Detecting and Treatment of Tumor Lysis Syndrome & SIADH

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Objectives

1. Define the electrolyte imbalances that occur with tumor lysis syndrome
2. List one treatment strategy for patients experiencing Tumor Lysis Syndrome (TLS)
3. List one treatment strategy for patients experiencing Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

Definition of TLS:

Tumor Lysis Syndrome: An oncological emergency caused by massive tumor cell lysis with the release of large amounts of potassium, phosphate, and nucleic acids into the systemic circulation.
Risk Factors

- **Tumor Related**
  - High grade lymphomas
  - Hematologic malignancies
  - Tumors with high growth fractions and treatment sensitive

- **Patient Related**
  - Large tumor burden/bulky tumors/extensive lymph node involvement
  - Elevated LDH, uric acid, potassium and phosphorus levels prior to treatment
  - Comorbid cardiac or renal disease
  - Metabolic conditions: diabetes, obesity, hypertension

- **Treatment Related**
  - Chemotherapy/Biotherapy/Hormonal
  - Radiation
  - Surgery

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**Onset of TLS:**
Usually within 6-72 hours after initiation of antineoplastic therapy

**Duration:**
May persist for 5-7 days post-therapy

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**TLS: Pathophysiology**

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**Prophylaxis Recommendations**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Low Risk Disease</th>
<th>Intermediate Risk Disease</th>
<th>High Risk Disease</th>
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</thead>
<tbody>
<tr>
<td>Monitoring</td>
<td>Monitoring</td>
<td>Monitoring</td>
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<tr>
<td>Hydration</td>
<td>Hydration</td>
<td>Hydration</td>
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<tr>
<td>Allopurinol</td>
<td>Allopurinol</td>
<td>Rasburicase</td>
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</tbody>
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**Key Terms**

- MM: Multiple myeloma
- CML: Chronic myeloid leukemia
- HL: Hodgkin lymphoma
- CLL: Chronic lymphoid leukemia
- AML: Acute myeloid leukemia
- ALCL: Anaplastic large cell lymphoma
- ULN: Upper limits normal
- 56 year old female
- Burkitt's lymphoma
- LDH < 2x UNL
- Creatinine/BUN WNL
- Plan: Hyper CVAD

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**Additional Notes**

- Up to date 2016
Cairo-Bishop TLS Classification System

**Monitoring**

- Based on laboratory & clinical findings
- Laboratory Diagnosis Definition:
  - 2 or more values
  - Increase or decrease 25% from baseline lab values
  - Within 3-7 days post initiation of chemo
- Clinical Diagnosis Definition:
  - Presence of laboratory TLS plus 1 or more of clinical TLS findings

<table>
<thead>
<tr>
<th>Laboratory TLS</th>
<th>Clinical TLS Grade 0-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uric acid: &gt; 8 mg/dl or 25% increase from baseline</td>
<td>Severe creatinine: 3.5 – greater than 6.5 times the upper limit of normal</td>
</tr>
<tr>
<td>Potassium: ≥ 6 mEq/L or 25% increase from baseline</td>
<td>Cardiac Arrhythmias: Life threatening (e.g., arrhythmia associated with HF, hypotension, syncope, shock) death</td>
</tr>
<tr>
<td>Phosphorus: &gt; 5.5 mg/dL for children and &gt; 5.5 mg/dL for adults or 25% increase from baseline</td>
<td>Seizures: one brief generalised seizure controlled or infrequent focal motor to any prolonged, repetitive or difficult to control, death</td>
</tr>
<tr>
<td>Calcium: &gt; 7 mg/dl or 25% decrease from baseline</td>
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</table>

<table>
<thead>
<tr>
<th>Complication</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine*</td>
<td>&lt;1.5xUNL</td>
<td>1.5-3.0 x UNL</td>
<td>&gt;3.0 x UNL</td>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac Arrhythmia</td>
<td>None</td>
<td>Intervention not indicated</td>
<td>Symptomatic &amp; aggressively controlled medically or controlled with device (e.g., defibrillator)</td>
<td>Life threatening arrhythmia associated with HF, hypotension, syncope, shock</td>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>Seizure*</td>
<td>None</td>
<td>One brief, generalized seizure controlled or infrequent focal motor seizures not interfering with ADL's</td>
<td>Seizure in which consciousness is altered; poorly controlled seizure disorder with breakthrough generalized seizures despite medical intervention</td>
<td>Seizure of any kind which are prolonged, repetitive or difficult to control, death</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Cairo-Bishop Grading**

