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CME MOC

Cleveland Clinic Journal of Medicine

Pursuing the diagnosis of low back pain

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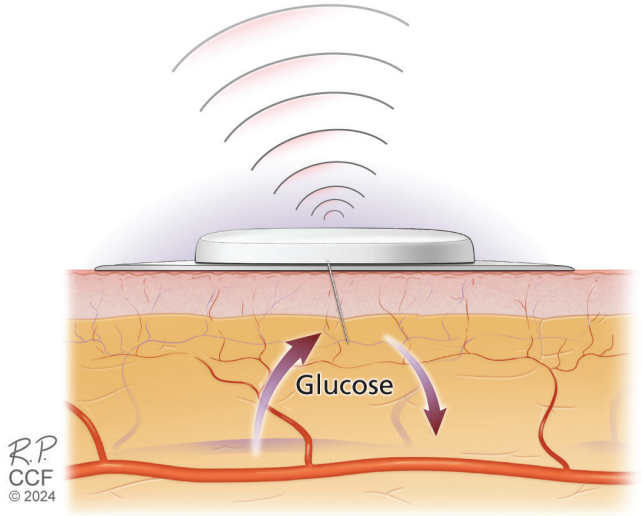

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Pursuing the diagnosis of low back pain

Low back pain is an extremely common reason for patients to seek medical evaluation. It has been estimated that approximately 80% of patients will have low back pain as a notable symptom at some point in their lives. Current guidelines from many international organizations share the recommendation for an initial conservative approach to management of patients with acute and subacute low back pain, even in the presence of symptomatic radiculopathy, and these recommendations generally include eschewing initial diagnostic imaging. The underlying basis for these recommendations is that the overwhelming majority of these patients will have "nonspecific" low back pain, which is variably operationally defined as pain without a clear structural etiology. Most, but clearly not all, of these episodes will have a self-limited course, and many patients will achieve apparent benefit from lifestyle and physiotherapeutic interventions.

But as all clinicians know, there are red flags associated with back pain that heighten concern for 1 of the serious causes of back pain, prompting the need for more immediate diagnostic evaluation. Skeletal malignancy, epidural or vertebral body infections, myelitis, cauda equina syndrome, vertebral compression fractures, and referred pain from a severe retroperitoneal pathology are some of these diagnoses. Hence, we routinely ask about documented fevers, weight loss, severe pain at night or pain at rest, trauma, use of corticosteroids, and a history of cancer other than nonmelanoma skin cancer. When exploring the strength of evidence supporting the use of these red flags, I found that it is weak.[1,2] Realizing the relative paucity (pretest likelihood) of these "do not miss" diagnoses compared with the high prevalence of nonspecific low back pain, this is not actually surprising. Despite the lack of robust data in support of the individual red flags, they should be sought when talking to the patient, and this should be accompanied by a physical examination (also with limited evidence for high sensitivity or specificity) focusing on looking for hints that may suggest any of the more worrisome diagnoses.

While this approach makes reasonable clinical sense, my sense from reading many of the guidelines is that a major reason for resisting the initial urge to pursue diagnostic testing in all patients with acute and subacute lower back pain is to reduce the cost to patients and the medical system. This is most certainly warranted. But from the clinician side, we must be comfortable that the likelihood of missing a significant clinical problem is low, and we must assure the patient that we have listened to their symptoms, have examined them looking for evidence of any severe problem that warrants immediate intervention, and will be available to them if their symptoms evolve or do not resolve as expected.

The clinical risks associated with imaging everyone with subacute back pain include radiation exposure, inconvenience, and discovering incidental findings that prompt additional concern, more studies, and more cost. This was highlighted years ago when it was clearly demonstrated that the presence of bulging and protruding spinal disks observed by magnetic resonance imaging in asymptomatic individuals is age-related and common,[3] and does not routinely warrant surgical intervention.

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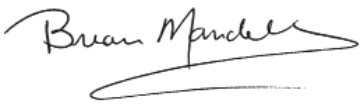
The above discussion relates to acute and subacute back pain, and this diagnostic strategy should be tempered in patients with more chronic pain. Depending on the age of the patient and the actual duration and characteristics of the back pain, most of the same red flag questions should be pursued. Many patients will ultimately have "nonspecific" back pain, but a modest proportion will have identifiable mechanical or anatomic causes, such as hip disease, spinal stenosis, and osteoporotic compression fractures. Some will have inflammatory spine disease, which may be identified by radiographic or magnetic resonance imaging. Clinical clues to the presence of spondylitis include fairly constant back pain or stiffness that is worse in the morning on awakening, personal or family history of inflammatory eye disease, nocturnal spine pain that can severely disrupt sleep resulting in fatigue, and diffuse periarticular pain (tendonitis, enthesitis). Presence of fatigue and seemingly generalized pain may suggest the diagnosis of fibromyalgia; careful examination and questioning should help in teasing these apart.

The significance of diagnosing spondylitis cannot be overstated. Multiple therapies are now available that, although costly, are generally extremely well tolerated and effective. In part due to direct-to-consumer and traditional physician-targeted advertising campaigns, there is an increased recognition of spondylitis as a condition that affects women as well as men and not infrequently is associated with underlying psoriasis or inflammatory bowel disease. Which brings me full circle to the value of imaging as a diagnostic tool.

In some patients with spondylitis, usually those who have had symptoms for a while, dedicated sacroiliac joint radiography may be diagnostic. But, importantly, standard hip or lumbar spine radiography may not reveal diagnostic findings, or they may be subtle and overlooked. If patients with suspected spondylitis have had previous computed tomography imaging of the abdomen, pelvis, or both, these images should be requested and reviewed again to see whether the sacroiliac joints can be evaluated; frequently they can be. Patients may require magnetic resonance imaging to demonstrate spondylitis, and this should be pursued if there is strong clinical suspicion but sacroiliac radiographs are normal. Even in the absence of inflammatory changes on imaging, some patients are diagnosed with spondylitis based on compelling history, physical examination, and often responsiveness to anti-inflammatory therapies, and may respond dramatically to biologics and other newer targeted therapies. These patients should be monitored over time.

There is a differential diagnosis for radiographic involvement of the sacroiliac joints. Not all patients with chronic back pain with sacroiliac imaging abnormalities have spondylitis, as nicely illustrated and discussed by Patel and Schils[4] in this issue of the *Journal*. But if spondylitis is not considered, it likely will not be diagnosed and successfully treated.



Brian F. Mandell, MD, PhD
Editor in Chief

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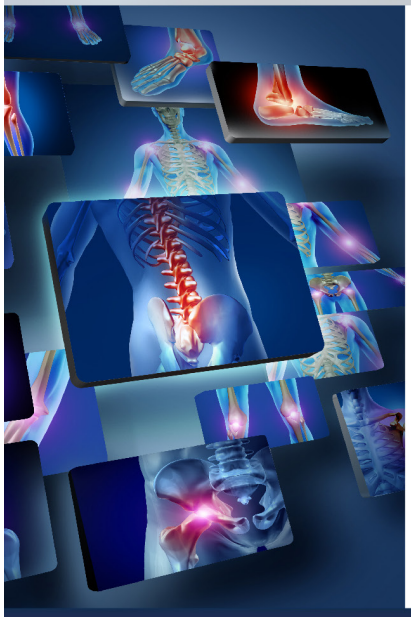

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Low back pain: Spondylitis?

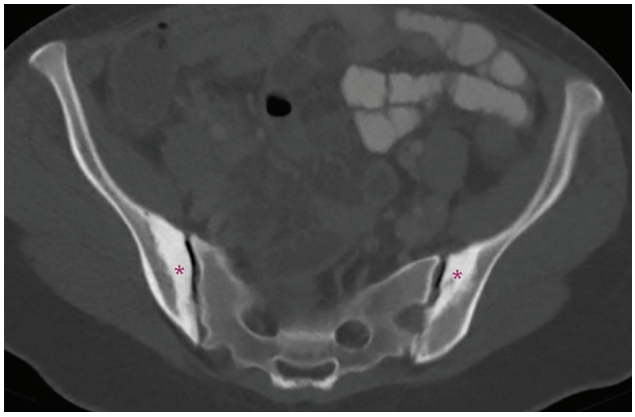

Figure 1. Computed tomography image from patient's evaluation for colitis. This axial view of the midsection of the sacroiliac joints shows bilateral subchondral sclerosis predominant on the iliac sides (asterisks), findings consistent with osteitis condensans ilii.

A 37-year-old woman was referred to the rheumatology clinic due to symptoms concerning for spondylitis. She had noted worsening low back pain about 18 months ago while pregnant with twins. At the time of evaluation in the clinic, she reported intermittent back pain episodes with right-sided groin pain that was exacerbated by working long hours and lifting heavy objects. She took nonsteroidal anti-inflammatory drugs for pain, which was beneficial. She denied difficulty with routine activities of daily living, morning stiffness, and nocturnal awakening due to low back pain. She had experienced no episodes of enthesitis, dactylitis, or inflammatory eye disease.

Years previously she had an episode of colitis with abdominal pain and rectal pressure. Computed tomography at that time was notable for colitis and abnormal sacroiliac joints with bilateral subchondral sclerosis (**Figure 1**). About 1 month later, she underwent a colonoscopy, which was unremarkable.

doi:10.3949/ccjm.91a.23086

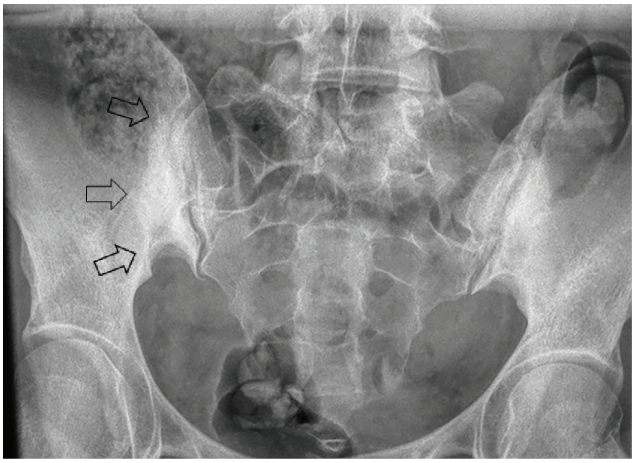

Figure 2. Radiograph of the sacroiliac joints from the patient's evaluation at the rheumatology clinic shows bilateral subchondral sclerosis on the iliac side, consistent with osteitis condensans ilii. The triangular-shaped area of sclerosis, a hallmark radiographic feature of osteitis condensans ilii, is best appreciated on the right side (arrows).

On physical examination at the rheumatology clinic, findings were notable for normal peripheral joints, normal range of motion in the spine, and no sacroiliac joint tenderness with a negative FABER (flexion, abduction, external rotation) stress test. There was no evidence of enthesitis, and her eye examination was normal.

Plain radiography showed dense bilateral subchondral sclerosis on the iliac sides of the mid portion of the sacroiliac joints (**Figure 2**). These radiography findings and the earlier computed tomography findings were consistent with osteitis condensans ilii (OCI).

OSTEITIS CONDENSANS ILII

OCI is a benign, noninflammatory cause of axial low back pain first described in 1926 by Sicard et al.[1] Its pathogenesis remains unclear. OCI has a predilection for

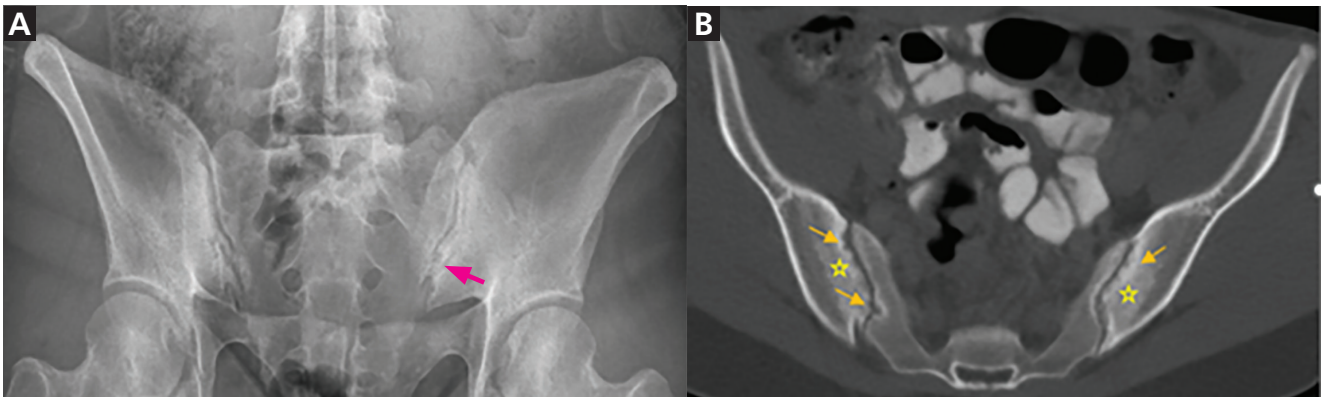

Figure 3. Imaging from a different patient showing radiographic features of ankylosing spondylitis. The (A) radiograph of the sacroiliac joints shows mild irregularity of the subchondral bone over the left inferior sacroiliac joint (pink arrow). The (B) axial computed tomography image of the sacroiliac joints shows bilateral erosions (yellow arrows) and sclerosis (yellow star) on the iliac side.

multiparous females, mean age 35 at time of diagnosis, leading some to propose vascular compression and resulting ischemia related to the physiologic changes of pregnancy, or mechanical laxity and sacroiliac joint overload during pregnancy, as potential mechanisms of injury.[1] Nevertheless, OCI does occur in nulliparous females and males.

Clues to the diagnosis

Patients with OCI complain of intermittent axial low back pain with occasional hip area pain.[2] This pain can be worse during the third trimester of pregnancy or post pregnancy. OCI can be an incidental radiographic finding in an asymptomatic patient. Radiographic findings of OCI include bilateral triangular (or oval) subchondral sclerosis predominant on the iliac side and the absence of erosions and ankylosis (**Figure 2**).[3] Computed tomography may also show sacral subchondral sclerosis.

The differential diagnosis

The differential diagnosis for OCI is sacroiliitis, which can be seen in other disease entities such as infection, ankylosing spondylitis, psoriatic arthritis, and osteoarthritis. In patients with chronic low back pain, particularly young patients, it is essential to look for features associated with spondyloarthritis, such as the following:

- Inflammatory back pain (age of onset < 40, insidious onset, improvement with exercise, no improvement with rest, and nocturnal awakening)
- Enthesitis (inflammation of insertion sites of tendons or ligaments into bone)
- Dactylitis (severe swelling of an entire finger or toe)
- Peripheral arthritis
- Extra-articular manifestations (eg, psoriasis, uveitis, inflammatory bowel disease)
- Family history of spondyloarthritis.[4]

OCI and inflammatory sacroiliitis are differentiated based on radiography findings. Imaging in a patient with ankylosing spondylitis shows bilateral symmetric sacroiliitis characterized by a variable combination of erosions, subchondral sclerosis, and ankylosis (**Figure 3**). Unilateral involvement can be seen in infection, destructive neoplastic processes, and psoriatic and reactive arthritis. Computed tomography can provide better evaluation of sacroiliac joints but is not necessary for diagnosis.

Treatment

Management is usually conservative, consisting of physical therapy and analgesics.[2] OCI is thought to resolve over years in most cases.[5]

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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Should an NPO order be placed for my patient with acute pancreatitis?

A 45-year-old man with a 10-year history of alcohol use disorder presents to the emergency department with constant severe pain in the epigastrium with radiation to the back. The abdominal pain is associated with fluctuating nausea without vomiting. His temperature on presentation is 99.1°F (37.28°C), blood pressure 142/77 mm Hg, heart rate 102 beats per minute, and oxygen saturation 99% on room air. Physical examination reveals a nondistended abdomen with decreased bowel sounds. Palpation of the epigastric area elicits voluntary guarding. Serum lipase is 591 U/L (reference range < 160 U/L). Computed tomography with intravenous contrast reveals an edematous pancreas with pancreatic fat-stranding and uniform enhancement of the pancreas without necrosis. A diagnosis of mild acute pancreatitis is made using the Atlanta criteria, given a lack of organ failure or acute complications. When is it safe to allow the patient to resume oral feeding?

A: Our patient has no contraindications to oral feeding, so he should resume oral feeding as soon as it is tolerated, ie, in the absence of emesis or severe pain.

Pancreatic rest through extended periods of nothing by mouth (NPO) status or total parenteral nutrition is no longer considered the standard of care.[1–3] Non-oral enteral nutrition is instituted instead of total parenteral nutrition if the patient does not tolerate oral feeding. Total parenteral nutrition and NPO status should be used only if there are contraindications to enteral nutrition, such as paralytic ileus.

GUT 'ROUSING' RATHER THAN REST

Historically, physicians treated acute pancreatitis with an NPO strategy, hoping to minimize pancreatic enzyme activation and thereby limit further pancreatic inflammation and injury.[1] Under normal physiologic conditions, oral or duodenal feeding stimulates pancreatic exocrine function. However, secretion of pancreatic exocrine enzymes, as measured through trypsin levels, is reduced in patients with acute pancreatitis compared with healthy controls. This reduction is associated with disease severity rather than nutrition intake, indicating that an oral feeding strategy would not exacerbate the enzymatic pathology of acute pancreatitis.[1,2]

The shift away from pancreatic rest to a new framework, called "gut rousing" by Petrov,[3] emphasizes the importance of restoring normal gut function as quickly as possible. Feeding through enteral routes rather than parenteral nutrition stimulates the gut and minimizes gut dysfunction, preventing complications of acute panceatitis.[3]

In a meta-analysis by Petrov et al[4] that included 5 randomized controlled trials with 95 patients who received enteral nutrition and 107 who received parenteral nutrition, the enteral group had lower rates of infectious complications, surgical interventions, and mortality. A meta-analysis by Chowdhury et al[5] found that patients who were immediately started on a full solid diet rather than having intake gradually increased through a stepwise diet had a shorter hospital length of stay; there were no differences between the groups in level of abdominal pain or rate of patients stopping their diet.

