Approach to poisoned patients with high anion gap metabolic acidosis in the emergency department - a case series

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ABSTRACT

Toxicology cases are frequent presentations in the emergency department (ED) and often their presentation can vary from a straightforward manner to a complex manner. In this case series we will discuss three cases that presented to the ED with a known, suspected, and unknown toxicological substance ingestion with the common denominator being high anion gap metabolic acidosis (HAGMA). HAGMA is a subcategory of metabolic acidosis. Categorizing metabolic acidosis as a high anion gap aids in identifying the underlying disease process and subsequently initiating appropriate treatment. There have been many broadly inclusive mnemonics used to list the common causes of High anion gap acidosis such as CAT MUDPILES which correspond to Carbon monoxide, Cyanide, Congenital heart disease, Aminoglycosides, Theophylline, Toluene, Methanol, Uremia, Diabetic ketoacidosis, Alcoholic ketoacidosis, Starvation, Acetaminophen, Phenformin, Paraldehyde, Iron, Isoniazid, Inborn errors of metabolism, Lactic acidosis, Ethanol, Ethylene glycol, and Salicylates, respectively. It is not uncommon to be faced with patients with an unclear clinical picture and a lack of clear toxicological ingestion. In such circumstances, the presence of a high anion gap acidosis is an important clue that should prompt investigating for uncommon toxicological causes not listed in the forementioned mnemonics, such as metformin, beta blockers, and CCBs.

Keywords: Metformin, calcium channel blocker (CCB), methanol, high anion gap metabolic acidosis (HAGMA), toxicology, poisoning

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Background

High Anion Gap Metabolic acidosis (HAGMA) is a subcategory of metabolic acidosis. Categorizing metabolic acidosis as high anion gap aids in identifying the underlying disease process and subsequently initiating appropriate treatment. There have been many broadly inclusive mnemonics used to list the common causes of High anion gap acidosis such as CAT MUDPILES which correspond to Carbon monoxide, Cyanide, Congenital heart disease, Aminoglycosides, Theophylline, Toluene, Methanol, Uremia, Diabetic ketoacidosis, Alcoholic ketoacidosis, Starvation, Acetaminophen, Phenformin, Paraldehyde, Iron, Isoniazid, Inborn errors of metabolism, Lactic acidosis, Ethanol, Ethylene glycol, and Salicylates, respectively.

The causes and mnemonics that are commonly considered and discussed do not usually include toxicological causes. Toxicological clinical scenarios, more common than not, pose unique diagnostic and management challenges due to the varied presentation. These toxicology scenarios range from an overdose of a confirmed and known drug to an unconfirmed and unknown drug exposure.

It is not uncommon to be faced with patients with an unclear clinical picture and a lack of clear toxicological ingestion. In such circumstances, the presence of a high anion gap acidosis is an important clue that should prompt investigating for uncommon toxicological causes not listed in the forementioned mnemonics, such as metformin, beta blockers, and calcium channel blockers (CCBs).

This case series will discuss three different cases, emphasizing on the importance of a systematic approach and widening the differential diagnosis for patients with HAGMA to include the less common toxicological causes particularly when there is a discrepancy between the history and clinical picture.

Case 1

A 41-year-old female, known to have type 2 diabetes mellitus presented to the ED with a three-day history of vomiting and dizziness. The patient had been consuming 4 tablets of Metformin, 500 mg each, rather than her usual

dosage of 2 tablets. The patient denied co-ingestion of other drugs and suicidal intentions.

The patient was vitally stable, except for a slightly low blood pressure of 97/59 mmHg. Her primary survey was significant for a Glasgow coma scale (GCS) of 12/15 and was severely agitated. Her random blood glucose was 229 mg/dl and venous blood gas (VBG) showed a pH was 7.237 with an anion gap of 22, and a lactic acid of 11.6 mmol/l. Blood ketones were negative.

The patient was seen by the toxicology service and in view of the history and laboratory findings, she was diagnosed with metformin-induced lactic acidosis (MILA) and the patient underwent urgent continuous renal replacement therapy (CRRT).

During her hospital stay, the patient's condition deteriorated as she became bradycardic and suffered the first of many cardiac arrests. CRRT was discontinued and her arterial blood gas (ABG) revealed worsening acidosis. She received intravenous (IV) sodium bicarbonate 250 mEq in total, IV Norepinephrine, and IV Vasopressin 40 units. Unfortunately, the patient's condition continued to worsen, and she passed away on the second day of admission in the intensive care unit (ICU).

