Aneurysmal Subarachnoid Hemorrhage

Carl Wherry RN MSN ACNP-bc
March 22, 2014
11:30am-12:45pm
CANP 37th Annual Conference
Disclosures

- none
Objectives

• Describe etiology and pathophysiology of aneurysmal subarachnoid hemorrhage (SAH).
• Discuss the grading scales used in the assessment of patients with aSAH.
• Understand the treatment modalities used for the prevention of morbidity and mortality that can follow SAH.
Overview

• Definition/epidemiology
• Disease process
• Current guidelines for management
• Case study
Epidemiology

- Adults over 30: 9 per 100,000 translates to 30k per year in the US.
- Female > Male (1.6x)
- ~12% will die before reaching the hospital
- 45% overall mortality

Basic Definitions

• Aneurysm

• What is it?

• Risk factors:
  Heredity
  HTN
  Tobacco

Figure:
www.brain-aneurysm.com
The Circle of Willis

Anterior (Front)
- Anterior Cerebral Artery A2 Segment
  ACA – A2
- Anterior Cerebral Artery A1 Segment
  ACA – A1
- Middle Cerebral Artery
  MCA
- Anterior Choroidal Artery
  AChA
- Posterior Communicating Artery
  PCoA
- Posterior Cerebral Artery
  P1 Segment
  PCA – P1
- Superior Cerebellar Artery
  SCbA

Posterior (Back)
- Posterior Cerebral Artery
  P2 segment
  PCA – P2
- Basilar Artery
  BA

Left Side
Right Side
Basic Definitions

- Subarachnoid Hemorrhage
Most common sites of intracranial saccular aneurysms

Incidence:
- <1%:
  - Pericallosal artery (4%)
  - Anterior communicating artery (30%)
  - Lateral carotid artery bifurcation (8%)
  - Middle cerebral artery (20%)
  - Posterior communicating artery (25%)
- 10%:
  - Basilar tip (7%)
- 20%:
  - Posterior inferior cerebellar artery (3%)

Author: Nicholas Zaorsky, M.D.
What are the current guidelines?

### Table 1. Applying Classification of Recommendation and Level of Evidence

<table>
<thead>
<tr>
<th>LEVEL A: Multiple populations evaluated</th>
<th>LEVEL B: Limited populations evaluated</th>
<th>LEVEL C: Very limited populations evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suggested phrases for writing recommendations</td>
<td>Suggested phrases for writing recommendations</td>
<td>Suggested phrases for writing recommendations</td>
</tr>
<tr>
<td>should is recommended is indicated is useful/effective/beneficial</td>
<td>is reasonable can be useful/effective/beneficial is probably recommended or indicated</td>
<td>m/w/might be considered m/w/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established</td>
</tr>
<tr>
<td>Comparative effectiveness phrases</td>
<td>Comparative effectiveness phrases</td>
<td>Comparative effectiveness phrases</td>
</tr>
<tr>
<td>treatment/strategy A is recommended/indicated in preference to treatment B</td>
<td>treatment/strategy A is probably recommended/indicated in preference to treatment B</td>
<td>treatment/strategy A is probably recommended/indicated in preference to treatment B</td>
</tr>
<tr>
<td>treatment A should be chosen over treatment B</td>
<td>It is reasonable to choose treatment A over treatment B</td>
<td>It is reasonable to choose treatment A over treatment B</td>
</tr>
</tbody>
</table>

**Size of Treatment Effect**

<table>
<thead>
<tr>
<th>CLASS I</th>
<th>CLASS IIa</th>
<th>CLASS IIb</th>
<th>CLASS III/No Benefit or CLASS III Harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefit &gt;&gt; &gt;&gt; Risk</td>
<td>Benefit &gt;&gt; &gt;&gt; Risk</td>
<td>Benefit ≥ &gt;&gt; Risk</td>
<td>Benefit ≥ &gt;&gt; Risk</td>
</tr>
<tr>
<td>Procedure/Treatment SHOULD be performed/administered</td>
<td>Additional studies with focused objectives needed IT IS REASONABLE to perform procedure/administer treatment</td>
<td>Additional studies with broad objectives needed: additional registry data would be helpful Procedure/Treatment MAY BE CONSIDERED</td>
<td>Recommendation that procedure or treatment is not useful/effective and may be harmful</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Recommendation’s usefulness/effectiveness less well established</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Greater conflicting evidence from multiple randomized trials or meta-analyses</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Evidence from single randomized trial or nonrandomized studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Recommendation that procedure or treatment is not useful/effective and may be harmful</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Evidence from single randomized trial or nonrandomized studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Recommendation that procedure or treatment is not useful/effective and may be harmful</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Evidence from single randomized trial or nonrandomized studies</td>
</tr>
</tbody>
</table>

