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# State-of-the-art TBI Resuscitation:
## Pressure, Oxygenation and Biomarkers


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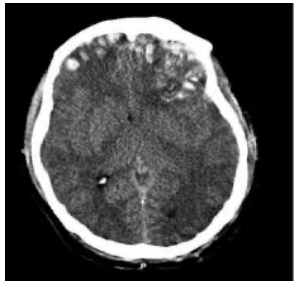
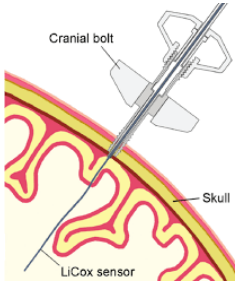
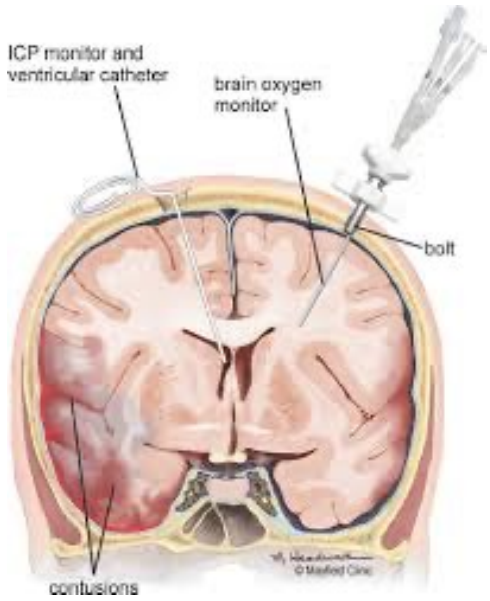
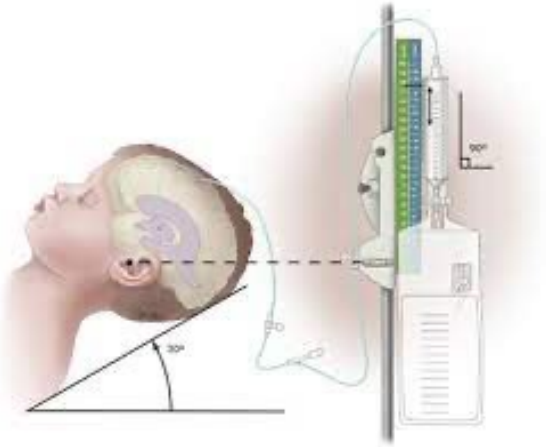


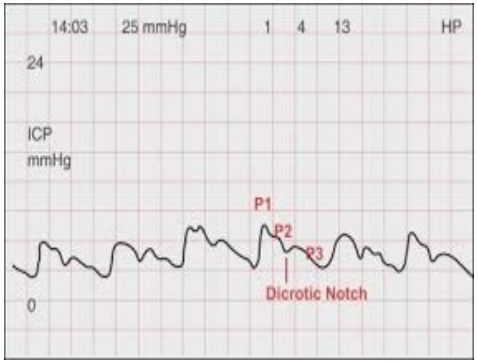


# Pressure

- Intracranial hypertension






- **Professor, “ICP is 35mmHg”**
- What do you do?
  A. Start 50gm of IV mannitol now
  B. Inject 30cc of 23.4% HTS IVP over 10min now
  C. Start 3% HTS at 100cc/h with Na target of 150
  D. Hyperventilate to target pCO2 of 30mmHg
  E. I need more data

# Answer: I need more data

- These are the questions you should have
  - Is the EVD working?
  - Is the ICP transient/ confounding factor
  - What is patient doing? Agitated/going for the tube? Neuro exam?

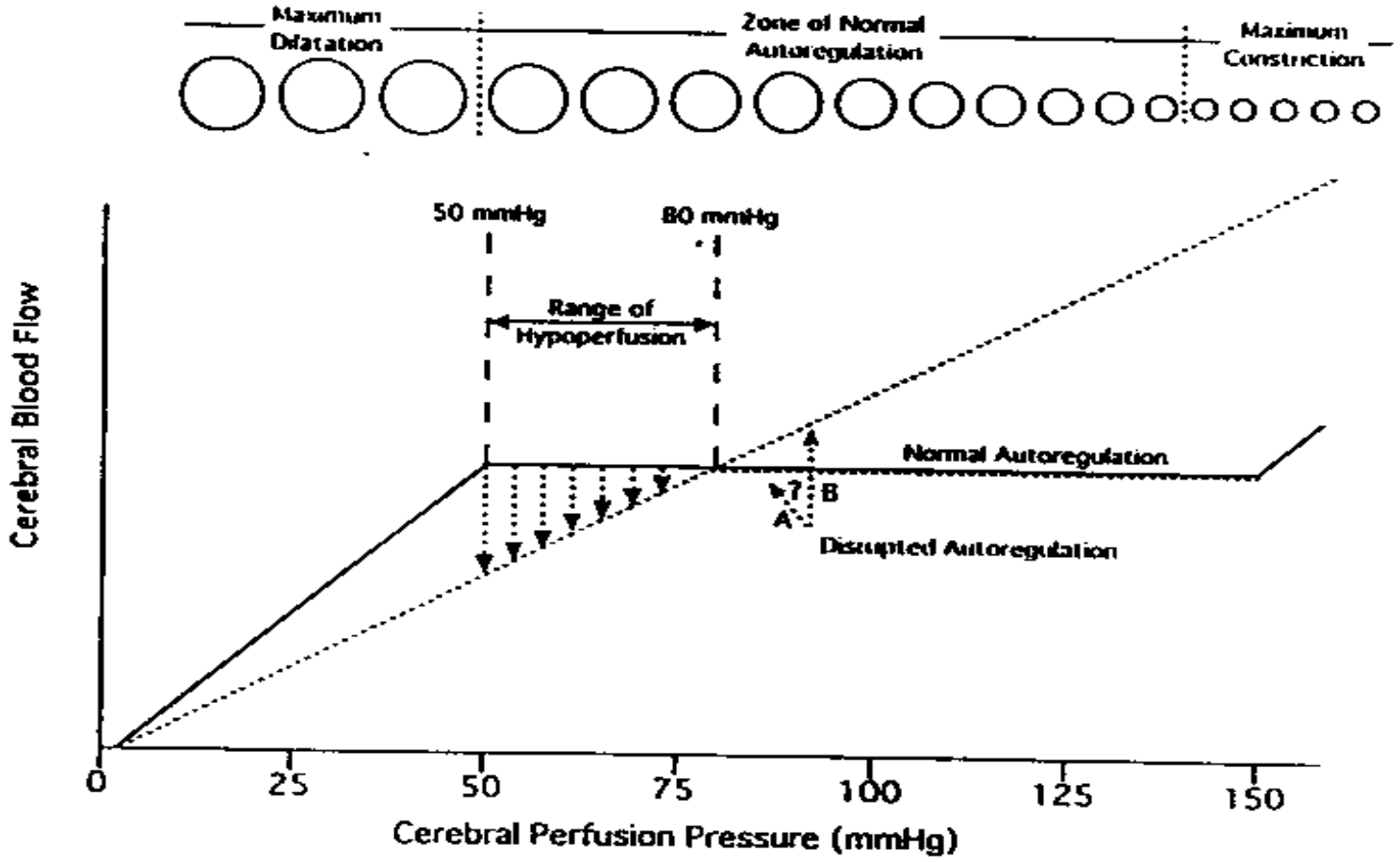
# After making sure all of the above, which case does your patient have?

- CPP optimized:
  - MAP 100, ICP 35, and CPP 65
  - You can relax and think about the etiologies for ICP elevation and consider therapies

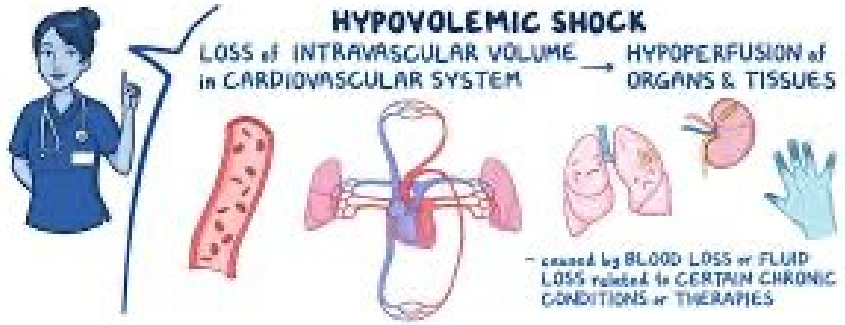
- CPP not optimized:
  - MAP 60, ICP 35, and CPP 25
  - You **SHOULD NOT** relax
  - What should you do immediately?

