Hyponatremia in the ICU: Morbidity, Mortality and Therapy

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Prevalence of dysnatremias at initial presentation to a health care provider
(data from 303,577 samples on 120,137 patients available for analysis)

Hyponatremia is an independent risk factor for in-hospital mortality

Study of 4,123 patients ≥65 years old admitted to a community hospital
3.5% had a serum $[\text{Na}^+] < 130$ mEq/L at admission
In this study, hyponatremia was found to be a predictor of in-hospital mortality (RR=2.0)

RR=relative risk.
Most recently...

Prospective cohort study of 98,411 adults hospitalized between 2000-2003
Assessed mortality in-hospital and at 1 and 5 years

Prevalence of serum Na+ < 135 meq/L was 14.5%
Those with hyponatremia: older (67 v. 63.1 yrs) and more comorbid conditions

# Odds-Ratio of Death in Hyponatremia

Serum sodium values (meq/L)

<table>
<thead>
<tr>
<th>In-hospital mortality</th>
<th>135-144</th>
<th>&lt; 135</th>
<th>130-134</th>
<th>125-129</th>
<th>120-124</th>
<th>&lt; 120</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (ref)</td>
<td>1.47</td>
<td>1.37</td>
<td>2.01</td>
<td>1.67</td>
<td>1.46</td>
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<td>1 (ref)</td>
<td>1.38</td>
<td>1.35</td>
<td>1.53</td>
<td>1.78</td>
<td>1.03</td>
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<tr>
<td>1 (ref)</td>
<td>1.25</td>
<td>1.24</td>
<td>1.33</td>
<td>1.29</td>
<td>1.09</td>
<td></td>
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</tbody>
</table>

1 year mortality

5 year mortality

Resolution of hyponatremia

In this study, more than one serum sodium level was available on 52,468 patients. Allowed investigators to look into the effects of resolution v. non-resolution of hyponatremia on mortality:

<table>
<thead>
<tr>
<th></th>
<th>Persistent (n = 4254)</th>
<th>Resolved (n = 3794)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mortality</td>
<td>6.2%</td>
<td>3.9%</td>
</tr>
<tr>
<td>1 year mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mortality</td>
<td>23.5%</td>
<td>18.5%</td>
</tr>
<tr>
<td>5 year mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mortality</td>
<td>40.8%</td>
<td>38.5%</td>
</tr>
</tbody>
</table>
Impact on length of stay and other outcomes

2 recent studies:

- LOS is increased from 1 to 2 days in patients with hyponatremia
- Patients with hyponatremia had between 12-58% increased risk of requiring an ICU stay (higher risk associated with lower initial sodium level)
- Total cost per admission increased from $1300 to $3500 (higher costs associated with lower sodium levels)

Callahan et al. Hosp Pract 2009; 121
Zilberberg et al. BMC Pulm Med 2008; 8:16
Does treatment matter?

Prospective review of lab and chart data over 6 months in a large teaching hospital

104 patients with serum [Na\(^+\)] <125 mEq/L identified

Only 28 (26%) had plasma osmolality measured, 29 (27%) urine osmolality, 11 (10%) urinary sodium, 8 (8%)

33% had “significant” management errors

- Fluid restriction and IV saline, fluid restriction in hypovolemia, hypotonic fluids in SIADH

27% mortality rate (28 of 104 patients)

- 20% mortality in patients managed appropriately
- 41% mortality in patients with management errors

Therapy of Hyponatremia

Two Key Questions
How much correction is enough to improve outcomes?
How much correction is too much?
Clinical Hyponatremia

- **Acute** (<48 hrs): Cerebral edema, seizures, death due to herniation especially in young women and children
- **Chronic** (>48 hrs): Adaptations minimize brain cell swelling, but reversibly alter neurologic function:
  - Nausea and vomiting
  - Confusion & personality changes
  - Gait disturbances
  - Seizures with very low serum sodium values
Acute Hyponatremia: Water Intoxication

Clinical symptoms first described in 1920’s and reproduced in experimental animals
Rowntree LG. Pharmacol Exp Ther 1926:29:135

First case of fatal cerebral edema from tap water by proctoclysis reported in 1935
Helwig FC. JAMA 1935:104:1569
Acute Hyponatremia

Normal study

Fatal hyponatremia
Clinical Hyponatremia: Rapid Correction

Rapid Correction

Acute hyponatremia: Generally well tolerated

Chronic hyponatremia (>48 hrs): Delayed onset of neurological deterioration associated with pontine and extrapontine demyelination
Central Pontine Myelinolysis

New disease of unknown etiology was found in four patients in Boston City Hospital and first reported in 1959. Dozens of case reports soon followed prompting a search for an etiology. Eventually an association with hyponatremia was made.

