NEUROCRIITICAL CARE MANAGEMENT OF ANEURYSMAL SUBARACHNOID HEMORRHAGE

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Disclosures: None
Epidemiology

- Aneurysmal SAHs cause 2% to 7% of all strokes
- 27% of stroke-related years of life lost before age 65
- Intracranial aneurysm prevalence 1-6% overall
- SAH incidence 6-7/ 100,000 in most populations
  - Up to 22-27/ 100,000 in Finland and Japan
- Mean age of presentation 49-55 years
- Female > Men (1.6 : 1)
- Non-white > White (2.1 : 1)
- Case fatality*: Decreased to 20% between 2004 to 2008
  Compared to 30% between 1979 to 1983

Aneurysm Rupture Risk

- Increases with age (peak 5th and 6th decades)
- Risk factors associated with aneurysm formation and rupture:
  - Hypertension
  - Smoking
  - ETOH, cocaine abuse
  - First degree relative with aSAH
Associated Conditions

- First degree relative
- Adult dominant polycystic kidney disease (ADPKD)
- Ehlers–Danlos disease (type IV)
- Alpha1-antitrypsin deficiency
- Sickle cell disease
- Pseudoxanthoma elasticum
- Hereditary hemorrhagic telangiectasia
- Neurofibromatosis type I
- Tuberous sclerosis
- Fibromuscular dysplasia
- Coarctation of the aorta
### Cumulative (5-Year) Aneurysm Rupture Risk by Size and Location

<table>
<thead>
<tr>
<th>Size of Aneurysm (mm)</th>
<th>No History of SAH and Anterior Circulation Aneurysm</th>
<th>No History of SAH and Posterior Circulation or PCOM Aneurysm</th>
<th>History of SAH and Incidental Aneurysm</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7</td>
<td>0</td>
<td>2.5</td>
<td>1.5 anterior circulation; 3.5 posterior circulation (including PCOM)</td>
</tr>
<tr>
<td>7–12</td>
<td>2.6</td>
<td>14.5</td>
<td>n/a</td>
</tr>
<tr>
<td>13–24</td>
<td>14.5</td>
<td>18.4</td>
<td>n/a</td>
</tr>
<tr>
<td>&gt;25</td>
<td>40</td>
<td>50</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Clinical Presentation

Signs and Symptoms

Classic (50%)
- Thunderclap headache
- Syncope
- Neck stiffness

Other
- Sentinel headache (20%)
- Nausea Vomiting
- Ophthalmoplegia
- Photophobia
- Seizures
- Visual Loss
- Subhyaloid / retinal hemorrhage
- Back/leg pain

19% of those with a normal mental status are initially misdiagnosed

Kowalski RG, et al. JAMA 2004
Noncontrast CT

Sensitivity:
- Up to 98.5% within 6 hours
- 95-100% <24 hours
- 80% by day 3
- 50% by 1 week

MRI (FLAIR and GRE)
- Up to 100% sensitivity 6-30 days

MRA and CTA (lower sensitivity for aneurysms < 3mm)
- May be useful for screening

Conventional catheter angiography (2D and 3D)
- Can be initially negative in 15 – 20%
- Multiple aneurysms in up to 30%
CSF Xanthochromia

- **RBC breakdown:**
  - OxyHgb and MetHgb (Red)
  - Bilirubin (Yellow)

- **OxyHgb** is released both in-vitro and in-vivo

- **Bilirubin formation requires in-vivo transformation**
  - Hemoxygenase (heme to biliverdin)
  - Biliverdin reductase (biliverdin to bilirubin) produced by ependymal cells

- **Using spectrophotometry,** the presence of OxyHgb is detected rapidly but bilirubin takes 6-12 hours
Typical presentation:
Severe headache with nausea and vomiting, meningismus, diminished level of consciousness, localizing neurologic signs

Atypical presentation:
Seizure, confusional state, associated head trauma

Head CT without contrast material

Subarachnoid hemorrhage

CT angiography or cerebral angiography

Aneurysm found

Prompt treatment

Normal

Repeat CT angiography in 1–3 wk

Image brain, brainstem, and spinal cord

No subarachnoid hemorrhage

Unequivocally abnormal (xanthochromia, elevated red cell count unchanged from tube 1 to tube 4)

Lumbar puncture

Abnormal but equivocal (elevated red cell count without xanthochromia or analysis of only 1 tube)

CT angiography or cerebral angiography

Aneurysm found

Prompt treatment

Normal

Stop

+ 6-12 hrs from onset
Severity, Outcome and Early Management
Clinical and Radiographic Grading Scales
## Modified Hunt and Hess Scale Mortality Trend

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Inpatient Mortality (%)</th>
<th>1968</th>
<th>1996-2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Asymptomatic or mild headache with normal neuro exam</td>
<td>11</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Moderate/severe HA with normal neuro exam or oculomotor palsy</td>
<td>26</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Lethargy, confusion or mild focal neuro signs</td>
<td>37</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Stupor</td>
<td>71</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>Coma</td>
<td>100</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>35</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>
### World Federation of Neurological Surgeons (WFNS)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Inpatient Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Unruptured aneurysm</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>GCS 15 and no motor deficit</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>GCS 13-14 and no motor deficits</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>GCS 13-14 and motor deficits</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>GCS 7-12 ± motor deficit</td>
<td>33</td>
</tr>
<tr>
<td>5</td>
<td>GCS 3-6 ± motor deficit</td>
<td>76</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I:</strong> “recommended”</td>
<td><strong>Quality of Evidence:</strong></td>
</tr>
<tr>
<td><strong>Class II:</strong> Conflicting evidence</td>
<td><strong>High:</strong> Further research is very unlikely to change our confidence in the estimate of effect.</td>
</tr>
<tr>
<td><strong>Class IIa:</strong> “reasonable”</td>
<td><strong>Moderate:</strong> Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</td>
</tr>
<tr>
<td><strong>Class IIb:</strong> “may be reasonable”</td>
<td><strong>Low:</strong> Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</td>
</tr>
<tr>
<td><strong>Class III:</strong> Not useful/effective and in some cases may be harmful. “not recommended”</td>
<td><strong>Very low:</strong> Any estimate of effect is very uncertain.</td>
</tr>
</tbody>
</table>

