emDocs

# The EM Educator Series

## The EM Educator Series: MALA

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**Case 1: A 38-year-old female presents with nausea, vomiting, and loose stools for 3 days. She has a history of HTN/DM and is on lisinopril and metformin. She has had difficulty with oral intake due to her symptoms and appears dehydrated on exam.**

**Case 2: A 52-year-old male presents from the outpatient clinic with complaints of "delirium and acute kidney injury". He is on a metformin for diabetes.**

**Case 3: A 58-year-old female is rushed back into the resuscitation area with suspected "septic shock" from the triage nurse. Her lactate returned at 16.**

**Questions for Learners:**

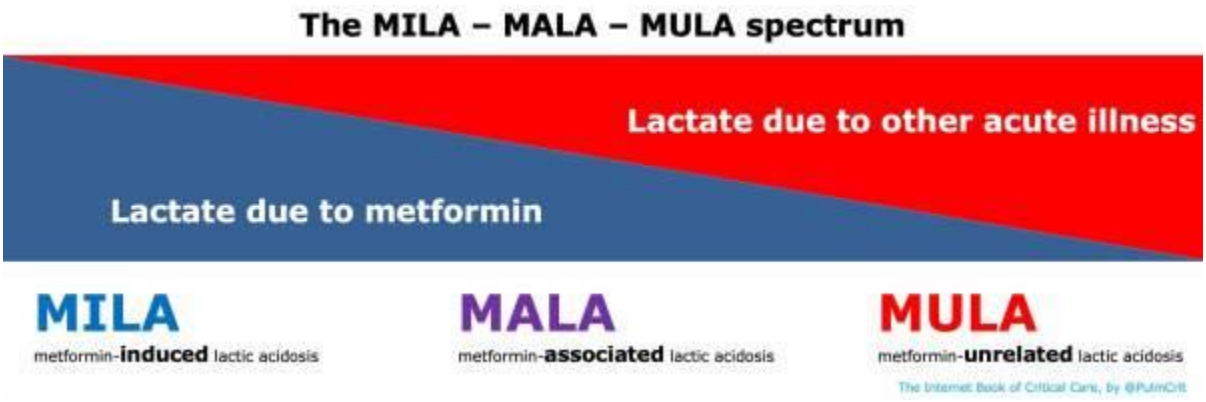
1. What are the differences between metformin-associated lactate acidosis (MALA), metformin-induced lactate acidosis (MILA), and metformin-unrelated lactate acidosis (MULA)?
2. How does MALA present?
3. What is the differential diagnosis for MALA?
4. What should you consider in the patients with a double-digit lactate and a single-digit bicarbonate?
5. What are the key components of managing MALA?

**Suggested Resources:**

- Articles
  - IBCC
  - emDocs ToxCard
  - Tox & Hound MALA
- Journal Articles
  - Clin Toxicol - Drug-induced hyperlactatemia
  - Pharmacotherapy - Medication-Induced Hyperlactatemia and Lactic Acidosis: A Systematic Review of the Literature
  - JEM - Metformin-Associated Lactic Acidosis Presenting Like Acute Mesenteric Ischemia
  - Critical Care Clinics - Toxicology of Medications for Diabetes Mellitus

**Answers for Learners:**

1. **What are the differences between metformin-associated lactate acidosis (MALA), metformin-induced lactate acidosis (MILA), and metformin-unrelated lactate acidosis (MULA)?**




**metformin-induced lactic acidosis (MILA)**

- High levels of metformin are the *primary* cause of illness.
- (1) Acute metformin overdose:
    - Acute poisoning may lead to MILA in the absence of renal dysfunction.
    - Precise amount of metformin required to do this is unclear, but seems to be high (e.g., >20 grams).(30126348)
    - Patients with acute ingestion look fine initially, but deteriorate subsequently (one example of a "toxin bomb").
- (2) Subacute accumulation of metformin due to renal failure:
    - Metformin is renally cleared.
    - Progressive renal failure (with GFR << 30 ml/min) eventually leads to metformin accumulation and toxicity.
    - These patients may present with marked lactic acidosis, yet have fairly preserved hemodynamics and look OK.

**metformin-associated lactic acidosis (MALA)**

- Definition:
    - Patient on metformin develops an acute life-threatening illness (e.g. ,septic shock, cardiogenic shock).
    - Metformin amplifies the degree of lactic acidosis, but it's not the *sole* cause of the illness.
- Risk factors include renal insufficiency, higher doses of metformin, and alcoholism.

