Chemotherapy in the Infusion Clinic: Patient Electrolyte Imbalance Considerations

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Learning Objectives

• Explore the benefits and harms of chemotherapy
• Discuss advantages and challenges of calcium and magnesium test methodologies
• Define laboratory diagnostic criteria for tumor lysis syndrome (TLS) and specimen handling considerations during patient treatment for TLS
• Describe similarities and differences between pseudohyperkalemia and "reverse" pseudohyperkalemia

Ambulatory Oncology Infusion Center

• Often high patient volume (e.g. UNC ~ 60 patients/day)
• Patient population
  o Solid cancer
  o Liquid/Hematologic cancer
• Infusion therapy is the intravenous administration of medications and nutrients
  o Chemotherapy
  o Electrolyte, vitamin and mineral replacement
  o Hydration and anti-emetics
  o Others
Traditional Chemotherapies
- Cytotoxic chemical agents → Systemically inhibit cell division / growth → Cell death
  
  Alkylating Agents (e.g. Cyclophosphamide, Cisplatin) / Anti-Metabolites (e.g. Methotrexate, 5-fluorouracil)
  
  Cytotoxic Antibiotics (e.g. Anthracyclines) / Mitotic Inhibitors (e.g. Taxanes)

Chemotherapy Toxicities
- Lacks selectivity in targeting cancer cells only

Chemotherapy Toxicities Diagram:
- Myelosuppression
- Cardiotoxicity
- Neurotoxicity
- Nephrotoxicity
- Hepatic Toxicity
- Bladder Toxicity
- Others
- Cytoreduction

Balancing Chemotherapy Treatment
- Adverse toxicities, side effects

Balancing Chemotherapy Treatment Diagram:
- Therapeutic Benefit
  
  Goal: Maximize therapeutic benefit and minimize or prevent possible toxicities and side effects
Laboratory Testing for the Infusion Center

- Body systems frequently monitored (vary with treatment)
  - Reproductive – e.g. hCG
  - Hematological – e.g. CBC with differential
  - Hepatic – e.g. Total bilirubin, AST, ALT, ALP, PT
  - Renal – e.g. Creatinine
  - Cardiovascular – e.g. cTh, BNP
  - Electrolyte imbalance – e.g. Na+, K+, Ca2+, Mg2+, PO4\textsuperscript{3-}

- Aide patient care management decisions
  - Monitor patients response to therapy
  - Assess toxicity
  - Aide in dosage modification

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Patient Case

- 22 year old male diagnosed with nasopharynx carcinoma is receiving chemoradiation treatment. Following 1\textsuperscript{st} cisplatin chemotherapy infusion he has had symptoms of nausea and vomiting with poor appetite. He presents 1 week later to the infusion clinic for his 2\textsuperscript{nd} infusion of cisplatin chemotherapy.

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Patient Case: Cisplatin Therapy

- Cisplatin is a platinum containing anti-neoplastic alkylating agent commonly used to treat solid tumors
- Mechanism of Action
  - Binds purine bases
  - DNA crosslinking
  - Cell cycle arrest
  - Apoptosis

- Side effects: Nephrotoxic, neurotoxic, ototoxic and can cause severe nausea and vomiting
  - Cisplatin dose-limiting side effect is nephrotoxicity

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Cisplatin Therapy and Electrolyte Imbalance

- Cisplatin can cause focal tubular necrosis
  - Renal injury can manifest with increase in creatinine values
  - Nephrotoxicity can be minimized or prevented with intravenous hydration
- Renal salt wasting is a complication of cisplatin therapy
  - Hypokalemia
  - Hypocalcemia
  - Hypomagnesemia
  - Hyponatremia
- Monitoring of electrolyte concentrations and replacement is recommended for patients receiving cisplatin

Patient Case

- Prior to chemotherapy infusion, medical staff perform a patient assessment and blood is collected for lab analysis
  - Electrolytes
  - Renal function
  - CBC

The patient sits in the infusion chair and waits...

