Aneurysms, Subarachnoidal Hemorrhage

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ANEURYSM

1. ETHIOPATHOPHYSIOLOGY, PATHOLOGY

2. Aneurysm growth

3. Giant saccular aneurysms

4. Multiplicity

5. Location

6. Pediatric aneurysms

7. FOLLOW-UP

8. CLINICAL FEATURES

9. Site specific clinical features

10. DIAGNOSIS

11. CT

12. CTA

13. MRI

14. MRA

15. Angiography

16. SCREENING

17. TREATMENT

18. FOLLOW-up

19. CLINICAL MANIFESTATIONS

20. Ruptured aneurysms

21. Unruptured (incidental) aneurysms

22. Subarachnoidal Hemorrhage (SAH)

23. Treatment

24. Prevention

25. Refractory vasospasm

26. Protocol

27. Aneurysm treatment

28. Timing of treatment

29. Methods

30. Surgical Clipping

31. Open Alternatives to Surgical Clipping

32. Endovascular Surgery

33. Special Situations

34. Recanalization (of previously treated aneurysm)

35. Multiple aneurysms

36. Wide-neck aneurysms

37. Aneurysm coexisting with AVM

38. Aneurysm causing CN3 palsy

39. Carotid stenosis associated with ICA aneurysm

40. Aneurysm perforation with coil

41. Carotid aneurysm within cavernous sinus

42. Recanalization in previous stent-assist coiled aneurysm

43. Cervical ICA aneurysms

44. ICA terminus aneurysms

45. ACA aneurysms

46. ACCom aneurysms

47. Aneurysm with arteroma

48. FOLLOW-up

49. PROGNOSIS

50. SAH

51. Unruptured aneurysms

52. Clipping

ANEURYSM

- pathologic focal blood vessel dilation (L. aneurysma - dilation).
- some lie entirely within subarachnoid space; others are buried in brain substance.
ETIOPATHOPHYSIOLOGY, PATHOLOGY

FALSE aneurysms (s. pseudoaneurysms) – encapsulation of perivascular hematoma – cavities that lack any component of vessel wall, but communicate with vessel lumen; cavity is lined by blood clot (periadventitial hematomas can be seen on imaging).

- caused by penetrating vessel injuries (most commonly; pseudoaneurysms grow in hours), periadventitial infections at multiple process sites
- N.B. intracerebral hematomas may harbor and simultaneously obscure traumatic aneurysm - angiography is diagnostic procedure of choice (esp. indicated for penetrating head injuries!, absolutely indicated in all stab wounds to head)

TRUE aneurysms – dilatations of vascular lumen caused by weakness of vessel wall (at least adventitia is present in aneurysm wall)

1. Saccular (“berry”) aneurysms (∼90%) – rounded outpouchings (i.e. neck with dome)

- why intracranial arteries are susceptible to aneurysm development:
  - 1) walls lack external elastic lamina
  - 2) very thin adventitia
  - 3) lie unsupported in subarachnoid space
  - sac is composed of only intima and adventitia.
  - media ends at junction of aneurysm neck with parent vessel.
  - intima is typically normal or thickened hyalinized (subintimal cellular proliferation is common).
  - internal elastic membrane is reduced or absent (normal internal elastic membrane can withstand pressures over 600 mmHg without bulging - as long as membrane remains intact, defects in media are inconsequential).
  - hemodynamics - adenolinden leukocytosis may infiltrate adventitia.
  - sac lumen often contains thrombotic debris.
  - athrosclerotic changes in parent vessel are common.
  - etiology
  - 1) developmental (congenital) - focal defects in media (present at birth); over period of years arterial pressure balloons out vessel wall (i.e. aneurysm is “congenital” in sense that defect in arterial wall is present from birth, but actual aneurysm develops over years after birth)
  - 2) hemodynamically induced degenerative vascular injury - hemodynamic shear stresses (esp. at bifurcation points) cause occurrence, growth, thrombosis, and rupture of aneurysms.
  - 3) high flow-related (caused by high flow states) – aneurysms occur along proximal* and distal** vessels feeding AVM.
  - do not increase risk of hemorrhage.
  - vascular perfusion pressures over 600 mmHg without bulging - as long as membrane remains intact, defects in media are inconsequential.
  - chromosomal loci associated with intracranial aneurysms.
  - 4) traumatic (< 5% all aneurysms) - caused by blunt vessel injuries. see Table 1
  - 5) anoxic - direct tumor invasion (e.g. meningioma) or implantation of metastatic emboli* (e.g. left atrial myxoma, chorriocarcinoma) – vessel wall infiltration – disruption.
  - intramural hematomas often involve peripheral cerebral vessels at gray-white junction
  - vascular lumen aneurysms exposed to arterial pressure - likely site for AVH hemorrhage (i.e. AVMs that bleed often have intra-nidal aneurysms)
  - 6) vasculopathy - fusiform aneurysms (mass effects are much more common).
  - 7) drug-related: COCAINE, HEROIN, AMPHETAMINE, METHAMPHETAMINE - can induce cerebral vasculitis - necrotizing angiitis (histologically similar to periarteritis nodosa) with focal arterial ectasias.

2. Fusiform (s. dolichoectatic) aneurysms (no identifiable neck):

- 1) atherosclerosis (7% all aneurysms) – unusual form of atherosclerosis damages media – arterial stretching and elongation that may extend over considerable length (may have serpentine, giant, bizarre shapes).
  - occur in older patients.
  - affect proximal arteries (vertebrobasilar system is commonly affected).
  - perforating branches often arise from entire length of aneurysm.
  - intraluminal clots are common (∼ occlusion of small size of perforating vessels → infarcts).
  - bleed rarely (mass effects are much more common).
  - frequent (0.5-3%) all aneurysms) - any aneurysm resulting from infectious process that involves (destroys) arterial wall:
    - septic emboli (e.g. IV drug abuse, bacterial endocarditis) → extension from infected sites.
    - meningitis → extension from periphery to lumen (e.g. aneurysms of basal circulation associated with fungal infections).
    - frequently multiple (20%), very friable – greater propensity to bleed! (rupture is fatal in 80% patients?)

3. Dissecting aneurysms – when intramural hematoma extends into subadventitial plane (e.g. in fibromuscular dysplasia, trauma, eldernal, ovoid, or saccular

- most affect extracranial segments of ICA, VA.

*aneurysms can be saccular, fusiform, or bizarre-looking mixture of both.

A. Dissected base of brain - aneurysm of ACA (arrow).
B. Dissected circle of Willis - large aneurysm.
ANEURYSMS, SUBARACHNOIDAL HEMORRHAGE

ANEURYSM GROWTH
- due to wall shear stress caused by rapid changes of blood flow direction (result of systole and diastole) - "water hammer effect".
- hemodynamic stresses continually damage intima at aneurysm cavity neck → progression of most saccular aneurysms.
- thrombosis and rupture are also explained by intra-aneurysmal hemodynamic stresses.
- arterial hypertension may contribute to, but is not only cause of, aneurysm formation and rupture; normal blood pressure in hemorrhagic stroke favors diagnosis of saccular aneurysm!

Geometric relationship between aneurysm and its parent artery:
Lateral aneurysms (e.g. arise directly from ICA) - blood moves into aneurysm at distal aspect of its ostium and exits at its proximal aspect, producing slow flow vortex in aneurysm center; lumen opacification proceeds in cranial-to-caudal fashion; pronounced contrast stagnation!

Aneurysms that arise at origin of branching vessels or terminal bifurcation - rapid intra-aneurysmal circulation; no vortex formation, no contrast stasis.

N.B. these patterns of intra-aneurysmal flow influence use of endovascular treatment devices.

GIANT SACCULAR ANEURYSM
- diameter > 2.5 cm.
- 3.5% of all intracranial aneurysms (3 times more common in women).
- slow growth occurs by recurrent intra-aneurysmal hemorrhages from highly vascularized membranous wall of aneurysm.
- giant sacs commonly contain multilayered laminated clots of varying ages and consistency, which occasionally are calcified.
- outer wall is fibrous and thick (seldom rupture into subarachnoid space) - giant aneurysms typically produce symptoms related to mass effect and distal thromboembolism.

MULTIPLEITY
Intracranial aneurysms are multiple in 10-30% cases (females : males = 5 : 1), of these:

- Berry aneurysm on ACA:

Histologic section at origin of aneurysm shows lack of internal elastic lamina:

ANEURYSM SHOWING HYALINIZED FIBROUS VESSEL WALL (H&E):


Three berry aneurysms:

Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>

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MULTIPLEITY
Intracranial aneurysms are multiple in 10-30% cases (females : males = 5 : 1), of these:
75% have 2 aneurysms
15% have 3 aneurysms
10% have > 3 aneurysms (females : males = 11 : 1)

- multiple aneurysms are common with vasculopathies (e.g. FMD).
- many are at mirror sites bilaterally.

LOCATION

Traumatic, mycotic aneurysms - distal sites in intracranial circulation.

Saccular aneurysms (developmental / degenerative) - proximal sites (bifurcations of major arteries) rupture into basal cisterns.

1. Anterior (carotid) circulation (86.5%)
   - AComA (25%)
   - PComA (25%)
   - MCA (20%)
   - ICA bifurcation (7.5%)
   - ACA (5%)
   - pericallosal/callosomarginal artery bifurcation (4%).

2. Posterior (vertebrobasilar) circulation (13.5%):
   - BA bifurcation (7%)
   - BA trunk (AICA origin, SCA origin) (3.5%)
   - PICA origin (3%) N.B. atherosclerotic aneurysms affect predominantly posterior circulation.

- carotid artery is affected most commonly in individuals < 18 yrs.

Ophthalmic complex aneurysms:
1. Dorsal ophthalmic – on ICA above ophthalmic branch
2. Ophthalmic artery
3. Superior hypophyseal artery

EPIDEMIOLOGY

PREVALENCE: ≈ 1-2% (0.3-6%) population.
- female : male ratio = 1.6 : 1

RISK FACTORS
1. Hypertension
2. Smoking

Exposure to exogenous estrogens in women - associated with a lower frequency of cerebral aneurysms, based on a retrospective case-control study.

CLINICAL FEATURES

Aneurysm rupture
minor aneurysmal hemorrhage (warning leak, k. sentinel bleed) - may be clinically silent (or headache with meningeal irritation), may precede rupture with wide variation in latency.

- SAH (significant morbidity and mortality) - must common presentation of intracranial aneurysm!

- intraparenchymal hematoma (more common with distal aneurysms) - direct rupture of aneurysm into brain, secondary rupture of subarachnoid hematoma into brain parenchyma.

Noncontrast CT can visualize large aneurysms (≥ 3 mm) or that contain calcium (mural calcification) with IV contrast.

- Aneurysm wall that is well-delimited, isodense → slightly hyperdense mass inside with subarachnoid space or sylvian fissure; large aneurysm of left MCA (see below):
  - partial thrombosis aneurysm
  - patent lumen inside thickened aneurysm wall that appears hypodense on CT.

- 30% of acute CN3 palsies are due to PComA aneurysms:
  - CN3 palsy (face & head)
  - hemisensory loss, aphasia / visual hemineglect
  - visual field deficits, pain in or behind eye and in low temple.

- Aneurysms typically become symptomatic in 40-60 years; peak incidence of SAH is 55-60 yrs.

- Risk of rupturing up to 1% per year.
  - aneurysms < 7 mm or aneurysms in anterior circulation = 0.05% per year.

- Risk factors for aneurysm growth and rupture:
  1. cigarette smoking
  2. female sex
  3. younger age
  4. hypertension
  5. aneurysm size (La Place law states that tension is determined by radius of aneurysm and pressure gradient across wall of aneurysm) - rupture rate is directly related to aneurysm size (≤ 5 mm - 2% risk of rupture; 6-10 mm - 40% have already ruptured upon diagnosis).