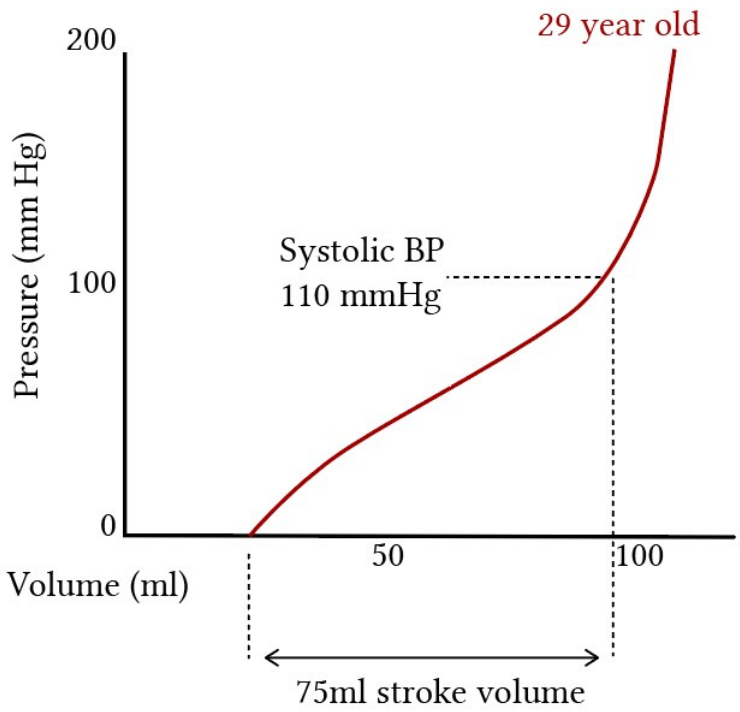
- So before you say “give mannitol”, ASK WHAT THE BLOOD PRESSURE IS

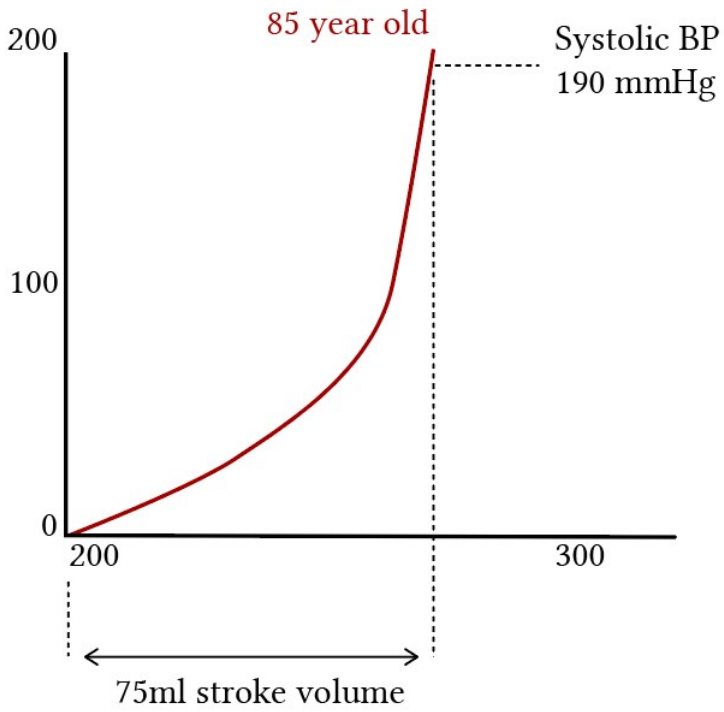
# CPP, CBP, and Vasoreactivity



# Intravascular volume



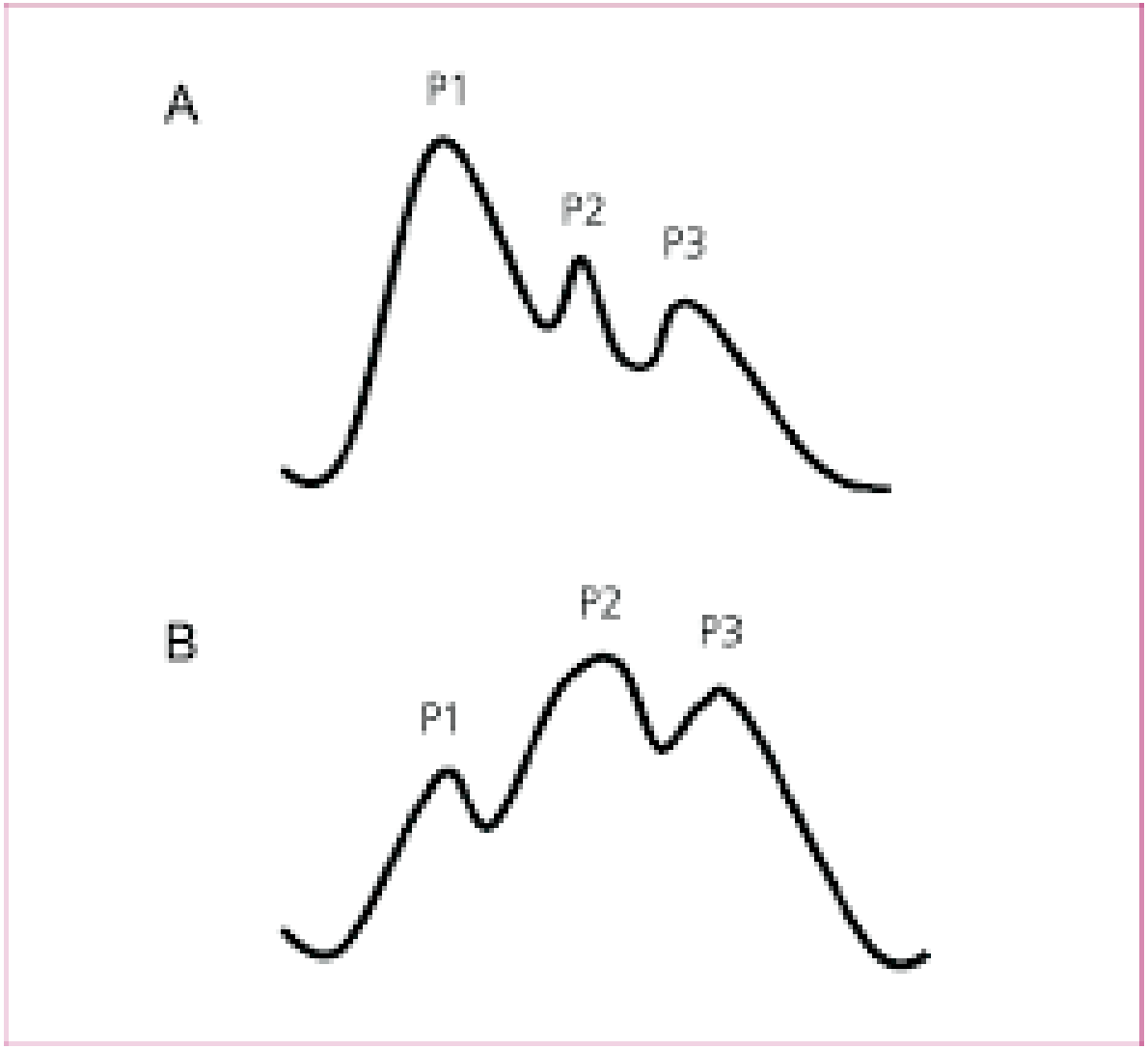

29 year old
200
100
0
Pressure (mm Hg)
Systolic BP
110 mmHg
50
100
Volume (ml)
75ml stroke volume


85 year old
Systolic BP
190 mmHg
200
100
0
200
300
75ml stroke volume

- Do not use pressor if hypovolemic
- Make the tank full and then press

- BRAIN COMPLIANCE

# ICP waveforms



# ORDERING CT HEAD….

- Don’t order CT head/MRI is waveform indicates poor compliance

- ICP may be ok now but may shoot up when you put the head down

# OK, CPP is ok

- OPTIMIZE SEDATION (prefer short acting)
  - Propofol
  - Fentanyl
  - Precedex
  - Ketamine
  - versed

# Management Strategies for Intracranial Pressure Crises in Subarachnoid Hemorrhage

- N Ravishankar, R Nuomman, M El-Hanem, V Thulasi, N Dangayach, K Lee, F Al-Mufti
- J ICM, 2018

# Sodium Bicarbonate


Hypertonic saline (3%, 7%, 23.4%) can lead to hyperchloremic metabolic acidosis

Neurocrit care publication 2010, N=7 with severe TBI

A single dose 8.4% Sodium bicarbonate lowers ICP in TBI

Mean ICP 28.5mmHg→10.3mmHg ($P<0.01$)

