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conference

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Emergency Medicine Pharmacotherapy with Resuscitation (EMPoweRx) Conference

Hypertonic Saline vs Mannitol:

A Frequent Debate in the Emergency Department: To Be Salty or Sweet

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- No one in control of the content of this activity has a relevant financial relationship (RFR) with an ineligible company.
  - As defined by the Standards of Integrity and Independence in Accredited Continuing Education definition of ineligible company. All relevant financial relationships have been mitigated prior to the CPE activity.

Learning Objectives

Describe	Describe the pathological processes underlying the formation of cerebral edema
Compare	Compare the available literature supporting the use of hypertonic saline and mannitol in the management of cerebral edema
Identify	Identify important considerations for implementing osmotherapy in the emergency department

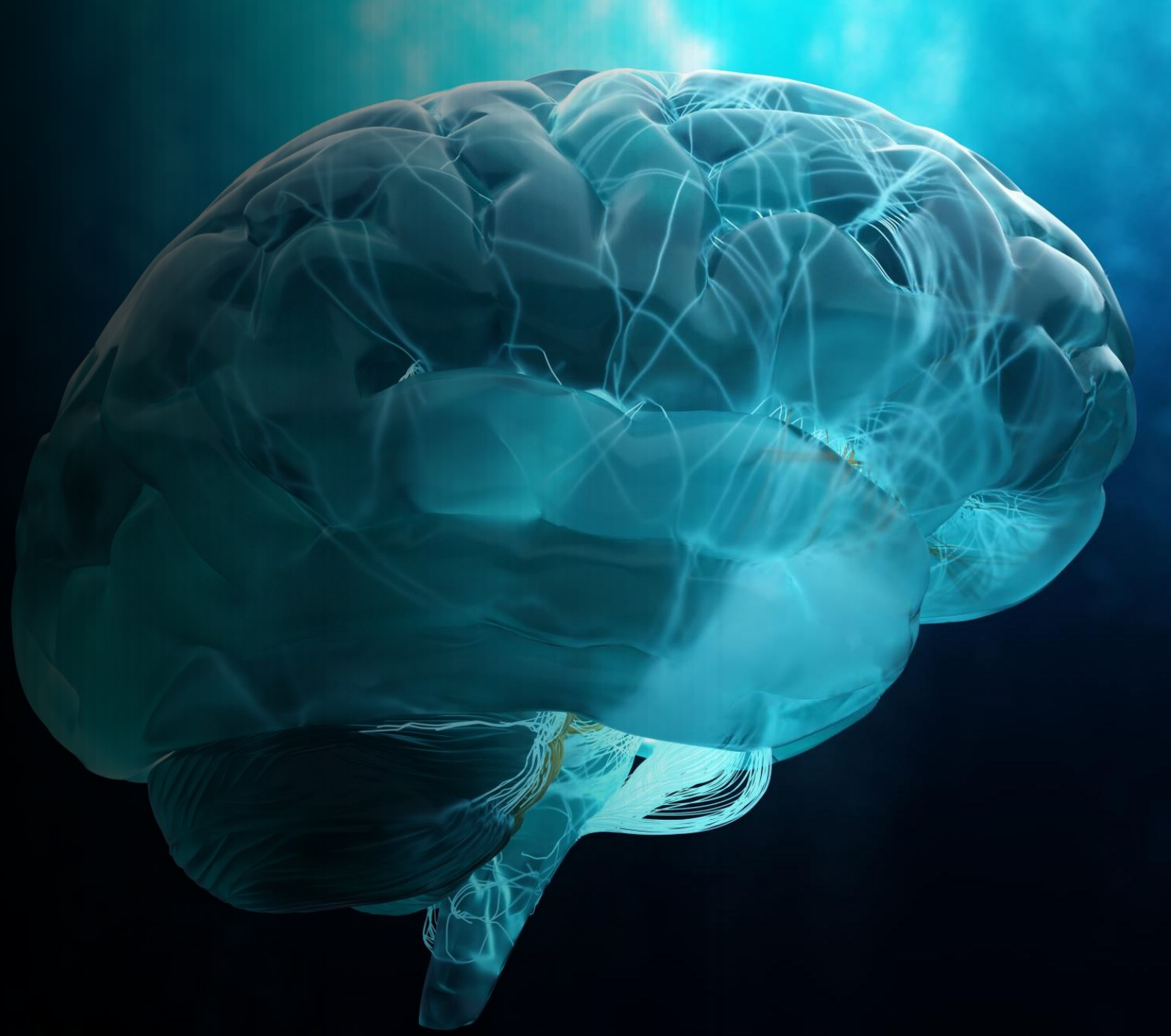
Patient Case: Wade Wilson

- 25-year-old (72 kg) male presents to the ED following a motor-vehicle collision
- Per report, patient was unrestrained and entrapped under the dashboard of the car. Heavy front-end damage was reported.
- EMS attempted intravenous (IV) access en route but were unsuccessful.
- The patient's GCS initially was a 4 in the field but improved to a 9 upon arrival.
- Physical Exam: Laceration/avulsion of the skin to the left temporal area; deformity to the right ankle; agitated, moaning, moving all four extremities but not following commands; right eye is noted to be deviated laterally

