1–42)
      d. Imaging and other tests (Stroke 2013;44:870-947)
      e. Noncontrast CT scan or magnetic resonance imaging (MRI) of the brain (to rule out bleeding)
      f. CT angiography (if intra-arterial thrombolysis or thrombectomy is contemplated)
      g. CT or MRI perfusion and diffusion imaging may be considered for patients outside the thrombolysis window.
      h. Chest radiography (if lung disease is suspected)
      i. Lumbar puncture (if SAH is suspected and CT scan is negative for blood)
      j. EEG (if seizures are suspected)
   2. Laboratory tests
      a. Blood glucose
      b. INR, activated partial prothrombin time (consider thrombin time, anti–factor Xa [anti-Xa] activity for newer oral anticoagulants)
      c. Complete blood cell count (CBC)
      d. Tests for hypercoagulable state

C. Causes
   1. Cardioembolic (29.1%)
   2. Large-artery atherosclerosis (16.3%)
   3. Lacunar infarcts (15.9%)
   4. Unknown (36.1%)
   5. Other (2.6%)

D. Treatment Considerations (Stroke 2013;44:870-947)
   1. Thrombolysis: Alteplase 0.9 mg/kg (maximum 90 mg) within 4½ hours of symptom onset; 10% of total dose as intravenous bolus, followed by 90% as 60-minute intravenous infusion

Table 11. Typical Inclusion/Exclusion Criteria for Intravenous Alteplase for Ischemic Stroke (exclusions are primarily based on the risk of systemic bleeding or hemorrhagic conversion of stroke)

Patient Selection Criteria	Patient History Excludes All Contraindications
Onset of symptoms < 4½ hr from drug administration	Recent intracranial or intraspinal surgery
Baseline CT head excludes intracerebral hemorrhage (ICH) or other risk factors	Head trauma or stroke < 3 months
Age > 18 yo	Active internal bleeding
	Symptoms suggest SAH
Vital signs and laboratory values:	Any history of ICH
INR ≤ 1.7	Intracranial neoplasm, arteriovenous malformation, or aneurysm
Platelet count ≥ 100,000/mm^3	Arterial puncture at noncompressible site < 1 wk
Blood glucose 50–400 mg/dL	Current use of novel anticoagulant agents with evidence of elevated sensitive laboratory tests
Blood pressure control (SBP < 185 mm Hg, DBP (diastolic blood pressure) < 110 mm Hg)	
	Additional exclusion criteria for 3- to 4½-hr window:
	Age > 80
	NIHSS > 25
	History of both stroke and diabetes
	Current treatment withoral anticoagulants (regardless of INR)

NIHSS = NIH Stroke Scale (score).

N Engl J Med 2008;359:1317-1329, Stroke 2013;44:870-947

   2. Permissive hypertension
      a. Reduction in blood pressure outside thrombolysis or recanalization is reasonable within the first 24 hours after onset of stroke.
      b. Cautiously to avoid hypotension or underperfusion of infarcted area (less than 15% blood pressure lowering)
      c. Resumption of home blood pressure medications is reasonable 24 hours after the onset of stroke.
      d. Recommended to treat blood pressure if it exceeds SBP greater than 220 mm Hg or diastolic blood pressure (DBP) greater than 120 mm Hg
   3. Seizure prophylaxis. Use of AEDs for seizure prophylaxis is not indicated after ischemic stroke.
   4. Secondary prevention
      a. Initiation of aspirin (325 mg x 1; then 81–325 mg/day), statin, intensive blood pressure regimen is necessary
         i. Ideally, as soon as feasible after the onset of stroke
         ii. Aspirin should not be initiated within 24 hours of alteplase.
      b. Control/modification of other disease states is often necessary.
      c. Hypertension: Typical blood pressure goal is less than 140/90 mm Hg.

d. Atrial fibrillation
    i. Rate or rhythm control
    ii. Anticoagulation (warfarin, new oral anticoagulants)
    iii. Typically, anticoagulant therapy is delayed until 5–14 days after stroke to reduce the risk of hemorrhagic conversion
    iv. Avoid using loading doses of warfarin.
e. Carotid artery stenosis: Stent versus endarterectomy (usually for patients with greater than 70% blockage and/or clinically evident symptoms)
f. Intracranial artery stenosis
g. Diabetes mellitus
h. Inherited or acquired hypercoagulable states

VIII. INTRACEREBRAL HEMORRHAGE

A. Epidemiology. Around 50,000 cases in the United States annually
    1. Diagnosis/pathogenesis
        a. Neurologic examination
        b. Vital signs
        c. NIH Stroke Scale and/or GCS score
    2. Imaging and other tests
        a. CT or MRI scan of the brain
        b. CT angiography or contrast-enhanced CT (to help identify patients at risk of hematoma expansion and to evaluate for underlying structural lesions)
        c. Medication history to identify agents that might produce coagulopathy
        d. Laboratory tests
        e. Blood glucose
        f. INR
        g. CBC

B. Causes
    1. Chronic/poorly treated hypertension
    2. Oral anticoagulant use
    3. Cocaine/other stimulant use
    4. Ischemic stroke
    5. Chronic alcohol intake
    6. Brain tumor
    7. Arteriovenous malformation
    8. Amyloid angiopathy

C. Clinical Impact – Death or major disability occurs in around 50% of patients.

D. Treatment Considerations (Stroke 2010;41:2108-2129)
    1. Coagulopathy reversal
    2. Prompt reversal is necessary. Reversal of laboratory values does not confirm hemostasis, especially with the newer oral anticoagulants.

Table 12. Anticoagulant Reversal Options

Anticoagulant	Reversal Agent and Dose	Adverse Effects
Warfarin	4f-PCC 25 units/kg (INR < 4), 35 units/kg (INR 4-6)or 50 units/kg (INR > 6) + vitamin K 10 mg intravenously Alternative: FFP 10–15 mL/kg + vitamin K 10 mg intravenously	Thrombosis, anaphylactoid reaction (vitamin K), pulmonary edema, or transfusion-related reaction (FFP)
Oral factor Xa inhibitors[a]	4f-PCC 50 units/kg or activated 4f-PCC (FEIBA) 50 units/kg	Thrombosis; limited data for reversal, especially with FEIBA
Oral direct thrombin inhibitorsa	4f-PCC 50 units/kg or activated 4f-PCC (FEIBA) 50 units/kg	Thrombosis; limited data for reversal, especially with FEIBA
Oral antiplatelets	Platelet infusion	Pulmonary edema or transfusion-related reaction (FFP)
Unfractionated heparin	Protamine (1 mg of protamine for each 100 units of heparin infused within the past 2–3 hours)	Hypotension, hypersensitivity
Low-molecular-weight heparins	Protamine 1 mg for each 1 mg of enoxaparin (within 8 hours of last dose)	Hypotension, hypersensitivity

[a]Reversal options have not been tested in patients with ICH and have variable degrees of coagulopathy reversal in experimental animal and human models.