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

**For comparative effectiveness recommendations (Class I and IIa, Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.**
Diagnosis and assessment

- Clinical Manifestations and Diagnosis of aSAH:
  1. aSAH is a medical emergency that is frequently misdiagnosed. A high level of suspicion for aSAH should exist in patients with acute onset of severe headache (Class I; Level of Evidence B).
  2. Acute diagnostic workup should include noncontrast head CT, which, if nondiagnostic, should be followed by lumbar puncture (Class I; Level of Evidence B).
  3. CTA may be considered in the workup of aSAH. If an aneurysm is detected by CTA, this study may help guide the decision for type of aneurysm repair, but if CTA is inconclusive, DSA is still recommended (except possibly in the instance of classic perimesencephalic aSAH) (Class IIB; Level of Evidence C). (New recommendation)
  4. Magnetic resonance imaging (fluid-attenuated inversion recovery, proton density, diffusion-weighted imaging, and gradient echo sequences) may be reasonable for the diagnosis of aSAH in patients with a nondiagnostic CT scan, although a negative result does not obviate the need for cerebrospinal fluid analysis (Class IIB; Level of Evidence C). (New recommendation)
  5. DSA with 3-dimensional rotational angiography is indicated for detection of aneurysm in patients with aSAH (except when the aneurysm was previously diagnosed by a noninvasive angiogram) and for planning treatment (to determine whether an aneurysm is amenable to coiling or to expedite microsurgery) (Class I; Level of Evidence B). (New recommendation)
Presenting Symptoms...
Evaluation of suspected subarachnoid hemorrhage

Sudden severe headache (Thunderclap)
With or without nausea/vomiting, photophobia, meningismus, altered mental state, seizures, motor or sensory deficits, cranial nerve palsies

CT brain without contrast

Consistent with SAH

CSF analysis for red blood cells and xanthochromia

Positive
Traumatic tap or uninterpretable results

CSF spectrophotometry (if available)

No bilirubin peak
No SAH

Bilirubin peak
SAH

SAH: subarachnoid hemorrhage.
Presenting Symptoms:  

