Role of Tranexamic Acid in the Management of Chronic Subdural Hematoma

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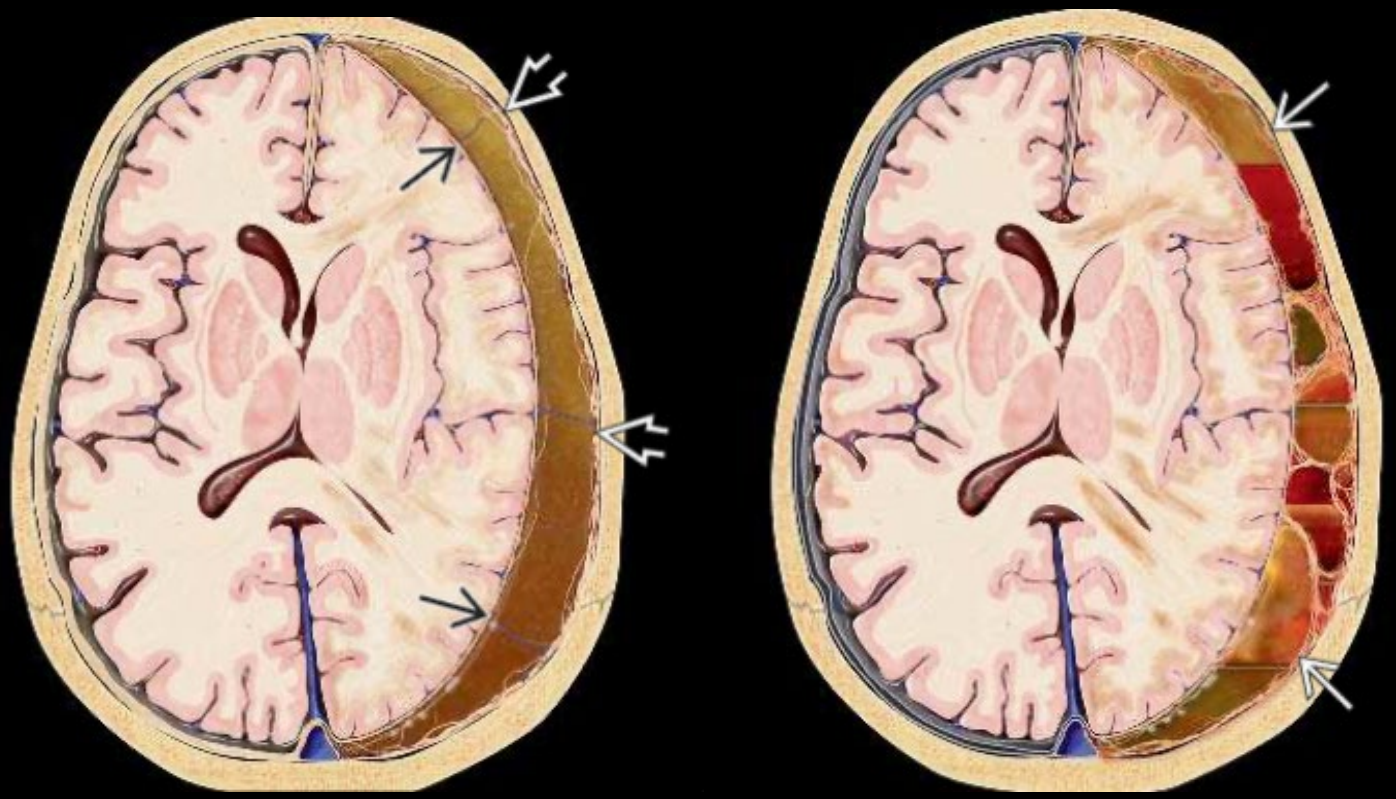
Chronic Subdural Hematoma

- Liquefied hematoma in the subdural space with a characteristic outer membrane and occurring, if known, at least 3 weeks after head injury



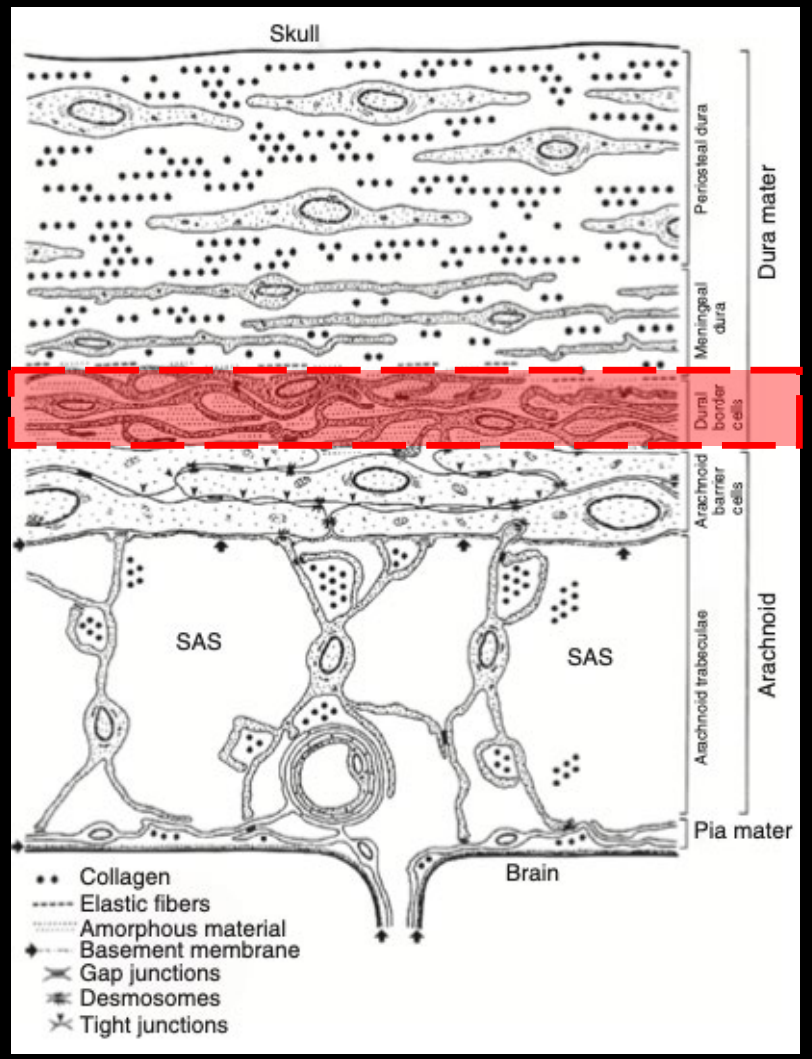
Abouzari M, Rashidi A, Rezaii J, et al. The role of postoperative patient posture in the recurrence of traumatic chronic subdural hematoma after burr-hole surgery. *Neurosurgery*. 2007;61(4):794-797.

Factors associated with increased risk

- Increasing age
- Alcohol consumption
- Male sex
- Use of antithrombotics
- Diseases presenting with brain atrophy
- Alzheimer's disease
- Dialysis
- Craniocerebral disproportion
- Post-VP shunting overdrainage
- Lumbar puncture
- Spinal anesthesia
- Spinal surgery complicated by dural tears

Beck J, Gralla J, Fung C, et al. Spinal cerebrospinal fluid leak as the cause of chronic subdural hematomas in nongeriatric patients. *J Neurosurg*. 2014;121(6):1380-1387.
Baechli H, Nordmann A, Bucher HC, et al. Demographics and prev- alent risk factors of chronic subdural haematoma: results of a large single-center cohort study. *Neurosurg Rev*. 2004;27(4):263-266.

