

# CLEVELAND CLINIC JOURNAL OF MEDICINE

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An unwelcome guest  
that won't leave

Scaly plaques from insulin injections

A tumorlike gingival lesion

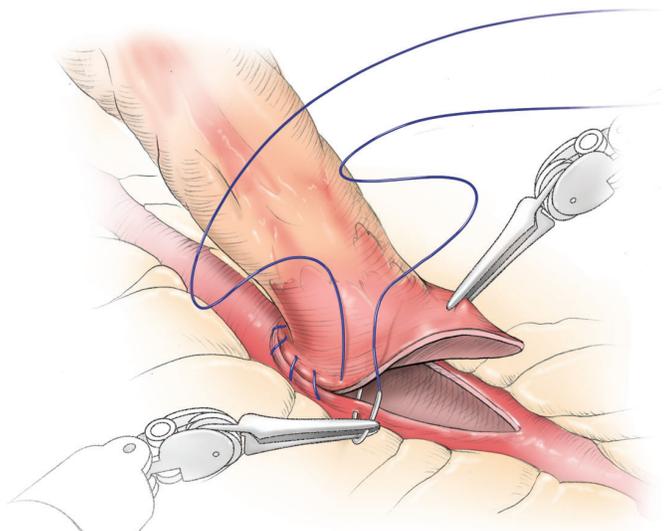
Vaccinating the unvaccinated adult

Quetiapine for primary insomnia:  
Consider the risks

## COVID-19 Brief perspectives from the front line

- Post-acute sequelae of SARS-CoV-2 infection
- What is causing the 'long-hauler' syndrome?

Coronary artery bypass grafting:  
When, why, and how?



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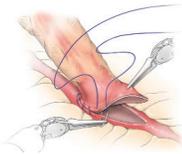
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## Upcoming Features

- Asthma management: The GINA report
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## COVID-19: An unwelcome guest that won't leave

The SARS-CoV-2 pandemic, with its multiple surges, is seemingly lasting forever, although it has actually been with us for a little more than a year. Despite recent setbacks, with difficulties in vaccine production and with safety concerns over a rare but potentially fatal (and possibly autoimmune) platelet activation-related coagulopathy with thrombosis and thrombocytopenia syndrome,<sup>1</sup> there is a sense that the end of the infection phase is within reach. Of course, tempering that optimism are the ongoing viral mutations that may exhibit increased virulence or vaccine resistance, and significant swaths of the population voicing “hesitancy” to get vaccinated and to wear a mask, which may slow the development of effective herd immunity.

But once the infectious phase of the pandemic eventually winds down, we will not be done with the pandemic. The effects of COVID-19 on our society and lifestyle and on our patients will linger far longer than the presence of infectious virions.

COVID-19 has had obvious direct and indirect effects on the fabric and behavior of our society in the United States, as well as internationally. The toll on the restaurant industry, on travel and tourism, on the entertainment industry, and on retail sectors of our economy has been striking and in some cases devastating—while at the same time warehousing, construction, and delivery sectors have boomed, and financial markets blossomed. The pandemic led to shortages of manufacturing supplies, while at the same time the need for selective products have skyrocketed. Conditions seem ripe to support a jump-started economic recovery in some sectors. But our economic and social landscapes will probably not be the same as before the pandemic.

As Christakis describes in his very readable book *Apollo's Arrow: The Profound and Enduring Impact of Coronavirus on the Way We Live*, past pandemics have provoked lasting societal change. The COVID-19 pandemic will be similar, though it will affect the post-pandemic world in ways different from the Spanish flu or the bubonic plague, in part because of its higher mortality rate in older people. How much societal PTSD will be expressed? How will younger vs older adults react in a post-infection reality while awaiting the next viral iteration and, likely, recommendations for ongoing vaccinations? We will see scattered wearing of facial masks in high-trafficked areas of cities, as has been the case in Asia for years. White-collar businesses and education venues will continue to utilize virtual technology to a far greater degree than before. There will be broader acceptance of a work-from-home option in many areas of professional life, with subsequent impact on geographic resettling, child care needs, home remodeling, new construction, office real estate, and the use of dining and other shared community spaces.

In clinical practice, we have experienced the scrambling to offer, monetize, and expand the utilization of telemedicine, perhaps (in my mind) more broadly than clinically optimal. In medical education, undergraduate and postgraduate, we have rapidly needed to cope with the challenges and advantages of virtual conferencing. For our medicine grand round lecture series, it has been easier to schedule desired speakers, and I have been fortunate to recruit several from Europe, while being forced to avoid inviting those on our West Coast, who would need to speak at 4:00 AM for those in our Eastern time zone. Consultant discus-

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sions, safety monitoring boards, and national education oversight committees have all met virtually. Travel expenses have almost disappeared.

But the adverse effects on the academic system are many and include the loss of personal interaction, dialogue with the opportunity to read facial expressions and body language, and interpersonal bonding. Trainees and other healthcare workers have experienced enormous emotional stress on the front lines, as well as the loss of educational opportunities and clinical experiences. The possibility for mentored introduction has almost disappeared, as has the opportunity for trainees and junior faculty to network with senior, nationally known academic leaders from other institutions. Still, stretched in ways we couldn't have imagined, we have not seen the total demise of our academic system, and only time will tell how we re-emerge in what is likely to be a hybrid in-person and virtual reality.

The long-lasting adverse effects on patients who have been infected with and have survived COVID-19 is a bit of a surprise—a major-league knuckleball tossed at us by SARS-CoV-2. Lingering pulmonary symptoms, dyspnea, chest pain, and nagging cough are easy to understand: after all, SARS-CoV-2 is a respiratory virus capable of damaging respiratory cells. But the post-infection symptoms experienced by “long-haulers” extend far beyond the thorax, as discussed by Vehar et al on page 267 in this issue. It is tempting to explain away the lingering constitutional and cognitive symptoms without evidence of biochemical or organ damage as a “functional” response to the stress reaction, buoyed by societal insecurity and mixed-message politicalization of public health measures, as well as by the very real threat of infection with resultant severe illness or even death—all occurring in an environment of economic insecurity and, for many, social isolation.

But as discussed by Sigal on page 273, there are also very real and complex biologic factors at play after infection with this virus. He draws comparisons with other infections that have triggered similar, lasting complications. We do not yet understand most of them, but research is elucidating the roles of specific cytokine reactions, abnormal activation of the clotting cascade, and stimulation and damage of the vasculature.



Brian F. Mandell, MD, PhD  
Editor in Chief

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## 2021

## MAY

**DIABETES DAY**  
May 20  
Live stream

**BIOLOGIC THERAPIES SUMMIT IX,  
AND VASCULITIS TREATMENT 2021**  
May 21–23  
Live stream

## JUNE

**CLEVELAND CLINIC SYMPOSIUM  
ON TRIGEMINAL NEURALGIA**  
June 4  
Live stream

**INNOVATIONS  
IN CEREBROVASCULAR CARE 2021**  
June 5  
Live stream

**INTENSIVE REVIEW  
OF INTERNAL MEDICINE**  
June 7–11  
Live stream

**MULTISYSTEM MANIFESTATIONS  
OF BRAIN DISEASES**  
June 12  
Live stream

**INTERNAL MEDICINE BOARD REVIEW**  
June 15–19  
Live stream

**WASOG/AASOG 2021:  
MULTIDISCIPLINARY MEETING  
FOR SARCOIDOSIS AND ILD**  
June 21–24  
Hollywood, FL

**MELLEN CENTER UPDATE  
IN MULTIPLE SCLEROSIS (MS)**  
June 26  
Live stream

## JULY

**MIDWEST MELANOMA  
AND HIGH-RISK SKIN CANCER  
SYMPOSIUM**  
July 16  
Cleveland, OH

## AUGUST

**HOSPITAL MEDICINE 2021**  
August 5–6  
Live stream

**NEUROLOGY UPDATE: A COMPREHENSIVE  
REVIEW FOR THE CLINICIAN**  
August 7–8  
Live stream

**INTENSIVE REVIEW OF CARDIOLOGY**  
August 14–15  
Live stream

**TRANSTHYRETIN CARDIAC AMYLOIDOSIS  
IN AFRICAN AMERICANS:  
WHAT PHYSICIANS NEED TO KNOW**  
August 24  
Live stream

**INTENSIVE REVIEW OF ENDOCRINOLOGY  
AND METABOLISM**  
August 27–29  
Live stream

## SEPTEMBER

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

**THE PRACTICE OF ECHOCARDIOGRAPHY  
AT CLEVELAND CLINIC 2021**  
September 11  
Live stream

**COMPREHENSIVE LIFELONG  
EXPEDITIOUS (CLE) CARE  
OF AORTIC DISEASE**  
September 17–18  
Cleveland, OH

**INTENSIVE REVIEW  
OF GASTROENTEROLOGY  
AND HEPATOLOGY**  
September 17–20  
Las Vegas, NV

**PRIMARY CARE WOMEN'S HEALTH:  
ESSENTIALS AND BEYOND**  
September 18  
Live stream

**GLOBAL EP**  
September 24  
Live stream

**GENETICS EDUCATION SYMPOSIUM –  
GENETICS AND GENOMICS:  
APPLICATIONS FOR THE PREVENTION,  
DETECTION, AND TREATMENT OF CANCER**  
September 30  
Live stream

## OCTOBER

**VIRTUAL NEPHROLOGY UPDATE**  
October 1  
Live stream

**PRACTICAL MANAGEMENT OF STROKE**  
October 1  
Live stream

**ADVANCES IN CONGENITAL  
HEART DISEASE SUMMIT**  
October 1–2  
Live stream

**WAKE UP TO SLEEP DISORDERS 2021:  
A CLEVELAND CLINIC SLEEP DISORDERS  
CENTER UPDATE**  
October 9–10  
Live stream

**PRIMARY CARE UPDATE**  
October 15–16  
Live stream

**CARDIOVASCULAR UPDATE  
FOR THE PRIMARY CARE PROVIDER**  
October 28–29  
Live stream

## DECEMBER

**MASTERING THE MANAGEMENT  
OF THE AORTIC VALVE**  
December 3–4  
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## 2022

## JANUARY

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## Prostate cancer screening

**To the Editor:** We read with interest the article about prostate specific antigen (PSA) and screening, “Prostate cancer screening and the role of PSA: A UK perspective” by Sooriakumaran in the January 2021 issue.<sup>1</sup> We are concerned with the author’s endorsement of unproven management options, an unreferenced claim that transperineal prostate biopsies curtail antibiotic resistance, and especially the generalized take-home point that “PSA screening saves lives.”

The European Randomised Study of Screening for Prostate Cancer (ERSPC), which the author used to justify screening, showed no such benefit. The relative risk for all-cause mortality was 1.00 (95% confidence interval 0.98–1.02,  $P = .82$ ).<sup>2</sup> Only a disease-specific benefit was detected: 570 men would need to be screened to prevent 1 death of prostate cancer at 16 years in the latest follow-up of the study.<sup>3</sup> For this marginal benefit, substantial costs are incurred. These include the psychological consequences of a cancer diagnosis, harms of prostate biopsies, and side effects of treatments including radiation, radical prostatectomy, and androgen deprivation therapy (eg, impotence or incontinence, or both). The US Preventive Services Task Force estimates that for 1,000 men ages 55 to 69 who are screened, 240 will experience the stress of an elevated PSA, 100 will be diagnosed with cancer, and at least 60 will suffer serious harm.<sup>4</sup>

Causing this harm is not inexpensive. A cascade of testing and procedures follows an elevated PSA, which by itself costs about \$40. However, additional fees can quickly add up—that of ultrasounds (\$150), specialist consultations (\$350), prostate biopsies (\$500), and more.<sup>5</sup> The United States wastes billions of dollars annually on nonbeneficial healthcare costs. We believe that higher value care is crucial for patient outcomes and for the sustainability of healthcare spending. The costs of PSA testing—both financial and to the patient’s well-being—are not worth it.

Sherry Zhang, MD  
University of California, San Diego

Ian Jenkins, MD  
University of California, San Diego

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doi:10.3949/ccjm.88c.05001

**To the Editor:** To make screening recommendations, including for PSA, one must consider an unbiased assessment of benefits, risks, and costs. Yet Sooriakumaran<sup>1</sup> fails to discuss current guidelines or the harms of screening, and falsely claims a mortality benefit. Gilligan’s accompanying editorial<sup>2</sup> fails to quantify those harms and briefly mentions the guidelines without giving the rationale to avoid screening. Both emphasize European Randomised Study of Screening for Prostate Cancer results showing a 20% relative risk reduction in disease-specific mortality.<sup>3</sup>

However, a better metric is absolute risk reduction (0.18% by our calculation), and the best metric is the absolute risk reduction for total mortality: none was noted.<sup>3</sup> And readers of both articles would not know that for every prostate cancer death avoided, 240 men face an elevated PSA, 100 experience a cancer diagnosis, 80 of those get treatment, and 65 suffer significant harm.<sup>4</sup>

The “shared decision-making” Gilligan advocates may sound reasonable. But for PSA screening, where the risk-benefit analysis is unfavorable in most patients,<sup>4</sup> shared deci-

sion-making is a chimera. If experts cannot fairly present the risks and benefits in the literature, much less agree on a strategy, how can lay people make an informed decision? “Punting” the decision to patients risks worsening their health outcomes at high costs, and may have profound implications for those who are unnecessarily harmed by their own decisions.<sup>5</sup>

Screening should be advised only if benefits clearly outweigh the risks. Sooriakumaran’s omission of risks and guidelines should have been addressed in Gilligan’s editorial. Together, the articles present a biased analysis of PSA screening that can cause patient harm, and the *Journal* should have published an article providing the case against screening.

Kevin Kurator, BS, BA  
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La Jolla, CA

Ian Jenkins, MD  
University of California, San Diego

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doi:10.3949/ccjm.88c.05002

**In Reply:** I appreciate the time and effort taken by Zhang and Jenkins and Kurator and Jenkins in reading and responding to my article “Prostate cancer screening and the role of PSA: a UK perspective.” As the final clause of this title states, my perspective is from the United Kingdom.

Kurator and Jenkins state that I falsely claim a mortality benefit. My article does not claim that PSA screening confers an overall mortality benefit, but there is clear evidence

from randomised trials of a disease-specific benefit for PSA screening, which I discuss. The authors go on to state that screening causes more harm than benefit, but this is their personal judgment, not a fact. It is true that prostate cancer screening leads to the diagnosis of more insignificant tumors that would otherwise have gone undetected without screening. It is also true that treatment of these insignificant tumors causes harm and thus must be avoided. But it is not true that detection of these tumors must lead to overtreatment.

In the United Kingdom, we have centralised cancer care services and developed cancer multidisciplinary teams such that management decisions regarding insignificant and low-risk tumors are made in consensus with urologists, oncologists, nurse specialists, and others. In the United Kingdom, the rate of surgery for low-risk prostate cancer is 4%, whereas it is around 25% in the United States. Hence, diagnosing prostate cancers early in the United Kingdom does not necessarily lead to “overtreatment” with its consequent harms.

We also know that PSA screening reduces deaths from prostate cancer. If we can reduce the risk of overtreatment, as we have done in the United Kingdom, the argument in favour of screening becomes much stronger. Without screening, the number of men presenting with metastatic (incurable) prostate cancer rises sharply. The use of PSA has vastly decreased these numbers, and therefore the advent of PSA screening and ad hoc testing is responsible for saving lives.

Zhang and Jenkins in their letter state that I did not reference my “claim” that transperineal prostate biopsies curtail antibiotic resistance. I apologise for this; there are simply too many references to choose from. Sticking needles up men’s rectums produces more infection than using needles that do not traverse fecal matter. Multiple studies have shown the lower infection rate with transperineal over transrectal biopsy, and again the former is advocated in specialist UK prostate cancer diagnostic practice. Clearly, having less infection means less antibiotics, which means less antibiotic resistance.

The use of multiparametric magnetic resonance imaging (MRI) before biopsy is also ubiquitous in the United Kingdom, and this strategy further improves diagnostic performance. PSA, MRI, and transperineal biopsies have revolutionized UK prostate cancer practice, with improved cancer detection of significant tumors, decreased detection of insignificant disease (due to targeted/fusion biopsies directed by prebiopsy MRI), and lower morbidity.

