Electrolyte Disturbances in Cancer Patients

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MD Anderson Cancer Center
Objectives

• Discuss a few interesting cases that highlight the importance and complexity of malignancy and treatment associated electrolyte disorders
• Provide rationale not only for specialized training for onconephrology, but importance of raising awareness among general nephrologists
• Share approaches and ideas from our experience at MD Anderson
Case

- 73yo Chinese male presented w hematuria
- L nephroureterectomy for papillary transitional cell carcinoma of the renal pelvis
- Due to disease progression on anti-metabolic therapy presented to MDACC
• Treated with nivolumab and ipilimumab
• Other than antihypertensives, no other meds
• 6 wks later seen at an outside ER for back pain and discolored urine; treated for a UTI
• Returned with weakness, unable to ambulate, difficulty eating

• CK 15,000
• SCr 3.5

• Received IVF, methylprednisolone; later infliximab
• History and urine should have immediately raised suspicion rhabdomyolysis
• Who is seeing our patients?
• How are they trained?
• Cancer is one of the leading causes of morbidity and mortality worldwide, with approximately 14 million cases/year (2\textsuperscript{nd} leading cause of death globally)
• Cancer incidence is increasing
• Improvement rate in 10 year survival have doubled or tripled in many types of cancer
• New agents available (e.g., targeted therapy, immunotherapy, CAR-T therapy, etc.)
Case

- 40 year-old man presented to his PCP with diffuse lower extremity bone pain and fatigue
- Pain management given but persisted; x-rays negative for abnormal findings
- Labs ordered:
  - SCr 1.0mg/dL
  - Ca 8.0mg/dL (nl albumin)
  - P 1.4mg/dL LOW
  - Alkaline phosphatase 232 (IU/dL)
  - PTH 80pg/mL
  - 25-vit D 30ng/mL
  - 1,25-vit D 10pg/mL LOW
• Lesion under tongue found
• Biopsy consistent with hemangiopericytoma
• Electrolyte abnormalities resolved after surgical resection
Tumor induced osteomalacia

• TIO is a rare disease characterized by excess FGF23, hyphosphatemia and secondary phosphaturia & impaired vit D synthesis
• In the last 2 years at MDACC we have had 20 cases
• P replacement and calcitriol when there is residual disease (high recurrence)
• Educational emphasis on cancer is needed in nephrology curriculum
Case

• 46 yo man with a history of widely metastatic melanoma to the liver, brain, lymph nodes, kidneys, and peritoneum

• He receives 1 dose of paclitaxel
Release of intracellular contents of tumor cells that exceeds the clearance capacity of the kidneys.
Original description

- 1st described by 2 Czech physicians Bedrna and Polcak in 1929
- Patients with chronic leukemia treated with irradiation
- TLS from spontaneous necrosis of a nonlymphomatous solid tumor was not described until 1977

Hyperuricemic Acute Renal Failure in Disseminated Carcinoma

David R. Crittendon, MD, George L. Ackerman, MD

A patient with widespread adenocarcinoma of gastrointestinal tract origin was seen in renal failure. He had extreme hyperuricemia, and at autopsy, uric acid crystals were demonstrated in many collecting structures of the kidney. To our knowledge, this is the first clinicopathologic description of hyperuricemic renal failure caused by spontaneous necrosis of a nonlymphomatous solid tumor. (Arch Intern Med 137:97-99, 1977)
Howard SC et al NEJM 2011
Newer targeted therapies can rapidly reduce WBC count and cause TLS; e.g., flavopiridol; ABT-199 (venetoclax)