<table>
<thead>
<tr>
<th>Neurological Feature</th>
<th>Day 0</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Percent</td>
<td>No.</td>
<td>Percent</td>
<td>No.</td>
</tr>
<tr>
<td>level of consciousness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fully alert</td>
<td>708</td>
<td>41.1</td>
<td>557</td>
<td>50.5</td>
<td>268</td>
</tr>
<tr>
<td>drowsy</td>
<td>557</td>
<td>32.4</td>
<td>393</td>
<td>35.6</td>
<td>121</td>
</tr>
<tr>
<td>stuporous</td>
<td>221</td>
<td>12.8</td>
<td>87</td>
<td>7.9</td>
<td>22</td>
</tr>
<tr>
<td>comatose</td>
<td>235</td>
<td>13.7</td>
<td>67</td>
<td>6.1</td>
<td>7</td>
</tr>
<tr>
<td>speech</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>normal</td>
<td>1150</td>
<td>66.8</td>
<td>873</td>
<td>79.1</td>
<td>372</td>
</tr>
<tr>
<td>dysphasic</td>
<td>167</td>
<td>9.7</td>
<td>97</td>
<td>8.8</td>
<td>17</td>
</tr>
<tr>
<td>no verbal response</td>
<td>404</td>
<td>23.5</td>
<td>134</td>
<td>12.1</td>
<td>29</td>
</tr>
<tr>
<td>orientation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>normal</td>
<td>902</td>
<td>52.4</td>
<td>670</td>
<td>60.7</td>
<td>305</td>
</tr>
<tr>
<td>impaired</td>
<td>819</td>
<td>47.6</td>
<td>434</td>
<td>39.3</td>
<td>113</td>
</tr>
<tr>
<td>response to commands</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>appropriate</td>
<td>1141</td>
<td>66.3</td>
<td>866</td>
<td>78.4</td>
<td>374</td>
</tr>
<tr>
<td>inappropriate</td>
<td>580</td>
<td>33.7</td>
<td>238</td>
<td>21.6</td>
<td>44</td>
</tr>
<tr>
<td>motor response</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>normal</td>
<td>1189</td>
<td>69.1</td>
<td>882</td>
<td>79.9</td>
<td>361</td>
</tr>
<tr>
<td>mild focal deficit</td>
<td>224</td>
<td>13.0</td>
<td>129</td>
<td>11.7</td>
<td>43</td>
</tr>
<tr>
<td>severe focal deficit</td>
<td>123</td>
<td>7.1</td>
<td>56</td>
<td>5.1</td>
<td>9</td>
</tr>
<tr>
<td>abnormal flexor</td>
<td>48</td>
<td>2.8</td>
<td>16</td>
<td>1.4</td>
<td>1</td>
</tr>
<tr>
<td>abnormal extensor</td>
<td>92</td>
<td>5.3</td>
<td>16</td>
<td>1.4</td>
<td>1</td>
</tr>
<tr>
<td>no response</td>
<td>45</td>
<td>2.6</td>
<td>5</td>
<td>0.5</td>
<td>3</td>
</tr>
<tr>
<td>meningeal signs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>225</td>
<td>13.1</td>
<td>75</td>
<td>6.8</td>
<td>31</td>
</tr>
<tr>
<td><strong>headache</strong></td>
<td>1142</td>
<td>66.4</td>
<td>791</td>
<td>71.6</td>
<td>313</td>
</tr>
<tr>
<td>stiff neck</td>
<td>1281</td>
<td>74.4</td>
<td>839</td>
<td>85.1</td>
<td>345</td>
</tr>
<tr>
<td>cranial nerve deficit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>1502</td>
<td>87.3</td>
<td>1003</td>
<td>90.9</td>
<td>371</td>
</tr>
<tr>
<td>third</td>
<td>161</td>
<td>9.4</td>
<td>61</td>
<td>5.5</td>
<td>30</td>
</tr>
<tr>
<td>other</td>
<td>71</td>
<td>4.1</td>
<td>46</td>
<td>4.2</td>
<td>19</td>
</tr>
<tr>
<td><strong>totals</strong></td>
<td>1721</td>
<td>48.9</td>
<td>1104</td>
<td>31.4</td>
<td>418</td>
</tr>
</tbody>
</table>


### Why early CT?

<table>
<thead>
<tr>
<th>CT Findings</th>
<th>Day 0</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>normal</td>
<td>51</td>
<td>68</td>
<td>62</td>
<td>20</td>
<td>9</td>
<td>288</td>
<td></td>
</tr>
<tr>
<td>decreased density</td>
<td>11</td>
<td>33</td>
<td>51</td>
<td>5</td>
<td>2</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>mass effect</td>
<td>124</td>
<td>14</td>
<td>11</td>
<td>2</td>
<td>3</td>
<td>211</td>
<td></td>
</tr>
<tr>
<td>aneurysm</td>
<td>73</td>
<td>33</td>
<td>11</td>
<td>5</td>
<td>0</td>
<td>173</td>
<td></td>
</tr>
<tr>
<td>hydrocephalus</td>
<td>248</td>
<td>33</td>
<td>47</td>
<td>6</td>
<td>3</td>
<td>527</td>
<td></td>
</tr>
<tr>
<td>intraventricular hematoma</td>
<td>312</td>
<td>51</td>
<td>23</td>
<td>2</td>
<td>2</td>
<td>578</td>
<td></td>
</tr>
<tr>
<td>intracerebral hematoma</td>
<td>294</td>
<td>70</td>
<td>43</td>
<td>14</td>
<td>6</td>
<td>601</td>
<td></td>
</tr>
<tr>
<td>subdural hematoma</td>
<td>28</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>subarachnoid hemorrhage†</td>
<td>1430</td>
<td>338</td>
<td>189</td>
<td>49</td>
<td>19</td>
<td>2940</td>
<td></td>
</tr>
<tr>
<td>diffuse</td>
<td>876</td>
<td>167</td>
<td>87</td>
<td>29</td>
<td>14</td>
<td>1684</td>
<td></td>
</tr>
<tr>
<td>thin</td>
<td>241</td>
<td>93</td>
<td>54</td>
<td>12</td>
<td>5</td>
<td>619</td>
<td></td>
</tr>
<tr>
<td>thick</td>
<td>587</td>
<td>116</td>
<td>68</td>
<td>15</td>
<td>6</td>
<td>1034</td>
<td></td>
</tr>
<tr>
<td>totals</td>
<td>1553</td>
<td>446</td>
<td>279</td>
<td>76</td>
<td>33</td>
<td>3451</td>
<td></td>
</tr>
</tbody>
</table>