Improved diagnosis of significant prostate tumors with reduced morbidity, avoidance of treating insignificant cancers, and fewer deaths from prostate cancer are reasons I continue to advocate for PSA screening. Perhaps once the United States adopts prebiopsy MRI, advanced biopsy techniques, and centralisation of cancer care such that appropriate management decisions are made for patients based on need rather than financial incentives, the case for PSA screening will become more apparent to my American colleagues.

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**In Reply:** I am grateful that Mr. Kurator and Dr. Jenkins took the time to read my commentary and to respond to it. The debate about prostate cancer screening remains fraught, and passions run high on both sides. Like screening for breast cancer, colon cancer, and cervical cancer, screening for prostate cancer has never been shown to have an impact on all-cause mortality in a randomized controlled trial. Some critics of cancer screening argue that without an overall survival benefit, screening should not be recommended. (It is worth noting that colon cancer and cervical

cancer screening can detect precancerous lesions and thus have the additional benefit of reducing the risk of needing more aggressive surgery.) The critics' argument, then, is that it is not enough to reduce your risk of dying of prostate cancer or breast cancer: screening should result in your living longer. The challenge is that any individual disease represents a very small fraction of all-cause mortality, and the disease-specific mortality benefit is thus lost in the noise. There is also the legitimate concern that screening may be increasing other causes of mortality and thus simply exchanging one cause of death for another. There is no space to rehash this argument here, but the disagreement about end points for cancer screening trials persists.

Whether the admittedly modest benefit of prostate cancer screening is worth the harms cannot be answered without including the patient in the discussion: the value placed on the different benefits and harms will vary from man to man. There are experts who are in favor of screening and experts who are opposed to screening, and it would be paternalistic to let patients hear only one side of the debate, hence the role of shared decision-making. It is also important for patients and clinicians to know that prostate cancer screening is evolving, and the decision-making about whom to biopsy and whom to treat has become more nuanced. The hope is that this will increase the benefits and decrease the harms, but that remains to be proven. In the meantime, each of us men needs to decide whether we will choose to be tested. I won't choose for you if you don't choose for me.

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# Koebner phenomenon from insulin injection



**Figure 1.** Erythematous, scaly plaques 5 cm by 5 cm at subcutaneous insulin injection sites.

**A** 68-YEAR-OLD MAN with psoriasis and type 2 diabetes mellitus was seen as an outpatient for management of his diabetes. On examination of subcutaneous insulin injection sites, 2 large erythematous scaly plaques were noted on the abdomen (Figure 1). The patient said he noticed these lesions shortly after he began injecting insulin in his abdomen 5 years ago. He had continued injecting insulin to the same sites on his abdomen. He had never had lesions on his abdomen before he started insulin injections.

Closer examination of the skin of the abdomen revealed 2 well-defined, erythematous, scaly plaques, measuring 5 cm by 5 cm.

The patient was prescribed a concentrated short-acting insulin and advised to change his injection sites to the arms, hips, or legs.

On a follow-up call 2 months later, he reported that the abdominal lesions had improved with a change in injection site and use of a topical steroid cream, and that no new lesions had developed.

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## KOEBNER PHENOMENON

Koebner phenomenon was first described by Heinrich Koebner in 1876 as the appearance of new psoriatic skin lesions at previously unaffected sites due to cutaneous trauma such as bruises, tattoos, and horse bites.<sup>1,2</sup> It has also been described in lichen planus and vitiligo.<sup>1–3</sup>

The pathogenesis of Koebner phenomenon is not well understood.<sup>1</sup> Our case demonstrates an isomorphic response or Koebner phenomenon due to trauma induced by subcutaneous insulin injections in a patient with preexisting psoriasis. The condition can occur at sites not previously affected by psoriasis, such as the abdomen in our patient.<sup>2</sup> The phenomenon can take from 3 days to 2 years to develop after trauma.<sup>2,3</sup>

The differential diagnosis includes conditions such as Wolf isotopic response, reverse Koebner phenomenon (also called Renböck, which is Koebner spelled backwards in German), pseudo-Koebner phenomenon, and pathergy. In Wolf isotopic response, new dermatosis appears in the same areas as previous cutaneous lesions. Reverse Koebner phenomenon involves clearing of skin lesions after trauma. Pathergy can lead to trauma-induced skin lesions like papules and pustules, unlike in Koebner phenomenon in which the skin lesion reflects the underlying skin condition.<sup>4,5</sup>

Koebner lesions are usually treated in the same way as the underlying dermatosis.<sup>4</sup>

## 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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# Fibrous epulis: A tumorlike gingival lesion

**A** 40-YEAR-OLD WOMAN presented with a 1-year history of an enlarging mass on the maxillary gingiva. The mass had been resected 4 years ago but had grown back. She said that she was otherwise in good health.

Examination revealed a nodule—well-circumscribed, smooth, elastic, hard, measuring 20 mm by 18 mm—on the left maxillary anterior gingiva (**Figure 1**). In addition, the left maxillary second incisor was hypermobile, with poor-quality dental restorations. Examination of the neck found no cervical lymphadenopathy.

Computed tomography showed a well-demarcated, rim-enhanced soft-tissue mass in the left maxillary anterior gingiva with slight bone resorption at the left maxillary second incisor (**Figure 2**).

Biopsy was performed, and histopathologic study revealed keratinized epithelium overlying fibrous connective tissue with infiltration of inflammatory cells.

Based on these findings, we diagnosed recurrent fibrous epulis, resected the nodule, and extracted the loose tooth. At follow-up 20 months later there was no evidence of recurrence.

## CLINICAL RECOGNITION AND DIAGNOSIS

Fibrous epulis, a type of inflammatory fibrous hyperplasia of the gingiva, is a relatively common tumorlike lesion.<sup>1,2</sup> The possible origin is the periosteum and the periodontal ligament.<sup>1,2</sup> Factors that lead to its development are local irritations such as poor-quality dental restorations, dental plaque, and calculus.<sup>2,3</sup>

The estimated prevalence of fibrous epulis is 0.09%. It occurs at a wide range of ages and in women more often than men.<sup>4</sup> Most lesions

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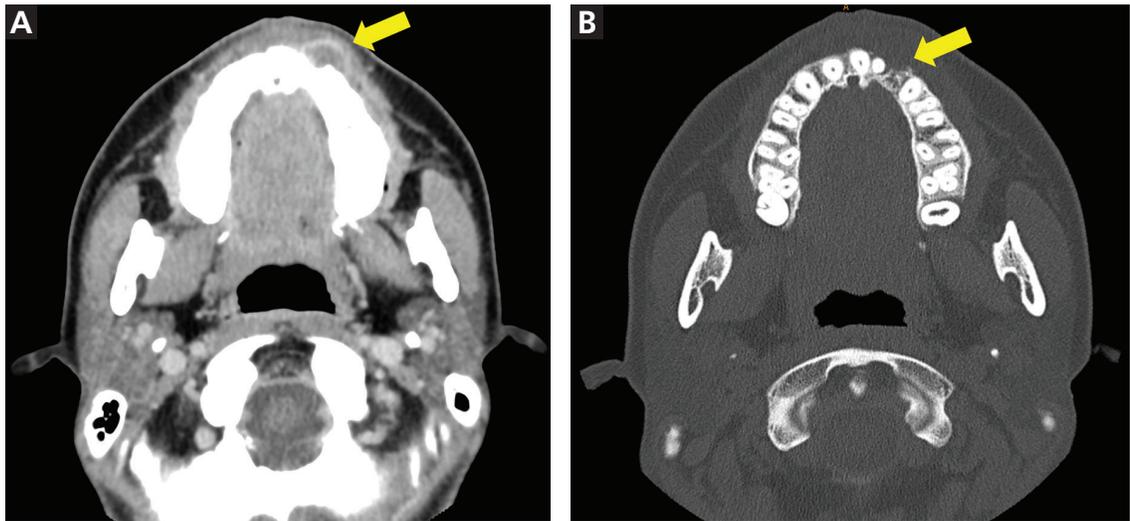
**Figure 1.** A well-circumscribed, smooth-surfaced, elastic, hard nodule, 20 mm by 18 mm, on the left maxillary anterior gingiva.

occur on the maxillary anterior interdental papilla.<sup>1,2,4</sup>

Clinically, fibrous epulis is an asymptomatic, exophytic, smooth-surfaced or focally ulcerated, mucosal-colored mass with a variable growth rate.<sup>2,3</sup> At presentation, most lesions are 10 mm to 20 mm in diameter; those that are large or grow rapidly tend to be misdiagnosed as neoplastic.<sup>2,3</sup>

On computed tomography, lesions appear as a soft-tissue mass in the gingiva with mild enhancement, and up to one-third contain calcifications that can be easily seen.<sup>1,3</sup> These calcified lesions are termed *mineralizing fibrous epulis* or *peripheral ossifying fibroma*.<sup>1</sup> Bone resorption is relatively uncommon.<sup>5</sup>

Histologically, fibrous epulis shows hyperplastic epithelium that overlies fibrous connective tissue.<sup>1</sup> Mineralized tissue, if present, consists of trabeculae or droplike metaplastic bone.<sup>1</sup>



**Figure 2.** Computed tomography shows a well-demarcated, rim-enhanced soft tissue mass in the left maxillary anterior gingiva (A, arrow), with slight bone resorption at the left maxillary second incisor (B, arrow).

The differential diagnosis includes pyogenic granuloma, peripheral giant cell granuloma, fibroma, peripheral odontogenic fibroma, fibrosarcoma, and squamous cell carcinoma.<sup>1,3,5</sup> A slowly growing mass on the interdental papilla with local irritations and calcifications detected by computed tomography should raise suspicion of fibrous epulis.<sup>3</sup> However, distinguishing fibrous epulis from the other conditions listed above may be difficult, and thus, histopathologic study is crucial.<sup>2,3</sup>

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■ TREATMENT

Complete excision and curettage of the lesion is the preferred treatment because the recurrence rate is high, from 7% to 45%.<sup>3</sup> Therefore, long-term follow-up is essential. Tooth extraction is not indicated unless there is underlying bone resorption. ■

■ 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 mass, resected 4 years ago, had grown back

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# Post-acute sequelae of SARS-CoV-2 infection: Caring for the ‘long-haulers’

**ABSTRACT**

An estimated 10% of COVID-19 survivors continue to experience symptoms several weeks to months after the appearance of initial symptoms, a condition termed post-acute sequelae of SARS-CoV-2 infection (PASC). These patients, also called “long-haulers,” most commonly report protracted symptoms of fatigue, cough, dyspnea, chest tightness, difficulty concentrating, arthralgia, olfactory dysfunction, and headache. While age, comorbid medical conditions, and COVID-19 severity are risk factors, young and previously healthy individuals with mild COVID-19 are also at risk. Recognition of symptoms, evaluation, supportive treatment, and attention to medical comorbidities are the cornerstones of medical management.

**KEY POINTS**

If a patient has COVID-19 symptoms at 4 weeks, assess for pulmonary, cardiac, neurocognitive, and psychiatric complications.

In patients with PASC, symptoms may persist for more than 60 days and as long as 6 months.

Focus treatment on managing comorbidities, pulmonary rehabilitation, and continued follow-up.

AS THE COVID-19 pandemic continues globally, there is increasing need to understand the entire disease spectrum and anticipate the long-term management of survivors. Early in the pandemic, adults with mild to moderate COVID-19 were believed to have a short-term course of acute illness lasting approximately 2 weeks, after which symptoms completely resolved. However, emerging data have described a subgroup of patients with a prolonged course of symptoms lasting several weeks to months.<sup>1</sup>

*See related article, page 273*

This protracted form of COVID-19 has been given several descriptive names, including the post-acute COVID-19 syndrome, long COVID, and long-haul COVID-19, with affected patients termed “long-haulers.” But most recently, the National Institutes of Health (NIH) called for a consensus terminology, ie, the post-acute sequelae of SARS-CoV-2 infection (PASC).<sup>2</sup> Although the definition seems to be evolving and is not yet formalized, we currently recognize PASC if symptoms persist for at least 28 days after the onset of COVID-19 symptoms. By building a consensus definition and terminology for PASC, the NIH aims to unify an initiative including \$1.15 billion in grant funding over the course of 4 years to investigate PASC and, hopefully, determine how to treat it.<sup>2</sup>

PASC should be recognized among other sequelae affecting COVID-19 survivors. For example, the postintensive care syndrome (PICS) describes a distinct group of patients who develop new or worsening cognitive, physical, or psychiatric health impairments after suffering critical COVID-19 symptoms

TABLE 1

**Prevalence of COVID-19 symptoms in a series of 143 cases**

Symptom	% of patients	
	At onset	At 60 days
Fatigue	79	56
Dyspnea	67	42
Joint pain	56	26
Chest pain	40	22
Cough	70	18
Anosmia	43	17
Sicca symptoms	22	16
Rhinitis	32	12
Red eyes	27	10
Dysgeusia	50	10
Headache	50	8
Sputum production	18	7
Lack of appetite	56	7
Sore throat	30	6
Vertigo	18	5
Myalgia	56	5
Diarrhea	30	2

Data from Carfi et al, reference 6.

requiring admission to the intensive care unit (ICU).<sup>3</sup> In contrast, PASC applies to the broad range of COVID-19 survivors, from those with mild acute illness who may have never required hospitalization to ICU survivors. Survivors of critical illness associated with COVID-19 can be viewed as likely having an overlap of PICS and PASC as part of the spectrum of post-COVID-19 complications.

**TRUE NUMBERS ARE HARD TO ASSESS**

A marked variability in reported symptoms, duration, and definitions of COVID-19 sequelae in studies makes it difficult to estimate the true incidence of PASC. However, by some estimates, at least 10% of patients who test positive for COVID-19 experience symptoms for longer than 3 weeks.<sup>4</sup>

Although advanced age, obesity, comorbid psychiatric conditions, and other chronic medical conditions are risk factors for PASC,

nearly 20% of suspected cases are in adults ages 18 to 34 with no chronic medical conditions.<sup>5</sup> Studies that included hospitalized patients report an even higher prevalence of protracted symptoms, with data suggesting more than two-thirds of these patients have continued symptoms 6 months after recovery from acute COVID-19.<sup>6,7</sup> We have insufficient data to directly attribute the prolonged symptoms in this population to PASC rather than to other causes of protracted symptoms in hospitalized patients, such as PICS. The prolonged symptoms are likely multifactorial and may be difficult to attribute to a single cause.

**MECHANISMS PROPOSED, BUT PATHOPHYSIOLOGY UNKNOWN**

The pathophysiology of the PASC is not known. Clinicians and researchers are exploring the possibilities of a persistent hyper-inflammatory state, inadequate antibody response, ongoing viral activity, and organ damage as a reflection of acute insult from the infectious phase.<sup>8</sup> Furthermore, it is likely that this syndrome represents a multifactorial presentation attributable to symptoms of underlying medical conditions, features of the acute disease state, and symptoms associated with physical deconditioning from precautionary isolation measures and acute illness.<sup>8</sup>

Despite the chronicity of symptoms, the US Centers for Disease Control and Prevention reports that most immunocompetent patients with mild to moderate COVID-19 are unlikely to be contagious at 10 days after symptom onset, or at 20 days for most immunocompromised patients and patients with severe illness, which allows for discontinuation of isolation precautions at those time points.<sup>9,10</sup>

**A RANGE OF SYMPTOMS**

Data on symptoms of PASC commonly include outpatients with mild to moderate disease severity, but many studies have included patients with severe COVID-19 who required hospitalization with or without ICU admission.<sup>1,8</sup> Most studies to date have recognized symptoms consistent with PASC as persisting after at least 14 to 21 days. Emerging reports are recognizing PASC as persisting symptoms at 28 days in COVID-19 survivors, although an official defi-

dition has not been clearly delineated.

