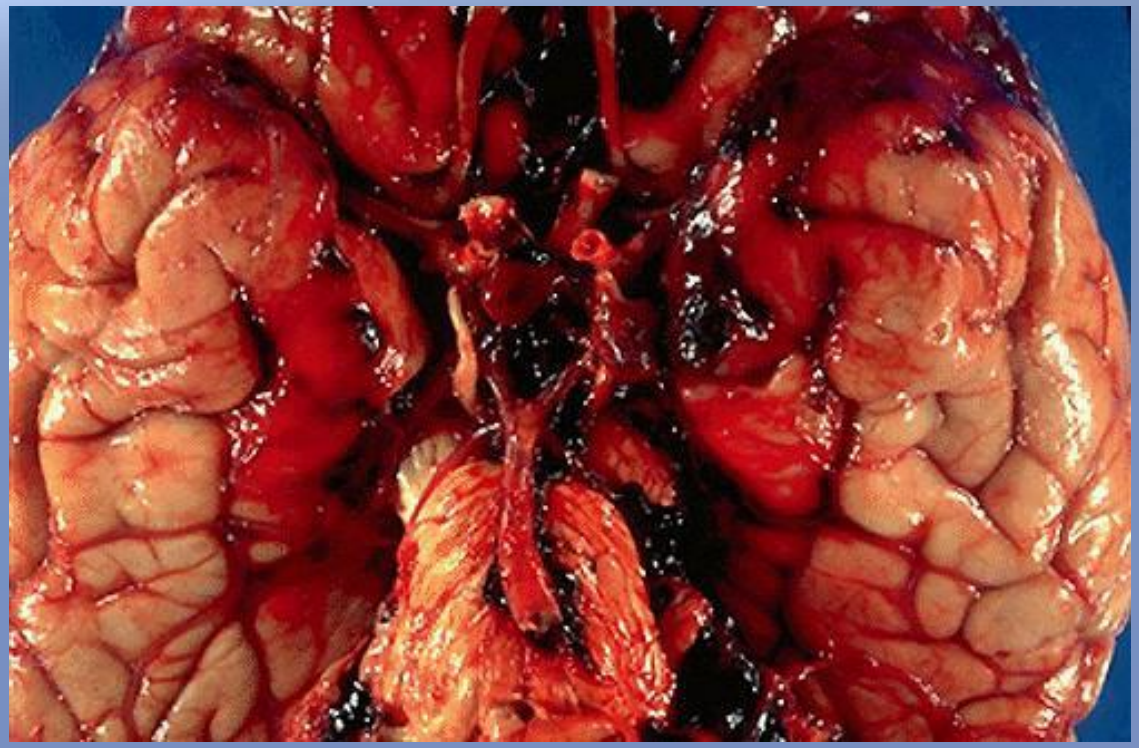
Subarachnoid Hemorrhage: Basics, Breakthroughs, and Beyond

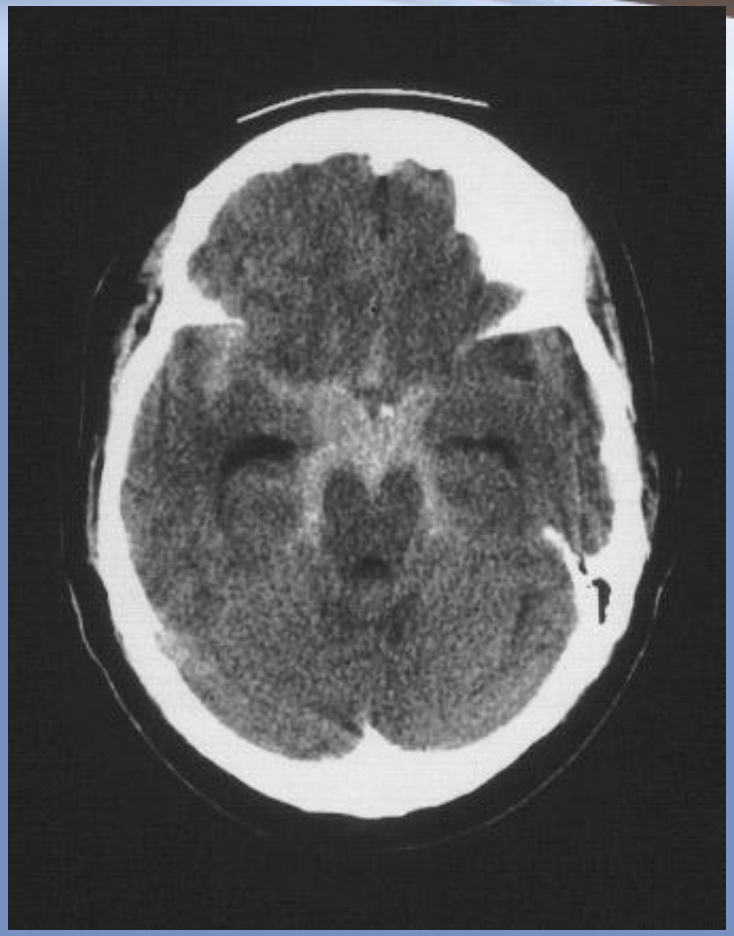
Tiffany Hoke, DNP, RN, RNP, APRN-RX, AGACNP-BC, SCRN, CNRN

International Neuroscience Nurses Symposium

Introduction

- Aloha!
- Why talk about subarachnoid hemorrhage (SAH)?
  - Demystify.
  - Empower through awareness promotion.





(Brisman, 2016, Image 4, 6)

Objectives

- Summarize **basic** science and management of SAH.

- Highlight recent **breakthroughs** related to the science and management of SAH and inspire us to go **beyond.**

Basics

Epidemiology

- 5% of all strokes.
- 30,000 people yearly in U.S.
  - Most between ages 40-60.
    - **Do NOT dismiss suspicion of SAH based on age of presenting individual.**
  - Women>men.
  - 12% **die** **before** receiving medical attention.
  - 20% **die** **after** admission.
  - 2/3rds **survive.**
    - ½ of survivors are permanently disabled.