**Level of Evidence - Therapeutic**

| A: Multiple RCT or meta-analysis | **Strength of Recommendation:** |
| B: Single RCT or observational study | **Strong or Weak** based on: |
| C: Consensus opinion of experts, case study, standard of care | Effect Size, confidence limits, relative value placed on each outcome, quality of the evidence |

**Level of Evidence - Diagnosis**

| A: Multiple prospective observational studies with a reference standard |  |
| B: single high quality study or 1+ case studies |  |
| C: Consensus opinion of experts |  |
**Initial management**

Medical stabilization

Prevention of re-bleeding
  - Blood Pressure Control
  - Aneurysm treatment

Control of intracranial pressure
Early brain injury (EBI)
- Sudden increase of ICP
- Decreased cerebral perfusion
- Transient global cerebral ischemia
  - Transient loss of consciousness or
  - Progressive intracranial hypertension.

Delayed cerebral ischemia (DCI)
- Change in neurological function that manifests most often between days 3 and 14
- DCI defined as a change in level of consciousness
  - 2 point decrease in GCS (or)
  - 2 point increase in NIHSS (or)
  - Development of new focal deficit lasting for at least 1 hour and not explained by other factors (e.g., systemic complications and hydrocephalus)

POOR OUTCOME
Early brain injury (EBI)

- Acute subarachnoid haemorrhage
  - Mechanical effects: Brain tissue destruction by ICH, mass effect, hydrocephalus
  - Intraventricular haemorrhage
  - Subarachnoid haemorrhage
    - Aneurysm
    - Intracerebral haemorrhage
      - Aneurysm bleeding or rebleeding
  - Aneurysm

- Early brain injury
  - CBF (microcirculatory constriction, microthrombosis, blood-brain barrier disruption, cerebral oedema, endothelial cell apoptosis, neuronal apoptosis, autophagy)
  - Cortical spreading ischaemia
    - Swollen neuron
    - Microthrombi

- Cellular changes
  - NO, K⁺, oxidative stress, increased ET-1, inflammation (increased cytokines, chemokines and adhesion molecules; activation of matrix metalloproteinases and apoptotic pathways; platelet activation and aggregation; ATP depletion; thrombin activation)

- Systemic complications
  - Sympathetic nervous system activation

- Acute global ischaemia
  - Causes CBF secondary to ICP, CPP, acute hydrocephalus
  - Can lead to microcirculatory constriction, microthrombosis
  - Pulmonary oedema
  - Cardiac dysfunction

- Systemic complications
  - Neurogenic pulmonary oedema, stunned myocardium, takotsubo cardiomyopathy, ECG changes, hyponatraemia, systemic inflammatory response syndrome
  - Microscopic
    - Contraction band necrosis
General ICU Management

- Airway protection
- Fluid resuscitation
- ICU admission
- Vascular access
- ECG, CXR, TTE, metabolic panel, CBC, PT/PTT, Troponin, Type and cross
- Bowel regimen
- VTE prophylaxis, initially with sequential compression devices (SCD’s)
Initial Blood Pressure Management

- Prior to securing aneurysm, it is reasonable to lower blood pressure in most circumstances
- Agents
  - Nicardipine
  - Clevidipine
  - Labetalol, esmolol
  - *Avoid NTG

- Presence of elevated ICP
- Integrity of cerebral autoregulation
- Presence of vasospasm, DCI
- End-organ dysfunction

<table>
<thead>
<tr>
<th>Hypertension management (unsecured aneurysm)</th>
<th>AHA/ASA</th>
<th>NCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;160 mmHg is reasonable (Class IIa; Level of Evidence C).</td>
<td>Modest elevations in blood pressure (mean blood pressure &lt;110 mmHg) do not require therapy. (Low QE; Strong Rec)</td>
<td></td>
</tr>
</tbody>
</table>
Re-bleeding and Prevention

- Most severe early complication
- Up to 15% in first 24 hrs
- Fatality rate up to 70%
- Cumulative risk 15-20%
- Poor grade at higher risk
- Early aneurysm repair
- ? Optimum timing
- Atleast within 72 hours
• **Clinical manifestations**
  – Acute or worsening headache
  – Decrease in the level of consciousness
  – Loss of brainstem reflexes, posturing
  – Respiratory arrest
  – Seizures

• **Other manifestations**
  – BP changes
  – Elevated ICP
  – Acute increase in external ventricular drainage or a change in the color of CSF

Confirm rebleeding by urgent non-contrast head CT
• Antifibrinolytic therapy can reduce risk of rebleeding
  – Tranexamic acid [No bolus; 1 g every 4 hours]
  – \(\varepsilon\)-aminocaproic acid (Amicar) [5-g IV bolus, followed by an infusion of 1.5 g/hour for 24 to 48 hours]

