CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will apply a systematic approach to diagnosing acid-base disturbances

SHYLAJA MANI, MD
Department of Internal Medicine, Cleveland Clinic

GREGORY W. RUTECKI, MD
Department of Internal Medicine, Cleveland Clinic

A patient with altered mental status and an acid-base disturbance

A 78-year-old black woman with a history of osteoarthrosis and chronic diffuse joint pain presents with altered mental status and tachypnea, which began 3 hours earlier. She lives alone, and her family suspects she abuses both alcohol and her pain medications. She has not been eating well and has lost approximately 10 pounds over the past 3 months. Her analgesic regimen includes acetaminophen and acetaminophen-oxycodone.

In the emergency department her temperature is 98.6°F (37.0°C), pulse 100 beats per minute and regular, respiratory rate 22 per minute, and blood pressure 136/98 mm Hg. She is obtunded but has no focal neurologic defects or meningismus. She has no signs of heart failure (jugular venous distention, cardiomegaly, or gallops), and examination of the lungs and abdomen is unremarkable.

Suspecting that the patient may have taken too much oxycodone, the physician gives her naloxone, but her mental status does not improve. Results of chest radiography and cranial computed tomography are unremarkable. The physician's initial impression is that the patient has "metabolic encephalopathy of unknown etiology."

The patient's laboratory values are shown in **Table 1**.

TABLE 1
The patient's laboratory values

Substance	Value	Reference range
Blood chemistry		
Sodium	132 mmol/L	136–144
Potassium	4.8 mmol/L	3.7–5.1
Bicarbonate	16.0 mmol/L	22–30[a]
Chloride	95 mmol/L	97–105
Blood urea nitrogen	23 mg/dL	7–21
Creatinine	1.3 mg/dL	0.58–0.96
Glucose	97 mg/dL	74–99
Lactate	1.1 mmol/L	0.5–2.2
Albumin	4.5 g/dL	3.9–4.9
Serum osmolality	318 mOsm/kg	275–295
Arterial blood gases		
pH	7.25	7.35–7.45
Pco_2	28 mm Hg	34–46[b]
Bicarbonate	16 mmol/L	22–26

[a]For acid-base problem-solving, a value of 25 mmol/L is considered normal.
[b]Healthier patients with better pulmonary function may attain lower Pco_2 values; for clinical problem-solving, a value of 40 mm Hg is considered normal.
Pco_2 = partial pressure of carbon dioxide

WHICH ACID-BASE DISORDER DOES SHE HAVE?

1 Which acid-base disorder does this patient have?

- ☐ Metabolic acidosis and respiratory alkalosis
- ☐ Metabolic acidosis and respiratory acidosis
- ☐ Metabolic acidosis with an elevated anion gap
- ☐ A triple disturbance: metabolic acidosis, respiratory acidosis, and metabolic alkalosis

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TABLE 2

'Rules of 5' for acid-base problem-solving

1 Determine the arterial pH status

pH < 7.40 is acidemic, pH > 7.44 is alkalemic
But a normal pH does not rule out an acid-base disorder

2 If the arterial pH is abnormal, determine whether the primary process is respiratory, metabolic, or both

	pH	Pco_2	Bicarbonate
Respiratory acidosis	Low	High	—
Metabolic acidosis	Low	—	Low
Mixed respiratory and metabolic acidosis	Low	High	Low
Respiratory alkalosis	High	Low	—
Metabolic alkalosis	High	—	High
Mixed respiratory and metabolic alkalosis	High	Low	High

3 Calculate the anion gap

Anion gap = sodium – (chloride + bicarbonate)

If serum albumin is low, add 2.5 mmol/L to the anion gap for every 1 g the serum albumin is below normal

An anion gap > 10 mmol/L is elevated

4 Check the degree of compensation (respiratory or metabolic)

Pco_2 and bicarbonate should move in the same direction

Nominal normal levels: bicarbonate 25 mmol/L and Pco_2 40 mm Hg

In respiratory acidosis, for every 10-mm Hg increase in Pco_2, bicarbonate should increase by 1 mmol/L in the first 48 hours and 4 mmol/L afterward

In metabolic acidosis, for every 1-mmol/L decrease in bicarbonate, Pco_2 should decrease by 1.3 mm Hg