The most commonly reported symptoms are fatigue, cough, shortness of breath, chest pain, difficulty concentrating, arthralgia, low-grade fever, and headache (Table 1).<sup>6-8,11</sup> Other reported symptoms include cognitive impairment (“brain fog”), olfactory and gustatory dysfunction, sleep difficulty, depression, anxiety, gastrointestinal upset, rashes, alopecia, and palpitations.<sup>4,6</sup> Persistent dermatologic manifestations have been described: in a multinational study of patients with dermatologic manifestations, pernio (“COVID toes”) was observed in 103 patients, and persisted at 60 days after diagnosis in 7% of them.<sup>12</sup>

Two studies noted symptoms at the 60-day follow-up in more than two-thirds of patients recovering from COVID-19.<sup>6,7</sup> In a study from Italy, Carfi et al<sup>6</sup> found that at 60 days after onset of COVID-19 symptoms, only 18 (12.6%) of 143 patients were completely free of any COVID-19-related symptom, 32% had 1 or 2 symptoms, and 55% had 3 or more symptoms. Other studies have shown at least 1 persistent symptom, most commonly fatigue or dyspnea, in more than half of patients at 110 days or 180 days, suggesting the longest duration has yet to be determined.<sup>13,14</sup>

Huang et al,<sup>14</sup> reporting on patients 6 months after their acute COVID-19 diagnosis, noted continued fatigue in 63%, sleep difficulties in 24%, and anxiety or depression in 23%. The level of persistent lung diffusion impairment and exercise intolerance at 6 months correlated with the severity of COVID-19 illness.

Of note, PASC affects patients across the spectrum of disease severity. Garrigues et al<sup>13</sup> found no statistically significant difference in the symptoms reported in patients with COVID-19 requiring hospitalization compared with those requiring admission to an ICU. On the other hand, a study from the United Kingdom found nearly twice the rate of psychological distress in patients who required ICU admission compared with those admitted to a general ward.<sup>11</sup>

In a study of outpatients with COVID-19,<sup>5</sup> 35% had not returned to their baseline health 2 to 3 weeks following positive testing for SARS-CoV-2.<sup>5</sup> This trend of protracted symptoms was consistent even in previously healthy patients: approximately 20% of those ages 18

to 34 without chronic medical conditions who were diagnosed with mild COVID-19 not requiring hospitalization reported that they had not returned to their baseline state of health 2 to 3 weeks after testing.<sup>5</sup> Even patients with dermatologic-dominant and otherwise mild COVID-19 have been reported to manifest dermatologic signs of pernio or livedo reticularis for as long as 150 days from initial diagnosis, again demonstrating the range of initial disease severity that variably becomes PASC.<sup>12</sup>

PASC has also had significant global economic impact. A single-center study in France reported that more than 25% of previously active workers (n = 41) discharged from the hospital ward (without ICU stay) had not returned to work after 110 days (mean 110.9 days).<sup>13</sup> An observational cohort study of patients discharged after recovery from COVID-19 in Michigan showed that 40% of previously employed individuals had not returned to work, and that another 15% returned with reduced hours or responsibilities at 60-day follow-up.<sup>15</sup>

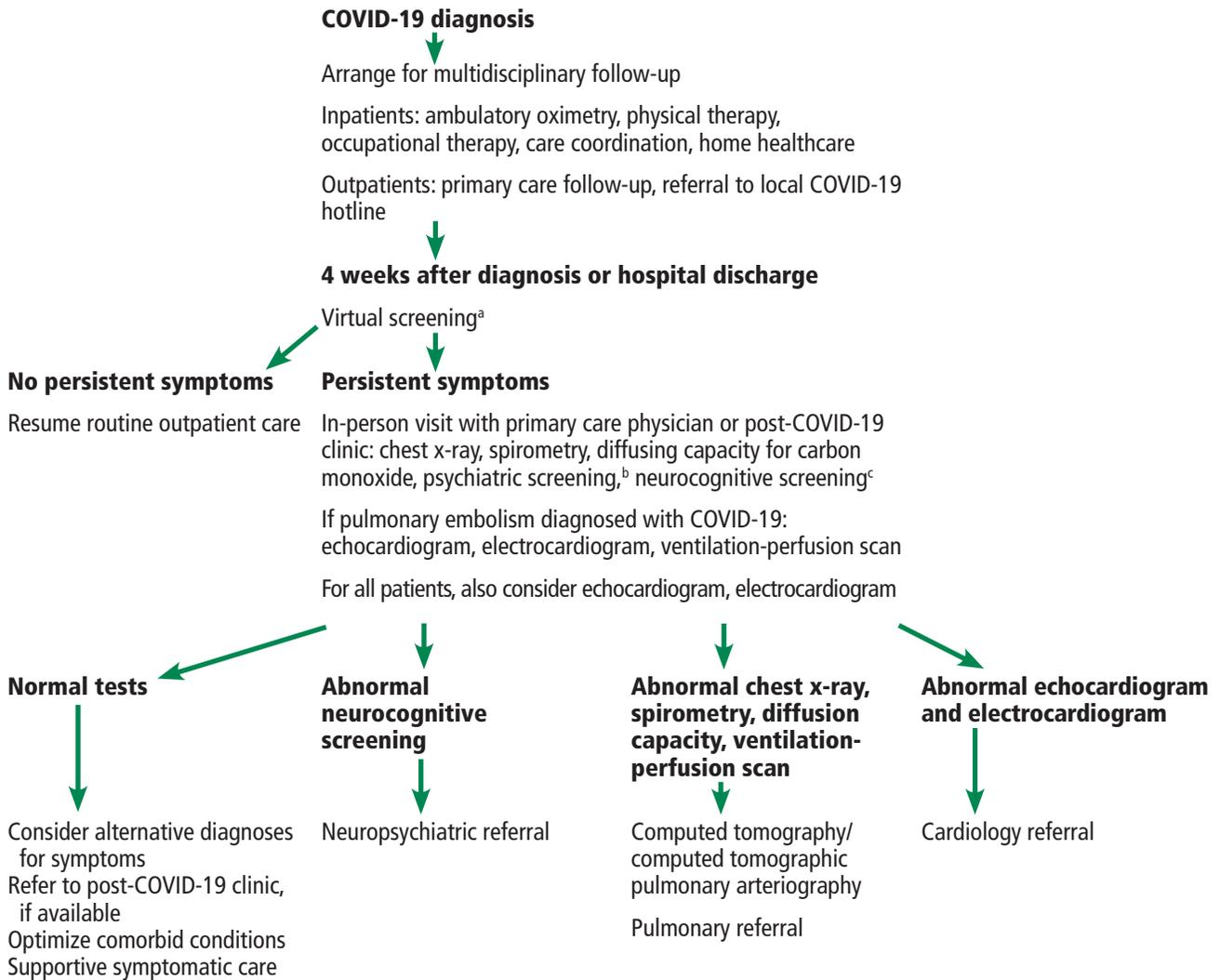
## EVALUATION OF LONG-HAULERS

Guidelines for evaluation of PASC are being developed. Several large centers have created post-COVID-19 clinics that offer a multidisciplinary approach to evaluation and management, including follow-up for noncritically ill patients and post-ICU care. Most clinics accept COVID-19 patients referred for persistent symptoms 1 month after symptom onset. Most use multiple screening measures, including the Montreal Cognitive Assessment, Hospital Anxiety and Depression Scale, and Impact of Event Scale-6, in addition to medication reconciliation, screening for rehabilitation needs, and pulmonary function testing.<sup>16</sup> A Post-COVID-19 Functional Status Scale has been created to grade the severity of symptoms, but it has not been validated or widely implemented.<sup>17</sup>

Multidisciplinary care teams typically include primary care, pulmonology, cardiology, infectious disease, neuropsychiatry, behavioral health, social work, physical and occupational therapy, pharmacy, and case management, but their involvement will vary depending on the particular needs of the patient.

**Nearly 20% of suspected cases are in young adults with no chronic conditions**

## COVID SEQUELAE



<sup>a</sup>Screening tools to consider: Post-COVID-19 Functional Status Scale, COVID-19 Yorkshire Rehabilitation Screen, University of Pennsylvania Post-COVID Screening Measures.

<sup>b</sup>Available psychiatric screening tools: General Anxiety Disorder-7 (GAD-7), Patient Health Questionnaire-9 (PHQ-9; for depression screening), PTSD Checklist for DSM-5 (PCL-5), Impact of Event Scale-6 (IES-R; for PTSD screening), Hospital Anxiety and Depression Score (HADS).

<sup>c</sup>Available neurocognitive screening tools: Montreal Cognitive Assessment (MoCA), Mini-Mental State Examination (MMSE), Cognitive Assessment Tool Rapid Version (CAT-rapid).

**Figure 1.** Care pathway for patients with the post-acute sequelae of SARS-CoV-2 infection.

The British Thoracic Society<sup>18</sup> published a guidance algorithm suggesting a follow-up chest radiograph at the 12-week follow-up. However, the timing of imaging tests must be tailored to the individual patient, with some algorithms suggesting chest radiography or computed tomography at 1 month. Our approach to follow-up evaluation and care is shown in **Figure 1**.

Evaluation of persistent or changing symp-

oms in patients recovering from COVID-19 should be done comprehensively but also judiciously. COVID-19 may unmask or exacerbate underlying disease processes such as chronic lung disease or cardiovascular disease, and may serve as motivation to seek medical care for patients who may not typically schedule routine visits. Basic management of chronic medical conditions is important.

## SPECIFIC TREATMENT FOR SYMPTOMS AND COMORBID CONDITIONS

At present, there are no specific treatments for PASC. But recognizing this syndrome is a key step toward seeking targeted treatment.

Management focuses on specific treatment of the most bothersome symptoms, such as fatigue or cognitive impairment, although efficacy data are lacking. Given the complexity and chronicity of the associated symptoms and their impact on several major organ systems, frequent routine follow-up, establishing rapport, and involving a patient's support system serve as the foundation of management in these patients. A comprehensive, multidisciplinary approach that incorporates detailed management of comorbid medical conditions is the cornerstone of care. Referral to a dedicated post-COVID-19 clinic is recommended, if available.

## LIMITATIONS OF CURRENT DATA, AND LESSONS LEARNED

There are significant limitations in the research efforts to understand the natural history of a pandemic that is merely 1 year old. Limitations include the relatively short time frame of follow-up and a heavy reliance on survey-reporting due to infection-prevention measures that limit in-person follow-up visits.

Reflecting on lessons learned from the out-

breaks of severe acute respiratory distress syndrome (SARS) and Middle East respiratory syndrome (MERS), both caused by related coronaviruses, clinicians should anticipate at least a similar range of long-term effects. Survivors of SARS and MERS have been found to have persistent respiratory compromise with abnormal pulmonary function test results, abnormal chest imaging, increased prevalence of psychological conditions, and fatigue that lasted several months.<sup>19</sup> Mainstays of their treatment included management of comorbid conditions, pulmonary rehabilitation, and ongoing multidisciplinary follow-up aimed at recognizing impairments and improving outcomes.

## FUTURE DIRECTIONS

As part of the PASC initiative, the NIH committed more than \$1 billion in grant funding toward several research initiatives to streamline efforts of the medical and scientific communities to improve our understanding and treatment of PASC. The SARS-CoV-2 Recovery Cohort will be established as a core resource to help investigate PASC as an important public health concern.

## 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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# What is causing the ‘long-hauler’ phenomenon after COVID-19?

COVID-19 HAS BEEN WITH US for more than 1 year (our *annus horribilis*), and many patients suffer long-term consequences. The term for this in the United Kingdom and Italy is *long COVID*; in Spain it is *Covid persistente*, and in Germany it is *mit Corona leben* (living with coronavirus). In the United States, it is commonly referred to as “long-hauler” COVID-19.

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“Brain fog,” tremors, limb stiffness, confusion, and signs and symptoms involving cognitive functions are becoming apparent in long-hauler patients with multiorgan complaints.<sup>1</sup> The frequency and severity of these features and of psychiatric findings are becoming clear.<sup>2</sup> Some speculate that COVID-19 may exacerbate underlying neurodegenerative syndromes such as Alzheimer disease, Parkinson disease, and multiple sclerosis.<sup>3</sup>

A study in London identified the following risk factors for long COVID<sup>4</sup>:

- Age (particularly > 50)
- Sex (women are less likely to develop severe COVID-19 but more likely to develop long-hauler COVID-19)
- Reporting more than 5 symptoms (ie, more than cough, fatigue, headache, diarrhea, loss of sense of smell) in the first week of infection
- Excess weight
- Asthma.

More risk factors are sure to be reported.<sup>5</sup>

## LONG-TERM NEUROLOGIC SEQUELAE OF OTHER INFECTIONS

There is a long history of patients describing chronic nonspecific symptoms after infection.

“Russian influenza,” so named because it apparently began in St. Petersburg in November 1889, is perhaps the first such example. This postinfluenza affliction, also called *grippe catalepsy*, *postgrippal numbness*, *psychosis*, *prostration*, and *inertia*, affected many of the leaders of the United Kingdom, including the prime minister. It kept coming back for over a decade, with an initial epidemic in 1893, and subsequent flares in 1893, 1895, 1898, and 1899–1900.<sup>6</sup>

Epstein-Barr virus infection is another infectious disease with varied long-term consequences. Some patients are ill for only a few weeks, while others experience debility that seems to know no end.

Lyme disease, due to infection with *Borrelia burgdorferi*, causes well-known clinical manifestations and responds to antibiotics—in most patients. A small proportion, however, report fatigue, brain fog, cognitive dysfunction, hallucinations, weakness, tachycardia, numbness, tingling, shortness of breath, “rolling waves of symptoms,” and other nonspecific symptoms that seem interminable. Given that there may be up to 476,000 new cases of Lyme disease per year in the United States,<sup>7</sup> even a small proportion is a large number.

Local outbreaks in which previously healthy people experience chronic and unrelenting nonspecific complaints after infections with *B burgdorferi*, Epstein-Barr virus, or other pathogens have been ascribed, without definitive evidence, to persisting infection. Controversies about the cause may relate directly to

**We are still early in our understanding of COVID-19 and the full spectrum of its manifestations**

this lack of definitive evidence, with patients and practitioners compelled to find a reason for this suffering. All too often, families and clinicians dismiss or minimize these chronic symptoms; and all too often, misguided therapies can lead to toxicity, frustration, and despair.

Similarly, for many years, researchers have sought evidence of prior infection as the cause of myalgic encephalopathy/chronic fatigue syndrome. And many patients with fibromyalgia recount a prior viral illness.

An explanation for the persistence of non-specific complaints, which often begin after an infectious illness, is that these symptoms are related to stress or anxiety, or both. In the current era, this theory was probably aided, if not initiated, by social media. Although postpolio syndrome, chronic brucellosis, epidemic neurasthenia, and epidemic myalgic encephalomyelitis were described long ago, more recent outbreaks have occurred at a time when respect for and trust in medical authority have waned, and many people place their trust in social media, a source of much that is inaccurate, unproven, and often harmful. If the media can stoke anger and resentment to the point of initiating insurrection, they can certainly stir stress, fatigue, and achiness into syndromic pots to serve many others.

Some have explained or dismissed these chronic complaints as being the result of “affective disorders,” a verdict that essentially precludes any further medical investigation as to etiology and mechanism of persistence.<sup>8</sup>

**■ HOW DOES INFECTION DAMAGE THE CENTRAL NERVOUS SYSTEM?**

How can an infection cause brain dysfunction, with long-term symptoms?

SARS-CoV-2 invades the host cell by first binding to angiotensin-converting enzyme 2 (ACE2) on the cell membrane. Entry activates Toll-like receptors 3, 7, and 8; viral RNA sensors in the endosome; and cytosolic receptors, including retinoic acid-inducible gene I, melanoma differentiation-associated gene 5, and nucleotidyl-transferase cyclic guanosine monophosphate-adenosine monophosphate synthase, which then induce secretion of interferons and other inflammatory cytokines.<sup>9</sup>

Then what happens?

**■ LOCAL INFECTION**

Local inflammation related to the immune response to the organism can be indiscriminate, both killing the organism and damaging cells of the nervous system: neurons, endothelial cells, or glial cells (from the Latin for “glue”) including oligodendrocytes, microglia, and astrocytes. Invasion of the brain by SARS-CoV-2 has been established.<sup>10</sup>

Loss of sense of smell, which is common in COVID-19 and occasionally its only clinically apparent feature,<sup>11</sup> may be due to local infection. The olfactory nerve may be an avenue of entry for the virus. SARS-CoV-2 appears to infect the olfactory ciliated cells of the nasal epithelium, causing deciliation<sup>12</sup> with subsequent loss of function.