- Traumatic aneurysms occasionally cause epistaxis.

Nonhemorrhagic symptoms (relatively uncommon):

- More common with giant aneurysms (diameter > 2.5 cm)
  1. Mass effect:
     - cranial neuropathies (e.g. CN5 palsy due to PComA aneurysm - requires urgent treatment!!)
     - visual loss (ophthalamic artery aneurysms compress CN2)
     - pituitary dysfunction (intrasellar aneurysms)
     - seizures
     - subarachnoid hemorrhage (aneurysmal expansion, thrombosis, intranidal hemorrhage)
     - brain stem compression (respiratory dysfunction, cardiovascular instability)
  2. Emboli → TIAs / cerebral infarction (esp. with large partially thrombosed MCA aneurysms)

- H. anticoagulation.

N.B. symptomatic aneurysms have significantly higher risk of rupture (6% per year).

**DIAGNOSIS**

**Angiography** - criterion standard preferred in patients with SAH.

**CTA** – preferred for unruptured intracranial aneurysms.

**MRA** – alternative to CTA (esp. in screening for aneurysm or following after coiling*).

*CTA would have lots of metal artefacts and difficult visualization of any recurrences.

Noncontrast CT can visualize large aneurysms (≥ 10 mm) or that contain calcium (mural calcification is uncommon, but both punctate and curvilinear types have been identified).

- Bone erosion in long-standing lesions near skull base.
- Patent aneurysms – well-delimited, isodense + slightly hyperdense mass in suprasellar subarachnoid space or sylvian fissure; IV contrast → enhance intensely and uniformly.
- Partially thrombosed aneurysm - patent lumen inside thickened (often partially calcified) wall that is lined with laminated clot.
  - residual lumen and outer rim of aneurysm may enhance strongly with IV contrast.
  - atherosclerotic debris in aneurysm wall appears hypodense on CT.

Contrast CT – laryngeal aneurysm of left MCA (arrowheads).
CTA
- sensitivity 97% in detecting aneurysms.
- important in detection of vasospasm.

MRI
- aneurysm appearance is highly variable and complex!
  - patent aneurysms - hypointense or hyperintense signals; well-delineated mass with high-velocity signal loss (flow void) on T1- and T2-weighted images; turbulent flow in aneurysm gives some signal heterogeneity (helps to differentiate aneurysms from other mass lesions).
    - IV contrast typically does not enhance patent aneurysms with high flow rates, but wall enhancement may occur.
  - partially thrombosed aneurysms - complex MRI signal - area of high-velocity signal loss in patent lumen with surrounding concentric layers of multilaminated clot.
    - larger aneurysms may have thick signal void rim (hemoglobin-containing mural thrombus and hemosiderin-laden fibrous capsule).
    - if intraluminal flow is slow/turbulent, residual lumen may be isointense with remainder of aneurysm.
  - completely thrombosed aneurysms - variable MRI findings;
    - recently thrombosed aneurysm may be isointense with brain parenchyma.
    - subacute thrombus is hyperintense on T1 and T2.
    - repeated episodes of intramural hemorrhage leave multilayered clots.

Giant aneurysm extending into suprasellar region:
- A) sagittal T1-MRI - heterogeneous mass resulting in upward compression of 3rd ventricle floor (arrow).
- B) coronal T1-MRI - large flow void (arrow) within lesion, indicating partially thrombosed giant suprasellar aneurysm.

MRA
- reliable 3D imaging of aneurysms ≥ 3 mm (sensitivity is 87% and specificity is 92%); most useful as screening tool.
  - for head – MRA without contrast (time-of-flight TOF protocol).
  - for neck – with gadolinium.

ANGIOGRAPHY
- criterion standard for revealing and delineating features of intracranial aneurysm.
  - aneurysms may be multiple - visualizing entire intracranial circulation (incl. AComA, PComA, both PICAs) is important.
  - 3D rotational angiography is preferable.
  - 6-vessel cerebral angiogram = both vertebral and internal carotid arteries + external carotid arteries (for dural AV fistula as cause of hemorrhage).
  - patent aneurysm - contrast-filled outpouching that arises from arterial wall or bifurcation.
  - thrombosed aneurysm - occasionally appears normal; large thrombosed aneurysm can cause avascular mass effect.
  - not indicated for benign perimesencephalic bleeds.

Aneurysms must be distinguished from:
1. Infundibulum (incomplete regression of fetal vessel);
   - most common location is at origin of PComA from ICA (less commonly - origin of anterior choroidal artery).
-- smooth funnel-shaped triangular dilatations ≤ 3 mm in diameter, regular in shape, distal vessel exits from apex.
-- found in 7-13% of otherwise normal arteriograms
-- rarely may bleed
-- 13 reported cases of progression to aneurysm
-- treat only if accessible during surgery for another reason – wrapping, or placing in encircling clip, or sacrificing artery if it can be done safely (infraduodenal lack true neck)


Features to take note of when analyzing angiogram:

1. Dose size:
   - aneurysm may be partially thrombosed and filling part may be much smaller than overall size (MRI or CT helps with this)
   - large aneurysms (≥ 15 mm diameter) are associated with lower rates of complete occlusion by coiling.

2. Neck size:
   - narrow necks < 5 mm are ideal for coiling (vs. broad necks ≥ 5 mm are associated with incomplete occlusion and recanalization with coiling)
   - *stent or balloon-assisted coiling may be needed

3. Dose: neck ratio ≥ 2 is associated with higher rate of coil occlusion

Giants basal tip aneurysm (AN = aneurysm, BA = basilar artery, LPCA = left posterior cerebral artery, RPCA = right posterior cerebral artery):
A. Townes view - large laterally pointing aneurysm
B. C. 3D surface shaded CTA projections - aneurysm relationship to PCA is more clearly shown.


SCREENING
- with MRA.

Indications:
1) ≥ 2 immediate relatives with intracranial aneurysms
2) AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD).

Other: family history of SAH, sudden death, stroke and migraine.

Target population – all adults > 30 years within one generation from index case.

Recommendations in literature (for ADPKD patients)

(i) no systematic screening of intracranial aneurysms in ADPKD patients
(ii) targeted screening in patients with a good life expectancy who present with a family history of intracranial aneurysms or SAH. patients with previous intracranial aneurysm rupture, those with high risk professions and anxious patients despite adequate information
(iii) the use of TOF MRI without gadolinium enhancement as the screening method of choice
(iv) rescanning at 5–10 year intervals in at-risk patients

Different opinions have also been published, advocating systematic screening for all patients with ADPKD as well as screening before major elective surgery or renal transplantation.

Jynarque (Tolvaptan) - selective vasopressin V2-receptor antagonist - first medicine to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD); due to possible liver injury Jynarque is available only through a restricted REMS.

TREATMENT

Treatment of ruptured aneurysms differ significantly from untreated aneurysms!

REPTURED ANEURYSMS
- treated surgically (within 72 h of hemorrhage): - to prevent rebleeding and to permit aggressive management of vasospasm (with HHH).
- see below (SAH) >>

UNREPTURED INTRACRANIAL ANEURYSMS
- managed electrically:
  a) close observation (e.g. annual CTA) – possible indications:
ANEURYSMS, SUBARACHNOIDAL HEMORRHAGE

Vas25 (8)

< 7 mm incidental aneurysms in anterior circulation have very low rupture risk in patients with no history of SAH

1) patient’s life expectancy < 5 years – any type of treatment carries 5% risk of complications; aneurysm rupture risk is 1%/year – to outweigh risks, patient must live > 5 years after treatment!
2) no previous SAH
3) aneurysm diameter < 5-10 mm (esp. if patient’s age > 50 yrs)
4) mycotic aneurysms – first treat with a/b (observe shrinkage with angiography q7-10 days; if aneurysm enlarges, it should be attacked surgically).
5) small AVM-related aneurysms (may disappear or shrink after successful treatment of AVM)

• educate such patients about:
  – warning signs and symptoms of SAH!
  – the only lifestyle modification that is necessary – to stop smoking!

b) TREATMENT (clipping or coiling*) – possible indications: see below (SAH) >>

1) young patients regardless of aneurysm size
2) symptomatic aneurysm (symptoms must be pathophysiologically related to aneurysm)
3) aneurysm growth (increase in diameter ≥ 1 mm) / change of configuration (e.g. development of bleb)
4) previous ruptured aneurysm

*endovascular approach is first line treatment

Management of incidental aneurysms:

N.B. posterior circulation aneurysms have higher risk of rupture!

• most neurosurgeons would treat ant. circulation aneurysms if they are > 4-5 mm (esp. young patient with newly discovered aneurysm vs. you would leave alone stable 7 mm aneurysm that was discovered 10 years ago in 85 yo patient).

International Study of Unruptured Intracranial Aneurysms (ISUIA)

- natural history of unruptured aneurysms + risks of treatment of unruptured aneurysms
- risk of rupture for a particular aneurysm over the patient’s remaining lifetime can be compared to the mortality/morbidity risk of treatment (7.1-12.6%).
- 5-year cumulative rupture rates (5 YRR): (multivariate analysis showed that age was not a factor)

< 7 mm aneurysms:

<table>
<thead>
<tr>
<th>Aneurysm Size</th>
<th>Cumulative 5 YRR</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 mm</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Type A risk factors</td>
<td>Young age</td>
<td>Symptomatic</td>
</tr>
<tr>
<td></td>
<td>Active smoking</td>
<td>Arterial hypertension</td>
<td>Posterter circulation aneurysms</td>
</tr>
<tr>
<td></td>
<td>Prior SAH</td>
<td>History of familial SAH</td>
<td>Aneurysm size ≥ 7 mm</td>
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7-12 mm aneurysms:

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<tr>
<td></td>
<td>Vertebralbasilar, PCA or PCC aneurysms</td>
<td>2-9%</td>
<td>3-4%</td>
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> 12 mm aneurysms:

<table>
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<th>Aneurysm Size</th>
<th>Cumulative 5 YRR</th>
<th>Group 1</th>
<th>Group 2</th>
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<tbody>
<tr>
<td></td>
<td>Vertebralbasilar, PCA or PCC aneurysms</td>
<td>14.5%</td>
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FOLLOW-UP

See below >>
SUBARACHNOID HEMORRHAGE (SAH)

- blood extravasation into subarachnoid space (between pia and arachnoid).

ETIOLOGY

1. Traumatic SAHs (most frequent SAHs)

2. Nontraumatic SAHs:

In 15-20% of SAH patients, angiography fails to identify an etiology!

a) 75-90% - aneurysm rupture (near at dome and ≤ 0.5 mm long); peak age 55-60 yrs (only 20% cases occur at age 15-45 yrs).

b) 4-10% - bleeding from AVM, most patients 20-30 yrs.

c) 5-15% - other

1) benign (nonaneurysmal) perimesencephalic SAH - bleeding immediately anterior to brainstem and adjacent areas (interpeduncular fossa, ambient cisterns) - rupture of small pontine or perimesencephalic veins (i.e. not arterial source - prognosis is excellent - no rebleeds reported!)

   • imaging - center of hemorrhage is anterior to midbrain with or without extension of blood to the anterior part of the ambient cistern or the basal part of the sylvian fissure, incomplete filling of the anterior interhemispheric fissure and no extension of the lateral sylvian fissure or the ventricles.

   • patients less commonly develop hydrocephalus, vasospasm, or other complications and have lower risk of recurrent bleeding - no need for repeat angiography.

