**Key Aspect of Medication Therapy in Neurocritical Care Patients: Current Viewpoints on Hyperosmolar Therapy**

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**Disclosure**

- I do not have (nor does any immediate family member have) a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.

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**Audience Participation**

- What is the osmotherapy of choice at your institution?
- When do you use osmotherapy?
- How do you administer mannitol or hypertonic saline?

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**Objectives**

- Review the pathophysiology of cerebral edema and intracranial hypertension
- Discuss principles of management of intracranial hypertension
- Compare and contrast the advantages and limitations associated with hyperosmolar therapy
- Formulate monitoring plans of therapeutic effects and complications associated with hyperosmolar therapy

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**Cerebral Edema**

- **Cytotoxic edema**
  - Intracellular
  - Secondary to energy failure; pump failure
  - Evolves over minutes to hours
- **Vasogenic edema**
  - Extracellular
  - Breakdown of BBB; increased vascular permeability
  - Evolves hours to days

**Location**
- Stroke (infarct)
- Brain tumor; brain abscesses, head injury, meningitis, stroke

**Proposed MOA**
- Intracellular
- Cellular injury, secondary to energy failure; pump failure

**Time course**
- Stroke (infarct): hours
- Brain tumor; brain abscesses, head injury, meningitis, stroke: days

**Common diseases**
- Stroke (infarct)
- Brain tumor; brain abscesses, head injury, meningitis, stroke

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**Cerebral Edema**

- The Monroe-Kellie doctrine
- Cranial vault
  - Blood
  - CSF
  - Brain tissue

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Cerebral edema alters CBV leading to increase in ICP

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Adapted from Unterberg AW, et al. Neuroscience 2004;129:1021
Global and Focal Edema

- Focal edema
  - Pressure gradient with adjacent regions
  - Tissue shift and herniation
  - Tumors, hematomas, and infarction
- Global edema
  - Diffusely affects the whole brain
  - Compromise perfusion → general ischemia
  - Cardiac arrest, severe TBI, and fulminate liver failure

Traumatic Brain Injury Guidelines

<table>
<thead>
<tr>
<th>Threshold to Treat</th>
<th>2007 BTF</th>
<th>2016 BTF</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICP &gt; 20 mmHg</td>
<td>Level II</td>
<td>Level IIB</td>
</tr>
<tr>
<td>CPP Goal</td>
<td>50 – 70 mmHg</td>
<td>60 – 70 mmHg</td>
</tr>
<tr>
<td>SBP Goal</td>
<td>N/A</td>
<td>50 – 69 mmHg</td>
</tr>
<tr>
<td>Avoid</td>
<td>SBP &lt; 90 mmHg</td>
<td>CPP &lt; 50 mmHg</td>
</tr>
<tr>
<td></td>
<td>SaO2 &lt; 90%; SjvO2 &lt; 50%</td>
<td>SjvO2 &lt; 30%</td>
</tr>
</tbody>
</table>

Management of ICP

- Head of bed elevated to >30º and head kept midline
- Use only isotonic fluids; avoid hypotonic fluids
- Corticosteroids shown no benefit on outcomes with more complications
- Maintain normothermia; prophylactic hypothermia is not recommended

Use of Osmotherapy

- Remain the cornerstone for ICP management
- Ideal properties of osmotic agent
  - Inert and nontoxic
  - Does not cross the cell membrane
  - Minimal systemic side effects
  - Excluded from an intact BBB [reflection coefficient]

History of Osmotherapy

- 1919: Weed and McKibben
- 1927: Fremont-Smith and Forbes
- 1962: Wise and Chater
- 1985: Todd and colleagues

Proposed Mechanism of Action

- Rheologic effects: immediate response
- Osmotic effects: delayed response
Other Theoretical Benefits

- Mannitol
  - Reduction in CSF production
  - Free radical scavenger
  - Inhibition of apoptosis
- Hypertonic Saline
  - Plasma expander
  - Restoration of normal membrane potential
  - Modulation of inflammatory response

