

CLEVELAND CLINIC JOURNAL OF MEDICINE



**The initial viral infection
may be only part of the story**

Abdominal pseudohernia

Leriche syndrome

**Dermatomyositis-related
interstitial lung disease**

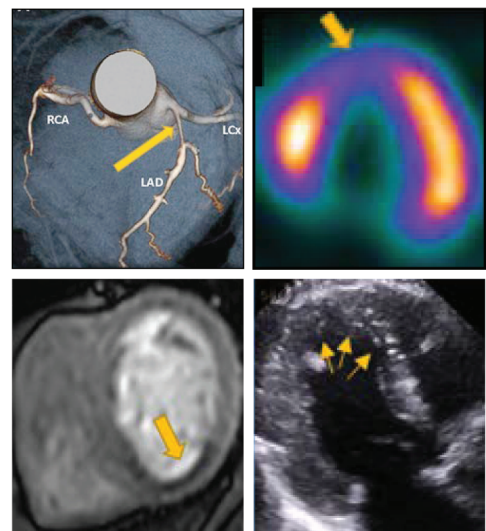
Clues on a 'normal' radiograph

**Teriparatide: Implications
of labeling changes**

**Right-sided headache
with vision loss**

End-of-life challenges in the ICU

**Stress testing and noninvasive
imaging: Choosing the best test**



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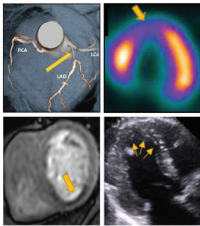
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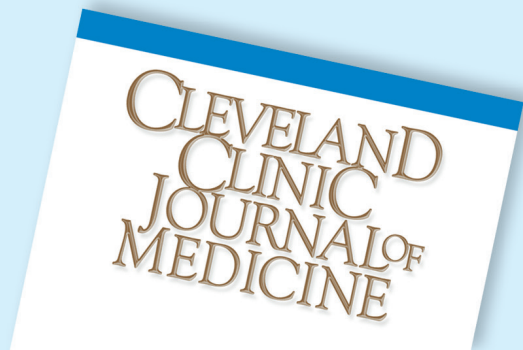
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The initial viral infection may be only part of the story

The concept of “long COVID” is now entrenched in our vocabulary and in the minds of our patients, but the pathogenesis of this protracted syndrome is thus far incompletely understood. Are there pockets of slowly dividing virus or incompletely cleared viral remnants driving a low-level inflammatory response? Is there a central nervous system reservoir of infected neurons contributing to an intense sense of fatigue, brain fog, and sometimes mood changes? Is there persistent infection of vascular cells impacting vascular regulation of blood flow to selected organs?

While we cannot answer these questions now, we clearly see that the coronavirus elicits pathologic syndromes far afield from the respiratory tissues that the virus primarily targets for infection.

A virus eliciting effects seemingly distinct from its primary infection is not a new concept at all, of course. Epstein-Barr virus is recognized as causing not only a lasting malaise in some patients, but also a reactivation syndrome and lymphoproliferative disorders. Hepatitis C and B virus infections are linked to the development of delayed hepatocellular carcinoma in the setting of hepatic fibrosis, as well as several systemic vasculitic disorders occurring during active infection. Parvovirus is associated with aplastic anemia and human papillomavirus is strongly linked to various carcinomas.

But the most common viral infection associated with delayed clinical events is the double-stranded DNA varicella-zoster alpha-herpesvirus (VZV), the causative agent for “chicken pox” and shingles. Seminal work from the laboratories of the late Dr. Don Gildea and others has demonstrated that the viral DNA exists in neurons, in a non-integrated form. Reactivation is best recognized by the appearance of pruritic, painful vesicles in an asymmetric dermatomal distribution. While often no definite trigger for reactivation with viral replication is recognized, it is felt that loss of cellular immunity is at least permissive, and this is increasingly recognized in a minority of patients treated with JAK inhibitors for rheumatoid arthritis and other inflammatory disorders. How a decrease in cellular immunity affects intracellular viral replication is not entirely clear, but more readily understood is that patients who are immunosuppressed often have a more difficult time containing and controlling the reactivation when it occurs. It is often said that stress may also bring about reactivation, and several fascinating studies have demonstrated that after space travel, astronauts experience a self-limited asymptomatic reactivation of VZV as detected by the presence of salivary viral DNA.¹

Postherpetic neuralgia is the best-known complication of dermatomal reactivation, and although some risk factors are known, we cannot predict who will develop it, nor do we know how to prevent it. The virus has been detected in cerebral blood vessels, and a VZV vasculopathy, often with giant cells and adventitial inflammation, has been associated with stroke syndromes and, controversially, with giant cell arteritis. VZV stroke syndromes may occur weeks or months after an episode of dermatomal zoster. VZV DNA or, more commonly, anti-varicella IgG antibody can be found in the cerebrospinal fluid of affected patients.

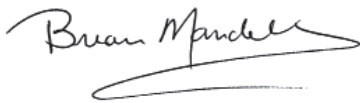
A myelopathy or segmental peripheral episode of motor weakness can follow an

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episode of typical zoster. Segmental weakness generally occurs in the area of the zoster outbreak, but not always. Myelopathy may affect legs and sphincter tone and has also been rarely described after infection with cytomegalovirus, another herpesvirus.

Since pain and neurologic complications before, during, or after VZV infection can occur in the absence of the classic skin findings (zoster sine herpette),² it is important to recognize the wide spectrum of regional VZV syndromes that can occur. How many times have I not recognized impending zoster in the setting of radiculopathy or an unusual regional pain syndrome? I know that I have on multiple occasions diagnosed pre-zoster rash-pain syndromes—oddly, it seems, more in family and friends than in patients in my office. (Patients these days probably cannot get an appointment in time before the vesicles appear.)

It is with this background in mind that I invite you to read the Clinical Picture in this issue by Dr. Mizumoto (page 480).³



Brian F. Mandell, MD, PhD
Editor in Chief

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2021

SEPTEMBER

STATE-OF-THE-ART DIAGNOSIS
AND TREATMENT OF DEMENTIA
September 9
Live stream

DIABETES, OBESITY,
AND CARDIOVASCULAR DISEASE
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September 9–11
Live stream

THE PRACTICE OF ECHOCARDIOGRAPHY
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September 18
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October 1
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IN THE ICU: CHALLENGES
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October 6–8
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GASTROENTEROLOGY UPDATE:
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IN THE ICU: CHALLENGES
AND OPPORTUNITIES
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IN THE ICU: CHALLENGES
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- Recognize the role of implementation science methods in guiding and studying delivery system change
- Discuss a specific care delivery implementation initiative to improve care for patients with STEMI

THE CLINICAL PICTURE

Junki Mizumoto, MD

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International Research Center for Medical
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The University of Tokyo, Tokyo, Japan

Abdominal pseudohernia due to herpes zoster

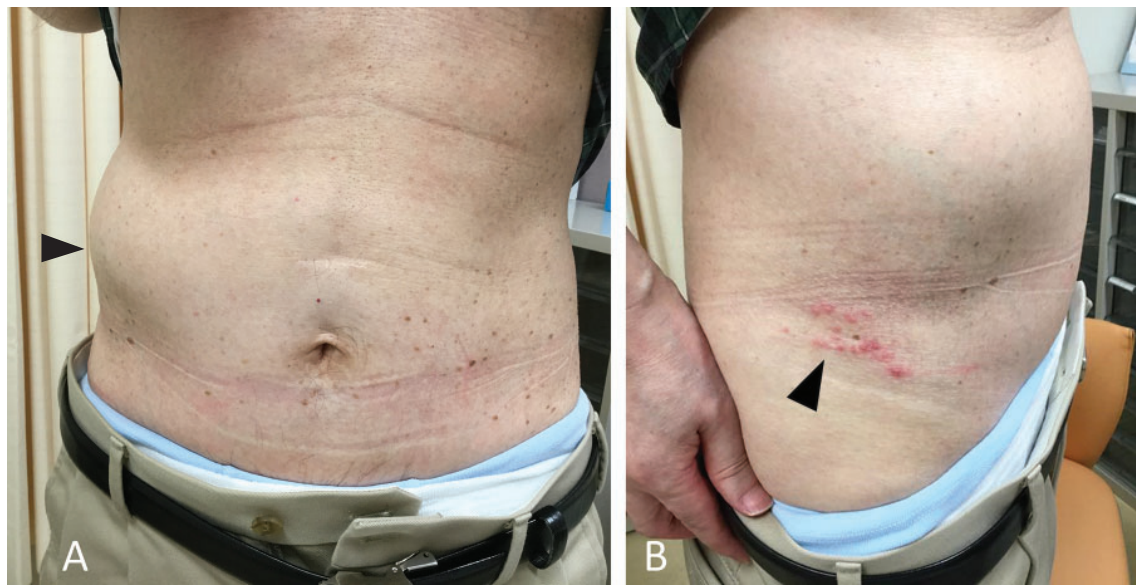


Figure 1. (A) Bulging of the right abdominal wall (arrowhead). (B) The papules aggregated in a row on the right side of the lower abdomen (arrowhead).

Thermal hypoalgesia was detected in a belt from the lower right side of the abdomen to the back

A 66-YEAR-OLD immunocompetent man presented with bulging and persistent burning pain in the right abdominal side for 4 days. Two days before the presentation, he went to another hospital and underwent abdominal computed tomography, which revealed no intraperitoneal abnormality.

On examination, the bulge was soft and nontender and did not have any palpable mass (**Figure 1A**). Thermal hypoalgesia was detected by alcohol swab in a belt from the lower right side of the abdomen to the back, a neurologic finding suggestive of zoster infection. No other neurologic deficit was seen. However, there were papules aggregated above the right groin (**Figure 1B**). The patient had

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been unaware of this rash until it was pointed out. The rash was thus presumed to have developed on the morning of the presentation day because the patient confirmed that there was no skin change when taking a bath the previous night.

The diagnosis of abdominal pseudohernia due to herpes zoster was made based on the physical findings.

Lesions of herpes zoster often progress through stages, in the course of 7 to 10 days, from red macules and papules (as in this patient) to vesicles, to pustules and crusts,¹ and then eventually subside spontaneously.² Our patient was reassured that the condition would resolve on its own. He was prescribed valacyclovir 3,000 mg/day for 7 days. The bulging gradually improved over several weeks.

■ NEUROLOGIC COMPLICATIONS OF INFECTION

Although skin neuralgia is a well-known complication of herpes zoster, the varicella-zoster virus can also cause motor neuron deficits, probably because of direct spread into spinal anterior horn cells and ventral roots.³

When the virus affects the lower thoracic spine, unilateral abdominal bulging may occur because of paresis of abdominal muscle.⁴ Most cases subside spontaneously,² and patients can be reassured and thus be spared unnecessary diagnostic tests or medications.

Causes of pseudohernia other than herpes include diabetic radiculoneuropathy; trauma, such as ventral root injury from tumor removal and prolapsed intravertebral disc; and infection, such as Lyme disease and poliomyelitis.^{5,6}

■ KEYS TO THE DIAGNOSIS

There are several keys to the diagnosis of abdominal pseudohernia due to herpes zoster.

First, the physician should not rule it out simply because there is no rash. Although the

condition is often termed postherpetic abdominal pseudohernia,^{3,4} the bulging precedes the herpetic rash in nearly 10% of patients.² This is why I prefer the term abdominal pseudohernia due to herpes zoster.

Second, a targeted history is important, eg, to rule out tick exposure and *Borrelia*-related neurologic complications.⁷

Third, imaging tests including magnetic resonance imaging may be indicated to check for mechanical compression of thoracic nerve roots if close follow-up does not reveal delayed-onset herpetic rash.

The combination of unilateral bulging of the abdominal wall and herpetic rash indicates abdominal pseudohernia due to herpes zoster. The rash may develop after the bulging, and thus, close follow-up may be of benefit. ■

Acknowledgments: We thank Robert Blakytyn, DPhil, from Edanz Group for editing a draft of this manuscript.

■ DISCLOSURES

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

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THE CLINICAL PICTURE

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Leriche syndrome

The syndrome presents as a triad of claudication, erectile dysfunction, and decreased distal pulses

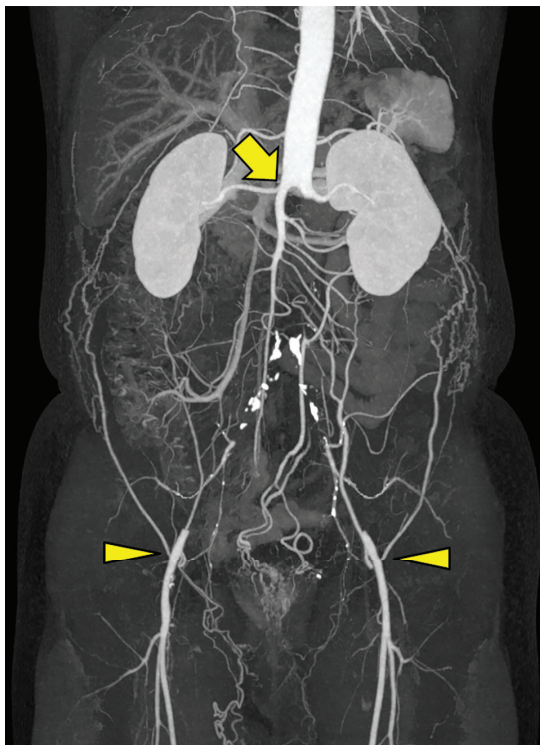


Figure 1. Abdominal contrast-enhanced computed tomography showed complete occlusion of the infrarenal abdominal aorta (arrow). The collateral pathways provided blood flow to both external iliac arteries (arrowheads).

A 53-YEAR-OLD MAN with a 2-month history of progressive pain and intermittent claudication of both lower extremities presented to the outpatient clinic. He was a smoker and had untreated diabetes mellitus, but he had no previous cardiovascular or gastrointestinal problems. He also denied any drug misuse, lead poisoning, ergotism, or abdominal injury.

His vital signs were normal. Physical examination revealed pallor of his toes, cold

extremities, dry skin, and absence of bilateral femoral pulses. He also disclosed that he had erectile dysfunction.

The ankle-brachial index was 0.28 on the right side and 0.47 on the left side, indicating severe bilateral vascular disease. Abdominal computed tomography with contrast enhancement revealed complete occlusion of the infrarenal abdominal aorta, with collateral pathways (**Figure 1**). Based on the clinical and radiographic findings, we made a diagnosis of aortoiliac occlusive disease, also called Leriche syndrome.

CLUES TO THE DIAGNOSIS

Leriche syndrome is a progressive disease that presents as a triad of claudication, erectile dysfunction, and decreased distal pulses. Risk factors are hypertension, diabetes mellitus, hyperlipidemia, and smoking. Some patients are asymptomatic because of sufficient collateral blood flow. Symptoms are often vague and include bilateral buttocks claudication, impotence, leg pain, pallor, and absent femoral pulses.

The differential diagnosis of Leriche syndrome includes abdominal aortic dissection, neuropathy, spinal canal stenosis, spinal disc herniation, and Guillain-Barré syndrome.¹

Measuring the ankle-brachial index is a noninvasive and inexpensive part of the evaluation of suspected Leriche syndrome. Imaging with Doppler ultrasonography, aortic angiography, and computed tomographic angiography can aid in confirming the diagnosis and the location of stenosis.

TREATMENT

Treatments for Leriche syndrome are aorto-bifemoral bypass, aortoiliac endarterectomy, extra-anatomic bypass grafting, and endovascular bypass.²

doi:10.3949/ccjm.88a.20179

Medical management to prevent progression of the disease should target hyperlipidemia, diabetes mellitus, and hyperglycemia, and smoking cessation is also important.³ Our patient quit smoking and was treated with aspirin and a statin.

Untreated Leriche syndrome is progressive and results in serious complications. Thus, early identification is essential. ■

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■ DISCLOSURES

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Dermatomyositis-related interstitial lung disease mimicking COVID-19 pneumonia

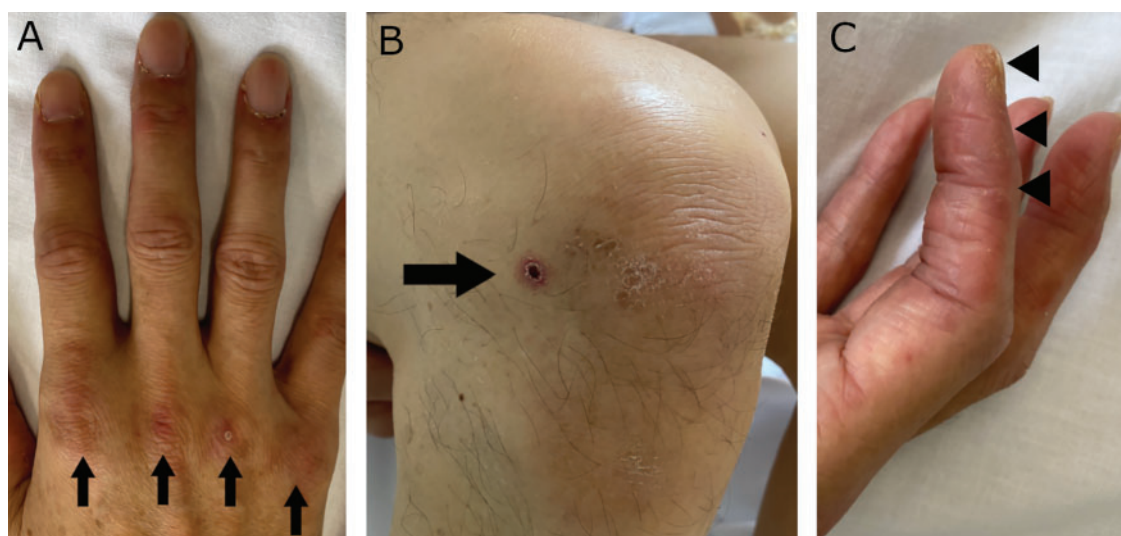


Figure 1. Examination of the patient revealed (A) Gottron sign (arrows), (B) ulceration on the right knee (arrow), and (C) linear hyperkeratotic lesions on the radial aspect of the index finger (“mechanic’s hands”).

A 51-YEAR-OLD MAN with no significant medical history presented to the emergency department with fever and dyspnea lasting for 10 days. On presentation, his body temperature was 36.6°C (97.9°F), respiratory rate 15 breaths per minute, and oxygen saturation 90% on 1 L per minute of oxygen.

