The Impact of Hyponatremia: 
*Role of the Pharmacist in Improving Care*

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OVERVIEW OF HYPONATREMIA

SCOPE OF THE PROBLEM
The Impact of Hyponatremia:  
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Learning Objective

• Examine the prevalence and clinical and economic consequences of hyponatremia

Hyponatremia

• The most common electrolyte disorder seen in clinical practice\(^1\)\(^-\)\(^3\)
• Commonly defined as serum sodium concentration ([Na\(^+\)] ≤135 mEq/L, but cut-off values vary

<table>
<thead>
<tr>
<th>Serum [Na(^+)], mEq/L</th>
<th>Severe hyponatremia</th>
<th>Moderate hyponatremia</th>
<th>Mild hyponatremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120</td>
<td>120-130</td>
<td>131-135</td>
<td></td>
</tr>
</tbody>
</table>

Hyponatremia: Incidence & Consequences

- Occurs in up to 3.2 to 6.1 million persons annually\(^1\)
- Estimated 1 million hospitalizations annually with 1\(^o\) or 2\(^o\) discharge diagnosis of hyponatremia\(^1\)
- Up to 15% of hospitalized patients, 24.5% of ICU patients\(^2,3\)
- Hospital-acquired hyponatremia is common, tends to be more severe
- Associated with significant morbidity in patients with a variety of underlying disease states\(^4\)
- May lead to death if not treated appropriately\(^4,5\)
- Incidence increases with age\(^6\)

ICU, intensive care unit.

Hyponatremia is Underreported

- Clinical laboratory values vs ICD-9 codes 1999-2000
- 2632 cases of hyponatremia identified using laboratory data alone
- 66% did not have appropriate ICD-9 code
  - 94% of moderately hyponatremic patients
  - 87% of severely hyponatremic patients
- Reported cases of hyponatremia from databases represent only 1/3 of cases

Hyponatremia is Often Mismanaged

- Review of 104 patients with serum [Na⁺] <125 mEq/L from 6-mo lab/chart data in a large teaching hospital
  - 49% of diagnoses inconsistent with clinical details
  - 33% had “significant” management errors


THE PATHOPHYSIOLOGIC MECHANISMS UNDERLYING HYPONATREMIA
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• Describe the pathophysiology of hyponatremia as well as its signs and symptoms

Role of Arginine Vasopressin (AVP) in Regulating Water Balance

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Receptor-Mediated Effects of AVP

<table>
<thead>
<tr>
<th>Receptor subtype</th>
<th>Site(s) of action</th>
<th>Activation effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1a</td>
<td>Vascular smooth muscle cells</td>
<td>Vasoconstriction, myocardial stimulation</td>
</tr>
<tr>
<td></td>
<td>• Platelets</td>
<td>• Platelet aggregation</td>
</tr>
<tr>
<td></td>
<td>• Lymphocytes and monocytes</td>
<td>• Cytokine release</td>
</tr>
<tr>
<td></td>
<td>• Liver</td>
<td>• Glycogenolysis</td>
</tr>
<tr>
<td>V1b</td>
<td>Anterior pituitary</td>
<td>ACTH and β-endorphin release</td>
</tr>
<tr>
<td>V2</td>
<td>Renal collecting duct principal cells</td>
<td>Renal free water absorption</td>
</tr>
</tbody>
</table>

Dysregulation of Normal AVP Response Complicates Many Disease States

<table>
<thead>
<tr>
<th>Disease State</th>
<th>Prevalence of Hyponatremia in Hospitalized Pts</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure (HF)</td>
<td>20% – 30%</td>
<td>Neurohormonal activation</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>30% – 40%</td>
<td>Neurohormonal activation</td>
</tr>
<tr>
<td>Community-acquired pneumonia</td>
<td>10% – 30%</td>
<td>SIADH ± reset osmostat</td>
</tr>
<tr>
<td>AIDS</td>
<td>38%</td>
<td>SIADH</td>
</tr>
<tr>
<td>Neurologic injury (TBI, SAH, infection, intracerebral hemorrhage, massive cerebral infarction, others)</td>
<td>2.3% – 36.6%</td>
<td>SIADH, idiopathic</td>
</tr>
</tbody>
</table>

During extreme exercise (marathons + triathlons), up to 29% of athletes develop hyponatremia.

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Classification Algorithm

- [Na⁺] <135 mEq/L
  - Assess serum osmolality
  - >295 mOsm/kg Hyperosmolar
    - Hyperglycemia
    - Mannitol
  - 275-295 mOsm/kg Normo-osmolar
    - Pseudohyponatremia
    - Na-free irrigant solutions
  - <275 mOsm/kg Hypo-osmolar
    - ≥100 mOsm/L (inappropriately concentrated)
      - Impaired water excretion
    - <100 mOsm/L (maximally dilute)
      - Polydipsia

Assess urine osmolality

- Assess volume status
  - Hypervolemia
    - Increased ECF volume
    - Hyperglycemia
    - Mannitol
    - Mannitol
  - Euvolemia
    - Normal ECF volume
    - SIADH
    - Tumors
    - CNS disorders
    - Drug-induced
    - Pulmonary diseases
    - Other
  - Hypovolemia
    - Reduced ECF volume
    - Hypertension
    - Renal failure
    - Sepsis
    - Pregnancy


Etiologies of Hypo-osmolar Hyponatremia

<table>
<thead>
<tr>
<th>Hypervolemia</th>
<th>Euvolemia</th>
<th>Hypovolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>SIADH</td>
<td>Thiazide diuretics</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Tumors</td>
<td>Cerebral salt wasting</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>CNS disorders</td>
<td>Mineralocorticoid deficiency</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>Drug-induced</td>
<td>Salt-wasting nephropathy</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Pulmonary diseases</td>
<td>Bicarbonaturia, glucosuria, ketonuria</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Other</td>
<td>Gastrointestinal losses</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Glucocorticoid deficiency</td>
<td>Third space losses</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
<td>Sweat losses</td>
</tr>
<tr>
<td></td>
<td>Primary polydipsia</td>
<td></td>
</tr>
</tbody>
</table>

