A 75-year-old female was admitted for symptomatic hyponatremia with a serum $[\text{Na}^+]$=123 mmol/L. She has a several year history of mild chronic hyponatremia, but recently has experienced confusion and dizziness. She was euvoletic on clinical exam, and was not taking antidepressants or diuretics. After 3 days on a confirmed 1,000 ml/d fluid restriction, serum $[\text{Na}^+]$=126 mmol/L, but the patient is still symptomatic and complains of thirst. Laboratory data on day 3 are:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[\text{Na}^+]$, mEq/L</td>
<td>126</td>
</tr>
<tr>
<td>$[\text{K}^+]$, mEq/L</td>
<td>4.0</td>
</tr>
<tr>
<td>$\text{Uosm}$, mOsm/kg $\text{H}_2\text{O}$</td>
<td>335</td>
</tr>
<tr>
<td>$\text{Posm}$, mOsm/kg $\text{H}_2\text{O}$</td>
<td>265</td>
</tr>
<tr>
<td>$\text{urine }[\text{Na}^+]$, mEq/L</td>
<td>45</td>
</tr>
<tr>
<td>$\text{urine }[\text{K}^+]$, mEq/L</td>
<td>70</td>
</tr>
<tr>
<td>BUN, mg/dL</td>
<td>6</td>
</tr>
<tr>
<td>creatinine, mg/dL</td>
<td>0.8</td>
</tr>
<tr>
<td>TSH, $\mu\text{IU}/\text{L}$</td>
<td>3.5</td>
</tr>
<tr>
<td>plasma cortisol, $\mu\text{g}/\text{dL}$</td>
<td>18</td>
</tr>
</tbody>
</table>

**Issues to be discussed:**

1. Diagnosis of SIADH
2. Appropriate selection of therapy in hyponatremic patients
3. When to use fluid restriction and predictors of failure of fluid restriction
SIADH: essential criteria

• true plasma hypoosmolality
• urine concentration inappropriate for plasma osmolality ($U_{osm} > 100$ mOsm/kg $H_2O$)
• clinical euvolemia, no diuretic therapy
• absent renal sodium conservation ($U_{Na} > 30$ mmol/L)
• normal thyroid, adrenal and renal function


---

plasma AVP levels are inappropriately elevated in $>95\%$ of patients with SIADH

HN Registry: diagnostic tests obtained in patients diagnosed with SIADH by the treating physicians

<table>
<thead>
<tr>
<th>Test</th>
<th>All SIADH (%)</th>
<th>US SIADH (%)</th>
<th>EU SIADH (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Test Performed</td>
<td>175 (11)</td>
<td>116 (11)</td>
<td>52 (11)</td>
<td>0.793</td>
</tr>
<tr>
<td>All Bartter diagnostic criteria</td>
<td>732 (47)</td>
<td>506 (49)</td>
<td>215 (44)</td>
<td>0.070</td>
</tr>
<tr>
<td>• Serum osmolality</td>
<td>1034 (67)</td>
<td>685 (66)</td>
<td>327 (67)</td>
<td>0.862</td>
</tr>
<tr>
<td>• Urine osmolality</td>
<td>1063 (68)</td>
<td>749 (72)</td>
<td>294 (60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>• Urine sodium</td>
<td>975 (63)</td>
<td>688 (67)</td>
<td>274 (56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Additional Labs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cortisol</td>
<td>506 (33)</td>
<td>356 (34)</td>
<td>141 (29)</td>
<td>0.030</td>
</tr>
<tr>
<td>• TSH</td>
<td>984 (63)</td>
<td>655 (63)</td>
<td>318 (65)</td>
<td>0.569</td>
</tr>
<tr>
<td>All of the above</td>
<td>329 (21)</td>
<td>222 (22)</td>
<td>102 (21)</td>
<td>.789</td>
</tr>
<tr>
<td>Serum Uric Acid</td>
<td>422 (28)</td>
<td>262 (25)</td>
<td>160 (33)</td>
<td>0.003</td>
</tr>
</tbody>
</table>