In respiratory alkalosis, for every 10-mm Hg decrease in Pco_2, bicarbonate should decrease by 2 mmol/L in the first 48 hours and 5 mmol/L afterward

In metabolic alkalosis, for every 1-mmol/L increase in bicarbonate, Pco_2 may increase by 0.6 mm Hg

5 If the patient has metabolic acidosis with an elevated anion gap, check whether the bicarbonate level has decreased as much as the anion gap has increased

In metabolic acidosis, the anion gap should increase by the same amount that bicarbonate decreases; a difference in these two changes is called a delta gap

Pco_2 = partial pressure of carbon dioxide

Based on information in reference 1

A 5-step approach

Acid-base disorders can be diagnosed and characterized using a systematic approach known as the "Rules of 5" (**Table 2**)[1]:

1. Determine the arterial pH status.
2. Determine whether the primary process is respiratory, metabolic, or both.
3. Calculate the anion gap.
4. Check the degree of compensation (respiratory or metabolic).
5. If the patient has metabolic acidosis with an elevated anion gap, check whether the bicarbonate level has decreased as much as the anion gap has increased (ie, whether there is a delta gap).

Let us apply this approach to the patient described above.

1. What is her pH status?

An arterial pH less than 7.40 is acidemic, whereas a pH higher than 7.44 is alkalemic. (*Acidemia* and *alkalemia* refer to the abnormal laboratory value, while *acidosis* and *alkalosis* refer to the process causing the abnormal value—a subtle distinction, but worth keeping in mind.)

Caveat. A patient may have a significant acid-base disorder even if the pH is normal. Therefore, even if the pH is normal, one should verify that the partial pressure of carbon dioxide (Pco_2), bicarbonate level, and anion gap are normal. If they are not, the patient may have a mixed acid-base disorder such as respiratory acidosis superimposed on metabolic alkalosis.

Our patient's pH is 7.25, which is in the acidemic range.

2. Is her acidosis respiratory, metabolic, or both?

Respiratory acidosis and alkalosis affect the Pco_2. The Pco_2 is high in respiratory acidosis (due to failure to get rid of excess carbon dioxide), whereas it is low in respiratory alkalosis (due to loss of too much carbon dioxide through hyperventilation).

Metabolic acidosis and alkalosis, on the other hand, affect the serum bicarbonate level. In metabolic acidosis the bicarbonate level is low, whereas in metabolic alkalosis the bicarbonate level is high.

Moreover, in mixed respiratory and metabolic acidosis, the bicarbonate level can be

low *and* the Pco_2 can be high. In mixed metabolic and respiratory alkalosis, the bicarbonate level can be high *and* the Pco_2 can be low (**Table 2**).

Our patient's serum bicarbonate level is low at 16.0 mmol/L, indicating that the process is metabolic. Her Pco_2 is also low (28 mm Hg), which reflects an appropriate response to compensate for the acidosis.

3. What is her anion gap?

Always calculate the anion gap, ie, the serum sodium concentration minus the serum chloride and serum bicarbonate concentrations. If the patient's serum albumin level is low, for every 1 gram it is below normal, an additional 2.5 mmol/L should be added to the calculated anion gap. We consider an anion gap of 10 mmol/L or less as normal.

Caveats. The blood sample used to calculate the anion gap should be drawn close in time to the arterial blood gas sample.

Although the anion gap is an effective tool in assessing acid-base disorders, further investigation is warranted if clinical judgment suggests that an anion gap calculation is inconsistent with the patient's circumstances.[2]

Our patient's anion gap is elevated (21 mmol/L). Her serum albumin level is in the normal range, so her anion gap does not need to be adjusted.

4. Is the degree of compensation appropriate for the primary acid-base disturbance?

The kidneys compensate for the lungs, and vice versa. That is, in respiratory acidosis or alkalosis, the kidneys adjust the bicarbonate levels, and in metabolic acidosis, the lungs adjust the Pco_2 (although in metabolic alkalosis, it is hard for patients to breathe less, especially if they are already hypoxic).

In metabolic acidosis, people compensate by breathing harder to get rid of more carbon dioxide. For every 1-mmol/L decrease in the bicarbonate level, the Pco_2 should decrease by 1.3 mm Hg.