• Systematic Review
  – 1399 patients from 9 trials
  – Antifibrinolytic agents reduced the risk of re-bleeding (odds ratio [OR], 0.55; 95%CI, 0.42–0.71)
  – But increased the risk of thromboembolism (OR, 1.39; 95%CI, 1.07–1.82)
  – No effect on neurologic outcome or mortality
### Preventing Rebleeding

<table>
<thead>
<tr>
<th>AHA/ASA</th>
<th>NCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>If unavoidable delay in obliteration of aneurysm, with significant risk of rebleeding, and no compelling medical contraindications, short term (&lt;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).</td>
<td>An early, short course of antifibrinolytic therapy prior to early aneurysm repair (begun at diagnosis; continued up to the point at which the aneurysm is secured or at 72 h post-ictus, whichever is shorter) should be considered (Low QE; Weak Rec).</td>
</tr>
<tr>
<td>Delayed (&gt;48 h after the ictus) or prolonged (&gt;3 days) antifibrinolytic therapy should be avoided (High QE; Strong Rec).</td>
<td>Antifibrinolytic therapy is relatively contraindicated in patients with risk factors for thromboembolic complications (Moderate QE; Strong Rec).</td>
</tr>
</tbody>
</table>
Securing Aneurysms
Surgical clipping versus Endovascular Treatment

- Anatomy, patient characteristics, and institutional expertise
- ISAT Trial (2005):
  - Lower rate of death or dependency with EVT Vs. Surgical clipping (23.7% vs. 30.6%, \( P = 0.0019 \)).
  - The risk of early re-bleeding was modestly higher in the EVT group.
  - Retreatment of aneurysms: EVT (17.4%) Vs. Surgery (3.8%)

- Barrow Ruptured Aneurysm Trial (BRAT), 6 year results (2015)
  - No significant difference in outcomes (\( p = 0.24 \)) was detected between the 2 treatment groups.
  - Complete aneurysm obliteration at 6 years: EVT (48%) Vs. Clipping (96%) (\( p < 0.0001 \))
  - Retreatment rates: EVT (16.4%) Vs. Clipping (4.6%) (\( p < 0.0001 \)).
## Preferences for treatment of Unsecured Aneurysms

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Preferred Treatment Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced age</td>
<td>Endovascular coiling</td>
</tr>
<tr>
<td>Poor clinical grade</td>
<td>Endovascular coiling</td>
</tr>
<tr>
<td>Multiple underlying systemic conditions</td>
<td>Endovascular coiling</td>
</tr>
<tr>
<td>Top-of-the-basilar aneurysm</td>
<td>Endovascular coiling</td>
</tr>
<tr>
<td>High surgical risk</td>
<td>Endovascular coiling</td>
</tr>
<tr>
<td>Patient preference</td>
<td>Endovascular coiling</td>
</tr>
<tr>
<td>Clinical equipoise</td>
<td>Endovascular coiling</td>
</tr>
<tr>
<td>Aneurysms with wide neck-to-body ratio</td>
<td>Surgical clipping</td>
</tr>
<tr>
<td>Normal arterial branches arising from dome or body</td>
<td>Surgical clipping</td>
</tr>
<tr>
<td>Middle cerebral artery aneurysm</td>
<td>Surgical clipping</td>
</tr>
<tr>
<td>Aneurysm associated with large parenchymal hematoma</td>
<td>Surgical clipping</td>
</tr>
</tbody>
</table>
Elevated Intracranial Pressure and Hydrocephalus

• Present on admission in up to 20%
  – Cerebral edema
  – Intra parenchymal hematoma
  – Acute communicating hydrocephalus – Up to 50% on admission
  – IVH
  – Aneurysm re-rupture
  – Complications related to aneurysm treatment
  – EBI, and DCI

➢ Severe derangements of cerebral metabolism
➢ Neurological deterioration
➢ Poor outcome
• Head of bed elevation (between 30° and 45°)
• Normoventilation
• Sedation and analgesia
• Surgical intervention for mass-occupying lesions
• ? Neuromuscular blockade

❖ CSF drainage
  o Acute symptomatic hydrocephalus: EVD or Lumbar Drainage (Class I, Level B)

❖ External Ventriculostomy Drainage
  o CSF drainage
  o ICP monitoring

❖ EVD insertion before aneurysm repair
  o Safe
  o Caution with CSF drainage
  o 30% of poor-grade SAH improve neurologically with EVD

❖ Late hydrocephalus, Shunt dependency (Class I, Level C)
Hypertonic saline versus mannitol for the treatment of elevated intracranial pressure: A meta-analysis of randomized clinical trials*

Hooman Kamel, MD; Babak B. Navi, MD; Kazuma Nakagawa, MD; J. Claude Hemphill III, MD, MAS; Nerissa U. Ko, MD

Mean quantitative reduction in ICP

Successful control of elevated ICP
• **Refractory ICP**
  
  – Barbiturates
    • Controls ICP
    • Medical complications: Electrolyte disorders, VAP, thrombocytopenia, septic shock
  
  – Induced hypothermia\(^1\)
    • Effective to control ICP in SAH
    • Not associated with improved functional outcomes
  
  – Decompressive craniectomy\(^2\)
    • Significant reduction in ICP
    • Improved cerebral oxygenation and metabolism
    • Decreased mortality