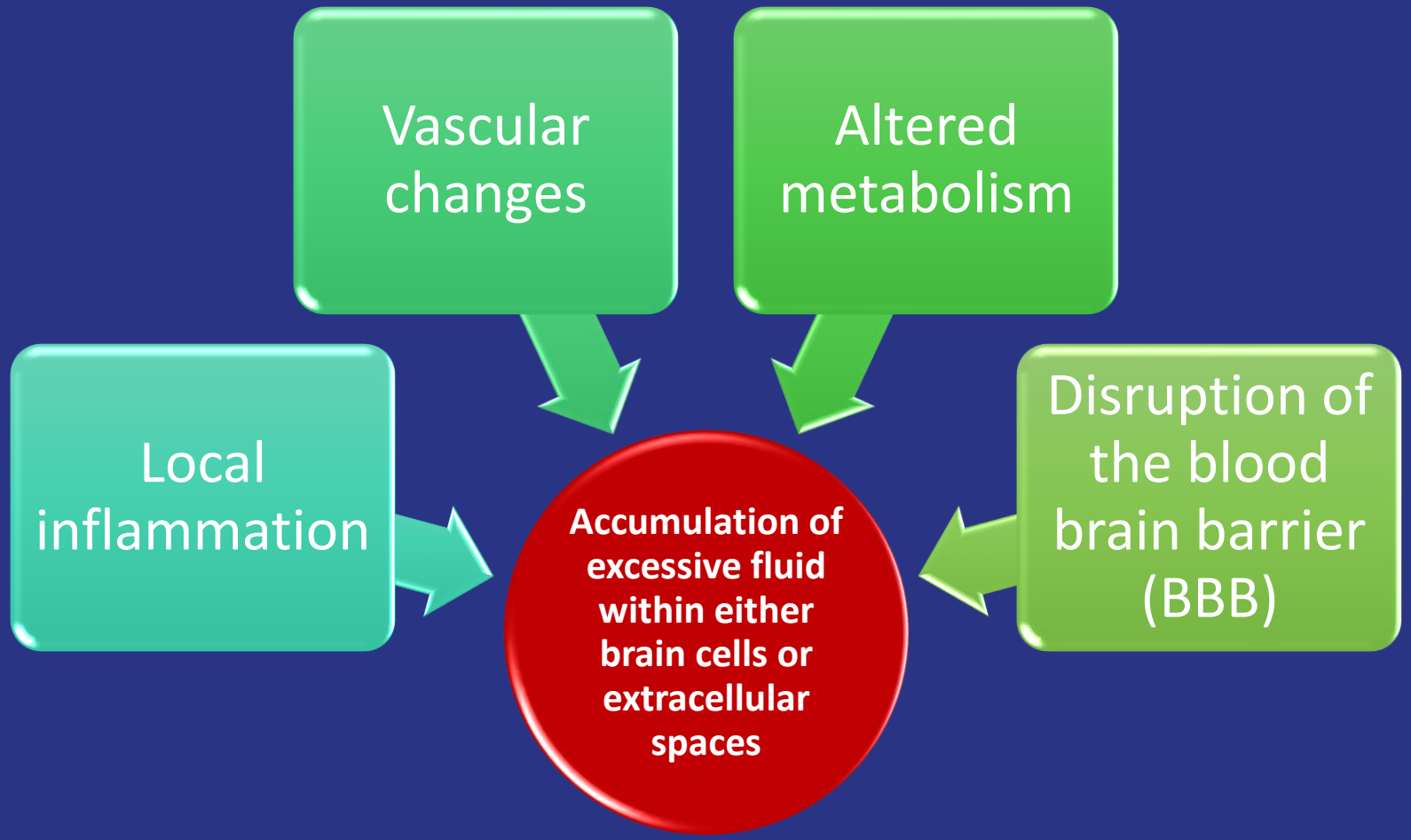
Patient Case: Wade Wilson

- Blood pressure: 90/75 mmHg
- Heart rate: 70 beats/min
- Respiratory rate: 10 breaths/min
- Labs pending intravenous (IV) access

Cerebral Edema

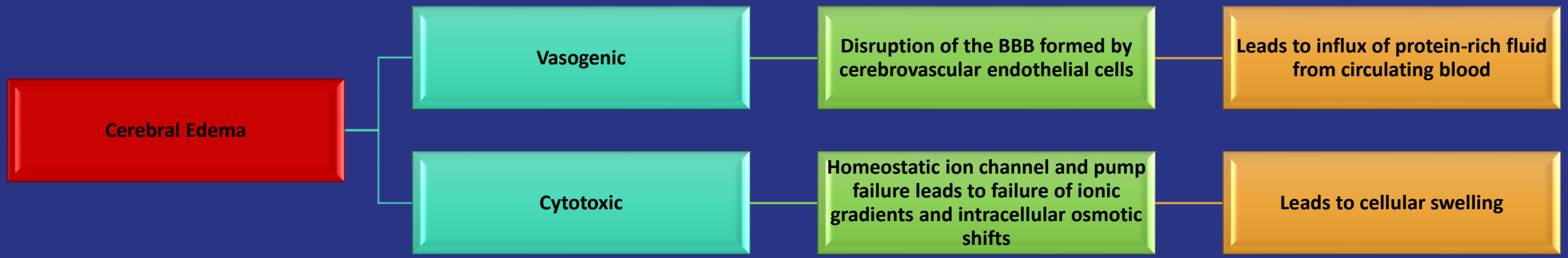


So what the heck is cerebral edema?