(Mayer, Bernardini, & Solomon, 2016; Ropper, Samuels, & Klein, 2014)

SAH Etiologies

- Trauma **= Most common cause of SAH.**
- **Aneurysmal**
- Idiopathic permesencephalic
  - Venous source
  - Posterior circulation aneurysm
  - Perforating artery rupture
- AVM
- Moyamoya
- Sympathomimetics
  - Methamphetamine
  - Cocaine
- Pituitary apoplexy
- Vasculitis
- Sickle Cell
- Coagulopathy
- Neoplasm

(Caplan, 2009; Edlow, Figaji, & Samuels, 2015; Mayer, Bernardini, & Solomon, 2016; Ropper, Samuels, & Klein, 2014)

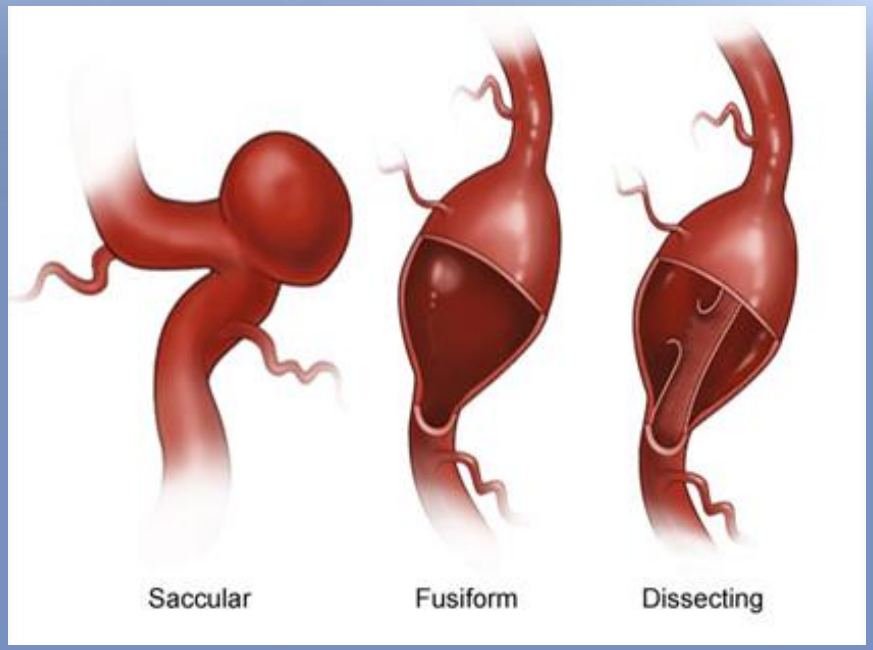
Aneurysmal Patho

- **Intracranial arteries higher risk than extracranial.**
  - Thinner
  - Less elastin.
  - No external elastic lamina.
  - Less supporting tissue.
  - Possible defects.
- **Size**
  - < 3 mm (very small).
  - 3-6 mm (small).
  - 7-12 mm (small-medium).
  - 13-25 (large).
  - > 25mm (giant).

(Brisman, 2016; Caplan, 2009; Mayer, Bernardini, & Solomon, 2016; Ropper, Samuels, & Klein, 2014; Szeder, Tateshima, & Duckwiler, 2016)

Aneurysmal Patho

- **Morphology or Types of Aneurysms**
  - **Saccular**
    - 80% of ruptured.
    - **Circle of Willis branches and bifurcations.**
  - **Fusiform**
  - **Dissecting**
  - **Mycoctic**
    - Septic emboli ->occlusion->wall weakening.
    - **Distal cerebral vessels.**



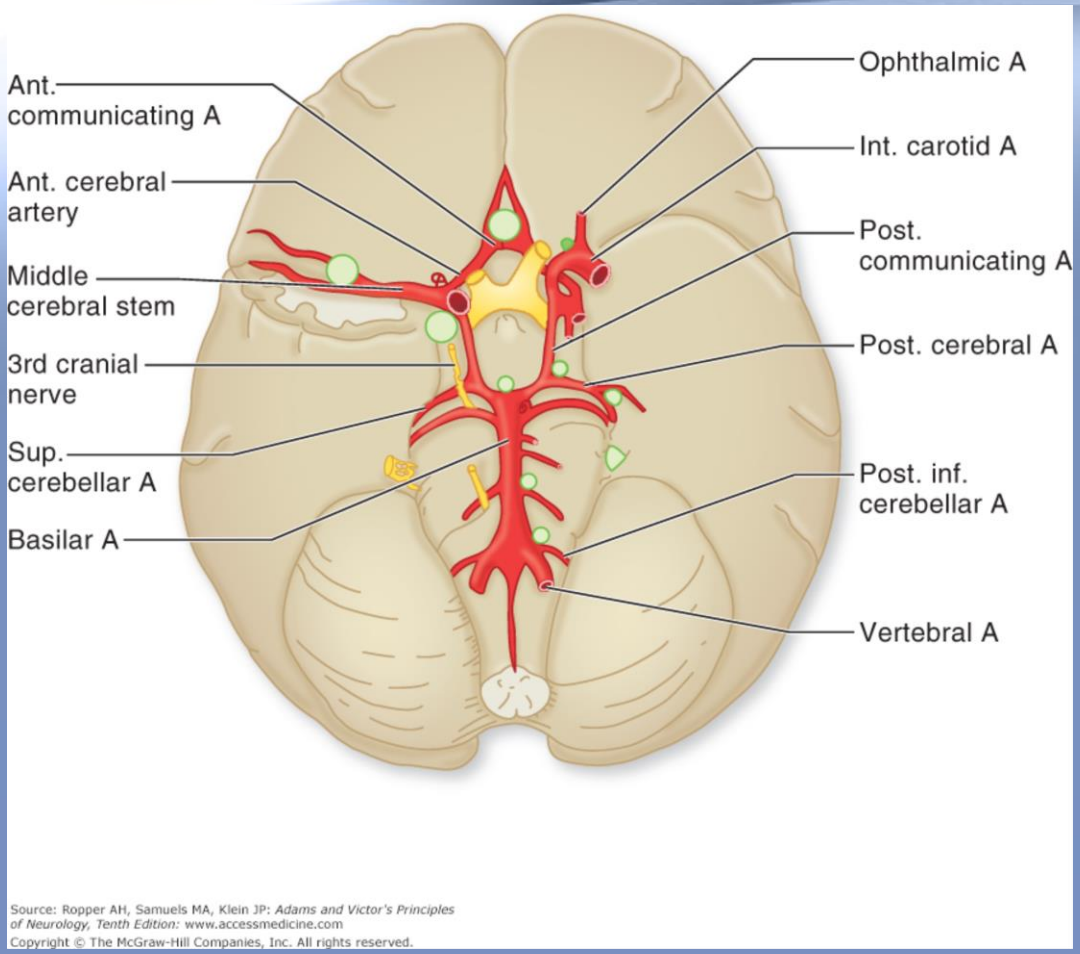
(Caplan, 2009; Mayer, Bernardini, & Solomon, 2016; Robert Wood Johnson University Hospital, 2016; Ropper, Samuels, & Klein, 2014; Szeder, Tateshima, & Duckwiler, 2016)

