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CME MOC
Recognizing a retirement, and a calcium deposition syndrome

This month, I want to devote the bulk of my editorial space to a personal note about changes in our CCJM editorial community. Ray Borazanian, who has been our managing editor for over 2 decades, is retiring as of April 2.

Upon reading (and editing) a retirement biosketch written by others for internal dissemination, Ray quipped in an e-mail that the “Borazanian guy appears to be a fine fellow.” That is as strong a self-promotional statement he has likely ever written. For ever the guy behind the curtain, he has quietly and competently translated clinicians’ writing into clear, readable, understandable English, in addition to verifying references and numbers and correcting tables. And he has done this with full realization that authors might take umbrage at having their stilted, plodding language “dumbed down” to simple and clearly expressed declarative statements. I recall my own reaction when receiving and reading the final galley proof of the first paper I submitted to CCJM. It was clearly not exactly what I had written—it was much clearer. Other journals I had published in had never edited like that. This CCJM approach to editing was equally driven, embraced, and enacted by other in-house editors Dave Huddleston and Phil Canuto, but I don’t think any took the pushback by authors harder and more personally than Ray. This “stylistic” editing, as I defended it to authors, paid off in many ways. These included getting surprise, unsolicited recognition by the Plain Language Action and Information Network (PLAIN), “an unfunded working group of federal employees from different agencies and specialties who support the use of clear written communication.” They wrote, “How did the editors of the Cleveland Clinic Journal of Medicine dramatically increase their readership? By replacing their journal’s dense, long-winded, jargon-filled style with an alternative style that incorporates the principles of plain language.”

Ray joined Cleveland Clinic as a research assistant in the Department of Hypertension and Nephrology in 1986. He coauthored several papers relating to hypertension with icons in the field, Ray W. Gifford, Jr., and Donald Vidt. He subsequently expanded his clinical editing activity and joined the CCJM as a manuscript editor. When Dave Huddleston, the Managing Editor at the time, left the Journal to do a stint in the Peace Corps, Ray quite ably assumed that position. Dave has long since returned to CCJM as Editorial Project Leader. With Ray’s retirement, Dave will, fortunately for all, now reprise his role as Managing Editor.

We have had other changes within our core editorial group over the past year, several of which I have previously noted in editorial comments. These changes were made more challenging by our pandemic-necessitated physical separation, with our nonphysician editorial team members all working from home. The personality of the Journal is fundamentally unchanged, something that I am personally quite thankful for and that I attribute in large part to the leadership of Peter Studer, our executive publisher. But changes there are, professional and personal.

As readers who are fans of classic British rock and roll may readily appreciate, it has been amusingly special to me to refer to our creative editing team of Ray and Dave.

doi:10.3949/ccjm.88b.04021
Although only those of a certain age will get what I am alluding to, I can’t do it any longer with Ray’s retirement. I have appreciated that neither of these musically adroit “fine fellows” has over the years red-penned out my editorial musical references.

Thank you, Ray. (And yes, I will try to remember that you do not like the use of parenthetic comments).

There is also clinical content in this issue of the Journal worth highlighting, relating to the biological and clinical impact of soft-tissue calcium deposition. Calcium deposition in articular and periarticular structures is associated with an odd paradox: it is both under- and over-attributed as a cause of specific clinical syndromes. Chondrocalcinosis is commonly seen on radiographs of knees and wrists, particularly in older patients. But its presence is not equivalent to the clinical syndrome of recurrent acute calcium pyrophosphate arthritis (pseudogout). Conversely, inflammatory chronic calcium pyrophosphate arthritis of the metacarpophalangeal joints and wrists, which is most reliably diagnosed by documenting the presence of calcium pyrophosphate crystals within neutrophil-predominant inflammatory synovial fluids, often in the absence of radiographic calcium deposition, can easily be misdiagnosed as seronegative rheumatoid arthritis if synovial fluid is not obtained and analyzed for the presence of crystals.

A unique calcium pyrophosphate crystal-associated inflammatory syndrome of the cervical spine, crowned dens syndrome, is discussed in 2 papers in this issue.²,³ This is a syndrome that I believe is underdiagnosed, recognized mainly in its florid presentation as a pseudomeningitis or pseudocervical spine abscess. And yet, as described in 2013 by Chang et al, a group led by Donald L. Resnick at University of California San Diego, in patients over age 60 the prevalence of atlantoaxial calcium pyrophosphate crystal deposition on computed tomography was 34%, jumping to 49% in patients age 80 and older.⁴ Often not recognized on magnetic resonance imaging, this calcium deposition should be looked for with computed tomography in the appropriate clinical context.

Brian F. Mandell, MD, PhD
Editor in Chief

The Symposium will provide up-to-date reviews of management strategies and research on the complications of diabetes. Key topic areas to be addressed include a review of therapeutic options to manage both type 1 and 2 diabetes and the complications, including a pump update, dual hormone therapies, sulfonylureas, GLP1 agonists, metformin, and the role of exercise and fasting. New this year is a discussion of the pathophysiologic impact of COVID-19.
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Want to know the symptoms, risk factors and prevalence of OSA? Jessica Vensel Rundo, MD, MS, discusses screening tools that can be used to assess for OSA risk.

**Sleep Apnea and the Heart**
Are you able to identify the physiology of sleep-heart interactions? Reena Mehra, MD, MS, describes the association of OSA and cardiovascular health.

**Beyond Heart Health: Consequences of Obstructive Sleep Apnea**
Ever wondered about the relationship between OSA and metabolic disease, and OSA and cognitive impairment? Harneet K. Walia, MD, presents OSA’s impact on one’s quality of life.

**Positive Airway Pressure: Making an Impact on Sleep Apnea**
Do you know the newest clinical trials and large observational studies related to PAP therapy for OSA? Colleen G. Lance, MD, discusses advanced PAP therapies, as well as the problem achieving PAP adherence.

**Treatment of Obstructive Sleep Apnea: Alternatives to PAP Therapy**
Want to know alternatives to PAP therapy? Tina Waters, MD, highlights conservative option, surgical interventions, oral appliance therapy, and nasal expiratory positive airway pressure therapy.

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Crowned dens syndrome: Caution about asymptomatic calcification

A 88-year-old Japanese man in a psychiatric hospital because of progressive Alzheimer disease developed fever, headache, and posterior neck pain. The symptoms persisted despite antibiotic therapy with 500 mg/day of oral levofloxacin and 500 mg/day of intravenous meropenem. He was transported to our emergency department 42 days after the onset of symptoms. Laboratory tests revealed a white blood cell count of $3.43 \times 10^9/L$ (reference range $3.59–9.64$) and a C-reactive protein level of $0.95$ mg/dL ($0–0.30$).

Computed tomography of the head and neck without contrast enhancement showed calcium deposition around the dens (Figure 1). Cerebrospinal fluid obtained by lumbar puncture was colorless and transparent and showed no red blood cells or white blood cells.

Based on the persistence of headache and neck pain despite antibiotic therapy and on calcification around the dens, a tentative diagnosis of crowned dens syndrome was made. The patient was prescribed a nonsteroidal anti-inflammatory drug (loxoprofen 60 mg), to be used as needed.

Bacterial culture of the cerebrospinal fluid came back 2 days later positive for Bacillus cereus. Therefore, the patient was diagnosed with bacterial meningitis, partially treated with previously administered antibiotics. He was quickly admitted to our hospital and started on intravenous vancomycin 750 mg every 24 hours and clindamycin 600 mg every 8 hours. His fever, headache, and cervical pain diminished gradually, and he was discharged to home on day 57.

**IS IT INFECTION OR CROWNED DENS?**

Crowned dens syndrome is characterized by acute-onset fever, head and cervical pain, and radiographic findings of calcium deposition around the dens. The calcification in our patient was thin, with no adjacent soft-tissue...
swelling. Advances in computed tomography enable the detection of slight calcifications; slight calcifications may be normal and should not raise unnecessary suspicion for crowned dens syndrome.

This patient’s case conveys the important message that calcium deposition in the atlantoaxial joint is not always symptomatic. It remained unclear whether the patient developed crowned dens syndrome with infection or just the infection.

Although crowned dens syndrome is relatively benign, infection of the central nervous system is a critical condition that needs prompt intervention. Physicians should not rule out infectious disease based only on a finding of calcium deposition.

■ HEEDING THE CLUES

Asymptomatic atlantoaxial calcium deposition is reportedly common in the aged population. In the present case, the prolonged period of fever was inconsistent with crowned dens syndrome, which usually develops acutely and subsides within a few days. In addition, inappropriate antibiotic use might lead to partial treatment of meningitis, pseudonegative cerebrospinal fluid findings, and, in this case, delayed diagnosis.

In summary, physicians should be aware that the combination of fever, headache, cervical pain, and calcium deposition around the dens does not always indicate crowned dens syndrome. Asymptomatic calcification is not rare, and physicians should not hesitate to perform lumbar puncture and other diagnostic tests to rule out life-threatening diseases such as bacterial meningitis.

Acknowledgments: I thank Dr. Hotaka Hara for engaging in useful discussion and providing clinical instruction. I also thank Kelly Zammit, BVSc, from Edanz Group (https://en-author-services.edanzgroup.com/ac) for editing a draft of this manuscript.

■ DISCLOSURES

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


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CORRECTION

SGLT-2 inhibitors for type 2 diabetes

In the January 2021 issue, in Tsushima Y, Lansang MC, Makin V. The role of SGLT-2 inhibitors in managing type 2 diabetes. Cleve Clin J Med 2021; 88(1):47–58. doi:10.3949/ccjm.88a.20088, a sentence on page 52 contained an error: “However, in January 2020, the 100-mg once-daily dose was approved for use in patients with eGFR 30 to 44 mL/min/1.73 m² with urinary albumin excretion less than 300 mg/day.” The 100-mg once-daily dose was approved for use in patients with eGFR 30 to 44 mL/min/1.73 m² with urinary albumin excretion more than 300 mg/day. This has been corrected online.
Calcium pyrophosphate deposition and crowned dens syndrome

Calcium pyrophosphate deposition disease (CPDD) was first described in the early 1960s in patients with acute inflammatory arthritis that looked like gout. This was just after the development of the polarized light microscope and before the common use of morphologic or birefringent properties to identify crystal types. Astute clinician-scientists noticed that some of the synovial fluid crystals from patients with goutlike arthritis were resistant to uricase, and later discovered that these uricase-resistant crystals were composed of calcium and pyrophosphate.

A description of a group of arthritis patients with radiographic chondrocalcinosis was also published around this time. Chondrocalcinosis appearing as finely stippled radiopaque deposits was shown to be a radiographic correlate of calcium pyrophosphate crystal deposition in tissues.

CPDD is still most commonly recognized as an acute inflammatory arthritis, formerly known as pseudogout. However, it has multiple clinical presentations, including a rheumatoid arthritis-like syndrome characterized by persistent inflammation of multiple large and small joints, as well as an osteoarthritis-like syndrome, with symptoms that are primarily degenerative but with a pattern of affected joints unusual for osteoarthritis. For example, shoulders, wrists, ankles, and metacarpophalangeal joints are commonly involved in CPDD, but this is relatively rare in osteoarthritis.

A NOT-SO-UNCOMMON FORM OF ARTHRITIS

While the true incidence and prevalence of CPDD are unknown, it is not an uncommon form of arthritis. Estimates of prevalence suggest that 10 to 15 million Americans have some evidence of this disease. It is typically associated with advanced age and is rare in people under age 60. Familial forms are known to cause premature severe disease. Conditions that predispose to CPDD include hyperparathyroidism, hemochromatosis, hypomagnesemia, and hypophosphatasia.

Factors that govern crystal formation and control their ability to induce inflammation remain poorly characterized. Consequently, no specific therapies to prevent crystal formation or dissolve existing crystals have been designed to date. Moreover, CPDD lacks specific therapeutic recommendations, as there are virtually no randomized clinical trials of this disease. We treat the acute inflammatory syndromes in a manner similar to acute gout, and we struggle to find effective therapies for patients with the more chronic forms of this disease.

LINK TO CROWNED DENS SYNDROME

Crowned dens syndrome is an underrecognized cause of acute neck pain and fever that is one of the more distinctive syndromes associated with CPDD.

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cant leukocytosis and dramatically elevated inflammatory markers. Delirium is also well described in these elderly patients.

Crowned dens syndrome is often misdiagnosed as menigitis or giant cell arteritis, and more rarely as polymyalgia rheumatica, spondylitis, or fever of unknown origin. The diagnosis is typically made by observing chondrocalcinosis surrounding the odontoid process on computed tomography of the cervical spine. Symptoms generally respond well to moderate or high doses of corticosteroids. Colchicine may be helpful, and cytokine-targeted anti-inflammatory drugs such as anakinra have also been used.1

■ CHALLENGES TO DIAGNOSIS

Crowned dens syndrome is considered rare, but little about its epidemiology is known, and it is likely that many cases are missed. Its diagnosis relies heavily on appropriate imaging. However, as in the case presented in this issue of the Journal by Mizumoto et al, a hasty diagnosis of crowned dens syndrome may result in missing a serious infection.

Conventional radiography and magnetic resonance imaging, often performed for musculoskeletal pain, will miss calcification around the dens. There are case reports of aspiration of local fluid collections that demonstrate calcium pyrophosphate crystals in crowned dens syndrome, but aspirations are rarely performed.

Conversely, the presence of calcific deposits in the periodontal ligament is not specific for the clinical symptoms of crowned dens syndrome and can occur in asymptomatic patients. This was illustrated nicely in a study of 513 patients undergoing computed tomography for acute trauma; the authors reported an overall 12.5% prevalence of atlantoaxial calcification, which increased to 34% in patients age 60 and older, and to 49% in those age 80 and older.

Improvements in imaging such as dual-energy computed tomography, which can chemically identify crystal deposits, will certainly aid in diagnosis. But until this type of test is widely available, increased clinical recognition of crowned dens syndrome as an important cause of acute neck pain with inflammatory signs and symptoms in older patients is essential.

■ REFERENCES


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Visit our web site at http://www.ccjm.org
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Tumoral calcinosis

A 47-year-old woman presented to our hospital with dyspnea and mild hip pain on ambulation. Chest radiography revealed multiple calcified masses on both shoulders. She had received peritoneal dialysis for 3.5 years because of chronic lupus nephritis. Her prescribed medications included prednisolone 5 mg daily, alfalcacidol 1 μg daily, and evocet (a new calcimimetic approved in Japan for secondary hyperparathyroidism in patients undergoing dialysis) 1 mg daily. She had an unremarkable family medical history, and she did not use tobacco or alcohol.