Hyponatremia: Risk Factors

**Miscellaneous conditions**
- Adrenal insufficiency
- Cirrhosis
- CNS impairment
- Heart failure
- Low body weight
- SIADH
- Surgery or injury
- Very old age
- Very young age

**Drugs**
- Antidepressants (TCAs, SSRIs, MAOIs)
- Antiepileptics
- Antihypertensives
- Antipsychotics
- Anticancer agents
- Diuretics
- NSAIDS
- Opiate derivatives
- Proton-pump inhibitors

TCAs, tricyclic antidepressants; SSRIs, selective serotonin reuptake inhibitors; MAOIs, monoamine oxidase inhibitors; CNS, central nervous system.

SSRI-Induced Hyponatremia

- Incidence: 0.5% – 32%¹
- Most cases during first few weeks of therapy¹
  - Normal serum [Na⁺] usually achieved within 2 weeks following discontinuation of drug
- Risk factors
  - Older age²
  - Concomitant diuretic therapy²
  - Low body weight¹
  - Baseline serum [Na⁺] <138 mEq/L²

Learning Objectives

- Examine the prevalence and clinical and economic consequences of hyponatremia

Consequences of Hyponatremia

- Osteoporosis and fractures
- Gait disturbances and falls
- Cerebral edema
- Seizures, coma
- Increased mortality risk
- Increased hospital LOS
- Increased rate of ICU admission
- Neurologic dysfunction and decreased mental function
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Hyponatremia & Neurologic Dysfunction

The SF-12 is a subset of the SF-36 Health Survey and has been shown to reproduce at least 90% of the variance in PCS-36 and MCS-36 in both general and patient populations.


SF-12 Mental Component Summary (MCS)

With Hyponatremia (SALT Data)

- Depression
- CHF Norm
- Liver/Kidney Disease Norm
- SIIADH
- Cirrhosis
- HypoNa+
- CHF HypoNa+

The SF-12 is a subset of the SF-36 Health Survey and has been shown to reproduce at least 90% of the variance in PCS-36 and MCS-36 in both general and patient populations.

Hyponatremia, Gait, & Falls

- Case-control study of 122 patients with asymptomatic chronic hyponatremia (serum [Na+] 126 ± 5 mEq/L), 244 matched controls
- Hyponatremic patients more often admitted for falls than controls (21.3% vs 5.3%; P < .001)
- Frequency of falls the same—regardless of the level of hyponatremia
- Gait instability significantly increased in patients with chronic hyponatremia
- Attention errors increased 1.2-fold (P = .001) in hyponatremic patients compared with normal controls
  - Comparable to increase observed after moderate alcohol intake in healthy volunteers

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**Correction of Hyponatremia Stabilizes Gait**

Gait stability assessed in 12 hyponatremic patients ([Na⁺] 124-130 mEq/L)
- Patients asked to walk on pressure mat.
- Skew from midline of path measured as length of walk.

Gait instability significantly increased in hyponatremia  
Gait stability normalized  

Correction of hyponatremia  


**Hyponatremia & Fractures in Ambulatory Falls**

- Case-control study of bone fractures after incidental fall¹
  - Patients presenting with falls and fractures had significantly higher incidence of hyponatremia (13.6%) than age-matched controls (3.9%)
  - Hyponatremia drug-induced in 53% (36% diuretics, 17% SSRI), due to SIADH in 37%
- Hyponatremia significantly associated with fracture occurrence (P<.01)²
  - Independent of age and gender²
- Even mild chronic hyponatremia increases fracture risk³

Bone quality should be assessed in all patients with chronic hyponatremia

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Symptoms Correlate With Severity & Rate of Decline in Serum [Na⁺]¹

- Asymptomatic presentation is common²
- May present with mild, nonspecific symptoms¹
- Degree of symptomatology is surrogate for duration of hyponatremia¹
- Symptoms from underlying disease process is also common¹


Increasing severity of hyponatremia and rate of [Na⁺] decline

Acute Versus Chronic Hyponatremia

- Symptomatic but less impaired: usually CHRONIC
- Life-threatening: usually ACUTE

<table>
<thead>
<tr>
<th>Acute (≤48 h)</th>
<th>Chronic (&gt;48 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms include:</td>
<td>Symptoms include:</td>
</tr>
<tr>
<td>• Cerebral edema</td>
<td>• Nausea/vomiting</td>
</tr>
<tr>
<td>• Seizures</td>
<td>• Confusion or personality changes</td>
</tr>
<tr>
<td>• Increased mortality risk</td>
<td>• Neurological dysfunction</td>
</tr>
<tr>
<td>Rapid correction reverses cerebral edema without sequelae</td>
<td>• Gait disturbances</td>
</tr>
<tr>
<td></td>
<td>• Seizures (with very low serum [Na⁺] levels)</td>
</tr>
<tr>
<td></td>
<td>Rapid correction may cause brain dehydration and osmotic demyelination syndrome (ODS)</td>
</tr>
</tbody>
</table>
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Acute Versus Chronic Hyponatremia

Pathophysiology

Hypotonic state

Acute hyponatremia (≤48 hours)

Extracellular Na+ decreases by Na+ loss or H2O gain

H2O moves into brain along osmotic gradients, causing symptomatic cerebral edema

When brain swelling >8%, it exceeds skull capacity

Herniation and death

Adaptation

Chronic hyponatremia (>48 hours)

Compensatory mechanism begins

Loss of electrolytes and osmolytes decreases brain solute content

Brain edema is virtually absent

H2O moves into brain along osmotic gradients, causing symptomatic cerebral edema

When brain swelling ≤8%, it is within skull capacity

Compensatory mechanism continues

TREATING HY PonATREMIA: CONVENTIONAL AND EMERGING THERAPEUTIC OPTIONS

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Learning Objective

• Compare and contrast the pharmacology, efficacy, and safety of conventional therapies as well as those of newer agents