Seizures in SAH patients

- Incidence 21% - 26%
- Seizure at onset: Predictor of poor outcome
  - Re-Bleeding
- Risk Factors:
  - Poor-grade admission WFNS
  - Thick cisternal blood clot
  - Clipping of unruptured aneurysm: Higher risk for seizures/epilepsy Vs. EVT
- Anticonvulsant prophylaxis:
  - Early prophylaxis does not prevent the long-term risk of epilepsy
<table>
<thead>
<tr>
<th>Antiepileptic Prophylaxis</th>
<th>AHA/ASA</th>
<th>NCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>AED prophylaxis may be considered in the immediate post-hemorrhagic period (Class IIb; Level B)</td>
<td>Routine use of anticonvulsant prophylaxis with phenytoin is not recommended after SAH (Low QE; Strong Rec).</td>
<td></td>
</tr>
<tr>
<td>Routine long-term use of anticonvulsants is not recommended (Class III; Level B)</td>
<td>Routine use of other anticonvulsants for prophylaxis may be considered (Very Low QE; Weak Rec).</td>
<td></td>
</tr>
<tr>
<td>Considered for patients with known risk factors for delayed seizure disorder, such as prior seizure, intracerebral hematoma, intractable hypertension, infarction, or aneurysm at the middle cerebral artery (Class IIb; Level B).</td>
<td>If anticonvulsant prophylaxis is used, a short course (3–7 days) is recommended (Low QE; Weak Rec).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>In patients who suffer a seizure after presentation, anticonvulsants should be continued for a duration defined by local practice (Low QE; Weak Rec).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Continuous EEG monitoring should be considered in patients with poor-grade SAH who fail to improve or who have neurological deterioration of undetermined etiology (Low QE; Strong Rec).</td>
<td></td>
</tr>
</tbody>
</table>
Delayed Cerebral Ischemia (DCI)

Prevention
Detection
Treatment
Early brain injury (EBI)
- Sudden increase of ICP
- Decreased cerebral perfusion
- Transient global cerebral ischemia
  - Transient loss of consciousness or
  - Progressive intracranial hypertension.

Delayed cerebral ischemia (DCI)
- Change in neurological function that manifests most often between days 3 and 14
- DCI defined as a change in level of consciousness
  - 2 point decrease in GCS (or)
  - 2 point increase in NIHSS (or)
  - Development of new focal deficit
  - Lasting for at least 1 hour and
  - Not explained by other factors (e.g., systemic complications and hydrocephalus)
Delayed cerebral ischemia (DCI)

Predictors of vasospasm and DCI after SAH

- Thickness, density, location, and persistence of subarachnoid blood
- Poor clinical grade
- Loss of consciousness at ictus
- Cigarette smoking
- Cocaine use
- Systemic Inflammatory Response Syndrome (SIRS)
- Hyperglycemia
- Hydrocephalus
- Incidence: 30% of SAH patients surviving initial hemorrhage
- Major predictor of mortality and disability

- Begins approximately 3 days
- Peaks 1 week after the hemorrhage
- Starts resolving after 2 weeks

- Reversible if treated promptly
- Can progress to cerebral infarction
  - CT or MRI within 6 weeks after SAH, or
  - Latest scan made before death within 6 weeks, or
  - Proven at autopsy
  - Not present on CT/MRI between 24 and 48 hours after early aneurysm occlusion
  - Not attributable to other causes such as surgical clipping or endovascular treatment
Challenges in clinical diagnosis of DCI

• Clinically difficult to detect in the poor-grade SAH
  – Decreased level of consciousness
  – Need for sedation (for ICP and mechanical ventilation management)

• Neurological wake-up tests
  – Interruption of sedation and analgesia
  – Safe: Not associated with changed in cerebral metabolism or oxygenation (CMD)
  – Sensitivity of neuroexam to detect DCI in poor grade SAH is low
  – 20% do not have clinical deterioration
<table>
<thead>
<tr>
<th>Lindegaard Ratio</th>
<th>Angiographic Vasospasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3</td>
<td>No spasm</td>
</tr>
<tr>
<td>3 - 4.5</td>
<td>Mild spasm</td>
</tr>
<tr>
<td>5.6 - 6</td>
<td>Moderate</td>
</tr>
<tr>
<td>&gt; 6</td>
<td>Severe spasm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Modality</th>
<th>Changes to trigger intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transcranial Doppler</td>
<td>(a) TCD mean flow velocity in the middle cerebral artery (FVMCA) of more than 50 cm/second over 24 hours or (b) Mean FVMCA of at least 200 cm/second or (c) Middle cerebral artery/ internal carotid artery ratio of more than 6 or both</td>
</tr>
<tr>
<td>CT and Conventional Angiography</td>
<td>Narrowing of at least 70 % from baseline</td>
</tr>
<tr>
<td>Perfusion CT/MR</td>
<td>(a) CBF of less than 25 ml/ 100 g/minute or (b) Mean transit times (MTTs) of more than 6.5 seconds or both</td>
</tr>
<tr>
<td>EEG</td>
<td>(a) Reduced alpha variability (b) Decreased alpha/delta ratio</td>
</tr>
<tr>
<td>Cerebral Metabolism</td>
<td>Abnormal brain tissue oxygen ($P_{ti}O_2 &lt;20$ mm Hg) CMD:</td>
</tr>
<tr>
<td>Cerebral Microdialysis</td>
<td>- Lactate/pyruvate ratio (LPR) &gt; 40</td>
</tr>
<tr>
<td></td>
<td>- Glucose &lt; 0.5 mM</td>
</tr>
<tr>
<td></td>
<td>- Glutamate &gt; 40 mM</td>
</tr>
</tbody>
</table>
# Diagnostic Accuracy: TCD Vs. Angiography
## Updated Meta Analysis, 2018