Intracranial Aneurysm Incidence and Prevalence

- **2% of adults have one.**
  - 90% small (< 10 mm) and asymptomatic.
- **20% of patients have 2+**
  - Often a contralateral mirror.

(Brisman, 2016; Mayer, Bernardini, & Solomon, 2016; Ropper, Samuels, & Klein, 2014)

Principle Sites



- **Anterior = 90%**
  - AComA=**40%**
  - PComA/ICA junction =**30%**
  - 1st MCA bifurcation=**20%**
- **Posterior**
  - Basilar apex
  - VA and PICA junction
  - Distal cerebral tree (rare)

(Ropper, Samuels, & Klein, 2014: Figure 34-24)

Associated Aneurysmal Risk Factors and Conditions

- Increases with age.
- Hypertension
- Smoking
- ETOH abuse.
- Sympathomimetic drugs.
- Atheroscelorsis
- AVMs
- Moyamoya
- Coarctation of aorta.
- Sickle cell
- Bacterial endocarditis.
- Fungal infection.
- Collagen-Connective Tissue Related Disorders.
- More

- **Positive family history**
  - **MRA screen.**
    - 2+ first degree relatives.
      - 5-10% **POSTIVE.**
    - PCKD

(Mayer, Bernardini, & Solomon, 2016; Ropper, Samuels, & Klein, 2014; Szeder, Tateshima, & Duckwiler, 2016)

Intracranial Aneurysm Rupture

- **Annual risk 0.7%.**
- **Risks**
  - Increasing size.
  - Prior aneurysmal SAH.
  - Basilar apex and pcomm aneurysms.
  - Smoking
  - Aneurysmal headache.
  - CN compression.
  - Heavy ETOH.
  - Family history of rupture.
  - Females
    - Menopausal.
  - Multiple aneurysms.
  - Hypertension
  - Sympathomimetic agents.

(Mayer, Bernardini, & Solomon, 2016)

Clinical Features

- **Headache**
  - Sudden, severe, and constant.
    - "Worst of my life." "Exploding."
  - Occipital or nuchal.
  - More rapid, longer than migraine.
    - Seconds to max.
  - After exertion or Valsalva.
  - Concurrent vomiting
  - Abrupt cessation of activity.
    - **Treatment response does not exclude diagnosis.**
- **Transient deficits**
  - Seizure
  - Ischemia
  - Sudden ICP increase as blood enters subarachnoid space.
- **40-50% = normal mental status.**

(Caplan, 2009; Edlow, Figaji, & Samuels, 2015)

Other Clinical Features

- Increased ICP
  - 3rd or 6th CN palsies.
  - Retinal hemorrhages.
- Nausea
- Vomiting
- Nuchal rigidity.
- Meningismus
- Back pain with sciatic radiation.
- Confusion
- Lethargy
- Amnestic to event.

(Caplan, 2009)

Focal Signs of Aneurysmal Rutpure

- **AComA**
  - Leg weakness.
  - Confusion
  - Bilateral Babinski.
- **PComA or SCA (ICA/PCA Junction)**
  - 3rd and 6th nerve palsies.
  - Weber's syndrome.
    - Contralateral hemiplegia due to midbrain compression.
    - Giant SCA.
- **Cavernous sinus**
  - Opthalmoplegia due to 3rd, 4th, 6th CN compression
- **PCA**
  - Homonymous hemianopia
- **MCA**
  - Aphasia
  - Hemiparesis
  - Anosognosia
  - Seizures
- **Basilar bifurcation**
  - Forward = Visual field defects and hypopituitarism.
  - Vertically = Amnesia, 3rd nerve palsy, bulbar signs, and quadriparesis.
- **Opthalmic artery**
  - Monocular visual disturbance.

(Calplan, 2009)

When to Scan?

- The headache = **INVESTIGATE.**
- New neuro findings = **INVESTIGATE**
- The headache + new neuro findings = **INVESTIGATE**.
- **Exam can be normal!**
  - 12-24% SAHs misdiagnosed!
  - 5% of 1st visit ED patients with HA misdiagnosed → worse outcomes.
    - Often due to failure to attain CT.
      - » If negative, low threshold for LP!
      - » If series LPs contain only positives, too few are being performed!