Treatment Overview

• Most important treatment factors
  – Severity of neurologic symptoms\(^1,2\)
  – Volume status\(^1,2\)
  – Acute vs chronic\(^2,3\)
  – Identify likely cause of hyponatremia\(^1,4\)

• Principles to guide treatment
  – Weigh risks and benefits\(^5\)
    • Neurologic consequences can follow both failure to promptly treat and excessively rapid rate of correction\(^3\)
    • Even modest improvement in serum [Na\(^+\)] have survival benefits\(^1,6\)
  – Monitor serum [Na\(^+\)] frequently\(^2,6\)
  – Address underlying disease and stop offending medications\(^1\)

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**Correct Serum [Na⁺] to Safe Level at Safe Rate**

- Insufficient correction\(^1\)
  - Cerebral edema

- Too aggressive correction\(^1\)
  - Osmotic demyelination syndrome (ODS)

- Raise [Na⁺] by <8-12 mEq/L in 1st 24 h\(^1,3\)
- Raise [Na⁺] by <18 mEq/L in 1st 48 h\(^1\)
- Symptomatic: 1 mEq/L/h until neurologic symptoms resolve or [Na⁺] ≥120 mEq/L or a total magnitude correction of 18 mEq/L is achieved\(^1,2\)


**Risks of Hyponatremia & Correction: A Balancing Act**

<table>
<thead>
<tr>
<th>Acute hyponatremia</th>
<th>Chronic symptomatic hyponatremia</th>
<th>Chronic asymptomatic hyponatremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marked brain edema</td>
<td>Some brain edema</td>
<td>Minimal brain edema</td>
</tr>
<tr>
<td>Minimal brain volume regulation</td>
<td>Partial brain volume regulation</td>
<td>Complete brain volume regulation</td>
</tr>
</tbody>
</table>

Correcting Hyponatremia

1. Add to the numerator

\[ \text{Serum } [\text{Na}^+] = \frac{\text{Na}^+ + \text{K}^+}{\text{Body water}} \]

2. Subtract from the denominator

\[ \text{Na}^+ + \text{K}^+ \]


Treatments for Hyponatremia

<table>
<thead>
<tr>
<th>Treatment\textsuperscript{1,2}</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| Saline infusion               | • Rapid response in symptomatic patients\textsuperscript{1}  
• Complex calculations\textsuperscript{1}  
• Not be used in edema-forming disorders\textsuperscript{2} |
| Fluid restriction             | • Inexpensive\textsuperscript{3}  
• Slow and limited response\textsuperscript{1,4}  
• Adherence concerns\textsuperscript{1,3} |
| Demeclocycline                | • No need to limit water intake\textsuperscript{1}  
• Targets excessive AVP\textsuperscript{1}  
• Slow response\textsuperscript{1,4}  
• Nephrotoxic in CHF and cirrhosis\textsuperscript{1,3,4} |
| Loop diuretics                | • Allows relaxation of fluid restriction\textsuperscript{4}  
• May cause volume, K\textsuperscript{+} and Mg\textsuperscript{2+} depletion\textsuperscript{1} |
| AVP receptor antagonists      | • Target excessive AVP\textsuperscript{4}  
• Aquaresis (solute free urine output)\textsuperscript{1,3}  
• Not to be used in hypovolemic states\textsuperscript{5} |

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### The Role of Hypertonic Saline (HTS)

- **When to consider hypertonic saline (3% NaCl)**
  - Symptomatic hyponatremia (seizure, coma)\(^1\)
  - Acute severe hyponatremia (<24 h, <120 mEq/L)\(^2\)
  - Hyponatremia worsening on normal saline (0.9% NaCl)\(^3\)
  - Induced hypernatremic states for prevention/treatment of cerebral edema\(^2\)
- **Discontinue HTS when serum [Na\(^+\)] reaches 120-130 mEq/L\(^3\)**
  - Exception: states of cerebral edema with Na\(^+\) augmentation
- **Safety concerns:** Requires ICU monitoring\(^2\)
- **Adrogué-Madias formula,** used to predict rise in [Na\(^+\)] after HTS, may underestimate correction rate, increasing risk for inadvertent overcorrection\(^1\)
- **No randomized trials performed\(^1\)**
- **HTS may or may not be combined with loop diuretic\(^1\)**

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### Fluid Restriction

- **Fluid restriction very patient-specific\(^1\)**
- **Standard procedure:** restrict fluid to <1 L/d\(^1\)**
- **Slow rate of improvement\(^2\)**
- **Poor patient adherence\(^2\)**
- **Predictors of failure\(^3\)**
  - High urine osmolality (>500 mOsm/kg H\(_2\)O)
  - Urine [Na\(^+\)] and [K\(^+\)] > serum [Na\(^+\)]
  - 24-h urine output <1,500 mL/d
  - Increase in serum [Na\(^+\)] <2 mEq/L in 24 h

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**Demeclocycline**

- Causes a nephrogenic form of diabetes insipidus, decreasing urine concentration even in the presence of high plasma AVP levels
- Dose: 600 to 1,200 mg/d in divided doses
  - Takes several days to achieve maximal diuretic effects
  - Wait 3 to 4 days before deciding to increase the dose
- Can cause
  - Reversible azotemia
  - Nephrotoxicity, especially in patients with cirrhosis
- Monitor renal function on a regular basis and discontinue if increasing azotemia


