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CME MOC

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Anorexia nervosa's deadly toll

C difficile: Detect, treat, prevent

Liposuction: Safety, concepts

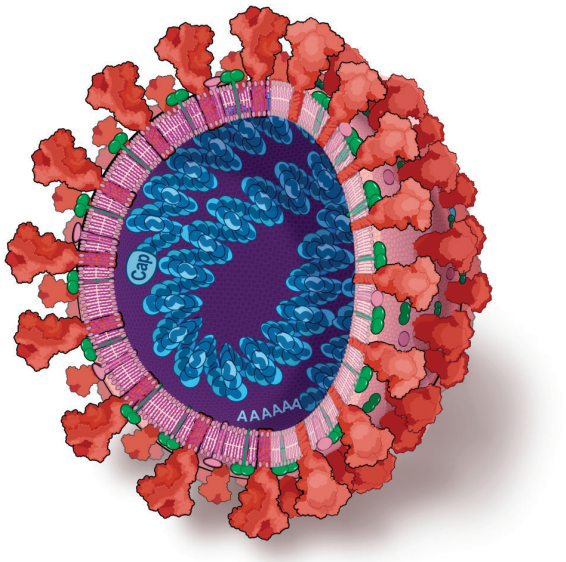
Biologics and surgery

Bone loss after stopping denosumab

Rigid airway

COVID-19
Brief perspectives from the front line

- Understanding the virus
- Serology: FAQs and caveats
- More at Curbside Consults www.ccjm.org



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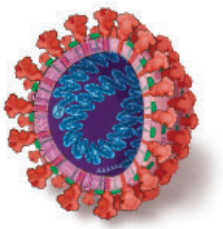

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- Glucocorticoid-induced bone loss
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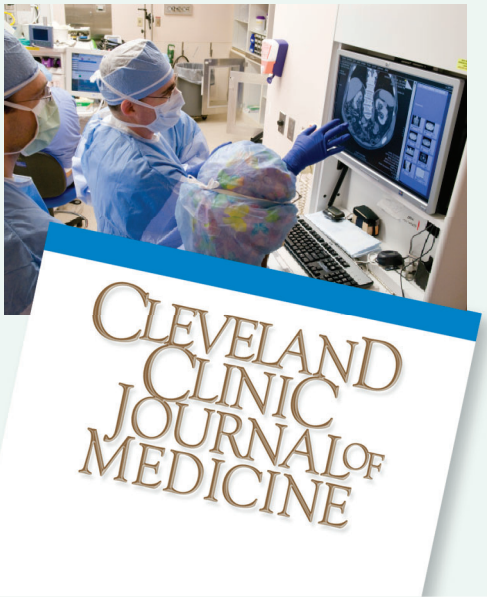

Perioperative infection: Are we sure what to focus on?

The relationship between immunosuppressants and infection is complex. True, these medications can increase the risk of opportunistic and perhaps routine infections. Some of the newer drugs increase the risk of reactivation of tuberculosis (and others are assumed to do so), some appear to increase the risk of activation of JC virus (an almost ubiquitous asymptomatic infection), and some predispose to *Pneumocystis* pneumonia or herpes zoster. But different agents do not equally increase the risk. Steroid therapy is the least precise weapon in our immunosuppressive arsenal and likely provokes the widest array of infections. We all are aware of this, but we continue to be gravely concerned about the risk of the newer biologics.

Then there is the seeming paradox that we can treat some severe infections with adjunctive immunosuppression; examples include bacterial meningitis, tuberculous pericarditis, *Pneumocystis* infection, and septic arthritis. Studies are under way using anti-interleukin 6 drugs to treat COVID-19 systemic inflammatory syndrome, so-called cytokine storm. We cannot assume that immunosuppression is always deleterious in the setting of otherwise appropriately managed infection, and specific scenarios need to be evaluated with attention to all potential confounders.

I don't imply that our newer biologics pose no significant risk of infection. They clearly do, although for some, I feel that the greater risk is that they mask clinical and laboratory signs of early infection. Thus, patients are actually sicker by the time the infection is recognized. For others, the body's ability to resolve a specific infection can indeed be significantly decreased. The different targeted inflammatory molecules and cells perform different roles in the inflammatory opera. We should not assume that disabling one will have the same effect as disabling another.

The discussion of whether to continue or withhold (and if so, for how long) immunosuppressive drugs before elective surgery has been going on for years. Two high-interest scenarios have been elective arthroplasty in patients with rheumatoid arthritis (RA) and abdominal surgery in patients with inflammatory bowel disease (IBD). Moosvi et al, in this issue of the *Journal* (page 343), weigh in with a discussion of whether to withhold biologics in patients undergoing intra-abdominal surgery for IBD. They argue nay for the most frequently used biologics, based on mixed and insufficient evidence of benefit of withholding, including a recent large nonrandomized prospective study of anti-tumor necrosis factor (TNF) agents. Interestingly, this trial[1] included analysis of whether the anti-TNF agents were detectable in the blood, which made no difference in risk of infection.

This recommendation differs from recent guidelines for management of biologics in the setting of elective arthroplasty[2] that suggested holding these drugs for one dosing cycle in advance of planned surgery. The evidence-based medicine jury has not weighed in that there definitely is an increased risk of infection if the drug is continued, as no large randomized prospective trial has compared continuing vs withholding the drug before arthroplasty, and it is not fair to compare outcomes of patients who

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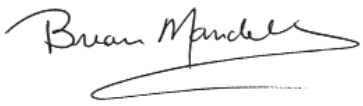
have been on biologic therapy with those who have never been on comparable therapy. Delaying one dose before totally elective joint surgery is often not associated with a major flare in inflammatory arthritis, but that may not be the case with an IBD patient requiring more semielective surgery. Concern over provoking a flare in the underlying disease, which may require steroid therapy to manage, has been an argument against withholding medications before elective surgery.

The historically conservative recommendations to withhold biologics before surgery are based on the fear of postoperative infection, especially of a prosthetic joint, in the absence of ideal data demonstrating safety.

But this reasoning has perhaps paid insufficient attention to the effect of corticosteroids on surgical and clinical outcomes. Steroid therapy has always been a known confounder of outcome studies, particularly of surgical outcome. Although it is well established that steroids are associated with increased risk of suboptimal outcomes of arthroplasty, patients with IBD, like those with RA, who need surgery to manage a complication of their disease have experienced, on average, more severe disease and have likely needed corticosteroid therapy. Recently, George et al[3] performed a retrospective review using Medicare administrative data of RA patients taking biologics and undergoing elective hip or knee surgery. There was no difference between the biologics. The authors did not assess whether use of any biologic increased the risk compared with patients who had never been on a biologic or if the biologic had been withheld preoperatively, although at least for intravenous infliximab that doesn't seem to make a big difference,[4] so this study doesn't shed direct light on the question addressed by Moosvi et al in this issue. However, the striking observation of George et al[3] was affirmation that even low doses of corticosteroids (prednisone equivalent > 5 mg) increased the risk of various postoperative infections and readmission within 30 days.

I don't know if lowering the steroid dose preoperatively to less than 5 mg will decrease that risk of infection, nor do I know whether patients will be at higher risk if they experience a flare in their IBD or arthritis and require a slight bump in their steroid dose due to withholding their biologic preoperatively. But I believe that we may have been a bit off target as we have focused so much on the biologics, and less on what we assumed to be low and safe doses of perioperative steroids.