(Edlow, Figaji, & Samuels, 2015)

ENLS SAH Protocol: The First Hour

- **Brain imaging.**
- **Labs**
  - PT/PTT
  - CBC
  - PLT
  - BMP
  - Troponin
  - Toxicology
- **EKG**
- **Establish BP goal.**
- **Address hydrocephalus.**

(Edlow, Figaji, & Samuels, 2015, Figure 1, Table 1)

Diagnostics

- **Non-contrast brain CT**
  - SAH in cisterns, around circle of Willis, major fissures, IVH.
    - Convexity usually nonaneurysmal, but remember mycotic.
  - **False negative.**
    - Too small.
    - Les sensitive over time.
      - 50% after 1 week.
    - Hematocrit < 30%
    - Technical factors.
- **CTA**
  - Circle of Willis aneurysms, and some distal.

(Edlow, Figaji, & Samuels, 2015)

Diagnostics

- **MRI/MRA**
  - Consider availability, cost, and required interpretation experience.
  - Relationship of aneurysm to adjacent brain structures.
  - Can detect aneurysms as small as 3-4 mm.
- **Which one bled?**
  - Largest.
  - Most irregular.
  - Most focal spasm.
  - Within vascular territory of focal signs.
  - Best correlates with blood collection on CT.

(Caplan, 2009; Edlow, Figaji, & Samuels, 2015)

Diagnostics

- **Lumbar Puncture**
  - If CT negative.
  - **Negative**
    - Large RBCs in initial tube clear by 4th= Traumatic tap.
    - Absence of xanthochromia.
      - Yellowish CSF
      - Hemoglobin breakdown.

- **Positive**
  - Large RBC not clearing by 4th.
  - Faint pink (4-5 hours out).
  - Xanthochromic (12 hours out).
  - Elevated protein.
  - Pleocytosis (WBC).
  - Elevated opening pressure.
  - Normal glucose.

(Caplan, 2009; Edlow, Figaji, & Samuels, 2015)

After Diagnosis Confirmed

- **Bedrest**
- **Cardiac monitor**
- **EKG**
- **Assure labs attained and review.**
- **Seek expert consultation**
  - Neurovascular or stroke specialist
  - Neurointensivist

- **Communicate**
  - Airway status.
  - Presentation
  - Hunt-Hess
  - Imaging/LP results.
  - Coagulopathy?
  - Hydrocephalus?
  - Meds given.
  - Other images?
  - Discuss BP goal.
  - Seizure prophylaxis?

(Edlow, Figaji, & Samuels, 2015)

After Diagnosis Confirmed

- **Monitor for decline.**
  - Neurocardiogenic shock
  - New hypoxia and acute respiratory failure.
  - Neurogenic pulmonary edema.
  - Seizure.
- **Correct coagulopathy.**
  - Consider risk versus benefit and related patient specifics.
  - INR goal < 1.4.
  - PLT goal > 50,000.
  - Antiplatelet reversal?

(Edlow, Figaji, & Samuels, 2015)

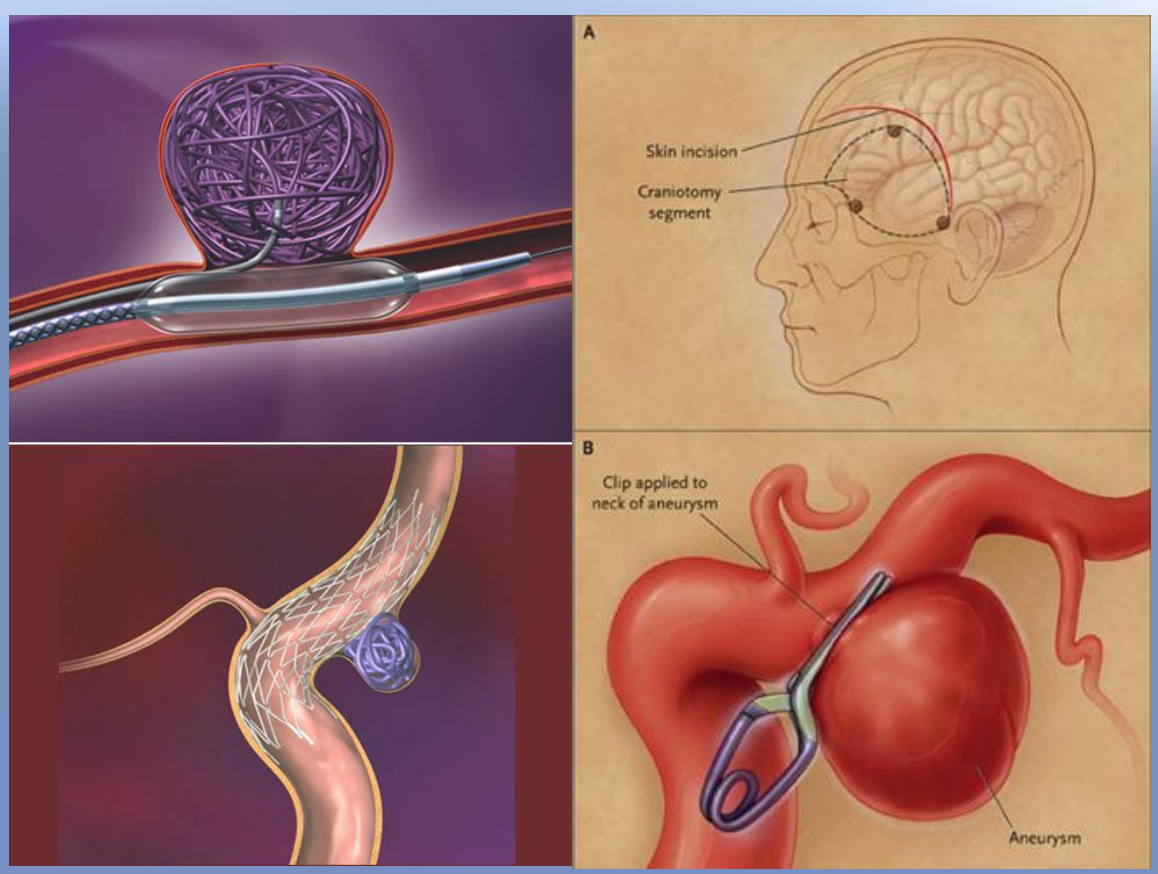
After Diagnosis Confirmed

- **Treat pain and anxiety.**
  - Avoid straining , Valsalva, stress.
  - Short acting IV analgesics (fentanyl).
  - Avoid over-medication.
    - Masks exam.
    - Reversal agents cause agitation and risk re-rupture.
- **Control BP**
  - Consider pre-morbid BP.
  - SBP < 140-160 or MAP < 110.
  - Nicardipine
    - Ease of titration.
  - No nitroprusside or nitroglycerin.