Case 2

A 47-year-old male who is known to be a chronic alcohol consumer was brought to the ED by emergency medical services (EMS), with complaints of vomiting, generalized body weakness, and visual loss. These complaints started 7 hours prior to ED presentation.

The patient was vitally unstable with a heart rate of 40 beats per minute, blood pressure of 80/20 mmHg, respiratory rate of 24 breaths per minute, and an oxygen saturation of 99% on room air. His primary survey was significant for tachypnea with bilateral crepitations on auscultation, warm extremities with faint peripheral pulses, and a fluctuating GCS of 13-14/15.

His Initial VBG showed a pH of <6.750 with an anion gap of 43, potassium of 6.7 mmol/l, and lactic acid of 24 mmol/l. His glucose level was 63 mg/dl for which he received oral glucose tablets and repeated serum glucose was 75 mg/dl. Laboratory findings are further detailed in Table 1.

The patient was intubated in the ED as clinical course deterioration was anticipated due to severe metabolic acidosis and received 1 l of IV Normal Saline. He then was started on IV Noradrenaline 0.5 mcg/kg/minute. A nasogastric tube was inserted and drained 200 ml of fresh blood followed by 300 ml of coffee ground fluid.

The patient was seen by the toxicology service and was started on CRRT. However, CRRT was discontinued as the patient continued to be persistently hypotensive in spite of optimal inotropic support and he was critically unstable to be shifted to a facility with extracorporeal membrane oxygenation capabilities. Unfortunately, the patient went into asystole on the same day in the ICU and was declared deceased.

Table 1. *Laboratory findings in patient 2.*

Blood osmolarity	337 mOsm/Kg
White blood cell (WBC)	19.3 × 10*3/ ul
Platelet count	123 × 10*3/ ul
Serum creatinine	1.7 mg/dl
Creatinine phosphokinase (CPK)	1989 U/l
Gamma glutamyl transferase (GGT)	425 U/l
Aspartate aminotransferase (AST)	119 U/l
Alkaline phosphatase (ALP)	89 U/l
Alanine transaminase (ALT)	68 U/l
Lipase	739 U/l
Fibrinogen	169 mg/dl
International normalized ratio (INR)	2.3

Case 3

A 54-year-old male, presented to the ED with the complaint of left sided, squeezing chest pain that was radiating to the left jaw and shortness of breath that began approximately 4 hours prior to his ED presentation.

In the ED, the patient had a blood pressure of 75/48 mmHg and a heart rate was 102 beats per minute. An electrocardiogram showed sinus tachycardia with no ST-T wave changes (Figure 1). Bedside echocardiogram revealed a left ventricular ejection fraction of approximately 40%, sclerotic aortic valve, mild mitral regurgitation, no pericardial effusion, mild hypokinesia in the apical region, and no evidence of aortic dissection.

The patient received 2 l of IV Normal Saline; however, his blood pressure did not improve. Norepinephrine infusion was started for him at 0.1 mcg/minute, which was then titrated up to 0.5 mcg/minute and his blood pressure slightly improved to 99/60 mmHg. Initial VBG showed a pH of 7.4, Bicarbonate of 22.8 mmol/l, anion gap of 15, lactic acid level of 2, and glucose level of 145 mg/dl.

He was admitted to the ICU with the diagnosis of non-ST elevation myocardial infarction in cardiogenic shock. Approximately 10 hours after admission, he developed persistent atrial fibrillation (Figure 2), not responding to treatment of amiodarone infusion 1 mg/minute. During this time, he had refused to undergo coronary angiography. An ABG after approximately 24 hours from ED presentation showed a pH of 7.28, with an anion gap of 23.

The patient's condition deteriorated as he developed an acute kidney injury where serum creatinine rose from 1.2 mg/dl to 4 mg/dl with low urine output and worsening of his metabolic acidosis with rising serum lactate levels reaching 8. During that time, as the clinical picture of the patient was not compatible with the history, he was queried again whether he took an overdose of any medication(s)