BRIAN F. MANDELL, MD, PhD
Editor in Chief

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2020

JUNE

INTERNAL MEDICINE BOARD REVIEW COURSE (LIVE STREAM)
June 16–20

WASOG/AASOG 2020: MULTIDISCIPLINARY MEETING FOR SARCOIDOSIS AND ILD (CANCELED)
June 24–27
Hollywood, FL

JULY

MULTIDISCIPLINARY APPROACH TO THE CONTEMPORARY MANAGEMENT OF HEART FAILURE (CANCELED)
July 31
Cleveland, OH

AUGUST

NEUROLOGY UPDATE: A COMPREHENSIVE REVIEW FOR THE CLINICIAN (LIVE STREAM)
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Washington, DC

INTENSIVE REVIEW OF CARDIOLOGY
August 15–19
Cleveland, OH

SEPTEMBER

MEDICAL DERMATOLOGY THERAPY UPDATE
September 3–5
Cleveland, OH

CLEVELAND CLINIC EPILEPSY UPDATE AND REVIEW COURSE
September 9–11
Cleveland, OH

PRIMARY CARE WOMEN'S HEALTH: ESSENTIALS AND BEYOND (CANCELED)
September 10–11
Cleveland, OH

WOMEN IN HEALTHCARE FORUM (CANCELED)
September 17
Beachwood, OH

GENETICS EDUCATION SYMPOSIUM—GENETICS AND GENOMICS: APPLICATIONS FOR THE PREVENTION, DETECTION, AND TREATMENT OF CANCER
September 24
Cleveland, OH

INTENSIVE REVIEW FOR THE GI BOARDS
September 25–28
Las Vegas, NV

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HOSPITAL MEDICINE 2020
October 1–2
Independence, OH

NEPHROLOGY UPDATE
October 1–3
Cleveland, OH

PRACTICAL MANAGEMENT OF STROKE
October 2
Cleveland, OH

STATE-OF-THE-ART ECHOCARDIOGRAPHY 2020
October 2–4
Cleveland, OH

INTENSIVE REVIEW OF ENDOCRINOLOGY AND METABOLISM
October 9–11
Cleveland, OH

CARDIOVASCULAR UPDATE FOR THE PRIMARY CARE PROVIDER
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FIRST EUROPEAN CLEVELAND CLINIC ENDOCRINOLOGY AND DIABETES UPDATE
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ORTHOBIOLOGICS SUMMIT 2020: SCIENCE AND EVIDENCE BEHIND BIOLOGICS IN ORTHOPEDICS
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Miami, FL

WAKE UP TO SLEEP DISORDERS 2020: A CLEVELAND CLINIC SLEEP DISORDERS CENTER UPDATE (LIVE STREAM)
October 16–17

PRIMARY CARE EVIDENCE-BASED MEDICINE
October 23–24
Beachwood, OH

DECEMBER

A CASE-BASED APPROACH TO MASTERING THE MITRAL VALVE: IMAGING, INNOVATION, INTERVENTION
December 4–5
New York, NY

2021

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SHAPING THE MANAGEMENT OF PARKINSON DISEASE: DEBATING THE MOST CONTROVERSIAL ISSUES AND DISCUSSING THE LATEST BREAKTHROUGHS
January 23–24
Lake Tahoe, NV

FEBRUARY

VALVE DISEASE, STRUCTURAL INTERVENTIONS, AND DIASTOLOGY: IMAGING SUMMIT
February 5–7
Orlando, FL

APRIL

MANAGEMENT OF ADVANCED AND RECURRENT OVARIAN CANCER
April 16–17
Cleveland, OH

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Familial hypercholesterolemia: Clarifications

To the Editor: The article by Shah and colleagues[1] is an excellent review of familial hypercholesterolemia (FH) and highlights an underdiagnosed condition on which clinicians can make a significant impact. I would like to clarify two points:

First, as the authors describe, tendon xanthoma is mostly pathognomonic for FH. Xanthelasma, however, is nonspecific for this condition and does not appear in any of the diagnostic criteria.

Second, the American Diabetes Association (ADA) was one of the societies involved in the 2018 American Heart Association/American College of Cardiology multisociety guidelines,[2] and the 2020 ADA Standards of Care still reflect a low-density lipoprotein cholesterol (LDL-C) threshold for intensification of 70 mg/dL in patients at very high risk.[3] I believe the authors meant to refer to the 2017 American Association of Clinical Endocrinologists/American College of Endocrinology guidelines that introduced a new category of "extreme risk" with an LDL-C treatment goal of less than 55 mg/dL, which includes patients with heterozygous FH and established atherosclerotic cardiovascular disease.[4] This treatment goal was mirrored by the 2019 European Society of Cardiology/European Atherosclerosis Society guidelines.[5]

TAHER MODARRESSI, MD
Diabetes & Endocrine Associates of Hunterdon
Flemington, NJ 08822

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In Reply: We thank Dr. Modarressi for bringing up those points, and we are grateful the review was found to be informative.[1]

We agree that, although tendon xanthomas are pathognomonic for familial hypercholesterolemia (FH), xanthelasmas are not. Xanthelasmas are rich cholesterol deposits in the skin of the eyelids that occur in the setting of hypercholesterolemia.[2] They are nonspecific, but can be seen in patients with FH because these patients often have extreme hypercholesterolemia. Therefore, we suggest in the article that xanthelasmas could be present in patients with FH as a physical finding, and we specifically state that xanthomas are the pathognomonic lesions. To the same effect, it is also possible to see a patient with FH without xanthomas or xanthelasmas.

We also agree with Dr. Modarressi that the low-density lipoprotein cholesterol goal of less than 55 mg/dL was based on the 2017 American Association of Clinical Endocrinologists/American College of Endocrinology guideline recommendations (reference 66).[3]

NISHANT P. SHAH, MD, FACC
Duke Heart Center
Durham, NC

HAITHAM M. AHMED, MD
AdvantageCare Physicians
New York, NY

W. H. WILSON TANG, MD
Heart and Vascular Institute
Cleveland Clinic

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Cornelia C. Bergmann, PhD
Department of Neuroscience, Cleveland Clinic Lerner Research Institute;
Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Robert H. Silverman, PhD
Department of Cancer Biology, Cleveland Clinic Lerner Research Institute; Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

COVID-19: Coronavirus replication, pathogenesis, and therapeutic strategies

Human coronaviruses, along with influenza virus, human metapneumovirus, respiratory syncytial virus, and rhinovirus, are endemic and cause approximately 15% to 30% of annual respiratory tract infections. Coronavirus infections are generally mild in healthy adults, obviating any urgent need to develop treatments or vaccines. However, outbreaks of acute respiratory distress syndrome (ARDS) due to novel, highly pathogenic strains—severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and now, SARS-CoV-2—have revealed the potency and danger of this expanding family of pathogens that have the capacity to kill many thousands of people around the world if not geographically contained.[1]

As in severe SARS and MERS disease, the mortality rate is disproportionately high in the elderly and patients with preexisting comorbidities such as heart disease, diabetes mellitus, hypertension, and renal disease.[2] Higher morbidity in the elderly may partly be attributed to muted interferon antiviral responses (although the suggestive study has not yet been peer-reviewed)[3] as well as overall lower adaptive immunity,[2] resulting, paradoxically, in longer courses of hyperactivity of the innate immune system ("cytokine storm").

A ZOONOTIC INFECTION

Bats have been implicated as the likely source of SARS-CoV-2, as both SARS-CoV and MERS-CoV are genetically similar to viruses recovered from bats, and bat coronaviruses can use human receptors for cell entry.[4] However, phylogenetic studies, looking at sequence-based virus evolution, suggest that the virus is not transmitted directly from bats to humans but rather first infects intermediate animal hosts in close contact with humans. In the case of SARS-CoV, these can be civets or raccoon dogs sold at crowded markets; for MERS-CoV, they can be domesticated dromedary camels.[4]

Transmission from bats to intermediate hosts and then to humans, as well as from human to human, all involve viral adaptation, slight changes in viral sequence to improve fitness in the new host. This is not unique to coronaviruses, as endemics and pandemics also occur when novel influenza A virus strains emerge in the human population from an animal host.[5] Similar to introduction of Ebolavirus and human immunodeficiency virus 1 by mammals, many other viruses circulating in wild animals have the potential for zoonotic transmission.[6]

Understanding of the virus and how it causes disease points the way to potential treatments

SARS-CoV-2, the causative agent for the pandemic corona virus disease of 2019 (COVID-19) outbreak, was first found in Wuhan, China, and initial analysis of viral RNA obtained from patients hospitalized in late 2019 revealed it was 96% identical at the whole-genome level to a bat SARS-like coronavirus.[7]