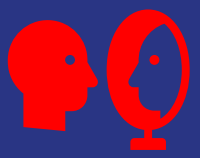
Neurosurg Clin N Am 2016;27:473-488

Types and Pathogenesis of Cerebral Edema



Neurosurg Clin N Am 2016;27:473-488

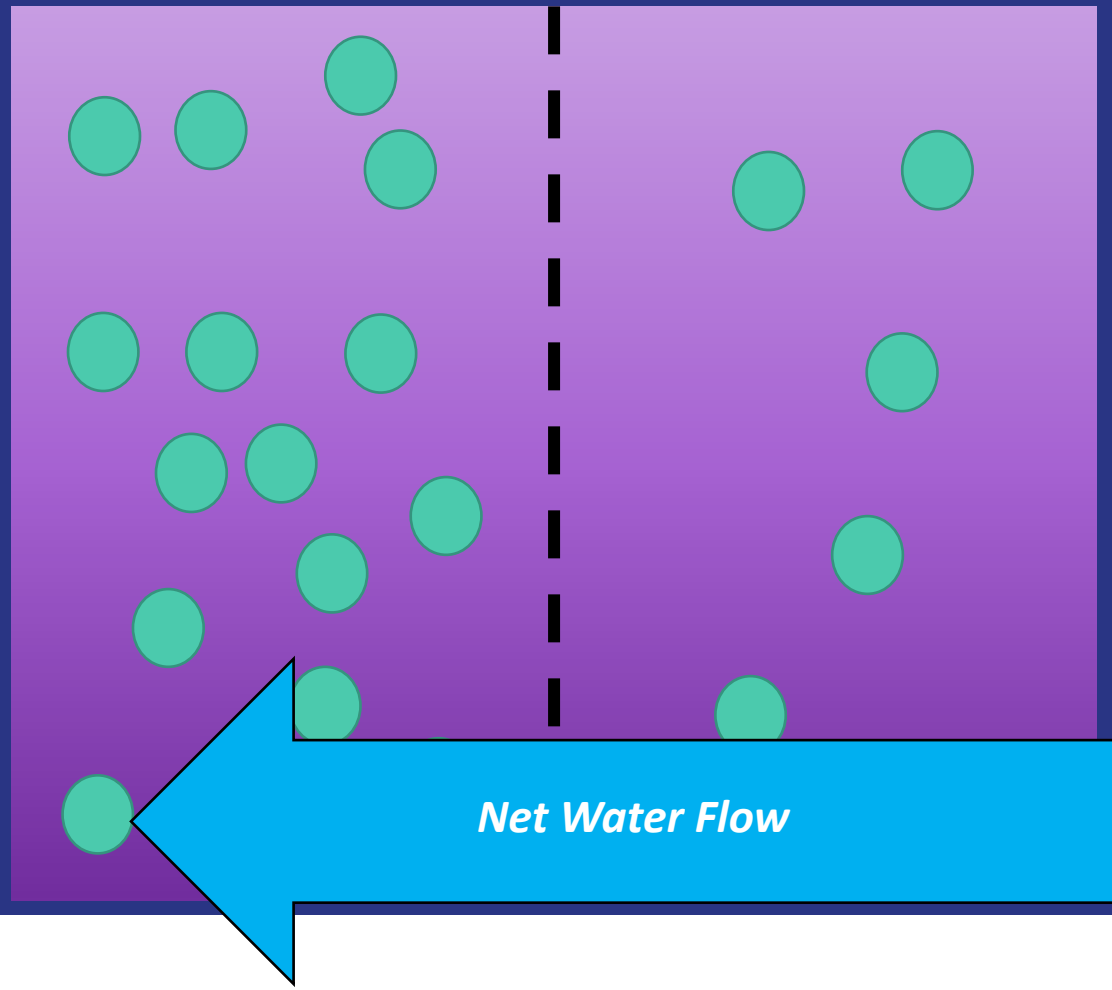
Obligatory Osmolality Slide



But depends on the reflection coefficient

Hyperosmotic side

- Higher solute concentration
- Lower free water concentration



Hypoosmotic side

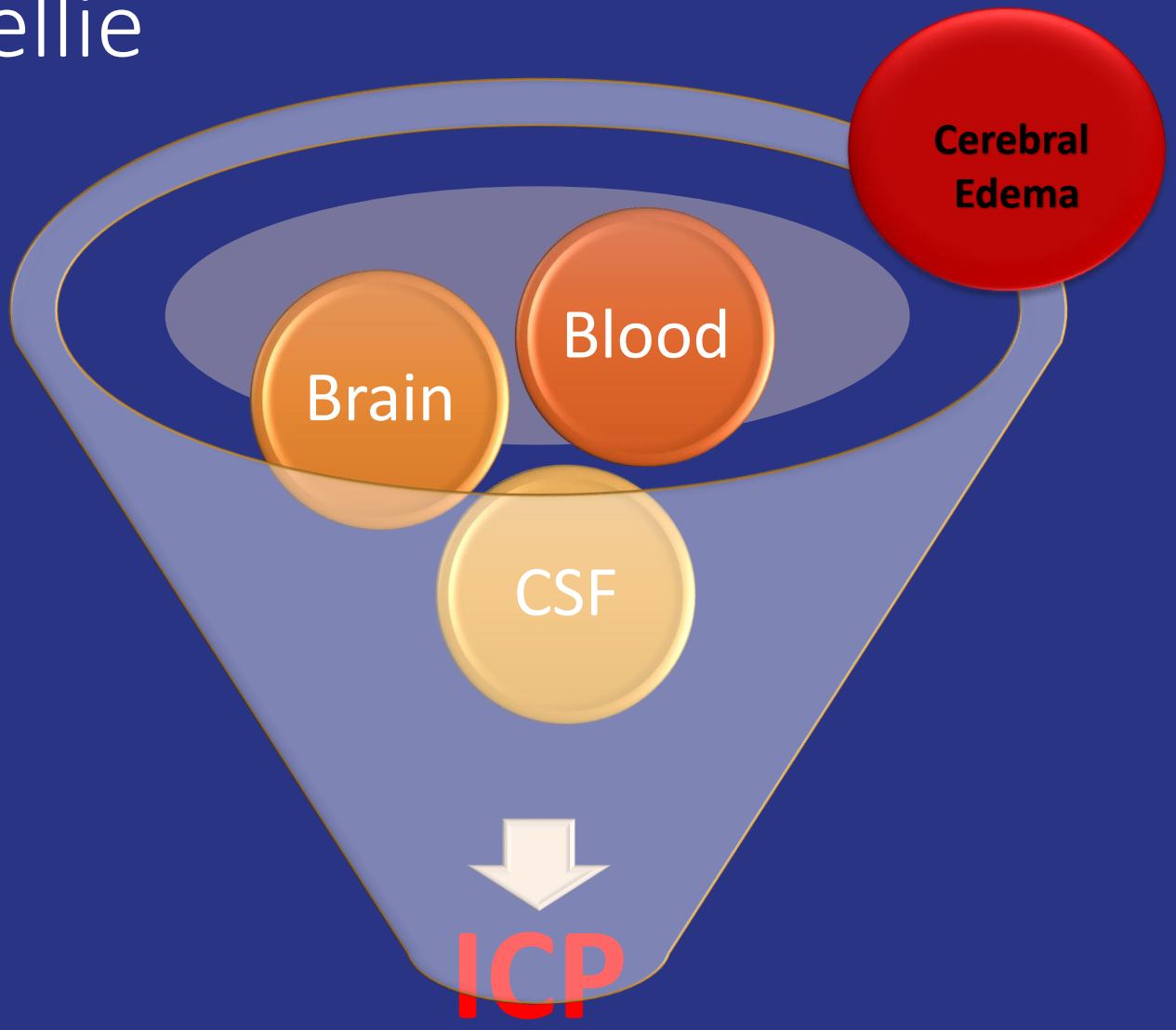
- Lower solute concentration
- Higher free water concentration

Serum Osmolality =

$$2\,[Na] + \frac{[BUN]}{2.8} + \frac{[Glucose]}{18}$$

Neurosurg Clin N Am 2016;27:473-488; Neurocrit Care 2020;32:636-640

Intracranial Pressure Indoctrination (ICP): Monro and Kellie



Neurosurg Clin N Am 2016;27:473-488

Example: Traumatic Brain Injury (TBI)

- Initially thought to arise predominantly from vasogenic mechanisms
  - Recent data has demonstrated that cytotoxic edema also plays a significant role
- Unique circumstance:
  - In the absence of vasogenic edema, a process that depends exclusively on cytotoxic edema would be self-limiting

Limiting edema to a problem of osmolarity is a reductionist view by omitting the mechanisms involved in cell volume regulation

Neurosurg Clin N Am 2016;27:473-488 ; Anaesth Crit Care Pain Med 2021;40:100929

Putting these concepts together: Initial Management of a Possible TBI Patient

Hypotensive patients should be treated with isotonic fluids