Normal olfaction does not always return; some patients are left with a perverted sense of smell—eg, coffee smells like barbecue. Possibly, in the process of healing in the nasal epithelium, the rewiring goes awry. This problem is sufficiently common and intrusive that it was the subject of an article in the *New York Times Magazine*.<sup>13</sup>

Other parts of the brain may also be susceptible to infection with SARS-CoV-2, although this is not yet proven. Postmortem studies have found that the ACE2 receptor is expressed broadly in blood vessels of a variety of sizes in the frontal cortex; ACE2 expression was upregulated in patients with hypertension and dementia.

In vitro, the virus did not kill primary human brain microvascular endothelial cells, but its spike protein altered the integrity of the human blood-brain barrier.<sup>14</sup> The spike proteins may trigger inflammatory changes in brain endothelium that alter blood-brain barrier function.<sup>15,16</sup> Subsequent passage of serum inflammatory proteins across the compromised blood-brain barrier may cause damage to the brain.

Inflammatory cells are also found in the brain in this setting.<sup>17</sup> Some of these inflammatory cells may actually be carrying the virus, a phenomenon known as a “Trojan horse,” with infected macrophages spreading the infection.<sup>18</sup> This phenomenon was previously noted in the spread of human immunodeficiency virus.

In the lungs, viral entry through the ACE2

**All too often, families and clinicians dismiss or minimize these chronic symptoms**

receptor into type 2 pneumocytes leads to cell damage and death. Local damage may be spread by toxic effects of cytokines liberated in the inflammatory response to the virus and to these dying cells.<sup>19</sup> A phenomenon of this sort in the brain could cause widespread dysfunction even if the infectious load is minimal.

Local infection might also damage the cells of the central nervous system by inducing changes in local biochemistry. In myalgic encephalopathy/chronic fatigue syndrome, there is evidence of brain inflammation (elevation of lactate in a variety of regions, and of choline, notably in the left anterior cingulate); this area plays an important role in cytokine-induced fatigue.<sup>20</sup> Also in this syndrome, researchers have found elevated temperatures in 5 areas of the brain, suggesting an increase in metabolism, perhaps related to local inflammation.<sup>20</sup> These phenomena have not been sought in COVID-19 long-hauler patients.

Brain damage due to changes in blood flow with stroke and hemorrhage was found in a review of 125 patients in the United Kingdom, as was encephalitis.<sup>2</sup> Paterson et al<sup>21</sup> reported similar findings. The long-term consequences of these phenomena are not yet clear.

### ■ AUTOIMMUNITY, MOLECULAR MIMICRY

Autoimmunity from SARS-CoV-2 infection is suspected to be a major force driving many of the features of COVID-19.<sup>22</sup> A component of the virus might resemble a component of human tissue, a phenomenon known as “molecular mimicry.” The immune response to the viral component then cross-reacts with the human tissue, resulting in a breakdown of tolerance, with subsequent autoimmune damage. Examples of this phenomenon with other pathogens include the following:

- Rheumatogenic *Streptococcus pyogenes* contains a component, M protein, that cross-reacts with heart and brain antigens, causing pancarditis and Sydenham chorea
- *Trypanosoma cruzi* cross-reacts with components of human heart and nerve cells, causing chagasic myocarditis and sensory and autonomic neuropathy
- *Campylobacter jejuni* has been implicated in some cases of the acute motor axonal neuropathy variant of Guillain-Barré syn-

drome; infection with *C jejuni* can elicit formation of antibodies to specific gangliosides, eg, GM1, GD1a, GalNac-GD1a, and GD1b, which are strongly associated with the acute motor axonal neuropathy.

The Miller-Fisher syndrome, a variant of Guillain-Barré syndrome manifesting as ataxia, areflexia, and ophthalmoplegia, has been reported following COVID-19. Immunoglobulin G antibodies to GD1b-IgG were detected in 1 of 2 patients with post-COVID Miller-Fisher syndrome reported from Spain.<sup>23</sup> It is likely that the immunogenetic background of an individual will determine if such autoimmunity occurs.

There are many possible examples of clinically significant molecular mimicry in COVID-19. Certain peptides of SARS-CoV-2 are similar to those of alveolar surfactant protein. SARS-CoV-1 also shares 6 minimal immune determinants with the Kawasaki antigen inositol triphosphate 3 kinase C,<sup>24</sup> of note because there have been reports of patients with COVID-19 developing a syndrome similar to Kawasaki syndrome.<sup>25-27</sup> Other human proteins with sequences similar to those of SARS-CoV-2 include interleukin 7 (a deficiency of which predisposes to severe lymphopenia) and histone-lysine *N*-methyl transferase C (linked to neurodevelopmental and behavioral abnormalities and seizures).<sup>24</sup>

Infection with SARS-CoV-2 damages cells as the virus replicates, having hijacked the cell's own mechanisms for protein synthesis. The cell ultimately ruptures, disgoring the new virus particles. During this cell lysis, cellular contents are released. In the correct immunogenetic background, these intracellular molecules, previously shielded from immune surveillance, could elicit an autoimmune response. A similar phenomenon occurs in “sympathetic ophthalmia,” in which unilateral ophthalmic trauma can lead to bilateral ophthalmic inflammation.<sup>28</sup>

### Antibodies induce antibodies, and so on ad infinitum: The id network

Another potential mechanism evolves from the normal method of dampening a humoral immune response. Idiotypes (ids) are the antigenic epitopes found in the antigen-binding portion of immunoglobulin molecules. The id is unique to

**Local infection of the brain may occur and cause damage or dysfunction, or both**

this newly produced antibody and, as a unique and new protein, is immunogenic, eliciting an antibody response, ie, anti-id antibodies. There is, similarly, a series of anti-anti-id antibodies and anti-anti-anti-id antibodies, each with a lower peak, ultimately dampening the response as a normal regulatory mechanism.

But what if the network that emanates includes an id reactive with human tissue? When *Escherichia coli* dextrin was given to mice, the anti-id network that emanated included an antibody to the human acetylcholine receptor,<sup>29</sup> an antibody linked to myasthenia gravis. In the humoral immune response to SARS-CoV-2, which binds to its ACE2 receptor, an immune response to the virus might lead to an anti-anti-id antibody that might mimic the viral spike protein binding site that plugs into the ACE2 molecule, thereby producing an antibody that binds to ACE2, thereby targeting the cell and perhaps activating complement that would then damage the targeted cells. This is called the “internal image” suggested in the initial development of the id-network therapy and now being used therapeutically.<sup>30</sup> There is as yet no evidence of this being relevant to COVID-19.

It is currently strongly suspected that COVID-19 induces autoimmunity in some patients, perhaps those with an underlying propensity for autoimmunity. There are now reports, often posted electronically before peer review, of patients having circulating antibodies to cells of the blood vessels, heart, and brain, and also autoantibodies to annexin A2, a molecule found in the small blood vessels of the lung, serving to stabilize cell membranes.<sup>31</sup> Immune cells such as B cells can also be targeted by autoantibodies,<sup>32</sup> as can be platelets, causing an autoimmune thrombocytopenia complicating COVID-19.<sup>33</sup> In one study, about 10% of SARS-CoV-2-infected patients had antibodies to type 1 interferon, a molecule that usually enhances immune responses.<sup>34</sup>

#### Antiphospholipid antibodies and thrombosis

The thrombophlebitis that often complicates COVID-19 and can cause serious morbidity may be autoimmune as well.

Many patients produce autoantibodies to phospholipids,<sup>35</sup> and some develop what appears to be an antiphospholipid antibody syn-

drome,<sup>36</sup> long known to cause thrombophlebitis, pulmonary embolism, thrombocytopenia, recurrent pregnancy loss, various neurologic deficits, cardiac valvulitis (Libman-Sacks endocarditis), renal damage, and skin lesions, notably livedo reticularis. Such antibodies have also been found transiently after other viral infections (eg, parvovirus B19, hepatitis C virus, human immunodeficiency virus, varicella zoster infections), although in most postinfectious cases these antibodies do not result in thrombosis or inflammation.<sup>37</sup> The reason for the propensity to thrombosis in COVID-19 infection is not yet clear.

In addition to autoantibodies, thrombosis may be promoted by neutrophil extracellular traps during COVID-19 infection.<sup>38</sup>

#### ■ CYTOKINE STORM

Systemic (and possibly local), poorly modulated production of excess cytokines can have an adverse effect on the brain. Alpha interferon given for hepatitis C virus infection caused profound fatigue and often depression. Interleukin 6, a notable cytokine in severe COVID-19, is produced by lymphocytes, monocytes, fibroblasts, and bronchial epithelium. In severely ill patients, elevated interleukin 6 levels cause an increase in levels of C-reactive protein and ferritin, as well as elevations of D-dimer. The cytokine pattern seen in COVID-19 cytokine storm<sup>39</sup> is similar to that seen in hemophagocytic lymphohistiocytosis.<sup>40</sup> Elevated levels of interleukins 1, 4, 7, 10, 12, and 17, tumor necrosis factor, granulocyte colony-stimulating factor, interferon gamma-inducible protein 10, monocyte chemoattractant protein 1, and macrophage inflammatory protein 1 alpha have also been reported as part of this cytokine storm.<sup>41</sup> Some of these cytokines may be produced within the central nervous system, but there is evidence that the SARS-CoV-2 spike protein can alter the blood-brain barrier.

There is evidence suggesting that interleukin 6 can regulate synaptic transmission and plasticity as well as other neuronal functions; in animal models, interleukin 6 has been found to influence cognitive function.<sup>42</sup> High levels of interleukin 6 and of C-reactive protein have each been found to be associated

**Cytokines, both local and systemic, may cause changes in central nervous system function**

with changes in local blood flow in the brain.

### COVID-19 AND BRAIN DAMAGE: SUMMING UP

We are still early in our understanding of COVID-19 and the full spectrum of its manifestations. Mechanisms whereby it could cause brain dysfunction and damage include but are not limited to the following:

- Local infection causing cell damage caused by the virus or “innocent bystander” inflammatory damage
- Autoimmunity
- Persistence of dysfunction due to cellular disarray and faulty regeneration
- Local production of cytokines with alteration of function
- Systemic cytokine effect through a dysfunctional blood-brain barrier
- Local tissue metabolic changes due to decreased blood flow
- Altered blood flow due to thrombotic occlusion.

An appreciation of these and other underlying causes of long-hauler COVID-19 may lead to targeted therapies.

### PEOPLE ARE SUFFERING

The current pandemic has been emotionally draining and very traumatic to many people. Long-term isolation, the constant worrying

about interactions and masks and hand sanitizers being sufficiently protective, the fear for oneself and for one’s parents and children—all certainly contribute to a heightened level of anxiety that is immunologically and spiritually damaging. After a year on high alert, people are experiencing an unparalleled combination of combat fatigue and posttraumatic stress, and these may contribute to, but are almost certainly not the entire cause of, the persistence of symptoms.

The long-hauler phenomenon calls for an enhanced and empathetic response to the people experiencing these symptoms and to their families. Simply because there is no specific test or finding to diagnose these patients does not mean they are not suffering and certainly does not mean that their suffering is not real. No mechanisms are yet proven, but recall that in the past, miasmatic air was thought to be the cause of malaria, rheumatoid arthritis was thought to be due to tuberculosis or gout, and scurvy due to “internal putrefaction” from faulty digestion related to the hardships of life at sea and the naval diet. With further research, explanations for long-hauler COVID-19 symptoms may become clearer.

### 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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# Vaccinating the unvaccinated adult

## ABSTRACT

The percent of US children who are not vaccinated has been increasing, and so have the rates of communicable diseases. As the unvaccinated and undervaccinated population ages, practitioners are likely to see more adult patients who have never been vaccinated. This article reviews the recommendations for vaccinating previously unvaccinated patients and addresses potential barriers and concerns adult patients may have about vaccines.

## KEY POINTS

The tetanus, diphtheria, and acellular pertussis (Tdap); mumps, measles, and rubella (MMR); and varicella vaccines are recommended for all unvaccinated adults.

Other vaccinations are not routinely recommended unless the patient meets certain criteria, eg, travels internationally, is a healthcare professional, or has no spleen.

Just over 7 in 10 children receive all the recommended vaccinations.

**A** 24-YEAR-OLD WOMAN with no known medical history presents at our outpatient clinic to discuss getting vaccinated for the first time. She hopes to get the mumps vaccine because of outbreaks at Temple University near her home in Philadelphia, PA. Her parents did not have her vaccinated as a child because of fears of vaccines causing illnesses, and she did not tell them that she wanted to get vaccinated, as she believed it would cause family strife.

She asks about our recommendations for vaccines for her.

## ■ INCREASING NATIONAL OUTBREAKS AND UNVACCINATED CHILDREN

In the United States, cases of communicable diseases are increasing, even those once considered eliminated. For example, from January 1 to August 1, 2019, 1,172 cases of measles in 30 states were reported to the US Centers for Disease Control and Prevention (CDC), the highest number since 1992, and drastically higher than the 372 cases reported in all of 2018.<sup>1</sup> The number of cases of mumps has also increased significantly during the past several years.<sup>2</sup>

As cases of measles and similar communicable diseases increase, the percentage of children who are unvaccinated is also increasing. Fortunately, more than 90% of US children age 19 to 35 months have received the vaccines for polio, for measles, mumps, and rubella (MMR), and for hepatitis B, according to the 2017 National Immunization Survey-Child (NIS-Child),<sup>3</sup> and more than 7 in 10 children received all the recommended vaccinations. Unfortunately, 1.3% of toddlers had received no vaccinations by 24 months of age, up from 0.3% in 2001.<sup>3</sup>

Vaccination rates were lowest in uninsured children, those insured by Medicaid, and those residing in more rural areas. While only 2.8% of children were reported as uninsured, they

**TABLE 1**

## Vaccinations recommended for unvaccinated adults

Vaccine	Dosing	Contraindications	Precautions
<b>Tetanus, diphtheria, acellular pertussis (TDaP)</b>	3 doses: 1–2 months between doses 1 and 2 and 6–12 months between doses 2 and 3  Give TD booster every 10 years after initial regimen completed	Prior severe allergic reaction to the vaccine or its components	Moderate or severe acute illness with or without fever  For pertussis-containing vaccines only, in patients with progressive or unstable neurologic disorder, uncontrolled seizures, or previous encephalopathy, defer use until a treatment regimen has been established and the condition stabilizes
<b>Measles, mumps, rubella (MMR)</b>	Give 1 dose if born in 1957 or later  Give 2 doses (no sooner than 4 weeks after initial dose) to high-risk groups: <ul style="list-style-type: none"> <li>• Any healthcare personnel</li> <li>• Students entering college</li> <li>• International travelers</li> </ul> If pregnant, MMR should be given postpartum	Prior severe allergic reaction to the vaccine or its components  Pregnancy or possible pregnancy within 4 weeks  Severe immunodeficiency (hematologic and solid tumors, active chemotherapy, congenital immunodeficiency, HIV with severe immunocompromise)	Moderate or severe acute illness with or without fever  If blood, plasma, and/or immunoglobulin were given in the last 11 months, follow the ACIP best practices <sup>14</sup>  History of thrombocytopenia or thrombocytopenic purpura
<b>Varicella (chickenpox)</b>	Give 2 doses: second dose 4–8 weeks after first dose; if delayed, do not start over, just give second dose	Prior severe allergic reaction to the vaccine or its components  Pregnancy or possible pregnancy within 4 weeks  People who are on long-term immunosuppression or are immunocompromised  Vaccine can be considered in patients with CD4 count $\geq$ 200 cells/mm <sup>3</sup>	Moderate or severe acute illness with or without fever  If blood, plasma, and/or immunoglobulin were given in last 11 months, follow ACIP best practices <sup>14</sup>  Recipient of specific antivirals (acyclovir, famciclovir, valacyclovir) 24 hours before vaccination  Use of aspirin-containing products as there is an increased risk of Reye syndrome

ACIP = Advisory Committee on Immunization Practices (part of the US Centers for Disease Control and Prevention); HIV = human immunodeficiency virus

Adapted from reference 16.

made up 17.2% of all unvaccinated children.<sup>3</sup>

There is evidence that most cases of vaccine-preventable diseases were in the unvaccinated population. A 2016 review of 18 measles studies found that 59.2% of cases (574 of 970 in which vaccination records were available) were in patients who were completely unvaccinated despite being vaccine-eligible, and many more were undervaccinated. Of the patients who were not vaccinated, 70.6% (405 of 574) had nonmedical exemptions to vaccination for various religious or philosophical reasons.<sup>4</sup>

In early 2019, a measles outbreak occurred in Clark County, Washington, with 53 re-

ported cases. Of the patients with measles, 47 (89%) were unvaccinated, 5 had unverified vaccination status, and just 1 had confirmed vaccination. The state of Washington is 1 of 15 US states that allows a philosophical exemption to vaccinations.<sup>5</sup> For the 2017–2018 school year, nearly 5% of children enrolled in Washington schools were not vaccinated because of philosophical exemptions, with numbers even higher in Clark County (7.9%).<sup>6</sup>

### ■ WHY ARE VACCINATION RATES SO LOW?

Several reasons account for the rising rates of nonvaccination and undervaccination.