---

treatments for hyponatremia

- isotonic saline infusion
- hypertonic saline infusion
- vaptan (conivaptan, tolvaptan) short-term
- fluid restriction
- demeclocycline
- furosemide + NaCl
- mineralocorticoids
- urea
- vaptan (tolvaptan) long-term
hyponatremia: symptom-based treatment recommendations

hyponatremia treatment algorithm based on neurological symptoms

**LEVEL 1 – NO OR MINIMAL SYMPTOMS:** difficulty concentrating, irritability, altered mood, depression, unexplained headache

**LEVEL 2 – MODERATE SYMPTOMS:** altered mental status, disorientation, confusion, unexplained nausea, gait instability

**LEVEL 3 – SEVERE SYMPTOMS:** coma, obtundation, seizures, respiratory distress, vomiting

\[ \text{ALL:} \] hypertonic NaCl\(^1\), followed by fluid restriction ± vaptan\(^2\)

\[ \text{HYPO:} \] solute repletion (isotonic NaCl iv or oral sodium replacement)\(^3\)

\[ \text{EU:} \] vaptan, limited hypertonic NaCl, or urea, followed by fluid restriction

\[ \text{HYPER:} \] vaptan, followed by fluid restriction

\[ \text{ALL:} \] fluid restriction, but consider pharmacologic therapy (vaptan, urea) under select circumstances:
  - inability to tolerate fluid restriction or predicted failure of fluid restriction (see table)
  - very low \([\text{Na}^+]\) (<125 mmol/L) with increased risk of developing symptomatic hyponatremia
  - need to correct serum \([\text{Na}^+]\) to safer levels for surgery or procedures, or for ICU/hospital discharge
  - unstable gait and/or high fracture risk
  - prevention of worsened hyponatremia with increased fluid administration
  - therapeutic trial for symptom improvement
choice of appropriate initial therapy


use of urine electrolytes to predict stringency of fluid restriction

<table>
<thead>
<tr>
<th>urine/plasma electrolyte ratio</th>
<th>recommended fluid consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1.0</td>
<td>0 mL</td>
</tr>
<tr>
<td>0.5–1.0</td>
<td>Up to 500 mL</td>
</tr>
<tr>
<td>&lt;0.50</td>
<td>Up to 1 L</td>
</tr>
</tbody>
</table>


*case #1: U/P electrolyte ratio = 85+50/120 = 1.12*
**fluid restriction**

- fluid restriction in patients with SIADH corrects hyponatremia by only 1-2 mmol/L/day, even when severe (<500 ml/day)

- in addition, fluid restriction is poorly tolerated because of increased thirst, with subsequent poor compliance


---

**success rates in treating hyponatremia by physicians in the HN Registry**

<table>
<thead>
<tr>
<th>diagnosis &amp; treatment</th>
<th>$\Delta [Na^+] \geq 5$ mmol/L</th>
<th>$[Na^+] \geq 130$ mmol/L</th>
<th>$[Na^+] \geq 135$ mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIADH, no rx (n=168)</td>
<td>41%</td>
<td>45%</td>
<td>20%</td>
</tr>
<tr>
<td>SIADH, FR (n=625)</td>
<td>44%</td>
<td>29%</td>
<td>10%</td>
</tr>
<tr>
<td>SIADH, NS (n=384)</td>
<td>36%</td>
<td>20%</td>
<td>4%</td>
</tr>
<tr>
<td>SIADH, tolvaptan (n=183)</td>
<td>78%</td>
<td>74%</td>
<td>40%</td>
</tr>
<tr>
<td>SIADH, 3% NaCl (n=78)</td>
<td>60%</td>
<td>25%</td>
<td>13%</td>
</tr>
</tbody>
</table>

at discharge, serum $[Na^+]$ was <135 mmol/L in 75% of patients, and ≤130 mmol/L in 43% of patients

decreases in serum [Na⁺] with fluid restriction and isotonic saline infusion


Nielsen et al., *JASN* 10:647-663, 1999
diuresis:
increased excretion of urine by the kidney; includes water and typically increased solute excretion as well

aquaresis:
increased excretion of water by the kidney without increased solute, i.e., electrolyte-sparing excretion of free water by the kidney

tolvaptan:
salt-water open label extension study

what aquareasis really looks like!