- 0.9% sodium chloride

Hypotonic fluids, such as D5W, should be avoided, as they may exacerbate brain edema

- If hypoglycemic, give D50W (50 mL IV push)

Neurocrit Care 2015;23:S143-S154

But doesn't just everyone LOVE Lactated Ringer's?!?!?!

Fluid	pH	Osmolarity (mOsm/L)	Sodium (mEq/L)	Chloride (mEq/L)	Dextrose (g/L)	Potassium (mEq/L)	Calcium (mEq/L)	Other
0.9% Sodium Chloride	5.5	308	154	154	0	0	0	
Lactated Ringer's	6.6	274	130	109	0	4	3	Lactate: 28 mEq/L
Plasma-Lyte	7.4	294	140	98	0	5	0	Magnesium: 3 mEq/L Acetate: 27 mEq/L Gluconate: 23 mEq/L
Dextrose 5% in Water	4.3	252	0	0	50	0	0	
Typical Human	7.4	285	140	104	0.8	4	2.3	Magnesium: 1.5 mEq/L Acetate: Negligible Gluconate: Negligible Lactate: Negligible

Transfus Apher Sci 2018;57:127-131; N Engl J Med 2013;369: 1243-1251

Patient Case: Wade Wilson

- Following obtainment of peripheral IV access the Trauma team inquires about what agent you would suggest for volume resuscitation considering the patient's low blood pressure (90/75 mmHg)
- Labs:

Sodium	**133 mEq/L**	**Potassium**	**4.5 mEq/L**
Chloride	**97 mEq/L**	**Carbon Dioxide**	**28 mg/dL**
BUN	**13 mg/dL**	**Serum Creatinine**	**0.7 mg/dL**
Glucose	**140 mg/dL**		

- Which of the following is the most appropriate agent to recommend for volume resuscitation in this setting?
  A. 0.9% Sodium Chloride
  B. Lactated Ringer's
  C. Hypertonic Saline 23.4%
  D. Hypertonic Saline 3%