**The Vaptans: Overview**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Receptor Selectivity/Affinity</th>
<th>Rte</th>
<th>T-1/2, h</th>
<th>Urine Volume</th>
<th>Urine Osmolality</th>
<th>FDA Approval Status</th>
<th>Therapy Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conivaptan</td>
<td>Mixed (V&lt;sub&gt;1A&lt;/sub&gt;+V&lt;sub&gt;2&lt;/sub&gt;);&lt;sup&gt;1&lt;/sup&gt; 10-fold higher affinity V&lt;sub&gt;2&lt;/sub&gt; vs V&lt;sub&gt;1A&lt;/sub&gt;&lt;sup&gt;2&lt;/sup&gt;</td>
<td>IV&lt;sup&gt;1&lt;/sup&gt;</td>
<td>3-8&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>↑↑&lt;sup&gt;3,4&lt;/sup&gt;</td>
<td>↓↓&lt;sup&gt;3,4&lt;/sup&gt;</td>
<td>Approved 2005&lt;sup&gt;5&lt;/sup&gt;</td>
<td>4 d&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tolvaptan</td>
<td>Selective for V&lt;sub&gt;2&lt;/sub&gt;&lt;sup&gt;3,4&lt;/sup&gt;; V&lt;sub&gt;2&lt;/sub&gt; affinity 1.8× native AVP; V&lt;sub&gt;2&lt;/sub&gt; affinity 29× that of V&lt;sub&gt;1A&lt;/sub&gt;</td>
<td>Oral&lt;sup&gt;1&lt;/sup&gt;</td>
<td>6-12&lt;sup&gt;1,6&lt;/sup&gt;</td>
<td>↑↑&lt;sup&gt;3,4&lt;/sup&gt;</td>
<td>↓↓&lt;sup&gt;3,4&lt;/sup&gt;</td>
<td>Approved 2009&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Long-term&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lixivaptan</td>
<td>V&lt;sub&gt;2&lt;/sub&gt;&lt;sup&gt;3,4&lt;/sup&gt;</td>
<td>Oral&lt;sup&gt;1&lt;/sup&gt;</td>
<td>7-10&lt;sup&gt;1&lt;/sup&gt;</td>
<td>↑↑&lt;sup&gt;3,4&lt;/sup&gt;</td>
<td>↓↓&lt;sup&gt;3,4&lt;/sup&gt;</td>
<td>Phase III&lt;sup&gt;4&lt;/sup&gt;</td>
<td>NA</td>
</tr>
</tbody>
</table>

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The Vaptans: Mechanism of Action

Conivaptan Double-Blind Clinical Trial

- Double-blind, placebo-controlled, randomized, multicenter study
- 84 patients euvoelemic/hypervolemic hyponatremia (serum [Na⁺] 115 to <130 mEq/L)
- Common etiology of hyponatremia
  - SIADH
  - Lung disease, abdominal infection, or malignancy
  - CHF
- All patients received ≤2 L/d fluid restriction
- Conivaptan administered 20 mg loading dose (over 30 min) with 4-d continuous infusion of either 40 mg/d or 80 mg/d infusion
- Serum or plasma [Na⁺] assessed at pre-dose (hour 0) and at 4, 6, 10, and 24 h post-dose on all treatment days

Conivaptan Double-Blind Clinical Trial (continued)

- Mean increase in serum [Na⁺] from baseline significantly higher with conivaptan at 24, 48, 72 h after treatment
  - Conivaptan 80 mg: 8.1–8.8 mEq/L
  - Conivaptan 40 mg: 6.4–6.9 mEq/L
  - Placebo: 0.4–1.9 mEq/L


Conivaptan Double-Blind Clinical Trial (continued)

- Mean free water clearance significantly higher from baseline to treatment Days 1 and 2 with conivaptan 40 + 80 mg/d ($P<.001$, $P=.03$, $P=.01$ vs placebo)
  - Greatest increase on treatment Day 1
- Most common adverse effects included hypotension, postural hypotension, infusion site inflammation, pyrexia, and hyperkalemia
  - No occurrence of ODS

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### Conivaptan Open-Label Trial: Serum \([\text{Na}^+]\) at Day 11 & Day 34

![Graph showing mean serum \([\text{Na}^+]\) at Day 11 & Day 34 for Vaprisol 20 mg/d (n=37) and Vaprisol 40 mg/d (n=214).]


### Tolvaptan for Hyponatremia: SALT-1 & SALT-2

- Double-blind, randomized, multicenter studies of 448 patients with euvolemic or hypervolemic hyponatremia (serum \([\text{Na}^+]\) <135 mEq/L) treated with placebo or tolvaptan, 15 mg/d
  - For first 4 d, dose could be increased from 15 to 30 mg or from 30 to 60 mg according to regimen designed for slow correction of serum \([\text{Na}^+]\) to ≥135 mEq/L
  - If serum \([\text{Na}^+]\) rose above 145 mEq/L or increased too fast (>12 mEq/L in 24 h or >8 mEq/L in 8 h on Day 1), the next dose was withheld or decreased, or fluid intake was increased
- Within 8 h after first tolvaptan dose, serum \([\text{Na}^+]\) levels significantly higher in tolvaptan group than in placebo group
  - 20% had normalized serum \([\text{Na}^+]\) vs 4% receiving placebo

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**Tolvaptan for Hyponatremia:**  
**SALT-1 & SALT-2** (continued)

- Increase in serum [Na+] in tolvaptan group sustained 30 d

<table>
<thead>
<tr>
<th>Serum [Na+] (mEq/L)</th>
<th>SALT-1</th>
<th>SALT-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>128.5 ± 4.5</td>
<td>129.0 ± 3.5</td>
</tr>
<tr>
<td>Day 4</td>
<td>133.9 ± 4.8</td>
<td>135.3 ± 3.6</td>
</tr>
<tr>
<td>Day 30</td>
<td>135.7 ± 5.0</td>
<td>135.9 ± 5.9</td>
</tr>
</tbody>
</table>

- Most common adverse effects included thirst, dry mouth, fatigue, polyuria, constipation, hyperglycemia
  - No occurrence of ODS