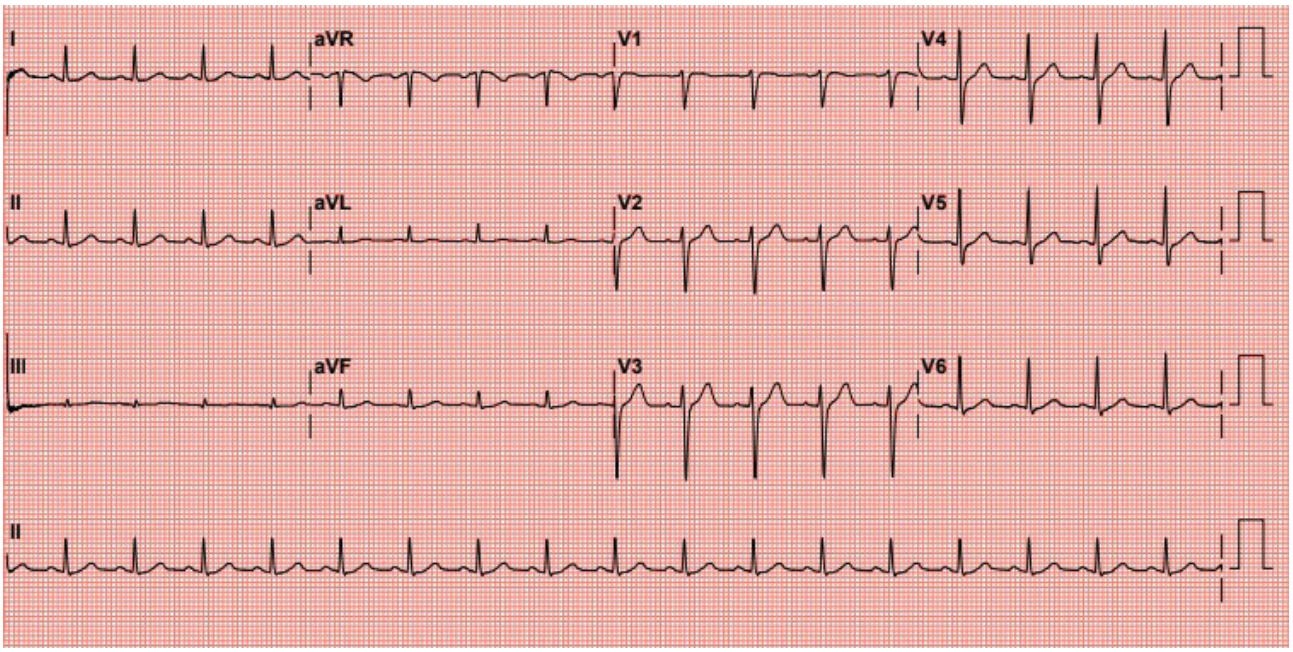

Figure 1. *ECG showing Sinus Tachycardia*

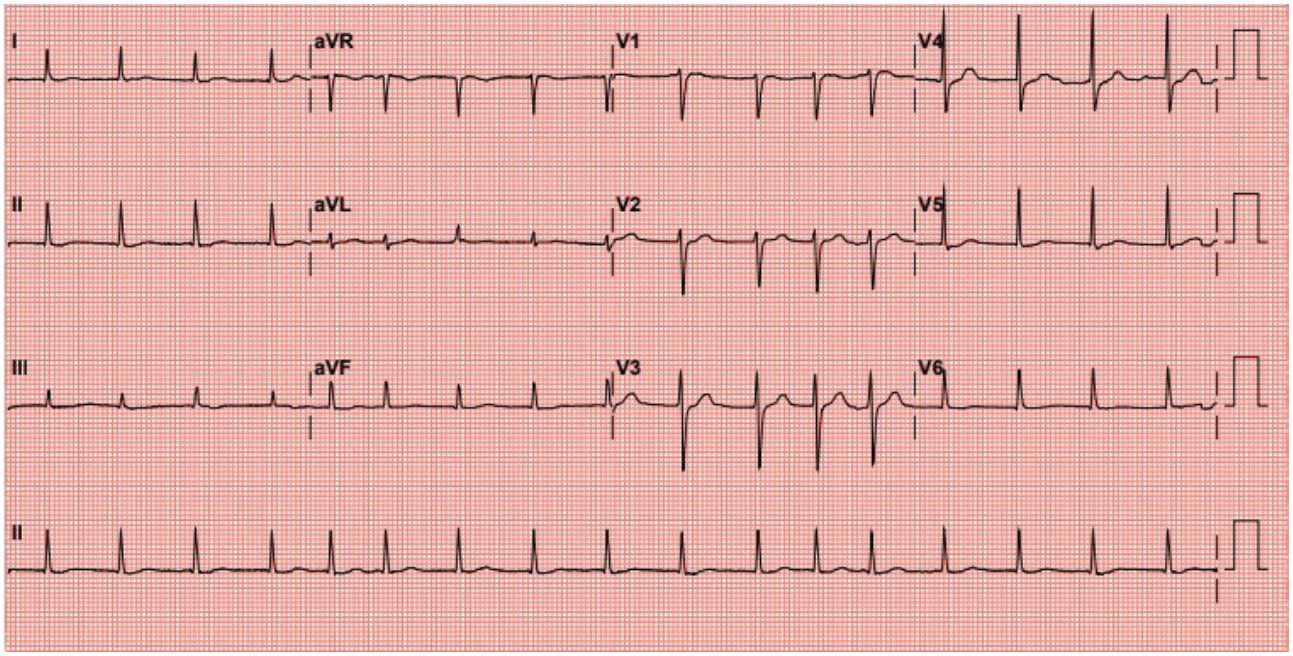

Figure 2. *ECG showing Atrial Fibrillation*

and he mentioned that he had taken 30 tablets of 10 mg per tablet Amlodipine on the evening that he had presented to the ED–A total of 300 mg of Amlodipine.

Toxicology services were consulted, and high dose insulin (HDI) therapy starting at 1 unit/Kg, titrating up to 10 units/Kg was started. The patient's clinical condition continued to deteriorate as he developed pulmonary oedema and was persistently hypotensive inspite of optimal inotropic support, thus he was orotracheally intubated and mechanically ventilated. Unfortunately, the patient went into pulseless electrical activity and was declared deceased.

Discussion

The cases mentioned in this case series can be classified into three categories: known ingestion, suspected ingestion, and unknown ingestion. As we will see further in the discussion, all three cases had different history and presentations, but the common denominator remained HAGMA (Figure 3).

The approach to such patients remains the same as to any patient in the ED with an ABCDE approach of Airway patency and maintainability, Breathing, Circulation, Disability, and Exposure. The addition to this approach would include the presence or absence of HAGMA; if it's