4f-PCC = 4-factor prothrombin complex concentrate; FEIBA = factor eight inhibitor bypassing activity; FFP = fresh frozen plasma.

E. Blood Pressure Management
   1. Prompt control of blood pressure is essential.
   2. Historically, caution may have been used in rapidly reducing blood pressure in chronically hypertensive patients because of concerns regarding accommodations in cerebral autoregulation.

Patient Case

3. A 61-year-old man is admitted with acute onset of difficulty speaking, confusion, and right-sided weakness. His NIH stroke scale score is 20. A CT scan of the head reveals a right parietal ICH. The patient's home medications include hydroxychloroquine, ibuprofen as needed, warfarin, amlodipine, and donepezil. His medical history includes a deep venous thrombosis (1 year ago), hypertension, early dementia, and arthritis. Serum laboratory values include Na 140 mEq/L, K 3.6 mEq/L, BUN 27 mg/dL, SCr 1.8 mg/dL, glucose 289 mg/dL, hematocrit 36.7%, platelet count 245,000/mm^3, and INR 2.8. His vital signs include blood pressure 163/101 mm Hg, heart rate 99 beats/minute, Sao_2 97%, and respiratory rate 20 breaths/minute. Which is the most appropriate initial therapy in addition to vitamin K for this patient's care?

   A. Reinitiate amlodipine.
   B. 6-pack infusion of platelets.
   C. 4-factor prothrombin complex concentrate (PCC) 25 units/kg intravenously x 1.
   D. Recombinant factor VIIa 90 mcg/kg intravenously x 1.

Patient Case *(continued)*

4. For this 61-year-old patient with ICH, which is the most appropriate initial antihypertensive therapy?
   A. Nitroprusside 0.5 mcg/kg/minute infusion to keep SBP less than 140 mm Hg.
   B. Nicardipine 5 mg/hour infusion to keep SBP less than 140 mm Hg.
   C. Labetalol 10 mg intravenously as needed to keep SBP less than 160 mm Hg.
   D. Esmolol 50 mcg/kg/minute infusion to keep SBP less than 180 mm Hg.

3. However, recent evidence suggests that the benefit of rapidly reducing the blood pressure (and thus reducing the risk of rebleeding) outweighs any concern for cerebral autoregulation issues and potential for ischemia.
4. INTERACT-2 – Large, prospective, randomized trial that compared levels of blood pressure control within 1 hour. (N Engl J Med 2013;368:2355-2365) SBP less than 140 mm Hg was as safe and effective as SBP less than 180 mm Hg (and may have had improved functional outcomes).

F. Seizure Prophylaxis. Use of AEDs for seizure prophylaxis is not indicated after intracerebral hemorrhage (ICH).

IX. SUBARACHNOID HEMORRHAGE

A. Epidemiology
   1. Occurs in around 15 of 100,000 people in the United States
   2. 60%–70% female, typical age 40–60 years

B. Diagnosis/Pathogenesis: Neurologic examination
   1. Vital signs
   2. NIH Stroke Scale and/or GCS

Table 13. SAH Severity Scale Scores

	Score Range	**Comments**
Hunt and Hess	0 (no rupture) to 5 (moribund)	Best correlated with risk of mortality
World Federation of Neurological Societies (WFNS)	1 (GCS score 15, no deficit) – 5 (GCS score 3–6)	Integrates risk of mortality and motor dysfunction
Fisher	1 (no blood visualized) to 4 (diffuse SAH, ICH, or intraventricular hemorrhage present)	Best correlated with risk of vasospasm

GCS = Glasgow Coma Scale.

C. Imaging (Stroke 2009;40:994-1025)
   1. CT scan of brain
   2. Lumbar puncture when CT scan of brain is negative for blood
   3. Digital subtraction (“conventional”) angiography
   4. May use CT angiography or magnetic resonance angiography if conventional angiography is not available

D. Medication History - to identify agents that might produce coagulopathy

E. Laboratory and Other Tests
   1. INR
   2. CBC
   3. Troponin
   4. ECG (electrocardiogram)
   5. Echocardiogram

F. Causes – Typically caused by cerebral aneurysm
   1. Modifiable risk factors for SAH
   2. Hypertension
   3. Smoking
   4. Illicit drug use

G. Clinical Impact
   1. Sudden death: Around 20% of patients die before hospitalization.
   2. Vasospasm and delayed ischemic neurologic deficits (DINDs)
      a. Presence of blood in subarachnoid space elicits a chemical meningitis-type inflammatory response and results in hemolysis of subarachnoid blood.
      b. Vasospasm (persistent vasoconstriction) occurs, causing a reduction on distal cerebral blood flow.
         i. Typical course is 3–14 days.
         ii. Vasospasm risk peaks at around 7–10 days.
      c. Several mechanisms of pathogenesis
         i. Inflammatory infiltration
         ii. Endothelin activation
         iii. Liberation of hemoglobin results in the scavenging of nitric oxide.
      d. Vasospasm is one of the main factors resulting in death or disability after acute SAH, aside from initial ictus.