Clinical Experience with Mannitol: TBI

Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Outcomes (RR; 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwartz et al. 1984</td>
<td>Mannitol: 31 Pentobarbital: 28</td>
<td>Death: 0.85 [0.52, 1.38]</td>
</tr>
<tr>
<td>Smith et al. 1986</td>
<td>Mannitol only ICP directed: 37 Neurological signs: 40</td>
<td>Death/disability: 0.88 [0.55, 1.38]</td>
</tr>
<tr>
<td>Sayre et al. 1986</td>
<td>Mannitol: 20 NS: 21</td>
<td>Death: 1.75 [0.48, 6.38]</td>
</tr>
<tr>
<td>Vidal et al. 2003</td>
<td>Mannitol: 10 7.5% Saline: 10</td>
<td>Death: 1.25 [0.47, 3.33]</td>
</tr>
</tbody>
</table>

Clinical Experience with Mannitol: Stroke

Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Santambrogio et al. 1978</td>
<td>Presumed AIS Mannitol (n=36) vs. control (n=41)</td>
<td>10-day clinical improvement: 35% mannitol; 39% control</td>
</tr>
<tr>
<td>Kalita et al. 2004</td>
<td>ICH (CT proven) Mannitol (n=12) vs. NS (n=9)</td>
<td>GCS improvement: 50% mannitol; 78% NS 1-month case fatality: 1 mannitol; 0 NS</td>
</tr>
<tr>
<td>Misra et al. 2005</td>
<td>ICH (CT proven) Mannitol (n=65) vs. NS (n=63)</td>
<td>Death/disability (OR; 95% CI): 1.28 [0.64, 2.56]</td>
</tr>
</tbody>
</table>

Sustained Use of Mannitol

- "Mannitol resistant" – lack of an osmotic response
- Retrospective analysis of prospectively collected data
- Patients who received scheduled mannitol only for ≥ 48 hr
  - 167 patients: ICH, SAH, brain tumor
  - 0.5-1.25 gm/kg mannitol Q4-8 hour ATC

Monitoring Mannitol Use

- Serum osmolality: 320 mOsm/L
- Osmotic gap: (Measured Osmo – Calculated Osmo)
  - Estimate serum mannitol levels
  - Formula: 1.86 * (Na + K) + (BUN/2.8) + (Gluc/18) +10
History of Osmotherapy

1919
- Weed and McKibben
- Intravenous administration of 30% saline

1927
- Fremont-Smith and Forbes
- Intravenous administration of concentrated urea

1962
- Wise and Chater
- Mannitol used for longer ICP control

1985
- Todd and colleagues
- Regenerated interest in hypertonic saline

1988
- Worthley and colleagues
- 2 TBI patients who failed mannitol

Adapted from Witherspoon B, et al. Nurs Clin N Am 2017;52:249

Clinical Experience with HTS

1.6% HTS vs. Lactated Ringer’s
- Prospective, randomized
- 34 TBI patients

7.2% HTS vs. Normal Saline
- Prospective, randomized, single-blinded
- 22 SAH patients

HTS vs. Mannitol: Meta-Analysis

2011 Kamel et al.
- 5 RCT; 112 mixed patients
- Equal osmolar doses
- ICP reduction favoring HTS

2012 Mortazavi et al.
- 36 studies: mixed adults and pediatrics
- HTS is more effective in decreasing ICP
- No differences in neurologic outcomes or mortality

2014 Rickard et al.
- 6 RCT; 171 TBI patients
- No significant difference in ICP reduction between HTS and mannitol

2015 Li et al.
- 7 studies; 169 TBI patients
- HTS was more effective in ICP reduction than mannitol in pooled analysis

2016 Burgess et al.
- 7 RCT; 191 TBI patients
- Unable to determine effect on mortality or neurological outcomes
- No difference in ICP reduction

23.4% HTS in Neurocritical Care

- Six studies were included for ICP reduction effect size analysis
- Decrease in ICP from baseline to 60 minutes or nadir: 55.6%; 95%CI 43.99, 67.12; p <0.0001

Unsolved Issues with HTS

- Optimal concentration/dose
- Timing: initiation of therapy
- Duration of therapy
- The best mode of administration
- Goals of therapy
- Clinical outcomes

