**Acute Hemorrhagic Stroke Introduction**

Hemorrhagic stroke is a critical and life-threatening condition that requires immediate attention and comprehensive management. As clinical pharmacists, our role in the management of this disease state is vital. Hemorrhagic stroke accounts for approximately 13% of all strokes and is characterized by bleeding within the brain. It is crucial to understand the clinical presentation, pathophysiology, diagnostic approach, and available management strategies to provide optimal care to patients.

In this chapter, we will explore the key aspects of hemorrhagic stroke to enhance your knowledge and prepare you for board certification. We will delve into the clinical presentation, discussing the typical signs and symptoms, risk factors, and demographic information of affected patients. Additionally, we will examine the underlying pathophysiology of hemorrhagic stroke, shedding light on the disease process and its impact on the body.

Understanding the diagnostic approach is essential for accurate and timely identification of hemorrhagic stroke. We will explore the various tests, examinations, and criteria used in the diagnosis. Furthermore, we will delve into the management strategies, discussing general approaches, pharmacotherapy options, and evidence-based guidelines for the treatment of hemorrhagic stroke.

By the end of this chapter, you will have a comprehensive understanding of hemorrhagic stroke, enabling you to provide effective and evidence-based care to patients. Let's dive into the clinical aspects and management of this challenging disease state.

**Clinical Presentation**

* Symptoms:
  + Sudden and severe headache
  + Nausea and vomiting
  + Decreased level of consciousness
  + Focal neurologic deficits corresponding to the location of bleeding (e.g., hemiparesis, sensory loss, visual disturbances)
  + Seizures
* Risk Factors:
  + Hypertension
  + Age (most common in individuals over 45 years old)
  + Previous history of hemorrhagic stroke
  + Cerebral amyloid angiopathy
  + Coagulopathies (e.g., hemophilia, thrombocytopenia)
  + Illicit drug use (e.g., cocaine, amphetamines)
  + Excessive alcohol consumption
  + Smoking
  + Family history of hemorrhagic stroke

Hemorrhagic stroke typically presents with sudden and severe symptoms, including a severe headache that is often described as the worst headache of the patient's life. Other symptoms may include nausea, vomiting, and a decreased level of consciousness. Focal neurologic deficits are common, and their specific nature depends on the location of the bleeding within the brain. Risk factors play a crucial role in the development of hemorrhagic stroke, with hypertension being the most significant risk factor. Age, previous history of hemorrhagic stroke, cerebral amyloid angiopathy, coagulopathies, illicit drug use, excessive alcohol consumption, smoking, and family history of hemorrhagic stroke also contribute to the risk. Early recognition of these symptoms and risk factors is essential for prompt diagnosis and management.

**Pathophysiology**

Hemorrhagic stroke occurs when there is bleeding within the brain, leading to the disruption of normal brain function. The two main types of hemorrhagic stroke are intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH), each with distinct pathophysiological mechanisms.

* Intracerebral Hemorrhage (ICH):
  + ICH is characterized by bleeding directly into the brain tissue. It is most commonly caused by the rupture of small blood vessels damaged by chronic hypertension.
  + The elevated blood pressure weakens the vessel walls, leading to vessel rupture and subsequent bleeding into the surrounding brain tissue.
  + The accumulation of blood within the brain parenchyma causes compression of adjacent structures, disrupts normal neuronal function, and results in neurologic deficits.
* Subarachnoid Hemorrhage (SAH):
  + SAH occurs when there is bleeding into the subarachnoid space, the area between the arachnoid and pia mater layers of the meninges.
  + The most common cause of SAH is the rupture of an intracranial aneurysm, a weakened and bulging area in the wall of a cerebral artery.
  + When an aneurysm ruptures, blood is released into the subarachnoid space, leading to an increase in intracranial pressure and subsequent neurologic symptoms.

Both types of hemorrhagic stroke can cause secondary brain injury through various mechanisms, including mass effect from the expanding hematoma, disruption of cerebral blood flow, ischemia from vasospasm, and inflammation in the surrounding brain tissue. These processes contribute to the development of cerebral edema, increased intracranial pressure, and further neurologic deterioration.

Understanding the pathophysiology of hemorrhagic stroke is crucial for guiding treatment decisions and implementing appropriate management strategies to minimize secondary brain injury and improve patient outcomes.

**Diagnostic Approach**

The diagnostic approach for patients presenting with hemorrhagic stroke involves a combination of clinical assessment, imaging studies, and laboratory investigations. Early and accurate diagnosis is essential to guide appropriate management strategies and determine the underlying cause of the hemorrhage.

