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**Treating anemia:
It's not just the erythropoietin**

**Oral hyperpigmentation, weakness,
and salt-craving**

**The devil is in the details:
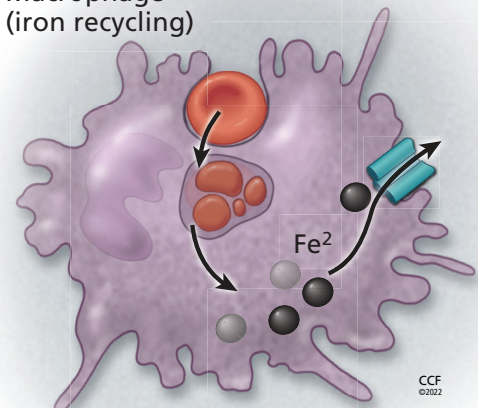Approach to refractory hypokalemia**

**Glycemic targets in the ICU:
A look back, and ahead**

**Glycemic control in the critically ill:
Less is more**

**Capsule endoscopy in
gastrointestinal disease:
Evaluation, diagnosis,
and treatment**

**Anemia of chronic kidney disease:
Will new agents deliver
on their promise?**

Macrophage
(iron recycling)

Fe^2

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Treating anemia:
It's not just the EPO

We are aerobic organisms. The ultimate component in our complex physiologic oxygen delivery system is the metabolically active, membrane-bound hemoglobin valet, the erythrocyte. So it is natural that we focus clinically on the readily measured hemoglobin and laboratory test derivatives of the red blood cell (RBC) count. A "normal" red cell count and hemoglobin are sufficient to support adequate physiologic function under even greater than routine demands, and there are multiple homeostatic controls that fine-tune the efficiency of oxygen delivery. The redundancy of these controls directed at RBC mass and hemoglobin concentration and function indicate that these values matter, and pharmacologic manipulation should have significant clinical effect.

In patients without advanced kidney disease, erythropoietin (EPO) levels begin to rise proportionately to restore the RBC mass as the hemoglobin falls below 12 to 13 g/dL. Erythrocyte 2,3-diphosphoglycerate levels rise with hypoxia or anemia, enabling more efficient release of oxygen from hemoglobin to peripheral tissue. Persistent exposure to a decreased external partial pressure of oxygen at elevated altitudes, or even intermittent exposure to relative hypoxia, as in patients with untreated sleep apnea, elicits an increased EPO with resultant elevated hemoglobin and hematocrit.

With all of these controls (and more) in place to maintain a normal capacity for oxygen delivery, it would seem clinically advantageous to therapeutically assist critically acute and chronically ill patients in maintaining close-to-normal RBC mass when their intrinsic controls are overwhelmed. And yet multiple studies, done in various settings, have demonstrated limited outcome benefits in utilizing a liberal RBC transfusion policy to reverse anemia and maintain a close-to-normal hemoglobin and hematocrit.

With knowledge of the transfusion experience, recognizing that the transfusion studies relate more to acute scenarios, perhaps it should not be a major surprise that pharmacologic efforts to normalize the anemia in patients with chronic inflammatory diseases, heart failure, and chronic kidney disease directly with EPO (or its derivatives) have had only modest outcome benefits. And these pharmacologic interventions are indirect and physiologically more complex than simple transfusion. As noted by Souaid et al[1] in this issue in their discussion of anemia of chronic kidney disease, normalizing the hemoglobin with EPO in clinical trials of patients with chronic kidney disease and heart failure has yielded only modest outcome benefits and has been fraught with complications including an increase in cardiovascular events.

Yet we have all had patients who have been extremely dependent on the maintenance of a higher hemoglobin and hematocrit in order to maintain their energy and a reasonable quality of life. So efforts to normalize anemia, as with most aspects of managing patients with chronic disease, must be individualized in the clinic.

Taking a step back and reviewing the biology and pathophysiology of the control of erythropoiesis and iron utilization, as Souaid et al do so clearly, I am struck by the interplay between inflammation, iron metabolism, and the renal production and bioefficacy of EPO. At the core of this complex molecular dance is the liver-derived
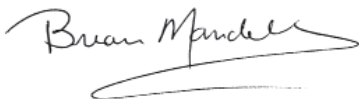
peptide hepcidin, which increases as part of the acute-phase inflammatory response and decreases in response to anemia and hypoxia. By decreasing the functionality of the major transmembrane iron transporter, hepcidin decreases both absorption of iron from the gut and release of macrophage iron stores. The biologic survival rationale for this may be to prevent iron overload and limit the availability of iron to invading microorganisms in the setting of sepsis—the ultimate inflammatory scenario. Elevated hepcidin levels in the setting of chronic inflammation result in a relative resistance to the desired marrow-stimulating effects of exogenously provided EPO. This may explain the limited benefits observed with EPO treatment in patients with chronic kidney disease, congestive heart failure, and inflammatory disease, and the higher EPO levels may cause off-target adverse effects. A challenge in translating the results of these clinical trials to clinical practice is our limited ability to accurately and routinely assess and interpret hepcidin levels and the adequacy of usable iron stores in individual patients. The routinely utilized iron, total iron-binding capacity, and ferritin tests have accuracy limitations. Furthermore, the unrecognized presence of functional iron deficiency, likely mediated in many patients by their elevated hepcidin levels, significantly reduces the marrow response to EPO. Provision of parenteral iron may benefit some of these patients.

The 2019 Nobel Prize in medicine and physiology was awarded to 3 investigators for their work in describing how intracellular oxygen levels are sensed and translated into cellular responses via hypoxia-inducible factor (HIF) transcription-mediated events. When oxygen levels decrease, intracellular HIF increases in many tissues, resulting in the induction and control of more than 50 genes, including EPO and others active in angiogenesis and cell growth. HIFs increase EPO production in the kidney and liver, enhance iron utilization, and promote effective erythropoiesis. Therapeutically increasing the HIF level demonstrably decreases the hepcidin level, which should augment iron availability and thus enhance the RBC response to the increased EPO,[2] especially in patients with elevated hepcidin levels due to chronic inflammation.

Souaid et al[1] summarize ongoing studies of a novel approach to increase HIF levels by stabilizing the HIF molecule by decreasing its prolyl hydroxylation, thus slowing its normally rapid proteasomal catabolism. But the long-term effects of treatment with these new oral inhibitors of prolyl hydroxylase will need to be carefully monitored, as prolyl hydroxylase is a key structural component of diverse proteins including collagens and mannose-binding lectin. The latter is an integral component of the protective innate immune response, and diminution of its function may have adverse infectious complications.

So while it is the erythrocyte-bearing hemoglobin that ultimately gets oxygen to our tissues, the mechanism by which we attempt to increase RBC mass may affect both efficacy and safety.

Brian F. Mandell, MD, PhD
Editor in Chief

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Oral hyperpigmentation with weakness and salt-craving
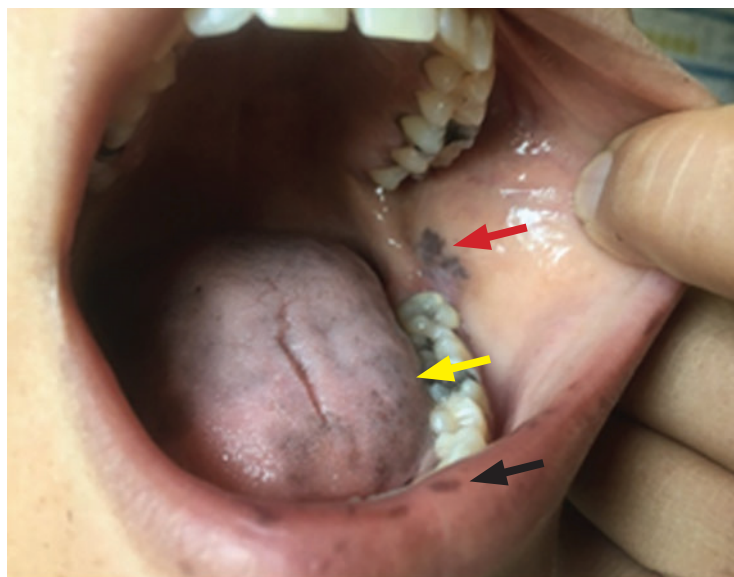
Figure 1. Hyperpigmented lesions involved the lower lip (black arrow), tongue (yellow arrow), and buccal mucosa (red arrow).

A 30-year-old woman came to the emergency department with episodes of weakness and presyncope, as well as constipation, nausea, vomiting, and salt-craving. The symptoms had begun 9 months earlier, after a miscarriage at 10 weeks of pregnancy, and had increased in frequency. She had also noticed dark colorations on her lower lip and inner cheek, which her primary physician had told her might be due to ink from a pen.

She also said that after searching the Internet for conditions that included her symptoms, she was convinced that she had Addison disease.

■ INITIAL MANAGEMENT AND WORKUP

Intravenous fluids were initiated for her symptoms of weakness and presyncope.

Physical examination demonstrated generalized cutaneous hyperpigmentation involving the lips, tongue, and buccal mucosa (**Figure 1**), as well as the gums and palmar creases.

Laboratory testing revealed a cortisol level of 0.8 μg/dL (reference range 3.10–22.40) and adrenocorticotropic hormone (ACTH) greater than 1,250 pg/mL (0.00–45.99). Intravenous saline and hydrocortisone succinate were initiated. The thyroid-stimulating hormone level was slightly elevated and, of note, her electrolytes and blood urea nitrogen-to-creatinine ratio were normal at the time of presentation to the emergency department. She was transitioned to hydrocortisone and fludrocortisone the next day.

■ ADDISON DISEASE: KEY FEATURES

In the United States and Western Europe, Addison disease has a prevalence of 1 in 20,000 persons, higher in women than in men.[1] The diagnosis is challenging due to the nonspecific constitutional symptoms, which are frequently mistaken for psychiatric disorders, extra-adrenal gastrointestinal endocrine disorders, or other endocrine disorders such as hypothyroidism.[2] The symptoms are subtle and often insidious and can include hyperpigmentation, anorexia, nausea, and fatigue. Elevated ACTH levels and lack of a rise in cortisol levels after an ACTH stimulation test confirm the diagnosis. In our patient, the almost undetectible cortisol level combined with extremely high ACTH level confirmed primary adrenal insufficiency and obviated the need for a formal ACTH-stimulation test.

The mainstay of treatment is lifelong oral hormone replacement therapy with glucocorticoids and mineralocorticoids at doses sufficient to keep electrolytes and plasma renin activity levels in the upper limits of normal.[3,4]

Addisonian crisis

Undiagnosed Addison disease may lead to addisonian crisis, a life-threatening acute cortisol deficiency presenting as a rapid clinical decompensation to obtundation, encephalopathy, and shock, requiring emergency administration of intravenous fluids and parenteral glucocorticoids to prevent circulatory collapse.[5,6] A high index of suspicion and early diagnosis are paramount.

Adrenal insufficiency causes hyponatremia through insufficient excretion of free water and sodium wasting.[7] In a retrospective multicenter study of patients with autoimmune Addison disease,[8] of 247 patients for whom sodium concentrations were available, hyponatremia was present in 84% (207) and was the most consistent biochemical finding of Addison disease. Many patients may have concurrent autoimmune thyroiditis with high levels of thyroid-stimulating hormone.[8] Introducing thyroxine replacement before steroid replacement may cause addisonian crisis.[8,9]

Hyperpigmentation

A hallmark sign of Addison disease is hyperpigmentation due to excess pituitary secretion of pro-opiomelanocortin, which is cleaved to ACTH, beta-endorphin, and melanocyte-stimulating hormone.[10,11] Intraoral pigmentation usually occurs before dermatologic pigmentation.[11]

■ CASE CONCLUSION AND TAKE-HOME MESSAGE

Our patient's case illustrates how misattributing hyperpigmented lesions on the lip, tongue, and buccal mucosa as due to pen ink in a patient with symptoms of weakness, presyncope, salt-craving, nausea, and vomiting delayed the diagnosis of this potentially life-threatening disease. In this case, the patient's own Internet search raised suspicion of adrenal insufficiency.

At 6 months after her presentation to the emergency department, she had gained about 10 pounds, with no recurrence of the periods of weakness. Her buccal hyperpigmentation also appeared to be lightening.

Thus, in a patient presenting with new onset of oral hyperpigmentation, clinicians should consider the pigmented lesions in the context of clinical symptoms with a high degree of suspicion for Addison disease. ■

■ DISCLOSURES

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The devil is in the details: Approach to refractory hypokalemia

A man with multiple medical problems presents with a serum potassium level of 2.1 mmol/L without symptoms

A 71-year-old man was told by his primary care physician to go to the emergency department for evaluation of asymptomatic hypokalemia detected on outpatient laboratory testing. He had a history of coronary artery disease, hypertension, gout, and atrial fibrillation. He reported that his father and brother had well-controlled hypertension diagnosed in adulthood. He was a former smoker but denied alcohol consumption. Recently, he had been exercising daily and following a diet to lose weight. He had visited his primary care physician because of new-onset lower-extremity edema.

The patient said that he had intentionally lost 20 pounds over 2 months by decreasing his caloric intake, and that he had experienced no vomiting, diarrhea, or abdominal pain. He did not use over-the-counter medications or herbal supplements. His home medications included warfarin 7.5 mg daily, clopidogrel 75 mg daily, atorvastatin 80 mg daily, lisinopril 20 mg daily, amiodarone 200 mg daily, and allopurinol 300 mg daily.

On physical examination, the patient was alert and oriented. He was not in any distress but appeared nervous. His temperature was 37.0°C (98.6°F), heart rate 84 beats per minute, blood pressure 186/100 mm Hg, respiratory rate 8 breaths per minute, and oxygen saturation 99% while breathing oxygen at 4 L/minute by nasal cannula. He had central obesity, with a body mass index of 34 kg/m^2. His heart rhythm was irregular, his lungs were clear to auscultation without crackles or wheezing, and gastrointestinal and neurologic examinations were unremarkable.

His initial serum potassium level was 2.1 mmol/L (reference range 3.5–5.0 mmol/L). Other initial laboratory values are listed in **Table 1**.

He was admitted to the hospital and received a total of 230 mmol of potassium intravenously and by mouth over the next 20 hours, but his serum potassium level increased to only 2.9 mmol/L. Therefore, the nephrology service was consulted to evaluate his refractory hypokalemia.

■ METABOLIC DISTURBANCES REVIEWED

1 What metabolic disturbance does the patient have?

☐ Metabolic alkalosis with respiratory acidosis
☐ Mixed metabolic and respiratory alkalosis
☐ Triple disorder with metabolic alkalosis, metabolic acidosis, and respiratory alkalosis
☐ Compensated metabolic alkalosis

Analyzing an acid-base disturbance is a 5-step process.

Step 1: Look at the pH. Our patient's arterial pH was 7.55, which, being higher than 7.45, shows a state of alkalemia.

Step 2: Determine if the primary process is metabolic or respiratory. In primary metabolic alkalosis, the serum bicarbonate level is high—and our patient's bicarbonate level was significantly elevated at more than 45 mmol/L (reference range 23–32 mmol/L). On the other hand, in primary respiratory alkalosis (as can occur during hyperventilation), the partial pressure of carbon dioxide (P_{CO_2}) is low—but our patient's breathing was slow and his P_{CO_2} was elevated, reflecting a compensatory process (see **Step 4**, below).

Step 3: Calculate the anion gap. Subtract the sum of the concentrations of the anions chloride and bicarbonate from the concentration of the most abundant cation, sodium. Importantly, the anion gap should be adjusted for the effect of an abnormal serum albumin concentration. The difference between the normal and the measured serum albumin concentrations in grams per deciliter is multiplied by 2.5, and the result is added to the calculated anion gap. In our patient's case, the anion gap adjusted for albumin was 5.25 mmol/L (reference range 8–16 mmol/L). The absence of an elevated anion gap ruled out concomitant metabolic acidosis.

Step 4: Assess compensation. In compensating for metabolic alkalosis, the breathing can slow down, and the Pco_2 can rise by as much as 0.7 mm Hg, from a normal of 40 mm Hg for every 1-mmol/L rise in the plasma bicarbonate concentration (from a normal level of 24 mmol/L). Therefore, as our patient's bicarbonate level was 45 mmol/L (21 mmol/L above normal), his Pco_2 could increase by about 15 mm Hg to approximately 55 mm Hg—for a measured value of 54 mm Hg. Note that this compensatory process of carbon dioxide retention involves slowing the respiratory rate, which is not always achievable. Also, this hypoventilation can result in hypoxemia, which was observed in our patient.