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  - D. Hypertonic Saline 3%

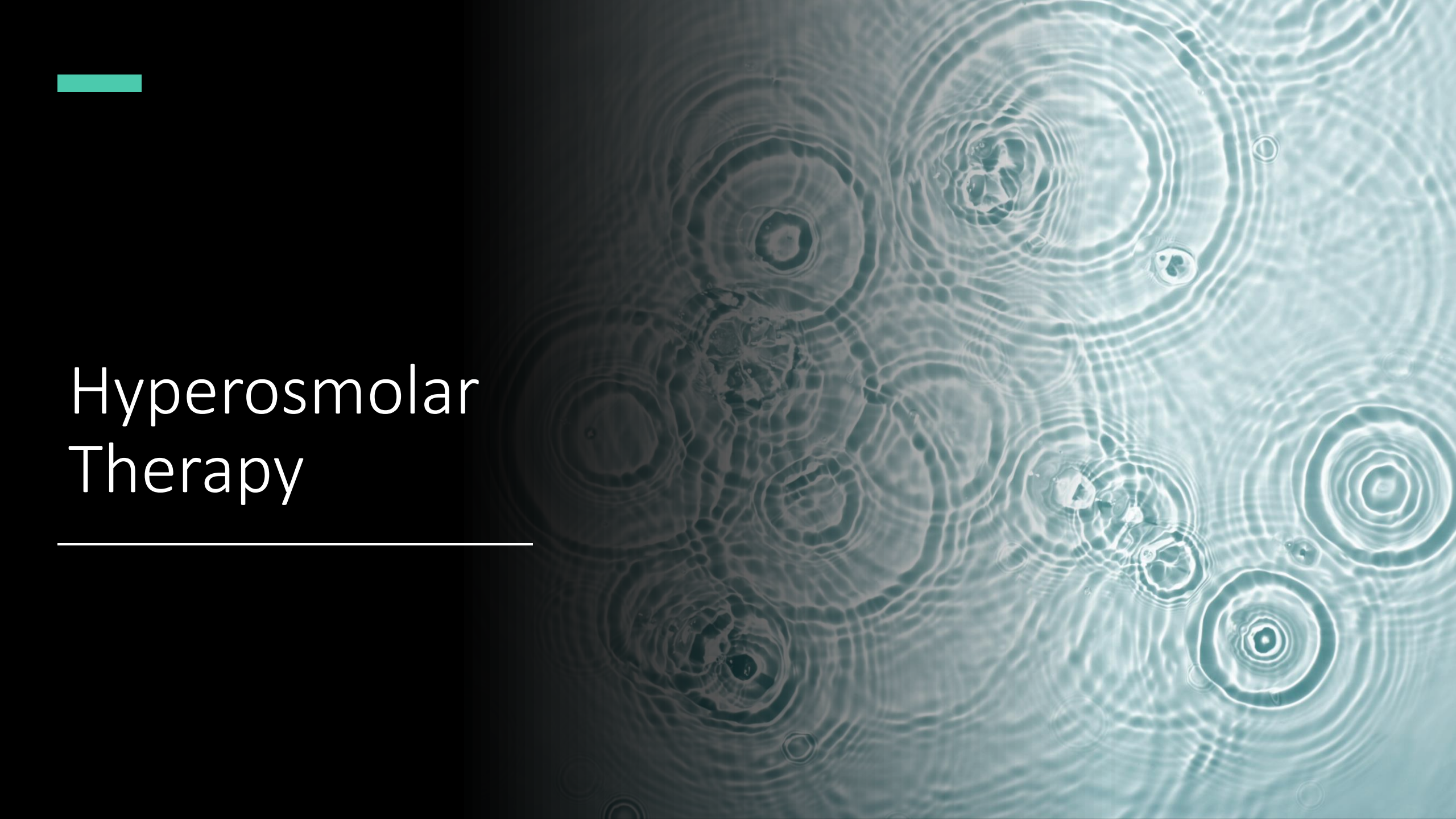
Patient Case: Wade Wilson

- His head computed tomography (CT) reveals a subdural hematoma and a traumatic subarachnoid hemorrhage. Based on these results and the patient's clinical status the team decides to intubate the patient to ensure patency of the airway.
- Following intubation, the patient is noted to have a fixed and dilated left pupil that was not present on the initial survey.