SOCIETY GUIDELINES

Multiple society guidelines support the use of enteral nutrition in acute pancreatitis.[6–9]

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The American College of Gastroenterology (ACG)[9] guidelinesfrom 2013 recommends oral feeding for mild acute pancreatitis. This recommendation was strengthened in the 2018[6] guideline with the removal of the qualifier "mild." The ACG recommendations allow for various diets, including diets low in fat or containing a normal amount of fat and diets consisting of solid or soft food, as tolerated, within 24 hours for all patients with acute pancreatitis. Oral feeding trials are preferred over NPO orders in patients with acute pancreatitis based on the combined results of 11 randomized controlled trials.[6]

The European Society for Clinical Nutrition and Metabolism (ESPEN) 2020 guideline[7] on clinical nutrition in acute pancreatitis includes the following recommendations:

- Nutrition decisions should not be based on serum lipase levels
- The oral diet should be low in fat and of soft consistency, as this type of diet provides more benefits and equal tolerability compared with clear liquid diets
- Enteral nutrition is recommended over parenteral nutrition for patients who are unable to tolerate oral feeding, which is in agreement with ACG guidelines
- Pancreatic enzyme replacement therapy should be started when patients present with clinical signs or symptoms of pancreatic insufficiency (eg, bloating, steatorrhea) or low fecal elastase, suggesting malabsorption.[7]

The guidelines of the UK Working Party on Acute Pancreatitis[8] largely agree with the above recommendations. For mild pancreatitis, the UK guidelines recommend starting oral feeding as soon as possible.[8] In regard to parenteral nutrition, the UK guidelines emphasize that enteral nutrition has better outcomes, but parenteral nutrition can be considered in certain scenarios, such as ileus persisting for more than 5 days.[8]

WHEN SHOULD ENTERAL NUTRITION BE STARTED IN PATIENTS WITH ACUTE PANCREATITIS?

The ACG guideline recognizes that not all patients will tolerate oral feeding because of pain, vomiting, or ileus.[6] A technical review of 12 randomized controlled trials that compared parenteral to enteral (oral or enteral tube) nutrition in patients with acute pancreatitis and inability to feed orally found enteral nutrition was associated with a decreased risk of infected peripancreatic necrosis and organ failure.[6] The meta-analysis by Petrov et al[4] also found that enteral feeding was associated with a decreased risk of necrosis.

Strong evidence or consensus on the optimal timing of enteral tube feeding is lacking. In the Pancreatitis, Very Early Compared with Selective Delayed Start of Enteral Feeding (PYTHON) trial[10] from the Netherlands, patients with severe acute pancreatitis at high risk for complications were randomized to nasoenteric feeding within 24 hours or an oral diet started after 72 hours with tube feeding if the oral diet was not tolerated. Infection rates and mortality did not differ between early nasoenteric feeding and oral diet.

If oral nutrition is not tolerated, the ESPEN guideline[7] indicates that enteral nutrition should be started via nasogastric or nasojejunal tube within 24 to 72 hours from admission. Nasogastric tubes are preferred because they cost less and have complication rates similar to nasojejunal tubes.[7] Absolute contraindications to enteral nutrition include ileus or bowel obstruction, open abdomen, and abdominal compartment syndrome.[7]

WHEN IS TOTAL PARENTERAL NUTRITION INDICATED?

The ESPEN guideline[7] lists several scenarios in which total parenteral nutrition is indicated over enteral routes, including bowel obstruction, abdominal compartment syndrome, prolonged paralytic ileus, and mesenteric ischemia. Approximately 20% of patients with severe acute pancreatitis may have an absolute or relative contraindication to enteral nutrition.[7] It is still important to emphasize that total parenteral nutrition and NPO orders should not be started without evidence of contraindications to enteral nutrition.[6]

THE BOTTOM LINE

Patients with acute pancreatitis should resume a solid diet as soon as it can be tolerated.[6] Guidelines recommend encouraging patients as soon as possible to start with an oral, nonliquid diet to minimize risk of infection and mortality, with initiation of enteral feeding through nasoenteral routes within 24 to 72 hours of insufficient oral intake.[6,7] Pancreatic enzyme supplementation should be started in patients with obvious signs of exocrine enzyme deficiency causing malabsorption.[7] Total parenteral nutrition and NPO orders should be placed only for patients with contraindications to enteral nutrition, such as prolonged paralytic ileus or bowel obstruction.[7]

DISCLOSURES

Dr. Sealock has disclosed serving as a co-principal investigator for Abbvie Pharmaceuticals. The other 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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A hidden cause of hypokalemia

A 21-year-old man presented to the emergency department with increasing fatigue and psychosis symptoms. He had experienced no nausea, vomiting, diarrhea, chest pain, dyspnea, or urinary symptoms. He was not on any prescribed or over-the-counter medications or herbal supplements, and he denied smoking and alcohol consumption. Recently, he observed a 20-lb weight gain over 6 weeks.

On examination, the patient was alert and oriented, with clear lungs on auscultation. His temperature was 37.0°C (98.6°F), heart rate 60 beats per minute, respiratory rate 11 breaths per minute, oxygen saturation 98% on room air, blood pressure 153/92 mm Hg, and body mass index 34 kg/m^2. Cardiovascular and gastrointestinal findings were unremarkable, and there were no focal neurologic abnormalities. Striae were noted over his abdomen and back.

Initial laboratory test results are listed in **Table 1**.

EVALUATION OF THE METABOLIC DISORDER

1 What is the most appropriate next step in investigating this patient's acid-base disorder?

- ☐ Random urine potassium
- ☐ Random urine chloride
- ☐ Random urine sodium
- ☐ Random urine urea

Our patient's blood gas analysis revealed a pH of 7.55 (indicating alkalemia), an elevated serum bicarbonate level of 34 mEq/L (suggesting a metabolic process), and an elevated partial pressure of carbon dioxide at 42 mm Hg (suggesting respiratory compensation). The patient's partial pressure of carbon dioxide was within the expected range, which in metabolic alkalosis can be calculated using the following formula: 0.7 × (bicarbonate level + 20) ± 5. Our patient's values were 0.7 × (34 + 20) = 44 ± 5, and he was diagnosed with primary metabolic alkalosis with respiratory compensation.

The urine chloride level is crucial to differentiate volume-responsive (urine chloride < 20 mmol/L) from volume-resistant (urine chloride ≥ 20 mmol/L) metabolic alkalosis.[1] In cases of alkalemia, urine chloride is a more reliable indicator of intravascular volume depletion than urine sodium. The kidneys respond to the increased filtered bicarbonate load during volume depletion by excreting bicarbonate in the urine. The negatively charged bicarbonate, in maintaining electroneutrality, pulls positively charged sodium and potassium ions into the urine. Consequently, urine sodium and potassium concentrations may be elevated in the setting of vomiting or nasogastric suction, making them less accurate indicators of the patient's volume status. In contrast, in a volume-depleted state urine chloride concentration remains low because low volume triggers activation of the renin-angiotensin aldosterone system, leading to increased reabsorption of sodium chloride in the proximal tubule. Therefore, the initial step in investigating metabolic alkalosis involves assessing spot urine chloride. Notably, urine urea plays no role in the evaluation of metabolic alkalosis.

Of note, serum sodium levels can aid in distinguishing various forms of metabolic alkalosis. Our patient's hypokalemia, metabolic alkalosis, and serum sodium concentration in the upper normal range suggest a volume-expanded form of metabolic alkalosis. In contrast, volume-contracted forms (such as vomiting) typically present with a low-normal serum sodium concentration due to volume contraction and antidiuretic hormone stimulation.

CASE CONTINUED: URINE STUDY RESULTS

The results of the patient's urine studies are listed in **Table 2**.

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TABLE 1
The patient's initial laboratory test results

Laboratory test (reference range)	Results[a]
White blood cell count (4.0–11.2 × 10^9/L)	**11.53**
Hemoglobin (12.5–15.9 g/dL)	**16.7**
Platelet count (130–380 × 10^9/L)	136
Sodium (136–145 mmol/L)	143
Potassium (3.5–5.1 mmol/L)	**2.5**
Chloride (98–107 mmol/L)	99
Bicarbonate (22–29 mmol/L)	**34**
Glucose (70–99 mg/dL)	**127**
Creatinine (0.67–1.17 mg/dL)	0.77
Blood urea nitrogen (6–23 mg/dL)	15
Calcium (8.6–10.2 mg/dL)	9
Albumin (3.5–5.2 g/dL)	4.2
Alanine aminotransferase (5–41 U/L)	**61**
Aspartate aminotransferase (5–40 U/L)	22
Alkaline phosphatase (40–129 U/L)	66
Bilirubin, total (0.2–1.2 mg/dL)	0.6
Arterial blood gasses	
pH (7.35–7.45)	**7.55**
Partial pressure of carbon dioxide (35–50 mm Hg)	42
Partial pressure of oxygen (75–100 mm Hg)	97

[a]Abnormal results are shown in bold.

TABLE 2
Urine studies

Laboratory test (reference range)	Results[a]
Urine potassium, random (11–80 mmol/L)	27
Urine chloride, random (30–260 mmol/L)	35
Urine creatinine, random (40–279 mg/dL)	62
Urine potassium, 24-hour (25–125 mmol/24 hours)	**275**

[a]Abnormal result is shown in bold.

EVALUATION OF HYPOKALEMIA IN VOLUME-RESISTANT METABOLIC ALKALOSIS

2 Considering these laboratory results, what would be the most appropriate next course of action for this patient?

- ☐ Check serum renin and aldosterone levels
- ☐ Obtain urine diuretic screen
- ☐ Seek consultation for genetic testing
- ☐ Check 24-hour urine calcium
- ☐ Check serum magnesium level

With a urine chloride level of 34 mmol/L, this patient had chloride-resistant (or volume-resistant) metabolic alkalosis along with hypokalemia. To assess the hypokalemia, urine electrolyte studies were needed to distinguish renal from extrarenal potassium losses. Although a random urine potassium level of 27 mmol/L may indicate renal potassium wasting, the accuracy of this measurement can be influenced by urine volume variations. This limitation can be overcome by evaluating the urine potassium-to-creatinine ratio or fractional excretion of potassium (calculated as [urinary potassium × serum creatinine] ÷ [serum potassium × urinary creatinine] × 100). The patient's spot urine potassium-to-creatinine ratio was 43.5 mmol/g (values > 15 mmol/g indicate renal potassium loss).[2] The fractional excretion of potassium was greater than 9.3%, indicative of inappropriate renal potassium wasting in the context of hypokalemia.[2] A 24-hour urine collection, the most accurate measurement of urinary potassium excretion, also was consistent with renal potassium loss.[2]

Given the presence of chloride-resistant metabolic alkalosis, renal potassium wasting, and hypertension, the most prudent next step would be to assess the patient's renin and aldosterone levels.

While diuretic abuse commonly induces hypokalemia through renal wasting and may lead to chloride-resistant metabolic alkalosis, patients typically exhibit hypotension or, at minimum, are not hypertensive. Consequently, a diuretic screen would not have been the most suitable next step in evaluating this patient.

Gitelman syndrome and Bartter syndrome are rare genetic disorders affecting the renal tubules and electrolyte balance. Gitelman syndrome is characterized by mutations in the *SLC12A3* gene, leading to defects in the thiazide-sensitive sodium-chloride co-transporter in the distal convoluted tubule. This results in excessive salt and water loss, leading to hypokalemia, metabolic alkalosis, and hypomagnesemia.[3] Bartter syndrome involves mutations in genes affecting the thick ascending limb of the loop of Henle, causing impaired sodium reabsorption. This leads to an electrolyte imbalance similar to that seen in Gitelman syndrome, but with hypercalciuria.[4] Most patients with these syndromes have normal to low blood pressure, but hypertension can be observed in certain instances. Given our patient's hypertension, the next sensible course of action was to evaluate his renin and aldosterone levels, not performing a 24-hour urine calcium

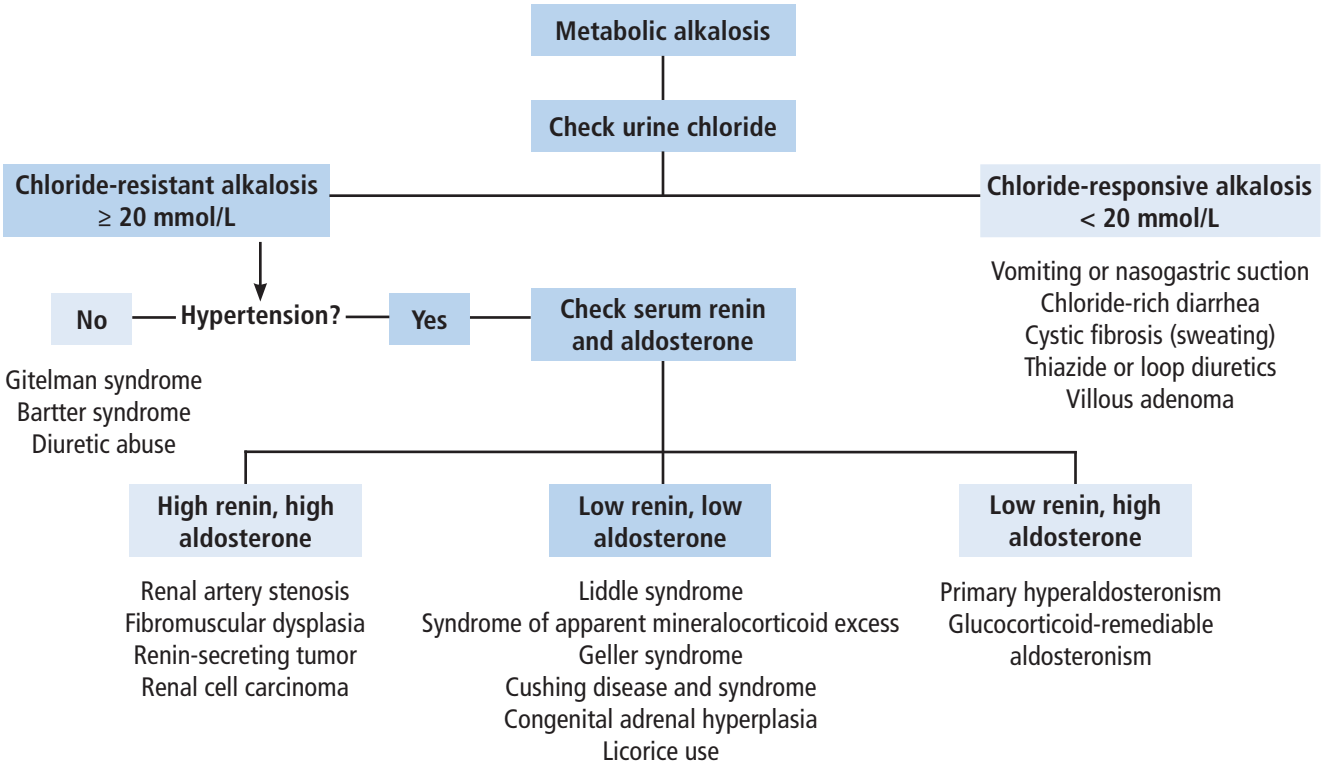

Figure 1. Algorithm for conducting a workup and differential diagnosis of metabolic alkalosis.

assessment as part of the investigation for Gitelman or Bartter syndrome.

Genetic testing might have been necessary in subsequent stages of the diagnostic process, but would have been premature at this point.[3,4]

Hypomagnesemia can induce hypokalemia by its effects on the renal outer medullary potassium channel, leading to increased potassium excretion through the apical tubular membrane.[5] Nevertheless, there is no association between hypomagnesemia and other metabolic abnormalities.

CASE CONTINUED: FURTHER TESTING

Further testing revealed a serum renin level less than 0.1 ng/mL per hour (0.5–4), serum aldosterone level 3.1 ng/dL (4–31), and serum magnesium level 2.0 mg/dL (1.7–2.2).

METABOLIC ALKALOSIS WITH INHIBITED SERUM ALDOSTERONE AND RENIN ACTIVITY

3 Based on the information at hand, the patient could have any of the following conditions except

- ☐ Syndrome of apparent mineralocorticoid excess (SAME)
- ☐ Liddle syndrome
- ☐ Cushing syndrome or disease
- ☐ Glucocorticoid-remediable aldosteronism

The additional investigation for this patient revealed inhibited serum aldosterone and renin activity. In Gitelman and Bartter syndromes, reduction of the extracellular fluid volume increases renin and aldosterone production, leading to hyperreninemia and secondary hyperaldosteronism.

SAME. Cortisol, the glucocorticoid synthesized by the adrenal gland, and aldosterone share a similar binding affinity for mineralocorticoid receptors in the principal cells of the cortical collecting duct. The renal enzyme 11 β-hydroxysteroid dehydrogenase (11β-HSD2) plays a crucial role in metabolizing cortisol to cortisone, preventing it from activating the mineralocorticoid receptor. In SAME, a mutation in the gene encoding 11β-HSD2 renders the enzyme ineffective.[6] Consequently, physiologic levels of cortisol activate mineralocorticoid receptors, leading to chloride-resistant metabolic alkalosis, renal potassium wasting, hypertension, and suppression of renin and aldosterone.