**SALTWATER Open-Label Extension: Increases in Serum [Na+] Maintained >2 Years**

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SALT Trials: 
Effect of Tolvaptan on SF-12

- **Mental Component Summary Score (MCS)**
  - Statistically greater mean improvement observed with tolvaptan than with placebo
  - Represents clinically meaningful improvement in mental function

- **Physical Component Summary Score (PCS)**
  - Changes between groups not significantly different
  - Improvement of hyponatremia in chronic illnesses does not dramatically change overall physical burden of the disease


EVEREST: Tolvaptan in CHF

- Randomized, double-blind, multicenter trial of 4133 patients hospitalized for ADHF and treated with tolvaptan (30 mg/d) or placebo for ≥60 d in addition to standard therapy. Only 8% of patients had hyponatremia (<134 mEq/L). HF hospitalization ≤48 h.
  - LVEF ≤40%
  - Fluid overload; ≥2 of the following
    - Jugular venous distention ≥10 cm
    - Pedal edema
    - Dyspnea
  - Exclusions
    - Creatinine >3.5 mg/dL; K+ >5.5 mEq/L; Hgb <9 g/dL
    - Recent or planned revascularization or device implant
    - Acute MI during hospitalization
    - Systolic blood pressure <90 mm Hg

EVEREST: Tolvaptan in CHF (continued)

- Short-term results favored tolvaptan vs placebo
  - Improved dyspnea by Day 1
  - Significant reductions in body weight due to fluid loss at Day 1 and Day 7/discharge
- Long-term results on morbidity and mortality showed no significant difference between tolvaptan and placebo

LVEF, left ventricular ejection fraction; Hgb, hemoglobin; STEMI, ST segment elevation myocardial infarction.

Post-hoc Exploratory Analysis EVEREST: CV Mortality & Morbidity

The Impact of Hyponatremia: 
*Role of the Pharmacist in Improving Care* 

Meta-analysis: Vaptans for Hyponatremia 

- 15 RCTs of vaptans with or w/o fluid restriction 
- Primary result: Normal or significant increase in serum [Na⁺] at 3-7 d 
- Vaptan treatment significantly increased 
  - Early response rate (11 trials): RR, 3.15; 95% CI, 2.27-4.37 
  - Late response rate (4 trials): RR, 2.27; 95% CI 1.79-2.89 
- Rates of hypernatremia (6 trials): 
  RR, 2.21; 95% CI, 0.61-7.96 
- No cases of ODS 


The Vaptans: Pharmacokinetics 

**Tolvaptan¹** 
- ≥40% of dose is absorbed 
- Peak concentrations between 2 and 4 h 
- Food does not impact bioavailability 
- Metabolized by CYP3A 
- Mean terminal half-life 12 h 

**Conivaptan²** 
- Mean terminal half-life 5-8.6 h 
- Mean clearance 9.5-18.7 L/h³ 
- Metabolized by CYP3A 

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**The Vaptans: Dosing**

**Tolvaptan**

- Should be initiated and reinitiated only in a hospital
- Initial oral dose of 15 mg administered once daily without regard to meals
- Increase to 30 mg once daily after at least 24 h
- Maximum dose 60 mg once daily
- Avoid fluid restriction during first 24 h of therapy

**Conivaptan**

- Loading dose: 20 mg IV over 30 min
- Maintenance infusion 20-40 mg over 24 h (if desired)
- May be administered for additional 1 to 4 d
- To minimize risk of vascular irritation
  - Administer through large veins
  - Change infusion site every 24 h

---

**Tolvaptan Administration via NG Tube**

- Bioavailability of tolvaptan 15 mg crushed and administered via NG tube vs oral tablet swallowed intact
  - Randomized crossover study in 28 healthy fasted adults
  - Each dose administered with 240 mL H₂O

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NG*</th>
<th>Oral*</th>
<th>Ratio, %</th>
<th>CI&lt;sub&gt;90%&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₁ (ng*h/mL)</td>
<td>381</td>
<td>512</td>
<td>74.3</td>
<td>68.1 – 81.0</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;∞&lt;/sub&gt; (ng*h/mL)</td>
<td>391</td>
<td>527</td>
<td>74.2</td>
<td>68.1 – 80.9</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>77.6</td>
<td>87.3</td>
<td>88.9</td>
<td>80.1 – 98.6</td>
</tr>
</tbody>
</table>

- CI<sub>90%</sub> for AUC not within 80%-125%, so bioequivalence could not be concluded
- May be viable alternative dosing route with clinical monitoring

---

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The Vaptans: Precautions

Conivaptan/Tolvaptan
- Do not use with potent CYP3A and PGP inhibitors
- Do not use in hypovolemic patients
- Use with caution in patients with hepatic or renal impairment
- Recommend frequent monitoring of serum [Na⁺] and volume
- Do not administer to anuric patients, as no benefit is expected

Tolvaptan¹
- Do not use in patients who are unable to sense or appropriately respond to thirst

Conivaptan²
- May cause significant infusion site reactions


The Vaptans: Drug-Drug Interactions

Tolvaptan¹
- Substrate of CYP3A
- Concomitant use of tolvaptan and potent CYP3A inhibitors (ketoconazole, itraconazole, clarithromycin, ritonavir, or indinavir) is contraindicated
- Does not significantly change pharmacokinetics of other CYP3A substrates
- Coadministration with digoxin results in a 1.3-fold increase in digoxin

Conivaptan²
- Substrate/inhibitor of CYP3A
- Concomitant use of conivaptan and potent CYP3A inhibitors (ketoconazole, itraconazole, clarithromycin, ritonavir, or indinavir) is contraindicated

The Impact of Hyponatremia:  
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Monitoring Patients on Conivaptan

- Only for use in hospitalized patients
- Administer through large veins, change infusion site every 24 h to minimize risk of vascular irritation
- Monitor serum [Na⁺] and neurologic status appropriately, as serious neurologic sequelae can result from overly rapid correction (>12 mEq/L in 24 h)
- Discontinue conivaptan if patient develops undesirably rapid rate of rise of serum [Na⁺], and carefully monitor serum [Na⁺] and neurologic status
  - If serum [Na⁺] continues to rise, do not resume treatment
  - If hyponatremia persists or recurs, and patient has had no evidence of neurologic sequelae of rapid rise in serum [Na⁺], conivaptan may be resumed at reduced dose

Vaprisol® (conivaptan hydrochloride injection) [prescribing information]. Deerfield, Ill; Astellas Pharma US, Inc.; February 2011.  