1. Clinical Assessment:

* A thorough history and physical examination are crucial in identifying symptoms, risk factors, and potential causes of hemorrhagic stroke.
* The assessment includes a detailed neurological examination to determine the location and extent of neurologic deficits.

2. Imaging Studies:

* Non-contrast Computed Tomography (CT) Scan: This is the initial imaging modality of choice for suspected hemorrhagic stroke. It helps identify the presence, location, and size of the hemorrhage, allowing for immediate intervention and differentiation from ischemic stroke.
* Computed Tomography Angiography (CTA): CTA is commonly performed to evaluate the blood vessels and detect underlying vascular abnormalities or aneurysms that may have caused the hemorrhage.
* Magnetic Resonance Imaging (MRI): MRI may be used to provide more detailed information about the brain and blood vessels, especially in cases where the CT scan is inconclusive or additional characterization is required.

3. Laboratory Investigations:

* Complete Blood Count (CBC): To assess platelet count and other blood cell parameters.
* Coagulation Studies: Including Prothrombin Time (PT), Activated Partial Thromboplastin Time (aPTT), and International Normalized Ratio (INR) to evaluate the coagulation profile.
* Additional Tests: Depending on the clinical context, other investigations such as genetic testing, bleeding disorder workup, or toxicology screening may be considered.

It is important to promptly initiate the diagnostic workup to determine the underlying cause of hemorrhagic stroke, as it can guide further management decisions and the implementation of appropriate preventive measures.

**Management – Overview**

The management of hemorrhagic stroke focuses on stabilizing the patient, minimizing further brain injury, and preventing complications. The overarching goals of treatment include controlling blood pressure, managing intracranial pressure, preventing rebleeding, and providing supportive care.

1. General Measures:

* Airway management: Ensure adequate oxygenation and ventilation.
* Hemodynamic stability: Maintain stable blood pressure and heart rate within target ranges.
* Intracranial pressure management: Monitor and control intracranial pressure to prevent further brain injury.
* Seizure prophylaxis: Administer antiepileptic drugs to prevent seizure activity, particularly in cases of intracerebral hemorrhage.
* Hematoma evacuation: In cases of significant hematoma causing mass effect or neurological deterioration, surgical removal of the clot may be necessary to relieve pressure on the brain and improve outcomes.
* Aneurysm or AVM treatment: For subarachnoid hemorrhage caused by an aneurysm or arteriovenous malformation, surgical clipping or endovascular coiling may be performed to prevent rebleeding.
* Blood pressure management is crucial in hemorrhagic stroke. The target blood pressure varies depending on the patient's clinical condition, the location and size of the hemorrhage, and the presence of comorbidities.
* Antihypertensive medications may be administered cautiously to maintain blood pressure within a safe range while ensuring adequate cerebral perfusion.
* Continuous neurologic assessment is essential to detect any changes in the patient's condition promptly. Monitoring includes Glasgow Coma Scale (GCS), pupillary response, motor function, and signs of increased intracranial pressure.
* Thromboembolic prophylaxis: Initiate prophylactic measures, such as subcutaneous heparin or pneumatic compression devices, to prevent deep vein thrombosis and pulmonary embolism.
* Temperature management: Maintain normothermia to avoid hyperthermia, which can exacerbate brain injury.

1. Surgical Intervention:
2. Blood Pressure Control:
3. Neurologic Monitoring:
4. Prevention of Complications:

The management of hemorrhagic stroke requires a multidisciplinary approach involving neurologists, neurosurgeons, critical care specialists, and pharmacists. Close monitoring, prompt intervention, and supportive care are essential components of the comprehensive management strategy.

**Pharmacotherapy**

The pharmacotherapy for hemorrhagic stroke aims to provide supportive care, prevent complications, and manage underlying conditions. As a clinical pharmacist preparing for board certification, it is essential to have a comprehensive understanding of the pharmacological interventions used in the management of hemorrhagic stroke. Here are the key pharmacotherapy considerations:

Blood Pressure Management:

* Goal SBP 130-150 mmHg is reasonable for most patients with ICH if tolerated. More intensive reduction to SBP <130 mmHg may be harmful.
* Intravenous agents like nicardipine, labetalol, or clevidipine are preferred for acute reduction in first 24 hours.
* Caution with excessive BP lowering in patients with very high baseline SBP or large ICH.
* Initial blood pressure control is crucial to prevent hematoma expansion and minimize the risk of rebleeding.
* Antihypertensive agents commonly used in hemorrhagic stroke include:
  + Nicardipine:
    - Intravenous calcium channel blocker.
    - Initial dose: 5 mg/hour IV infusion.
    - Titrate by 2.5 mg/hour every 5-15 minutes to achieve target blood pressure.
    - Maximum dose: 15 mg/hour.
    - Labetalol:
      * Non-selective beta-blocker with alpha-blocking properties.
      * Initial dose: 10-20 mg IV over 1-2 minutes.
      * May repeat every 10-20 minutes if necessary.
    - Clevidipine:
      * Intravenous dihydropyridine calcium channel blocker.
      * Initial dose: 1-2 mg/hour IV infusion.
      * Titrate by doubling the dose every 2-5 minutes to achieve target blood pressure.
      * Maximum dose: 21 mg/hour.
    - Oral agents like captopril, labetalol, or nimodipine can be used for BP maintenance after the first day.
    - Caution with excessive reduction in patients with very high baseline SBP or large ICH to avoid hypoperfusion.
    - Minimize SBP fluctuations and achieve smooth sustained control.

Anticoagulation Reversal

Patients on anticoagulant therapy like warfarin or DOACs are at high risk of hematoma expansion. Rapid reversal is critical but should not delay other acute ICH care.

Warfarin Reversal

* 4-factor PCC is preferred over FFP for warfarin reversal. Provides faster increase in factor levels.
* Dose is 25-50 IU/kg or fixed 1500 IU for ICH. Maximum dose not established.
* Always give 5-10 mg IV vitamin K regardless of PCC use to sustain effect.
* Monitor INR to guide dosing. Target INR <1.3.
* Adverse effects like DVT/PE are rare if appropriate dosing used.

Dabigatran Reversal

* Idarucizumab 5 g IV (two 2.5 g boluses) effectively binds dabigatran and reverses anticoagulation.
* Normalization of dilute thrombin time or ecarin clotting time confirms reversal.
* No need to wait for coagulation test results if recent dabigatran ingestion.
* Adverse effects are rarely reported. Hypersensitivity is possible.

Factor Xa Inhibitors

* Andexanet alfa preferred for reversal of apixaban, rivaroxaban, edoxaban.
* IV bolus followed by 2 hour infusion. Dose per specific Xa inhibitor and timing since last dose.
* 4-factor PCC reasonable option if andexanet unavailable. Dose 50 IU/kg.
* aPCC also suggested but less evidence than 4-factor PCC.
* Monitor anti-Xa levels. Target <0.1 IU/mL for apixaban, <0.2 IU/mL for rivaroxaban.
* Thrombosis risk 5-10%. Higher with andexanet compared to PCC.

Heparin Reversal

* For UFH, 1 mg IV protamine sulfate reverses 100 units of heparin. Maximum 50 mg over 10 minutes.
* For LMWH, 1 mg protamine per 1 mg enoxaparin. Only partial reversal.
* Monitor aPTT. Target 40-60 seconds.
* Seizure Prophylaxis:
  + Seizure activity can exacerbate brain injury; therefore, prophylactic antiepileptic drugs (AEDs) may be administered.
  + In patients with spontaneous ICH, impaired consciousness, and confirmed electrographic seizures, antiseizure drugs should be administered to reduce morbidity
    - In patients with spontaneous ICH without evidence of seizures, prophylactic antiseizure medication is not beneficial to improve functional outcomes, long-term seizure control, or mortality.

* Commonly used AEDs for seizure treatment include
  + Phenytoin:
    - Loading dose: 15-20 mg/kg IV at a rate of 50 mg/minute.
    - Maintenance dose: 300-400 mg/day in divided doses.
    - Levetiracetam:
      * Loading dose: 1000-3000 mg IV over 15 minutes.
      * Maintenance dose: 1000 mg twice daily or 500 mg twice daily in renal impairment.
    - Phenobarbital:
      * Loading dose: 10-20 mg/kg IV at a rate of 1 mg/kg/minute.
      * Maintenance dose: 1-3 mg/kg/day in divided doses.