TABLE 3
Cortisol hormone studies

Tests (reference range)	Results[a]
Cortisol, morning level (2.7–18.4 µg/dL)	**49.5**
Urinary cortisol excretion, 24-hour (< 32 µg/24 hours)	**5,904.8**
Adrenocorticotropic hormone (7.2–63.3 pg/mL)	**258**

[a]Abnormal results are shown in bold.

Usually, this genetic defect follows an autosomal recessive pattern, with affected individuals manifesting symptoms at a notably younger age, including failure to thrive and severe hypertension.[6] Additionally, inhibition of 11β-HSD2 by substances such as licorice products[6–9] and certain antifungal agents such as posaconazole and itraconazole[8,9] can mimic the effects of SAME.

Liddle syndrome is an uncommon autosomal dominant disorder arising from mutations in the genes encoding the subunits of the epithelial sodium channel in the collecting tubule.[10] This condition is characterized by an overactive epithelial sodium channel, resulting in excessive sodium reabsorption and potassium excretion, leading to chloride-resistant metabolic alkalosis, hypokalemia, hypertension, and low serum renin and aldosterone levels.[10] Typically, patients present during childhood, often with a supportive family history.[10] Due to variable penetrance, however, the clinical presentation and severity can vary widely. Diagnosis of Liddle syndrome usually requires genetic testing.[10]

Cushing syndrome is marked by the overproduction of cortisol, stemming from either endogenous sources such as a tumor (as seen in pituitary Cushing disease or other ectopic tumors causing Cushing syndrome) or exogenous sources such as medications.[11] Elevated levels of circulating cortisol overpower the activity of 11β-HSD2, enabling cortisol to exert its mineralocorticoid effect on the collecting ducts.[12] This results in sodium resorption and potassium excretion. Consequently, both Cushing disease and Cushing syndrome are associated with chloride-resistant metabolic alkalosis, hypokalemia, hypertension, and low serum renin and aldosterone levels.[13]

Glucocorticoid-remediable aldosteronism, also referred to as familial hyperaldosteronism type I, is an autosomal dominant condition marked by adrenocorticotropic hormone (ACTH)–sensitive aldosterone production in the zona fasciculata.[14] Diagnosis often occurs in childhood, with many patients having a family history of hypertension and cerebrovascular and cardiovascular complications.[14] While glucocorticoid-remedial aldosteronism is a cause of volume-resistant metabolic alkalosis, aldosterone levels are elevated in this condition, distinguishing it from the other causes being considered.[14]

Figure 1 shows an algorithm for conducting a workup and differential diagnosis of metabolic alkalosis.

CASE CONTINUED: HORMONE TESTING

The results of cortisol hormone studies are listed in **Table 3**. The 24-hour urine cortisol and serum ACTH levels were elevated. Therefore, the decision was made to proceed with the high-dose dexamethasone suppression test.

Administering an 8-mg dose of dexamethasone, more than 10 times the amount of cortisol produced daily, is anticipated to suppress ACTH secretion from pituitary tumors. These tumors usually retain some sensitivity to high-dose glucocorticoid negative feedback inhibition. In contrast, nonpituitary tumors that ectopically produce ACTH lack active glucocorticoid receptors and typically do not respond to glucocorticoid negative feedback.[15]

The high-dose dexamethasone suppression test resulted in less than 50% suppression of serum cortisol, with a baseline of 66.7 µg/dL dropping to 45.2 µg/dL after an 8-mg dose of dexamethasone was administered. This finding suggested ectopic ACTH production.

Computed tomography with intravenous contrast of the chest, abdomen, and pelvis did not identify an ectopic source of ACTH production. Magnetic resonance imaging of the brain revealed a 5-mm pituitary adenoma (**Figure 2**).

NEXT STEPS IN MANAGEMENT OF HYPERCORTISOLISM

4 Considering the updated information, what would be the most appropriate course of action?

- ☐ Start treatment for depression
- ☐ Inferior petrosal sinus sampling (IPSS)
- ☐ Refer to neurosurgery for pituitary adenoma resection
- ☐ Start empiric treatment with metyrapone

Individuals with hypercortisolism may exhibit various neuropsychological manifestations, as was observed in our patient.[16] Although elevated cortisol levels can also be associated with depression, the concurrent presence of metabolic alkalosis, hypertension, and hypokalemia is highly unusual in cases of depression.[17] Consequently, depression appeared less probable in our patient.

The clinical presentation, characterized by significantly elevated ACTH, less than 50% suppression of serum cortisol on the high-dose dexamethasone suppression test, profound hypokalemia, and metabolic alkalosis, appeared more consistent with ectopic Cushing syndrome. However, it is possible that the 5-mm pituitary adenoma could produce enough cortisol to cause the severe excess seen in this patient, especially considering that the computed tomography results of the chest, abdomen, and pelvis were normal.

Bilateral IPSS is the definitive test to distinguish between pituitary and ectopic ACTH–dependent Cushing syndrome.[18] This diagnostic procedure measures ACTH levels in both the pituitary and peripheral venous drainage.[18] A pituitary source is identified by a central-to-peripheral ACTH gradient of 2 or greater at baseline and 3 or greater after corticotropin-releasing hormone or desmopressin is administered, given the expectation of higher ACTH concentrations near the pituitary gland.[18] Conversely, the absence of a petrosal-to-peripheral ACTH gradient indicates an ectopic ACTH source.[18]

If the presence of a functional pituitary adenoma is confirmed on IPSS, the patient should be referred to neurosurgery for adenoma resection. The prevalence of nonfunctioning pituitary adenomas in the population is estimated to be approximately 7 to 41.3 per 100,000.[19]

Given the presence of a pituitary adenoma and the inability to identify an ectopic source of ACTH production, we proceeded with IPSS to differentiate between pituitary and ectopic ACTH–dependent Cushing syndrome.

Metyrapone, a steroidogenesis inhibitor, is employed in the treatment of hypercortisolism. It is an adjunctive therapy to lower cortisol levels while awaiting surgery or as an initial option for patients with unresectable, occult, or metastatic disease.[20] Metyrapone should not be started until all diagnostic evaluations are completed because it may influence the results of IPSS.

CASE CONTINUED

The findings from IPSS indicated a nonfunctional adenoma, supporting the diagnosis of an ectopic ACTH source as the root cause of hypercortisolism. Our patient then underwent gallium-68 dotatate positron emission tomography, revealing an anomalous tracer-avid left lung perihilar nodule with somatostatin receptor positivity (**Figure 3**). This finding conclusively established the diagnosis of a pulmonary carcinoid tumor.

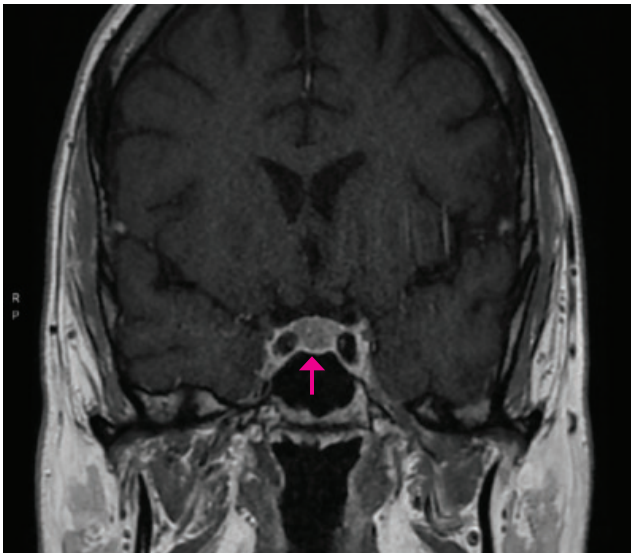

Figure 2. Magnetic resonance imaging of the brain showed a 5-mm pituitary adenoma.

TREATING HYPERTENSION IN ECTOPIC ADRENOCORTICOTROPIC SYNDROME

5 What is the optimal approach to managing our patient's hypertension as he awaits resection of the lung nodule?

- ☐ Losartan
- ☐ Hydrochlorothiazide
- ☐ Verapamil
- ☐ Eplerenone

Hypertension commonly develops as a complication of ectopic ACTH syndrome, and the preferred course of action in such cases is complete resection of the ACTH-secreting tumor. Nevertheless, it is crucial to manage blood pressure while awaiting the optimal therapy.

Losartan functions as an angiotensin II receptor blocker, reducing aldosterone while elevating renin and angiotensin II levels. In Cushing syndrome, hypertension is driven by excessive cortisol rather than an abundance of aldosterone. Consequently, effectively managing blood pressure necessitates targeted therapy for hypercortisolism, often involving mineralocorticoid receptor antagonists.

Thiazides and loop diuretics should be avoided because they may exacerbate hypokalemia.

Verapamil, a nondihydropyridine calcium channel blocker, may be less efficacious in this scenario because it does not influence the mineralocorticoid pathway.

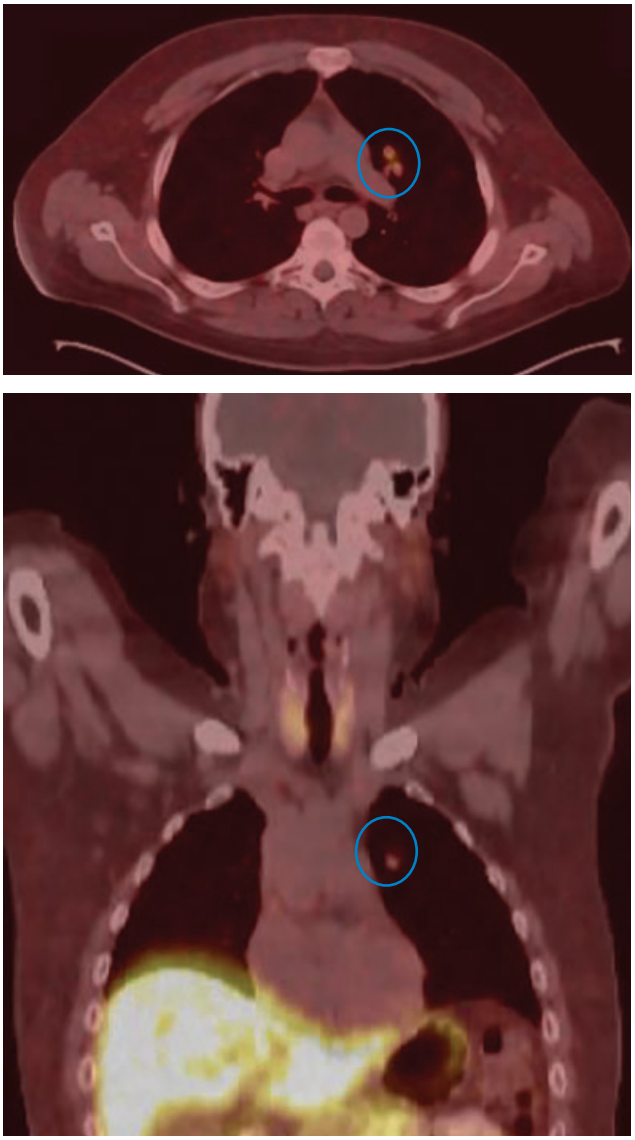

Figure 3. Left lung perihilar nodule (blue circles) revealed by gallium-68 dotatate positron emission tomography.

Eplerenone, a synthetic steroid and aldosterone receptor antagonist, hinders the activation of the mineralocorticoid receptor by excess cortisol.[21] Eplerenone is effective in managing hypertension in Cushing syndrome and can ameliorate aldosterone-mediated metabolic alkalosis and hypokalemia.[22]

CASE CONCLUSION

Our patient started treatment with eplerenone and metyrapone, in addition to potassium supplements. Subsequently, he underwent resection of the left hilar lung nodule. Surgical pathology revealed a 1.2-cm typical carcinoid tumor immunohistochemically labeled with ACTH. After the tumor was removed, ACTH levels decreased, leading to resolution of both hypokalemia and hypertension. Both eplerenone and metyrapone were discontinued after surgery, and the patient no longer required potassium supplements.

Ectopic ACTH syndrome, though rare, accounts for a minority of Cushing syndrome cases. While ectopic ACTH syndrome is associated with various malignancies, neuroendocrine tumors are the most common cause.

TAKE-HOME POINTS

- Begin the assessment of metabolic alkalosis by obtaining a spot urine chloride.
- For patients with chloride-resistant metabolic alkalosis (urine chloride ≥ 20 mmol/L) accompanied by hypertension and low levels of serum renin and aldosterone, consider Liddle syndrome, SAME, Geller syndrome, Cushing disease and syndrome, congenital adrenal hyperplasia, and licorice use in the differential diagnosis.
- Employ bilateral IPSS as the gold standard test to distinguish between pituitary and ectopic ACTH-dependent Cushing syndrome.
- Recognize that ectopic ACTH syndrome, although rare, constitutes a minority of Cushing syndrome cases. It is associated with various malignancies, but neuroendocrine tumors are the most common cause of ectopic ACTH syndrome.
- Choose aldosterone receptor antagonists as the primary antihypertensive for individuals with ectopic ACTH syndrome during the presurgery period.

DISCLOSURES

Dr. Hanouneh has disclosed teaching and speaking for Alexion, Astra Zeneca, BI/Lilly, and Bayer. The other 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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Diabetes technology: A primer for clinicians

ABSTRACT

Diabetes technology is evolving rapidly and is changing the way both patients and clinicians approach the management of diabetes. With more devices gaining US Food and Drug Administration approval and insurance coverage expanding, these new technologies are being widely adopted by people living with diabetes. We provide a summary of the commonly available devices in the market today that clinicians will likely encounter. This includes continuous glucose monitors (CGMs); connected insulin pens, caps, and buttons; and insulin pumps. Clinicians' awareness of and familiarity with this technology will enhance its accessibility for patients with diabetes.

KEY POINTS

CGMs measure interstitial glucose and transmit data wirelessly to a receiver. Evidence supports their use in patients on insulin therapy or who are at a high risk of hypoglycemia.

Connected insulin pens, caps, and buttons act as bridges between traditional insulin pens and insulin pumps. The technology allows patients to calculate how much insulin to take, accounting for carbohydrate intake, glucose level, and, in some models, previous insulin dose.

Insulin pumps deliver rapid-acting insulin continuously via the subcutaneous route either independently (open loop) or in association with CGMs (automated insulin delivery).

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Technology in diabetes management has come a long way. Devices measure glucose levels continuously (continuous glucose monitors, or CGMs), make it easier for patients to calculate insulin doses (smart pens, caps, buttons), and deliver insulin based on an algorithm (hybrid closed-loop insulin pumps). These devices help patients manage their diabetes in a manner consistent with their goals and lifestyle.

CGMs are increasingly available, providing information that clinicians can use to adjust medication doses or recommend lifestyle modifications. Insulin pump initiation and management traditionally has been the domain of endocrinologists. The introduction of newer, more simplified pumps, such as those that deliver basal insulin only or mealtime insulin only, however, may allow for increased management in primary care settings. Further, nonspecialty clinicians who are aware of pump basics can respond appropriately in urgent situations.

This review of the basics of various diabetes management devices is intended to enhance clinicians' comfort level in helping patients use these technologies. It is especially advisable to develop a working knowledge of CGMs, which are widely available. We acknowledge that there are other devices available in the market that are beyond the scope of this review, and more devices may become available through FDA approval after this article is published.

CONTINUOUS GLUCOSE MONITORS

A CGM system consists of a sensor, transmitter, and receiver. All models measure glucose in the interstitial fluid, with most doing so

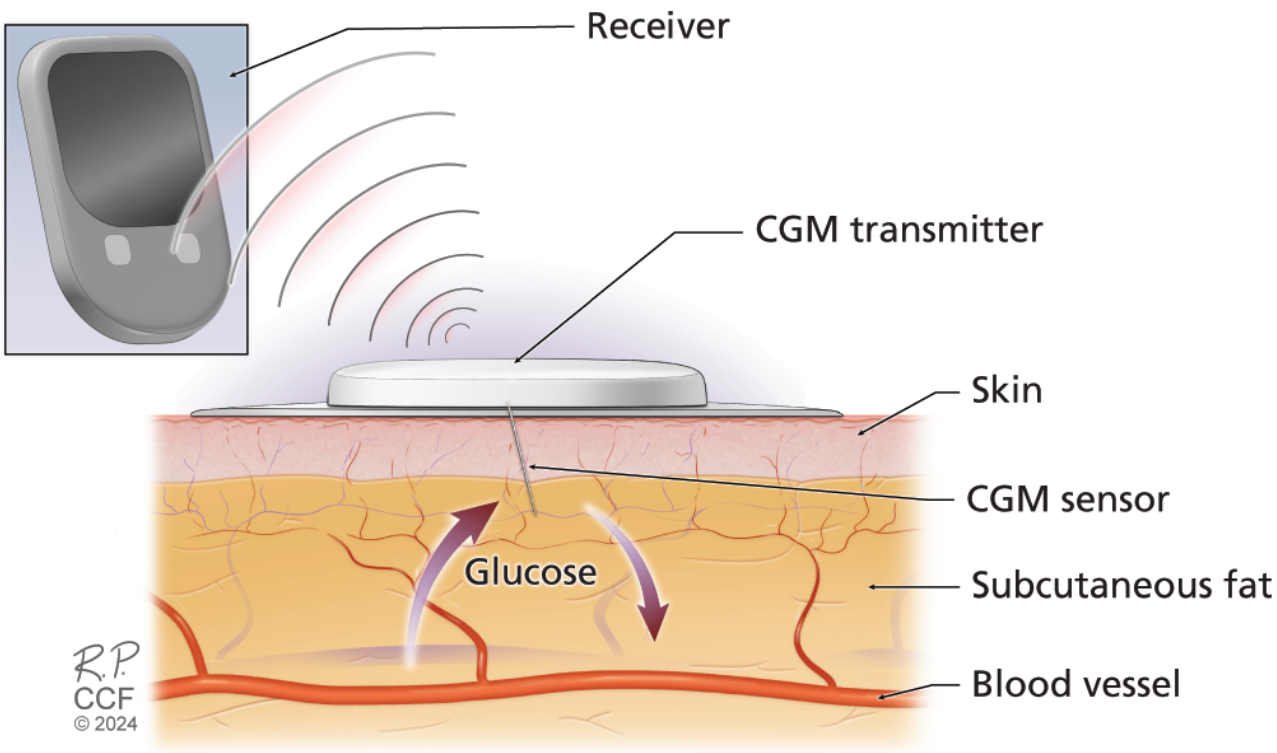

Figure 1. Schematic illustration of components of a continuous glucose monitor (CGM) system.

via a filament-like sensor inserted through the skin (**Figure 1**); one model is implanted subcutaneously via a tiny incision.[1] Data from the sensor are transmitted wirelessly to the receiver, either a cell phone or a dedicated reader.[2] In some models, the sensor and transmitter are 1 combined piece that is disposable. Other systems have reusable transmitters that may need to be charged.