Uniquely, SARS-CoV-2 can be transmitted by people who are infected but have no symptoms, not just by symptomatic patients. Concern about potential spread of SARS-CoV-2 to household cats has emerged from a news report of infection in a tiger in the Bronx Zoo. Ferrets can be infected, with intraspecies transmission,[8] and cats can also be infected and transmit the virus to other cats, while dogs have low susceptibility. However, it is unknown if any of these animals can transmit the virus to humans.[9]

Disclosure: Dr. Silverman is a Scientific Advisory Board member of Sator Therapeutics, LLC (Cleveland).

doi:10.3949/ccjm.87a.20047

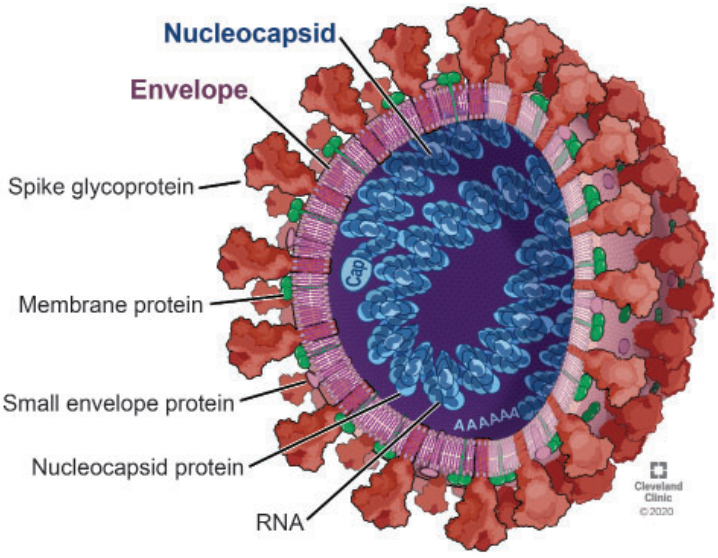

Figure 1. Structure of coronaviruses.

STRUCTURE AND GENOME OF CORONAVIRUSES

Coronaviruses are spherical enveloped viruses containing a single strand of positive-sense RNA (similar to host mRNA) of approximately 26 to 32 kb.[10] Their defining morphologic features are club-shaped projections from the viral envelope resembling a crown or a solar corona and made of a highly glycosylated protein named spike protein. Their other 3 structural proteins are the envelope, membrane, and nucleocapsid proteins (**Figure 1**).

Only a few changes are needed to adapt an animal virus to humans

The first two-thirds of the genome consists of 2 large overlapping open reading frames that encode 16 nonstructural proteins, including proteases, RNA-dependent RNA polymerase (prRdRp), RNA helicase, primase, and others, that form the viral replicase complex, a platform to propagate viral mRNAs. These nonstructural proteins are all potential targets for therapies, which would in theory work against all coronaviruses (**Figure 2**).[1,8,10–15]

The remaining portion of the genome includes interspersed open reading frames for the structural proteins, as well as a number of accessory proteins generally nonessential for replication in tissue culture but capable of suppressing immune responses and enhancing pathogenesis.[10,16]

HOW THE VIRUS GETS IN

Features of coronavirus transmission, replication, and pathogenesis are determined by both the viral genome and the human host.

Coronavirus spike proteins are key determinants for virus attachment and entry into target cells. The receptor for both SARS-CoV and SARS-CoV-2 is angiotensin-converting enzyme 2 (ACE2),[11,12] a cell-surface enzyme contributing to control of blood pressure. SARS-CoV cell entry is independent of ACE2 catalytic activity.

Entry involves 2 spike protein subunits, which mediate distinct functions. The S1 subunit mediates ACE2 attachment through the receptor-binding domain. The S2 subunit, containing the fusion peptide and transmembrane domains, drives fusion of viral and host cell membranes. To be activated for fusion, the spike protein must be cleaved at 2 sites directly at the cell membrane, through endosomes, or both. The sequence of the cleavage sites, one located at the border of S1 and S2 subunits, the other (S2′) within S2 just upstream of the fusion peptide, provide substrates for a variety of cellular proteases and determine cleavage efficiency.

The route or routes of infection thus depend on the proteases available in different cell types and the protease cleavage sites.[17] This is also demonstrated by involvement of the cellular serine protease TMPRSS2 (transmembrane protein serine protease 2) and activities of furin and endosomal cathepsins B and L in SARS-CoV-2 entry.[11] TMPRSS2 activity is also involved in viral spread and pathogenesis in SARS-CoV-infected and MERS-CoV-infected mouse models.[18]

Host proteases that cleave the S protein are also potential targets for antiviral drugs. A higher rate of SARS-CoV-2 infections compared with SARS-CoV infections may be at least partially explained by a higher affinity of spike protein for ACE2.[12] The sequence divergence in both the receptor-binding domain and cleavage domains in the spike protein between SARS-CoV-2 and the bat virus highlight how only a few changes are needed to adapt an animal virus to humans.[7,11,12,19]

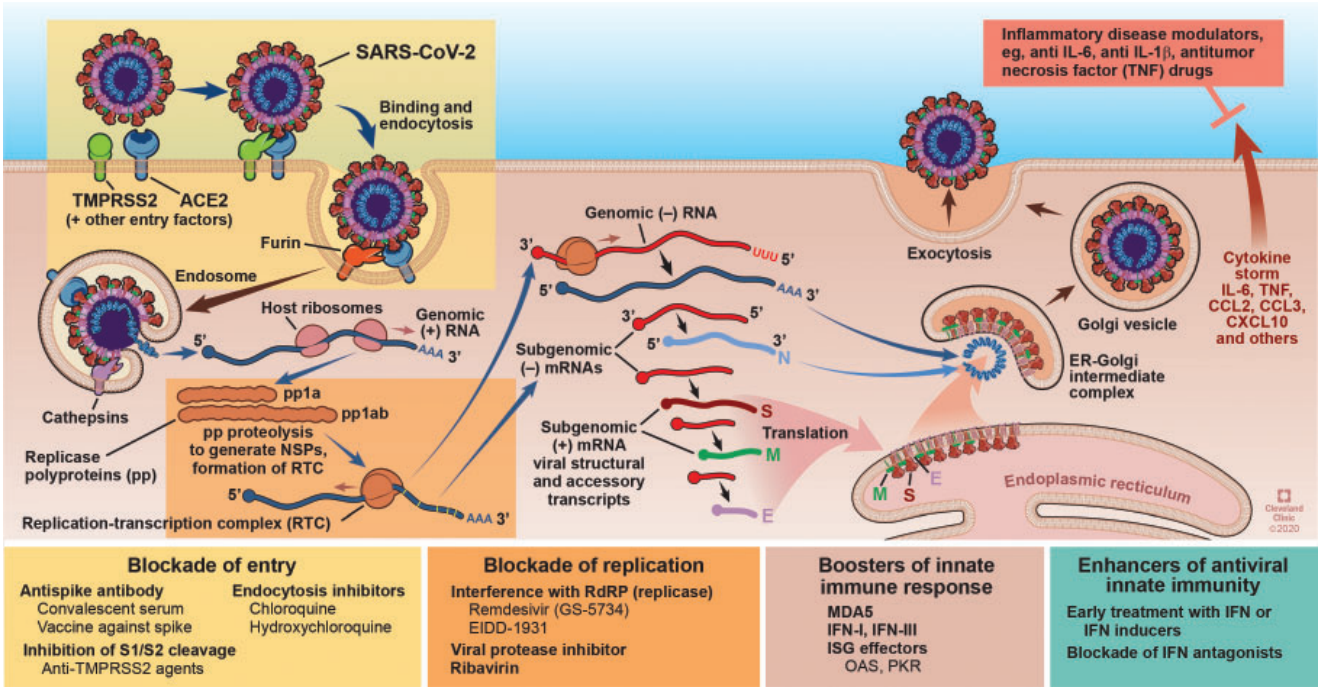

Figure 2. Overview of COVID-19, SARS-CoV-2 replication, and therapeutic targets.