H. Treatment Considerations (Stroke 2012;43:1711-1737)
   1. Agents for preventing vasospasm or DINDs
      a. Nimodipine (British Medical Journal 1989;298:636-642)
         i. Lipophilic dihydropyridine calcium channel blocker
         ii. "Cerebrovascular-specific"
         iii. 60 mg orally or per tube every 4 hours x 21 days
         iv. Only U.S. Food and Drug Administration (FDA) label-approved medication to reduce DINDs associated with SAH
         v. Clinical trials did not show a large effect of nimodipine on the occurrence of vasospasm (though the effects of DINDs were still significantly less).
         vi. Possibly neuroprotective
      b. Statins
         i. Preservation of nitric oxide balance as heme is liberated during SAH hemolysis
         ii. Phase II data with pravastatin and simvastatin
         iii. Phase III trial (STASH) did not show benefit of applying statins in aneurysmal SAH. (Lancet Neurol 2014;13:666-675)
         iv. Abrupt withdrawal of statins in patients who were taking before SAH may result in a withdrawal effect and increase the risk of vasospasm.

c. Others?
    i. Magnesium – No utility in attaining magnesium concentrations 3–4 mEq/L. Maintaining magnesium at normal concentrations (i.e., preventing hypomagnesemia) is advisable.
    ii. Clazosentan – No utility in blocking endothelin-1
    iii. Albumin – Not beneficial and may be associated with an increase in pulmonary edema

2. Treatment of vasospasm
    a. Intra-arterial therapies (see below)
    b. Triple-H therapy (hypertension, hypervolemia, hemodilution)
        i. No longer recommended in the traditional format. Euvolemia is better than hypervolemia – Similar outcomes in clinical trials, less pulmonary edema
        ii. Hyperperfusion therapy
            (a) Better descriptor for the goal of therapy
            (b) Vasospasm causes distal vasoconstriction to the point of ischemia.
            (c) Maximizing cerebral blood flow mitigates ischemia.
        iii. Contemporary therapy includes:
            (a) Euvolemia
            (b) Vasopressors (blood pressure targets are ill defined, but are also typically patient- and symptom-dependent)
            (c) Inotropes (milrinone)

3. Seizure prophylaxis
    a. Use of AEDs for seizure prophylaxis is controversial after an SAH.
    b. One small study suggests 3 days of prophylactic phenytoin after aneurysm clipping is helpful in reducing the seizure rate.
    c. SAH guidelines permit prophylaxis, according to this study.
    d. Some evidence suggests that phenytoin use in aneurysmal SAH is associated with worse outcomes and increased in-hospital complications.

X. INTERVENTIONAL ENDOVASCULAR MANAGEMENT

A. Intra-arterial Therapies (Pharmacotherapy 2010;30:405-417)
    1. Administration technique
    2. Typically administered during cerebral angiography. Catheter advanced to vessels with lesion/vasospasm, and drug is infused locally (“super-selective infusion”)
    3. Calcium channel blockers
        a. Typically used for cerebral vasospasm associated with SAH
        b. Direct, local infusion typically results in immediate vasodilation.
        c. Usually effective in proximal and distal vessels

Table 14. Typical Agents for Intra-arterial Use for Cerebral Vasospasm

Agent	Typical Dose	Adverse Effects
Nicardipine	1–10 mg (usually 1–2 mg)	Systemic hypotension Increased ICP
Verapamil	1–8 mg (usually 1–2 mg)	Systemic hypotension Bradycardia Increased ICP
Milrinone	8 mg	Systemic hypotension
Papaverine	150–600 mg	Increased ICP Systemic hypotension Neurologic deterioration

ICP = intracranial pressure.

B. Thrombolysis
   1. Most often used in patients with ischemic stroke
   2. Limited evidence to support combining with intravenously alteplase as a standard of care
   3. Current roles
      a. Combination with mechanical thrombectomy
      b. Rescue therapy in patients having received intravenously alteplase
      c. Large hemispheric infarction
         i. Dose is not well defined.
         ii. Typically applied until thrombus has resolved
         iii. Alteplase less than 20 mg

Patient Case

A 49-year-old woman presents to an urgent treatment center with the "worst headache of her life." She is sent to your ED, where a CT scan of the head reveals a diffuse SAH. The patient takes no home medications and has an insignificant medical history other than a 20 pack-year history of smoking.

5. Which therapy is most appropriate to prevent ischemic complications from SAH?
   A. Nimodipine for 21 days.
   B. Euvolemia and permissive hypertension for 14 days.
   C. Simvastatin for 14 days.
   D. Aminocaproic acid infusion for 48 hours.

6. On hospital day 5, the patient has reduced alertness, and her GCS score decreases by 2 points. The digital subtraction angiography suggests cerebral vasospasm. Which treatment modality is best to initiate first?
   A. 1 unit of packed RBCs to increase hemoglobin to 10 g/dL.
   B. Norepinephrine 0.05 mcg/kg/minute to increase MAP to 90 mm Hg.
   C. 0.9% sodium chloride boluses to increase central venous pressure to 14 mm Hg.
   D. Milrinone 0.375 mcg/kg/minute infusion to increase cardiac index to 5 L/minute/m^2.

C. Stent Deployment and Antiplatelet Agents
   1. Intracranial stents often deployed in place of coils or to support coils for complex aneurysms
   2. Intracranial circulation is different from coronary circulation.
      a. Blood vessels are generally smaller and more tortuous.
      b. Flow rate is lower.
      c. Epithelialization of stent takes longer.
   3. Dual antiplatelet therapy is typically used around the time of stent placement.
      a. Clopidogrel plus aspirin
      b. Current evidence suggests up to 3 months in duration (not 4 weeks like after percutaneous coronary intervention)
      c. Platelet testing may be necessary in some individuals to evaluate their pharmacogenetic response to clopidogrel.
      d. No gold standard for platelet reactivity in this setting
      e. Patients may require higher/additional loading doses of clopidogrel peri-procedurally or if procedural thrombosis occurs.
      f. Prasugrel is not recommended in patients with high on-treatment platelet reactivity because of warnings about use in patients with a history of stroke – Increased bleeding
      g. Ticagrelor may have a role in patients with a variable response to clopidogrel.

Patient Case

A 52-year-old woman is admitted to your ICU after a single vehicle crash. She has many orthopedic injuries to her lower extremities and a subdural hematoma, which will require an emergency craniotomy for evacuation. Her home medications include metoprolol, rivaroxaban, lisinopril, and atorvastatin. Her medical history is significant for atrial fibrillation. Laboratory values were obtained on admission and were notable for hematocrit 31.2% and platelet count 577,000 mm^3.

7. Which would be the most appropriate laboratory tests to obtain to evaluate the extent of anticoagulation from rivaroxaban?
   A. INR.
   B. Anti-Xa activity level.
   C. Activated partial thromboplastin time.
   D. VerifyNow PRUTest measurement.