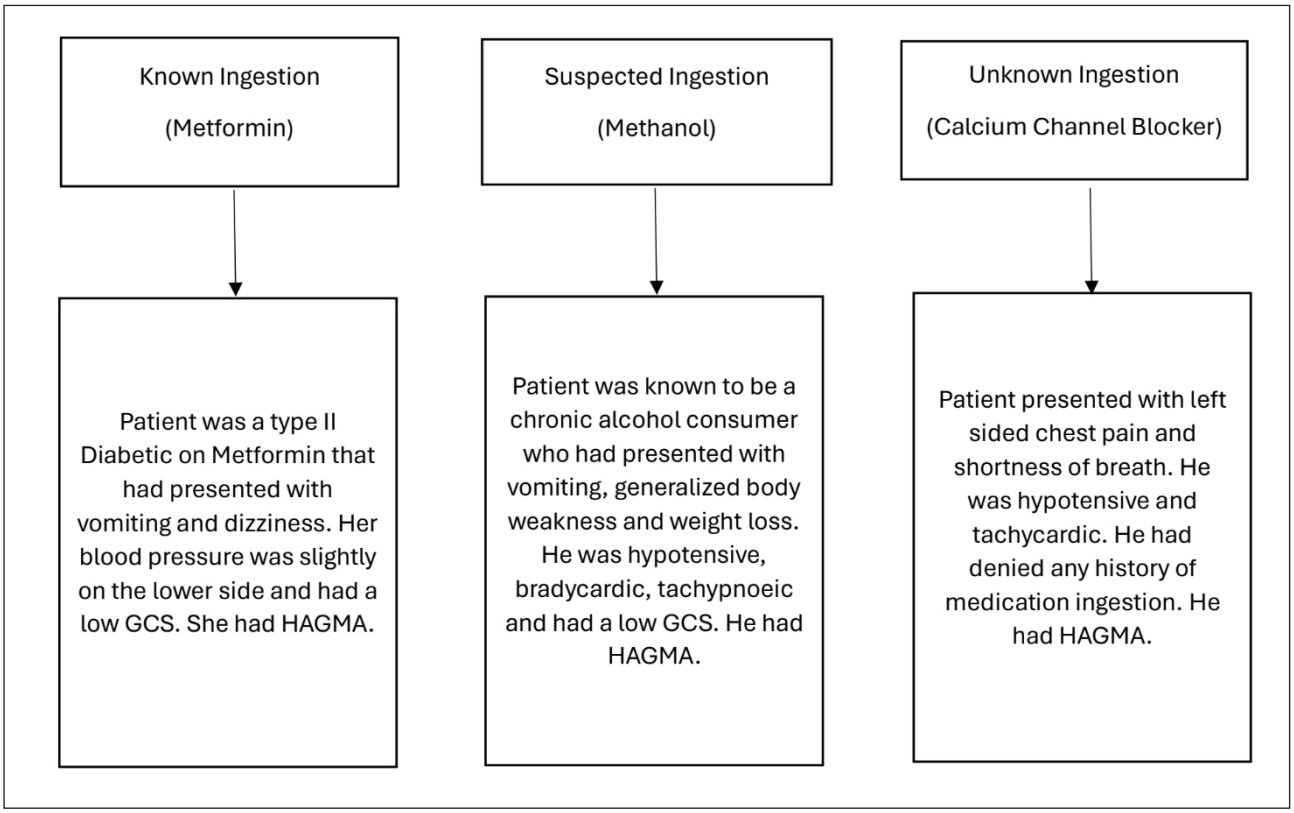

Figure 3. *Classification of the cases and brief history*

absent then to reassess the patient and if present to apply CAT MUDPILES/KLUTZ and treat the patient according to the known substance ingested. If there is HAGMA present but a discrepancy between the history or clinical findings of the patient, or suspicion of a toxicological substance being ingested then the patient is to be treated as a case of suspected or unknown toxic ingestion and managed accordingly. Figure 4, describes the suggested toxicological approach.

Metformin overdose induces both hyperlactemia as well as metabolic acidosis. Increased levels of metformin induces oxidative phosphorylation by inhibiting complex I in the mitochondrial respiratory chain. It also inhibits pyruvate carboxylase, which leads to increased lactate production and in turn reduced adenosine triphosphate (ATP). Similarly, AMP is increased which inhibits fructose-1-6-bisphophatase impairing gluconeogenesis. This leads to accumulation of lactate due to reduced hepatic clearance [1]. Two types of lactate isomers exist: D- lactate and L-lactate. D-lactate accumulates when there is impaired hepatic clearance, for example in liver disease, toxic alcohols as well as with medications such as paracetamol and metformin. L-lactate concentrates when there is insufficient tissue perfusion such as in sepsis. Moreover, due to the inhibition of complex I, the mitochondria loses its ability to recycle and buffer hydrogen ions. Eventually these accumulate causing metabolic acidosis which may lead to HAGMA and shock [2]. About 90% of metformin is renally cleared, hence in patients with chronic or newly diagnosed renal insufficiency, there is prolonged plasma elimination [2].

Patients with acute metformin toxicity is often present with vague symptoms such as gastrointestinal upset such as diarrhea and vomiting, however, in extreme cases may present with altered mental status or even coma [1]. Our patient complained of dizziness and vomiting for 3 days. Other nonspecific signs include tachypnea, tachycardia, and hypotension which our patient had.

It's essential to clinically differentiate between metformin associated lactic acidosis (MALA) wherein metformin levels are high due to a systemic disease, metformin unrelated lactic acidosis (MULA) where metformin levels are either normal or low, MILA which is solely caused by metformin, and lactic acidosis in metformin therapy (LAMT) which occurs in small amounts in metformin treated patients. In literature, these terms are interchangeably used and may often become confusing [3]. Our patient suffered from MILA, regardless of her diabetes status, as there was clear history provided of metformin overdose supported by the VBG which revealed lactic acidosis. Thus far, pH and lactate have not been proven to be of prognostic value in those with chronic metformin use [2]. Initially, our patient had a pH of 7.237 and lactate of 11.6 mmol/dl with minimal symptoms. Though, they may be useful in monitoring disease progression and treatment response.

The treatment for metformin is mainly supportive as there is no antidotal therapy. Nevertheless, metformin is a