pH did go up 7.45→7.5

# Sodium Bicarbonate

- Raises the sodium

8.4% 50meq/50mL
(1meq/mL) inject the
Entire 50mL (50cc) via IV
Over 1-2 minutes


1. Serum sodium 140→142-143
2. Repeat lab 6h and then inject 50mL
   143→145

# Hypothermia

- may reduce ICP in SAH, TBI and even in malignant edema due to MCA infarcts

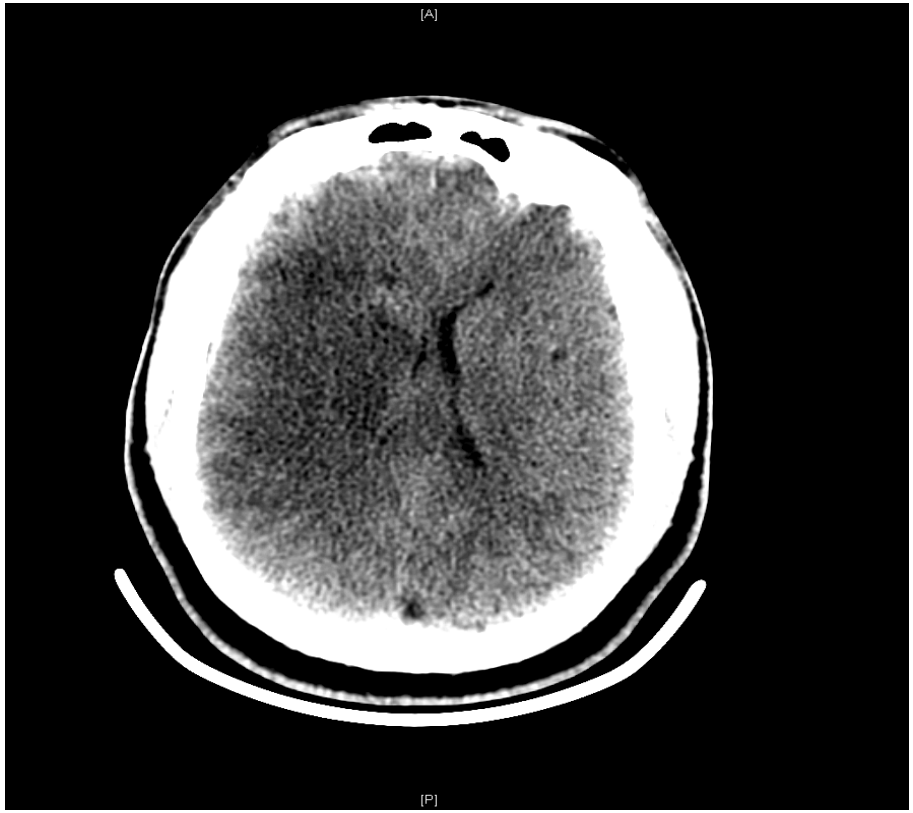
# 2012 Brain Inj

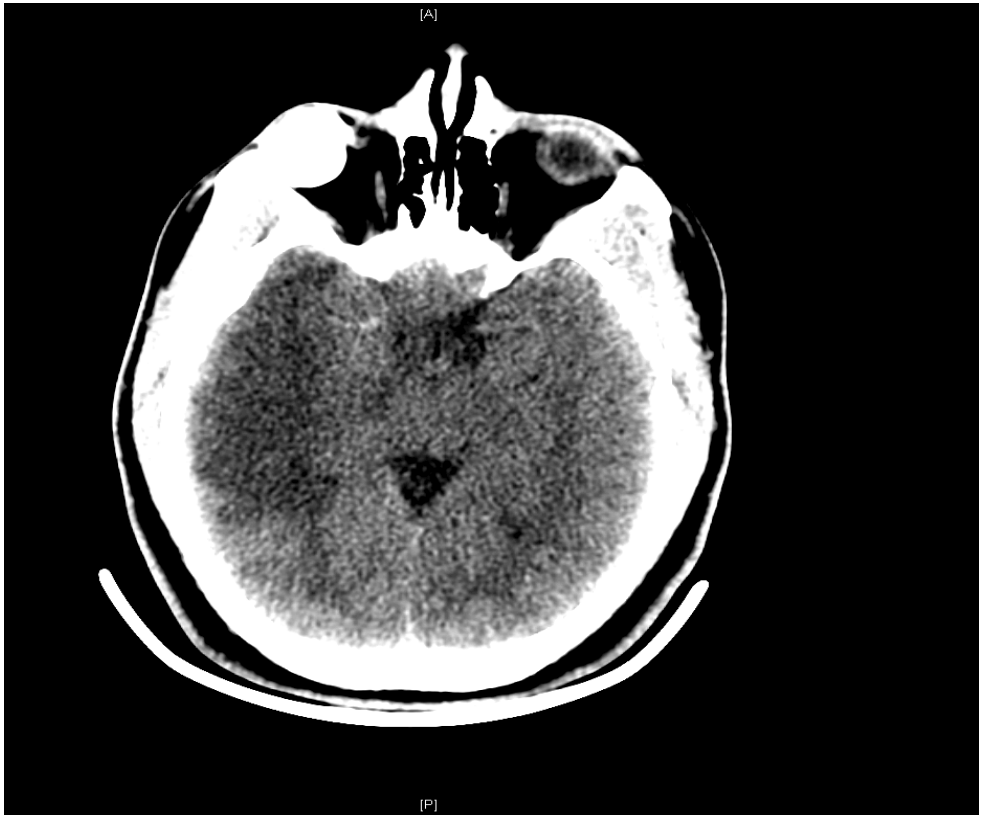
- Therapeutic Hypothermia for the Management of ICP in severe TBI
- Review of 13 RCT and 5 observational studies
- 33-35C lowered ICP significantly in all of the patients

# 27 year old with malignant R MCA infarct

- Somnolent but arousable
- Left hemiplegic
- R forced gaze deviation

- Would you do hemicraniectomy? It is now 30 hours out


[A]
[P]


[A]
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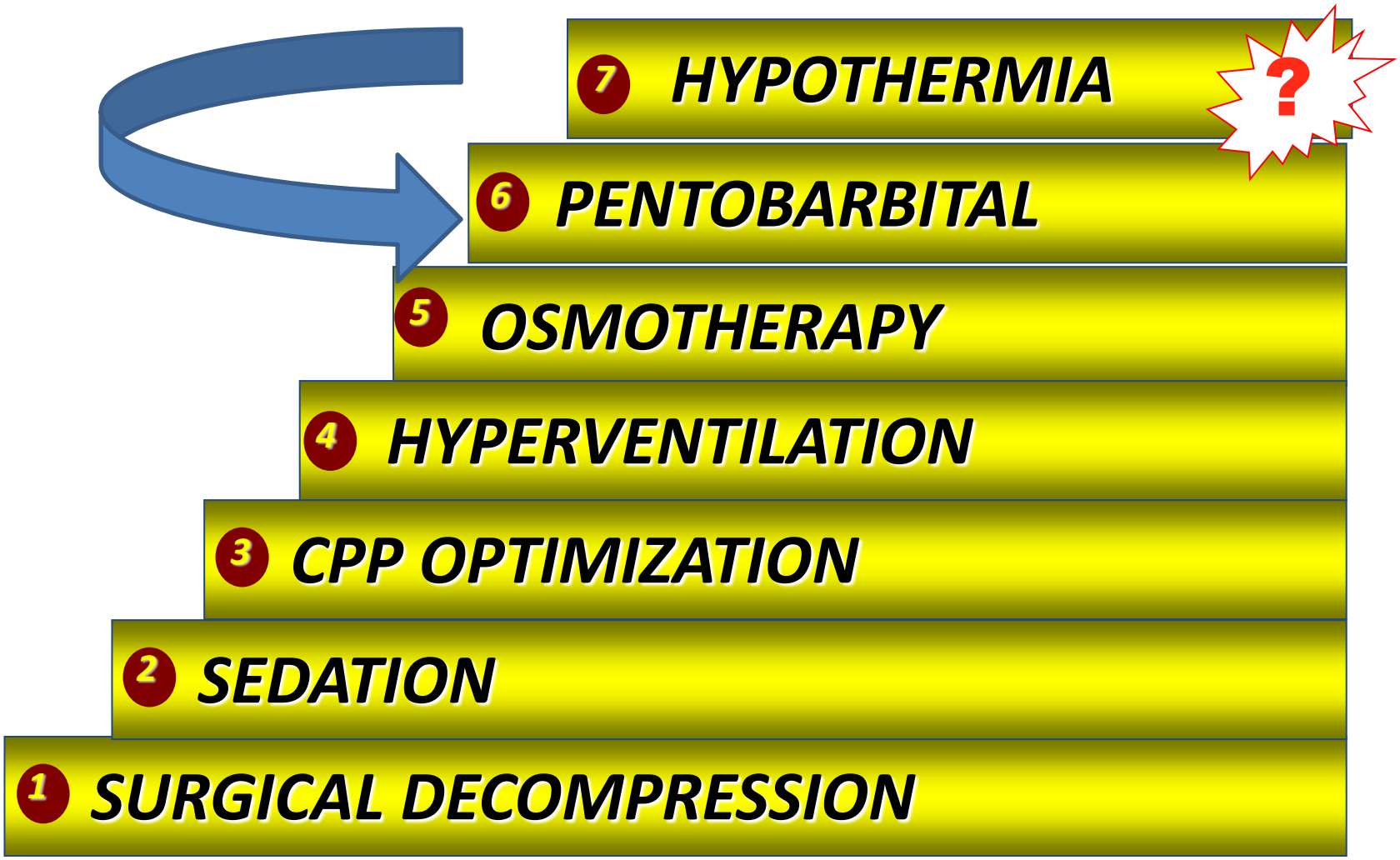
# Well, I didn’t

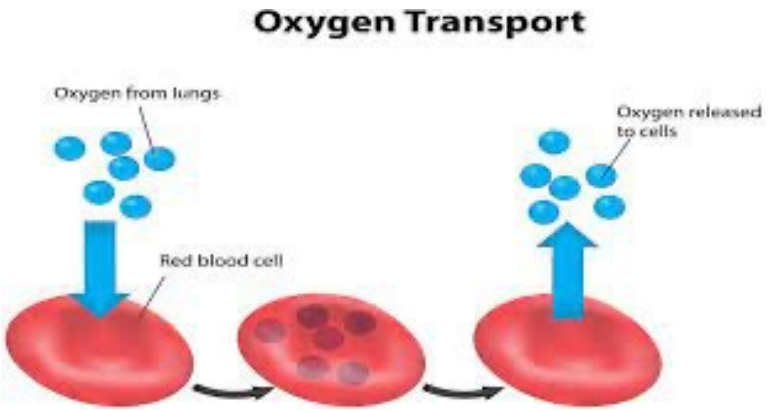
- Hypertonic saline: Na target 150
- Mild hypothermia: Temp target 36C

- He did not herniate!