Step 5: Calculate the delta gap in cases of metabolic acidosis. Our patient had metabolic alkalosis, not acidosis, and therefore did not need this step.

In conclusion, the patient had metabolic alkalosis with appropriate respiratory compensation.[1]

■ FURTHER EVALUATION OF METABOLIC ALKALOSIS

2 What is the best next step to further evaluate this patient's metabolic disorder?

☐ Random urine chloride measurement
☐ Random urine sodium measurement
☐ Random urine potassium measurement
☐ Random urine ammonium measurement

Metabolic alkalosis should first be evaluated by obtaining a random urine chloride measurement (**Figure 1**). This helps classify metabolic alkalosis as either volume-responsive (urine chloride < 20 mmol/L) or volume-resistant (urine chloride ≥ 20 mmol/L).[1]

Urine chloride is more accurate than urine sodium as an indicator of intravascular volume depletion because chloride has a negative charge. In states of hypovolemia, sodium and chloride are reabsorbed from the urine as a consequence of activation of the renin-angiotensin-aldosterone system. In metabolic alkalosis, the kidneys respond by excreting bicarbonate in the urine. The negative charge of bicarbonate, particularly in early stages of volume-depleted metabolic alkalosis, drags the

TABLE 1

The patient's laboratory values on admission

Test	Results[a]	Reference range
Sodium	140 mmol/L	132–148 mmol/L
Potassium	**2.1 mmol/L**	3.5–5.0 mmol/L
Chloride	**93 mmol/L**	98–111 mmol/L
Bicarbonate	**> 45 mmol/L**	23–32 mmol/L
Blood urea nitrogen	**30 mg/dL**	10–25 mg/dL
Creatinine	1.11 mg/dL	0.7–1.4 mg/dL
Calcium	**8.0 mg/dL**	8.4–10.5 mg/dL
Albumin	**2.7 g/dL**	3.5–5.0 g/dL
Hemoglobin A1c	**6.8%**	< 5.7%
Hemoglobin	14.5 g/dL	12–16 g/dL
White blood cell count	**14.3 × 10⁹/L**	3.7–11.0 × 10⁹/L
Platelet count	**79 × 10⁹/L**	140–400 × 10⁹/L
Alanine aminotransferase	**79 U/L**	0–45 U/L
Aspartate aminotransferase	**81 U/L**	7–40 U/L
Alkaline phosphatase	129 U/L	40–150 U/L
Bilirubin, total	1.4 mg/dL	0–1.5 mg/dL
Arterial blood gasses		
pH	**7.55**	7.35–7.45
Pco_2	**54 mm Hg**	35–45 mm Hg
Po_2	**34 mm Hg**	75–100 mm Hg
Bicarbonate	**47 mmol/L**	18–23 mmol/L

[a] Abnormal results are shown in bold.

Metabolic alkalosis
Arterial pH > 7.44
Bicarbonate > 30 mmol/L

↓

Measure urine chloride

↙   ↘

Low (< 20 mmol/L)   **High** (≥ 20 mmol/L)

↓   ↘

Volume- or chloride-responsive alkalosis   **Volume- or chloride-resistant alkalosis**

↓   ↙   ↘

Congenital chloride-losing diarrhea
Diuretics (late effect)
Gastric fluid losses (vomiting, nasogastric suction)
Nonabsorbable anion delivery
Posthypercapnea

Hypertension present:
Congenital adrenal
  hyperplasia

Cushing disease or
  syndrome

Geller syndrome

Hyperaldosteronism
  (primary or secondary)

Liddle syndrome

Renovascular disease

Renin-secreting tumor

Apparent mineralo-
  corticoid excess

Hypertension absent:
Bartter syndrome

Gitelman syndrome

Diuretics (early effect)

Severe potassium
  depletion

Figure 1. Metabolic alkalosis should first be evaluated by obtaining a random urine chloride. This step helps classify it as volume-responsive (urine chloride < 20 mmol/L) or volume-resistant (urine chloride ≥ 20 mmol/L). The latter is further divided based on the presence or absence of hypertension.

positively charged ions sodium and potassium into the urine to maintain electroneutrality. Therefore, urine sodium and potassium levels are elevated in the first 24 to 72 hours of volume depletion, but after 72 hours they drop.

Urine ammonium is measured when evaluating non-gap metabolic acidosis but has no role in states of alkalosis.[2]

■ **CASE CONTINUED: RESULTS OF FURTHER TESTING**

Results of additional testing (**Table 2**) showed a urine chloride level of 32 mmol/L, indicating his metabolic alkalosis was volume-resistant.

Further, his urine potassium level was 68 mmol/L and his urine creatinine level was 80

mg/dL. (ie, 7.04 mmol/L) Therefore, his urine potassium-to-creatinine ratio was 9.66—and values greater than 1.5 indicate urinary loss of potassium.

Several days later, the patient's renin level was measured and was normal, and his aldosterone level was low. Note that he was taking lisinopril at home. Angiotensin-converting enzyme (ACE) inhibitors such as lisinopril block production of angiotensin II, thereby interrupting the negative feedback loop of the renin-angiotensin-aldosterone cascade and stimulating renin synthesis.[3] However, a state of hypercortisolemia will suppress renin levels, which in our patient might appear artificially normal due to the concomitant use of an ACE inhibitor.

■ CAUSES OF VOLUME-RESISTANT METABOLIC ALKALOSIS WITH LOW RENIN AND ALDOSTERONE

3 All of the following conditions can cause volume-resistant metabolic alkalosis with low renin and low aldosterone levels except which one?

☐ Liddle syndrome
☐ Apparent mineralocorticoid excess
☐ Cushing syndrome
☐ Glucocorticoid-remediable aldosteronism

Liddle syndrome is an autosomal-dominant condition characterized by hyperactivity of the epithelial sodium channel. More than 30 variants of the genes that code for the 4 subunits of this channel have been described, and the clinical features of Liddle syndrome can differ significantly, as it has variable penetrance.[4,5]

The epithelial sodium channel is found in the principal cell of the cortical collecting duct of the distal nephron. If activity of this channel is increased, the abnormality will resemble a high-aldosterone state by causing excessive sodium reabsorption and potassium excretion. The high sodium load leads to volume expansion and hypertension.[1,2] Therefore, this syndrome usually presents as early-onset hypertension, hypokalemia, volume-resistant metabolic alkalosis, and a low-renin and low-aldosterone state, since these hormone levels are suppressed. Due to its variable penetrance, the severity of the hypertension and the age of onset can differ.[4,5]

Apparent mineralocorticoid excess is an autosomal-recessive disease caused by a deficiency of the enzyme 11-beta hydroxysteroid dehydrogenase type 2.[6,7] This enzyme converts cortisol to one of its inactive metabolites, cortisone, in aldosterone target organs such as the collecting tubules in the kidney.[1]

Cortisol and aldosterone have the same affinity for the mineralocorticoid receptor, but cortisol circulates in the system in a higher concentration (**Figure 2**). Therefore, this enzyme limits cortisol from acting as the major endogenous mineralocorticoid.[1,2] Licorice and medications like posaconazole can also inhibit this enzyme, resulting in a state of excess cortisol that activates the mineralocorticoid

TABLE 2

Additional workup

Tests	Results[a]	Reference range
Urine potassium, random	68 mmol/L	17.0–99.0 mmol/L
Urine chloride, random	32 mmol/L	30–260 mmol/L
Urine creatinine, random	80 mg/dL	40–278 mg/dL
Serum renin	2.17 ng/mL	0.25–5.82 ng/mL
Serum aldosterone	**< 1 ng/dL**	3–16 ng/dL

[a] Abnormal results are shown in bold.

receptors and clinically resembles primary hyperaldosteronism.[1,6] Volume-resistant metabolic alkalosis, hypokalemia, low renin, and low aldosterone levels are characteristic of this syndrome.[7]

Cushing syndrome is a state of cortisol excess caused by ectopic production of adrenocorticotropic hormone (ACTH).[8,9] ACTH stimulates the zona fasciculata of the adrenal gland, leading to excessive production of cortisol.[8] The excess cortisol overwhelms the 11-beta hydroxysteroid dehydrogenase enzyme in the distal tubules and activates the mineralocorticoid receptors, producing a clinical picture of primary hyperaldosteronism.[1] The most common sources of ectopic ACTH production include small-cell lung cancer and carcinoid tumors.[9,10] As described above, this excessive activation of the mineralocorticoid receptor presents with volume-resistant metabolic alkalosis with low renin and low aldosterone levels.

Glucocorticoid-remediable aldosteronism is an autosomal-dominant condition in which chimeric gene duplication leads to crossover between the 11-beta hydroxylase and aldosterone synthase genes.[11] As a result, aldosterone is produced ectopically in the zona fasciculata solely under the stimulation of ACTH.[2,11] The clinical picture is characterized by early-onset severe hypertension, and cerebrovascular and cardiovascular complications with a mean age of 32 at the time of the initial event.[11]

Even though this is another cause of volume-resistant metabolic alkalosis, glucocorticoid-remediable aldosteronism is a mineralocorticoid-excess state in which aldosterone

Potassium infusions and supplements failed to raise his potassium level
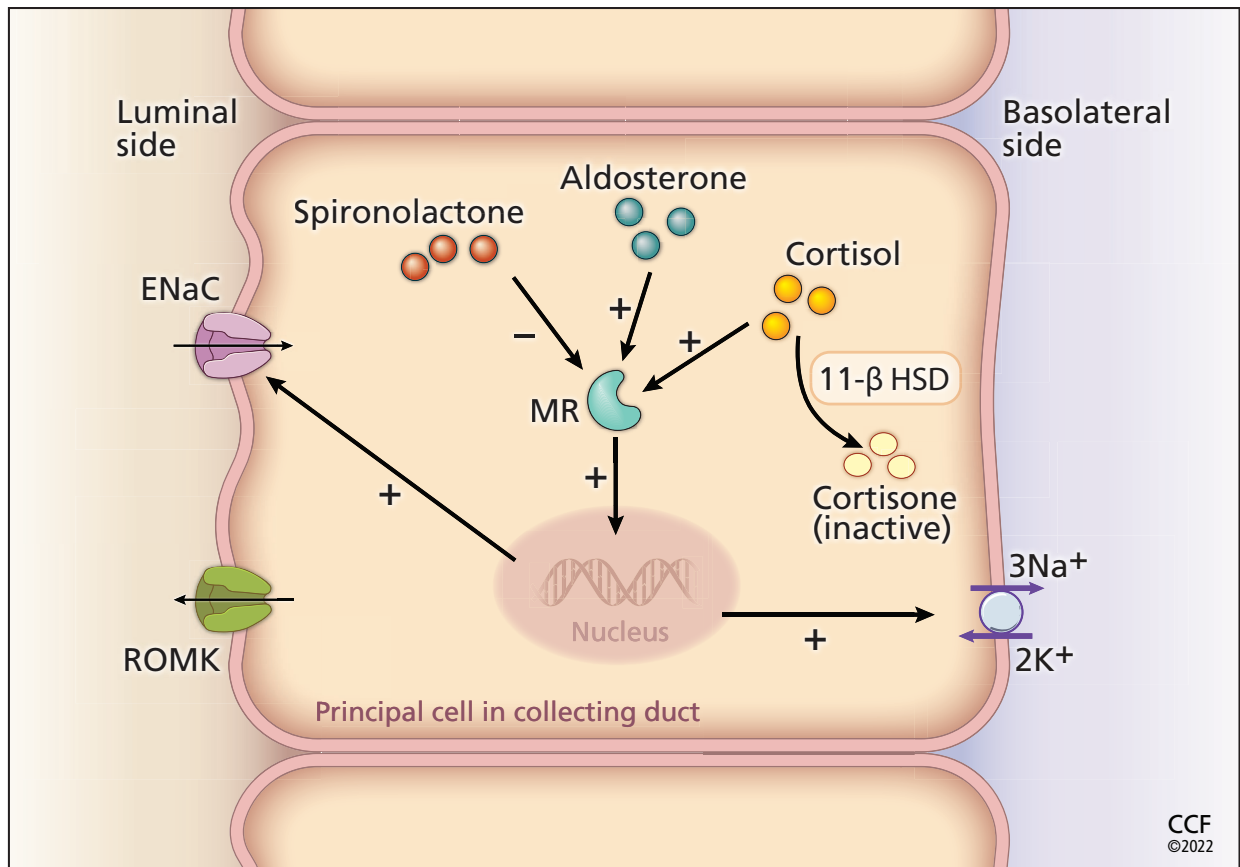
Figure 2. Processes of mineralocorticoid excess and effect of spironolactone. In the principal cells in the collecting ducts of the kidney, activation of the mineralocorticoid receptor (MR) increases the transcription, translation, and insertion of more epithelial sodium channels (ENaC) in the luminal side. Cortisol and aldosterone have the same affinity for the mineralocorticoid receptor, but aldosterone is present in higher concentrations. Activation of the mineralocorticoid receptor stimulates a cascade of intracellular reactions that results in increased expression of the epithelial sodium channel. Spironolactone blocks the mineralocorticoid receptor. The enzyme 11-β hydroxysteroid dehydrogenase (HSD) type 2 converts cortisol to its inactive metabolite, cortisone. This enzyme can be absent in apparent mineralocorticoid excess, or it can be inhibited by licorice or posaconazole. Notably, the increased number of epithelial sodium channels leads to sodium (Na^+) reabsorption from the tubular lumen. To maintain electroneutrality, another positive ion (K^+) is secreted into the tubular lumen through the renal outer medullary potassium channel (ROMK).

levels are elevated and renin is suppressed. Therefore, this is the correct answer to the question above. Of importance, hypokalemia is uncommon in glucocorticoid-remediable aldosteronism, and when it occurs, it is usually triggered by a potassium-wasting diuretic agent.[2,11]

The diagnosis of this condition is based on confirming that aldosterone is suppressed when glucocorticoids are given, on genetic testing, or on detecting high levels of C-18 oxidation products of cortisol in the urine.[2,11]

■ **CASE CONTINUED: A CANCER DIAGNOSIS**

Liddle syndrome is characterized by early-onset hypertension and a strong family history, making this condition less likely in our patient. Along the same lines, the inherited form of apparent mineralocorticoid excess presents in early childhood, while its acquired form, caused by inhibition of the enzyme 11-beta hydroxysteroid dehydrogenase type 2, is triggered by medications such as antifungals or by licorice, which our patient was not consuming.

Because Cushing syndrome was strongly suspected in this patient, further evaluation was pursued (**Table 3**), and ultrasonography of the liver was performed to evaluate the patient's elevated aminotransferase levels and thrombocytopenia. Multiple hepatic masses were detected, the largest being 5 cm. This was followed by computed tomography of the chest, abdomen, and pelvis, which revealed a right suprahilar pulmonary nodule measuring 2.7 cm, bilateral diffuse adrenal nodularity (the probable source of his excess cortisol), and liver and pancreatic masses. Magnetic resonance imaging did not show any metastases in the brain or pituitary gland. Liver biopsy revealed metastatic small-cell lung cancer.

◼ ANTIHYPERTENSIVE THERAPY IN HYPERMINERALOCORTICOID STATES

4 Which medication would be indicated to address this patient's hypertension?

☐ Spironolactone
☐ Verapamil
☐ Losartan
☐ Aliskiren

Spironolactone is a synthetic steroid that competes with aldosterone. It also has affinity for steroid receptors, specifically those of progesterone and androgen systemically.[12]

In the kidney, spironolactone is delivered through the blood to the distal nephron, where it penetrates the basolateral membrane and binds the mineralocorticoid receptor, located in the cytosol (**Figure 2**).[13] When aldosterone activates this receptor, a cascade of intracellular reactions is triggered, culminating in a decrease in degradation of the epithelial sodium channel.[14] As a result, aldosterone increases sodium reabsorption and volume expansion, and its antagonist, spironolactone, blocks these effects.[13,14]

Importantly, in the absence of mineralocorticoid excess, other potassium-sparing diuretics such as amiloride (an epithelial sodium channel blocker) are preferred to minimize renal losses of potassium, as they are better tolerated.