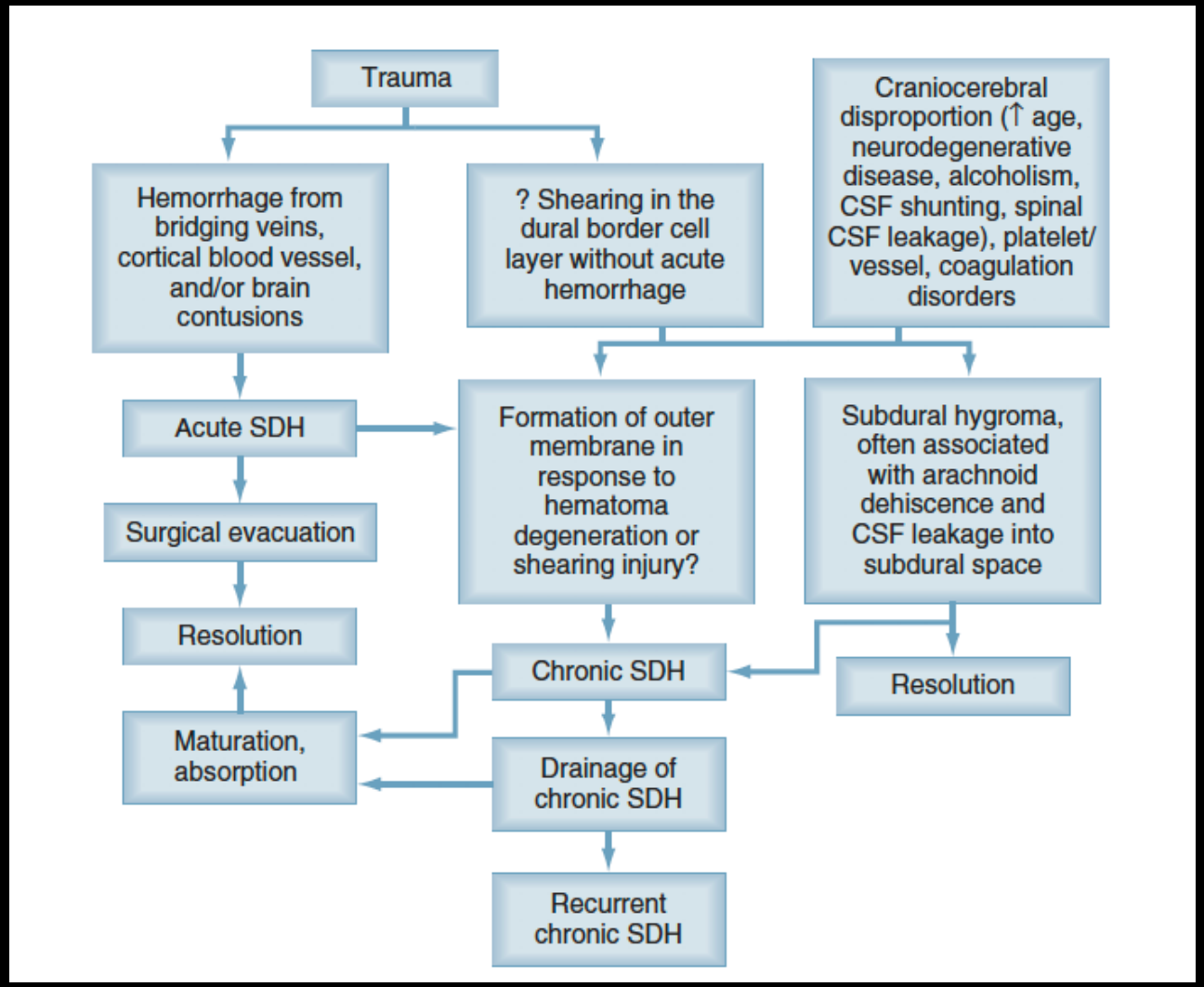
Relevant Anatomy



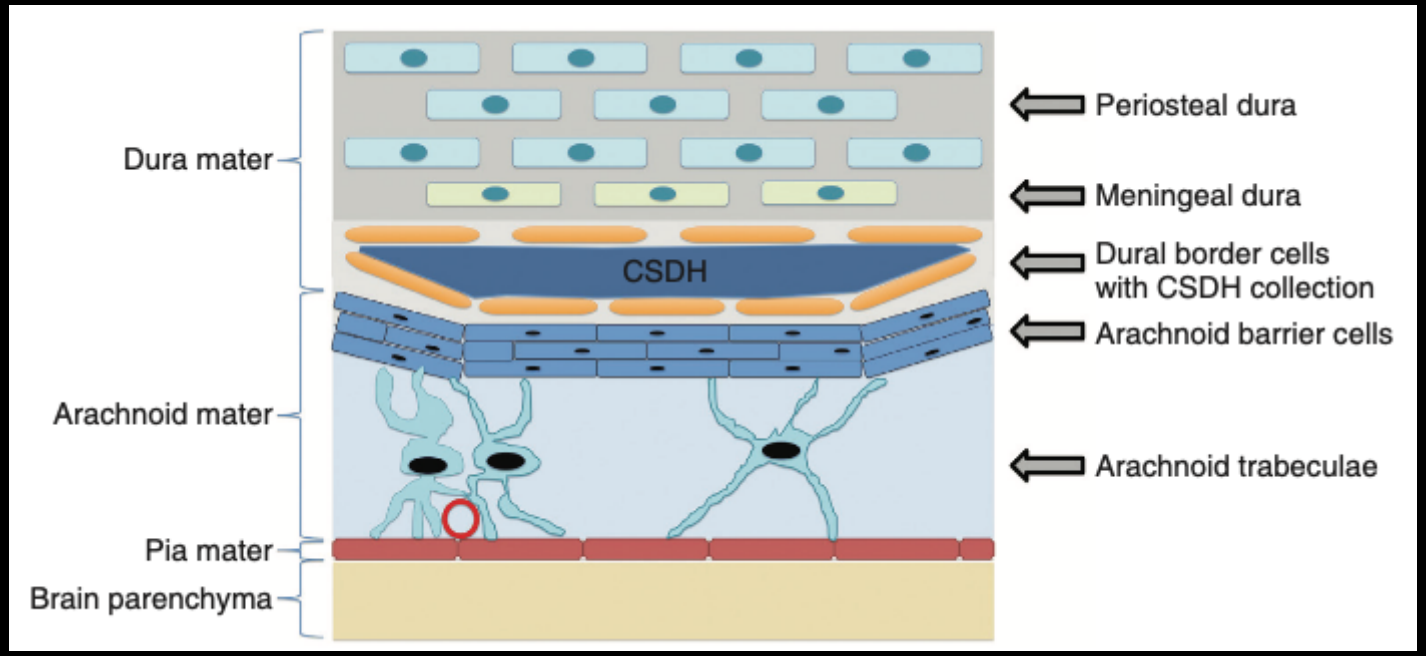
- The subdural space does not exist in healthy individuals
- The dura mater is separated from the arachnoid by a thin layer of dural border cells
- The dural border cell layer contains flattened, elongated cells connected by desmosomes with amorphous ECM and limited collagen fibers → *natural cleavage plane* in which the dura is easily separated from the arachnoid

Haines DE. On the question of a subdural space. *Anat Rec. 1991;230(1):3-21*

Pathogenesis



Macdonald R. Pathophysiology of chronic subdural hematomas. *Youmans and Winn Neurological Surgery*. Elsevier. 2017.



