



Marshfield  
Clinic

# An Unusual Case of Elevated Anion Gap Metabolic Acidosis

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# Introduction

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- ▶ Acute acetaminophen hepatotoxicity causes anion gap metabolic acidosis secondary to lactic acidosis and renal failure
- ▶ However, chronic ingestion of therapeutic doses of acetaminophen can sometimes cause elevated anion gap metabolic acidosis through glutathione depletion and 5-oxoproline accumulation



# History

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- ▶ 63 y/o female smoker who has been feeling **increasingly weak** over the past 2 weeks presents to the hospital with unresponsiveness
- ▶ Has been taking **acetaminophen at therapeutic doses** for chronic pain, arthralgia and fibromyalgia
- ▶ **Intubated** en route to the hospital for agonal breathing



# Past Medical History

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- ▶ **Chronic calcific pancreatitis** secondary to chronic alcohol abuse
  - ▶ H/O alcohol abuse, abstinent for more than 2 years
  - ▶ Pancreatic insufficiency leading to **severe malnutrition**
  - ▶ **Type 2 diabetes mellitus**
  - ▶ Depression
  - ▶ Polyarthralgia/Fibromyalgia
  - ▶ Chronic back pain
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# Physical Exam

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- ▶ **VITAL SIGNS:** Temperature 96 F, PR: 95, **RR: 28**, O2 100% on **60% FiO2**, BP: 117/73 ; Weight: **33 kg**
  - ▶ **GENERAL:** **Emaciated, not responsive to any stimuli**
  - ▶ **HEENT:** Atraumatic. Pupils equal, round, and nonreactive to light. Mild pallor present
  - ▶ **LUNGS:** **Coarse breath sounds right > left**
  - ▶ **CVS:** S1 and S2, RRR. No murmurs, rubs, or gallops
  - ▶ **Abdomen:** Soft, nontender, nondistended. Bowel sounds +. No organomegaly.
  - ▶ **EXTREMITIES:** Slightly cool to touch; 2+ pulses. No pitting pedal edema.
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# Labs

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- ▶ **CMP:** T Bil: 0.2, AST: 43, ALT: 15, Alkaline phosphatase: 164, **Albumin: 2.6**, Ca: 7.8, Na: 134, K: 4.8, Cl: 108, **HCO<sub>3</sub>: 3**, **Urea: 24**, **Creat: 1.6**, **Glucose: 384**
- ▶ **CBC:** **WBC: 51.1**, Hemoglobin: 9.4, Platelets: 629
- ▶ **Urine drug screen:** Tricyclics + Barbiturates
- ▶ **Urinalysis:** Unremarkable
- ▶ **Rapid blood screen:** Alcohol: NEG; Salicylates: 2.5 (2.0-29.9); **Acetaminophen 13 (0-10)**
- ▶ **ABG:** **pH: 6.81**, **pCO<sub>2</sub>: 27**, pO<sub>2</sub>: 389
- ▶ **Lactate: 0.5 (0.0-1.6)**

## Labs cont...

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- ▶ **Blood osmolality:** 319 (282-305) mOsm/kg
- ▶ **Calculated blood osmolality:** 298 mOsm/kg
- ▶ **β-hydroxybutyrate:** 4.04 (0.03-0.3)
- ▶ **High sensitivity troponin I:** 37
- ▶ **Blood cultures:** No growth



# Imaging

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- ▶ **Chest x-ray:** Multifocal air space opacities
- ▶ **Head CT scan:** No evidence of mass, intracranial hemorrhage, or large distribution acute infarction





# Hospital Course

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- ▶ Broad spectrum antibiotics
- ▶ Bicarbonate infusions followed by continuous drip
- ▶ Resuscitation fluids
- ▶ Vasopressors
- ▶ Regular insulin drip as per DKA protocol



# What is Going on Here?

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# Causes of Anion Gap Metabolic Acidosis

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- ▶ M – Methanol
- ▶ U – Uremia
- ▶ D – DKA, drugs (Metformin, Stavudine, Topiramate)
- ▶ P – Paraldehyde, phosphate
- ▶ I – Iron, Isoniazid, ischemia
- ▶ L – Lactic acidosis
- ▶ E – Ethylene glycol
- ▶ S – Salicylates, starvation



# Hospital Course cont...

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- ▶ IV N-acetylcysteine
- ▶ Urine 5-oxoproline levels
- ▶ Hemodialysis



## Hospital Course cont...

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- ▶ Urine 5-oxoproline levels – **8800  $\mu\text{mol/mol}$**  creatinine (reference range **<50**)
- ▶ Very high peak of urine acetaminophen