On physical examination, the jugular veins were distended, and heart and lung auscultation revealed an S3 gallop and bibasilar crackles. There were no palpable masses or tenderness of the shoulders, but range of motion of hip joints was limited.

Results of laboratory studies were as follows:
- Average serum calcium 7.5 mg/dL (reference range 8.8–10.1)
- Phosphate 4.8 mg/dL (2.7–4.6)
- Blood urea nitrogen 35 mg/dL (8–20)
- Serum creatinine 6.9 mg/dL (0.46–0.79)
- Total protein 5.5 g/dL (6.6–8.1)
- Albumin 2.7 g/dL (4.1–5.1)
- Intact parathyroid hormone 390 pg/mL (10–60)
- Normal white blood cell count.

Chest and hip radiographs demonstrated cardiomegaly with pulmonary congestion, as well as large, irregular, calcified masses adjacent to both shoulders, below the right lower ribs (Figure 1), on the left side of the lower lumbar spine, at the hip joints, and superimposed over both ischial tuberosities (Figure 2).

Multiple calcified masses on radiography suggested tumoral calcinosis, the differential diagnosis.

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diagnosis of which includes calcific tendinitis, synovial osteochondromatosis, and osteosarcoma. Extensive calcification beyond the tendons and synovia of multiple joints made these conditions less likely, and osteosarcoma usually affects children and adolescents. In our patient’s case, the diagnosis was tumoral calcinosis associated with chronic kidney disease, along with congestive heart failure.

She began temporary hemodialysis, which improved her heart failure symptoms, and then peritoneal dialysis was reintroduced with an increase in frequency. Her evocalcet was increased to 2 mg daily.

**FEATURES OF TUMORAL CALCINOSIS**

Tumoral calcinosis is an uncommon disorder characterized by calcium salt deposition around large joints, resulting in irregular, large, lobulated calcified masses. Histologic examination of the mass demonstrates extensive amorphous calcium deposits within a fibrous stroma with giant multinucleated foreign-body cells and inflammatory infiltrates.

Tumoral calcinosis is divided into primary and secondary types, and chronic kidney disease is the leading cause of the secondary type. The incidence of secondary tumoral calcinosis in patients undergoing peritoneal dialysis has been estimated as 1.6%.

Although the precise mechanism is unknown, risk factors include hypercalcemia, hyperphosphatemia, increased calcium-phosphate product, hyperparathyroidism, calcium-containing phosphate binders, and activated vitamin D.

Common clinical manifestations are joint tenderness, limited range of motion of joints, and skin ulcerations. In one report, 14% of patients (1 of 7) with secondary tumoral calcinosis had no symptoms.

**TREATMENT OPTIONS**

Treatment should focus on correcting risk factors to optimize calcium and phosphate homeostasis. Medical management includes restricting dietary calcium and phosphorus, using low-calcium dialysate, and giving non-calcium-containing phosphate binders.

Excision of calcified masses is indicated in cases refractory to conservative medical care. Renal transplant has been reported to produce complete remission. Parathyroidectomy has been tried but reported to be unsatisfactory.

**DISCLOSURES**

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

**REFERENCES**


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A 37-year-old man presented to the rheumatology clinic for evaluation of swelling of his fingers and hands. The symptoms began 8 months earlier and at first were intermittent, but in the last 4 months, they had become persistent. The swelling started in the right (nondominant) hand, and then affected the left hand within a few weeks.

He reported limited range of motion in his fingers and wrists, with loss of hand dexterity and difficulty picking up objects or putting on socks and shoes. He denied any features suggestive of systemic sclerosis, including Raynaud phenomenon, ischemic digital ulcers, heartburn, dysphagia, dry cough, and exertional shortness of breath. He reported no other chronic medical illness.

He said he smoked marijuana and half a pack of cigarettes per day. After 2 years of sobriety, he had restarted using intravenous (IV) drugs (opiates and methamphetamine) about 1 month earlier.

On examination, the dorsal and palmar aspects of both hands, fingers, and wrists were diffusely swollen with limited range of motion (Figure 1). However, there was no clinical evidence of inflammation (synovitis) of the wrist and finger joints, ie, no joint swelling, tenderness, heat, or redness.

Laboratory studies revealed a normal complete blood cell count, comprehensive metabolic panel, C-reactive protein, and thyroid-stimulating hormone level. Other tests with negative results included urine tox-
cology screen, hepatitis B and C and human immunodeficiency virus serology, and testing for rheumatoid factor, anti-cyclic citrullinated peptide antibody, antinuclear antibody, and antibodies to extractable nuclear antigens.

A radiograph of the right hand showed diffuse soft-tissue swelling (Figure 2). Computed tomography of the right hand also showed diffuse soft-tissue edema and skin thickening, most prominent over the dorsal side. There was no enhancing fluid collection or gas in the soft tissues and no bony cortical destruction. Based on the presentation, the history, and the evaluation, the diagnosis was puffy hand syndrome.

### A COMPLICATION OF IV DRUG USE

Puffy hand syndrome, a common complication of IV drug use, is not a well-recognized condition among general practitioners. However, addiction specialists, dermatologists, and vascular medicine specialists are familiar with this syndrome.

In patients who do not volunteer a history of IV drug use, a rheumatologist may also be consulted, as the differential diagnosis includes scleroderma, mixed connective tissue disease, and the syndrome of remitting seronegative symmetrical synovitis with pitting edema (RS3PE).1

### DIAGNOSTIC CLUES

The precise pathogenesis of puffy hand syndrome remains unknown. Hand edema, which is initially pitting, becomes more indurated over time, as there is progressive fibrosis of the subcutaneous tissues. The swelling is asymmetric and intermittent at first, often affecting the nondominant hand; over time, it becomes persistent and symmetric, as in this patient.1

Repeated injection of agents that can induce vascular and dermal sclerosis results in an inflammatory reaction with granuloma formation, similar to a foreign-body granulomatous reaction. Over time, the dense dermal fibrosis obscures the superficial veins and the extensor tendons on the dorsum of the hands.2 The edema is painless and nonpitting2 and is unaffected by elevation.2 Edema may also affect the feet when injection drug users use veins in the feet, legs, or groin.

Risk factors and underlying processes

The main risk factors are repeated injections in the superficial veins on the dorsum of the hands (preferred by IV drug users because of easy access), and not using a tourniquet during the injections.3 The condition is more common in females. The risk increases with unsterile injection practices, suggesting that repeated local infections also contribute to
the lymphatic destruction and consequent lymphedema.

Neviaser et al. performed venography, lymphangiography, and deep-skin biopsies in 4 patients with puffy hand syndrome. Deep venous patterns were entirely normal. In contrast, lymphangiograms showed extensive collateralization at the elbow, suggesting the destruction of deep lymphatic channels. Biopsy studies showed extensive fibrosis in the subcutaneous tissues.

This study indicated that puffy hand syndrome results primarily from lymphatic obstruction, and that there may be concomitant local scarring resulting from inflammatory reactions at injection sites. Venous obstruction does not appear to play a primary role but can coexist in some cases. Repeated insults are needed for swelling to develop.

■ A BROAD DIFFERENTIAL DIAGNOSIS

The differential diagnosis of puffy hand syndrome is broad and includes conditions that cause anasarca, such as congestive heart failure, nephrotic syndrome, cirrhosis of the liver, and severe hypoalbuminemia. Other causes include upper-extremity venous thrombosis, deep palmar space infection, complex regional pain syndrome, lymphedema resulting after axillary lymph node removal or irradiation, and filariasis.

Rheumatologic diseases causing puffy hands include rheumatoid arthritis, crystal arthropathies, systemic sclerosis, mixed connective tissue disease, nephrogenic systemic fibrosis, and RS3PE syndrome.

A thorough history and physical examination, followed by judicious use of laboratory and other investigations, should help determine the underlying cause of puffy hands.

TREATMENT OPTIONS

Treatment is mostly symptomatic. Intravenous drug use should stop permanently. Long-term use of low-stretch bandages and elastic compression gloves may be useful in decreasing the puffiness of the hands and fingers.

■ PATIENT OUTCOME

Our patient quit IV drug use and is currently undergoing drug rehabilitation and psychiatric counseling. So far, he has not regained much movement in his hands and fingers.

Acknowledgment: The author thanks the patient for providing permission to share his information.

■ DISCLOSURES

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

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Visit WWW.CCJM.ORG Test your knowledge of clinical topics
Q: Is it safe to start steroids at home for a COPD exacerbation after virtual assessment in the COVID-19 era?

A: A 63-YEAR-OLD MAN with chronic obstructive pulmonary disease (COPD), using an albuterol inhaler as needed, called our nurse triage line in October 2020 because his chronic cough had worsened over the past 7 days. In this time, he occasionally had wheezing when breathing, but he noted no increase in shortness of breath. The nurse advised him to be tested for coronavirus and scheduled a follow-up virtual visit for 3 days later.

By then, his symptoms were worse. The cough was productive, associated with occasional mucoid expectoration, and now interfered with sleep. He said he still occasionally had wheezing on respiration but did not have worsened shortness of breath, fever, sore throat, myalgias, or diarrhea. Because he lacked transportation and social support, he could not undergo the recommended coronavirus test. He had never undergone pulmonary function testing at our institution, and had never been hospitalized for similar concerns.

On virtual examination, he appeared comfortable. His respiratory rate was 24 breaths per minute, and he did not appear to be using accessory muscles of respiration. No wheezing could be heard.

Based on the impression that the patient was experiencing an acute exacerbation of COPD, should he be prescribed a corticosteroid, and can this be done safely?

The answer to both questions is yes.

In acute exacerbations of COPD, systemic corticosteroids have been shown to accelerate improvement in airflow, delay the time to recurrence, and, in hospitalized patients, reduce the length of stay. A 5-day course of prednisone 40 mg/day has been shown to be noninferior to a longer (14-day) course and is generally well tolerated.

The dilemma posed by our patient—new cough and phlegm in a patient with COPD—poses a common challenge in the COVID-19 pandemic, as the differential diagnosis also includes COVID-19.

Virtual visits are appropriate during the pandemic, given the risk a potentially infected individual poses to others. The use of virtual visits has expanded rapidly during the pandemic. Yet a virtual assessment of a patient with COPD who is suspected of having an acute exacerbation is limited in some ways.

COPD VS COVID-19: DIAGNOSTIC CHALLENGE

The clinical features of acute exacerbation of COPD—worsened shortness of breath and cough—overlap with those of COVID-19, and this was the reason for recommending COVID-19 testing in our patient. Compounding this diagnostic dilemma, COPD is a risk factor for severe COVID-19 and adverse clinical outcomes of COVID-19. Managing acute exacerbations of COPD during this pandemic is further complicated by increased demands for healthcare, limited access to healthcare, and heightened reluctance of patients to go to the hospital.

Hospital admissions for acute exacerbations of COPD have declined recently, likely because patients don’t want to go to the hospital, and hospitals are admitting only the sickest patients. Another reason may be that there are fewer COPD exacerbations due to less air pollution because people are working...
from home and not traveling as much. Also, patients with chronic cough can be reflexively suspected of having COVID-19, and in-office visits are sometimes discouraged based on the infectious risk.

Together, these factors have made virtual visits a mainstay of managing patients with COPD during the pandemic.

### Virtual Assessment of Acute Exacerbations of COPD

**Table 1**

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count the respiratory rate</td>
<td>A rate &gt; 30 breaths/minute indicates increased work of breathing</td>
</tr>
<tr>
<td>If possible, note increased activity of accessory muscles</td>
<td>Increased accessory muscle activity indicates ongoing respiratory distress</td>
</tr>
<tr>
<td>Assess mentation and look for flapping tremors (asterixis)</td>
<td>Changes in mentation and presence of asterixis suggest ongoing acute respiratory failure</td>
</tr>
</tbody>
</table>

*There is no clear guidance on the assessment of acute exacerbation of chronic obstructive pulmonary disease (COPD) through a virtual visit. This table is to help clinical assessment through virtual visits and is drawn from the Global Initiative for Chronic Obstructive Lung Disease recommendations for assessment of exacerbation of COPD for hospitalized patients.*

Based on information in reference 7.

Virtual visits have provided a portal for healthcare access while mitigating infection risks. They can allow one to form a clinical impression and to decide whether the patient needs emergent, in-person care vs continued virtual management. On the other hand, virtual visits also limit the clinician's assessment, eg, confining the physical examination to observation and not allowing direct examination, laboratory work and, in some cases, pulse oximetry.

Though studies have examined the value of self-management strategies for COPD with on-line and telephonic backup, to our knowledge, no published report has specifically addressed best practices in virtual visit assessment of patients with COPD.

A careful history is important to elicit a history of exposure to individuals known to have SARS-CoV-2, and also to assess whether the current illness resembles prior exacerbations the patient may have experienced.

Visual inspection is critical and plays an even more important role during a virtual visit. Drawing from the Global Initiative for Chronic Obstructive Lung Disease 2020 guidelines for managing acute exacerbations of COPD, assessing the patient’s respiratory rate, use of accessory muscles, mentation, and oxygenation and observing for asterixis are especially important during a virtual visit (Table 1). Establishing whether the patient has a normal respiratory rate (< 30 breaths per minute), has obvious cyanosis, is using accessory muscles of respiration, has asterixis, and has normal mentation helps determine the urgency of care, and the normal findings in our patient are reassuring.

Close serial follow-up with frequent reassessments to gauge the trajectory of the patient’s illness becomes more important when the initial assessment is limited, as in a virtual visit. Conversely, worrisome findings on initial assessment such as tachypnea, gross cyanosis, accessory muscle use, paradoxical inward motion of the abdomen on inspiration, asterixis, or confusion should prompt a recommendation to go to the nearest emergency room or call 911.

### Treating Acute Exacerbations of COPD in the COVID-19 Era

We could not confidently exclude COVID-19 in this case. Because corticosteroids are indicated in acute exacerbations of COPD, the current case prompts 2 questions:

- Should corticosteroids be prescribed (eg, prednisone 40 mg daily for 5 days, as was used in the Reduction in the Use of Corticosteroids in Exacerbated COPD [REDUCE] trial)?
- Would corticosteroids adversely affect outcomes if the patient actually has COVID-19?