(Edlow, Figaji, & Samuels, 2015)

SAH Treatment

- Aneurysm securement.
- Complication prevention.
- Complication treatment.



(Brisman, 2016, Images 11, 19)

Clinical Course Complications

- Hydrocephalus
- Aneurysmal re-rupture
- Vasospasm and delayed cerebral ischemia (DCI)
- Multi-system abnormalities

(Caplan, 2009; Edlow, Figaji, & Samuels, 2015)

Hydrocephalus

- **Altered CSF dynamics.**
  - Blocked flow (obstructive)
  - Impaired absorption due to attachment of blood to arachnoid granulations.
- 30% first 3 days.
- May be asymptomatic
- Increasing headache, lethargy, incontinence, and decreased spontaneity.
- CT scan
- EVD

(Caplan, 2009; Edlow, Figaji, & Samuels, 2015)

Aneurysmal Re-rupture

- Highest risk within first 12-24 hours.
  - 20% in first 2 weeks.
- Mortality rate = 50%.
- IPH and SAH.
- Sudden, abrupt, severe changes.
- Rapid coma.

- **Prevent**
  - Bedrest.
  - Minimize stimuli.
  - Pain control.
  - Bowel regimen.
  - BP regulation.
  - Early securement

(Caplan. 2009; Edlow, Figaji, & Samuels, 2015)

Vasospasm

- **Substance release into CSF -> Vasoconstriction -> arterial wall necrosis.**
  - Hemolysis (oxyhemoglobin).
  - Endothelial factors.
  - Coagulation cascade.
  - Abnormal smooth muscle contraction or failed relaxation.
- **Can cause delayed cerebral ischemia (DCI).**
- **Risk Factors:**
  - Large amount of blood and thick blood clots in cisterns.
  - Small arterial lumen < 0.5mm with low distal perfusion.
  - Decreased LOC.
  - IVH
  - Elevated BNP.

(Caplan, 2009; Francoeur & Mayer, 2016)

Vasospasm

- **Early signs**
  - Tachycardia.
  - Hypertension.
  - EEG abnormalities.
  - Decreased LOC.
- **Diffuse**
  - Headache
  - Stupor
  - Confusion
- **Focal signs**
  - Indicate artery involved.
- **Surveillance and Prevention**

(Caplan, 2009)

Vasospasm

- **Transcranial Doppler (TCD)**
  - Day 3-10 increasing velocity.
  - Day 5-9 peak.
  - Usually resolved by 2 weeks, but max velocities can persist ≥ 20 days.
  - MCA > 140 cm/s = Mild on angiography.
  - MCA > 200 cm/s = Severe.
- **Suspect?**
  - **CTA**
    - Absence of vasoconstriction has negative predictive value of 95%.
  - **CT perfusion.**
    - Assess for signs of DCI, salvageable penumbra, or stroke?
  - **Angiography**
    - Diagnostic and therapeutic
    - Not without risk.
    - 50% positives are asymptomatic.

(Caplan, 2009)

Other Neuro Complications

- **Global cerebral edema**
  - Poor-grade SAH
  - LOC at bleeding onset.
  - Increased mortality, disability, and cognitive dysfunction.
  - **Early brain injury** on MRI within 72 hours.
    - Symmetric ischemic injury in 70% of Hunt-Hess 4-5.
    - Usually ACA territories.
    - Acute ischemia, reperfusion injury, microvascular dysfunction, inflammation.
- **Seizures**
  - Tonic-clonic
    - 5% during hospitalization.
    - 10% 1 year post D/C.
  - NCSE
    - 20% of poor-grade.
- **Fever**
  - 80%
  - Central (poor-grade).

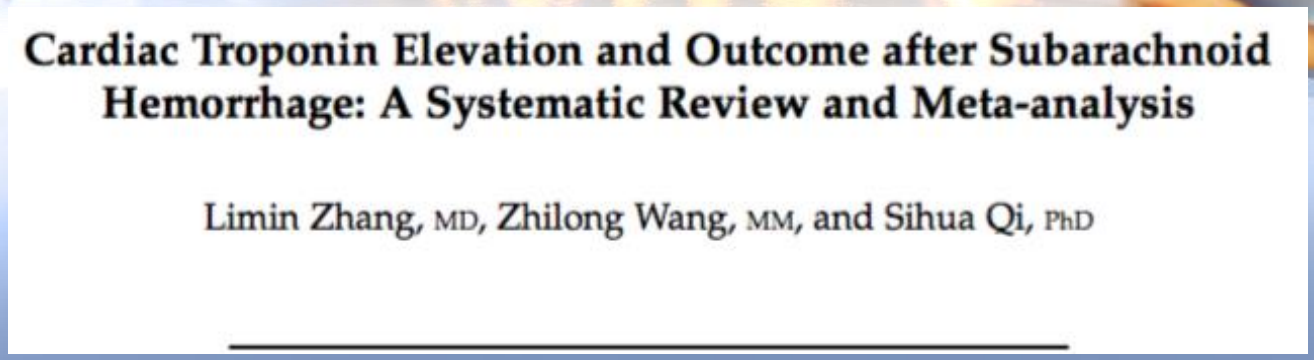
(Mayer, Bernardini, & Solomon, 2016)

Cardiac Complications

- Transient echo abnormalities 50-100%.
- Systemic hypertension
- Heart failure
- Arrhythmia
- Myocardial myoctyolysis
    - Serum catecholamines and sympathetic discharges from hypothalamus.
        - Subendocardial hemorrhage.
        - Myofibrilllary degeneration.
        - Contraction band necrosis.
- Myocardial infarction
- Hypovolemia
- Site hematoma.