On physical examination, fine crackles were heard bilaterally at the base of the lungs. No evidence of muscle weakness was observed. Skin examination (**Figure 1**) revealed Gottron papules at the knees, elbows, and metacarpophalangeal joints of the hands, a skin ulcer at the knee, hyperkeratosis of the lateral aspect of the index finger of both hands, peri-

ungual erythema, and palmar papules.

Results of initial laboratory testing were as follows:

- Leukocyte count $10.7 \times 10^9/L$ (reference range $3.3\text{--}8.6 \times 10^9/L$)
- Creatine kinase 257 IU/L (reference range 59–248 IU/L)
- Ferritin 841.8 ng/mL (reference range 39–340 ng/mL)
- C-reactive protein 5.5 mg/dL (reference range 0–0.14 mg/dL).

Chest computed tomography (CT) (**Figure 2**) revealed bilateral peripheral subpleural ground-glass opacities in the upper and lower lobes.

In the emergency department, interstitial

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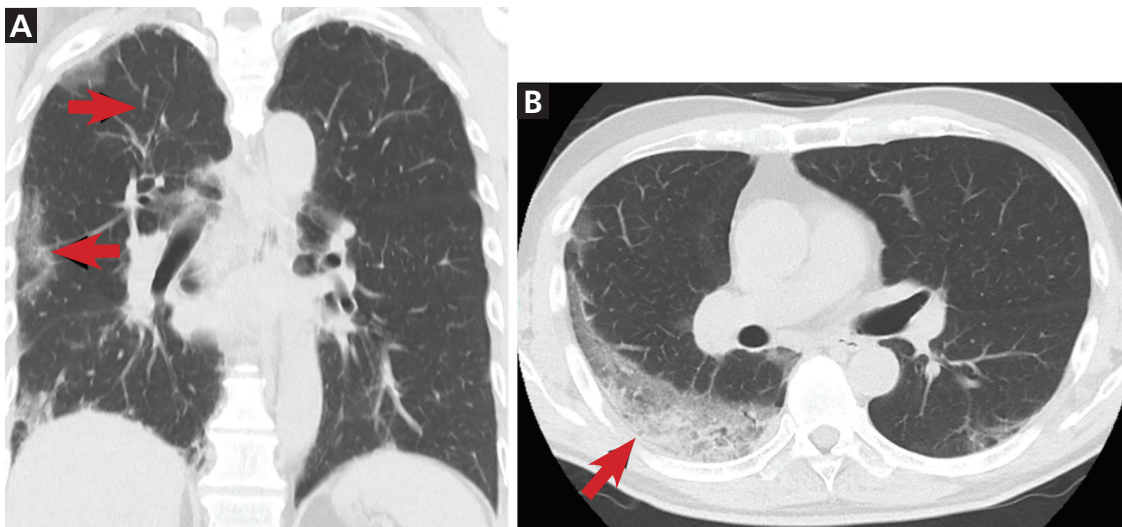


Figure 2. Computed tomography of the chest revealed peripheral subpleural ground-glass opacities in the right upper lobe (A, arrows) and right lower lobe (B, arrow).

pneumonia including COVID-19 pneumonia was suspected, but SARS-CoV-2 real-time polymerase chain reaction testing of nasopharyngeal swabs and a sputum specimen was negative. Consultation with the rheumatology department and review of the clinical findings led to a diagnosis of rapidly progressive interstitial lung disease (ILD) associated with dermatomyositis.

The hyperkeratosis of the lateral digit suggested “mechanic’s hands.” The characteristic skin findings, lack of muscle symptoms, and progressive pneumonia led to the clinical diagnosis of amyopathic dermatomyositis. In addition, we ordered testing for anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibody on admission, but results were not immediately available.

Treatment with methylprednisolone pulse therapy, intravenous cyclophosphamide pulse therapy, and tacrolimus was promptly initiated, and his respiratory status gradually improved. Later, the test for anti-MDA5 was confirmed positive, thus further refining the diagnosis to anti-MDA5-positive dermatomyositis with ILD.

■ ANTI-MDA5-POSITIVE DERMATOMYOSITIS AND THE DIFFERENTIAL DIAGNOSIS OF ILD

Anti-MDA5-positive dermatomyositis is a subtype of myositis with characteristic skin rashes and ulcers, amyopathic or hypomyopathic

symptoms, and rapidly progressive ILD.^{1,2} It is associated with a poor prognosis, with 6-month survival rates of 33% to 50%.²⁻⁴

Early diagnosis and early intervention are necessary to improve the prognosis.^{4,5} Although standard treatment has not been established, combination therapy of high-dose glucocorticoids (1 mg/kg), a calcineurin inhibitor (cyclosporine A or tacrolimus), and intravenous cyclophosphamide should be considered as first-line therapy.^{4,5} In refractory cases, concomitant use of rituximab as salvage therapy has been reported to be effective.⁵ For patients who do not respond to combination therapy, nonpharmacologic therapies such as plasma exchange and intravenous immunoglobulin are considered options, but their efficacy has not yet been proven.⁵

CT in our patient showed bilateral peripheral subpleural ground-glass opacities in the lower lobes, with findings similar to those of viral pneumonia or ILD.^{1,2}

Anti-MDA5-positive dermatomyositis with ILD triggered by a viral infection has been reported, although viral infection has not been directly proven as the mechanism underlying this condition.²

■ DIFFERENTIATING ILD FROM COVID-19

In the context of the COVID-19 pandemic, a detailed history and physical examination are particularly important for the differential di-

COVID-19 also shows a variety of skin findings, such as pernio-like lesions and urticarial and morbilliform rashes, but cutaneous ulceration is rare

ILD MIMICKING COVID-19 PNEUMONIA

agnosis of ILD. Muscle weakness and elevated muscle enzyme are often absent or scant in anti-MDA5-positive dermatomyositis, making the diagnosis of dermatomyositis difficult.

The key to diagnosis is the characteristic skin findings such as Gottron papules, skin ulcers, palmar papules, and lateral digit hyperkeratosis. It is important not to overlook the minor skin findings that are present with pneumonia.²

COVID-19 also shows a variety of skin findings such as perniolike lesions and urticarial and morbilliform rashes, but cutane-

ous ulceration is rare.⁶ Cutaneous ulceration overlying Gottron papules is one of the most characteristic signs and is present in 83% of patients with anti-MDA5-positive dermatomyositis.²

Anti-MDA5-positive dermatomyositis with ILD mimics COVID-19 and is a reminder of the importance of careful physical examination for diagnosis. ■

DISCLOSURES

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

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THE CLINICAL PICTURE

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An uncommon cause of chest pain

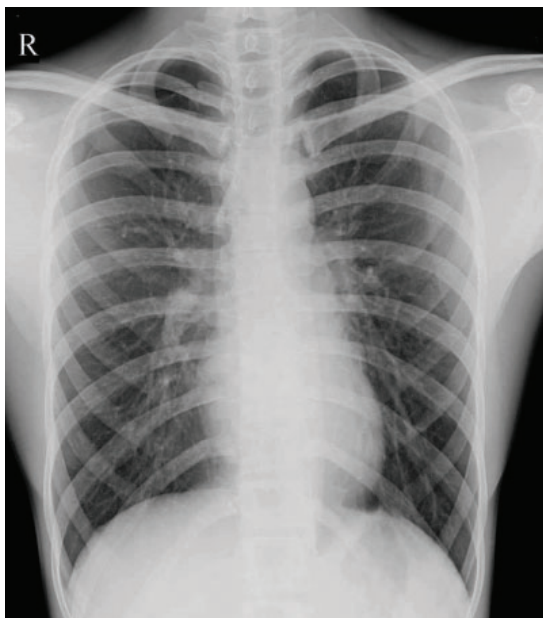


Figure 1. The chest radiograph taken at another facility was ruled to be normal.

A 20-YEAR-OLD MAN was referred to the chest pain unit with acute-onset right-sided chest pain. A chest radiograph taken at another facility (Figure 1) had been reported as normal, and electrocardiography had revealed “T inversion in lead III.” The patient was referred because of this finding.

The patient had no history of significant medical illness. He was lean and thin-built. Clinical examination in the emergency department revealed no significant findings, with normal oxygen saturation on room air. Echocardiography showed no regional wall-motion abnormality, and acute coronary syndrome and aortic dissection were ruled out.

However, re-review of the chest radiograph from the previous facility noted a mild displacement of the pleural line, with absence of lung markings in the right upper lung zone,

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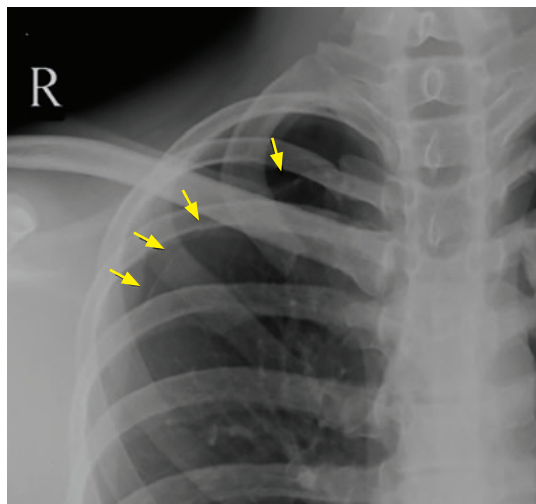


Figure 2. On re-review of the chest radiograph from another facility, magnification showed a thin visceral pleural marking (arrows) displaced from the chest wall at the right apex, indicating a small right apical pneumothorax.

suggestive of a small apical pneumothorax (Figure 2). Based on this finding, on the absence of a precipitating cause or other significant finding, and on his chest pain atypical for angina, a diagnosis of small spontaneous primary pneumothorax was made.

The patient was treated conservatively with high-flow oxygen for several hours, his cardiorespiratory status stabilized, and he was discharged.

■ SPONTANEOUS PNEUMOTHORAX: RISK FACTORS AND DIAGNOSIS

A small pneumothorax can be easily missed on a chest radiograph unless there is a strong index of clinical suspicion.

Pneumothorax is considered spontaneous if there is no apparent precipitating cause. Spontaneous pneumothorax is considered

“primary” if it occurs in individuals with no underlying lung disease. Primary spontaneous pneumothorax typically occurs in tall, thin individuals. Other risk factors are male sex and cigarette smoking. Spontaneous rupture of a subpleural bleb or bulla is usually the cause.

Patients typically present with an abrupt onset of chest pain that is usually pleuritic, with or without breathlessness. Some patients may experience shoulder-tip pain.

Posteroanterior chest radiography is the standard view in patients with suspected primary spontaneous pneumothorax and may be combined with lateral radiographs in difficult cases. Expiratory films, though traditionally believed to enhance diagnostic sensitivity, may not be routinely necessary.^{1,2} The radiographic hallmark is displacement of the pleural line and the absence of lung markings between the edge of the pleura and chest wall. If these features are difficult to see on the posteroanterior radiograph, a lateral decubitus view with the affected side up would clearly show the lung “falling away” from the chest wall, demonstrating the pneumothorax.

Computed tomography is more sensitive in the detection of pneumothorax but is not usually required. Bedside lung ultrasonography has emerged as a new sensitive tool to diagnose pneumothorax in the emergency department, especially in trauma and critically ill patients.¹

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TREATMENT

Conservative management with observation for 6 hours is recommended if the patient is clinically stable and no enlargement of the pneumothorax is noted on repeat radiographs. An outpatient follow-up visit 2 days after discharge is desirable.^{3,4}

High-flow oxygen may be administered to hasten absorption of intrapleural air.⁴ Additional inpatient care and pleural drainage may be necessary for patients with larger pneumothoraces (distance from lung apex to visceral pleura ≥ 3 cm, or $\geq 15\%$ of thoracic volume)³⁻⁵ or patients who are clinically unstable due to hypotension, respiratory distress, or significant oxygen desaturation ($< 92\%$).

Primary spontaneous pneumothorax typically occurs at rest. Therefore, there is no need to recommend avoiding exercise to prevent recurrences.

The acute nature of the presentation can mimic an acute coronary syndrome or an acute aortic syndrome and therefore requires a strong index of suspicion for the diagnosis. A small pneumothorax can be easily missed on chest radiography and should be sought in the appropriate clinical setting.

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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COMMENTARY

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Teriparatide: Label changes and identifying patients for long-term use

The osteoporosis agent teriparatide (Forteo) no longer carries a boxed warning about the risk of osteosarcoma, and dosing is no longer limited to 24 months of lifetime use. These labelling changes have left clinicians with the challenge of identifying patients for consideration of long-term treatment.

Teriparatide was initially approved based on only 19 months of data on fracture reduction, in contrast to the 3 years required for all other osteoporosis drugs. Given the lack of clinical trial data, in this article we offer suggestions for selecting patients for extended use of teriparatide based mostly on our extensive experience treating patients with teriparatide, some patients for longer than 2 years.

■ CHANGES TO THE LABEL

In November 2020, the US Food and Drug Administration (FDA) approved changes to the label for the parathyroid hormone (PTH) analogue teriparatide (PTH 1-34), by removing the 2-year lifetime treatment limitation and the boxed warning about the potential risk of osteosarcoma.¹ The lifetime limitation had been established because 24 months was the longest that any woman had been treated with teriparatide in the labeling clinical trial.²

Osteosarcoma boxed warning

The deleted boxed warning (not a contraindication) regarding osteosarcoma was based on studies in Fischer 344 rats showing that high doses of teriparatide—3 times greater than the approved human dosing based on milligrams per kilogram of body weight—administered over most of a rat lifespan (about 24 months) were associated with the development of osteo-

sarcoma. Based on this observation, which occurred while the clinical trial for teriparatide was ongoing, the trial was terminated early. As a result, study participants received teriparatide for an average of 19 months, with a mean observation time of 21 months.²

In the 18 years since teriparatide was approved, no increase in osteosarcoma risk has been reported in studies in animals with bone remodeling similar to that in humans (eg, monkeys). However, considering the rarity of osteosarcoma (about 1 in 250,000 adults per year), the sample size of about 60 monkeys in a study by the manufacturer of Forteo³ was too small to provide conclusive data.

In humans treated with teriparatide, there is no evidence of an increased risk of osteosarcoma. The observed incidence of osteosarcoma during a 15-year postmarketing surveillance study was no different than the background incidence rate for individuals not treated with teriparatide.⁴

The boxed warning has not been removed for abaloparatide (Tymlos), a synthetic analogue of PTH-related protein (PTHrP 1-34), but at the time of this writing, the FDA is in discussions with the manufacturer about removing the boxed warning. Another PTH 1-34 product (Bonsity) has also not had any recent label change.

The duration of dosing

The revised teriparatide label states that use “for more than 2 years during a patient’s lifetime should only be considered if a patient remains at or has returned to having a high risk for fracture.”¹ Now that the teriparatide label permits use for longer than 2 years, there are practical clinical questions about the selection of patients for an extended use.

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■ **BEHIND THE ORIGINAL FDA APPROVAL**

Teriparatide is derived from splitting the biologically active 1-34 amino-acid fragment from the intact PTH 1-84 molecule. The labeling trial for teriparatide was a placebo-controlled study with the primary end point of new vertebral compression fracture (VCF) over 3 years.² The FDA requires evidence that pharmacologic treatment of women with postmenopausal osteoporosis reduces fracture risk over a 3-year period compared with placebo, with a favorable balance of benefits and risks.

Are there osteosarcoma risks?

When osteosarcoma was observed in the Fischer 344 rats receiving teriparatide, the study sponsor halted the human trial while the rat data were evaluated. After the FDA concluded that the osteosarcoma risk was confined to the rats, they encouraged the manufacturer to resume the clinical trial. However, by this time, approximately 50% of the patients who had been enrolled in the initial registration trial had switched to treatment with alendronate, resulting in loss of statistical power as defined by the study design. Nevertheless, a subsequent evaluation of the clinical data found that teriparatide was effective in preventing fractures and well tolerated.²

■ **WHY THE TIME-LIMIT CHANGE FOR DOSING?**

The FDA approved teriparatide for the treatment of postmenopausal women with osteoporosis who are at high risk for fracture, with a 24-month lifetime limit of use. High fracture risk was described as a history of osteoporotic fracture or multiple risk factors for fracture, or as failure of or inability to tolerate osteoporosis therapy.¹

In 2020, 18 years after the FDA approval of teriparatide, the incidence of osteosarcoma in patients treated for 2 years was reported as being lower than the natural incidence rate of osteosarcoma in adults.⁴ Use of teriparatide for more than 2 years during a patient's lifetime should be considered only if a patient remains at or has returned to having a high risk for fracture.¹ Determination of high risk, therefore, is a clinical decision to be made by the clinician.

The 2019 Endocrine Society clinical practice guidelines included patient profiles representing examples of high and very high fracture risk⁵:

- High risk: T-score of minus 2.5 or below, or prior hip or vertebral fracture, or high fracture probability by the fracture risk assessment tool (FRAX) (10-year probability of major osteoporotic fracture \geq 20%, or 10-year probability of hip fracture \geq 3%)
- Very high risk: T-score of minus 2.5 or below and 1 or more fractures, or multiple vertebral fractures, or severe vertebral fracture.

The Endocrine Society guidelines suggest that anabolic therapy with teriparatide or abaloparatide be considered the first-line for treatment for up to 2 years in postmenopausal women with osteoporosis who are at very high risk of fracture.⁵

For initial therapy in patients at high risk, there is evidence that teriparatide should be started first, followed by an antiresorptive agent (eg, bisphosphonate, estrogen, selective estrogen receptor modulator, calcitonin, denosumab) because the bone formation effects of teriparatide are blunted by initiating therapy with an antiresorptive agent. Thus, the sequence of treatment is important.^{6,7}

Abaloparatide is a molecular modification of PTH-related protein that is synthesized with 76% homology to human PTH-related protein. This modification conveys to abaloparatide a different binding configuration to its receptor (PTH receptor type 1) than teriparatide. In clinical practice, the resulting stimulation of osteoblasts by abaloparatide results in faster and greater increases in bone mineral density (BMD) than with teriparatide.⁸

Use for glucocorticoid-induced osteoporosis

In the teriparatide clinical trial that led to the regulatory approval of teriparatide for the treatment of glucocorticoid-induced osteoporosis, participants were randomized to receive teriparatide or alendronate for a total of 3 years.⁹ The primary end point was change in BMD at the lumbar spine, and vertebral fracture risk reduction was a secondary outcome measure.