**metformin-unrelated lactic acidosis (MULA)**

- Metformin is an innocent bystander. Metformin levels are *low*.
- Clinically it may be impossible to differentiate this from MALA.
    - Differentiation of MULA from MALA requires measurement of metformin levels, which isn't available at most hospitals.

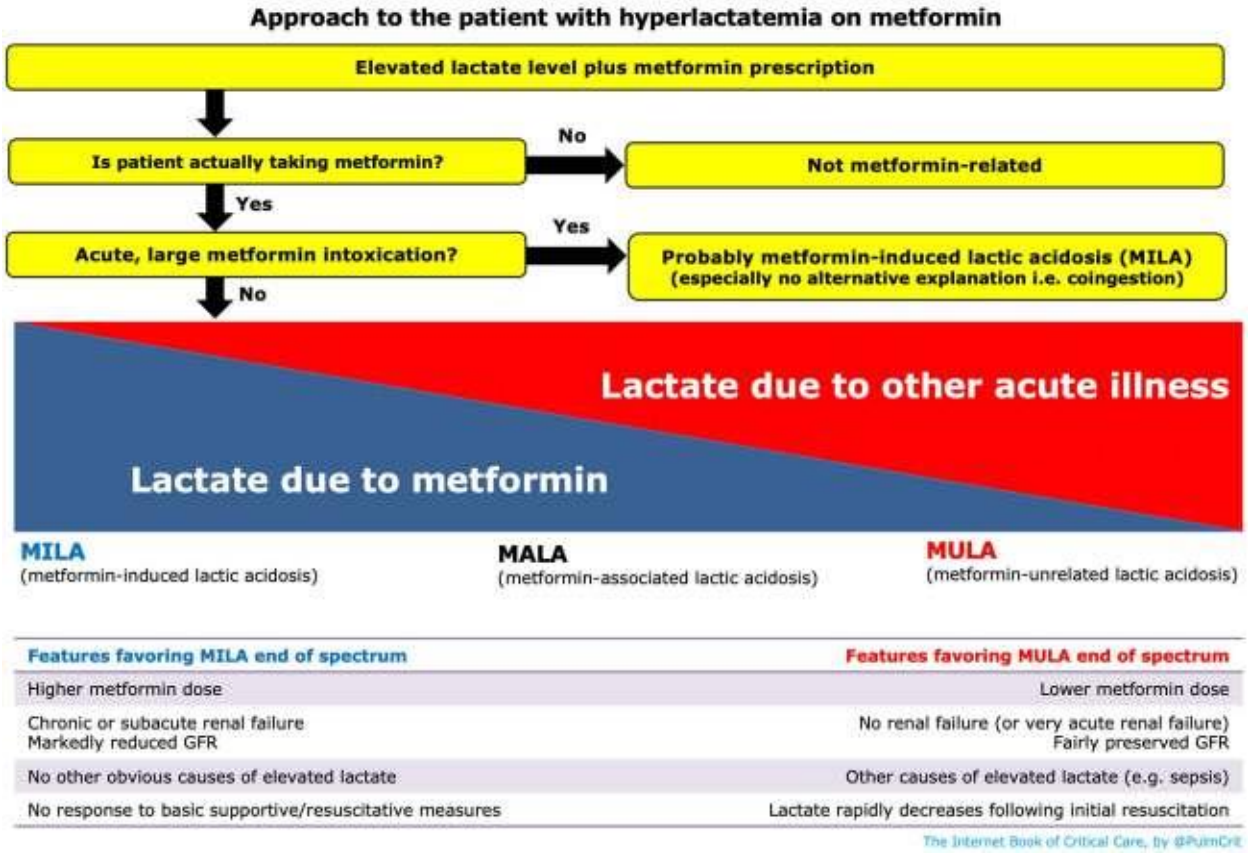
**2. How does MALA present?**

Mild toxicity: non-specific symptoms including nausea, vomiting, diarrhea, abdominal pain, pancreatitis, malaise, myalgias, and dizziness.

Severe toxicity:

a. Onset may be subtle with non-specific symptoms
b. Patients may also develop encephalopathy, blindness, shortness of breath, hypothermia, hypotension, and death.