Administration: bolus vs. continuous infusion

- Potential complications with continuous infusion
  - Associated with increased BUN/Scr but not renal failure; not related to DVT
  - Associated with increased cardiac arrhythmia, heart failure, pulmonary edema, and renal failure as control
  - Two studies suggested increased in-hospital mortality
  - Available literatures with large variations
  - 11 studies of continuous infusion: 3 RCT
  - 26 studies of bolus dosing: 7 RCT
Serum Na Level and ICP

- 27 patients: TBI, post-neurosurgery, ischemic stroke, intracranial hemorrhage
- 3% hypertonic saline/acetate at 75-150 ml/hr
- Goal of therapy: Na level 145-155 mEq/L

Monitoring HTS Use

- Serum sodium level: 145 – 155 mEq/L
- Linear regression analysis of mean serum Na concentrations and GCS: R² = 0.8, p = 0.01
- Monitor every 4-6 hours
- Serum osmolality: 310 – 320 mOsm/L

Na Threshold: how high is too high?

Severe hypernatremia is an independent predictor of mortality.

Complications

<table>
<thead>
<tr>
<th>Mannitol</th>
<th>Hypertonic saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial complications</td>
<td>Rebound edema, Central pontine myelinolysis</td>
</tr>
<tr>
<td>Extracranial complications</td>
<td>Dehydration, Hypertension, Renal failure, Electrolyte abnormalities</td>
</tr>
</tbody>
</table>

Hyperosmolar Therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mannitol</th>
<th>Hypertonic Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolus Dosing</td>
<td>0.25 – 1 gm/kg*</td>
<td>30 - 60 ml 23.4%; 250 ml 3%; 2-4 ml/kg 7.5%</td>
</tr>
<tr>
<td>Continuous Infusion</td>
<td>Not recommended</td>
<td>2-3 ml/h</td>
</tr>
<tr>
<td>Peak Effect</td>
<td>15-30 min</td>
<td>15-30 min</td>
</tr>
<tr>
<td>Duration of Effect</td>
<td>1 – 5 hr</td>
<td>2 – 6 hr</td>
</tr>
<tr>
<td>Risk of Hypovolemia</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Summary

- Osmotic agent is routinely used for ICP management
- Mannitol and HTS are therapeutic options available
- HTS demonstrates a favorable effect on both ICP and hemodynamic effects
- Many issues remain unknown regarding HTS
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Current Viewpoints on Hyperosmolar Therapy
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Objectives
- Describe the blood-brain barrier (BBB) and pharmacologic properties of antimicrobials that facilitate CNS penetration
- Discuss disease states that affect CNS penetration of antimicrobials
- Describe administration routes and dosing of antimicrobials to ensure adequate CNS penetration

Meningitis & Ventriculitis
- Microbiology:
  - Fungal infection rare (Candida spp.)
- Diagnostic signs & labs
  - ↓ CSF glucose  ↑ CSF protein  CSF pleocytosis  ↑ CSF culture
  - Fever  Meningism  ↓ LOC  Photophobia
  - Seizure  ↑ Procalcitonin  Phonophobia
- Cell index > 10
  - Cell index = (WBC CSF - RBC CSF) / (WBC Blood - RBC Blood)

Decreasing Incidence…
But Increasing Costs

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>1997*</th>
<th>2010</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumococcus spp.</td>
<td>50,734</td>
<td>82,283</td>
<td>0.03</td>
</tr>
<tr>
<td>Meningococcus spp.</td>
<td>25,021</td>
<td>55,251</td>
<td>≪ 0.01</td>
</tr>
<tr>
<td>Staphylococcus spp.</td>
<td>56,921</td>
<td>86,080</td>
<td>0.16</td>
</tr>
<tr>
<td>Gram negative</td>
<td>41,677</td>
<td>105,060</td>
<td>≪ 0.01</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>24,319</td>
<td>53,735</td>
<td>0.09</td>
</tr>
</tbody>
</table>