8. Which would be the most appropriate therapy to reverse rivaroxaban before the emergency craniotomy for this patient?
   A. 4-factor PCC 50 units/kg intravenously x 1.
   B. Vitamin K 10 mg intravenously x 1.
   C. Fresh frozen plasma 15 mL/kg intravenously x 1.
   D. Recombinant factor VIIa 90 mcg/kg intravenously x 1.

XI. ACUTE SPINAL CORD INJURY (NEUROSURGERY 2013;60 SUPPL 1:82-91)

A. Epidemiology – Annual incidence of 15–40 cases per 1 million people in the United States

B. Diagnosis/Pathogenesis
   1. Diagnostic tests
   2. Neurologic examination

C. Imaging (Neurosurgery 2013;60 Suppl 1:82-91)
   1. CT scan of spine
   2. Many views of spine radiography are necessary when a CT scan is unavailable.

D. Causes
   1. 40%–50% are caused by motor vehicle collisions.
   2. Falls (20%), violence (14%), recreational and work activities

E. Clinical Impact
   1. Mortality
      a. Ranges from 50% to 75% at the time of injury
      b. Hospital mortality 4.4%–16%
   2. Morbidity
      a. Paralysis and loss of sensation
      b. Spasticity
      c. Neurogenic shock
      d. Orthostatic hypotension
      e. Autonomic dysreflexia
      f. Venous thromboembolism
      g. Decubitus ulcers
      h. Respiratory insufficiency
      i. Bowel and bladder dysfunction
      j. Sexual dysfunction
      k. Treatment considerations
      l. Neurogenic shock
         i. Hypotension often occurs after injury (50%–90% of cervical spine injuries).
         ii. May be associated with malperfusion of the spinal cord and worsened outcome
         iii. Etiology of shock is decreased sympathetic nervous system outflow. Continues to be counterbalanced by parasympathetic outflow, which is not affected by SCI
         iv. Results in hypotension and bradycardia

F. Blood Pressure Management
   1. Typical recommendations after acute SCI are to maintain MAP 85–90 mm Hg x 7 days to ensure adequate spinal perfusion.
   2. Little high-quality evidence supports this recommendation, but it is included in the SCI guidelines as a treatment option.
   3. Often requires judicious fluid resuscitation and vasopressor support.

G. VTE Prophylaxis
   1. Occurs in 80%–100% of patients without pharmacologic prophylaxis
   2. LWMHs are the drugs of choice for prophylaxis and should be initiated within the first 36 hours post injury.
   3. Duration of prophylaxis is typically about 8 weeks.

H. Role of High-Dose Methylprednisolone (NEJM 1990;322:1405-1411, J Neurosurg 1992;76:23-31, JAMA 1997;277:1597-1604, J Neurosurg 1998;89:699-706, Neurosurgery 2013;60 Suppl 1:82-91)
   1. Controversial topic related to NASCIS-II and NASCIS-III trials
   2. Methylprednisolone 30 mg/kg intravenously x 1, followed by 5.4 mg/kg/hour within 8 hours of injury for 24 or 48 hours
   3. Both trials suggested a modest benefit in the first 6 weeks or 6 months (which often did not persist at 1 year) and a modest risk (primarily related to infection). Current guidelines do not support administering high-dose methylprednisolone.
   4. NASCIS-II split enrolled population in half (those who received the drug before the median time to administration [8 hours] and those who did not).
      a. Subgroup analysis may not have been powered to show benefit.
      b. Used motor and sensory scores from one side of the body, not both. The investigators later said there was no difference, but they have not allowed others to examine the raw data.
   5. Consistently showed risk (GI bleeding, infection) and inconsistently showed benefit
   6. Potential treatment effects may have been caused by early surgery or additional benefit of high-dose methylprednisolone therapy in combination with early surgery.
   7. NASCIS-III used a functional independence measure (FIM) score to show how improvement in muscle strength might translate to improved outcome. Failed to show a difference in FIM score
   8. If a practitioner does choose to use high-dose steroids in SCI:
      a. Must use methylprednisolone; no other steroids
      b. Must use NASCIS-II or NASCIS-III dosing
      c. Must give within 8 hours of injury

XII. BRAIN TUMORS

A. Epidemiology
   1. Primary brain tumors (from brain cells such as meninges and neural tissues)
   2. 17,000–20,000 cases per year in the United States
   3. Glioblastoma
   4. Meningioma
   5. Pituitary adenoma
   6. Astrocytoma
   7. Metastases – Common neoplasms that result in spread to brain
      a. Lung (40%–50%)
      b. Breast (15%–20%)
      c. Melanoma (5%–10%)
      d. Colon (4%–6%)
      e. Renal cell carcinoma
      f. CNS lymphoma

B. Diagnosis/Pathogenesis – Diagnostic tests
   1. Contrast-enhanced MRI is the most common test.
   2. Biopsy is often necessary to elucidate the specific histology.

C. Clinical Impact – Mortality is often high, depending on the nature and grade of the tumor.

D. Treatment Considerations
   1. Corticosteroids (and adverse drug reactions) for brain edema
      a. Dexamethasone commonly used for vasogenic edema associated with tumor
         i. Reduces peritumoral edema and symptoms associated with increased ICP. Temporarily reduces symptoms (neurologic dysfunction, seizures, headache)
         ii. Dose commonly 4 mg intravenously every 6 hours – 1st dose prior to antibiotics
      b. May use other corticosteroids at comparable doses
      c. Use of acid-suppressive agents may be helpful with concomitant steroid use to reduce the risk of GI complications. (Wien Med Wochenschr 1988;138:97-101)
      d. Consideration for glycemic control and gastric protection with prolonged use
      e. Induction of phenytoin metabolism (because of increased metabolic rate)
      f. Metabolism induced by phenytoin (because of increased cytochrome P450 [CYP] activity)
   2. VTE prophylaxis and treatment
      a. High risk of VTE
      b. Consider using combination pharmacologic/mechanical prophylaxis.
      c. Enoxaparin is superior to warfarin for treatment of VTE in oncology patients.
   3. Seizure prophylaxis
      a. Not typically indicated
      b. AEDs often necessary (seizures may occur often) – Around 50% of patients with primary brain tumor present with seizure.
      c. Phenytoin, carbamazepine, levetiracetam often recommended
      d. Phenytoin may be problematic for some chemotherapy agents (CYP enzyme induction).