* Fifteen patients underwent CT scanning after Day 5; 70 patients did not have a CT scan.
† Classification was determined according to Fisher, et al.**
• How to describe our patients and risk stratify for complication
Basic Definitions

- **Glasgow Coma Scale**
  - Motor (1-6)
    1 None
    2 Decerebrate
    3 Decorticate
    4 Flexion Withdrawal
    5 Localize
    6 Follows Commands
  - Eye Opening (1-4)
    1 None
    2 To Pain
    3 To Voice
    4 Spontaneous

- **Verbal 1-5**
  1 None
  2 Moans
  3 Unintelligible words
  4 Confused Conversation
  5 Oriented
Hunt and Hess Scale

- Grade 0: Asymptomatic
- Grade I: Slight Headache, No Deficit
- Grade II: Severe Headache, No Deficit (may have cranial nerve palsy)
- Grade III: Drowsiness and mild deficit
- Grade IV: Stupor, Moderate to severe hemiparesis, and possible early rigidity
- Grade V: Deep coma, decerebrate rigidity, moribund appearance
Fischer Grade

- Based on imaging

- Grade 1: No Blood noted on Computed Tomography (CT) scan
- Grade 2: <1mm blood in subarachnoid space
- Grade 3: >1mm blood in subarachnoid space
- Grade 4: Blood in subarachnoid space with extension into ventricular or parenchymal space
Let's Practice Grading a SAH
Another scale to be aware of:

- World Federation of Neurologic Surgeons (WFNS)
  - 1: GCS 15 no focal deficit
  - 2: GCS 13-14, no focal deficit
  - 3: GCS 13-14 with focal deficit
  - 4: GCS 7-12 with or without focal deficit
  - 5: GCS <7 with or without focal deficit
Management Guidelines

• Medical Measures to Prevent Rebleeding After aSAH: Recommendations

• 1. Between the time of aSAH symptom onset and aneurysm obliteration, blood pressure should be controlled with a titratable agent to balance the risk of stroke, hypertension-related rebleeding, and maintenance of cerebral perfusion pressure (Class I; Level of Evidence B). (New recommendation)

• 2. The magnitude of blood pressure control to reduce the risk of rebleeding has not been established, but a decrease in systolic blood pressure to <160 mm Hg is reasonable (Class IIa; Level of Evidence C). (New recommendation)

• 3. For patients with an unavoidable delay in obliteration of aneurysm, a significant risk of rebleeding, and no compelling medical contraindications, shortterm (<72 hours) therapy with tranexamic acid or aminocaproic acid is reasonable to reduce the risk of early aneurysm rebleeding (Class IIa; Level of Evidence B). (Revised recommendation from previous guidelines)
Surgical and Endovascular Methods of Treatment of Ruptured Cerebral Aneurysms:

1. Surgical clipping or endovascular coiling of the ruptured aneurysm should be performed as early as feasible in the majority of patients to reduce the rate of rebleeding after aSAH (Class I; Level of Evidence B).

2. Complete obliteration of the aneurysm is recommended whenever possible (Class I; Level of Evidence B).

3. Determination of aneurysm treatment, as judged by both experienced cerebrovascular surgeons and endovascular specialists, should be a multidisciplinary decision based on characteristics of the patient and the aneurysm (Class I; Level of Evidence C). (Revised recommendation from previous guidelines)

4. For patients with ruptured aneurysms judged to be technically amenable to both endovascular coiling and neurosurgical clipping, endovascular coiling should be considered (Class I; Level of Evidence B). (Revised recommendation from previous guidelines)
• 5. In the absence of a compelling contraindication, patients who undergo coiling or clipping of a ruptured aneurysm should have delayed follow-up vascular imaging (timing and modality to be individualized), and strong consideration should be given to retreatment, either by repeat coiling or microsurgical clipping, if there is a clinically significant (eg, growing) remnant (Class I; Level of Evidence B). (New recommendation)