Verapamil is a nondihydropyridine calcium channel blocker that causes peripheral vasodilation and cardiac depression.[15] It is a

<table>
<tr><td colspan="3">TABLE 3

Further additional workup</td></tr>
<tr><td>Tests</td><td>Results[a]</td><td>Reference range</td></tr>
<tr><td>Cortisol, AM level</td><td>125 µg/dL</td><td>6–26 µg/dL</td></tr>
<tr><td>24-hour urinary cortisol excretion</td><td>16,080 µg/24 hours</td><td>4–50 µg/24 hours</td></tr>
<tr><td>Adrenocorticotropic hormone</td><td>1,140 pg/mL</td><td>6–50 pg/mL</td></tr>
<tr><td colspan="3">[a] Abnormal results are shown in bold.</td></tr>
</table>

therapeutic option for hypertension, but it does not affect the mineralocorticoid pathway.

Losartan is a selective inhibitor of the angiotensin II receptor. Angiotensin II induces vasoconstriction and the release of hormones like aldosterone, as well as catecholamines and arginine vasopressin.[16] Consequently, angiotensin II receptor blockers (ARBs) lower aldosterone levels and, due to negative feedback, they increase renin and angiotensin II levels.[3]

Even though ARBs are excellent therapeutic options in states of excess renin-angiotensin-aldosterone activation, specific conditions of mineralocorticoid excess are better addressed by targeted therapy with mineralocorticoid receptor antagonists such as spironolactone.[17] Furthermore, the hypertension in Cushing syndrome is not mediated by an excess of aldosterone but by excess cortisol.[8]

Aliskiren is a direct renin inhibitor that binds to renin at its active site, thereby stopping the cleavage of angiotensinogen that produces angiotensin I. In normal conditions, angiotensin I is converted by ACE to angiotensin II. Therefore, aliskiren blocks the renin-angiotensin-aldosterone system at an earlier stage than ACE inhibitors, ARBs, or spironolactone.[18] As mentioned above, Cushing syndrome causes hypertension through an excess of cortisol, which directly activates the mineralocorticoid receptor.

◼ CASE CONCLUSION

The patient was treated with spironolactone, and his hypertension and hypokalemia improved. Weeks later, he was readmitted to

The patient was treated with spironolactone, and his hypertension and hypokalemia improved

start chemotherapy and received etoposide and carboplatin. Because the cancer was advanced and unresectable, adrenalectomy to treat the hypercortisolemia was ruled out, and the 11-beta hydroxylase inhibitor metyrapone was added to his regimen with the goal of decreasing the conversion of 11-deoxycortisol to cortisol.

Unfortunately, the patient developed septic shock and kidney failure secondary to disseminated aspergillosis and died less than 2 months after his initial presentation with asymptomatic, refractory hypokalemia.

■ TEACHING POINTS

- Severe hypokalemia (serum potassium level < 3 mmol/L) or symptomatic hypokalemia warrants prompt repletion and closer monitoring of serum levels to determine response to therapy. A lower serum potassium threshold should be applied for patients with heart disease, due to increased risk for arrhythmias, as in our patient.
- The expected respiratory compensation for metabolic alkalosis is a 0.7-mm Hg increase in Pco_2 from a normal Pco_2 of 40 mm Hg for every 1-mmol/L rise in the plasma bicarbonate concentration from a normal level of 24 mmol/L.
- Chloride is the best urine electrolyte to measure to evaluate volume status in metabolic alkalosis, allowing it to be classified as either volume-responsive (urine chloride < 20 mmol/L) or volume-resistant (urine chloride ≥ 20 mmol/L).
- Liddle syndrome, apparent mineralocorticoid excess, and Cushing syndrome can cause volume-resistant metabolic alkalosis with low renin and low aldosterone levels.
- Spironolactone, a mineralocorticoid receptor antagonist, is the drug of choice for hypertension in states of mineralocorticoid excess. ■

■ DISCLOSURES

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Glycemic targets in the ICU: A look back, and ahead

INPATIENT HYPERGLYCEMIA is associated with significant morbidity and mortality, including in the intensive care unit (ICU). However, when it comes to optimal blood glucose targets, controversy abounds. In this issue, Alhatemi et al[1] reflect on how we arrived at the current blood glucose targets and offer important insights on the future of glycemic monitoring and targets in critically ill patients.

■ HISTORICAL INSIGHTS

While a number of studies reported the association between hyperglycemia and poorer outcomes for patients in the ICU, 2 studies in Leuven, Belgium,[2,3] were the first to look at how achieving intensive glucose control affects clinical outcomes. The positive effect of glucose control on mortality and morbidity noted in those studies led to attempts to achieve even tighter glycemic control in patients in the ICU. But this movement came to a halt in 2009 with the publication of the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study,[4] which demonstrated increased mortality in critically ill patients with intensive glucose control.

Alhatemi et al nicely outline the basic differences between the Leuven studies and the NICE-SUGAR study. It is worth noting that caloric intake was higher in the Leuven studies, which may have mitigated some of the hypoglycemia seen in the NICE-SUGAR study. Furthermore, there was less overlap in glucose values between the intensive-control and conventional-control groups in the Leu-

ven studies than in the NICE-SUGAR study, which may have enhanced the detection of outcome differences in the Leuven studies.[5]

Ultimately, the divergent findings of these trials serve to highlight a very important point—that there may not be a one-size-fits-all approach to glycemic targets.

■ THE IMPORTANCE OF CONTEXT

The question that naturally arises then is whether there actually *is* a group of patients in the ICU who benefit from an intensive glucose control strategy? The answer appears to be that critically ill patients with well-controlled diabetes mellitus or without preexisting diabetes benefit from a more intensive glucose control strategy while, conversely, rapidly lowering glucose values in patients with poorer preadmission diabetes mellitus control is actually deleterious.

Egi et al[6] examined how preexisting hyperglycemia influenced the association between glycemia and mortality in a study of 415 critically ill patients with diabetes. They found that in patients with higher preadmission hemoglobin A1c (> 7%), the higher the level of acute glycemia during the ICU stay, the lower the rate of in-hospital mortality as opposed to patients in the ICU with lower preadmission hemoglobin A1c levels (< 7%).

Naraba et al[7] considered blood glucose target time-in-range (TIR) and 28-day mortality in 1,230 critically ill patients. In patients with a preadmission hemoglobin A1c < 6.5%, a lower TIR of 70 to 180 mg/dL was associated with increased mortality, an association not seen in patients with a hemoglobin A1c ≥ 6.5%.

While these trials suggest an interaction

> **Divergent trial findings highlight a very important point—that there may not be a one-size-fits-all approach to glycemic targets**

between preadmission glycemic state and response to intensive glucose control in patients in the ICU, the Glycemic Stability During the Intraoperative Period Among Patients With DM Undergoing CABG Surgery (GLUCO-CABG) study[8] demonstrated this principle in prospective randomized fashion. Overall, intensive glucose control did not improve outcomes after cardiac surgery, but subsequent subgroup analysis revealed a lower rate of complications in patients without diabetes but with intensive glucose control. The physiologic basis for this is not clear, although one might postulate that there is a relative neuroglycopenia when patients with suboptimal glycemic control receive intensive glucose control.[9]

■ CONTINUOUS GLUCOSE MONITORING: THE FUTURE?

As Alhatemi et al[1] point out, increasing attention is being paid to TIR and glycemic variability as targets for intervention for patients in the ICU. The studies done thus far on measurements of glycemic control have typically been extrapolated to TIR and glycemic variability from point-of-care glucose readings as opposed to using true continuous glucose monitoring.

An approach with the potential to significantly alter inpatient glycemic management is the use of current outpatient continuous glucose monitoring devices in the inpatient setting. Currently, 2 devices are approved for use in the hospital (GlucoScout and OptiScanner 5000).[10] However, their availability in ICUs is limited, and they require a dedicated central or peripheral access for blood sampling. However, the COVID-19 pandemic has opened the doors to the testing and use of outpatient glucose monitoring devices in the hospital, showing that even in the ICU, outpatient devices can be used, although calibration is needed.[11,12] This allows us to envision, in addition to telemetry for cardiac monitoring, the use of glucose tracings with alarms to monitor for hyperglycemia and hypoglycemia in hospital inpatients.

Much work still needs to be done to better understand the nuances of glycemic targets in critically ill patients, and to learn how to take advantage of evolving technology to improve appropriate glycemic control in the ICU. ■

■ DISCLOSURES

The author reports no relevant financial relationships which, in the context of her contributions, could be perceived as a potential conflict of interest.

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Glycemic control in the critically ill: Less is more

ABSTRACT

Hyperglycemia is associated with poor clinical outcomes in critically ill patients. Initial clinical trials of intensive insulin therapy targeting blood glucose levels of 80 to 110 mg/dL showed improved outcomes, but subsequent trials found no benefits and even increased harm with this approach. Emerging literature has evaluated other glycemic indices including time-in-target blood glucose range, glycemic variability, and stress hyperglycemia ratio. These indices, while well described in observational studies, have not been addressed in the initial trials. Additionally, the patient's preexisting diabetes status and preadmission diabetic control may modulate the outcomes of stringent glycemic control, with worse outcomes of hyperglycemia being observed in patients without diabetes and in those with well-controlled diabetes. Most medical societies recommend less stringent glucose control in the range of 140 to 180 mg/dL for critically ill patients.

KEY POINTS

Hyperglycemia is associated with increased morbidity and mortality in critically ill patients and should be treated.

Enhancing the amount of time glucose levels are in the target range and minimizing glycemic variability have been associated with improved outcomes in critically ill patients.

Hypoglycemia has been independently associated with an increased risk of death in critically ill patients.

Although the optimal blood glucose target for patients in the intensive care unit is not known, a target of 140 to 180 mg/dL is the most acceptable.

HYPERGLYCEMIA HAS BEEN ASSOCIATED with adverse clinical outcomes in critically ill patients, regardless of diabetes status.[1–7] Proposed causes of stress hyperglycemia include excessive counterregulatory hormones (corticosteroid, glucagon, growth hormone, catecholamines) and release of cytokines tumor necrosis factor (TNF)-alpha and interleukin (IL)-1. These factors can promote a transient state of insulin resistance that can lead to decreased insulin action on suppressing gluconeogenesis and also to decreased uptake of insulin-mediated skeletal muscle glucose.[8] Factors contributing to hyperglycemia in hospitalized patients include medications (steroids, catecholamines), parenteral nutrition, and intravenous medications diluted in dextrose.[9]

Further, hyperglycemia itself induces production of inflammatory cytokines (IL-6, IL-8, and TNF-alpha) and reactive oxygen species.[10] It also impairs the neutrophil functions of chemotaxis and bactericidal activity.[11] Additionally, hyperglycemia and hyperinsulinemia have been shown to increase tissue procoagulant activity that may add to the procoagulant state.[12] These mechanisms may explain the poor outcomes observed with hyperglycemia.

Initial single-center randomized clinical trials (RCTs) of intensive insulin therapy targeting blood glucose levels in the fasting range (80–110 mg/dL) (referred to as the Leuven trials) found significant mortality and morbidity benefit,[13,14] and this strategy gained popularity. However, subsequent multicenter RCTs[15–17] failed to replicate these findings, and the larg-

est RCT, the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial,[17] reported evidence of harm with this intervention.

Other glycemic indices have shown independent impacts on outcomes in the intensive care unit (ICU). In fact, the time-in-range (TIR, the amount of time the glucose level is in the target range), glycemic variability, and the modulation effect of preexisting diabetes status, although thoroughly evaluated by observational studies, were not examined in the early RCTs. This may explain potential differences in outcomes between these trials.

This review will discuss findings from the major RCTs, metrics of glycemic control, and recommendations of professional medical societies for target blood glucose ranges in critically ill patients.

■ METRICS OF GLYCEMIC CONTROL

Hyperglycemia
In observational study results published from 2003 to 2009, hyperglycemia was generally associated with adverse clinical outcomes in critically ill patients in various settings (medical, surgical, trauma, and neurologic).[1–7] For example, in one retrospective analysis,[4] hyperglycemia had a graded effect on hospital mortality. In other trials,[1,5–7] trauma patients with hyperglycemia had increased mortality rates, hospital length of stay, ICU length of stay, and incidences of nosocomial infection. Moreover, hyperglycemia was associated with worse neurologic outcomes and elevated intracranial pressure in patients with severe traumatic brain injury, and early hyperglycemia was an independent predictor of worse scores on the Glasgow Coma Scale.[3]

The relationship between hyperglycemia and mortality in ICU patients is modulated by their diabetes status. Observational studies[2,18–20] have shown that the greatest reduction in mortality associated with intensive insulin therapy (target goal 80–110 mg/dL) was seen in patients without diabetes. In Egi et al,[18] multivariate logistic regression analysis showed greater reduction in odds of mortality (odds ratio 0.45) when 80–110 mg/dL was used in patients without diabetes compared

with other blood glucose targets. In contrast, for patients with diabetes, the mortality benefit had a poor correlation. The cohorts of critically ill patients with diabetes were not identical. Thus, preadmission diabetic control as evidenced by hemoglobin A1c (HbA1c) levels might have a differential impact on the hyperglycemia-mortality relationship. For instance, in a retrospective observational study of patients with HbA1c levels obtained at admission,[21] for patients with a low HbA1c level (< 7%), increases in mean blood glucose values were associated with increased mortality risk; the risk was decreased when the HbA1c was above 7%.[21] This may signify that patients with poorly controlled diabetes may benefit from a less stringent glucose target.

In addition to mortality outcomes, early hyperglycemia (defined as elevated blood glucose on hospital day 1 or 2),[5] hyperglycemia at admission,[6,7] and worsening or highly variable hyperglycemia[1] were associated with higher rates of infectious complications in critically ill patients. After correction for severity of illness and other variables including age, elevated glucose was an independent predictor of increased infectious morbidity in these studies.[1,5–7]

To study the complex interplay between acute and chronic hyperglycemia on mortality in hospitalized patients, Roberts et al[22] developed the stress hyperglycemia ratio, calculated as the blood glucose level at admission divided by the estimated average glucose, which was inferred from the HbA1c as follows: the estimated average glucose equals HbA1c × 1.59, minus 2.59.[23] In Roberts et al,[22] the stress hyperglycemia ratio but not admission hyperglycemia was associated with adverse outcomes. These findings were corroborated by other cohort studies,[24,25] demonstrating that the stress hyperglycemia ratio was independently associated with increased risk of death and additional complications.

Time in the target glucose range
The TIR had been proposed as a "unifying" metric of glycemic control because it is affected by hyperglycemia, hypoglycemia, and glycemic variability. The Glucontrol study[16] was the only RCT that explicitly reported TIR. A subsequent post hoc analysis of data from this study showed that a TIR greater than 50% for

The relationship between hyperglycemia and mortality in ICU patients is modulated by diabetes status

a glucose target of 140 to 180 mg/dL was independently associated with increased rate of survival.[26] A series of single-center studies using the SPRINT (Specialized Relative Insulin Nutrition Tables) protocol, a tight glycemic control intervention, examined the effect of TIR (termed "cumulative time in band") on organ failure and mortality in critically ill patients receiving intensive insulin therapy.[27–29] Reduced organ failure, as evidenced by a reduction in the SOFA (Sequential Organ Failure Assessment) score, was associated with a TIR greater than 50%,[27] while a TIR greater than 70% was independently associated with improved survival.[29]

A subsequent prospective study of patients after cardiac surgery showed improved outcomes in decreased duration of both mechanical ventilation and ICU length of stay in those with a TIR greater than 80%, regardless of diabetes status. The incidence of sternal wound infections was significantly higher in patients with a TIR below 80% vs patients with a TIR above 80%.[30]

The effect of diabetes status on TIR outcomes has been studied by Krinsley and Preiser.[31] In their retrospective analysis of the prospectively collected data, and independent of severity of illness and ICU length of stay, a TIR greater than 80% for a blood glucose of 70 to 140 mg/dL was strongly associated with increased survival in critically ill patients without diabetes but not in patients with diabetes. One could argue that the design of the study did not include data on baseline glycemic control before ICU admission, and so it questions whether poorly controlled diabetes has any impact on the benefits of a high TIR.

A more recent landmark retrospective multicenter study by Lanspa et al[32] published in 2019 sought to examine this effect and found that a TIR greater than 80% for a blood glucose target of 70 to 139 mg/dL was independently associated with reduced mortality in patients with or without diabetes. However, when diabetes status was stratified into well-controlled and poorly controlled disease (based on HbA1c), the TIR effect was not significant in patients with poorly controlled diabetes.[32] This finding suggests that antecedent poor glucose control may potentially confound the effects of tight glycemic control if not taken into consideration.