**Table 1. Risk Assessment Based on Disease Type**

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Leukemia</strong></td>
<td>AML with WBC &lt; 25 x 10⁹/L</td>
<td>Leukemia</td>
</tr>
<tr>
<td>CLL receiving only alkylating agents</td>
<td>CLL receiving targeted and/or biological therapies</td>
<td>ALL</td>
</tr>
<tr>
<td>CML (excluding blast crisis)</td>
<td></td>
<td>AML with WBC ≥ 25 x 10⁹/L</td>
</tr>
<tr>
<td><strong>Lymphoma</strong></td>
<td>DLBCL with LDH &gt; ULN (non-bulky)</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Anaplastic large-cell lymphoma</td>
<td>Mantle cell lymphoma (blastoid variants) with LDH &gt; ULN (non-bulky)</td>
<td>Advanced Stage lymphoblastic lymphoma</td>
</tr>
<tr>
<td>DLBCL with LDH WNL</td>
<td>Peripheral T-cell lymphoma with LDH &gt; ULN (non-bulky)</td>
<td>Burkitt’s lymphoma</td>
</tr>
<tr>
<td>Mantle cell lymphoma (blastoid variants) with LDH WNL</td>
<td>T-cell lymphoma with LDH &gt; ULN (non-bulky)</td>
<td>DLBCL with LDH &gt; ULN (bulky)</td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma with LDH WNL</td>
<td>Transformed lymphoma with LDH &gt; ULN (non-bulky)</td>
<td>Mantle cell lymphoma (blastoid variants) with</td>
</tr>
<tr>
<td>T-cell lymphoma with LDH WNL</td>
<td>Early Stage lymphoblastic lymphoma with LDH &lt; 2x ULN</td>
<td>LDH &gt; ULN (bulky)</td>
</tr>
<tr>
<td>Transformed lymphoma with LDH WNL</td>
<td></td>
<td>Peripheral T-cell lymphoma with LDH &gt; ULN</td>
</tr>
<tr>
<td>Cutaneous T-cell lymphoma</td>
<td></td>
<td>(bulky)</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td></td>
<td>Transformed lymphoma with LDH &gt; ULN (bulky)</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mantle cell lymphoma (non-blastoid variants)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marginal zone B-cell lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small lymphocytic lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Neuroblastoma</td>
<td>Other</td>
</tr>
<tr>
<td>Solid tumors (excluding neuroblastomas, germ-cell tumors, and small cell lung cancer)</td>
<td>Germ-cell tumors</td>
<td>Myeloma with extramedullary disease and LDH &gt; ULN</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>Small cell lung cancer</td>
<td>Myelofibrosis - Intermediate-2 risk or High-risk disease</td>
</tr>
<tr>
<td>MDS</td>
<td></td>
<td>Plasma cell leukemia</td>
</tr>
</tbody>
</table>

*Renal dysfunction elevates the patient to the next risk level; Bulky disease is defined as any mass ≥ 10 cm*
Cairo-Bishop Criteria

Patients must meet more than two of four laboratory criteria during the same 24 h period within 3 days before the start of chemotherapy or up to 7 days afterward. A 25% change from baseline laboratory values is also acceptable. Clinically TLS is defined as the presence of laboratory TLS plus any one or more of the above-mentioned criteria.

<table>
<thead>
<tr>
<th>Incidence depends on population and tumor type</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Laboratory TLS 40-70%</td>
</tr>
<tr>
<td>• Clinical TLS 3-25%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3. Classification of TLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTLS (≥2 laboratory changes ≤3 days after cytotoxic therapy)</td>
</tr>
<tr>
<td>Uric acid ≥8 mg/dL or 25% increase from baseline</td>
</tr>
<tr>
<td>Potassium ≥6 mEq/L or 25% increase from baseline</td>
</tr>
<tr>
<td>Phosphorus ≥6.5 mg/dL (children) or ≥4.5 mg/dL (adults), or 25% increase from baseline</td>
</tr>
<tr>
<td>Calcium ≤7 mg/dL or 25% decrease from baseline</td>
</tr>
<tr>
<td>CTLS (LTLS + ≥1 clinical complication)</td>
</tr>
<tr>
<td>Creatinine 1.5 × ULN</td>
</tr>
<tr>
<td>Cardiac arrhythmia or sudden death</td>
</tr>
<tr>
<td>Seizure</td>
</tr>
</tbody>
</table>

CTLS: clinical tumor lysis syndrome; LTLS: laboratory tumor lysis syndrome; TLS: tumor lysis syndrome; ULN: upper limit of normal.

