Detecting and Treatment of Tumor Lysis Syndrome & SIADH

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Definition of TLS:

Tumor Lysis Syndrome: On 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
  • Pre-existing renal conditions/dehydration prior to treatment

• Treatment Related
  • Chemotherapy/Biotherapy/Hormonal
  • Radiation
  • Surgery

Onset:

Usually within 24-48 hours after initiation of antineoplastic therapy

Duration:

May persist for 5-7 days post-therapy

Results:

• Hyperuricemia
• Hyperkalemia
• Hypophosphatemia
• Secondary Hypercalcemia

TLS: Pathophysiology
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

Prophylaxis Recommendations

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

Hydration

Monitoring

Allopurinol

Rasburicase

Cairo-Bishop TLS Classification System

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

Cairo-Bishop Grading

- Based on laboratory & clinical findings
  - Laboratory TLS
    - Serum creatinine: ≥ 1.5 - greater than 6 times the upper limit of normal
  - Potassium: ≥ 5 mEq/L or 25% increase from baseline
  - Phosphorus: ≥ 6 mg/dL for children and ≥ 9.5 mg for adults or 25% increase from baseline
  - Calcium: ≤ 2 mg/dL or 25% decrease from baseline

Prophylaxis and Monitoring:

- Often asymptomatic initially
- Detected initial via abnormalities in blood chemistries (Uric Acid, Potassium, Calcium, Phosphate, BUN, Creatinine)
- Signs & symptoms depend on extent of metabolic abnormalities
  - Hyperkalemia
  - Hyperuricemia
  - Hyperphosphatemia
  - Hypocalcemia
Prevention: IV Hydration

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

Patient Considerations:
- Fluid overload
- Intravenous access
- Kidney and cardiac status

Hydration Recommendations

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

Diuretics:
- Can be used but 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:
- Patients on steroids: 5% dextrose % NS induction (potential sodium retention and hypertension)
- Hyponatremia or volume depletion: Isotonic saline is initial choice
- Due to risk of hyperkalemia and hyperphosphatemia with calcium phosphate precipitation once tumor breakdown begins, potassium and calcium should be withheld initially
- No guidelines address optimal duration of hydration

Urinary Alkalization: Controversial

Acetazolamide and/or Sodium Bicarbonate

pH of 6.5-7.0 or higher

Fallen Out of Favor Due To:
- Lack of evidence demonstrating efficacy of approach. Experimental study suggest hydration with NS alone is as effective
- Alkalization 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
- Metabolic alkalosis

Panel Conclusions:
- Sodium bicarbonate is only indicated in patients with metabolic acidosis
- No consensus in patients who receive treatment with allopurinol
- Not required in patients receiving Rasburicase
- Still seen in practice: Sodium bicarbonate added to IV fluid (50-100 meq/liter)

Hyperuricemia Signs & Symptoms

Catabolism of Nucleic Acid to Uric Acid

Hyperuricemia:
- uric acid > 7.0 mg/dL
- Serum > 35 mg/dL
- Crystals/nephrolithiasis
- Decreased renal flow
- Acute/chronic renal failure
- Nausea, vomiting
- Fever
- Metabolic acidosis
- Pancreatitis
- Uric acid nephropathy
- Nucleated red blood cells
- Arthritis
- Uric acid diuresis
- Uric acid crystals

Precipitation in Renal Tubules

Inflammation

Renal Vasodilation

Oxidation

Impaired Autoregulation

Decreased Renal Flow

Oliguria, anuria, azotemia, hematuria, crystalluria
- Nausea, vomiting
- Arthritis
- Uric acid nephropathy
- Uric acid diuresis
- Uric acid crystals
- Nephrolithiasis
- Acute/chronic renal failure
- Metabolic acidosis
- Pancreatitis
- Fever
- Nucleated red blood cells

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

Allopurinol or Rasburicase

Allopurinol:
- Inexpensive and orally administered
- Begin 24 hour 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)

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

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, ≤100 mg/dose at extended intervals for creatinine clearance <3 mL/minute in adults

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

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 ≤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
- Rasburicase within blood samples: Blood should be collected in a pre-chilled tube, immediately placed on ice, and the assay completed 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

Hyperkalemia
Serum K+ >6.5 mEq/L
Guidelines: >6mEq/L

Early cardiac:
- Tachycardia
- EKG Changes: Prolonged QT and ST segment, lowering and inversion of T wave