Results showed that BMD increased significantly more with teriparatide than with alendronate, and new radiographic and clinical vertebral fractures were reduced to a greater extent. These findings supported the

Teriparatide use for more than 2 years during a lifetime should be considered only if a patient is at high risk for fracture

FDA approval of teriparatide to treat glucocorticoid-induced osteoporosis, although the recommended 24-month lifetime treatment duration was not extended.

The superior effects of teriparatide over alendronate are biologically plausible, as glucocorticoids inhibit osteoblast recruitment and activity,^{10,11} while teriparatide stimulates osteoblastic bone formation and alendronate inhibits it.

■ CLINICAL IMPLICATIONS OF EXTENDED USE

In our opinion, long-term use of teriparatide can be considered in high-risk patients receiving long-term glucocorticoid therapy. However, we still need more data on the safety and efficacy of long-term use.

What about hypercalcemia?

Hypercalcemia was seen more often in the pivotal clinical trial with teriparatide (6.1%) than with abaloparatide (3.4%).⁸ Serum calcium ideally should be drawn 16 hours or more after the injection to avoid measuring transient calcium elevations that are probably not clinically relevant. A common clinical practice protocol is to measure the serum calcium 1 month and 3 months after starting teriparatide. If no hypercalcemia appears during that time, it is very rare for hypercalcemia to appear later.

Prolonged treatment with teriparatide seems logical for patients with glucocorticoid-induced osteoporosis who cannot be managed with antiresorptive medications. Although there is a dose-response relationship with glucocorticoids and fractures, even low doses of glucocorticoids (eg, prednisone 2.5 mg/day) are associated with elevated fracture risk compared with no glucocorticoids.¹²

What about measuring bone quality?

Glucocorticoids induce a decline of BMD and have adverse effects on bone quality independent of BMD. Bone quality has been described as the non-BMD properties of bone, such as architecture, turnover, damage accumulation, mineralization, and material properties that also determine bone strength.^{13,14}

While we can accurately measure and monitor BMD with dual-energy x-ray absorptiometry (DXA),^{15,16} we lack the capacity to measure bone quality in clinical practice. The trabecular bone

score is a measurement derived from DXA of the lumbar spine that is a surrogate for trabecular microarchitecture, an important component of bone that is an independent predictor of fracture risk.¹⁷ The development of the trabecular bone score is a major advance in fracture risk predictability, and it is included in the FRAX algorithm to estimate the 10-year probability of fracture.

Although the trabecular bone score may improve with anabolic therapy for osteoporosis (eg, with teriparatide), it does not reliably increase with antiresorptive agents.¹⁸ Antiresorptive agents, however, may improve some aspects of bone quality, but this effect has not been systematically validated in human beings.¹⁹

While the capacity to measure bone quality in clinical practice is limited, there are measurements, used mostly in research settings, that may be helpful. Transiliac nondecalcified double tetracycline-labeled bone biopsy provides quantitative bone histomorphometry,²⁰ and high-resolution peripheral quantitative computed tomography measures bone trabecular structure at peripheral skeletal sites with a resolution of 82 μm .²¹ The tomography test, however, is a research tool that is not currently applicable to clinical practice. Neither of these methodologies is widely available.

Which patients are most likely to benefit from long-term teriparatide use?

When considering the clinical benefit of continuing teriparatide beyond 2 years, there are no published studies addressing this issue (notwithstanding the 3-year data with teriparatide for glucocorticoid-induced osteoporosis⁹). Interestingly, a review of clinical data on teriparatide treatment over time showed that while BMD declined rapidly after discontinuing teriparatide, fracture rates did not increase for as long as 18 months after teriparatide discontinuation.²² There is no definitive explanation for this observation, although it suggests that improvements in bone quality with teriparatide persist longer than the increases in BMD.

In our opinion, there are clinical features that identify patients who may benefit from long-term administration of teriparatide (Table 1). Current glucocorticoid users are at high risk for fractures and remain at high or very high risk as long as they use glucocorticoids. Additionally, patients at high risk for fracture who

Long-term use of teriparatide can be considered in high-risk patients on long-term glucocorticoid therapy, but more data on safety and efficacy are needed

TABLE 1

Features of patients who may benefit from long-term teriparatide use

- Very high fracture risk, unable to come off glucocorticoid therapy
- High fracture risk, with P1NP level that remains high after 2 years on teriparatide
- High fracture risk, with multiple vertebral compression fractures at baseline but none while on teriparatide
- Adynamic renal bone disease
- Severe chronic obstructive pulmonary disease and vertebral compression fractures

P1NP = procollagen type 1 *N*-terminal propeptide

Patients at high or very high fracture risk who have severe COPD and vertebral compression fractures may be candidates for long-term teriparatide therapy

have a level of the bone-formation marker procollagen type 1 *N*-terminal propeptide (P1NP) that remains above the upper limit of the reference range after 2 years of treatment with teriparatide should continue therapy because the elevated P1NP indicates that new bone formation is continuing. An increase of P1NP of more than 10 µg/L from baseline while on teriparatide therapy is correlated with improvements in BMD and bone strength.²³

As with all osteoporosis medications, the BMD or the bone turnover marker may not always change over time while the patient is on therapy. However, because a stable BMD may be an acceptable response and the P1NP may not increase, we feel that as long as the patient does not suffer a fracture, treatment should be continued. Furthermore, patients at high or very high fracture risk who have multiple VCFs at baseline but no incidence of VCF while on teriparatide may be candidates for treatment longer than 2 years, especially if a bone formation marker such as P1NP is still above the reference range.

Data show that VCFs are associated with a high risk of more VCFs and non-VCFs in untreated patients²⁴ and a high 10-year mortality.²⁵ In its labeling clinical trial,² teriparatide reduced VCF incidents by about 80% over 19 months, similar to the VCF risk reduction with abaloparatide.⁸

Renal-associated adynamic bone disease.

There are reports suggesting that patients at high or very high fracture risk who have adynamic renal bone disease may respond to treatment with teriparatide.^{26–29} Idiopathic adynamic renal bone disease is a form of renal bone disease characterized on bone biopsy as very low bone turnover, very low bone formation, and poor osteoid development with an increased risk for low-trauma fractures.^{26,27}

Many patients who have stage 4 or 5 or 5D chronic kidney disease (especially with diabetic renal disease), who have bone-biopsy-documented adynamic renal bone disease have serum PTH levels below 100 to 150 pg/mL, and who have a bone-specific alkaline phosphatase in the lower quartile of the reference range have a high positive predictive value for having adynamic bone disease.²⁸ Although there have been a few case reports of teriparatide improving bone formation parameters measured by paired bone biopsies in this patient population,^{30,31} data are needed from prospective clinical trials or large observational trials to validate its long-term efficacy.

Severe chronic obstructive pulmonary disease (COPD) and VCFs. Finally, patients at high risk or very high risk of fracture who have severe COPD and VCFs may be candidates for long-term use of teriparatide. Patients with COPD and VCFs are at high risk for more fractures and have increased mortality risk.²⁵ For each VCF in these patients, there is a loss of about 8% of vital capacity.^{32–34} These patients cannot afford any additional loss of lung function.

Long-term use of teriparatide seems justified in these patients to reduce mortality risk by preventing more VCFs. In our opinion, teriparatide or abaloparatide should be the initial therapy in these patients, given that anabolic agents reduce the incidence of VCF to a greater extent than bisphosphonates.³⁵

CONTINUING CHALLENGES

With the labeling changes to teriparatide, clinicians face the challenge of identifying patients for longer treatment. Although the evidence for guiding such a decision is limited, we have suggested clinical circumstances in which long-term teriparatide may be appropriate.

It is unclear how long to continue teripa-

ratide beyond 2 years. We suggest that practitioners consider continuing treatment as long as PINP levels remain appropriately elevated and the patient has not had new VCFs.

Finally, we encourage the development and implementation of clinical investigations to explore the potential additional benefits of

longer-term use of teriparatide and other anabolic agents.

DISCLOSURES

Dr. Schwartz has disclosed consulting, membership on advisory committee or review panels, and teaching and speaking for Amgen; and consulting, research/independent contracting, membership on advisory committee or review panels, and teaching and speaking for Radius Health. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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An 86-year-old man with unexplained right-sided headache and vision loss

AN 86-YEAR-OLD MAN presented to a local hospital ophthalmologist with headache and pain in his right temple without vision loss. Laboratory values for complete blood cell count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were normal. The medical history was remarkable only for a remote history of diverticulitis. He reported social consumption of alcohol and smoking in the past.

Although reassured, the patient returned 2 weeks later with acute loss of vision in his right eye, preceded by eye discomfort, floaters, flashing lights, and worsening right temporal pain and headache. On physical examination, he had no fever and was normotensive. Extraocular movements and visual fields were normal, and visual acuity was unchanged. Heart, lung, joint, and skin examinations were unremarkable.

Given the patient's age and presentation, giant cell arteritis (GCA) was suspected. Key clinical features of GCA in patients over age 50 include abrupt new headache, scalp pain and tenderness, jaw claudication, visual symptoms, polymyalgia rheumatica, temporal artery abnormalities, and elevated ESR or CRP, or both.^{1,2} Anterior ischemic optic neuropathy due to occlusion of the posterior ciliary artery is the cause in 85% of cases of vision loss in GCA.³

EVALUATING AND MANAGING SUSPECTED GIANT CELL ARTERITIS

1 What is the most appropriate first step for a patient with suspected GCA?

- Oral glucocorticoid therapy
- Biopsy of the temporal artery
- Measurement of serum ESR and CRP
- Duplex ultrasonography of the temporal artery
- Ophthalmologic assessment

If GCA is strongly suspected, high-dose systemic glucocorticoids should be started promptly to prevent irreversible vision loss and involvement of the other eye.⁴ Urgent referral for specialist management, ophthalmologic assessment, and temporal artery biopsy are recommended but should not delay administration of glucocorticoids. Temporal artery biopsy is the preferred method of confirming GCA, although a negative result does not rule out disease in cases of high clinical suspicion.¹

Initiating glucocorticoids should lead to significant improvement in symptoms. If this does not occur, one should evaluate for alternative diagnoses.

CASE CONTINUED: SYMPTOMS PROGRESS DESPITE STEROIDS

The patient was started on oral prednisone 60 mg for presumed GCA and admitted to the local hospital. ESR and CRP were repeated, and results again were within normal range. A right-sided temporal artery biopsy was per-

If giant cell arteritis is strongly suspected, high-dose systemic glucocorticoids should be started promptly

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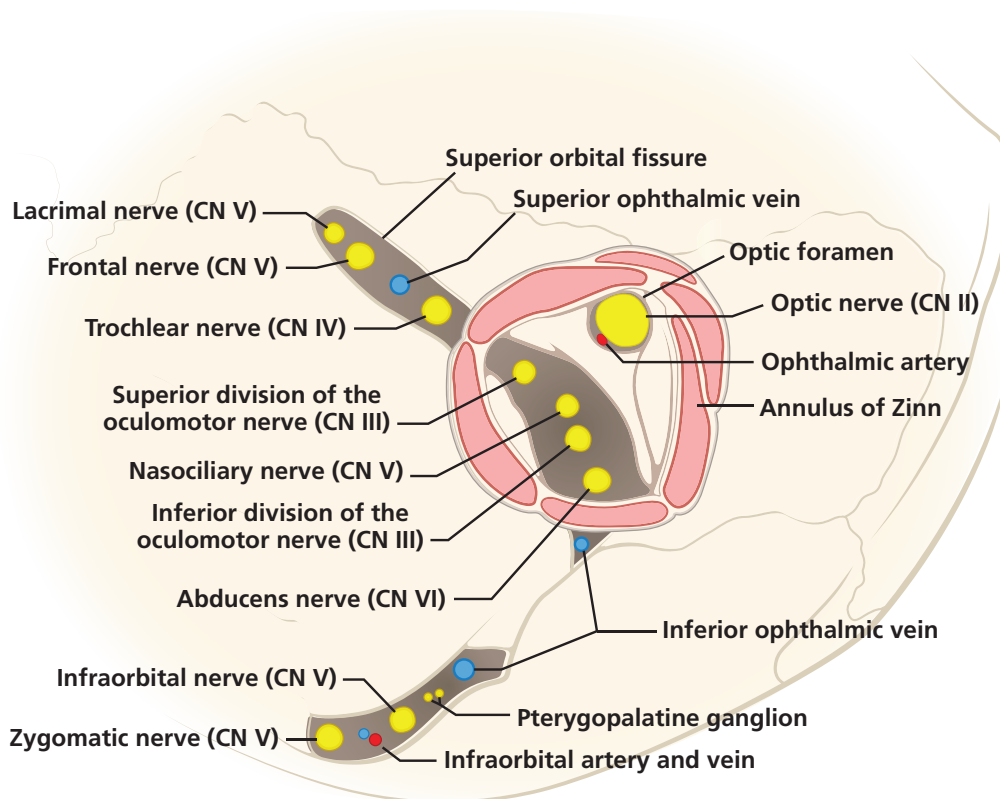


Figure 1. The anatomy of the orbital apex, the most posterior aspect of the orbit. The unilateral cranial nerve (CN) deficits in this patient point to disruption of structures of the orbital apex including the optic, oculomotor, trochlear, and abducens nerves. The optic foramen contains the optic nerve, ophthalmic artery, and associated sympathetic nerves. The nasociliary, frontal, and lacrimal branches of the ophthalmic nerve, superior ophthalmic vein, and cranial nerves III, IV, and VI pass through the superior orbital fissure.

The orbital apex is the posterior-most end of the orbit and comprises bony, neural, and vascular structures

formed but showed no evidence of active or healed arteritis. Magnetic resonance imaging (MRI) and computed tomography (CT) angiographic imaging of the head and neck were unremarkable.

The patient was discharged. The diagnosis of GCA was considered unlikely, but prednisone was continued out of concern for possible vision loss in the unaffected eye while other causes were being evaluated. Prednisone was up-titrated to 70 mg due to lack of symptom improvement, with no improvement in vision or headache severity reported.

The patient was referred to the ophthalmology department at a nearby large academic hospital for further workup. On presentation 1 month after his hospitalization, a variety of new signs and symptoms had developed. Ophthalmologic examination revealed right-sided ptosis, eyelid swelling, and chemosis (ie, swelling of the conjunctiva). The

right eye was unable to gaze superiorly, inferiorly, or laterally. Vision in the right eye was completely absent, with no light perception. The right pupil was nonreactive to light, and an afferent pupillary defect was present. The fundus appeared normal on dilated fundus examination. Intraocular pressures were 20 mm Hg (reference range 12–22 mm Hg) in both eyes. Tenderness to palpation was noted over the right eyebrow, temple, and forehead. All findings in the left eye were normal.

The patient was admitted for additional workup. Initial laboratory investigations revealed a white blood cell count of $10.47 \times 10^9/L$ (reference range $3.70\text{--}11.00 \times 10^9/L$) with 90.9% neutrophils, 5.9% lymphocytes, 3.1% monocytes, 0% eosinophils, and 0.1% basophils. A complete metabolic panel was within normal limits except for an elevated blood glucose level of 170 mg/dL (reference range 74–99 mg/dL), which was attributed

to steroid therapy. The ESR was 4 mm/hour (reference range < 30 mm/hour) and CRP was 0.15 mg/dL (reference range < 0.30 mg/dL).

Given the lack of response to prednisone, the normal ESR and CRP levels, and the negative temporal artery biopsy, the diagnosis of GCA was ruled out, and evaluation for other causes continued.

■ CRANIAL NERVE PATTERN PROVIDES CLUES

2 Involvement of the neural structures at which of these locations best explains the pattern of cranial nerve deficits seen on this patient's examination?

- Orbital apex
- Cavernous sinus
- Optic nerve
- Retina
- Superior orbital fissure

The pattern of neurologic deficits localizing unilaterally to cranial nerves II (optic), III (oculomotor), IV (trochlear), and VI (abducens) seen in this patient is most consistent with disruption of structures at the orbital apex.⁵ The orbital apex is the posterior-most end of the orbit and is made up of bony, neural, and vascular structures (**Figure 1**). Within the orbital apex are 2 orifices in the sphenoid bone:

- The optic foramen, which contains the optic nerve, the ophthalmic artery, and associated sympathetic nerves
- The superior orbital fissure, a bony cleft lateral to the optic foramen, through which pass the nasociliary, frontal, and lacrimal branches of the ophthalmic nerve (V_1 , ie, first division of cranial nerve V [trigeminal]), superior ophthalmic vein, and cranial nerves III, IV, and VI.

The annulus of Zinn is the common tendinous origin of the recti muscles and surrounds the optic foramen and the central portion of the superior orbital fissure. The contents of this annulus are the optic nerve, ophthalmic artery, oculomotor nerve, abducens nerve, and nasociliary nerve. Because of their confinement, these structures are at greater risk of compression or shear injury.⁶

The presence of multiple nerve palsies in this patient's presentation indicated that his

condition was unlikely due to a primary pathology at the retina or optic nerve.⁷ In addition, on dilated fundus examination there was no optic nerve pallor and no finding suggestive of central retinal artery occlusion or retinal detachment.

3 Which of these syndromes is most likely to cause optic nerve dysfunction?

- Orbital apex syndrome
- Cavernous sinus syndrome
- Superior orbital fissure syndrome
- Rochon-Duvigneaud syndrome

Orbital apex syndrome is the constellation of signs and symptoms resulting from a disease process affecting the orbital apex structures characterized by involvement of cranial nerves II, III, IV, VI, and V_1 . The most common presenting features are vision loss, ophthalmoplegia, and blurred vision.^{8,9} Involvement of the oculomotor, abducens, and trochlear nerves causes ophthalmoplegia and diplopia owing to disruption of innervation to the extraocular muscles. Oculomotor nerve palsy also causes ipsilateral ptosis and mydriasis. Involvement of cranial nerve V_1 results in hypoesthesia or pain of the ipsilateral forehead and upper eyelid, along with absence of corneal reflex and sensation. Inflammation due to infectious, inflammatory, or neoplastic processes may cause proptosis. Variations in presentation of orbital apex syndrome are common owing to the large number of structures involved.

Due to close anatomic proximity, overlapping clinical features are found in two additional syndromes: cavernous sinus syndrome and superior orbital fissure syndrome (also known as Rochon-Duvigneaud syndrome).⁸⁻¹¹ The names of these three syndromes correlate with the anatomic location of their disease processes.