**Monitoring:**

- Labs: Uric Acid, Potassium, Calcium, Phosphate, BUN, Creatinine, Etc.
  - Hyperkalemia
  - Hyperuricemia
  - Hyperphosphatemia
  - Hypocalcemia
- Cardiac Monitoring
- Neurological Assessment
- Clinical exam
- Intake and Output
Prophylaxis: IV Hydration

Goal: improve renal perfusion and glomerular filtration and induce a high urine output to prevent kidney damage

Patient Considerations:
- Kidney and cardiac status
- Comorbid conditions
- Fluid volume status
- Intravenous access

Hydration Recommendations

Rate/Volume:
- 2-3 L/m² per day or 200 mL/kg per day in children weighing ≤10 kg
- Monitor closely and maintained within 80-100 mL/m² per hour (2 mL/kg per hour for children and adults, 4 to 6 mL/kg per hour if ≤10 kg)

Diuretics:
- Contraindicated in patients with hypovolemia or obstructive uropathy
- Should not be required in patients with normal renal and cardiac function
- The best diuretic is unknown. Loop diuretics (Furosemide/Lasix®) appear preferable due to diuresis and potential increased potassium secretion

Solution & Duration:
- Steroids: 5% dextrose ¼ NS induction (potential sodium retention and hypertension)
- Hyponatremia or volume depletion: isotonic saline is initial choice
- Once tumor breakdown begins, potassium and calcium should be withheld due to risk of hyperkalemia and hyperphosphatemia with calcium phosphate precipitation
- No guidelines address optimal duration of hydration

Urinary Alkalization: Controversial

Acetazolamide and/or Sodium Bicarbonate:
- pH of 6.5-7.0 or higher (maximum solubility of urate 7.5, solubility of xanthine and hypoxanthine decreases over a pH of 6.5; may predispose patients to xanthine neuropathy)
- Fallen Out of Favor Due To:
  - Lack of evidence demonstrating efficacy. Experimental study suggest hydration with NS alone is as effective
  - Alkalinization of the urine has the potential of promoting calcium phosphate deposition in the kidney, heart, and other organs in patients who develop marked hyperphosphatemia once tumor breakdown begins
  - Bicarb has vesicant potential and multiple incompatibility issues
  - Sodium bicarbonate is only indicated in patients with metabolic acidosis
  - No consensus in patients who receive treatment with allopurinol

Nucleic Acids
- Purines
- Hypoxanthine
- Xanthine
- Uric Acid
- Alkalosis

How many of you still see?

Sodium bicarbonate added to IV fluid (50-100 mEq/liter)
- Bicarb has vesicant potential and multiple incompatibility issues
- Metabolic alkalosis

Panel Conclusions:
- Sodium bicarbonate is only indicated in patients with metabolic acidosis
- No consensus in patients receiving Rasburicase
- Not required in patients receiving allopurinol

How many of you still see?
Hyperuricemia Signs & Symptoms (Onset 48-72 hours)
Catabolism of Nucleic Acid to Uric Acid

Hyperuricemia
- Serum uric acid >10 mg/dl
- Severe = >20 mg/dl
- Guidelines: > 476 micromole/L (8mg/dL)

- Oliguria, anuria, azotemia, hematuria, crystaluria
- Edema, hypertension
- Acute/Chronic renal failure
- Nausea, vomiting
- Flank pain, gout

Preventative Hyperuricemia Agents

Allopurinol or Rasburicase

- Allopurinol:
  - Inexpensive and orally administered
  - Begin 24-48 hours prior to therapy
  - Blocks uric acid production by inhibiting xanthine oxidase (liver enzyme)
  - Prevents uric acid precursors from converting to Uric acid, ↓ risk uric acid crystallization

- Rasburicase:
  - Catalyzes oxidation of uric acid to the much more water-soluble compound allantoin which is excreted by the kidneys
  - Urate oxidase is present in most mammals but not humans.