**3. What is the differential diagnosis for MALA?**




| Features favoring MILA end of spectrum | Features favoring MULA end of spectrum |
|---|---|
| Higher metformin dose | Lower metformin dose |
| Chronic or subacute renal failure<br>Markedly reduced GFR | No renal failure (or very acute renal failure)<br>Fairly preserved GFR |
| No other obvious causes of elevated lactate | Other causes of elevated lactate (e.g. sepsis) |
| No response to basic supportive/resuscitative measures | Lactate rapidly decreases following initial resuscitation |

The Internet Book of Critical Care, by @PulmCrit

*Many patients may be ill due to a combination of metformin plus an acute illness. Therefore, a thorough search must always be made for any additional causes of physiologic stress.*

metformin-induced lactic acidosis vs. DKA

- Compared to isolated DKA, patients with metformin-induced lactic acidosis have greater degree of hyperlactatemia, with less extensive ketoacidosis.
- However, it can be difficult to sort this out (and patients can have a combination of both processes). When in doubt, treat both conditions (the treatment for DKA may actually improve MILA/MALA). More on treatment of this below.

other causes of lactic acidosis, for example:

- Shock of any etiology (e.g., septic shock, adrenal insufficiency, cardiogenic shock).
- Acute mesenteric ischemia.
- Seizure.
- Liver failure.
- Thiamine deficiency.
- Medications:

- HIV antiretrovirals.
- Linezolid.
- Propylene glycol.
- Propofol infusion syndrome.
- Beta-adrenergic medications (e.g., albuterol, epinephrine).
- Massive acetaminophen overdose.

**4. What should you consider in the patients with a double-digit lactate and a single-digit bicarbonate?**

Double-digit lactate: dead bowel (or something is dead); cancer; cardiac arrest; seizures; acute liver failure; MALA; cyanide tox; multifactorial shock

Single-digit bicarb: sick ketoacidotic syndromes; severe kidney injury; severe liver injury; double-digit lactate (as above); multifactorial shock; toxic alcohols; severe salicylate tox; severe acetaminophen tox; other toxins

**5. What are the key components of managing MALA?**

- The mainstay of treatment is good systematic and supportive care.
- Patients should be monitored closely, as clinical worsening can occur rapidly
- Consider early consultation with toxicologist and nephrologist.
- Decontamination: Consider activated charcoal early following an acute ingestion in patients that can protect their airway or are intubated.
- Airway management: Patients with metformin toxicity rarely require intubation, but it is important to remember tachypnea may reflect compensation for metabolic acidosis as opposed to impending respiratory failure, and clinicians should be conscious of ventilator rate settings (i.e. don't set the ventilation rate too low).
- Hypotension:
    - IV fluids, vasopressor therapy
    - Persistent hypotension suggests profound toxicity, in which case hemodialysis is often necessary.
- Hypoglycemia:
    - Dextrose supplementation
    - If hypoglycemia occurs, evaluate for other causes such as concurrent insulin or sulfonylurea exposure, as metformin alone rarely causes hypoglycemia.
- Metabolic acidosis:
    - Sodium bicarbonate usage for acidosis is controversial.
    - Can consider IV sodium bicarbonate if serum bicarbonate concentration less than 5 mEq/L.
    - Dose: 1-2 mEq/kg IV bolus, then infusion titrated to pH greater than 7.2.
- Hemodialysis:
    - In cases of severe metformin toxicity, dialysis can be utilized.
    - Intermittent hemodialysis is preferred initially; continuous renal replacement therapy may be considered if hemodialysis is not feasible.
    - EXTRIP's criteria for dialysis include any one of the following:
        - Severely elevated lactate greater than 20 mmol/L
        - Severe metabolic acidosis with pH less than or equal to 7.0

        - Failure to improve (pH, lactate, clinical status) with standard supportive care within 2-4 hours
    - Dialysis may also be considered under the following conditions according to EXTRIP[4]:
        - Elevated lactate greater than 15 mmol/L
        - pH 7.0-7.1
        - Shock
        - Decreased level of consciousness
        - Comorbidities: kidney injury, liver failure with coagulopathy, encephalopathy
    - Disposition:
        - Asymptomatic acute ingestions:
            - 4–6-hour observation period for immediate-release overdose, 8-12-hour observation with extended-release formulations; medically clear if remain asymptomatic without metabolic acidosis, lactate elevation, hypoglycemia, or renal injury
            - Some recent studies have suggested longer observation times up to a minimum of 12 hours following acute overdose.
        - Symptomatic ingestions with mild elevation of lactate and increased anion gap:
            - Can medically clear if all symptoms and laboratory abnormalities resolve after a period of observation with instructions to discontinue metformin, get follow-up labs with primary care physician if they are prescribed metformin.
            - Observation or hospital admission if symptoms or laboratory abnormalities unresolved.
        - Severe Toxicity:
            - Admission to an intensive care unit
            - Trend electrolytes and lactate frequently (Ex: every 2 hours or less)
            - Trend ABG/VBG
            - Consider hemodialysis