Cavernous sinus syndrome presents similarly to orbital apex syndrome but also involves the maxillary nerve (V_2). This results in hypoesthesia of the cheek and lower eyelid, along with facial pain extending farther inferiorly than the periorbital region innervated by the ophthalmic branch.¹⁰ On examination, the most useful distinction between cavernous sinus syndrome and orbital apex syndrome is involvement of the optic nerve, which is rare

Possible causes of orbital apex syndrome are numerous and varied

in cavernous sinus syndrome.¹¹ Also of note, cavernous sinus syndrome may cause Horner syndrome (manifested by ptosis, miosis, and anhidrosis) due to the involvement of the sympathetic chain adjacent to the cavernous segment of the internal carotid artery. Vascular etiologies of cavernous sinus syndrome are classically associated with a pulsatile proptosis.⁸

Superior orbital fissure syndrome occurs with a lesion directly anterior to the orbital apex, affecting structures coursing through the superior orbital fissure at this location. The presentation is similar to that of orbital apex syndrome but without optic nerve impairment. Superior orbital fissure syndrome can be progressive, and patients may go on to develop orbital apex syndrome or cavernous sinus syndrome.⁸

EVALUATING THE CAUSE OF ORBITAL APEX SYNDROME

Possible causes of orbital apex syndrome are numerous and varied (Table 1)^{8,10} In the absence of recent surgery or trauma, inflammatory, infectious, vascular, and neoplastic etiologies must be considered.

Tolosa-Hunt syndrome is a common inflammatory cause of orbital apex syndrome. It presents with periorbital pain and limited eye movements, most often unilaterally.

Immunoglobulin G4-related disease is a systemic inflammatory condition that can include salivary gland enlargement, lymphadenopathy, retroperitoneal fibrosis, and pancreatitis. Ocular involvement most commonly includes chronic lid swelling and proptosis, but may include visual disturbances from orbital apex syndrome.¹²

Both Tolosa-Hunt syndrome and immunoglobulin G4-related disease have characteristic findings on neuroimaging and generally respond to steroids.

Vasculitides associated with antineutrophil cytoplasmic antibody (ANCA) (eg, granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis) generally present with pulmonary, gastrointestinal, and neurological involvement but can also have ocular involvement like orbital apex syndrome, as well as corneal ulceration, episcleritis, scleritis, and

TABLE 1

Causes of orbital apex syndrome

Inflammatory

Sarcoidosis, systemic lupus erythematosus, antineutrophil cytoplasmic antibody vasculitis (granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, microscopic polyangiitis), Tolosa-Hunt syndrome, giant cell arteritis, orbital inflammatory pseudotumor, thyroid orbitopathy, immunoglobulin G4-related disease

Infectious

Fungi: Aspergillosis, mucormycosis

Bacteria: *Streptococcus* species, *Staphylococcus* species, *Actinomyces* species, gram-negative bacilli, anaerobes, *Mycobacterium tuberculosis*

Spirochetes: *Treponema pallidum*

Viruses: Herpes zoster ophthalmicus

Neoplastic

Head and neck tumors: nasopharyngeal carcinoma, adenoid cystic carcinoma, squamous cell carcinoma

Neural tumors: neurofibroma, meningioma, ciliary neurinoma, schwannoma

Metastases: lung, breast, renal cell, malignant melanoma

Hematologic: non-Hodgkin lymphoma, leukemia

Perineural invasion of cutaneous malignancy

Iatrogenic

Sinonasal surgery, orbital-facial surgery

Traumatic

Orbital apex fracture, retained foreign body, penetrating or nonpenetrating injury

Vascular

Carotid cavernous aneurysm, carotid cavernous fistula, cavernous sinus thrombosis, sickle cell anemia

Other

Mucocele

Adapted from reference 8.

retinal vascular occlusion.

Sarcoidosis is a granulomatous inflammatory disease that primarily affects the lungs. The most common ocular involvement of sarcoidosis is anterior uveitis, although cases of sarcoid granulomas eroding into the orbital apex have been reported.¹³

Because immunosuppressive therapy is indicated for inflammatory causes, infectious etiologies should first be considered so as not to exacerbate them with treatment.

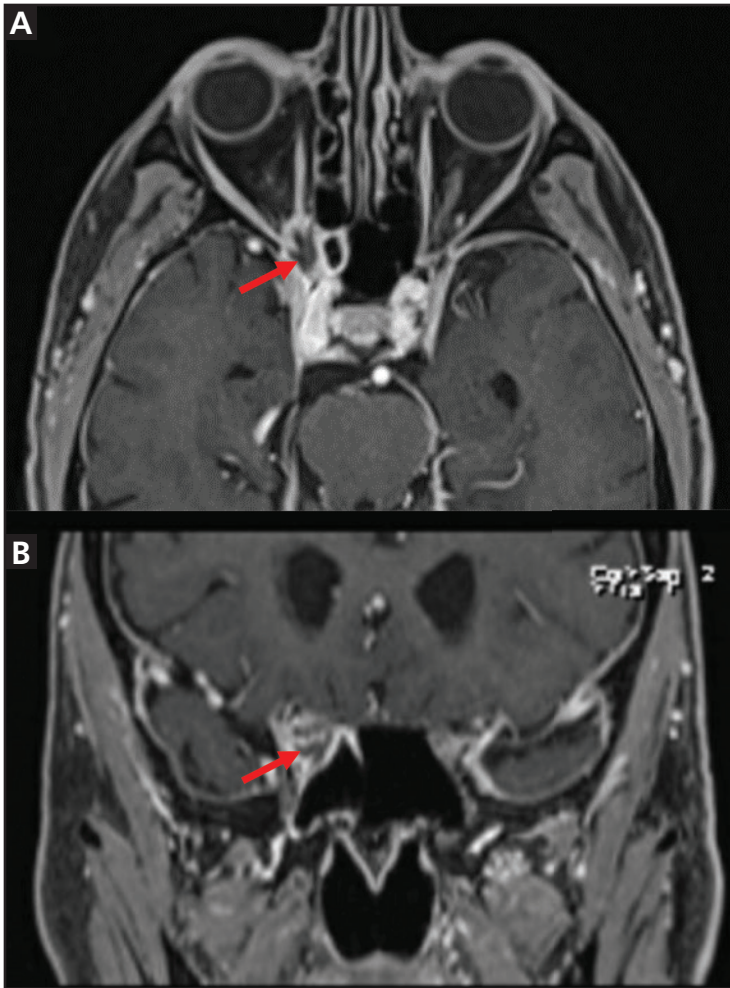


Figure 2. Magnetic resonance imaging of the orbit showed lesions (arrows) in axial T1-weighted fat-suppressed series (A) and coronal multiplanar reformation (B) views.

Bacterial and fungal infections of the paranasal sinuses can spread to the contiguous orbital apex. Fungal infections are primarily found in immunocompromised patients.

Neoplastic etiologies include meningeal infiltration of leukemia or lymphoma, as well as nasopharyngeal carcinoma, which portends a poor prognosis.¹⁴

■ **CASE CONTINUED: FURTHER EVALUATION**

A serologic vasculitis workup including ANCA, antinuclear antibodies, and double-stranded DNA antibodies was negative. Human immunodeficiency virus testing was negative. Lumbar puncture was performed to evaluate for evidence of inflammatory, infec-

tious, and neoplastic processes in the central nervous system. Cerebrospinal fluid analysis showed no white blood cells, normal protein, elevated glucose (122 mg/dL, reference range 45–80 mg/dL), and no growth on cultures.

■ **IMAGING THE ORBITAL APEX**

4 What is the preferred imaging method for evaluating lesions of the orbital apex?

- MRI
- CT
- Ultrasonography
- Radiography

High-resolution MRI with and without contrast is preferred for evaluating most lesions of the orbital apex.⁸ MRI provides superior soft-tissue contrast compared with other imaging methods, and orbital fat suppression can also improve lesion visibility.¹⁵ A short-tau inversion recovery image or T2-weighted fat-suppressed series can be included to evaluate for inflammatory edema and purulent fluid collections.¹⁶

CT is useful for evaluating bone involvement at the orbital apex, especially in the setting of trauma.¹⁰ It is also used for patients with magnetic foreign bodies, surgical clips, or other MRI contraindications.

■ **CASE CONTINUED: DIAGNOSTIC IMAGING AND BIOPSY**

Brain MRI revealed an irregularly shaped lesion with peripheral enhancement and a central nonenhancing region just inferior to the right optic nerve at the orbital apex (**Figure 2**). It was thought that this finding might represent a small abscess or area of necrosis. Scattered paranasal sinus mucosal thickening and increasing asymmetric enlargement of the right anterior cavernous sinus relative to previous images were also noted.

Sinus CT showed corresponding heterogeneous soft tissue at the right orbital apex with smooth bony remodeling and subtle erosive changes, raising suspicion for a neoplasm, infection, or an inflammatory entity. There appeared to be thinning and convexity of the right sphenoid sinus roof in addition to erosion of the right optic strut and along the inferior margin of the right anterior clinoid process.

An endoscopic transnasal intracranial biopsy was performed. An incision made within the right orbital apex inferior to the optic nerve returned purulent material. Frozen sections from the right orbital apex were negative for neoplasm but showed invasive fungal hyphae within fragments of fibrous tissue with focal necrosis. On Grocott-Gomori methenamine silver stain, the organism morphologically resembled aspergillus species. *Aspergillus fumigatus* was confirmed by fungal culture.

The patient was then diagnosed with invasive orbital aspergillosis with involvement of the orbital apex and cavernous sinus.

■ ORBITAL FUNGAL INFECTIONS

5 Which pair of organisms most commonly cause orbital mycoses?

- Aspergillus* and *Mucor*
- Mucor* and *Candida*
- Aspergillus* and *Candida*
- Candida* and *Fusarium*

Aspergillosis and mucormycosis are the most common causes of orbital fungal infections.¹⁷

Candida species are the most common etiologic pathogens of keratitis. *Fusarium* species are also one of the predominant causes of corneal fungal infections and are the most likely fungal pathogen to cause infection following eye trauma.¹⁸

Orbital mycoses are most often a result of contiguous spread from the paranasal sinuses.¹⁰

Rhizopus species are the most common cause of mucormycosis, which is classically associated with diabetes.^{19,20}

Orbital aspergillosis

A flavus and *A fumigatus* are the most common species of aspergillus that affect the orbit.²¹ Orbital aspergillosis presents in invasive and noninvasive forms.

Noninvasive aspergillosis typically does not display fungal infiltration of tissue but can produce a thick material known as allergic mucin along with extramucosal mycotic proliferations known as fungus balls, which are seen primarily in patients who are immunocompetent. If located in the posterior sphenoid or ethmoid sinus, a large fungus ball may

compress the optic nerve and cause vision loss and even orbital apex syndrome.²²

Invasive aspergillosis is characterized by bone invasion and fungal tissue that behaves similarly to an inflammatory or malignant process.²³ Locally, there is invasion of nearby structures and blood vessels, causing thrombosis and tissue necrosis. In the fulminant form of invasive aspergillosis, there is embolization and multiorgan involvement, potentially leading to death.²¹ Risk factors for invasive aspergillosis include total neutrophil count of less than 1,000/mm³, T-cell defects (eg, from human immunodeficiency virus), defective phagocytosis, hematologic malignancy, immunosuppressive agents, diabetes mellitus, prosthetic devices, trauma, excessive environmental exposure, residence in an endemic area (eg, Sudan), and advanced age.²⁰ While incidence of invasive disease is much greater in immunocompromised patients, cases have also been reported in immunocompetent hosts.^{21–30}

■ TREATING INVASIVE ASPERGILLOSIS

6 Which antifungal medication is preferred for the initial treatment of invasive aspergillosis?

- Amphotericin B deoxycholate
- Voriconazole
- Isavuconazole
- Echinocandins

The Infectious Diseases Society of America 2016 update of practice guidelines for diagnosis and management of aspergillosis recommends voriconazole for initial medical therapy for invasive sinus aspergillosis.³⁰ For patients who are intolerant to voriconazole, the best alternative is a lipid formulation of amphotericin B or isavuconazole. Treatment is recommended for a minimum of 6 to 12 weeks, depending on the degree of immunosuppression, infection location, and evidence of improvement.

Lipid formulations of amphotericin B are less likely to cause nephrotoxicity compared with amphotericin B deoxycholate. Amphotericin B deoxycholate is not recommended for use in invasive aspergillosis unless lipid formulations of amphotericin or other mold-active antifungals (such as voriconazole) are

High-resolution MRI with and without contrast is preferred for evaluating most lesions of the orbital apex

unavailable.³⁰ Hyperbaric oxygen and retrobulbar amphotericin B injections are less commonly used to treat orbital mycoses, but there is some evidence for their viability.^{31–33} Retrobulbar injections may be useful if aggressive orbital debridement is not favored or if the burden of orbital disease is not substantial.³³

In general, combination therapy is not recommended, but the use of voriconazole with an echinocandin may be considered for patients with severe disease, hematologic malignancy, or profound persistent neutropenia.³⁰

In addition to medical therapy, surgical debridement is usually required and may involve exenteration (ie, surgical removal of the entire globe and surrounding structures) in cases of orbital apex involvement.^{22,30}

PROGNOSIS

Invasive aspergillosis carries a significantly worse prognosis than the noninvasive form. Invasion of bone and blood vessels makes surgical access and drug penetration challenging and allows the fungus to spread intracranially. The reported mortality rate associated with invasive aspergillosis is 40%, rising to 50% when there is central nervous system involvement.³⁴

Prognosis is often worsened by initial misdiagnosis owing to presenting features that are largely nonspecific. Initial administration of corticosteroids is also associated with a poorer prognosis as a result of iatrogenic potentiation of the infection.¹⁷

CASE CONCLUSION

The patient was started on voriconazole and tapered off prednisone. CT of the chest was performed to investigate the lungs for additional areas of infection and was negative. Oculoplastic surgery was consulted regarding the benefit of right orbital exenteration. Because the infection had already spread to the cavernous sinus, it was determined that exenteration would not improve survival and was therefore deferred.

Three weeks after discharge, the patient continued to experience retro-orbital headaches but rated the pain as 1/10 instead of 10/10, as he had consistently rated it before treatment. His right-sided ptosis was slightly

improved, but his right eye blindness, afferent pupillary defect, and complete loss of extraocular movements persisted.

TAKE-HOME POINTS

- Suspected GCA should be treated immediately with glucocorticoids, but lack of improvement, negative temporal artery biopsy, and normal ESR and CRP should prompt investigation of an alternative diagnosis.
- The orbital apex is the posterior-most end of the orbit and contains bony, neural, and vascular structures.
- Orbital apex syndrome is characterized by involvement of cranial nerves II, III, IV, VI, and V₁.
- Cavernous sinus syndrome and superior orbital fissure syndrome present similarly to orbital apex syndrome; specific cranial nerve palsies can help differentiate them on physical examination.
- Etiologies of orbital apex syndrome are numerous but fit into these main categories: inflammatory, infectious, neoplastic, iatrogenic, traumatic, and vascular.
- MRI is the best imaging method for visualizing the orbital apex, but CT is useful when examining bone involvement or if the patient has MRI contraindications.
- Orbital mycoses are most often a result of contiguous spread from the paranasal sinuses and are most commonly caused by aspergillosis or mucormycosis.
- Patients with immunodeficiency are at much greater risk of contracting invasive aspergillosis, which carries a significant risk of mortality that further increases with central nervous system involvement.
- Treatment of invasive aspergillosis involves a combination of antifungal management and surgical debridement.
- Voriconazole monotherapy is the preferred initial medical therapy for invasive sinus aspergillosis, with isavuconazole or lipid formulations of amphotericin B being viable alternatives. ■

DISCLOSURES

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Voriconazole monotherapy is the preferred initial medical therapy for invasive sinus aspergillosis

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REVIEW

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Stress testing and noninvasive coronary imaging: What's the best test for my patient?

ABSTRACT

Coronary artery disease (CAD) causes significant morbidity and mortality. Accurate noninvasive evaluation is important to facilitate appropriate diagnosis and treatment. The ubiquitous nature of CAD requires all practitioners, regardless of their specialty, to be familiar with noninvasive diagnostic modalities. This article reviews currently available tests, including specific features, diagnostic and prognostic value, strengths, and limitations.

KEY POINTS

Noninvasive cardiac imaging (stress testing or anatomic evaluation) is warranted in patients who present with symptoms suspected to be cardiac, and in asymptomatic patients in clinical scenarios in which possible CAD needs to be assessed or excluded.

Patients with symptoms and low to intermediate pretest probability for CAD are ideal candidates for electrocardiography exercise stress testing, stress echocardiography, or coronary computed tomography angiography.

Myocardial perfusion imaging is particularly useful in patients with known underlying CAD to determine if ischemia is present, and positron emission tomography stress imaging provides greater accuracy in those who are obese.

CORONARY ARTERY DISEASE (CAD) is the leading cause of death in both men and women in the United States.¹ Its diagnosis and risk stratification are an important aspect of medical care for all practitioners, regardless of specialty.

Coronary catheterization has been the technical standard for the diagnosis of CAD and is the recommended pathway for patients who are at high risk or who present with acute coronary syndrome.^{2,3} However, given that chest pain and anginal-equivalent symptoms are frequent in patients presenting to community clinics and emergency rooms and on inpatient wards, many practitioners need the skills and knowledge to conduct cardiac risk evaluation.

Noninvasive testing is often used to categorize patients as being at lower risk or having noncardiac chest pain vs those who are likely to have ischemia or obstructive CAD, which may require invasive coronary catheterization for further evaluation or intervention.

Testing for CAD may be functional or anatomic (Table 1). In this article, we review what each test measures, its specific features, diagnostic and prognostic value, clinical utility, and limitations. These considerations help practitioners select the best test for a patient in a given setting or provide answers to a specific clinical question.

■ CORONARY ARTERY DISEASE

CAD is an inflammatory pathologic process that starts as fatty streaks in the intimal layers of coronary arteries, then progresses to nonobstructive and then obstructive atherosclerotic

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plaques. The process is driven by genetic and environmental cardiovascular risk factors.⁴ Ischemia occurs when coronary atherosclerotic plaque becomes severely stenotic or obstructive (generally if stenosis is $\geq 50\%$ in the left main coronary artery and $\geq 70\%$ in the other epicardial coronary arteries), and it may be associated with symptoms of angina or dyspnea.⁴

Moderate stenosis (50%–70%) may also cause ischemia and anginal-equivalent symptoms due to lesion characteristics such as location and length of plaque, presence of endothelial dysfunction, and presence of microvascular disease.⁵ Both obstructive and nonobstructive coronary stenosis may be complicated by acute plaque rupture and thrombosis, leading to acute loss of blood flow to the myocardium and myocardial infarction.⁴

Clinical scores incorporate variables such as age, sex, cardiovascular risk factors (hypertension, hyperlipidemia, diabetes, history of smoking, family history of CAD), changes on electrocardiography (ECG), cardiac enzyme levels, and symptoms. These scores help determine if patients have a low, intermediate, or high pretest probability of CAD.^{2,3,6}

Chest pain may be classified as noncardiac, atypical angina, and typical angina. Women and patients with diabetes may present without chest pain but with anginal-equivalent symptoms such as shortness of breath on exertion or arm pain, or they may also have silent ischemia.