- Adjusted for inflation with average consumer price index to 2010 dollars

- Larger absolute cost increase for gram-negative bacteria
- Average length of stay longest with gram-negative bacteria (15.8 days)
- Gram-negative, Staphylococcus spp., Pneumococcus spp. most costly
- Gram-negative, Staphylococcus spp. usually nosocomial causes

Causes of Nosocomial Meningitis

- Implanted CSF shunts
- Ventriculoperitoneal (VP) most common
- External ventricular drains
- Intrathecal infusion pumps
- Deep brain stimulators
- Neurosurgical procedures
- Cranial trauma

BBB - Macrophysiology

Solute & Water diffusion occur between:
- Blood and extracellular fluid (ECF)
- Blood and epithelium of choroid plexus
- Across ependymal
- Across pia-glial membranes
e&f) Across cell membranes of neurons & glia

BBB Molecule Distribution

- Tight junctions → leaky
- CSF outflow decreases
  - Less CSF production
- Inhibited efflux pumps
- Increased antibiotic distribution

Pharmacologic Properties Affecting CNS Absorption

- Molecular size
  - CNS penetration ↓ as √ molecular mass ↑
- Lipophilicity
- Protein binding
- Ionization
- Active transport
- CNS metabolism

Effects of Meningeal Inflammation

- Tight junctions → leaky
- CSF outflow decreases
  - Less CSF production
- Inhibited efflux pumps
- Increased antibiotic distribution
### Effects of Meningeal Inflammation on Antibiotics

**Antibiotic Class**

<table>
<thead>
<tr>
<th>Antibiotic Class</th>
<th>[CSF] &gt; MIC</th>
<th>Systemic Toxicity</th>
<th>CNS Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-Lactams</td>
<td>+/-</td>
<td>Low</td>
<td>High – seizure</td>
</tr>
<tr>
<td>Beta-Lactamase Inhibitors</td>
<td>-</td>
<td>Low</td>
<td>High – seizure</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>+/- Unknown</td>
<td>High</td>
<td>Mad – ototoxicity</td>
</tr>
<tr>
<td>Colistin</td>
<td>-</td>
<td>High</td>
<td>Mad – ototoxicity</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>+/- Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>+</td>
<td>Low</td>
<td>Unknown</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>+/- Low</td>
<td>Low</td>
<td>Unknown</td>
</tr>
<tr>
<td>Linezolid</td>
<td>+/- Low</td>
<td>Low</td>
<td>Unknown</td>
</tr>
<tr>
<td>Methronidazole</td>
<td>+</td>
<td>Low</td>
<td>Unknown</td>
</tr>
<tr>
<td>Rifamycins</td>
<td>+</td>
<td>Low</td>
<td>Unknown</td>
</tr>
<tr>
<td>SMX/TMP</td>
<td>+/- Low</td>
<td>Low</td>
<td>Unknown</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>+/- Low</td>
<td>Low</td>
<td>Unknown</td>
</tr>
</tbody>
</table>


*Effects of Meningeal Inflammation on Antifungals*

**Antifungal**

<table>
<thead>
<tr>
<th>Antifungal</th>
<th>[CSF] &gt; MIC</th>
<th>Systemic Toxicity</th>
<th>CNS Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>+</td>
<td>High</td>
<td>Unknown</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>+</td>
<td>Low</td>
<td>Unknown</td>
</tr>
<tr>
<td>Micafungin</td>
<td>+/- Low</td>
<td>Low</td>
<td>Unknown</td>
</tr>
</tbody>
</table>


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### The Ideal Antimicrobial...

- Easily penetrates the CNS
- Has a high [CSF]/MIC ratio
- Has minor systemic adverse effects
- Has good evidence of clinical cure

**Why not instill directly into the CNS?**

- Invasive
- Possible adverse effects
- Dosing and administration concerns

**When to consider IVT:**

- Indwelling hardware
- Resistant organism(s)
- Lack of response to standard therapy

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### Aminoglycosides

- Gentamicin, tobramycin, amikacin all have clinical data
  - Limited to Level III evidence
- Gentamicin
  - Dosing: 5-20 mg
  - [CSF ventricular] > 4 mg/L for most of 24 hour dosing interval
- Tobramycin
  - Dosing: 5-20 mg
  - [CSF ventricular] 13-40 during first 6 hours w/ 5 mg dose
- Amikacin
  - Dosing: 10-50mg
  - Least studied
  - Possible ototoxicity, not reported in any case series