(Caplan 2009; Mayer, Bernardini, & Solomon, 2016)

Cardiac Complications



Cardiac Troponin Elevation and Outcome after Subarachnoid Hemorrhage: A Systematic Review and Meta-analysis

Limin Zhang, MD, Zhilong Wang, MM, and Sihua Qi, PhD

- Troponin elevation in 30%.
- Increased risk of
  - DCI
  - Poor outcome
  - Death

(Zhang, Wang, Qi, 2015)

Pulmonary Complications

- **Acute respiratory failure.**
- **Neurogenic pulmonary edema (NPE).**
  - Under recognized.
  - Rapid onset.
  - Proteinaceous fluid.
  - Acute ICP elevation->massive autonomic discharge -> increased cerebral perfusion -> accumulation of fluid within lungs -> hypoxemia
  - Treatment
    - Lower ICP
    - Cautiously eliminate excess fluid.

(Caplan, 2009)

Fluid and Electrolyte Complications

- **Higher risk with AComA aneurysms.**
- **Hyponatremia**
  - 2-fold increase in length of stay->cost->nosocomial complications.
  - Associated with vasospasm.
- **Cerebral salt wasting (CSW).**
- **Hypervolemia**
  - Usually iatrogenic.
  - Can challenge management of NPE and heart failure.
- **Goal euvolemia and normonatremia.**

(Caplan, 2009; Mapa et al., 2016)

Other Complications

- **Endocrine Complications**
  - Hypoperfusion of hypothalmic-pituitary blood supply.
  - SIADH
  - Diabetes insipidus.
- **Hematologic Complications**
  - Anemia
    - Reduced O2 delivery

(Caplan 2009; Mayer, Bernardini, & Solomon, 2016)

Breakthroughs and Beyond

DCI

- **Most preventable cause of mortality and poor neuro outcome.**
- **30%**
- **High Risk and Poorer Outcomes.**
  - Severe initial SAH.
  - More cisternal blood and IVH.
  - Poor post resuscitation exam.

- **Paradigm Shift**
  - Large-vessel not required for DX.
  - Think early brain injury, microcirculatory dysfunction, loss of autoregulation, and micro thrombosis.
  - Post-mortem infarcts correlate with microthrombi more than vasospasm or aneurysm location.

(Francoeur & Mayer, 2016)

DCI

- **Prevention**
  - Nimodipine
  - Euvolemia and normonatremia.
    - Isotonics
    - Fludrocortisone (0.2-0.4 mg/day).
    - Hypertonic saline (3%) for acute correction of symptomatic hyponatremia.
- **Detection and Diagnosis.**
  - **Clinical exam: Most reliable.**
    - **Poor grades: Less consistent manifestations.**
  - **TCD**
    - MCA < 120 cm/s: High negative predictive value.
    - MCA > 180 cm/s: High positive predictive value.
    - Limitations
      - No assessment of distal vasculature.
      - Operator dependent.
      - 10% have no bone windows.
      - 40% with DCI have MCA < 120 cm/s.

(Francoeur & Mayer, 2016)

DCI

- **Detection and Diagnosis (cont.)**
  - **Vascular imaging.**
    - **CTA: First line screening tool.**
      - Day 4 (high risk patients).
      - Day 8 (lower risk patients).
        - » Lack of spasm on day 8 = low risk of subsequent DCI.
          - » Decreased ICU days and LOS.
    - **CT perfusion.**
      - Coupled with CTA.
      - Detects salvageable penumbra.

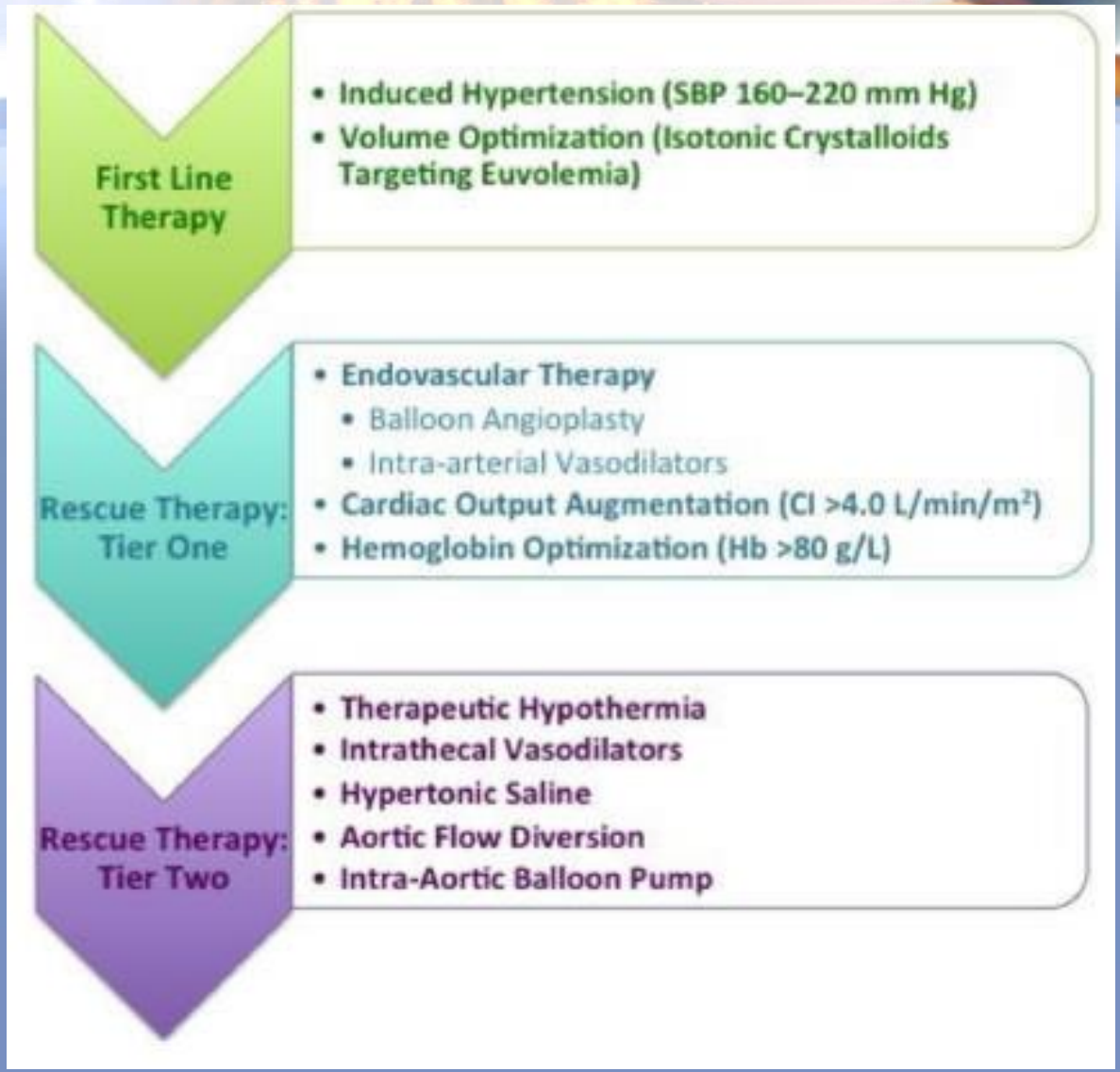
(Francoeur & Mayer, 2016)