Glycemic variability

Glycemic variability is defined as the fluctuation of blood glucose or other parameters of glucose homeostasis over a given time. The most frequently used metrics for assessing short-term within-day glycemic variability are the following:
- Standard deviation of glucose
- Coefficient of variation for glucose
- Mean amplitude of glycemic excursions.[33]

Ryan et al[34] proposed another metric for glycemic variability in type 1 diabetes, termed the glycemic lability index, based on the change in glucose level over a 4-week period. A discussion of the interpretation and reference values of these indices is beyond the scope of this review.

There is strong evidence that high glycemic variability is associated with increased short-term and long-term mortality and hospital length of stay in heterogeneous cohorts of critically ill patients,[35–39] with 1 study[36] showing a higher mortality rate with increasing glycemic variability in patients with sepsis when the glycemic lability index was divided into deciles. Increased rates of bacteremia,[40] nosocomial infections,[41] and surgical site infections[42] have also been linked to increased glycemic variability. For example, Atamna et al[40] found that increased glycemic variability (expressed as coefficient of variation for glucose) increased the risk of bacteremia in non-ICU patients hospitalized for acute infectious illnesses. Donati et al[41] found that in critically ill patients, increased glycemic variability in all 3 indices noted above were significantly associated with infectious morbidity and mortality, with the highest quartile of the glycemic lability index having the strongest association with ICU-acquired infection. Subramaniam et al[42] reported that postoperative glycemic variability in the first 24 hours after cardiac surgery carried the highest rate of a composite of postoperative adverse events, including superficial and deep sternal wound infections.

Several studies have evaluated the effects of antecedent diabetes status as well as hypoglycemia.[20,43,44] Interestingly, when Krinsley et al[20,43] stratified patients based on their prior diagnosis of diabetes, a high glycemic variability (using the coefficient of variation for glucose) was associated with increased mortality and

There is strong evidence that high glycemic variability is associated with increased short-term and long-term mortality rates and hospital length of stay in critically ill patients

shortened survival in acutely ill patients without diabetes but not in patients with diabetes. The landmark study by Lanspa et al[44] used a standardized electronic insulin protocol to minimize interphysician variability in insulin titration. They found that even though the coefficient of variation was independently associated with 30-day mortality, this association was higher for patients without diabetes than for those with diabetes. Although these studies were adequately powered and their populations were stratified for diabetes state, their potential weakness is that the stratification was made based on either chart review[20,43] or the International Classification of Diseases (ICD)-9 codes[44] without including the HbA1c. Thus, diabetes diagnoses could have been missed. In addition, the effect of glycemic variability was not studied in patients with well-controlled vs poorly controlled diabetes, based on HbA1c values, as was done for the TIR.

The effect of glycemic variability on mortality outcomes, though potentially confounded by hypoglycemia, was also proven to be a strong independent predictor of mortality when adjusting for hypoglycemia and disease severity.[44,45] In fact, in 1 study,[46] the risk of hypoglycemia was 3.2 times higher in patients with increased glycemic variability.

Glycemic variability, though potentially confounded by hypoglycemia, is a strong independent predictor of mortality

■ HYPOGLYCEMIA: A COMPLICATING FACTOR

The American Diabetes Association defines hypoglycemia as a blood glucose level below 70 mg/dL and classifies it as follows:
- Level 1: 70 to ≥ 54 mg/dL
- Level 2: < 54 mg/dL
- Level 3: a clinical event characterized by altered mental or physical status requiring assistance for treatment of hypoglycemia.[47]

In observational studies, hypoglycemia has been independently associated with increased risk of death in critically ill patients.[48–52] In RCTs, a pooled analysis of the NICE-SUGAR study[53] and the study by Meyfroidt et al[54] showed that hypoglycemia increased the odds of mortality. In one study,[52] mild hypoglycemia (defined as < 70 mg/dL) was associated with increased mortality regardless of diabetes status and diagnosis of conditions (medical, surgical, or trauma). In

a retrospective study, Bagshaw et al[48] found that early hypoglycemia (defined as within 24 hours of ICU admission) and its severity were associated with increasing mortality in a dose-dependent fashion. Interestingly, mortality was higher in patients with 2 episodes of hypoglycemia than in those with only 1 episode.[48] Saliba et al[55] examined outcomes based on whether hypoglycemia was induced by medication (iatrogenic) or was spontaneous during the course of critical illness. When results were stratified based on the cause of hypoglycemia, they found that the effects on mortality rates were equally harmful and that the cause did not have a significant impact.[55]

■ GLYCEMIC TARGETS IN CLINICAL STUDIES

Single-center trials
In 2010, Meyfroidt et al[54] published results of a retrospective analysis of data first published in 2001 by Van den Berghe et al.[13] In that trial, 1,548 patients (mainly with cardiac disease) admitted to the surgical ICU were randomized to receive either intensive insulin therapy (glucose goal of 80–110 mg/dL) or hyperglycemia treatment only when it reached the renal threshold (180–220 mg/dL). Reductions in mortality, critical illness polyneuropathy, acute renal failure, transfusion requirement, and bloodstream infections were more significant in the intensive insulin therapy group than in the "tolerating-hyperglycemia" group. However, hypoglycemia was more frequent in the intensive treatment cohort.[13]

In 2006, Van den Berghe et al[14] published results from a similar trial in 1,200 exclusively medical ICU patients. The insulin infusion protocols and nutritional strategies were the same as in the study of surgical patients. Results showed that intensive insulin therapy did not decrease hospital mortality rates. However, the group had significant reductions in length of ICU and hospital stay, mechanical ventilation duration, and acute renal failure. As in the first trial, hypoglycemia was significantly more prevalent in the intensive insulin treatment group.[14]

Multicenter trials
Subsequent multicenter RCTs failed to confirm the mortality benefits of intensive insulin

therapy reported by Van den Berghe et al[13,14] and Meyfroidt et al.[54] The Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis study (VISEP)[15] was conducted in medical and surgical ICU patients with sepsis, with results published in 2008. One year later, results were published from the Glucontrol study,[16] conducted in a similar population. However, both studies were terminated prematurely due to increased hypoglycemia in the intensive therapy arm in VISEP[15] and a high rate of unintended protocol violations in Glucontrol.[16]

Enthusiasm for strict glycemic control was further reduced by the 2009 publication of results from the international multicenter NICE-SUGAR study,[17] which randomized 6,104 patients. In NICE-SUGAR, the intensive insulin therapy cohort (glucose target 81–108 mg/dL) had higher 90-day mortality rates and a higher incidence of severe hypoglycemia (< 40 mg/dL) than the conventional therapy group (glucose target 144–180 mg/dL). Moreover, there was no reported difference between the groups in ICU or hospital length of stay, duration of mechanical ventilation, or need for renal replacement therapy. In a 24-month follow-up study of NICE-SUGAR,[56] no differences were detected in favorable neurologic outcomes or mortality in patients with traumatic brain injury.

■ EXPLAINING DISCREPANCIES IN STUDY RESULTS

Difference in blood glucose targets
The Leuven studies[13,14] and VISEP[15] used target glucose levels of 80 to 110 mg/dL (stringent) in the intervention groups and 180 to 200 mg/dL (loose) in the control groups. In contrast, the Glucontrol study used 80 to 110 mg/dL for the intervention group (stringent) and 140 to 180 mg/dL (intermediate) for the controls,[16] and the NICE-SUGAR study[17] used 81 to 108 mg/dL (stringent) for the interventional arm and 144 to 180 mg/dL (intermediate) for the controls. Thus, comparisons between stringent and intermediate glucose targets have not been addressed by adequately powered RCTs.

In attempts to find an optimal blood glucose target, Yamada et al[57] and Yatabe et al[58] performed network meta-analyses of published RCTs comparing insulin regimens in critically ill adults with hyperglycemia. Unlike the standard pairwise meta-analysis, a network meta-analysis has the advantage of comparing the efficacy of more than 2 interventions, using direct and indirect or mixed comparisons for the intervention groups.[59] Using a common comparator, indirect comparisons can examine intervention arms that had no prior direct head-to-head comparisons in clinical trials. The 2 meta-analyses[57,58] divided study groups into 4 interventions based on different blood glucose targets: tight (80–100 mg/dL), moderate (110–140 mg/dL, 110–144 mg/dL), mild (140–180 mg/dL, 144–180 mg/dL), and loose (> 180 mg/dL). Results revealed no significant difference relevant to the mortality risk for any comparison. However, these findings should be interpreted with caution, as the validity of indirect and mixed comparisons is built on the assumption that there are no differences between trials other than the intervention or treatment (in this case, a target blood glucose value), which is clearly a limitation given the methodologic differences of the key trials.

Differences in other glycemic control metrics and diabetes status
The TIR, glycemic variability, preexisting diabetes status, and preadmission glycemic control play important modifying roles on the benefits of stringent insulin therapy on mortality outcomes, as discussed above. Apart from the Glucontrol trial that reported TIR and glycemic variability,[16] earlier RCTs based comparisons solely on the blood glucose target, which can potentially confound the results.

Differences in methods of glucose measurement
Inaccurate glucose measurement can lead to insulin dosing errors that can cause hypoglycemia. A review article by Inoue et al[60] found that the first Leuven trial[13] used precise blood-gas analyzers, which are more accurate than traditional point-of-care capillary glucose meters. Subsequent trials—medical Leuven,[14] VISEP,[15] Glucontrol,[16] and NICE-SUGAR[17]—used both arterial and capillary analyzers. The point-of-care glucose meters, while having the advantage of ease of use and rapidity, can be affected by anemia,[61] arterial oxygen tension,[62]

Enthusiasm for strict glycemic control was diminished by results from the NICE-SUGAR study

TABLE 1

Recommendations for blood glucose targets for insulin therapy

Professional society	Year	Recommendations
American Diabetes Association[70]	2021	Insulin therapy should be initiated for treatment of persistent hyperglycemia at a threshold 180 mg/dL.
		Once insulin therapy is started, a target blood glucose range of 140–180 mg/dL is recommended for most critically ill patients.
		More stringent goals, such as 110–140 mg/dL, may be appropriate for selected patients if they can be achieved without significant hypoglycemia.
American College of Physicians[71]	2014	Best practice advice 1: Clinicians should target a blood glucose level of 140–200 mg/dL if insulin therapy is used in surgical or medical patients in the intensive care unit.
		Best practice advice 2: Clinicians should avoid targets < 140 mg/dL because harms are likely to increase with lower glood glucose targets.
Society of Critical Care Medicine[72]	2012	A blood glucose level ≥ 150 mg/dL should trigger initiation of insulin therapy, titrated to keep the level < 150 mg/dL for most adult intensive care unit patients, and to maintain blood glucose values absolutely < 180 mg/dL using a protocol that achieves a low rate of hypoglycemia (blood glucose ≤ 70 mg/dL) despite limited impact on patient mortality.

We hypothesize that a standardized computer-based insulin protocol can minimize interclinician variability and enhance compliance of the treating team

and the patient's medications,[63] especially given the outdated glucose monitors used in these studies.

Continuous glucose monitoring was not available at the time of the initial RCTs. This technology can offer a significant benefit in improving glycemic control,[64,65] using a wide range of metrics such as TIR, time above range, and time below range, which can provide more precise data on glycemic control than conventional intermittent glucose monitoring.[66] Clinical trials evaluating continuous glucose monitoring in hospitalized patients have been mainly confined to the intravascular route,[67,68] and thus, minimally invasive devices have not been thoroughly studied. We believe that use of continuous glucose monitoring can probably provide more objective information on optimal blood glucose targets for future trials, especially when combined with validated computerized insulin protocols.

Differences in insulin administration protocols

The Leuven trials[13,14] and VISEP[15] used a strict algorithm for insulin titration. In contrast, the NICE-SUGAR[17] trial protocol was less standardized, allowing physicians to use their discretion and thus introducing interclinician variability in insulin administration, which can jeopardize TIR and increase glycemic variability.

In a multicenter international RCT published in 2017,[69] a clinically validated computer algorithm for insulin infusion was compared with a nurse-driven protocol. Results showed that the computerized protocol achieved higher quality of blood glucose control as evidenced by lower hypoglycemia rates, high TIR, and low glycemic variability than the nurse-driven protocol. We hypothesize that a standardized computer-based insulin protocol can minimize interclinician variability and enhance compliance of the treating team.

■ WHAT DO MEDICAL SOCIETIES RECOMMEND?

Several medical societies have guidelines on blood glucose targets for insulin therapy (**Table 1**).[70–72]

The American Diabetes Association,[70] citing the NICE-SUGAR trial results,[17] recommends that insulin therapy be started for persistent hyperglycemia (> 180 mg/dL) with a target glucose range of 140 to 180 mg/dL in most critically ill patients, and notes that more aggressive goals (110–140 mg/dL) may be more appropriate for specific groups of patients (eg, postsurgical patients or patients with cardiac surgery) if these targets can be achieved without significant hypoglycemia. On the other hand, glucose concentrations above 180 mg/dL may be acceptable in terminally ill patients, in patients with severe comorbid conditions, and in inpatient care settings where frequent glucose monitoring or close nursing supervision is not feasible.[70]

The American College of Physicians[71] recommends targeting a blood glucose range of 140 to 200 mg/dL in surgical and medical ICU patients, avoiding targets below 140 mg/dL due to likely increased harm.

Guidelines of the Society of Critical Care Medicine[72] suggest a blood glucose value of 150 mg/dL or greater to trigger the use of insulin therapy, with the goal of maintaining a glucose level below 150 mg/dL for most critically ill patients and maintaining the glucose level absolutely below 180 mg/dL.

■ TAKE-HOME MESSAGE

The optimal blood glucose target for patients in the ICU remains unknown, but a target of 140 to 180 mg/dL is the most acceptable for critically ill patients. We believe that future studies investigating the optimal target for ICU patients should do the following:

- Include other glycemic metrics
- Take into account preadmission diabetes diagnosis and premorbid glycemic control (based on the HbA1c)
- Use accurate blood glucose monitoring methods combined with a standardized validated insulin algorithm.

This will enable studies to shed light on appropriate glycemic targets and may lead to a more individualized approach for the critically ill patient rather than a universal approach. ■

■ DISCLOSURES

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Capsule endoscopy in gastrointestinal disease: Evaluation, diagnosis, and treatment

ABSTRACT

Capsule endoscopy, also known as wireless capsule endoscopy or video capsule endoscopy, is a noninvasive procedure that uses a swallowed capsule-shaped miniature camera for direct visual and diagnostic evaluation of gastrointestinal (GI) disease. Although originally intended as a tool to examine the small intestine, which is mostly beyond the reach of conventional endoscopy, capsule endoscopy is now also being used to examine the entire length of the GI tract.

KEY POINTS

Currently, capsule endoscopy is useful in diagnosing occult GI bleeding in the small bowel, celiac disease, Crohn disease, small-bowel tumors, and nonsteroidal anti-inflammatory drug-induced enteropathy in the small and large bowel.

Capsule endoscopy is not recommended as a routine screening tool for colon cancer.

Sedatives and pain medications are not required for capsule endoscopy, essential medications need not be withheld on the day of studies, and patients can go about their usual activities of daily living.

A significant drawback of capsule endoscopy is the inability to fully control the movement of the device, perform suction, or obtain a biopsy.

In the future, endoscopic capsules will allow obtaining biopsy samples, analyzing and coagulating lesions, and even treating them.

CAPSULE ENDOSCOPY WAS CONCEIVED as a tool to examine the small intestine, which is beyond the reach of conventional endoscopes, but it is now being used to diagnose and monitor diseases throughout the entire gastrointestinal (GI) tract. Although conventional endoscopy remains the gold standard for looking at the esophagus and stomach proximally and the colon distally, capsule endoscopy has the advantage of being noninvasive.

Thus, although capsule endoscopy is mainly used to look for sources of obscure bleeding in the small bowel, it is also being used in the evaluation and diagnosis of celiac disease, Crohn disease, small-bowel tumors, nonsteroidal anti-inflammatory drug (NSAID)-induced enteropathy, and esophageal, gastric, and large-bowel diseases. It is also used in monitoring treatment outcomes. A limitation of current capsules is that they cannot perform inflation, suction, or biopsy.

In this article, we review the current role of capsule endoscopy in the evaluation, diagnosis, and treatment of GI disease in adults.

■ CHALLENGES OF EXAMINING THE SMALL INTESTINE

The GI tract is about 30 feet (9 m) long from mouth to anus. The small intestine makes up about two-thirds of the entire tract and is subject to diseases such as bleeding, ulcers, malabsorption, inflammation, strictures, polyps, and cancer.