Regarding the latter question, the Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial demonstrated that, in hospitalized patients with COVID-19 needing supplemental oxygen or mechanical ventilation, fewer patients died who received dexamethasone 6 mg daily for up to 10 days compared with usual care alone. Neither ben-
benefit nor excess harm with dexamethasone was shown for patients with COVID-19 not needing supplemental oxygen and not on a ventilator, supporting the recommendation that inhaled corticosteroids not be withdrawn in COPD patients who contract COVID-19 and that systemic steroids, whether dexamethasone or other steroids in equivalent doses, can be used when indicated.5

Notably, prednisone 40 mg is roughly equivalent to dexamethasone 6 mg in glucocorticoid potency, though the duration of treatment for a COPD exacerbation (5 days) is less than that for severe COVID-19 disease (up to 10 days).10

■ BACK TO THE PATIENT

The patient was started on oral prednisone 40 mg for 5 days for what was presumed to be an acute exacerbation of COPD. He was later able to get a polymerase chain reaction-based test for SARS-CoV-2, which was negative. On follow-up 1 week after the initial virtual visit, his symptoms had dramatically improved, and he reported being back to his usual state of health.

■ VIRTUAL VISITS ARE VALUABLE

In summary, clinically differentiating acute exacerbation of COPD from COVID-19 poses challenges that are exaggerated by some limitations of the virtual visit. But despite the limitations, taking a systematic approach to the history and maximizing visual assessment, as with this patient, can help the patient safely get through the acute illness. It is prudent to plan frequent short-term virtual reassessments to assess the course of the patient’s illness, especially when diagnostic evaluation is limited.

Although the efficacy of virtual visits has not been established for patients with COPD in general nor for those experiencing an exacerbation that might resemble COVID-19, this experience supports the value of virtual visits, coupled with a careful history and clinical observation during the visit.

■ DISCLOSURES

Dr. Stoller has disclosed consulting for Dicerna Pharmaceuticals. All other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

■ REFERENCES


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Update in perioperative cardiac medicine 2021

ABSTRACT
Several studies published in the last year have shed light on the preoperative assessment of perioperative cardiovascular risk and on the need for anticoagulation in patients with postoperative atrial fibrillation, which are reviewed here.

KEY POINTS
The American University of Beirut HAS2 Index and the Updated Cardiac Risk Score are new, simple-to-use risk-stratification tools for patients undergoing various types of surgical procedures.

Incorporating the Duke Activity Status Index into the preoperative evaluation helps identify patients at intermediate to high risk who may need modifications in perioperative care.

Another method of assessing exercise capacity is simply to ask patients if they can walk up 2 flights of stairs.

Preoperative measurement of N-terminal pro-brain natriuretic peptide also adds accuracy to the preoperative assessment, but the optimal cutoff value remains under study.

A study in patients with new-onset postoperative atrial fibrillation questions the efficacy of anticoagulation for preventing strokes while highlighting the bleeding risk.

THE CHOICE OF CALCULATORS to predict perioperative cardiac risk, assessment of a patient’s exercise capacity, role of preoperative biomarkers, and need for anticoagulation after postoperative atrial fibrillation are controversial topics in perioperative medicine, and the evidence continues to evolve. This update will highlight new information in these areas based on publications from the past year.

CARDIAC RISK CALCULATORS
Current guidelines recommend the use of either the Revised Cardiac Risk Index, Myocardial Infarction or Cardiac Arrest Calculator, or American College of Surgeons Surgical Risk Calculator to estimate the risk of postoperative cardiac complications. Other calculators designed specifically for geriatric patients or for vascular surgery are also available. Most of these tools were developed retrospectively from databases or have not been externally validated.

What’s new? Two new calculators
Two new prospectively developed calculators were recently reported, the American University of Beirut (AUB)-HAS2 Index and the Updated Cardiac Risk Score (UCRS).

The AUB-HAS2 Index
Dakik et al prospectively derived the AUB-HAS2 Index from 3,284 adult patients undergoing noncardiac surgery at the American University of Beirut Medical Center and validated it in 1,167,414 patients from the American College of Surgeons National Surgical Quality Improvement Program database. The primary outcome included death, myocardial infarction, or stroke at 30 days after surgery. The index and “HAS2” acronym are based on the following risk factors:

1. Age
2. Heart history
3. Diabetes
4. Smoking
5. Kidney function
6. Allergies
7. Previous surgery

Additional factors may be included based on the surgeon or hospital’s risk profile.

Preoperative measurement of N-terminal pro-brain natriuretic peptide also adds accuracy to the preoperative assessment, but the optimal cutoff value remains under study.

A study in patients with new-onset postoperative atrial fibrillation questions the efficacy of anticoagulation for preventing strokes while highlighting the bleeding risk.

Steven L. Cohn, MD, MACP, SFHM
Professor Emeritus, Department of Medicine,
University of Miami Miller School of Medicine,
Miami, FL
• History of heart disease
• Symptoms of heart disease (angina or dyspnea)
• Age 75 or older
• Anemia (hemoglobin < 12 mg/dL)
• Vascular surgery
• Emergency surgery.

The index stratifies risk in patients undergoing noncardiac surgery into 3 groups:
• Low risk (score 0–1)
• Intermediate risk (score 2–3)
• High risk (score > 3).

The AUB-HAS2 Index was subsequently validated in a prospective cohort of 1,918 patients at the American University of Beirut, although the primary outcome occurred in only 13 patients (0.7%).

Using 1,167,278 patients from the National Surgical Quality Improvement Program database, the performance of the AUB-HAS2 index was studied in 9 surgical specialty groups and in 8 commonly performed site-specific surgeries, compared with the Revised Cardiac Risk Index using receiver operating characteristic curves, and was superior overall (area under the curve 0.818 vs 0.716, \( P < .001 \)) as well as in all surgical subgroups (areas under the curve ranged from 0.71 in vascular and thoracic surgery to > 0.80 in orthopedic, general, and plastic surgery). Additionally, it identified a large low-risk group of patients (score = 0) and a high-risk group (score ≥ 3) with complication rates less than 1% and more than 10%, respectively.

Of note, there were differences between the AUB-HAS2 and Revised Cardiac Risk Index, limiting a true direct comparison but potentially enhancing applicability towards the overall population undergoing noncardiac surgery. The former included emergency surgery as well as some low-risk procedures, and the outcomes studied included stroke and all-cause mortality at 30 days, which were not included in the Revised Cardiac Risk Index.

The Updated Cardiac Risk Score
Scorcu et al\(^5\) derived the UCRS from 4,600 patients age 40 or older and validated it in another 2,735 patients in the Preoperative Assessment of Cardiovascular Risk in Patients Undergoing Elective Noncardiac Surgery, an observational prospective cohort study in Italy.

Outcomes included cardiovascular death, cardiac arrest, acute myocardial infarction, acute heart failure, atrioventricular block requiring cardiac pacing, and stroke within 30 days after surgery.

Four variables were significantly associated with the risk of a major perioperative cardiovascular event:
• High-risk surgery
• Preoperative glomerular filtration rate less than 30 mL/min/1.73 m\(^2\)
• Age 75 or older
• History of heart failure.

Four risk classes were created, and their corresponding risks of a major cardiovascular complication were:
• 0.8% (95% confidence interval [CI] 0.5–1.7)
• 2.5% (95% CI 1.6–5.6)
• 8.7% (95% CI 5.2–18.9)
• 27.2% (95% CI 11.8–50.3).

The areas under the curve were higher for the UCRS than the Revised Cardiac Risk Index in both the derivation cohort (0.86 vs 0.79) and the validation cohort (0.77 vs 0.72).

This study evaluated a wider range of complications than did the Revised Cardiac Risk Index, but like the Revised Cardiac Risk Index, it was a single-institution study and used creatine kinase-MB, not troponin, for postoperative surveillance. Once again, a true direct comparison is limited.

In summary, the AUB-HAS2 and UCRS are new, simple-to-use tools that accurately stratified risk in patients undergoing various types of surgical procedures. External validation is awaited using high-sensitivity troponin for postoperative surveillance.

■ EXERCISE CAPACITY

Estimating a patient’s exercise capacity is part of the American College of Cardiology perioperative guideline algorithm,\(^1\) which suggests using at least 4 metabolic equivalents (METs) as a cutoff for adequate exercise capacity. Historically, this was done by asking patients how many blocks they could walk or flights of stairs they could climb, to determine their activity level.

However, the Measurement of Exercise Tolerance Before Surgery (METS) study\(^6\) demonstrated that a clinician’s subjective assess-
ment had a low discriminative ability to define poor exercise capacity compared with the gold standard of cardiopulmonary exercise testing, and it did not correlate well with postoperative cardiac complications. Instead, the study suggested using a more objective method, the Duke Activity Status Index score, which was more predictive of these complications.

**Duke Activity Status Index improves preoperative evaluation**

Wijeysundera et al, in a follow-up METS substudy, evaluated the ability of a specific cutoff value of the Duke Activity Status Index to predict complications after noncardiac surgery. In this nested cohort analysis of 1,546 patients age 40 and older from the METS study, a score of 34 was identified as a threshold for distinguishing patients at risk for myocardial injury, myocardial infarction, moderate-to-severe complications, and new disability. However, although 97% of patients with scores of 35 or higher were deemed to have moderate or good functional capacity, only 15% with scores of 34 or lower were judged as having poor functional capacity.

The authors urged caution in converting a score to a specific number of METs because in this study, a Duke Activity Status Index score of 34 corresponded to 5 METs, whereas the recommended conversion formula in a non-surgical setting yields 7 METs.

Fleisher, in a subsequent editorial, suggested that if a 50% increased rate of events is considered clinically as opposed to statistically significant (since the absolute number of complications was low), then a Duke Activity Status Index score of less than 25 points (approximately 4 METs) would be a second cutoff to identify the subgroup in whom further testing should be considered if it would change management.

One of the limitations noted was that there was a bias excluding high-risk patients due to the study’s requirement for strenuous preoperative exercise, which may have resulted in a low rate of myocardial infarction and death (only 26 patients, 1.7%).

**Summary.** Incorporation of Duke Activity Status Index scores into preoperative evaluation helps to improve the accurate identification of intermediate-to-high-risk patients who warrant modifications in perioperative care. Using a cutoff of 34 was suggested by the study, although 25 may be an acceptable alternative.

**Can you climb 2 flights of stairs?**

Lurati Buse et al performed a predefined secondary analysis of self-reported ability to walk up 2 flights of stairs and perioperative cardiovascular complications in 4,560 consecutive patients age 65 and older, or age 45 and older with a history of coronary artery disease, peripheral arterial disease, or stroke undergoing in-patient noncardiac surgery in Switzerland. The primary end point was a composite of cardiac death and cardiac events at 30 days. Secondary end points included the same composite at 1 year, all-cause mortality, and myocardial injury.

Inability to climb 2 flights of stairs was independently associated with major adverse cardiac events and all-cause mortality at both 30 days (hazard ratio 1.63, 95% CI 1.23–2.15) and 1 year. The addition of functional capacity information to the Revised Cardiac Risk Index improved risk classification. Although the use of a binary cutoff of 2 flights, while not addressing the impact of other daily activities or applying a validated formal functional capacity assessment tool (like the Duke Activity Status Index) was a limitation, the estimation based on “cut-off” daily activities is used by the guidelines.

**Summary.** Compared with the METS study, this study was larger, included high-risk patients, and confirmed the association of self-reported exercise capacity with major adverse cardiac events. Additional information on self-reported exercise capacity will be forthcoming later in 2021 with the publication of the METREPAIR study of more than 15,000 patients across Europe.

**PREOPERATIVE NATRIURETIC PEPTIDES**

Multiple small studies have suggested that elevated levels of the natriuretic peptides brain natriuretic peptide (BNP) and N-terminal-proBNP (NT-proBNP) before surgery are associated with postoperative cardiac complications, and that measuring these peptides may improve risk prediction over using the Revised Cardiac Risk Index alone.

Although the American College of Cardi-
ology guidelines\(^\text{1}\) did not recommend obtaining preoperative biomarkers, the Canadian Cardiovascular Society guidelines\(^\text{11}\) did recommend them for patients with a baseline risk of 5%, which included those age 65 and older, those age 45 and older with cardiovascular risk factors, and those with a Revised Cardiac Risk Index of 1 or more undergoing noncardiac surgery. They also recommended postoperative troponin surveillance in patients whose NT-proBNP level was 300 pg/mL or higher.

**What’s new?**

**Lower NT-proBNP cutoff suggested**

In a large study, Duceppe et al\(^\text{12}\) evaluated the utility of measuring NT-proBNP in predicting postoperative cardiac complications and suggested a different cutoff value.

This nested substudy of the prospective cohort Vascular Events in Noncardiac Surgery Patients Cohort Evaluation study evaluated 10,402 adults age 45 and older to determine whether preoperative NT-proBNP had additional predictive value beyond the Revised Cardiac Risk Index.

The primary end point, a composite of myocardial injury after noncardiac surgery or vascular death within 30 days after surgery, occurred in 12.2%, but a more rigid outcome of myocardial infarction or all-cause mortality occurred in only 4.3%. Stratified by preoperative NT-proBNP values, the incidence of the primary outcome was as follows:

- 100–199 pg/mL, 12.3% (226 of 1,843)
- 200–1,499 pg/mL, 20.8% (542 of 2,608)
- ≥ 1,500 pg/mL, 37.5% (223 of 595).

Adding NT-proBNP thresholds to clinical stratification using the Revised Cardiac Risk Index improved net absolute reclassification by 25.8%. Preoperative NT-proBNP values were also statistically significantly associated with 30-day all-cause mortality.

**Summary.** Compared with the Canadian guideline\(^\text{11}\) threshold of 300 pg/mL and over to identify patients at higher risk, this study found that a threshold of 200 pg/mL and over was associated with a risk greater than 5%, but this cutoff needs to be validated externally.