- Need for lab speed
  - Workflow varies from institution to institution
  - Pre-infusion testing with physician office visit
  - Stat testing in lab
  - Satellite lab
  - Some point-of-care testing

Calcium

- Physiology:
  - Ca^{2+} plays key role in bone mineralization, coagulation, muscle contraction, hormone secretion, glycogen metabolism, cell division, others...
- Body’s calcium:
  - 99% calcium resides in bone
  - Calcium in circulation:
    - 45% free ionized (physiologically active)
    - 45% protein bound (primarily albumin)
    - 10% complexed with anions (e.g. phosphate, lactate, citrate)
Calcium

- Calcium test methodologies:
  - Colorimetric assays measure total Ca²⁺
- Colorimetric reagents:
  - O-cresolphthalein complexone (OCP)
  - Aresenazo III
  - Methylthymol blue
  - NM-BAPTA

- Pros:
  - Readily available with most automated testing platforms
  - Heparinized plasma (faster TAT) or serum are acceptable

- Cons:
  - Total Ca²⁺ concentration influenced by protein (albumin) concentration
  - Analytical interferences (e.g. gadolinium)


Total Ca²⁺ Assays: Gadolinium Interference

- Gadolinium contrast agents may interfere with total Ca²⁺ measurement using colorimetric assays

Interference considerations:
- Contrast type and dose
- Patient renal function
- Time of sample collection

Prince et al. Radiology 2003; 227:639-646

Total Ca²⁺ Assays: Gadolinium Interference

- Gadolinium contrast agents may interfere with total Ca²⁺ measurement using colorimetric assays

Interference considerations:
- Contrast type and dose
- Patient renal function
- Time of sample collection
- Assay colorimetric reagent


<table>
<thead>
<tr>
<th>Study</th>
<th>Contrast agent</th>
<th>Method</th>
<th>Result</th>
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<td>Nemmar et al.</td>
<td>Gadobenate</td>
<td>OCP</td>
<td>Negative</td>
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<td>Umar et al.</td>
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<td>Groenela et al.</td>
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</table>
Calcium

- Calcium test methodologies:
  - Ion selective electrode measures **free ionized Ca**
  
  - **Pros:**
    - Measures physiologically active free ionized Ca measurement that is independent of albumin concentration
    - Whole blood acceptable and supports rapid TAT
    - Blood-gas and electrolyte analyzers can be performed at the point-of-care, satellite lab or in the lab (options for rapid TAT)

  - **Cons:**
    - Anaerobic handling of specimens is a must!
      - Air bubbles: Loss of CO2 \( \rightarrow \) pH \( \rightarrow \) iCa
    - Rapid analysis needed or transport on ice
    - Minimize glycolysis (lactate) \( \rightarrow \) pH \( \rightarrow \) iCa


Magnesium

- Physiology:
  - Mg is a key cofactor for > 300 enzymes (e.g. Na-K ATPase)
  - Mg is needed for appropriate oxidative-phosphorylation, glycolysis, cell replication, protein biosynthesis, nerve conduction, others...

- Body's magnesium:
  - ~70% resides in bone
  - 2nd most abundant intracellular cation
  - ~1% in circulation:
    - ~60% free ionized (physiologically active)
    - ~30% protein bound (primarily albumin)
    - ~10% complexed with with anions (e.g. bicarb, phosphate)


- Additional considerations:
  - Hemolysis: Mg^2+ concentration due to intracellular release
  - Mg^2+ test results may not reflect cellular Mg^2+ status

Lab Results Are Ready: Back to the Patient

- 22 year old male diagnosed with nasopharynx carcinoma
  - Symptoms of nausea and vomiting
  - Waiting for cisplatin chemotherapy

- Select lab results:

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Patient Results</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺</td>
<td>129</td>
<td>135-149 mmol/L</td>
</tr>
<tr>
<td>K⁺</td>
<td>2.6</td>
<td>3.5-5.0 mmol/L</td>
</tr>
<tr>
<td>Tot Ca²⁺</td>
<td>9.1 (2.3)</td>
<td>8.5-10.2 mg/dL</td>
</tr>
<tr>
<td>Tot Mg²⁺</td>
<td>1.6 (0.7)</td>
<td>1.6-2.2 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.39 (52)</td>
<td>0.70-1.30 mg/dL</td>
</tr>
</tbody>
</table>

- Treatment plan: Hold cisplatin chemotherapy → Intravenous KCl replacement with 0.9% NaCl Infusion

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Next Patient

- 39 year old man diagnosed with B-cell acute lymphoblastic leukemia received 1st cycle of chemotherapy
- 3 days follow-up examination: Patient symptoms include worsening fatigue, nausea, vomiting, muscle cramps and perioral numbness

- Select lab findings:

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient Result</th>
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</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>36X10⁹</td>
<td>3.5 - 10.5X10⁹/L</td>
</tr>
<tr>
<td>K⁺</td>
<td>6.3</td>
<td>3.6 - 5.2 mmol/L</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>6.3 (1.6)</td>
<td>8.9 - 10.1 mg/dL</td>
</tr>
<tr>
<td>PO₄³⁻</td>
<td>7.6 (2.5)</td>
<td>2.5 - 4.5 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>2.3 (203)</td>
<td>0.8 - 1.3 mg/dL</td>
</tr>
<tr>
<td>Uric acid</td>
<td>15.6 (928)</td>
<td>3.7 - 8.0 mg/dL</td>
</tr>
<tr>
<td>Urinalysis</td>
<td></td>
<td>Absent</td>
</tr>
</tbody>
</table>

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Tumor Lysis Syndrome

- Tumor lysis syndrome (TLS) in oncolytic emergency
  - Hyperkalemia: Cardiac arrhythmias, seizures
  - Hypocalcemia: Renal failure
  - Hyperphosphatemia: Renal failure
  - Hyperuricemia: Cardiac arrhythmias, seizures

- 2008 American Society Clinical Oncology TLS guideline:
Tumor Lysis Syndrome

- Clinical TLS = Lab TLS + clinical complication

### Pathophysiology: Tumor Lysis Syndrome

- Rapid tumor lysis → release of intracellular contents
  - Rapid release of purines → hyperuricemia
  - Uric acid crystal deposition in renal tubules → renal failure

- ~98% K⁺ is intracellular under physiological conditions
  - Rapid release → hyperkalemia

- Malignant cells can contain 4 X's intracellular phosphate
  - Rapid release → hyperphosphatemia
  - Exacerbated in renal failure

- Hypocalcemia is secondary to hyperphosphatemia in TLS
  - Precipitation of calcium-phosphate crystals in renal tubules can exacerbate renal failure and lead to hypocalcemia

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TLS Treatment: Risk Stratification

- Best treatment for TLS is prevention
- 2010 Expert TLS Panel Consensus
  - Algorithms incorporating tumor type, tumor burden, renal function and electrolytes are used to risk stratify patients

- Patients at-risk for lab TLS should have electrolytes and chemistries monitored at least every 6 h
- Forced diuresis may reduce uric acid deposition in renal tubules

Rasburicase Warning for Uric Acid Testing

- Potential rasburicase interference with uric acid testing
  - Uric acid lab testing: Colorimetric detection common
    - 2H2O + uric acid \rightarrow allantoin + H2O2 + CO2
    - H2O2 + leuco-dye \rightarrow dye + 2H2O
  - Elitek® (rasburicase) WARNING:
    - Rasburicase may cause spuriously low uric acid measurement
    - Special handling of blood specimens is needed to prevent ex vivo uric acid degradation
Next Patient
- 75 year old man was diagnosed with chronic lymphoblastic leukemia (CLL) 9 years previously and presents to the infusion center for chemotherapy
- 2 days follow-up examination: Worsening clinical condition
- Select lab findings

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient Result</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>479 X 10⁹</td>
<td>3.5 - 10.5 X 10⁹/L</td>
</tr>
<tr>
<td>Platelets</td>
<td>17 X 10⁹/L</td>
<td>140 - 400 X 10⁹/L</td>
</tr>
<tr>
<td>Serum K⁺</td>
<td>9.8</td>
<td>3.4 – 5.0 mmol/L</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>6.3 (1.6)</td>
<td>8.9 – 10.1 mg/dL (2.2 – 2.5 mmol/L)</td>
</tr>
<tr>
<td>PO₄³⁻</td>
<td>7.6 (2.5)</td>
<td>2.5 - 4.5 mg/dL (0.8 – 1.5 mmol/L)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.5 (133)</td>
<td>0.6 – 1.3 mg/dL (53 – 115 mmol/L)</td>
</tr>
<tr>
<td>Uric acid</td>
<td>11.8 (702)</td>
<td>3.5 - 8.0 mg/dL (208 – 479 µmol/L)</td>
</tr>
</tbody>
</table>

- Diagnosis: Leukemic blast crisis with TLS

Patient Case (Continued)
- Patient did not exhibit signs or symptoms of hyperkalemia
- Hyperkalemia investigation:
  - No ECG findings consistent with systemic hyperkalemia
  - Repeat K⁺ measurement
    - Serum K⁺ – 9.8 mmol/L
    - Plasma K⁺ – 4.1 mmol/L
- **Pseudohyperkalemia** - Elevated serum K⁺ artifact
  - Generally attributed to platelet degranulation during clotting
  - Specimen collection: Hemolysis, prolonged tourniquet, fist clenching
  - Specimen transport: Trauma to cells during pneumatic tube transport