The GI tract can be examined indirectly by radiologic studies such as contrast barium swallow, small-bowel follow-through, and barium enema, but these offer no opportunity to obtain biopsy specimens or perform treat-

ment. On the other hand, fiberoptic upper endoscopy, colonoscopy, and enteroscopy ("push enteroscopy," for part of the small intestine) offer direct visualization.

But it is not possible to examine the entire small intestine with routine endoscopy. Single-balloon, double-balloon, and spiral endoscopes have been invented for this purpose, but it can be a challenge even with antegrade and retrograde balloon enteroscopic techniques. Further, these techniques usually require general anesthesia, long procedure times, advanced skills, and fluoroscopy, which exposes the patient to radiation. Therefore, the need to directly visualize the entire small intestine led to the birth of the capsule endoscope.

■ INVENTION OF THE CAPSULE ENDOSCOPE

Capsule endoscopy began in 1981, when Gavriel Iddan, an engineer from the Israeli Defense Ministry, collaborated with gastroenterologist Eitan Scapa while both were on sabbatical studies in Boston, MA. Further collaboration with Paul Swain, an English gastroenterologist, and Shuji Nakamura's invention of the light-emitting diode as a light source for optical devices (for which he won the Nobel Prize in 2014) led to further refinement of the capsule endoscope for evaluating small-bowel disease.[1]

The basic components of capsule endoscopy are the following:

- The capsule, containing one or more cameras, a light source, battery, and transmitter
- In most systems, sensors placed on the surface of the patient's abdomen similar to electrocardiographic leads on the chest, or contained in a belt worn by the patient that is connected to a recorder
- Software to process and display images to be reviewed by a physician.

Devices have improved over the years, with wider fields of view (140°–360°), more cameras (up to 4 in some models), longer battery life, and variable frame rates so that the capsule can take as few as 2 frames (pictures) per second when traveling slowly through the stomach and intestines and up to 35 per second when traveling quickly through the distal esophagus.

In its journey through the GI tract, the capsule can acquire 50,000 to 60,000 images,

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TABLE 1

Current indications for capsule endoscopy in adults

In the small bowel
Finding the source of obscure gastrointestinal bleeding

Evaluating iron-deficiency anemia in which a gastrointestinal source is suspected and upper and lower endoscopy are negative

Crohn disease: diagnosis and surveillance of disease activity

Celiac disease: diagnosis and evaluation of refractory disease

Assessing mucosal healing

Surveillance of polyposis syndrome

Diagnosing small-bowel tumors

Detecting arteriovenous malformation

Evaluating drug-induced injury, eg, from nonsteroidal anti-inflammatory drugs

In the esophagus[a]
Diagnosing Barrett esophagus

Diagnosing variceal bleeding

In the colon
Screening in cases of incomplete colonoscopy

Screening in patients at high risk from sedation, pain medications, and anesthetics

[a] Capsule endoscopy is used if upper-gastrointestinal endoscopy cannot be tolerated.

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which can take from 30 to 90 minutes to review. Software allows for a quick preliminary review and single or group viewing of 2 or 4 images. Real-time viewing is particularly important in detecting active GI bleeding.

Detailed reports of the procedure should be generated and at a minimum include patient demographic information, the indication for the procedure, type of device used, the diagnosis based on findings, and management recommendations.

■ EXPANDING ROLES FOR CAPSULE ENDOSCOPY

Current indications for capsule endoscopy of the small intestine in adults (**Table 1**) include diagnosis of obscure GI bleeding and chronic iron-deficiency anemia, small-bowel tumors, and NSAID-induced enteropathy, and diagnosis and assessment of treatment outcomes

TABLE 2

Contraindications to capsule endoscopy for small-bowel disease

Cognitive disorders in which the patient may not follow instructions for the procedure, resulting in biting the capsule, damaging teeth or the capsule

Gastroparesis (but the capsule can be placed distally with an endoscope)

Esophageal stricture or swallowing disorders (but the capsule can be placed endoscopically)

Zenker diverticulum of the esophagus

Partial or intermittent small-bowel obstruction, chronic adhesions

History of strictures from inflammatory bowel disease

Pregnancy

Active Crohn disease

Left ventricular assist devices (but pacemakers and automatic implantable cardiac defibrillators are no longer contraindicated)

Numerous diverticula

Advantages of capsule endoscopy: it is noninvasive, does not require sedation, and does not require essential medications to be withheld on the day of the procedure

of celiac and Crohn disease. It is also used in screening for and surveillance of familial adenomatous polyposis syndrome, Barrett esophagus, and esophageal varices. In addition, there is interest in using capsule endoscopy to manage acute GI bleeding, both in the emergency department to help in deciding whether the patient needs to be admitted to the hospital, and after admission to the hospital.

In the large bowel, capsule endoscopy is indicated only in cases when colonoscopy was started but could not be completed and in patients at moderate to high risk from sedation or severe cardiopulmonary conditions. It is not for routine colon cancer screening.

Capsule endoscopy has multiple contraindications that include cognitive impairment, risk factors for capsule retention, and active Crohn disease (**Table 2**). It should be used with caution in patients who have cardiac implantable electronic devices such as pacemakers, automatic implantable cardiac defibrillators, or left ventricular assist devices. These devices can possibly cause electromagnetic interference that can produce image artifacts, but the capsule does not affect the cardiac device.[2]

Chief advantages of capsule endoscopy are that it is noninvasive, does not require sedation, and does not require that essential medications be withheld on the day of the procedure (**Table 3**). Images are of high quality, with 1:8-fold magnification, which can show individual villi (**Figure 1a**).[3] A drawback is the lack of suctioning, flushing, or biopsy capability, and therapeutic interventions are not possible with current devices. In addition, results may be prone to overinterpretation by readers.[4] Its learning curve is steep: accuracy is higher in diagnosing prominent intraluminal lesions, active bleeding ulcers, tumors, and stenosis, and lower with subtle lesions, erosions, angiodysplasias (also called angioectasias), and diverticula (**Figure 1b**).[3,5]

A consensus committee of the Canadian Association of Gastroenterology has offered a list of recommendations for and against capsule endoscopy for various conditions (**Table 4**).[6]

■ CAPSULE ENDOSCOPY IN SMALL-BOWEL DISEASE

Capsule endoscopy has evolved to the point that different capsules are available to examine different parts of the GI tract. Capsules optimized for the small intestine include the following:

PillCam SB3 (Given Imaging), a third-generation device that weighs less than 4 g, measures 11 mm by 26 mm, has higher resolution than earlier models, and has variable frame rates—up to 6 frames per second when going through fast areas such as the duodenum, and down to 2 frames per second when stationary or moving slowly. It also has a blood detector to help identify sites of bleeding.

Olympus Endocapsule 10 (Olympus), which measures 11 mm by 26 mm, weighs 3.3 g, has a 160-degree wide-view camera with 4 lights, takes 2 frames per second, takes higher-resolution pictures for better clarity, and provides software-mediated 3-dimensional views of the small intestine. Both PillCam SB3 and Endocapsule 10 have battery lives of about 8 to 12 hours.

Micro Cam (IntroMedic) and **OMOM** (Jinshan Science & Technology) are other capsule endoscopes used worldwide.

All small-bowel capsule endoscopes have comparable diagnostic yields.[7]

Obscure gastrointestinal bleeding and chronic iron-deficiency anemia

GI bleeding is called obscure when traditional upper and lower endoscopy and radiography fail to find the source. It is the most common reason capsule endoscopy is performed. Of note, GI bleeding can be both obscure and overt, ie, manifested clinically by hematemesis (vomiting blood), hematochezia (blood in stool), and melena (black stool).

Bleeding from the small bowel is uncommon, accounting for only 5% to 10% of cases of GI bleeding, but it is responsible for up to 80% of cases of obscure GI bleeding and can manifest as iron-deficiency anemia.[8] Most of these lesions are angiodysplasias (**Figure 1c**),[3] which are tufts of abnormal vessels caused by abnormal connections between arteries and veins that bypass the capillary system. They are small, bleed intermittently, and share similarities with other angiodysplasias that have never bled.[9–11]

In a study of 911 patients who underwent evaluation for obscure GI bleeding,[11] capsule endoscopy found the source of the obscure bleeding in 509 (56%) of the 911 patients: 203 patients (22%) had small-bowel disease, 88 (10%) had ulcerations, 70 (8%) had tumors, 24 (3%) had varices, and 73 (8%) had blood in the small bowel with no lesions identified. Lesions of the esophagus or stomach were found in 97 patients (11%).[11]

A systematic review of 22,840 procedures in 227 studies of capsule endoscopy[12] found a detection rate of 61% for obscure small-bowel bleeding. Angiodysplasia was the most common cause.

The timing of capsule endoscopy is important in detecting the source of obscure GI bleeding, as the detection rate decreases with time: 55% within 1 day of admission vs 18% 5 days after admission.[13]

The cause of obscure GI bleeding sometimes goes undiagnosed even with capsule endoscopy. But the chances of rebleeding in such cases appears to be low and does not warrant further invasive investigations.[14]

Celiac disease

Celiac disease is an autoimmune enteropathy characterized by an immunologic response to gluten, which is ubiquitous in food and addi-

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TABLE 3

Advantages of capsule endoscopy

Can directly visualize areas of gastrointestinal tract not easily reachable with fiberoptic endoscopy

Convenient for patients, with no loss of work hours

No bowel preparation needed for the most upper-gastrointestinal studies

No need to withhold crucial medications

Minimal to no fasting

Inexpensive

No sedation or pain medications needed

No restriction for cardiopulmonary conditions (except concerns for cardiac devices)

Fewer complications such as bleeding or perforation

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tives; it usually responds to a gluten-free diet. Diagnosis relies on symptoms (eg, chronic diarrhea, bloating, abdominal discomfort), characteristic biomarkers, histologic analysis, and response to a gluten-free diet. Screening tests include tissue transglutaminase antibodies and deamidated gliadin peptide antibodies.

The diagnostic test of choice is upper-GI endoscopy with duodenal biopsy. Celiac disease causes architectural changes in the villi, and villous atrophy is common.[15–17] Capsule endoscopy can show villous atrophy in its magnified images. However, villous atrophy can also be seen in conditions such as Crohn disease, lymphoma, amyloidosis, human immunodeficiency virus infection, food allergies, drugs, and chemotherapy.[18]

Capsule endoscopy is indicated in patients who have positive serology or symptoms suggestive of celiac disease but are unable or unwilling to undergo routine upper endoscopy. It is also indicated in patients with normal duodenal histology to identify distal small-bowel lesions. In patients with celiac disease, it helps detect serious complications such as ulcerative jejunoileitis, celiac-associated lymphoma, and adenocarcinoma, and can be used to monitor unexplained symptoms due to inadvertent gluten use, which is seen in about 48% of patients with nonresponsive celiac disease.[19,20]

Capsule endoscopy is also of value when

Obscure gastrointestinal bleeding is the most common reason capsule endoscopy is performed

Figure 1. Capsule endoscopy of the small bowel. A, normal; B, diverticula; C, angiodysplasia; D, erosions of Crohn disease; E, a 10-mm pedunculated polyp; and F, ulcerative colitis.

Capsule endoscopy can detect Crohn disease through 3 findings: mucosal inflammation, disease extension, and strictures

clinical symptoms are highly suspicious for celiac disease despite negative serology, as is seen in 5% of patients.[19]

Crohn disease

Crohn disease is an inflammatory bowel disease that can affect any part of the GI tract from the mouth to the anus. About 50% of patients have disease in the colon and terminal ileum, 30% in the small bowel, and 20% in the colon only.[21] The disease is complicated by fistulas, strictures, obstruction, and risk of colonic malignancies. The diagnosis is based on clinical, biochemical, radiologic, histologic, and endoscopic findings.

Characteristic symptoms of Crohn disease include diarrhea or abdominal pain for more than 6 weeks, low-grade fever, weight loss, and fatigue. Laboratory signs include elevated C-reactive protein, elevated erythrocyte sedimentation rate, elevated fecal calprotectin, anemia, and hypoalbuminemia.[22]

Computed tomographic (CT) enterog-

raphy with small-bowel follow-through and magnetic resonance enterography can aid in determining the location and extent of Crohn disease. The characteristic findings include segmental mural hyperenhancement, wall-thickening, intramural edema, strictures, and ulcerations. But direct ileocolonoscopy remains the gold standard because it directly visualizes the intestinal mucosa and can be used to obtain a biopsy. Crohn disease is suggested endoscopically by mucosal inflammation, ulceration (linear or aphthous), cobblestone appearance of the mucosa, and stenosis.

Capsule endoscopy can detect Crohn disease through 3 findings: mucosal inflammation, disease extension, and strictures (**Figure 1d**).[3] Difficulty in describing the lesions with capsule endoscopy has led to the development of 2 scoring systems, the Lewis score[23] and the Capsule Endoscopy Crohn's Disease Activity Index.[24]

Capsule endoscopy can detect disease in the terminal ileum with a sensitivity approach-

TABLE 4

Canadian Association of Gastroenterology consensus recommendations for and against capsule endoscopy[a]

For gastrointestinal bleeding, capsule endoscopy is recommended:

In patients with documented overt gastrointestinal (GI) bleeding (excluding hematemesis and negative findings on high-quality upper-GI endoscopy and colonoscopy)

As soon as possible in patients with an overt, obscure bleeding episode

Possibly as part of a repeat study (with endoscopy or colonoscopy) in patients with previous negative capsule endoscopy results who continue to have obscure bleeding

In selected patients with suspected obscure GI bleeding and unexplained mild chronic iron-deficiency anemia

For celiac disease, capsule endoscopy is recommended:

In patients with unexplained symptoms despite treatment and appropriate investigations

… But capsule endoscopy is discouraged:

To make a diagnosis in patients with suspected celiac disease

For Crohn disease, capsule endoscopy is recommended:

In patients presenting with clinical features consistent with Crohn disease and negative ileocolonoscopy and imaging studies

In patients with Crohn disease and clinical features unexplained by ileocolonoscopy or imaging studies

In patients with Crohn disease, when the assessment of small-bowel mucosal healing (beyond the reach of ileocolonoscopy) is needed (conditional recommendation)

In patients with a suspected small-bowel recurrence of Crohn disease after colectomy, undiagnosed by ileocolonoscopy or imaging studies

For polyposis, capsule endoscopy is recommended:

For ongoing surveillance in patients with polyposis syndromes who require small-bowel studies (conditional recommendation)

For colon studies, capsule endoscopy is discouraged:

As a routine substitute for colonoscopy

As a substitute for colonoscopy in patients with inflammatory bowel disease to assess the extent and severity of the disease

[a]The strength of these recommendations is strong, except for the 2 conditional recommendations noted. However, the quality of evidence is low or very low for all.

Based on information in reference 6.

ing 100%, superior to that of CT enterography or magnetic resonance enterography,[25] and it can detect jejunal lesions, which have a high risk of relapse.[26]

Therefore, capsule endoscopy is recommended in patients with known, suspected, or relapsed Crohn disease with unexplained symptoms when ileocolonoscopy and imaging studies are negative or when reassessment is beyond the reach of ileocolonoscopy. It is also

of value in Crohn disease recurrence or progression after small-bowel colectomy.[6]

Small-bowel tumors

The small bowel is the site of 2% of all gastrointestinal tumors and 10% of occult gastrointestinal bleeding. Benign tumors include leiomyoma, adenoma, lipoma, and hemangioma, while malignant lesions include adenocarcinoma, neuroendocrine tumors, gastrointesti-

nal stromal tumors, and lymphoma. The most common sites in the small bowel are the ileum, followed by the duodenum and jejunum.[27] Signs of small-bowel tumors on capsule endoscopy include protruding masses, mucosal disruption, irregular surfaces, discolored areas, and white villi. Capsule endoscopy is less sensitive in detecting small-bowel tumors in the duodenum because of anatomic variability (bulges can be mistaken for masses) and rapid transit of the capsule (preventing adequate visualization). Also, the ampulla of Vater has a higher frequency of malignant transformation, but capsule endoscopy visualizes it poorly and cannot distinguish adenomas from anatomic variations around that site.[28]

Intestinal polyposis syndromes are rare and include familial adenomatous polyposis and hamartomatous polyposis syndromes such as Peutz-Jeghers syndrome. When intestinal polyposis syndromes are diagnosed early, outcomes are better with surveillance, and capsule endoscopy can be very useful in this function, as it is noninvasive and obtains images of the entire small intestine.[29,30]

NSAID-induced enteropathy

Adverse effects of NSAIDs include abdominal pain, nausea, indigestion, bleeding, constipation, and abdominal distention. The broad spectrum of pathology of NSAID-induced enteropathy includes petechiae, reddened folds, denuded mucosa, mucosal breaks, angiodysplasias, and strictures from chronic use. Multiple ulcers and lesions are common with both acute and chronic NSAID use, even with low doses and enteric-coated preparations.