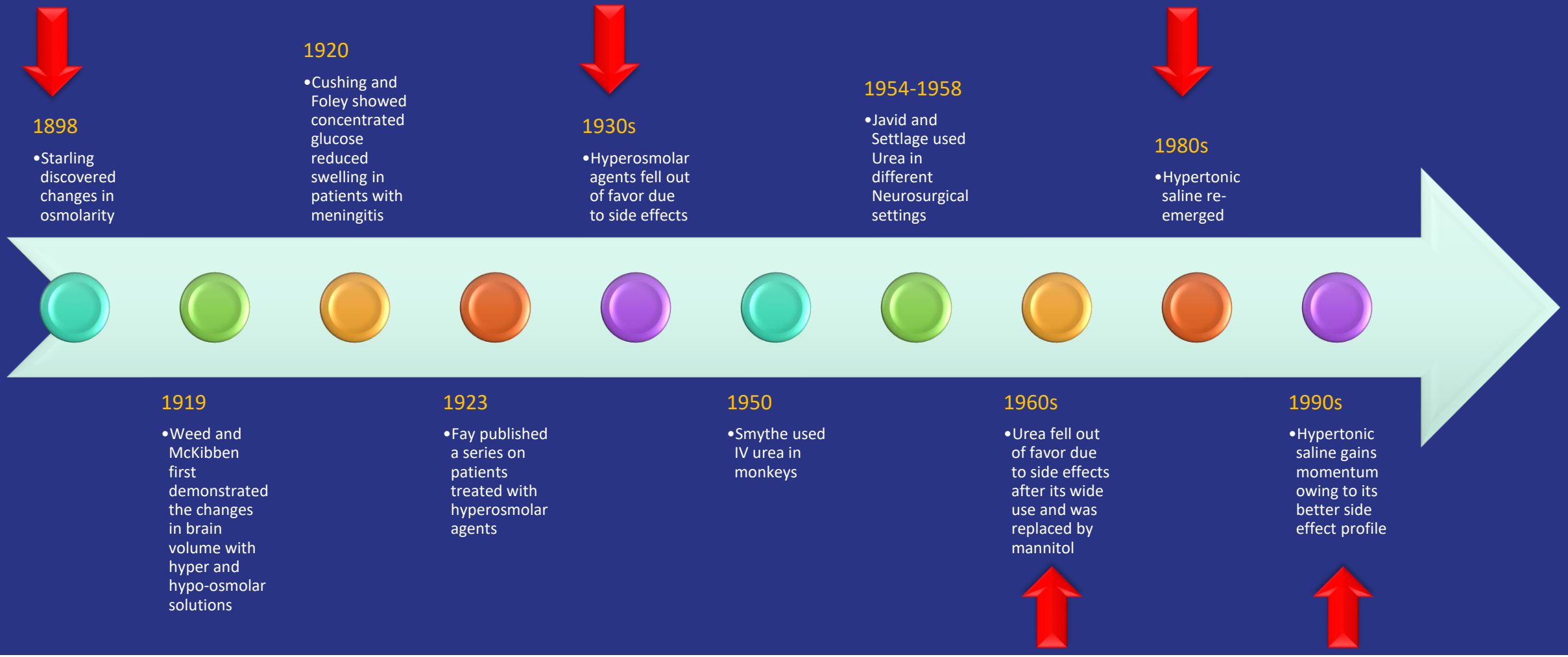
- Signs of intracranial hypertension or brain herniation
  - Dilated and nonreactive pupils
  - Asymmetric pupils
  - Motor exam that demonstrates extensor posturing
  - Progressive decline in neurologic condition that are not associated with non-TBI causes
  - Cushing reflex (hypertension, bradycardia, irregular respirations)

- Everybody: "@$%&#*, so what now?!?!?!?!"

Hyperosmolar Therapy



The Osmotherapy History You Didn't Know You Needed!!



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Clin Neuro Neurosurg 2021;206:106704

Hyperosmolar Therapy Options

- Hypertonic Saline (HTS)
  - Sodium chloride…just lots of it
  - Serum Osmolality = **2 [Na]** + $\frac{[BUN]}{2.8}$ + $\frac{[Glucose]}{18}$
- Mannitol
  - Sugar Alcohol
  - Osmotic diuretic
  - Serum Osmolality = 2 [Na] + $\frac{[BUN]}{2.8}$ + $\frac{[Glucose]}{18}$ + **Mannitol**

	Equi-Osmolar Dose	Osmolarity
Sodium Chloride 3%	5.34 mL/kg	1026 mOsm/L
Sodium Chloride 23.4%	0.68 mL/kg	8008 mOsm/L
Mannitol 20%	1 gm/kg	1098 mOsm/L

Neurocrit Care 2015;23:S76-S82

Recommended Dosing

Hypertonic Saline	Mannitol
Concentration dependent* • 3%: 5 mL/kg over 5-20 mins • 5%: 3 mL/kg over 5-20 mins • 7.5%: 2 mL/kg over 5-20 mins • 23.4%: 0.6 mL/kg (typically 30 mL) over 10-20 mins *Concentrations listed are approximately equal osmolar to mannitol 1 g/kg	0.5-1 g/kg over 5-15 min every 4-6 hrs

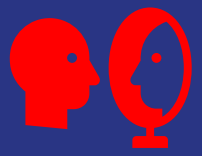
Neurocrit Care 2020;32:636-640; J Emerg Trauma Shock 2020;13:252-256

Reported Adverse Reactions

Hypertonic Saline	Mannitol
Pulmonary edema Heart Failure Acute kidney injury Coagulopathy Hypernatremia Metabolic acidosis Thrombophlebitis Osmotic demyelination syndrome	Rebound ICP elevation with abrupt discontinuation* Acute kidney injury Dehydration Hypotension Electrolyte imbalances *Associated with high, repeated dosing