Compensation does not return pH to normal; rather, it mitigates the impact of an acid or alkali excess or deficit. If the pH is normalized with an underlying acid-base disturbance, there may be mixed acid-base processes rather than compensation.

Our patient's bicarbonate level is 16 mmol/L, which is 9 mmol/L lower than normal (for acid-base calculations, we use 25 mmol/L as the nominal normal level). If she is compensating appropriately, her Pco_2 should decline from 40 mm Hg (the nominal normal level) by about 11.7 mm Hg (9×1.3), to approximately 28.3 mm Hg. Her Pco_2 is, indeed, 28 mm Hg, indicating that she is compensating adequately for her metabolic acidosis.

If we use Winter's formula instead (Pco_2 = [1.5 × the bicarbonate level] + 8 ± 2),[3] the lowest calculated Pco_2 would be 30 mm Hg, which is within 2 mm Hg of the Rules of 5 calculation. Other formulas for calculating compensation are available.[3]

This information rules out the first two answers to question 1, ie, metabolic acidosis with respiratory alkalosis or acidosis.

5. Is there a delta gap?

Although we know the patient has metabolic acidosis with an elevated anion gap, we have not ruled out the possibility that she may have a triple disturbance. For this reason we need to check her delta gap.

In metabolic acidosis with an elevated anion gap, as the bicarbonate level decreases, the anion gap should increase by the same amount. If the bicarbonate level decreases more than the anion gap increases, the additional decline is the result of a second process—an additional normal-anion-gap acidosis. If the bicarbonate level does not decrease as much as the anion gap increases, there is an additional metabolic alkalosis.

Our patient's bicarbonate level decreased 9 mmol/L (from the nominal normal level of 25 to 16), and therefore her anion gap should have increased approximately the same amount—and it did. (A normal anion gap for problem-solving is 10, and this patient's anion gap has increased to 21. A difference of ± 2 is insignificant.) This conclusion verifies that a triple acid-base disturbance is not present, so the last answer is incorrect.

So, the correct answer to the question posed above is metabolic acidosis with an elevated anion gap (that is, metabolic acidosis with appropriate respiratory compensation).

The patient lives alone, and her family suspects she abuses alcohol and pain medications

TABLE 3

'MUD PILES' then and now: Metabolic acidosis with elevated anion gap

Then	Now
Methanol	**M**ethanol
Uremia	**U**remia
Diabetic ketoacidosis[a]	**D**iabetic ketoacidosis
Paraldehyde	**P**yroglutamate and **p**ropylene glycol[c]
Isoniazid	**I**soniazid and **i**ngestions
Lactic acidemia (L and D)[b]	**L**actic acidemia[d]
Ethylene glycol	(di)**E**thylene glycol
Salicylates	**S**alicylates

[a]Ketoacidosis can be a complication of alcoholism (betahydroxybutyric acid).
[b]D-Lactate is a consequence of short-bowel syndrome. If more common causes of metabolic acidosis are not present and the patient has a history suggesting short-bowel syndrome, D-lactate can be considered.
[c]If the patient is older, female, and has a history of acetaminophen ingestion—and if more common causes of metabolic acidosis are not present—consider pyroglutamic acid metabolic acidosis as an etiology.
[d]D-Lactate can also be a consequence of propylene glycol metabolic acidosis.

A patient may have a significant acid-base disorder even if the pH is normal

'MUD PILES': FINDING THE CAUSE OF ANION GAP METABOLIC ACIDOSIS

The possible causes of metabolic acidosis with an elevated anion gap (as in our patient) can be summarized in the mnemonic MUD PILES (**m**ethanol, **u**remia, **d**iabetes, **p**araldehyde, **i**soniazid, **l**actate, **e**thylene glycol, and **s**alicylates), which has been used for many years. Parts of it are no longer useful, but rather than discard it, we propose to update it (**Table 3**).

Methanol and ethylene glycol

We will address toxic ingestion of methanol and ethylene glycol (the "M" and "E" of MUD PILES) at the same time.

In cases of suspected ingestion of toxic substances such as these, it is useful to examine the osmol gap, ie, the difference between the calculated and the measured serum osmolality. Serum osmolality (in mOsm/kg) is calculated as the sodium concentration in mmol/L times 2, plus the glucose concentration in mg/dL divided by 18, plus the blood urea nitrogen concentration in mg/dL divided by 2.8 (**Table 4**). If the measured osmolality is higher than this calculated value, the difference may be due to solutes in the blood that should not be there such as ethylene glycol, diethylene glycol, methanol, and their many metabolic products.