In a study in which 40 healthy volunteers underwent capsule endoscopy at baseline and then took the NSAID diclofenac for 2 weeks, repeat capsule endoscopy showed new lesions in 27 (68%).[31]

There are no biomarkers of NSAID-induced enteropathy. The diagnosis is based on a history of NSAID use in the previous month, an endoscopic finding of mucosal damage, and improvement of clinical course after stopping the drug in the absence of other inflammatory bowel diseases. Findings on capsule endoscopy include ulcers, erosions, scar formations, luminal stenosis, and diaphragmatic disease of the intestine (characterized by multiple thin,

concentric, diaphragm-like strictures in the large and small intestine, which are pathognomonic of NSAID damage).

Evaluation of chronic abdominal pain and diarrhea

Chronic abdominal pain and diarrhea are common reasons for healthcare visits and are mostly caused by irritable bowel syndrome or functional dyspepsia.[32] The role of capsule endoscopy of the small bowel in evaluating chronic abdominal pain and diarrhea was highlighted in a meta-analysis of 21 studies in 1,520 patients by Xue et al.[33] The pooled diagnostic yield was 21%, but in those patients with known underlying inflammatory conditions the yield was 78%.

Biomarkers of inflammation such as erythrocyte sedimentation rate and C-reactive protein increase the yield of capsule endoscopy in finding the cause of chronic abdominal pain and diarrhea.[34] Capsule endoscopy is therefore not recommended in the evaluation of patients who have chronic abdominal pain or diarrhea but no supportive positive biomarkers such as C-reactive protein.

Infiltrative diseases such as lymphoma, adenocarcinoma, amyloidosis, or sarcoidosis have no pathognomonic features on capsule endoscopy, and tissue biopsies are necessary to diagnose them.

■ CAPSULE ENDOSCOPY OF THE ESOPHAGUS AND STOMACH

Neoplastic and nonneoplastic diseases in the upper-GI tract have been evaluated with barium studies, fluoroscopy, CT, and magnetic resonance imaging. Conventional upper-GI endoscopy remains the diagnostic tool of choice in evaluating these diseases, and the yield is increased with the use of endoscopic ultrasonography. While capsule endoscopy is noninvasive and appeared attractive, earlier capsule devices could not adequately visualize the distal esophagus because they moved through it too quickly. This has been improved with newer capsule devices such as the following:

PillCam UGI (Medtronic) has a battery life of 90 minutes, a variable frame rate of 1 to 35 frames per second, and 2 cameras at each end.

CapsoCam (CapsoVision) has 4 cameras

NSAIDs can cause ulcers even with low doses, enteric coating, and short-term use

to provide 360° views, a battery life of 15 hours, and an embedded recorder that eliminates the need for external receiver equipment. The patient retrieves the capsule from the stool with a magnetic wand supplied in a special kit and brings or mails it back to the clinic to be uploaded and interpreted.[35]

Both devices are used to evaluate the esophagus, stomach, and small bowel.

Capsule endoscopy is used in diagnosing various diseases in the esophagus, such as ulcers, varices, and Barrett esophagus, which is a risk factor for esophageal cancer if left untreated. However, although capsule endoscopy is useful in screening for Barrett esophagus, it is not cost-effective in diagnosing and treating it compared with direct visualization with fiberoptic endoscopy.[36]

The role of capsule endoscopy in diagnosing gastric lesions is limited because of the large surface area of the stomach and the inability to control the capsule's movements as it tumbles, even with tedious patient positional strategies.

Esophageal varices and other bleeding complications
Esophageal varices and bleeding are complications of portal hypertension and decompensated liver disease. Traditional evaluation of varices is with fiberoptic endoscopy, which allows for concurrent treatment with ligation, banding, and sclerotherapy.

The potential role of capsule endoscopy in managing varices was noted in a meta-analysis of 1,328 patients.[37] The diagnostic accuracy was 90%, pooled sensitivity 83%, and specificity 85%. The authors concluded that capsule endoscopy could not replace upper endoscopy as the initial procedure of choice for patients with varices or variceal bleeding, but that it may have a role if patients decline or cannot undergo upper-GI endoscopy.

Capsule endoscopy in the emergency department
Capsule endoscopy has been studied in patients with acute upper-GI bleeding in the emergency department to determine the need for hospital admission. In a study of 71 patients,[38] 30 (81%) of the 37 patients initially evaluated with capsule endoscopy were discharged from the emergency department, while all patients who were not evaluated with capsule endoscopy were admitted to the hospital. Rates of recurrent bleeding and death at 30 days were similar between the 2 groups

These findings have significant cost implications and suggest that capsule endoscopy may help screen patients with GI bleeding before they are admitted to the hospital. Although it increases the length of stay in the emergency department, it reduces overall hospital costs by decreasing hospital admissions and length of stay in the hospital.

Capsule endoscopy is also being used to look for the source of bleeding after admission to the hospital. A randomized trial[39] in patients admitted to the hospital because of GI bleeding without hematemesis found a 64% detection rate of the source of bleeding with early capsule endoscopy compared with 31% with routine care (standard direct upper endoscopy followed later by other studies). There were no differences in mortality or rebleeding rates between the 2 groups after discharge. However, early capsule endoscopy detected more vascular lesions such as angiodysplasias (19% compared with 4.4% in the routine-care group). Angiodysplasias are characteristically small, bleed intermittently, and do not leave any mucosal footprints of recent bleeding, and those lesions that bleed have a higher rate of rebleeding.[39]

■ CAPSULE ENDOSCOPY OF THE COLON
Colonic capsule endoscopes include the following:

PillCam Colon (Given Imaging) has 2 cameras, one at each end. It is about 5 mm longer than the small-bowel capsule, guaranteeing that the entire surface of the colon is examined with a wide angle of view of 172° per camera. The capsule frame rate is adjustable, from 4 frames per second to 35 frames per second, and can take up to 30,000 pictures before the battery runs out. It has 2 approved indications from the US Food and Drug Administration. One indication is for incomplete colonoscopy, which occurs in about 5% of the 14 million colonoscopies each year. The other indication is detection of colon polyps in patients with evidence of lower-GI bleeding in whom colonoscopy or moderate sedation

Earlier devices could not evaluate the esophagus because they moved through it too quickly

would pose major risks, but in whom colonoscopy can still be tolerated if a clinically significant abnormality is found.

PillCam Crohn's Capsule has dedicated rapid software and the ability to detect subtle mucosal lesions. The small bowel is divided into 3 segments (tertiles) and scored using the Lewis score.[23] The left and right colon are similarly scored for severity and extent of disease, strictures, and response to treatment.

Colorectal cancer
Colorectal cancer is the third most common cause of cancer-related death in men (after lung and prostate cancer) and also the third most common cause in women (after lung and breast cancer). About 148,000 new cases are diagnosed yearly, 105,000 in the colon and 43,000 in the rectum.[40]

When colorectal cancer is diagnosed at an early stage, the 5-year survival rate is 90%. Screening tools include flexible sigmoidoscopy, CT colonography, and fecal testing, but colonoscopy remains the gold standard diagnostic test, with its ability to survey the entire colon, obtain tissue biopsies, and remove polyps. Patients often put off or avoid colonoscopy because they perceive it to be invasive, embarrassing, and uncomfortable, and because it requires long bowel preparation, sedation, and often pain medication, and because it poses risks of perforation, bleeding, and cardiopulmonary complications.

CT colonoscopy (virtual colonoscopy) is an outpatient imaging procedure that can take from 30 to 60 minutes and requires air or carbon dioxide inflation of the colon for optimal visualization of colonic mucosa. It does not require anesthesia. However, traditional colonoscopy is needed if a lesion is found or if incidental findings warrant further testing, and it exposes the patient to ionizing radiation.

Capsule endoscopy is less invasive. Although sedation is not needed, the colonic cleansing preparation must be close to perfect to provide excellent images since it has no suctioning or flushing capability. Bowel preparation with 4 L of polyethylene glycol solution in split doses in the evening and morning before the procedure or with a low-volume sodium phosphate agent is sometimes employed for better preparation and for enhanced movement of the device.

Colonic capsule endoscopy was used for polyp detection in a prospective study of 884 patients without symptoms who underwent this procedure followed by conventional colonoscopy. Capsule endoscopy had a sensitivity of 81% and a specificity of 93% for polyps 6 mm or larger, and a sensitivity of 80% and specificity of 97% for polyps 10 mm or larger (**Figure 1e**).[3] Serrated polyps accounted for 25% of missed polyp diagnoses.[41]

Other uses
In a study of cases of incomplete colonoscopy in which capsule endoscopy was done the same day,[42] capsule endoscopy detected additional significant findings in 36% of cases. However, performing capsule endoscopy the same day can be logistically difficult.

In patients with ulcerative colitis (**Figure 1f**),[3] capsule endoscopy underestimates the amount of disease involvement in the large intestine, and colonoscopy is still the gold standard with its ability to obtain tissue for analysis.[3]

Recommendations
Capsule endoscopy should not be used to screen for or diagnose colon cancer in the general population, and especially not in those with a family history of colon cancer or alarm symptoms of anemia, bleeding, or weight loss, in whom the risk of malignancy is 5 to 10 times greater (**Table 4**).[6]

■ PATIENT PREPARATION FOR CAPSULE ENDOSCOPY

Iron supplements that can discolor the mucosa should be stopped at least 7 days before the procedure, and patients should generally fast for 12 hours before the procedure.

Capsule endoscopy can be done with or without laxatives for small-bowel studies, but drinking 1 gallon (4 L) of a polyethylene glycol solution (eg, Miralax) appears to allow for higher-quality images. Other strategies to improve image quality include simethicone to reduce bubbles and N-acetylcysteine to break up mucus. For large-bowel studies, as mentioned above, the cleansing preparations must be close to perfect, since the capsule has no suction or flushing capabilities.

Capsule endoscopy should not be used to screen for or diagnose colon cancer in the general population

Routine laboratory testing and radiography are not needed.

Informed consent must be obtained and should detail the benefits of the procedure and possible complications (see below).

Sensor arrays are contained in a belt worn by the patient or are placed as 8 leads similar to electrocardiographic leads, attached by adhesive pads to the abdomen and connected to a recorder worn on a belt.

Removing the capsule from its holder activates it, and it is then swallowed with water. In patients who have difficulty swallowing or had previously retained capsules in the stomach, the capsule can be deployed directly into the small intestine using an upper-GI endoscope.

Patients can start to take clear liquids 2 hours after swallowing the capsule, and medications after 4 hours. They can go about their activities of daily living, and the belt and recording devices are removed after 8 hours to be reviewed.

■ COMPLICATIONS OF CAPSULE ENDOSCOPY

Capsule endoscopy is relatively safe, with rare complications.

Capsule retention, ie, the capsule getting stuck somewhere along the GI tract, is the most common complication and occurs in about 2% of all studies.[43] Normally, the capsule is expelled within 3 to 7 days, and therefore capsule retention is defined as occurring when the capsule remains inside for a minimum of 2 weeks.

Most cases of retention are asymptomatic. Risk factors include small-bowel obstruction, strictures, history of small-bowel surgery, abdominal or pelvic radiation therapy, and inflammatory bowel disease (**Table 5**).

Since radiography and magnetic resonance imaging cannot be relied on to detect significant obstructions, Medtronic has developed a dissolvable "patency capsule" to be given to patients before they undergo capsule endoscopy, to try to identify any areas where the video capsule could get stuck. The patency capsule contains a radiofrequency identifier chip covered with cellophane-filled barium and lactose, with time-released biodegradable plugs at both ends that fully dissolve in 40 to 80 hours if the capsule gets stuck in the GI tract. Passage of the retention capsule by 30 hours suggests no obstruction to

TABLE 5
Risk factors for capsule retention
Crohn disease
Nonsteroidal anti-inflammatory drug-induced strictures
Obstructing tumors of the small and large bowels
Radiation-induced enteritis
Surgical anastomosis stricture
History of adhesions
Enteric tuberculosis
Ulceration in colon
Peptic ulcer with scarring

impede the use of capsule endoscopy.

In a study of 106 patients,[44] all patients who successfully excreted the patency capsule underwent successful capsule endoscopy, and none retained the video capsule.[44]

In treating capsule retention, watchful waiting is suggested, and various radiographic studies may help locate the retained capsule. In patients with inflammatory bowel disease, the use of steroids has facilitated the passage of retained capsules.[45] However, leaving the capsule in for a long time may expose the patient to complications of obstruction, perforation, and capsule fragmentation, and shared decision-making with the patient may be necessary for retrieval after 2 weeks even though passage of an intact capsule has been reported after 4.5 years.[46]

Retained capsules can be retrieved surgically, but this approach is being marginalized by device-assisted enteroscopy, which has proven to be 90% to 100% effective in most cases.[47]

Other complications include battery failure, missed lesions, bowel obstruction, bowel perforation, and aspiration of the capsule into the trachea and bronchial tree.[48]

■ COST-EFFECTIVENESS

The cost-effectiveness of capsule endoscopy is difficult to ascertain and depends on various factors such as region of the country, type of procedure, inpatient vs outpatient setting, insurance coverage, facility fees, physician fees,[49] and effect on length of stay.

Capsule endoscopy is relatively safe, with rare complications

Nevertheless, capsule endoscopy appears to be most cost-effective if performed for a disease-specific indication. For example, in surveillance of Crohn disease, capsule endoscopy proved to be cost-effective in a study by Lobo et al.[50] In another study,[51] the authors projected that early use of capsule endoscopy to assess upper-GI bleeding without hematemesis could lead to earlier hospital discharge, at 0.88 days compared with 1.63 days with standard care.

■ FUTURE CAPSULES WILL DO MORE

Passage of the video capsule depends on the unpredictable and unreliable peristaltic contractility of the GI tract, and so the inability to control and guide the movement of the capsule presents a major challenge. Research is under way to give future capsules the ability to stop, inspect, biopsy, review, tamponade, coagulate, and provide treatment with drug-delivery systems. Devices under study include MACE (Magnetic Activated Soft Capsule Endoscope), NEMO (Nano-based Capsule Endoscopy), and VECTOR (Versatile Endoscopy Capsule for Gastrointestinal Tumor Recognition and Therapy).[52] ■

■ DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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Anemia of chronic kidney disease: Will new agents deliver on their promise?

ABSTRACT

Anemia is a well-known complication of chronic kidney disease, and its treatment remains a challenge. Although erythropoiesis-stimulating agents (ESAs) raise hemoglobin levels, their benefits appear to be limited to decreasing the number of blood transfusions needed and perhaps improving quality of life. The newly developed prolyl hydroxylase inhibitors (PHIs)—agents that increase endogenous erythropoietin production—promise to improve outcomes for patients with anemia of chronic kidney disease. Randomized controlled trials have found these drugs to be at least as effective as ESAs, and the drugs are used in other countries. However, PHIs have yet to be approved in the United States.

KEY POINTS

The approval of the first of the ESAs in 1989 was a turning point in treating anemia of chronic kidney disease, but the only proven benefit of ESAs is reducing the need for blood transfusions.

Of the recently developed PHIs (also known as hypoxia-inducible factor stabilizers), roxadustat is the most studied in phase 2 and 3 randomized control trials.

PHIs seem to be as effective as ESAs in raising hemoglobin levels and potentially more effective in inflammatory states, but there are lingering concerns about their cardiovascular safety.

Anemia is a common complication of chronic kidney disease. Its prevalence increases as the glomerular filtration rate decreases,[1] and most patients with a rate lower than 30 mL/min/1.72 m^2 develop anemia.[2] Older studies linked anemia of kidney disease to numerous complications, including the onset and progression of left ventricular hypertrophy, heart failure, decreased quality of life, faster progression of chronic kidney disease, and death.[3–6]

Subsequently, several randomized controlled trials shed light on the benefits and limitations of iron supplements and erythropoiesis-stimulating agents (ESAs). This allowed the development of iron supplementation and hemoglobin targets. In addition to traditional ESAs, newer therapies have been developed and are now being used in clinical practice.

In this article, we discuss the pathophysiology of anemia of chronic kidney disease, the major clinical trials, and novel therapies.