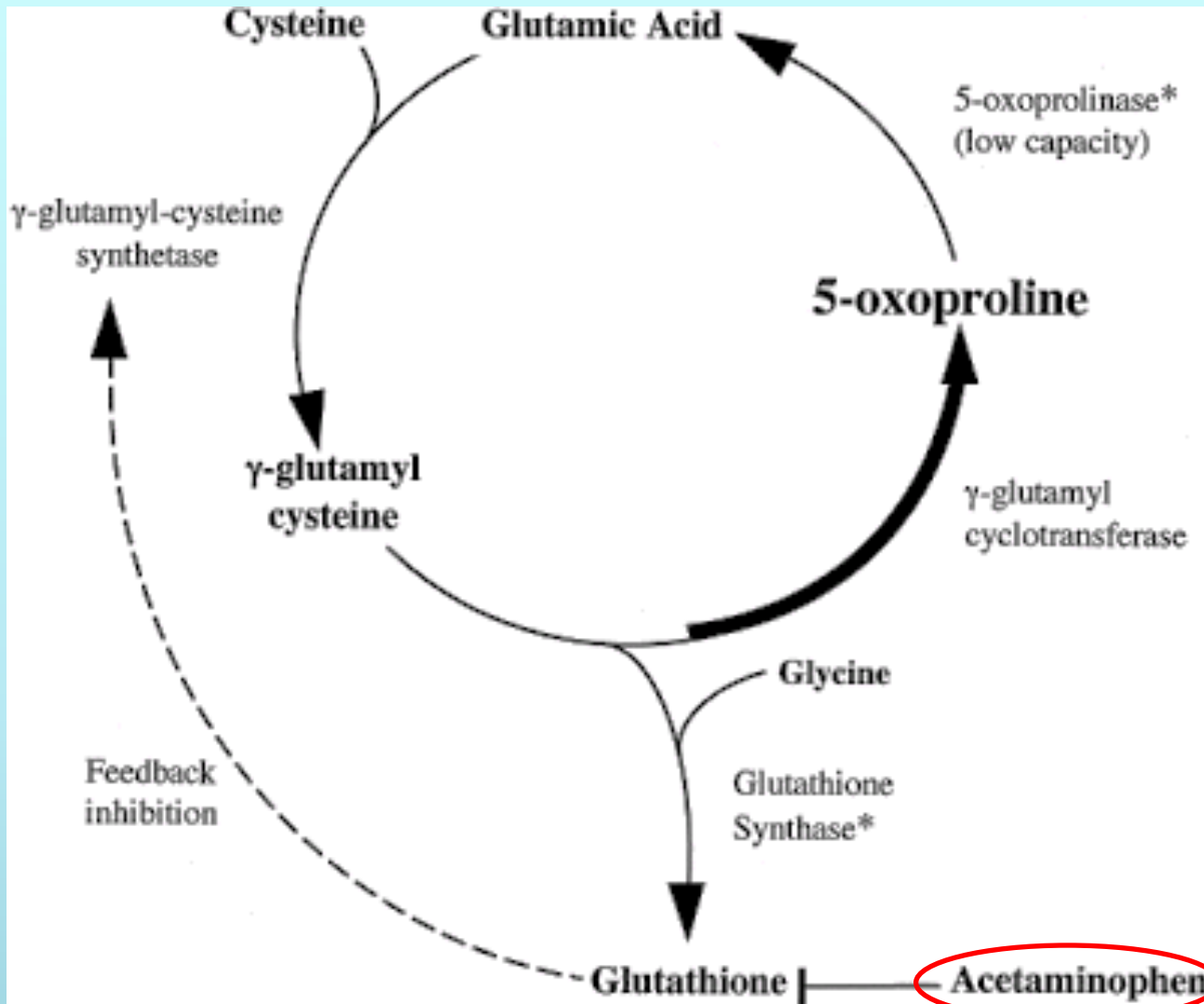


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Increased Anion Gap Metabolic  
Acidosis as a Result of 5-Oxoproline  
(Pyroglytamic Acid)



# $\gamma$ -Glutamyl Cycle



# Acetaminophen and 5-Oxoproline

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## ▶ Contributory factors:

- ▶ Severe malnutrition (limited glycine and cysteine availability)
- ▶ Pregnancy
- ▶ Strict vegetarian diet
- ▶ Diabetes mellitus type 2
- ▶ Liver disease
- ▶ Renal failure



# Diagnosis

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- ▶ Urine/blood organic acid levels – 5-Oxoproline
- ▶ Glutathione synthetase activity
- ▶ Supra-therapeutic/toxic levels of acetaminophen are not required to cause 5-oxoprolinuria



# Treatment of 5-Oxoprolinemia

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- ▶ No convincing evidence for N-acetylcysteine
- ▶ Bicarbonate infusions and drips



# Take Home Points

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- ▶ In severely malnourished patients, especially women with multiple underlying co-morbidities, chronic ingestion of therapeutic doses of Acetaminophen can cause unexplained severe anion-gap metabolic acidosis with normal lactate levels and elevated serum osmolality.
- ▶ If high suspicion get serum/urine 5-oxoproline levels, withdraw medication and start N-acetylcysteine and bicarbonate drip.



# Replace MUDPILES?

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- ▶ G – Glycols
- ▶ O – Oxoproline
- ▶ L – L-lactate
- ▶ D – D-lactate
- ▶ M – Methanol
- ▶ A – Aspirin
- ▶ R – Renal failure
- ▶ K – Ketoacidosis

# Questions?

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