In our patient, ingestion of both methanol and ethylene glycol should be considered, since she lives alone and has been suspected of alcohol and opioid abuse. Her calculated osmol gap is 278 mOsm/kg. Her measured osmolality is 318 mOsm/kg (**Table 1**). The osmol gap is 40 mOsm/kg (normal is ≤ 10).[4,5] Therefore, her osmol gap is elevated.

Identifying the specific substance the patient ingested that caused metabolic acidosis with anion gap may be difficult. Poisonings with these agents do not always increase the osmol gap.[6] A high index of suspicion is essential. It is helpful to have the family search for any sources of ethylene glycol and methanol at home and initiate treatment early if an ingestion is suspected, using fomepizole (an alcohol dehydrogenase inhibitor) or parenteral ethanol and hemodialysis.[7] Liquid chromatography identifies these two toxins, but results are not available emergently.

Diethylene glycol ingestion should also be considered.[8] Since it is diagnosed and treated like ethylene glycol intoxication, it can be placed with the "E" of (di)ethylene glycol in the mnemonic.

Uremia

Renal failure can lead to metabolic acidosis.[9] Our patient has no history of kidney disease, but her blood urea nitrogen and creatinine concentrations are above normal, and her estimated glomerular filtration rate by the Modification of Diet in Renal Disease formula is 48 mL/min/1.73 m^2—low, but not uremic.

Rhabdomyolysis (suspected by elevated creatine kinase values) should be considered in any patient with mental status changes, suspected toxic ingestion, and metabolic acidosis (see the "I" in MUD PILES below). Compartment syndromes with muscle necrosis may present in a subtle fashion. Therefore, renal failure from rhabdomyolysis may complicate this patient's course later, and should be kept in mind.

Diabetes

The patient has no history of diabetes and has a normal blood glucose level. Blood testing did not reveal ketones. She is not taking metformin (alleged to cause lactic acidosis) or a sodium-glucose cotransporter 2 inhibitor (which

have been associated with ketoacidosis).[10]

There is another, less common cause of ketoacidosis: alcohol.[11] Although alcoholism is common, alcoholic ketoacidosis is uncommon, even in heavy drinkers. Ethyl alcohol causing metabolic acidosis is similar to metabolic acidosis with (di)ethylene glycol and methanol, and if suspected it should be treated empirically (first with thiamine, then dextrose and saline, and correcting other electrolyte disturbances such as hypokalemia and hypomagnesemia) before specific identification is made. Ketones (predominantly beta-hydroxybutyrate) may persist up to 2 weeks after alcohol ingestion has stopped.[11] Ketosis in the setting of alcoholic ketoacidosis is frequently accompanied by other markers of alcohol target organ injury: elevated bilirubin, aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transferase levels. The term "ketohepatitis" has been suggested as an alternative to alcoholic ketosis.[11]

This patient did not have an elevated blood ethanol level, and her liver markers were otherwise normal.

THE NEW MUD PILES

2 Which of the following is (are) true? Regarding the remaining letters of the MUD PILES mnemonic:

- ☐ The "P" (paraldehyde) has been replaced by pyroglutamic acid (5-oxoproline) and propylene glycol.
- ☐ There are two isomers of lactate (dextro and levo), and consequently two clinical varieties of lactic acidosis.
- ☐ Isoniazid is no longer associated with metabolic acidosis with elevated anion gap.
- ☐ Salicylates can paradoxically be associated both with elevated and low anion gaps.

Isoniazid is still associated with metabolic acidosis with elevated anion gap, and so the third answer choice is false; the rest are true.

Paraldehyde, isoniazid, lactate

The "P," "I," and "L" (D-lactate) of the revamped MUD PILES acronym are less common than the others. They should be considered when the more typical causes of metabolic acidosis are not present, as in this patient.