TABLE 2

**Vaccinations not routinely recommended for unvaccinated adults**

Vaccine	Indications	Dosing	Contraindications
<b>Hepatitis A</b>	<ul style="list-style-type: none"> <li>• Desire to be protected from hepatitis A virus (HAV)</li> <li>• Travel or work outside of United States</li> <li>• Chronic liver disease, use of injected or noninjected drugs, homeless, receiving clotting-factor concentrates, works with HAV in laboratory, food handlers when appropriate</li> <li>• Close contact with international adoptee from country where HAV is endemic during the first 60 days after adoptee's arrival</li> </ul>	<p>2 doses, 6–18 months apart depending on brand</p> <p>If second dose is delayed, do not start over, just give dose</p>	<p>Prior severe allergic reaction to the vaccine or its components</p> <p>Cautions: Moderate or severe acute illness with or without fever</p>
<b>Hepatitis B</b>	<ul style="list-style-type: none"> <li>• Wants to be protected from hepatitis B virus</li> <li>• Has close household contact of hepatitis B surface antigen-positive people, chronic liver disease, injects drugs, sexually active with multiple partners, male who has sex with men, human immunodeficiency virus-positive, hemodialysis patients or may soon need dialysis, diabetes and younger than 60</li> <li>• Is a healthcare worker or person exposed to blood, inmates of long-term correctional facilities</li> </ul>	<p>Heplisav-B: 2 doses, 1 month apart</p> <p>Engerix-B and Recombivax HB: 3 doses (1 mL each) at 0, 1, 6 months</p> <p>If patient is receiving hemodialysis or is immunocompromised:</p> <ul style="list-style-type: none"> <li>• Recombivax HB: 1 dose of 4 mL at 0, 1, 6 months</li> <li>• Engerix-B: 2 doses of 2 mL given simultaneously at 0, 1, 2, 6 months</li> <li>• Heplisav-B: 2 doses 1 month apart</li> </ul> <p>If schedule delayed, do not start over, continue from where schedule was interrupted</p>	<p>Prior severe allergic reaction to the vaccine or its components</p> <p>Cautions: Moderate or severe acute illness with or without fever</p>
<b>Haemophilus influenzae type B</b>	<ul style="list-style-type: none"> <li>• Anatomic or functional asplenia</li> <li>• Undergoing elective splenectomy</li> <li>• Received a hematopoietic stem cell transplant (HSCT)</li> </ul>	<p>Give 1 dose of any <i>H influenzae</i> type B conjugate vaccine</p> <p>If received HSCT, 3 doses at least 4 weeks apart beginning 6–12 months after transplant</p>	<p>Prior severe allergic reaction to the vaccine or its components</p> <p>Cautions: Moderate or severe acute illness with or without fever</p>
<b>Inactivated polio</b>	Plans to travel to areas where exposure to wild-type virus is likely	0, 2, 4, 16 months 4–6 year schedule with minimum interval of 4 weeks between doses	<p>Prior severe allergic reaction to the vaccine or its components</p> <p>Cautions: Moderate or severe acute illness with or without fever; pregnancy</p>
<b>Meningococcal conjugate</b>	<ul style="list-style-type: none"> <li>• Student younger than age 21 living in residence hall</li> <li>• Has anatomic or functional asplenia, is HIV-positive, or has persistent complement component deficiency</li> <li>• Travel to countries where meningococcal disease is endemic</li> <li>• Microbiologist routinely exposed to isolates of <i>Neisseria meningitidis</i></li> </ul>	<p>If college student age 19–21 living in residence hall, give 1 dose</p> <p>If asplenic, give 2 initial doses at 0 and 2 months with booster every 5 years</p> <p>If traveling or has exposure risk, give 1 initial dose with booster every 5 years</p>	<p>Prior severe allergic reaction to the vaccine or its components</p> <p>Cautions: Moderate or severe acute illness with or without fever</p>
<b>Meningococcal serogroup B</b>	<ul style="list-style-type: none"> <li>• Anatomic or functional asplenia or persistent complement component deficiency</li> <li>• Microbiologist routinely exposed to isolates of <i>N meningitidis</i></li> <li>• At risk because of a serogroup B meningococcal outbreak</li> </ul>	<p>Bexsero at 0 and 1 months</p> <p>OR</p> <p>Trumenba at 0, 1–2, and 6 months</p>	<p>Prior severe allergic reaction to the vaccine or its components</p> <p>Cautions: Moderate or severe acute illness with or without fever</p>

Adapted from reference 16.

### Autism link discredited, but some people still believe it

Foremost in the minds of many vaccine-hesitant parents is a controversial case series published in 1998 that suggested that the MMR vaccine may lead to behavioral regressions and developmental disorders, including autism.<sup>7</sup> The case series itself was significantly flawed in having a small sample size of 12 patients, an uncontrolled design, and conclusions that were largely speculative.

There was an almost immediate backlash, and several epidemiologic studies refuted the series' conclusions.<sup>8-10</sup> Shortly afterward, 10 of the 12 coauthors offered a retraction, concluding that no link existed between the vaccine and developmental disorders, including autism. There were further ethical implications after it was revealed that the lead author failed to disclose that he received funding from lawyers involved in lawsuits against vaccine manufacturers.

In 2010, the publisher (*Lancet*) officially retracted the original article,<sup>11</sup> and the lead author was removed from the UK medical registry,<sup>12</sup> but by then the damage was done. For example, a review of the 2011 NIS-Child (N = 12,259) found that 21.4% of parents of unvaccinated children and 9.9% of parents of children who received at least 1 MMR dose believed that the vaccine is linked to autism.<sup>13</sup>

### Religious and philosophical objections

Many state vaccination laws allow religious exemptions or philosophical exemptions to vaccination.<sup>5</sup>

### Lack of access is probably the biggest reason

A 2015 multivariable analysis using data from the 2010–2013 NIS-Child and NIS-Teen suggested that reasons other than negative vaccine-related beliefs accounted for most of the unvaccinated children and adolescents.<sup>13</sup> In fact, the authors found that 74.6% of parents of unvaccinated children did not have negative opinions of vaccines, and only 34.6% refused vaccines. What they did find was that compared with vaccinated children, unvaccinated children were more likely to be uninsured, to be of lower socioeconomic class, and to have unmarried parents.

This analysis suggests that missed opportunities to vaccinate are more common than parents overtly refusing vaccination. Reviewing a patient's vaccination records at every visit as well as sending patients reminders via cell phone have been shown to improve immunization rates and combat missed vaccine opportunities.<sup>13</sup>

### TDaP, MMR, AND VARICELLA FOR ALL UNVACCINATED ADULTS

Our patient had asked which vaccines we would recommend for her as a vaccine-naive adult. The CDC has comprehensive vaccination recommendations on its website<sup>14</sup>; however, they do not speak directly to the growing population of unvaccinated adults. The Immunization Action Coalition, a nonprofit organization partially funded by the CDC, has recommendations for adult vaccinations that are more simplified.<sup>15</sup>

For our patient, a few vaccines are absolutely recommended (**Table 1**), and some are generally not recommended except under certain circumstances (**Table 2**).<sup>16</sup> Only the tetanus, diphtheria, and acellular pertussis (TDaP), MMR, and varicella vaccines are recommended for all unvaccinated adults.

**The TDaP vaccine** is given in a 3-dose series, with the second dose 1 to 2 months after the first dose and the third dose 6 to 12 months after the second dose. A tetanus booster should be given every 10 years after the series is completed.

**The MMR vaccine** is given only if the patient was born in 1957 or later. It is given as a single dose unless the patient works in healthcare, is a student entering college, or travels internationally. In those situations, the patient should receive a second dose 4 weeks after the first dose.

**The varicella vaccine** is given as a 2-dose series, with the second dose 4 to 8 weeks after the initial dose.

All 3 of the recommended vaccinations can be given safely at the same time.<sup>17</sup>

### OTHER VACCINES, FOR SOME PEOPLE

The remaining vaccinations are not routinely recommended unless the patient meets certain criteria, eg, travels internationally, is a

Only the TDaP, MMR, and varicella vaccines are recommended for all unvaccinated adults

healthcare professional, or is asplenic (Table 2). Patients can receive those vaccinations when specifically requested. Additional vaccinations including influenza, human papillomavirus infection, and pneumococcal vaccines should be encouraged, if indicated.

Providers should also check for contraindications to the live attenuated vaccines (ie, MMR, varicella, herpes zoster, rotavirus, yellow fever, and intranasal influenza vaccines). These vaccines should be avoided in patients who are pregnant or may become pregnant within 4 weeks after administration; these patients should be counseled to use contraceptives for 1 month after vaccination.

Live attenuated vaccines should also be avoided in patients with severe immunodeficiency, including hematologic and solid malignancies, active chemotherapy, congenital immunodeficiencies, and human immunodeficiency virus. Other less common examples of immunosuppression are listed on the CDC website.<sup>18</sup>

### ■ ADDRESSING PATIENT CONCERNS

Patients presenting to discuss vaccinations may have questions, concerns, and anxieties pertaining to the vaccines. They may be concerned about acute postvaccination reactions as well as potential long-term adverse reactions, regardless of their vaccination history. For these patients, it is important to maintain a calming presence while addressing each question and concern honestly. It can be helpful to start by asking, “What specific questions do you have about the vaccines?”

Patients should be assured that they cannot get the disease from the vaccine. They should also be informed that reactions such as soreness and redness at the injection site and low-grade fever, if they occur, are not serious, and usually last no longer than 48 hours.<sup>19</sup> Even patients with known egg allergy can be vaccinated without restriction or observation, as the rate of anaphylaxis is just over 1 in 1 million.<sup>20</sup>

If patients have questions about vaccine preservatives such as aluminum and mercury-containing thimerosal, you can explain that those preservatives help prevent vaccine contamination or growth of microbes, as

well as allow for multiuse vials. If patients are concerned that preservatives in vaccines can cause diseases such as autism or can lead to mercury poisoning, you can inform them that multiple international studies have found preservatives to be safe in both childhood and adult vaccines.<sup>21,22</sup> More information on addressing reasons for vaccine reluctance was published in the *Cleveland Clinic Journal of Medicine* in December 2019.<sup>23</sup>

With the increasing use of single-dose containers, thimerosal is used much less frequently. In fact, reformulations have focused on significantly reducing mercury-containing preservatives as strictly precautionary measures, not because of safety concerns. If a patient is still hesitant, recommended vaccines are available in formulations that do not contain thimerosal.<sup>24</sup>

Other patients may be concerned about receiving multiple vaccinations at the same time. As we have mentioned, data show that the recommended vaccinations can be administered together safely. If necessary, vaccinations can be given at different appointments and time intervals based on the patient’s specific preferences and availability. There are many online resources for patients that discuss common concerns and misconceptions in simplified language, notably the CDC and the Immunization Action Coalition.<sup>25–27</sup>

### ■ VACCINATION IN THE TIME OF COVID-19

The current COVID-19 pandemic and subsequent rapid development and availability of effective COVID-19 vaccines have amplified the discussions around the safety and necessity of adult vaccination. Even before this pandemic, the World Health Organization recognized vaccine hesitancy as a top threat to global health.<sup>28</sup>

The factors that lead to hesitancy over COVID-19 vaccination are similar to those with other vaccines, but also include the rapidity of vaccine development, as well as political factors that reflect the larger political polarization of the pandemic.<sup>29</sup>

In a large study of adult Americans,<sup>30</sup> over 20% of respondents reported vaccine hesitancy, with racial and ethnic minorities having higher reported vaccine hesitancy in group

**Online resources for patients about common concerns and misconceptions, in simplified language, include the CDC and the Immunization Action Coalition**

comparisons, as did patients living in rural areas, those with lower household incomes, and those with lower levels of education.

Focus group discussions with Black participants living in communities of high COVID-19 prevalence suggested that vaccine skepticism was driven by a number of factors, including historical mistreatment of the Black community, the accelerated timeline of vaccine development, and limited data on long-term side effects.<sup>31</sup> These same focus group discussions also demonstrated that acceptance increased if the recommendation for vaccination came from a trusted healthcare provider, a finding that has also been seen in other studies.<sup>32</sup>

Ultimately, at the individual clinician level, concerns over the COVID-19 vaccines should be addressed in much the same way as concerns over other vaccines—by eliciting questions and concerns in a nonjudgmental,

patient-centered way, and addressing the concerns compassionately and honestly. In order to address COVID-19 vaccination hesitancy, clinicians will need to be equipped with current, accurate information, which will likely come from both self-directed learning and institutional support and training.<sup>29</sup>

## CASE CONCLUSION

After counseling and reassurance, our patient successfully received the 3 recommended vaccines (MMR, TDaP, and varicella) without issue and is scheduled to return to complete the regimens. The patient agreed to devote time at future visits to discuss human papillomavirus vaccination and to consider an influenza vaccination when it is due.

## 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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## REVIEW

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# Quetiapine for primary insomnia: Consider the risks

## ABSTRACT

The second-generation antipsychotic drug quetiapine (Seroquel) is increasingly being used off-label for treating insomnia in the general population, possibly to avoid standard medications with known addictive qualities and adverse side effects. However, evidence to support using it in this way is scant, and quetiapine is associated with weight gain and other metabolic effects. It must be used cautiously and with appropriate monitoring for adverse effects and abuse.

## KEY POINTS

Quetiapine affects multiple central nervous system receptors, resulting in a variety of effects, including sedation.

The use of quetiapine to treat insomnia should be confined primarily to patients with comorbid mood or schizophrenia spectrum disorders.

Compared with many other antipsychotic drugs, quetiapine is less associated with dystonia and extrapyramidal side effects but tends to cause weight gain, metabolic syndrome, and QTc prolongation.

Body mass index, weight, blood pressure, fasting glucose, and lipid levels should be measured before starting treatment and then regularly monitored, even for low doses.

Despite having no euphoric effects, quetiapine is often abused to enhance or counter side effects of illicit drugs.

Quetiapine carries particular risks for elderly patients.

PRESCRIPTIONS FOR QUETIAPINE (Seroquel), a second-generation antipsychotic medication, have risen sharply in recent years.<sup>1,2</sup> Despite its approval by the US Food and Drug Administration (FDA) only for the treatment of schizophrenia, bipolar disorder (depression, acute mania, and maintenance), and major depressive disorder (as an adjunct medication),<sup>3</sup> only a minority of patients filling prescriptions for quetiapine have these diagnoses. Rather, quetiapine is increasingly being used off-label, including for insomnia, anxiety, agitation, and posttraumatic stress disorder (PTSD).<sup>4</sup> It is generally regarded as being nonaddictive and having a good safety profile. However, its cardiometabolic effects and potential for abuse warrant caution for its off-label use.

This article focuses on the use of quetiapine for treating insomnia, its basic pharmacology, evidence of efficacy, and adverse effects, and it provides recommendations for clinical monitoring of patients receiving the drug.