Allopurinol: Dose and Administration (Zyloprim, Lopurin)

**Oral Dose:**
- Adults: 100 mg/m² every eight hours (maximum 800 mg per day)
- Children 50 to 100 mg/m² every eight hours (maximum 300 mg/m² per day) or 10 mg/kg per day in divided doses every eight hours

**IV Formulation:**
- 200 to 400 mg/m² per day, in 1-3 divided doses (maximum dose 600 mg per day)

**Reduced Dose:**
- 50% in the setting of acute kidney injury (potential accumulation of allopurinol & metabolites)
- Manufacturer’s labeling: Reduce to 200 mg daily for creatinine clearance 10 to 20 mL/minute, ≤100 mg daily for creatinine clearance 3 to 10 mL/minute, and ≤100 mg/dose at extended intervals for creatinine clearance <3 mL/minute in adults
- Generally initiated 24 to 48 hours before the start of induction chemotherapy
- Continued for 3-7 days afterwards until there is normalization of serum uric acid and other laboratory evidence of tumor lysis (e.g., elevated serum LDH levels)
Allopurinol Considerations

- For preexisting hyperuricemia (serum uric acid ≥7.5 mg/dL) Rasburicase, is preferred
- May increase serum concentration of other purines and promote formation of active thioguanine nucleotides. Mercaptopurine or azathioprine should be reduced by 1/3-1/4 of the usual dose if used concomitantly
- Drug interactions include: cyclophosphamide, bendamustine high-dose methotrexate, ampicillin, amoxicillin, carbamazepine, loop diuretics, and thiazide diuretics.
- Associated with hypersensitivity reactions, including vasculitis and Stevens-Johnson syndrome.

Febuxostat: Dose and Administration (Uloric)

<table>
<thead>
<tr>
<th>Oral Dose: Selective inhibitor of xanthine oxidase approved for management of chronic hyperuricemia in gout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults: 120 mg/day</td>
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</tbody>
</table>

Differences from Allopurinol:
- Not a purine base analog. Inhibits both reduced and oxidized forms of xanthine oxidase, and has minimal effects on other enzymes involved in purine and pyrimidine metabolism
- Dose adjustment is not needed in patients with mild to moderate renal impairment
- Fewer drug-drug interactions
- More expensive

Place in treatment:
- Available data of efficacy and safety are insufficient to use as an alternative to allopurinol to prevent TLS in patients at intermediate to high risk
- May be used judiciously in patients with hyperuricemia who cannot tolerate allopurinol in a setting in which rasburicase is either not available or contraindicated

Rasburicase: Dose and administration (Elitek/Fasturtek outside USA)

Dose:
- 0.2 mg/kg once daily for 5 (FDA) or 7 (EMA) days
- Expert panel alternative dose recommendations based upon risk stratification
  - High-risk patients or baseline uric acid level >7.5 mg/dL = 0.2 mg/kg
  - Intermediate-risk patients with baseline uric acid 5-7.5 mg/dL = 0.15 mg/kg
- Supplied in 1.5 or 7.5 mg vials
- Generally rounded up to the closest number of full vials.
- In adults a flat dose of 3 mg is commonly used
- If tumor lysis is massive, an increase to twice daily dosing may be needed

Allopurinol treatment can also be started once the serum uric acid is brought down to adequately low or normal levels.
Rasburicase:

- CONTRAINDICATED in patients with G6PD deficiency. Consider an enzyme assay or genetic testing in males with a history of drug-induced hemolytic anemia and/or a racial/ethnic background associated with G6PD deficiency (African-American, Mediterranean, or Southeast Asian).
- Anaphylaxis may occur with the initial dose but is more common with repeated courses.
- Methemoglobinemia:
  - Methemoglobin (metHb): a form of hemoglobin that contains ferric iron (Fe$^{3+}$) and has decreased ability to bind oxygen.
  - If elevated in red blood cells tissue hypoxia can occur.
  - Blood has a bluish or chocolate-brown color.
  - Signs and symptoms: Shortness of breath, cyanosis, mental status changes (50%), headache, fatigue, exercise intolerance, dizziness.
- Treatment:
  - Supplemental oxygen.
  - Methylene blue 1% solution (10mg/mL) 1-2 mg IV slowly over 5 minutes.
  - Dose may be repeated in one hour.