Neurocrit Care 2020;32:636-640

Obligatory Osmolality Slide

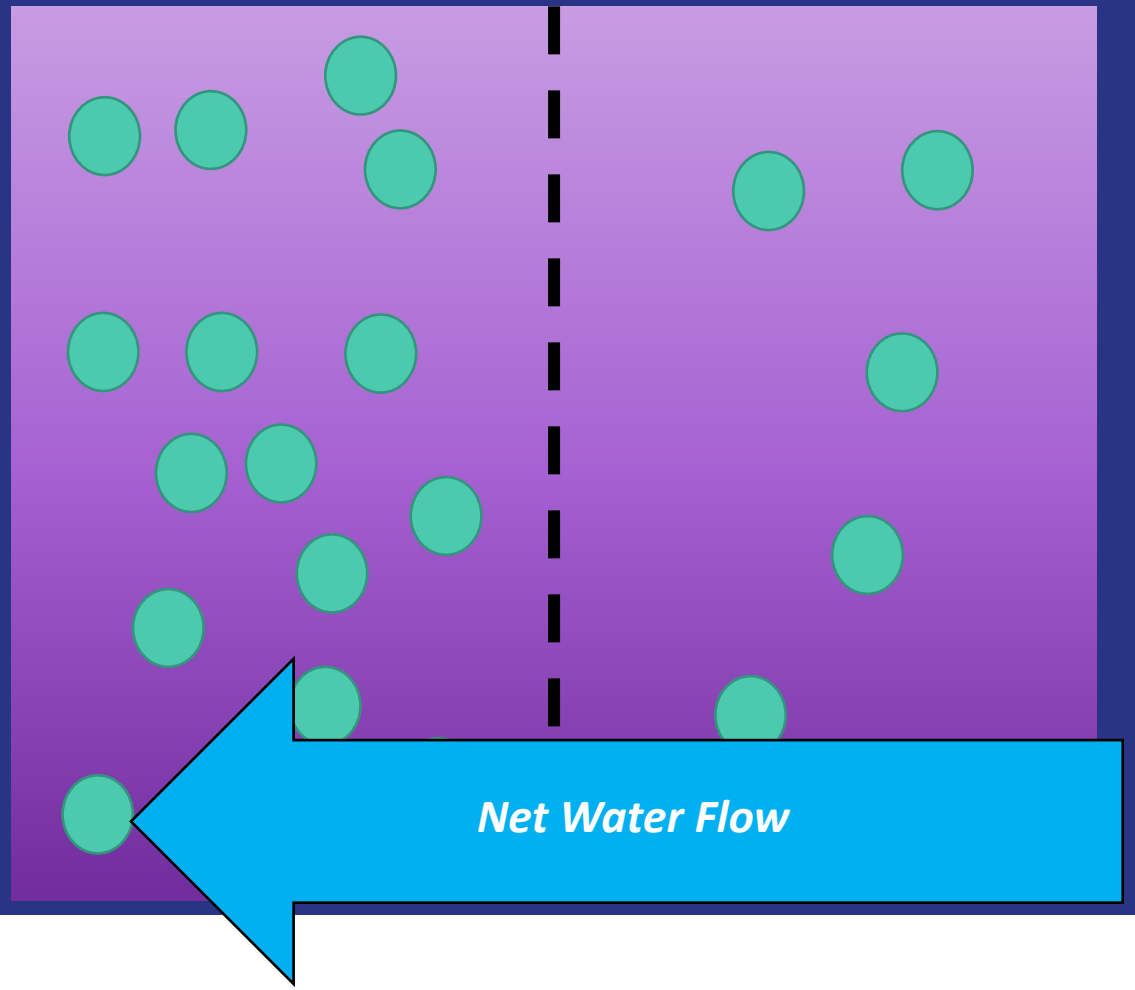


Reflection Coefficient

- Hypertonic Saline = 1.0
- Mannitol = 0.9

Hyperosmotic side

- Higher solute concentration
- Lower free water concentration



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Neurosurg Clin N Am 2016;27:473-488; Neurocrit Care 2020;32:636-640


But how do we choose?

Just what we need to answer our question!!

- *A systematic review of RCTs Comparing HTS and Mannitol for TBI*
  - 326 articles screened
    - 7 trials enrolling 191 patients met inclusion criteria
- Underpowered to detect significant differences in mortality or neurological outcomes
- No difference between HTS and mannitol was observed for mean ICP reduction
  - Risk of ICP treatment failure favored HTS
    - Risk ratio = 0.39; 95% CI = 0.18-0.81
- Conclusion:
  - Clinically important differences between the agents was not observed
    - HTS appears to lead to fewer ICP treatment failures

Ann Pharmaco 2016;50:291-300

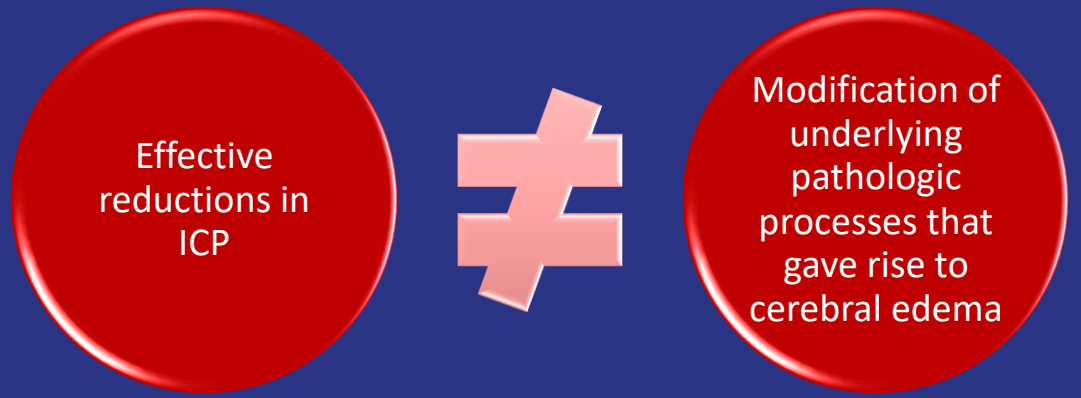
Ok, well how about this one?!?!

- *Effects of HTS vs Mannitol in Patients with TBI: Systematic Review and Meta-Analysis*
  - 352 articles screened
    - 4 trials enrolling 125 patients met inclusion criteria
- No significant difference between risk of death
- No significant differences between the two groups in the other secondary outcomes
- Conclusion:
  - No significant difference in all-cause mortality
    - No significant differences between groups in the reductions of ICP and serum sodium concentrations

J Intensive Care 2020;8:61

Well fine…what do the experts recommend?!?!?