• 6. Microsurgical clipping may receive increased consideration in patients presenting with large (>50 mL) intraparenchymal hematomas and middle cerebral artery aneurysms. Endovascular coiling may receive increased consideration in the elderly (70 years of age), in those presenting with poor-grade (World Federation of Neurological Surgeons classification IV/V) aSAH, and in those with aneurysms of the basilar apex (Class IIb; Level of Evidence C). (New recommendation)

• 7. Stenting of a ruptured aneurysm is associated with increased morbidity and mortality, and should only be considered when less risky options have been excluded (Class III; Level of Evidence C). (New recommendation)
Clip versus Coil

- Aneurysm clip
- Aneurysm
- Artery
- Aneurysm neck
- Aneurysm coils

© Mayfield Clinic
Treatment and Care

• Clip vs Coil
  Based on size and morphology of Aneurism
  Dome to neck ratio
  Medical stability of patient

• 2005 International Subarachnoid Aneurysm Trial (ISAT)
  Only multicenter, randomized trial
  2143 patients
ISAT cont.

Trial profile
SAH—subarachnoid haemorrhage. *Based on those centres that returned ascertainment logs. †Based on patients randomised before Dec 1, 2001. ‡Based on patients randomised before Feb 1, 2001.
Results of ISAT

- 23% (coil) vs 31% (clip) with death or severe disability at 1 year.
- Possible increased risk for re-bleed w endovascular therapy 5% vs 4%.
- Results favor coil embolization (but caveat).
Hospital Characteristics and Systems of Care: Recommendations

• 1. Low-volume hospitals (eg, <10 aSAH cases per year) should consider early transfer of patients with aSAH to high-volume centers (eg, >35 aSAH cases per year) with experienced cerebrovascular surgeons, endovascular specialists, and multidisciplinary neuro-intensive care services (*Class I; Level of Evidence B*). (Revised recommendation from previous guidelines)

• 2. Annual monitoring of complication rates for surgical and interventional procedures is reasonable (*Class IIa; Level of Evidence C*). (New recommendation)

• 3. A hospital credentialing process to ensure that proper training standards have been met by individual physicians treating brain aneurysms is reasonable (*Class IIa; Level of Evidence C*). (New recommendation)
Complications

- Hydrocephalus
- Delayed Ischemic Deficits
- Medical Complications
Hydrocephalus

- Disturbance in CSF reabsorption
Management of Hydrocephalus Associated With aSAH: Recommendations

1. aSAH-associated acute symptomatic hydrocephalus should be managed by cerebrospinal fluid diversion (EVD or lumbar drainage, depending on the clinical scenario) (Class I; Level of Evidence B). (Revised recommendation from previous guidelines)

2. aSAH-associated chronic symptomatic hydrocephalus should be treated with permanent cerebrospinal fluid diversion (Class I; Level of Evidence C). (Revised recommendation from previous guidelines)

3. Weaning EVD over >24 hours does not appear to be effective in reducing the need for ventricular shunting (Class III; Level of Evidence B). (New recommendation)

4. Routine fenestration of the lamina terminalis is not useful for reducing the rate of shunt-dependent hydrocephalus and therefore should not be routinely performed. (Class III; Level of Evidence B). (New recommendation)
Delayed Ischemic Deficit

- Vasospasm
- Time of onset 5-7 days
- Duration may last up to 14 days
- Role of Nimodipine
Management of Cerebral Vasospasm and DCI After aSAH: Recommendations

1. Oral nimodipine should be administered to all patients with aSAH ([Class I; Level of Evidence A]). (It should be noted that this agent has been shown to improve neurological outcomes but not cerebral vasospasm. The value of other calcium antagonists, whether administered orally or intravenously, remains uncertain.)

2. Maintenance of euvolemia and normal circulating blood volume is recommended to prevent DCI ([Class I; Level of Evidence B]). (Revised recommendation from previous guidelines)

3. Prophylactic hypervolemia or balloon angioplasty before the development of angiographic spasm is not recommended ([Class III; Level of Evidence B]). (New recommendation)

4. Transcranial Doppler is reasonable to monitor for the development of arterial vasospasm ([Class IIa; Level of Evidence B]). (New recommendation)
Cerebral Vasospasm and DCI cont:

• 5. Perfusion imaging with CT or magnetic resonance can be useful to identify regions of potential brain ischemia (*Class IIa; Level of Evidence B*). (New recommendation)