Rasburicase: Blood Samples:

- Collect in a pre-chilled tube.
- Immediately placed on ice.
- Complete assay within four hours.
- Samples left at room temperature may result in low serum uric acid concentrations, and hence miss the diagnosis of ongoing TLS.

Teratogenicity: No studies in pregnant or lactating women. Animal studies suggest it can cause fetal malformations at all dose levels.

Hyperkalemia: Signs & Symptoms (Onset 6 hours):

<table>
<thead>
<tr>
<th>Hyperkalemia</th>
<th>Early cardiac:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum K+ &gt;6.5 mEq/L</td>
<td>- Tachycardia</td>
</tr>
<tr>
<td>Guidelines: &gt; 5.5 mEq/L</td>
<td>- EKG Changes: Prolonged QT and ST segment lowering and inversion of T wave</td>
</tr>
<tr>
<td></td>
<td>- Bradycardia</td>
</tr>
<tr>
<td></td>
<td>- EKG Changes: Shortened QT, elevated T wave, wide QRS</td>
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<tr>
<td></td>
<td>- Ventricular tachycardia, ventricular fibrillation, cardiac arrest</td>
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<table>
<thead>
<tr>
<th>Hypermagnesemia</th>
<th>Late cardiac:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Nausea/vomiting</td>
<td></td>
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<tr>
<td>- Diarrhea</td>
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<tr>
<td>- Increased bowel sounds</td>
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</tr>
<tr>
<td>- Twitching</td>
<td></td>
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<tr>
<td>- Muscle cramps</td>
<td></td>
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<tr>
<td>- Weakness</td>
<td></td>
</tr>
<tr>
<td>- Paresthesia</td>
<td></td>
</tr>
<tr>
<td>- Lethargy</td>
<td></td>
</tr>
<tr>
<td>- Syncope</td>
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</tbody>
</table>

- Early cardiac:
  - Tachycardia
  - EKG Changes: Prolonged QT and ST segment lowering and inversion of T wave
  - Bradycardia
  - EKG Changes: Shortened QT, elevated T wave, wide QRS
  - Ventricular tachycardia, ventricular fibrillation, cardiac arrest

- Late cardiac:
  - Nausea/vomiting
  - Diarrhea
  - Increased bowel sounds
  - Twitching
  - Muscle cramps
  - Weakness
  - Paresthesia
  - Lethargy
  - Syncope
Hyperkalemia Treatments:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate &amp; Asymptomatic (&gt;6.0 mEq/L)</td>
<td>Avoid IV and oral potassium, ECG &amp; cardiac rhythm monitoring, Sodium polystyrene sulfonate: Adult: 15-30 grams orally; Pediatric: 1 gram/kg orally. Onset 1-2 hours. Repeat every 4 to 6 hours up to four times daily as needed based on serum K+ levels.</td>
</tr>
<tr>
<td>Severe (&gt;7.0 mEq/L and/or symptomatic)</td>
<td>Add: For ECG changes (worsening of the QRS complex, loss of p-waves but not peaked t-waves alone), calcium gluconate by slow IV infusion to prevent life-threatening arrhythmias. Calcium gluconate: Adult: 1 gram (10 mL of 10% solution); Pediatric: 50-100 mg/kg. Slow IV infusion (max 50-100 mg/minute) in large vein. May repeat in 5-10 minutes if ECG changes persist. Insulin and dextrose: To temporarily shift potassium into cells. Adult: regular insulin (10 units) IV plus 100 mL of 50% (D50) dextrose solution IV. Pediatric: regular insulin (0.1 unit/kg) IV plus 20% (D25) dextrose 0.5 g/kg IV over 10 minutes. May repeat after 30-60 minutes. Monitor finger stick glucose closely. Sodium bicarbonate: Given to induce influx of potassium if patient is acidic. Sodium bicarbonate and calcium are incompatible and need separate lines. Sodium bicarbonate: Adult: 45-50 mEq; Pediatric: 1-2 mEq/kg. Slow IV infusion over 5-10 minutes. Beta 2 agonist inhalation: Albuterol (per nebulizer or metered dose inhaler) Adult: 10-20 mg in 4 mL saline nebulized over 20 minutes or 10-20 puffs per metered dose inhaler over 10-20 minutes. Pediatric: 0.1-0.3 mg/kg per nebulization.</td>
</tr>
</tbody>
</table>