<table>
<thead>
<tr>
<th>Estimate and Number of Studies</th>
<th>Transcranial Doppler</th>
<th>Transcranial Color-Coded Duplex Doppler</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Middle Cerebral Artery</td>
<td>Anterior Cerebral Artery</td>
</tr>
<tr>
<td>n studies</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Pooled sensitivity</td>
<td>66.7% (55.9–75.9)</td>
<td>32.7% (10.9–65.7)</td>
</tr>
<tr>
<td>p^, %</td>
<td>57.8</td>
<td>78</td>
</tr>
<tr>
<td>Pooled specificity</td>
<td>89.5% (80.3–94.7)</td>
<td>89.6% (48.2–98.7)</td>
</tr>
<tr>
<td>p^, %</td>
<td>89</td>
<td>65</td>
</tr>
<tr>
<td>Positive LR</td>
<td>6.86 (3.57–12.50)</td>
<td>5.77 (0.55–25.60)</td>
</tr>
<tr>
<td>Negative LR</td>
<td>0.38 (0.27–0.50)</td>
<td>0.79 (0.41–1.33)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>93.7% (88.9–96.6)</td>
<td>87.4% (57.8–98.3)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>53.4% (46.7–60.9)</td>
<td>35.4% (24.6–50.6)</td>
</tr>
</tbody>
</table>

LR = likelihood ratio.
Positive predictive value and negative predictive value were calculated with a prevalence of 70%. Numbers in parenthesis represent 95% CI.

*p^ = comparison between Transcranial Doppler and transcranial color-coded duplex Doppler for the middle cerebral artery.
• Systematic review of 26 studies
  – TCD vs. angiography
  – If MCA mean CBFV >120 cm/s
    o 99% specificity and 67% sensitivity to identify angiographic VSP of ≥25%
• Retrospective study of 101 patients:
  • MCA MFV >120 cm/s:
    o 72% specificity and 88% sensitivity to detect angiographic VSP ≥33%
  • MCA MFV <120 cm/s:
    o NPV of 94%.
  • MCA MFV >200 cm/s:
    o 98% specificity, 27% sensitivity, PPV 87% for detection of angiographic VSP of ≥33%.

DCI: Pharmacological Prophylaxis

Nimodipine

- **Cochrane Database Systematic Review 2007**
  - 16 RCT of calcium antagonists in SAH, 3361 patients
  - Relative risk reduction of poor outcome at 3 months with oral nimodipine compared with placebo (0.67; 95% CI, 0.55–0.81)

- Benefit not seen with IV nimodipine or other calcium antagonists.

- Oral nimodipine 60 mg every 4 hours for 21 days should be administered to all patients (Class I-A/ High QE; Strong Rec)
Randomized, Open-Label, Phase 1/2a Study to Determine the Maximum Tolerated Dose of Intraventricular Sustained Release Nimodipine for Subarachnoid Hemorrhage (NEWTON [Nimodipine Microparticles to Enhance Recovery While Reducing Toxicity After Subarachnoid Hemorrhage])

Daniel Hänggi, MD; Nima Etminan, MD; Francois Aldrich, MD; Hans Jakob Steiger, MD; Stephan A. Mayer, MD; Michael N. Diringer, MD; Brian L. Hoh, MD; J Mocco, MD; Herbert J. Faleck, DO; R. Loch Macdonald, MD; on behalf of the NEWTON Investigators

- Safe and tolerable to 800 mg
- Associated with reduced delayed cerebral ischemia and rescue therapy
- Rate of favorable clinical outcome was greater in the intraventricular arm compared to oral nimodipine.

(Stroke. 2017;48:145-151. DOI: 10.1161/STROKEAHA.116.014250.)
DCI: Pharmacological Prophylaxis

Magnesium

- 7 RCT and meta-analysis reported no effect on poor outcome
- Magnesium is not recommended for prevention of DCI (Class I, level A)