Upper left. Virus entry entails binding the angiotensin-converting enzyme 2 (ACE2) receptor and cleavage by the serine protease TMPRSS2 (in green) to allow fusion with the host membrane. Other cellular proteases, eg, furin (in orange), facilitate pH-dependent entry through the endocytic pathway. The predominant entry routes are cell type-specific and dependent on availability of select proteases.

Middle. Following uncoating and release of viral RNA into the cytoplasm, translation of open reading frame 1a (ORF1a) and ORF1ab produces the polyproteins pp1a and pp1ab. These in turn are processed by viral proteases (encoded by ORF1a) to yield 16 nonstructural proteins. Formation of the RNA replicase–transcriptase complex (RTC) uses rough endoplasmic reticulum (ER)-derived membranes. The RTC drives synthesis of (–)RNAs. Full-length (–)RNA copies of the genome provide templates for full-length (+)RNA genomes. Transcription further produces a subset of subgenomic RNAs, including those encoding all structural and accessory proteins.

Right. The translated structural proteins and genomic RNA are assembled into the viral nucleocapsid and envelope in the ER–Golgi intermediate compartment, and are subsequently released by exocytosis.

Bottom. Potential strategies for treatment. Anti-TMPRSS2 or chloroquine treatment in experimental animals will reveal efficacy of targeting select proteases or entry pathways in limiting infection, while simultaneously monitoring effects on innate and adaptive immunity. The replication cycle can be blocked at several stages using single or combined treatment paradigms: virus entry can be inhibited by antispike antibodies elicited by vaccines to block attachment or by preventing fusion using relevant protease inhibitors.[11] RTC formation and transcription-replication events can be targeted using viral protease inhibitors or nucleoside analogues (GS-5734 or EIDD-1931).[15] Interferon (IFN) responsiveness can be increased by early exogenous IFN treatment,[13] IFN inducer treatment, repression of viral IFN antagonists, and enhancement of host antiviral IFN pathways. The "cytokine storm" induced as a host response to rampant virus replication may be targeted by administration of select anti-inflammatory immune modulators, which are already given to patients with inflammatory disorders. Drugs targeting viral replication may also be combined with treatments that control detrimental immune responses. The ferret model will provide a useful tool to test multiple therapeutic and preventive treatments.[8]

Based on information in references 1, 10, 12, and 14

THE BODY MOUNTS AN INNATE IMMUNE RESPONSE

Interferons I and III are cytokines with critical roles in the innate immune response against viral infections.[20] Virus-infected cells induce and secrete interferon I molecules that bind to the cell surface receptor IFNAR (interferon III uses a different receptor), thereby triggering the Jak-Stat (Janus kinase/signal transducer and activator of transcription) signaling pathway that switches on many antiviral genes. The interferon-stimulated genes are then transcribed into RNA and translated into proteins that suppress viral replication and spread.

HOW THE VIRUS EVADES THE HOST RESPONSE

During coevolution with their hosts, viruses have learned to counteract the interferon antiviral response. Like other human coronaviruses, SARS-CoV-2 can at least partly evade innate immunity to gain a foothold in humans, a critically important step in the infection cycle. Although mechanistic insights are as yet unavailable, we do have a good understanding of how other coronaviruses evade interferon's antiviral activity,[21] and also how we could engage antiviral factors to promote interferon activity.[22]

During coevolution with their hosts, viruses have learned to counteract the interferon antiviral response

In general, coronaviruses can potently antagonize antiviral innate immunity by interfering with both interferon production and the cellular antiviral response.[23] For instance, mouse coronaviruses and MERS-CoV have accessory proteins that block an interferon response pathway that degrades the viral RNA (by oligoadenylate synthetase and ribonuclease L).[24,25]

The large number of host antiviral mechanisms and distinct viral antagonism at different steps in the virus replication cycle have made it difficult to identify the most relevant ones. Not only does each type of coronavirus encode different accessory proteins responsible for allowing the virus to escape cellular innate immune mechanisms, but distinct cell types may respond differently.

While we are only just beginning to understand the functions of the SARS-CoV-2 accessory proteins, it is clear that there are similarities and differences between the accessory proteins of SARS-CoV-2 and those of its closest human pathogen relative, SARS-CoV. A better understanding of the precise functions of the SARS-CoV-2 accessory proteins, especially their interaction with innate immune pathways, could lead to novel antiviral drugs that promote the innate immune response. The finding (not yet peer-reviewed)[26] that SARS-CoV-2 was more sensitive to interferon than SARS-CoV raises hope that giving interferon or interferon inducers very early in the infection could be beneficial, and, perhaps, less likely to cause harm than using interferon later in COVID-19.[13]

WHY DO SOME PEOPLE GET SO SICK, BUT OTHERS ARE FINE?

One of the most problematic features of SARS-CoV-2 infection is the broad spectrum of disease, ranging from no symptoms to mild flu-like symptoms, anosmia, fever, nonproductive cough, dyspnea, and fatigue to acute respiratory distress syndrome, the main cause of death. While multiple organs, including the heart, kidneys, liver, and gastrointestinal tract, are injured, it remains to be resolved to what extent tissues are damaged by infection, hypoxia, or the immune response. Complications may also involve the central nervous system, either by direct infection or secondary damage.[27,28]

Different ACE2 expression? ACE2 is expressed in various cell types of the lung, including alveolar epithelial cells, pneumocytes, and bronchial transient secretory cells, as well as enterocytes of the small intestine, heart (pericytes), and kidney. These are the same tissues that the virus affects, but studies with SARS-CoV indicate that ACE2 expression is not the only determinant of susceptibility.[29–32] More research is needed to assess to what extent ACE2 surface expression or polymorphisms, or other coreceptors and proteoglycan moieties, are markers of tissue susceptibility.

Renin-angiotensin system dysregulation? The finding that ACE2 is a primary SARS-CoV-2 receptor has further led to extensive discussion of dysregulation of the renin-angiotensin system, which regulates blood pressure and electrolyte balance.[33–35] Conversion of angiotensin I to angiotensin II by angiotensin-converting enzyme (ACE) activates pathways

that lead to inflammation, vasoconstriction, oxidation, and fibrosis. ACE2 activity counterbalances this pathway by cleaving both angiotensin I and angiotensin II to shorter peptides, which use distinct receptors to promote vasodilation, as well as anti-inflammatory, antioxidant, and antifibrosis activity.

ACE inhibitors and angiotensin II receptor blockers are thus commonly used in patients with cardiovascular diseases, hypertension, and diabetes, promoting the protective effects of ACE2. However, increased expression of ACE2 by use of antihypertensive drugs in animal models raised concerns of higher virus infection risk for patients receiving these drugs. Nevertheless, current recommendations are to continue treatment.[34,35] The complexity of the renin-angiotensin system will require more extensive retrospective analysis of larger and ethnically diverse patient groups.

Protective host features? The apparently large percentage of infections that are asymptomatic is unique to SARS-CoV-2, but many of the pathogenic features resemble those observed in SARS and MERS-CoV infections. The protective host features underlying the asymptomatic infections are currently unknown, as testing within many countries is limited to people presenting with symptoms such as severe shortness of breath, coughing, and fever. Retrospective studies incorporating serum antibody testing and health status will provide much-needed insights.

Cytokine storm? Severe disease is associated with lymphopenia and an uncontrolled systemic inflammatory response called a cytokine storm, which ultimately leads to multiple organ failure and death.[36,37] Autopsy results reveal severe damage to endothelial tissue, vasculitis-like manifestations, and atrophy of secondary lymphoid tissues.[37] Early studies in COVID-19 patients showed higher plasma levels of interleukin 2 (IL-2), IL-7, granulocyte colony-stimulating factor, C-X-C motif chemokine 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1a (chemokine [C-C motif] ligand 2), and tumor necrosis factor (TNF), but also anti-inflammatory IL-10, higher in intensive care patients than in nonintensive care patients.[38] Several reports also confirm high levels of IL-6 in severely ill patients.[2,39] Retrospective clinical investigation of more patient cohorts without or with preexisting conditions and of those being treated with distinct anti-inflammatory immune modulators—eg, anti-TNF, anti-IL-6, anti-IL12/IL23, or anti-IL-1 beta—for immune-mediated inflammatory conditions will provide much-needed guidance on treatment to stem severe COVID-19.