# Stepwise Protocol for Raised ICP



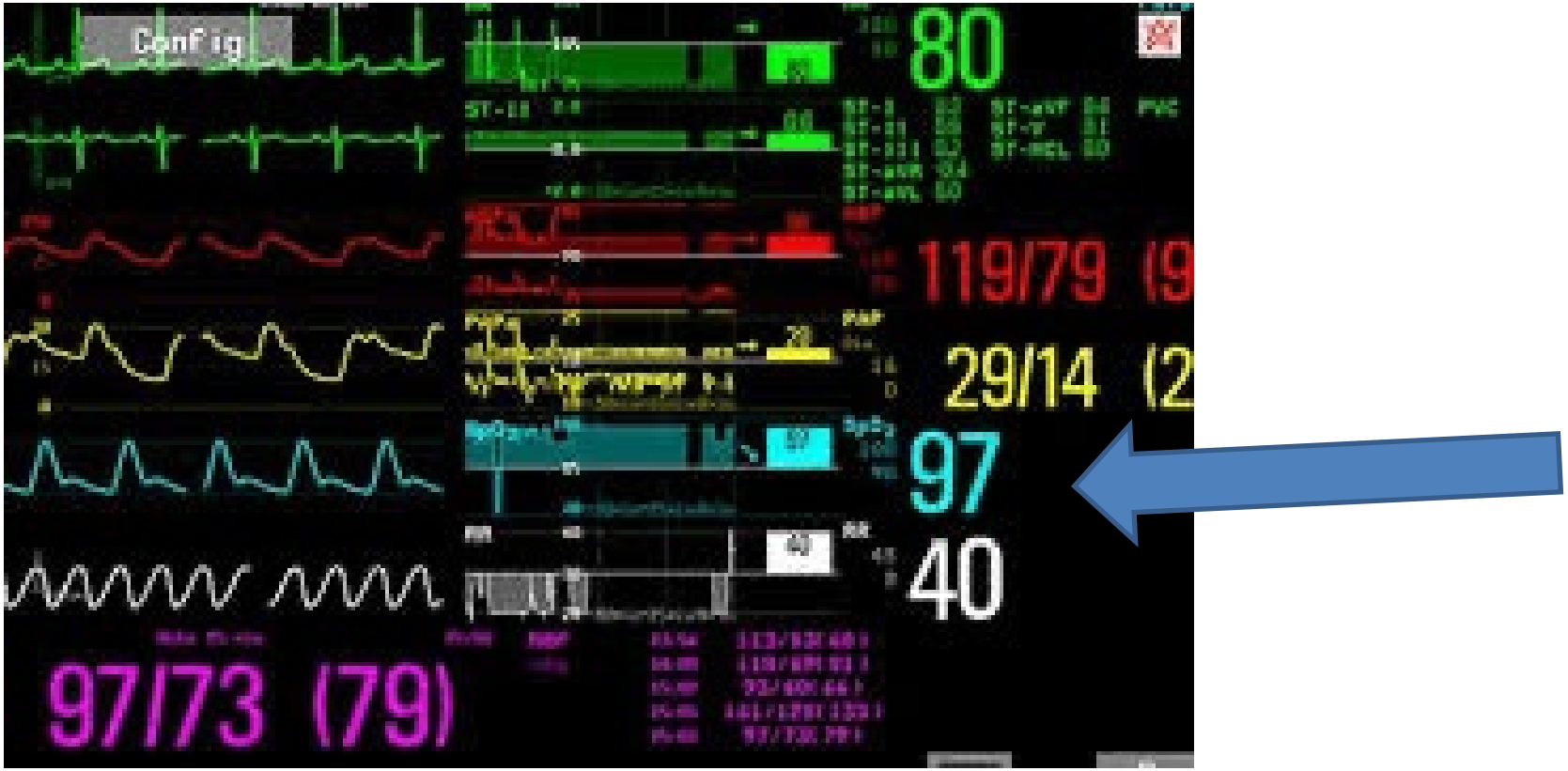
- Oxygenation



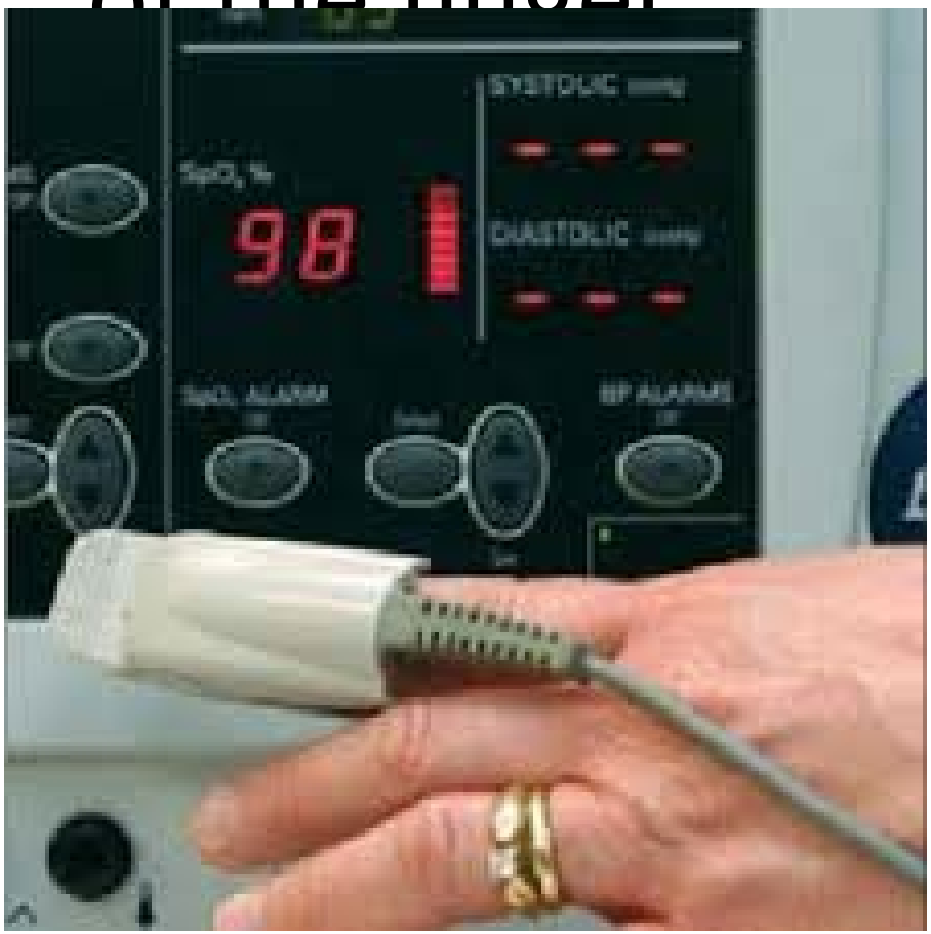
- Brain needs oxygen: Normally we can talk to people, do neuro exam..
- Contused brain needs oxygen: Severe TBIs- they don’t have good exams-

- HOW DO WE KNOW THE BRAIN IS GETTING ENOUGH O2?

# Well, we can look at the monitor and say: “Oxygen saturation is 97%”



# Well, that's the oxygen saturation of the finger



# Is this ok?

- BP = 120/60mmHg
- HR = 78/min sinus
- O2 saturation = 98% at FiO2 40=%
- ICP = 15mmHg

- **PbtO2 = 5mmHg….. I would say it is NOT ok**

# What is it?

- LICOX Brain tissue monitoring: Continuous measurement of brain oxygen partial pressure (PbtO2) and intracranial temperature

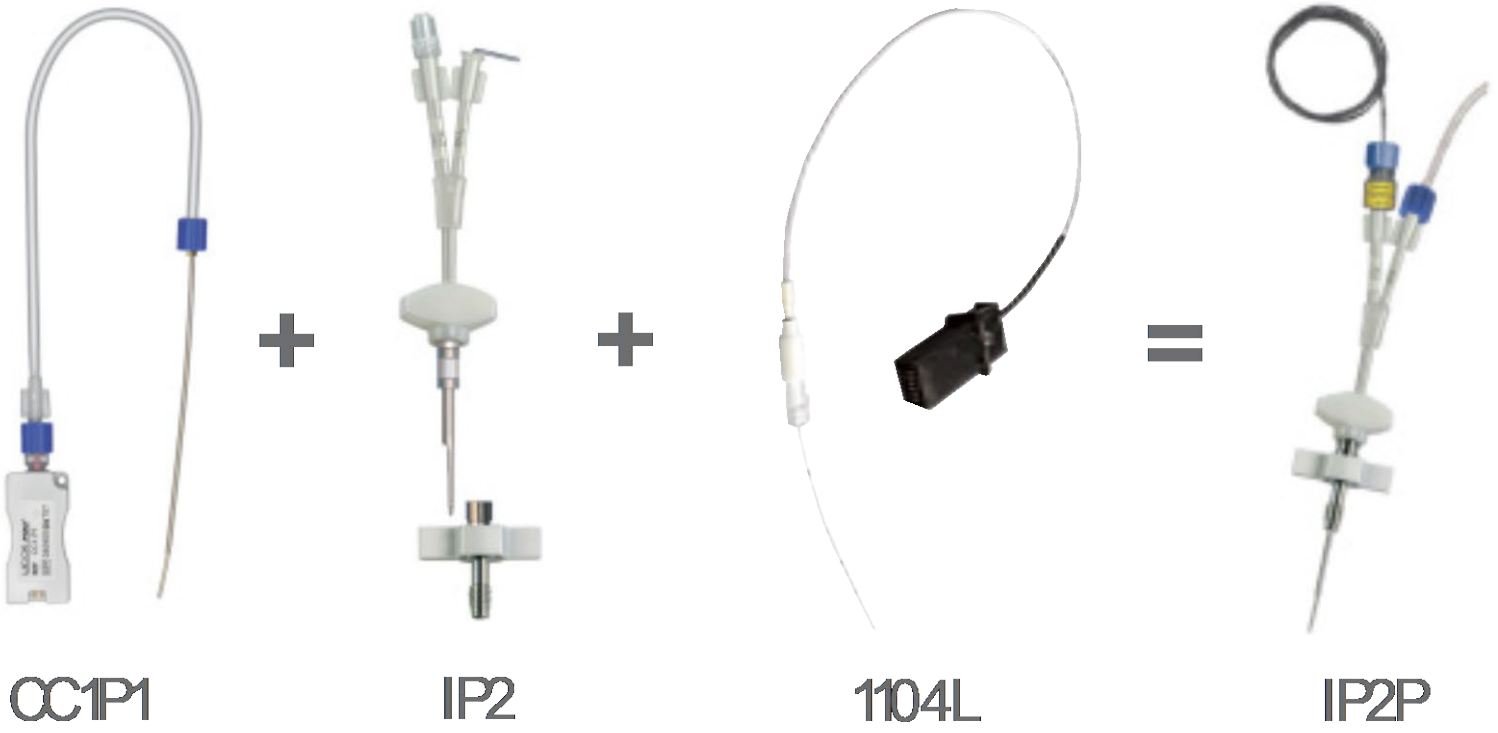
- IM3STEU: Bolted, or IT2EU: Tunneled


LCXO2


OR

IT2EU

# Would use ICP and PbtO2 together




PbtO2+temp  2 lumens  ICP camino  ICP, Pbt2, temp

# EVIDENCE

- No level I or II recommendation for advanced monitoring
- Only Class III evidence for reducing mortality and better outcomes for AVDO2 monitoring
- Class 2 study: Martini 2009 PbtO2+ICP (N=503)v. ICP only (N=123): retrospective observational showed how PtO2 monitoring and treatment group actually did worse (bias: PbtO2 group was the sicker group, but after adjustment, mortality still did not get better
- Class III studies