Late cardiac:
- Bradycardia
- EKG Changes: Shortened QT, elevated T wave, wide QRS
- Ventricular tachycardia, ventricular fibrillation, cardiac arrest

Methemoglobinemia

Rasburicase: Hyperkalemia: Signs & Symptoms

Hyperkalemia Treatments:

**Hyperkalemia**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate &amp; Asymptomatic (K+&lt;6.0mEq/L)</td>
<td>Avoid IV and oral potassium</td>
</tr>
<tr>
<td>ECG &amp; cardiac rhythm monitoring</td>
<td></td>
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<tr>
<td>Sodium polystyrene sulfonate: Adult: 15-30 grams orally; Pediatric: 1 gram/kg orally.</td>
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<tr>
<td>Calcium gluconate (Adult): 1 gram (10mL of 10% solution): Pediatric: 50-100 mg/kg.</td>
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<tr>
<td>Sodium bicarbonate: Adult: 45-50 mEq; Pediatric: 1-2 mEq/kg.</td>
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</tbody>
</table>

Severe (K+>6.0mEq/L and/or symptoms):
ADD: For ECG Changes (widening 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.

**Hyperphosphatemia & Hypocalcemia**

Hyperphosphatemia
Serum PO4 >5 mg/dl
Guidelines: 6.5 mg/dl for children or 4.5 mg/dl for adults

Secondary Hypocalcemia
Serum Ca++ < 8.7 mg/dl
Guidelines: 7 mg/dl

**Hypokalemia**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperphosphatemia</td>
<td>Anuria</td>
</tr>
<tr>
<td>Oliguria</td>
<td></td>
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<tr>
<td>Acetemia</td>
<td></td>
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<tr>
<td>Edema</td>
<td></td>
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<tr>
<td>Hypertension</td>
<td></td>
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<tr>
<td>Acute renal failure</td>
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**Hypocalcemia**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Increased bowel sounds</td>
<td></td>
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<tr>
<td>Twitching</td>
<td></td>
</tr>
<tr>
<td>Muscle cramps</td>
<td></td>
</tr>
<tr>
<td>Weakness</td>
<td></td>
</tr>
<tr>
<td>Paresthesia</td>
<td></td>
</tr>
<tr>
<td>Lethargy</td>
<td></td>
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<tr>
<td>Syncope</td>
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</table>

Insulin and dextrose: To temporarily shift potassium into cells
- Adult: regular insulin (10 units) IV plus 100 mL of 50% dextrose solution IV:
- Pediatric: regular insulin (0.1 unit/kg) IV plus 25% dextrose 0.5 gram/kg IV over 30 minutes.

May repeat after 30-60 minutes.

Monitor finger stick glucose closely

Sodium bicarbonate: Given to induce influx of potassium if patient is diabetic.
Sodium bicarbonate and calcium are incompatible and need separate lines.

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 20 minutes
  - Pediatric: 0.1-0.3 mg/kg per nebulization

Cardiac:
- Tetany |
| Ventricular arrhythmias |
| Prolonged QT interval, inverted T wave |
| Heart block |
| Cardiac arrest |
### Hyperphosphatemia Treatment:

<table>
<thead>
<tr>
<th>Moderate (≥6.5 mg/dL)</th>
<th>Restrict oral and IV phosphate intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphate Binders:</td>
<td></td>
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<tr>
<td>- Calcium acetate</td>
<td>Adult: 2-3 tabs (1334 to 2668 mg) with each meal or</td>
</tr>
<tr>
<td>- Calcium carbonate</td>
<td>Adult: 1-2 grams with each meal; Pediatric: 30-40 mg/kg with each meal or</td>
</tr>
<tr>
<td>- Sevelamer</td>
<td>Adult: 800-1600 mg with each meal; Pediatric: 40-54 mg/kg with each meal or</td>
</tr>
<tr>
<td>- Lanthanum carbonate</td>
<td>Adult: 300-1000 mg with each meal or</td>
</tr>
<tr>
<td>- Aluminum hydroxide</td>
<td>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)</td>
</tr>
</tbody>
</table>

**Severe = Dialysis**

- CARH: Continuous arterial-venous hemofiltration
- CVVH: Continuous venous-venous hemofiltration
- CARHD: Continuous arterial-venous hemodialysis
- CVVHD: Continuous venous-venous hemodialysis

### Hypocalcemia Treatment

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

- **Asymptomatic:** No therapy
- **Symptomatic:**
  - Calcium gluconate: Adult: 1 gram (10 mL of 10% solution); Pediatric: 50-100 mg/kg in 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