**Hypophosphatemia & Hypocalcemia Signs & Symptoms**

*Onset 24-48 hours*

<table>
<thead>
<tr>
<th>Hypophosphatemia</th>
<th>Hyperphosphatemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum PO₄ &lt; 3 mg/dL</td>
<td>Serum PO₄ &gt; 5 mg/dL</td>
</tr>
<tr>
<td>Guidelines: 3.5 mg/dL for children or 4.5 mg/dL for adults</td>
<td>Guidelines: 6.5 mg/dL for children or 6.5 mg/dL for adults</td>
</tr>
<tr>
<td>Anuria</td>
<td>Oliguria</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Atelectasis</td>
</tr>
<tr>
<td>Edema</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Acute renal failure</td>
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<table>
<thead>
<tr>
<th>Secondary Hypocalcemia</th>
<th>Neurological/Neuromuscular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Ca²⁺ &lt; 7 mg/dL</td>
<td>Tetany</td>
</tr>
<tr>
<td>Guidelines: 7 mg/dL</td>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td>Muscle cramps &amp; weakness</td>
<td>Proximal Q1 interval, inverted T wave</td>
</tr>
<tr>
<td>Anxiety, depression</td>
<td>Heart block</td>
</tr>
<tr>
<td>Carpopedal spasms</td>
<td>Cardiac arrest</td>
</tr>
<tr>
<td>Seizures</td>
<td></td>
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</tbody>
</table>
Hyperphosphatemia Treatment:

<table>
<thead>
<tr>
<th>Level</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate &gt;6.5mg/dL</td>
<td>Restrict oral and IV phosphate intake</td>
</tr>
</tbody>
</table>

**Phosphate Binders:**
- **Calcium acetate** Adult: 2-3 tabs (1334 to 2668 mg) with each meal or
  Pediatric: 30-40 mg/kg with each meal or
- **Calcium carbonate** Adult: 1-2 grams with each meal; Pediatric: 30-54 mg/kg with each meal or
- **Sevelamer** Adult: 800-1600 mg with each meal; Pediatric: 30-40 mg/kg with each meal or
- **Lanthanum carbonate** Adult: 300-600 mg with each meal; Pediatric: 12.5-37.5 mg/kg four times daily with meals (avoid in patients with renal insufficiency)

**Severe = Dialysis**
- CAVH: Continuous arterial-venous hemofiltration
- CVVH: Continuous venous-venous hemofiltration
- CAVHD: Continuous arterial-venous hemodialysis
- CVVHD: Continuous venous-venous hemodialysis

Hypocalcemia Treatment

**Hypocalcemia, total serum calcium < 7mg/dL or ionized calcium < 3.2 mg/dL**

**Asymptomatic** No therapy

**Symptomatic**
- **Calcium gluconate** Adult: 1 gram (10mL of 10% solution); Pediatric: 50-100 mg/kg slow IV infusion (max 50-100 mg per minute) in large vein.
- Administer slowly with ECG monitoring
- Patients with acute hypocalcemia and hyperphosphatemia should not be treated with calcium until the hyperphosphatemia is corrected (unless they have tetany or a cardiac arrhythmia from hypocalcemia)
- May repeat after 5-10 minutes if symptoms or ECG changes present

Summary: Monitoring Guidelines

- Despite optimal care, severe acute kidney injury develops in some patients, requiring renal replacement therapy.
- Indications for renal replacement therapy are similar to those in patients with other causes of acute kidney injury, although lower thresholds are used because of potentially rapid potassium release and accumulation, particularly if urine output is low.
- Indications for renal replacement therapy in patients with TLS are:
  - Severe oliguria or anuria
  - Persistent hyperkalemia
  - Hyperphosphatemia-induced symptomatic hypocalcemia
  - Calcium-phosphate product ≥70 mg/dL²