## ■ AN INCREASINGLY POPULAR DRUG

Second-generation antipsychotic use has increased worldwide, with quetiapine, risperidone, and olanzapine being the most frequently prescribed.<sup>1</sup> In Canada, prescriptions written by family physicians for quetiapine increased 300% from 2005 to 2012, with a 10-fold increase in its use for sleep disorders.<sup>2</sup> The pattern was similar in the United States from 1996 to 2003, with up to 70% of prescriptions for second-generation antipsychotics being written for conditions other than psychosis.<sup>4</sup>

Bertisch et al,<sup>5</sup> using US National Health and Nutrition Examination Survey data from 1999 to 2010, found that nearly 3% of 32,328 respondents reported having used a common-

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TABLE 1

**Quetiapine activity in the central nervous system**

Doses	Low (25–100 mg daily)		Medium (300–600 mg daily)	High (> 800 mg daily)
Receptors	Histamine 1	Alpha 1/alpha 2 adrenergic	5-HT1A, 5-HT2A/B, 5-HT2C	D2
Activity	Antihistaminergic	Antiadrenergic	Serotonergic	Antidopaminergic
Effect	Sedation		Antidepressant properties	Antipsychotic properties

ly prescribed insomnia medication over the previous month. Quetiapine ranked fourth among frequently prescribed medications, following the “Z-drugs” (the benzodiazepine receptor agonists zolpidem, zaleplon, and eszopiclone), trazodone, and benzodiazepines.<sup>5</sup>

Prescriptions for quetiapine to treat sleep disturbances have also increased in Australia, New Zealand, and the United Kingdom.<sup>6–8</sup>

**POTENTIAL FOR ABUSE**

Quetiapine, used alone, does not produce euphoria or other pleasurable effects typically associated with drugs of abuse, but it can enhance or counter the side effects of substances such as marijuana, cocaine, and heroin,<sup>9</sup> a practice that is colloquially referred to as “seroquelling.” Although the mechanism underlying its rewarding effects remains elusive, misuse of the drug may be driven by its ability to counteract overstimulation caused by other substances of abuse.<sup>10</sup> There are also reports of quetiapine use for “self-detoxification,” in an effort to mitigate withdrawal symptoms from other substances such as alcohol, cocaine, benzodiazepines, and opioids.<sup>9</sup> These trends appear to be more prevalent in correctional facilities (where commonly abused drugs are not readily available) and among patients with a previous history of substance abuse.<sup>9</sup> Those who abuse quetiapine typically consume high doses, which has led to several cases of accidental overdose, some of which have been fatal.<sup>9</sup>

These emerging patterns of abuse, along with the drug’s potential metabolic and cardiac complications, signal the need for caution for use in the general patient population.

**DIFFERENT DOSES HAVE DIFFERENT EFFECTS**

Quetiapine works similarly to other second-generation antipsychotics, but its uniqueness lies in the various affinities of the drug and its active metabolite (norquetiapine) for multiple central nervous system receptors in a dose-dependent manner (Table 1). Lower dosages primarily affect histaminergic (H1) and alpha 1 and alpha 2 adrenergic receptors, mediating sedative effects.<sup>11</sup> Medium and high doses have an additive affinity for serotonergic receptors (5-HT1A, 5-HT2A, 5-HT2B, 5-HT2C) and the dopamine D2 receptors, causing mood stabilization and improvements in anxiety, deep sleep, and psychosis.<sup>12</sup>

This quality of increasing doses causing different effects has led to the “Goldilocks” analogy: “Papa Bear” doses (> 800 mg daily) are for treatment of schizophrenia, “Mama Bear” doses (300–600 mg daily) are for mood disorders, and “Baby Bear” doses (25–100 mg daily) are for sedative-hypnotic effects.<sup>13</sup>

Among antipsychotics drugs, quetiapine is the least potent binder of the D2 receptor and has the fastest dissociation time from it, which explains the larger doses required for achieving antipsychotic effects as well as its lower incidence of extrapyramidal side effects.<sup>12,14</sup>

**PHARMACOKINETIC PROFILE LENDS ITSELF TO ABUSE**

Quetiapine is available as an oral tablet in an immediate-release formulation (time to peak plasma level 1.5 hours) and an extended-release formulation (6 hours).<sup>2,15</sup> Its half-life, about 6 hours, is the shortest of all the second-generation antipsychotics.

**Cardiometabolic effects and potential for abuse warrant caution for its off-label use**

The short duration to peak plasma concentration with the immediate-release formulation is generally comparable with that of many of the approved hypnotics, including Z-drugs and benzodiazepines.<sup>16</sup> At peak plasma levels, H1-receptor occupancy is more than 90% at just 50 mg of the immediate-release formulation,<sup>13</sup> which is consistent with the receptor profile for strong hypnotic effects even at the lowest therapeutic doses.

Quetiapine's pharmacokinetic profile may make it more attractive for abuse, especially for crushing tablets for intravenous injection or intranasal snorting. It can also be mixed with other drugs of abuse<sup>9</sup> to achieve faster and more intense effects, such as sedation and relaxation. Quetiapine taken through such alternative routes is associated with an increased risk of neuroleptic toxicity.<sup>10</sup>

### ■ ADVERSE EFFECTS

#### Weight gain, metabolic effects

Common adverse effects of second-generation antipsychotics include weight gain and motor symptoms.<sup>17</sup> Clozapine and olanzapine are more recognized for causing weight gain, but long-term use of quetiapine is also associated with moderate weight gain (10 kg on average), as well as development of metabolic syndrome.<sup>18</sup> The mechanism behind weight gain in this class of drugs is unclear, but antihistaminergic effects may be causing enhanced appetite.

Second-generation antipsychotics also increase levels of blood glucose and low-density lipoprotein cholesterol, effects that seem to resolve when treatment is stopped.<sup>19,20</sup> While weight gain alone is concerning, the metabolic changes associated with second-generation antipsychotic use can lead to higher risk of cardiovascular disease and stroke, with quetiapine among the antipsychotic drugs associated with the largest metabolic effects.<sup>21</sup>

#### Low doses not totally harmless

Whether quetiapine's metabolic effects occur even at low doses has been investigated in retrospective studies. Cates et al<sup>22</sup> studied 43 patients taking low-dose quetiapine for insomnia. About two-thirds of them gained weight: daily dosages below 200 mg at bedtime used for an average of 11 months were associated

with an average weight gain of 4.9 lb ( $P = .037$ ) and a body mass index (BMI) increase of  $0.8 \text{ kg/m}^2$  ( $P = .048$ ).

Carr et al<sup>23</sup> studied 403 veterans taking low-dose quetiapine (average daily dose 116.8 mg) for an average of 44 months. Statistically significant increases were found in systolic blood pressure (1.95 mm Hg,  $P = .036$ ), diastolic blood pressure (1.97 mm Hg,  $P = .001$ ), BMI ( $0.52 \text{ kg/m}^2$ ,  $P = .001$ ), weight (1.88 kg,  $P = .002$ ), and fasting blood glucose ( $6.71 \text{ mg/dL}$ ,  $P = .002$ ).

Williams et al<sup>24</sup> investigated low-dose quetiapine ( $< 100 \text{ mg}$  daily for at least 1 month) in 534 patients in military hospitals. The mean weight gain was  $5.56 \pm 1.25 \text{ lb}$  ( $P < .001$ ) at 6 months and  $10.58 \pm 2.20 \text{ lb}$  ( $P < .001$ ) at 12 months compared with baseline.

#### Extrapyramidal effects

The low affinity of quetiapine for the D2 receptor, as well as a preference for binding to D2 receptors in the limbic pathway over the striatum, make movement disorders a less prominent side effect.<sup>25</sup> However, extrapyramidal adverse effects do occur,<sup>19</sup> with reports of restless legs syndrome, tardive dyskinesia, akathisia, and periodic leg movement disorder.<sup>14</sup> In studies of quetiapine for bipolar disorder, the incidence of extrapyramidal symptoms increased in a dose-dependent manner, occurring in around 7% to 12% of patients.<sup>26,27</sup>

#### QTc prolongation

Quetiapine's labeling carries a warning for QTc prolongation. Risk is dose-dependent.

#### Sedation

Given their action on histamine receptors, second-generation antipsychotics commonly cause sedation. Quetiapine also has sleep latency-enhancing properties (reducing the time from being fully awake to falling asleep), attributable to its serotonergic action, leading to the drug's off-label use for insomnia.<sup>11</sup> Outside of this context, sedation is generally considered to be an undesirable side effect for most patients.<sup>18</sup>

#### Some side effects lessened

Quetiapine's low affinity for D2 receptors results in fewer of the endocrine side effects associated with antipsychotic drugs, namely, prolactin elevation and associated amenor-

Use of second-generation antipsychotics has increased worldwide

rhea, galactorrhea, sexual dysfunction, and osteoporosis.<sup>12,14,18</sup>

**■ CONCERNS FOR THE ELDERLY**

Use of second-generation antipsychotics is becoming more widespread in the elderly as clinicians try to avoid adverse effects (particularly extrapyramidal symptoms) of traditional antipsychotics.<sup>28</sup> However, use of second-generation antipsychotics comes with its own set of risks in this population. Second-generation antipsychotics have received FDA black-box warnings for a nearly twofold increase in incidence of cardiovascular events, stroke, and overall mortality.<sup>21</sup> The American Geriatrics Society 2019 Beers Criteria note an increased rate of cognitive decline associated with antipsychotics in patients with dementia and strongly recommends avoiding their use in this population.<sup>29</sup>

Given its action on adrenergic receptors, quetiapine can be associated with orthostatic hypotension, especially in the elderly.<sup>12</sup> Syncope from hypotension can lead to hip fractures, transient ischemic attacks, myocardial infarction, and even death.<sup>21</sup> A 2013 study investigating 4 second-generation antipsychotics to treat psychiatric conditions in patients over age 40 found a high incidence of side effects (50% of participants) and life-threatening conditions (24%), noting that adverse effects were twice as common with quetiapine than with the other drugs.<sup>30</sup> Furthermore, quetiapine’s clearance is about 40% lower in elderly patients than in younger patients.<sup>25</sup> In view of the increasing use of second-generation antipsychotics in the elderly, these findings are especially worrisome.

**■ STANDARD INSOMNIA MEDICATIONS HAVE DISADVANTAGES**

The *Diagnostic and Statistical Manual of Mental Disorders, fifth edition*<sup>31</sup> defines insomnia as difficulty initiating sleep, difficulty maintaining sleep, or early morning awakening, resulting in significant physical or emotional distress. Insomnia affects about 30% of the population worldwide, and 10% have symptoms that severely affect their daily function.<sup>32</sup> People with insomnia often experience irritability, fatigue, physical distress, and impaired cognition.<sup>32</sup> The disorder has been linked with poor academic

and work functioning as well as cardiovascular disease, cancer, diabetes, and hypertension.<sup>32</sup> Therapeutic goals for patients with insomnia include improving sleep and daytime function and reducing distress.<sup>32</sup>

**Benzodiazepines and Z-drugs**

Benzodiazepines and Z-drugs have been approved by the FDA for treating insomnia. They enhance gamma-aminobutyric acid (GABA) neurotransmission, leading to sedation, reduced sleep latency, and increased sleep efficiency. While benzodiazepines non-specifically bind to GABA receptors in the central nervous system, Z-drugs preferentially bind to the GABA receptor alpha-1 subunit, making them less sedating. This subunit mediates sleep effects while appearing to confer a better safety profile for the Z-drugs.<sup>11</sup> However, to varying degrees, both classes are associated with cognitive and memory impairments, rebound insomnia, risk of dependence and misuse, as well as car accidents, falls, and workplace accidents.<sup>11</sup>

Because benzodiazepines are associated with tolerance and subsequent withdrawal, treatment is recommended for only 2 to 4 weeks at a time.<sup>33</sup> Given these risks and limitations, as well as the status of these drugs as schedule IV controlled substances requiring prescription monitoring, physicians are often hesitant to prescribe them to patients in favor of alternatives.<sup>6</sup>

**■ IS QUETIAPINE THE ANSWER?**

Quetiapine is increasingly being turned to as an off-label alternative for treating insomnia, owing to its well-known sedative and sleep-promoting effects at low doses.

**Study in healthy men**

In a seminal 2004 study, Cohrs et al<sup>34</sup> explored the effects of quetiapine on sleep architecture and subjective sleep quality in 14 healthy men, using self-assessment and polysomnography recordings 3 times (4 days apart) for 3 consecutive nights. In the second set (standard sleep conditions) and third set (acoustic stress conditions), treatment was given on the first and second night, consisting of either placebo, quetiapine 25 mg, or quetiapine 100 mg by mouth 1 hour before sleep.

**Second-generation antipsychotics increase weight, glucose, and low-density lipoprotein cholesterol**

Relative to placebo, quetiapine 25 mg and 100 mg significantly improved subjective sleep quality and sleep initiation, duration, and efficiency, with a dose-dependent increase in stage 2 sleep. Periodic leg movements during sleep were noted with quetiapine 100 mg.

### Studies in mood and psychotic disorders

Guidelines from the American Academy of Sleep Medicine<sup>35</sup> and others agree that off-label use of antipsychotics should be avoided, although quetiapine may be useful for insomnia in patients with psychiatric disorders.

In 2009, Wine et al<sup>36</sup> reviewed 10 controlled studies and case reports assessing the effects of immediate-release quetiapine on sleep in patients with bipolar disorder, schizophrenia, history of trauma, or depression. Their analysis suggested that quetiapine improved total sleep time, efficiency, and subjective sleep within a dose range of 12.5 mg to 800 mg; however, decreased rapid-eye-movement sleep was noted in some populations. Notable adverse events included akathisia, metabolic changes, and periodic leg movements.

In 2014, Anderson and Vande Griend<sup>37</sup> analyzed studies investigating quetiapine for insomnia, including a review of the 2010 EM-BOLDEN II (Efficacy of Seroquel for Bipolar Depression) trial,<sup>38</sup> which found that quetiapine improved sleep in patients with bipolar depression over 8 weeks. Despite this, Anderson and Vande Griend argued that given the insufficient evidence of efficacy for treating insomnia and potential risks associated with the drug, they did not recommend quetiapine for insomnia even in patients with psychiatric disorders.

In 2008, Endicott et al<sup>39</sup> conducted a secondary analysis of the large multicenter, randomized, placebo-controlled BOLDER (Bipolar Depression) I and II trials, which had demonstrated efficacy of quetiapine for acute bipolar depression.<sup>26,27</sup> In a secondary analysis, they found sleep quality and total sleep time to be improved among patients treated with quetiapine.

### Studies in posttraumatic stress disorder

Some data support the use of quetiapine for PTSD symptoms such as nightmares and insomnia. A 2005 study<sup>40</sup> in 20 postwar veterans with PTSD found that adding low-dose quetiapine resulted in significant improvements in sleep quality, latency, duration, night ter-

rors, and nightmares.

A 2016 randomized controlled trial<sup>41</sup> investigating quetiapine monotherapy for treatment of PTSD found a statistically significant reduction in the total Clinician-Administered PTSD Scale score ( $P = .02$ ) and its re-experiencing ( $P = .0004$ ) and hyperarousal ( $P = .007$ ) subscale scores compared with placebo. No statistically significant differences in weight or blood pressure were found between groups, but quetiapine use was associated with increased somnolence and sedation.

Byers et al<sup>42</sup> compared prazosin and quetiapine for treating nighttime symptoms in veterans with PTSD ( $N = 237$ ) and found that short-term effectiveness of the 2 drugs was similar at 60%. However, patients taking prazosin were significantly more likely to remain in the study, and those in the quetiapine group were likelier to stop the medication because of side effects.

### Studies for primary insomnia

A 2012 summary of a 2011 Agency for Healthcare Research and Quality review of safety and efficacy data of off-label uses for atypical antipsychotics<sup>17</sup> was inconclusive concerning the use of quetiapine for insomnia. Only 1 relevant study met the authors' inclusion criteria: a 2010 study<sup>43</sup> in just 13 patients with primary insomnia conducted in Thailand. In this randomized, double-blinded, placebo-controlled trial, participants received either quetiapine 25 mg or placebo each night for 2 weeks. There were nonsignificant trends for longer total sleep time and shorter sleep latency in the quetiapine group.