### Colistin & Polymyxin B

- Colistin (Polymyxin E): case reports/series and one retrospective cohort study
  - Fotakopoulos, et al.
  - 23 patients IVT + IV vs. 11 patients IV alone
  - MDR in 76% of cases
  - Mean dose: 170,000 IU (13.6 mg) x 16 days
  - Cure rate significantly improved in combo group (87% vs. 28%, p=0.001)
  - Gilbert, et al.
  - Case series of 7 patients over 7 years
  - Dose: 10mg IVT daily
  - 100% clinical cure, 0 adverse effects
  - Polymyxin B
  - Case reports (Level III)
  - Dose: 50,000-100,000 IU (5-10 mg) IVT Daily
  - Most common dose: 5 mg
  - Adverse effects: aseptic meningitis, reversible loss of bladder and bowel control
Vancomycin

• Most widely studied IVT antibiotic
  • Mostly case reports and case series (Level III), a few prospective studies
  • Dosing: 10-50 mg IVT Q24H
  • Routine monitoring not necessary in most cases
  • Prospective trial (Pflaumer, et al.)
    • Vancomycin 500mg IV Q6H vs. vancomycin 10mg IVT Q24H
    • 10 patients enrolled w/ EVD-associated ventriculitis
    • [Vancomycin serum] levels in IVT group mostly undetectable
      → Mean IVT [Vancomycin CSF] = 565 → 3.74 mcg/mL
    • IV [vancomycin CSF] = 2.71 → 0.82 mcg/mL
    • CSF clearance in 3-4 days in both groups
    • No adverse effects reported


Other IVT Antimicrobials

Quinupristin/Dalfopristin
  • Case reports
    • 58 yo F w/ SAH, E. faecium
    • 2 mg IVT + 7.5 mg/kg IV Q8H
    • CSF clearance on day 3
    • Some reports of failure w/ 1-2 mg doses
    • No reports of adverse effects


Amphotericin B
  • Good CNS penetration when given IV
  • Liposomal preferred
  • IVT → deoxycholate
  • Fever/nausea common
  • Can give with 5 mg methylprednisolone to decrease headaches


Adverse Effects

Aminoglycosides
  • Hearing loss (temporary), seizure, aseptic meningitis, eosinophilic CSF pleocytosis

Amphotericin B
  • Tinnitus, fever, shivering, parkinsonian syndrome

Colistin
  • Meningitis, seizures, loss of appetite, agitation, eosinophilia, edema, pain, aseptic meningitis

Daptomycin
  • Fever

Vancomycin
  • Hearing loss (temporary), headache

Administration

- Clamp EVD for 1 hour, then open to drain
- Instill antibiotic followed by flush of sterile, PF normal saline (green top vials)
- Remove CSF equivalent to amount in syringe or 10 mL
- Don mask, sterile gloves and gown
- Clean EVD port with chlorhexidine

PF = preservative free

When to Consider Intraventricular

- Indwelling hardware
- Lack of response to IV therapy
- Resistance to standard agents

Other Considerations

- Optimize dosing of intravenous antibiotics
  - CIV/EI beta lactams may have better [CSF]
  - IV + IVT > IV alone in MDR gram negative
- Little evidence to guide duration
  - Risk of contamination vs. under-treatment
  - Clinical response

Summary

- There are significant pharmacologic and physiologic barriers to CNS antimicrobial penetration
- Limited data on intraventricular administration of antimicrobials exists
- Consider adjunct intraventricular therapy if no response to several days of standard intravenous therapy
- Extra steps in preparation and administration are necessary to ensure aseptic delivery

Objectives

- Describe the blood-brain barrier (BBB) and pharmacologic properties of antimicrobials that facilitate CNS penetration
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Key Aspects of Medication Therapy in the Neurocritical Care Patient

CNS Penetration of Antimicrobials
Michael Erdman, PharmD, BCPS