XIII. CRITICAL ILLNESS POLYNEUROPATHY

A. Epidemiology
   1. Exact incidence is unknown because of inconsistent monitoring and diagnosis.
   2. May be as high as 60% in patients with acute respiratory distress syndrome, 77% in long ICU stay (greater than 7 days), 80% in patients with multiorgan failure

B. Diagnosis/Pathogenesis – Diagnostic tests
   1. Typically suspected when patients do not wean well from the ventilator or if their limbs are weak/flaccid
   2. Electrophysiologic studies or muscle biopsy may provide a more precise diagnosis. Differential diagnosis includes evaluation for critical illness myopathy, Guillain-Barré syndrome, electrolyte abnormalities

C. Causes
   1. The cause of critical illness polyneuropathy is unknown, but several hypotheses exist.
      a. Mitochondrial dysfunction in critical illness may cause energy stress in vulnerable neurons.
      b. Microcirculatory ischemia
      c. Protein catabolism in severe critical illness/immobility may cause muscle wasting.

2. Often associated with:
    a. Sepsis
    b. Multiorgan dysfunction
    c. Hyperglycemia
    d. Renal failure
    e. Neuromuscular blockade
    f. Duration of vasopressor or corticosteroid therapy
    g. Duration of ICU stay

D. Clinical Impact
1. Limb and diaphragm weakness may persist for weeks to months.
2. About 33% of patients with critical illness polyneuropathy ultimately cannot independently ambulate or breathe.

E. Treatment Considerations
1. No specific treatments have been shown to be effective.
2. Intravenous immunoglobulin may play a role. (The Lancet Neurology 2008;7:136-144)
3. Intensive glycemic control may reduce critical illness neuropathy.
4. Passive mobilization/early physical therapy in the ICU
5. Daily awakening/less time on the ventilator
6. Limiting risk factors as much as possible

XIV. GUILLAIN-BARRÉ SYNDROME

A. Epidemiology
1. 1.11 cases per 100,000 person-years
2. Men > women (almost 2:1)

B. Diagnosis/Pathogenesis – Diagnostic tests
1. Bilateral symmetric progressive weakness of limbs
2. Generalized hyporeflexia or areflexia
3. Nerve conduction studies may provide a more precise diagnosis.

C. Causes
1. Typically associated with *Campylobacter jejuni* infection. Also associated with Epstein-Barr virus, varicella-zoster, and *Mycoplasma pneumoniae* infections
2. Swine flu vaccine in 1976 caused increased risk of Guillain-Barré syndrome.

D. Clinical Impact
1. Progressive weakness over 3–4 weeks
2. 20% of patients remain severely disabled.
3. Mortality rate around 5%
4. Respiratory failure
5. Autonomic dysfunction resulting in arrhythmia, hypertension, hypotension

E. Treatment Considerations (The New England journal of medicine 1992;326:1123-1129)
1. Intravenous immunoglobulin versus plasma exchange
2. Therapies are essentially equivalent.

3. Plasma exchange: Five treatments over 2 weeks
4. Intravenous immunoglobulin: 0.4 g/kg intravenously daily x 5 days
5. Combination of therapies no better than single therapy alone
6. Steroids are not particularly effective.

F. Supportive Care
1. VTE prophylaxis is imperative.
2. Careful ventilation strategies to minimize barotrauma and prevent pneumonia
3. Dysphagia is common, so enteral feeding access is necessary in most cases.
4. Neuropathic pain is common; use opiates with caution to avoid respiratory depression.

XV. MYASTHENIA CRISIS

A. Epidemiology
1. Annual incidence of myasthenia gravis (MG) is 1 or 2 per 100,000.
2. 15%–20% of patients with MG will develop myasthenia crisis within the first year of illness.

B. Diagnosis/Pathogenesis
1. Patients with myasthenia crisis typically present with respiratory failure caused by muscle weakness.
2. Autoimmune disease targeting acetylcholine receptors at the neuromuscular junction
3. Myasthenia crisis is usually preceded by a predisposing factor.
   a. Respiratory infection
   b. Emotional stress
   c. Aspiration
   d. Changes in MG medication regimen
   e. Other physiologic stress (trauma, surgery)

C. Treatment Considerations
1. Intravenous immunoglobulin versus plasmapheresis
2. Intravenous immunoglobulin 0.4 g/kg/day x 3–5 days
3. Plasmapheresis 20–25 mL/kg plasma x 5 exchanges every other day x 10 days
4. Similarly effective; can choose according to patient risk factors, etc.
5. Corticosteroids moderately effective

D. Supportive Care – Consider discontinuing cholinergic therapies while the patient is acutely ill. May increase pulmonary secretions and complicate ventilator/ICU management

XVI. SEROTONIN SYNDROME (NEUROCRIT CARE 2014;21:108-113)

A. Presentation
1. Autonomic hyperactivity (hypertension, tachycardia)
2. Mental status changes
3. Hyperthermia – Diaphoresis
4. Neuromuscular abnormalities
5. Rigidity
6. Hyperreflexia and clonus

Table 15. Medications Associated with Serotonin Syndrome

Antidepressants	SSRIs (sertraline, fluoxetine, citalopram, paroxetine) Trazodone Nefazodone Buspirone Venlafaxine MAOIs (phenelzine)
Anticonvulsants	Valproic acid
Migraine agents	Sumatriptan
Antibiotics	Linezolid
Cough suppressants	Dextromethorphan
Herbal products	St. John's wort Tryptophan Ginseng
Antiemetics	Ondansetron Metoclopramide
Analgesics	Meperidine Fentanyl

MAOI = monoamine oxidase inhibitor; SSRI = selective serotonin reuptake inhibitor.