■ HOW CHRONIC KIDNEY DISEASE LEADS TO ANEMIA

Anemia of chronic kidney disease is multifactorial and can be caused by decreased erythropoietin production by the peritubular interstitial cells of the kidney, higher circulating levels of uremia-induced inhibitors of erythropoietin, shorter red blood cell life span, and relative iron deficiency.[7] However, measuring serum levels of erythropoietin is of no diagnostic utility in pa-

tients with anemia of chronic kidney disease, as there is no clear threshold defining a low value, especially in uremia, which can induce resistance to erythropoietin.[8,9]

Absolute iron deficiency results from decreased iron stores, whereas functional iron deficiency is characterized by sufficient iron stores but inadequate incorporation of iron into erythroid precursors.[10] Hepcidin, a liver peptide and crucial regulator of iron homeostasis, is thought to play a key role in this process. Mobilization of iron into the circulation from enterocytes, iron-recycling macrophages, and hepatocytes requires transport across the cellular membrane by a transporter called ferroportin.[11] Binding of hepcidin to ferroportin degrades the channel and inhibits iron mobilization out of the cell.

Normally, hepcidin levels decrease in conditions such as anemia, absolute iron deficiency, and hypoxia, in which more iron is needed for erythropoiesis. Conditions of systemic inflammation, such as chronic kidney disease, result in elevated hepcidin levels, diminished iron mobilization, and relative iron deficiency.[12,13] The result is less iron available for erythropoiesis, with resistance to the action of ESAs (**Figure 1**).[14–16]

■ ESAs ARE THE MAINSTAY, BUT HAVE LIMITED BENEFIT

Before erythropoietin was discovered, anemia of chronic kidney disease was treated with red blood cell transfusions and androgens. Frequent red blood cell transfusions led to iron overload, transmission of viral infections, and allosensitization to human lymphocyte antigens, with potential adverse effects on transfusion responsiveness and importantly, transplant candidacy and outcomes. Androgen therapy was the only potentially transfusion-sparing option, and it was used in the 1970s.[17]

After approval of the first of the ESAs by the US Food and Drug Administration (FDA) in 1989, studies continued to demonstrate benefits of the drugs. In a study published in 1990, the ESA recombinant human erythropoietin showed promising results, raising hemoglobin levels by more than 5 g/dL and keeping them there after 2 months of therapy in 10 patients on hemodialysis whose mean baseline hemoglobin level was 6.3 g/dL.[18] A year later, a double-blind, randomized placebo-controlled trial in 118 patients on hemodialysis with hemoglobin levels less than 9 g/dL found improvements in quality of life and exercise capacity.[19]

By 2006, ESAs had become the treatment of choice of renal anemia, along with oral and intravenous iron supplementation, and were being given to most patients on dialysis in the United States.[20]

Clinical trials dampen enthusiasm for normalizing hemoglobin levels with ESAs

However, then came 4 randomized controlled trials[21–24] using ESAs to raise hemoglobin levels to higher vs lower target levels in patients with chronic kidney disease, some of whom were on dialysis and some not. Except for reducing the number of transfusions needed and perhaps improving quality of life (the results differed), the trials found no benefits of treating to higher targets, and indeed highlighted higher risks of cardiovascular and cerebrovascular events and worsening of cancer outcomes (**Table 1**).[21–25]
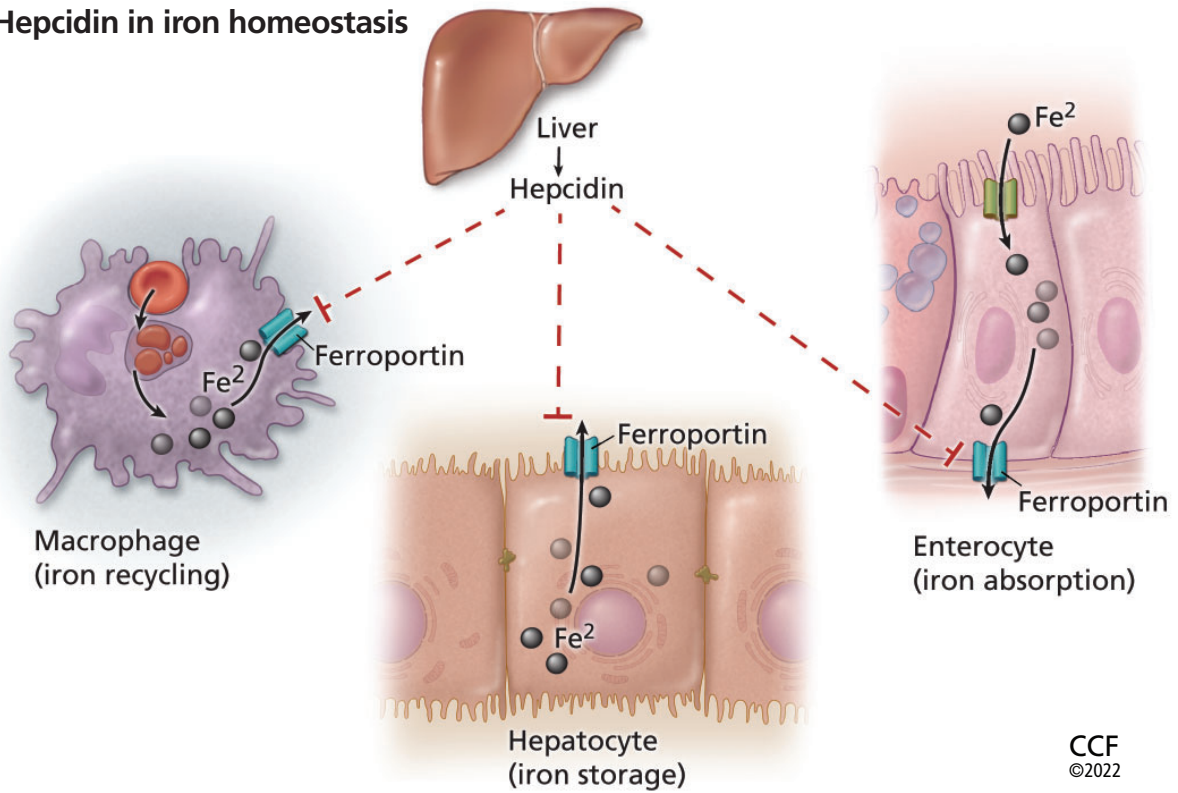
In view of these results, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines[26] strongly advised against trying to raise hemoglobin to normal levels (eg, higher than 13.5 g/dL in men, 12 g/dL in women), instead recommending a target of 10 to 11.5 g/dL in patients with end-stage kidney disease. The guidelines also advised that the decision to start ESAs should be individualized for patients with chronic kidney disease with a hemoglobin level less than 10 g/dL.[26]

In addition, a closer look at the data identified a "hyporesponsive" group in whom ESAs failed to achieve a higher hemoglobin target despite increasing doses. Interestingly, patients who received higher doses of ESAs had a higher rate of adverse events.[27,28] Therefore, the KDIGO guidelines recommend using the lowest ESA doses needed to achieve the hemoglobin goal, realizing the only proven benefit is avoiding transfusions.[29] Other possible benefits (again, the data conflict) include lessening of anemia-related symptoms, higher quality of life,[30–32] and reduction in left ventricular hypertrophy.[33] **Table 2** summarizes the potential risks and benefits of ESA therapy.[18,21–24,29–33]

The KDIGO guidelines strongly advised against trying to raise hemoglobin to normal levels
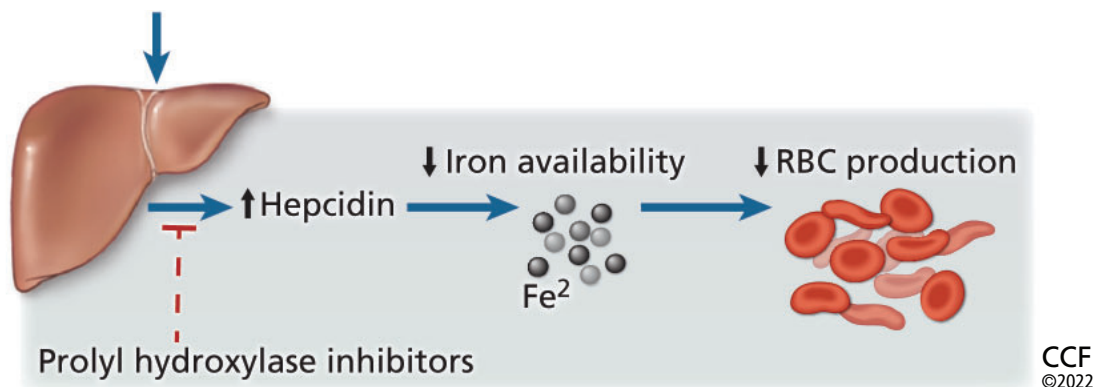
Figure 1. Hepcidin limits erythropoiesis. (A) Hepcidin plays a key role in iron homeostasis. It is produced by the liver and acts to degrade the iron transporter ferroportin, thus preventing release of iron (Fe^2) from enterocytes, hepatocytes, and macrophages into the circulation. (B) In chronic kidney disease, hepcidin levels are elevated as a result of the underlying occult inflammatory state and as a result of decreased renal clearance of hepcidin. This makes less iron available for erythropoiesis and can lead to resistance to erythropoiesis-stimulating agents. Prolyl hydroxylase inhibitors (PHIs) decrease liver production of hepcidin, which may improve iron metabolism and lead to efficient management of anemia of chronic kidney disease. (RBC = red blood cell.)

TABLE 1

Clinical trials of erythropoiesis-stimulating agents to increase hemoglobin to different targets in chronic kidney disease

Trial	Normal HCT[21]	CHOIR[22]	CREATE[23]	TREAT[24]
Population	Patients with chronic heart failure and end-stage kidney disease on dialysis (N = 1,233)	Chronic kidney disease (N = 1,432)	Chronic kidney disease (N = 603)	Chronic kidney disease with diabetes (N = 4,038)
Hemoglobin targets	10 vs 14 g/dL	13.5 vs 11.3 g/dL	> 13 vs 11 g/dL	> 13 vs 9 g/dL
Target achieved?	No	No	Yes	No
Primary outcomes	Time to death or first myocardial infarction	Composite of death, myocardial infarction, hospitalization for chronic heart failure, stroke	Time to first cardiovascular event	Composite of death or a cardiovascular event, or Composite of death or end-stage kidney disease
Results with higher hemoglobin target	Higher risk of primary outcome[a]	Higher risk of primary outcome[b]	Trend toward higher risk of primary outcome (not statistically significant)	No increase or reduction in risk of primary outcome
Other results with higher target	Higher rate of thrombosis		Improved quality of life	Higher rates of stroke and malignancy-associated mortality; less need for blood transfusions

[a] Risk ratio 1.28, 95% confidence interval 1.06–1.56, P = .01.
[b] Hazard ratio 1.34, 95% confidence interval 1.03–1.74, P = .03.

CHOIR = Correction of Hemoglobin and Outcomes in Renal Insufficiency trial; CREATE = Cardiovascular Risk Reduction by Early Anemia Treatment With Epoetin Beta trial; HCT = hematocrit; TREAT = Trial to Reduce Cardiovascular Events With Aranesp Therapy

Commonly used ESAs are recombinant human erythropoietin (epoetin alfa), darbepoetin alfa (which has a longer half-life),[34,35] and a recently approved form of pegylated recombinant human erythropoietin (**Table 3**).[36–39]

ESAs continue to be the mainstay in managing anemia of chronic kidney disease. The newer ESAs were developed by increasing the glycosylation or pegylation of recombinant human erythropoietin to prolong its half-life and affinity for the erythropoietin receptor. However, their mechanism of ac-

tion is essentially the same, and they carry the same potential risks, ie, adverse cardiovascular events, thrombosis, stroke, and poor cancer outcomes.

■ A NEW CLASS OF DRUGS: PROLYL HYDROXYLASE INHIBITORS

The hypoxia-inducible factor (HIF) pathway was a revolutionary discovery, and drugs that target it promise to improve outcomes in diseases that include anemia of chronic kidney disease.

TABLE 2

Potential benefits and risks of erythropoiesis-stimulating agents

Benefits

Higher hemoglobin levels[18]

Decreased blood transfusion needs[29]

Better quality of life[23,30–32]

Reduction in left ventricular hypertrophy[33]

Risks

Cardiovascular events[21,24]

Malignancy-associated mortality[24]

Thromboembolic events[21,24]

Hypertension[21–24]

Hemodialysis vascular-access thrombosis[21]

HIF is a heterodimer consisting of an alpha and a beta subunit. Heterodimerization of the 2 subunits activates transcription of numerous genes and regulates a multitude of biologic and metabolic processes such as angiogenesis, cell growth and differentiation, and erythropoiesis.[40,41] The transcriptional activity of HIF is controlled primarily by its degradation rate.[42]

Stable HIF leads to more erythropoietin

While the beta subunit of HIF is constitutively expressed (ie, it is present all the time), the alpha subunit is regulated by oxygen tension. At normal oxygen levels, the proline residue of HIF alpha is hydroxylated (ie, receives a hydroxyl [OH–] group) by the enzyme prolyl hydroxylase, leading to ubiquitylation (inactivation by binding to ubiquitin) and proteasomal degradation.[43] This impedes formation of alpha-beta heterodimers, preventing erythropoietin transcription. The opposite happens in hypoxic states, in which HIF alpha is no longer degraded, and HIF heterodimers bind to the hypoxia-response elements, increasing erythropoietin transcription.

Prolyl hydroxylase inhibitors (PHIs), also known as HIF stabilizers, prevent hydroxylation of HIF alpha and its subsequent degradation. Thus, they stabilize the HIF alpha-beta

Drugs targeting the hypoxia-inducible factor pathway hold promise to improve outcomes in diseases that include anemia of chronic kidney disease

heterodimer and enhance downstream expression of the erythropoietin gene EPO, leading to increased endogenous erythropoietin production (**Figure 2**).

■ TRIALS OF THE NEW AGENTS IN PATIENTS NOT ON DIALYSIS

In 2015, a phase 2 randomized clinical trial compared an oral PHI (roxadustat) with placebo in patients with anemia of chronic kidney disease not on dialysis who had never received an ESA.[44] An effective hemoglobin increase from baseline (arbitrarily defined as ≥ 1 g/dL) occurred in all 20 of the 20 patients receiving roxadustat 2 mg/kg 2 to 3 times per week compared with 3 (13%) of the 23 patients receiving placebo. Notably, roxadustat raised endogenous erythropoietin and lowered hepcidin levels.

In 2019, in an 18-week, double-blind, randomized, open-label, phase 3 trial in China in 154 patients with anemia of chronic kidney disease who were not on dialysis, those receiving roxadustat had a higher mean hemoglobin level than those receiving placebo after 8 weeks, with maintained efficacy afterwards.[45] In this study, roxadustat reduced cholesterol levels.

In 2020, in the ANDES study,[46] a phase 3 global randomized clinical trial in 916 anemic patients with nondialysis-dependent chronic kidney disease (analyzed by an intention-to-treat model), oral roxadustat given 3 times per week was superior to placebo in hemoglobin correction and maintenance, with the same overall tolerability.

In OLYMPUS,[47] another recent phase 3 randomized clinical trial, in 2,781 patients, roxadustat significantly raised hemoglobin levels and decreased the need for blood transfusions, with a side-effect profile similar to that of placebo.

Additionally, the ALPS study,[48] a phase 3, multicenter, randomized, double-blind, placebo-controlled trial in 594 patients, found that roxadustat was superior to placebo with regard to hemoglobin response rate and change in hemoglobin level from baseline, with a comparable adverse-event profile.