- Uremic/renal dysfunction
  - Fluid and electrolyte management
  - Uric acid & phosphate management
  - Adjust renally excrated drug doses
  - Dialysis (hemo- or peritoneal)
  - Hemofiltration (CAVH, CVVH, CAVHD, CVVHD)
Summary: Monitoring Guidelines

Not evidence-based: Expert Panel recommendations for monitoring patients at high risk of TLS

• High risk patients:
  • should be in a position to be readily transferred to an ICU
  • should be tested for laboratory and clinical TLS parameters 4-6 hours after the initiation of chemotherapy and every 4-8 hours thereafter

• Rasburicase/Allopurinol:
  • Serum uric acid should be reevaluated 4 hours after administration of the first dose of Rasburicase, and every 6-12 hours thereafter until normalisation of serum LDH and uric acid levels
  • If not used, electrolytes should be measured 8 hours after chemotherapy and one-night hospital stay considered.

• Intermediate risk adults
  • should be monitored for at least 24 hours after completion of chemotherapy, for multi-agent regimens, 24 hours after administration of the final agent of the 1st cycle of therapy.
  • Others suggest an algorithmic approach to monitoring and management
  • If TLS has not occurred within 72 hours of multi-agent chemotherapy, the likelihood of TLS is very low.

Sample Algorithmic Approach

SIADH: Syndrome of Inappropriate Antidiuretic Hormone Secretion
Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH):

**AKA:** Schwartz-Bartter syndrome, SIAD: Syndrome of Inappropriate Antidiuresis

**Definition:** Excessive release of antidiuretic hormone from the posterior pituitary gland or another source. The result is often dilutional hyponatremia in which the plasma sodium levels are lowered and total body fluid is increased.

**Incidence:**
- 1-2% of all cancer patients
- 75% are bronchogenic cancer especially SCLC (15-50%)
- Head and Neck 1.5-3% (majority of squamous cell origin)

**Characterized By:**
- Erratic, unregulated release of ectopic antidiuretic hormone
- Fluid and electrolyte imbalance

**SIADH: Causes**

- Ectopic tumor secretion of ADH or ADH-like substances by tumor cells
- Abnormal secretion of ADH
- Chemotherapy
- Other Medications
- Non-Malignant Causes

**SIADH Risk Factors**

- **Malignancy**
  - Small Cell Lung
  - Head and neck
  - Olfactory neuroblastoma
  - Bladder
  - Breast
  - Cervix
  - Colon
  - Duodenum
  - Ovary
  - Pancreas
  - Prostate
  - Rectum
  - Small intestine
  - Lung
  - Thyroid

- **Nonmalignancy**
  - Hypothyroidism
  - Pulmonary disorders
  - Asthma
  - Acute respiratory failure
  - Pneumothorax
  - Acute respiratory distress syndrome
  - Chronic obstructive pulmonary disease
  - Tuberculosis
  - Hematologic malignancies
  - Genetic disorders
  - Pharmacologic agents
  - Surgery
  - Elderly
  - Systemic lupus erythematosus

- **Neurogenic**
  - Stroke
  - Encephalitis
  - Guillain-Barre syndrome
  - Herniation
  - Congestive heart failure

- **Pulmonary disorders**
  - Pneumonia
  - Atelectasis
  - Acute respiratory failure
  - Pneumothorax
  - Chronic obstructive pulmonary disease
  - Tuberculosis
  - Pulmonary fibrosis
  - Pulmonary edema
  - Pulmonary hypertension

- **Miscellaneous**
  - Anxiety
  - Nausea
  - Positive end-expiratory pressure breathing devices
  - Severe pain
  - Stress
  - Trauma

* Cerebral Salt Wasting: usually requires the administration of hypertonic saline, either oral or intravenous saline.
Medication's