Statins

- 7 RCTs; 1 systematic review (not including the STASH trial) found no effect of statin treatment on poor outcome.
- Administer statins only if the patient was already receiving them at time of SAH (Class I, level A)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Status</th>
<th>Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clazosentan</td>
<td>Endothelin A receptor</td>
<td>4 RCT and MA. Clazosentan reduced angiographic vasospasm without a significant effect on outcome.</td>
<td>After the publication of the CONSCIOUS trials and following meta-analysis, clazosentan infusion will not be recommended for patients with SAH, as a Class I, level A</td>
</tr>
<tr>
<td></td>
<td>antagonist</td>
<td></td>
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</tr>
<tr>
<td>Fasudil</td>
<td>Rho-kinase inhibitor</td>
<td>8 RCT</td>
<td>Approved in Japan and China, not USA or EU</td>
</tr>
</tbody>
</table>
|           |                             |                                             | Treatment significantly reduced the incidence of angiographic vasospasm and cerebral infarction and improved the odds ratio for good recovery compared with placebo or nimodipine and other drugs |}
<p>| Dantrolene | Inhibits ryanodine receptors | 1 dose escalation study Reduced cerebral blood-flow velocities | Experimental                                                                                                                              |</p>
<table>
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<tr>
<td>Intrathecal thrombolytics</td>
<td>Fibrinolytic</td>
<td>5 RCTs and a meta-analysis. Thrombolysis was associated with significant reductions in angiographic vasospasm, DND, hydrocephalus, and poor outcome.</td>
<td>Not addressed</td>
</tr>
<tr>
<td>(urokinase, r-tPA)</td>
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</tr>
</tbody>
</table>
| Antiplatelet                | Inhibition of platelet aggregation | 7 RCT, MA.  
- Trends toward reduction in poor outcome  
- Increased ICH | Not addressed. Cannot be recommended |
| - ASA                       |                      |                                                                        |                    |
| - Dipyridamole              |                      |                                                                        |                    |
| - Ticlopidine               |                      |                                                                        |                    |
| Albumin                     | Multiple             | One open-label dose-escalation trial. Trend toward improved outcome with 1.25 g/kg per day | Experimental       |
| Erythropoietin              | Multiple             | 2 RCT.  
- One negative study  
- One showing reduction in cerebral infarcts, shorter duration of autoregulatory dysfunction, and better clinical outcome. | Experimental       |
| Cilostazol                  | PDE-3 I              | RCT, MA. Cilostazol significantly reduced angiographic vasospasm, cerebral infarction and poor outcome | Large RCT required |
|                            |                      |                                                                        |                    |
Hemodynamic Prophylaxis (hypervolemia, hypertension and haemodilution)?
Volume status and fluid management

- Depends on factors
  - Status of the aneurysm
  - Presence of vasospasm, DCI
  - Cerebral edema
  - Cerebral salt wasting, SIADH

✓ Avoid hypovolemia
✓ Avoid prophylactic hypervolemia (high QE; strong rec)
✓ Goal euvolemia with CVP between 5-8 mmHg (Class IIa-LevelB)
✓ Avoid hypotonic fluids (0.45% saline, 5% dextrose in water (D5W) (Class III-LevelB)
✓ Isotonic crystalloids are preferred agents
✓ Persistent negative fluid balance, use of fludrocortisone or hydrocortisone may be considered (Moderate QE; weak rec)
New focal deficit or global decline in mental status without a known cause

Bolus 500 mL to 1000 mL of crystalloid solution

No Known Vasospasm

Known Vasospasm

If no improvement in 2 hours or therapy is not tolerated, proceed to endovascular therapy

If no improvement after fluid challenge and induced hypertension, add inotrope and titrate to cardiac index > 4.5 L/min/m² to 6.0 L/min/m²
<table>
<thead>
<tr>
<th>AHA/ASA</th>
<th>NCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Pressure management Delayed Cerebral Ischemia</td>
<td>✓ Patients clinically suspected of DCI should undergo a trial of induced hypertension <em>(Moderate QE; Strong Rec)</em></td>
</tr>
<tr>
<td></td>
<td>✓ The choice of vasopressor should be based on the other pharmacologic properties of the agents (e.g., inotropy, tachycardia) <em>(Moderate QE; Strong Rec)</em></td>
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<tr>
<td></td>
<td>✓ Blood pressure augmentation should progress in a stepwise fashion with assessment of neurologic function at each MAP level to determine if a higher blood pressure target is appropriate <em>(Low QE; Strong Rec)</em></td>
</tr>
<tr>
<td></td>
<td>✓ If nimodipine administration results in hypotension, then dosing intervals should be changed to more frequent lower doses. If hypotension continues to occur, then nimodipine may be discontinued <em>(Low QE; Strong Rec)</em></td>
</tr>
<tr>
<td>AHA/ASA</td>
<td>NCS</td>
</tr>
<tr>
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</tbody>
</table>
| **Vasospasm/ DCI Management** | **Imaging/ Monitoring:**  
- TCD (Class IIa – B)  
- Perfusion CT/MR to identify regions of potential brain ischemia (Class IIa -B) | **Imaging/ Monitoring:**  
- Imaging and/or perfusion can be used to confirm a diagnosis of DCI in monitored good grade patients who show a change in neurologic exam or TCD variables (High QE-Strong Rec)  
- CTA can be used for screening for vasospasm, and due to its high specificity may reduce the need for DSA studies (Low QE; Weak Rec)  
- DSA is the gold standard for detection of large artery vasospasm (High QE; Strong Rec)  
- CTP findings of elevated MTT > 6.4 s may be additive to CTA findings in predicting DCI (Low QE; Weak Rec).  
- EEG, PbtO2 monitoring, and CMD may all be useful physiological monitors for DCI detection. Relative value of these monitors individually versus as part of a multi-modality monitoring strategy is not known  
- (Low QE; Weak Rec) |
<table>
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<th>AHA/ASA</th>
<th>NCS</th>
</tr>
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<tbody>
<tr>
<td><strong>Vasospasm/ DCI Management</strong></td>
<td><strong>Prophylaxis:</strong></td>
</tr>
<tr>
<td></td>
<td>• Oral nimodipine for all aSAH patients <em>(Class I-A)</em></td>
</tr>
<tr>
<td></td>
<td>• Euvolemia <em>(Class I-B)</em></td>
</tr>
<tr>
<td></td>
<td>• Prophylactic hypervolemia or balloon angioplasty before the development of angiographic spasm is not recommended <em>(Class III-B)</em></td>
</tr>
<tr>
<td><strong>DCI Treatment:</strong></td>
<td><strong>DCI Treatment:</strong></td>
</tr>
<tr>
<td>• Induced hypertension <em>(Class I-B)</em></td>
<td>• Endovascular treatment using intra-arterial vasodilators and/or angioplasty <em>(Moderate QE; Strong Rec)</em></td>
</tr>
<tr>
<td>• Cerebral angioplasty and/or selective intra-arterial vasodilator therapy (patients not responding to HTN therapy) <em>(Class II a-B)</em></td>
<td>• Timing of rescue therapy: a complex decision which should consider the aggressiveness of the hemodynamic intervention, the patients’ ability to tolerate it, prior evidence of large artery narrowing, and the availability of and the willingness to perform angioplasty or infusion of intra-arterial agents <em>(Moderate QE; Strong Rec)</em></td>
</tr>
</tbody>
</table>
**Initial treatment**
- Early aneurysm repair
- CT/CTA/CTP on admission and on days 3–5, days 7–10
- Oral nimodipine
- Systolic BP <160 mm Hg before aneurysm repair
- Euvolemia
- Hemoglobin >8 g/dL