Monitoring Patients on Tolvaptan

- The medication MUST be started in the hospital
- Obtain serum [Na⁺] every 4-6 h for 48 h
  - While no cases of ODS have been reported, there are many instances where the correction rate can be too fast
- After 48 h, the vast majority reach a steady state and can be safely discharged with outpatient monitoring
- Check serum [Na⁺] once a week for the first month, then monthly once stable
- As many as 20%-30% of patients (especially those with the highest urine osmolalities) may need concomitant water restriction to see a rise in serum [Na⁺]

The Impact of Hyponatremia: 
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The Vaptans: Postdischarge Therapy

Need for postdischarge vaptan therapy should be based on the etiology of SIADH and the risk of chronic SIADH

<table>
<thead>
<tr>
<th>SIADH Etiology</th>
<th>RR of Chronic SIADH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumors producing AVP ectopically</td>
<td>High</td>
</tr>
<tr>
<td>Drug-induced, agent continued</td>
<td></td>
</tr>
<tr>
<td>Brain tumors</td>
<td></td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td></td>
</tr>
<tr>
<td>Inflammatory brain lesions</td>
<td></td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td></td>
</tr>
<tr>
<td>Nausea, pain, prolonged exercise</td>
<td></td>
</tr>
<tr>
<td>Drug-induced, agent discontinued</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
</tr>
<tr>
<td>Postoperative hyponatremia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low</td>
</tr>
</tbody>
</table>


Treatment Algorithm

<table>
<thead>
<tr>
<th>Euvolemic hyponatremia</th>
<th>Hypervolemic hyponatremia</th>
<th>Hypovolemic hyponatremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid restriction; vaptan under select circumstances:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Inability to tolerate fluid restriction or failure of fluid restriction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Prevention of worsened hyponatremia with increased fluid administration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Unstable gait and/or high fracture risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Serum [Na+] &lt;125 mEq/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Need to correct serum [Na+] to safer levels for surgery / procedures or ICU / hospital discharge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Therapeutic trial for symptom relief</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level 1: No or minimal symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid restriction; vaptan under select circumstances:</td>
</tr>
<tr>
<td>* Inability to tolerate fluid restriction or failure of fluid restriction</td>
</tr>
<tr>
<td>* Prevention of worsened hyponatremia with increased fluid administration</td>
</tr>
<tr>
<td>* Unstable gait and/or high fracture risk</td>
</tr>
<tr>
<td>* Serum [Na+] &lt;125 mEq/L</td>
</tr>
<tr>
<td>* Need to correct serum [Na+] to safer levels for surgery / procedures or ICU / hospital discharge</td>
</tr>
<tr>
<td>* Therapeutic trial for symptom relief</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level 2: Moderate symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaptan ± fluid restriction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level 3: Severe symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertonic NaCl followed by fluid restriction ± vaptan</td>
</tr>
</tbody>
</table>


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The Impact of Hyponatremia: 
Role of the Pharmacist in Improving Care

Learning Objective

- Examine the prevalence and clinical and economic consequences of hyponatremia
# The Impact of Hyponatremia: 
*Role of the Pharmacist in Improving Care*

## Impact of Hyponatremia on Selected Hospital Outcomes

<table>
<thead>
<tr>
<th>Type of Hyponatremia</th>
<th>In-hospital Mortality</th>
<th>Discharge to Short- or Long-term Care</th>
<th>Prolongation in LOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community-Acquired Hyponatremia (37.9%)</td>
<td>OR 1.52 (CI, 1.36-1.69)</td>
<td>Higher likelihood of discharge to short- or long-term care (37.5% vs 33.7%)</td>
<td>14% prolongation in LOS</td>
</tr>
<tr>
<td>Hospital Aggravated Hyponatremia (5.7%)</td>
<td>OR 2.30 (CI, 1.75-3.02)</td>
<td>Higher likelihood of discharge to short- or long-term care</td>
<td>Prolonged LOS</td>
</tr>
<tr>
<td>Hospital-Acquired Hyponatremia (38.2%)</td>
<td>OR 1.66 (CI, 1.39-1.98)</td>
<td>Higher likelihood of discharge to short- or long-term care (45.7% vs 31.9%)</td>
<td>Increase in LOS (median, 5 vs 4 d)</td>
</tr>
</tbody>
</table>

Admission $[Na^+] < 138$ mEq/L  
Decline in admission $[Na^+]$ at least 2 mEq/L  
Serum $[Na^+]$ nadir $< 138$ mEq/L


## Hyponatremia is an Independent Risk Factor for In-Hospital Mortality

- 1-year study of 4123 patients ($\geq 65$ y) admitted to community hospital; 3.5% had admission serum $[Na^+] < 130$ mEq/L\(^1\)
  - Linear trend in mortality evident as serum $[Na^+]$ decreased
  - Admission hyponatremia significant predictor of in-hospital mortality (RR, 1.95; \(P < .006\))
- Even mild hyponatremia is associated with increased in-hospital mortality\(^2\)

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**Failure to Measure Plasma & Urinary Osmolalities Associated With Increased Hyponatremia Mortality**

- 113 patients with severe hyponatremia (serum [Na⁺] ≤120 mEq/L)
- Relationship between lack of investigation for hyponatremia and increased mortality