Macdonald R. Pathophysiology of chronic subdural hematomas. *Youmans and Winn Neurological Surgery*. Elsevier. 2017.

Santarius T, Kirkpatrick PJ, Kolias AG, et al. Working toward rational and evidence-based treatment of chronic subdural hematoma. *Clin Neurosurg*. 2010;57:112-122

Injury splitting the dural border cell layer

- Inflammation → Dysregulated coagulation and fibrinolysis
- Poor angiogenesis → Vascular leakage

3-4 weeks → Chronic subdural hematoma

Clinical Presentation

- Heterogeneous presentation
- Headache, limb and gait disturbance, hemiparesis/hemiplegia, cognitive decline and confusion
- in majority of cases, a history of trauma may be elicited
- 20-30% may be completely asymptomatic
- 20% with intake of anticoagulants
- 32% with intake of antiplatelets

Santarius T, Kirkpatrick PJ, Ganesan D, et al. Use of drains versus no drains after burr-hole evacuation of chronic subdural haematoma: a randomised controlled trial. *Lancet*. 2009;374:1067-1073.

INITIAL MANAGEMENT

Imaging

- Plain cranial CT scan is fast and more accessible
    - hyperacute – isodense to adjacent cortex (<24hrs)
    - acute – crescentic, homogenously hyperdense (Days 1-2)
    - subacute – decreasing density (Days 3-21)
    - chronic – hypodense (≥3 weeks old)
    - acute on top of chronic – both acute (hyperdense) and chronic (hypodense) components, (+) layering

Osborn A. (2018). *Osborn's Brain Imaging, Pathology and Anatomy 2nd edition*. Philadelphia; Elsevier.
Cooper, P and Golfinos, J. *Head Injury, 4th edition*. McGraw-Hill. 2000.

Imaging

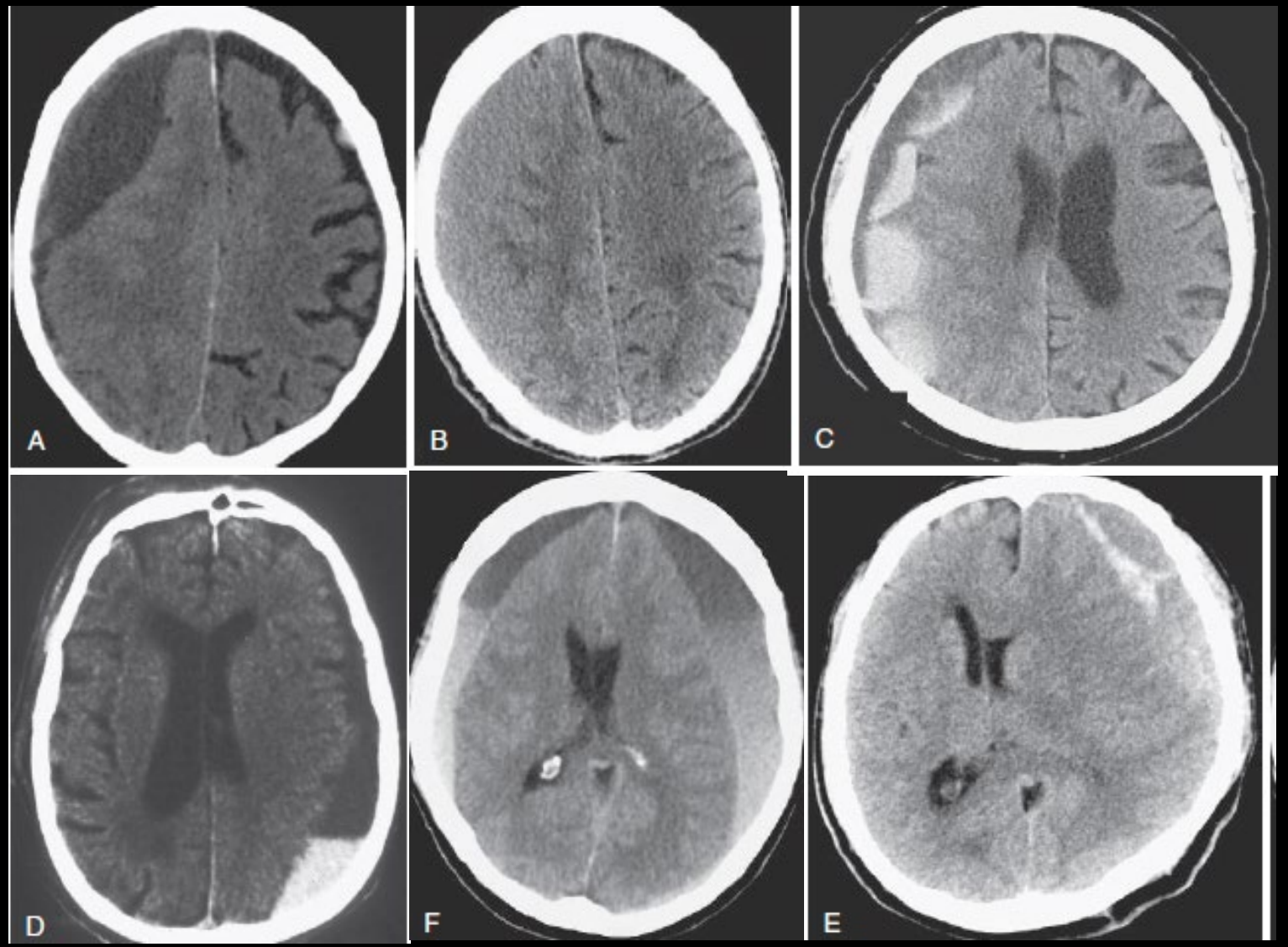
- MRI is done for accurate hematoma localization and to visualization of parenchymal abnormalities that might be missed on CT scan
- signal intensity is variable across sequences
- T1: hypontense to isointense
- T2: hypointense to isointense
- FLAIR: hyperintense to CSF (most sensitive sequence)
- GRE: blooming if blood clots are still present

Osborn A. (2018). *Osborn's Brain Imaging, Pathology and Anatomy 2nd edition*. Philadelphia; Elsevier.
Cooper, P and Golfinos, J. *Head Injury, 4th edition*. McGraw-Hill. 2000.

Homogeneous hypodense

Homogeneous isodense

Trabeculated



Layering separated

Layering gradated

Laminar

Macdonald R. Pathophysiology of chronic subdural hematomas. *Youmans and Winn Neurological Surgery*. Elsevier. 2017.

Nakaguchi H, Tanishima T, Yoshimasu N. Factors in the natural history of chronic subdural hematomas that influence their postoperative recurrence. *J Neurosurg*. 2001 Aug;95(2):256-62.

Predictors of CSDH Recurrence

- Variable rate (9-26%)
- Defined as increase in hematoma volume in the ipsilateral subdural space with neurologic deficits
- Brain atrophy, increasing age (≥75 years), bilateral CSDH, alcoholism, obesity (BMI ≥ 25kg/m2)
- Presence of thick membranes or septations, persistent midline shift, poor perioperative brain expansion, pneumocephalus
- Intake of antithrombotics *does not* significantly increase recurrence

Torihashi K, Sadamasa N, Yoshida K, Narumi O, Chin M, Yamagata S (2008) Independent predictors for recurrence of chronic subdural hematoma: a review of 343 consecutive surgical cases. Neurosurgery 63(6):1125–1129.
Chari A et al. Medical and surgical management of chronic subdural hematomas. *Youmans and Winn Neurological Surgery*. Elsevier. 2017.