Source: References 28, 29.
Tumor Lysis Syndrome

Management

• Prophylaxis
  – High Risk  *IVF with rasburicase 3 mg*
  – Moderate Risk  *IVF with allopurinol*
  – Low Risk  monitor  *IVF +/- allopurinol*

• Treatment
  – Isotonic fluid +/- diuretics  *UOP 100 ml/hr*
  – Rasburicase (various regimens)
  – Alkalinization of urine with IV alkalai or acetazolamide
  – Hemodialysis or CRRT Peritoneal Dialysis
Exogenous Calcium

- Reserve for tetany, electrocardiographic changes, or cardiac arrhythmia
- Ca-P deposition and worsening AKI
Rasburicase

The recommended dose and schedule of ELITEK is 0.20 mg/kg as a single daily dose for 5 days.

- Recombinant urate oxidase
- Derived from Aspergillus flavus gene
- Catabolizes uric acid to allantoin (5-10x more soluble in urine)
- Onset of action within hours
- G6PD deficiency ➔ hemolytic anemia or MetHb
- Abs detected in 14% of pts after administration

Non-recombinant urate oxidase
Figure 3. Median Serum Uric Acid following Single Dose Administration per Episode

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Episodes (N)</th>
<th>Initial</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>RRT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Post-implementation Period</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixed 3-mg</td>
<td>106</td>
<td>9.0</td>
<td>4.2</td>
<td>3.3</td>
<td>3.6</td>
<td>3.5</td>
<td>3.6</td>
<td>&lt; 1% (1/106)</td>
</tr>
<tr>
<td>Fixed 6-mg</td>
<td>259</td>
<td>7.8</td>
<td>3.4</td>
<td>1.0</td>
<td>2.0</td>
<td>2.8</td>
<td>3.0</td>
<td>2.7% (7/259)</td>
</tr>
<tr>
<td>Weight-based</td>
<td>18</td>
<td>11.0</td>
<td>3.0</td>
<td>0.6</td>
<td>1.4</td>
<td>2.0</td>
<td>3.2</td>
<td>0% (0/18)</td>
</tr>
<tr>
<td><strong>Pre-implementation Period</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixed 3-mg</td>
<td>38</td>
<td>7.5</td>
<td>4.7</td>
<td>3.3</td>
<td>3.0</td>
<td>3.7</td>
<td>4.1</td>
<td>2.6% (1/38)</td>
</tr>
<tr>
<td>Fixed 6-mg</td>
<td>18</td>
<td>11.0</td>
<td>3.0</td>
<td>0.6</td>
<td>1.4</td>
<td>2.0</td>
<td>3.2</td>
<td>0% (0/18)</td>
</tr>
</tbody>
</table>

RRT: renal replacement therapy, ULN: upper limit of normal
• 700 TLS cases that were treated with rasburicase at MDACC in the last 2 years
• Examined 239 cases
• Most common malignancy was AML
• Mean rasburicase dose 3mg
• 26% given repeated dose
• Regression analysis showed higher SCr and uric acid determinants of repeated dosing
Tumor Lysis Syndrome

Take Home Points

• TLS risk highest in heme malignancies, sensitive tumors, bulky dz, intensive tx

• Alkalization of urine no longer recommended

• Rasburicase 3 mg fixed dose may be just as effective as weight based dose.
• A 58-year-old man with small-cell lung carcinoma presents with severe confusion and lethargy and found to have a SNa of 112mmol/L.
• He is given 1L of 0.9%NS and 2 hours later repeat sodium is 110mmol/L.
• What happened?
SIADH

- Inappropriate urinary response to hypo-osmolality (urine Osm >100mOsm/kg H₂O); fixed urine osmolality

\[ U_{osm} = \frac{\text{Urine Solute Load}}{\text{Urine Volume}} \]

Urine Volume = \( \frac{308\text{mmol} (154\times2)}{616\text{mmol/L}} \) = 0.5L

All solute dumped into \( \frac{1}{2} \) Liter of urine and there is retention of 500mL worsening hypoNa

KDIGO
Case 2

- A 48-year-old woman with CNS lymphoma is in the hospital ward for post-chemo monitoring. Patient has had chronic hyponatremia, but now SNa is 121 despite 1L water restriction
- What is happening?
Patients with SIADH has negative electrolyte free water clearance and therefore have tendency to retain water.