ONCE YOU GET IT, ARE YOU IMMUNE FOR LIFE?

Another critical unresolved aspect of COVID-19 is the establishment of adaptive immunity. Lessons from the SARS-CoV epidemic indicate that CD4 and CD8 T-cell memory lasts for up to 11 years in recovered individuals.[40–42] A study of a limited number of patients hospitalized with mild or severe COVID-19 revealed humoral immunoglobulin M (IgM) and immunoglobulin G (IgG) serum responses to the viral nucleocapsid and spike proteins emerging at 10 days after symptom onset, with serconversion in a sizable majority of patients by 3 weeks.[2,43,44] Moreover, the IgG levels correlated with virus neutralization titers.

Transfusion of convalescent plasma from recovered patients had beneficial outcomes in a small number of SARS and COVID-19 cases.[45] Based on preliminary results of convalescent serum as well as in vitro and in vivo neutralization studies, clinical trials will be launched to evaluate the efficacy of spike protein-based vaccines.

A concern is the mutation rate of the virus as it spreads through the population. Viral genomes are being analyzed throughout the world and compiled in large, publicly available databases, which collate sequenced isolates and look at relationships (https://nextstrain.org/ncov/global). Although such databases currently reflect a population naïve to the virus, similar studies can be conducted once vaccines become available to test the effects of immune pressure on the virus.

There are at least 4 potential therapeutic strategies against COVID-19

VIRAL AND HOST TARGETS FOR THERAPIES AND VACCINES

There are at least 4 potential therapeutic strategies against COVID-19, apart from supportive and oxygenation therapies such as use of ventilators:

- Direct antiviral drugs against SARS-CoV-2 (eg, remdesivir)
- Indirect antiviral agents (eg, interferon I, interferon inducers, and drugs that target host proteins required for infections)
- Convalescent plasma that contains antibodies against SARS-CoV-2
- Drugs that tamp down the pathogenic hyperactive inflammatory response and cytokine storm later in disease progression.

However, we would like to emphasize that at present, these strategies are investigational only, including the off-label use of existing drugs, and may prove to show no efficacy and could be harmful in controlled clinical trials.

The emergence of 3 highly pathogenic human coronaviruses within the past 20 years predicts that more of them will continue to come along. As the timing is unpredictable, monitoring and transparent reporting of local outbreaks is imperative for early intervention.

With respect to currently circulating SARS-CoV-2 and limited overall testing, it is also unknown whether the virus is affected by seasonal changes. While physical distancing is an effective control measure to limit acute infection rates, asymptomatic carriers will likely continue to spread the virus, leading to ongoing hotspots of symptomatic infection.

A major factor influencing the future of COVID-19 is the ability of recovered people to develop protective immunity. However, the ongoing yearly infection rates by historically circulating coronaviruses,[46] as well as evidence for already distinct SARS-CoV-2 variants[47] suggest that established immunity may be insufficient to avoid recurring infections.

Clinical trials with drugs targeting viral proteins will reveal tolerance of the SARS-CoV-2 to selective pressure and guide in development of strategies that target host proteins required for replication.[48] Efficacy of vaccination strategies to elicit protective antibodies may further uncover the potential need for seasonal vaccines like those for circulating influenza viruses.

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***Addresses**:*
Cornelia Bergmann, PhD, Department of Neurosciences, NC30, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; bergmac@ccf.org
Robert Silverman, PhD, Department of Cancer Biology, NB40, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; silverr@ccf.org

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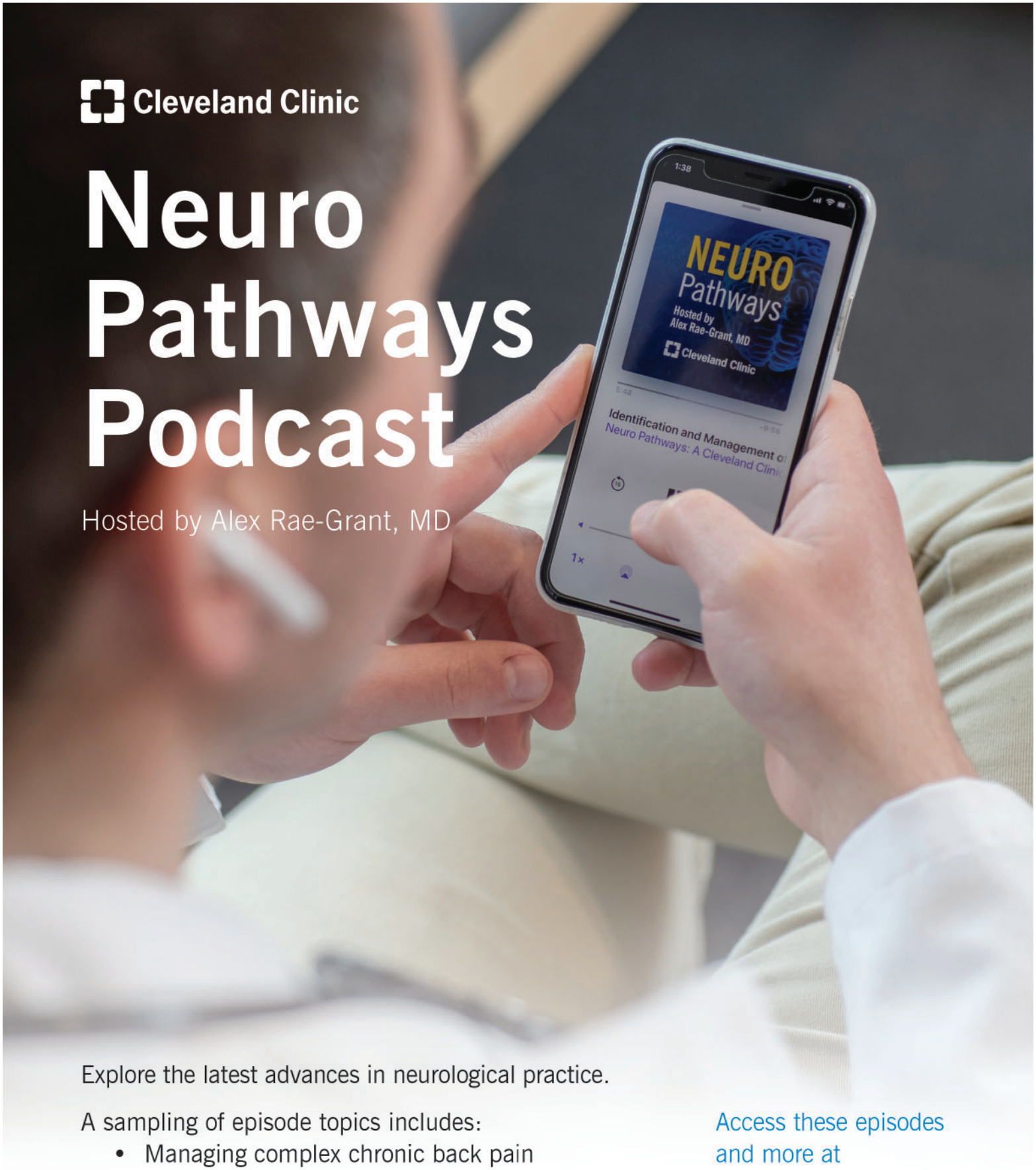

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COVID-19 serologic testing: FAQs and caveats

There has been an immense amount of discussion regarding the potential usefulness of serologic testing for COVID-19. Serologic testing has never been routinely used for diagnosing infections with "respiratory viruses" such as influenzae, parainfluenzae, respiratory syncytial viruses, adenoviruses, or metapneumovirus, nor was it used routinely for diagnosis during the global epidemics of severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and H1N1 influenza. However, the pandemic status of COVID-19 and the shortage of nucleic acid detection kits and swabs in certain areas raise the prospect of resorting to serology as an alternative to direct testing for the virus, and it is relevant to ask how useful it may be. The Infectious Diseases Society of America has recently issued a clear statement on COVID-19 serology.[1]

The following addresses some common questions regarding serologic testing for COVID-19.