**Anticoagulation for postoperative atrial fibrillation**

New-onset postoperative atrial fibrillation occurs most frequently after cardiac and thoracic surgery, followed by vascular and major general surgery. It is also more common in the elderly and patients with underlying atherosclerotic cardiovascular disease and is associated with an increased risk of stroke and death within 30 days after surgery.\(^\text{13}\)

New-onset atrial fibrillation was previously thought to be transient and benign; however, recent systematic reviews and meta-analyses reported an increased long-term risk for atrial fibrillation recurrence as well as for cardiovascular and cerebrovascular events.\(^\text{13,15}\) Although most patients with postoperative atrial fibrillation persisting more than 48 hours tend to receive anticoagulation, it is unclear whether they or patients with transient postoperative atrial fibrillation require anticoagulation or for what duration.\(^\text{14,15}\) Unknown is the long-term risk of cerebrovascular events in these patients and whether they should be treated similarly to patients with chronic nonvalvular atrial fibrillation, as the benefit of preventing thromboembolism must be balanced against the risk of bleeding with anticoagulation.

**What’s new?**

**Anticoagulation questioned**

A new study in patients with new-onset postoperative atrial fibrillation questions the efficacy of anticoagulation for preventing stroke while highlighting the bleeding risk.\(^\text{16}\)

Because how to manage new-onset postoperative atrial fibrillation after noncardiac surgery is unclear, Elharram et al\(^\text{16}\) performed a retrospective cohort study of 22,007 patients in Quebec from 1990 through 2015 to determine the association between oral anticoagulation use and hospitalization or emergency department visits for thromboembolic events and major bleeding.

The 6,475 of 22,077 patients (29%) started on oral anticoagulation (81% warfarin, 19% direct oral anticoagulants) within 30 days of discharge had higher CHA2DS2–VASc scores and lower HAS-BLED scores than those not given oral anticoagulation. A thromboembolic event occurred in 1,099 of 22,007 patients (5%), and anticoagulation use was not associated with a lower risk (adjusted hazard ratio 0.89; 95% CI 0.73–1.07) and did not differ based on class of anticoagulant.
A major bleeding event occurred in 3,250 patients (15%). Bleeding risk correlated with HAS-BLED scores, and anticoagulation use was associated with a higher risk of bleeding (hazard ratio 1.14; 95% CI 1.04–1.25). Bleeding risk was higher in those on warfarin vs direct oral anticoagulants and those who had undergone thoracic surgery vs noncardiothoracic surgery.

Summary. Despite the increased risk of cardiovascular and cerebrovascular events after postoperative atrial fibrillation, in this study it appears that the thromboembolic risk in surgical patients differs from those with chronic nonvalvular atrial fibrillation.

In contrast to a Danish study,\textsuperscript{17} the Elharram study showed that oral anticoagulation did not reduce thromboembolic events but did increase major bleeding. Until further data are available, the risk of chronic atrial fibrillation in patients with new-onset postoperative atrial fibrillation may be warranted only in patients with a thromboembolic risk above 1.5%, the cutoff suggested by the Canadian Cardiovascular Society guidelines,\textsuperscript{11} which in the Elharram study correlated with a \textit{CHA}_2\textit{DS}_2–\textit{VASc} score of 4 or higher, as opposed to a score higher than 2 in patients with chronic nonvalvular atrial fibrillation.

\section*{REFERENCES}


\section*{DISCLOSURES}

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

\section*{Anticoagulation did not statistically significantly lower the risk of thromboembolism in postoperative atrial fibrillation}
Our evolving understanding of primary aldosteronism

Primary aldosteronism is the most common endocrine cause of hypertension, and is often associated with treatment-resistant hypertension. It is characterized by autonomous aldosterone production independent of renin activity, potassium level, or volume status. Its prevalence has been debated, and studies are fraught with limitations, including reliance on tests that do not confirm the diagnosis. It has been identified as a public health issue, and the urgency in identifying and treating it is heightened by its strong association with adverse kidney and cardiovascular outcomes.

Multiple studies have pointed to limitations of our current screening strategies, which may be missing a great many patients who have the disease. In particular, newer evidence highlights shortcomings of the long-accepted screening strategy that uses the spot aldosterone-to-renin ratio.

In this commentary, we review the current understanding of primary aldosteronism and the current landscape of screening practices. We will highlight the emerging evidence suggesting that renin-independent hyperaldosteronism is best viewed as a continuum that extends across the spectrum of blood pressure severity. We also describe a proposed approach to optimize case detection of primary aldosteronism.

Serum potassium is not always low

Primary aldosteronism was first described in 1954 by Dr. Jerome Conn, who noted a syndrome of periodic muscle weakness, hypokalemia, alkalosis, and hypertension with elevated urinary aldosterone levels.

Subsequently, hypokalemia came to be viewed as an important component of this condition, to the point that it became almost a sine qua non for the diagnosis. Although primary aldosteronism was classically suspected in patients presenting with the triad of hypertension, hypokalemia, and metabolic alkalosis, this phenotype likely describes an extreme form of the condition. In fact, only 9% to 37% of patients with primary aldosteronism have hypokalemia, and the most common presentation is normokalemic hypertension. Hypokalemia often alerts the clinician to a possible diagnosis of primary aldosteronism; however, the absence of hypokalemia holds a poor negative predictive value for diagnosis and should not be used to exclude the presence of the disorder.

More common than thought, but true prevalence is unclear

The prevalence of primary aldosteronism varies significantly among published reports, and its true prevalence remains unclear. What is becoming clear, however, is that the old notion that this condition accounts for fewer than 1% of cases of mild to moderate hypertension is not true. The variability in the reported prevalence stems primarily from the populations being studied, i.e., the general population vs hypertensive patients vs those with resistant hypertension. Most experts now accept that the prevalence of primary aldosteronism is between 5% and 10% among all hypertensive patients, and up to 20% in those with resistant hypertension.

A major challenge in studying the epidemiology of primary aldosteronism is that there is no gold standard for diagnosing it. The de-
fault standard has been the aldosterone-renin ratio, but the diagnostic cutoff varies across practices and has not been validated in prospective trials. Liberalizing or restricting the diagnostic cutoffs can have significant effects on the perceived prevalence.

CURRENT GUIDELINES FOR SCREENING AND DIAGNOSIS

First step: Screening with the ratio of aldosterone to renin

The current Endocrine Society guidelines for detecting and diagnosing primary aldosteronism, published in 2016, recommend the aldosterone-renin ratio as the most reliable screening test. The reporting should include the plasma aldosterone concentration and the plasma renin activity or direct renin concentration, along with the aldosterone-renin ratio. Patients are at high risk of primary aldosteronism and should be screened for it if they have any of the following:

- Sustained hypertension, with blood pressure above 150/100 mm Hg on 3 or more occasions
- Hypertension with blood pressure above 140/90 mm Hg despite the use of 3 or more medications
- Controlled blood pressure less than 140/90 mm Hg on 4 or more medications
- Hypertension with spontaneous or diuretic-induced hypokalemia
- Hypertension with obstructive sleep apnea
- Hypertension with an adrenal mass
- Hypertension with a family history of early-onset hypertension or cerebrovascular accident before age 40
- Hypertension with a first-degree relative diagnosed with primary aldosteronism.

The guidelines acknowledge that the threshold defining a high aldosterone-renin ratio (and thus a positive screen) varies by practice, but the most common one is a ratio of 30 ng/dL per ng/mL/hour or higher with a plasma aldosterone concentration of 15 ng/dL or higher (Table 1).

In the interest of convenience and automation, many laboratories have switched from the traditional plasma renin activity assay to a direct renin concentration assay. While the

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TABLE 1

Positive thresholds of biochemical testing for primary aldosteronism

<table>
<thead>
<tr>
<th>Screening tests</th>
<th>More conservative</th>
<th>Most widely accepted</th>
<th>More liberal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldosterone-renin ratio (ng/dL per ng/mL/hour)</td>
<td>≥ 40</td>
<td>≥ 30</td>
<td>≥ 20</td>
</tr>
<tr>
<td>Plasma aldosterone concentration (ng/dL)</td>
<td>≥ 20</td>
<td>≥ 15</td>
<td>≥ 10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Confirmation aldosterone suppression tests</th>
<th>More conservative</th>
<th>More liberal</th>
</tr>
</thead>
<tbody>
<tr>
<td>With oral salt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-Hour urinary aldosterone excretion rate (μg)</td>
<td>&gt; 12–14</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>With intravenous saline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma aldosterone concentration (ng/dL)</td>
<td>&gt; 10</td>
<td>&gt; 5</td>
</tr>
<tr>
<td>With fludrocortisone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seated plasma aldosterone concentration (ng/dL)</td>
<td>&gt; 6</td>
<td>&gt; 6</td>
</tr>
<tr>
<td>with plasma renin activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 ng/mL/hour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With captopril</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma aldosterone concentration, decrease from baseline</td>
<td>&lt; 30%</td>
<td>&gt; 30</td>
</tr>
<tr>
<td>Aldosterone-renin ratio (ng/dL per ng/mL/hour)</td>
<td>&gt; 30</td>
<td>&gt; 20</td>
</tr>
</tbody>
</table>

Based on information in references 2 and 11.
MEHDI AND COLLEAGUES

2 assays generally correlate well with one another, conversion factors vary slightly among different laboratories. A discussion of the advantages and disadvantages of each assay is beyond the scope of this commentary. Practitioners, however, must consult with their laboratory when interpreting direct renin concentration and converting to plasma renin activity.

Second step: Confirmatory testing
Patients who have a positive (high) result on the aldosterone-renin ratio screening test should then undergo a confirmatory diagnostic test to definitively confirm or exclude primary aldosteronism.

The guidelines describe 4 confirmatory testing procedures: oral sodium suppression, saline infusion suppression, fludrocortisone suppression, and captopril challenge test. All these tests hinge on the premise that aldosterone should normally be suppressed with the above interventions. Persistent aldosterone production would be indicative of autonomous renin-independent aldosteronism, thus confirming primary aldosteronism.

The cutoffs used to define a positive result on a confirmatory test again vary by practice (Table 1).2,11

The guidelines note an exception to the need for the confirmatory step. Patients with spontaneous hypokalemia, suppressed renin, and a plasma aldosterone concentration higher than 20 ng/mL on the screening test can be confidently given the diagnosis of primary aldosteronism without confirmatory testing.

After the diagnosis of primary aldosteronism is confirmed, patients proceed with subtype evaluation, including computed tomography of the adrenal glands and, potentially, adrenal venous sampling to further classify the primary aldosteronism as being due to adenoma vs hyperplasia. This information can then guide the therapeutic strategy of surgery (adrenalectomy) vs medical therapy with a mineralocorticoid receptor antagonist. Our commentary is limited to case detection, and we acknowledge that subtype classification and treatment of primary aldosteronism is another area of intense discussion and yet another element in the changing landscape of primary aldosteronism.

LIMITATIONS OF CURRENT STATE
Current guidelines recommend screening for primary aldosteronism only in patients with relatively severe hypertension. But restricting screening to this population allows less severe and, possibly, early cases to go undetected for many years, if they are ever diagnosed.

Monticone et al12 screened 1,672 patients referred to a hypertension center in Italy. Using relatively conservative thresholds for positive results on screening (aldosterone-renin ratio > 30 ng/dL per ng/mL/hour and a plasma aldosterone concentration > 10 ng/dL), confirmatory testing with intravenous saline suppression identified primary aldosteronism in 10% to 12% of patients who met the screening criteria. More importantly, 4% of patients with untreated hypertension (blood pressure 140–159/90–99 mm Hg) were also found to have primary aldosteronism. These patients did not meet any screening criteria and would not have been tested outside a research setting.

Other studies show that even in high-risk groups in which screening is recommended, rates of screening and eventual diagnosis remain unacceptably low.5,6

The limitations in screening are further confounded by the arbitrary aldosterone-renin ratio cutoffs used. As noted, the most widely accepted threshold for a positive screening test is an aldosterone-renin ratio of 30 ng/dL per ng/mL/hour or higher with a minimum plasma aldosterone concentration of 15 ng/dL or higher. However, multiple studies have repeatedly demonstrated higher detection rates when the criteria were more relaxed.11 In particular, in patients with low plasma renin activity (< 1 ng/mL/hour), plasma aldosterone concentration cutoffs of 9 ng/dL,2 or even as low as 6 ng/dL,13 have increased the number of cases detected.

A practice-changing study
The strongest evidence yet of the limitation of our screening test of choice comes from a study by Brown et al.7 The study cohort was derived from 5 study protocols across the United States representing a spectrum of blood pressure phenotypes ranging from normotension to resistant hypertension. A total of 1,846 patients were included in the study.

Blood pressure medications were with-
drawn, except in patients with resistant hypertension, in whom medications aside from mineralocorticoid receptor antagonists and epithelial sodium channel inhibitors were continued. Then, all patients underwent oral salt loading for 3 days, after which plasma renin activity, plasma aldosterone concentration, and 24-hour urinary aldosterone excretion were measured. The authors used a conservative threshold aldosterone excretion rate of 12 μg/24 hours to define “biochemically overt primary aldosteronism” in the context of high sodium balance and suppressed renin activity.

The rates of primary aldosteronism were high, reaching 11.3% in normotensive patients. In hypertensive patients, the rates were 15.7% in those with untreated stage 1 hypertension, 21.6% in those with untreated stage 2, and 22% in those with resistant hypertension. In the subset of patients with suppressed renin, the rates were even higher, reaching 51.6% in those with resistant hypertension.

However, these rates are perhaps not the most important takeaway from this study. What was remarkable was how poorly the currently accepted screening protocol performed. In patients with confirmed overt primary aldosteronism, the sensitivity (26.9%) and negative predictive value (31.8%) of an aldosterone-renin ratio greater than 30 were low. Even after relaxing the aldosterone-renin ratio cutoff to a more liberal 20, the sensitivity was a mere 42.3%. Importantly, in the patients with resistant hypertension and confirmed primary aldosteronism, 24.5% had a plasma aldosterone concentration less than 10 ng/dL and would have been missed had the standard screening criteria been used.