Next Patient
- 64 year old man was diagnosed with chronic lymphoblastic leukemia (CLL) and presents to the infusion center for first cycle of chemotherapy
- 1 day post-chemo examination: Patient denies fatigue
- Select lab findings

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<thead>
<tr>
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<th>Patient Result</th>
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</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>367 X 10⁹</td>
<td>4.5 – 11.0 X 10⁹/L</td>
</tr>
<tr>
<td>Platelets</td>
<td>73 X 10⁹/L</td>
<td>150 - 350 X 10⁹/L</td>
</tr>
<tr>
<td>Plasma K⁺</td>
<td>7.7</td>
<td>3.5 - 5.0 mmol/L</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>8.2 (2.1)</td>
<td>8.2 – 10.2 mg/dL (2.1 – 2.6 mmol/L)</td>
</tr>
<tr>
<td>Mg²⁺</td>
<td>1.9 (0.8)</td>
<td>1.7 – 2.6 mg/dL (0.7 – 1.1 mmol/L)</td>
</tr>
<tr>
<td>PO₄³⁻</td>
<td>6.2 (2.0)</td>
<td>2.5 - 4.5 mg/dL (0.8 – 1.5 mmol/L)</td>
</tr>
<tr>
<td>Uric acid</td>
<td>6.6 (393)</td>
<td>4.0 - 8.0 mg/dL (228 – 479 µmol/L)</td>
</tr>
</tbody>
</table>

Patient Case (Continued)

- Patient did not exhibit signs or symptoms of hyperkalemia
- Hyperkalemia investigation:
  - No ECG findings consistent with systemic hyperkalemia
  - Repeat K+ measurement
    - Plasma K+ = 8.1 mmol/L
    - Plasma K+ = 10.7 mmol/L
    - Serum K+ = 3.6 mmol/L
  - "Reverse" Pseudohyperkalemia - Elevated plasma K+ artifact
    - Mechanism remains unknown
    - Potential causes:
      - Mechanical stressors - Pneumatic tube transport, vacuum tube
      - Heparin-induced cell lysis in setting of hematological malignancy

Summary

- Traditional chemotherapy agents promote cell death in rapidly proliferating cells (non-specific)
- Rapid lab testing can provide useful information for clinical management of patients in the infusion center
- Electrolyte imbalances are common in patients receiving chemotherapy
  - Tumor lysis syndrome is an oncolytic emergency
  - Laboratorians play a key role in investigating potential pseudo-electrolyte concentration artifacts
- Total Ca²⁺ and Mg²⁺ are commonly measured using colorimetric assays, but assay interferences and abnormal albumin concentrations are confounding factors
- Free ionized Ca²⁺ is commonly measured using ISE methodology, though careful specimen collection and handling are needed

Assessment Question

A heparinized-syringe whole blood sample is received in the laboratory for blood-gas and electrolyte testing. Upon careful examination, the medical technologist notices frothy air bubbles in the sample. What impact, if any, may air bubbles have on pH and free iCa²⁺ results using ISE methodology?

A. No effect
B. Falsely ↓ pH and ↑ iCa²⁺
C. Falsely ↓ pH and ↓ iCa²⁺
D. Falsely ↑ pH and ↑ iCa²⁺
E. Falsely ↑ pH and ↓ iCa²⁺
Assessment Question

Patients exhibiting tumor lysis syndrome have electrolyte imbalances characterized by:

A. ↑ K⁺, ↑ Ca²⁺, ↑ PO₄³⁻, ↑ uric acid
B. ↓ K⁺, ↑ Ca²⁺, ↑ PO₄³⁻, ↑ uric acid
C. ↑ K⁺, ↓ Ca²⁺, ↑ PO₄³⁻, ↑ uric acid
D. ↑ K⁺, ↑ Ca²⁺, ↓ PO₄³⁻, ↑ uric acid

[↑ = above reference range  
↓ = below reference range]

Assessment Question

Reverse pseudohyperkalemia is characterized by:

A. Elevated serum K⁺ artifact
B. Elevated plasma K⁺ artifact
C. Elevated K⁺ artifact in both serum and plasma
D. Physiologically elevated K⁺ concentration