B. Treatment Considerations
   1. Removal of precipitating drugs/factors
   2. Control of agitation – Benzodiazepines
   3. Control of autonomic hyperactivity – Hypotension treatment with direct-acting sympathomimetics
   4. Control of hyperthermia
      a. Cooling blanket
      b. Sedation, neuromuscular paralysis, intubation
      c. Avoid succinylcholine.
   5. Serotonin-2a antagonist blocks serotonin receptors implicated with serotonin syndrome.
      a. Cyproheptadine 12–32 mg/24 hours by mouth or per feeding tube. A 12-mg loading dose 2 mg every 2 hours as symptoms continue
      b. Chlorpromazine 50–100 mg intramuscularly

XVII. NEUROLOGIC MONITORING DEVICES

A. ICP Monitors
   1. Goal ICP is typically less than 20 mm Hg.
   2. Catheters are typically inserted under sterile conditions at the bedside.
   3. Temporary catheters
      a. Used primarily in the ICU
      b. Ventriculostomy (aka external ventricular drain) – Diagnostic and therapeutic
         i. Catheter inserted into frontal horn of lateral ventricle
         ii. Transduces ICP
         iii. Higher infection rate compared with intraparenchymal catheter; insertion is more difficult (particularly with brain swelling)

iv. Permits drainage of CSF, intraventricular hemorrhage (IVH) drainage
v. Permits intraventricular drug administration

c. Intraparenchymal catheter
i. Wire that sits in brain tissue
ii. Transduces ICP
iii. Low infection rate, fewer complications with insertion
iv. Cannot zero, experience "drift" after prolonged use. May not be entirely accurate for duration of use

d. Brain tissue oxygen monitor (Licox®)
i. Intraparenchymal catheter
ii. Optimal location of placement is not well defined (injured vs. non-injured tissue).
iii. Transduces $PbtO_2$
(a) Goal $PbtO_2$ is usually greater than 15%.
(b) Concept similar to SvO_2 values systemically
iv. Desaturation shows increased ICP or reduced oxygen delivery.
v. Typically, will be used in combination with other monitoring modalities

e. Subarachnoid bolt
i. Single-lumen screw inserted through a burr hole into the subarachnoid space
ii. Transduces ICP
iii. Associated with increased CNS infection

4. EEG
a. Scalp electrodes are placed externally.
b. Permits evaluation of cortical electrical activity
c. Standard of care for seizure monitoring

5. Transcranial Doppler
a. Ultrasound of intracranial vessels
b. Used in monitoring for cerebral blood flow velocity or vasospasm
c. Threshold values
i. 125 cm/second may be suggestive of vasospasm.
ii. 200 cm/second typically suggestive of severe vasospasm
iii. Lindegaard ratio: Ratio of target blood vessel (usually middle cerebral artery) to carotid (internal carotid artery) transcranial Doppler values – Three suggestive of vasospasm

6. Bispectral index (BIS) monitor
a. Scalp electrodes are placed externally.
b. Uses EEG information to derive a number
c. BIS 0–100 (100 being completely wakeful)
d. Little correlation with BIS values and ICP control or extent of pharmacologic coma

REFERENCES

1. Adrogue HJ, Madias NE. Hyponatremia. N Engl J Med 2000;342:1581-9.
2. Alldredge BK, Gelb AM, Isaacs SM, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. N Engl J Med 2001;345:631-7.
3. Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med 2013;368:2355-65.
4. Baguley IJ, Perkes IE, Fernandez-Ortega JF, et al. Paroxysmal sympathetic hyperactivity after acquired brain injury: consensus on conceptual definition, nomenclature, and diagnostic criteria. J Neurotrauma 2014;31:1515-20.
5. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41:263-306.
6. Bederson JB, Connolly ES Jr, Batjer HH, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage. Stroke 2009;40:994-1025.
7. Bracken M, Shepard M, Collins W, et al. A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal cord injury: results of the Second National Acute Spinal Cord Injury Study (NASCIS-2). N Engl J Med 1990;322:1405-11.
8. Bracken M, Shepard M, Collins W, et al. Methylprednisolone or naloxone treatment after acute spinal cord injury: 1-year follow up data—results of the Second National Spinal Cord Injury Study. J Neurosurg 1992;76:23-31.
9. Bracken M, Shepard M, Holford T, et al. Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury: results of the Third National Acute Spinal Cord Injury Study. JAMA 1997;277:1597-604.
10. Bracken M, Shepard M, Holford T, et al. Methylprednisolone or tirilazad mesylate administration after acute spinal cord injury: 1-year follow-up—results of the Third National Spinal Cord Injury Randomized Controlled Trial. J Neurosurg 1998;89:699-706.
11. Brain Trauma Foundation. Management of severe traumatic brain injury. J Neurotrauma 2007;24 (suppl 1):S1-S95.
12. Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care 2012;17:3-23.
13. Connolly ES Jr, Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage. Stroke 2012;43:1711-37.
14. Cook AM, Mieure KD, Owen RD, et al. Intracerebroventricular administration of medications. Pharmacotherapy 2009;29:832-45.
15. Cook AM, Peppard A, Magnuson B. Nutrition considerations in traumatic brain injury. Nutr Clin Pract 2008;23:608-20.
16. de Gans J, van de Beek D; European Dexamethasone in Adulthood Bacterial Meningitis Study Investigators. Dexamethasone in adults with bacterial meningitis. N Engl J Med 2002;347:1549-56.
17. Edwards P, Arango M, Balica L, et al. Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury—outcomes at 6 months. Lancet 2005;365:1957-9.
18. Ellison DH, Berl T. Clinical practice. The syndrome of inappropriate antidiuresis. N Engl J Med 20007;356:2064-72.
19. Friederich JA, Butterworth JF 4th. Sodium nitroprusside: twenty years and counting. Anesth Analg 1994;81:152-62.
20. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008;359:1317-29.
21. Hirschl M. Report of experience with stomach-protective therapy in high-dosage corticosteroid treatment of patients with brain tumors [in German]. Wien Med Wochenschr 1988;138:97-101.
22. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2 suppl): e152S-184S.
23. Hughes RA, Donofrio P, Bril V, et al. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory

demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial. Lancet Neurol 2008;7:136-44.
24. Hurlbert RJ, Hadley MN, Walters BC, et al. Pharmacological therapy for acute spinal cord injury. Neurosurgery 2013;72(suppl 2):93-105.
25. Jauch EC, Saver JL, Adams HP Jr, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44:870-947.
26. Kelly DF, Goodale DB, Williams J, et al. Propofol in the treatment of moderate and severe head injury: a randomized, prospective double-blinded pilot trial. J Neurosurg 1999;90:1042-52.
27. Kirkpatrick PJ, Turner CL, Smith C, et al. Simvastatin in aneurysmal subarachnoid haemorrhage (STASH): a multicentre randomised phase 3 trial. Lancet Neurol 2014;13:666-75.
28. Lee P, Jones R, Center JR. Successful treatment of adult cerebral salt wasting with fludrocortisone. Arch Intern Med 2008;168:325-6.
29. Liu-DeRyke X, Rhoney DH. Cerebral vasospasm after aneurysmal subarachnoid hemorrhage: an overview of pharmacologic management. Pharmacotherapy 2006;26:182-203.
30. Morgenstern LB, Hemphill JC III, Anderson C, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2010;41:2108-29.
31. Pedavally S, Fugate JE, Rabinstein AA. Serotonin syndrome in the intensive care unit: clinical presentations and precipitating medications. Neurocrit Care 2014;21:108-13.
32. Pickard JD, Murray GD, Illingworth R, et al. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. Br Med J 1989;298:636-42.
33. Rabinstein AA, Benarroch EE. Treatment of paroxysmal sympathetic hyperactivity. Curr Treat Options Neurol 2008;10:151-7.
34. Rhoney DH, Parker D Jr. Considerations in fluids and electrolytes after traumatic brain injury. Nutr Clin Pract 2006;21:462-78.
35. Roberts I, Yates D, Sandercock P, et al. Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. Lancet 2004;364:1321-8.
36. Sarode R, Milling TJ Jr, Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. Circulation 2013;128:1234-43.
37. Silbergleit R, Durkalski V, Lowenstein D, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. N Engl J Med 2012;366:591-600.
38. Spasovski G, Vanholder R, Allolio B, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Intensive Care Med 2014;40:320-31.
39. Taylor SJ, Fettes SB, Jewkes C, et al. Prospective, randomized, controlled trial to determine the effect of early enhanced enteral nutrition on clinical outcome in mechanically ventilated patients suffering head injury. Crit Care Med 1999;27:2525-31.
40. Temkin NR, Dikmen SS, Anderson GD, et al. Valproate therapy for prevention of posttraumatic seizures: a randomized trial. J Neurosurg 1999;91:593-600.
41. Temkin NR, Dikmen SS, Wilensky AJ, et al. A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. N Engl J Med 1990;323:497-502.
42. Treggiari-Venzi MM, Suter PM, Romand JA. Review of medical prevention of vasospasm after aneurysmal subarachnoid hemorrhage: a problem of neurointensive care. Neurosurgery 2001;48:249-61; discussion 261-242.
43. Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med 1998;339:792-8.
44. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. Clinical Infectious Diseases 2004;39:1267-84.
45. van de Beek D, de Gans J, McIntyre P, et al. Corticosteroids for acute bacterial meningitis. Cochrane Database Syst Rev 2007;1:CD004405.
46. van der Meche FG, Schmitz PI. A randomized trial comparing intravenous immune globulin and

plasma exchange in Guillain-Barre syndrome. Dutch Guillain-Barre Study Group. N Engl J Med 1991;326:1123-9.

47. Walters BC, Hadley MN, Hurlbert, RJ, et al. Guidelines for the management of acute cervical spine and spinal cord injuries: 2013 update. Neurosurgery 2013;60(suppl 1):82-91.
48. Weant KA, Ramsey CN III, Cook AM. Role of intraarterial therapy for cerebral vasospasm secondary to aneurysmal subarachnoid hemorrhage. Pharmacotherapy 2010;30:405-17.

ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: C

C is correct because Lorazepam is the agent of choice, as recommended by the status epilepticus guidelines. (Neurocrit Care 2012; 17: 3-23). Answers A, B, and D are incorrect because phenytoin is less effective than lorazepam as the initial agent. Although valproic acid and levetiracetam have not been formally compared with lorazepam as the initial agent for status epilepticus, their use is supported by less clinically rigorous evidence.

2. Answer: A

A is correct because mannitol is an agent of choice for treating elevated ICP according to the TBI guidelines. Clinical evidence supports the safety and efficacy of mannitol as a first-line therapy in this situation. (Journal of Neurotrauma 2007; 24: S1-S95) B is incorrect because although hypertonic saline is an option, but the typical dose of 23.4% sodium chloride is 20–30 mL. C and D (Pentobarbital and midazolam) are not ideal selections for this patient because of the likelihood of hypotension.

3. Answer: C

C is correct because warfarin is well reversed by 4-factor PCC products in a much more timely and complete manner than is vitamin K in the acute setting. (Chest 2012; 141: e152S-184S, Circulation 2013; 128: 1234-1243). A is incorrect because although blood pressure control is important for this patient, amlodipine is unlikely to have timely effects immediately after ICH. B is incorrect because platelets are minimally effective for reversing ibuprofen. D is incorrect because rFVIIa is not recommended for reversal of warfarin due to thrombosis risks.

4. Answer: B

B is correct because nicardipine is a recommended agent for reducing blood pressure after ICH and the threshold for treatment is correct based on the INTERACT 2 study. (N Engl J Med 2013; 368: 2355-2365) A is incorrect because although nitroprusside may be considered in this case, but it is typically not recommended unless the SBP exceeds 220 mm Hg. In addition, this patient's renal dysfunction may increase the patient's risk of thiocyanate accumulation. C and D are incorrect because labetalol and esmolol are also effective at reducing blood pressure, but the optimal SBP goal after ICH is less than 140 mm Hg. (Stroke 2010; 41: 2108-2129)

5. Answer: A

A is correct because nimodipine is the only agent with an FDA indication for preventing ischemic complications related to SAH. (British Medical Journal 1989; 298: 636-642, Stroke 2012; 43: 1711-1737) B is incorrect because prophylactic Triple-H therapy or variants thereof are not effective for preventing ischemic complications—rather, hyperperfusion therapies are used when vasospasm develops. C is incorrect because clinical trials investigating the efficacy of statins for preventing vasospasm have failed. (Lancet Neurol 2014; 13: 666-675) D is incorrect because aminocaproic acid may in fact increase the risk of stroke in patients with an SAH.

6. Answer: B

B is correct because induction of hypertension with a vasopressor such as norepinephrine appears to improve cerebral perfusion. Titration of the infusion to MAP values that result in improvedment of neurologic symptoms is often necessary. (Pharmacotherapy 2006; 26: 182-203, Stroke 2012; 43: 1711-1737). A is incorrect because data are limited to support transfusing blood to a high hemoglobin (in fact, blood transfusion appears to be a risk factor for vasospasm). In addition, fluid resuscitation to hypervolemic levels is not beneficial. C is incorrect because when hypervolemia is compared with euvolemia, neurologic outcomes are no different, but patients receiving hypervolemia develop more pulmonary edema. D is incorrect because milrinone is not first-line therapy for the treatment of vasospasm.