<table>
<thead>
<tr>
<th>Analgesics</th>
<th>Antidepressants</th>
<th>Chemotherapy/Biotherapy</th>
<th>Other Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Imipramine</td>
<td>Cisplatin</td>
<td>Bromocriptine</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Monoamine oxidase Inhibitors</td>
<td>Cyclophosphamide</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>General analgesics</td>
<td>Selective serotonin reuptake inhibitors</td>
<td>Decetaxel</td>
<td>Chlorpropamide</td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
<td>Ifosfamide</td>
<td>Haloperidol</td>
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<tr>
<td>Meperidine</td>
<td></td>
<td>Melphalan</td>
<td>Thiourea diuretics</td>
</tr>
<tr>
<td>Nicotine</td>
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<td>Vinblastine</td>
<td>Amiodarone,</td>
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<tr>
<td>NSAIDs</td>
<td></td>
<td>Vinorelbine</td>
<td>Ciprofloxacin</td>
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<tr>
<td>Acetaminophen</td>
<td></td>
<td>Carboplatin</td>
<td>&quot;Ecstasy&quot;</td>
</tr>
</tbody>
</table>

Antidiuretic Hormone (ADH) a.k.a. Vasopressin

- Normally released from posterior pituitary
- Regulates water output and reabsorption by kidneys
- When plasma osmolality goes above the normal set point
  - "Osmoreceptors" in hypothalamus stimulate ADH release
  - ADH → acts on collecting ducts → causes kidneys retain water → restores plasma osmolality to its set point

Pathophysiology

Despite normal serum osmolality and plasma volume, the kidneys inappropriately conserve water:

End Result: plasma hyposmolality, urine hyperosmolality, elevated urinary sodium concentrations and dilutional serum hyponatremia

In an attempt to equalize osmotic pressure Water moves from the extracellular fluid to the intracellular fluid End Result: Cerebral Edema which causes profound neurologic changes
SIADH: Diagnostic Criteria

**Lab Values Adults**

- **Serum sodium:** (136-145 mEq/L)
  - < 130 mEq/L
- **Serum osmolality:** (285-295 mOsm/kg H₂O)
  - < 280 mOsm/kg
- **Urine Osmolality:**
  - > 100 mOsm/kg
- **Urinary sodium:** (40-220 mEq/L/d)
  - > 20 mEq/L

**Other**

- Clinical euvoemla
- Normal thyroid function
- Normal adrenal function
- Radiographic studies, if indicated
  - CXR
  - Computed tomography scan of head

**Other Clinical euvolemia**

- Normal thyroid function
- Normal adrenal function
- Radiographic studies, if indicated
  - CXR
  - Computed tomography scan of head

SIADH: Clinical Manifestations

- Depend on:
  - Severity of hyponatremia
  - Rate of change in plasma sodium concentrations
  - Osmotic gradient between intracellular and extracellular fluids
- Rapidly falling sodium
  - Can cause life-threatening symptoms
- Chronic low-grade hyponatremia
  - May not develop signs & symptoms unless sodium level drops below 125 mEq/L

SIADH: Treatment

- Identify & treat underlying cause if possible
  - Medications
  - Disease
    - Chronic
    - Acute
- Therapy to correct hyponatremia (based on severity, symptoms, & cause)
  - Chronic treatment may be necessary for SIADH caused by cancer
SIADH: Clinical Manifestations*

<table>
<thead>
<tr>
<th>Type</th>
<th>Serum Sodium Levels</th>
<th>Signs/Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal sodium</td>
<td>135 – 145 mEq/L</td>
<td>-</td>
</tr>
<tr>
<td>Mild hyponatremia</td>
<td>131 – 134 mEq/L</td>
<td>Nonspecific or none, Thirst, anorexia, nausea, fatigue, weakness, muscle cramps, headache, combativeness, irritability, abdominal cramps, oliguria</td>
</tr>
<tr>
<td>Moderate hyponatremia</td>
<td>126 – 130 mEq/L</td>
<td>Weight gain, oliguria, progressive neurologic symptoms</td>
</tr>
<tr>
<td>Severe hyponatremia</td>
<td>&lt; 120 mEq/L</td>
<td>Signs &amp; symptoms related to cerebral edema: papilledema, delirium, hypactive reflexes, ataxia, gait disturbances, seizures, coma, death</td>
</tr>
</tbody>
</table>

*Varies depending on the rate of onset of hyponatremia; signs of fluid depletion or overload are absent.