* Prevention of Complications:
  + Thromboembolic Prophylaxis:
    - Subcutaneous heparin or low-molecular-weight heparin should be initiated to prevent deep vein thrombosis and pulmonary embolism in patients with reduced mobility.
    - Dosage and frequency depend on the specific agent used and patient characteristics. Consult guidelines for appropriate dosing.
  + Acid Suppression:
    - Proton pump inhibitors (PPIs) such as pantoprazole or omeprazole may be prescribed to prevent stress ulcers and gastrointestinal bleeding.
    - Dosage and frequency depend on the specific PPI used. Consider renal and hepatic function when determining dosing.
  + Glycemic Control:
    - Maintaining optimal blood glucose levels is crucial in reducing the risk of secondary brain injury.
    - Regular blood glucose monitoring and insulin therapy may be initiated to achieve tight glycemic control.
* Underlying Condition Management:
  + If an underlying condition, such as an arteriovenous malformation (AVM), is identified as the cause of the hemorrhage, referral to neurosurgery for further evaluation and potential intervention is necessary.
  + Management of comorbidities, including hypertension, diabetes, and dyslipidemia, is essential to optimize long-term outcomes and reduce the risk of recurrent strokes.
  + Refer to specific guidelines and consult with the healthcare team for detailed drug selection, dosing, and monitoring considerations.

**Key Guidelines and Evidence**

In the management of hemorrhagic stroke, several key guidelines and landmark trials provide evidence-based recommendations. Familiarizing yourself with these guidelines and studies is essential for clinical pharmacists preparing for board certification. Here are the key guidelines and evidence-based practices for the management of hemorrhagic stroke:

1. American Heart Association (AHA)/American Stroke Association (ASA) Guidelines:

* AHA/ASA guidelines provide comprehensive recommendations for the management of hemorrhagic stroke, including blood pressure management, surgical intervention, prevention of complications, and secondary prevention strategies.
* Key recommendations include controlling blood pressure to target ranges, considering surgical hematoma evacuation in cases of significant mass effect or deterioration, implementing thromboembolic prophylaxis, and managing underlying conditions.
* Reference: AHA/ASA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage.

2. INTERACT-II Trial:

* The INTERACT-II trial demonstrated that early intensive blood pressure lowering in patients with acute intracerebral hemorrhage resulted in improved functional outcomes.
* This trial supports the importance of aggressive blood pressure management in patients with hemorrhagic stroke.
* Reference: Anderson CS et al., "Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage." N Engl J Med. 2013 Jun 20;368(25):2355-65.

3. STICH Trial:

* The STICH (Surgical Treatment for Intracerebral Hemorrhage) trial evaluated the role of early surgical evacuation of supratentorial intracerebral hemorrhage.
* The trial found no significant difference in functional outcomes between early surgical evacuation and conservative medical management.
* Reference: Mendelow AD et al., "Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): A randomised trial." Lancet. 2005 Jan 29-Feb 4;365(9457):387-97.

4. ATACH-2 Trial:

* The ATACH-2 (Antihypertensive Treatment of Acute Cerebral Hemorrhage II) trial investigated the optimal blood pressure target in patients with acute intracerebral hemorrhage.
* The trial found no significant difference in functional outcomes between intensive blood pressure reduction (systolic target <140 mmHg) and standard blood pressure reduction (systolic target <180 mmHg).
* Reference: Qureshi AI et al., "Intensive blood-pressure lowering in patients with acute cerebral hemorrhage." N Engl J Med. 2016 Jun 8;375(23):2277-89.

5. MISTIE-III Trial:

* The MISTIE-III (Minimally Invasive Surgery Plus rt-PA for Intracerebral Hemorrhage Evacuation) trial evaluated the efficacy and safety of minimally invasive surgery combined with recombinant tissue plasminogen activator (rt-PA) for the evacuation of intracerebral hemorrhage.
* The trial demonstrated that minimally invasive surgery with rt-PA resulted in greater reduction in hematoma volume compared to medical management alone.
* Reference: Hanley DF et al., "Minimally invasive surgery plus recombinant tissue-type plasminogen activator for intracerebral hemorrhage evacuation: MISTIE III Trial." JAMA Neurol. 2019 Aug 5;76(12):1426-1433.

6. Neurocritical Care Society Guidelines:

* The Neurocritical Care Society provides evidence-based guidelines for the management of intracerebral hemorrhage, including recommendations for blood pressure management, intracranial pressure monitoring, and prevention of complications.
* These guidelines offer valuable insights into the pharmacological and non-pharmacological approaches to optimize patient outcomes.
* Reference: Hemphill JC 3rd et al., "Guidelines for the management of spontaneous intracerebral hemorrhage: A guideline for healthcare professionals from the American Heart Association/American Stroke Association." Stroke. 2015 Jul;46(7):2032-60.