- **Not evidence-based:** Expert Panel recommendations for monitoring in patients at high risk of TLS
  - High risk patients should be in a position to be readily transferred to an ICU
  - High risk patients should be tested for laboratory and clinical TLS parameters (Uric acid, PO₄, K⁺, Creat, Ca²⁺, and LDH, as well as T & O) 4-6 hours after the initiation of chemotherapy and every 4-8 hours thereafter
  - Serum uric acid should be reevaluated 4 hours after administration of the first dose of rasburicase, and every 6-12 hours thereafter until normalization of serum LDH and uric acid levels
  - If rasburicase is not used, electrolytes should be measured 8 hours after chemotherapy and one-night hospital stay considered.
  - If TLS has not occurred within 72 hours of multi-agent chemotherapy, the likelihood of TLS is very low.
  - 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
Sample Algorithmic Approach

Summary: Monitoring Guidelines

Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH):

SIADH: Causes

- Ectopic tumor secretion of ADH or ADH-like substances
  - Small cell lung cancer (accounts 75% SIADH associated with cancer)
  - Non-small cell lung cancer, mesothelioma, lymphoma
- Abnormal secretion of ADH 3 to inflammation, neoplasm, vascular lesions or drugs
  - Chemotherapy
  - Other Medications
  - Non-Malignant Causes

AKA: Schwartz-Barter syndrome, SIAD: Syndrome of Inappropriate Antidiuresis

Definition: Characterized by excessive release of antidiuretic hormone from the posterior pituitary gland or another source. The result is often dilutional hypotnatremia 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

- Fluid and electrolyte management
- Uric acid & phosphate management
- Adjust renally excreted drug doses
- Dialysis (hemo or peritoneal)
- Hemofiltration (CAVH, CVVH, CAVHD, CVVHD)
**SIADH Risk Factors**

<table>
<thead>
<tr>
<th>Neoplastic</th>
<th>Nonmalignancy</th>
<th>Neurologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Cell Lung</td>
<td>Malignancy</td>
<td>Syndrome</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>Nonmalignancy</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>Bladder</td>
<td>Pneumonia (viral/bacterial)</td>
<td>Hemorrhage</td>
</tr>
<tr>
<td>Breast</td>
<td>Asthma</td>
<td>Trauma</td>
</tr>
<tr>
<td>Cervix</td>
<td>Ataxia</td>
<td>Psychosis</td>
</tr>
<tr>
<td>Ducts/ducts</td>
<td>Acute Respiratory Failure</td>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Ovary</td>
<td>Pneumothorax</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Brain</td>
<td>Chronic obstructive pulmonary disease</td>
<td>Nausea</td>
</tr>
<tr>
<td>Paranasal</td>
<td>Tuberculosis</td>
<td>Positive end-expiratory pressure breathing devices</td>
</tr>
<tr>
<td>Primary</td>
<td>Hereditary SIADH (genetic disorder V2 receptor gene)</td>
<td>Severe pain</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>Surgery (transsphenoidal pituitary 21-35%)</td>
<td>Stress</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Older age</td>
<td>Trauma</td>
</tr>
<tr>
<td>Lymphomas</td>
<td></td>
<td></td>
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<tr>
<td>Multiple</td>
<td></td>
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<tr>
<td>Myeloma</td>
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<tr>
<td>Pancreas</td>
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<tr>
<td>Prostate</td>
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</tr>
<tr>
<td>Carcinoid</td>
<td></td>
<td></td>
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<tr>
<td>Testes</td>
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<tr>
<td>Thyroid</td>
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</tbody>
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**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, causing kidneys to retain water, restoring plasma osmolality to its set point

**Pathophysiology**

- Normally:
  - ADH
  - Urine Concentration

- SIADH:
  - Water retention
  - Lower Na concentration
  - Transiently expands extracellular fluid volume and organs increased urinary Na excretion

- Despite normal serum osmolality and plasma volume, the kidneys inappropriately conserve water
- End Result: plasma hyposmolality, urine hyperosmolality, elevated urinary sodium concentration and dilutional serum hyponatremia