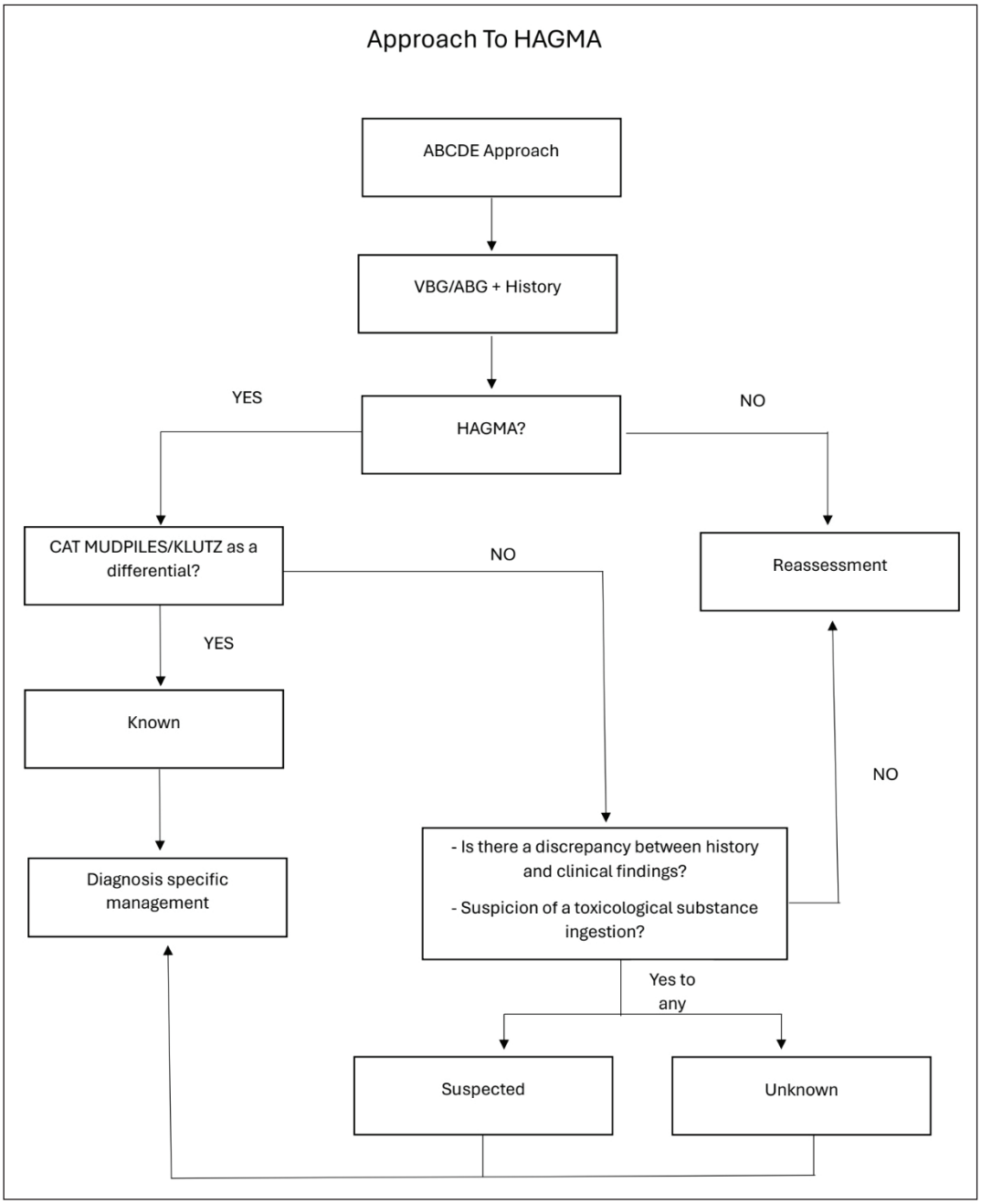

Figure 4. *Approach to HAGMA*

dialyzable drug. Evidence shows that prolonged intermittent hemodialysis (HD) is more efficient in clearing lactate and metformin compared to continuous therapy if they fit the criteria [4,5]. Many papers also recommend the use of bicarbonate infusion if the pH falls below 7.20, particularly if the patient is unstable. Large doses accompanied by dialysis have proven to significantly reduce mortality [2].

As with patient 2, Methanol (CH3OH) (also known as wood alcohol) is a toxic alcohol found in multiple households and industrial agents such as windshield washer fluid, gas line anti-freeze, perfumes, food warming fuels, and other types fuels. Exposure to methanol can be extremely dangerous, leading to high morbidity and mortality rates if left untreated.