Patients presenting with the acute coronary syndrome, high pretest probability of CAD, or concerning clinical features proceed straight to invasive coronary angiography. Noninvasive imaging (stress testing or anatomical evaluation) is warranted in those who present with symptoms that are suspected to be cardiac, particularly if the patient has an increased pretest probability of CAD.

Table 2 lists the common indications for stress testing and coronary computed tomography (CT) angiography.^{3,7–10}

■ ELECTROCARDIOGRAPHY EXERCISE STRESS TESTING

Test features

ECG exercise stress testing is the workhorse in community and hospital practices as an initial functional test to evaluate chest pain and sus-

TABLE 1

Testing for coronary artery disease

Functional	Electrocardiography exercise stress test
	Stress echocardiography
	Nuclear medicine myocardial perfusion imaging techniques
	Single-photon emission computed tomography
	Positron emission tomography
	Cardiac magnetic resonance imaging with stress perfusion
Anatomic	Coronary computed tomography angiography
	Invasive coronary catheterization

pected CAD. Patients with low or intermediate pretest probability for CAD are ideal candidates for ECG exercise stress testing.¹¹

The Bruce protocol is the most commonly used format. It starts the patient on a treadmill at a speed of 1.7 miles per hour and a 10% incline. Every 3 minutes, the speed and angle of incline are increased.

Standard 12-lead ECG is used. If motion artifact occurs, moving the extremity electrodes to the torso and ensuring good electrode contact with the skin (eg, shaving if required) may help.

Baseline ECG is taken before starting. The stress test continues until the patient is fatigued and asks to stop or develops cardiac symptoms, significant ECG changes, or other high-risk features.

An ECG stress test is considered diagnostic if the patient achieves at least 85% of the maximum age-predicted heart rate. If a test is terminated before achieving this threshold because of positive findings but the results meet the ECG criteria for ischemia, then the results are still considered positive for ischemia. However, if a test is terminated before achieving 85% of the predicted heart rate and there are no ECG changes, it is considered nondiagnostic as it is not known whether ischemic changes would have occurred if the patient had continued to the required workload.

Diagnostic and prognostic features

An ECG stress test is considered positive for ischemia if there is at least a 1-mm horizontal or down-sloping ST-segment depression. Up-sloping ST-segment depression is not considered a positive finding. An ST-segment elevation greater than 1 mm is highly suggestive of significant ischemia.

An ECG stress test is positive for ischemia if there is at least a 1-mm horizontal or down-sloping ST-segment depression

TABLE 2

Common indications for stress testing and coronary computed tomography angiography

Assessment for coronary artery disease

- Angina or anginal equivalent symptoms and negative cardiac enzymes
- Atypical symptoms in patients with diabetes or with high probability of diabetes
- New diagnosis of cardiomyopathy (to define whether the cause is ischemic or nonischemic)
- New or increasing heart failure symptoms despite adherence to medical therapy
- Re-evaluation of known heart failure (systolic or diastolic) in patients with a change in clinical status without a clear precipitating change in medication or diet
- Arrhythmias such as ventricular tachycardia or atrial fibrillation (to exclude ischemia as the cause) or new left bundle-branch block
- To exclude severe ischemia prior to noncardiac surgery in those with increased coronary artery disease risks, angina symptoms, or poor exercise capacity (< 4 metabolic equivalents)
- To define presence or absence of ischemia in those with moderate coronary stenosis (stress test or fractional flow reserve-computed tomography)
- Evaluation of anomalous coronary arteries

Stress testing for indications other than coronary artery disease assessment

- Valve assessment
 - Mitral valve stenosis or regurgitation severity (exercise stress echocardiography)
 - Low-flow low gradient aortic stenosis (dobutamine stress echocardiography)
- Exercise-induced pulmonary hypertension or diastolic dysfunction (exercise stress echocardiography)
- Hypertrophic cardiomyopathy to demonstrate provokable left ventricular outflow tract obstruction (exercise stress echocardiography)
- Exercise-induced arrhythmia or chronotropic incompetence (exercise stress echocardiography)
- To define cardiopulmonary disease and aerobic exercise capacity (metabolic stress test)

Data from references 3 and 7–10.

Functional capacity is the strongest prognostic marker of an ECG stress test

A meta-analysis of 24,074 patients in 147 studies found that ECG stress testing for detecting CAD has a sensitivity of 68% and specificity of 77%.¹² The Coronary Artery Surgery Study database suggested that the development of ST depression and functional capacity (duration of exercise) are the 2 most prognostic markers.¹³

Functional capacity is the strongest prognostic marker of an ECG stress test.^{7,14} It is estimated by metabolic equivalents (METs), which approximate oxygen uptake during exercise, with 1 MET representing 3.5 mL/kg/min. Laboratories estimate functional capacity from exercise duration in a specific exer-

cise protocol based on published nomograms. Prognostic markers from an ECG stress test are shown in **Table 3**.^{7,13–19}

The Duke treadmill score²⁰ is reported by many laboratories and predicts 5-year mortality risk in patients without known CAD. It incorporates variables that include degree of ST change and symptoms, with lower scores associated with higher mortality and increased likelihood of significant CAD.²⁰

Limitations

An ECG stress test result positive for ischemia usually has ST-segment depressions mostly in the inferior and precordial leads, and it may

TABLE 3

Prognostic indicators on electrocardiography stress testing

Indicator	Comments
Functional capacity	Strongest prognostic indicator, reported as metabolic equivalents. ^{7,14}
ST-segment depression or elevation	> 1-mm ST deviation is suggestive of ischemia. ¹³
Exercise-induced hypotension	Defined as systolic blood pressure that is lower during exercise than while standing at rest before exercise, reflecting failure of cardiac output to increase during exercise. Associated with severe coronary artery disease or left ventricular systolic dysfunction. ¹⁵
Chronotropic incompetence	Failure of heart rate to increase as expected during exercise, defined as achieving < 80% of predicted heart rate (or < 62% for patients taking beta-blockers). ¹⁶ Associated with increased all-cause and cardiovascular mortality. ¹⁷
Impaired heart rate recovery	Heart rate fails to decrease normally after cessation of exercise. Predicts all-cause mortality and cardiovascular events, including sudden death. ¹⁸
Ventricular arrhythmia	Sustained ventricular tachycardia or ventricular fibrillation. Associated with significant coronary artery disease or left ventricular dysfunction. ¹⁹

not necessarily correspond to specific coronary artery territories.

An ECG stress test should not be used if any of the following abnormalities are found on ECG: complete left bundle-branch block or paced ventricular rhythm (limits interpretation of the test), pre-excitation syndrome, or greater than 1 mm of resting ST-segment depression.²¹ Pronounced left ventricular (LV) hypertrophy or use of digoxin therapy can affect stress-related results. Patients with impaired mobility such as amputees or those with severe arthritis may not be able to safely exercise on the treadmill or go long enough to complete a diagnostic test. False-positive results may be more frequent in women.

Many of these limitations can be overcome by adding an imaging component to the stress test or performing a pharmacologic stress test in those who cannot exercise.

■ STRESS ECHOCARDIOGRAPHY

Test features

Stress echocardiography uses imaging with echocardiography after exercise or pharma-

cologically induced stress to show coronary abnormalities. Ischemia is identified if there is a new or worsening regional wall-motion abnormality, which generally correlates with stenosis in the corresponding coronary territory. Stress echocardiography is most often used to diagnose CAD in patients in whom an ECG stress test would be contraindicated, uninterpretable, or nondiagnostic, or if their CAD risk is sufficient to warrant an imaging component to enhance the sensitivity and specificity of the test.

Images are typically obtained from standard views including the parasternal long-axis and short-axis views, and apical long-axis and apical 2- and 4-chamber views to show the wall motion in each of the LV walls before and after stress (**Figure 1**). Results are analyzed and scored using a 17-segment model of the LV (divided into apical, mid, and basal segments), with each segment graded on a 4-degree scale of regional wall-motion analysis (normokinesis, hypokinesis, dyskinesis, and akinesis).²²

On stress echocardiography, ischemia is identified if there is a new or worsening regional wall-motion abnormality

Intravenous (IV) echo contrast agents can be used to improve visualization of the endocardium if the image quality is suboptimal, particularly in patients with large body habitus or lung disease, or if more than 2 contiguous myocardial segments have poor endocardial definition. Echo contrast agents do not contain iodine and have been shown to improve the accuracy of the assessment of ventricular volume and ejection fraction, enhance recognition of wall-motion abnormalities, and improve reproducibility.²³

Stress echocardiography can be exercise-based on a treadmill or bicycle, or pharmacologically based with dobutamine infusion. Treadmill stress tests most often use the Bruce protocol.

It is important to obtain postexercise imaging as soon as possible after exercise stops, as regional wall-motion abnormalities that persist into recovery become less pronounced and resolve as the heart rate comes down.²² As such, the patient is moved immediately from the treadmill to the imaging bed in a left lateral decubitus position for poststress imaging.

Stress echocardiography using a bicycle (supine or upright), although less frequent, is quieter, which permits sensitive precordial measurements with less motion artifact and allows imaging while the patient is exercising at different stages during the stress test. When used, it is often for valvular or hemodynamic assessment.

Exercise stress echocardiography may allow for hemodynamic evaluation in addition to that for ischemia. Doppler assessment may be helpful in patients with dyspnea and suspected exercise-induced diastolic dysfunction or pulmonary hypertension²⁴ or in those with mitral valve stenosis or regurgitation that is clinically suspected to be more severe than a resting echocardiogram suggests. Stress echocardiography can also assess for dynamic LV outflow-tract obstruction in hypertrophic cardiomyopathy.

Pharmacologic stress echocardiography can assess for ischemia in patients who cannot exercise or can help define the severity of aortic stenosis, particularly when low-flow, low-gradient severe aortic stenosis is suspected. This is performed predominantly with dobutamine infusion, although it is possible to use di-

pyridamole or adenosine for ischemia testing. Dobutamine is a synthetic catecholamine that stimulates beta-1 adrenergic receptors causing a chronotropic effect (increase in heart rate) and an inotropic effect (increase in myocardial contractility), resulting in increased oxygen demand. The typical dobutamine stress protocol consists of continuous IV infusion of dobutamine in 3-minute increments, starting with 5 mg/kg/min and increasing to a maximum of 40 mg/kg/min.²⁵ Dobutamine may have an arrhythmogenic or hypertensive effect, and requires monitoring throughout. Patients with severe conduction disorders or advanced asthma or airway disease are not affected by dobutamine.

Diagnostic and prognostic features

Stress echocardiography results are reported by description of wall motion as normal, ischemic, viable, or scarred myocardium. Normal myocardium has normal motion of segments at rest, and after stress, all segments demonstrate either normal motion or hyperkinesia, with overall increase in ejection fraction. When the myocardium is ischemic, contractile function goes from normal to hypokinetic, akinetic, or dyskinetic after stress, in at least 2 adjacent segments for the test to be positive.²⁶ When myocardium is scarred (due to previous MI), resting dysfunction (hypokinesis or akinesis) remains fixed after stress.

The myocardium is considered viable when segments with resting hypokinesis show either a maintained improvement with stress (indicating the presence of “stunning”) or improvement during an early stress phase with subsequent deterioration in contractility at peak (ie, biphasic response), which portends potential improvement with revascularization.²⁷

Other features that may suggest significant ischemia are a decrease in LV ejection fraction after exercise (instead of an increase) or an increase in the LV cavity size after stress (expected to decrease as a result of increased contractility).

A meta-analysis has demonstrated that stress echocardiography with exercise, dobutamine, dipyridamole, and adenosine has a sensitivity of 83%, 81%, 72%, and 79%, respectively, and a specificity of 84%, 84%, 95%, and

On stress echocardiography, a decrease in LV ejection fraction after exercise or an increase in LV cavity size after stress can suggest significant ischemia

91%, respectively.²⁸ Stress echocardiography is generally considered more specific than nuclear perfusion imaging, although nuclear perfusion imaging is considered more sensitive.²⁹

A strength of stress echocardiography is improved diagnostic accuracy compared with stress ECG alone without ionizing radiation exposure. As such, it is often the preferred test for middle-aged women who may have symptoms and intermediate cardiovascular risk. It may also be desirable in patients who have dyspnea, in whom other hemodynamic evaluation can be done in the same test.

Stress echocardiography has prognostic value. A normal test with no regional wall-motion abnormalities confers a less than 1% per year cardiac event rate. Increasing severity of regional wall-motion abnormalities after peak stress corresponds to higher clinical event rates.⁸

Limitations

As with all imaging, interpretation of a stress echocardiogram may be affected by subjectivity. Thus, it is important to have good imaging protocols and quality acquisitions along with experienced practitioners to interpret the images. Stress echocardiography may miss mild ischemia that is due to small, distal, or branch-vessel disease, and it is considered slightly less sensitive than nuclear imaging.³⁰ Patients with obesity or emphysema may have poor acoustic windows, resulting in suboptimal images.

■ NUCLEAR MEDICINE MYOCARDIAL PERFUSION IMAGING

Test features

Nuclear myocardial perfusion imaging (MPI) may be performed by either single-photon emission CT (SPECT) or positron emission tomography (PET). As with stress echocardiography, MPI stress testing may be exercise or pharmacologically induced. MPI involves IV administration of radioactive tracers. A gamma camera detects radio emissions from the tracer that perfuses the myocardium. Tracer uptake depends on flow dynamics as well as myocyte membrane integrity. Color-coded images of myocardial perfusion pre- and post-stress are generated in different axes to allow assessment for each coronary distribution.³¹

The radioisotopes and cameras used in

PET and SPECT differ. PET generally uses rubidium or ammonia radionuclides for perfusion imaging, and fluorodeoxyglucose (FDG) may be used to assess myocardial viability and inflammation. SPECT scanners predominantly use technetium 99 (sestamibi) for perfusion imaging. Thallium has been phased out because of associated high radiation.

PET carries advantages over SPECT including superior image quality, due to more favorable tracer characteristics and count statistics. Positron-emitting radiotracers used in PET can produce higher-energy photons than those produced by SPECT radiotracers, resulting in less attenuation artifact. PET can also detect smaller and more subtle perfusion defects (typically 4–7 mm) owing to its higher spatial resolution than SPECT (typically 12–15 mm).³² Other advantages of PET over SPECT include a lower radiation burden and shorter scan time.

Stress MPI can be exercise-induced (using the treadmill Bruce protocol, which has the added value of providing functional capacity data that is prognostic) or pharmacologic for those unable to exercise. Vasodilators are the most frequently used stress agents, primarily regadenoson (which has a more favorable profile) or dipyridamole and adenosine. Vasodilators increase coronary blood flow through their effect on the adenosine A_{2A} receptor, which increases blood velocity and flow rate in normal vessels compared with a lesser response in stenotic vessels that are already maximally dilated, thus decreasing subendocardial flow to regions supplied by diseased vessels. Dobutamine infusion may also be used, although it is rare in MPI practice.

Diagnostic and prognostic features

MPI enables clinicians to assess the physiologic significance of coronary stenosis by measuring heterogeneity in coronary flow. The ability to maintain the maximum flow (“coronary flow reserve”) is impaired when there is more than 50% coronary stenosis.³³ Normal myocardial perfusion is shown by homogeneous radiotracer distribution on both stress and rest images. In general, perfusion defects in a coronary territory that occur after stress with normal flow at rest suggest inducible ischemia, whereas a fixed defect in perfusion both at rest

MPI enables clinicians to assess the physiologic significance of coronary stenosis by measuring heterogeneity in coronary flow

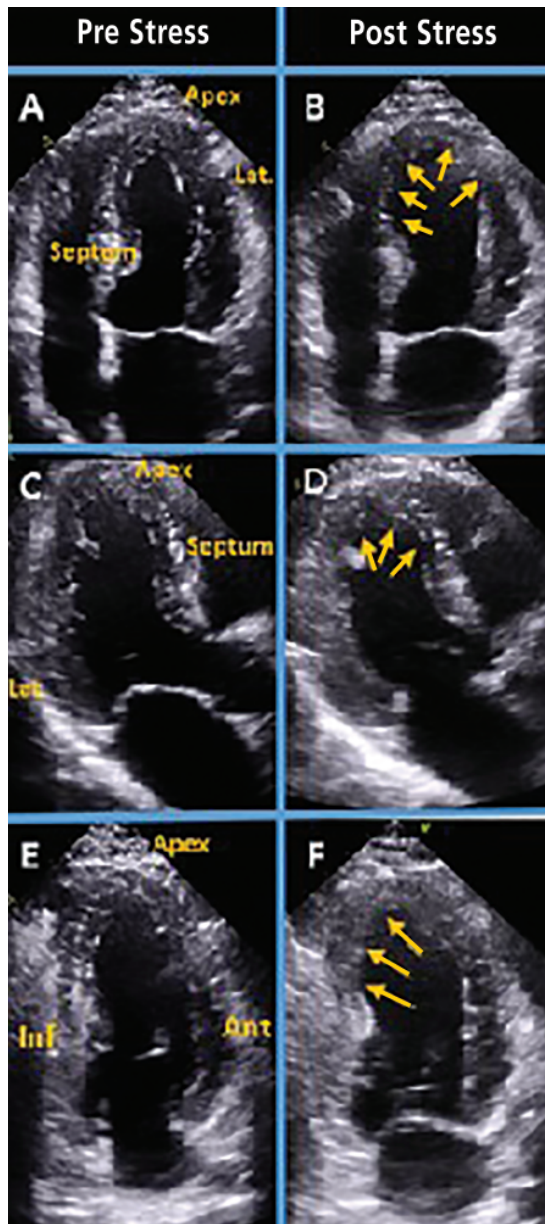


Figure 1. Stress echocardiogram from a 54-year-old woman with chest pain shows ischemia in the left anterior descending artery and right coronary artery territories. Panels A and B show the 4-chamber view before and after the stress test. On the poststress image (B), the arrows point to hypokinesis at the apex and distal septum; enlargement of left ventricular cavity suggests significant ischemia. In the long-axis view (C, D), arrows point to hypokinesis at the apex and distal septum. In the 2-chamber view (E, F), arrows point to hypokinesis on the mid and apical inferior wall.

and after stress in a coronary distribution suggests either scarred myocardium (from prior myocardial infarction) or hibernating myocardium (which may improve in function if revascularized).³⁴

MPI defects are generally reported with reference to the following:

- Defect size or extent: small (< 10% of LV myocardium affected), medium (10%–20% affected), or large (> 20% affected)
- Severity of perfusion defect (mild, moderate, severe)
- Extent of reversibility (reversible, irreversible)
- Location (based on 17-segment LV model and coronary artery territory).

