Update and Innovations in the Care of Patients with Hyponatremia
A Clash of Titans 2018

Qi “The Rochester Rocket” Qian
Versus

Jimmy “The Tumlinator” Tumlin
“The Atlanta Redneck”

A Fight to the Death
Here is what we agree upon:

“Understanding the physiology and pathophysiology of the disease is central to its proper treatment!”
Water regulation by the kidney: AVP & TonEBP

AVP – production, regulation and mechanisms of action

**Physiological regulations of AVP:**
1. Serum osmolality - sensitive, less potent
2. Volume status - less sensitive but more potent
3. Circadian rhythmicity – habit forming

*Modified from: Nat. Rev. Endocrinol (2016)*
V2 AVP Receptors: Water-Urea Transport

Medullary Concentration Gradient

AVP: Facilitates Na+/Urea transport: Maximizes medullary hyperosmolality and Osmotic diffusion capacity

Aquaporin-2 in sub-brush Border vesical
CT Changes of Water Intoxification: Brain Edema

Normal CT

Brain Edema

Diagram showing the changes in water content and sodium concentration in brain tissue under different conditions of sodium and water balance.
Efflux of Idiogenic Osmoles: Neurologic Accommodation of Chronic Hyponatremia

Arieff et al. Medicine 55:121 1976

Brain research 567(2) 274-82 1991

Retention Time (Min)

Brain Osmolyte Content (mmol/kg DW)

Verbalis, J G
Efflux of Idiogenic Osmoles: Neurologic Accommodation of Chronic Hyponatremia

Table 1  Brain organic osmolytes

<table>
<thead>
<tr>
<th>Major</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutamate</td>
<td>Aspartate</td>
</tr>
<tr>
<td>Glutamine</td>
<td>Threonine</td>
</tr>
<tr>
<td>Taurine</td>
<td>Alanine</td>
</tr>
<tr>
<td>$\text{myo-}$-Inositol</td>
<td>GPC</td>
</tr>
<tr>
<td>Glutamine</td>
<td>Glycine</td>
</tr>
<tr>
<td>Lysine</td>
<td>Betaine</td>
</tr>
<tr>
<td>Serine</td>
<td>Choline</td>
</tr>
</tbody>
</table>

| Other          | Phosphocreatine |

This page contains a diagram showing the efflux of idiogenic osmolytes in chronic hyponatremia. The diagram includes major and minor osmolytes such as Glutamate, Glutamine, Taurine, $\text{myo-}$-Inositol, and their respective minor counterparts like Aspartate, Threonine, Alanine, GPC, Glycine, Betaine, Choline, and Phosphocreatine.
Clinical Manifestations of Hyponatremia:

“Here is where it gets tricky!”
Pharmacokinetics of DDAVP

- **Half-life:** Healthy volunteers 74 minutes
- **Half Life:** 10+ hrs in severe renal failure
- **Reduces renal clearance:** 1-2%
- **D5W Infusions**
Round #1

People Die FROM Hyponatremia
Not just WITH Hyponatremia

Qi

Tumlin
PRO: Tumlin

CON: Qi
“Severe Hyponatremia with Altered Sensorium”
Neurologic Sequelae After Treatment of Severe Hyponatremia: A Multicenter Perspective’

- Study Objective: To determine the cause, presenting symptoms, rate of correction, and neurologic sequelae of patients with severe (<105 meq/L) hyponatremia.
- Study Design: Survey- questionnaire sent to 4100 ASN members requesting clinical information on patients with confirmed Na+<105 within 5 yrs
- Clinical and Therapeutic Endpoints:
  - Use hypertonic saline
  - Rate of Na+ correction-mM/L/Hr
  - Time to correction of Na+>120

Neurologic Sequelae After Treatment of Severe Hyponatremia: A Multicenter Perspective’