A short-cut for the above equation is:

\[
\frac{(UNa + UK)}{PNa}
\]

>1 means unlikely to improve even with very restrictive measures; try another other strategy.
# Prescriptive guide to water restriction

<table>
<thead>
<tr>
<th>(UNa+UK)/PNa</th>
<th>Insensible Water Losses (ml)</th>
<th>Water Loss beyond Insensible Losses (ml)</th>
<th>Recommended Fluid Restriction (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1</td>
<td>800</td>
<td>0–800*</td>
<td>0</td>
</tr>
<tr>
<td>0.5–1</td>
<td>800</td>
<td>300–800</td>
<td>≤500</td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>800</td>
<td>300–800</td>
<td>≤1000</td>
</tr>
</tbody>
</table>

Bayou City Bean Club

Journal Club and Case Discussions

Designed for fellows; high impact topics, low stress environment, food

Get your burning questions about nephrology topics answered and have opportunity to contribute

Planning committee:
Rajeev Raghavan (BCM)
Dia Waguespack (UT-H)
Hassan Ibrahim (TMH)
Biruh Workeneh (MDACC)
Clinic addressing low sodium levels opening Oct. 6

Thursday, September 28, 2017

If you’re concerned that a patient may be suffering from low sodium levels, you can now refer them to our Hyponatremia Clinic, opening on Fridays beginning Oct. 6.

Hyponatremia is the most common electrolyte disorder seen in cancer patients, and it can lead to other health concerns if not treated. Many treatments and comorbidities can cause low sodium levels, and it’s important to address quickly.

What to look for

Hyponatremia is most often seen in patients with small cell cancer, though it can be present in any patient. Mild symptoms can lead to attention deficits and unsteady gait, which can cause falls and more serious conditions.

Mild symptoms of hyponatremia include:

- Headaches
- Nausea
- Hiccups

Patients should get a referral to the Hyponatremia Clinic if their sodium level is less than 133.

More severe symptoms (lethargy, confusion, seizures, and coma) should go directly to the Emergency Center.

Make a referral
Case

- 64yo man with metastatic cholangiocarcinoma
- SNa persistently 120-125mmol/L
- Exam vitals stable; no edema; no offending agents
- Fluid restriction attempted, but failed to correct
- He is “asymptomatic”; what do we do?
‘Asymptomatic’ Hyponatremia

• Mild chronic hyponatremia is defined as SNa >72 hours between 125 and 135 mEq/L without apparent symptoms
• Most patients ambulatory and the condition is generally perceived as inconsequential
Hyponatremia impacts cancer survival

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Cancer type</th>
<th>n of patients</th>
<th>Definition of hyponatremia</th>
<th>Median OS in univariate analysis</th>
<th>p-value</th>
<th>Outcome in multivariate analysis</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kimura et al. (2001) [18]</td>
<td>Japan</td>
<td>NSCLC Good PS subset</td>
<td>109</td>
<td>Not reported</td>
<td>4.40 versus 6.95 mos</td>
<td>.0019</td>
<td>Not reported</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>76</td>
<td></td>
<td>4.4 versus 9.5 mos</td>
<td>.0281</td>
<td>RR, 2.4; 95% CI, 1.1–5.4</td>
<td>.0302</td>
</tr>
<tr>
<td>Kim et al. (2007) [22]</td>
<td>Korea</td>
<td>Gastric cancer</td>
<td>39</td>
<td>≤133 mEq/L</td>
<td>25 versus 87 days</td>
<td>.002</td>
<td>RR, 4.57; 95% CI, 1.99–10.52</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Jacot et al. (2008) [19]</td>
<td>France</td>
<td>NSCLC</td>
<td>301</td>
<td>Not reported</td>
<td>4.1 versus 18.7 mos</td>
<td>&lt;.0001</td>
<td>HR, 1.99; 95% CI, 1.04–3.77</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Vasudev et al. (2008) [20]</td>
<td>UK</td>
<td>RCC</td>
<td>212</td>
<td>&lt;130 mEq/L</td>
<td>Not reported</td>
<td>&lt;.10</td>
<td>HR, 1.18; 95% CI, 1.05–1.30</td>
<td>.004</td>
</tr>
<tr>
<td>Jeppesen et al. (2010) [21]</td>
<td>Denmark</td>
<td>RCC</td>
<td>123</td>
<td>&lt;136 mEq/L</td>
<td>5.5 versus 18.6 mos (HR, 2.43; 95% CI, 1.51–3.92)</td>
<td>&lt;.001</td>
<td>HR, 1.86; 95% CI, 1.12–3.11</td>
<td>.014</td>
</tr>
<tr>
<td>Aggerholm-Pedersen et al.</td>
<td>Denmark</td>
<td>GIST</td>
<td>80</td>
<td>&lt;135 mEq/L</td>
<td>15 versus 61 mos</td>
<td>&lt;.01</td>
<td>HR, 3.3</td>
<td>&lt;.04</td>
</tr>
</tbody>
</table>