The 2014 Anderson and Vande Griend<sup>37</sup> analysis of studies investigating quetiapine for insomnia concluded that data were insufficient to make a decision regarding safety and efficacy for this use. Existing literature was scarce, consisting of studies that included only small numbers of patients with specific conditions, and few studies used objective sleep quality measures such as polysomnography. They concluded that given its high side-effect profile and lack of data on efficacy, quetiapine should not be used to treat insomnia.

In 2018, Atkin et al<sup>11</sup> reviewed the evidence for multiple pharmacologic agents used for insomnia and compared their effect on sleep physiology. The authors concluded that there was

**Detecting  
metabolic  
effects  
requires  
vigilance**

limited evidence to support the use of quetiapine for insomnia in the general population, but there may be a role for using it to improve sleep in patients with conditions that can be treated with quetiapine, such as psychotic or mood disorders. They also concluded that compared with other medications used for insomnia, quetiapine poses a low risk of dependence.

**■ MANY BELIEVE OFF-LABEL QUETIAPINE TO BE SAFER THAN ALTERNATIVES**

Why do some clinicians prescribe quetiapine off-label?

In 2017, Chow et al<sup>44</sup> reviewed the use of nighttime-only quetiapine in 83 children and adolescents treated in an inpatient psychiatric setting. Forty seven (57%) received it for insomnia alone, and 21 (25%) received it for insomnia plus another indication. Youths in the first group had longer lengths of stay and were more likely to be female and have anxiety, eating disorders, or borderline personality disorder. Hence, quetiapine probably was prescribed in an effort to target multiple issues (eg, mood, anxiety, sleep) while avoiding polypharmacy.

In 2018, Kelly et al<sup>45</sup> investigated outpatient prescribing of quetiapine among family physicians. Quetiapine was generally reserved for patients who had not responded to other therapies or had psychiatric comorbidities or difficult social backgrounds. Many physicians prescribed it to avoid benzodiazepine use and minimize risk for abuse. Many physicians interviewed believed that low doses of quetiapine were generally safe, so they did not monitor patients for side effects.

**■ CLINICAL RECOMMENDATIONS**

**Considerations for use for primary insomnia**

Given the scant evidence in favor of using quetiapine in the general population to treat insomnia and the risk of metabolic side effects even at low doses, the drug should be used with caution and only after other drug options have been exhausted. Practitioners should also consider prescribing it only in short courses in an effort to limit its long-term effects.<sup>20</sup> For patients currently using it, providers should look for opportunities to discontinue it if clinically indicated.

**TABLE 2**

**Recommendations for monitoring during quetiapine treatment**

**At baseline**

- Body mass index
- Waist circumference
- Blood pressure
- Fasting glucose
- Fasting lipids

**After initiation**

- Electrocardiography
- Potassium level
- Extrapyramidal side effects (using the Abnormal Involuntary Movement Scale [AIMS])

**At 4, 8, and 12 weeks after initiation**

- Body mass index

**Three months after initiation**

- Blood pressure
- Fasting glucose
- Fasting lipids

**Routinely at follow-up visits**

- Body mass index
- Extrapyramidal side effects (using AIMS)
- Signs of misuse, abuse, or other drug-seeking behavior

**Annually**

- Blood pressure
- Fasting glucose
- Fasting lipids

**With dose or risk factor changes**

- Electrocardiography
- Potassium level

Based on information in reference 20.

Before prescribing quetiapine, one should compare its expected benefits (improved mood, sleep, functioning) and risks (metabolic syndrome, motor side effects, abuse).<sup>21</sup>

Age and comorbidities should be considered, particularly personal and family history of obesity, diabetes, dyslipidemia, hypertension, and cardiovascular disease.<sup>20</sup>

Given its reduced drug clearance in older individuals, caution should be used when dosing quetiapine for patients over age 65.

Patients at risk of QTc prolongation (those with heart disease, advanced age, taking other QTc-prolonging medications, electrolyte abnormalities, bradycardia, con-

genital long QT syndrome) should have an electrocardiogram and potassium level obtained after initiation and any time the dose or risk factors change.<sup>21</sup>

As with other second-generation antipsychotic drugs, signs of agranulocytosis should be monitored.

In pregnancy, antipsychotics may increase the risks of gestational diabetes, hypertension, and congenital malformation, although evidence for the safety of quetiapine in this setting is limited and conflicting.<sup>21</sup>

### Monitor for metabolic changes

Detecting metabolic effects requires vigilance. Recommendations from the American Diabetes Association and allied organizations in 2004 are outlined in **Table 2**.<sup>20</sup> In patients with existing metabolic or cardiovascular disease or in those who gain 5% or more of their initial weight, alternative medications or closer monitoring is required.

### Monitor for movement disorders

Patients should also be monitored for extrapyramidal side effects (**Table 2**), as some may be irreversible (eg, tardive dyskinesia) or otherwise cause distress (eg, restless legs syndrome, akathisia). Emergence of abnormal movements is most commonly monitored using the Abnormal Involuntary Movement Scale,<sup>46</sup> a survey consisting of 12 physical examination findings related to movement disorders. The scale can be employed routinely to detect tardive dyskinesia and monitor its severity over time. Provider familiarity with the scale as well as regular monitoring during follow-up visits is imperative to detect tardive dyskinesia early.<sup>46</sup>

### Consider potential for abuse

Risk of drug abuse should be considered when weighing the risks and benefits of prescribing quetiapine.<sup>10</sup> It is important to identify patients who are at high risk of drug abuse (eg, prisoners, patients with a history of anxiolytic, sedative, or hypnotic misuse or abuse) at the onset of treatment, and to continue to monitor risk throughout treatment.<sup>47</sup> Pa-

tients should be monitored for signs of tolerance, such as increasing dose or seeking other drugs.<sup>2</sup>

However, the risk of misuse, abuse, and dependence with quetiapine is not as high as with benzodiazepines and Z-drugs, which require extensive follow-up and monitoring, possibly including in-person visits every 6 months to 1 year (minimum of every 3 months if the patient is also taking other controlled medications), yearly drug screening, monitoring in a state prescription monitoring and reporting system, limitations on quantity prescribed, and 2-point identification for prescribers, depending on local legislation.<sup>33,48</sup> Second-generation antipsychotics do not require this level of monitoring.

### ■ BOTTOM LINE

In general, with proper monitoring, quetiapine may help to treat insomnia in patients with comorbid schizophrenia or mood disorders. Some data also support the use of quetiapine for nightmares and insomnia related to PTSD.

Evidence is insufficient to support the broad use of quetiapine to treat insomnia in the general patient population. Several organizations—including the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity, and the American Geriatric Society—have cautioned against using quetiapine off-label for sleep.<sup>20,35</sup>

Physicians need alternatives when facing difficult decisions about managing highly distressed patients. Other FDA-approved medications for sleep should be tried before quetiapine. And nonpharmacologic strategies, such as meditation, cognitive behavioral therapy for insomnia, and sleep hygiene, should always be recommended before drugs are given. ■

### ■ DISCLOSURES

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

**Always  
recommend  
nonpharmacologic  
strategies  
for sleep  
before giving  
drugs**

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## CORRECTION

### Update in perioperative cardiac medicine 2021

In the April 2021 issue, in Cohn SL. Update in perioperative cardiac medicine 2021. *Cleve Clin J Med* 2021; 88(4):216–220, doi:10.3949/ccjm.88a.21014, in the final paragraph, the sentence, “Until further data are available, the risk of chronic atrial fibrillation in patients with new-onset postoperative atrial fibrillation may be warranted only in patients with a thromboembolic risk above 1.5%...” should read as follows: “Until further data are available, the risk of chronic anticoagulation in patients with new-onset postoperative atrial fibrillation may be warranted only in patients with a thromboembolic risk above 1.5%...” This has been corrected online.

## REVIEW

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# CABG: When, why, and how?

## ABSTRACT

Coronary revascularization has matured as a field since coronary artery bypass grafting (CABG) was first developed over 50 years ago, with diagnostic and treatment methods having advanced dramatically. CABG remains the standard of care for obstructive coronary artery disease, particularly for patients with multivessel disease or diabetes. It is now recognized that not all CABG is created equal—operative strategy, including conduit choice for bypass grafts and target coronary selection, affects survival. A multidisciplinary approach including surgeons with a special interest in CABG is recommended to optimize treatment selection and outcomes.

## KEY POINTS

The main criteria guiding the selection of revascularization therapy are disease stability, procedural risk, patient comorbidities, atherosclerotic burden, and lesion complexity.

In general, CABG is preferred over percutaneous coronary intervention in patients with a heavy atherosclerotic burden and diabetes, and those without multiple significant baseline comorbidities, frailty, or short life expectancy.

CABG with arterial grafts can improve patient longevity, particularly with appropriate patient and coronary artery target selection.

Multiple arterial grafts should be considered over single thoracic artery and multiple vein conduits.

Less-invasive strategies are emerging.

Guideline-directed medical therapy in coronary artery disease is essential for improved outcomes in primary and secondary prevention.

CORONARY ARTERY BYPASS GRAFTING (CABG) has been performed for more than 50 years. And even though the procedure is increasingly being used for older and higher-risk patients, outcomes have improved substantially over time. The surgery has developed beyond a “cookie-cutter” generic cardiac operation, and the use of a multidisciplinary, experienced heart team approach has become important.

This review briefly describes:

- The evolution of CABG
- Guidance for diagnosing coronary artery disease and determining the best strategy for intervention
- Conduit selection for CABG, including evidence supporting multiple arterial grafting
- The emergence of less-invasive strategies
- Enhanced recovery after surgery protocols
- The importance of medications.

## NEED FOR CABG IS GREAT

Every year, about 18 million Americans are diagnosed with coronary artery disease, the most common cause of death in the United States.<sup>1</sup> The estimated annual incidence of new myocardial infarctions is 720,000, in addition to about 335,000 recurrent infarctions.<sup>1</sup> Isolated CABG is the most common cardiac surgical procedure in North America.<sup>2</sup>

## EVOLUTION OF A SURGERY

In 1968, Cleveland Clinic established CABG as the standard of care for obstructive coronary artery disease.<sup>3</sup> Two years later, a Cleveland Clinic team led by René Favaloro<sup>4</sup> reported on the workup and favorable outcomes of more than 300 patients who underwent “venous autograft reconstruction” with appropriate follow-up.<sup>4</sup>

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All-venous-conduit CABG reigned from 1968 until January 1986, when Loop et al<sup>5</sup> demonstrated improved graft patency and a 10-year actuarial survival with internal thoracic artery (ITA) grafts compared with saphenous venous grafts anastomosed to the left anterior descending (LAD) coronary artery (86.6% vs 75.9% survival). The authors acknowledged that a randomized controlled trial would be beneficial to confirm their findings, but that this would not be possible because “present knowledge about late patency rates would bias the offering of the internal mammary [thoracic] artery and saphenous vein as comparable conduits in a trial.”<sup>5</sup> And they were right.

Pursuit of improved outcomes has intensified in the current era of public reporting. Perioperative mortality rates have been reported nationally at 2% (and at < 1% at some centers of excellence).<sup>3</sup> But beyond perioperative mortality and morbidity, interest in improving long-term outcomes has grown. Debate continues about the use of bilateral ITA grafting and other multiarterial grafting strategies. Minimally invasive options and robotic assistance are also evolving.<sup>6</sup> Given all these highly technical approaches requiring high-volume surgeon experience, some have recently called for coronary revascularization to be recognized as a subspecialty within cardiac surgery.<sup>7,8</sup>

### ■ DIAGNOSTIC METHODS HAVE ADVANCED

Coronary angiography remains the gold standard for diagnosing coronary artery disease.<sup>9</sup> Optical coherence tomography, intravascular ultrasonography, fractional flow reserve, cardiac computed tomographic angiography, and cardiac magnetic resonance imaging (MRI) are newer diagnostic methods that provide more than a simple subjective visual estimation of coronary narrowing; they provide information on granular anatomic and physiologic features of coronary lesions and the downstream effect on the myocardium.

#### Role of fractional flow reserve

Stenosis seen by 2-dimensional angiography does not always reflect a flow-limiting lesion.<sup>10</sup> In fact, residual stenosis determined by coronary angiography does not affect outcomes

if the patient is completely revascularized by fractional flow reserve criteria.

In the setting of percutaneous coronary intervention (PCI) in multivessel coronary artery disease, fractional flow reserve has been found to be superior to coronary angiography. Unfortunately, this has not been rigorously studied for surgical revascularization.<sup>10,11</sup> Extrapolating the utility of fractional flow reserve to CABG entails the risk of erroneously downgrading a multivessel disease scenario or underestimating disease severity and forgoing CABG for a less invasive but also less durable therapy.

We have only limited data to correlate fractional flow reserve with graft patency. While venous grafts are not vulnerable to competitive flow from native coronary vessels, arterial grafts are at risk for failure when bypassing less-than-severe lesions. Compared with radial grafts, ITAs appear to be less vulnerable to competitive flow, with no clear stenosis cut-off and with excellent long-term patency rates even when used to bypass moderately diseased vessels.<sup>12</sup> Radial grafts should only be used to bypass occluded or severely diseased vessels.<sup>13</sup>

### Cardiac MRI has evolved dramatically

Late gadolinium enhancement cardiac MRI is a noninvasive nonstress test that has become the most sensitive and specific viability test. Image resolution is superior to that of single-photon-emission computed tomography, and it identifies smaller, more distinct areas of fibrosis. Acutely, late gadolinium enhancement cardiac MRI can overestimate infarcts early due to tissue edema, but a transmural uptake of less than 50% infers functional improvement.

### ■ TREATMENT CONSIDERATIONS

Three main factors should be considered when deciding on an intervention strategy.

**Disease stability.** Stability of coronary artery disease and presentation—ie, ST-elevation myocardial infarction (STEMI), non-STEMI, or stable angina—are factored into the management algorithm. PCI is the treatment of choice for STEMI; for non-STEMI and stable angina, recommendations are more nuanced. In patients with stable coronary artery disease and low-risk anatomic features,

**A multidisciplinary, experienced heart team approach to CABG is important**

PCI has failed to show convincing evidence of benefit beyond a modest reduction in angina.<sup>14,15</sup> Comparisons of CABG and medical therapy are dated, and emphasis now is on complementary rather than competing therapies.<sup>16,17</sup> Medical treatments (eg, high-intensity statins, dual antiplatelet therapy, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and novel glucose-lowering agents) are transforming primary and secondary cardiovascular prevention in patients with stable angina, resulting in reduced event rates in recent years.<sup>18</sup> Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for patients with type 2 diabetes mellitus and renal impairment are associated with reduced disease progression and recurrent ischemic events.<sup>19</sup>

**Procedural risk and patient comorbidities.** CABG risk is most commonly and reliably estimated by the Society of Thoracic Surgeons risk calculator, which estimates the risk of perioperative mortality and major morbidity.<sup>20</sup> The latter includes stroke, with about a 1% perioperative rate, which is slightly higher than the risk associated with PCI.<sup>21</sup> Advanced age is an important risk factor for stroke and periprocedural mortality, but it should be considered in the context of other risk factors when choosing between therapies.

Risk models perform well at a population level but are limited for estimating risk for individuals, particularly for patients with rare comorbidities (eg, cirrhosis) or unique risk profiles. Patients with significant baseline comorbidities, frailty (not captured by the Society of Thoracic Surgeons calculator), and reduced life expectancy are best suited for PCI.