All 56 patients presented with some degree of neurologic compromise

Percentage (%) Patients with Clinical Endpoint

- Dysthria: 35.7%
- HA-N/V: 17.6%
- Seizures: 14.3%
- Obtused: 13.2%
- Impaired: 10.7%
- Unarousable: 8.9%
Neurologic Sequelae After Treatment of Severe Hyponatremia: Rate Matters


- Rate Na+ Correction in (meq/L/hr)
  - Permanent: 2.44 meq/L/hr
  - Transient: 1.24 meq/L/hr

- Serum Na+ at 48 hours
  - Neurologic Sequelae
  - No Neurologic Sequelae

Qi
“You Can’t Be Serious!!”
Study Objective: To document the mortality and clinical outcomes patients with hyponatremia (<128 meq/l) and neurologic impairment

Study Design: Retrospective analysis of 65 patients seen in renal consultation:

- **Group-1:** Hyponatremia < 12 hrs
  - 14 patients
- **Group-2:** Hyponatremia > 12 hrs NO neuro-impairment
  - 27 patients
- **Group-3:** Hyponatremia > 12 hrs + neuro-impairment
  - 24 patients

Clinical Response: Treatment with or without Hypertonic Saline
Neurologic Complications Correlated with Decreasing Serum Sodium (Na+)

Neurologic Complications and Mortality of ACUTE (<12 Hour) Onset of Hyponatremia

Arief et. al. Medicine; 55(2), 121-129, 1976

Mean Na+ 112

% Coma 100%

% Seizures 28.5%

28.5% Mortality

75.0% Mortality

Number of Clinical Events

Serum Na+ % Coma % Seizures 3% Rx No 3% Rx
Neurologic Complications and Mortality of ACUTE (>12 Hour) WITH Neurologic Impairment


Number of Clinical Events

- Mean Na+ 115
- % Coma 58.3%
- % Seizures 8.3%
- 0.0% Mortality
- 12.5% Mortality

Arief et.al. Medicine; 55(2), 121-129, 1976
Neurologic Complications and Mortality of ACUTE (>12 Hour) WITHOUT Neurologic Impairment

Arief et.al. Medicine; 55(2), 121-129, 1976
“But Just Wait if You Think That’s Scary”
Study Objective: To compare the safety and efficacy of Na+ replacement vs fluid restriction in patients with hyponatremia and CNS manifestations.

Study Design: Prospective non-randomized study of 53 post-menopausal women: mean Na+ 111 X 5.2 days.

Intervention:
- Group-1: IV saline Prior to intubation
- Group-2: IV saline After intubation
- Group-3: Fluid Restriction

Primary Objectives: Determine overall patient mortality and long-term neurologic functionality.
Chronic Hyponatremic Encephalopathy in Postmenopausal Women: Time to Respiratory Failure

Ayus & Arief et al. JAMA. 281:2299-2304, 1999

Recovery
Impaired
Nursing Home
Coma
Death

Delta Na+: 22 meq/l
Rate of Correction: 10 meq/36 hrs
100% Survival

Delta Na+: 30 meq/l
Rate of Correction: 6.0 meq/41 hrs
63% Dead-Coma

Delta Na+: 3.0 meq/l
Rate Correction: 2.0 meq/41 hrs
93% Dead-Coma

Pre-Intubation
Post-Intubation
Fluid Restriction

Tumlin
So now what do you think of 3% Saline?
“But Wait There’s More”
Acute Postoperative Hyponatremic Encephalopathy: Differential Gender Effect

Study Objective: To determine the clinical outcome and factors that contribute the development of acute post-operative hyponatremic encephalopathy

Study Design:
- Patient Source: 76,678 consecutive surgical cases
- Baylor University Hospital
- Intervention: Post-Operative Hyponatremia: Definition < 128 meq/l
  - 739 cases: unadjusted incidence: 0.96%
- Non-Encephalopathic Controls:
  - 674 patients with Na+,128 without encephalopathy
- Encephalopathic Cases: 0.96%
  - 65 patients with postoperative encephalopathy

Acute Postoperative Hyponatremic Encephalopathy: Differential Gender Effect

Acute Postoperative Hyponatremic Encephalopathy: Marked Predilection for Female Gender


Tumlin
Sodium Chloride: NOT always your Enemy
Where we Agree!!: “If its Goofy Treat it”
Interim Summary

- Hyponatremia with Encephalopathy is associated with increased mortality and permanent neurologic impairment.