Hospital-admitted cohorts

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Cancer type</th>
<th>n of patients</th>
<th>Definition of hyponatremia</th>
<th>Median OS in univariate analysis</th>
<th>p-value</th>
<th>Outcome in multivariate analysis</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hampshire et al. (2009) [25]</td>
<td>UK</td>
<td>Hematological malignancies</td>
<td>7,869</td>
<td>&lt;130 mEq/L</td>
<td>Not performed</td>
<td>–</td>
<td>OR, 2.47; 95% CI, 1.70–3.60</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Waikar et al. (2009) [26]</td>
<td>USA</td>
<td>Metastatic cancers</td>
<td>6,612</td>
<td>&lt;135 mEq/L</td>
<td>Not performed</td>
<td>–</td>
<td>OR, 2.05; 95% CI, 1.67–2.53</td>
<td>.005</td>
</tr>
<tr>
<td>Doshi et al. (2012) [27]</td>
<td>USA</td>
<td>All cancers</td>
<td>3,357</td>
<td>130–134 mEq/L</td>
<td>Not reported</td>
<td>–</td>
<td>HR, 2.04; 95% CI, 1.42–2.91</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>120–129 mEq/L</td>
<td>Not reported</td>
<td>–</td>
<td>HR, 4.74; 95% CI, 3.21–7.01</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;120 mEq/L</td>
<td>Not reported</td>
<td>–</td>
<td>HR, 3.46; 95% CI, 1.05–11.44</td>
<td>.04</td>
</tr>
</tbody>
</table>

What happens in the brain?

- Adaptive response to hyponatremia
- Cerebral loss of osmolytes including neurotransmitters (e.g., glutamate); induces neurocognitive effects
- Threshold \([\text{Na}]\) at which deficits consistently appear is 132mEq/L

Adrogué/Madias, NEJM 2000.
Neurocognitive deficits present in mild hyponatremia

Table 2. Studies reporting the association of mild chronic hyponatremia and neurocognitive deficits

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Cohort Size</th>
<th>Mean PNa ± SD (mEq/L)</th>
<th>Neurocognitive Assessment Tool</th>
<th>Outcomes of Hyponatremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renneboog et al. (18)</td>
<td>Crossover</td>
<td>16</td>
<td>128±3</td>
<td>Battery of attention test&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Median latencies increased by 58 ms (&lt;0.001) and no. of errors increased 1.2-fold (&lt;0.001)</td>
</tr>
<tr>
<td>Gooch et al. (19)</td>
<td>Retrospective case control</td>
<td>258</td>
<td>128±3.2</td>
<td>MMSE and CC</td>
<td>In multivariate analysis, hyponatremia was a significant predictor for abnormal scores on the MMSE (&lt;0.04; OR, 1.96; 95% CI, 1.05 to 3.68) and CC (&lt;0.02; OR, 2.57; 95% CI, 1.19 to 5.55)</td>
</tr>
<tr>
<td>Gunathilake et al. (20)</td>
<td>Prospective cohort</td>
<td>2550</td>
<td>135 versus 130&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ARCS</td>
<td>Scores were, on average, 4.67 units significantly lower (&lt;0.01)</td>
</tr>
</tbody>
</table>

PNa, plasma sodium concentration; MMSE, Mini-Mental State Examination; CC, Clock Completion test; ARCS, Audio Recording Cognitive Screening tool; OR, odds ratio; 95% CI, 95% confidence interval.

<sup>a</sup>Study compared patients with PNa of 135 versus 130 mEq/L. No mean PNa was provided.