Methanol is rapidly absorbed via the gastrointestinal tract. It gets absorbed directly into the total body water compartment as it does not bind to any protein. Serum concentrations peak immediately post-absorption and follow a zero-order elimination rate. It goes through hepatic metabolization in a two steps oxidation process by alcohol dehydrogenase and aldehyde dehydrogenase enzyme. Methanol gets converted into formaldehyde then into formic acid by the effect of aldehyde dehydrogenase enzyme. The oxidation process results in reduction of NAD to NADH. The end product of formic acid results in bodily accumulation as it doesn't get eliminated. The remaining unmetabolized methanol doesn't get sufficiently cleared through the kidneys or lungs, and it has an

effective half-life up to 30—85 hours. Methanol toxicity results in decrease in osmolar gap and increase in anion gap metabolic acidosis as formic acid is the primary toxic metabolite resulting in end-organ damage.

Methanol toxicity can be lethal with a minimum dose of 30 ml of 40% methanol. Permanent visual damage occurs with minimum ingestion of 10 ml of methanol resulting in optic nerve damage [6]. It is unclear for the putaminal neurons and optic discs to share the risk of being affected by methanol intoxication, but it is attributed to their relatively high metabolic rates [6].

The aforementioned presentation of the patient with methanol toxicity is one of the textbook-like clinical presentations, as he presented with Gastrointestinal symptoms, which were followed by alteration of mental status, drop in GCS, and hyperventilation as a result of the metabolic acidosis.

Moreover, the patient complained of sudden loss of vision, which is more evident due to bilateral optic nerve damage. On the other hand, symptoms caused by basal ganglia lesions may not be detected early during the illness course due to the drop in GCS.

The mainstay of management of methanol toxicity cases is supportive care. The use of fomepizole or ethanol as an anti-dote therapy depends on the availability of resources. Fomepizole acts as an anti-dote for toxic alcohol by inhibiting the effect of alcohol dehydrogenase enzyme. Theoretically, ethanol has a similar mechanism of action on alcohol dehydrogenase enzyme.

In cases of toxicity, it is advocated to consider HD, as methanol is dialyzable due to the lack of ability to bind proteins.

In cases of refractory hypotension, evidence has shown that methylene blue to be used as a vasopressor over the last decade, as it prevents smooth muscle relaxation by inhibiting the nitric oxide synthase. Nitric oxide is known to be an endothelial-derived smooth muscle relaxant, resulting in vasodilation, hence hypotension [7].

The use of methylene blue in this case was part of the supportive management as the patient was persistently hypotensive, which lead to stoppage of the CRRT, hence delaying the clearance of the toxic metabolites.

This leads us to the third patient; as CCBs are a commonly prescribed medication [8]. Three subclasses of CCBs have been described: Phenylalkylamines, Benzothiazepines, and Dihydropyridines [8]. Amlodipine is a long acting dihydropyridine [9].

The patient had presented with a history and symptoms suggestive of cardiac disease. He was diagnosed with NSTEMI and heart failure. There was no suspicion of drug overdose initially as the patient had denied taking any medications.

This patient's presentation is one of the most common presentations of cardiotoxins. In this case, it was a CCB that acts by blocking the L-type voltage gated calcium channels which are predominantly found in the Sino Atrial node and atrio ventricular (AV) node.

CCBs toxicity can vary in presentation from being asymptomatic to dizziness, fatigue, and lightheadedness, and in severe cases as altered mental status, coma, and fatal shock.

ECHO findings of adequate EF and refractory hypotension despite IV fluids and inotropes must raise the suspicion of a possible toxicological cause, as evident in our patient [8]. This was evident in our patient as he had hypotension not responding to IV fluids as well as vasopressors. In an overdose, amlodipine can cause profound vasodilation, hypotension, and vasopressor-resistant shock [9]. Profound bradycardia and hypotension that is refractory to standard medications used for circulatory support can be found in severely poisoned patients [10]. The state of shock can be attributed to myocardial depression and/or peripheral vasodilation [10,11].

CCBs and Beta blockers account for more than 65% of death from cardiovascular medications [9]. Although severe cardiovascular toxicity has been commonly related to the non-dihydropyridine class of CCBs, the dihydropyridine drugs such as Amlodipine, cause reflex tachycardia [11]. This phenomenon was seen in our patient as he had presented to the ED with the complaint of chest pain was in sinus tachycardia initially that later transitioned into Atrial fibrillation.