- Hyponatremic encephalopathy with associated respiratory failure is life-threatening condition and immediate intervention.

- Female patients have a higher incidence & increased rate of neurologic sequelae compare to males.

- If patient is altered hypertonic saline should be considered.
“What about less severe Sodium Levels?”
Mortality & Serum Sodium: What is the Cut Off?

- Study Objective: To determine whether hyponatremia alone or concurrent with other co-morbid conditions contribute to patient mortality.

- Study Design: Retrospective analysis of 45,693 hospital admissions at Rochester General Hospital with serum Na+ <135 meq/L.

- Chart review of 53 with hospital death: Mean Na+<120
- Chart review of 38 patients surviving: Mean Na+<110

- Study Endpoints:
  - Patient mortality over range of Hyponatremia
  - Identification of confounding co-morbidities contributing to increased mortality

Mortality & Serum Sodium: Do Patients Die from or with Hyponatremia?

Impact of Hospital-Associated Hyponatremia on Selected Outcomes

15% Risk In-Hospital Mortality with serum Na+ < 110

Hyponatremia: < 138 meq/L admitted to Tufts Medical Center 200-2007 53,236

Impact of Hospital-Associated Hyponatremia on Selected Outcomes

Unadjusted Odds Ratio for Clinical Outcome

- In Hospital Mortality
- Transfer to Long-term Care

Peak Mortality 120-124
Chawla & Sterns et.al. CJASN 2011

Admission Serum Na⁺ (meq/l)

- >138
- 133
- 128
- 123
- 118
- <118

1.0 1.45 2.49 3.33 3.17 3.18
1.0 1.11 1.35 1.53 1.94 1.78
1.0 1.11 1.35 1.53 1.94 1.78
1.0 1.11 1.35 1.53 1.94 1.78
1.0 1.11 1.35 1.53 1.94 1.78
1.0 1.11 1.35 1.53 1.94 1.78

“Why would mortality be Higher with moderate hyponatremia?”
Mortality of “Mild” Hyponatremia Driven By Associated Co-Morbidities

<table>
<thead>
<tr>
<th>Serum Na+ Range</th>
<th>Percentage Died</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>110-125 meq/l</td>
<td>73%</td>
<td>51% Sepsis, 60% AKI</td>
</tr>
<tr>
<td>126-134 meq/l</td>
<td>66%</td>
<td></td>
</tr>
<tr>
<td>Na+ &lt; 110 meq/l</td>
<td>81%</td>
<td></td>
</tr>
</tbody>
</table>

73% patients Na+ < 110 were being treated with HCTZ or SSRI.

Mild Hyponatremia: Risk for Myocardial Infarction Among Community Subjects

Increased Incidence of Acute Myocardial Infarction with Mild Hyponatremia

- $42\%$
- $23\%$
- $14\%$

Take That Dr. Tumlin!
<table>
<thead>
<tr>
<th>Qi Con</th>
<th>Tumlin</th>
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</thead>
</table>

<table>
<thead>
<tr>
<th>Proposition #3</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Correction of Mild Hyponatremia in Patients with Congestive Heart Failure Should be Standard of Care Therapy”</td>
</tr>
</tbody>
</table>
Effects of Tolvaptan in Hospitalized Patients With Worsening Heart Failure