Surgical Techniques

	Indications	Technique	Remarks
Twist drill craniostomy <10mm	For patients who cannot tolerate GA Elderly patients with multiple comorbids Poor candidates	Local anesthesia infiltrated Place 1-2 drill holes over the maximum width of hematoma Pierce dura and outer membrane and place drainage system for 48hrs	May be performed at bedside Lowest morbidity and mortality but higher recurrence
Burr hole craniostomy (10-30mm)	Most frequently performed Most efficient (recurrence vs M&M)	1-2 Burr holes placed over the maximum width of the hematoma, dura and outer membrane incised releasing hematoma fluid, subdural space liberally irrigated until effluent runs clear; drain inserted into subdural space	No difference in outcome between 1 and 2 burr holes
Craniotomy (>6cm) or minicraniotomy (<6cm)	Significant acute component, multiple membranes, recurrent CSDH	Free bone flap of varying sizes is created to provide maximal access, dura and outer membrane incised releasing hematoma fluid, subdural space liberally irrigated until effluent runs clear; drain inserted into subdural space	Reserved for recurrent CSDH with extensive organization and membrane formation

Chari A et al. Medical and surgical management of chronic subdural hematomas. *Youmans and Winn Neurological Surgery*. Elsevier. 2017.
Ducruet AF, Grobelny BT, Zacharia BE, et al. The surgical management of chronic subdural hematoma. *Neurosurg Rev*. 2012;35:155- 169.

Surgical Techniques – Comparison

- *Twist-drill craniostomy* has lowest morbidity and mortality, but recurrence higher
- *Burr hole craniostomy* results in best cure to complication ratio
- SDH with significant membranes, acute component, multiple recurrences, or calcification are best evacuated by *craniotomy*

TABLE 34-2 Comparison of Efficacy, Morbidity/Complications, Recurrence, and Mortality of the Different Techniques in Contemporary Meta-analyses[14,45,74]

		Successful Outcome	Morbidity/Complications	Recurrence	Mortality
Almenawer et al.[74] (2014)	BHC	86.0%	7.2%	10.5%	3.5%
	TDC	90.2%	5.5%	14.5%	3.6%
	Craniotomy	80.3%	10.2%	6.2%	6.8%
Ducruet et al.[14] (2012)	BHC	84.9%	9.3%	11.7%	3.7%
	TDC	93.5%	2.5%	28.1%	5.1%
	Craniotomy	74.4%	3.9%	19.4%	12.2%
Weigel et al.[45] (2003)	BHC	79.1%	3.8%	12.1%	2.7%
	TDC	88.1%	3.0%	33.0%	2.9%
	Craniotomy	67.8%	12.3%	10.8%	4.6%

BHC, bur-hole craniostomy; TDC, twist-drill craniostomy.

Chari A et al. Medical and surgical management of chronic subdural hematomas. *Youmans and Winn Neurological Surgery*. Elsevier. 2017.

Ducruet AF, Grobelny BT, Zacharia BE, et al. The surgical management of chronic subdural hematoma. *Neurosurg Rev*. 2012;35:155- 169.

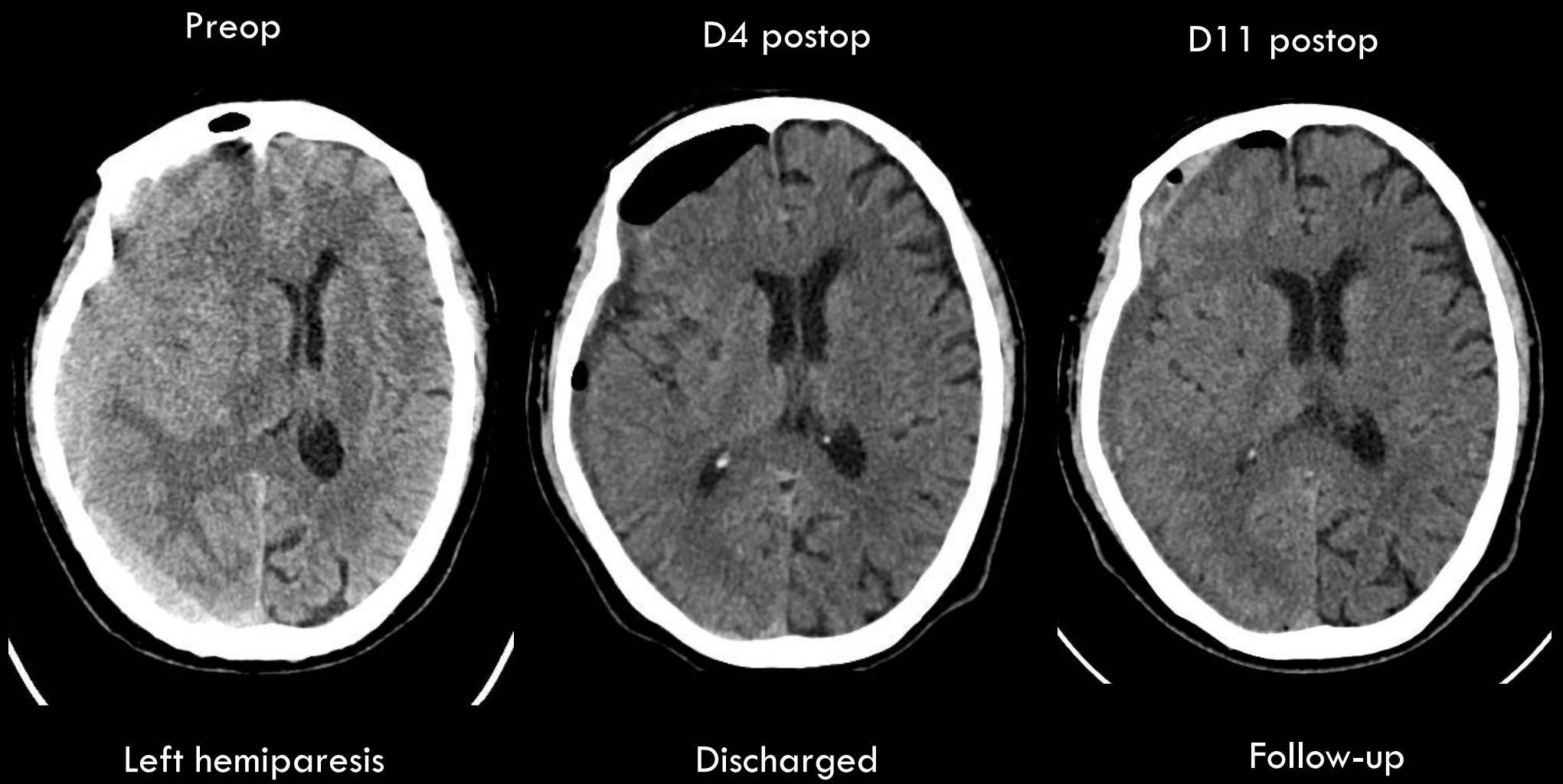
Almenawer SA, Farrokhyar F, Hong C, et al. Chronic subdural hematoma management: a systematic review and meta-analysis of 34829 patients. *Ann Surg*. 2014;259:449-457.