• 6. Induction of hypertension is recommended for patients with DCI unless blood pressure is elevated at baseline or cardiac status precludes it (*Class I; Level of Evidence B*). (Revised recommendation from previous guidelines)

• 7. Cerebral angioplasty and/or selective intra-arterial vasodilator therapy is reasonable in patients with symptomatic cerebral vasospasm, particularly those who are not rapidly responding to hypertensive therapy (*Class IIa; Level of Evidence B*). (Revised recommendation from previous guidelines)
Nimodipine

Nimodipine,

\[ C_{21}H_{26}N_2O_7 \]

\[
\begin{align*}
\text{Nimodipine} & : & \\
\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_7 & : & \\
\end{align*}
\]

![Nimodipine structure]

![Nimotop tablets]
Nimodipine

Dihydropyridine calcium channel blocker
Protein bound
Time to peak activity – 1 hour
Medication half life – 8-9 hours
Side Effects: hypotension, nausea, diarrhea, cramping
Prevention of Delayed Ischemic Deficit (DID)

Data in early 80s demonstrated efficacy of drug in limiting DID despite continued angiographic vasospasm

Strength of Effect began to be called into question

Mechanisms:
- Vasodilation
- Cytoprotective/Free radical scavenger
- Potentiation of collateral flow
Early data:

- NEJM 1983
- 125 patients randomized, double blind, placebo control
- 21 day outcomes.
- Death or severe disability occurred 8 of 60 in placebo vs 1 of 56 in Nimodipine arm. P=0.03
Efficacy of prophylactic nimodipine for delayed ischemic deficit after subarachnoid hemorrhage: a metaanalysis

Fred G. Barker II, M.D., and Christopher S. Ogilvy, M.D.

Brain Tumor Research Center, Department of Neurological Surgery, University of California at San Francisco, San Francisco, California; and Cerebrovascular Surgery, Neurosurgical Service, Massachusetts General Hospital, and Department of Surgery, Harvard Medical School, Boston, Massachusetts
Methods

Medline Search and abstract review
Trials needed to be randomized and compare nimodipine vs placebo in a prophylactic setting

Endpoints:

- Glasgow Outcome Scale – some scales converted
- New deficit
- Death
- Radiological Infarct rate – CT based
- Hunt and Hess Grade

Intention to treat analysis
Outline of metaanalyses performed*

<table>
<thead>
<tr>
<th>Metaanalysis No.</th>
<th>Outcome Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>good outcome vs. all other grades</td>
</tr>
<tr>
<td>2</td>
<td>good or fair outcome vs. other grades</td>
</tr>
<tr>
<td>3</td>
<td>overall mortality</td>
</tr>
<tr>
<td>4</td>
<td>deficit or mortality attributed to vasospasm or DID</td>
</tr>
<tr>
<td>5</td>
<td>mortality attributed to vasospasm or DID</td>
</tr>
<tr>
<td>6</td>
<td>cerebral infarction rate (as assessed by CT)</td>
</tr>
<tr>
<td>7</td>
<td>deficit or mortality attributed to rebleeding</td>
</tr>
<tr>
<td>8</td>
<td>mortality attributed to rebleeding</td>
</tr>
</tbody>
</table>

* Abbreviations: CT = computerized tomography; DID = delayed ischemic deficit.
Studies that met specifications

<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>No. of Patients Randomized</th>
<th>No. of Patients Analyzed</th>
<th>No. of Patients Excluded</th>
<th>Method of Nimodipine Administration</th>
<th>Duration of Treatment (days)</th>
<th>Hunt &amp; Hess Grades Included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen, et al., 1983</td>
<td>121</td>
<td>116</td>
<td>5</td>
<td>PO</td>
<td>21</td>
<td>I &amp; II</td>
</tr>
<tr>
<td>Philippon, et al., 1986</td>
<td>81</td>
<td>70</td>
<td>11</td>
<td>PO</td>
<td>21</td>
<td>I-III</td>
</tr>
<tr>
<td>Messeter, et al., 1987</td>
<td>20</td>
<td>20</td>
<td>0</td>
<td>IC, IV</td>
<td>9</td>
<td>I-III</td>
</tr>
<tr>
<td>Mee, et al., 1988</td>
<td>75</td>
<td>75†</td>
<td>0†</td>
<td>IC, PO</td>
<td>21</td>
<td>I-V</td>
</tr>
<tr>
<td>Petruk, et al., 1988</td>
<td>188</td>
<td>154</td>
<td>34</td>
<td>PO</td>
<td>21</td>
<td>III-V</td>
</tr>
<tr>
<td>Pickard, et al., 1989</td>
<td>555</td>
<td>554</td>
<td>1</td>
<td>PO</td>
<td>21</td>
<td>I-V</td>
</tr>
<tr>
<td>Öhman, et al., 1991</td>
<td>215</td>
<td>213</td>
<td>2</td>
<td>IV, PO</td>
<td>21</td>
<td>I-III</td>
</tr>
<tr>
<td>total</td>
<td>1255</td>
<td>1202†</td>
<td>53†</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* Abbreviations: IC = intracisternal (during craniotomy); IV = intravenous; PO = oral; — = not applicable.
† Twenty-five patients were excluded from the trial reported by Mee, et al., in Metaanalyses 4, 5, 7, and 8.