7. Answer: B

B is correct because the anti-Xa activity level is the laboratory value that best correlates with rivaroxaban activity. A and C are incorrect because neither the INR nor the activated partial thromboplastin time is typically affected by rivaroxaban alone. D is incorrect because the VerifyNow PRUTest measurement is more specific to antiplatelet agents such as aspirin or clopidogrel.

8. Answer: A

A is correct because the most consistent reversal effects, albeit with low-quality evidence, occur with 4-factor PCC. (Circulation 2013; 128: 1234-1243). A and C are incorrect because vitamin K and fresh frozen plasma have no effect on reversing factor Xa inhibitors. D is

incorrect because factor VII may have some utility, but reversal is incomplete, and factor VII is associated with an increased risk of thrombosis.

ANSWERS AND EXPLANATIONS TO SELF-ASESSMENT QUESTIONS

1. Answer: B

B is correct because sodium supplementation is effective for treating hyponatremia. Although hypervolemia is no longer advocated, ensuring euvolemia is important. A and C are incorrect because water restriction or tolvaptan is not desirable in a patient who is 4 days after ictus for SAH because of the importance of maintaining adequate cerebral perfusion. (Stroke 2012; 43: 1711-1737) Hyponatremia may be deleterious in a patient with a new stroke such as an SAH caused by cerebral edema, making Answer D incorrect. (N Engl J Med 2007; 356: 2064-2072)

2. Answer: D

D is correct because vancomycin and ceftriaxone effectively cover the common pathogens for a woman this age who has community-acquired meningitis. A is incorrect because acyclovir is not indicated for this patient because viral meningitis or herpetic encephalitis is not suggested by the lumbar puncture results. B is incorrect because anti-Pseudomonal coverage with cefepime is unnecessary for this patient based on her risk factors. C is incorrect because ampicillin is not indicated for this patient because this patient's age is not within the risk category for *Listeria* infection. (Clinical Infectious Diseases 2004; 39: 1267-1284)

3. Answer: B

B is correct because the optimal CPP varies with each individual, but the typical recommended target range is 50–70 mm Hg. (Journal of Neurotrauma 2007; 24: S1-S95) Patients with TBI have gastric intolerance but benefit greatly from early enteral nutrition, making Answer A incorrect. (Nutrition in Clinical Practice 2008; 23: 608-620) C is incorrect because dextrose-containing fluids may increase cerebral edema in TBI. (Nutrition in Clinical Practice 2006; 21: 462-478) D is incorrect because high-dose methylprednisolone therapy increases mortality in patients with TBI. (Lancet 2004; 364: 1321-1328)

4. Answer: B

B is correct because this patient meets the criteria for receiving alteplase and has no obvious contraindications. The more timely the administration of alteplase, the more likely the patient will benefit (and the less risk). (N Engl J Med 2008; 359: 1317-1329, Stroke 2013; 44: 870-947) A is incorrect because aspirin should be initiated within the first 24–48 hours after stroke, but not necessarily immediately. C is incorrect because the blood pressure may be slightly elevated (SBP less than 185 mm Hg, DBP less than 110 mm Hg) before alteplase administration or immediately after stroke in general (so-called permissive hypertension to ensure adequate cerebral perfusion). Nicardipine is not necessary for this patient at this point. D is incorrect because reversal of warfarin with vitamin K is not recommended in the setting of an acute thrombosis in the brain.

5. Answer: C

C is correct because current guidelines do not recommend high-dose methylprednisolone therapy because of the inconsistency of beneficial effects and the relatively consistent risk of adverse effects (GI bleeding, infection) shown in clinical trials. (Neurosurgery 2013; 72 Suppl 2: 93-105). B is incorrect because high-dose methylprednisolone does not augment spinal perfusion. A and D are incorrect because although the NASCIS-III study showed some potential benefit for patients who received a bolus and a 47-hour infusion when it was initiated between 3 and 8 hours after injury, particularly for incomplete injuries. (J Neurosurg 1998; 89: 699-706), the therapy is no longer recommended.

6. Answer: A

A is correct because of the other agents listed, buspirone is the only one that acts to increase CNS serotonin concentrations. (Neurocrit Care 2014; 21: 108-113) B, C and D would not be expected to increase CNS serotonin concentrations. Cyproheptadine is a potential therapeutic agent for patients with serotonin syndrome.

7. Answer: B

B is correct because given this patient's vital signs and monitoring values, she is likely having a cerebral vasospasm with increased ICP. Therapy should be targeted at optimizing cerebral perfusion (fluid bolus or increase in MAP) and reducing ICP. Hypertonic saline will address both issues, causing an increase in intravascular volume to improve perfusion and possibly increase blood pressure while lowering ICP through osmotic effects. (Neurosurgery 2001; 48: 249-261; discussion 261-242,

Pharmacotherapy 2006; 26: 182-203) A is incorrect because verapamil would need to be given super-selectively in the angiography suite. One possible adverse effect of verapamil is cerebral vasodilation, which might lead to increased ICP, and ICP would be undesirable in this patient right now. (Pharmacotherapy 2010; 30: 405-417) C is incorrect because mannitol may act to decrease ICP, but it will also cause diuresis, which is not desirable in a patient with ongoing cerebral vasospasm. D is incorrect because although a blood transfusion may theoretically increase oxygen-carrying capacity to the brain (enhancing perfusion), blood transfusion may in fact cause a risk of cerebral vasospasm. In addition, it is unlikely to affect ICP.

8. Answer: D

D is correct because propofol represents an almost-ideal agent for sedation with its quick onset and offset of activity and relative lack of dependence on organ function for clearance; however, boluses and large dose titrations should be avoided because of the risk of hypotension. (Journal of Neurosurgery 1999; 90: 1042-1052, Crit Care Med 2013; 41: 263-306) A and C are incorrect because long-acting sedating agents such as lorazepam and morphine are not desirable in patients with neurologic injury because of their propensity to obscure the neurologic examination for prolonged periods. B is incorrect because midazolam (and other benzodiazepines) is associated with increased delirium. In addition, midazolam may accumulate when used for a prolonged period because of its long context-sensitive half-life.