TABLE 4

Increasing diagnostic utility of the osmol gap

The osmol gap is the difference between the calculated serum osmolality and measured osmolality

Calculated serum osmolality =
(Sodium x 2) + (Glucose/18) + (Blood urea nitrogen/2.8)

An elevated osmol gap indicates osmotically active solutes in plasma that are not typically present under normal conditions, such as ethylene glycol, diethylene glycol, methanol, and their many metabolic products

UPDATING THE 'P' IN MUD PILES

Paraldehyde is rarely prescribed anymore. A PubMed search on December 21, 2015 applying the terms paraldehyde and metabolic acidosis yielded 17 results. Those specific to anion gap metabolic acidosis were from 1957 to 1986 (n = 9).[12–20]

Therefore, we can eliminate paraldehyde from the MUD PILES mnemonic and replace it with pyroglutamic acid and propylene glycol.

5-Oxoproline or pyroglutamic acid, a metabolite of acetaminophen

Anion gap: sodium minus chloride minus bicarbonate (normal ≤ 10)

Acetaminophen depletes glutathione stores in acute overdoses, in patients with inborn errors of metabolism, and after chronic ingestion of excessive, frequent doses. Depletion of glutathione increases metabolic products, including pyroglutamic acid, which dissociates into hydrogen ions (leading to metabolic acidosis and an anion gap), and 5-oxoproline, (which can be detected in the urine).[21,22]

Risk factors for metabolic acidosis with acetaminophen ingestion include malnutrition, chronic alcoholism, liver disease, and female sex. In fact, most cases have been reported in females, and altered mental status has been common.

Metabolic acidosis with pyroglutamic acid can occur without elevated acetaminophen levels. Serum and urine levels of pyroglutamic acid may assist with diagnosis. Since identification of urine pyroglutamic acid usually requires outside laboratory assistance, a clinical diagnosis is often made initially and corroborated later by laboratory results. When the anion gap metabolic acidosis is multifactorial, as it was suspected to be in a case reported by

Tan et al,[23] the osmol gap may be elevated as a consequence of additional toxic ingestions, as it was in the reported patient.

No controlled studies of treatment have been done. N-Acetylcysteine may be of benefit. Occasional patients have been dialyzed for removal of excess pyroglutamic acid.

Propylene glycol, a component of parenteral lorazepam

Lorazepam is a hydrophobic drug, so when it is given parenterally, it must be mixed with a suitable solvent. A typical formulation adds propylene glycol. In patients receiving high doses of lorazepam as relaxation therapy for acute respiratory distress syndrome in the intensive care unit, or as treatment of alcohol withdrawal, the propylene glycol component can precipitate anion gap metabolic acidosis.[24,25]

Although nearly one-half of the administered propylene glycol is excreted by the kidneys, the remaining substrate is metabolized by alcohol dehydrogenase into D,L-lactaldehyde, then converted into D- or L-lactate. L-Lactate can be metabolized, but D-lactate cannot and leads to anion gap metabolic acidosis. This is another toxic metabolic acidosis associated with an elevated osmol gap. An increasing osmol gap in the intensive care unit can serve as a surrogate marker of excessive propylene glycol administration.[23]

An elevated osmol gap may be due to solutes in the blood that should not be there

Isoniazid

Although it is uncommon, there are reports of isoniazid-induced anion gap metabolic acidosis,[26] either due to overdoses, or less commonly, with normal dosing. Isoniazid should therefore remain in the mnemonic MUD PILES and may be suspected when metabolic acidosis is accompanied by seizures unresponsive to usual therapy. The seizures respond to pyridoxine.

The "I" should also be augmented by newer causes of metabolic acidosis associated with "ingestions." Ecstasy, or 3,4-methylenedioxymethamphetamine, can cause metabolic acidosis and seizures. Ecstasy has been associated with rhabdomyolysis and uremia, also leading to anion gap metabolic acidosis.[27] A newer class of abused substances, synthetic cathinones ("bath salts"), are associated with metabolic acidosis, compartment syndrome, and renal failure.[28]

Lactic acidosis

Lactic acidosis and metabolic acidosis can result from hypoperfusion (type A) or other causes (type B). Not all lactic acidosis is contingent on L-lactate, which humans can metabolize. Metabolic acidosis may be a consequence of D-lactate (mammals have no D-lactate dehydrogenase). D-Lactic acidosis as a result of short bowel syndrome has been known for more than a generation.[29] However, D-lactic acidosis occurs in another new setting. The new "P" in MUD PILES, propylene glycol, can generate substantial amounts of D-lactate.[29]

D-lactic metabolic acidosis is always accompanied by neurologic manifestations (slurred speech, confusion, somnolence, ataxia, abusive behavior, and others).[30] With short bowel syndrome, the neurologic manifestations occur after eating and clear later.[30]

Although our patient's anion gap is more than 20 mmol/L, her blood level of lactate is not elevated, and she had no history to suggest short-bowel syndrome.