Mild Hyponatremia & General Care

- Fluid restrictions not to exceed 800 – 1,000 mL/day
- Monitor electrolyte levels, especially sodium and potassium
- Educate patients and caregivers about the importance of fluid restriction
- Provide an easy method to measure oral fluid intake
- Review medications and discontinue potentially offending drugs
- Control thirst and dry mouth (hard candy, artificial saliva, avoid alcohol-based mouthwashes)
- Maintain a diet high in sodium
- Educate on signs and symptoms to report: muscle weakness/cramps, mental changes, nausea, headache, anorexia

Moderate Hyponatremia

- Oral medications as ordered. May be given alone or in conjunction with fluid restriction of 500-1000mL/day. Observe for side effects
- Monitor electrolyte levels, urine output, and renal function
- Document response to treatment: fluid weight loss, increased serum sodium and osmolality
- Relieve pain, anxiety, and stress with relaxation techniques and educate patients and caregivers about the use of opioids, barbiturates and tricyclic antidepressants
### Medications Used in Treatment of Moderate

<table>
<thead>
<tr>
<th>Medication</th>
<th>Nursing Considerations</th>
</tr>
</thead>
</table>
| Demeclocycline 600-1200 mg/day PO | - Polyuria may develop.  
- Nephrogenic diabetes insipidus occurs in 60-70% of patients in 2-5 days  
- SE include nausea, ascites, and skin photosensitivity  
- Close monitoring of renal function  
- One hour prior or two hours after meals  
- Avoid antacids containing aluminum, calcium, or magnesium and iron-containing preparations (impairs absorption) |

| Lithium 900 – 1,200 mg/day PO | - Nephrogenic diabetes insipidus occurs in 30% of patients  
- Approximately four days to be effective  
- Serum lithium levels must be monitored  
- Limited use due to low efficacy and side effects: hypothyroidism and tremor  
- Swallow the capsule or tablet whole |

| Urea 30 g/day | - Poor palatability  
- Azotemia at higher doses  
- Limited availability in the US |

### Severe Hyponatremia

- Patients are usually hospitalized  
- Hypertonic (3% or 5%) saline infused SLOWLY (0.5 mL/kg/hr.)  
- Adjust on basis of every 1-2 hour plasma sodium levels  
- Goal to increase serum sodium:  
  - < 10 mEq/L in 1st 24 hrs.  
  - < 18 mEq/L in 1st 48 hrs.  
- Furosemide as ordered to increase diuresis, monitor potassium levels  
- Assess for adequate symptom management related to pain, anxiety, depression, nausea, and vomiting  
- Assess coping abilities  
- Monitor for signs of central pontine myelinolysis which is often delayed 2-6 days after correction of hyponatremia

### Vasopressin-Receptor Antagonists

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage</th>
<th>Side Effects</th>
</tr>
</thead>
</table>
| Conivaptan (Vaprisol®) | Loading dose: 20 mg infusion over 30 minutes  
Continuous infusion: 20 – 40 mg/24 hours | Thirst  
Dry mouth  
Nausea  
Risk of osmotic demyelination  
Polyuria |
| Tolvaptan (Samsca®) | Loading dose: 15 – 25 mg PO/IV Q day | Same as above |
Nursing Priorities SIADH

- Keep patient safe
- Increase serum sodium levels

SIADH: Nursing Interventions

- Monitor laboratory values
  - Serum & urine electrolytes and osmolality (severe hyponatremia – initially Q2h)
- Monitor for neurologic changes
  - LOC, behavior
  - Seizure precautions
- Watch for signs of central pontine myelinolysis (may be delayed 2-6 days after correction of hyponatremia)
- Patient Education & Support

References

- Up to Date: 9/30/2016; Treatment and Management of TLS and expert panel approach & Treatment of Hyponatremia: SIADH and reset osmostat
- Kaplan Marcella, SOEH, CHCN-01 Kaplan (Ed.). Understanding non-malignant myeloma enzymes: A summary for nurses. 2nd ed. (pp. 11-12). Chebungh, NY: ONS.
- TLS and SIADH evidence-based practice template reference tool available on the PSONS website