<sup>b</sup>Visual Vigilance, Working Memory or Digit Span, Go/No Go, Intemodal Comparison, Divided Attention, and Phasic Alert.
Hyponatremia increases Fall Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Cohort Size</th>
<th>Mean PNa ±SD (mEq/L)</th>
<th>Fall Risk (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renneboog et al. (18)</td>
<td>Cross-sectional</td>
<td>366</td>
<td>126±5</td>
<td>67.43 (95% CI, 7.5 to 607)</td>
</tr>
<tr>
<td>Bun et al. (21)</td>
<td>Retrospective case control</td>
<td>248</td>
<td>131.82±2.99</td>
<td>4.38 (95% CI, 1.33 to 14.46)</td>
</tr>
<tr>
<td>Gunathilake et al. (20)</td>
<td>Prospective cohort</td>
<td>2550</td>
<td>135 versus 130*</td>
<td>1.32 (95% CI, 1.04 to 1.64)</td>
</tr>
</tbody>
</table>

PNa, plasma sodium concentration; OR, odds ratio; 95% CI, 95% confidence interval.
*Study compared patients with PNa of 135 versus 130 mEq/L. No mean PNa was provided.

Rondon/Berl. CJASN, 2015.
Hyponatremia is a significant risk factor for Fracture.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Cohort Size</th>
<th>Definition of Hyponatremia (mEq/L)</th>
<th>Mean PNa ± SD (mEq/L)</th>
<th>All Fracture Risk (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gankam Kengne et al. (22)</td>
<td>Retrospective case control</td>
<td>1026</td>
<td>&lt;134</td>
<td>131±3</td>
<td>4.16 (95% CI, 2.2 to 47.71)</td>
</tr>
<tr>
<td>Sandhu et al. (23)</td>
<td>Retrospective case control</td>
<td>728</td>
<td>&lt;135</td>
<td>131±2</td>
<td>2.34 (95% CI, 1.24 to 4.35)</td>
</tr>
<tr>
<td>Kinsella et al. (24)</td>
<td>Retrospective case control</td>
<td>1408</td>
<td>&lt;135</td>
<td>132.2±1.8</td>
<td>2.25 (95% CI, 1.24 to 4.09)</td>
</tr>
<tr>
<td>Hoorn et al. (11)</td>
<td>Prospective cohort</td>
<td>5208</td>
<td>&lt;136</td>
<td>133.4±2</td>
<td>1.34 (95% CI, 1.08 to 1.68)</td>
</tr>
<tr>
<td>Tolouian et al. (25)</td>
<td>Retrospective case control</td>
<td>293</td>
<td>&lt;135</td>
<td>a</td>
<td>4.8 (95% CI, 1.06 to 21.67)</td>
</tr>
<tr>
<td>Jamal et al. (26)</td>
<td>Prospective cohort</td>
<td>5122</td>
<td>&lt;135</td>
<td>132.3±1.8</td>
<td>3.48 (95% CI, 1.76 to 6.87)</td>
</tr>
</tbody>
</table>

PNa, plasma sodium concentration; OR, odds ratio; 95% CI, 95% confidence interval.

*Mean PNa not provided in the publication.

^Hazard ratio for nonvertebral fractures.

^OR for hip fracture.

^Hazard ratio for hip fracture.

Rondon/Berl. CJASN, 2015.
Osteoporosis

- In experimental models of hyponatremia, animals had a reduction of bone mass of 30% compared with fluid-restricted controls.
- Hyponatremia increases the number of osteoclasts per bone area compared with controls, suggesting that increased bone resorption, rather than decreased bone formation, is the predominant mechanism.
- Recently, V2R (ADH receptors) were found to present in osteoblasts and osteoclasts, indicating ADH may have a direct contributory role.

Available interventions

- Treat xerostomia (e.g., biotene, neutrasal, cevimeline)
- Fluid restriction
- Hypertonic saline (2-5% solution)
- Loop diuretics + salt tabs
- Vaptans
- Urea
- Dialysis
- Demeclocycline*
Back to our case
Urea for hyponatremia?