![Graph showing mortality rates for serum, urine, and paired osmolality measurements.](Image)


**Impact of Hyponatremia on Cost in Hospitalized Patients With Heart Failure**

![Cost graph showing attributable costs for various levels of hyponatremia.](Image)

Effect of Serum [Na⁺] & Tolvaptan on LOS in Hospitalized Patients With HF

- Objectives of this post-hoc analysis of EVEREST trial
  - Compare LOS between normonatremic (n=1789) and hyponatremic (n=216) patients who were randomized to placebo
  - Evaluate the effect of tolvaptan (n=225) compared with placebo (n=216) on LOS in hyponatremic patients
- LOS in hyponatremic vs normonatremic patients
  - Serum [Na⁺] <135 mEq/L: LOS + 3.06 d (P<.001)
  - More severe hyponatremia: LOS + 5.17 d (P<.001)
- LOS tolvaptan vs placebo
  - 1.72 d shorter vs placebo (P=NS)
  - 2.12 d shorter in patients with more severe hyponatremia (P=NS)


Economic Benefit of Tolvaptan in Hyponatremic HF Patients

- Hospital cost and LOS for DRG hospitalizations of adult HF patients with complications, comorbidities estimated from HCUP 2008 NIS database
- Reductions in LOS associated with tolvaptan estimated from EVEREST trial data for hyponatremic patients
- Cost offset model used to evaluate impact of tolvaptan on LOS and hospital cost
  - LOS reduced 0.81 d among HF hospitalizations
  - $265 total cost savings per admission (based on wholesale acquisition cost of $250/d)
  - Supports clinical and economic benefit of tolvaptan use
  - Study limitation: Clinical trial patient profiles and relative LOS reductions may not be applicable to real-world patient populations

DRG, diagnosis-related group; HCUP, Healthcare Cost and Utilization Project; NIS, Nationwide Inpatient Sample.
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### SIADH Cost Analysis

- **Cost estimate methods**
  - HCUP 2009 Nationwide Inpatient Sample database
    - 21,718 patients hospitalized for SIADH: mean LOS of 5.7 d, mean total hospital costs of $8667
  - Used tolvaptan treatment duration of 4 d at cost of $250/dose
  - LOS reduction estimate based upon SALT-1 and SALT-2 trials
    - SIADH patients receiving tolvaptan had shorter hospital LOS (4.98 vs 6.19 d)
- **Results**
  - Cost offset model estimated LOS reduction of 1.11 d and total cost offset of $694 per admission
    - 95% CI for cost offset using Monte Carlo simulation was $73–$1405
  - Cost-neutral break-even mean duration of tolvaptan inpatient use: 6.78 d
  - Applying data to the 21,718 patients identified in the HCUP population, use of tolvaptan to treat these patients would result in total cost offset >$15 million


### Many Roles of the Pharmacist

- Monitor for hyponatremia development + resolution
- Participate in clinical decision making
- Participate in formulary decision making and address cost-containment concerns beyond acquisition costs
- Consider a more pathophysiologic approach to diagnosis and treatment
- Ensure optimal management of hyponatremia
- Educate clinicians on hyponatremia
- Consider drug-related causes of hyponatremia
- Ensure appropriate monitoring for morbidities of hyponatremia
- Development of preventative hospital systems directed toward hyponatremia

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Top 10 Take-Aways

1. When hyponatremia is present, consider drug-related causes
2. Be vigilant for cognitive dysfunction at any level of hyponatremia
3. Chronic consequences of hyponatremia
4. Impact of hyponatremia on costs and outcomes is real
5. Role of AVP in pathophysiology of SIADH and hypervolemia
6. Treatment algorithm
7. Rate of serum [Na⁺] correction
8. Monitor, monitor, monitor during [Na⁺] correction for safety
9. Vaptans are necessary "tool" in treatment algorithm for hyponatremia
10. Vaptan AEs, drug interactions
The Impact of Hyponatremia: 
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Costs of Hyponatremia

- Direct costs estimated at $1.6 to $3.6 billion annually\(^1\)
  - Hospitalization costs account for \(\approx 70\%\)
- Associated with worse clinical and economic outcomes\(^2\)
- Patients with hyponatremia have
  - 12\% to 58\% increased risk of requiring ICU stay\(^2,3\)
  - Adjusted mean LOS of 3.06 d longer\(^4\)
  - 12\% to 64\% increased risk of requiring discharge to short- or long-term care facility\(^5\)
  - 41.2\% higher cost at 6 mo; 45.7\% higher at 1 y\(^6\)

LOS, length of stay.

10 Most Common Diagnoses Among Hospitalized Patients With Hyponatremia

<table>
<thead>
<tr>
<th>ICD-9-CM Discharge Code</th>
<th>Hyponatremia Present (n=10,899)</th>
</tr>
</thead>
<tbody>
<tr>
<td>486 Pneumonia, Organism Unspecified</td>
<td>6.0%</td>
</tr>
<tr>
<td>038 Septicemia</td>
<td>5.5%</td>
</tr>
<tr>
<td>276 Disorders of Fluid, Electrolyte, and Acid-base Balance(^4)</td>
<td>5.3%</td>
</tr>
<tr>
<td>428 Heart Failure</td>
<td>5.3%</td>
</tr>
<tr>
<td>250 Diabetes Mellitus</td>
<td>5.0%</td>
</tr>
<tr>
<td>584 Acute Renal Failure</td>
<td>3.9%</td>
</tr>
<tr>
<td>410 Acute Myocardial Infarction</td>
<td>3.2%</td>
</tr>
<tr>
<td>966 Complications Peculiar To Certain Specified Procedures</td>
<td>2.1%</td>
</tr>
<tr>
<td>518 Other Diseases Of Lung</td>
<td>2.0%</td>
</tr>
<tr>
<td>491 Chronic Bronchitis</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