  6 studies, all mixed and inconsistent results

# Brain tissue oxygen monitoring and management in severe traumatic brain injury (BOOST-II): A phase II Randomized trial

- Crit Care Med 2017 Nov;45(11): 1907-1914
- Randomized prospective 10 ICUs in USA
- N=119 severe TBI
- Randomized to: treatment based on ICP+PbtO2 vs ICP alone
- “Trend” towards lower mortality and better outcomes in ICP+PbtO2 group

# Just because there is no evidence, does that mean we can't do anything?

- Actually, we need to do more if patients are really sick
- Often, we need better judgment than poorly designed studies or lack of "evidence"
- We did mechanical thrombectomy for many decades before it was proven by class I studies
- It makes sense to optimize (as opposed to depriving) brain oxygenation for injured brains

- Brain oxygenation depends on
  1. O2 content in the arterial blood

     (Hg, Pa/SaO2)
  2. Cerebral blood flow

     (blood volume, cardiac output)
  3. Cerebral metabolic activity

     (Oxygen demand/OEF)

# Delivery of oxygen

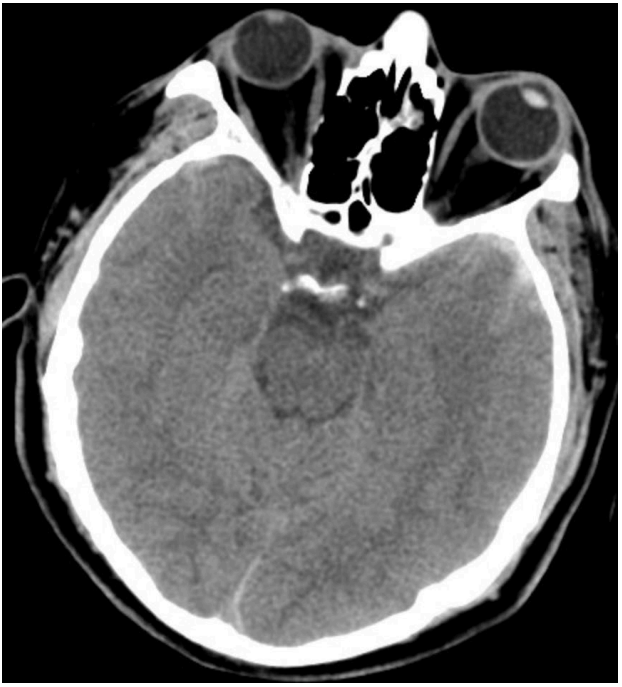
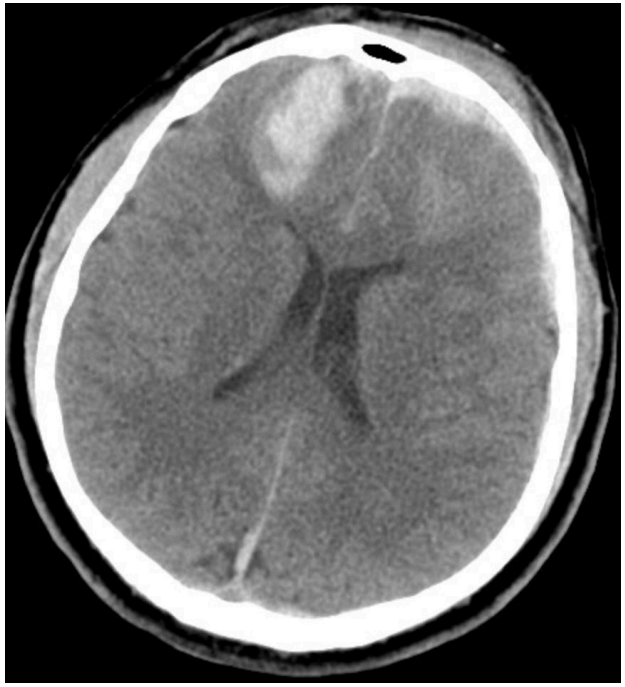
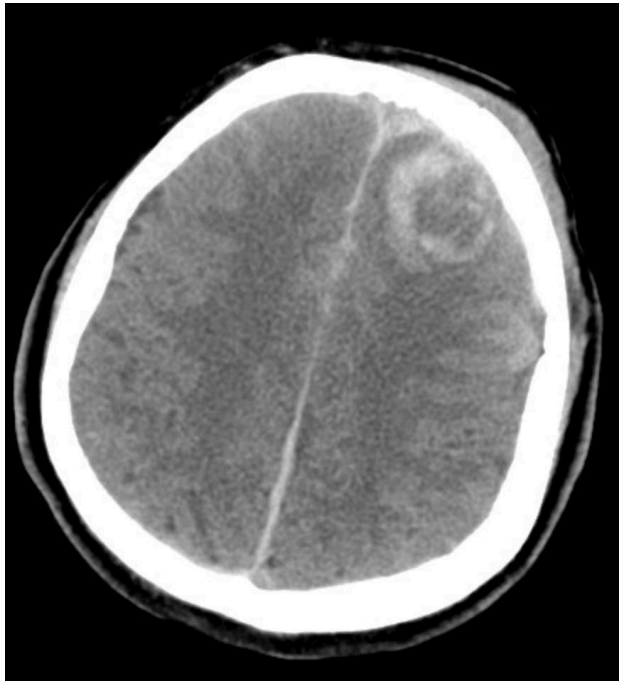
$$DO2 = [1.39 \times Hb \times SaO_2 + (0.003 \times PaO_2)] \times CO$$

36M no PMH presented s/p assault while intoxicated with EtOH with +LOC. Intubated in field for agitation and airway protection.

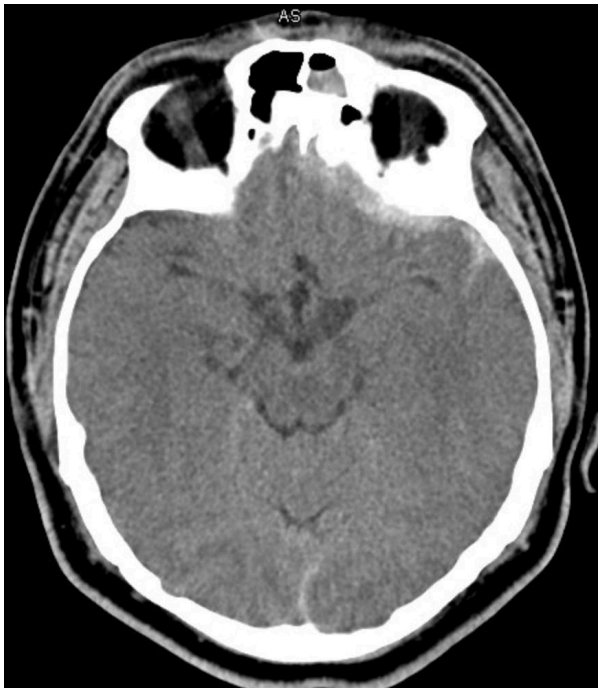
Initial exam: Intubated, EO to noxious, no commands, PERRL, MAEx4 purposefully

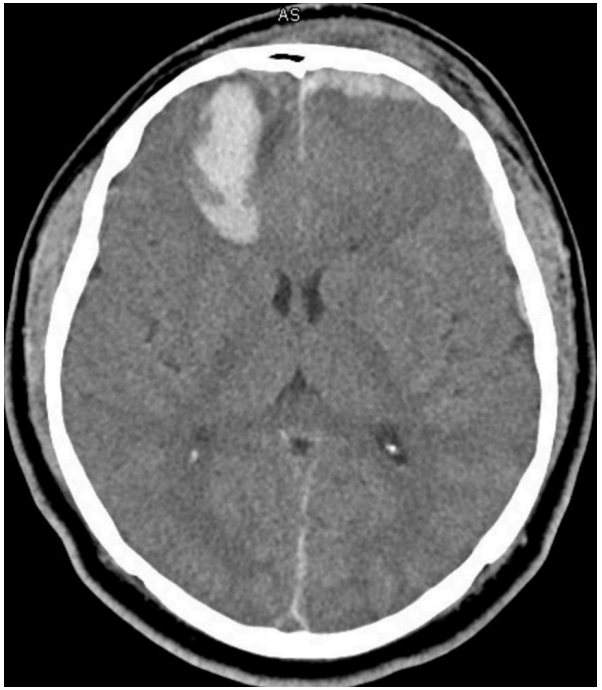
Initial CT was notable for bifrontal contusions.

