A Multifactorial Lactic Acidosis in the ICU
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Introduction
Lactic acidosis is a common occurrence in the ICU setting, and is usually attributable to states of hypoperfusion, such as shock. Type B lactic acidosis occurs in normotensive and normocapnic conditions, with etiologies including medications, toxins, and underlying conditions. Among these are metformin-induced lactic acidosis (MALA) and the malignancy-associated Warburg effect.

Case
An unidentified middle aged Asian male was brought to the ICU, having been intubated for altered mental status in the field and started on norepinephrine for hypotension.

Exam
- Vital signs: T 95.2 | HR 126 | BP 102/51 | SpO2 99%
- Gen: Well developed, well nourished male, intubated, sedated
- HEENT: No scleral icterus. Pupils equal, round, reactive.
- CV: Tachycardic, regular rate, no murmurs
- Pulm: Coarse ventilator sounds
- Abd: Hypoactive, soft, nontender, no organomegaly
- Ext: No pitting edema. Warm and well perfused
- Skin: Multiple tattoos. No jaundice

Labs
- EKG: Sinus tachycardia. Peaked T waves. No ST changes
- TTE: LVEF 66%, no wall motion abnormalities
- MRI abdomen (see below): Heterogenous infiltrative mass in right hepatic lobe with extension into porta hepatitis. Bulky portaocaval adenopathy. Multiple osseous metastases. No abscesses.

Case, continued
- The patient was identified as a 56 year-old Laotian male with a history of diabetes and metastatic cholangiocarcinoma refractory to palliative chemotherapy.
- Medications (last known): Metformin, long acting morphine.
- HIDA scan: No uptake of trace in gallbladder or cystic duct
- MRI abdomen: (last known): Metformin, long acting morphine.

Discussion
Lactate is the end product of glycolysis; pyruvate is preferentially reduced to lactate under hypoxic conditions. Lactic acidosis (serum lactate level >5 mmol/L and pH <7.35, usually with an increased anion gap) occurs when production exceeds utilization or clearance. Type A lactic acidosis refers to conditions of inadequate oxygen delivery, such as hypotension, hypoxia, and anemia. Type B lactic acidosis refers to conditions of inadequate oxygen utilization, which can occur in malignancy or congenital mitochondrial myopathies; medications such as metformin and antiretrovirals; and toxins such as ethanol and propylene glycol.

Metformin, a common diabetes medication, is mainly readily cleared. It can inhibit part of the mitochondrial respiratory transport chain, as well as impair hepatic clearance of lactate. This is compounded in cases of acute renal failure, which is present in the majority of cases of metformin-associated lactic acidosis (MALA). Although rarely seen, even in the ICU setting, it is associated with a high mortality (50%), with lactate levels ranging from 2.9 to 30 mmol/L. Dialysis has its proponents given the adverse effects associated with sodium bicarbonate (volume overload, hypernatremia, paradoxical intracellular acidosis); however one case series showed no difference in mortality between the two.

Type B lactic acidosis is described in malignancies, with most of these being hematologic (87%). The etiology is partially explained by liver dysfunction from metastases (in 45% of cases). The Warburg effect refers to the altered glucose metabolism in neoplastic cells wherein glycolysis is favored even within an aerobic environment. Dialysis and bicarbonate infusions may be used as temporizing measures until the underlying malignancy can be treated. Mortality is very high (81%).

Teaching Points
- The differential for lactic acidosis should include both Type A (inadequate oxygen delivery) and Type B (inadequate oxygen utilization or lactate clearance) causes.
- Type B lactic acidosis etiologies include medications (e.g., metformin) and malignancy.
- Metformin-associated lactic acidosis (MALA) is usually associated with acute kidney injury, has a high mortality rate, and may be treated with sodium bicarbonate or dialysis.
- The lactic acidosis associated with malignancy (hematologic > solid tumor) is due to a combination of liver dysfunction, ischemia, and altered glucose metabolism (Warburg effect).

References