**Atherosclerotic burden and disease complexity.** Coronary artery disease complexity is often assessed using the Synergy Between PCI With TAXUS and Cardiac Surgery (SYNTAX) trial score,<sup>22</sup> which is incorporated in the American College of Cardiology–American Heart Association criteria for treatment selection. A heavy atherosclerotic burden favors CABG over PCI.<sup>23</sup>

### ■ LEFT MAIN DISEASE

Historically, the mortality rate in untreated left main coronary artery disease is about

50% at 3 years.<sup>24</sup> It is a heterogeneous condition that may involve the ostia, midshaft, bifurcation, or trifurcation. The specific areas involved affect the feasibility and success of PCI but have no bearing on CABG success or durability. The role of PCI vs CABG in left main disease is controversial, with 2 recent trials showing seemingly different findings. However, neither favored PCI over CABG.<sup>16</sup>

The 5-year Evaluation of XIENCE vs Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial showed noninferiority of PCI and CABG for left main disease, but an increased rate of all-cause mortality with PCI at 5 years.<sup>25</sup>

The 5-year Nordic-Baltic-British Left Main Revascularization (NOBLE) trial, while not powered for mortality, showed that PCI was inferior to CABG for left main disease for reintervention and nonprocedural myocardial infarction, a marker of mortality.<sup>26</sup>

About 10% of STEMIs involve the left main coronary artery. In STEMI or hemodynamic instability, PCI is the treatment of choice. In non-STEMI and stable ischemia, the American College of Cardiology–American Heart Association guidelines give the highest recommendation for CABG for all SYNTAX levels (class I, level of evidence A)<sup>27</sup>; PCI is recommended at this level only for low-risk SYNTAX scores.

### ■ MULTIVESSEL DISEASE

Left main and multivessel coronary artery disease are treated as different entities in the literature, even though less than 15% of lesions are isolated left main disease. SYNTAX 10-year data show an all-cause mortality benefit for CABG over PCI in patients with 3-vessel disease (21% vs 28%).<sup>28</sup>

Current guidelines recommend CABG over PCI for multivessel coronary artery disease in patients with diabetes and for those with left ventricular dysfunction.<sup>27</sup> Even for severe left ventricular dysfunction (ejection fraction < 35%), CABG is associated with improved long-term outcomes, including survival, compared with PCI for patients with indications for CABG and who can tolerate the stress of surgery.<sup>29</sup>

Why CABG improves outcomes for left

**Isolated CABG is the most common cardiac surgical procedure in North America**

main and multivessel coronary artery disease is likely multifactorial. The distal insertion of a bypass graft is downstream from where most future atherosclerotic disease might develop. In addition, use of arterial grafts that are resistant to atherosclerosis enhances long-term patency. Data suggest that the incremental benefit of CABG is strongly associated with the use of the ITA.<sup>30</sup> Finally, surgical revascularization more frequently achieves complete revascularization, which is associated with improved survival.

### ■ CONDUIT SELECTION FOR CABG

Conduit selection is a current topic of debate.

**Saphenous vein.** Attrition of the saphenous vein graft, the Achilles' heel of CABG, occurs in phases. The first phase is nearly immediate and likely related to a technical factor. This can be avoided with intraoperative evaluation of the bypass graft. Transit-time flow meters can identify low graft flows due to thrombosis, kinking, conduit dissection, coronary dissection, or anastomosis stenosis, all of which are potentially correctable.<sup>31</sup> Subsequent phases of vein graft failure include intimal hyperplasia and atherosclerosis. Saphenous vein graft attrition rates of 1% to 2% per year for the first 6 years and 4% per year for the next decade have been reported.<sup>32</sup>

**Arteries vs veins.** Dimitrova et al<sup>33</sup> reported that angiography over a 15-year period revealed that coronary territories bypassed with arteries had less disease progression compared with territories bypassed with veins. The internal elastic lamina of arterial grafts protects them from disease progression. Native coronary disease is also protected by arterial grafts for unclear reasons, but possibly due to the downstream effect of vasoactive signals.<sup>34</sup>

**ITA and radial artery grafts.** At 15 years, right ITA graft patency is reported to be more than 90% and left ITA graft patency more than 95%.<sup>35</sup> The Society of Thoracic Surgeons guidelines<sup>13</sup> recommend the following:

- ITA grafts should be used to bypass the LAD artery when bypass of the LAD artery is indicated (class of recommendation [COR] I, level of evidence [LOE] B)
- As an adjunct to a left ITA graft, a second arterial graft (right ITA or radial artery)

should be considered in appropriate patients (COR IIa, LOE B)

- Use of arterial grafts (including specific targets, number, and type) should be a part of the discussion of the heart team in determining the optimal approach for each patient (COR I, LOE C).

In 2019, RADIAL study 5-year data showed a benefit for using the radial artery rather than the saphenous vein for graft occlusion and target revascularization.<sup>36</sup> Rates of myocardial infarction and repeat revascularization were also superior for radial arteries, and a mortality benefit was reported in a follow-up study.<sup>37</sup>

### ■ SINGLE VS MULTIPLE ARTERIAL GRAFTING

#### Evidence favors multiarterial options

In 2019, the Arterial Revascularization Trial (ART) 10-year intention-to-treat data showed no difference in survival or event-free survival for bilateral vs left ITA. However, a 14% crossover rate, excellent medical compliance, and a radial artery conduit in more than 20% of patients possibly clouded the results.<sup>38</sup> A post hoc as-treated analysis showed improved mortality and major adverse cardiac and cerebrovascular events with multiple arterial grafting. Additionally, a 5-year post hoc analysis found that radial artery grafting improved outcomes in both groups.<sup>39</sup>

Since 2001, 5 major systematic reviews and 1 meta-analysis found that bilateral ITA grafting offered a survival advantage over left ITA grafting, including long-term survival, reduced hospital mortality, reduced cerebrovascular accidents, and reduced revascularization.<sup>38</sup>

Despite evidence of the benefits of multiple arterial grafting and the professional association recommendations to encourage its use, only a small percentage of patients undergoing CABG in the United States receive multiarterial grafts. Reasons for this include additional technical complexity, prolonged operative times, and potential for complications.<sup>40</sup>

#### Regional practice differences

In California, receipt of a second arterial graft decreased from 10.7% of isolated CABG operations in 2006 to 9.1% in 2011, with the use of a radial artery graft falling from 7.8%

Stenosis seen by 2-dimensional angiography does not always reflect a flow-limiting lesion

to 6.6% and a right ITA graft from 3.0% to 2.4%.<sup>41</sup> Despite these trends, there is a clear survival advantage for multiarterial grafting 7 years after surgery.

Chikwe et al<sup>42</sup> performed a retrospective cohort analysis with propensity matching. Of patients undergoing CABG between 2005 and 2012, 14% received multiarterial grafting, a nearly 50% higher rate than was found in the California study. Patients receiving multiarterial grafts were younger and healthier at baseline. After propensity matching, those receiving multiarterial grafts had better 10-year survival and lower 10-year myocardial infarction and reintervention rates. However, the study also identified subgroups of patients, including those with advanced age or renal disease, who might not realize additional benefits from multiarterial grafting.

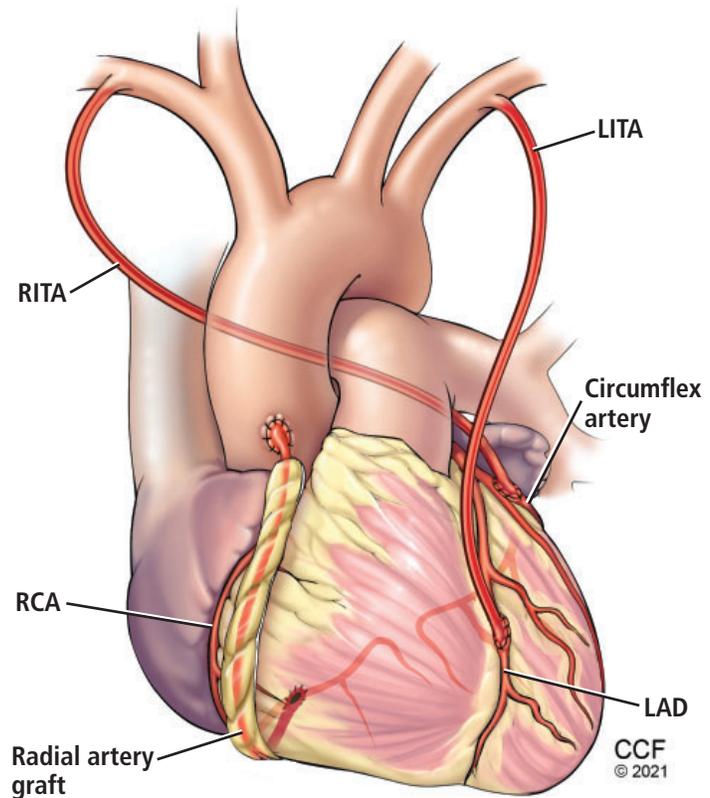
#### Ongoing trial may provide standard

The ongoing Randomization of Single vs Multiple Arterial Grafts (ROMA) trial is expected to be the definitive prospective randomized trial comparing multiple arterial grafting vs a single ITA to the LAD artery with saphenous vein graft bypasses to the remaining targets.<sup>43</sup> The enrollment goal is 4,300 patients, and the composite outcomes include death, stroke, myocardial infarction, and repeat revascularization.

#### Optimizing success of multiarterial grafts

Multiple arterial grafting (Figure 1) is not without its nuances, including conduit choice and intended target coronary vessel. For example, radial artery grafts are best used to bypass severely diseased target vessels to minimize competitive flow and optimize graft patency.<sup>13</sup> The myocardial mass supplied by a diseased vessel is also critically important. Important target vessels extend more than 75% of the way to the apex of the heart. Matching important vessels (extending more than 75% to the apex) with the second arterial graft has a long-term mortality benefit.<sup>44</sup>

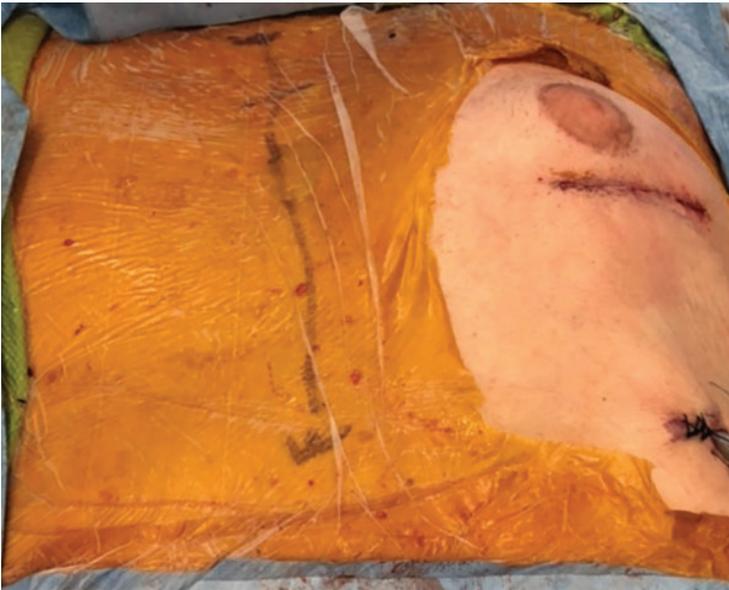
The feared risk of sternal wound complications associated with bilateral ITA harvesting can be mitigated by meticulous harvesting techniques and ITA skeletonization.<sup>45</sup> Skeletonization separates the ITA from adjacent tissues, with the surgeon staying close to the ITA wall throughout the dissection, thereby



**Figure 1.** An example of multiarterial coronary artery bypass grafting. The left internal thoracic artery (LITA) is used to bypass the left anterior descending artery (LAD), the right internal thoracic artery (RITA) to bypass the circumflex artery, and the radial artery to bypass the right coronary artery (RCA).

reducing adjacent tissue damage and preserving collateral routes of blood flow to the sternum compared with techniques that take the ITA as a pedicle that incorporates adjacent chest wall tissues. There is a theoretical risk of increased ITA injury in the hands of inexperienced harvesters, but data on the differential patency rates between skeletonized vs pedicled ITAs are limited.

The importance of an experienced coronary surgeon in decision-making and the performance of CABG cannot be overstated.<sup>7,8</sup> A specific volume-outcome relationship has been described for bilateral ITA grafting.<sup>46</sup> The increased risk associated with surgery for complex revascularization procedures such as redo CABG is well documented<sup>47</sup> but is mitigated by surgical expertise.<sup>48</sup> In addition, a focused interest in CABG facilitates innova-



**Figure 2.** Example of minimally invasive coronary artery bypass grafting, performed through a small left thoracotomy incision, in which the left internal thoracic artery is bypassed to the left anterior descending artery without use of a heart-lung machine. The patient's head is toward the top, and the skin marking is where a traditional sternotomy incision is placed.

**Opioid-sparing techniques are improving outcomes and decreasing length of stay; minimizing opioid use also reduces the incidence of delirium**

tion and the development of less invasive approaches.

### ■ LESS-INVASIVE CABG STRATEGIES

Off-pump CABG avoids use of cardiopulmonary bypass and is physiologically less invasive than traditional on-pump CABG. Off-pump CABG can benefit select high-risk patients not typically enrolled in trials. Surgical experience is critical in mitigating reduced graft patency and incomplete revascularization associated with off-pump CABG.<sup>49</sup> Widespread adoption is ill-advised, and indeed, use of off-pump CABG has declined.

Robotic CABG accounts for less than 1% of CABG operations in the United States.<sup>6</sup> Data supporting use of these procedures outside of select specialized centers are currently limited. Technology is lagging, and it is difficult to teach robotic multiarterial CABG and reliably achieve complete revascularization.

Hybrid CABG uses robotic or minimally invasive left ITA harvest with a direct hand-sewn left ITA-to-LAD artery anastomosis through a minithoracotomy (**Figure 2**). Non-

LAD artery stenosis is then addressed with drug-eluting stents. Theoretical benefits are lower occurrence of stroke, decreased infection, sternal sparing, fewer transfusions, and faster recovery. The Safety and Efficacy of Hybrid Revascularization in Multivessel Coronary Artery Disease study (POL-MIDES) found no difference between traditional and hybrid CABG in outcomes at 1 and 5 years.<sup>6</sup> Other trials are ongoing, and more are expected in the future.

### ■ OPTIMIZING RECOVERY AFTER SURGERY

Enhanced recovery after surgery relies on evidence-based protocols designed to improve outcomes and cost-savings based on rigorous data review and protocol development.<sup>50</sup> Post-operative goal-directed hemodynamic resuscitation algorithms reduce 30-day major adverse cardiovascular events in high-risk patients.<sup>51</sup> Similarly, fast-track early extubation protocols decrease time on a ventilator. Shorter extubation times are associated with decreased length of stay and hospital cost.<sup>52</sup>

### Opioid-sparing pain management

In this era of opioid abuse, pain management has come under global public scrutiny. More importantly, opioid-sparing techniques are improving patient outcomes and decreasing length of stay. Minimizing opioid use also reduces the incidence of delirium. Some form of delirium can occur in nearly 50% of post-operative cardiac surgery patients, increasing hospital mortality and readmission and decreasing long-term survival.<sup>50</sup> Many causes of delirium are reversible, and frequent delirium screening by bedside nurses and critical care teams improves outcomes.

### Glycemic control

Multiple mechanisms to deal with postoperative complications secondary to hyperglycemia exist. Goal blood glucose levels of 80 to 110 mg/dL are well established.<sup>53</sup> Glucose levels over 160 to 180 mg/dL managed with insulin infusions have improved outcomes, including reduced infections.

### ■ SECONDARY PREVENTION

Optimal medical management for secondary prevention and improved long-term outcomes

after CABG has been increasingly recognized.<sup>54</sup> Discharge prescriptions for beta blockers and statins are process measures tracked by the Society of Thoracic Surgeons as part of its program quality ratings. The benefits of beta blockers include a potential decrease in long-term mortality after CABG.<sup>55</sup> In patients receiving radial artery grafting, use of antispasmodic medications, including calcium channel blockers, is associated with improved outcomes.<sup>56</sup> Statin use after surgery is associated with decreased readmissions and late death from myocardial infarction or stroke.<sup>57</sup>

Dual antiplatelet therapy is now recommended for 6 months in patients with acute coronary syndrome undergoing CABG. Additionally, in patients who had coronary stenting prior to CABG, dual antiplatelet therapy may

prolong stent patency and prevent thrombus development and propagation.<sup>58</sup>

Comprehensive rehabilitation programs have been developed to prevent readmissions and improve treatment compliance and quality of life after discharge. Medication adherence dramatically improves outcomes regardless of coronary revascularization strategy.<sup>59</sup> For patients who do not adhere to medications, CABG leads to improved major cardiac event-free survival. New methods of improving treatment adherence are currently being evaluated; they include wearable technology, educational tools, and increased use of virtual visits. ■

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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