Professional CGMs are owned by a hospital or a practice and are worn temporarily by the patient. Patient-owned, or personal, CGMs are becoming more common; these are classified as intermittently scanned or real-time.[3] Most CGMs (eg, Freestyle Libre 2, Freestyle Libre 3, Dexcom G6, and Dexcom G7) do not need calibration with fingerstick blood glucose monitors, although some, like Eversense E3 and Guardian Connect, need 1 to 2 calibrations daily to enhance sensor accuracy (**Table 1**).[4–13]

Intermittently scanned CGM devices

Intermittently scanned devices measure glucose levels and capture data continuously throughout the day. To save the data, the devices' sensors must be manually scanned with a smartphone or reader at least every 8 hours.[1]

The **Freestyle Libre 2** is a coin-shaped intermittently scanned device with an easy applicator for applying the sensor to the body. The patient needs to scan the sensor with a compatible reader or smartphone. The sensor lasts for 14 days and has a 1-hour warm-up time (the time from applying the sensor to display of the first available glucose reading). Advantages of the device are its affordability and availability, but if the patient does not scan the sensor at least every 8 hours, the resulting gaps in data transmission make interpretation more difficult.

The **Freestyle Libre 2 Plus** is a recently announced modification of the Libre 2 system. Significant changes include 15-day wear time, higher vitamin C threshold (1,000 mg) before interactions (falsely elevated glucose readings) occur, and integration with insulin pumps, ie, the ability of the sensor to communicate with an insulin pump.[4] This modification also has a lower mean absolute relative difference (MARD) of 8.2%. MARD is the difference of the CGM reading from the reference or standard-of-care measurement; a lower MARD indicates greater accuracy. The Freestyle Libre 2 Plus transmits CGM data via Bluetooth to the insulin pump without a scan, but the patient needs to

TABLE 1
Continuous glucose monitors

	Dexcom G6	Dexcom G7	Freestyle Libre 2	Freestyle Libre 2 Plus	Freestyle Libre 3	Eversense E3	Guardian Connect
Maximum wear time (days)	10	10.5	14	15	14	180	7
Warm-up time	2 hours	30 minutes	1 hour	1 hour	1 hour	24 hours	Up to 2 hours
MARD[4–7,10,13]	9%	8.2%	9.2%	8.2%	7.9%	8.5%	9% (arm), 10.5% (abdomen)
Calibrations required	0	0	0	0	0	2 per day for 21 days, then 1 per day	2 per day
Integration[a] with insulin pumps, smart pens, caps, buttons	t:slim X2, Omnipod 5, iLet, Tempo Smart Button	InPen (available only for Apple iOS), t:slim X2, iLet, Tempo Smart Button	Bigfoot Unity smart cap	t:slim X2	Insulin pumps FDA-cleared but not yet available	None	None
Display device	Smartphone or reader	Smartphone or reader	Smartphone or reader	Smartphone or reader	Smartphone or reader	Smartphone only	Smartphone only
Drug interactions	Hydroxyurea	Hydroxyurea	Vitamin C > 500 mg	Vitamin C > 1,000 mg	Vitamin C	Tetracycline antibiotics, mannitol	Acetaminophen, hydroxyurea
FDA-cleared sites	Abdomen	Upper arm	Upper arm	Upper arm	Upper arm	Upper arm	Upper arm, abdomen
Approved in pregnancy	No	Yes	Yes	Yes	Yes	No	No

[a]Integration is the communication ability between the glucose monitor sensor and pump or other device.

FDA = US Food and Drug Administration; MARD = mean absolute relative difference

Based on information from references 4–13.

scan the sensor to display a blood glucose reading on the display device.

Real-time CGMs

Real-time CGMs, which also capture glucose data continuously throughout the day, need no participation from the patient except when the sensor needs to be replaced. Data are transmitted wirelessly to the patient's smartphone or reader. While many sensors work with smartphones, it is important to verify compatibility with the patient's smartphone. If a sensor is incompatible, then the standalone reader would need to be prescribed. Most manufacturers specify the compatibility of their devices on their websites.

The **Freestyle Libre 3** sensor lasts for 14 days. This real-time CGM can be used with the Freestyle Libre 3 application on a smartphone, but also works with a standalone reader. Freestyle Libre 3 has an improved MARD compared with Freestyle Libre 2.[5] The Freestyle Libre 3 uses Bluetooth, improving its connectivity and data transfer compared with Libre 2, which uses near-field communication, a wireless technology that requires a distance of 4 cm or less between devices for connection to occur.

The latest models of the Dexcom system are G6 and G7.[6,7] **Dexcom G6** requires 2 replaceable parts to function: a sensor that needs to be replaced every 10 days and a transmitter that needs to be replaced every 3 months. Its warm-up time—how long until a glucose reading is available after the CGM is inserted—is 2 hours.[6] A smartphone or reader is needed to collect data.[8] **Dexcom G7**, cleared by the US Food

and Drug Administration (FDA) in December 2022,[9] has several advantages over its predecessor. It has a shorter warm-up period (30 minutes), the MARD is lower (8.2% vs 9.0%), and the sensor and transmitter have been integrated into a single device that requires replacement every 10 days, with a 12-hour grace period.

Eversense E3 is unique among CGMs in that its sensor is implanted in the patient's subcutaneous tissue for long-term (up to 6 months) glucose monitoring. The sensor communicates via a rechargeable transmitter that is attached to the skin over the sensor using an adhesive patch and wirelessly (Bluetooth) transmits data to a mobile device. The glucose data are displayed on a smartphone application; no dedicated reader is available. A trained healthcare professional can manage the insertion and replacement process during an office visit.[10,11]

Guardian Connect consists of a sensor and transmitter that act as a standalone CGM. It works exclusively with smartphone applications; the sensor lasts for 7 days and needs to be calibrated twice daily (ie, at least every 12 hours) with a fingerstick glucose monitor to maintain accuracy. The transmitter needs to be charged weekly and is typically used for 1 year or longer.[12,13]

Which patients are candidates for a CGM?

The distinct advantage CGMs have over traditional fingerstick glucose checks is fewer severe hypoglycemic and hyperglycemic episodes.[3] CGMs were developed for patients who were using insulin pumps or needed multiple daily insulin injections. Now, with increased availability of CGM devices and their ability to support meaningful lifestyle changes, patients with diabetes can benefit from continuous glucose monitoring regardless of medication regimens, glucose patterns, or risks of hypoglycemia. Even patients with a "smoldering" hemoglobin A1c of 7.5% to 8.5% may benefit from a CGM. While hemoglobin A1c is a good tool for assessing glycemic control, it does not provide detailed analyses such as postprandial spikes or undetected early morning hypoglycemia during sleep.[14] CGMs can be useful in this setting, even in seemingly stable patients with diabetes, to guide medication and behavioral changes.

The patient's preference, comfort and ease with technology, willingness to engage with the device, caregiver support, interacting medications, and insurance coverage, along with device affordability, are important factors in determining which CGM is appropriate.[3,15]

Except for Eversense E3, CGM sensors must be removed for computed tomography scans and magnetic resonance imaging.[16] The Eversense E3 transmitter must be removed, however. Certain drugs can interfere with readings: vitamin C can affect readings from Freestyle Libre CGMs, particularly at high doses[17]; acetaminophen at doses greater than 4 g daily along with hydroxyurea can affect readings from Guardian Connect and Dexcom G6 and G7[16,18]; and tetracycline and mannitol can affect Eversense E3 readings.[11,19]

PENS, CAPS, AND BUTTONS

Smart insulin pens and associated smart caps and buttons can help address hurdles such as missed doses and suggest correction doses for hyperglycemia. These devices can act as a bridge for patients on insulin who are interested in insulin pumps but are not ready to adopt them yet.

Smart insulin pens

Most people with diabetes face challenges regarding timing of injections and administering the correct dosage of insulin. Bluetooth- or near-field communication–enabled smart insulin pens communicate with smartphone applications to monitor insulin administered at different times of day. Smart insulin pens keep track of insulin doses administered and active insulin on board; many have an insulin bolus calculator that enables the user to calculate mealtime insulin doses based on the amount of carbohydrates they are about to consume and their glucose level prior to the meal. Specialized short-acting insulin cartridges like Humalog and NovoLog need to be prescribed separately for use with these devices.

The **InPen** is a good example of a smart insulin pen available in the United States. It can communicate with CGM applications (eg, Guardian Connect, Dexcom G6, Dexcom G7) to keep track of both blood glucose levels and administered insulin.[20,21] It can also alert the user to a missed basal or bolus insulin dose, thus preventing large fluctuations in blood glucose levels.

Smart caps and buttons

The **Bigfoot Unity** diabetes management system offers smart caps, devices that attach to commercially available short- or long-acting disposable insulin pens. In this system, the patient scans the Freestyle Libre 2 sensor with a smart cap that is attached to the insulin pen. The cap captures the glucose data and suggests a correction dose based on predetermined settings defined by the healthcare team and programmed into the mobile application. The cap also records the timing of insulin administration to prevent stacking of insulin doses, and will not recommend an additional correction dose within 3 hours of a previous dose.[22]

The Bigfoot Unity application combines the glucose data from the CGM with insulin doses administered and makes it available at a single location for the patient and clinician. The application, which has alarms set for hypoglycemia and missed insulin doses, is currently FDA-cleared for both type 1 and type 2 diabetes.[22] The pen caps, white for rapid-acting insulin and black for long-acting insulin, are rechargeable. This system historically has required clinics or hospitals to subscribe to the company to use its devices; however, it is projected to be available through pharmacies in the near future.

The **Tempo Smart Button** device attaches to a prefilled custom-made manufacturer-branded insulin pen. When the patient presses the button to deliver insulin, it shares data via Bluetooth with a smartphone application, recording the type of insulin, dose, and time of administration. Each button lasts for up to 8 months. The smartphone application integrates insulin dosing data, glucose data obtained from Dexcom G6 or G7, and food, exercise, and sleep data. The application also delivers customized alerts to patients to view their glucose data on a daily or weekly basis and provides alerts on missed doses.[23]

Which patients are candidates for smart pens, caps, or buttons?

A person living with diabetes who needs multiple daily insulin injections and has access to a smartphone and suitable applications might consider smart pens, caps, or buttons as an alternative to insulin pumps. These devices are most useful for patients who struggle with dose calculations or who miss or forget doses and may benefit from missed-dose alerts.[24,25] These options also might be preferable for patients who are less comfortable with technology.

PUMPS AND CONTINUOUS INSULIN INFUSION

Insulin pumps, used for continuous subcutaneous insulin infusion, deliver rapid-acting insulin at a preset per-hour dose throughout the day for basal needs. Patients must self-administer mealtime boluses with the pump itself based on the amount of carbohydrates in their upcoming meal. Most currently available pumps have a reservoir that stores the insulin and tubing that connects the reservoir to a cannula inserted into the skin. Examples of available pumps are the t:slim X2, Mobi, MiniMed, and iLet ACE. Omnipod DASH and Omnipod 5 are examples of tubeless, or patch, pumps.

Insulin pumps can be broadly divided into systems based on their level of automation and interaction with CGMs.

Manual or open loop

These systems deliver basal insulin based on predetermined settings without regard to CGM readings. In such systems, the CGM device and insulin pump act as separate entities and do not interact.

Automated insulin delivery

With these systems, CGMs and insulin pumps are programmed to share information, allowing for insulin administration based on CGM data.

Low glucose suspend systems are insulin pumps that shut off insulin delivery to minimize hypoglycemia. They do this in 1 of 2 ways:

- Suspend at low glucose value. The MiniMed Paradigm series, no longer available for purchase in the Unites States, suspends insulin delivery and alerts the user when a preprogrammed low glucose threshold is reached; the MiniMed 670G, 770G, and 780G pumps can suspend insulin delivery in manual mode (in manual mode, the pump does not take into account the glucose values from the CGM and delivers insulin via basal rates independently)
- Suspend at predicted low glucose value. Pumps such as the **t:slim X2 with Basal-IQ** predict the onset of hypoglycemia and suspend insulin delivery before it occurs; the MiniMed 670G, 770G, and 780G pumps can also do this in manual mode.

Hybrid closed-loop systems use readings from a CGM and deliver basal insulin using a proprietary algorithm, with or without the need to input basal insulin rates into the pump. Alternatively, the endocrinology team inputs basal rates and the pump uses an algorithm to deliver a fraction of a correction dose hourly to counteract hyperglycemia. Over time, in pumps such as the MiniMed 780G or Omnipod 5, the pump targets a glucose level rather than a preset basal rate. Insulin delivery is reduced or stopped when patients are predicted to develop hypoglycemia. Hybrid closed-loop systems require patients to push buttons to tell the pump to deliver mealtime insulin boluses.

Examples of hybrid closed-loop pumps include **MiniMed 670G**, **770G**, and **780G**, **t:slim X2**, **Mobi with Control-IQ**, and **Omnipod 5**. The MiniMed pumps work in closed loop only with the proprietary Guardian sensor. The t:slim X2 and Omnipod 5 are cleared by the FDA to work with the Dexcom G6 glucose monitor. The FDA has also cleared the Dexcom G7, Freestyle Libre 2 Plus, and Libre 3 CGMs, as well as interoperable CGMs (which can integrate with insulin pumps form various manufacturers), for integration with certain insulin pumps. These

integrations are currently available with the t:slim X2 (with the Freestyle Libre 2 Plus and Dexcom G7 CGMs) and iLet ACE or Bionic Pancreas (with Dexcom G7) in the US market.[9,26]

The **Mobi** is smaller than other available pumps. It has a shorter (5-inch) tubing option and can be taped onto the skin and controlled with a compatible smartphone. Although FDA-cleared, the Mobi is not yet available in the consumer market. Because the Mobi uses the same "Control IQ" algorithm as the t:slim X2, it integrates with Dexcom G6 and it is anticipated that it will integrate with Dexcom G7. Integration of the Mobi pump with the Freestyle Libre 2 Plus CGM has not yet been announced.[27]

The **iLet Bionic Pancreas**, a hybrid closed-loop insulin pump, was cleared by the FDA in May 2023 for patients with type 1 diabetes.[28] Its algorithm uses the patient's body weight and glucose targets to determine basal insulin rates; instead of entering carbohydrate values, the patient indicates their meal size (usual, smaller or larger than usual).The device can be used with Dexcom G6 and G7.

Do-it-yourself hybrid closed-loop systems are open-source software systems that use a smartphone application and bridging devices to simulate hybrid closed-loop communication between a CGM and insulin pump. In 2023, the Tidepool application, which originated from a do-it-yourself program, received FDA clearance.[29]

Closed-loop systems, currently being researched and not yet available, would require no user input and ideally would calculate mealtime bolus dosing automatically. The highest-level closed loop system should counteract hypoglycemia by administering glucagon.

Patch pumps

Mechanical disposable patches such as **V-Go** and **Simplicity** contain rapid-acting insulin like lispro or aspart. V-Go delivers insulin at a steady rate for 24 hours through a needle. When bolus insulin is needed at mealtime, the patient clicks a button on the pump to deliver 2 units of insulin. V-Go does not require a battery. It has different fixed-dose capacities consisting of 20, 30, and 40 units delivered at a uniform rate over 24 hours. It can deliver up to 36 units of bolus insulin in a 24-hour period. The patient needs to change the pump every day.[30] The Simplicity patch is a bolus-only pump. It can be worn for 3 days and holds up to 200 units of rapid-acting insulin. Patients may use it to deliver a bolus before meals; each click delivers 2 units of insulin. These devices can be useful when patients do not want to use pens or needles and prefer discretion in public places.[31]

Basal-only patch pump. Apart from the Omnipod DASH and Omnipod 5 discussed above, the **Omnipod GO** is a standalone tubeless pump that delivers rapid-acting insulin in 7 different preprogrammed rate options over 72 hours. It was cleared by the FDA in April 2023.[32]

Which patients are candidates for insulin pumps?