Weigel R, Schmiedek P, Krauss JK. Outcome of contemporary surgery for chronic subdural haematoma: evidence based review. *J Neurol Neurosurg Psychiatry*. 2003;74:937-943

Case 1

MC
83/M

Subacute
SDH
HTN, DM,
BPH

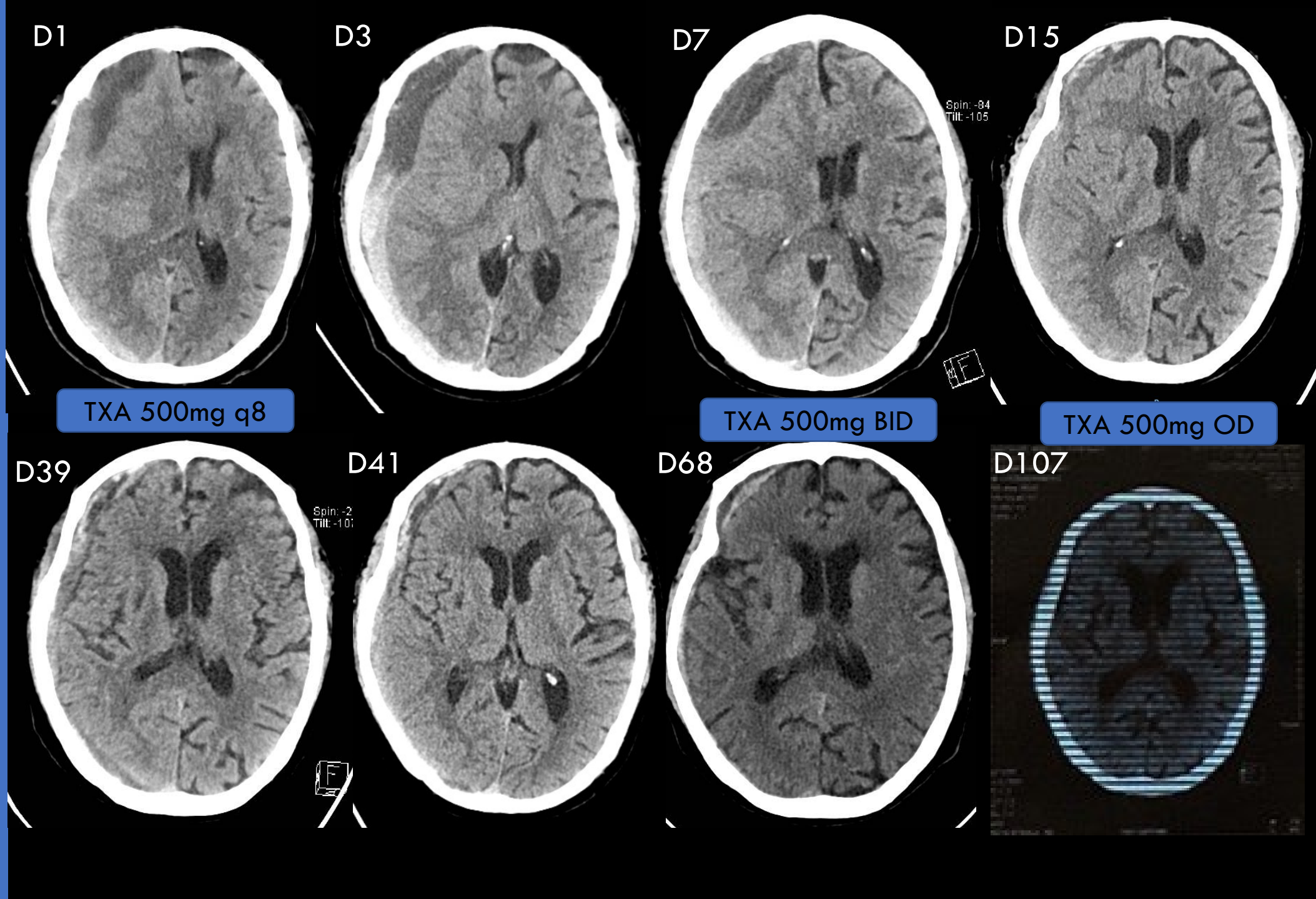


s/p Right Frontal and Parietal Burr
Craniectomy, Evacuation of Hematoma

Case 1

MC
83/M

Recurrent CSDH at D17 postop



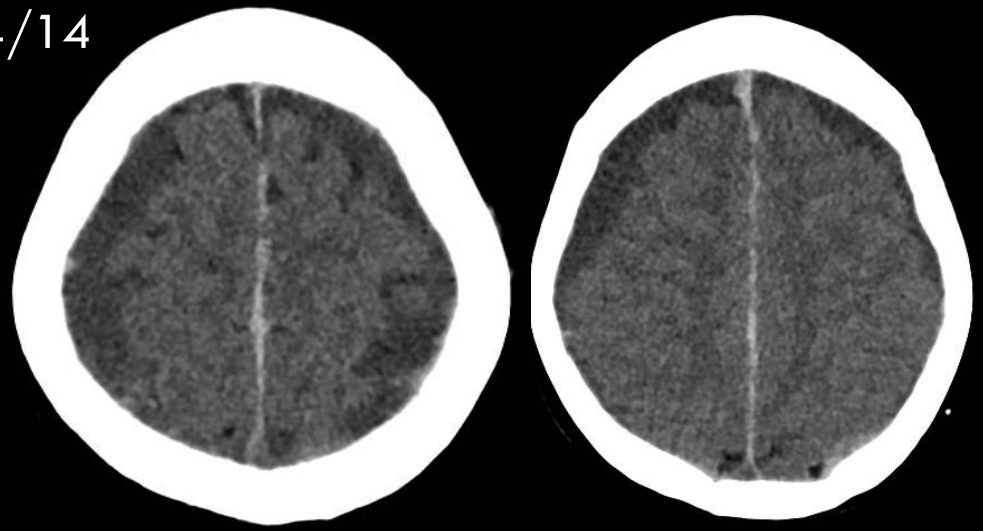
Case 2

AD

58/F

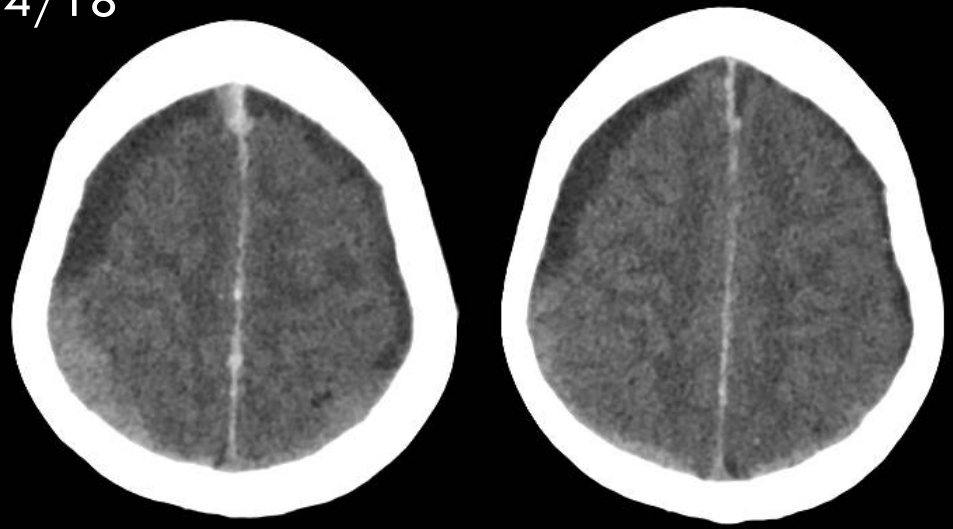
Papillary thyroid Ca, Anterior mediastinal cellulitis, COVID Pneumonia