2) occult aneurysm (initially compressed by hematoma or did not opacify because of vasospasm or clot); H. repeat angiography (1 wk later), indication for 3rd angiogram:

   a) blood just in front of brainstem - benign perimesencephalic SAH

   b) blood more widely distributed - 3rd angiogram 6 weeks later: 4-5% chance of detecting aneurysm.

   3) intracranial artery dissection

   4) bleeding from tumor (such as pituitary adenoma).

   5) spinal cord aneurysm or AVM

   6) dural malformation

   7) toxic drugs (e.g. cocaine)

   50% patients who have drug abuse problem along with CNS symptoms have SAH (of these 50% have underlying abnormality such as aneurysm or vascular malformation; others are due to hypertensive response to drugs)

8) amyloid angiopathy, bleeding diatheses, sickle cell anemia, pituitary apoplexy

relationship between hypertension and aneurysmal SAH is uncertain.

Hypertension per se is not significant risk factor, but aneurysms do rupture under conditions associated with sudden BP rise (coitus, athletic events, etc).

evidence for association with smoking is indirect.

EPIDEMIOLOGY

INCIDENCE has not decreased over decades (unlike for other stroke categories), but survival improved:

- 10-fold variation in age-adjusted incidence: from 2.0 cases / 100,000 population / year in China to 22.5 cases / 100,000 / year in Finland (a little bit less in Japan)

   rate of aneurysmal SAH in western populations: 6.8-18,000 population / year

   - incidence increases with age and peaks at 50 yrs.

   80% SAHs occur in people aged > 40 yrs.

   15% in people aged 20-40 yrs.

   4.5% in people aged 10-20 yrs.

   0.5% in children < 10 yrs.

significant risk factors for aneurysmal SAH:

1) smoking (risk of SAH increased 3-6-fold; risk increased 6-fold if positive family history of aneurysmal SAH).

2) hypertension (conflicting data - see above)

3) North American blacks (2.1 times greater risk than in whites)

4) females (1.24: 1)

5) 3rd trimester of pregnancies - SAH is leading cause of maternal mortality (5-25% maternal deaths during pregnancy)

75% from aneurysms (esp. older multiparous women)

25% from AVMs (esp. younger multiparous women)

*recent reviews have suggested that, contrary to conclusions from prior retrospective studies, risk of SAH is not increased during pregnancy.

6) hormone replacement therapy in postmenopausal women

7) heavy alcohol consumption (controversial)

8) reduced lung function, reduced FEV1, reduced FEV1/FVC - significantly associated with increased incidence of SAH - comparable with effects of hypertension and smoking

9) long-term (esp. > 3 years) low-dose ASPRIN has protective effective against SAH and does not increase risk of intracranial hemorrhage.

aneurysm size matters; AComA aneurysm size correlates linearly with risk of rupture.

oral contraceptives, hormone replacement therapy, hypercholesterolemia, physical activity are not significantly related!

PATHOLOGY

- surrounding brain parenchyma - brownish pigmentation and fibrous adhesions.

- aneurysm size may be diminished postmortem.

- ruptured fundus may be visualized with calefactions of aneurysm wall and intraluminal thrombus.

- SAH may be complicated by:

   - intracerebral hemorrhage (20-40%)

   - intraventricular hemorrhage (13-28%)

   - subdural hematoma (2-5%) - over convexity (most commonly due to PComA aneurysm) or interhemispheric (dural ACA).

Ruptured berry aneurysm in circle of Willis.
CLINICAL FEATURES

• 10-50% patients had premonitory symptoms 10-20 days (few hours ± few months) prior to rupture (due to sentinel leaks, aneurysm expansion, embolization).

  Sentinal SAH headache should be considered in differential diagnosis of all new headaches!

• 30-40% patients are at rest at time of SAH (e.g. sleeping);

  remaining 60-70% are at physical / emotional strain (defecation, coitus, head trauma, etc).

1. Sudden excruciating headache ("thunderclap headache") - "most in patient’s life") – localized (to side of aneurysm) or generalized.

  • reaches maximum intensity within 1 minute.
  • location of headache is variable - does not give clue as to site of hemorrhage.
  • present in 97% cases; absence of headache represents anemia for event.

*N.B. thunderclap headache is not limited to SAH and may be seen with cerebral venous thrombosis, reversible cerebral vasospasm syndromes, crush injury, benign organic cephalgia - lack of SAH evidence should prompt MRV. CTA, angiography no longer recommended.

2. Arterial blood (pressure 100-150 mmHg) squinting into CSF space (pressure ± 10-15 mmHg) → sudden ICP elevation (± transient abrupt generalized vasospasm, seizures) → transient* alteration in consciousness (syncope in 33-50% cases at onset**).

  *10% patients are comatose for several days
  **massive SAH, in contrast to other kinds of stroke, may cause sudden death!

Deterioration of consciousness few days after hemorrhage:

  a) rebounding (sudden worsening)
  b) vasospasm (gradual deterioration)
  c) hydrocephalus (gradual deterioration)

3. Blood induces STERILE MENINGITIS → meningeal irritation signs (neck stiffness, photophobia, nausea & vomiting, low back pain) - may take several hours to manifest, may become more severe during first week (blood breakdown in CSF).

  *irritation oftumbhar nerve roots by dependent blood

4. Focal neurological findings:

  a) CN3 palsy is most frequent (PCoM aneurysm).
  b) CN6 palsy is due to ICP↑ (false localizing sign).
  c) classis clinical can localize ruptured aneurysm in only ± 30% patients.

5. Focal or generalized seizures (10-25%) - most occur within 24 hours (sudden ICP rise + direct cortical irritation by blood).

6. Autonomic disturbances (due to subarachnoid accumulation of blood degradation products – CHEMICAL HERIC MENINGITIS) – fever (!), nausea & vomiting (!), sweating, cardiac arrhythmias / ischemia.

7. Ocular hemorrhage (20-40%) - elevated ICP causing venous hypertension and disruption of retinal veins:

  1) subhyaloid (periretinal) hemorrhage - seen funduscopically in 11-33% cases as bright red blood near optic disc that obscures underlying retinal vessels.
  2) intra/retinal hemorrhage: may surround fovea
  3) hemorrhage within vitreous humor (Terson syndrome):

  • funduscopy reveals vitreous opacity
  • usually bilateral
  • complications: elevated intraocular pressure, retinal membrane formation → retinal detachment, retinal folds.

  • vitrectomy if vision fails to improve spontaneously in 6-12 mos
  • long-term prognosis for vision is good

GRADING CLINICAL SEVERITY

Hunt & Hess scale (on admission and pre-op):

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical Findings</th>
<th>Survival Rate</th>
<th>Vasospasm Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Unruptured aneurysm</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Asymptomatic (or minimal headache and slight nuchal rigidity)</td>
<td>70%</td>
<td>22%</td>
</tr>
<tr>
<td>2</td>
<td>Focal neurological deficits</td>
<td>55%</td>
<td>60%</td>
</tr>
<tr>
<td>3</td>
<td>Focal or generalized seizures</td>
<td>25%</td>
<td>35%</td>
</tr>
<tr>
<td>4</td>
<td>Severe headache, focal neurological deficits, or both</td>
<td>10%</td>
<td>50%</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>
Add one grade for serious systemic disease (HTN, DM, COPD, severe atherosclerosis) or severe vasospasm on angiography.

International Cooperative Aneurysm Study:
Grades 1 and 2 were operated upon as soon as aneurysm was diagnosed; Grade 3 managed until condition improved to Grade 2 or 1 (exception: life threatening hematoma or multiple bleeds which were operated on regardless of grade).

Study results:
- with normal consciousness. H&H grades 1 and 2 had identical outcome; hemiparesis and/or aphasia had no effect on mortality.
- mortality: admission H&H grade 1 or 2: 20%. patient taken to OR (for any procedure) at H&H grade 1 or 2: 14%. major cause of death in Grade 1 or 2 is rebleed. signs of meningeal irritation increases surgical risk.

World Federation of Neurological Surgeons (WFNS) Scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Glasgow Coma Scale</th>
<th>Clinical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>Headache, no focal defects</td>
</tr>
<tr>
<td>II</td>
<td>13-14</td>
<td>Headache, no focal defects</td>
</tr>
<tr>
<td>III</td>
<td>13-14</td>
<td>Headache, no focal defects</td>
</tr>
<tr>
<td>IV</td>
<td>7-12</td>
<td>Headache, no focal defects</td>
</tr>
<tr>
<td>V</td>
<td>3-6</td>
<td>Headache, no focal defects</td>
</tr>
</tbody>
</table>

*a=aphasia, hemiparesis / hemiplegia

**NEW VERSION** World Federation of Neurological Surgeons (WFNS) Scale:

<table>
<thead>
<tr>
<th>Grade</th>
<th>GCS</th>
<th>Major focal defects*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>15</td>
<td>No focal defects</td>
</tr>
<tr>
<td>II</td>
<td>13-14</td>
<td>No focal signs</td>
</tr>
<tr>
<td>III</td>
<td>13-14</td>
<td>No focal signs</td>
</tr>
<tr>
<td>IV</td>
<td>7-12</td>
<td>No focal signs</td>
</tr>
<tr>
<td>V</td>
<td>3-6</td>
<td>No focal signs</td>
</tr>
</tbody>
</table>

*b=aphasia, hemiparesis / hemiplegia

**DIAGNOSIS**

Algorithm in suspected SAH

CT without contrast

1. *positive angiography* ↓ subsequent LP

2. *negative angiography* ↓ subsequent LP

3. Suspect SAH if: persistent headache, nuchal rigidity, fever, photophobia, new focal deficit

CT sensitivity decreases to 80% at 72 hours, 50% at 1 week

Negative CT does not preclude SAH!!!

For subtle SAH, look in occipital horns of lateral ventricles and dependent portions of Sylvian fissures.

CT sensitivity 95-98% (maximum sensitivity is within 12-48 hours)

If CT is negative, but SAH is still suspected → lumbar puncture or repeat CT later or FLAIR MRI

In patients with minimal symptomatology (e.g. sentinel leaks), lumbar puncture is considerably more accurate than CT!

N.B. you have only one chance with LP – if you repeat it, it will be false-positive from small amount of blood from first LP

**Bleeding site localization**

N.B. blood may quickly spread diffusely throughout CSF spaces, providing little clue to its site of origin.

- supraependymal cisterns blood is common from many bleeding sites.
- blood within cisterns of lamina terminalis, anterior interhemispheric fissure – AComA.
- blood within Sylvian fissure – MCA or PcomA.
- blood predominantly in preptentum or peduncular cistern – basilar apex or SCA.
- lateral sylvian Blood – AComA.
- 3rd ventricle blood – basilar tip.
- 4th ventricle blood – posterior fossa aneurysms (esp. at PICA takeoff) – almost pathognomonic for PIACA!!!
- surrounding edema and inflammation may be appreciated with IV contrast following noncontrast CT.

Blood in basal cisterns, Sylvian fissure, or intracerephalic fissur - saccular aneurysm rupture; blood over convexities or within superficial brain parenchyma - AVM or mycotic aneurysm rupture.

**HINDS score** - amount of cisternal and ventricular blood seen on CT.

**Fishers grade** - amount of blood seen on CT (predicts vasospasm):

- Fisher 1 - no blood detected
- Fisher 2 - diffuse thin (< 1 mm) layer, no clots
- Fisher 3 - localized clot and/or vertical layer (≥ 1 mm) – high risk of vasospasm! Fisher 4 - intracerebral or intraventricular clot with diffuse or no SAH.

Only Fisher 3 is associated with clinical vasospasm (amount of blood in cisterns and fissures is important prognosticator for vasospasm?)