**Medication's**

<table>
<thead>
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<th>Antidepressants</th>
<th>Chemotherapy/Biotherapy</th>
<th>Other Medications</th>
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</thead>
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<tr>
<td>Aspirin</td>
<td>Imipramine Monoamine oxidase inhibitors</td>
<td>Cisplatin</td>
<td>Bromocriptine</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Bupropion</td>
<td>Cyclophosphamide</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>General anesthetics</td>
<td>Selective serotonin reuptake inhibitors</td>
<td>Docetaxel</td>
<td>Chlorpropamide</td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
<td>Ifosfamide</td>
<td>Haloperidol</td>
</tr>
<tr>
<td>Meperidine</td>
<td></td>
<td>Melphan</td>
<td>Thalidomide</td>
</tr>
<tr>
<td>Nicotine</td>
<td></td>
<td>Vincristine</td>
<td>Antipsychotics</td>
</tr>
<tr>
<td>NSAIDs</td>
<td></td>
<td>Vinorelbine</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td></td>
<td>Carboplatin</td>
<td>Ciprofloxacin</td>
</tr>
</tbody>
</table>

**Medication List**

- Aspirin
- Barbiturates
- Bupropion
- Cisplatin
- Docetaxel
- Ifosfamide
- Melphan
- Vincristine
- Vinorelbine
- Carboplatin
- Imatinib
- Methotrexate
- Interferon-alfa and -gamma
- Bromocriptine
- Carbamazepine
- Chlorpropamide
- Haloperidol
- Thalidomide
- Antipsychotics
- Amiodarone
- Ciprofloxacin

**Edelman's Classic Equation**

\[ \text{PNa} = \text{NaE} + \text{K_E} \times \frac{\text{Total body water}}{\text{Plasma Na concentration/Exchangeable sodium and potassium}} \]

- ADH
- Water retention
- Lower Na concentration
- Transiently expands extracellular fluid volume and organs increased urinary Na excretion
- Returns extracellular volume toward normal and further lowers the plasma Na concentration
**SIADH: Diagnostic Criteria**

- **Lab Values Adults**
  - **Serum sodium**: (136-145 mEq/L)
    - < 130 mEq/L
  - **Serum osmolality**: (285-295 mOsm/kg \(H_2O\))
    - < 280 mOsm/kg
  - **Urine Osmolality**:
    - > 100 mOsm/kg
  - **Urinary sodium**: (40-220 mEq/L/d)
    - > 20 mEq/L

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

**SIADH: Clinical Manifestations**

- **Type**
  - **Serum Sodium Levels**
  - **Signs/Symptoms**
  - **Normal sodium**: 135 – 145 mEq/L
    - Non-specific or none
    - Thirst, anorexia, nausea, fatigue, weakness, muscle cramps, headache, irritability, abdominal cramps, oliguria
  - **Mild hyponatremia**: 131 – 134 mEq/L
    - Weight gain, oliguria, progressive neurologic symptoms
  - **Moderate hyponatremia**: 126 – 130 mEq/L
    - Weight gain, oliguria, progressive neurologic symptoms
  - **Severe hyponatremia**: < 120 mEq/L
    - Signs & symptoms related to cerebral edema: papilledema, delirium, hypoactive reflexes, ataxia, gait disturbances, seizures, coma, death

- **Other**
  - **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
- Therapy to correct hyponatremia (based on severity, symptoms, & cause)
- Chronic treatment may be necessary for SIADH caused by cancer

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*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 frequently, 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 Hyponatremia

<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 50-70% of patients in 2-5 days  
• Side effects include nausea, asthenia 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 (impair 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  
• Asthenia 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
- Safety Measures: Assist with ADL’s and seizure precautions
- 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>
<tbody>
<tr>
<td><strong>Conivaptan</strong></td>
<td>Loading dose: 20 mg infusion over 30 minutes</td>
<td>Thirst, Dry mouth, Nausea, Risk of osmotic demyelination Polyuria</td>
</tr>
<tr>
<td></td>
<td>Continuous infusion: 20 – 40 mg/24 hours</td>
<td></td>
</tr>
<tr>
<td><strong>Tolvaptan</strong></td>
<td>Loading dose: 15 – 25 mg PO/IV Q day</td>
<td>Same as above</td>
</tr>
</tbody>
</table>

**Contraindications:**
- Concurrent use of ketoconazole, itraconazole, ritonavir, clarithromycin, indinavir or other potent CYP3A inhibitors.
- Hypersensitivity to corn or corn products.

**References**
- Up to Date. 2015. Treatment and management of TLS and expert panel approach & Treatment of hyponatremia, SIADH and acute renal failure.

### Nursing Priorities SIADH

- Keep patient safe
- Increase serum sodium levels
- Reduce intracellular water

### 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)