The authors emphasized the insensitivity of a single aldosterone-renin ratio compared with a 24-hour urine collection, given the known pulsatile nature of aldosterone secretion and the unrecognized fact that adrenocorticotropic hormone is a secretagogue of aldosterone leading to diurnal fluctuations.7

It is now clear that the current aldosterone-renin ratio screening test and long-accepted cutoffs are far from being the right answer. In an editorial accompanying the above study, Dr. John Funder ultimately labels the spot measurement of plasma aldosterone concentration and aldosterone-renin ratio “not merely useless, but actually misleading.”14

### THE LOW-RENIN PHENOTYPE

The limitations in our current understanding do not stop here. The designation of “biochemically overt primary aldosteronism” relies yet again on arbitrary cutoffs for the confirmatory testing (generally accepted as an aldosterone excretion rate of 12 to 14 μg/24 hours in the case of the oral salt loading test).2 The issue with this definition is that even milder renin-independent aldosterone production that fails to meet these cutoffs might not be entirely benign.

The concept of “nonclassical” or “subclinical” primary aldosteronism has been proposed over the past few years, describing a milder phenotype of dysregulated renin-independent aldosterone production. Indeed, the risk of incident hypertension is reported to be higher in normotensive individuals with a high aldosterone-renin ratio and plasma aldosterone concentration values not meeting the criteria for primary aldosteronism.15 A follow-up study also showed that the rate of incident hypertension was high in participants with the lowest renin concentrations.16 Brown et al17 reported similar outcomes in another cohort, in which suppressed renin activity (≤ 0.5 ng/mL/hour) was associated with significantly higher risk of incident hypertension among normotensive participants compared with those with unsuppressed renin. Importantly, incident hypertension correlated positively with the plasma aldosterone concentration even at levels considered to be in the normal range.

Interest in the low-renin profile is not new. In 1969, Woods et al18 reported that hypertensive patients with the low-renin phenotype responded to adrenal blockade with significant decreases in blood pressure. The clinical significance of this suppressed renin phenotype is further highlighted in the PATHWAY-2 study,19 which showed that spironolactone was the most effective add-on medication in resistant hypertension. Importantly, primary aldosteronism was excluded by a specialist before patients entered this study. In a follow-up analysis,20 there was favorable blood pressure response to spironolactone when renin was
suppressed, and the response correlated positively with plasma aldosterone concentration and aldosterone-renin ratio (even within the “normal” range).20 This analysis raises the question as to whether this population of patients with resistant hypertension included some with a milder form of primary aldosteronism who simply did not meet the current criteria for diagnosis of the disease.

In data presented at the American Society of Nephrology in 2019 (unpublished), we evaluated 1,142 patients with chronic kidney disease in whom renin and plasma aldosterone concentration values were obtained. After excluding patients with primary aldosteronism, patients with suppressed renin values had more resistant hypertension and faster decline in glomerular filtration rate than those with un-suppressed renin. We speculate that some of these patients with suppressed renin may actually have a milder form of primary aldosteronism.

HYPERALDOSTERONISM AS A SPECTRUM

Dysregulated aldosterone production is not just a cause of resistant hypertension; even at levels below the currently accepted criteria for primary aldosteronism, it is associated with adverse cardiovascular, metabolic, and kidney outcomes.17,21 In the study by Brown et al,7 a clear continuum of renin-independent aldosterone production was observed in each of the 4 blood pressure categories (normotension, stage 1 hypertension, stage 2 hypertension, and resistant hypertension) despite the high sodium balance. As expected, the magnitude of aldosterone production was progressively higher across the blood pressure spectrum. Importantly, a continuous relationship was observed between the magnitude of the renin-independent aldosterone production as well as signs of excess mineralocorticoid activity (systolic and diastolic blood pressure, serum potassium level, and urinary potassium-to-sodium ratio).

Given the above, the authors call for reframing our terminology of primary aldosteronism and the arbitrary binary cutoffs to highlight the spectrum of this condition characterized by renin-independent aldosterone production—one that goes from a subclinical form where patients can be normotensive, to milder clinically significant phenotypes not meeting current diagnostic criteria, and all the way to an overt phenotype of severe hypertension and hypokalemia.11

WHERE DO WE GO FROM HERE?

Current screening practices likely capture only a small portion of the more severe phenotype of primary aldosteronism. Given the potential cardiometabolic and kidney implications of even the milder forms of primary aldosteronism, the current guidelines need to be reexamined. This is particularly important, as these risks are potentially modifiable with targeted therapy with mineralocorticoid receptor antagonists. In Figure 1, we propose an approach to screening and diagnosing primary aldosteronism.

New practice guidelines will, hopefully, address the following issues:

Greater awareness in the general medical community is needed to emphasize that primary aldosteronism is not a rare disorder and that it is particularly common in the high-risk population in which screening is classically recommended.

Identifying populations to screen other than the classic high-risk populations. This decision will have to balance the cost-effectiveness of expanding screening practices against the risks of missing cases of primary aldosteronism with associated adverse implications. Particular attention should at least be given to severe but not resistant hypertension, hypertension at a young age, and hypertension with concomitant early-onset cardiovascular disease or atrial fibrillation.

Less reliance on the aldosterone-renin ratio. Clearly, the current screening test with single spot aldosterone-renin ratio testing along with the accepted threshold is misleading. At the minimum, the classic high-risk populations should forgo spot testing and pursue confirmatory dynamic testing directly (with oral salt loading, for example).

Looser screening cutoffs. For screening outside the classic high-risk groups, the cutoffs for a positive screen for both the aldosterone-renin ratio and the plasma aldosterone concentration should be liberalized. Given the diurnal variation in aldosterone production,
repeat screening should be strongly considered in some patients, particularly those with a low-renin phenotype. Clinicians should also have a low threshold to pursue confirmatory testing, given the low sensitivity of spot screening.

**Streamlined testing.** Whether these expanded populations being screened should also bypass the screening test and proceed directly to confirmatory testing will also need to be considered. Cost-effectiveness analyses will be needed.

**Looser confirmatory cutoffs.** The thresholds for positive confirmatory testing will have to be liberalized as well, particularly in the context of suppressed renin.

**New diagnostic tools.** Results of evaluation of novel biomarkers of aldosterone excess and mineralocorticoid receptor activation including urinary exosomes and steroid metabolome profiling are awaited.

### EVOLVING UNDERSTANDING

Our understanding of primary aldosteronism has changed dramatically over the past few years. Formerly seen as a rare syndrome
of resistant hypertension and hypokalemia, primary aldosteronism should now be viewed as a spectrum of autonomous renin-independent aldosterone production that is prevalent across the continuum of blood pressure severity. This condition is associated with higher cardiovascular, metabolic, and renal morbidity, even in its milder phenotypes.

Current screening and diagnostic guidelines capture only a fraction of the more severe forms of primary aldosteronism and with very poor overall sensitivity. A revamping of current practice guidelines is needed, informed by our newer understanding of this disorder.

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

■ REFERENCES

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Pregnancy in a woman with congenitally corrected transposition of the great arteries

A 28-year-old woman with a history of complex congenital heart disease presents to an urgent care center with nausea and emesis, which have been worsening for 3 days. She also reports 2 weeks of constipation, with bowel movements occurring approximately every 3 days. Her most recent medical contact was 3 weeks ago for management of sinusitis that had failed to improve with azithromycin therapy. One week before the current presentation, she was prescribed trimethoprim-sulfamethoxazole for this issue. She says she has had no recent fever, lightheadedness, shortness of breath, or chest pain.

Her medical history is remarkable for congenitally corrected transposition of the great arteries (CC-TGA) with a ventricular septal defect and subpulmonic stenosis. At 5 years of age, she underwent initial surgical repair that included subpulmonic resection to relieve right ventricular outflow obstruction and closure of the ventricular septal defect to prevent chronic left-to-right shunting, a situation that could eventually lead to pulmonary vascular remodeling and pulmonary hypertension (Eisenmenger syndrome).

At age 24, she underwent implantation of a mechanical tricuspid valve to prevent the development of systemic ventricular dysfunction related to chronic, severe systemic atrioventricular valve regurgitation. Her postoperative course was complicated by complete heart block, requiring placement of a dual-chamber permanent pacemaker. Transthoracic echocardiography performed 2 months after the valve replacement demonstrated normal systemic ventricular function and no significant prosthetic valve stenosis or regurgitation. She has not undergone repeat cardiac imaging since that time.

FIRST STEP IN EVALUATION

Based on the patient's presentation, what is the most appropriate next step?

- Computed tomography of the abdomen
- Right heart catheterization
- Urine or serum pregnancy test
- Abdominal radiography

A pregnancy test is essential before a woman of childbearing age undergoes any diagnostic testing involving radiation exposure, especially if she has symptoms that could possibly be due to pregnancy. While all the above options may help with diagnosis, computed tomography, right heart catheterization, and abdominal radiography require exposure to radiation. The most appropriate and cost-effective first test to evaluate this patient's symptoms is a urine or serum pregnancy test.

CASE CONTINUED: A POSITIVE PREGNANCY TEST

The patient says she has had no abdominal cramping, bloating, or vaginal bleeding since her last menstrual period, which was about 7 weeks before this presentation.

Her pulse is 68 beats per minute, blood pressure 112/70 mm Hg, oral temperature 36.8°C (98.2°F), and respiratory rate 16 breaths per minute.
She is alert, well-nourished, and in no acute distress. Her mucous membranes are moist. Her abdomen is without tenderness, rebound pain, guarding, or palpable masses. Auscultation of the heart reveals a crisp mechanical S1 and a grade 2 of 6 systolic ejection murmur at the left lower sternal border.

A rapid serum quantitative human chorionic gonadotropin test is positive for pregnancy.

**HEMODYNAMIC CHANGES OF PREGNANCY**

Which of the following is a normal hemodynamic adaptation of pregnancy?

- Increased cardiac output
- Reduced blood volume
- Decreased heart rate
- Increased systemic vascular resistance

Cardiac output increases during pregnancy, as the maternal cardiovascular system must undergo dynamic adaptations to meet increased metabolic demands and to support fetal growth and development through the uteroplacental circulation. Because nitric oxide is upregulated by circulating gestational hormones and the placental bed has low resistance, systemic and pulmonary vascular resistance decreases by about 30% early in pregnancy, resulting in decreased mean arterial blood pressure. Beginning early in the second trimester, maternal circulating plasma volume increases by 30% to 50%, peaking at the beginning of the third trimester and resulting in relative anemia and reduced blood viscosity. Heart rate also increases during that time due to increased sympathetic tone. Also related to sympathetic tone and increased preload, stroke volume increases by an average of 25%. These physiologic changes cause cardiac output to increase steadily throughout pregnancy, peaking in the third trimester at about 50% above prepregnancy levels.

Labor and delivery bring additional maternal hemodynamic changes that can challenge the cardiovascular system. Pain and anxiety lead to increased mean arterial blood pressure and oxygen consumption. With each uterine contraction, circulating blood volume further increases by up to 500 mL. These rapid changes result in a further rise in maternal cardiac output to about 80% above prepregnancy levels, in some women reaching more than 10 L/min. Some of these hemodynamic shifts can be mitigated with the use of adequate analgesia.

After delivery, with the uterus no longer compressing the inferior vena cava, venous return increases. This, in combination with intrapartum blood shifts related to uterine contractions and a sudden increase in systemic vascular resistance following delivery of the placenta, leads to relative elevation of intracardiac filling pressures. Spontaneous diuresis occurs in most women over the first 24 to 48 hours after delivery. Maternal hemodynamics typically require 2 to 6 weeks to return to baseline after vaginal delivery, and usually longer after cesarean delivery.

**EFFECTS OF TRANSPOSITION OF THE GREAT ARTERIES**

Which of the following statements about TGA is correct?

- In infants with dextro-transposition, a shunt is essential for survival

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**Figure 1.** (Left) Congenitally corrected transposition of the great arteries (CC-TGA). The right ventricle pumps oxygenated blood in the systemic circulation, while the left ventricle pumps deoxygenated blood in the pulmonary circulation. No intervention may be needed. (Right) Dextro- or D-TGA. Pulmonary and systemic blood flows are separate, leading to rapid clinical deterioration in the first day of life unless a communication between the circulations exists or is created.
PREGNANCY IN CONGENITAL HEART DISEASE

□ A patient with CC-TGA may develop heart failure due to dysfunction of the systemic right ventricle
□ A patient with CC-TGA may develop regurgitation of the systemic atrioventricular (morphologic tricuspid) valve
□ Heart block can occur in up to a third of patients with CC-TGA
□ All of the above are correct
All the above statements are correct.

In dextro-transposition, two separate circulations
In TGA, the aorta arises from the right ventricle and the pulmonary artery from the left ventricle (Figure 1). In complete TGA (dextro- or D-TGA), the normal relationship between the atria and the ventricles is preserved: the right atrium empties into the right ventricle through the tricuspid valve, and the left atrium empties into the left ventricle through the mitral valve. Thus, the pulmonary circulation is separate from the systemic circulation. As a result, infants develop cyanosis and rapidly clinically deteriorate within the first day of life unless a communication between the systemic and pulmonary circulation exists through either an atrial septal defect, ventricular septal defect, patent ductus arteriosus, or atrial septostomy.7

In CC-TGA, normal oxygenation
In CC-TGA, also known as levo- or L-TGA, the right atrium empties into the left ventricle through the mitral valve and the left ventricle in turn empties into the pulmonary artery, while the left atrium empties into the right ventricle through the tricuspid valve, and the right ventricle in turn empties into the aorta.

The condition is described as “congenitally corrected” because, unlike D-TGA, the pulmonary and systemic circulations exist in series, and hence, oxygenated blood does reach the systemic circulation. In fact, the only functional difference between CC-TGA and normal anatomy is that the right ventricle is responsible for pumping oxygenated blood into the systemic circulation while the left ventricle pumps deoxygenated blood into the pulmonary circulation. Hence, patients with isolated CC-TGA do not commonly require surgical or transcatheter intervention.

Cardiac output peaks in the third trimester at about 50% above prepregnancy levels

Figure 2. Electrocardiogram demonstrating complete heart block with a junctional escape rhythm in a patient with CC-TGA. The typical findings in patients with CC-TGA found here include Q waves in the inferior leads (II, III, and aVF) and right limb lead (aVR), and the absence of Q waves in V5 and V6.

From Yoon et al, reference 9.
CC-TGA: Associated anomalies, conduction abnormalities
CC-TGA is associated with other congenital cardiac anomalies in up to 90% of patients. The most common include deformities of the tricuspid valve, ventricular septal defects, and subpulmonic ventricular outflow obstruction. CC-TGA can also be associated with abnormalities of the cardiac conduction system.