Continuous subcutaneous insulin infusion demands more patient involvement than multiple injected doses. Factors to consider include the patient's prior adherence to treatment, mental and psychological status, device preferences, and availability for follow-up visits, as well as device affordability for the patient.[3,15,33] Automated insulin delivery systems are now the standard of care for patients living with type 1 diabetes.[34] Automated insulin delivery- or sensor-augmented pumps may also be considered in other forms of insulin-deficient diabetes, including type 2 diabetes.

There are important considerations regarding insulin pumps. Patients must remove insulin pumps before undergoing computed tomography and radiography (none are radiation-safe), magnetic resonance imaging, and other imaging modalities. When using airport security, patients should avoid full-body scanners and request manual pat-downs and metal detectors. If insulin infusion is suspended for more than 1 to 2 hours, the patient needs to inject long-acting insulin to avoid complications such as diabetic ketoacidosis.

CLOSING THOUGHTS

The American Diabetes Association recommends that automated insulin delivery systems be offered to patients with type 1 and other forms of insulin-deficient diabetes, with the choice based on the patient's circumstances, preferences, and needs.[34] Clinical trials provide evidence of reduced A1c levels and improved time in goal range.[3] Time below the desired glucose range is often reduced as well through features that can decrease or suspend insulin delivery based on predicted low glucose levels.[35] Pivotal clinical trials for available systems show that all can achieve the recommended time-below-range targets of less than 4% of time spent below 70 mg/dL and less than 1% of time below 54 mg/dL. However, there are few head-to-head comparisons, and the patient populations and trial designs differed, so it is a challenge to make direct comparisons in terms of hypoglycemia.[36]

Several device options can improve outcomes or decrease the mental burden in people living with diabetes. Increased comfort level with this technology among clinicians will benefit patients. We encourage primary care physicians to work with endocrinology colleagues to identify patients who are candidates for these devices, ensure that patients who are candidates for these devices are offered the options to use them, and arrange timely access to them.

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REVIEW

CME MOC

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Preexposure prophylaxis for preventing HIV infection: Routine practice in primary care

ABSTRACT

An estimated 1.2 million people in the United States have human immunodeficiency virus (HIV) infection per US Centers for Disease Control and Prevention 2021 data. The highest risk of HIV transmission occurs during injection drug use with needle sharing and during sexual activity, most significantly in condomless, receptive anal intercourse. Preexposure prophylaxis (PrEP) for the prevention of HIV infection is part of a larger biobehavioral strategy that uses antiretroviral medication, an oral formulation taken daily or during anticipated exposure events, or an injectable formulation administered every 8 weeks. PrEP consists of 3 possible regimens: emtricitabine/tenofovir disoproxil fumarate, emtricitabine/tenofovir alafenamide, or injectable cabotegravir. Primary care clinicians are strategically positioned to provide PrEP education and access.

KEY POINTS

- The 3 available PrEP regimens are emtricitabine/tenofovir disoproxil fumarate, emtricitabine/tenofovir alafenamide, and injectable cabotegravir.
- The highest risk of HIV transmission occurs during injection drug use with needle sharing and during sexual activity, most significantly in condomless receptive anal intercourse.
- Conducting a sexual history is a first step in identifying behaviors that may place patients at risk for, or protect them from, exposure to HIV.

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The US Centers for Disease Control and Prevention 2021 data estimate that 1.2 million people in the United States have human immunodeficiency virus (HIV) infection,[1,2] and that 766,000 people have died from complications of HIV infection between the first report of HIV in 1981 and 2019.[2,3] Despite a downturn in new cases of HIV infection in the United States over the past decade, 30,635 new infections were reported in 2020.[2,4] While this is a 17% decrease from 2019, 36,136 new infections were reported in 2021, an 18% increase,[5] possibly owing to healthcare disruption during the COVID-19 pandemic.[1,4] Of these new cases, about 80% are in adolescents (age ≥ 13) and adult men, and 68% are in men who have sex with men (MSM).[2,4]

Social disparity contributes to the epidemiology of HIV infection.[1,2,5,6] Black or Hispanic persons, transgender individuals (specifically transgender women), and persons who inject drugs are disproportionately affected compared with the general population.[2,5,6] The highest risk of HIV acquisition occurs during injection drug use with needle sharing and during sexual activity, most significantly in condomless receptive anal intercourse. The likelihood that a specific activity will result in HIV infection is related to the detectable viral load of a partner with HIV, compounded by concurrent inflammatory sexually transmitted infections.[2,7]

Preexposure prophylaxis (PrEP) for the prevention of HIV infection is part of an effective biobehavioral intervention that includes

TABLE 1
Suggested questions for obtaining a sexual history

Questions	Comments and follow-up questions
Are you sexually active?	Explore what sexual activity means for the patient
Who are your sexual partners?	Ask in an anatomic- and gender-inclusive manner: partner with a penis, partner with a vagina, only male, only female, transgender men, transgender women, gender nonconforming
Do you have a current partner or partners?	Does your partner have multiple partners?
How many partners have you had in the past 6 months?	
How do you typically meet partners?	Specifically inquire regarding online, app, casual hookup, anonymous sexual encounters, sex workers, or friends
What sexual activities do you participate in?	Specifically inquire regarding oral, vaginal, anal, top (insertive), bottom (receptive)
Do you use condoms or barriers with steady or new partners?	Guide to quantify as never, rarely, 50%, or always
Do you or your partner(s) have a history of sexually transmitted infections?	Any infections in past 6 months?
Do you have plans for prevention of pregnancy?	Are you using or interested in contraception?
Do you have a history of commercial sex work?	

Based on information from reference 21.

antiretroviral medication taken daily or during anticipated exposure events.[6,8] Currently, there are 3 PrEP regimens available: emtricitabine/tenofovir disoproxil fumarate, emtricitabine/tenofovir alafenamide, and injectable cabotegravir. In 2021 it was estimated that only 30% of the 1.2 million people who could benefit from PrEP were prescribed this therapy.[9] Although evidence does demonstrate occurrence of drug-resistant HIV infection during PrEP therapy, the incidence is rare. Most resistant cases were reported when treatment was started during an undiagnosed acute HIV infection or during inconsistent PrEP use.[10] When adherence to PrEP regimens is at least 70%, the approximate reduction of risk of HIV infection is 75% (approximate number needed to treat = 33).[11]

Primary care clinicians are positioned to provide PrEP education and access.[12]

PrEP IN PRACTICE

Screening

The US Preventive Services Task Force recommends screening all adults and adolescents age 15 or older for HIV.[13] All sexually active persons should be informed about PrEP for the prevention of HIV infection.[14] PrEP is recommended if behaviors indicate risk of HIV acquisition, as it is a safe and effective prevention strategy.[15]

Patients often do not disclose stigmatized sexual or substance use behaviors to clinicians, especially when not asked.[14] Routinely taking a sexual history creates an opportunity to provide appropriate sexual healthcare.[15,16] Often this history is not completed due to urgency of other medical conditions, time constraints, clinician discomfort and bias of sexual practice, and lack of experience and familiarity in discussing sexual healthcare topics.[12,14,17–20] Using a sexual history framework based on cultural humility, context, and open conversation helps to develop rapport and trust, especially in a sexual and gender minority population. A guided discussion of sexual history increases the effectiveness of the conversation and may decrease the associated anxiety of both patient and clinician.[21]

Conducting a sexual history is a first step in identifying behaviors that may place patients at risk for, or protect them from, exposure to HIV.[2,13] Elements of a complete history include sex assigned at birth with organ inventory; gender identity; sexual orientation, practices, and partners; transactional or commercial

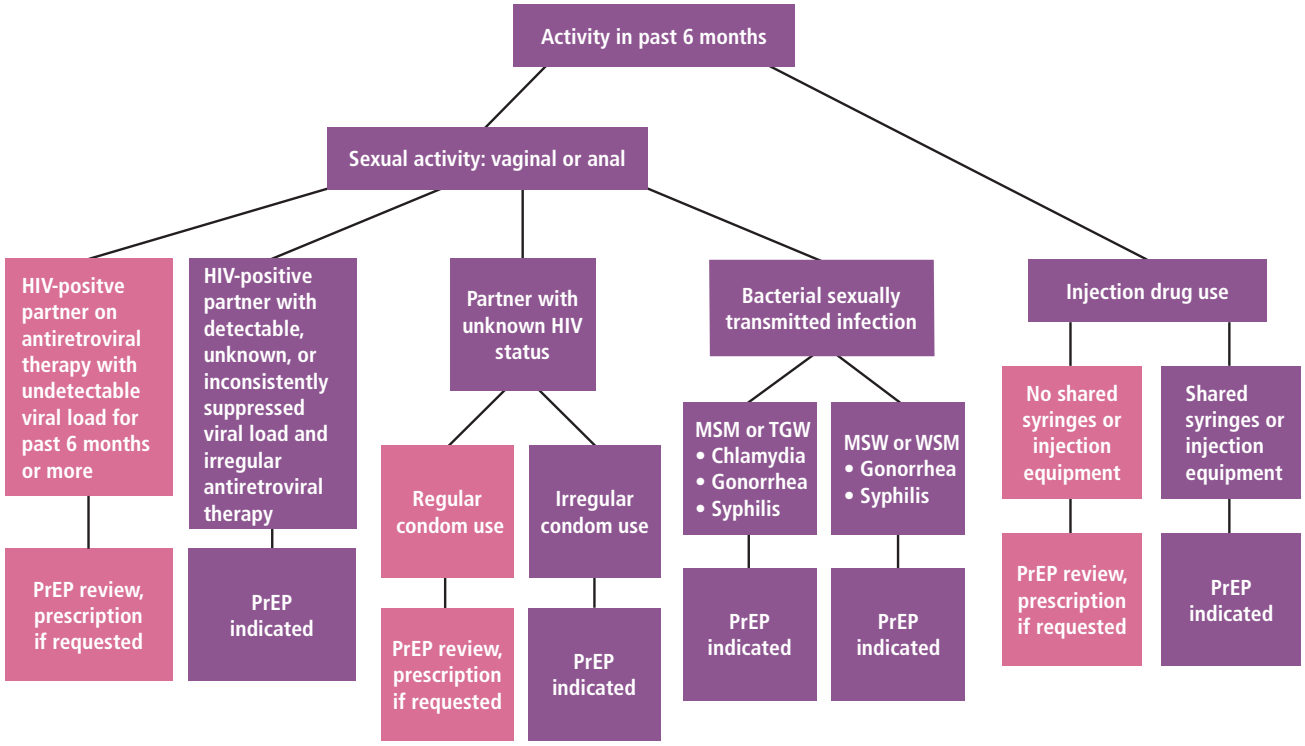

Figure 1. Considerations for initiation of preexposure prophylaxis.

HIV = human immunodeficiency virus; MSM = men who have sex with men; MSW = men who have sex with women; PrEP = preexposure prophylaxis; TGW = transgender women; WSM = women who have sex with men

Based on information from references 2,6,14,22–25.

sex work; sexually transmitted infections; protective practices; intention of pregnancy; and prevention methods (**Table 1**).[2,8,14,21]

Screening for alcohol use disorder, use of noninjecting illicit drugs, and receptive sharing of syringes and injection equipment of illicit drugs also helps determine risk of HIV acquisition and whether PrEP therapy may be considered.[2,14] Further, referrals should be placed for substance-use support and harm-reduction interventions.[6,14]

Indications for PrEP

Indication for PrEP can be assessed using the strategy illustrated in **Figure 1**.[2,6,14,22–25] Vaginal or anal sexual activity or history of injection drug use with shared syringes or injection equipment in the past 6 months directs care. If no activity is disclosed, information about PrEP should be reviewed. Regardless of disclosed or identified risk behaviors, any patient who requests PrEP should be offered this therapy.[2,6,14]

Sexual activity with an HIV-positive partner receiving antiretroviral therapy with an undetectable viral load (ie, less than 200 copies/mL) for at least the previous 6 months prompts PrEP review and prescription, if requested. This is noted in the 2016 Prevention Access Campaign's health equity initiative, using the slogan Undetectable = Untransmittable or U = U, signifying that an individual with an undetectable viral load cannot sexually transmit the virus to others.[22,26] PrEP is indicated in the following scenarios:

- A partner's viral load is detectable, not known, or inconsistently suppressed, or if use of antiretroviral therapy is irregular
- The patient is sexually active with any partner without knowing the partner's HIV status, or with irregular condom use; consistent condom use directs PrEP review and prescription, if requested
- The patient has had a bacterial sexually transmitted infection in the past 6 months, specifically chlamydia, gonorrhea, or syphilis in MSM and transgender women, and gonorrhea or syphilis in men who have sex with women and women who have sex with men.[2]

TABLE 2
Testing in patients prescribed preexposure prophylaxis for HIV prevention

PrEP medications	Emtricitabine/tenofovir disoproxil fumarate	Emtricitabine/tenofovir alafenamide	Cabotegravir
Initial testing			
Human immunodeficiency virus (HIV) antigen/antibody	X	X	X
HIV RNA	X	X	X
Creatinine/estimated creatinine clearance	X	X	X
Rapid plasma reagin syphilis screening	X	X	X
Gonorrhea/chlamydia nucleic acid amplification testing[a]	X	X	X
Hepatitis A virus specific immunoglobulin G	X	X	X
Hepatitis B surface antigen	X	X	X
Hepatitis B surface antibody	X	X	X
Hepatitis B core antigen	X	X	X
Hepatitis C virus-specific immunoglobulin G	X	X	X
Pregnancy test[b]	X		X
One month			
HIV antigen/antibody	X	X	X
HIV RNA			X
Every 2 months			
HIV antigen/antibody			X
Rapid plasma reagin syphilis screening[c]	Not applicable	Not applicable	X
Gonorrhea/chlamydia nucleic acid amplification testing[a,c,d]			X
Pregnancy test[b]			X
Every 3 months			
HIV antigen/antibody	X	X	
Creatinine[e]	X	X	
Rapid plasma reagin syphilis screening	X	X	Not applicable
Gonorrhea/chlamydia nucleic acid amplification testing[a,d]	X	X	
Pregnancy test[b]	X		
Annually			
Creatinine[e]	X	X	X
Hepatitis C virus-specific immunoglobulin G[f]	X	X	X
Lipid panel		X	

[a]3-site testing of self-collected urine or vaginal specimen, pharyngeal swab, and rectal swab.
[b]Urine pregnancy testing if childbearing potential.
[c]Testing intervals may be extended to every 4 months.
[d]Gonorrhea testing semiannually and chlamydia testing at least yearly for cisgender women.
[e]Renal function testing may be performed semiannually.
[f]Hepatitis C virus immunoglobulin G may be tested more regularly and as requested.

Based on information from references 2,6,14,22–25.

Although there is no indication for PrEP for reducing HIV risk from injection drug use with shared syringes or injection equipment within the past 6 months, guidelines note that patients who engage in such activity likely benefit from these medications.[2] If patients do not endorse drug use activity or sharing of items, PrEP should be reviewed and prescribed if requested.

TESTING GUIDELINES

HIV testing

The US Centers for Disease Control and Prevention and the US Preventive Services Task Force recommend that MSM, persons who inject drugs, patients with an HIV-positive sexual partner, and persons at substantial risk of HIV transmission have annual HIV testing.[2,14]

If additional risk factors are present, testing every 3 to 6 months is recommended.

Documented, confirmed negative HIV-testing results within the week are required before starting PrEP therapy, and HIV testing should be repeated at intervals after PrEP initiation.[2,14] Testing options include an HIV antigen-antibody assay, viral load and nucleic acid (or RNA) laboratory testing, or US Food and Drug Administration (FDA)–approved point-of-care fingerstick antigen-antibody blood tests.[2,14] If point-of-care testing is used, a laboratory antigen-antibody test should always be ordered with baseline laboratory screening, as point-of-care testing has lower sensitivity. This practice increases detection of an unrecognized acute infection.[2,14]

Testing for bacterial sexually transmitted infections

Testing for gonorrhea, chlamydia, and syphilis is recommended at least annually.[2,6,14] For gonorrhea and chlamydia, 3-site testing of self-collected urine or vaginal specimens, pharyngeal swabbing, or rectal swabbing is recommended at PrEP initiation and for MSM at quarterly visits.[2,14] Semiannual gonorrhea and annual chlamydia testing is recommended for cisgender women. Chlamydia infection, in contrast to syphilis and gonorrhea, does not have a strong correlation with risk of HIV transmission and may be screened for less frequently.

Gonorrhea or chlamydia infection in men who have sex with women and women who have sex with men warrants consideration of expedited partner therapy. Based on limited data regarding expedited partner therapy in MSM and the incidence of other bacterial sexually transmitted coinfections, shared clinical decision-making regarding expedited partner therapy is recommended.[2,14] In cases of syphilis or HIV diagnoses, referral for partner services is advised.

Syphilis screening, commonly performed with a rapid plasma reagin test, is recommended at least annually for those at increased risk of infection based on high-risk sexual and injection drug use behaviors and during each pregnancy.[2,6] Periodic testing may be performed every 3 to 6 months and as requested.

Laboratory testing

Estimated creatinine clearance rate (mL/min) calculation and serum creatinine testing should be done for patients on oral PrEP because decreased renal function is a potential safety issue.[2,27] Renal function should be assessed every 6 to 12 months.