courtesy nephology fellows, Lenox Hill Hospital, New York, NY

SALT: mean increases in serum [Na+] after 30 d in patients with cirrhosis, HF, and SIADH

hyponatremia: osmotic demyelination syndrome

osmotic demyelination syndrome: clinical manifestations

- tremor
- incontinence
- hyperreflexia, pathological reflexes
- quadriplegia, quadriplegia
- dysarthria, dysphagia
- cranial nerve palsies
- mutism, locked-in syndrome
central pontine myelinolysis:
white areas in the middle of the pons indicate massive demyelination of descending axons (corticobulbar and corticospinal tracts)

Wright, Laureno & Victor
Brain 102:361-385, 1979

differentiating goals from limits of correction of hyponatremia
re-lowering of serum [\(\text{Na}^+\)] is only recommended in patients with high risk of ODS

patients at high risk of ODS

Table 3  Factors That Place Patients at High Risk of Developing the Osmotic Demyelination Syndrome with Correction of Chronic Hyponatremia

<table>
<thead>
<tr>
<th>High Risk of Osmotic Demyelination Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Serum sodium concentration ≤105 mmol/L</td>
</tr>
<tr>
<td>• Hypokalemia*</td>
</tr>
<tr>
<td>• Alcoholism*</td>
</tr>
<tr>
<td>• Malnutrition*</td>
</tr>
<tr>
<td>• Advanced liver disease*</td>
</tr>
</tbody>
</table>

L = liter; mmol = millimole.
*Unlike the rate of increase in serum sodium concentration, neither the precise level of the serum potassium concentration nor the degree of alcoholism, malnutrition, or liver disease that alters the brain’s tolerance to an acute osmotic stress have been rigorously defined.


osmotic demyelination syndrome (ODS)

one case of CPM has been reported following correction of hyponatremia using a vaptan as monotherapy in >5,000 patients to date; two cases of ODS have been reported with combined use of tolvaptan and hypertonic (3%) NaCl

reported case of ODS using a vaptan as monotherapy

A healthy 25-year-old female just completed her first marathon race. She felt ill toward the end of the race, but was able to walk back to her hotel unassisted. Six hours later, her roommate noticed that she was not making sense. She was taken to the nearby ER where she was found to be disoriented and confused but without focal neurological deficits. Vital signs were stable except for an increased respiratory rate to 32 and the patient was euvolemic by clinical exam. Laboratory data from the ER are:

| [Na⁺], mEq/L | 122 | Uosm, mOsm/kg H₂O | 412 |
| [K⁺], mEq/L | 3.5 | urine [Na⁺], mEq/L | 50 |
| Posm, mOsm/kg H₂O | 254 | urine [K⁺], mEq/L | 20 |
| BUN, mg/dL | 12 | glucose, mg/dL | 140 |
| creatinine, mg/dL | 0.8 | |

Issues to be discussed:
1. Exercise-associated hyponatremia
2. Time course and symptoms of EAH
3. Therapy of acute hyponatremias
EAH: definition

EAH is the occurrence of hyponatremia in individuals engaged in prolonged physical activity and is defined by a serum or plasma sodium concentration ([Na⁺]) below the normal reference range of the laboratory performing the test; for most laboratories, this is a [Na⁺] < 135 mmol/L.

EAH can occur during or after physical activity, and most commonly occurs in events lasting longer than four hours, although a few cases have been reported during shorter duration events.

London marathon, April 22, 2007

“A 22-year-old man died after completing his first London Marathon because he drank too much water. David Rogers collapsed at the end of the race and died yesterday in Charing Cross Hospital.”