Nimodipine given orally in 5 trials
Meta-analysis Outcome

Higher chance of good outcome with nimodipine  
(P = 0.004 OR 1.86 99% CI 1.07-3.25)
Assuming 52% good outcome rate among placebos, one additional good outcome was gained with treatment of 7 patients

Higher chance of good to fair outcome with nimodipine  
(p < 0.0007, OR 1.67 99% CI 1.13-2.46)
Assuming rate of deficit or death of 28% in placebo group, one additional good or fair outcome for treatment of 10 patients
Nimodipine had no impact on mortality $p=0.1$
Nimodipine treated patients had a significantly lower incidence of death or deficit related to vasospasm ($p < 0.00001$, OR 0.46, CI 0.31-0.68)
Assuming a 28% rate of deficit or death attributable to delayed ischemia or vasospasm, treatment of 8 patients would result in one fewer death
Radiological Infarction

Nimodipine treated patients had less infarcts ($p = 0.001$, OR 0.58, CI 0.38-0.90) Assuming a 32% radiographic infarction rate, treatment with nimodipine would prevent 1 stroke every 10 treated patients.
Re-bleeding

Permanent deficit or death from re-bleeding

No reduction in permanent deficit or death from rebleeding

No reduction in death due to rebleeding

Death due to Re-bleeding
Data from 2007 used for guidelines:

Cochran Review

- The meta-analysis included 16 studies with a total of 3361 patients (1665 in the treatment group and 1696 in the control group).
- The number of patients per trial ranged from 20 (Messeter 1987) to 906 (Haley 1993).
- Comparison of:
  1. Poor Outcome
  2. Mortality
  3. Secondary Ischemia
  4. Rebleeding
Cochran Review, the results:

- Reduction of poor outcome (defined as death or dependency in activities of daily life) after SAH, though the reduction of case fatality alone is not statistically significant.
- Reduction in the frequency of secondary ischemia.
- Not associated with an increased frequency of rebleeding.
- Intravenous administration of calcium antagonists is more expensive and potentially hazardous in view of hypotensive effects, and is therefore not recommended.

Therefor:

- oral Nimodipine (60mg every four hours, to be continued for three weeks) as standard treatment in patients with aneurysmal subarachnoid hemorrhage.
ICU monitoring and therapies

- Neurologic Exam
- Role of cEEG
- CSF drainage
- Transcranial Doppler
- Triple H Therapy
Medical Complications

- Therapies not without regard to patient
Medical Complications

Figure 2. Frequency of medical complications in the total subarachnoid hemorrhage (SAH) population (676 patients) and among patients with poor outcome (220 patients; mRS 4-6) at 3 months.

Subarachnoid hemorrhage complications Wartenberg and Mayer 2006
Management of Medical Complications Associated With aSAH: Recommendations

1. Administration of large volumes of hypotonic fluids and intravascular volume contraction is not recommended after aSAH (Class III; Level of Evidence B).

2. Monitoring volume status in certain patients with recent aSAH by some combination of central venous pressure, pulmonary wedge pressure, and fluid balance is reasonable, as is treatment of volume contraction with crystalloid or colloid fluids (Class IIa; Level of Evidence B).

3. Aggressive control of fever to a target of normothermia by use of standard or advanced temperature modulating systems is reasonable in the acute phase of aSAH (Class IIa; Level of Evidence B). (New recommendation)

4. Careful glucose management with strict avoidance of hypoglycemia may be considered as part of the general critical care management of patients with aSAH (Class IIb; Level of Evidence B).
Management of Medical Complications cont.