4/14

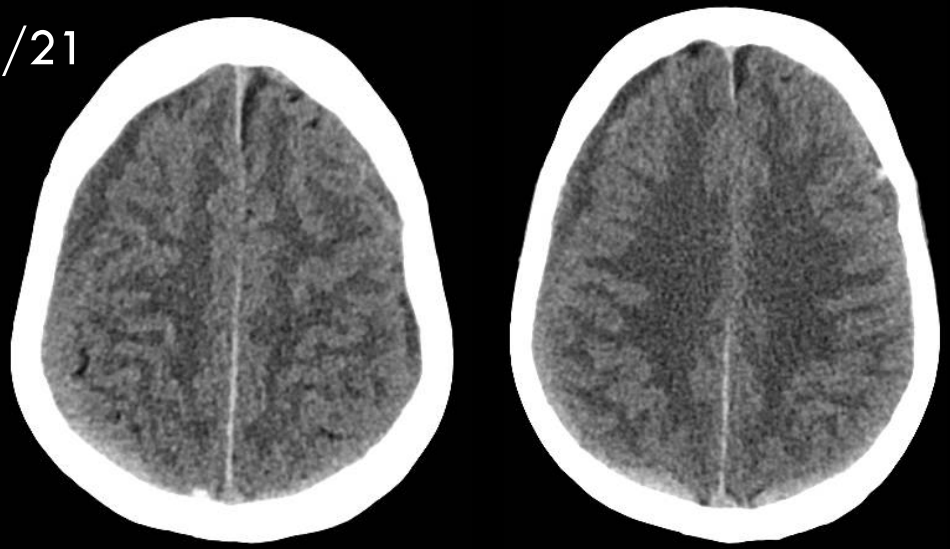


Mannitol 150ml q6
Dexamethasone 5mg q8

4/18

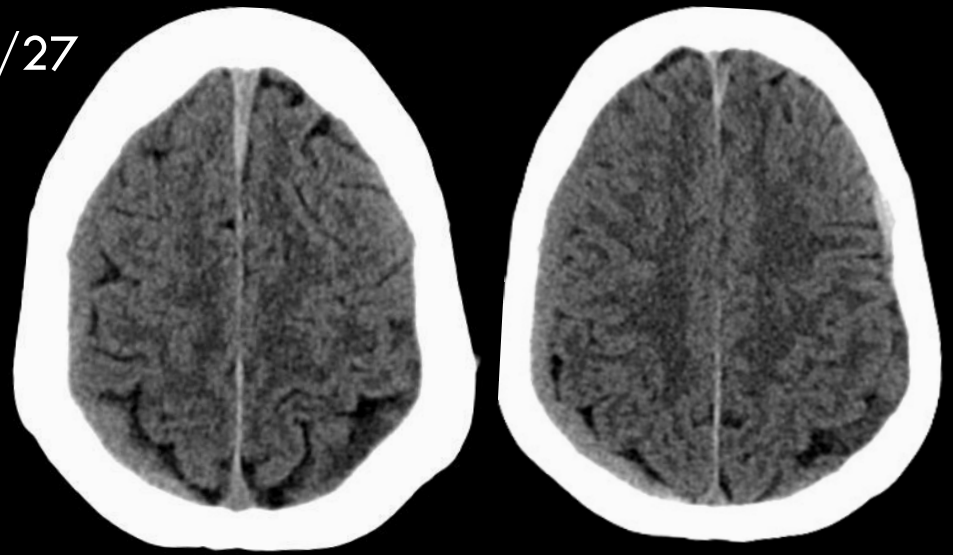


4/21



COVID-positive
Tranexamic acid 500mg q8

4/27



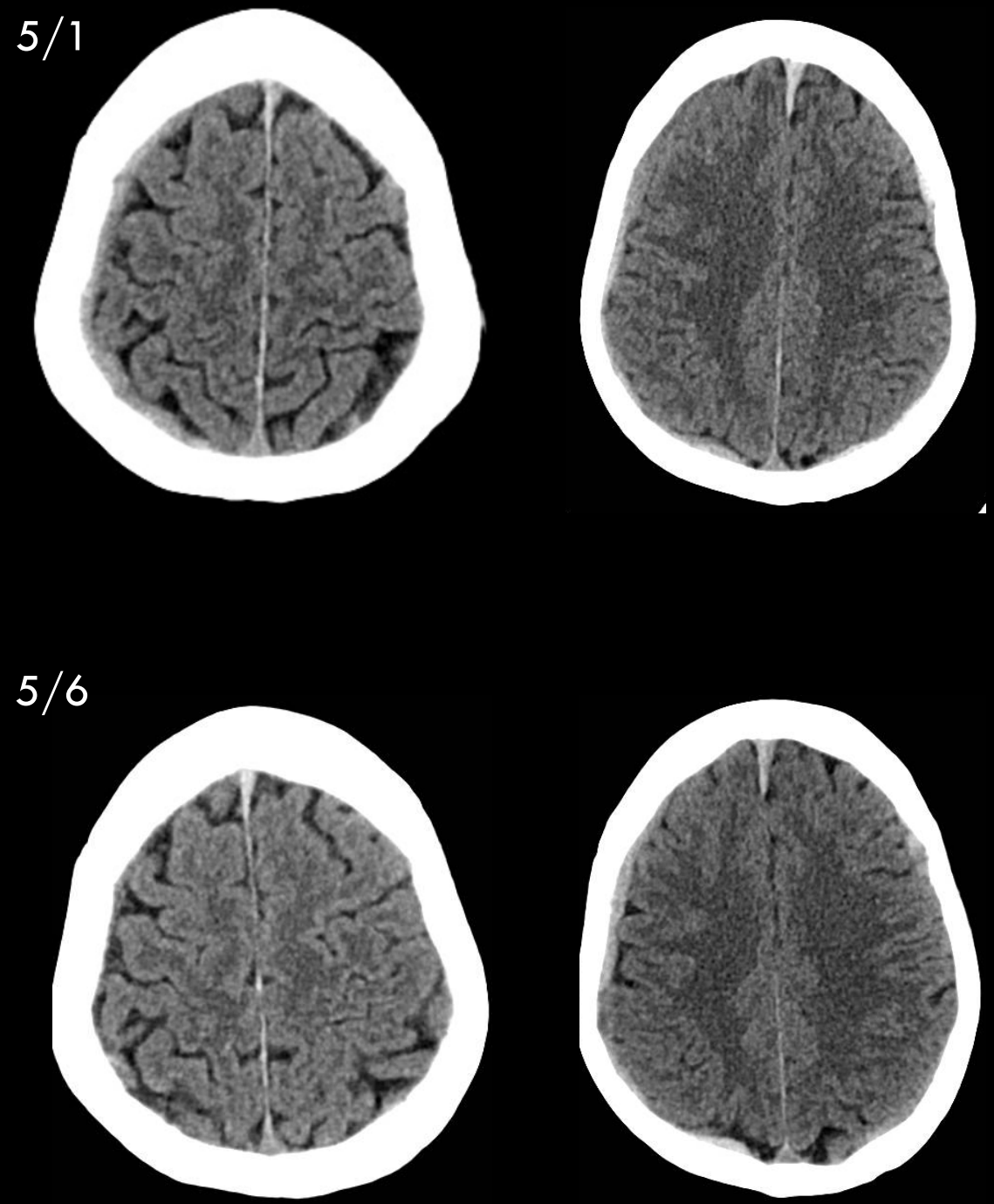
Discontinued TXA

Case 2

AD

58/F

Papillary thyroid Ca, Anterior mediastinal cellulitis, COVID Pneumonia



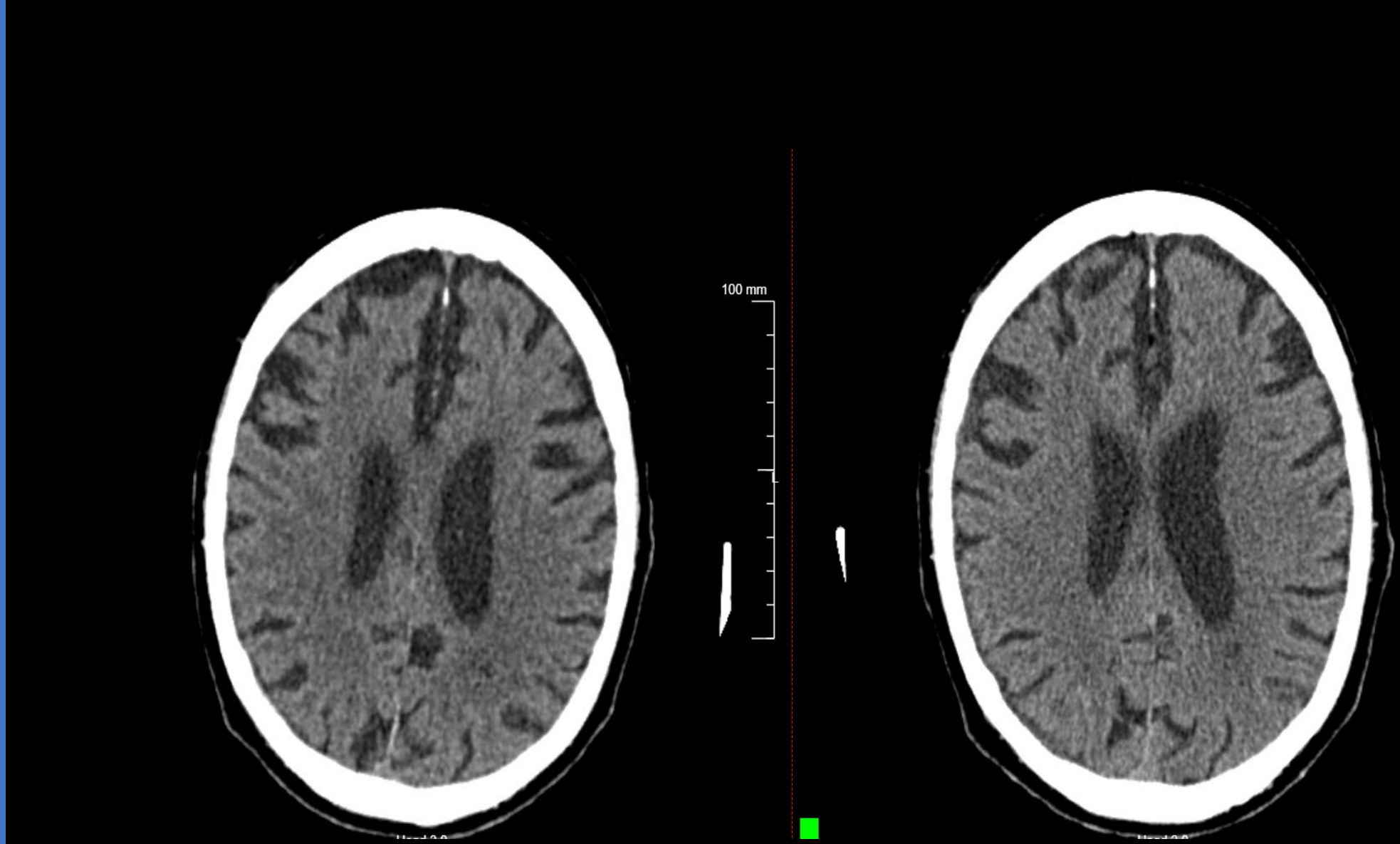
Stable sensorium, generally weak but with no focal deficits

Intubated due to respiratory failure from COVID pneumonia with concomitant pulmonary embolism