Is IgM/IgA serology reliable for diagnosing acute symptomatic COVID-19?

Based on recent publications,[2] the appearance of detectable immunoglobulin M (IgM) antibodies after infection with COVID-19 is delayed, resulting in abysmal sensitivity ranging from 17% to 50% in the first 10 to 14 days after the "onset" of symptoms. Note that this is not days after exposure or infection, but rather days after the onset of clinical symptoms. Unfortunately, the results may not be clinically useful because COVID-19 often progresses very quickly within the first 7 to 10 days.[3] Thus, by the time of seroconversion, patients could be critically ill with septic shock or multiorgan failure, or they could die before seroconverting.

Most hospitalized patients typically receive the diagnosis of COVID-19 by nucleic acid testing before admission or up to 24 hours after admission. Unfortunately, by the time of serologic diagnosis, the patient may have inadvertently infected innumerable contacts.

There are no carefully peer-reviewed studies regarding the specificity of IgM and IgA tests, even though numerous point-of-care and non-point-of-care enzyme immunoassays (EIAs) are commercially available. IgM serologic tests, in general, have an inherent predisposition to false-positive results. Viruses as distantly related as Dengue virus have been reported to cause false-positive IgM results in COVID-19 point-of-care serologic tests.[4]

COVID-19 IgA EIAs had false-positive results in 20% of samples from 2,018 patients in the United States (author's personal communications). The potential for a rapidly progressing clinical course of COVID-19, combined with the low sensitivity of IgM testing during the first 10 days of clinical infection, makes this low specificity of IgA testing a concern, since class-switching to IgA typically occurs after the appearance of IgG.

Is IgG serology a reliable option for diagnosing acute or convalescent COVID-19?

IgG seroconversion is delayed after the onset of symptoms (more than 35 days in some cases), but typically occurs in 2 to 3 weeks, at which time it can be detected if the test specificity is high. Commercially available serologic assays, typically enzyme-linked immunosorbent assays (ELISAs), require validation with a plaque-reduction neutralization test (PRNT).

In brief, PRNT requires mixing live viruses with serially diluted serum followed by

The pandemic status of COVID-19 and the shortage of supplies raise the possibility of serologic testing as an alternative to direct testing

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cell cultures to view cytopathic effect. PRNT is a functional assay that requires significant expertise and a biosafety level 3 facility (not available in hospitals), and it is not amenable to automation; however, it is necessary when any new assay is being validated. Ideally, this test should be done by manufacturers prior to US Food and Drug Administration submission; if this is a lab-developed test, the onus is on the lab to ensure PRNT is done on-site or in collaboration with a reference lab that has PRNT capability. Additionally, PRNT needs to be done head-to-head against other known coronaviruses, particularly those that are commonly acquired in the community (eg, 229E, OC43, NL63, HKU1), which have always been detected using nucleic acid amplification tests. Thus far, none of the published studies or commercially available kits have documentation of such validation.

That said, PRNT has its limitations. Previous exposure to common coronaviruses may lead to an early and high-titer humoral immune response to SARS-CoV-2. As time elapses, however, the humoral response probably becomes more specific to SARS-CoV-2. Studies have shown greater than 90% seroprevalence of common coronaviruses in the United Sates. Interestingly, Wölfel et al[2] report finding a significant degree of serologic cross-reactivity between SARS-CoV-2 and common coronaviruses. Further, IgG responses were much stronger and appeared earlier than IgM responses. It seems that exposure to SARS-CoV-2 triggers previous memory response to all common coronaviruses. Based on the current information, it is not clear which target provides the best specificity, but specificity should increase over time as the immune response becomes more fine-tuned. This, however, will be well beyond the recovery time and, thus, of no use for diagnostic purposes.

By the time of seroconversion, the patient could be critically ill or dead

In addition to cross-reactivity with common coronaviruses, false-positive results are seen using serum with elevated antinuclear antibody titers. Elevated titers are relatively common in patients over age 50, which happens to overlap with the median age for COVID-19 diagnosis. False-positive results have also been documented with serum from patients with influenza or influenza vaccine recipients. Flu vaccine recipients constitute a large population—45% of the adult US population, according to the US Centers for Disease Control and Prevention (CDC)—who may have overlapping signs and symptoms of influenza and COVID-19.

On the IgG side, false-positives using both EIA and point-of-care testing kits also have been observed in serum samples from patients with herpes simplex virus type 1, human metapneumovirus, enterovirus, parvovirus B19, and sera-positive rheumatoid factor, among others. Finally, even if IgG is to be used with a highly specific ELISA for diagnosing acute COVID-19 infection, one still has to wait several weeks to see a minimum 4-fold rise in antibody levels. This would be too late to be of clinical use. And testing requires a minimum of 2 blood draws (acute and convalescent), exposing sick patients to even more healthcare environments.

Is IgG serology reliable for evaluating infectivity and clinical immunity to reinfection with COVID-19?

No one knows. Patients with a positive IgG result may still be sick and can shed the virus through their respiratory secretions or stools. SARS-CoV-2 is an enveloped RNA virus belonging to the Coronaviridae family, which includes common coronaviruses such as 229E, OC43, NL63, HKU1, and several that infect animals. Upper respiratory samples can remain positive for viral RNA for a few weeks after onset, when patients are supposed to have IgG antibodies. Viral shedding in stool has been reported for up to 47 days, which speaks against authentic neutralizing capacity of tissue-transudated IgG and secretory IgA antibodies.[5] SARS-CoV (a SARS-CoV-2 sister virus) has been grown in cultures from upper respiratory samples in 54% of cases at 2 weeks after symptom onset and in 16% of cases at 3 weeks after symptom onset, despite documented seroconversion in more than 92% of patients assessed by PRNT that detected "neutralizing antibodies."[6] Thus, having circulating neutralizing antibodies may not ensure lack of infectivity. This has yet to be shown in SARS-CoV-2.

As of this writing, the CDC has not established guidelines for occupational health isola-

tion disposition based on serologic testing, other than using 2 consecutive negative nucleic-acid amplification tests at least 24 hours apart.[7]

Regarding COVID-19, the correlate of protection is not known, although these levels have been established for many other viral diseases. For example, the correlate of protection for hepatitis B is a surface antibody level at or very close to 10 mIU/mL, and this measure is routinely used for occupational health purposes. For COVID-19, the correlate of protection has to be established in large, well-designed randomized controlled trials, which have not been conducted. Therefore, determination of "immune status" of individuals, including healthcare workers, to SARS-CoV-2 cannot be established at this time using serology. To further confound matters, all individuals can be infected and become sick with common coronaviruses in the community in almost every season and sometimes several times during a season. This suggests that immunity to some coronaviruses is short-lived, and lingering IgG antibodies from previous seasons does *not* mean an individual is necessarily immune to infection with the same coronaviruses. Furthermore, cell-mediated immunity (typically mediated through CD8+ memory T cells) also plays a role.

More recently, it has been shown that 20% of individuals do not mount neutralizing antibodies and over 50% mount only low titer neutralizing antibodies with geometric titer of 142. The rest (< 30%) are able to mount high-titer neutralizing antibodies, but whether they will last and whether they are protective is not known.[8]

Is IgG serology reliable for screening a COVID-19-convalescent donor?

The discussions in the previous 2 items provide a segue to answer this question. First, we do not know if EIA results correlate well with PRNT (ie, ELISA antibodies vs neutralizing antibodies). And if they do correlate well, then second, we do not know if the so-called neutralizing antibodies are neutralizing enough to confer immunity.

Shen et al[9] gave critically ill patients infusions of 400 mL of convalescent plasmas collected from donors with clinically resolved COVID-19. Interestingly, the critically ill recipients' pretransfusion neutralization titers were approximately only 1 dilution different than those of the donors (pretransfusion neutralizing antibody geometric titers of 192 and 80, in donors and patients, respectively). Further, Duan et al[10] found that severely ill patients had neutralization titers as high as 1:640 before receiving transfusions of convalescent plasma. Healthy and COVID-19-resolved donors had titers higher than 640.