“Today it emerged the fitness instructor from Milton Keynes died from hyponatraemia, or water intoxication. This is when there is so much water in the body that it dilutes vital minerals such as sodium down to dangerous levels. It can lead to confusion, headaches and a fatal swelling of the brain.”

p[Na⁺] = 122 mmol/L
drank Lucozade
fatal EAH: cerebral edema

normal brain  hyponatremic brain


brain volume regulation:

1. true loss of brain solute
2. can reduce or eliminate brain edema despite severe hypoosmolality
3. time dependent process
**EAH: incidence/prevalence**

- >100 reported cases, 9 documented deaths
- **runners requiring medical assistance:**
  - 6-40% (Cape town, Houston, San Diego, Pittsburgh)
- **prospective studies:**
  - Hawaii ironman triathlon, 1991: 9/30 (30%)
  - New Zealand ironman triathlon, 1997: 43/330 (18%; 45% of females)
  - Houston marathon, 2000: 33/117 (28%; 39% of females)
  - Boston marathon, 2002: 62/488 (13%; 22% of females)

**ALL PROSPECTIVE STUDIES: 15.2%**

Hyponatremia can be caused by **dilution** from retained water, or by **depletion** from electrolyte losses in excess of water.
Overhydration

Normonatremia

Biochemical Hyponatremia

Clinically significant hyponatremia

n = 2135
r = 0.32
P < 0.0001

Collaborative study: Auckland; Boston; Cape Town; Christchurch; Houston.

Boston marathon, 2002

Almond et al, *NEJM* 352:1550-1556, 2005

P<0.001 (Hyponatremia)
P<0.001 (Severe hyponatremia)
1. **DRINK BIG.** Drink, drink and drink some more. Not just on race day but every day.

2. **TIMING’S EVERYTHING.** About four hours before the race drink 80-100 oz of fluid.

3. **Don’t skip the sports drink at the aid stations even if you are not thirsty.**

4. **Get down as much sports drink at every aid station along the way.**

5. **PRACTICE, PRACTICE.** Like training for your big race you need to train yourself to drink lots of fluids before, during and after the race. Remember, practice makes perfect.

### Hyponatremia Treatment Algorithm Based on Neurological Symptoms

**LEVEL 1 – NO OR MINIMAL SYMPTOMS:** difficulty concentrating, irritability, altered mood, depression, unexplained headache

**LEVEL 2 – MODERATE SYMPTOMS:** altered mental status, disorientation, confusion, unexplained nausea, gait instability

**LEVEL 3 – SEVERE SYMPTOMS:** coma, obtundation, seizures, respiratory distress, vomiting

**HYPO:** solute repletion (isotonic NaCl iv or oral sodium replacement)^3  
**EU:** vaptan, limited hypertonic NaCl, or urea, followed by fluid restriction

**HYPER:** vaptan, followed by fluid restriction

**ALL:** hypertonic NaCl^1, followed by fluid restriction ± vaptan^2

**ALL:** fluid restriction, but consider pharmacologic therapy (vaptan, urea) under select circumstances:
- inability to tolerate fluid restriction or predicted failure of fluid restriction (see table)
- very low $[\text{Na}^+] <$125 mmol/L with increased risk of developing symptomatic hyponatremia
- need to correct serum $[\text{Na}^+]$ to safer levels for surgery or procedures, or for ICU/hospital discharge
- unstable gait and/or high fracture risk
- prevention of worsened hyponatremia with increased fluid administration
- therapeutic trial for symptom improvement

---

^1: Hyponatremia treatment algorithm based on neurological symptoms.
hypertonic saline correction

- choose desired correction rate of plasma [Na⁺] (e.g., 1.0 mEq/L/h)
- obtain or estimate patient’s weight (e.g., 70 kg)
- multiply weight X desired correction rate and infuse as ml/h of 3% NaCl (e.g., 70 kg X 1.0 mEq/L/h = 70 ml/h infusion)

OR:

- 100-200 ml bolus infusion (5-10 min) of 3% NaCl, repeat every 30 min until goal reached

FOR ALL SALINE CORRECTIONS:

- follow serum [Na⁺] and urine output every 2-4 hrs during the active correction

SUMMARY STATEMENT

For those athletes presenting with signs and symptoms consistent with EAHE, emergent intravenous treatment therapy with hypertonic saline is indicated and should not be delayed pending laboratory measurement or other diagnostic testing (Grade 1B).

differentiating goals from limits of correction of hyponatremia
re-lowering of serum [Na⁺] is only recommended in patients with high risk of ODS