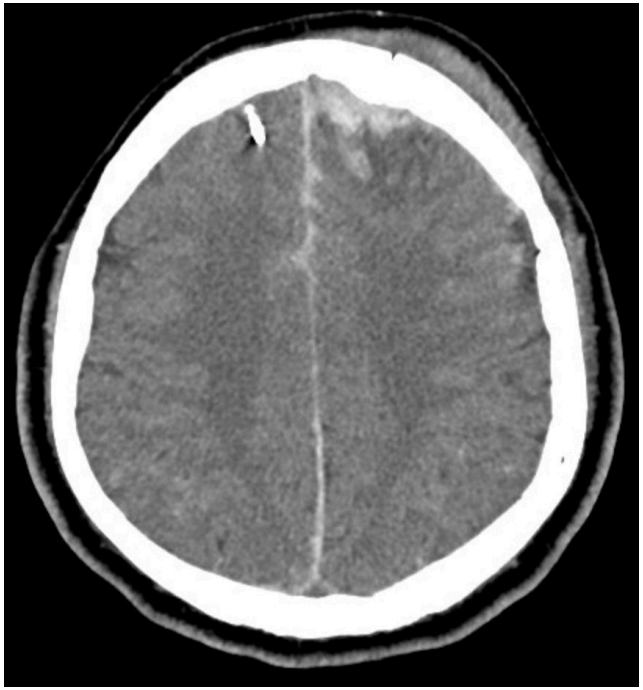
# Initial CT

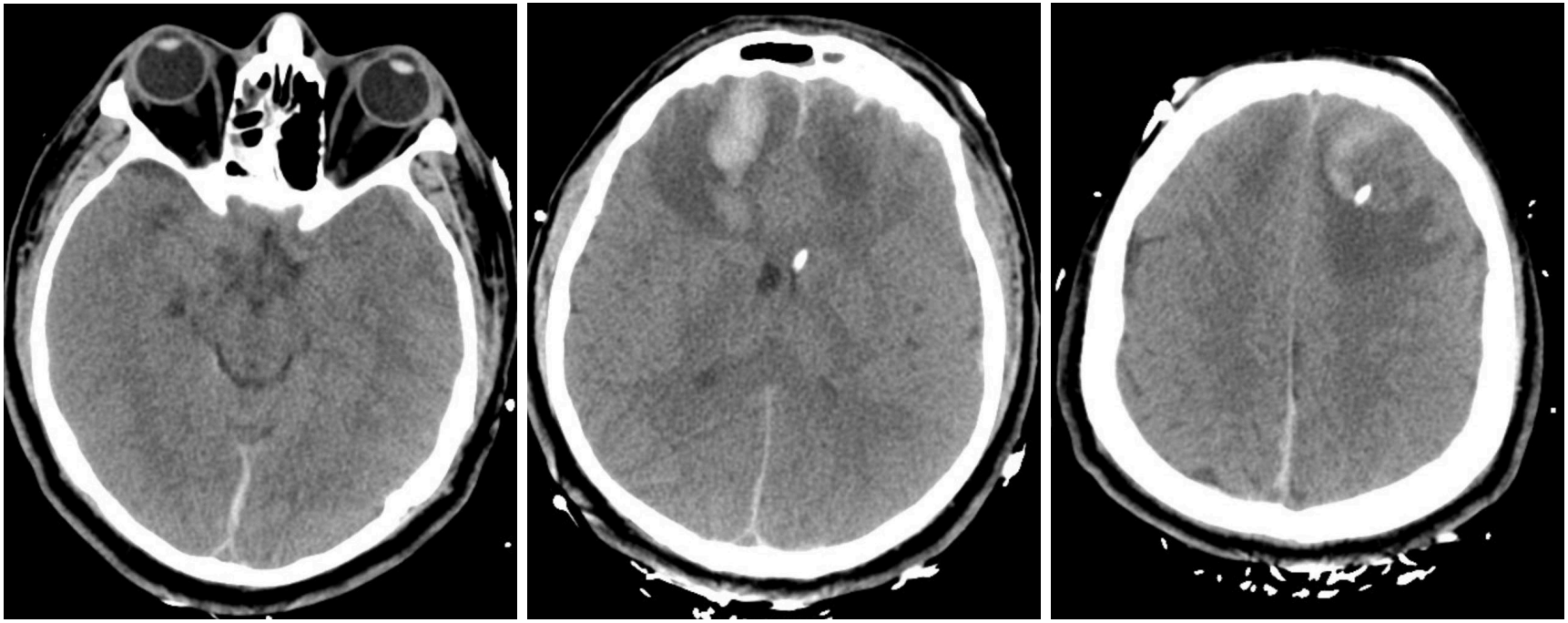
# CT s/p ICP Monitor (Post-Trauma Day #1)



# DAY #7: NOW Contusion PLUS **THE EDEMA**



# ICP bolt, EVD, Sedation, Na 155, Temp 36

ICP is still high
Comatose
Lots of edema
Pentobarb coma

What next?

# ICP+PbtO2

ICP = 44 mmHg,

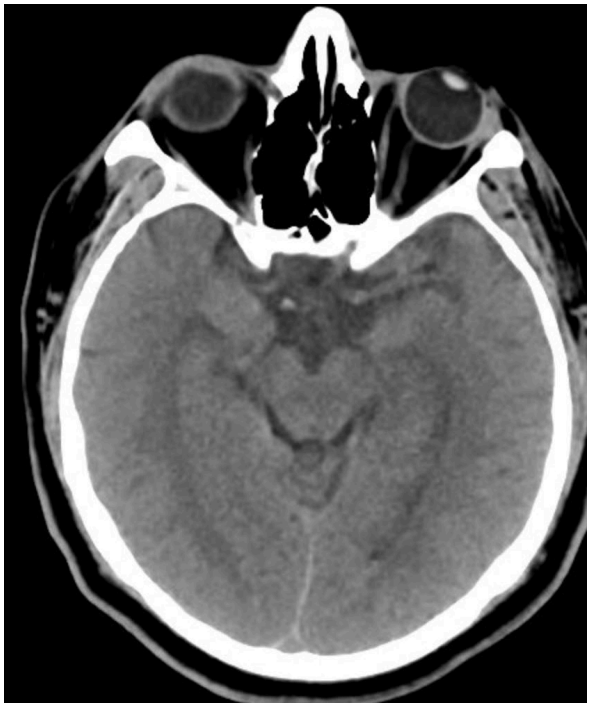
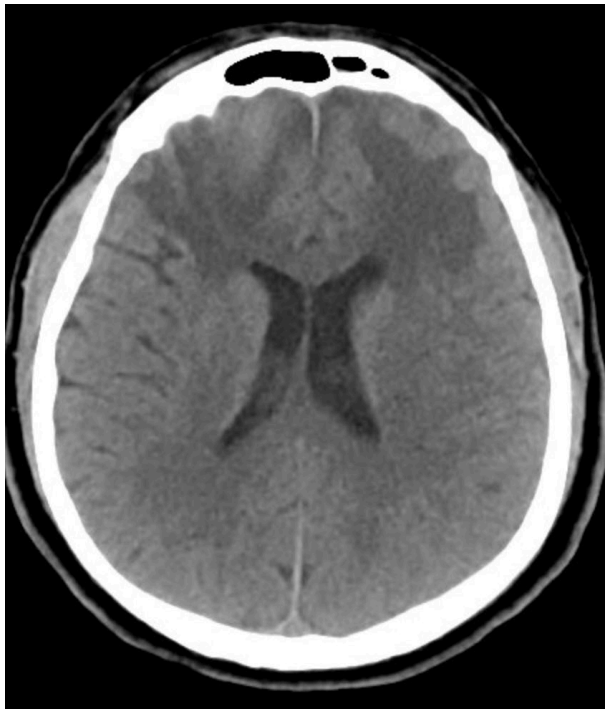
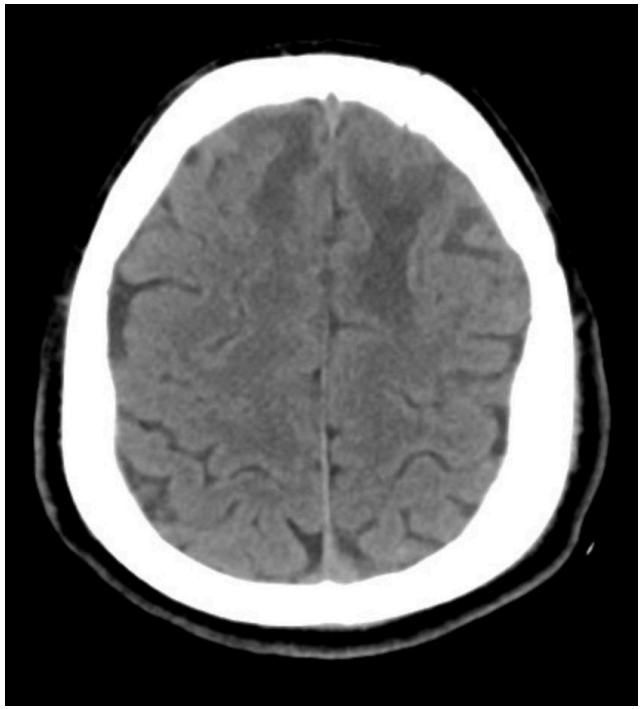
PtO2 = 2 mmHg

- MAP=90

- (MAP-ICP=CPP)
- (90-44= 46)

- FiO2, MAP (thus CPP) were increased, and PtO2 climbed to 20-25 range
- Licox removed after 5 days

# Final CT (PTD #21)

# Prognostication

Mild vs Severe TBI….. Prognosis?

Mild means good, and severe means bad?

- **Withdrawal of support in intracerebral hemorrhage may lead to self-fulfilling prophecies**
- K J Becker et al. Neurology 2001

- "Attitudes" about futility of care were examined among members of the departments of neurology and neurosurgery through a written survey and case presentations.

# Attitudes

- **Results:**
- N =87 supratentorial ICH
- mortality =  34.5%
- Mortality was 66.7% (18/27) in patients with Glasgow Coma Score < or = 8 and ICH volume > 60 cm(3).
- Medical support was withdrawn in 76.7% (23/30) of patients who died.
- Survey results suggested that practitioners tend to be overly pessimistic in prognosticating outcome based upon data available at the time of presentation.

# Conclusions

- **The most important prognostic variable in determining outcome after ICH is the level of medical support provided.**

- Our data show that individual patients in traditionally "poor outcome" categories can have a reasonable neurologic outcome when treated aggressively.