Osmotic Demyelination Syndrome

Question #1

How much correction of hyponatremia is “enough” to prevent complications in severe acute hyponatremia?
Consensus Conference on Treatment of Acute Hyponatremia in Marathon Runners

**Recommended Therapy:**

In the field: 3% saline 100 ml over 10 minutes, repeated x 2 if needed

In hospital: 3% saline 100 ml or 1 ml/kg bolus followed by 100 ml/hr or 1-2 ml/kg/hr

Therapeutic hypernatremia for cerebral edema

30 ml bolus of 23.4% saline (equivalent to 238 ml 3% saline)

$\Delta$ Serum Na = 5 mEq/L

Reversed clinical signs of brain herniation in most cases

Decreased intracranial pressure by 40%

Hypertonic Saline for Seizures, Coma or Cerebral Edema: Data @ ≤ 4 hours

<table>
<thead>
<tr>
<th>Study</th>
<th>Etiology</th>
<th>Age/Sex</th>
<th>Seizure</th>
<th>Cerebral Edema</th>
<th>Initial Sodium Level, mmol/L</th>
<th>Post-Treatment Sodium Level, mmol/L</th>
<th>Time Between Laboratory Values, h</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Worthley and Thomas⁹²</td>
<td>Postoperative</td>
<td>65 M</td>
<td>Yes</td>
<td>Unknown</td>
<td>109</td>
<td>116</td>
<td>0.5</td>
<td>Recovered</td>
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<tr>
<td>Worthley and Thomas⁹⁹</td>
<td>Postoperative</td>
<td>47 F</td>
<td>Yes</td>
<td>Unknown</td>
<td>109</td>
<td>117</td>
<td>0.5</td>
<td>Disabled*</td>
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<td>Postoperative</td>
<td>28 F</td>
<td>Yes</td>
<td>Unknown</td>
<td>100</td>
<td>109</td>
<td>0.5</td>
<td>Recovered</td>
</tr>
<tr>
<td>Worthley and Thomas⁹²</td>
<td>Burns</td>
<td>45 M</td>
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<td>Unknown</td>
<td>106</td>
<td>112</td>
<td>0.5</td>
<td>Recovered</td>
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<tr>
<td>Worthley and Thomas⁹⁴</td>
<td>Psychosis/polydipsia</td>
<td>67 F</td>
<td>Yes</td>
<td>Unknown</td>
<td>99</td>
<td>106</td>
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<tr>
<td>Drescher et al⁹³</td>
<td>Psychosis/polydipsia</td>
<td>63 F</td>
<td>Yes</td>
<td>Unknown</td>
<td>100</td>
<td>108</td>
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<tr>
<td>Snell and Bartley⁹¹</td>
<td>Hypoadrenal/polydipsia</td>
<td>25 M</td>
<td>Yes</td>
<td>No</td>
<td>111</td>
<td>117</td>
<td>3.6</td>
<td>ODS/recovered†</td>
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<td>Runner</td>
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<td>Yes</td>
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<td>121</td>
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<td>Hew-Butler et al⁹⁹</td>
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<td>116</td>
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<tr>
<td>Rae⁹⁸</td>
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<tr>
<td>Schreiber et al⁹²</td>
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<td>Fisher et al¹⁰⁰</td>
<td>SSRI (outpatient)</td>
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<td>Unknown</td>
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<td>112</td>
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Abbreviations: ODS, osmotic demyelination syndrome; DDAVP, desmopressin; SSRI, selective serotonin reuptake inhibitor.

*Given additional 90-ml bolus of 29.2% saline after resolution of seizures; 31-mmol/L increase in serum sodium level over 8 hours.

†Water diuresis after adrenal replacement; 28-mmol/L increase in serum sodium level in 42 hours.