- Study Objective: Determine the short and intermediate effects of Tolvaptan in patients hospitalized for heart failure
- Study Design: Randomized, prospective, Phase II dose finding study - 319 patients with LV dysfunction (EF<40%) and heart failure resistant to standard therapy
- Intervention: Oral Tolvaptan 30, 60, or 90mg vs placebo Plus diuretics and standard therapy for 60 days.
- Primary Objectives: Change in body weight at 24 hrs Worsening CHF (Death, re-hospitalization or unscheduled visits within 60 days

Effects of Tolvaptan in Hospitalized Patients With Worsening Heart Failure


Tolvaptan Doses

<table>
<thead>
<tr>
<th>Mg Doses Tolvaptan</th>
<th>Standard Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>90</td>
<td>90</td>
</tr>
</tbody>
</table>

Change in Body Wt (Kg) From Admission

Day-1

Discharge

Last Visit

PLB
Short-term Clinical Effects of Tolvaptan an Oral Vasopressin Antagonist, in Hospitalized Patients with Heart Failure: EVERST Trial

● Study Objective: To determine the safety and efficacy of oral Tolvaptan in patients hospitalized for Heart Failure

● Study Design: Two identical prospective, randomized, double-blind, placebo-controlled trials. Sites-359: North-South America, & Europe in 2048 (trial A) and 2085 (trial B) patients hospitalized with heart failure

● Intervention: Patients randomized to 30 mg Tolvaptan or matching placebo, 48 hours of admission

● Primary End Point: Body weight at day 7 or discharge

Secondary endpoints: Dyspnea Day-1 Edema

Short-term Clinical Effects of Tolvaptan an Oral Vasopressin Antagonist, in Hospitalized Patients with Heart Failure: EVERST Trial

Short-term Clinical Effects of Tolvaptan an Oral Vasopressin Antagonist, in Hospitalized Patients with Heart Failure: EVEREST Trial

Note: 60% of patient experience minimal or no improvement in Dyspnea

Correction of Hyponatremia with Tolvaptan Does NOT Alter All-Cause or Cardiovascular Mortality

EVEREST Trial

Proposition #2 “Apart from Neurologic Impairment, there is no real need to correct Hyponatremia”
“Now Hold on a Minute”
Mild Hyponatremia Contributes to Falls and Traumatic Fractures Among Elderly

- **Study Objective:** Determine whether “Hyponatremia” is associated with gait and attention deficits resulting in higher frequency of traumatic bone fractures.

- **Study Design:** Case control study of 513 patients > 65 years evaluated for falls and traumatic bone fractures.

- **Controls:** Randomly selected age-sex matched controls with hyponatremia but without h/o of fall or fracture.

- **Main Endpoint:** Odds ratio (OR) of bone fracture after incidental fall associated with hyponatremia.

Mild Hyponatremia Contributes to Falls and Traumatic Fractures Among Elderly

Mild Hyponatremia Contributes to Falls and Traumatic Fractures Among Elderly

Chronic Hyponatremia Induces Total Hip & Femoral Neck Bone Loss

- BMD Density reduced by 30%
- BMD reduced by 80% by micro CT,
- BMD reduced 60% by bone histomorphometry
Hyponatremia: Correlation and Diagnosis of Associated Neurologic Sequelae

Table 1. Classifications of hyponatremia

<table>
<thead>
<tr>
<th>Classification</th>
<th>Criteria</th>
<th>Limitations of Clinical Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate (125–129 mmol/L) versus severe/profound&lt;sup&gt;a&lt;/sup&gt; (&lt;125 mmol/L)</td>
<td>Absolute $S_{Na}$ concentration</td>
<td>Symptoms do not always correlate with degree of hyponatremia</td>
</tr>
<tr>
<td>Acute versus chronic</td>
<td>Time of development (cutoff 48 h)</td>
<td>Time of development not always known</td>
</tr>
<tr>
<td>Symptomatic versus asymptomatic</td>
<td>Presence of symptoms</td>
<td>Many symptoms aspecific; chronic hyponatremia may be symptomatic</td>
</tr>
<tr>
<td>Hypotonic, isotonic, or hypertonic</td>
<td>Measured serum osmolality</td>
<td>Ineffective osmoles (e.g., urea, ethanol) are also measured</td>
</tr>
<tr>
<td>Hypovolemic, euvolemic, hypervolemic</td>
<td>Clinical assessment of volume status</td>
<td>Clinical assessment of volume status has low sensitivity and specificity</td>
</tr>
</tbody>
</table>