- Urine therapy has been used for centuries.
- Oral urea first used as a diuretic in 1892, and in advanced heart failure in 1926.
- Decaux and colleagues reported first use of oral urea to treat hyponatremia in the modern era in 1980.
- Published accounts demonstrating its efficacy.
Mechanism of Action

- Induces osmotic diuresis and electrolyte-free water loss
• Cost savings over tolvaptan (Samsca®):
  1 month tolvaptan (15mg daily) = $12,000
  1 month of urea (15g bid) = $228
• Hepatotoxicity with long-term vaptan therapy
• Protection against osmotic demyelination syndrome when overcorrection of serum sodium occurs

Kengne et al. Kidney Int. 2015 Feb;87(2):323-31
Urea is **Safe** and Effective

**Methods**

- Retrospective EHR review
- 4 hospitals within UPMC system, Jul 2016 – Aug 2017
- Plasma Na < 135 mEq/L
- ≥ 1 Urea dose

**Conclusions**

In this retrospective review of urea use in the hospital, urea was safe, well-tolerated, and effective for the correction of hyponatremia.

**Sub-group matched control**

<table>
<thead>
<tr>
<th>Treated only with urea</th>
<th>Treated without urea</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=12</td>
<td>N=12</td>
</tr>
<tr>
<td>Na change at 24h</td>
<td>Final Na ≥ 135 mEq/L</td>
</tr>
<tr>
<td>+ 2.5 mEq/L</td>
<td>33%</td>
</tr>
</tbody>
</table>

Case

- 20yo man from Saudi Arabia, who has a history of T-cell ALL since childhood, and is s/p 2 bone marrow transplants (alloTx from brother)
- His medical course has been complicated by the development of graft-versus-host disease, bilat AVN, BK viremia, TMA (failed eculizumab), and ESRD; receiving HHD
- Chronic hip pain, vertebral compression fx and severe osteoporosis
- Started on denosumab
Prolonged hypocalcemia after denosumab

Denosumab 60 mg
SQ x 1 dose on 7/29

Presented to the EC

KDIGO
Denosumab

- Prevents osteoclast maturation, function, survival
- Sustained response > 3 mos
- N/V/D, edema, dyspnea, anemia most common SE
- Risk of hypocalcemia
  - Vit D deficiency
  - GFR <= 30 ml/min
  - Hx of Hypoparathyroidism
Case

- 60 y/o male with hx of metastatic rectal cancer to bladder and colon
- S/p coloproctostomy and diverting ileostomy, resection of the prostate and bladder with creation of an ileal conduit
- Presents with weakness, diarrhea
- Na 131; K 2.9; bicarbonate 8mmol/L; nl anion gap; SCr 2.1
Types of Urinary Diversion

ILEAL CONDUIT
(incontinent diversion to skin)

CONTINENT CUTANEOUS RESERVOIR
(continent diversion to bladder)

ORTHOTOPIC NEOBLADDER
(continent diversion to urethra)
Bowel segment matters!

- The electrolyte imbalance that occurs depends on the segment of bowel interposed to create the urinary diversion system.
  - Stomach: metabolic alkalosis + hypoK
    - Due to H/K antiport
    - Treat with H2 blockade
  - Jejenum: hyponatremia
    - Increased sodium and chloride secretion causes volume depletion; often hypoNa or AKI
  - Ileum or colon: metabolic acidosis + hypoK
    - Absorption of ammonium chloride; sodium/bicarbonate excreted for HCl
MBD issues with ileal conduits

- Not well studied
- Due to poor absorption of calcium and vitamin D
- Calcium wasting in the urine occurs as well; metabolic acidosis
Case

- 25yo woman with h/o ALL, s/p allo-SCT 10d ago, in the ICU with hypotension. She is fatigued, but alert, eating/drinking
- BP 90/55 HR 102
- +ansasarca
- Receiving NS 150cc/hr for intravascular volume depletion
Body compartments