DCI

- **Detection and Diagnosis (cont.)**
  - **Multimodality monitoring (MMM)**
    - Real time early detection.
    - Early autoregulatory failure = poor outcomes.
    - **ICP monitoring.**
      - 80% poor grade SAH have intracranial HTN.
      - CPP > 70 = lesser risk of brain metabolic crsis and hypoxia.
    - **PbtO2**
      - Detects cerebral compromise in absence of elevated ICP or low CPP.
      - Early detection of silent infracts.
      - Higher mean = improved survival.
    - **Microdialysis**
      - Interstitial fluid composition and cellular metabolism.
      - Derangements precede silent infarction by few hours.
        - » Lactate > 4 mmol = DCI.

(Francoeur & Mayer, 2016)

Active DCI Stepwise Approach



(Francoeur & Mayer, 2016, Figure 2)

Cardiac Output Augmentation

- Target CI >4.0
- Dobutamine and phenylephrine
  - Can increased CBF by 50% in SAH with severe vasospasm.
- Milrinone
  - More effective inotropy in neurogenic stunned myocardium
    - Decreased beta-receptor sensitization.

(Francoeur & Mayer, 2016)

Neuroinflammation Research

- **Heparin**
  - Reduced inflammation and apoptosis in models.
- **Glyburide**
  - Reduced inflammation and behavioral deficits in models.
- **Inflammatory cytokines mediate vasospasm.**
  - Rosiglitazone: Antioxidant reduced vasospasm and improved outcome in models.
  - Glutamate modulation reduced vasospasm in models.

(Lucke-Wold et al., 2016)

Autophagy-Lysosomal System

- **Self-catabolic process**
  - Removes dysfunctional or unnecessary intracellular components degraded by lysosomal enzymes.
  - Activated in ipsilateral frontobasal cortex.
  - Duration 0-3 days.
- **Under or over function is bad.**
  - Appropriate activity = pro-survival mechanism.
  - Excessive self-digestion->cell death.
- **Melatonin stimulated autophagy and suppressed apoptic cell death->deficit amelioration in models.**

(Wu et al., 2016)

Radiogenomics

- **Neuroimaging + molecular approaches = Radiogenomics.**
- **Aneurysmal pathophysiology directly related to regional blood flow.**
- **Non-invasive analysis of aneurysm morphology and hemodynamics.**
- **Ferumoxytol-enhanced MRI.**
  - Aneurysmal inflammation.
  - Predicted instability and increased 6-month rupture risk.
  - Biomarker indicating more urgent intervention.
- **Diagnostic CSF biomarkers for vasospasm**
  - Endothelin-1
  - Interleukin-6
- **Personalized medicine protocols in treatment and prevention of vasospasm.**

(Achrol & Steinberg, 2016)