Tomograms are also produced on MPI studies that estimate LV ejection fraction. The presence of transient ischemic dilation is a sign of severe ischemia. It refers to the enlargement of the LV poststress instead of decrease of cavity size as would be expected with increased contractility.

Myocardial blood flow and myocardial flow reserve offer a quantitative assessment of myocardial perfusion³⁵ and, in some cases, may help identify the presence of microvascular disease. Some centers routinely include these measures on clinical PET reports, and similar quantitative measures may also be available for SPECT in the future.

A systematic review reported sensitivity and specificity of SPECT for the diagnosis of CAD of 82% and 76%, respectively, and 91% and 89% for PET, with the difference accounted for by superior spatial resolution and attenuation correction of PET.³⁶ SPECT is considered more sensitive than stress echocardiography but less specific. PET is generally accepted as the most accurate noninvasive functional test for ischemia.

MPI provides clinically helpful prognostic information. For those with normal MPI results, the 2-year clinical event rate for cardiac death or myocardial infarction is less than 1%.³⁷ The presence of perfusion defects is prognostic for clinical myocardial infarction and mortality.

MPI is useful in symptomatic patients with suspected CAD to show the presence or absence of ischemia (**Figure 2**), as well as in those with known CAD to evaluate if stenosis is functionally significant. In addition,

Positron emission tomography is generally accepted as the most accurate noninvasive functional test for ischemia

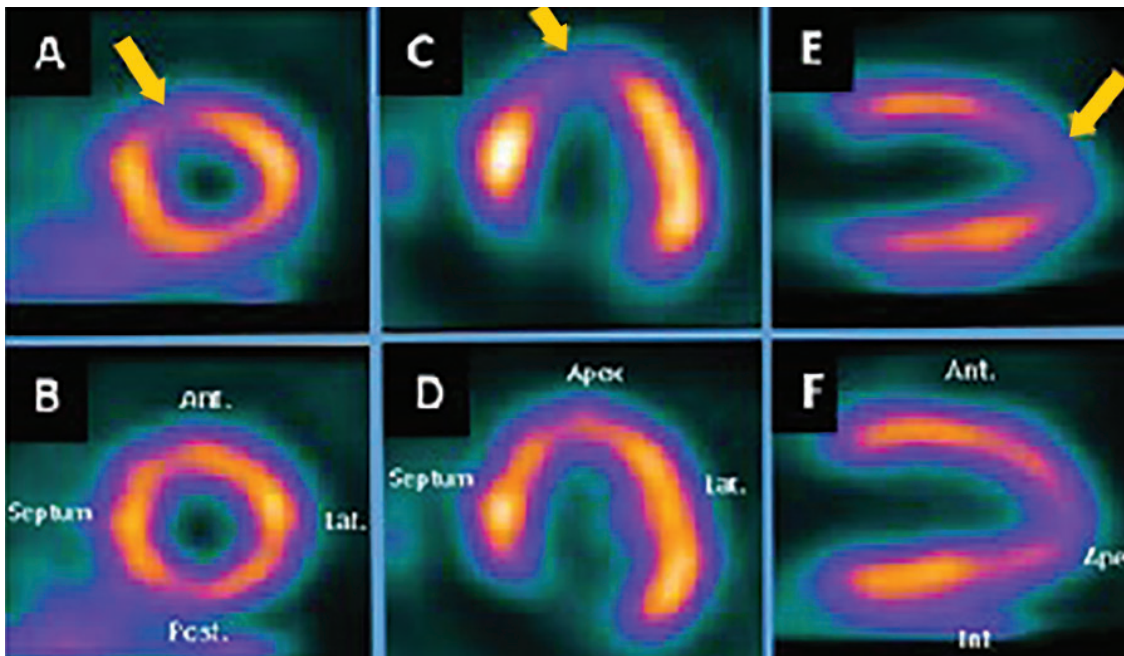


Figure 2. Single-photon emission CT myocardial perfusion imaging in a 62-year-old man with diabetes and a 2-month history of dyspnea shows moderate left anterior descending coronary artery ischemia. Panels A, C, and E are poststress images that show perfusion defects in the apex, apical septum, and apical anterior wall (arrows). Panels B, D, and F show relatively normal perfusion at rest at the corresponding levels.

those with impaired LV systolic function may also have viability concurrently assessed during MPI imaging, particularly with FDG-PET techniques, which may help guide revascularization decisions. Those with left bundle-branch block may be suitable candidates for regadenoson pharmacologically induced SPECT or PET (as an ECG exercise stress test would be nondiagnostic). For obese patients, PET MPI is the superior modality.

Limitations

MPI techniques involve radiation exposure, and there needs to be sufficient clinical value to justify testing. SPECT may be more prone to artifact from diaphragmatic attenuation or gut scatter that may result in false-positive results being identified in the inferior LV wall, particularly in patients who are obese. This is less of an issue with PET.

The main limitations for PET are higher cost and limited availability. Only healthcare facilities with an on-site cyclotron to produce isotopes daily (due to their short half-life) can offer PET imaging.³²

Finally, a normal result on MPI suggests the absence of obstructive CAD. However, it does not exclude mild to moderate atherosclerosis that may not be contributing to symptoms but nonetheless may warrant aggressive preventive measures. Identifying coronary calcium on CT scout images before an MPI may help flag for the presence of subclinical coronary atherosclerosis.

■ CORONARY CT ANGIOGRAPHY

Test features

Coronary CT angiography (CCTA) is an anatomic noninvasive modality that can identify and assess the severity of CAD. It differs from stress testing in that it directly visualizes the coronary arteries and can quantify the degree of stenosis and assess plaque characteristics (Figure 3). In contrast, stress testing assesses LV wall-motion abnormalities or perfusion defects to determine if obstructive CAD is present.

Adequate patient preparation is needed to enable high-quality image acquisition and improve accuracy. Ideally, the heart rate needs

Coronary CT angiography can identify and assess the severity of CAD by quantifying the degree of stenosis and assessing plaque characteristics

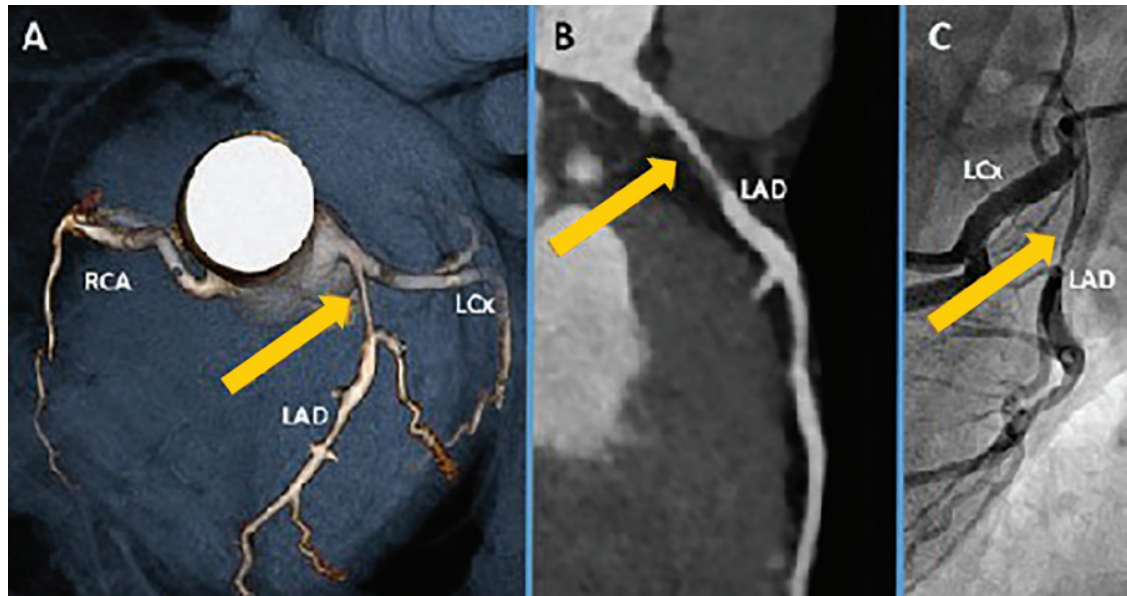


Figure 3. Coronary computed tomography angiography in a 40-year-old man who smoked and had a family history of premature coronary artery disease. Panel A is a 3-D rendering showing proximal left anterior descending (LAD) coronary artery stenosis (arrow). Panel B is a multiplanar reconstruction showing proximal LAD coronary artery stenosis with predominantly soft (lipid-laden) noncalcified plaque (arrow). Panel C shows the corresponding LAD lesion (arrow) on coronary catheterization.

LCx = left circumflex artery; RCA = right coronary artery

Coronary CT angiography can identify plaque features that suggest the plaque is more vulnerable to rupture

to be less than 60 beats per minute, although less than 70 beats per minute is acceptable on more advanced scanners. A beta-blocker or calcium channel blocker may be administered orally or intravenously to help achieve the target heart rate.

Sublingual nitroglycerin is given just before scanning to help dilate the coronary arteries and improve the image quality. Then an iodinated contrast agent is administered through an IV line in the cubital fossa, and CT images are acquired with ECG gating. To reduce radiation exposure, it is preferable to use a prospective acquisition protocol for CCTA scans in which images are obtained at a point in end diastole (or sometimes end systole) when cardiac and coronary motion is least, thus reducing motion artifact.

Diagnostic and prognostic features

Images are reconstructed and analyzed for the presence, degree, and location of coronary stenosis. Plaque composition (whether calcified, noncalcified, or mixed) and high-risk plaque features, if present, are also reported. The So-

ciety of Cardiovascular CT recommends using the CAD reporting and data system to standardize CCTA reports.³⁸ It categorizes coronary segments as having no stenosis, minimal (0%–24%), mild (25%–49%), moderate (50%–69%), or severe (70%–99%) stenosis, or total occlusion (100%).³⁸

High-risk plaque features include low Hounsfield unit attenuation (signifying more lipid-laden plaque), high plaque volume, positive remodeling (plaque extending outwards from the vessel wall and not just into the lumen), or spotty calcification within the plaque. These features suggest that plaque is more vulnerable to rupture and, thus, the patient has a greater likelihood of clinical events such as myocardial infarction.³⁹ These features are mandated for clinical reporting in the Society of Cardiovascular CT guidelines.³⁸

Numerous meta-analyses have confirmed the diagnostic accuracy of CCTA, including reported sensitivity of 99% and specificity of 89%.⁴⁰ As such, it has excellent negative predictive value and can accurately rule out CAD. The European Society of Cardiology 2019

guidelines give CCTA a class 1 indication to assess for (or rule out) CAD in symptomatic patients with low to intermediate cardiovascular risk, and a class IIa indication if functional testing is not diagnostic or is equivocal.³ UK guidelines recommend CCTA as first-line testing for evaluating stable chest pain.⁴¹

CCTA results are prognostic. Patients with obstructive CAD identified by CCTA have worse outcomes than those with nonobstructive CAD,⁴² who, in turn, have a higher clinical event rate than those without CAD. CCTA is useful clinically, as it may identify patients with nonobstructive CAD (such as 50% stenosis), which a stress test would call normal, as nonobstructive lesions are not flow-limiting.

In addition, identification of nonobstructive CAD by CCTA offers an opportunity for aggressive risk factor modification, including statin therapy.⁴³ CCTA can be also used for the assessment of coronary artery bypass graft patency, and is excellent in the assessment of suspected anomalous coronary arteries.

Although CCTA is predominately used for anatomic coronary assessment, techniques such as fractional flow reserve CT (FFR-CT) and stress perfusion imaging by CT are now available to determine the functional significance of a moderate coronary lesion (eg, whether a 50% to 70% stenosis on CT is flow-limiting or nonobstructive). FFR-CT has additional costs, and the images are sent off-site for analysis. In addition, CT perfusion requires higher radiation and contrast doses and longer scan time, limiting its widespread adoption.

Another advance is surrogate imaging markers for inflammation such as attenuation in coronary perivascular fat on CCTA, which may be predictive of cardiac mortality and thus may play a clinical role in prevention.⁴⁴ Anticipated developments in artificial intelligence and radiomic assessment are expected to enhance automated image evaluation and quantitative assessment of CCTA, with improvements in workflow and diagnostic accuracy.⁴⁵ These are expected to have a significant impact on clinical practice.

Limitations

CCTA involves exposure to ionizing radiation. It requires an iodinated contrast agent, which needs premedication in patients with

iodine allergy. And its use is limited in those with renal insufficiency.

CCTA is generally less useful for evaluating coronary stents because of blooming artifact from the metal struts, limiting its ability to assess for in-stent restenosis unless the stent is large in caliber.

Arrhythmias, including atrial fibrillation and ectopy, make it more difficult to obtain a quality image, requiring adjustment of protocols. More rapid heart rate also reduces image quality.

Heavy calcification can result in segments being uninterpretable for stenosis, potentially limiting the utility of CCTA in elderly or dialysis patients. Patients unable to adequately hold their breath would not be suited for CCTA.

■ CORONARY ARTERY CALCIUM SCORE

Test features

A coronary artery calcium (CAC) score is widely accepted and used for CAD risk stratification in *asymptomatic* patients. It is a surrogate marker for the presence and the burden of CAD as it quantifies coronary calcification and, hence, the extent of atherosclerotic disease. It involves rapid CT scan acquisition without contrast, with the field of view focused on the heart. Axial slices with 3-mm thickness are acquired prospectively with ECG gating in mid to late diastole. The CAC Agatston score takes into account the amount and density of calcium, with more than 130 Hounsfield units or at least 3 adjacent voxels needed to generate a numeric score.⁴⁶

Diagnostic and prognostic features

There are strong data to support the prognostic value of CAC, and it enhances risk stratification incremental to traditional clinical cardiovascular risk factors.⁴⁷ In absolute terms, a calcium score of 0 is associated with excellent prognosis; scores in categories of 1 to 99, 100 to 299, and 300 and above are associated with respective increased risks of mortality.⁴⁷ However, risk prediction is often reported as a percentile with adjustment for age, sex, and ethnicity.

The CAC score may be useful in the clinical decision-making process for patients who are asymptomatic with borderline (5%–7.5%) or intermediate (7.5%–20%) 10-year risk ac-

A coronary artery calcium score is used for CAD risk stratification in asymptomatic patients

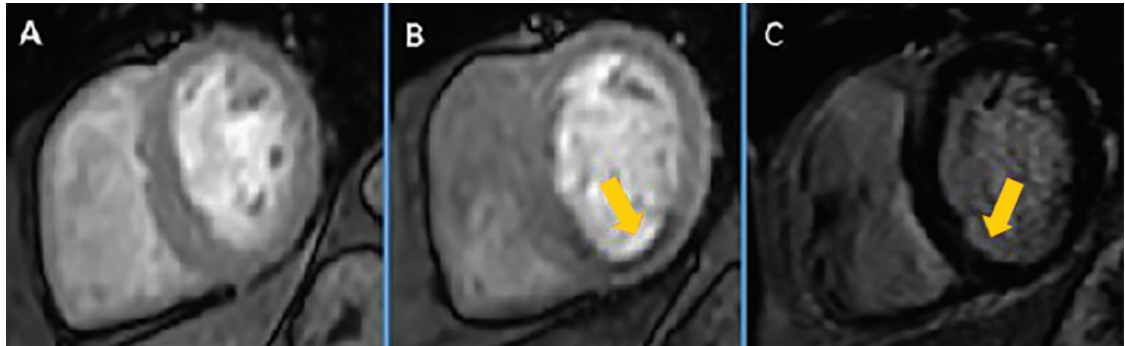


Figure 4. Stress cardiac magnetic resonance imaging in a 67-year-old woman with diabetes and chest pain shows normal perfusion at rest (A). Panel B shows a poststress image with a perfusion defect in the inferior and inferoseptal segments (arrow), suggestive of ischemia in the right coronary artery territory. Panel C is a delayed gadolinium-enhanced image showing mild subendocardial enhancement (arrow) in the corresponding region, consistent with a small area of scar.

Stress cardiac MRI compares favorably with established noninvasive tests in terms of accuracy for detecting CAD

cording to the atherosclerotic cardiovascular disease (ASCVD) risk calculator, and in whom the benefit of a statin is in question.⁶ The 2019 American College of Cardiology/American Heart Association guidelines recommend initiating a statin in patients with diabetes or in those age 40 to 75 with an ASCVD risk above 7.5% over 10 years.⁶ In this latter group, the CAC score may be used to re-stratify the risk either up or down and better guide statin initiation. For example, a patient with borderline or intermediate ASCVD risk and a CAC score of 0 would not be started on a statin. However, if the CAC score were above 100 (or \geq 75th percentile for age/sex/race), then the risk would be re-stratified up, clearly defining a patient who would benefit from a statin.⁶

Limitations

It must be stressed that although the CAC score has use in prognostication in asymptomatic patients, if anginal-equivalent symptoms are being evaluated, then the CAC score has no role as it cannot determine whether a calcified coronary plaque is stenotic, and other tests would need to be considered.

■ STRESS CARDIAC MAGNETIC RESONANCE IMAGING

Test features

Stress cardiac magnetic resonance imaging (MRI) is a promising modality, with advantages such as good spatial and temporal resolu-

tion, wide field of view, and ability to acquire images in different planes.⁴⁸ It uses gadolinium contrast rather than iodinated contrast and does not use ionizing radiation. MRI perfusion images can be assessed for perfusion defects (Figure 4), just as is done with nuclear MPI before and after stress. In addition, cine images from MRI can be assessed for regional wall-motion abnormalities as is done with stress echocardiography. MRIs also provide morphologic information including quantification of ventricular and valvular function.⁴⁹ However, current technology limits MRI anatomic assessment of the coronary arteries in adults to visualization of only the proximal portions.