<sup>a</sup>$S_{Na} < 125$ mmol/L is defined as “severe hyponatremia” by the United States guideline, and as “profound hyponatremia” by the European guideline.<sup>7,9</sup>
Chronic Hyponatremia Slows Cognition, Neural Recognition and Visual Response Times

Visual Response latencies improve following correction of hyponatremia
Correcting hyponatremia may not directly reduce cardiovascular mortality in heart failure but may alter mortality associated with the indirect consequences of chronic hyponatremia.
ROUND #4

Qi Con

Tumlin Con

“Correction of Mild Hyponatremia – Use of Vaptans to Treat Cirrhosis Associated Hyponatremia is Standard of Care Therapy”
Pharmacodynamic Effects of a Nonpeptide Antidiuretic Hormone V2 Antagonist in Cirrhotic Patients With Ascites

Fig. 3. Urine sodium excretion during 24 hours after dose (mEq/24 h). Although not significantly dose related, there was an increase of urine sodium levels in patients given VPA-985.

Fig. 4. Urine potassium excretion during 24 hours after dose (mEq/24 h). Although not significantly dose related, there was an increase of urine potassium levels in patients given VPA-985.

V2 antagonist – excretes Na and K

HEPATOLOGY, Vol. 36, No. 5, 2002

49 cirrhotic patients with hyponatremia, Tolvaptan 15 mg daily
48 patients, without Tolvaptan

RESULTS:

Twenty-three (47%) patients in the tolvaptan group and 17 (35%) in the control group had normal serum sodium on day 7 (p = 0.25).

Serum sodium improved in 30 (61%) patients in the tolvaptan group versus 17 (35%) patients in the control group (p = 0.011).

Na: from < 125 to ≥ 125 or 125-134 to ≥ 135mmol/L on day 7.

Adverse events occurred in 46-47% of patients in both groups, and tolvaptan was not associated with worsened liver function.

Zero 30 day mortality in patients with normal serum Na+ on day 7 died versus 16% 30-day mortality in those with persistent hyponatremia

CONCLUSION: Short-term tolvaptan treatment is safe and can improve serum sodium level in cirrhotic patients with hyponatremia.

Annals Hepatology 2017 Jan-Feb;16(1):123.
## Clinically Approved Uses of Vaptans: US European Union and Japan

<table>
<thead>
<tr>
<th>Drug</th>
<th>United States (FDA)</th>
<th>European Union (EMA) indications</th>
<th>Japan (PMDA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolvaptan</td>
<td>Hypervolemic or euvoletic hyponatremia (≤125 mEq/L or symptomatic and resistant) in SIADH and heart failure. No more than 30 days.</td>
<td>Hyponatremia secondary to SIADH</td>
<td>Volume overload resistant to diuretics in heart failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fluid retention resistant to diuretics in hepatic cirrhosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ADPKD patients with large and rapidly increasing kidney volumes</td>
</tr>
<tr>
<td>Conivaptan</td>
<td>Hypervolemic or euvoletic hyponatremia in hospitalized patients</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Mozavaptan</td>
<td>None</td>
<td>None</td>
<td>Hyponatremia in paraneoplastic SIADH</td>
</tr>
</tbody>
</table>
Are there other treatments apart from 3% saline and the Vaptans?
Urea: How does it work?