**Avoid**
- Hypotension
- Increased ICP
- Low CPP
- Fever
- Hypovolemia
- Hyperglycemia
- Hypoglycemia
- Hyponatremia
- Hypomagnesemia
- Hypocarbia
- Hypoxia
- Anticonvulsants unless documented seizures
- Low-volume center without access to endovascular specialists and multidisciplinary neurocritical care

**Low risk**
- WFNSS 1, 2, no or thin SAH, no IVH, older age
  - Neurologic assessment every 4 hours, fluid balance every 2 hours, TCD every second day
  - No change neurologically, normal TCD and CTP
  - Low risk: Consider transfer to lower-level monitoring 5–10 days after SAH
    - Elevated TCD velocities (>120 cm/s or Lindegaard ratio >3), increased vigilance for DCI
      - Detect causes of neurologic deterioration
        - Correct identified causes (eg, seizures, increased ICP, hydrocephalus, hyponatremia, infections)
            - No major elevation of MTT or angiographic vasospasm; or deficit resolves
            - Continue monitoring

**High risk**
- WFNSS 1–3, no or thin SAH with IVH or thick SAH without IVH
  - Neurologic assessment every 2 hours, fluid balance every 12 hours, TCD every second day
  - No change neurologically, normal TCD and CTP
  - Consider transfer to lower-level monitoring 7–10 days after SAH
    - Elevated TCD velocities (>120 cm/s or Lindegaard ratio >3), abnormal CTP, neurologic deterioration
      - Detect causes of neurologic deterioration
        - No major identified causes for deterioration: CTA/CTP or catheter angiogram
          Consider empiric induced hypertension if aneurysm has been repaired
        - CTP elevated MTT or angiographic vasospasm, persisting deficit
          Induced hypertension, fluid boluses as necessary, vigilant monitoring
        - Deficit persists >60 minutes or patient cannot tolerate induced hypertension
          Consider catheter angiography and balloon and/or pharmacologic angioplasty

**High risk**
- Inaccessible due to sedation or WFNSS 3–5, thick SAH with IVH
  - Neurologic assessment hourly, fluid balance every 6 hours, consider fluidrocortisone, daily weight, TCD daily, brain tissue oxygen and blood flow monitor, arterial catheter
  - Consider transfer to lower-level monitoring 14 days after SAH
Pulmonary Complications & Ventilatory Management

- Pulmonary complications in up to 30%
- Increased A-a gradient in up to 80%\(^1\)
- ARDS in up to 27% of high grade cases\(^2\)
- Potential mechanisms:
  - Hypersympathetic state
  - Neurogenic pulmonary edema
  - Cardiogenic pulmonary edema
- Lung protective ventilation
  - Plateau pressure <30 cm H20
  - Monitor PCO2. Avoid hyper/hypo carbia
  - Application of PEEP may reduce VILI
  - ?Diuretics

1. Vespa and Bleck Neurocritical care 2004
2. Kahn JM et al. CCM 2006;34:196–202
Neurogenic Myocardial Injury

- Sympathetic surge
- TTE evidence in 25%
- High troponin I in 35%
- ECG changes in ~50%
- Associated with high grade SAH
- Reversible LV dysfunction due to myocytolysis (contraction band necrosis)
- May require inotropic support
  - Dobutamine
  - Levosimendan
  - Milrinone
  - Intra-aortic balloon pump
- ACE-I/ARB use associated with improved survival

Maiti A. N Engl J Med 2017; 377:e24
Fever

- Common in SAH patients
- Associated with poor outcome
  - Exacerbation of cerebral edema
  - Elevated ICP
  - Vasospasm
- Noninfectious etiologies
  - Venous thromboembolism
  - Intraventricular hemorrhage
  - Drug effect
  - Central fever
- Maintain normothermia
- Optimal method?
<table>
<thead>
<tr>
<th><strong>Fever</strong></th>
<th><strong>AHA/ASA</strong></th>
<th><strong>NCS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>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).</td>
<td>While the efficacy of most antipyretic agents (acetaminophen, ibuprofen) is low, they should be used as the first line of therapy (Moderate Quality Evidence; Strong Recommendation). Surface cooling or intravascular devices are more effective and should be employed when antipyretics fail in cases where fever control is highly desirable (High quality evidence—strong recommendation). Use of these devices should be accompanied by monitoring for skin injury and venous thrombosis (Weak quality evidence; Strong Recommendation).</td>
</tr>
</tbody>
</table>
Glucose

- Hyperglycemia\(^1\)
  - Longer ICU stay
  - Symptomatic vasospasm
  - Poor discharge outcome, worse GOS