Diagnostic and prognostic features

Stress cardiac MRI compares favorably with established noninvasive modalities in terms of accuracy for detecting CAD. Studies show stress-induced wall-motion abnormality imaging by MRI has a sensitivity of 83% and specificity of 86%.⁴⁸ Perfusion imaging with MRI has a sensitivity of 91% and specificity of 81%.⁴⁸

Stress cardiac MRI that is negative for ischemia has prognostic value and is associated with very low risk of cardiovascular death and myocardial infarction (less than 1% combined rate per annum).⁵⁰

Limitations

Stress cardiac MRI is relatively new and is the least frequently used compared with the other modalities discussed. Its availability and

access may be limited, with practical experience still nascent and limited in most centers. Other potential limitations include cost and long duration of scanning, which may be intolerable for those with significant claustrophobia or inability to hold their breath. It may be contraindicated in those with metal devices or prostheses, or in those with severe renal dysfunction due to risk of nephrogenic systemic fibrosis.⁵¹

■ APPROPRIATE USE CRITERIA

Appropriate-use criteria (AUC) guidelines are available for each imaging modality. They summarize the evidence and provide broad recommendations for given clinical scenarios by way of categorization as appropriate, may be appropriate, inappropriate, or rarely appropriate.

In 2019, a group of healthcare societies released consensus AUC guidelines for cardiac multimodality imaging including stress testing that address appropriateness of test selection in broad categories.⁹ The 2014 AUC guidelines, however, are more focused on testing for CAD and give more of a detailed and extensive list of scenarios for appropriate use,¹⁰

although additional evidence has accrued since then. Nevertheless, both guidelines are useful in improving understanding for appropriate test selection. Ultimately, AUC guidelines cannot determine a single best test, and a physician must take into account the whole clinical picture and test features when making a selection.

■ TAKE-HOME MESSAGE

Both stress testing with ECG, echocardiography, nuclear perfusion imaging, and MRI and anatomical evaluation with coronary CT provide details for evaluating CAD in at-risk patients. Results can help in risk stratification and assist with prognostication. Appropriate test selection is based on the patient's clinical picture, including the nature of symptoms, the risk profile, the clinical question being asked, and the strengths and limitations of the testing modality. Other factors that may influence test selection include local expertise, availability and access to a given modality, cost, and patient preference. ■

■ DISCLOSURES

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

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Medical, ethical, and legal aspects of end-of-life dilemmas in the intensive care unit

ABSTRACT

Physicians in the intensive care unit face a myriad of ethical dilemmas involving end-of-life care, yet they receive only minimal training about their jurisprudential obligations, and misconceptions about legal responsibilities abound. In particular, significant uncertainty exists among critical care physicians as to ethical and legal obligations for terminally ill patients. This paper presents 3 hypothetical cases to elucidate the medical, ethical, and legal considerations in common end-of-life situations encountered in the intensive care unit.

KEY POINTS

Addressing end-of-life care dilemmas requires careful analysis, an understanding of basic ethical and legal principles and perspectives, and access to reliable consultants.

Adults with decision-making capacity are entitled to refuse medical care, including life-sustaining interventions, but it is important to make sure such refusals are reasonably well informed.

When a patient lacks decision-making capacity, the care team should attempt to locate someone who can speak to the patient's wishes and values.

AMID THE VARIOUS CLINICAL DECISIONS that must be made for critically ill patients in the intensive care unit (ICU), physicians must often confront complex circumstances involving end-of-life care. Most deaths in the ICU occur within the context of medical orders limiting treatment, such as do-not-resuscitate (DNR) and do-not-intubate (DNI) orders, or measures instituted to ensure patient comfort such as comfort care.¹ These directives originate from the ethical and legal imperatives to honor the decisions of patients or designated surrogates to consent or refuse medical treatment, and from physician judgments about the benefits, burdens, and effectiveness of those treatments.²

Physicians receive minimal training about their jurisprudential obligations in determining end-of-life care, and misconceptions abound regarding their legal responsibilities in this area.³ Moreover, each state in the United States maintains its own medicolegal system, and many physicians practice medicine in multiple clinical settings and geographic areas, all of which complicate their ability to master the law. In addition, clinical terminology often differs substantially from legal language (Tables 1 and 2), making a synthesis of these 2 areas highly challenging.

These factors can contribute to significant uncertainty among critical care physicians regarding their ethical and legal obligations for terminally ill patients. Concerned with facing malpractice lawsuits, physicians may err on the side of aggressive treatment or overtreatment rather than forgoing treatments they

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TABLE 1

Select clinical ethics terms and definitions

Term	Definition
Autonomy	A patient's right to self-determination and to make personal medical decisions.
Justice	Similarly situated patients should be treated similarly. The distribution of resources should be fair and based on medical need and the likelihood of a "good" medical outcome.
Beneficence	Medical treatments should be provided to benefit a patient.
Nonmaleficence	The principle of "do no harm." This pertains to the potential burdensomeness of medical treatments. A balance between beneficence and nonmaleficence should always be considered when providing medical treatments and care.
Decision-making capacity	A patient's cognitive abilities to understand information and communicate medical decisions.
Implied consent	A situation in which a reasonable person would consent to medical care. It is relevant in a situation where a patient is unable to make his or her preferences known, no surrogate decision-maker can be identified, and failure to immediately provide medical care would risk loss of life or limb.
Medical futility	"Inability of a medical intervention to fulfill any of the patient's expressed goals and/or achieve any beneficial physiologic outcomes." ^a Note: this is a concept that can be difficult to define or quantify and is often an area of uncertainty, subject to debate.

^aFrom Chow GV, Czarny MJ, Hughes MT, Carrese JA. CURVES: a mnemonic for determining medical decision-making capacity and providing emergency treatment in the acute setting. *Chest* 2010; 137(2):421–427. doi:10.1378/chest.09-1133

judge to be medically inappropriate or overly burdensome.^{3,4} These practices persist despite a rich and consistent legal precedent that runs contrary to this perception (Table 3).

We present 3 hypothetical cases to elucidate the medical, ethical, and legal considerations in common end-of-life situations encountered in the ICU. After placing the cases in their medical and ethical contexts, a broad legal overview at the federal and state levels will be provided. It is the authors' hope that these case presentations and accompanying discussions will help inform the practice of physicians who deal with similar scenarios and increase awareness and understanding of medicolegal concerns in similar complex cases.

The information we present here is intended only for general informational purposes. It does not constitute legal advice and should not be construed as such.

■ CASE 1: A PATIENT WITH DECISION-MAKING CAPACITY REFUSES RECOMMENDED EMERGENCY MEDICAL CARE

A 22-year-old woman with severe refractory asthma is admitted to the medical ICU for a severe asthma exacerbation. The critical care team believes she requires emergency intubation and mechanical ventilation. However, she refuses intubation stating, "I am sick of living with this disease and don't want any more treatment." Her attending physician determines that she has decision-making capacity (DMC) and that she understands that refusing intubation may result in her death.

Medical perspective

In general, obtaining informed consent is a legal and ethical imperative incumbent on physicians before they initiate therapies or perform procedures.⁵ The process of informed consent can only be undertaken with patients who

Many patients in the ICU lack decision-making capacity

TABLE 2

Select medicolegal terms and definitions

Term	Definition
Medical law or health law	An area of law, which can be construed broadly to pertain to medicine and healthcare, including confidentiality, negligence, termination of treatment, and torts in the practice of medicine and clinical care.
Competency proceedings	Hearings conducted to determine a person’s mental capacity.
Negligence	The omission to do something that a reasonable person would do, or the doing of something that a reasonable and prudent person would not do. The failure to use such care as a reasonably prudent and careful person would use under similar circumstances. Actionable negligence involves the breach or nonperformance of a legal duty; essential elements are duty, breach, proximate cause, and harm.
Malpractice	Professional misconduct or unreasonable lack of skill. Failure of one rendering professional services to exercise that degree of skill and learning commonly applied under all the circumstances in the community by the average prudent reputable member of the profession.
Medical futility	Varies by jurisdiction and may be fact-specific. There is no overarching, agreed-upon legal definition.
Medical directive	A document that expresses a patient’s wishes regarding various types of medical treatment in several different situations where the patient may become incapacitated and thus unable to make or communicate such decisions on their own. This document can grant a power to make medical care decisions to another by means of a power of attorney, healthcare proxy, or living will.
Surrogate medical decision-maker	A person empowered by a medical directive, statutory law, or a court of competent jurisdiction with making medical decisions for a patient who lacks decision-making capacity.
Implied consent	Consent that is not expressed and manifested by explicit and direct words but is gathered by implication or necessary deduction from the circumstances or from the conduct of the parties. One example is an adult patient with decision-making capacity who voluntarily offers his arm to a healthcare provider for a vaccination.

Any procedure that alleviates discomfort or provides palliation should not be considered futile

have the cognitive abilities to comprehend, reflect, and communicate effectively. Patients are determined to have DMC if they can:

- Communicate a specific decision
- Demonstrate an understanding of relevant clinical information
- Recognize the consequences of accepting or declining recommended therapy
- Elaborate on how a decision was reached.⁵

Nonverbal communication can be an acceptable means to meet these criteria.

A robust informed consent process includes educating a patient in understandable and transparent terms about the nature, purpose, risks, benefits, and alternatives of a proposed treatment or intervention and the likely consequences of refusing the proposed intervention. This informed consent and educative process relies on the patient having adequate DMC for the specific decision under consideration.⁶

Although not impossible in most critical care situations, a robust informed consent

TABLE 3

Select legal decisions related to end-of-life care

Case	Decision
Terry Schiavo, 1990–2005	A series of federal and state court decisions, ending in 2005 when a court decision allowed the removal of a feeding tube from an incompetent patient who had suffered an anoxic brain injury. The patient's husband requested withdrawal of the patient's feeding tube and the trial court found that there was clear and convincing evidence that Ms. Schiavo would not have wanted a feeding tube, based on prior oral statements Ms. Schiavo had made to family members.
Texas Advance Directives Act, 1999	Provides in relevant part that, "A physician, or a health professional acting under the direction of a physician, who participates in withholding or withdrawing life-sustaining treatment from a qualified patient in accordance with this subchapter is not criminally liable or guilty of unprofessional conduct as a result of that action unless the physician or health professional fails to exercise reasonable care when applying the patient's advance directive." (§ 166.044) and that, "If an attending physician refuses to honor a patient's advance directive or a health care or treatment decision made by or on behalf of a patient, the physician's refusal shall be reviewed by an ethics or medical committee. The attending physician may not be a member of that committee. The patient shall be given life-sustaining treatment during the review" (§ 166.046).
Death With Dignity Act, 1994	Permits mentally competent, terminally ill patients to obtain a prescription from their physician for a lethal dose of drug provided certain conditions are met.
Patient Self Determination Act, 1990	Applies to institutions that receive Medicare or Medicaid funding and requires that patients must be informed of their rights regarding medical decision making, including the right to refuse life-sustaining treatment. Such institutions are also required to inquire as to whether patients have an advance directive and to document any advance directive in the patient's medical record.
Cruzan v. Director, Missouri Department of Health, 1990	US Supreme Court Case holding that, "(1) the United States Constitution did not forbid Missouri from requiring that clear and convincing evidence of an incompetent's wishes to the withdrawal of life-sustaining treatment; (2) state Supreme Court did not commit constitutional error in concluding that evidence adduced at trial did not amount to clear and convincing evidence of patient's desire to cease hydration and nutrition; and (3) due process did not require state to accept substituted judgment of close family members absent substantial proof that their views reflected those of patient."
Bouvia v. Superior Court, 1986	California decision that a competent 28-year-old quadriplegic patient had right to removal of nasogastric feeding tube inserted against her will.
Bartling v. Superior Court, 1984	California decision that a competent 70-year-old, seriously ill man had right to the removal of respirator.
California Natural Death Act, 1976	First state law establishing a formal procedure to allow certain terminally ill competent adult patients to refuse or have withdrawn life-sustaining interventions.
Quinlan, 1976	Supreme Court of New Jersey decision (70 N.J. 10, 355 A.2d 647 (NJ 1976)) holding that, "upon the concurrence of the guardian [here, the patient's father] and family of Karen [Quinlan], should the responsible attending physicians conclude that there is no reasonable possibility of Karen's ever emerging from her present comatose condition to a cognitive, sapient state and that the life-support apparatus now being administered to Karen should be discontinued, they shall consult with the hospital 'Ethics Committee' or like body of the institution in which Karen is then hospitalized. If that consultative body agrees that there is no reasonable possibility of Karen's ever emerging from her present comatose condition to a cognitive, sapient state, the present life-support system may be withdrawn and said action shall be without any civil or criminal liability therefor on the part of any participant, whether guardian, physician, hospital or others."

process is extremely challenging to put into operation⁷ due to the severity of the patient's underlying illness or the effects of sedation, or both. The presence of an endotracheal tube can also complicate matters as it may preclude meaningful verbal communication. If a patient is intubated, awake, and not unduly influenced by sedatives, communication can be accomplished through nonverbal means such as gesturing and writing and the use of word or letter charts and electronic devices. However, these alternative modes of communication can be cumbersome and time-consuming and are only effective when there is sufficient time to decipher the information.

Informed consent in an ICU must typically be obtained through disclosures and communication with surrogate decision-makers. If the patient has not previously appointed a surrogate decision-maker, the clinical team must identify the individual who would best reflect the patient's goals of care, which is deemed substituted judgment. Other considerations related to a patient's DMC include cognitive impairment (eg, severe depression, dementia), emotional status (eg, frustration with disease or treatment), and prior experiences. Issues specific to critically ill patients that do not necessarily affect DMC but may still impact decision-making include a patient's clinical condition and acuity and the general ICU environment.

It is advisable to obtain a second medical opinion when possible if there is any question or dispute about the patient's DMC. This second opinion should come from a provider who has appropriate expertise but who is not a member of the care team that is recommending treatment. When the specialized skill of a mental health professional is needed or when there is significant disagreement or uncertainty regarding the patient's DMC, it can help to have psychiatry, neuropsychology, or specialized providers from other relevant disciplines conduct a DMC evaluation. For example, although a cognitive evaluation can show a patient is unable to balance a checkbook, he or she may still be capable of understanding and appreciating the consequences of refusing intubation.

Because healthcare decisions can be influenced by the way information is presented, the perspectives, perceptions, and support of the clinical team can play a significant role. A

physician who has made a clinical judgment about a recommended treatment can appear to a patient or surrogate to be selling a care plan. Physicians must balance their role as experts who provide advice and recommendations with respect for a patient's right to voluntarily consent to or refuse treatment.

Clinicians should also consider obtaining and documenting additional information from the patient. For example, why is the patient refusing intubation? What is it about this intervention or this moment in time that has resulted in the patient's refusal? What is it about living with asthma that the patient finds burdensome and unacceptable? If any underlying issues can be effectively addressed and remediated (eg, concerns about pain or frequency of hospital admissions), the patient might consent to intubation. The ICU team should consider how to appropriately include the patient's surrogate or surrogates in this conversation (with the patient's authorization) because it could result in additional information that clarifies the patient's overall situation.

For the case described above, the clinician should try to persuade the patient within the time available to accept intubation and ventilation for a time-limited trial.⁸ The clinician should assure the patient that her comfort will be paramount and that the ventilator can be discontinued and nature allowed to take its course if the weaning process becomes unlikely or is overly prolonged, or if the ventilator becomes unacceptably burdensome to the patient or her surrogates. Family members or loved ones might be helpful allies in this process of persuasion and negotiation.

If the above interventions are unsuccessful, the clinician is faced with a young patient with a controllable disease and a potentially reversible acute condition who is declining a lifesaving measure. Her physician and care team are faced with a high-stakes dilemma: Should they honor an informed refusal of an adult patient with DMC, the result of which could be the patient's death?

Ethical perspective

Respect for persons and their autonomy is a hallmark of clinical practice in the United States and in many other parts of the world. This ethical principle is the foundation for

It is advisable to obtain a second medical opinion when possible if there is any question or dispute about the patient's decision-making capacity

the emphasis placed on obtaining a patient's informed consent before a clinical intervention. A corollary to informed consent is the always-present possibility of informed refusal by patients. In fact, a kind of moral maxim or rule of thumb has emerged in this regard: informed adult patients with DMC have the right to refuse treatment, including lifesaving and life-sustaining treatments. One example is the right of an informed adult patient who is a Jehovah's Witness to refuse blood products.

Ultimately, if efforts to persuade the patient to accept a time-limited trial of ventilator support are unsuccessful, the patient's refusal of life-sustaining treatment should be honored. From an ethical perspective, in this case and similar cases, if a negotiated middle-ground option cannot be reached, a patient's autonomy and informed refusal would trump the physician's judgment of what would be in the patient's best interests.

Legal perspective

Adults with DMC are entitled to consent to or refuse medical care, including life-sustaining interventions. From a historical and legal perspective, informed consent developed over time as a method accepted by the medical and legal communities of documenting patient consent to actions that, if done without consent, could be considered battery or assault, or both.

To the extent reasonably possible, it is important to ensure that such refusals are informed refusals. For instance, sometimes patients may clearly refuse an intervention but in actuality are refusing because of an effect that they believe is unavoidable (eg, pain, suffering, discomfort) rather than because they are not interested in the intervention per se. In order to make a responsible decision in this realm, it is important for clinicians to understand the reason for a patient's refusal.

This is not to say that patients are not permitted to refuse for any reason or for no reason, nor should unknown reasons be presumed to apply. For instance, it would be incorrect to presume that all patients who refuse intubation do so related to concerns about suffering. While respecting the general right of adult patients with DMC to refuse medical interventions, clinicians should also attempt, to the extent possible, to understand the patient's reasoning. In

that way, the clinician can be more assured of addressing a patient's actual concerns.

When a legal challenge to DMC is presented, the law will often require proof of a DMC evaluation and, if DMC is absent, the extent and detail of the deficit. Judicial decisions are also subject to being informed by the patient's values and the patient's desired goals of care. Therefore, it is generally advisable that the patient's DMC and information about the patient's values and goals of care be documented in the patient's medical record, including a detailed description of communications held with the patient regarding the proposed interventions, the patient's goals, the patient's understanding of the care plan, and the proposed interventions. Further, medical record documentation should indicate all patient and clinician communications regarding refusal of medical interventions and the patient's understanding of the consequences of refusal.

Proving DMC in a legal context can involve disagreement among the patient's surrogate, family members, and the clinical team. Thus, physicians should document any questions, concerns, or comments in the medical record that were articulated by the patient during relevant discussions. It is also advisable to provide documentation of the patient's historic expression of goals of care and any information regarding interventions of a similar nature or with a similar clinical goal that have been consented to or refused by the patient.