A pooled analysis of the ANDES, OLYMPUS, and ALPS trials concluded that roxadustat was effective at increasing hemoglobin

TABLE 3

The most widely used erythropoiesis-stimulating agents in the United States

Drug	Half-life (hours)		Dosage in adults
	Intravenous	Subcutaneous	
First-generation			
Epoetin alfa[36]	4–13	5–24	Initial 50–100 U/kg 3 times weekly intravenously or subcutaneously Maintenance individualized
Second-generation			
Darbepoetin alfa[37]	21	35–139	Initial 0.45 µg/kg weekly, adjusted as needed to maintain hemoglobin 11–13 g/dL Do not adjust dose more frequently than once a month unless clinically indicated
Third-generation			
Methoxypolyethylene glycol–epoetin beta[38]	119	124	Initial 0.6 µg/kg every 2 weeks intravenously or subcutaneously
Epoetin zeta[39]	Similar to first-generation epoetin alfa		

levels in anemic patients with chronic kidney disease not on dialysis, reduced the need for blood transfusions, and did not demonstrably increase the risk of major adverse cardiac events.[49,50]

■ TRIALS IN PATIENTS ON DIALYSIS

The first phase 2 clinical trial of oral PHI therapy to report hemoglobin correction in patients on dialysis who had never received ESAs, published in 2016, was an open-label study of roxadustat (with no placebo group).[51] The mean hemoglobin level increased by at least 2.0 g/dL within 7 weeks, independent of initial hemoglobin level, iron-repletion state, iron supplementation, C-reactive protein level, and dialysis type (hemodialysis or peritoneal), and hepcidin concentrations decreased. This was the first study to challenge the historical notion that anemia in dialysis-dependent chronic kidney disease was a result of loss of the cells that produce endogenous erythropoietin. Instead, it showed that the mechanism remains intact but was suppressed in the uremic milieu.

In 2019, a randomized phase 3 study of 305 patients in China with dialysis-dependent chronic kidney disease on ESAs found that oral roxadustat was noninferior to intravenous epoetin alfa.[52] A notable result also seen in the 2016 phase 2 trial[51] was that inflammation (assessed by C-reactive protein levels) did not affect the hemoglobin-correcting effect of roxadustat, whereas ESAs produce less of a response in inflammatory states.[53]

In 2021, the HIMALAYAS study[54] explored the efficacy and safety of roxadustat in a phase 3 open-label trial using epoetin alfa as the control treatment in 1,043 patients with anemia who had never received an ESA before and who had recently started on dialysis (from 2 weeks up to 4 months before randomization). Roxadustat was noninferior to epoetin alfa in correcting and maintaining hemoglobin levels, with comparable adverse-event rates with either treatment.[54]

■ BENEFITS AND SIDE EFFECTS OF PHIs

PHIs are promising drugs, as they are at least as effective as ESAs in raising hemoglobin
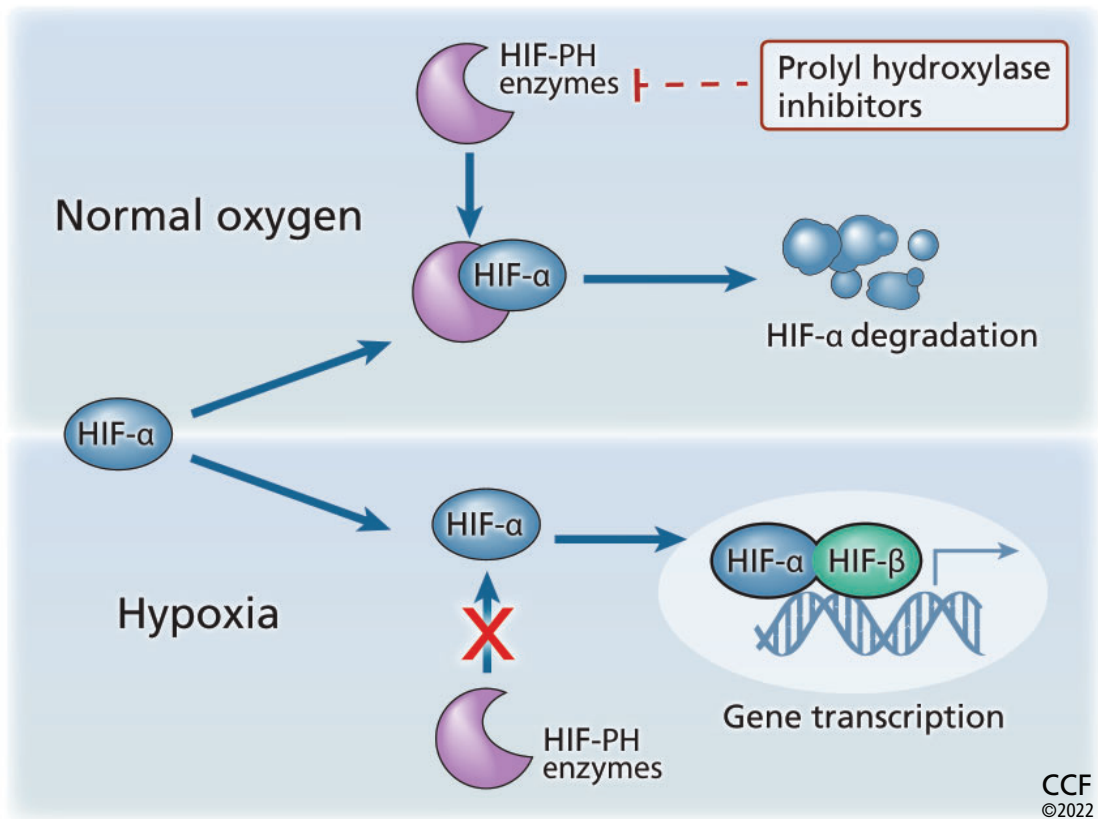
Figure 2. Prolyl hydroxylase (PH) inhibitors increase erythropoiesis. Hypoxia-inducible factor (HIF) is a heterodimer consisting of 2 subunits, alpha and beta (HIF-α, HIF-β). Under normal oxygen tension, the proline residue of HIF-α is hydroxylated and subsequently degraded. This prevents the formation of the heterodimer and stops subsequent erythropoietin transcription. When oxygen tension is low, HIF-α is not degraded, thus allowing HIF heterodimers to form. This leads to an increase in erythropoietin transcription. By preventing hydroxylation of HIF-α, PHIs prevent its degradation and stabilize the HIF-α/HIF-β heterodimer. This leads to increased downstream gene expression with increased production of endogenous erythropoietin.

PHIs are promising drugs, as they are at least as effective as ESAs in raising hemoglobin levels in patients with chronic kidney disease on or off dialysis

levels in patients with chronic kidney disease either on or off dialysis. They increase iron availability by decreasing hepcidin levels, thus potentially reducing the need for intravenous iron. Most importantly, they seem to remain effective in inflammatory states. This is a striking difference from ESAs, which require higher doses in inflammatory states and often fail to achieve target hemoglobin values.[21,22,24] This ESA resistance and the higher required doses are likely responsible for the negative cardiovascular outcomes in hyporesponsive patients.[27,28]

Additional advantages of PHIs include ease of administration (oral dosing, especial-

ly advantageous in patients not on dialysis or who are on home hemodialysis), cheaper manufacturing with less stringent transportation logistics (ESAs need to be kept refrigerated),[55] and less immunogenicity (a concern with ESAs), given that they are not protein-based. Also, roxadustat seemed to lower cholesterol levels, though the mechanism remains to be understood.[45]

Adverse effects of PHIs

So far, no major serious adverse effects have been found in clinical trials. The serious adverse events that happened in phase 2 trials were not considered drug-related or were deemed

TABLE 4

Published phase 2 and 3 trials of roxadustat

Trial	No.	Patients	Effect on hemoglobin
Besarab et a[44]	104	Not on dialysis	Better than placebo
Chen et al[45]	154	Not on dialysis or ESAs	Better than placebo
ANDES[46]	922	Not on dialysis or ESAs	Better than placebo
OLYMPUS[47]	2,781	Not on dialysis	Better than placebo
ALPS[48]	594	Not on dialysis or ESAs	Better than placebo
Besarab et al[51]	60	On dialysis, or ESAs	Better than baseline
Chen et al[52]	305	On dialysis and ESAs	As good as epoetin alfa
HIMALAYAS[54]	1,043	New to dialysis	As good as epoetin alfa
Akizawa et al[66]	303	On dialysis	As good as darbepoetin alfa
Akizawa et al[67]	56	On dialysis	Better than baseline
Akizawa et al[68]	239	On dialysis	Better than baseline in those not on ESAs
Akizawa et al[69]	99	Not on dialysis or ESAs	Better than baseline
Provenzano et al[70]	145	Not on dialysis	Better than baseline
Provenzano et al[71]	90	On dialysis	As good as epoetin alfa

ESA = erythropoiesis-stimulating agent

"within expected range," as they happened at comparable rates in comparable patients who were not on these drugs.[56] However, studies of the PHI FG-2216 were suspended after a patient died of hepatic necrosis, making it the only drug of this class for which a study was halted due to safety concerns.[57]

Hyperkalemia. The two Chinese phase 3 trials[45,52] showed an increased risk of hyperkalemia with roxadustat. Hyperkalemia has also been reported in trials of daprodustat in patients on hemodialysis.[58] Thus, use of PHIs in patients predisposed to hyperkalemia should be approached with caution.

Upper respiratory tract infections and metabolic acidosis have also been reported. More side effects may emerge with larger and longer studies.

Cardiovascular safety. A pooled post hoc analysis compared roxadustat with epoetin alfa in 1,530 patients newly started on dialysis.[49] Although the results suggested a lower risk of death, myocardial infarction, and stroke in the roxadustat group, an analysis with prespecified stratification factors had shown attenuated benefits and wider confidence intervals,[59] leading to the results of this study being called into question.[60] Thus, the cardiovascular superiority of PHIs is yet to be fully established.

Theoretical risk of malignancy. To date, no animal or human study has shown PHIs to increase the risk of kidney cancer or other malignancies. However, HIF activation may enhance the proliferation, invasion, and metastatic potential of cells, as HIFs appear to be linked to metastasis in several malignancies (breast, prostate, lung, bone, and colorectal cancer).[61]

Diabetic retinopathy (either its induction or progression) is another potential adverse effect. HIF-1 alpha can induce vascular endothelial growth factor, which is involved in the progression of this disease. No such cases have been reported, but because many trials excluded patients at high risk of retinal hemorrhage, PHIs should be used with caution in

this population.[42]

Progression of autosomal dominant polycystic kidney disease. In theory, PHIs could raise the risk of cyst growth, since HIF expression levels have been correlated in human and rat models with increased cyst burden.[62] Until better evidence is available, some experts suggest limiting PHI use in patients with this disease who are not on dialysis.[63]

PHI DRUGS: CURRENT STATUS

Roxadustat is currently approved for use in anemia of chronic kidney disease in nondialysis-dependent and dialysis-dependent patients in China, Japan, and Chile, and recently received a positive opinion by the Committee for Medicinal Products for Human Use of the European Medicines Agency.[64]

However, concerns about its cardiovascular safety prompted the FDA Cardiovascular and Renal Drugs Advisory Committee to vote against the approval of roxadustat in July 2021. In August 2021, the FDA responded to roxadustat's New Drug Application by asking for a new clinical trial to assess the safety of this drug in both nondialysis- and dialysis-dependent chronic kidney disease.[64] Therefore, it seems unlikely that roxadustat will be available in the United States in the immediate future.

Although other PHIs have been approved for clinical use in Japan,[65] roxadustat is the most studied to date. The 14 published phase 2 and 3 trials of roxadustat[44–48,51,52,54,66–71] are summarized in **Table 4**. (See ccjm.org for an expanded version of **Table 4**.)

KEY QUESTIONS REMAIN

More research is needed to answer the following important questions about PHIs:

- Given their ability to achieve hemoglobin targets at physiologic plasma erythropoietin levels, could they be used to treat hyporesponsive patients more effectively and safely?
- Given their effects on iron mobilization, can they reduce the need for intravenous iron in patients with anemia of chronic kidney disease?
- Will their cholesterol-lowering properties prove clinically relevant?
- What is the future of roxadustat in light of the recent FDA decision?

However, regardless of the lingering questions, the exploration and exploitation of the HIF pathway opens the door to multiple possibilities. Will PHIs deliver on the promises? We certainly hope so. It would be great to have 1 more tool at our disposal to treat anemia in patients with kidney disease. ∎

DISCLOSURES

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CORRECTION

In the February 2022 issue, in *Bartolomeo K, Tan XY, Fatica R. Extraosseous calcification in kidney disease. Cleve Clin J Med 2022; 89(2):81–90. doi:10.3949/ccjm.89a.21073*, an error appeared in Figure 1 on page 83, relative to phosphate excretion and phosphate absorption. The correct figure appears below:
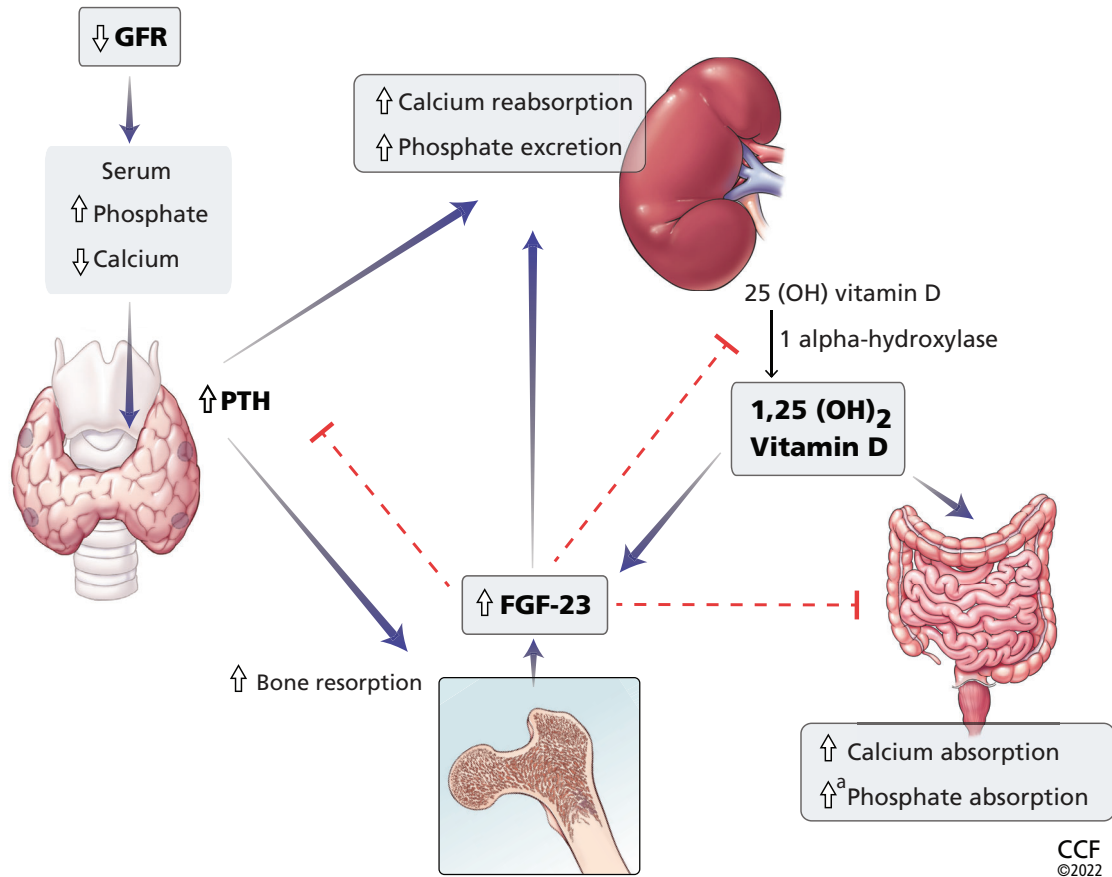
Figure 1. Calcium and phosphate metabolism in chronic kidney disease. Decreased glomerular filtration rate (GFR) leads to changes in serum calcium and phosphate, triggering release of parathyroid hormone (PTH) from the parathyroid glands and fibroblast growth factor 23 (FGF-23) from osteoblasts and osteocytes. These hormones have complex downstream effects on the kidney, gut, and bone, both from direct effects on the tissue and from indirect effects through modulation of enzyme activity in vitamin D conversion.

[a] Minimally increased.

25(OH) vitamin D = 25-hydroxycholecalciferol; 1,25(OH)$_2$ vitamin D = 1,25-dihydroxycholecalciferol

This is now correct on ccjm.org.

CORRECTION

In the February 2022 issue, an error appeared in *Chapman T, Sinz E, McGillen B. Does my hospitalized patient need an NPO-after-midnight order preoperatively? Cleve Clin J Med 2022; 89(2):69–70. doi:10.3949/ccjm.89a.21061*. In the reference list on page 70, reference 3, the citation information was incorrect. The reference should have read as follows: Black MK, Lupa MC, Lemley LW, Dreesen EB, Deaton AM, Wardrop RM 3rd. Things we do for no reason: NPO after midnight. J Hosp Med 2021; 16(6):368–370. doi:10.12788/jhm.3537. This is now correct on ccjm.org.

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