Tenofovir and emtricitabine are used to treat chronic hepatitis B virus infection. Patients with chronic hepatitis B who discontinue PrEP may experience a significant hepatitis flare. Hepatitis B virus testing allows for this risk to be considered and patients counseled accordingly if screening is positive. Screening for hepatitis B virus infection is performed by measuring hepatitis B surface antigen, hepatitis B surface antibody, and total antibody to hepatitis B core antigen.[2,27] Ideally, this triple-panel screening should be performed before PrEP is started, but screening should not delay therapy. Initiating PrEP in patients with chronic hepatitis B virus infection should be done in consultation with an expert in hepatitis B virus treatment.[2,27]

Hepatitis C screening is recommended at least once in a lifetime for all adults age 18 or older and during each pregnancy.[28] Annual and periodic testing may be performed for persons with ongoing high-risk behaviors, including persons who inject drugs or participate in receptive condomless anal sex, or as requested.

Annual lipid panel monitoring should be performed for patients on emtricitabine/tenofovir alafenamide as clinical trials have shown greater weight gain and elevation in triglyceride levels in MSM and transgender women taking this medication than in those taking emtricitabine/tenofovir disoproxil fumarate.[2,14] This increased risk may be considered when treating patients with preexisting cardiovascular risk.

Dual-emission x-ray absorptiometry scans should be considered in patients with a history of osteopenia or pathologic bone fracture.[22]

Recommended testing for patients starting and taking PrEP therapy is summarized in **Table 2**.[2,6,14,22–25]

PRESCRIBING: ORAL MEDICATION

Two oral PrEP medications, both 2-drug combinations of HIV-1 nucleoside analogue reverse transcriptase inhibitors, are approved by the FDA, and have a Grade A recommendation from the US Preventive Services Task Force (**Table 3**).[2,6,14,22–25,29] In men at risk for sexual exposure to HIV, oral PrEP medications have high efficacy (up to 99% when taken as prescribed) and good safety profiles.[14,22,23,30] PrEP is not approved for expedited partner therapy.

In 2021 the US Department of Health and Human Services established that some federal health programs and most commercial insurers must provide oral PrEP medication, indicated laboratory tests, and clinic visits with no out-of-pocket cost to patients.[14] However, navigating insurance coverage of PrEP can be challenging. Prior authorizations are commonly required, and copay

TABLE 3
Preexposure prophylaxis prescribing, safety, and other considerations

PrEP medications			
Generic name	Emtricitabine/tenofovir disoproxil fumarate	Emtricitabine/tenofovir alafenamide	Cabotegravir
Dosing	200/300 mg daily or on-demand	200/25 mg daily	600-mg gluteal intramuscular injection
Population	Cisgender women/cisgender men,[a] transgender women, transgender men,[a] persons who inject drugs	Cisgender men,[b] transgender women[b]	Cisgender women,[a] cisgender men,[b] transgender women[b]
Prescribing	30-day initial prescription 90-day maintenance	30-day initial prescription 90-day maintenance	Optional lead-in 30-mg oral daily for 4 weeks Initial injection, then second injection in 4 weeks Maintenance injection every 8 weeks
Safety			
Side effects	Headaches, abdominal pain, nausea, weight loss	Diarrhea, weight gain	Tenderness and redness at injection site
Renal function	Estimated creatinine clearance > 60 mL/minute	Estimated creatinine clearance > 30 mL/minute	No renal restrictions
Drug interactions	Drugs compromising renal function (antivirals, aminoglycosides, and high-dose nonsteroidal anti-inflammatory drugs) may increase concentration	St. John's wort may decrease concentration Antibiotics rifabutin and rifapentine should not be coadministered May consider rifampin if benefit outweighs risk	Carbamazepine, oxcarbazepine, phenytoin, phenobarbital, rifampicin, and rifapentine may decrease concentration May consider rifabutin if benefit outweighs risk
Other concerns	Avoid use with osteopenia or osteoporosis or with renal impairment	Avoid use with osteopenia or osteoporosis	Caution if gluteal fillers or if at increased bleeding risk Caution with end-stage kidney disease not yet receiving dialysis
Other			
Missed dose	Continue daily dosing	Continue daily dosing	> 7 days late: oral preexposure prophylaxis bridging until next injection > 8 weeks late: restart administration

[a]Includes insertive and receptive vaginal or anal sex.
[b]Insertive vaginal or anal sex and receptive anal sex; not approved for risk from receptive vaginal sex.

Based on information from references 2,6,14,22–25,29.

amounts vary. Employing diagnosis codes, such as those suggested by the HIV Medicine Association (**Table 4**), is recommended.[31] Use of thoughtful, nonstigmatizing nomenclature provides additional rapport and trust between clinician and patient.

Daily Regimens

Emtricitabine/tenofovir disoproxil fumarate is a fixed-dose combination (200/300 mg) daily medication for use in healthy (estimated creatinine clearance rate > 60 mL/minute) cisgender and transgender adults

TABLE 4
Commonly used preexposure prophylaxis diagnosis codes

ICD-10 code	Description	Use
Z01.812	Encounter for preprocedural laboratory examination	Pretreatment testing
Z20.6	Contact with and (suspected) exposure to human immunodeficiency virus	PrEP initiation and monitoring
Z20.2	Contact with and (suspected) exposure to infections with a predominantly sexual mode of transmission	PrEP initiation and monitoring Sexually transmitted infections screening
Z11.4	Encounter for screening for human immunodeficiency virus	Human immunodeficiency virus screening
Z11.3	Encounter for screening for infections with a predominantly sexual mode of transmission	Sexually transmitted infections screening

ICD-10 = *International Classification of Disease, Tenth Revision, Clinical Modification*; PrEP = preexposure prophylaxis

and adolescents (≥ 35 kg) at risk of acquiring HIV infection.[14,22,32] Emtricitabine/tenofovir disoproxil fumarate is available in generic and brand name forms. It is FDA-approved for use in MSM, transgender women, and cisgender women, including those seeking to conceive or who are pregnant or breastfeeding. Data are not available regarding transgender men, genderqueer, or nonbinary individuals who become pregnant and deliver while taking PrEP. Concentrations of emtricitabine/tenofovir disoproxil fumarate may be increased with medications that reduce renal function (antivirals, aminoglycosides, and high-dose nonsteroidal anti-inflammatory drugs).[14,22] In patients taking feminizing hormones, studies report potential reduction in rectal tissue concentration, but the effect on efficacy is unclear.[14]

Emtricitabine/tenofovir alafenamide is a fixed-dose combination (200 mg/25 mg) daily medication for use in men and transgender women at sexual risk for acquiring HIV infection.[14,23] It is available only in brand formulation and is approved for use in persons with an estimated creatinine clearance rate of at least 30 mL/minute.[14,23] Emtricitabine/tenofovir alafenamide is not an FDA-approved PrEP medication for use by women at risk of acquiring HIV through receptive vaginal sex, as research has not been reported in this population.[2,14,23,24] Several medications may decrease the concentration of emtricitabine/tenofovir alafenamide and should not be coadministered, including St. John's wort and the antibiotics rifabutin and rifapentine.

The time from initiation of daily oral PrEP to maximum protection against HIV infection is not clear. Although pharmacokinetic studies show that intracellular concentration occurs after 7 to 20 days of daily oral dosing, depending on tissue type, exactly when maximal tissue protection takes place is not known.[2,14] Use of condoms is recommended during this time; in fact, promoting consistent use of condoms is a component of successful PrEP treatment.[2,9,14]

The most-reported side effects with oral PrEP include headache, nausea, diarrhea, and weight change.[2,22,23] Barriers to adherence to oral PrEP should be reviewed.[2,6,20,33] Daily alarms and routines have been found to be helpful, as has acknowledging the incidence of occasional missed doses.

On-demand PrEP

On-demand PrEP, or the 2-1-1 regimen (also called event-driven or intermittent), times dosing of oral emtricitabine/tenofovir disoproxil fumarate in relation to sexual intercourse events.[9,14] The regimen consists of 2 pills taken 2 to 24 hours before sex, preferably closer to 24 hours, 1 pill taken 24 hours after the initial 2-pill dose, and 1 pill taken 24 hours after this. Should sex occur on the consecutive day after the 2-1-1 doses are completed, an additional 1 pill per day should be taken until 48 hours after the last sexual event. If there are fewer than 7 days until the next sexual event, the patient should resume taking 1 pill daily. If 7 days or more have passed, the patient should restart 2-1-1 dosing.

Negative HIV testing is required before starting on-demand PrEP, and a prescription should be for no more than 30 days, with follow-up testing required for continuation of medication.[6,14] Testing for bacterial sexually transmitted infections is also recommended with on-demand dosing, at intervals similar to the testing intervals for daily dosing.

The 2-1-1 regimen is advantageous for use in cisgender men who have sex less than once per week and can take the initial dose at least 2 hours before anticipated sex.[6,19] On-demand dosing should be taken for every episode of sexual activity, not selectively. Although the 2-1-1 regimen is not FDA-approved for MSM, studies have shown that it is effective for HIV prevention in MSM, and the International Antiviral (formerly AIDS) Society-USA panel has recommended 2-1-1 dosing as an optional, off-label alternative to daily dosing for MSM.[8,34]

Same-day prescribing

Initiation of PrEP therapy may be delayed because of the multiple healthcare visits required to receive a prescription; same-day prescribing can help mitigate this barrier to starting PrEP for those at substantial risk of acquiring HIV infection.[6,8,35] Same-day prescribing can only be offered in clinics that provide HIV point-of-care testing or provide same-day results for HIV and creatinine laboratory testing. Ideally, screening for sexually transmitted infections should also be performed at this time. Clinics considering same-day PrEP prescribing must be able to provide rapid-result follow-up, follow-up appointment scheduling, and patient navigation support for prescription payment assistance.[8]

Eliminating serial visits to healthcare facilities for initiation of PrEP may benefit patients who have confidently made the decision to start treatment, can complete a blood draw, and have no renal or other medical conditions that may decrease adherence with PrEP therapy. Reliable contact information, having the ability to acquire prescribed medication, and not having had recent HIV exposure are required.[20] Those with recent HIV exposure without acute symptoms should be evaluated for postexposure prophylaxis (outside the scope of this review).

Follow-up

Patients on oral PrEP should follow-up every 3 months for HIV testing, screening for sexually transmitted infections, and support for medication adherence and risk-reducing behaviors.[32] When starting PrEP therapy, the option of a 30-day prescription and 1-month follow-up for repeat HIV testing and counseling may be pursued. Prescriptions for daily PrEP medication should not exceed 90 days.[14]

The COVID-19 pandemic led to disruptions in clinical care services, including HIV treatment and PrEP therapy, and shortages of HIV testing reagent and materials,[7,29] but it also led to an increase in telehealth services. Telehealth has become a prominent healthcare delivery tool that can help patients hesitant to access in-person clinical services. It has led to adaptations in starting and continuing oral PrEP treatment, overcoming potential barriers to access.[1] Additionally, telemedicine may reduce potential stigma associated with initiation and continuation of PrEP therapy, reduce transportation time and cost, and reduce the financial penalty of loss of work hours for patients.[7] All told, mitigation of these barriers could substantially improve access to PrEP therapy. Testing for HIV infection and sexually transmitted infections as well as renal function testing can be done virtually by using at-home testing or scheduling with available laboratories.[29]

PRESCRIBING: INJECTABLE MEDICATION

One FDA-approved injectable PrEP medication, an HIV-1 integrase strand transfer inhibitor, is now available.[25] The current recommendation from the US Preventive Services Task Force for PrEP does not apply to injectable formulations. Cabotegravir injections may be considered for cisgender men, cisgender women, and transgender women (> 35 kg) who have difficulty taking daily oral PrEP medications, have renal impairment, or prefer injectable therapy.[6,24,26] Oral cabotegravir 30 mg daily is available for an optional 4-week lead-in before starting injectable therapy.[25] Nonadherence to the lead-in course creates a potential vulnerability for HIV acquisition.[6] Patients taking daily oral PrEP can start cabotegravir injection if they test negative for HIV infection.

Cabotegravir is administered as a 600-mg gluteal intramuscular injection.[6,29,36] Time from initiation of cabotegravir to maximum protection against HIV infection is not yet known.

Follow-up

A negative HIV test is required within the week before starting cabotegravir and during maintenance dosing.[36] The next dose after initiation is administered 1 month later, and thereafter maintenance doses are scheduled every 2 months.[35] Screening for sexually transmitted infections is recommended at regular intervals. If injections are more than 7 days late, an oral PrEP bridge is recommended to maintain protection until the next injection. With any injection more than 8 weeks late, a reloading dose schedule with 4-week intervals should be followed. HIV-1 RNA testing should be performed at the time of oral PrEP bridge and restart of injections.[6,14,37]

TABLE 5
Preexposure prophylaxis education and prescribing resources

Clinician prescribing resources
• PrEPline: National Clinician's Consultation Center (https://nccc.ucsf.edu/clinical-resources/prep-resources/prep-quick-guide)
• Integrating HIV Care, Treatment & Prevention Services into Primary Care—A Toolkit for Health Centers (https://bphc.hrsa.gov/media/p4c-toolkit-2018.pdf)
• HIV Nexus Centers for Disease Control and Prevention Resources for Clinicians (www.cdc.gov/hiv/clinicians/index.html)
• The AIDS Education and Training Center (AETC) Program National Coordinating Resource Center (https://aidsetc.org)
• The National Network of STD Clinical Prevention Training Centers (http://nnptc.org)
Patient education resources
• US Preventive Services Task Force. Let's Talk About It: Preventing HIV with PrEP (www.uspreventiveservicestaskforce.org/uspstf/sites/default/files/inline-files/hiv-prep-prevention-discussion-guide.pdf)
• US Department of Health and Human Services Office of the Assistant Secretary for Health (OASH). Ready, Set, PrEP (http://readysetprep.hiv.gov)
• Centers for Disease Control and Prevention. PrEP 101. PrEP Access. Is PrEP Right For Me? (www.cdc.gov/hiv/pdf/basics/prep/cdc-hiv-stsh-prep-brochure-english.pdf)

HIV = human immunodeficiency virus; PrEP = preexposure prophylaxis

DISCONTINUATION OF PrEP

Situational life changes, nonadherence to daily dosing, nonadherence to follow-up or laboratory testing, intolerance to medication, or acquisition of HIV infection may prompt discontinuation of PrEP. HIV status and the reason for discontinuation should be documented. HIV infection protection wanes in 7 to 10 days after oral PrEP is discontinued, and patients with chronic hepatitis B should be monitored for flares.[37] Methods to reduce risk for HIV acquisition should be discussed, as should indications for postexposure prophylaxis. Changes prompting a restart of PrEP, which follow the same guidelines as original initiation, need to be documented.[2,14,22,23,36]

Discontinuation of cabotegravir includes a tail period as protective levels decline. There is a possibility of false-negative HIV testing during this time and risk of developing drug-resistant HIV infection.[14] HIV testing should continue every 3 months for 12 months. If risk remains and PrEP continues to be indicated, daily oral PrEP should be started within 8 weeks of the last injection.[6,14,25]

PREVENTIVE HEALTHCARE OPPORTUNITIES

Providing PrEP opens opportunities to provide preventive healthcare during the required frequent visits. Mental health, nicotine, alcohol and drug use, and intimate partner violence screenings should be conducted. Anatomy-specific screenings for cervical, chest or breast, colorectal, and prostate cancers are recommended per the US Preventive Services Task Force guidelines.[38] Anal cancer screening is recommended per the International Anal Neoplasia Society consensus guidelines.[39] The Advisory Committee on Immunization Practices recommends discussing immunizations against hepatitis A, hepatitis B, mpox (formerly monkeypox) virus, human papillomavirus, meningitis B, influenza, COVID-19, pneumonia, respiratory syncytial virus, and shingles.[40]

PrEP IN PRIMARY CARE

Primary care clinicians are strategically positioned to deliver sexual healthcare, including PrEP therapy, to their communities.[8,15] The impact of local and accessible continuity of care cannot be overstated as the benefit of PrEP therapy is significant and far reaching. Primary care clinicians who can confidently conduct a thorough sexual history and know the benefits and prescribing practice of PrEP may significantly help reduce the incidence of new HIV infection. Education resources for clinicians and patients are listed in **Table 5**.

DISCLOSURES

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

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REVIEW

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Gastroparesis for the nongastroenterologist

ABSTRACT

Gastroparesis is a heterogeneous motility disorder characterized by nausea, vomiting, and postprandial fullness. Its diagnosis requires objective documentation of delayed gastric emptying of solid food and exclusion of mechanical obstruction. Its epidemiology is unclear, and the main causes are diabetes mellitus and idiopathic disease. Cardinal symptoms often co-occur. Management involves nutritional assessment, dietary changes, drug evaluation, glycemic control (for patients with diabetes mellitus), and symptom relief. In this review, we explore challenges nongastroenterologists may encounter and how they can use current recommendations to manage patients with gastroparesis.

KEY POINTS

The diagnosis of gastroparesis requires specific symptoms and objective documentation of delayed gastric emptying of solid food without mechanical obstruction, which should be excluded by upper gastrointestinal endoscopy or imaging studies.

Cardinal symptoms of gastroparesis such as nausea, vomiting, early satiety, postprandial fullness, bloating, belching, and upper abdominal discomfort usually present in clusters or combinations.

Management of gastroparesis aims to improve symptoms and gastric emptying. It includes improving nutritional status through dietary modifications, minimizing or avoiding drugs such as opioids, achieving glycemic control in patients with diabetes, treating underlying causes, and instituting pharmacologic and nonpharmacologic options when indicated.