- “vertical layer” refers to blood within “vertical” subarachnoid spaces including interhemispheric fissure, insular cistern, ambient cistern

**REFERENCES and ANEURYSMS, SUBARACHNOID HEMORRHAGE**

[Page 25 of 11]
ANEURYSMS, SUBARACHNOID HEMORRHAGE

• reflux of blood into ventricles frequently indicates obstruction of CSF circulation, and is associated with high incidence of hydrocephalus

Things that can mimic SAH on CT:
1. Pus
2. Contrast (IV and especially intrathecal)
3. Pachymeningeal thickening seen in spontaneous intracranial hypotension

Nonenhanced CT - massive SAH in basal cisterns and supracerebellar cistern and lesser amounts in sylvian fissures bilaterally. Blood reflux into ventricular system, and acute hydrocephalus.

Acute diffuse SAH within suprasellar cistern, ambient cistern, and frontal and temporal sulci. There is dilation of both temporal horns of lateral ventricles associated with communicating hydrocephalus.

SDH due to ruptured right PCoM aneurysm:

LUMBAR PUNCTURE:
- most sensitive test for SAH - indicated if CT is negative - nonclotting hemorrhagic CSF with xanthochromic supernatant (may be absent within first few hours; 100% present after ≥ 12 hours).
SAH (subarachnoid hemorrhage)

- opening pressure? (remains for many days), proteins!
- proportion of WBCs to RBCs is that of peripheral blood (if SAH count increases after 24 hours (chemical meningitis), also [glucose] decreases.
- LP should not be performed if CT demonstrates SAH.
- you have only one chance; repeat LP may be xanthochromic from previous LP.
- differential of xanthochromia: jaundice, high protein levels in CSF.

Angiography
- indicated in all patients after SAH diagnosis
- explore all 4 vessels.
- signs of ruptured aneurysm (if ≥ 1 aneurysm is found - which aneurysm needs to be treated acutely)
  1) contract extravasation (pathognomonic but extremely rare)
  2) larger aneurysm will be site of rupture more frequently than smaller one – most important (practically) criterion! (all others below – only soft signs)
  3) mass effect adjacent to aneurysm (focal parenchymal or cisternal hematoma)
  4) focal vasospasm (but subarachnoid bleeding quickly spreads along basal cisterns)
  5) irregularly shaped aneurysm (fetal daughter dome)

Murphy's“rule,”“ill,” or “excruciation” - Dr. Francis Murphy (the Semmes-Murphey Clinic in Memphis. Dr. Murphy did not formally publish this important work) recognized that a focal sacculation on the dome of an aneurysm may be angiographic evidence of a culpable aneurysm in the setting of SAH with multiple intracranial aneurysms present.

N.B. acute angiography occasionally yields negative results (e.g. due to thrombosis or vasospasm) - repeat angiography 1 and 4 weeks later

Before-celling angiogram negative, one must
1) visualize both PICA origins (via one VA injection if there is enough reflux down contralateral VA).
2) visualize AComA*: if both ACAs fill from one side, this is satisfactory.
* perform cross compression AP study with carotid injection (first, rule-out plaque in carotid to be compressed), or use a higher injection rate to facilitate flow
3) see no infundibulum (see above) co-localized to SAH

- trial balloon occlusion of parent artery - for giant and fusiform aneurysms that may need to be surgically “trapped” because they lack defined neck for surgical clipping.

Diagnostic yield in angiographically negative SAH
- one must
  1) visualize both PICA origins (via one VA injection if there is enough reflux down contralateral VA).
  2) visualize AComA*: if both ACAs fill from one side, this is satisfactory.
  3) see no infundibulum (see above) co-localized to SAH

- after first negative angiogram, order cerebral MRI to rule out cerebral AVM / AVF as source of SAH.

Cerebral AVM

- trial balloon occlusion of parent artery - for giant and fusiform aneurysms that may need to be surgically “trapped” because they lack defined neck for surgical clipping.

Diagnostic yield in angiographically negative SAH

<table>
<thead>
<tr>
<th>Parameter</th>
<th>&quot;Traumatic Tap&quot;</th>
<th>SAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xanthochromia</td>
<td>Absent</td>
<td>Onset: 4-6 hr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Still present in 40% at 4 wks</td>
</tr>
<tr>
<td>RBC count (serial tubes)</td>
<td>Decreasing</td>
<td>Constant</td>
</tr>
<tr>
<td>Blood clot formation</td>
<td>Rapid</td>
<td>Slower</td>
</tr>
</tbody>
</table>

* angiograms still give 4% false-negatives; 4-week angiogram is indicated if SAH blood pattern is compatible with benign perimesencephalic bleed

Dr. Francis Murphey (the Semmes-Murphey Clinic in Memphis. Dr. Murphy did not formally publish this important work) recognized that a focal sacculation on the dome of an aneurysm may be angiographic evidence of a culpable aneurysm in the setting of SAH with multiple intracranial aneurysms present.

* angiograms still give 4% false-negatives; 4-week angiogram is indicated if SAH blood pattern is compatible with benign perimesencephalic bleed
NEURYSMS, SUBARACHNOID HEMORRHAGE

A. Carotid angiogram - distal ICA berry aneurysm 4 x 6 mm (arrow)
B. Postoperative angiogram shows clip placement (arrow) with total aneurysm obliteration.

A. Ventral angiogram - basilar tip aneurysm.
B. Angiogram after placement of coils with excellent aneurysm obliteration and preservation of adjacent vessels.

MRI
- not sensitive for SAH within first 48 hours

N.B. fast fluid-attenuated inversion recovery (FLAIR) sequences detect SAH with sensitivity that is equal to or greater than that of CT (subarachnoid hemorrhage produces dramatic hyperintensity in normally hypointense CSF).

- useful to diagnose AVMs.
- useful for diagnosing and monitoring unruptured aneurysms.
- MRI with gadolinium IV bolus better than CTA visualizes previously coiled / clipped aneurysms (lots of metal artifacts on CT).
- cases of repeated bleeding show areas of SUPERFICIAL HEMOSIDEROSIS (i.e. subpial black T2 hemosiderin):
  Axial T2-FLAIR - pons, mesial temporal lobes and cerebellar folia are outlined by low signal intensity hemosiderin rim indicating repeated SAHs.

TRANSCRANIAL DOPPLER
- to assess for vasospasm, done routinely every day until risk of vasospasm decreases (patient “beyond window” of vasospasm).
- disadvantage – monitors only major branches of Willis circle.
- index of Lindegaard may be more specific.

FUNDOSCOPY
1) papilledema
2) Terson syndrome - pathognomonic of SAH - subhyaloid hemorrhages (25%; often bilateral) between retina and vitreous membrane – due to blood dissection along optic nerve sheath + subarachnoid blood around optic nerve compresses central retinal vein at its exit from nerve:

CARDIAC MANIFESTATIONS
- SAH causes circulating catecholamines and autonomic stimulation:
  1) subendocardial myocardial ischemia
  2) peaked P waves, prolonged QT, tall or inverted T waves, U waves
  3) arrhythmias (tachy-, brady-)

TAKOTSUBO CARDIOMYOPATHY - transient stress cardiac syndrome (due to circulating catecholamines) that involves left ventricular apical akinesis and mimics acute coronary syndrome.
  - patients often present with chest pain, ST elevation, and ↑ cardiac enzymes
  - on cardiac angiography, left ventricular apical ballooning is present and there is no significant coronary artery stenosis.

Japanese word takotsubo translates to “octopus pot” resembling shape of left ventricle during systole on imaging studies.
VENTRICULOGRAM - typical appearance of - left ventricle during diastole and end-systole - aneurysmal dilatation (ballooning) of both apical and inferior segments of the left ventricle (arrows):

**COMPLICATIONS**

**VASOSPASM**

- due to irritation by blood - delayed narrowing of large capacitance arteries at base of brain (radiographic vasospasm) that can lead to delayed ischemic neurologic deficit (DIND) - clinical (asymptomatic) vasospasm.

  - Most significant cause of disability and death! (causes death in 7% SAH patients) - must be aggressively treated.

  - Vasospasm develops earlier in patients with previous SAH.

  - Clinical vasospasm resolves by day 12 → gradual radiographic resolution over 3-4 weeks.

  - Angiographic incidence 30-70% (on bleed day 7); of these, only 20-50% patients become symptomatic.

- More blood is surrounding arteries, more likely there will be vasospasm; vasospasm risk correlates with:

  1. Amount of blood in SA space:
     - if CT fails to demonstrate blood or shows only thin layer, vasospasm is unlikely.
     - if CT shows clot ≥ 5 x 3 mm, severe spasm follows in nearly all cases.

  2. Speed of blood clearance - one of reasons to have EVD.

- Pathogenesis: arterial blood at high pressure contacts vessels at base of brain (vasospasm is rare in SAH with distribution limited to cerebral convexity).

- Putative responsible agent - ENDOTHELIN (other candidates - OXYHEMOGLOBIN, SEROTONIN, CATECHOLAMINES, PROSTAGLANDINS, SUBSTANCE P, CALCITONIN GENE PEPTIDE, PLATELET-DERIVED GROWTH FACTOR).

- Risk factors: higher HH grade, more blood on CT (clots are especially spasmogenic when in direct contact with proximal 9 cm of ACA and MCA) and thus antifibrinolytic therapy, age↑, preceding hypertension, history of active cigarette smoking, hypovolemia.

- Angiographic dye can exacerbate spasm.

- Most common sites - terminal ICA, proximal ACA > proximal MCA; more distal arteries become involved later.

- N.B. involved territory is not related to location of ruptured aneurysm! (Greenberg says there is good but not perfect correlation)

- Vasospastic vessels show medial necrosis and inflammation within first few weeks, and later medial atrophy, subendothelial fibrosis, intimal thickening.

- Vasospasm is chronic condition with definite long-term changes in morphology of involved vessels!

**CLINICAL FEATURES** (may develop over few days and fluctuate; 10% present abruptly) - DIND (delayed ischemic neurologic deficit): headache, deterioration in mental status, new-onset focal neurologic deficits.

- Lethargy (with or without focal neurological deficit) is vasospasm, until proven otherwise! → emergency CT to rule out other pathology (vasospasm may be clinically indistinguishable from rebleeding!)

**MONITORING**

1) Routine serial neuro exams

2) Routine daily TCD (normal velocities are < 100); alternative - continuous EEG (look for asymmetry)

3) Baseline and follow-up perfusion CT, CTA

**DIAGNOSIS**

- arterial narrowing with slowing of contrast filling: 1) CTA (with pCT) - first test to do if SAH patient develops any neuro deficit*; some neurosurgeons do it routinely (e.g. at SAH bleed day 10 or if TCDs???)
1. AP left ICA angiogram - routed anterior communicating artery aneurysm (arrow).
2. AP right ICA angiogram - absent A1 segment of right anterior cerebral artery and no vasospasm.
3. AP right ICA angiogram 7 days after admission - severe vasospasm of M1 segment of right middle cerebral artery (MCA) (ap arrow) and suprachiasmatic right ICA (left arrow).
4. Perfusion CT cerebral blood flow (CBF) map - vasospasm-induced decreased CBF (blue areas) within right frontal lobe (arrows).
5. AP right ICA angiogram after intra-aortic urea - improved MCA (ap arrow) and ICA (left arrow) vessel caliber.
6. Follow-up portal CT scan in level as in D - returned CBF to right frontal arterial lobe on CBF color map (arrows).

---

**PREVENTION**
- see below >>

**TREATMENT**
- see below >>

### REBLEEDING (RERUPTURE)
- From aneurysm rupture:
  - Clinically - new headache, sudden neurologic worsening, sudden ICP↑, bright blood in EVD.
  - Diagnosis - CT show presence of new blood in subarachnoid space.
  - EVD increases risk of rebleeding of unsecured aneurysms
- N.B. rebleeding carries mortality ≈ 51-85% !!!