The major arrhythmogenic complication of CC-TGA is conduction system disease. Due to the presence of atrioventricular discordance, the atrioventricular node is unable to connect normally to the bundle of His. A second anteriorly positioned atrioventricular node, therefore, typically develops and gives rise to an elongated His bundle that is vulnerable to fibrosis over time. The risk of complete heart block is around 2% per year, with a cumulative lifetime incidence of 30%. Patients with CC-TGA should undergo a surveillance electrocardiogram at least yearly to screen for development of conduction system disease (Figure 2).

■ CASE CONTINUED: THE PATIENT CONSULTS A SPECIALIST

Once pregnancy is confirmed, the patient is surprised, as she had been regularly using a barrier method of contraception. She is excited, as this is her first pregnancy, but becomes concerned about potential complications that she might experience due to her preexisting heart disease. She promptly schedules an appointment with her adult congenital heart disease specialist to discuss this.

■ CARDIOVASCULAR RISK IN PREGNANCY

Which of the following conditions pose the highest risk of pregnancy-associated maternal mortality?

- Eisenmenger syndrome
- Mechanical prosthetic valve
- Subaortic atrioventricular valve regurgitation with preserved subaortic ventricular function
- Moderate pulmonary valve stenosis

Eisenmenger syndrome poses the highest risk of maternal mortality of the conditions listed.

Hemodynamic changes during pregnancy, delivery, and the postpartum period may be poorly tolerated in women with congenital or acquired heart disease. Cardiovascular conditions are the leading cause of maternal mortality in the United States: 25% to 30% of pregnancy-related deaths between 2011 and 2016 were attributable to preexisting cardiovascular disease.

All women of childbearing age with preexisting heart disease should receive regular counseling regarding their individual risk of adverse pregnancy-related outcomes. The updated 2018 American Heart Association-American College of Cardiology guideline recommends that all women with congenital heart disease receive pregnancy counseling with input from a congenital heart disease specialist to determine maternal cardiac, obstetric, and fetal risks, as well as potential long-term risks to the mother (recommendation class 1 [strong recommendation], evidence level C [based on expert consensus, case studies, or standard of care]).

It is vitally important for physicians to understand the pregnancy risks associated with specific cardiac lesions and disease states. The risk for adverse pregnancy-related events in women with preexisting cardiovascular disease can be estimated based on the type and severity of the underlying cardiac disease, as well as preconception functional status.

Several clinical tools are available to assist in patient-specific preconception risk assessment. The Cardiac Disease in Pregnancy II (CARPREG II) risk score, which was derived from 1,938 pregnancies between 1994 and 2014, is the most contemporary. Ten predictors of adverse pregnancy-related events were identified and correlated to a weighted-point system to assist in counseling patients:

- Previous cardiac events or arrhythmias: 3 points
- Baseline New York Heart Association class III or IV heart failure or cyanosis: 3 points
- Mechanical valve: 3 points
- Ventricular dysfunction: 2 points
- High-risk left-sided valve disease or left ventricular outflow tract obstruction: 2 points
- Pulmonary hypertension: 2 points
- Coronary artery disease: 2 points
- High-risk aortopathy: 2 points
- No prior cardiac intervention: 1 point
- Late pregnancy assessment: 1 point.

Isolated CC-TGA does not commonly require surgical or transcatheter intervention.
Patients with CC-TGA should have an ECG at least yearly to screen for conduction system disease.

The risk of a primary cardiac event is calculated from the total points:
- 0–1 points: 5%
- 2 points: 10%
- 3 points: 15%
- 4 points: 22%
- > 4 points: 41%.

The World Health Organization has also developed a maternal cardiovascular risk classification, which is based on expert opinion (Table 1). The risk of a primary cardiac event is calculated from the total points:

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Uncomplicated, small or mild pulmonary stenosis, patent ductus arteriosus, or mitral valve prolapse; successfully repaired simple lesions (atrial or ventricular septal defect, patent ductus arteriosus, anomalous pulmonary venous return) Cardiovascular risk: No increased risk of maternal mortality, possible mild increase in morbidity</td>
</tr>
<tr>
<td>II</td>
<td>Unrepaired atrial or ventricular septal defect; repaired tetralogy of Fallot; supraventricular tachycardia Cardiovascular risk: Small increased risk of maternal mortality, moderate increase in morbidity</td>
</tr>
<tr>
<td>II–III</td>
<td>Mild left ventricular dysfunction; native or tissue valvular heart disease not considered World Health Organization class I or IV; Marfan syndrome without aortic dilation; aorta less than 45 mm in association with bicuspid aortic valve; repaired coarctation of the aorta; hypertrophic cardiomyopathy Cardiovascular risk: As in class II or III, depending on individual</td>
</tr>
<tr>
<td>III</td>
<td>Mechanical valve; systemic right ventricle with good or mildly reduced function; Fontan circulation without complication; unrepaired cyanotic heart disease; other complex congenital heart disease; aortic dilation 40 to 45 mm in Marfan syndrome; aortic dilation 45 to 50 mm in bicuspid aortic valve disease; previous peripartum cardiomyopathy with complete recovery of ventricular function Cardiovascular risk: Significantly increased risk of maternal mortality or severe morbidity. Expert counseling required. If pregnancy continues, intensive specialist cardiac and obstetric monitoring needed throughout pregnancy, childbirth, and for 6 weeks afterwards</td>
</tr>
<tr>
<td>IV</td>
<td>Pulmonary arterial hypertension from any cause; severe systemic ventricular dysfunction (ejection fraction &lt; 30%, New York Heart Association functional class III-IV); systemic right ventricle with moderate or severely reduced function; Fontan circulation with any complication; severe mitral stenosis; severe symptomatic aortic stenosis; Marfan syndrome with aortic dilation more than 45 mm; aortic dilation more than 50 mm in bicuspid aortic valve disease; native severe coarctation of the aorta; previous peripartum cardiomyopathy without complete recovery of ventricular function Cardiovascular risk: Pregnancy is contraindicated because of extremely high risk of maternal mortality or severe morbidity. If pregnancy occurs, discuss termination. If pregnancy continues, care as for class III</td>
</tr>
</tbody>
</table>

Information from reference 13.
prevalence of congenital heart disease is 0.8% in the general population; risk increases up to 10-fold if congenital heart disease is also present in a first-degree relative. Rates of transmission are higher when the mother is affected compared with the father. In patients with autosomal dominant conditions, such as Marfan syndrome, there is a 50% chance of transmission to the fetus.

**COMPLICATIONS IN PREGNANCY IN WOMEN WITH CC-TGA**

What is the most common pregnancy-associated cardiovascular complication in women with CC-TGA?

- □ Symptomatic heart failure
- □ Worsening systemic atrioventricular valve regurgitation
- □ Arrhythmia
- □ Endocarditis

With medical management, most women with CC-TGA reach childbearing age and are healthy enough to consider pregnancy. Patients and their physicians should understand their specific risks so that they can carefully consider the appropriateness and timing of pregnancy.

Although helpful, global risk assessment tools such as CARPREG II developed to predict pregnancy-associated maternal cardiovascular risk typically do not account for the presence of a systemic right ventricle. In the maternal World Health Organization classification system, patients with a systemic right ventricle with normal or mildly reduced function are categorized as class III, consistent with significantly increased risk of maternal mortality or severe morbidity, and patients with moderately to severely reduced systemic right ventricular dysfunction should be advised against pregnancy (class IV).

**Arrhythmia risk poses challenges**
The most common pregnancy-associated cardiovascular complication seen with CC-TGA is supraventricular arrhythmia. It presents a management challenge, as few antiarrhythmic medications have been studied for safety and efficacy in pregnancy. Beta-blockers, especially metoprolol succinate and labetalol, are acceptable in pregnancy. However, they should be used with caution in patients with CC-TGA, who have an increased predisposition for heart block, which these drugs can exacerbate. In a minority of cases, supraventricular arrhythmias can lead to maternal hypoxia, which can be associated with premature delivery and low birth-weight infants.

**Risk of heart failure depends on baseline function**
Systemic right ventricular dysfunction and resulting congestive heart failure symptoms are common by the third decade of life and increase in frequency as patients age. The World Health Organization classification of risk in patients with a systemic right ventricle is derived from the idea that the systemic right ventricle is not designed to support systemic blood flow, predisposing patients to systemic ventricular dysfunction and other cardiovascular complications of pregnancy. Although pregnancy-related changes in cardiovascular hemodynamics may provoke new-onset or worsening systemic ventricular dysfunction, most women with CC-TGA who have normal systemic ventricular function before conception do not develop symptomatic heart failure during pregnancy or postpartum.

**CASE CONTINUED: ANTICOAGULATION IN PREGNANCY**
The patient engages in detailed discussions with a specialist in adult congenital heart disease and the high-risk obstetrics team about her potential risks during pregnancy. She next asks about additional considerations regarding her mechanical systemic atrioventricular valve. She currently takes warfarin 7.5 mg daily to prevent mechanical valve thrombosis. Her international normalized ratio (INR) is within the therapeutic range.

6 How should anticoagulation be immediately handled in this patient?

- □ Continue warfarin at her current dose of 7.5 mg daily
- □ Because anticoagulation can lead to fetal
Complications, she should stop and remain off of all anticoagulants until after delivery.

- Switch to low-molecular-weight heparin during the first trimester.

Mechanical heart valves are associated with elevated maternal and fetal risk, irrespective of additional structural heart disease. Thrombotic and hemorrhagic complications occur at higher rates during pregnancy in women with mechanical heart valves than in patients with congenital heart disease or bioprosthetic valves. Serious pregnancy complications occur in up to 40% of women who have a mechanical valve.19

Therapeutic systemic anticoagulation is necessary throughout pregnancy for women with a mechanical heart valve. Pregnancy is a hypercoagulable state due to increased circulating levels of fibrinogen, plasminogen activator inhibitor, and factors VII, VIII, and X. Increased platelet adhesiveness, resistance to activation of protein C, and decreased fibrinolysis also contribute to hypercoagulability in pregnancy.20,21

Warfarin and heparin both entail risk. Warfarin, a vitamin K antagonist, is the most effective anticoagulant in preventing thrombotic complications in pregnant women with mechanical heart valves and is associated with lower rates of adverse maternal events compared with heparin products. However, it has traditionally been associated with fetal teratogenicity, leading to limited use during pregnancy during fetal organogenesis. Furthermore, warfarin crosses the placenta into the fetal circulation, causing systemic anticoagulation in the fetus.

Heparin products do not cross the placenta and so are considered to pose less risk to the fetus. But dosing and monitoring of heparin products during pregnancy are difficult, and heparin therapy is associated with higher rates of valve thrombosis and maternal mortality than warfarin.22

Steinberg et al23 found that women who require 5 mg or less of warfarin daily to achieve therapeutic anticoagulation have a similar risk of adverse fetal outcomes compared with women using low-molecular-weight heparin. The current American College of Cardiology/American Heart Association guideline on valvular heart disease management24 recommends warfarin in preference to heparin products in pregnancy if 5 mg or less of warfarin per day is required to achieve therapeutic anticoagulation, even during the first trimester. If a higher dose is required, low-molecular-weight heparin with close monitoring of anti-Xa levels is recommended during early pregnancy. If warfarin is used, patients should be transitioned back to heparin products in the last weeks of pregnancy to minimize the risk of fetal bleeding during labor and delivery.

In addition to systemic anticoagulation, aspirin 81 mg daily should be given to all pregnant women who have a mechanical heart valve.

**CASE CONTINUED: POSSIBLE DECOMPENSATION**

Because our patient requires more than 5 mg of warfarin daily to achieve therapeutic anticoagulation, her warfarin is discontinued, and low-molecular-weight heparin is initiated and continued until the 12th week of pregnancy, with close monitoring of anti-Xa levels. At the beginning of the second trimester, warfarin is restarted and low-molecular-weight heparin is discontinued after the patient achieves a therapeutic INR. Unfortunately, her INR proves difficult to maintain within the therapeutic range (2.5–3.5). A plan is made to resume low-molecular-weight heparin at 35 weeks of gestation in anticipation of delivery.

During a routine follow-up visit at 19 weeks of gestation, the patient reports very mild dyspnea on exertion. Her N-terminal pro-brain natriuretic peptide (NT-proBNP) level is 124 pg/mL (reference range < 125 pg/mL).

Transthoracic echocardiography demonstrates mild to moderate dilation of the systemic ventricle with low-normal systolic function. The subpulmonic ventricle is normal in size and function. There is moderate residual subpulmonic stenosis (peak gradient 45 mm Hg; mean gradient 28 mm Hg). A possible residual restrictive ventricular septal defect is also noted. Her mechanical valve is functioning normally, without evidence of regurgitation or stenosis.

As pregnancy progresses, she continues
to experience mild dyspnea with activity. By the 34th week of pregnancy, she notes mild lower-extremity edema. She says she has no paroxysmal nocturnal dyspnea, palpitations, cough, or chest pain. Her blood pressure is 114/70 mm Hg. Serial echocardiograms and NT-proBNP measurements remain unchanged, despite her persistent and worsening symptoms.

Based on the patient’s current symptoms and echocardiogram, what is the most appropriate next step in her management?

- □ Start a diuretic to address signs of heart failure
- □ Perform right-heart catheterization to assess heart failure
- □ Perform transesophageal echocardiography to evaluate for prosthetic valve thrombosis
- □ No change in management at this time; continue to monitor closely

A change in management is not necessary at this time, but the patient should continue to be monitored closely.

Symptoms such as shortness of breath, orthopnea, lower-extremity edema, and sinus tachycardia may be considered normal in some women during pregnancy owing to expected hemodynamic changes. Likewise, echocardiographic chamber size, transvalvular flow velocity, and valvular regurgitation are also expected to increase as pregnancy progresses. It can be difficult to differentiate these symptoms and imaging changes from cardiac decompensation in women with heart disease.25

Serial NT-proBNP measurement can be helpful in differentiating whether worrisome symptoms and echocardiographic changes should be considered pathologic. On the other hand, reduced ventricular function is never considered normal during pregnancy. As such, it is important to evaluate each patient’s cardiac function before determining whether a change in management strategy is necessary.

CASE CONTINUED: A HEALTHY BABY

Given her stable cardiac imaging and NT-proBNP measurements, it is deemed unlikely that the patient’s symptoms represent cardiac decompensation. She continues to be monitored closely without additional medical therapy.