Neurology 2001 Mar 27;56(6):766-72.

- Do you REALLY know the future?
  - Good outcome vs. Bad outcome

# Do we really know the stock future?
# Or House prices of the Gangnam?

# Prognostic value of day-of-injury plasma GFAP and UCH-L1 concentrations for predicting functional recovery after traumatic brain injury in patients from the US TRACK-TBI cohort: an observational cohort study

Frederick K Korley [1], Sonia Jain [2], Xiaoying Sun [2], Ava M Puccio [3], John K Yue [4], Raquel C Gardner [5], Kevin K W Wang [6], David O Okonkwo [3], Esther L Yuh [7], Pratik Mukherjee [7], Lindsay D Nelson [8], Sabrina R Taylor [9], Amy J Markowitz [4], Ramon Diaz-Arrastia [10], Geoffrey T Manley [4]; TRACK-TBI Study Investigators

THE LANCET

The prognostic value of **glial fibrillary acidic protein (GFAP)** and **ubiquitin C-terminal hydrolase L1 (UCH-L1)** as day-of-injury predictors

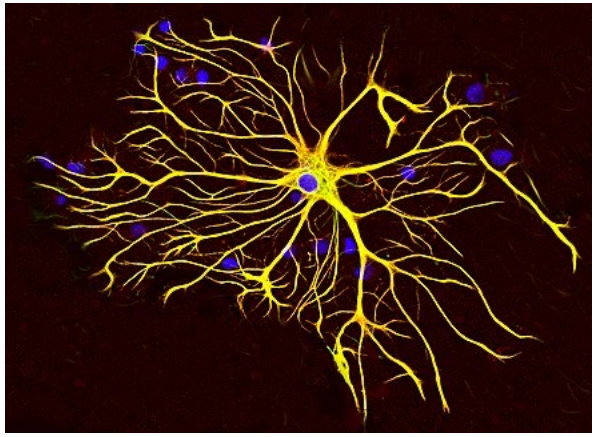
GFAP is a protein found in glial cells and UCH-L1 is found in neurons, and these biomarkers have been cleared to aid in decision making regarding **whether brain CT should be performed** after TBI

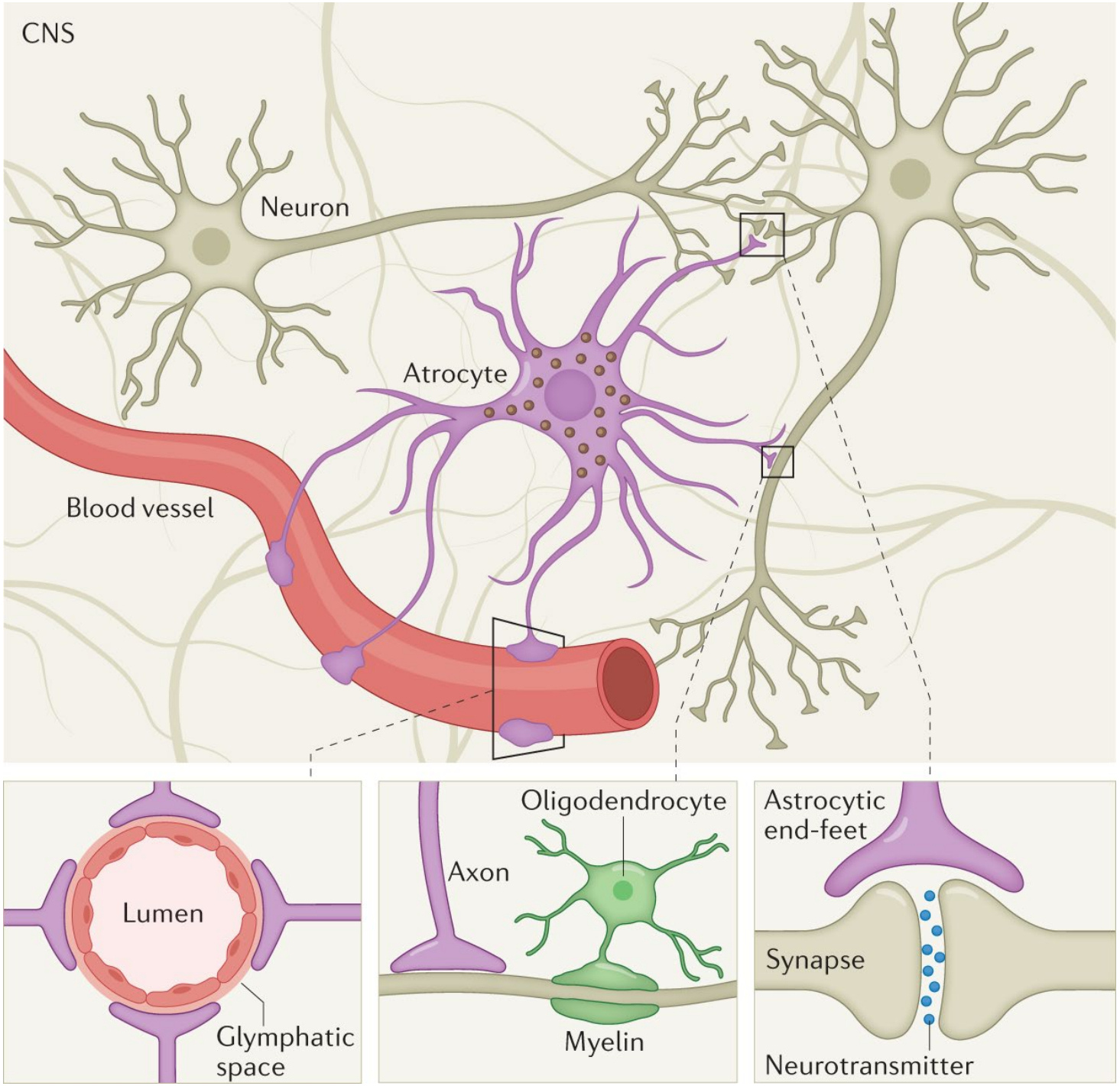
Lancet 2022 Sep;21(9):803-813.

THE LANCET

# Glial Fibrillary Acidic Protein (GFAP)

- Type III intermediate filament protein that is expressed by many cells in CNS (eg. Astrocytes, ependymal cells)
- Blood biomarker: elevated in acute injuries

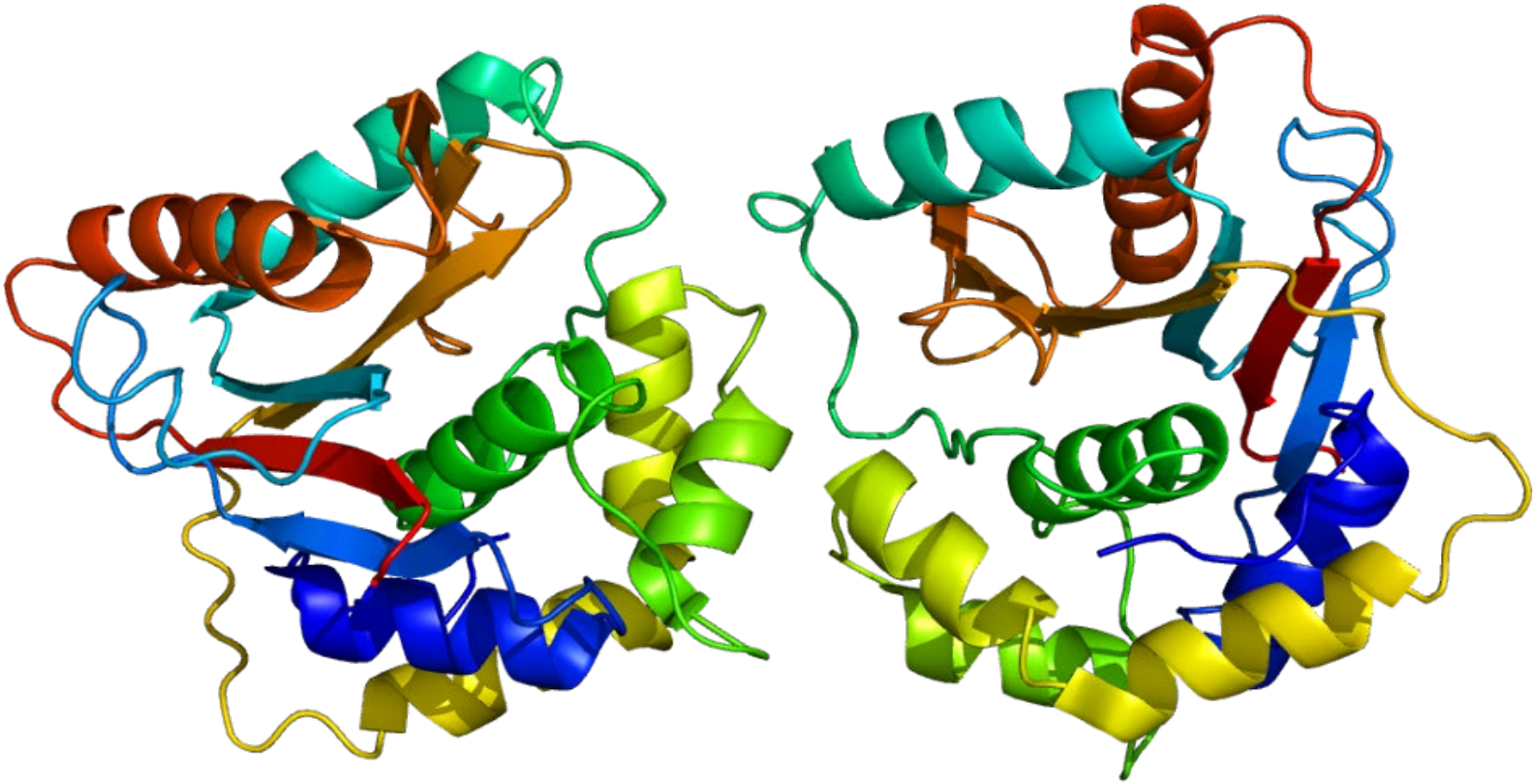



CNS
Neuron
Atrocyte
Blood vessel
Lumen
Glymphatic space
Oligodendrocyte
Axon
Myelin
Astrocytic end-feet
Synapse
Neurotransmitter