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Gastroparesis is a chronic motility disorder and a heterogeneous syndrome with significant variability in its symptoms, causes, severity, and response to treatment. It is defined by symptoms such as nausea, vomiting, postprandial fullness, and upper abdominal discomfort; objective documentation of delayed gastric emptying of solid food; and exclusion of mechanical obstruction.[1]

Delayed gastric emptying was first reported in patients with diabetes by Boas[2] in 1925, and the term "gastroparesis diabeticorum" was used by Kassander[3] in 1958 to describe asymptomatic gastric retention in patients with diabetes. Although diabetes mellitus accounts for more than one-third of all cases of gastroparesis,[4] other risk factors include gastrointestinal surgery, medications, and neurologic and autoimmune disorders. Moreover, in many patients no underlying cause is found,[5] making this condition even more variable.

Regardless of the cause and despite advances in understanding of the pathogenesis (which has unresolved questions), gastroparesis poses a challenge in diagnosis and management for gastroenterologists and nongastroenterologists alike.

This review focuses on the most relevant challenges encountered when approaching patients with this condition, current recommendations for diagnosis and treatment, and how nongastroenterologists such as primary care clinicians can use these to help manage patients.

PREVALENCE VARIES IN DIFFERENT STUDIES AND COUNTRIES

A 2023 systematic review reported that the overall standardized prevalence of gastroparesis

ranged widely (from 13.8 to 267.7 per 100,000 adults) in studies from 1994 to 2019.[6] However, many of these studies used a broad definition of gastroparesis ("probable and/or possible gastroparesis") solely based on diagnosis codes and without objective evidence of delayed gastric emptying.

Community-based studies with a strict case definition (objective evidence of delayed gastric emptying, typical symptoms, and absence of mechanical obstruction)[1] appear to offer a more accurate estimate. For instance, 2 US studies using community-based databases reported a prevalence of 21.5 per 100,000 adults[7] and 24.2 per 100,000 adults.[8] In contrast, a study conducted using a community database from the United Kingdom and a strict case definition reported a prevalence of 13.8 per 100,000 persons.[9] Similarly, a study from Israel showed a crude prevalence of 13.6 per 100,000 persons.[10] The incidence has been reported to be around 6.3 per 100,000 person-years in the United States[8] and 1.9 per 100,000 person-years in the United Kingdom.[9]

The difference in prevalence in different studies and countries can be attributed to several factors. First, epidemiologic studies classify gastroparesis inconsistently: some rely solely on diagnosis codes while others consider specific diagnostic criteria. Second, the diagnosis of gastroparesis may vary among regions and countries, influenced in part by differences in the methodology of gastric emptying studies and variations in clinical practice.[6] Lastly, diabetes mellitus is a major contributor to gastroparesis, and its prevalence is notably higher in the United States (11.6%)[11] than in the United Kingdom (7%)[12] and Israel (2.6%),[13] potentially contributing to the overall higher prevalence of gastroparesis in the United States.

The mean age of patients with gastroparesis has been reported as between 45.4 and 58.9 years, and the proportion who are White from 46.7% to 90.1%.[6] In several reports, most patients (63.7% to 76.4%) were female,[6] with an age-adjusted female-to-male ratio of 3.9:1.[8] Although this female predominance has been attributed to factors such as sex hormones, it has not been accurately described or researched.[6]

The mortality rate is higher in patients with gastroparesis than in the general population, the most common causes of death being cardiovascular disease, respiratory failure, and malignancy, although some studies reported that inpatient mortality rates have been falling over time.[6]

The most common comorbidities also differ among regions and countries. For instance, in the United States the most common comorbidities were hypertension, smoking history, obesity, chronic pulmonary disease, and cerebrovascular disease, regardless of the cause of gastroparesis, while in the United Kingdom chronic pulmonary disease was most common, followed by renal disease and malignancy.[7,9]

DIABETES AND OTHER CAUSES

Diabetes and idiopathic disease are the most common causes of gastroparesis. However, the etiology differs among studies and populations.

A large national claims database study from the United States (N = 82,574,650) reported diabetes mellitus as the most common cause, involving 57.4% of all cases, with type 2 diabetes (51.7%) being more prevalent than type 1 (5.7%).[7] Second was surgery (15%), mostly esophageal, gastric, and duodenal surgeries, although there are anecdotal cases involving cardiothoracic surgery, mainly vagus nerve resection.[7] Third (11.8%) were drugs that can impair gastric emptying (opioids, anticholinergic agents, calcium channel blockers, glucagon-like peptide 1 [GLP-1] receptor agonists, cyclosporine). Unknown causes came fourth (11.3%).[7] Other causes such as autoimmune diseases (scleroderma, systemic lupus erythematosus), hypothyroidism, Parkinson disease, cerebral palsy, and multiple sclerosis account for less than 5% of all cases.

Other studies had different findings. For instance, another US study found that the most common causes were idiopathic (49.4%), diabetes mellitus (25.3%), drugs (22.9%), and surgery (7.2%).[8] In another large population-based study in the United States (N = 43,827,910), diabetes was the most common cause (71.7%), followed by idiopathic (28.3%).[14] However, the investigators relied solely on diagnosis codes from medical records for gastroparesis classification.

Interestingly, the etiology varies in other countries and regions. For instance, in the UK study, idiopathic disease was the most common cause of gastroparesis (39.4%), followed by diabetes (37.5%)[9]; in the study in Israel,[10] diabetes accounted for 17.2% of all cases and the rest (82.8%) were classified as idiopathic (the authors excluded cases due to other causes).

Differences in the etiology of gastroparesis across countries can be partly explained by differences in the prevalence of diabetes mellitus, which is probably the most common cause where its prevalence is higher. Additionally, in some studies, the differentiation of the etiology is poor, with subgroup analyses that classify all nondiabetic gastroparesis cases (postsurgical, drug-induced) as idiopathic.[6]

Evidence regarding certain risk factors or causes of gastroparesis lacks consensus. For example, hypothyroidism has been reported to be associated with 4.0% of cases.[7] Some studies suggest hypothyroidism may affect esophageal and gastric motor activity, leading to upper gastrointestinal symptoms that can be improved with thyroid hormone replacement.[15,16] However, a group of experts from European gastroenterology societies could not reach consensus on hypothyroidism as a cause of gastroparesis.[5] Similarly, this group did not reach consensus on whether viral infections can cause gastroparesis.[5] Nonetheless, gastroparesis has been (rarely) associated with viruses such as Epstein-Barr, norovirus, herpes, and cytomegalovirus, and viral illness has been linked to poor prognosis if there is evidence of autonomic dysfunction, such as postural hypotension.[4]

Recent findings highlight that gastrointestinal motility disorders presenting with gastroparesis symptoms can occur in patients with generalized autoimmune dysautonomia.[17] Several antibodies have been associated with autoimmune disorders that manifest gastroparesis-like symptoms, including antibodies targeting ganglionic nicotinic acetylcholine receptors containing alpha 3 subunits or antibodies against calcium channels.[17]

For instance, autoimmune gastrointestinal dysmotility is a limited form of autoimmune dysautonomia that can occur as an idiopathic or paraneoplastic phenomenon. It has various presentations: hypermotility or hypomotility, such as colonic inertia, pyloric obstruction, anal spasm, and gastroparesis.[17] It is believed that an unknown number of "idiopathic" gastroparesis cases may fall within this category, leading to consideration of immunotherapy as a treatment option.[17] However, stronger evidence regarding the immune profiles and response to immunotherapy of this group of patients is needed. The latest American College of Gastroenterology guideline does not recommend routine clinical use of autoimmune therapy in the management of gastroparesis.[1]

GASTROPARESIS OFTEN PERSISTS DESPITE TREATMENT

More than two-thirds of patients receiving treatment for gastroparesis do not have significant symptom improvement during 1 year of follow-up.[18,19]

Gastroparesis is associated with increased emergency department visits and hospitalizations due to exacerbation of symptoms such as vomiting, electrolyte abnormalities, abdominal pain, and malnutrition. Higher healthcare resource utilization has been shown within 2 years of gastroparesis diagnosis.[10]

Gastroparesis predominantly affects women, who are more likely to have idiopathic gastroparesis with more severe symptoms of postprandial fullness, early satiety, bloating, and upper abdominal pain, and are less likely to improve after 48 weeks of follow-up.[18,19]

Some predictors of improvement over 48 weeks include age 50 and older, moderate or severe gastroparesis (> 20% gastric retention at 4 hours), and onset of gastroparesis following an infectious prodrome. Predictors associated with lack of improvement include being overweight or obese, severe abdominal pain, concomitant gastroesophageal reflux (eg, pyrosis, dysphagia, chest pain, chronic cough), and depression.[18,19]

Gastroparesis in patients with type 1 diabetes mellitus is associated with higher hemoglobin A1c levels, longer duration of gastrointestinal symptoms, greater gastric retention, and more hospitalizations due to gastroparesis. Patients with type 2 diabetes mellitus and gastroparesis are older and heavier and have more comorbidities. More than 40% of patients with type 2 diabetes who require insulin therapy have delayed gastric emptying.[18]

Improvement in glycemic control is associated with a decreased incidence of microvascular complications, and it is expected to be associated with a lower incidence of diabetic gastroparesis.[4] Indeed, diabetic gastroparesis seems to be associated with poor glycemic control and vascular and neurogenic complications.[20] But once delayed gastric emptying is established, it may persist for up to 25 years despite improved glycemic control.[21]

GASTRIC EMPTYING IS COMPLEX, AND SO IS GASTROPARESIS

In diabetic and idiopathic gastroparesis, the main alterations that lead to delayed gastric emptying and symptoms are impaired accommodation of the gastric fundus and body, antral hypomotility, impaired pyloric relaxation, and dysmotility in the small intestine.[18]

Emptying a meal from the stomach into the small bowel requires complex coordination involving the fundus, antrum, and pylorus. Swallowing induces relaxation of the gastric fundus, allowing it to accommodate the food. Then, steady increases in fundic tone propel gastric contents toward the pylorus, where phasic contractions facilitate the grinding of digestible solids.[18] The antral contractions are regulated by the interstitial cells of Cajal, generating a basal electrical rhythm. This process reduces digestible solids to particles 2 mm or smaller, forming the chyme. Small bowel function is also crucial to complete gastric emptying, as emptying

requires coordination between the antrum and pylorus, and inhibitory signals from the small bowel modulate emptying rates based on chyme composition.[18]

Fewer inhibitory neurons expressing nitric oxide synthase (nitrergic neurons) may play an important role in impaired accommodation and pyloric relaxation.[4,18] The interstitial cells of Cajal and cells positive for platelet-derived growth factor receptor-alpha (fibroblast-like) in the gastric smooth muscle layer are considered the pacemakers that convey the stimulation from extrinsic vagal fibers and intrinsic enteric nerves to the gastric smooth muscle cells (multicellular electrical syncytium), resulting in coordinated contractions towards the antropyloric region.[4] Reduced numbers of interstitial cells of Cajal and fibroblast-like cells and altered expression of smooth muscle cell contractile protein have been found in patients with gastroparesis, and this may explain the antral hypomotility that interferes with peristalsis, trituration, and gastric emptying.[4]

Immune alterations seem to play an important role in the mechanism of injury. Injury and loss of the interstitial cells of Cajal, smooth muscle cells, and fibroblast-like cells, comprising the electrical syncytium of the gut, have been associated with reduced numbers of anti-inflammatory M2 macrophages, which mediate cell repair.[4,18] Losing M2 macrophages reduces the protection of neural tissue from oxidative stress and inflammation—both involved in diseases such as diabetes mellitus.[4]

NAUSEA, VOMITING, EARLY SATIETY

The main symptoms of gastroparesis are nausea, vomiting, early satiety, postprandial fullness, bloating, belching, and upper abdominal discomfort.[4] These cardinal symptoms are usually present in clusters or combinations, eg, abdominal pain with early satiety and heartburn; heartburn with bloating, early satiety, nausea, and vomiting; and regurgitation with bloating, nausea, and vomiting.[4,22]

Severe early satiety and postprandial fullness are reported by 50% to 60% of patients, and 95% experience nausea, which is the predominant symptom in 29% of cases.[18] Nausea is related to food intake in at least three-quarters of patients; in 40% of cases, nausea lasts most of the day.[18]

Vomiting and early satiety are often the initial symptoms in diabetic gastroparesis. Patients with diabetic gastroparesis may experience greater nausea and longer periods of vomiting than those with idiopathic gastroparesis.[18,23]

Abdominal pain is often the initial presentation of idiopathic gastroparesis.[23] Two-thirds of patients report it, and it is associated with nonacute onset of gastroparesis, bowel disturbances, and opiate and antiemetic use. In addition, patients in whom pain is the predominant symptom have greater impairment in quality of life than those in whom nausea and vomiting predominate.[18]

Bloating is more significant in women, individuals who are overweight, and those using probiotics, regardless of the etiology.

DIAGNOSIS REQUIRES SYMPTOMS PLUS STUDIES

The diagnosis of gastroparesis requires 3 criteria:

- Symptoms of gastroparesis
- Exclusion of mechanical obstruction such as pyloric stenosis with esophagogastroduodenoscopy or a radiographic study
- Evidence of delayed gastric emptying of solids.

There are currently 2 gold-standard tests to document delayed gastric emptying: gastric emptying scintigraphy and the stable isotope gastric-emptying breath test.

Gastric emptying scintigraphy

Gastric emptying scintigraphy measures gastric emptying of a solid meal using an egg or protein-based (western-style) or rice-based (Asian-style) meal containing a radioisotope, usually technetium Tc 99m. A gamma camera is used to scan the gastric area (anteroposterior view) at baseline and 30 minutes, 1 hour, 2 hours, 3 hours, and 4 hours after the meal. Normally, more than 90% of the solid meal should be emptied at 3 hours. Retention of more than 10% at 4 hours is considered diagnostic for delayed gastric emptying.[1] The assessment of severity based on gastric emptying scintigraphy is as follows[24]:

- Grade 1 (mild): 11% to 20% retention at 4 hours
- Grade 2 (moderate): 21% to 35% retention
- Grade 3 (severe): 36% to 50% retention
- Grade 4 (very severe): > 50% retention.

While this reporting method is the most commonly used, the results can be presented in other ways such as half-time of emptying or rate of emptying (percent per minute), and the test may be conducted under varied protocols. This lack of standardization complicates the clinical utility of the test and poses a challenge for physicians and patients, particularly when interpreting tests from different institutions.[24] A unified protocol that can be implemented in all institutions and nuclear medicine facilities would be optimal.

The test has other limitations. Radiation exposure limits its use in pregnant or breastfeeding women; patients with severe symptoms or allergies may not tolerate a solid

meal; and special equipment and rooms are needed.[4,18] Hyperglycemia can delay gastric emptying and thus confound the test; hence, the test should not be done if the fasting blood glucose level is above 200 mg/dL.[4]

Medications that affect gastric emptying should be withheld before the test (**Table 1**).[25] This includes marijuana (the time frame is unknown).

Glucagon-like peptide-1 (GLP-1) receptor agonists and gastric inhibitory polypeptide receptor agonists, commonly used for managing diabetes mellitus and obesity, are associated with nausea and vomiting attributed to delayed gastric emptying. However, there are no clear guidelines on how long to withhold these medications before a gastric emptying test. While the American Society of Anesthesiologists advises skipping 1 weekly dose of GLP-1 receptor agonists before endoscopy, the American Gastroenterological Association at this time does not endorse this recommendation and suggests tailoring the approach for each patient based on the indication for the GLP-1 agonist and clinical symptoms before endoscopy.[26] While not officially recommended for gastric emptying scintigraphy, the guidelines above may serve as a reference for clinicians ordering the test. The decision to withhold GLP-1 agonists before gastric emptying scintigraphy seems to be based on institutional guidelines and clinician experience.

TABLE 1
Medications to discontinue 48 to 72 hours before gastric emptying scintigraphy

Prokinetics
Metoclopramide, cisapride, domperidone, erythromycin

Anticholinergics, antispasmodics
Dicyclomine, donnatal, hyoscyamine, glycopyrrolate

Opioids
Meperidine, codeine, morphine, oxycodone

Laxatives
Any laxative (discontinue 24 hours before)

Gastric acid suppressants, aluminum-containing antacids
Aluminum hydroxide

Calcium channel blockers
Amlodipine, nifedipine

Agents that may affect gastric emptying
Atropine, benzodiazepines, octreotide, progesterone, theophylline, phenylamine

Adapted from reference 25.

The stable isotope gastric-emptying breath test

The stable isotope gastric-emptying breath test involves the patient ingesting a meal containing a carbon 13-labeled substrate such as *Arthrospira (Spirulina) platensis* (edible blue-green algae) or octanoic acid (a medium-chain fatty acid).[27] Then, breath samples are taken to calculate the carbon 13 carbon dioxide excretion rate for approximately 4 hours, usually at 45, 90, 120, 180, and 240 minutes. At any time point, the carbon 13 carbon dioxide excretion is proportional to the rate of gastric emptying, so that increasing excretion means increasing rates of gastric emptying. Patients with delayed gastric emptying will have carbon 13 carbon dioxide excretion rates lower than references values.[27]

This test is relatively easy to perform. It can be done in the office or at the bedside and does not require elaborate detection equipment. Because it does not involve radiation exposure, it is safer than scintigraphy, which is especially important in pregnant or breastfeeding women and children.[28] On the other hand, it may be inaccurate in patients with malabsorption or liver or lung diseases.[1,27] Physical activity influences carbon dioxide production, and hence, measurements of the breath test. Therefore, it is recommended that patients be at rest through the entire test.[27]

Other tests

American College of Gastroenterology guidelines[1] recommend against using whole-gut motility tests such as the radiopaque marker test as well as the wireless motility capsule to measure gastric emptying. The main reason that the radiopaque marker and the nondigestible wireless motility capsule are not recommended is that they do not empty with the solid food from the stomach and hence may give a false-positive result of delayed gastric emptying.[5] There is evidence that the capsule empties during phase III of the migrating motor complex, similar to a nondigestible solid, which occurs after digestion of solid food.[29]

Electrogastrography may complement the identification of pathophysiologic mechanisms in gastric function, as it reveals distinct patterns and electrical waves associated with specific motility disorders such as gastroparesis, functional dyspepsia, and cyclic vomiting. However, the clinical significance of this information remains unclear,[1] and as a result, it is not routinely requested. More research will help to clarify its role in clinical practice.