These results raise the question as to why patients who already had mounted neutralizing antibody titers were still critically ill. This could be explained by the phenomenon called *antibody-dependent enhancement*, in which viruses can gain access to Fc gamma receptor-expressing cells via antibody-recognizing receptors as opposed to viral receptors and proliferate or trigger those cells to respond with a vigorous and potentially harmful cytokine release (cytokine storm). More recently, Wölfel et al[2] grew SARS-CoV-2 in upper and lower respiratory samples from onset until day 8 but not beyond that. This suggests that transfusion of convalescence-phase plasma may not have a role beyond day 8 after onset. This is important, as passive immunotherapy is typically considered in critically ill patients who are well beyond this time point.

Patients with a positive IgG may still be sick and can shed the virus

Antibody-dependent enhancement has been shown in coronaviruses, which may potentially lead to more severe subsequent coronaviral diseases. Although this may have implications for vaccine design (similar to those of Dengue vaccine), it may also lead to potential adverse outcomes for convalescent plasma therapy. At this juncture, we do not have any evidence that plasma from patients who have recovered offers clear clinical benefit, as it showed mixed results for SARS or MERS.[11] Further, SARS-CoV and SARS-CoV-2 can cause syncytium formation among lung epithelial cells, thereby paving the way for cell-to-cell transmission of the virions. In this way, virions may be protected from antibody neutralization.

Using a serologic test with poor or unknown performance characteristics to "green-light" distributing blood products (plasma) is not really an undertaking for hospital labs. The

US Food and Drug Administration (FDA),[12] however, recommends neutralizing antibody titers of at least 1:160, but a titer of 1:80 may be considered acceptable if an alternative matched unit is not available. The FDA also recommends that convalescent plasma be considered only for patients with severe or immediately life-threatening COVID-19. The FDA further clarifies that, although promising, convalescent plasma has not yet been shown to be effective in every disease studied. It is therefore important to determine through clinical trials, before routinely administering convalescent plasma to patients with COVID-19, that it is safe and effective to do so.[12]

In short, at this point, using serology to screen COVID-19-convalescent donors is fraught with risk, not only because there is no robust science to back it up, but also because there are no FDA-approved products for donor screening. Further, the correlation between neutralization assays and other test formats has been poor,[2] making it hard to use commercial assays for this purpose.

Is IgG serology reliable for SARS-CoV-2 serosurveys?

At this point, using serology to screen COVID-19-convalescent donors is fraught with risk

Maybe, but it very much depends on the specificity of the assay. Serology may only be good for surveillance or seroepidemiologic studies, which is a public health function or an academic project. Once fine-tuned assays are available and resources allow, impact assessments will need to be done on a large scale in collaborative studies performed using well-balanced and unbiased samples that include multiple age, sex, and geographic cohorts.

Another aspect here is to assess what percentage of infected individuals remain asymptomatic and to calculate the case-fatality rate (CFR). The former is helpful as background epidemiologic knowledge, but the CFR is even more important, although it comes at a potential cost. The cost is that taking asymptomatic cases into account when the CFR is calculated amid an outbreak, a sudden drop in the publicly announced CFR would potentially lead to loosening precautionary measures such as social distancing by the general public, which may lead to further spread of the infection.

Here's some math to consider. As of May 13, 2020, there were 1,420,581 cases in the United States. Also, let's say only 20% of cases become severely symptomatic, which is a gross underestimation because according to the *Morbidity and Mortality Weekly Report*, 87% will be symptomatic.[13] Thus, at most, we'll have a total of 7,102,905 infected cases in the United States so far. Given the 2019 US population of 328.2 million, this means a seroprevalence of 2.16%. An ideal IgG kit (for serosurveys) with a sensitivity of 100% and specificity of 95%, used in a context of a pretest probability of 2.16%, would give us a positive predictive value (PPV) of 30% (best-case scenario). Although a very big claim to make, even a specificity of 99% would yield a PPV of 69%, meaning out of 100 positive IgG results, between 31 and 70 of them are more likely false-positive. This is of course for the whole country; a state such as New York can immensely skew the calculations, given the disproportionately high number of cases.

The seroprevalence in the State of Ohio is estimated as about 1.06% (based on published state government data as of May 13, 2020). Therefore, the PPV will be 17%, based on specificity of 95%, and 51% based on a specificity of 99%. Again, all of these are calculated very generously.

Let's take a recent example from the media on coronavirus infections in Northern California.[14] This study by Stanford University researchers suggested a seroprevalence of 2.5% to 4.2% in Santa Clara County. According to the above calculations and based on the premise for the test performance (sensitivity 100%, specificity 95%), the PPV for the California study would be 33% to 46%, which is translated to a large false alarm. Another way to look at this is to compare their claim with peer-reviewed literature. According to this serosurvey, the actual numbers of cases is estimated to be 50 to 85 times higher than what the county has announced. This roughly means that only 1.17% to 2% of infected individuals become symptomatic.

On a related note, according to a CDC study from the state of Washington, 87% of coronavirus-infected individuals became symptomatic.[13] This finding (87%) is in sharp contrast with the results of the Stanford University serosurvey estimates. A subsequent study by Arons et al[15] reported that 94% of residents of a skilled nursing facility with confirmed sta-

tus became symptomatic. More recently, the CDC reported that of 4,336 exposed healthcare workers (median age 42) with confirmed COVID-19 diagnosis (by RNA testing), only 8% did not report any symptoms.[16] It should also be mentioned that according to an earlier study, also from California, about 5% of individuals with flulike illness tested positive for COVID-19 by RNA testing.[17]

Serosurveys may help with understanding herd immunity. With a minimum calculated basic reproduction number of 2.2, a minimum of 55% of the population is needed to be immune to prevent large outbreaks. With current interventions we may never reach such a point unless an effective vaccine becomes available. Therefore, a serosurvey may not necessarily help with this aspect.

Finally, according to a large epidemiologic joint report from China and the World Health Organization,[18] only 1% of cases were asymptomatic based on typical symptoms; of symptomatic cases, 81% were mild or moderate and 19% were severe or critical. This was also reviewed and summarized later by Wu and McGoogan[19]; although in almost all jurisdictions severe and critical cases get tested for RNA (as are less-severe cases based on expanded other indications), it is relatively safe to multiply the announced number of confirmed cases by 5 to arrive at the estimated total number.

All in all, a careful analysis of harm and cost vs benefit needs to be done prior to conducting such large-scale serosurveys, if needed at all.

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***Address**: Kamran Kadkhoda, PhD, Department of Laboratory Medicine, LL3-3, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; kadkhok@ccf.org*

Masaki Itagane, MD
Division of Rheumatology, Department of Internal Medicine, Okinawa Chubu Hospital, Okinawa, Japan

Hiroyuki Yano, MD
Division of Rheumatology, Department of Internal Medicine, Okinawa Chubu Hospital, Okinawa, Japan

Tomoo Kishaba, MD
Division of Pulmonary Disease, Department of Internal Medicine, Okinawa Chubu Hospital, Okinawa, Japan

Mitsuyo Kinjo, MD, MPH
Division of Rheumatology, Department of Internal Medicine, Okinawa Chubu Hospital, Okinawa, Japan