Urea induces an osmotic diuresis and increases free water excretion.
Urea Reduces Neurologic Sequelae of Chronic Hyponatremia Compared with Lixivaptan

Rat Model Hyponatremia: Liquid diet with vasopressin

Really? What Now?
What should we do?

Aristotelian Logic

Law of Identity

Either Here  Or Here

Null Set (Law of Excluded Middle)

Law of Non-Contradiction (Either-Or)

Law of Logic Inferences

Over Here

No, this way

STOP  KEEP MOVING
Table 2. Comparison of the United States and European guidelines

<table>
<thead>
<tr>
<th>Subject</th>
<th>United States Guideline</th>
<th>European Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute or symptomatic hyponatremia</td>
<td>Severe symptoms: Bolus 3% NaCl (100 ml over 10 min × 3 as needed)</td>
<td>Severe symptoms: Bolus 3% NaCl (150 ml over 20 min 2–3 times as needed)</td>
</tr>
<tr>
<td></td>
<td>Moderate symptoms: Continuous infusion 3% NaCl (0.5–2 ml/kg per h)</td>
<td>Moderate symptoms: Bolus 3% NaCl (150 ml 3% over 20 min once)</td>
</tr>
<tr>
<td>Chronic hyponatremia SIAD</td>
<td>Fluid restriction (first line)</td>
<td>Fluid restriction (first line)</td>
</tr>
<tr>
<td></td>
<td>Demeclocycline, urea, or vaptan (second line)</td>
<td>Urea or loop diuretics + oral NaCl (second line)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Do not recommend or recommend against vaptan&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recommend against lithium or demeclocycline</td>
</tr>
<tr>
<td>Hypovolemic hyponatremia</td>
<td>Isotonic saline</td>
<td>Isotonic saline or balanced crystalloid solution</td>
</tr>
<tr>
<td>Hypervolemic hyponatremia</td>
<td>Fluid restriction</td>
<td>Fluid restriction</td>
</tr>
<tr>
<td></td>
<td>Vaptans&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Recommend against vaptan</td>
</tr>
<tr>
<td>Correction rates</td>
<td>Minimum: 4–8 mmol/L per d, 4–6 mmol/L per d (high risk of ODS)</td>
<td>No minimum</td>
</tr>
<tr>
<td></td>
<td>Limits: 10–12 mmol/L per d, 8 mmol/L per d (high risk of ODS)</td>
<td>Limit: 10 mmol/L per d</td>
</tr>
<tr>
<td>Management of overcorrection</td>
<td>Baseline $S_{Na} \geq 120$ mmol/L: probably unnecessary</td>
<td>Start once limit is exceeded</td>
</tr>
<tr>
<td></td>
<td>Baseline $S_{Na} &lt; 120$ mmol/L:</td>
<td>Consult an expert to discuss</td>
</tr>
<tr>
<td></td>
<td>start relowering with electrolyte-free water or desmopressin after correction exceeds 6–8 mmol/L per d</td>
<td>infusion containing electrolyte-free water (10 ml/kg) with or without 2 μg desmopressin iv</td>
</tr>
</tbody>
</table>

<sup>a</sup>“Do not recommend” when $S_{Na} < 125$ mmol/L, “recommend against” when $S_{Na} < 125$ mmol/L.

<sup>b</sup>In liver cirrhosis, restrict to patients where potential benefit outweighs risk of worsened liver function.
CUTTING THROUGH THE FOG
Reality can be so complex that equally valid observations from differing perspectives can appear to be contradictory.
Qi and Tumlin approach:

- IV 3% NaCl when dealing symptomatic/severe hyponatremia
- Investigate and target etiology whenever possible.
- Limit correction <10 mmol/L per day, regardless of presumed onset of duration.
- Don’t trust calculation. Rely on measurements.
- Consider vaptan when all others failed and when expected treatment duration is short (patient with late stage cancer).
- Urea - a potential option --
Thank you!

That's all Folks!