As pregnancy progresses, she develops severe pelvic pain due to suspected symphysis pubis separation, as well as hemorrhoids, for which she is managed supportively.

Warfarin is continued until 35 weeks of gestation, at which time she is transitioned to low-molecular-weight heparin.

At 37 weeks, she presents with spontaneous rupture of membranes while fully anticoagulated with low-molecular-weight heparin. Despite counseling regarding bleeding risks, she opts for a primary cesarean delivery because of her concerns about the potential of worsening symptoms related to pubic symphysis separation, as she cannot be managed with neuraxial anesthesia owing to her anticoagulated state.

She undergoes primary cesarean delivery under general anesthesia. The procedure is uncomplicated and results in the delivery of a healthy infant boy with Apgar scores of 9 (of a maximum possible 10) at both 1 and 5 minutes.

Her postpartum course is uneventful. Anticoagulation with intravenous heparin is reinitiated 12 hours after delivery. Warfarin is restarted on postoperative day 3, while continuing intravenous heparin until a therapeutic INR is achieved. She is discharged on postoperative day 7 receiving warfarin (INR 2.5) and aspirin 81 mg daily. A nonhormonal intrauterine device is recommended for contraception.

CLINICAL PEARLS

- CC-TGA is a form of congenital heart disease characterized by ventriculoarterial and atrioventricular discordance. This makes the morphologic right ventricle responsible for pumping the systemic circulation.
- The maternal cardiovascular system must undergo tremendous hemodynamic adaptations during pregnancy, which can lead to clinical decompensation in women with cardiovascular disease.
- Risk of adverse pregnancy-related cardiovascular events in women with preexisting cardiovascular disease should be deter-
PREGNANCY IN CONGENITAL HEART DISEASE

Main text:

- Patients with CC-TGA can carry a pregnancy successfully without complication. The most common pregnancy-associated cardiovascular complication in patients with CC-TGA is supraventricular arrhythmia. They are also at risk for worsening systemic ventricular dysfunction and decompensated heart failure.
- Managing anticoagulation in women with a mechanical heart valve to prevent valve thrombosis during pregnancy can be difficult. When 5 mg or less of warfarin is required to achieve therapeutic anticoagulation, it should be continued even in the first trimester. If low-molecular-weight heparin is needed, anti-Xa levels should be followed closely to ensure therapeutic anticoagulation.

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DISCLOSURES

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

REFERENCES


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Update on medical management of acute hip fracture

ABSTRACT

Morbidity and mortality rates associated with acute hip fracture remain high. Over the past decade, the management of hip fracture has shifted to emphasize prompt surgical treatment, multimodal analgesia to reduce opioid use, and incorporation of enhanced recovery pathways. Preoperative evaluation focuses on acutely correctable problems, with the understanding that delaying surgery may worsen the outcome. Prophylaxis of venous thromboembolism, treatment of preoperative anemia and acute kidney injury, and cardiac stabilization are important measures to reduce morbidity. Multimodal analgesia incorporating regional anesthesia techniques may help prevent delirium and facilitate early participation in physical therapy to reduce complications.

KEY POINTS

Follow evidence-based guidelines to minimize unnecessary testing and delay of surgery.

To minimize delirium and facilitate postoperative ambulation, consider multimodal analgesia, including peripheral nerve blocks that help minimize the need for opioids, in enhanced recovery pathways.

The best outcomes are achieved with prompt surgical repair, which should ideally be completed within 24 hours of presentation but not later than 48 hours, except in rare cases when critical medical optimization is needed.

The use of antiplatelet agents, warfarin, and direct oral anticoagulants should not delay surgery unless the benefit of spinal over general anesthesia is overwhelming.

HIP FRACTURES ARE THE MOST COMMON reason for urgent surgery in the elderly and often lead to long-term institutional care.1 Despite advances in perioperative management, postoperative mortality rates remain high, up to 10% in the first 30 days and 8% to 36% in the first year after repair.2 Even 10 years after fracture repair, the mortality rate due to comorbid medical conditions remains higher than in age-matched controls.3

IS NONSURGICAL MANAGEMENT AN OPTION?

Without repair, the risk of death is exceedingly high due to infectious, thrombotic, and cardiopulmonary complications related to immobility. Unless the perioperative risk of death is exceptionally high due to severe comorbid illness, repair is recommended.1 Without surgery, patients are left with significant pain, immobility, and a shortened leg.

In those who are terminally ill, cannot walk, have severe dementia, or have serious comorbid conditions, nonoperative management can be considered if pain is adequately controlled and the patient is comfortable. However, a large cohort study reported that the in-hospital mortality rate may be as high as 17.2% in those treated conservatively.4

TIMING OF HIP FRACTURE REPAIR

A landmark retrospective cohort study in 42,230 adults demonstrated that wait time (time from emergency department arrival until surgery) greater than 24 hours was associated with a higher risk-adjusted likelihood of death within 30 days (6.5% vs 5.8%).5 The composite outcome of other medical complications (myocardial infarction, deep vein thrombosis,
ACUTE HIP FRACTURE

If the patient’s functional capacity is poor or unknown, use the physical examination and ECG to assess for high-risk cardiac conditions.

RISK STRATIFICATION IN THE GERIATRIC PATIENT

The preoperative assessment should focus on stabilizing medical conditions that can be corrected, such as dehydration, hypovolemia, anemia, hypoxia, electrolyte disturbances, and arrhythmias. It should aim at recognizing chronic conditions that could modify the postoperative course, such as cognitive disorders and chronic cardiac, respiratory, and renal failure.

A targeted preoperative evaluation is included in Table 1. Some of the major issues of particular significance in the elderly are discussed below.

Diabetes, hypoglycemia
Avoidance of hypoglycemia in the elderly is essential, as it is associated with a longer length of hospital stay and higher risk of death, and elderly patients undergoing surgical interventions often have reduced oral intake.

For patients with diabetes with blood glucose levels greater than 180 mg/dL, the recommended total daily dose of insulin is 0.1–0.15 U/kg/day, given mainly as basal insulin, with correctional insulin coverage for glucose levels above 180 mg/dL.

Anemia
The prevalence of preoperative anemia due to bleeding from the fracture ranges from 24% to 44%, and that of postoperative anemia is even higher at 51% to 87%.

The FOCUS trial (Functional Outcomes

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preoperative evaluation of acute hip fracture</strong></td>
</tr>
<tr>
<td>Preoperative condition or organ system</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Fall</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Anemia, thrombocytopenia</td>
</tr>
<tr>
<td>Anticoagulation before admission</td>
</tr>
<tr>
<td>Respiratory</td>
</tr>
<tr>
<td>Renal</td>
</tr>
<tr>
<td>Cardiovascular</td>
</tr>
</tbody>
</table>
in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair) was a randomized controlled trial designed to address a transfusion goal for patients over age 50 with hip fracture who had a history of or risk factors for ischemic heart disease. A postoperative hemoglobin transfusion threshold of 8 g/dL in the absence of symptomatic anemia was considered acceptable in elderly patients with or at risk of ischemic heart disease.

Acute kidney injury
Hong et al reported that patients who experienced acute kidney injury during hospitalization had significantly longer hospital stays and higher in-hospital and long-term mortality rates. A low preoperative albumin level, use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), the need for blood transfusion, and coronary artery disease were found to be independent risk factors for acute kidney injury.

Aggressive hydration with isotonic fluids should be started early, and ACE inhibitors or ARBs should be held before surgery to prevent intraoperative hypotension and acute kidney injury. Doses of antihypertensive and rate-control drugs should be reduced to avoid hypotension. However, routine use of normal saline infusion per standing orders without evidence of dehydration or acute kidney injury should be avoided, as it can lead to peripheral fluid overload and decompensated heart failure.

Cardiovascular risk
The American College of Cardiology/American Heart Association and the Canadian Cardiovascular Society (CCS) guidelines caution about indiscriminate use of preoperative testing that, in many circumstances, does not serve to reduce the patient’s risk but may instead delay needed surgery. It is our policy to screen patients on admission for high-risk conditions and to use cardiology consultation or preoperative testing only when it would lead to a change in perioperative management, because delays are associated with increased mortality.

The impact of preoperative testing in terms of delaying surgery is substantial. In acute hip fractures, preoperative echocardiography and nuclear stress testing can delay surgery by up to 6 days, leading to further postoperative complications. In one study, echocardiography alone led to a delay of surgery of 32 to 48 hours without a demonstrable difference in complications or mortality.

In terms of preoperative cardiac screening, cardiac consultation delayed surgery by a mean of 9.9 hours due to an overestimation of cardiac risk. Preoperative subspecialty consultation was associated with delays to surgery of over 24 hours, and only 37% of the time did consultation lead to an identifiable change in treatment.

The main role of cardiology consultation should be to assist in the management of the patient who has a high-risk or unstable cardiac condition, to advise regarding risk-reduction strategies, and to assist with postoperative management.

A good exertional capacity is an excellent prognostic feature. However, if the patient has a poor or unknown functional capacity, objective data such as the physical examination and electrocardiogram should be used to assess for high-risk cardiac conditions.

We typically obtain an expedited preoperative transthoracic echocardiogram if the patient has any of the following conditions:
- Physical signs or symptoms of acute heart failure, including recently worsened dyspnea on exertion, orthopnea, and pulmonary or lower extremity edema
- Signs or symptoms suggestive of severe pulmonary hypertension
- A newly discovered murmur that raises concern for an obstructive process (eg, left ventricular intracavitary obstruction, hypertrophic obstructive cardiomyopathy)
- Clinical signs or symptoms suggesting critical aortic stenosis, such as a systolic murmur or unexplained syncope, or severe mitral stenosis in a patient who has not had an echocardiogram in the past 12 months.

The finding of critical aortic stenosis, hypertrophic obstructive cardiomyopathy, or severe pulmonary hypertension may affect the anesthetic plan, including the choice of general or regional anesthesia, placement of invasive monitors, and use of vasoactive medications. We usually perform transthoracic echocardiography to estimate the degree of valve stenosis and left ventricular dysfunction. Even if severe aortic stenosis is detected in a patient who has no symptoms, hip repair surgery may be safely performed, and reduction of risk can be at-
tempered on an individualized basis.

While preoperative balloon aortic valvuloplasty to reduce the degree of valve stenosis has been suggested as an approach to lower the perioperative risk, the delay in surgery and the complication rate of the valvuloplasty must be considered. We do not believe that transcatheter aortic valve replacement before emergency hip surgery is a practical option, given the delay to fracture repair. Transcatheter aortic valve replacement requires a comprehensive evaluation including coronary angiography and is rarely done as an emergency procedure.

Arrhythmias
Patients with rapid atrial fibrillation, atrial flutter, or supraventricular tachycardia can proceed to surgery after the ventricular rate is controlled. Patients with advanced atrioventricular block—e.g., second-degree (Mobitz type II) atrioventricular block or third-degree atrioventricular block—may require temporary pacemaker placement before surgery. Placement of a permanent pacemaker may be indicated before discharge.

Medications
ACE inhibitors and ARBs may be withheld during the 24 hours before surgery to avoid perioperative hypotension if being prescribed for essential hypertension. For patients receiving an ACE inhibitor or ARB as treatment for chronic heart failure, we weigh the risks vs benefits of their discontinuation with the patient’s outpatient physician, if possible, and with the anesthesiology team.

Because there is a risk of bradycardia and hypotension, we do not initiate beta blockers for patients not already receiving them in the immediate preoperative period. For patients with chronic systolic heart failure taking beta blockers before surgery, we continue these agents unless there is evidence of decompensated heart failure.

Troponin
Troponin T and troponin I are measured to evaluate the diagnosis of an acute cardiac injury. A troponin level is often drawn on admission to evaluate for a possible ischemic cause of syncope. Troponin is frequently elevated in patients with renal insufficiency in the absence of acute myocardial injury. It may be elevated due to chronic congestive heart failure and should be considered a marker of poorer prognosis. Troponin elevation with a significant increase is concerning for type 1 or type 2 myocardial infarction. If preoperative troponin is elevated and the elevation attributed to myocardial injury or the etiology is unclear, cardiology consultation should be considered.

Most perioperative myocardial infarctions are not accompanied by classic chest pain or ST-segment elevation. In this situation, we treat patients using the same guideline-directed approach as for non-ST-elevation myocardial infarction in the nonoperative setting.

Isolated perioperative troponin elevation, without other features of myocardial infarction, is deemed myocardial injury after non-cardiac surgery. In general, the risk of death within 30 days is higher in patients in whom this happens. Currently, the clinical significance of isolated troponin elevation in a patient who has sustained a hip fracture is unknown. If the patient is hemodynamically stable, we typically proceed to hip repair surgery with enhanced surveillance in the postoperative period. After surgery, we decide whether an assessment of myocardial perfusion is warranted for risk assessment.

Risk assessment
Repair of an acute hip fracture is urgent surgery, and hip fracture is considered an intermediate-risk surgery, with a 1% to 5% risk of major adverse cardiac events. Elderly patients with hip fractures are frail, and many have a poor or unknown functional status and risk factors for cardiac disease. Urgent surgery increases the risk of a perioperative cardiovascular event.

As preoperative pharmacologic stress testing leads to delays without a clear benefit in acute hip fractures, we follow the CCS guidelines, which do not include pharmacologic stress testing preoperatively for perioperative cardiovascular risk estimation. Instead, they recommend risk stratification using the Revised Cardiac Risk Index. The CCS also uses preoperative N-terminal pro-brain natriuretic peptide or B-type natriuretic peptide (BNP) measurement to aid in risk stratification and recommends postoperative troponin measurement to detect myocardial infarction.
In our practice, we consider the elderly patient with hip fracture to be at increased risk; we do not order preoperative BNP testing but proceed as if the BNP were elevated and follow serial troponin levels postoperatively in the patients at highest risk.

Shared decision-making, involving the patient and the family, is critical in a patient with a high-risk cardiac condition to explain the elevated risk of morbidity and death. We offer surgery for high-risk patients, involving cardiac anesthesiology in the management, and admission to the intensive care unit postoperatively if needed.

### PERIOPERATIVE INTERVENTIONS THAT MAY AFFECT OUTCOMES

#### Anesthesia type

Studies comparing anesthesia techniques for hip fracture repair have had conflicting results. One large database study found that regional anesthesia reduced the incidence of pulmonary complications and conferred lower odds of mortality than general anesthesia. However, the same researcher in a subsequent retrospective database study reported no difference in mortality based on anesthesia technique.