An 80-year-old female was seen as an outpatient for chronic hyponatremia with a serum [Na⁺] that ranged from 125-129 mmol/L. Her main complaint was feeling unsteady on her feet, and she had a history of several falls in the past 2 years. Her only medication is HCTZ 25 mg/d for systolic hypertension. A recent DXA scan confirmed a diagnosis of osteoporosis in the LSS (T-score=-3.3) and hip (T-score=-2.7). Laboratory data:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Na⁺], mEq/L</td>
<td>127</td>
</tr>
<tr>
<td>[K⁺], mEq/L</td>
<td>3.9</td>
</tr>
<tr>
<td>Posm, mOsm/kg H₂O</td>
<td>263</td>
</tr>
<tr>
<td>BUN, mg/dL</td>
<td>10</td>
</tr>
<tr>
<td>creatinine, mg/dL</td>
<td>1.2</td>
</tr>
<tr>
<td>Uosm, mOsm/kg H₂O</td>
<td>480</td>
</tr>
<tr>
<td>urine [Na⁺], mEq/L</td>
<td>75</td>
</tr>
<tr>
<td>urine [K⁺], mEq/L</td>
<td>52</td>
</tr>
<tr>
<td>TSH, μU/L</td>
<td>2.9</td>
</tr>
<tr>
<td>plasma cortisol, μg/dL</td>
<td>18</td>
</tr>
</tbody>
</table>

Issues to be discussed:
1. Is chronic “asymptomatic” hyponatremia benign?
2. Gait instability and falls in chronic hyponatremia
3. Hyponatremia-induced osteoporosis
4. Other possible adverse effects of chronic hyponatremia
**hyponatremia:** association with adverse clinical outcomes

**relationship between hospital admission serum [Na⁺] and in-hospital mortality**

correcting hyponatremia improves mortality

 Corona et al. PLOSone, 10(4) Apr 23, 2015

hyponatremia: association with fractures
hyponatremia increased the risk of fracture in CKD independently of osteoporosis

1,408 female patients from Cork, Ireland adjusted for age, T-score, amenorrhea, steroid use, liver disease, smoking and EtOH use, liver disease, and osteoporosis treatments


chronic hyponatremia is also associated with increased adverse outcomes

increased mortality over a 12-year period of outpatient follow-up

significantly increased risk of fracture

six independent international studies have shown increased fracture rates in patients with hyponatremia – there seems little question about this – the real question now is: why does this occur and via what mechanisms?

increased risk of falls with “asymptomatic” hyponatremia

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>% Falls</th>
<th>Odds ratio</th>
<th>Adjusted odds ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>“asymptomatic” chronic hyponatremia</td>
<td>122</td>
<td>21.3%</td>
<td>9.45 (2.64–34.09)</td>
<td>67.43 (7.48–607.42)</td>
</tr>
<tr>
<td>normonatremic controls</td>
<td>244</td>
<td>5.35%</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*adjusted for age, sex and covariates

correction of hyponatremia normalizes gait stability in “asymptomatic” hyponatremia

serum $[\text{Na}^+] = 130$ mEq/L

serum $[\text{Na}^+] = 139$ mEq/L


chronic hyponatremia induced marked bone loss in rats

normonatremic

$[\text{Na}^+] = 140$

hyponatremic

$[\text{Na}^+] = 115$

bone micro-CT of rat femurs after chronic hyponatremia

[Na⁺] = 140 mmol/L

[Na⁺] = 114 mmol/L

Verbalis, Barsony et al. *JBMR* 25:554-663, 2010

hyponatremia induces a 5-fold increase in osteoclasts compared to normonatremic controls by TRAP staining

odds ratio for hyponatremia as a predictor of osteoporosis in NHANES III database

bone mineral density by of hip measured by DEXA; results adjusted for age, sex, BMI, physical activity, serum vitamin D (ng/mL) and diuretic use

mean serum [Na⁺] = 133.0 ± 0.2 mmol/L

Verbalis, Barsony, et al. JBMR 25:554-663, 2010

Syndrome of Inappropriate ADH Secretion and Severe Osteoporosis

Anne-Sophie Sejling, Ulrik Pedersen-Bjergaard, and Pia Eiken
Department of Cardiology, Nephrology, and Endocrinology, Hillestad Hospital, DK-3400 Hillerød, Denmark