Again, as an adult with DMC, the patient generally has a legal right to refuse medical interventions, including intubation and other life-sustaining measures. The patient's goals, desires, and values should form the touchstone of understanding in this milieu. Clinicians should scrupulously avoid replacing the patient's goals, desires, and values with those of others. The ICU team should do everything possible to ensure that a patient's refusal is reasonably well informed, but should also not infringe on a patient's right to autonomy. The strategy of moving forward with an intervention a patient refuses in order to establish more evidence that a patient is well-informed is generally highly suspect. This can lead to a violation of patient rights and can result in a clinical course in which the patients' ability to communicate future wishes about their care

A corollary to informed consent is the always-present possibility of informed refusal by the patient

will be significantly compromised. Such decisions should be carefully reviewed to make sure they are not an oblique strategy to override the patient's wishes in favor of others' values and goals.

■ CASE 2: A PATIENT WITHOUT DMC AND WITHOUT AN IDENTIFIED SURROGATE DECISION-MAKER

A 78-year-old woman with a history of multiple strokes and severe dementia is admitted to the medical ICU from an extended-care facility for treatment of septic shock. The patient never completed an advance directive and has no family members or friends. A number of urgent management decisions must be made, including intubation. The attending physician believes that shifting to comfort care is appropriate.

Medical perspective

Physicians often care for patients for whom discussions and decisions about goals of care have not been established. The discomfort many physicians experience when discussing matters pertaining to end-of-life care and the ambiguity about which clinical service is responsible for holding such discussions (eg, primary care, geriatrics, palliative medicine) also contribute to the lack of established goals of care.⁹

Physicians caring for patients with life-limiting clinical conditions must carefully distinguish between interventions that are beneficial and those that are overly burdensome and potentially medically inappropriate or futile. Although physicians are not obligated to provide futile therapy, there is little consensus for the definition of medical futility.¹⁰ Brody and Halevy categorized 4 conceptual definitions of futility¹¹:

- Physiologic futility: the intervention is unlikely to have any clinical effect
- Imminent demise futility: the patient will likely die soon regardless of the intervention
- Lethal condition futility: the patient's underlying disease is likely to impede long-term survival
- Qualitative futility: the intervention is unlikely to restore a patient's meaningful quality of life.

Any procedure that alleviates discomfort or provides palliation should not be considered futile.¹²

While these categories of futility are generally relevant, patients often have their own perception of what they believe to be futile. Some terminally ill patients may not want life-prolonging therapies (lethal condition futility) while others desire any and all interventions until the point of physiologic futility. In the absence of a pre-existing physician-patient relationship and without detailed knowledge of the patient's life and goals, patient preferences for managing clinical situations are often unknown or uncertain.

In the case of this 78-year-old patient, the physician must decide whether treatment is beneficial. If the physician feels that treatment would be beneficial, then he or she would provide all indicated treatments to the patient while simultaneously searching for more guiding information. On the other hand, the physician may find the treatment to be futile or nonbeneficial. A declaration of futility is not performed through a standardized procedure or algorithm but rather is determined on a case-by-case basis. At times, physicians invoke an arbitrary 6-month predicted survival metric used by the US Centers for Medicare and Medicaid Services to define a terminal condition.¹³ Most often, however, futility is a clinical judgment made in partnership with a patient or the patient's surrogates, in view of achievable goals of care. If the physician feels the therapy is futile, then he or she is not obligated to provide any therapy that would be considered futile, harmful, or nonbeneficial.

Because failing to intubate the patient may result in immediate death or death within a very short time, the magnitude of this consequence could argue for using temporary intubation to create a window of time to attempt to locate someone who can speak to the patient's wishes and values. If it is not possible to locate such a person after a thorough and diligent search, then clinically appropriate next steps should be taken as they would for any patient. Policies, procedures, and applicable laws and regulations regarding patients without surrogate decision-makers should be followed. This approach is not without its pitfalls, however, because the physician and other clinicians are likely to feel uneasy about providing treatments that could have little or no benefit and be overly burdensome.

Although physicians are not obligated to provide futile therapy, there is little consensus for the definition of medical futility

Further, there is also a societal responsibility to distribute resources in a fair manner based on medical need and the likelihood of a good medical outcome, however defined. Providing futile treatment may also be economically unreasonable.⁹ Physicians should aim to provide care and treatment that will likely lead to a successful patient outcome. Judgments and conclusions about futility should be consistent with the reality of patients' medical conditions and prognoses.

Ethical perspective

How should the physician manage this patient without DMC whose previously expressed wishes are unknown, and who currently has no one to speak on her behalf? What would be an ethically and legally supportable treatment plan for this patient?

The physician must do what is best for the patient. Beneficence is the driving principle for the patient-physician relationship and often aligns with its corollary to avoid harm (nonmaleficence). As such, the physician, as the expert in the matter, must undertake a risk-benefit assessment within each situation to determine if interventions pose more potential harm than benefit, or vice versa.

Moreover, irrespective of the potential short-term outcomes, the clinician must determine if the interventions are clinically indicated or futile in the broader picture. The balance between beneficence and nonmaleficence depends on the clinical condition of the patient and the patient's values. Ideally, clinical decision-making proceeds through a partnership between patients, physicians, and other members of the clinical team. Patients bring to the decision-making process their knowledge and expertise about their values, preferences, wishes, and goals, whereas clinicians and other members of the care team bring their knowledge and expertise about clinical interventions and treatments, diagnoses, and prognoses.¹⁴ Within this partnership model, patients and healthcare professionals negotiate agreements and decisions about treatments and goals of care. This relationship-centered communication has been demonstrated to have a therapeutic effect in and of itself.¹⁵

The gold standard for the partnership model for clinical decision-making occurs when a

patient has DMC and can participate directly in the process. The silver standard comes into play when a patient lacks DMC but surrogates or advance directives such as a living will are available to provide a substituted judgment on behalf of the patient and what he or she would want.¹⁶ In the case of this patient, neither the gold nor silver standard for decision-making can be actualized. By default, the ICU physician and team must use a bronze standard of making decisions based on the patient's best interests, which entails maximizing benefits and minimizing burdens of treatment.¹⁷

On a practical level, there are ethically supportable strategies for clinical management aimed at promoting a patient's best interests. Often, but not always, hospitals have policies and procedures to guide clinicians' decisions for patients lacking DMC in the absence of healthcare proxies. For this 78-year-old patient, it would also be appropriate to include a social worker to further explore the existence of family members, friends, and others who may know something about the patient's values, lifestyle, and activities of daily living prior to her strokes and dementia. For example, the social worker could contact the extended-care facility to see if the patient had visitors while there or if there is a record of an advance directive or next of kin. Finally, the hospital's ethics consultation service¹⁸ should be asked to review the case and to provide ethically supportable recommendations. Throughout the patient's ICU stay, intensive efforts should be given to ensure the patient's comfort.

Legal perspective

As noted above, for adult patients who have DMC, legal considerations are significantly guided by the patient's goals, desires, and values regarding medical interventions. If the patient lacks DMC or cannot communicate this information, an effort should be made to determine whether the patient has historically communicated this information to anyone else. For instance, the patient may have an advance directive that provides such information, or the patient may have had discussions at some time in the past with a clinician, including a primary care provider, another member of the clinical team, a surrogate medical decision-maker, or a care provider or loved one who may be able to

Ideally, decision-making proceeds through a partnership between patient, physician, and other members of the clinical team

offer insight into the patient's perspective.

However, the patient's goals, desires, and values should form the touchstone of understanding how the patient would like to proceed in this milieu, and clinicians should be cautious not to substitute their own values or goals or those of family members, surrogates, or others for those of the patient. This is not to say that the values and goals of others should not receive respect, but it should be recognized that these are distinct from those of the patient. The care a patient receives should not be infringed upon based on the goals, desires, and values of others if they contradict the patient.

Additionally, clinicians' assessments regarding the utility of specific interventions is an important part of the legal analysis pertaining to whether proposed clinical interventions will achieve the patient's desired goals of care and comfort within the context of the patient's values and desires. A common way to emphasize consensus among physicians is to provide notation by a second independent physician confirming the plan of care. A more robust discussion of the legal considerations in cases of physician-determined futility follows in case 3.

The care a patient receives should not be infringed upon based on the goals, desires, and values of others if they contradict the patient

■ **CASE 3: A PATIENT WITHOUT DMC, BUT THE SURROGATE DECISION-MAKER WANTS MEDICALLY FUTILE TREATMENT**

A 92-year-old man with metastatic prostate cancer is admitted to the medical ICU with hypoxic respiratory failure and sepsis. The source of the sepsis is found to be a lower urinary tract obstruction. He is intubated and placed on vasopressors. After 6 days of treatment, the ICU team believes he will not achieve a meaningful recovery. The patient's resuscitation status is "full code." His son, who is also the surrogate medical decision-maker appointed by a medical power of attorney, wants to continue with intensive therapies including chemotherapy to shrink the prostate and possibly relieve the obstruction. The patient has a cardiac arrest and the son is not present. Should the team attempt cardiopulmonary resuscitation (CPR)?

Medical perspective

The initial responsibility of the care team is to assess the clinical status of the patient and the utility of the intervention. For example, car-

diac arrest stemming from a reversible cause such as hypovolemia or a vasovagal reaction would differ from cardiac arrest secondary to generalized worsening of the patient's clinical status. If the clinical judgment of the team, confirmed by ancillary information or testing, is that there is no reversible cause to the arrest, then the team would be justified in believing that further resuscitative efforts would be futile. It goes without saying that the medical team's primary responsibility is to communicate this medical knowledge to the family and, in the name of transparency and intent, to explain the clinical and scientific rationale for their opinions.

There are 2 separate but related issues in this scenario: whether to honor a family member's request for interventions unlikely to favorably impact the patient's long-term survival, and whether to initiate a DNR order without family consent, based on the belief that CPR would be medically inappropriate, overly burdensome, or futile. Requests by family members or surrogates to provide ineffective therapy is a common situation in an ICU. Discordance between clinical teams and families can result from different levels of knowledge, poor communication, different expectations, cultural and religious beliefs, and family dynamics. Respectful interactions with the family or surrogates, including multidisciplinary conferences, will often help to identify differences of opinion, perspectives, and achievable goals and can build trust.

The importance of clear, consistent, compassionate communication cannot be overemphasized in helping to navigate these differences. More concretely, the American Medical Association's Council on Ethical and Judicial Affairs recommends the following steps to deliberate and resolve potential conflicts¹⁹:

- Negotiate an understanding of what constitutes futile care in advance of such a situation arising
- Strive for joint decision-making
- Enlist the assistance of a consultant or patient representative, or both, to facilitate discussions
- Involve an institutional ethics committee
- Transfer the patient's care to another physician or institution.

The effectiveness of CPR in providing

meaningful recovery has been overstated in popular culture and the media. For example, a study of CPR performed for cardiac arrest on 2 popular television programs showed survival rates significantly higher than those reported in the literature, ie, a success rate for short-term survival of 75% on television vs 40% in the literature.²⁰ A number of factors make meaningful recovery less likely, including old age, the presence of a terminal condition, and the absence of a discernible electrical rhythm.²¹

The perception and expectation among healthcare professionals is that CPR should be attempted for all patients after cardiac or pulmonary arrest, regardless of comorbidities or prognosis, unless otherwise specified to the contrary by a DNR order.³ However, as with all other medical interventions, physicians should be cognizant of the clinical circumstances and likelihood of success of CPR before initiating it. The critical process of risk-benefit analysis is no less applicable to CPR than to other clinical procedures. Even if CPR is not physiologically futile, eg, a patient recovers spontaneous circulation and has a prolonged survival, it may still meet criteria for other categories of futility and will not ultimately and favorably impact the patient's overall outcome. Therefore, providing CPR could be unreasonable and professionally objectionable because it promises more than medicine can deliver.²²

Each hospital has different policies on how to deal with this situation. To the extent permissible under local laws and hospital policies, the physician should clearly communicate to the patient and family that futile therapy will not be offered, and this communication should be documented. An order for DNR should be written, and CPR should subsequently not be offered. Some hospitals require a written opinion from a second physician to place a unilateral DNR order in the chart, and some jurisdictions and hospitals do not permit unilateral DNR orders. If the family insists on care that the clinical team deems unreasonable, attempts should be made to transfer the patient to another physician or facility.

Ethical perspective

Patients and families at times disagree about the plan of care recommended by clinicians. These disagreements may be unavoidable,

especially in situations involving diverse religious and cultural values. These disagreements may be a natural consequence of an attempt by a family member or surrogate to participate in the care of a loved one being treated by strangers.

The word futility should be used cautiously and viewed as a relative (or "relational") term, because an action can be considered futile only in relation to a specified goal. In clinical settings, treatments or interventions such as CPR, intubation, and dialysis can only be appropriately described as futile after a specific goal for that treatment has been identified and there is virtual certainty that the medical intervention cannot achieve the identified goal.²³

In the case of the 92-year-old man, if his goal is to stay alive and to have his physiologic life extended regardless of quality of life or his ability to interact with his children or his environment, then continued treatment in the ICU including intubation and ventilation would not be strictly futile. However, that does not mean that continued ICU care is necessarily medically appropriate. There may be other ethically supportable reasons and other strategies for communication and negotiation (such as the steps recommended by the American Medical Association) that should be used in this case.¹⁹

At the core of many medical futility dilemmas is a conflict between patient autonomy and a physician's obligation to maintain professional standards of care.²⁴ However, many such conflicts can often be prevented by optimizing communication, providing comprehensive clinical information, and conveying realistic expectations for a patient's outcome. When aiming to optimize communication, clinicians should never label or talk about the patient's care as futile. Some authors discourage clinicians from using the word futility altogether, replacing the term with "potentially inappropriate."²⁵

The word futility should only be used to describe the inability (or virtually certain inability) of a specific treatment to achieve an identified goal of the patient.

In the event that a conflict emerges, the participation of third-party mediators such as palliative medicine specialists and ethics consultants may be helpful. If hospital per-

Effectiveness of CPR in providing meaningful recovery has been overstated in popular culture and the media

sonnel perceive a pattern of such conflicts arising related to CPR, it would be appropriate to proactively address these issues in the hospital's DNR policy, procedures, and guidelines. The patient's surrogates should be made aware of any relevant hospital protocols and policies.

Ideally, the issue of providing or not providing CPR should have been addressed proactively with the patient's son. If the ICU team preemptively judged that CPR would not benefit the patient or would be overly harmful to him, this should have been communicated to the son and a DNR order strongly recommended. If the ICU team had no intention of providing CPR in the event of cardiac or respiratory arrest (which could have been ethically supportable), this should have been clearly communicated to the son. There is no ethical justification for deceiving the son by performing a "show code" or "slow code" on the patient.²⁶

For case 3, based on relevant CPR outcomes data and on the clinical judgment of the ICU physician, there is ethical support for not attempting CPR immediately after the cardiac arrest. This is the official position of the American Medical Association Council on Ethical and Judicial Affairs.¹⁹

Legal perspective

Absent a law that provides an affirmative obligation or circumstances in which a physician agrees to take on an affirmative obligation, physicians are generally not obligated to provide treatment that in their professional medical judgment is deemed inappropriate.^{27,28} This general construct applies to CPR as well as other medical interventions. However, different jurisdictions have different laws about end-of-life issues, including CPR and DNR orders, and healthcare facilities and organizations differ in their policies and procedures pertaining to CPR and DNR orders. Different states may also have different laws on whether the consent of patients or their surrogates is required for DNR orders. Clinicians should be familiar with applicable laws, regulations, and institutional policies for CPR and DNR orders. If they are unfamiliar with these matters or have questions about how they might apply in any given circumstance, legal counsel

should be sought.

Physicians in this context may have questions about whether or not they can be sued for certain actions or inaction, particularly when their care plan runs counter to the wishes of the patient, family, or surrogate decision-maker. Clinical decisions in end-of-life situations tend to be fact-specific, and laws can vary widely depending on the jurisdiction. Physicians with questions or concerns about the legal impact of their decisions would be wise to consult with appropriate medical, ethical, and legal experts. This is especially true in any patient-care situation that involves withholding or withdrawing life-sustaining treatment where there is not clear agreement between the clinical team and the patient or, if the patient lacks DMC, the patient's surrogate medical decision-maker.

Practically speaking, physicians may be able to mitigate their risk by taking the following steps:

- Appropriately documenting the futility of a specific intervention that they believe is inappropriate, as well as the clinical basis for an intervention they believe is appropriate
- Seeking a well-documented second opinion from an appropriately objective and qualified physician regarding the intended intervention or nonintervention, and proceeding only to the extent that the second physician opinion is in agreement with the intended intervention or nonintervention
- Responding appropriately to any dissonance that might arise in medical opinions regarding a particular patient's care
- Including the hospital's or healthcare institution's ethics consultation service and legal counsel in the decision-making process.

However, whether or not such actions provide legal mitigation in any particular set of circumstances or for any particular individual is a question for legal counsel.

An appropriate surrogate medical decision-maker (eg, a person appointed as a patient's surrogate through a valid legal process, such as a medical power of attorney or a court order) is often permitted the same decision-making authority as the patient. But such legal vehicles for conveying surrogacy can

Clinicians should be familiar with applicable laws, regulations, and institutional policies for CPR and DNR orders

be written in a manner that is more or less limiting, so it is important to make sure that the actual legal document is a fully executed legal document. This means that it is read in consultation with legal counsel as appropriate and that there is a full and complete understanding as to the legal powers the document conveys. The overarching role of a surrogate medical decision-maker is to communicate what the patient would have wanted, if known, and if not known, to communicate information about the patient that assists the clinical team in making decisions that reflect the patient's goals, desires, and values in the healthcare context.

■ TAKE-HOME POINTS

Critical care is rife with medical, ethical, and legal dilemmas involving end-of-life care. The

physician must be acutely aware of the ethical and jurisprudential considerations that should be balanced in navigating these sensitive situations. The cases presented here provide a small sampling of common issues that arise in clinical practice, although they clearly represent only the tip of the ethical and legal iceberg. Addressing these dilemmas requires careful analysis, an understanding of basic ethical and legal principles and perspectives, and reliable consultants to assist physicians and other clinicians in their time of need. A synthesis of medical, ethical, and legal concerns unique to each case is necessary to provide the most appropriate care to patients and families. ■

■ DISCLOSURES

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

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