Current practices vary by institution, and the decision is typically made after the patient, surgeon, anesthesiologist, and consultants discuss the risks and benefits of each technique as they relate to the specific patient.

#### Pain control

An opioid-sparing strategy is recommended for optimal perioperative pain control. Neuraxial blockade and peripheral nerve blocks provide the best combination of pain control with the least amount of sedation.

---

**TABLE 2**

<table>
<thead>
<tr>
<th>Pain control in acute hip fracture</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>First line: nonopioid analgesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral nerve block (femoral nerve block, fascia iliaca block)</td>
<td>Ropivacaine 0.5%, 15–20 mL in primary block; if catheter placed, infusion may be run with ropivacaine 0.2% at 8–10 mL/hour</td>
<td>Quadriceps weakness can be a limitation</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>1,000 mg intravenously or orally every 6 hours</td>
<td>For patient weighing &lt; 50 kg, orally 650 mg every 6 hours</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>200 mg orally twice a day</td>
<td>Use if glomerular filtration rate is &gt; 60 mL/min</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>400 mg by mouth every 6 hours</td>
<td>Use if glomerular filtration rate is &gt; 60 mL/min</td>
</tr>
<tr>
<td>Opioids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>50 mg orally every 6 hours as needed for mild to moderate pain</td>
<td>Use 25 mg if creatinine clearance rate is &lt; 60 mL/min</td>
</tr>
<tr>
<td>Oxycodeone</td>
<td>2.5–5 mg orally every 4–6 hours as needed for severe pain</td>
<td>Start with 2.5 mg if creatinine clearance rate is &lt; 60 mL/min</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.25 mg intravenously every 4–6 hours as needed</td>
<td>Preferable to morphine, since morphine’s metabolites can accumulate in patients with impaired renal function Respiratory depression, delirium, urinary retention, sedation, nausea and vomiting, and constipation are side effects of all opioids. Elderly patients may be particularly vulnerable to changes in mental status with opioids</td>
</tr>
</tbody>
</table>
Enhanced recovery protocols have been used in Europe for 20 years over a wide range of surgeries.

Acetaminophen, in scheduled intravenous or oral doses, is associated with shorter hospital stay, lower pain levels, less opioid use, fewer missed physical therapy sessions, and higher rate of discharge to home.25

Nonsteroidal anti-inflammatory drugs provide effective analgesia but can be problematic in elderly patients with stage 3 chronic kidney disease (glomerular filtration rate < 60 mL/min) or higher, given the risk of perioperative acute kidney injury.26 In a cohort of geriatric trauma patients over a 6-year period, these drugs were associated with decreased opioid requirements without an overall increase in bleeding.27 We generally avoid nonsteroidal anti-inflammatory drugs in patients with preexisting renal dysfunction.

Gabapentinoids have not been shown to help with pain and may not have a favorable risk-benefit ratio in the elderly.28 Muscle relaxants, anticholinergics, and benzodiazepines may increase the risk of delirium when used for perioperative pain.

Table 2 lists the preferred pain control regimens used at our institution.

Nerve blocks
Peripheral nerve blocks provide better analgesia than opioids alone. Common targets include the femoral nerve and fascia iliaca. Benefits are lower risk of pneumonia, shorter time to ambulation, less postoperative cognitive dysfunction, lower analgesia cost, and less opioid use. To date, studies have been small, and there are not enough data to determine if other outcomes such as delirium are affected.24 Effective control of postoperative pain using multimodal analgesia prevents delirium, encourages early participation in physical therapy, and reduces length of stay, hospital-acquired complications, and subsequent institutionalization.29

Delirium
The incidence of delirium after surgery ranges from 10% to 65%,29 and increases total cost by 50% as a result of longer length of stay, more nursing care, and more testing.30 Risk factors include multiple medical comorbidities, prolonged hospitalization, decreased mobility, and need for discharge into a facility.29 A Cochrane review of comprehensive geriatric assessments did not find an improvement in the incidence of delirium with nonpharmacologic interventions, but did find high-quality evidence for reduction in discharges to institutional facilities and moderate-quality evidence for mortality reduction.31

Simple nonpharmacologic interventions to prevent delirium include an adequate sleep protocol, use of eyeglasses or hearing aids, minimizing urinary catheters, early mobility and daily physical activity, maintaining hydration, and avoidance of constipation. Prophylactic antipsychotics are not recommended.31

■ PREOPERATIVE ANTICOAGULATION MANAGEMENT

Hip fracture repair carries an intermediate risk of bleeding, for which transfusion is often required. Anticoagulation management is discussed below.32

Antiplatelet agents
Patients receiving aspirin as primary prevention of cardiovascular disease. Aspirin may be discontinued even though the effect on bleeding is negligible.32

Patients receiving antiplatelet drugs as secondary prevention. Aspirin should be continued, as the effect on perioperative bleeding is minimal. Clopidogrel, used by itself, should also be continued, as there is no significant increase in bleeding, mortality, need for blood transfusion, length of surgery, or length of stay.32

In a prospective study of 1,225 patients receiving clopidogrel, delaying hip fracture repair led to a higher mortality rate: 29% for those who had surgery delayed vs only 4% for those who had immediate repair.33

Patients on dual antiplatelet therapy: aspirin plus clopidogrel, ticagrelor, or prasugrel. It is essential to know why the patient is receiving dual antiplatelet therapy. Typical reasons include an acute coronary syndrome during the previous 12 months, and a coronary stent implant.

Recommendations on dual antiplatelet therapy
• After a recent acute coronary syndrome event: ideally, dual antiplatelet therapy should be continued for 12 months after an event. If no stents are placed, the P2Y12 inhibitor (eg, clopidogrel) may be stopped earlier.32
After recent coronary stenting, with or without a recent acute coronary syndrome event: minimum of uninterrupted dual antiplatelet therapy for 1 month after bare-metal stent placement, or 3 to 6 months of uninterrupted dual antiplatelet therapy for a drug-eluting stent.32

There are few studies of dual antiplatelet therapy in acute hip fracture repair. In a study of 122 patients on dual antiplatelet therapy at the time of hip fracture repair, there was a similar risk of transfusion, independent of time to operation.34 Dual antiplatelet therapy was associated with a higher probability of major complications in early surgery. Delays to surgery for those on dual antiplatelet therapy led to higher mortality rate at 30 days.34 It is unclear if the higher complication rate from early surgery was from blood loss or from the medical complications resulting from the fracture.

The guidelines of the American Society of Regional Anesthesia and Pain Medicine suggest waiting 5 to 7 days before performing spinal anesthesia in patients taking clopidogrel or ticagrelor, and 7 to 10 days for patients taking prasugrel. Thus, it is impractical to delay surgery in order to perform spinal anesthesia, especially given the equivocal evidence thus far.35 We follow the guidelines outlined above on continuation of dual antiplatelet therapy through the perioperative period.32 For indications other than coronary stents or recent acute coronary syndrome, we typically continue aspirin alone in the perioperative period.

### Warfarin

For a patient taking warfarin, we typically withhold 1 dose and consider giving vitamin K 2.5 to 5 mg if the international normalized ratio (INR) is greater than 1.8 before surgery;
the goal ratio is 1.5 for surgery, and within normal range if neuraxial anesthesia is planned. In a retrospective study of patients on warfarin, delaying surgery by more than 48 hours to allow INR normalization increased the risk of mortality 1.5 times over those sent to surgery within 48 hours.36

For the patient at very high thrombotic risk (Table 3),37,38 heparin is used as an anticoagulation bridge. Timing of bridging should involve multidisciplinary conversation with orthopedics and cardiology.37,38

Direct-acting oral anticoagulants
Surgery must be delayed for 24 hours. For patients with acute renal failure, there should be a discussion between orthopedics, cardiology, and anesthesiology regarding delaying the procedure for 48 hours or using a reversal agent. Patients receiving these drugs have experienced longer delays to surgery than those receiving warfarin (6.9 hours vs 39.4 hours).39

PREVENTING VENOUS THROMBOEMBOLISM

According to the 2012 American College of Chest Physicians guidelines for prevention of venous thromboembolism in orthopedic surgery patients, the following medications have been approved for prophylaxis after hip fracture surgery: enoxaparin, fondaparinux, aspirin, and vitamin K antagonists. Table 4 presents dosing recommendations.

Enoxaparin is first-line, as it is highly effective and poses a low risk of bleeding.37 We use it as our preferred agent.

Data are lacking on the use of direct-acting oral anticoagulants in patients with acute hip fracture, and they are not yet approved for this by the US Food and Drug Administration. Most studies involving these agents included only patients undergoing elective total hip and knee replacement.39

Prophylaxis should be continued for 35 days, because the risk of venous thromboembolism is high (4.3%) in the first 5 weeks after hip fracture without prophylaxis.37,40

An intermittent pneumatic compression device should be used for 18 hours per day in addition to pharmacologic prophylaxis.37 If surgery is delayed, enoxaparin should be initiated at the time of presentation and continued up until 12 hours before surgery. Venous thromboembolism prophylaxis should be resumed 12 hours postoperatively, except for warfarin, which should be started the night of surgery.

Aspirin is also an option.37 However, a meta-analysis of 8 randomized controlled trials comparing aspirin and anticoagulants in patients undergoing major lower extremity orthopedic surgery found a nonsignificant trend toward fewer episodes of deep vein thrombosis with anticoagulants after hip fracture repair, although the risk of bleeding was lower with aspirin.41

ENHANCED RECOVERY PATHWAYS

Enhanced recovery protocols have been used in Europe for about 20 years over a wide range of surgeries. Many of the recommendations in this review are aligned with such protocols, which have been shown to benefit the geriatric population.42

Principles of enhanced recovery pathways include avoiding a preoperative catabolic fasting state and resultant hypoglycemia.42 Clear carbohydrate drinks up to 2 hours before surgery can reduce delirium and acute kidney injury and minimize thirst and anxiety. Reduction of opioid use and the use of regional anesthesia whenever possible are other principles.

Intraoperatively, the goal is euvoemia without fluid overload. Postoperatively, the emphasis is on early removal of drains and tubes, continued use of peripheral nerve blocks, and multimodal analgesia to minimize need for opioids, as well as on early mobilization and ambulation and adequate nutrition. Oral nutritional supplementation is recommended in patients with hip fracture who are malnourished or at risk of undernutrition, as these factors increase the risks of fracture non-union and death.26

A large multicenter study43 of an enhanced recovery pathway in 5,002 patients with acute hip fractures found significantly higher rates of discharge to home with early ambulation and decreased opioid use.

COMANAGEMENT

Comprehensive interdisciplinary care in a geriatric ward has been shown to significantly
improve mobility, activities of daily living, and quality of life compared with routine care in an orthopedic ward. The length of stay and complications were significantly reduced in the comprehensive geriatric care group, and significantly more patients in this group were discharged directly home.

We recommend consideration of geriatric medicine consultation if there is no geriatric ward or unit for acute care for elderly patients available, to improve outcomes in this population such as discharge to home and reduction in mortality.

■ TAKE-HOME MESSAGES
In the elderly, acute hip fracture poses significant risks of illness and death. An expedited medical evaluation to ensure operative repair within 24 to 48 hours of admission is recommended for improved outcomes, and the patient’s use of anticoagulants before admission should not delay surgery. Guidelines regarding consultation and cardiac testing should be followed, as routine testing is unlikely to produce a measurable impact on outcomes.

Multimodal analgesia, regional anesthesia, enhanced recovery pathways, and delirium precautions are paramount to producing the best outcomes.

Risk factors contributing to acute hip fracture such as chronic osteoporosis and frailty are often not addressed during the inpatient stay. On discharge, patients should be referred for pharmacologic treatment of osteoporosis, advised on calcium and vitamin D supplementation, and referred for physical therapy to prevent future fractures.

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

### TABLE 4

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing and route of administration</th>
<th>FDA-approved for VTE prophylaxis?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-molecular-weight heparin</td>
<td>Enoxaparin 40 mg subcutaneously daily</td>
<td>Yes</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>2.5 mg subcutaneously daily</td>
<td>Yes</td>
</tr>
<tr>
<td>Warfarin</td>
<td>3–5 mg by mouth daily for goal international normalized ratio 2–3</td>
<td>Yes</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>5,000 U every 8 hours, every 12 hours for patients weighing &lt; 50 kg Use if creatinine clearance rate is &lt; 230 mL/min</td>
<td>Yes</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Unclear, dosing ranges from 81 mg orally twice a day for creatinine clearance rate &lt; 30 mL/min, to 325 mg orally twice a day</td>
<td>No</td>
</tr>
<tr>
<td>Apixaban</td>
<td>2.5 mg orally twice a day</td>
<td>No</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>150 mg orally daily</td>
<td>No</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>10 mg orally daily</td>
<td>No</td>
</tr>
</tbody>
</table>

FDA = US Food and Drug Administration; VTE = venous thromboembolism

Based on information in reference 37.

Interdisciplinary care in a geriatric ward significantly improves mobility, activities of daily living, and quality of life.
REFERENCES


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- **American Board of Anesthesiology (ABA) MOC:** 1.0 Lifelong Learning MOC points in the ABA MOCA 2.0® Maintenance of Certification in Anesthesiology Program®.
- **American Board of Internal Medicine (ABIM) MOC:** 1.0 Medical Knowledge MOC points in the ABIM MOC Assessment Recognition Program.
- **American Board of Pathology (ABPath) CC:** 1.0 Lifelong Learning credits in the ABPath Continuing Certification Program.
- **American Board of Pediatrics (ABP) MOC:** 1.0 Lifetime Learning & Self-Assessment MOC points in the ABP Maintenance of Certification Program.
- **American Board of Surgery (ABS) CC:** 1.0 Accredited CME & Self-Assessment credits toward ABS Continuous Certification Program.

Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity.

It is the CME activity provider’s responsibility to submit participant completion information to ACCME for the purpose of granting ABA, ABIM, ABPath and ABP credit. Credit will be reported within 30 days of claiming credit.

**ABS:** It is the participant’s responsibility to self-report their participation per current board policy.

**Please Note:** To receive MOC you must select the MOC option during the online credit claiming process and complete the required steps.