TABLE 2
Differential diagnosis of gastroparesis

Disorder	Clinical presentation and differentiation from gastroparesis	Treatment
Functional dyspepsia	Less nausea and vomiting Often indistinguishable	*Helicobacter pylori* eradication, proton pump inhibitors, tricyclic antidepressants, prokinetics, consider psychotherapy[29]
Rumination syndrome	Effortless and repetitive regurgitation of ingested food	Behavioral modification: deep-breathing exercises, diaphragmatic breathing
Cyclic vomiting syndrome	Absence of symptoms between vomiting episodes Compulsive hot bathing or showering Strong association with personal or family history of migraines	Acute attacks: ondansetron, triptans, aprepitant Prophylaxis: tricyclic antidepressant, topiramate, aprepitant, zonisamide, levetiracetam
Cannabinoid hyperemesis syndrome	Absence of symptoms between vomiting episodes Compulsive hot bathing or showering Cannabis use Gastric emptying scintigraphy might be normal	Benzodiazepines, tricyclic antidepressants, haloperidol, droperidol, promethazine, prochlorperazine, ondansetron, corticosteroids, capsaicin Cannabis cessation
Anorexia or bulimia	Binge and purge behavior (bulimia), and severe caloric restriction (anorexia)	Psychotherapy, selective serotonin reuptake inhibitors
Anxiety disorder toward food (avoidant restrictive food intake disorder)	Immediate postprandial nausea and vomiting when patients see the food or put it in their mouth	Cognitive behavioral therapy, cyproheptadine
Narcotic bowel syndrome	Chronic or intermittent colicky abdominal pain that worsens when the narcotic effect wears off Constipation is common	Clonidine, benzodiazepines, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, laxatives, methylnaltrexone

Based on information from references 30–32.

CONSIDER OTHER FACTORS, DISORDERS

During the assessment, it is important to consider manageable factors that could explain gastroparesis symptoms. This includes reviewing the patient's medical history, assessing medications that may affect gastric emptying (eg, opioids, GLP-1 receptor agonists), and obtaining thyroid function tests. In addition, sensory or motor disorders of the upper gastrointestinal tract may have similar symptoms as gastroparesis.

Some functional gastrointestinal disorders can have a clinical presentation similar to that of gastroparesis. Hence, it is important to properly differentiate among them (**Table 2**).[30–32] Functional dyspepsia, rumination syndrome, cyclic vomiting syndrome, and others should be considered in the differential diagnosis.

Functional dyspepsia can be indistinguishable from gastroparesis.[30] It is defined by similar symptoms, eg, early satiety, postprandial fullness, bloating, and epigastric discomfort or pain, and approximately 25% to 35% of patients may have delayed gastric emptying.[4] Two categories or subtypes are recognized: epigastric pain syndrome and postprandial distress syndrome, with postprandial distress syndrome having more similarities to symptoms of gastroparesis.[30]

Distinguishing between functional dyspepsia and gastroparesis is important, since functional dyspepsia has different treatments and a better prognosis.[1]

Rumination syndrome presents with effortless, repetitive regurgitation, chewing, and reswallowing, or spitting out previously digested food.[4,30] It can be

diagnosed with combined high-resolution manometry–impedance monitoring, revealing a pattern of low-pressure gastric straining followed by regurgitation.[31] Treatment of rumination syndrome is also different, with education and behavioral modification (diaphragmatic and deep-breathing exercises).[30,31]

Cyclic vomiting syndrome (associated with a personal or family history of migraines) and **cannabinoid hyperemesis syndrome** (associated with heavy cannabis use) should be considered in the differential diagnosis. Both present with episodic attacks of severe nausea and vomiting, usually associated with dehydration and electrolyte imbalance.[4,31]

Eating disorders such as anorexia and bulimia nervosa should be considered because a low body mass index is associated with delays in gastric emptying and disturbed gastric functioning. Treatment involves psychotherapy and nutrition enforcement, but not prokinetics.[31]

Anxiety disorder toward food, also known as avoidant restrictive food intake disorder, can mimic gastroparesis. However, patients with this disorder have immediate nausea and vomiting as soon as they see food (before eating), while those with gastroparesis have delayed symptoms (20 to 30 minutes after eating). This condition is treated with psychotherapy and neuromodulators.[30]

Narcotic bowel syndrome can be considered in the differential diagnosis, since it is characterized by a progressive and somewhat paradoxical increase in abdominal pain (accompanied by bloating and nausea) despite continued or escalating doses of opioids.[31,32]

Conditions that present with constipation as the predominant syndrome should also be considered. In this case, upper gastrointestinal symptoms and delayed gastric emptying may be the result of constipation, and the symptoms improve when it resolves.[30]

MANAGEMENT: A COMPREHENSIVE STRATEGY

A comprehensive strategy for managing gastroparesis includes optimizing nutritional status (balance between nutrients acquired from food and beverages and their use by the body for essential functions), improving gastric emptying, reversing iatrogenic causes, and achieving glycemic control in patients with diabetes.[1,18,33] It is crucial to avoid medications that exacerbate the gastric emptying delay, such as opioids and GLP-1 receptor agonists. The different strategies for management are summarized in **Table 3**.

Diet and nutrition

The first-line approach is to educate patients on a small-particle diet.[34] This consists of foods with a small particle size or those that can be processed into small particles (eg, soups, smoothies, apple sauce). Foods that are initially not in a small-particle form such as corn, peas, and onions should be avoided, but these foods can be included when they are processed to smoothie consistency.[34]

A registry study found that only one-third of patients with gastroparesis had received nutritional counseling, and just 2% adhered to dietary recommendations for patients with gastroparesis.[35] Even though obesity is increasingly prevalent among patients with gastroparesis, 64% of patients in the registry reported consuming calorie-deficient diets, leading to various vitamin and mineral deficiencies.[35] Consequently, it is important to include a thorough assessment of caloric intake and provide dedicated nutritional counseling for these patients.

In cases of severe gastroparesis despite medical and nutritional interventions, it may be necessary to consider inserting a jejunal feeding tube to bypass the stomach and deliver the formula directly into the small bowel.[33,36] The preferred approach involves placing feeding tubes directly into the jejunum, by either endoscopy or laparoscopy, instead of using percutaneous endoscopic gastrostomy tubes.[33] It is crucial to allow for a gradual adaptation period, incrementally increasing the infusion rate over a few days until the desired feeding rate is achieved.[33,36] Prolonged use of enteric tubes is typically regarded as safe, but there can be infrequent complications such as clogging, dislodgment, malfunction, tip migration, and site infections.[36]

Patients with severe gastroparesis frequently need hospitalization to address their condition, including intravenous hydration to correct metabolic imbalances, nasoenteric decompression, and temporary parenteral nutrition for those experiencing significant weight loss and difficulties with oral intake.[18,33] Total parenteral nutrition can be considered for advanced cases of gastroparesis; however, reinstating oral intake is generally recommended when feasible to reduce the risk of complications such as central-line infections.[1,33]

Prokinetic medications

Pharmacologic therapy of gastroparesis involves prokinetics, antiemetics, and neuromodulators. Prokinetics act by stimulating nonsphincteric muscle contractility. They are classified into different pharmacologic classes, including dopamine (D2) receptor antagonists, serotonin (5-hydroxytryptamine 4 [5-HT4]) receptor agonists, cholinesterase inhibitors, motilin-like agents, and ghrelin-like agents, although many drugs have multiple mechanisms of action.[18,33]

Metoclopramide is the only US Food and Drug Administration (FDA)–approved medication for

TABLE 3
Management strategies for gastroparesis

Exclude iatrogenic causes (eg, opioids, surgery, glucagon-like peptide 1 receptor agonists)		
Diet modification Small-particle diet to improve symptom relief and facilitate gastric emptying		
Pharmacologic therapy		
	Dosage	**Side effects**
Prokinetics		
Metoclopramide[a]	10 mg 3 times a day, 30 minutes before meals, for a maximum of 3 months, or 70-µL spray 30 minutes before meals and at bedtime for 2–8 weeks	Extrapyramidal symptoms (1%–25%, higher in elderly and young), tardive dyskinesia (around 0.1% per 1,000 patient-years)
Erythromycin	250 mg 3 times a day for 1 to 2 weeks	Tachyphylaxis after 4 weeks
Domperidone[b]	10 mg 3 times a day	QTc interval prolongation (6%)
Antiemetics		
5-HT3 receptor antagonists (granisetron, ondansetron)	Same dosage as that used to manage nausea or emesis, or as needed per patient	QTc interval prolongation, second-degree heart block (< 1%)
Neurokinin antagonists (aprepitant, tradipitant)	Aprepitant dose tested in clinical trials is 125 mg once daily	Fatigue, constipation (> 10%)
Neuromodulators		
Levosulpiride	Start with minimum effective dose	Sedation, hypotension, dyskinesia
Buspirone	Start with minimum effective dose	Dizziness, drowsiness
Mirtazapine	Start with minimum effective dose	Somnolence, xerostomia, weight gain
Haloperidol	Start with minimum effective dose	Extrapyramidal symptoms
Nonpharmacologic therapies Gastric electrical stimulation ("gastric pacemaker"), acupuncture		
Pyloric interventions		
Endoscopic functional luminal imaging probe	Used to evaluate pyloric function and predict treatment outcomes following gastric peroral endoscopic myotomy	
Intrapyloric injection of botulinum toxin	Not recommended	
Laparoscopic (Heineke-Mikulicz) pyloroplasty	Safe and enhances gastric emptying with short-term improvement in symptoms	
Gastric peroral endoscopic myotomy	Improves gastric emptying and is equivalent to laparoscopic pyloroplasty	

[a]Only medication approved by US Food and Drug Administration (FDA) for gastroparesis; nasal spray is FDA-approved for diabetic gastroparesis.
[b]Available through the FDA's program for expanded access to investigational drugs.

gastroparesis management. It works by blocking D2 receptors and partly activating 5-HT4 receptors, exerting both prokinetic and central antiemetic effects. Initially it enhances gastric emptying of liquids in diabetic gastroparesis, but its symptomatic efficacy is likely secondary to its central antiemetic effect.

Long-term use is limited due to decreasing effectiveness and the risk of central nervous system side effects, including reversible involuntary movements and irreversible tardive dyskinesia. Recent data show a risk of tardive dyskinesia of around 0.1% per 1,000 patient-years.[37] Typically, metoclopramide is prescribed at 10 mg 3 times a day, taken 30 minutes before meals, for a maximum of 3 months.[1,18,33]

Metoclopramide is also FDA-approved as a nasal spray for diabetic gastroparesis, offering several advantages such as faster and predictable absorption and better symptom control than the oral preparation. As with the oral preparation, extending treatment with the nasal spray longer than 12 weeks should be avoided.[38]

Erythromycin is a motilin agonist and enhances gastric emptying when taken orally at a dosage of 250 mg 3 times a day for 1 to 2 weeks. However, its prokinetic effects are restricted by tachyphylaxis after 4 weeks.[33]

Domperidone, another D2 antagonist, is as effective as metoclopramide for relief of symptoms, and it does not cross the blood-brain barrier in sufficient quantity to cause the neurologic side effects seen with metoclopramide.[18,39] It is typically prescribed at a dosage of 10 mg 3 times a day. However, it should be used with caution, as it causes relative prolongation of the QTc interval.[18] Domperidone is available for prescription through the FDA's program for expanded access to investigational drugs.[1,39]

Prucalopride, a 5-HT4 receptor agonist used to treat chronic constipation, recently has been shown to also exert a gastrokinetic effect and to improve symptoms in a relatively small number of patients with idiopathic gastroparesis.[40]

Several experimental medications are currently in development for the treatment of gastroparesis. These include felcisetrag (a 5-HT4 agonist), tradipitant (a neurokinin-1 antagonist), relamorelin (a ghrelin agonist), and trazpiroben (a dopamine D2/D3 receptor antagonist).[33]

Antiemetic medications

5-HT3 receptor antagonists such as granisetron and ondansetron are known for their effectiveness in managing chemotherapy-induced nausea and vomiting. They reduce nausea without affecting gastric compliance or postprandial accommodation and can be considered for patients with dysmotility disorders primarily characterized by nausea and vomiting.[18,33]

Neurokinin antagonists like aprepitant and tradipitant have been shown to alleviate nausea.[33]

Although both **marijuana and dronabinol** can slow gastric emptying, many patients still turn to THC (tetrahydrocannabinol), found in marijuana, for relief from their nausea.[33]

Neuromodulators

Levosulpiride, an antipsychotic agent, promotes gastric emptying through its dual action as an antidopaminergic and a 5-HT4 agonist.[41]

Buspirone, an anxiolytic medication acting as a 5-HT1A agonist, enhances gastric accommodation and alleviates postprandial symptoms independently of its anxiolytic properties.[42]

Mirtazapine, an antidepressant with central adrenergic and serotonergic effects, has been shown to improve symptoms of nausea, vomiting, and loss of appetite.[43]

Haloperidol, given intravenously, has demonstrated efficacy in reducing abdominal pain and nausea in severely ill patients with gastroparesis in the emergency department.[44]

Tricyclic antidepressants have generated conflicting data in the context of gastroparesis treatment due to their anticholinergic effects, which could potentially lead to delayed gastric emptying. Notably, nortriptyline demonstrated no discernible difference compared with placebo in patients with idiopathic gastroparesis.[45]

Nonpharmacologic therapy

Gastric electrical stimulation has demonstrated a reduction in the frequency of vomiting, although its mechanism of action remains unclear.[1,18]

Acupuncture, as a stand-alone treatment or when combined with prokinetic drugs, may offer benefits for symptom management in those with diabetic gastroparesis.

Herbal therapies such as rikkunshito or STW5 are not recommended for the treatment of gastroparesis.[1]

Brain-gut therapies such as hypnotherapy and cognitive behavioral therapy are widely used in gastrointestinal disorders in which pain and nausea and vomiting are primary symptoms, such as functional dyspepsia, irritable bowel syndrome, and rumination syndrome. While it is intuitive to consider their applicability to gastroparesis, evidence supporting their role in gastroparesis treatment is limited. However, given their primary use in patients with anxiety and depression—common comorbidities in gastroparesis—they likely play an important role in gastroparesis management in some patients.[46]

Pyloric interventions

Both diagnostic (endoscopic functional luminal imaging probe) and therapeutic pyloric interventions

(intrapyloric injection of botulinum toxin and pyloromyotomy) are available for gastroparesis. They are indicated in cases of refractory gastroparesis not responding to conservative therapy.

Endoscopic functional luminal imaging probe is an innovative diagnostic method employed to evaluate pyloric function and predict treatment outcomes after peroral pyloromyotomy, also known as gastric peroral endoscopic myotomy (G-POEM).[1]

Intrapyloric injection of botulinum toxin was initially applied for achalasia and subsequently extended to gastroparesis. However, based on randomized controlled trials, this intervention has not shown symptom improvement and is not recommended for patients with gastroparesis.[1,33]

Laparoscopic (Heineke-Mikulicz) pyloroplasty involves creating a longitudinal incision across the pylorus, followed by a transverse closure. This surgical approach results in the division of both the longitudinal and circular muscle layers. Laparoscopic pyloroplasty is considered a relatively safe procedure and has been shown to enhance gastric emptying while bringing about short-term improvements in symptoms such as nausea, vomiting, bloating, and abdominal pain.[1,18,33,47]

G-POEM is a novel endoscopic procedure that divides the pylorus from the mucosal surface and presumably cuts predominantly the circular muscle layer while maintaining the longitudinal muscle to avoid perforation.[33] G-POEM has been proven effective in treating gastroparesis, leading to improved gastric emptying. It has demonstrated superiority over gastric electrical stimulation for gastroparesis in terms of duration of clinical response (time from the procedure to clinical recurrence, with recurrence defined as symptoms refractory to medical treatment requiring hospitalization along with Gastroparesis Cardinal Symptom Index score ≥ 3 for 6 months),[48] and has shown results equivalent to surgical pyloroplasty in patients with medically refractory gastroparesis.[49]

TAKE-HOME POINTS

- Primary care clinicians continue to be crucial in providing first-line treatment for patients with mild to moderate gastroparesis, particularly those with obesity or overweight and diabetes mellitus. This includes offering ongoing education and counseling on dietary changes to effectively manage symptoms.
- To assess the risk of diabetic gastroparesis and ensure optimal glycemic control, continuous glucose monitoring can provide valuable insights. Further studies examining the associations between glucose metrics derived from continuous glucose monitoring and diabetic gastroparesis are warranted.
- A better understanding of the etiology of idiopathic gastroparesis is needed.
- A meticulous medical history and relevant workup are needed to accurately diagnose idiopathic gastroparesis. Also, autoimmune disorders associated with neuronal antibodies such as autoimmune gastrointestinal dysmotility should be suspected in patients with dysautonomic manifestations. This requires referral to a gastroenterologist trained in motility disorders. Strong evidence is needed before considering immunotherapy for patients with autoimmune gastrointestinal dysmotility.

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