- *Neurocritical care Guidelines: TBI*
  - *"We suggest using hypertonic sodium solutions over mannitol for the initial treatment of elevated ICP or cerebral edema in patients with TBI."*
    - Conditional recommendation, low-quality evidence
  - *"We suggest that neither HTS nor mannitol be used with the expectation for improving neurological outcomes in patients with TBI."*
    - Conditional recommendation, low-quality evidence



Neurocrit Care 2020;32:647-666; Neurosurg Clin N Am 2016;27:473-488

But why?!?!
Rationale Behind the Neurocritical Care Guidelines

- The consistency of the literature suggested HTS was at least as safe and effective as mannitol
- Some potential advantages of HTS over mannitol have been observed:
  - May have a quicker onset of action
    - 6 min vs 8.7 min ($p<0.0002$)
  - More robust and durable ICP reduction
    - 57% vs 48% ($p<0.01$)

Neurocrit Care 2020;32:647-666; Crit Care 2005;9:R530-R540

Neurocritical Care Guidelines: Hypertonic Saline Use Considerations

- *"We suggest that severe hypernatremia and hyperchloremia during treatment with HTS be avoided due to the association with acute kidney injury (AKI)."*
  - Recommendations:
    - Upper serum sodium range of 155-160 mEq/L
    - Upper serum chloride range of 110-115 mEq/L
- Consider all HTS solutions with either a chloride, lactate, or bicarbonate salt effective
  - 3% hypertonic saline vs 3% hypertonic saline buffered with sodium acetate
    - Increase in serum osmolality: 21.1 mOsm/kg vs 20.3 mOsm/kg
    - Decrease in serum chloride by an average of 2.5 mEq/L after switching from 3% HTS

Neurocrit Care 2020;32:647-666; Clin Neurol Neurosurg 2021;201:106435

Neurocritical Care Guidelines: Poor Mannitol

- *"We suggest that the use of mannitol is an effective alternative in patients with TBI unable to receive hypertonic sodium solutions."*
  - Conditional recommendation, low-quality evidence
- Mannitol Use Considerations
  - *"We suggest using osmolar gap over serum osmolarity thresholds during treatment with mannitol to monitor for the risk of AKI."*
    - Recommendations:
      - Although an osmolar gap of 20 mOsm/kg has been used in clinical practice, no data to supports this threshold
      - Evidence suggests that an osmolar gap of 55 mOsm/kg or higher is most correlated with serum mannitol concentrations

Neurocrit Care 2020;32:647-666

Osmolar Gap: Measuring Mannitol Molecules

Osmolar gap =

$$\text{measured osmolality} - \left(2\,[Na] + \frac{[BUN]}{2.8} + \frac{[Glucose]}{18}\right)$$

Serum Osmolality =

$$2\,[Na] + \frac{[BUN]}{2.8} + \frac{[Glucose]}{18}$$

Osmolar gap = measured osmolality – estimated osmolality

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Neurocrit Care 2020;32:647-666

Patient Case: Wade Wilson

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- His head computed tomography (CT) reveals a subdural hematoma and a traumatic subarachnoid hemorrhage. Based on these results and the patient's clinical status the team decides to intubate the patient to ensure patency of the airway.
- Following intubation, the patient is noted to have a fixed and dilated left pupil that was not present on the initial survey.
- The team would like to start osmotherapy on this patient. Which of the following is an appropriate recommendation for this patient?
  A. Mannitol 20% 140 grams IV x 1
  B. Hypertonic Saline 3% 280 mL IV x 1
  C. Mannitol 20% 70 mg IV x 1
  D. Hypertonic Saline 3% 60 mL IV x 1

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Mannitol Pearls

Requires in-line filter (precipitates/crystals)

May require warming to dissolve

May be given via peripheral access

Duration of effect: 90 mins – 6 hrs

Monitor through osmotic gap

Goal <20-55 mOsm/kg

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Neurocrit Care 2020;32:647-666

Hypertonic Saline Pearls

3%-5% may be given via peripheral access	Central line ‘required’ for 23.4% bolus
Duration of effect 90 min- 4 hr	
Controversy exists over whether continuous infusion is helpful	Not recommended in guidelines
Monitor serum sodium every 4-6 hrs	Avoid prolonged hypernatremia >160 mEq/L

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Neurocrit Care 2020;32:647-666

I can’t you say?? Here, hold my salt shaker…

Hypertonic Saline 23.4% via Peripheral Venous Access

299 administrations (242 central, 57 peripheral)

No documented occurrence of soft tissue injury or necrosis in any patient

No significant difference in median ICP reduction between routes

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Neurocrit Care 2021;35:845-852

Patient Case: Wade Wilson

- You go to remove the above agent from your automated dispensing cabinet and discover that you are all out of hypertonic saline, but you still have mannitol available. So you grab this bag and take it to bedside.
- What administration considerations are important to convey to the bedside nurse?
  A. Infuse with an inline filter
  B. Only infuse in a central line
  C. Only infuse in a distal site
  D. Protect from light

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Conclusion

- Cerebral edema is a heterogenous consequence of multiple etiologies and is associated with significant morbidity and mortality
- In clinical practice, treatment of cerebral edema is largely limited to hyperosmolar therapy
- Available data does not clearly support one hyperosmolar agent over another and both mannitol and hypertonic saline are considered equivalent
  - Consensus opinion would recommend hypertonic saline over mannitol
- Multiple unique physiochemical, administration, and monitoring considerations should be entertained when implementing either therapy
- These interventions lack the ability to modify the underlying pathologic processes that resulted in cerebral edema

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