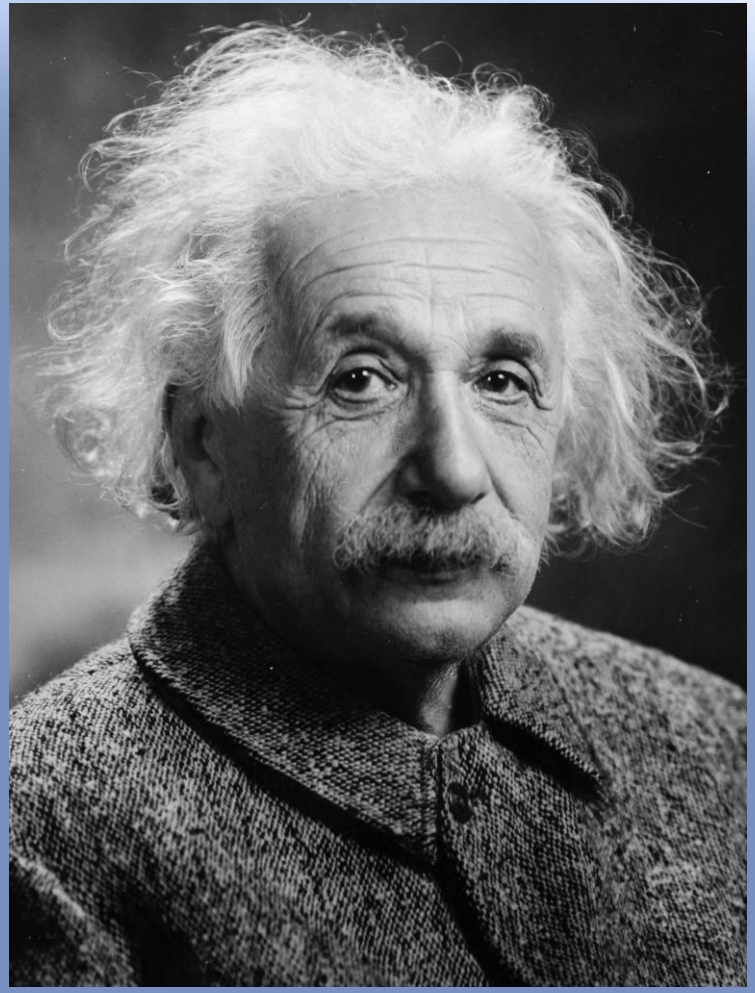
Bright Side

- Improved survival over 30 years.
  - Reduced fatality from 50% to 20% in high volume centers.
- We can go beyond.

(Mayer, Bernardini, & Solomon, 2016)

Super Scientific AND Inspirational Closing Quotes

- "I have no special talents. I am only passionately curious."
  - **Be curious.**
- "For us believing physicists, the distinction between past, present, and future is only a stubborn illusion."
  - **Abandon illusions; actualize solutions.**



(Albert Einstein, n.d.; Turner, 1947)

Conclusion

- **Additional Resources**
  - Neurocritical Care Society
    - **www.neurocriticalcare.org**
    - Family & Patient Resources > Stories of Hope
  - Brain Aneurysm Foundation
    - www.bafound.org

- **Mahalo**!

(Brain Aneurysm Foundation, 2016; Neurocritical Care Society, 2016)

References

- Albert Einstein. (n.d.). Retrieved November 3, 2016 from https://en.wikiquote.org/wiki/Albert_Einstein
- Achrol, A.S. & Steinberg, G.K. (2016). Personalized medicine in cerebrovascular neurosurgery: precision neurosurgical management of cerebral aneurysms and subarachnoid hemorrhage. *Frontiers in Surgery, 3(34). doi:10.3389/fsurg.2016.00034*
- Brain Aneurysm Foundation. (2016). *Brain aneurysm foundation.* Retrieved from http://www.bafound.org
- Brisman, J.L. (2016). Neurosurgery for cerebral aneurysm. Retrieved from http://emedicine.medscape.com/article/252142-overview
- Caplan, L.R. (2009). Subarachnoid hemorrhage, aneurysm, and vascular malformations. In *Caplan's stroke: A clinical approach* (4th ed.). Retrieved from https://www-clinicalkey-com.ezproxy4.library.arizona.edu/#!/content/book/3-s2.0-B9781416047216500146Mayer, S.A., Bernardini, G.L., & Solomon, R.A. (2016). Chapter 39. Subarachnoid hemorrhage. In E.D. Louis, S.A. Mayer, & L.P. Rowland (Eds.), *Merritt's neurology* (13 ed.). Retrieved from http://online.statref.com/Document.aspx?fxId=501&docId=331
- Edlow, J.A., Figaji, A, Samuels, O. (2015). Emergency neurological life support: subarachnoid hemorrhage. *Neurocritical care, 23,* S103-S109. doi:0.1007/s12028-015-0183-0
- Francoeur, C.L., & Mayer, S.A. Management of delayed cerebral ischemia after subarachnoid hemorrhage. *Critical Care, 20:277.* doi:10.1186/s13054-016-1447-6
- Lucke-Wold, B.P., Logsdon, A.F., Manoranjan, B., Turner, R.C., McConnell, E., Vates, G.E., . . . Simard., J.M. (2016). Aneurysmal subarachnoid hemorrhage and neuroinflammation: A comprehensive review. International Journal of Molecular Sciences. doi:10.3390/ijms17040497

References

- Neurocritical Care Society (2016). *Stories of hope*. Retrieved from http://www.neurocriticalcare.org/Family-Patient-Resources/Stories-of-Hope
- Robert Wood Johnson University Jospital. (2016). What is a brain aneurysm. Retrieved from http://www.rwjuh.edu/brain-aneurysm/brain-aneurysm-overview.aspx
- Ropper A.H., Samuels M.A., Klein J.P. (2014). Chapter 34. Cerebrovascular diseases. In A.H. Ropper, M.A. Samuels, J.P. Klein (Eds.), *Adams & Victor's Principles of Neurology* (10 ed.). Retrieved from http://accessmedicine.mhmedical.com.ezproxy4.library.arizona.edu/content.aspx?bookid=690&Sectionid=50910885
- Szeder, V., Tateshima, S., & Duckwiler, G.R. (2016). Intracranial aneurysms and subarachnoid hemorrhage. In R.B. Darroff, J. Jankovic, J.C. Mazziotta, & S.L Pomerory (Eds.), *Bradley's neurology in clinical practice* (7th ed.). Retrieved from https://www-clinicalkey-com.ezproxy2.library.arizona.edu/#!/content/book/3-s2.0-B9780323287838000673
- Turner, O.J. (1947). *Albert einstein, 1879-1955* (Digital photograph]. Retrieved from https://www.loc.gov/item/2004671908/
- Zhang, L, Wang, Z., & Qi, S. (2015). Cardiac troponin elevation and outcome after subarachnoid hemorrhage: A systematic review and meta-analysis. *Journal of Stroke and Cerebrovascular Diseases, 24*(10), 2375-2384. doi:10.1016/j.jstrokecerebrovasdis.2015.06.030
- Wu, H., Niu, h. Wu, C., Li, Y., Wang, K., Zhang, J., . . . Yang, S. (2016). The autophagy-lysosomal system in subarachnoid hemorrhage. *Journal of Cellular and Molecular Medicine, 20*(9), 1770-1778. doi:10.1111/jcmm.12855