• 5. The use of packed red blood cell transfusion to treat anemia might be reasonable in patients with aSAH who are at risk of cerebral ischemia. The optimal hemoglobin goal is still to be determined (*Class IIb; Level of Evidence B*). (New recommendation)

• 6. The use of fludrocortisone acetate and hypertonic saline solution is reasonable for preventing and correcting hyponatremia (*Class IIa; Level of Evidence B*).

• 7. Heparin-induced thrombocytopenia and deep venous thrombosis are relatively frequent complications after aSAH. Early identification and targeted treatment are recommended, but further research is needed to identify the ideal screening paradigms (*Class I; Level of Evidence B*). (New recommendation)
Case Study #1:

• 56yo Woman presents w acute onset HA started 1 hour ago.
• “Worst headache of my life”.
• Hx: HTN
• 10/10, frontal, onset less than 1 minute.
• Acute onset while doing her morning yoga
Work-up?

- What kind of imagining should we use to work-up?
  A) None, she has sinusitis, f/u w primary care provider in 1 week
  B) CT brain (non-contrast)
  C) MRI brain
  D) CT brain with contrast
Next steps

- Blood pressure is 184/92, HR 72, NSR
- Is this ok?
Initial management
Initial management
What do we need to monitor for now?

- A) Nothing, aneurysm is stable, patient can be discharged to home.
- B) Hydrocephalus
- C) Delayed Ischemia related to cerebral vasospasm
- D) B and C
Therapies to prevent DIND:

- Nimodipine 60mg PO q 4 hrs x 21 days.
- We continue drainage of CSF via external ventricular drain. Daily transcranial doppler to assess velocities. What kind of fluid management should be implement?
  - A) prophylactic hypertension using norepinephrine gtt to push SBP 160-200.
  - B) PRBC and 0.45% NaCl to push volume status at least 2 liters positive balance.
  - C) titration of ivf to maintain euvoolemic status.
Outcome:

- Fluid balance maintained, Na balance maintained.
- Normothermia goal.
- Daily TCDs without elevation through post bleed day 14.
- Tapering and removal of EVD.
- PT/OT and transfer from ICU.
Case #2

• **HPI:** 67 y.o. female with a history of hypertension, who presents with a subarachnoid hemorrhage.

• The patient reports she has had headaches on and off for the last month, in the past week she has had gradual onset of a severe headache associated with nausea and vomiting. She lives alone and at first tried to self medicate with Aleve, aspirin, and Tylenol but with no relief. In the last two days, she's felt the headache has been especially unrelenting and she's had little PO intake due to nausea and this prompted her to call 911. She was taken to an outside hospital, where CT revealed subarachnoid hemorrhage with blood in the R sylvian fissure, parafalcine sulci bilaterally, and prepontine basilar cisterns; no IVH was seen. The patient was given platelets and ddAVP for reversal of platelet dysfunction from aspirin use and started on nicardipine gtt. She was then transferred to our facility for further management.

• She denies any numbness, weakness, vertigo, diplopia, or dysarthria.
Imagining:
What happens next:

• She undergoes coil embolization of a L PCOM aneurysm. She is monitored in the ICU post embolization. Day 2 p embolization, she becomes increasingly sleepy.
• What should we be worried about?
• A) Nothing, she is in the icu where every 2 hours a nurse barges into the room to wake her up and ask her orientation questions.
• B) Hydrocephalus.
• C) Delayed cerebral ischemia due to cerebral vasospasm.
• D) B and C.
• She is intubated for airway protection, receives an external ventricular drain.
• TCDs demonstrate elevated velocities.
• What should we do regarding:
  Blood pressure goal?
  Fluid management?
  Other physiology issues to control?
ICU management continues:

- Daily cerebral angiogram to administer intraarterial therapy.
- Despite aggressive measures...
Outcomes

• Unfortunate
Dr. Bleck clarifies

- ... a realistic evidence based rating scale:
  - Class 0: Things I believe
  - Class 0a: Things I believe despite the available data
  - Class 1: Randomised controlled clinical trials that agree with what I believe
  - Class 2: Other prospectively collected data
  - Class 3: Expert opinion
  - Class 4: Randomised controlled clinical trials that don't agree with what I believe
  - Class 5: What you believe that I don't.

BMJ. Jul 22, 2000; 321(7255): 239.
Thanks