Salicylates

Salicylate overdose can cause a mixed acid-base disorder: metabolic acidosis with elevated anion gap and respiratory alkalosis.

Although our patient does not have respiratory alkalosis, an aspirin overdose must be considered. A salicylate level was ordered; it was negative.

Despite the typical association of salicylates with an elevated anion gap, they may also cause a negative anion gap.[31] Chloride-sensing ion-specific electrodes contain a membrane permeable to chloride. Salicylates can increase the chloride permeability of these membranes, generating pseudohyperchloremia, and consequently, a negative anion gap.

WHAT ELSE MUST BE CONSIDERED?

3 In view of her anion gap metabolic acidosis, elevated osmol gap, and absence of diabetes, renal failure, or lactate excess, what are the remaining diagnoses to consider in this patient? (Choose all that are potential sources of metabolic acidosis and an increased anion gap.)

☐ Methanol, ethylene, or diethylene glycol
☐ Excessive, chronic acetaminophen ingestion
☐ Salicylate toxicity
☐ Alcoholic ketoacidosis

All of the above can potentially contribute to metabolic acidosis.

A search of the patient's home did not reveal a source of methanol or either ethylene or diethylene glycol. Similarly, no aspirin was found, and the patient's salicylate levels were not elevated. The patient's laboratory work did not reveal increased ketones.

Since none of the common causes of metabolic acidosis were discovered, and since the patient had been taking acetaminophen, the diagnosis of excessive chronic acetaminophen ingestion was suspected pending laboratory verification. Identification of 5-oxoproline in the urine may take a week or more since the sample is usually sent to special laboratories. Acetaminophen levels in this patient were significantly elevated, as were urinary oxyproline levels, which returned later.

The patient was diagnosed with pyroglutamic acid metabolic acidosis. She was treated supportively and with N-acetylcysteine intravenously, although there have been no controlled studies of the efficacy of this drug. Seventy-two hours after admission, she had improved. Her acid-base status returned to normal.

GOLD MARK: ANOTHER WAY TO REMEMBER

Another mnemonic device for remembering the causes of metabolic acidosis with elevated anion gap is "GOLD MARK": **g**lycols (ethylene and propylene), **o**xoproline (instead of pyroglutamic acid from acetaminophen), L-lactate, D-lactate, **m**ethanol, **a**spirin, **r**enal failure, and **k**etoacidosis).[32]

ACID-BASE DISORDERS IN DIFFERENT DISEASES

Diverse diseases cause distinctive acid-base abnormalities. Matching the appropriate acid-base abnormality with its associated disease may lead to more timely diagnosis and treatment:

Type 2 diabetes mellitus, for example, can lead to lactic acidosis, ketoacidosis, or type 4 renal tubular acidosis.[33]

Heart failure, although not typically framed in the context of acid-base physiology, can lead to elevated lactate, which is associated with a worse prognosis.[34]

Acquired immunodeficiency syndrome. Abacavir can cause normal anion gap metabolic acidosis.[35,36]

Cancer[37,38] can be associated with proximal tubular renal tubular acidosis and lactic acidosis.

An expanding array of toxic ingestions

Metabolic acidosis may be the most prominent and potentially lethal clinical acid-base disturbance. When metabolic acidosis occurs in certain disease states—lactic acidosis with hypoperfusion or methanol ingestion with metabolic acidosis, for example—there is increased morbidity and mortality.

As reflected in the revisions to MUD PILES and in the newer GOLD MARK acronym, the osmol gap has become more valuable in differential diagnosis of metabolic acidosis with an elevated anion gap consequent to an expanding array of toxic ingestions (methanol, propylene glycol, pyroglutamic acid-oxoproline, ethylene glycol, and diethylene glycol), which may accompany pyroglutamic acid-oxoproline.

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***ADDRESS**: Gregory W. Rutecki, MD, Department of Internal Medicine, G10, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; ruteckg@ccf.org*