In a published report of a patient with an Amlodipine overdose, not only did the patient present with hypotension and sinus tachycardia but has also developed transient pulmonary oedema after a relatively low-volume fluid resuscitation [12]. Another published report described a patient going into pulmonary oedema because of iatrogenic congestion and amlodipine vasoplegia after receiving 2 L of IVF and increasing noradrenaline requirement [9]. Our patient also developed pulmonary oedema after receiving the same amount of IV fluids as above. This can be reasoned by these patients not being fluid depleted. These patients are usually euvolemic and therefore no excess of 1 – 2 l of intravenous fluids (IVF) administration should be given to treat the hypotension [11]. A question that arises is whether inferior vena cava (IVC) measurement can guide fluid resuscitation in such patients to prevent fluid overload and one published report mentions that in fact a dilated IVC of more than 2.1 cm with no variability in respiration is seen in patients with cardiogenic shock whereas an IVC of less than 2 cm with a collapsibility of more than 50% is seen in patients with hypovolemic shock [13].

This patient initially had a pH of 7.4, PCO2 35.3 mmHg, PO2 48.3 mmHg, Bicarbonate 22.8 mmol/l, anion gap of 15, and lactic acid level of 2. CCBs are believed to cause lactic acidosis by ATP hydrolysis and mitochondrial activity inhibition which all interferes with glucose metabolism.

Although gastrointestinal (GI) decontamination methods such as activated charcoal and Whole bowel irrigation, in immediate release (IR) and slow release substances, respectively, have a role in such a patient, with the latter being of no role once symptoms of toxicity ensue [11], they were not applied to our patient as he had only declared his Amlodipine overdose more than 24 hours after ingestion and had been symptomatic since his ED presentation. Urinary alkalinization and HD have no role in CCBs toxicity due to their lipophilic nature and large volume of distribution [7].

The cornerstone management of CCB toxicity is HDI therapy of IV bolus of 1.0 unit/kg followed by a 0.5–2.0 unit/kg/hour infusion, a hyperinsulinemic euglycemia (HIE) state. In a prospective observational study, 3 of the patients who had received HDI therapy showed an improvement in their hemodynamics, and systolic blood pressure to be more precise [14,15]. Calcium, which causes an influx through available L-type calcium channels by increasing the extracellular availability, is mentioned in one report as an effective agent in reversing myocardial conduction depression and elevating the blood pressure if used in conjunction with other inotropic agents whereas another report mentions it to be deficient in severe toxicity [8,11]. These regimens were started in our patient; however, they were of no benefit as evidenced by the outcome of this patient.

Conclusion

Causes of HAGMA have been summarized into many mnemonics for ease of remembrance such as GOLDMARK and CAT MUDPILES. In addition to keeping a wide list of differential diagnoses, it is critical to have a systematic approach whereas primary survey is applied to all the patients as well as a toxicological approach. It is also crucial to consider the limitations in such cases in terms of limited clinical history. Consequently, a clinician must always have the suspicion of toxicological etiologies when the clinical presentation does not match a specific pathology, and aim for ideal resuscitation and inclusive supportive management, as early intervention helps in drastically reducing morbidity and mortality. Finally, approaching patients in a systematic and comprehensive manner by using local protocols or available evidence-based algorithms would aid in reducing the rate of missed unusual presentations or cases of unknown ingestion.

What is new?

Toxicology cases more than often are challenging. Therefore, the authors have formulated an algorithm to aid Emergency Physicians with their approach to patients presenting with HAGMA to help minimize the number of missed cases, particularly the inconspicuous presentations.

List of Abbreviations

ATP	Adenosine Triphosphate
ABG	Arterial Blood Gas
CCB	Calcium Channel Blocker
CRRT	Continuous Renal Replacement Therapy
ED	Emergency Department
GCS	Glasgow Coma Scale
HD	Hemodialysis
HAGMA	High Anion Gap Metabolic Acidosis
HDI	High Dose Insulin
IVCInferior Vena Cava	
ICU	Intensive Care Unit
IV	Intravenous ()
MILA	Metformin Induced Lactic Acidosis ()
PEA	Pulseless Electrical Activity
VBG	Venous Blood Gas

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this case series.

Funding

None.

Consent for publication

A waiver of consent was obtained due to the patient's demise and inability to locate and contact next of kin.

Ethical approval

Ethical approval was granted by the Hospital Institutional Review Board via reference number: MBRU IRB-2024-275, dated 26/08/2024 as "Exempt".

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Summary of the case

1	Patient (gender, age)	Male, 54 Male, 47 Female, 41
2	Final diagnosis	Metformin toxicity, calcium channel blocker toxicity, Methanol toxicity
3	Symptoms	HAGMA
4	Medications	Antidotes/supportive therapy
5	Clinical procedure	Antidotes/supportive therapy
6	Specialty	Toxicology/Emergency medicine