\(^4\)Includes the 4-digit code for Hyponatremia (276.1).
The Impact of Hyponatremia: 
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Change in Serum [Na⁺] & Mortality

Crude Mortality, %

<table>
<thead>
<tr>
<th></th>
<th>In-hospital</th>
<th>1-year</th>
<th>5-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normonatremia (n=42176)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Resolution of Hyponatremia (n=3794)</td>
<td>1.26</td>
<td>1.19</td>
<td>1.18</td>
</tr>
<tr>
<td>Persistent Hyponatremia (n=4524)</td>
<td>2.37</td>
<td>1.55</td>
<td>1.32</td>
</tr>
<tr>
<td>Acquired Hyponatremia (n=1974)</td>
<td>2.44</td>
<td>1.54</td>
<td>1.4</td>
</tr>
</tbody>
</table>


Role of AVP in Edematous Disorders

CHF
- Cardiac output

Cirrhosis
- Peripheral resistance due to splanchnic vasodilation

Arterial underfilling
Stimulation of arterial baroreceptors
Nonosmotic release of AVP
Impaired H₂O excretion
Hypervolemic hyponatremia


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SIADH: Pathophysiology

- Caused by excessive levels of AVP as a result of disease, drug-induced pituitary release of AVP, or ectopic production of AVP
- AVP secretion not suppressed appropriately when plasma osmolality falls below the osmotic threshold\(^1\,^2\)
- The inability to suppress AVP secretion results in:
  - Impaired renal water excretion
  - Increased total body water
  - Hyponatremia
- “Dilute serum, nondilute urine”

Essential Criteria for Diagnosis of SIADH

- ↓ Effective osmolality of the ECF (\(P_{\text{osm}} < 275 \text{ mOsm/kg H}_2\text{O}\))
- Inappropriate urinary concentration (\(U_{\text{osm}} > 100 \text{ mOsm/kg H}_2\text{O}\)) with normal renal function at some level of hypo-osmolality
- Clinical euvolemia (no signs of hypovolemia or hypervolemia)
- Elevated urinary Na excretion despite normal salt and H\(_2\)O intake
- No other potential causes of euvoletic hypo-osmolality

\(P_{\text{osm}}\): plasma osmolality; \(U_{\text{osm}}\): urinary osmolality.


**The Impact of Hyponatremia:**
*Role of the Pharmacist in Improving Care*

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**Morbidities in Hospitalized Patients With Symptomatic Hyponatremia**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered sensorium</td>
<td>51.7</td>
</tr>
<tr>
<td>Seizures</td>
<td>22.5</td>
</tr>
<tr>
<td>Nausea &amp; vomiting</td>
<td>4.8</td>
</tr>
<tr>
<td>Gait disturbance &amp; falls</td>
<td>3.6</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>2.2</td>
</tr>
<tr>
<td>Coma</td>
<td>2.2</td>
</tr>
</tbody>
</table>


---

**Hyponatremia Associated With Increased Mortality in Patients in the ICU**

- Retrospective study in 77 medical, surgical, and mixed ICUs in Austria
- 151,486 adults admitted consecutively over 10 years (1998-2007)
  - Borderline (130 ≤ [Na⁺] <135 mEq/L) hyponatremia: 13.8%
  - Mild hyponatremia (125 ≤ [Na⁺] <130 mEq/L): 2.7%
  - Severe hyponatremia ([Na⁺] <125 mEq/L): 1.2%
- Independent mortality risk with increasing severity of hyponatremia
  - Borderline: OR, 1.32 (95% CI, 1.25-1.39)
  - Mild: OR, 1.89 (95% CI, 1.71-2.09)
  - Severe: OR, 1.81 (95% CI, 1.56-2.10)

## Impact of Hyponatremia on Mortality in Hospitalized Patients With Heart Failure

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>[Na(^+)], mEq/L</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe hyponatremia</td>
<td>6117</td>
<td>≤130</td>
<td>1.78</td>
<td>1.59-1.99</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>18,445</td>
<td>131-135</td>
<td>1.29</td>
<td>1.19-1.40</td>
</tr>
<tr>
<td>Normonatremia (ref)</td>
<td>87,682</td>
<td>136-145</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>3725</td>
<td>&gt;145</td>
<td>1.55</td>
<td>1.34-1.80</td>
</tr>
</tbody>
</table>

\(^a\)All \(P<.0001\)


## Impact of Hyponatremia on Survival in Cirrhosis

The Impact of Hyponatremia:  
*Role of the Pharmacist in Improving Care*

### Healthcare Costs Determinants

- **Direct** (medical and nonmedical)
- **Intangible** (emotional pain + suffering, inconvenience)
- **Indirect** (morbidity, mortality)
- **Opportunity** (lost opportunity, foregone revenue)

### Costs of Admission Hyponatremia

- **32% ICU admission**  
  - Moderate-Severe (≤129 mEq/L)  
  - 8 Day LOS  
  - Total costs $19,519

- **22% ICU admission**  
  - Normal (135-145 mEq/L)  
  - 6 Day LOS  
  - Total costs $17,085

- **26% ICU admission**  
  - Mild-Moderate (130-134 mEq/L)  
  - 8 Day LOS  
  - Total costs $18,054

**Difference**
- $2434 (Moderate-Severe vs Normal)
- $969 (Moderate-Severe vs Mild-Moderate)

The Impact of Hyponatremia:
Role of the Pharmacist in Improving Care

Costs Associated With Hyponatremia in the United States

• Direct cost of treating hyponatremia estimated as $1.6 to $3.6 billion annually\(^1\)
  – Based on inpatient hospital discharge data, published literature, an expert consensus panel

• 1-year medical costs for patients with hyponatremia were $19,215 vs $9,257 for normonatremic patients\(^2\)
  – Data from managed care database of >162,000 patients

• In hospitalized patients, $2,289 increase in costs attributable to hyponatremia\(^3\)
  – Based on data from 39 hospitals and 198,281 patients