**Rebleeding risk of unsecured aneurysms:**
1st day - 5%
- each next day during first 2 weeks - 1.5%** (2 wks cumulative ～20%, 6 mos cumulative ～50%)
- after 6 months - bleeding risk returns to baseline (1-3%/yr)
- *blow out* hemorhages - due to unstable thrombus
- *lysis of clot* sitting over ruptured site

**N.B.** Risk of rebleeding in SAH of unknown etiology:
- SAH with AVMs, SAH with incidental multiple unruptured aneurysms, are all similar at 1-3%/yr
- Prevention:
  - N.B. bed rest does not prevent rebleeding!
  - Control HTN
  - Do not drain EVD below 10
  - Tranexamic Acid (Cyklokapron®) 1 g q8h IV (e.g. if patient needs to be transferred before securing aneurysm)
  - Epsilon-Aminocaproic Acid (Amicar®) 10 g IV loading dose → IV 48 g/d, incidence of hydrocephalus and stroke is increased with prolonged use!

### SEIZURES
- Seizure INDECISIVE (excluding seizures at time of hemorrhage) - 312% of SAH patients have seizures during acute illness
- Majority of seizures are nonconvulsive (cannot be detected without EEG)
- N.B. seizure burden (number of hours of seizures) is associated with unfavorable functional (mRS 4-6) and cognitive outcome - every hour of seizure on cEEG is associated with odds ratio of 1.10 (95% CI 1.01-1.21, p = 0.04) to 3-month disability and mortality!!!
10.5% incidence of seizures in 5 years follow-up (20% for MCA, 9% for PCA, 2.5% for ACA aneurysms)

**ACUTE OBSTRUCTIVE HYDROCEPHALUS**
- blood within ventricles blocks foramen of Monro, sylvian aqueduct, blood within basal cisterns blocks 4th ventricular outlets.
  - develops in 15-20% cases acutely
  - most present within first 24 hours (or within first 7 days).
  - most reliable clinical measure is level of consciousness; any change in level of consciousness → emergent CT (dilated ventricles* → immediate ventriculostomy).
  - N.B. ventriculostomy increases risk of rebleeding (if aneurysm is unprotected!);
    therefore:
    - keep EVD drainage at least at 10 (when aneurysm is secured – may drop to 0)
    - patients with dilated ventricles (but no compromise of level of consciousness) should be treated conservatively.
  - blood may obstruct ventriculostomy catheter (H: intraventricular injection of tPA or urokinase 10,000-12,000 U followed by clamping drain for 1 h and then opening tube).
  - hydrocephalus resolution is assessed periodically by clamping EVD while monitoring ICP/ neuro status.

**DELAYED COMMUNICATING HYDROCEPHALUS**
- blood in subarachnoid space obliterates arachnoidal villi;
  - develops in 8-45% cases
  - develops ≥ 10 days after SAH – incontinence, gait instability, cognitive deterioration (abulia).
  - prophylaxis: EVD (clears blood from CSF).
  - treatment: ventriculoperitoneal shunt.
  - N.B. usually it is temporary condition and prolonged EVD/LD helps to avoid shunt in some patients; some experts would even use intermittent LP with multiple passes to create CSF leak in spine as temporary “safety valve” until condition resolves.

**NON-NEUROLOGICAL**

**SAH-INDUCED HYponATREMIA**
- develops in 10-34% cases
- majority of cases are due to cerebral salt wasting (atrial natriuretic peptide↑?); the rest – due to SIADH
  - may be first sign of vasospasm!
  - treatment: see p. 2514 >>
    - SIADH – fluid restriction
    - CSW: fluid repletion with normal saline or slightly hypertonic (1.5-3%) NaCl at rates above maintenance requirements, hydrocortisone f fludrocortisone, salt tabs.
    - hyponatremic patients have 3 times incidence of delayed cerebral infarction than normonatremic patients!

**ACUTE NEUROGENIC PULMONARY EDEMA**
- unrelated to HHH therapy.
- almost universal in severe SAH.
- H: gentle diuresis, dobutamine, PEEP.

Patients undergoing triple-H therapy can develop cardiogenic pulmonary edema as they “fall off” Starling curve with volume expansion!

**NEUROGENIC STUNNED MYOCARDIUM (S. TAROKTSUBO CARDIOMYOPATHY)**
- myocardial hypokinesis (↓ ejection fraction) not attributable to coronary artery disease or myocardial abnormalities.
- putative mechanism: hypothalamic ischemia → local (myocardial) catecholamine surge (peak 2 days to 2 weeks post SAH).
- clinically: hypotension (may be compensated by 1SVR), CHF, arrhythmias.
- reverses completely in most cases within about 5 days; 10% progress to MI.
to prevent cerebral ischemia may exacerbate myoccardial ischemia; therapy for myocardial ischemia (nitrates) may increase ICP and exacerbate cerebral ischemia.

2D echocardiography is more sensitive in detecting myocardial ischemia than is ECG.

CEREBROVASCULAR ANEURYSM

Aneurysm is secured

Vasospasm prevention

Heparin

SAH

Neurogenic sympathetic hyperactivity → ischemia

myonecrosis)

Neurogenic sympathetic hyperactivity → ischemia

Neurogenic sympathetic hyperactivity → ischemia

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Neurogenic sympathetic hyperactivity → ischemia

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in acute crisis, PENTANYL is OK – short acting and does not release histamine (does not elevate ICP)! Avoid Demerol® - lowers seizure threshold!

- glucocorticoids may help reduce head & neck ache (irritative effect of subarachnoid blood); no good evidence that they are neuroprotective - routine use is controversial.

**BP GOALS**

- SBP goal: unsecured aneurysm < 140, secured (clipped / coiled) 100-160; up to 180-220 (if secured and in vasospasm).
- maintain BP in range that allows for sufficient cerebral perfusion* yet limits risk of rebleeding:
  - β-blockers (labetalol / Ca-antagonists (nicardipine) / NA at agents of choice ⇒ start short-acting ACEI
  - most clinicians avoid nitrates (NITROPRUSIDE, NITROGLYCERIN) which elevate ICP.
- state of consciousness may be used as guide to level of cerebral perfusion - administer hypotensive medications up to level that patient begins to experience drowsiness.

Avoid HYPOVOLEMIA!

Arterial line indications: hemodynamically unstable, stuporous or comatose, difficult to control hypertension, requiring frequent labs (e.g. ventilator patients).

- pulmonary-artery catheter (aka Swan-Ganz catheter) is out of favor.

**OXYGENATION**

- must be adequate.
- some experts target for early moderate hyperoxemia in intubated patients; studies show no benefit on outcomes.

**ANTIEPILEPTICS** - controversial

- generalized seizure may be devastating in presence of transient aneurysm – seizures increase risk of rebleeding.
- AEDs are given by many authorities at least for 1 week post-op
- Keppra® (LEVETIRACETAM) start with 500 mg PO or IV q 12 hours alternative - PHENYTOIN (load with 17 mg/kg, maintenance of 100 mg TID)
- some prophylaxis is provided by barbiturates (e.g. PHENOBARBITAL) when given for sedation or burst suppression.

**FEVER CONTROL**

- nonthermia, particularly in immediate post event period (14 days), is crucial, and lack of maintenance may negatively affect outcomes.
- very aggressive fever control beyond Tylenol and external cooling measures) may improve outcomes without causing significant harm (maybe pneumonia?).

**NOT TO USE**

- antiﬁbrinolytics (e.g. tranexamic acid) reduce rebleeding from 19-24% to 9-11%, but do not improve or even worsen outcome:
  1. delay clot lysis → vasospasm, hypothermia, cerebral ischemia↑
  2. all sort of ischemic complications

  Vermeulen M et al. Antiﬁbrinolytic treatment in subarachnoid hemorrhage. N Engl J Med 1984; 311: 421. - A randomised, placebo-controlled, double-blind study in 479 patients with subarachnoid hemorrhage showed a signiﬁcant (p < 0.001) reduction in the rate of rebleeding (from 24% in placebo-treated patients to 9% in those who received tranexamic acid). This difference was maintained for the first week and for 4 weeks thereafter. However, a significant increase in the incidence of cerebral ischemia (15% in the placebo treated group vs 24% in patients who received active treatment).

  Kasell NF, Torres JC, Adams Jr BH. Antiﬁbrinolytic therapy in the acute period following aneurysmal subarachnoid hemorrhage: preliminary observations, from the Cooperative Aneurysm Study 1. J Neurosurg 1984; 64, 221-30

  In an analysis of 672 patients participating in the International Cooperative Study on the Timing of Aneurysm Surgery, in which patients who received antiﬁbrinolytic therapy (tranexamic acid or EACA) and those who did not were compared, inhibition of ﬁbrinolysis was associated with a signiﬁcant reduction in the incidence of rebleeding (11.7 vs 19.4%; p = 0.01). However, signiﬁcant increases in rates of ischemic deﬁcit (52.4% vs 22.7%; p = 0.001) and hydrocephalus (13.5% vs 6.8%; p = 0.02) were also reported.

  Findings of other studies published during the 1970s and early 1980s have been inconsistent in terms of clinical beneﬁt of tranexamic acid or EACA.

- antiplatelets and anticoagulants are contraindicated; exceptions:
  1. heparin in prophylactic doses
  2. anticoagulants after stent-assisted coiling (but usually it is not used in case patient will need second surgery – shunt placement); some experts start Aspirin® after all coiling (even if patient has EVD or may need EVD in near future), especially if there is some coil protrusion into vessel lumen.

Aspirin may be associated with reduced DCI risk

Post-treatment Antiplatelet Therapy Reduces Risk for Delayed Cerebral Ischemia due to Aneurysmal Subarachnoid Hemorrhage. Marvin Darthau Oopph et al. Neurosurgery, Volume 85, Issue 6, December 2019; Pages 827-833

- aspirin use after aneurysm treatment was independently associated with reduced DCI risk (P < 0.001, adjusted odds ratio = 0.41, 95% confidence interval 0.24-0.65) and favorable outcome (P = 0.02, adjusted odds ratio = 1.78, 95% confidence interval 1.06-2.9).
- aspirin was associated only with minor bleeding events (P = 0.02 vs P = 51 for major bleeding events).
- caffeine (e.g. Fioricet), nicotine patch, vasopressin – vasocostractor properties.

**VASOSPASM prophylaxis**

For all SAH patients!!!

NIMODIPINE - Ca²⁺ channel blocker

- 60 mg PO q4h or 30 mg PO q2hr (to avoid periodic dips in IBP)
- start within 96 h of SAH, no effect on reversing chronic vasospasm once that has started.
N.B. does not alter radiographic vasospasm, and there is no statistically significant difference in mortality; however, there is risk of strokes and outcome are improved.

- for 21 d or until patient is discharged home in good neurological condition, whichever occurs first.
- early impressions that nimodipine prevents vasospasm have not been confirmed (i.e. actual mechanism of action unknown but may involve brain protection against ischaemia - blocking Ca²⁺ influx into damaged neurons).
- if capsule cannot be swallowed, hole can be made at both ends of capsule with 18-G needle, and contents extracted into syringe → empty contents into nasogastric tube in situ and wash down tube with 30-mL isotonic saline.
- contraindications: systolic BP < 90 mmHg; sick sinus syndrome; 2–3° AV block (except when using pacemaker).
- dosage is halved for liver failure.
- drug interactions: 
  - β-blockers - increased depressive effects on myocardium and AV conduction; 
  - PENTANYL - may cause severe hypotension; 
  - CIMETIDINE - may increase blood [nimodipine].