Sterns, Semin Nephrol 29:282-299
Hypertonic Saline for Seizures, Coma or Cerebral Edema: Data @ ≤ 4 hours

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<td>109</td>
<td></td>
<td></td>
</tr>
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4 to 6 mEq/L Increase Appears To Be “Enough”

Abbreviations: ODS, osmotic demyelination syndrome; DDAVP, desmopressin; SSRI, selective serotonin reuptake inhibitor.
*Given additional 90-mL bolus of 29.2% saline after resolution of seizures; 31-mmol/L increase in serum sodium level over 8 hours.
†Water diuresis after adrenal replacement; 28-mmol/L increase in serum sodium level in 42 hours.

Sterns, Semin Nephrol 29:282-299
Therapy of Hyponatremic Emergencies- Summary

Goal: 4 to 6 mEq/L increase in serum sodium concentration
2 ml/kg bolus of 3% saline for severe symptoms (repeated if necessary) or
1 to 2 ml/kg infusion of 3% saline for 2 to 3 hours
Question #2

How much correction of hyponatremia is “enough” to cause complications in severe chronic hyponatremia?
How much is too much?
# How Much is Too Much?

**CPM by Autopsy (Fatal cases)**

<table>
<thead>
<tr>
<th>Author</th>
<th>Δ Na/day</th>
<th>Δ Na/2 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norenberg¹</td>
<td>20 mEq/L</td>
<td></td>
</tr>
<tr>
<td>Ayus²</td>
<td>25 mEq/L</td>
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</tr>
</tbody>
</table>

**Non-fatal cases**

<table>
<thead>
<tr>
<th>Author</th>
<th>Δ Na/day</th>
<th>Δ Na/2 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterns¹,²,³</td>
<td>12 mEq/L</td>
<td>18 mEq/L</td>
</tr>
<tr>
<td>Ellis⁴</td>
<td>10 mEq/L</td>
<td></td>
</tr>
<tr>
<td>Karp⁵</td>
<td>10 mEq/L</td>
<td>21 mEq/L</td>
</tr>
</tbody>
</table>

². Ann Internal Med 1987; 107:656  
³. JASN 1994;4:1522  
⁴. QJM 1995; 88:905  
⁵. Medicine 1993; 72:359
Serum Na ≤ 105 mEq/L
Rate of Correction and Outcome

Data from Sterns
JASN 1994;4:1522
Serum Na ≤ 105 mEq/L
Rate of Correction and Outcome

Data from Sterns
JASN 1994;4:1522
Treatment of Chronic Hyponatremia

- Limits are not goals
- Target therapy to stay well clear of limits
  - 6 to 8 mEq/L daily
- Use special care in patients at high risk for osmotic demyelination:
  - Chronic hyponatremia
  - Alcoholism
  - Malnutrition
  - Liver disease
  - Burns
  - Hypokalemia
  - Serum Na ≤ 105 mEq/L
Avoiding Inadvertent Rapid Correction

Reversibly impaired water excretion
- Volume depletion
- DDAVP
- Hypocortisolism
- Thiazide diuretics
- SSRI’s
- Nausea & alcohol withdrawal

In these cases, the stimulus for impaired water excretion is corrected quickly, and a rapid water diuresis then ensues.

Maximally dilute urine increases the serum sodium concentration by > 2 mEq/L/hr
Continued vigilance with frequent measurements of the serum sodium concentration and attention to urine output is essential in all patients with very low serum sodium concentrations.
Equations - serious pitfalls

\[ \Delta SNa \text{ after 1 liter of infusate } = \]

\[ \frac{\text{Infusate Na} - \text{Serum Na}}{\text{Total Body Water} + 1} \]

Assumes all of the infusate is retained; does not consider urine losses of electrolyte or water

Must be vigilant to watch for water diuresis which will lead to much more rapid correction than predicted

3% Saline for Serum Na <120 mEq/L

\[ \Delta \text{Serum [Na]} \text{ with 1 L infusate} = \frac{\text{Infusate [Na]} - \text{[Na]}}{\text{Total Body Water} + 1} \]

Mohmand et al, CJASN 2:1110-1117, 2007
3% Saline for Serum Na <120 mEq/L

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Mohmand et al, CJASN 2:1110-1117, 2007
Lower Serum Na = Higher Risk of Overcorrection