- Avoid hypoglycemia (<80 mg/dL) (Class IIb-LevelB)
- Maintain blood glucose <200 mg/dL (Moderate QE; Strong rec)

Nutrition

- No data on early nutrition for SAH
- Enteral route preferred

---

Hyponatremia

- Most common electrolyte abnormality
- Up to 50% of all SAH patients
  - SIADH
  - Cerebral Salt Wasting
- Treatment of SIADH with fluid restriction is not recommended
- Fludrocortisone acetate
- Hypertonic saline

Anemia

- Optimal hemoglobin unknown
- Maintain hemoglobin above 8-10 g/dL (Moderate / Strong Recommendation)
<table>
<thead>
<tr>
<th>VTE prophylaxis</th>
<th>AHA/ASA</th>
<th>NCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIT and DVT are relatively frequent complications after aSAH</td>
<td>Early identification and targeted treatment are recommended (Class I; Level of Evidence B).</td>
<td>Patients treated with antifibrinolytic therapy should have close screening for deep venous thrombosis (Moderate QE; Strong rec).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sequential compression devices should be routinely used in all patients (High QE; Strong rec).</td>
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<td></td>
<td>The use of LMW heparin or unfractionated heparin for prophylaxis should be withheld in patients with unprotected aneurysms and expected to undergo surgery (Low QE; Strong rec).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The use of unfractionated heparin for prophylaxis could be started 24 h after undergoing surgery (Moderate QE; Strong Rec).</td>
</tr>
</tbody>
</table>
Overall Risk for any medical complication by Sex and Mechanical Ventilation Status

Adapted from Mahapatra AK et al. Temporal trends in medical complications and mortality following subarachnoid hemorrhage in the United States from 2004–2013
April 18, 2017; 88 (16 Supplement)
Temporal trends in Medical Complications, aSAH

Adapted from Mahapatra AK et al. Temporal trends in medical complications and mortality following subarachnoid hemorrhage in the United States from 2004–2013. April 18, 2017; 88 (16 Supplement)
Mortality Trends, aSAH

Adapted from Mahapatra AK et al. Temporal trends in medical complications and mortality following subarachnoid hemorrhage in the United States from 2004–2013 April 18, 2017; 88 (16 Supplement)
Dedicated Neurologic/Neurosurgical Intensive Care Unit

- Improved long-term outcomes in ABI
- SAH
  - Hospital caseload
  - Better outcomes happen in high-volume centers (> 60 patients per year)
  - Six-month mortality is inversely associated with hospital annual caseload
  - 24 % reduction in mortality for each 100 patients admitted per year
- Regardless of initial grade, early transfer to a high-volume center is safe and cost-effective and should be pursued.
### Prevention, Detection & Treatment of DCl

**Common causes of delayed neurological deterioration**
1. Progression of early brain injury
2. Hydrocephalus
3. Re-bleeding
4. Seizures
5. Cerebral ischemia (DCI)
6. Systemic conditions (e.g., fever and infections, respiratory failure, electrolyte abnormalities)

**Prevention of DCl**
1. Maintenance of Euvolema and Normonatremia
   - Risk of SIADH and cerebral salt wasting syndrome
   - Consider fludrocortisone (0.2 mg every 12 hrs)
2. Calcium Channel Blockers
   - Nifedipine 60 mg orally every 4 hours
3. Do not reduce BP after aneurysm obliteration
4. Avoid Hyperglycemia (> 10 mmol/L or 180 mg/dL)
5. Avoid Hypoglycemia (< 3.9 mmol/L or < 70 mg/dL)
6. Maintenance of Normothermia (core T ≤ 37.5°C)
7. Attempts to avoid anemia
   - Hgb ≥ 8 g/dL; however, blood transfusions may be detrimental

**Definition of DCl**
- GCS ≥ 2 points or ↑ NIHSS ≥ 2 points

**DCI Management**
A. Rule out confounding factors (e.g., fever, hypnatenemia, infection, seizures)
B. Initiation as soon as possible of Hemodynamic Augmentation (stepwise SBP/MAP titration to neurologic response)
C. Mild hypervolemia reasonable in patients with symptomatic vasospasm/DCI
D. If no improvement, consider urgent endovascular therapies (transluminal balloon angioplasty and super-selective intra-arterial infusion of vasodilators)

### Control of Intracranial Pressure

1. Verify ICP measurement
2. Check and treat systemic causes of increased ICP
   - Vasodilation of cerebral vessels
   - Fever
   - Seizures
   - Hypercapnia
   - Hypoxemia
   - Hypotension
3. Increased arterial pressure
   - Pain
   - Cellular edema
   - Hypnatenemia
4. Increased venous pressure
   - Neck tension or compression
   - Pneumothorax
   - Ventilator asynchrony
   - Increased abdominal pressure
3. Initiate or intensify ICP-directed treatment
   - Consider repeat brain injury and surgical removal of intracranial mass lesions
   - HOB 30-45°
   - Normoventilation (PaCO₂, 35-40 mmHg)
   - Normothermia (core T ≤ 37.5°C)
   - CSF drainage
   - Increase analgesia and sedation
   - Hypersomolar therapy
   - Consider manipulation of CPP
   - Consider hyperventilation (PaCO₂, 28-32 mmHg)
   - Increase analgesia and sedation
   - Consider paralytics
   - Decompressive craniectomy + duraplasty
   - Mild Hypothermia (32-34°C)
   - Metabolic suppression (barbiturates)