British Aneurysm Nimodipine Trial


- class I evidence.
- at 3 months nimodipine reduced the incidence of: 
  - cerebral infarction by 1/3 (22% with nimodipine vs 33% with placebo, p = 0.014);
  - poor outcomes by 40% (20% vs 33%, p < 0.001).
- no significant effect on mortality between the groups.

NEWTON (Nimodipine microspheres to Enhance Recovery While Reducing Toxicty after subarachnoid hemorrhage) study

- EG-1962 (Edge Therapeutics, Inc.) - polymer-based microcapsule containing nimodipine.
- delivered as single dose, delivers high and sustained concentrations of nimodipine over 21 day period.

Although other calcium antagonists, such as NIFEDIPINE, have been investigated, there is a Cochran review of 27 RCTs that concluded that there was only evidence to support the prophylactic use of nimodipine. Dorhout Mees SM et al. Calcium-antagonists for subarachnoid haemorrhage. Cochrane database of systematic reviews 2007, Issue 1. Art. No.: CD002777. DOI: 10.1002/14651858.CD002777.pub3

PRAVASTATIN 40 mg/dl for 21 day

Prazanatin in the prevention of vasospasm


- trend for more post-operative deficits in the prazastatin group (p = 0.115) but a trend for more deaths in the placebo group (again, not significant).
- prazastatin reduced vasospasm-related DIDs by 83 % (p < 0.001) and mortality by 75 % (p = 0.037).
- beneficial effects were still present at 6 months (Tseng et al. 2007).


Peter Kilpatrick: “There is no place for the generalized treatment of SAH patients with simvastatin during the acute stage.”

High Dose Simvastatin in Subarachnoid Hemorrhage (HIDS-SAH)

40 mg vs. 80 mg of simvastatin

G Wang. MD: no difference between the 2 doses:

- MANGANESE SULFATE 64 mmol IV for 14 days – neuroprotective agent; beneficial for treatment of eclampsia, which shares pathophysiologic mechanisms with delayed cerebral ischaemia after aneurysmal SAH.

Manganese for Aneurysmal Subarachnoid Hemorrhage trial (MASH-2)

- safe but no benefit compared with placebo (and no subgroup of patients who might benefit from manganese).

CLAZOSERTAN (Prexelar®) – intravenous endotelin receptor antagonist.

- currently, in pivotal Phase III study.

FASUDIL - Rho kinase (ROCK) inhibitor - approved in Japan for treatment of cerebral vasospasm after aneurysm rupture.

- may reduce lesion burden in patients with cerebral cavernous malformation (CCM), study in mice suggests.

Clot removal during surgery or via EVD drainage (up to subarachnoid irrigation with thrombolytic agents)

Triple H therapy – not recommended (as prophylaxis)!

IMPROVES (intensive Management of Blood Pressure or Volume Expansion in Subarachnoid Hemorrhage) - volume expansion or blood pressure augmentation for prevention of delayed cerebral ischemia, did not result in significant differences in neuropsychological outcomes at 6 months vs. patients with normovolemia and normotension;
- blood pressure augmentation was associated with worse neurobehavioural outcome;
- hypervolaemia caused 4-fold increase in risk of adverse event.

VASOSPASM treatment

1. Drop EVD drainage to 0.

2. Aggressive HHH s. hypodynamic therapy (aims to maintain cerebral perfusion pressure in setting of impaired cerebrovascular autoregulation):
   - hypertension (ZOPHINE; NOREPINEPHRINE) – keep MAP 70-130 mmHg, systolic BP high (e.g. 180-240 mmHg; 160 mmHg if aneurysm is unsecured);
   - if tachycardia> 140-150 add PRONESTIL
   - if SBP still low (esp. if SVR > 800 and PCWP 12-14 mmHg*) add DOPRAMINE.

   *in severe vasospasm may increase to 18-21 mmHg (risk of pulmonary edema!)

2) hypervolaemia

   - target CVP > 10 mmHg) – NS* = 200 mL/hr (plus, boluses of colloid, e.g. ALBUMIN)** if UO > 200 mL/hr Greenberg recommends DDAVP; some add FLOMIDOFORTSINE.

   **ALISAHAB study: ALBUMIN in doses up to 1.25 g/kg/d×7 days is tolerated and may be neuroprotective in SAH.

Dextran and Hetastarch are not used - may induce coagulopathy!

- hemodilution (optimal hematocrit is 30-33%); for Hct < 25% give packed RBCs, Mannitol 20% at 0.25 gm/kg/hr may improve cerebral properties. N.B. use of pHbC transfusion to treat anemia is reasonable, although optimal hemoglobin goal is still underdetermined (maintain Hct ~ 30%)
- central venous pressure (CVP) should be maintained at 10-12 mmHg.
- Swan-Ganz catheterisation is indicated - target pulmonary capillary wedge pressure (PCWP) to 14-20 mmHg (in normovolaemia = 10-12 mmHg).

- risks of HHH therapy:
  - 1) rebleeding (if aneurysm is still not treated!)
  - 2) pulmonary edema
  - 3) myocardial ischemia
  - 4) dilutional hyponatraemia

Hypertension/hyponatraemia for symptomatic vasospasm


- reversal of deficits was seen within 1 hr in 81%.
- Ht is most effective for patients with mild deficits.

REFRACTORY VASOSPASM

- endovascular methods:
  a) transmural balloon angioplasty – method of choice! (contraindicated if stroke already happened)
  b) intra-arterial medications (for vasospasm in distal vasculature, where balloons may not access)

VIRAPAMIL – 8 mg injected over 2 min; takes 30 min for full effect; effect lasts 24 hrs. NURAPROINE – 10-40 mg per procedure. PAPYRINE: 200-300 mg infused over 30 mins – effect short-lived, more adverse side effects than angioplasty, largely abandoned because of limited success.

PROTOCOL

TCID! (close to 200) – triple H; from symptomatic – maximum therapy for 1 hour; if still symptomatic – angiography

ANEURYSM treatment

Unruptured (incidental) aneurysms – see above >>
All ruptured aneurysms are treated to avoid disastrous rebleeding (rare exceptions - hemodynamic instability, extreme old age, clinical condition approaching brain death).

TIMING OF TREATMENT

- ruptured aneurysm is treated ASAP ideally within 24H of SAH. (to prevent rebleeding* and to allow HHH therapy for vasospasm) even in patients with grade 5 – in absence of compressing hematoma, it is not necessary to operate during nighttime.
- e.g. pregnant patients - risk of rebleeding during delivery when aneurysms are unclipped

- formerly, surgery was delayed until 2-3rd week after SAH; arguments against early surgery:
  1) inflammation and brain edema are most severe immediately following SAH.
  2) presence of solid clot complicates surgery.
  3) risk of intraoperative rupture of fragile aneurysm.
  4) risk of vasospasm due to mechanotrauma to vessels.
Although operative mortality (of early surgery) is higher, overall patient mortality rate is lower (than of delayed surgery).

- do not delay treatment, if patient presents ≤ 10 days after SAH.
- treatment after 10 days is associated with worse outcome (regardless of treatment modality)
  - there is significant risk for rebleeding (and no compelling medical contraindications) — short-term (< 72 hours) TRANSAXIC Acid or AMINOCAPRIC Acid (Class IIa, Level B)
  - patient presents ≤ 7 days after SAH — coiling has better results (after day 9, coiling = clipping).

International Cooperative Study on the Timing of Aneurysm Surgery

- 3521 SAH patients admitted within 3 days since bleed (83%, i.e. 2922 had aneurysm surgery).
- 68 centers in 14 countries (24 in USA).
- only 6 months of follow up.

- conclusions:
  - good grade → early surgery by day 3.
  - poor grade, older age, pre-existing medical conditions = very poor prognosis — should not be operated on before day 10.

    - main difference today is that we now have the option of endovascular treatment (often performed in poorer grade patients within the vasospastic period, largely because it is less risky to do).
    - early surgery decreases risk of rebleeding but does not prevent vasospasm (however, vasospasm can be treated aggressively)
    - risk of waiting for delayed surgery: 12% rebleed, 30% vasospasm with DIND.

METHODS
N.B whereas coiling is somewhat safer than clipping for both ruptured and unruptured aneurysms (at least in acute perioperative period), clipping is slightly more durable:
  - coiling (vs. clipping) is associated with less risk of vasospasm.

Advantages
  - Clipping vs. coiling carries lower risk of vasospasm (due to endothelial damage during angiographic manipulation — less endothelin release?)

Complications
  - (5% after clipping, 10% after clipping)
  - Seizures: 8.3% — after coiling
  - 13.6% — after clipping
  - MCA aneurysm location increased risk of seizures in both groups.

Morbidity and mortality (strongly correlates with patient’s age):
  - clipping of unruptured aneurysms — morbidity 4-10.9%, mortality 1.3% (higher for ruptured aneurysms, but still ≤ 5%).
  - coiling of aneurysms — morbidity 3.7-5.3%, mortality 1.1-1.5%.

  - Long-term outcomes or similar decision to coil or clip should be made on individual basis

  - long-term rebleed rates might be slightly higher in coiling patients; thus, in patients < 40 yo clipping might be better.

International Subarachnoid Aneurysm Trial (ISAT)
1-yr disability or death:
  - 30.9% — clipping
  - 23.5% — coiling

International Study of Unruptured Intracranial Aneurysms (ISUIA)
in patients with no prior history of subarachnoid hemorrhage, the overall 1-yr morbidity and mortality:
  - 12.6% — clipping
  - 9.8% — coiling

ISAT (International Subarachnoid Aneurysm Trial)

- class 1 evidence that there is a greater impact on treatment of ruptured aneurysms than any other study; trial has led to a huge shift from surgery to endovascular treatment in some centers.
- 2143 patients (1073 coiled, 1070 clipped).
- inclusions: SAH within 28 days, good enough clinical state to justify treatment, aneurysm judged to be suitable for either technique (opinion of both surgeon and neuroradiologist) with equipoise regarding which method would be best.
- rates of rebleeding are higher after coiling (no statistical significance at 1 yr) but poor outcomes (mortality, dependence) are more common after clipping (coiling gives 22.6% relative risk reduction for poor outcome)

- critique:
  - trial is biased towards small anterior circulation aneurysms (97.5%).
  - it is not a trial of “the best possible surgery vs the best possible endovascular treatment” but a trial of what the best option is for an “average patient” (i.e. trial compares good interventional neuroradiologists to “average” neurosurgeons rather than neurosurgeons who “concentrate” on neurosurgical surgery)
  - primary endpoints were measured at 1 year
    - surgical group may just be slower to recover

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  • primary endpoints were measured at 1 year
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SURGICAL CLIPPING
- clip across neck of aneurysm – to exclude aneurysm from circulation (without occluding normal vessels).
  - Dandy performed first successful clipping in 1937, using clip designed by Harvey Cushing.
  - all clips after 2000 are made of titanium – MRI compatible.

Indications:
1) wide aneurysm neck (as is often in MCA bifurcation aneurysms) – alternative – pCOnA device
2) vessel branching off from dome – better eliminates symptomatic mass effect created by aneurysm!
3) if aneurysm contacts cranial nerve (causing neuropathy) it is more important to eliminate pulsations that mass itself.

Approach:

ANTERIOR CIRCULATION aneurysms:
1) pericallosal (fronto-parietal) approach – opening of Sylvian fissure damages small veins → “brain retraction” ischemic changes in postoperative CT
2) minimally invasive approach – performed in Day Surgery unit.

POSTERIOR CIRCULATION aneurysms:
- head of BA (BA bifurcation above dorsum sellae) – modified pericallosal approach.
  - head of BA (BA bifurcation below dorsum sellae) – subtemporal approach.
  - BA trunk – posterior subtemporal approach.
  - lower BA trunk and midline VA – fat lateral inferior approach.
  - VA where it pierces dura – midline suboccipital approach.