Mohmand et al, CJASN 2:1110-1117, 2007
Serum Sodium (mmol/l)

Urine Osmolality (mOsm/kg)

Reversing Overcorrection

Storns, R. Kidney Int August, 2009
Re-Induction of Hyponatremia Prevents Myelinalysis

<table>
<thead>
<tr>
<th></th>
<th>Rapid Correction</th>
<th>Rapid Correction Plus Re-Lowering</th>
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</thead>
<tbody>
<tr>
<td>SNa Pre-Rx</td>
<td>108 ± 2 mmol/l</td>
<td>104 ± 2 mmol/l</td>
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<tr>
<td>ΔSNa at 12 hrs</td>
<td>--</td>
<td>29 ± 1 mmol/l</td>
</tr>
<tr>
<td>ΔSNa at 24 hrs</td>
<td>29 ± mmol/l</td>
<td>14 ± 1 mmol/l</td>
</tr>
<tr>
<td>Sx’s Day 5</td>
<td>12/12</td>
<td>1/16</td>
</tr>
<tr>
<td>Deaths Day 10</td>
<td>12/12</td>
<td>1/16</td>
</tr>
</tbody>
</table>

Vasopressin Receptor Antagonists
## AVP-Receptor Subtypes

<table>
<thead>
<tr>
<th>Receptor Subtype</th>
<th>Site of Action</th>
<th>Pharmacologic Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_{1A}$</td>
<td>Vascular smooth muscle</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td></td>
<td>Platelets</td>
<td>Platelet aggregation</td>
</tr>
<tr>
<td></td>
<td>Lymphocytes and monocytes</td>
<td>Coagulation factor release</td>
</tr>
<tr>
<td></td>
<td>Hepatocytes</td>
<td>Glycogenolysis</td>
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<tr>
<td>$V_{1B}$</td>
<td>Anterior pituitary</td>
<td>ACTH and $\beta$-endorphin release</td>
</tr>
<tr>
<td>$V_{2}$</td>
<td>Renal collecting duct cells</td>
<td>Free water absorption</td>
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</tbody>
</table>

ACTH=adrenocorticotropic hormone
# Nonpeptide AVP Receptor Antagonists

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Tolvaptan</th>
<th>Lixivaptan</th>
<th>Satavaptan</th>
<th>Conivaptan</th>
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<tr>
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<td>V&lt;sub&gt;2&lt;/sub&gt;</td>
<td>V&lt;sub&gt;2&lt;/sub&gt;</td>
<td>V&lt;sub&gt;2&lt;/sub&gt;</td>
<td>V&lt;sub&gt;1a/V&lt;sub&gt;2&lt;/sub&gt;&lt;/sub&gt;</td>
</tr>
</tbody>
</table>

| Route of administration | Oral | Oral | Oral | IV |

| Urine volume | ↑ | ↑ | ↑ | ↑ |
| Urine osmolality | ↓ | ↓ | ↓ | ↓ |

| Na<sup>+</sup> excretion/24 h | ↔ | ↔ for low dose | ↑ for high dose | ↔ | ↔ |

Serum Sodium by Visit

Severe Hyponatremia Group

SIADH Responded Better to Tolvaptan Than CHF and Cirrhosis

Mean increase of the serum sodium between baseline and day 30 in cirrhosis, CHF, and SIADH

![Bar chart showing the mean increase of serum sodium between baseline and day 30 in cirrhosis, CHF, and SIADH. The chart indicates that SIADH responded better to tolvaptan than CHF and cirrhosis.]
Conivaptan in Euvolemic Hyponatremic Patients

**Change From Baseline in Serum [Na+]**

Mean (SE) change from baseline in serum [Na+] with intravenous conivaptan

Treatment of Hyponatremia

Summary

Acute hyponatremia:
- *Prompt* correction may avoid morbidity and mortality from cerebral edema
- *Adequate* correction: 4 to 6 mmol/l

Chronic symptomatic hyponatremia:
- *Limited* correction avoids iatrogenic neurologic injury: <10 mmol/l/24 hrs; <18 mmol/l/48 hr; <20 mmol/l/72 hrs