Case 3

HC
86/M

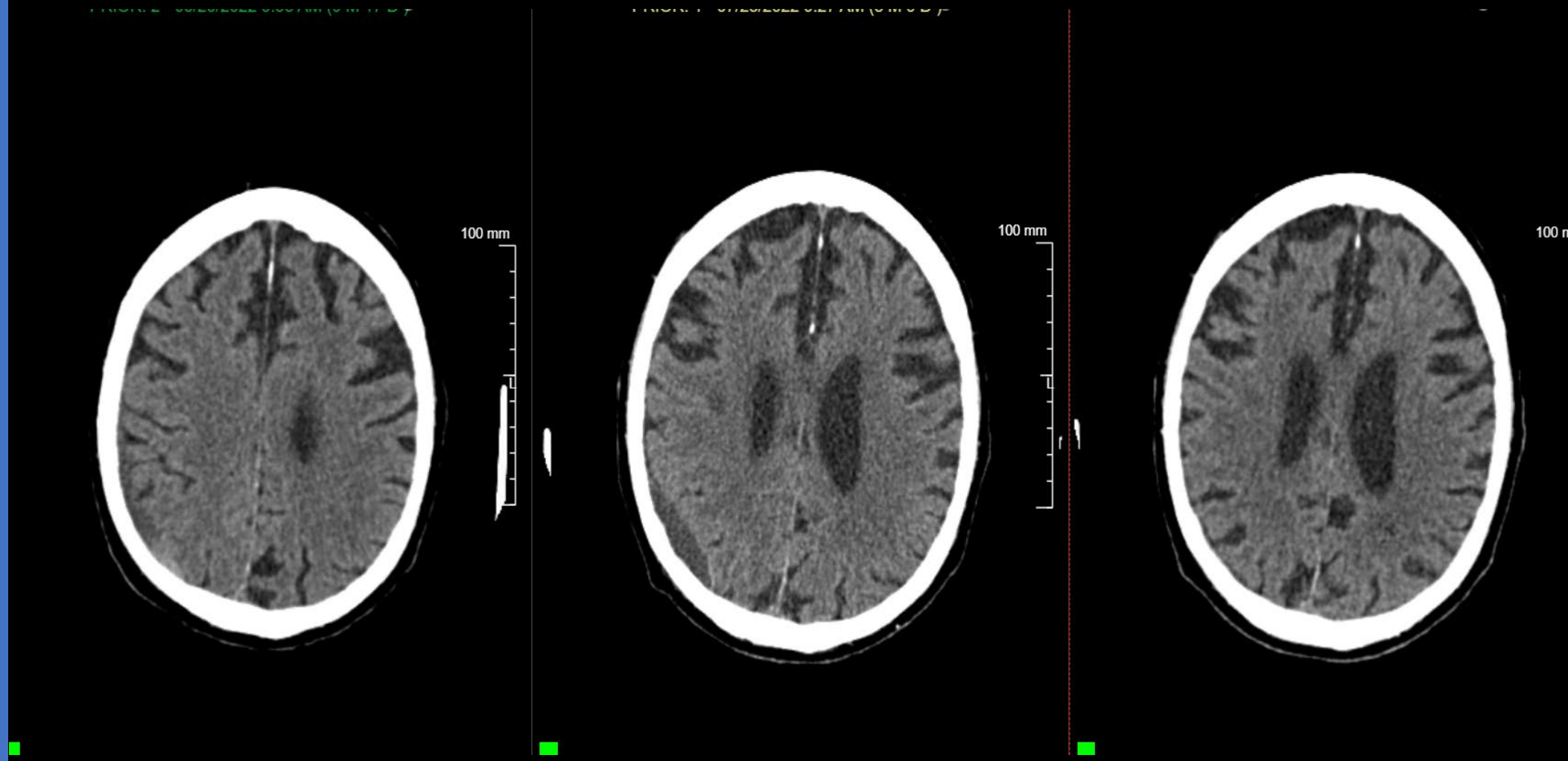
Hx of fall, CHF



Case 3

HC
86/M

Hx of fall, CHF



Conservative Management

- Offered to patients in whom operative risks outweigh the benefits of surgery
- Asymptomatic patients with small subdural collections
    - serial CT scans
- Moribund patients with poor baseline function
- Patients who refuse surgery

Chari A et al. Medical and surgical management of chronic subdural hematomas. *Youmans and Winn Neurological Surgery*. Elsevier. 2017.