Prep and drape neck for rapid carotid proximal control – absolutely for ophthalmic aneurysms, strongly recommended for PCoM aneurysms.

for pCOnA aneurysms, check CTA prep – if fetal circulation, cannot sacrifice pCOnA!

Details:
- first identify parent artery (for possible temporary clipping in event of aneurysmal rupture).
- use operative microscope to detect aneurysm neck free from feeding vessels without rupturing aneurysm.
- if loss of blood clots around – irrigate with saline.
- aneurysmal sac volume can be decreased (to soften aneurysm and facilitate manipulation):
  - temporary clips (with low closing force) on parent artery & aspiration of aneurysm sac (suction device placed over cotton pad)
  - systemic hypotension
- incise arachnoid overlying aneurysm with tip of #11 blade.
- with small aneurysm dissector or spatula aneurysm walls are dissected away from perforating vessels.
- mobilize aneurysm in all directions – for visualization of any perforating vessels (that might inadvertently be incorporated by clip misplacement).
- clips are in various types, shapes, sizes, and lengths and currently are MRI compatible titanium.
  - giant aneurysms or aneurysms with calcified neck require specialized clips with added strength (tandem or booster clips – add force to closing of original clip).
  - use clip as small as possible.
  - jaws of clip applicer are of same metal as clip, so as to avoid transfer of different metal type to clip.
  - avoid placing clip too close to parent artery (may cause tear in aneurysmal sac).
  - if tear does occur – repair with clip graft (risk of damage to perforating vessels).
  - suture in close proximity to aneurysm can result in damage to parent artery.
  - if an aneurysm is located at vessel bifurcation making T (like MCA bifurcation or ICA terminus) – apply clip parallel (not perpendicular) to T – to minimize constriction.
  - for left pCOnA aneurysms, use pCOnA-applicator. 
  - INTRAOPERATIVE FLUORESCEIN ANGIOGRAPHY is used (confirms aneurysm occlusion and patency of nearby vessels).
  - alternative – immediate POSTOPERATIVE ANGIOGRAPHY
  - gently open basal cisterns – carefully remove as much of subarachnoid blood as possible (suction, lavage, a cisternal infusion of 2% Ringer's)
  - advantages – reducing likelihood of vasospasm & hydrocephalus;
  - disadvantages – clot aspiration is usually suboptimal & may initiate traumatic to pial surfaces and small vessels.

- after successful obliteration of ruptured aneurysm, patient remains at significant risk for vasospasm, hydrocephalus, and medical complications – must remain in ICU for at least 7-10 days.

Measures to avoid INTRAOPERATIVE ANEURYSMAL Rupture (principal surgical complication):
1) minimal brain retraction – paramount in aneurysm surgery! - use one blade only self- retaining retractor (e.g. Yasargil, Greenbe, Sugita)
2) induced systemic hypotension, daunreics
3) lumbar CSF drainage
4) hyperventilation
5) hypothermia (+ circulatory arrest)

Key moment in aneurysm surgery – establishment of proximal vascular control!

Measures for CEREBRAL PROTECTION (surgery often requires temporary reduction / suspension of cerebral blood flow, either regionally or globally):
1) continuous EEG monitoring
2) hyporosmonal agents: 20% MINITHERM 1 g/kg IV 5 min prior to temporary clipping of parent artery – to slow ischemic cerebral tissues from infarction for 30 min.
3) anesthetic agents: BISULFATE – preferred anesthetic agent for aneurysm surgery - effective in protecting against infarction during temporary ischemia.
4) barbiturates – have protective effects other than anesthetic agents – redistribute blood flow to ischemic regions (“reversed steal” phenomenon); THIOPENTAL (EEG burst suppression is dosage end point).
5) hypothermia with cardiopulmonary bypass – aneurysm can be opened and debulked in bloodless field; disadvantage – small perforating branches become transparent and blend unperceptively with aneurysm wall so that origin of perforator near neck cannot be visualized (safe dissection may be impossible). H: low perfusion rather than total cerebral arrest.
  - bypass can be achieved by open thoracotomy or cannulation of femoral artery and vein.
  - times of estimated safe circulatory arrest: (1) 37°C 3.5 min, (2) 19°C < 31 min, (3) 13°C < 65 min; therefore, as much dissection as possible is completed before arrest is instituted.

Perioperatively
AED (e.g. L vegan TRACAT) for 7 days.

Outcomes, prognosis after clipping – see below >>
A. **Open Alternatives to Surgical Clipping** (if aneurysm cannot be clipped because of nature of aneurysm or poor medical condition):

- **Endovascular Penetration**
  - Coiling procedure
  - Systems

- **Distal and proximal arterial interruption with direct surgery (ligation or occlusion with clip)**; trial balloon occlusion assesses which cases necessitate extracranial-intracranial (EC-IC) bypass to maintain flow distal to trapped segment.

- **Huniterian principle (proximal ligation of parent artery)** (reduces intravascular pressure on aneurysm) – for uncontrollable broad-based or giant aneurysms (esp. ICA in cavernous sinus).
  - clump is applied ≥ 2 cm below CCA bifurcation.
  - **Adjustable clumps** (gradual occlusion) allow time for collateral circulation to increase.
  - if patient fails to tolerate CCA occlusion — extracranial-intracranial bypass can augment collateral flow.

- **Aneurysm excision** (for giant MCA aneurysms) — end-to-end or branch reconstruction of parent artery.

**Endovascular Surgery**

A. **Indications** (and of feeding artery) (e.g. for onotic aneurysms) - pioneered in mid 1970s by Sberjensko at Moscow Institute of Neurosurgery.

B. **Direct obliteration of aneurysmal lumen**

### Systems

a. **detachable balloon (silicon and latex)**

b. **liquid embolic agents (glues)**

c. **Guglielmi detachable coil (GDC)** - primary treatment modality of aneurysms in many centers! - can be used to treat most aneurysms (initially used for aneurysms not amenable to surgical clipping).

- FDA approved in 1995.

- Soft flexible® platinum microcoils are detached from stainless steel guide by passing very small direct current that causes electrolysis at solder junction — separation occurs within 2-10 minutes after satisfactory coil placement (some newer generation coils involve detachment strategies that do not involve electrolysis — takes only 20-30 seconds).

- Can be contoured to configuration of aneurysm.

- **Coil sizes** range 2-2.2 mm in diameter and 2-30 cm in length.

- **Coil induced electrothrombosis** - positively charged electrode attracts negatively charged blood components (WRBCs, RBCC, platelets, fibrinogen).

- Platinum is 3-4 times more thrombogenic than stainless steel.

- Technical limitations - aneurysms with wide necks or complex morphologies.

- Coils can protrude into parent vessel and can compromise it (H balloon-assisted and stent-assisted coil placements)

- **High rates of recurrence to coil compaction** — see below >>

- **ePAX Aneurysm Treatment System** (NeuroVasx) - FDA approved; advantages:
  - Can detach at any point chosen by clinician (platinum coils have fixed detachment zone)
  - Continuous filling capability (decreases number of devices and amount of time required for treatment)
  - Polymetric material allows for noninvasive MRI and CT without metallic artifact.

- **HydroCoil Embolic System (HES; MicroVention, Inc)** - platinum core with integrated hydraulic first generation — extradiscal coating — difficult handling; second generation — expandable hydraulic within the coil (once in contact with blood, expands to fill the lumen).

- Developed to reduce recurrence through enhancing packing density and healing within the aneurysm.

- Hydrogel Endovascular Aneurysm Treatment Trial (HEAT) — 2nd generation HES; randomized 600 patients (28% with ruptured aneurysms).
  - Assist devices (balloons and stents) were permitted at the discretion of the performing physician, flow diverters, however, were not permitted!
  - Recurrence occurred in 4.4% subjects in the HES arm and 15.4% subjects in the base platinum coil (RPC) arm (P = .002).
  - **Initial occlusion rate** was higher with RPC (17.8% vs 28.3%, P = .003).
  - Packing density and both major and minor recurrence rates were in favor of HES.
  - **Second primary endpoints** (adverse events, retreatment, hemorrhage, mortality, and clinical outcome) did not differ between arms.

### Indications for coiling:

- **Poor clinical grade**
- **Medically unstable**
- **Increased surgical risk** (e.g. cavernous sinus and many basilar tip aneurysms)
- **Posterior circulation aneurysms**
- **Non-tortuous feeding vessels** (i.e. endovascularly accessible aneurysm)
- **Early vasospasm**
- **Aneurysm without defined surgical neck** (although these are also difficult to “coil”); threshold for choosing coiling vs. clipping is 1 / 2 neck to corpus ratio.
- **Basilar artery aneurysms** (practically impossible to clip)

### Coiling procedure:

- Ideally under general anesthesia.
- Complete patient immobilization (and thus general anesthesia) is mandatory.
- Arterial access via puncture of femoral artery.
- Intravenous HEP (10U/kg) achieves targeted coagulation time > 250 seconds (in ruptured aneurysms, patients may not receive heparin until first coil is deployed).
- **6F guide catheter** is placed in cervical ICA or VA.
- Find projection that allows optimal visualization of parent artery in relation to aneurysm.
- **Microcatheter** is navigated into aneurysm cavity using magnified road-mapping technique (computer-generated technique that allows for real-time visualization of endovascular equipment superimposed over map of intracranial arteries).
- Microcatheter should not touch walls of aneurysm.
- Coils of decreasing sizes are delivered into aneurysm cavity and detached.
- First coil (framing coil) should be slightly smaller than diameter of aneurysm, and it should cross neck of aneurysm several times to form receptacle.
- **Angiogram** are obtained before each coil is detached to ensure preservation of parent vessel.

**BENEFITS**

- **Better result** vs surgical clipping.
- **Reduces memory** of aneurysm.
- **Risks** of surgery (ligation or occlusion with clip).
- **Immediate and sustained occlusion** of aneurysm (giant MCA aneurysms).
- **Low recurrence rate**.
- **Surgical mortality** and **morbidity** reduced.
- **Avoids brain resection**.
- **Lower cost** of medical care.
- **Reduce length of hospital stay**.
- **Improves quality of life**.
- **Surgical morbidity** reduced.

**LIMITATIONS**

- **Intracranial hemorrhage**.
- **Increased** risk of coil embolization into parent artery.
- **High** rate of recurrence.
- **High** cost of medical care.
- **Lower** quality of life.
- **Surgical morbidity** increased.
- **Wider** size of neck of aneurysm required.
- **Increased** risk of surgery (ligation or occlusion with clip).
- **Lower** rate of immediate and sustained occlusion of aneurysm.
Anejurysms, Subarachnoidal Hemorrhage

- process is continued until maximal angiographic obliteration of aneurysm cavity is achieved.
  - check percentage at www.angiocalc.com
  - complete packing of aneurysmal sac and neck is possible with small aneurysms.
  - in larger aneurysms, neck cannot be occluded completely - higher risk of recurrence (H: balloon-assisted or stent-assisted technique).
  - withdraw microcatheter cautiously from aneurysm → final angiogram.
  - may reverse heparinization with Protamine.
  - patient is transferred to neurologic ICU.
  - some experts start aspirin immediately (was important with older generation more thrombogenic coils; now – only if coils are too close to normal vessel lumen).