Table: Key AHA/ASA Guideline Recommendations for Hemorrhagic Stroke Management

| **Recommendation** | **Class** | **Evidence Level** |
| --- | --- | --- |
| Reduce SBP to 130-150 mmHg | IIa | B-R |
| Reduce blood pressure within 2 hours of ICH and reach target BP within 1 hour can be beneficial | IIa | B-R |
| Reverse warfarin with IV vitamin K and 4PCC | I | B-R |
| Reverse dabigatran with idarucizumab | IIa | B-NR |
| Reverse Xa inhibitors with andexanet alfa | IIa | B-NR |
| Reverse Xa inhibitors with 4PCC may be considered | IIb | B-NR |
| Careful titration to ensure continuous smooth and sustained control of BP, avoiding peaks and large variability in SBP can be beneficial for improving outcomes | IIa | B-NR |
| In patients taking aspirin going for surgery, platelet transusion might be considered to reduce postoperative bleeding and mortality | IIb | C-LD |
| In patients taking antiplatelets, the effectiveness of desmopressin  with or without platelets transfusions to reduce the expansion of hematoin is uncertainmight be considered to reduce postoperative bleeding and mortality | IIb | C-LD |

Legend:  
Level B-R: Moderate quality evidence from ≥1 randomized controlled trials  
Level C-LD:randomized or nonrandomized observational or registry studies with limitation of design or executio  
Class I: Benefit >>> Risk  
Class IIa: Benefit >> Risk

Understanding and incorporating these guidelines and evidence-based practices into your practice as a clinical pharmacist will enhance your ability to provide optimal care to patients with hemorrhagic stroke.

**Clinical Scenarios**

Clinical Scenario 1:

* A 58-year-old male with a history of poorly controlled hypertension presents to the emergency department with a sudden severe headache and decreased level of consciousness. CT scan reveals a large intracerebral hemorrhage in the left basal ganglia. Blood pressure on admission is 180/110 mmHg. How should the blood pressure be managed?
* Key Learning Point: Aggressive blood pressure control is essential in the management of hemorrhagic stroke to prevent hematoma expansion and further neurological injury. In this scenario, the blood pressure should be lowered to a target systolic blood pressure of <140 mmHg using intravenous antihypertensive agents such as nicardipine or labetalol.

Clinical Scenario 2:

* A 65-year-old female with a history of atrial fibrillation presents with sudden-onset right-sided weakness and slurred speech. CT scan reveals a left-sided intracerebral hemorrhage with intraventricular extension. The patient is hemodynamically stable, and systolic blood pressure on admission is 160 mmHg. What pharmacological prophylaxis should be considered in this patient?
* Key Learning Point: Thromboembolic prophylaxis is crucial in patients with reduced mobility to prevent deep vein thrombosis and pulmonary embolism. In this scenario, subcutaneous low-molecular-weight heparin or unfractionated heparin should be prescribed as thromboembolic prophylaxis.

Clinical Scenario 3:

* A 72-year-old male with a known history of cerebral amyloid angiopathy presents with a sudden-onset severe headache and vomiting. CT scan reveals subarachnoid hemorrhage with multiple small subcortical hemorrhages. Blood pressure on admission is 200/120 mmHg. How should blood pressure be managed in this patient?
* Key Learning Point: Blood pressure management is crucial in patients with subarachnoid hemorrhage. In this scenario, blood pressure should be lowered to a target systolic blood pressure of <140 mmHg using intravenous antihypertensive agents such as nicardipine or labetalol.

These clinical scenarios highlight important management decisions and considerations in the pharmacotherapy of hemorrhagic stroke. They emphasize the need for prompt and tailored interventions to optimize patient outcomes.

**Acute Hemorrhagic Stroke Summary**

Hemorrhagic stroke is a critical condition that requires prompt and comprehensive management. Clinical pharmacists play a crucial role in optimizing patient outcomes through their involvement in the pharmacotherapy and overall care of patients with hemorrhagic stroke.

The clinical presentation of hemorrhagic stroke is characterized by sudden and severe symptoms, including headaches, decreased level of consciousness, and focal neurologic deficits. Risk factors such as hypertension, age, and history of hemorrhagic stroke contribute to the development of this condition.

The diagnostic approach to hemorrhagic stroke involves clinical assessment, imaging studies (such as non-contrast CT scan and CTA), and laboratory investigations. Early and accurate diagnosis is crucial for timely intervention and determining the underlying cause of the hemorrhage.

Management strategies for hemorrhagic stroke focus on stabilizing the patient, controlling blood pressure, preventing complications, and managing underlying conditions. Pharmacotherapy plays a significant role in achieving these goals, including antihypertensive agents for blood pressure control, antiepileptic drugs for seizure prophylaxis, and thromboembolic prophylaxis to prevent deep vein thrombosis and pulmonary embolism.

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