TBW ~42L

Intracellular ~28L  Extracellular ~14L

Extravascular fluid ~11L  Intravascular fluid ~3L

Venous volume 2L

Arterial volume 500-1L
<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient characteristics</th>
<th>Methodology</th>
<th>Key results*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anand IS et al. [3]</td>
<td>8 untreated CHF pts, with evidence of volume overload on physical examination vs. 24 normal controls</td>
<td>Radio-labeled albumin</td>
<td>• PV of CHF pts was increased to 134% of controls (57.9±2.9 ml/kg vs. 43.2±3.0 ml/kg, <em>p</em>=0.0012)</td>
</tr>
<tr>
<td>(1989)</td>
<td></td>
<td></td>
<td>* before treatment, PV of CHF pts was increased to 129±19% of normal</td>
</tr>
<tr>
<td>James KB et al. [4]</td>
<td>10 pts with decompensated CHF (mean EF 19%±10%), evaluated before and after treatment with diuretics, ACEI, beta blockers, vasodilators, and inotropic agents</td>
<td>Radio-labeled albumin</td>
<td>• after treatment (12–24 h), PV of CHF pts was decreased, but still greater than normal (126±16%)</td>
</tr>
</tbody>
</table>
### Table 2 Summary of studies assessing intravascular volume in patients with nephrotic syndrome (NS)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient characteristics</th>
<th>Serum albumin/plasma oncotic pressure (POP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meltzer et al. [18] (1979)</td>
<td>5 NS pts, adults, edematous (3 with MCD and high renin activity; 2 with membranous and low renin activity)</td>
<td>High renin (n=3): albumin=1.4 g/dL</td>
</tr>
<tr>
<td>Dorhut Mees EJ et al. [9] (1979)</td>
<td>10 NS pts, adults, all with MCD, edematous, on low-salt diet without diuretics, studied before and after steroid-induced remission</td>
<td>Low renin (n=2): albumin=1.7 g/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Albumin, before and after remission=1.58 and 3.67 g/dL, respectively</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Methodology</th>
<th>Results*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radio-labeled albumin</td>
<td>• PV of NS pts in high renin group was decreased compared to low renin group (38.9±7.1 ml/kg vs. 49.0 ml/kg±2.1)</td>
</tr>
<tr>
<td>Radio-labeled albumin</td>
<td>• PV of NS pts was normal or increased during the edematous phase</td>
</tr>
<tr>
<td></td>
<td>• PV of NS pts decreased significantly by 0.3 L following remission</td>
</tr>
<tr>
<td></td>
<td>• BV of NS pts was increased to 108% (5.71 L vs. 5.27 L)</td>
</tr>
</tbody>
</table>
Table 3  Summary of studies assessing intravascular volume in patients with cirrhosis

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patient characteristics</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murray JF et al. [19] (1958)</td>
<td>24 cirrhotic pts vs. 14 controls</td>
<td>Evans blue dye</td>
</tr>
<tr>
<td>Moller S et al. [24] (1995)</td>
<td>39 cirrhotic pts (12 Child-Turcotte class A, 14 class B, and 13 class C) vs. 6 controls</td>
<td>Radio-labeled albumin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Methodology</th>
<th>Results&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evans blue dye</td>
<td>• BV in cirrhotic pts was increased to 115% of controls (&lt;span style='font-size:0.7em'&gt;3.13±0.52 L/m² vs. 2.72±0.25 L/m², p&lt;0.05&lt;/span&gt;)&lt;br&gt;• BV was significantly greater in cirrhotic pts with vs. without evidence of portal systemic shunting</td>
</tr>
<tr>
<td>Radio-labeled albumin</td>
<td>• PV in cirrhotic pts was increased to 118% of controls, irrespective of Child-Turcotte class (&lt;span style='font-size:0.7em'&gt;3.92±0.24 L [class A], 3.86±0.29 L [class B], 3.93±0.26 L [class C] vs. 3.3±0.1 L&lt;/span&gt;)&lt;br&gt;• administration of colloid increased central BV in class A cirrhotic pts (18%), but not in class B or class C cirrhotic pts (1–3%)</td>
</tr>
</tbody>
</table>
Summary

- Electrolyte complications of cancer and cancer therapy are common; the consequences of ignorance can be deadly.
- The pace of drug development is unprecedented and there is need to immediately characterize observed complications.
Oslerisms

• Medicine is learned by the bedside and not in the classroom

• If you cannot imagine what disease your patient may have, you will never arrive at the diagnosis
Eternal vigilance is our only insurance