Techniques for Stent Assisted Coil Embolization of Aneurysms

C. Stent-assisted coiling (SAC) - results in significantly lower rates of recanalization and rehemorrhage!

  Indication - "wide neck" aneurysm:
  a) neck width > 4 mm
  b) dome-to-neck ratio < 2

Generally, not used for ruptured aneurysms – because unable to use antiplatelets after procedure! (not due to rebleeding risk* but if patient will need EVD or shunting)

*aneurysmal bleeding is arterial and unaffected by platelet function

- stent prevents coil protrusion into parent vessel - allows for coil embolization of wide-necked aneurysms that might otherwise not be amenable to endovascular therapy.
- stent allows denser coil packing.
- adds need for dual antiplatelet therapy - predisposes to delayed hemorrhagic complications; discontinuation of dual antiplatelet therapy → delayed thromboembolic complications.

pCONus device (PhenoX) - stent acts as a device for aneurysm neck protection for wide-neck aneurysm coiling, e.g. at MCA bifurcation (traditionally, treated surgically):
D. Balloon-assisted coiling (BAC)
- rates of hemorrhagic, thromboembolic, and overall procedural complications, plus rate of favorable outcomes are not significantly different between SAC and BAC.

E. Endovascular flow disruptors - act from within the lesions.
- dual antiplatelet therapy is not required.

Woven EndoBridge (WEB; Microvention, Aliso Viejo, California)

Medina (Medtronic, Dublin, Ireland)

Artisio (formerly LUNA; Medtronic)

Contour (Cerus Endovascular, Fremont, California)
Aneurysms, Subarachnoid Hemorrhage

F. Flow-diverting* endoluminal stent - operate from within the parent artery, i.e. do not catheterize aneurysm sac – reduced risk of rupture!

*term flow diverter, itself, may be a misnomer: though the flow diverter may contribute to the initial thrombus formation in the aneurysm, the final sequestration of the aneurysm from the parent vessel occurs only with endothelialization - this could be the reason why the devices may not work as well in the elderly, where the endothelium may not have the same regenerative capacity, or in thrombosed aneurysms, where inflammatory mediators and proteases secreted by the thrombus impede endothelialization.

- mechanism of action: provide a scaffold for endothelial cells growth while inducing intra-aneurysmal thrombosis - bimetallic microfabricate braid provides flexible yet supportive structure across aneurysm neck - scaffolding promotes endothelial re-pavement, excluding aneurysm from circulation.

Silk flow diverter (SFD; Balt Extrusion)
Flow Re-Direction Endoluminal Device (FRED; Microvention)
Surpass flow diventer (Stryker Neurovascular)
Pipeline™ Embolization Device (PED, Covidien/ev3) - moves therapy from mere endosaccular occlusion to true parent vessel remodeling.

Indications:
- a) wide-necked aneurysms (neck > 4 mm) with unfavorable dome/neck ratios (< 1.5)
- b) fusiform / dissecting aneurysms

- FDA approved for carotid artery - can block giant and wide-necked aneurysms.
- aneurysm occlusion rates 84-94% (if aneurysm is going to occlude it happens within 6 months; still wait total 12 months - then coil)
- jailed side branches preserve patency - incidence of major supraclinoid ICA branch occlusion after treatment is 0-7% and these events are not associated with new neurological deficits.

- can also use in basilar artery (preserves perforators) but not at the basilar tip.
- Safe in posterior circulation!
- flexible (allows it to be used in tortuous anatomy) mesh tube made of nickel-cobalt chromium alloy and platinum.
- may place multiple devices, one inside another (customized constructs with variable degrees of aneurysm coverage and flow disruption); but wait > 1 year for first stent effect (if see stagnant flow in aneurysm during angio, it is enough to thrombose aneurysm over time)
- 70% of aneurysms remain obstructed, without significant arterial stenosis 1 year after PED implantation.
- some experts use successfully also for ruptured aneurysms.
- patients should start dual antiplatelet therapy before implantation* → PLAVIX for 6 months + ASPRIN indefinitely.
- preferably 5 days of Plavix 75 mg/d; check assay on the day of surgery: if < 90 – do not proceed (if bleeding happens it will be catastrophic); if nontherapeutic, proceed with ReoPro intraop, then prasugrel (Effient) postop
- New stems are under development with laser-smoothed surfaces – will not need antiplatelet agents at all!
- contraindicated in active infection, inability to take antiplatelet therapy.

Cerus devices (Cerus Endovascular, Fremont, California)
Adding coils to pipeline device increases rate and fastens aneurysm occlusion (rupture risk↓) and decreases risk of stent prolapse into wide-necked aneurysm cavity.

N.B. do not pack coils densely (need only to promote thrombosis) – thrombotic mass effect on pipeline will cause stent stenosis (H: intrastent angioplasty)

**SPECIAL SITUATIONS**

**Recanalization of previously treated aneurysm**

Risk factors for recanalization:
1. large volume (> 600 mm³) aneurysms
2. low volume (< 20%) packing.

- high rates (15-33% at 18 mos) of recurrence (recanalization).
- mechanisms: coil compaction, unorganized unstable thrombus formation, absence of neointima formation at the neck of coiled aneurysms.

**Raymond-Ray (RR) occlusion scale**

- **COMPLETE**
  - Complete aneurysm occlusion
- **RESIDUAL NECK**
  - Residual aneurysm neck
- **RESIDUAL ANEURYSM**
  - Residual aneurysm dome

**Meyers’s occlusion grading system**

- Grade 0: complete and total aneurysm occlusion
- Grade 1: 90-99% volumetric aneurysm occlusion
- Grade 2: 70-89% volumetric aneurysm occlusion
- Grade 3: 50-69% volumetric aneurysm occlusion
- Grade 4: 25-49% volumetric aneurysm occlusion
- Grade 5: < 25% volumetric aneurysm occlusion

When to treat? If remnant keeps enlarging at each follow up (threshold to treat is lower for previously ruptured aneurysms).
- re-coiling is fairly safe technique
- additional techniques: complex shaped coils, balloon and stent technology, bioactive coils* coated with various substances (swell within aneurysm, promote fibrous tissue formation) - enhanced thrombus permanency.

**MULTIPLE ANEURYSMS**

- a) if incidental aneurysm is in field of surgical approach, it can be clipped along with ruptured aneurysm.
- b) if incidental aneurysm is on contralateral side, then it can be clipped electively at another time (to prevent bilateral vascular injury at the same time).

**WIDE-NECK ANEURYSMS**

- now amenable to endovascular treatment with pCONus device – see above

Grade 0: complete and total aneurysm occlusion. Grade 1: ≥90% volumetric aneurysm occlusion. Grade 2: 70-89% volumetric aneurysm occlusion. Grade 3: 50-69% volumetric aneurysm occlusion. Grade 4: 25-49% volumetric aneurysm occlusion. Grade 5: <25% volumetric aneurysm occlusion.
ANEURYSM COEXISTING WITH AVM (4-18% cases) – AVM excision may precipitate rupture of associated aneurysm (aneurysm subjected to increased flow resistance).

ANEURYSM CAUSING CN3 PALSY – better results with clipping (than coiling).

CAROTID STENOSIS ASSOCIATED WITH ICA ANEURYSM – stenosis may have “protective effect” on aneurysm - endarterectomy can expose aneurysm to increased hemodynamic stress and potential rupture; H. elective aneurysm clipping → endarterectomy.

ANEURYSM PERFORATION WITH COIL during endovascular coiling procedure; H: BP↓ and don’t stop, continue coiling; place EVD.

CAROTID ANEURYSM WITHIN CAVERNOUS SINUS – if ruptures, bleeding is contained but risk of CC fistula.

Differential from paraclinoid aneurysm (i.e. intradural) – CTA in coronal plane: look at optic strut (bony structure running transversely as floor of optic canal): PARACLINOID aneurysm – above optic strut; CAVERNOUS aneurysm – below optic strut

Treatment indications:
1) diameter > 1 cm (risk of erosion through dura → SAH in case of rupture)
2) symptomatic
   a) CC fistula
   b) CN palsies
   c) thalamoperforals (from turbulent flow within aneurysm)

Treatment modalities:
- stand-alone coil embolization or balloon remodeling technique
- stent-assisted coil embolization
- flow-diverter (pipeline)
- clipping
- bypass/trapping

RECANALIZATION IN PREVIOUS STENT-ASSIST COILED ANEURYSM – attempt clipping again.
- if needs clipping, may need to open aneurysm sac to remove coils to allow neck clipping.

CERVICAL ICA ANEURYSM – treatment not indicated.

ICA TERMINUS ANEURYSM – high rate of recurrence after treatment.

ACHA ANEURYSMS
- AChA supplies posterior limb of internal capsule and optic radiation.
- treatment of AChA aneurysms poses particular challenges - complex anatomy of aneurysm + relatively small diameter of AChAs.
- limitation of vessel manipulation should be used to improve outcomes.

ALOSA ANEURYSMS
- aneurysms are known to rupture at nearly any size – risk proportional to size!

ANEURYSM WITH ATHEROSMA
- even after clipping contrast may go in (neck is too stiff): H: place second reinforcing clip (piggyback on first clip).

FOLLOW UP
N.B. MRI with gadolinium IV bolus better than CTA or MRA visualizes previously coiled / clipped aneurysms (lots of metal artifacts on CT).
At some point perform simultaneous angiography and MRA so that in the future, aneurysm recurrence can be monitored using MRI.

After coiling
1. 4-vessel angiogram - 6 months after coiling (if it was stent-assisted coil embolization, patient may discontinue PLAVIX, but will remain on ASPRIN for life)
2. 4-vessel angiogram - 18 months (1.5 years) + 42 months (3.5 years) after coiling.
3. Later – MRA / CTA every 4 years for life

After clipping (there is currently no standard protocol); recurrence risk is 0.26-0.053% / year
2 weeks – clinical
6 weeks – clinical
1 year – angiography every 4-5 years – CTA

Risk for de novo aneurysm is 0.84-1.8% / year

PROGNOSIS
- risk and treatment of recanalization – see above >>
1/4 of patients with aSAH die, and roughly half of survivors are left with some persistent neurological deficit.

- overall MORTALITY is 45% (range: 32-67%):
  10-15% die before reaching medical attention
  20-25% die within 24 hours
  50% deaths occur within 1 month
- prognosis is worse for:
  1) women
  2) blacks
  3) age > 70 yrs
  4) smokers - smoking increases risk of aneurysm rupture 3-6 times!
  5) posterior circulation aneurysms
  6) higher clinical grades
  7) aneurysms (vs. AVMs)
- causes of death:
  1) direct effect of aneurysm rupture (25%)
  2) rebleeding (17.6-25%) - mortality = 51-85% !!! = 15-20% aneurysmal SAHs rebleed in first 2 weeks – see above
  3) delayed ischemia due to vasospasm (7-32%)
  4) neurogenic pulmonary edema
  5) neurogenic stunned myocardium
- 25-50% survivors have moderate to severe neurological deficits.
- 66% of those who have successful aneurysm clipping never return to the same quality of life as before SAH.

Mortality after SAH has improved (Danish study):

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>30-day mortality (%)</td>
<td>38</td>
<td>25</td>
</tr>
<tr>
<td>1-year mortality (%)</td>
<td>42</td>
<td>31</td>
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<tr>
<td>5-year mortality (%)</td>
<td>51</td>
<td>37</td>
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**UNRUPTURED ANEURYSMS**

CLIPPING:

- 10.1% of craniotomies result in a complication leading to a modified Rankin Scale score >1 at 12 months.
- significant risk factors for complications:
  1) age (odds ratio, 1.04; 95% CI, 1.02-1.06)
  2) size (odds ratio, 1.12; 95% CI, 1.09-1.15)
  3) posterior circulation location (odds ratio, 2.95; 95% CI, 1.82-4.78).
- cumulative 10-year risk of retreatment or rupture - 3.0% (95% CI, 1.3-7.0).

**BIBLIOGRAPHY** for ch. “Neurovascular Disorders” → follow this LINK >>

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Please visit website at www.NeurosurgeryResident.net