# Ubiquitin C-terminal Hydrolase L1 (UCH-L1)

- Hydrolyze small C terminal ubiquitin to generate ubiquitin monomer
- Abundantly present in all neurons
- Known to increase in cancer
- Interact with alpha-synuclein (Parkinson's)

# UCH-L1



- **Methods:**
- Traumatic Brain Injury (TRACK-TBI) observational cohort study.
- Age: 17-90 years with TBI at 18 level 1 trauma centers in USA
- **Day-of-injury plasma level of GFAP and UCH-L1**
- 6-month outcome

- **N = 2,552 patients**
- **2014-2018**
- **1696 participants data at baseline and at 6mo**
- 120 (7·1%) died (GOSE-TBI=1),
- 235 (13·9%) had an unfavorable outcome (ie, GOSE-TBI ≤4),
- 1,135 (66·9%) had incomplete recovery (ie, GOSE-TBI <8),
- 561 (33·1%) recovered fully (ie, GOSE-TBI=8)

- The area under the curve (AUC) of GFAP for predicting
  - death at 6 months was 0·87 (95% CI 0·83-0·91),
  - unfavorable outcome was 0·86 (0·83-0·89),
  - incomplete recovery was 0·62 (0·59-0·64).

- The corresponding AUCs for UCH-L1
  - 0·89 (95% CI 0·86-0·92) for predicting death
  - 0·86 (0·84-0·89) for unfavorable outcome,
  - 0·61 (0·59-0·64) for incomplete recovery at 6 months.
- **AUCs were higher for GCS 3-12 than GCS 13-15.**

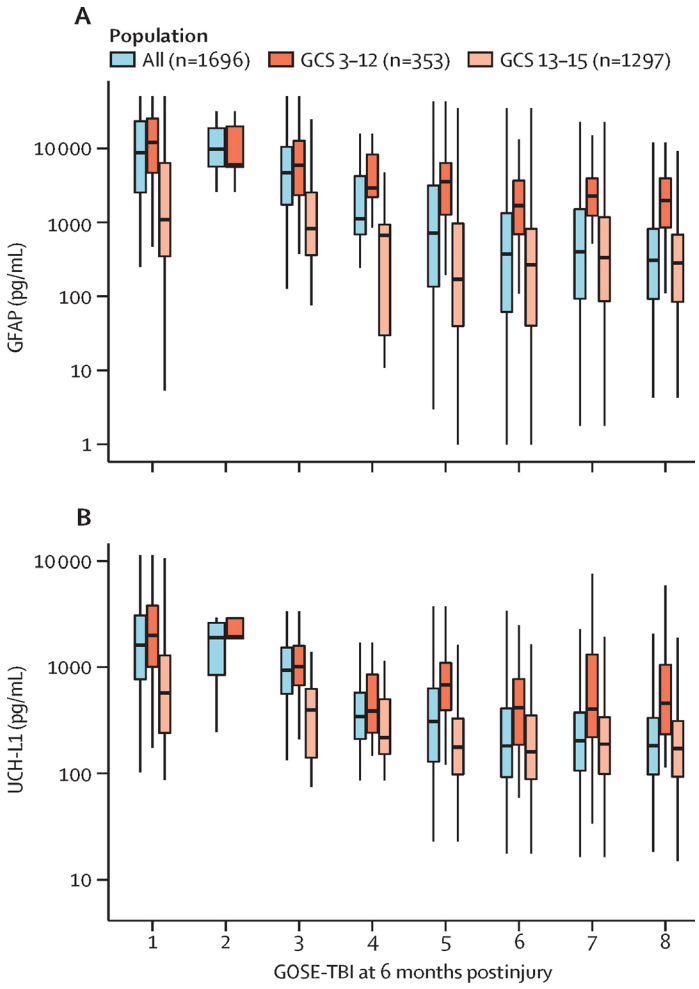
- GCS score of 3-12 (n=353): adding GFAP and UCH-L1 (alone or combined) **significantly** increased their AUCs for predicting death (AUC range 0·90-0·94) and unfavorable outcome (AUC range 0·83-0·89).
- GCS score of 13-15 (n=1297): adding GFAP and UCH-L1 to the UPFRONT study model **modestly** increased the AUC for predicting incomplete recovery (AUC range 0·69-0·69, p=0·025).

# Outcome measures

- Glasgow Outcome Scale (GOS): 5
  1. Dead
  2. Vegetative
  3. Severe disability
  4. Moderate disability
  5. Good recovery

- Glasgow Outcome Scale Extended (GOSE):8
  1. Dead
  2. Vegetative
  3. Lower severe disability
  4. Upper severe disability
  5. Lower moderate disability
  6. Upper moderate disability
  7. Lower Good recovery
  8. Upper good recovery

# GFAP and UCH-L1 to 6 months outcome



# Interpretation

- Day-of-injury GFAP and UCH-L1 plasma concentrations have good to excellent prognostic value for predicting death and unfavorable outcome, but not for predicting incomplete recovery at 6 months.
- These biomarkers contribute the most prognostic information for participants presenting with a **GCS score of 3-12.**

- Eur J Trauma Emerg Surg 2022 May 7.
- **The diagnostic and prognostic value of glial fibrillary acidic protein in traumatic brain injury: a systematic review and meta-analysis**
- Yunlong Pei[1,2], Xiaojia Tang[3], Enpeng Zhang[1,2], Kongye Lu[1], Boming Xia[4], Jun Zhang[5], Yujia Huang[2], HengZhu Zhang[2], Lun Dong[6]

- **Objectives:** prognostic value of glial fibrillary acidic protein (GFAP) for TBI patients.
- **Methods:** The online databases up to May 2021.

# Over 3 thousand patients

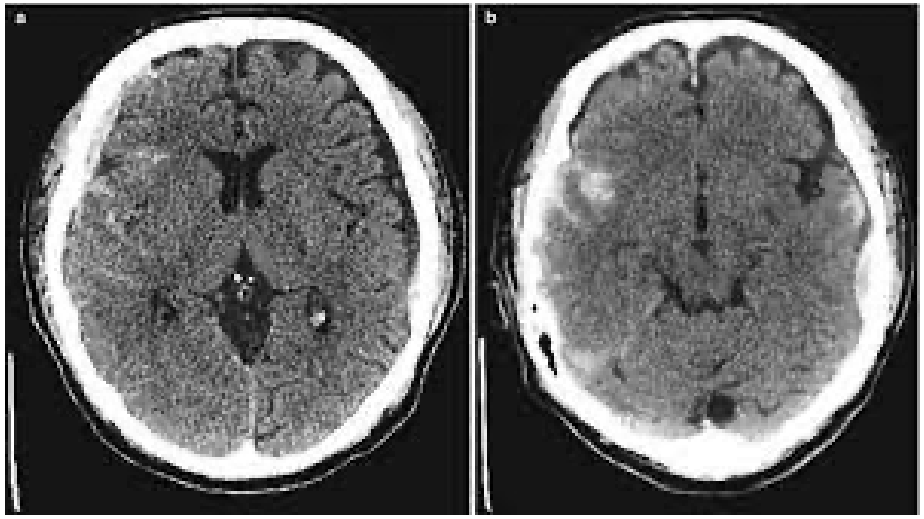
- **Results:**
- 22 studies, N= 3,709 in meta-analysis.
- serum GFAP had a value **in detecting traumatic intracranial lesions** (AUC 0.81; 95% CI 0.77-0.84; $p < 0.00001$).
- The pooled sensitivity and specificity were 0.93 (95% CI 0.81-0.98), and 0.66 (95% 0.53-0.77; $p < 0.00001$)-→ **Highly sensitive, meaning low GFAP→ chances are you don't have any intracranial lesions!**

- Besides, **GFAP exhibited a significant value in predicting mortality** (AUC 0.81; 95% CI 0.77-0.84; $p < 0.00001$), with high sensitivity and specificity

- **Conclusions:** Our meta-analysis indicated that GFAP had diagnostic and prognostic value for TBI patients, especially during the early TBI.

# “Mild” TBI because of GCS of 14

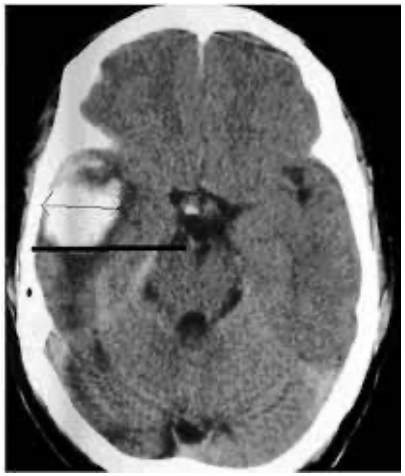
- Maybe it is really “mild” and has good prognosis because CT looks ok



- GFAP = 200 pg/ml

# Same “Mild” TBI with GCS of 14

- This person **may not have the same good prognosis** CT shows bigger contusion



- GFAP = **3,200** pg/dl

- Not all “Mild” or good GCS will have good outcomes

- Not all “severe” or bad GCS will have bad outcomes

# US FDA approves rapid handheld blood test (<15min) for GFAP and UCH-L1 which can predict TBIs better than CT

- A negative test using the handheld device could rule out the requirement of getting a CT scan to test for a TBI, a positive result would mean they should get a CT scan to confirm if it is a TBI and how severe it is so that they can get the clinical care they need.

"Mild TBI because GCS 15"
You need images and biomarkers to be more accurate
Maybe GCS will drop to 8 in 2 hours due to hematoma expansion