• 36-yr-old male was diagnosed with SIADH at age 22
• sodium levels remained low from 111–130 mmol/L
• diagnosed with osteoporosis at age of 34 after a MRI scan showed compression fractures at T9–11 and L2
• DXA scan showed Z-scores of −3.9 at the lumbar spine (L3–L4) and −1.3 in the total hip
• no other known risk factors for osteoporosis
• urinary excretion of calcium and sodium elevated
• plasma AVP level was inappropriately elevated

Osteoporosis by DXA is higher in patients with time-averaged hyponatremia across all bone areas.

Afshinnia et al. Osteoporosis Int 26:2291-2298, 2015

Osteoporosis and fractures are both 2.6-fold increased in a large U.S. hospital system (MedStar, Washington DC).

Chronic hyponatremia is associated with a 3.987 O.R. of osteoporosis.

Usala et al.  
*J Clin Endocrinol Metab*  
100:3021-31, 2015

Recent hyponatremia is associated with a 3.079 O.R. for fragility fractures.

Usala et al.  
*J Clin Endocrinol Metab*  
100:3021-31, 2015
A 3-month-old male was admitted for irritability, generalized seizures and failure to thrive. An MRI scan of the brain was read as WNL, and a general work-up was unrevealing for any underlying abnormality. There is no family history of metabolic or electrolyte abnormalities. Laboratory data on admission are:

| [Na⁺], mEq/L | 118 | Uosm, mOsm/kg H₂O | 720 |
| [K⁺], mEq/L  | 3.7 | urine [Na⁺], mEq/L | 75 |
| Posm, mOsm/kg H₂O | 247 | urine [K⁺], mEq/L | 50 |
| BUN, mg/dL    | 3   | TSH, μIU/L         | 2.0 |
| glucose, mg/dL | 90  | plasma cortisol, μg/dL | 22 |

**Issues to be discussed:**

1. Diagnosis of nephrogenic syndrome of inappropriate antidiuresis (NSIAD)
2. Treatment of NSIAD
3. Prevalence of NSIAD in adults as a potential cause of SIADH with low plasma AVP levels

---

**SIADH: essential criteria**

- true plasma hypoosmolality
- urine concentration inappropriate for plasma osmolality ($U_{osm} > 100$ mOsm/kg H₂O)
- clinical euvolemia, no diuretic therapy
- absent renal sodium conservation ($U_{Na} > 30$ mmol/L)
- normal thyroid, adrenal and renal function

plasma AVP levels are inappropriately elevated in most patients with SIADH


nephrogenic SIAD caused by an activating mutation of the AVP V2R at the same site that also can cause DI via an inactivating mutation

treatment of NSIAD with oral urea


<table>
<thead>
<tr>
<th>Table II. Blood and urine studies in 4 patients with chronic SIAD treated with oral urea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
</tr>
<tr>
<td>Oral Urea Dose g/kg/day</td>
</tr>
<tr>
<td>Patient</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>Normal Range</td>
</tr>
</tbody>
</table>

ND = not done; Nd = not applicable; BUN = blood urea nitrogen.

family tree illustrating transmission of the mutated vasopressin receptor type 2 (AVPR2) gene responsible for nephrogenic syndrome of inappropriate antidiuresis (NSIAD) over five generations

update of hyponatremia treatment guidelines first published in 2007

Diagnosis, Evaluation, and Treatment of Hyponatremia: Expert Panel Recommendations

Joseph G. Verbalis, MD,1 Steven R. Goldsmith, MD,2 Arthur Greenberg, MD,3 Cynthia Korzelius, MD,4 Robert W. Schrier, MD,5 Richard H. Sterns, MD,5 Christopher J. Thompson, MD, FRCP(C)5

1Georgetown University Medical Center, Washington, DC; 2University of Minnesota, Minneapolis, MN; 3Duke University Medical Center, Durham, NC; 4Tufts University School of Medicine, Boston, MA; 5University of Colorado, Denver, CO; 6University of Rochester, Rochester, NY; 7Royal College of Surgeons in Ireland School of Medicine, Dublin, Ireland