Emerging Role of Tranexamic Acid

- *Level of TPA found to be higher in hematoma fluid vs. plasma*
- MOA: synthetic lysine analogue antifibrinolytic that blocks the activation of plasminogen to plasmin via competitive inhibition
- CSDH can be treated non-surgically (750mg OD) with no adverse events (Kageyama et al), given daily until with resolution
- Can be safely administered in trauma patients with reduction in all-cause mortality (CRASH-2)
- Tranexamic acid 1g IV q8 within the first 3 hours reduces head-injury related deaths (CRASH-3)
- Ongoing RCTs: TRACS, TORCH

Chuk Kit Ng, W., Jerath, A., & Wasowicz, M. (2015). Tranexamic acid: a clinical review. *Aneasthesiology Intensive Therapy* , 1-32.

Kageyama, H., & Toyooka, T. (2013). Nonsurgical treatment of chronic subdural hematoma with tranexamic acid. *JNeurosurg 119*, 332–337.

Roberts, I., H, S., & Coats, T. (2013). The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. *Health Technol Assess*, 1-79.

Roberts, I., & H, S. (2019). Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. *The Lancet*, 1713-1723.

Steroids

- MOA: inhibit TPA activity, IL-6, IL-8 and VEGF expression, inhibit growth of neomembranes
- Associated with lower recurrence rate and reduced hospital stay
- Dexamethasone 4mg q8, re-evaluated after 48-72 hrs and gradually tapered *(Delgado-Lopez et al)*
- Dexamethasone 4mg q6 for 21 days *(Sun et al)*
- Hyperglycemia is the most common complication (27.8%)
- *Not* associated with higher incidence of complications and treatment-related deaths

Sun, T.F.D., Boet, R., Poon, W.S.: Non-surgical primary treatment of chronic subdural haematoma: preliminary results of using dexamethasone. Br J Neurosurg 2005; 19: 327-333.

Delgado-Lopez et al. Dexamethasone treatment in chronic subdural hematoma. *Neurocirugía* 2009; 20: 346-359

Berghauser L. et al. Clinical Factors Associated With Outcome in Chronic Subdural Hematoma: A Retrospective Cohort Study of Patients on Preoperative Corticosteroid Therapy. *Congress of Neurological Surgeons*. 2012; 70: 873-880.

Glover D, Labadie EL. Physiopathogenesis of subdural hematomas. Part 2: Inhibition of growth of experimental hematomas with dexamethasone. *J Neurosurg*. 1976 Oct; 45(4):393-7.

The role of osmotherapy

- Mannitol is metabolically inert and could theoretically facilitate hematoma absorption by increasing the osmotic pressure of blood
- Decrease in ICP and CSF drainage might cause further retraction of draining veins in SDH patients → hematoma expansion
- Give to herniating patients at a dose of 1g/kg

Meagher R. (5 Aug 2020). Subdural Hematoma Medication. Retrieved from *Medscape*.
Huang K et al. The Neurocritical and Neurosurgical Care of Subdural Hematomas. *Neurocrit Care* (2016) 24:294–307.
Huang J, et al. Drug treatment of chronic subdural hematoma. *Expert opinion on pharmacotherapy*. 2020.

Atorvastatin

- MOA: HMG-COA reductase inhibitor, found to reduce inflammation and promote angiogenesis
- Dose of 20mg OD for 8 weeks has been found to reduce volume of hematoma and improve neurologic function
- Reduces post-op recurrence
- Ongoing RCTS: REACH, ATOCH2

Edlmann E. et al. Systematic review of current randomised control trials in chronic subdural haematoma and proposal for an international collaborative approach. *Acta Neurochirurgica*. 2020.
Xu M, et al. Effects of Atorvastatin on Conservative and Surgical Treatments of Chronic Subdural Hematoma in Patients. *World Neurosurg*. 2016;91:23-28.
Jiang R, Zhao S, Wang R, et al. Safety and efficacy of atorvastatin for chronic subdural hematoma in chinese patients: a randomized clinical trial. *JAMA Neurol*. 2018 1;75(11):1338–1346.

ACE Inhibitors

- Theoretically, block immature angiogenesis and reduce bleeding from immature blood vessels
- Contradicting evidence: inhibiting ACE → elevated bradykinin → increased vascular permeability → higher hematoma volume and recurrence rate
- Impact and potential yet to be determined

Holl et al. Pathophysiology and non-surgical treatment of chronic subdural hematoma: from past to present to future. *World Neurosurgery*. (2018).

Weigel R, Hohenstein A, Schlickum L, Weiss C, Schilling L. Angiotensin converting enzyme inhibition for arterial hypertension reduces the risk of recurrence in patients with chronic subdural hematoma possibly by an antiangiogenic mechanism. Neuro- surgery. 2007 Oct;61(4):788-92.

Middle Meningeal Artery Embolization

- Minimally invasive technique to treat CSDH and prevent reaccumulation
- Polyvinyl alcohol particles are injected to seal off this portion of the artery and prevent any further blood flow into the subdural hematoma
- Two RCTS ongoing (USA and China)

Edlmann E. et al. Systematic review of current randomised control trials in chronic subdural haematoma and proposal for an international collaborative approach. *Acta Neurochirurgica*. 2020.

Haldrup, M., *et al*. Embolization of the middle meningeal artery in patients with chronic subdural hematoma—a systematic review and meta-analysis. *Acta Neurochir* **162**, 777–784 (2020).

Surgical

- BHC preferred surgical method *(C)*
- TDC under local anesthesia preferred for high-risk patients *(C)*
- cSDH with significant membranes, multiple recurrences or calcifications best evacuated by craniotomy *(C)*
- single BHC as good as double BHC *(C)*
- irrigation role in recurrence still unclear, might lead to less recurrence, no impact on M&M *(C)*
- closed system drainage leads to lower recurrence *(A)*
- subperiosteal as good as subdural drainage *(C)*
- immediate mobilization may lead to higher recurrence rate, but may prevent medical complications from immobilization *(A)*

Medical

- Asymptomatic patients can be observed and managed conservatively with serial imaging
- Correction of coagulopathy and thrombopathy crucial to prevent hematoma expansion
- Consider adjunctive therapies Tranexamic acid, Dexamethasone, Atorvastatin
- AED prophylaxis for those a thigh risk for seizures *(C)*
- Mannitol generally not useful for CSDH patients except for those with impending herniation
- For high-risk patients, anticoagulation may be resumed safely within 72 hours *(B)*