Rigid airway

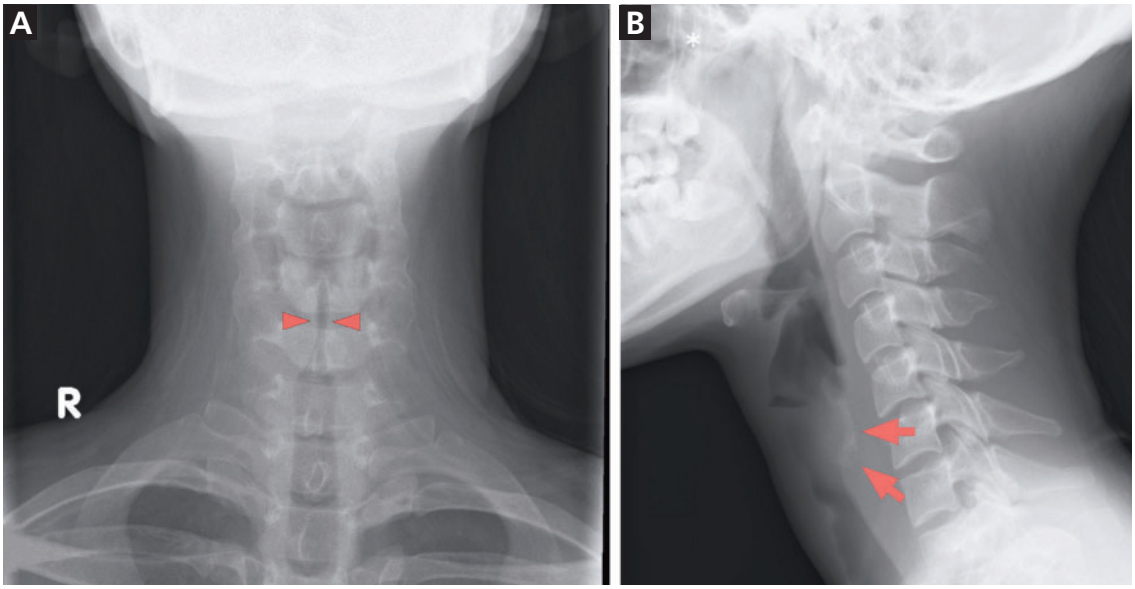

Figure 1. Radiography showed (A) narrowing of the upper trachea (arrowheads) and (B) calcification of tracheal cartilage (arrows).

A 23-year-old previously healthy woman presented with nonproductive cough and shortness of breath

A 23-year-old previously healthy woman presented with a 2-month history of nonproductive cough. Two weeks before her presentation, she developed shortness of breath on talking, followed by nasal congestion and epistaxis without a precedent episode of infection.

Her past medical and family history was noncontributory.

On examination, she was alert. Her temperature was 36.9 °C (98.4 °F), blood pressure 100/60 mm Hg, pulse 104 beats per minute, respiratory rate 18 breaths per minute, and oxygen saturation on ambient air 100%. There was audible stridor. Her eyes were not injected. Her ears and nose were not swollen with purulent nasal discharge.

Heart and lung examinations were normal. Laboratory testing showed elevated C-reactive protein at 2.37 mg/dL (reference range < 0.14), and the erythrocyte sedimentation rate was 25 mm/h (3–15). Chest radiography and electrocardiography were unremarkable. Neck radiography showed narrowing of the upper trachea and calcification of tracheal cartilage in the lateral view (**Figure 1**).

Computed tomography (CT) of the head and neck showed a thickened nasal septum, severe subglottic stenosis extending 2 cm in length, and dystrophic mural calcification along the bilateral dorsolateral margins of the trachea, but sparing the posterior membranous portion of the wall (**Figure 2**).

Rhinoscopy showed swelling of nasal mucosa and epistaxis. Fiberoptic laryngoscopy revealed severe subglottic narrowing with no exudation and normal-appearing mucosa (**Figure 3**). Pulmonary function testing was deferred because of severe airway compromise.

doi:10.3949/ccjm.87a.19129

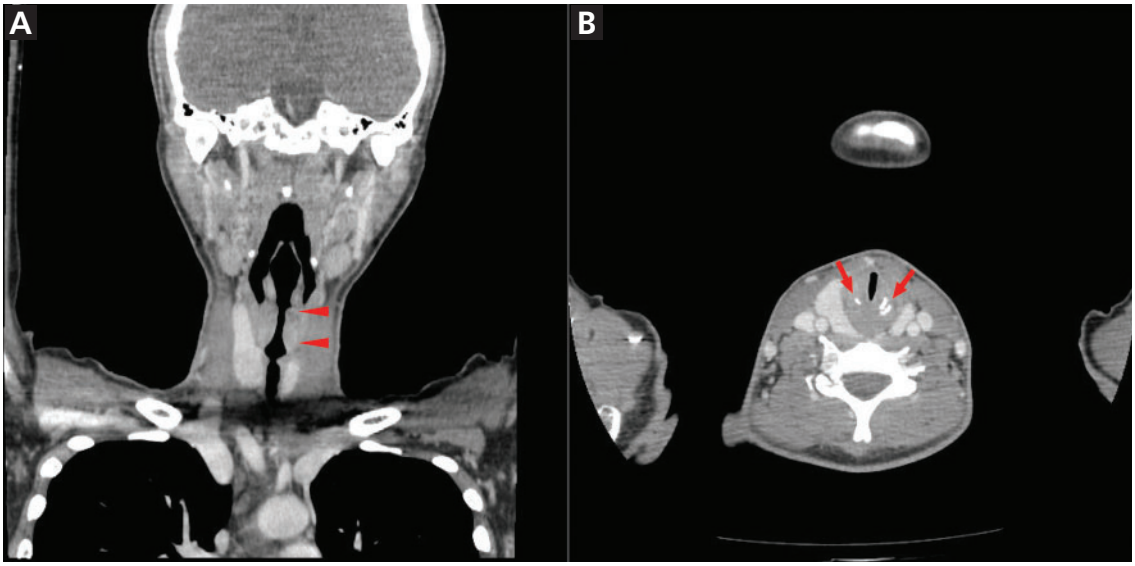

Figure 2. Computed tomography coronal (A) and axial (B) views of the head and neck showed severe subglottic stenosis (arrowheads), from which stenosis extended 2 cm in length, and tracheal calcification with sparing of the membranous posterior portion of trachea (arrows).

SEARCHING FOR THE CAUSE OF SUBGLOTTIC NARROWING

The differential diagnosis of subglottic narrowing includes relapsing polychondritis, granulomatosis with polyangiitis, idiopathic subglottic stenosis, lymphoma, sarcoidosis, amyloidosis, and bronchial tuberculosis. Interferon gamma-releasing assay for tuberculosis was negative, as was testing for myeloperoxidase and proteinase 3 antineutrophil cytoplasmic antibodies, antinuclear antibody, rheumatoid factor, and anticyclic citrullinated peptide antibody.

Nasal septal tissue biopsy study showed areas of lymphocytic infiltrates without evidence of vasculitis or granuloma. CT showed thickening of the tracheal wall of greater than 6 mm (reference range < 2 mm) and sparing of the posterior membranous (noncartilaginous) portion of the trachea, features highly typical of relapsing polychondritis rather than granulomatosis with polyangiitis, as the lack of associated clinical features for lymphoma, sarcoidosis, amyloidosis, and bronchial tuberculosis made them less likely.[1,2]

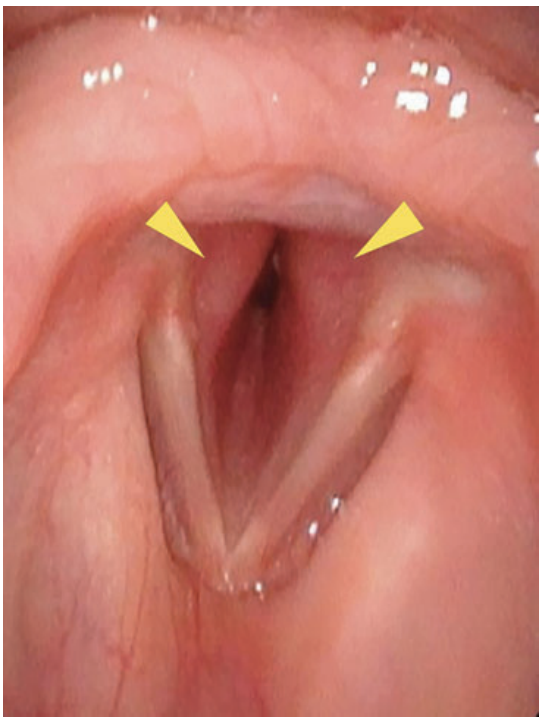

Figure 3. Fiberoptic laryngoscopy revealed severe subglottic narrowing.

Only 10% of patients have respiratory symptoms at presentation, but 50% eventually develop airway problems

TREATMENT

Prednisolone 50 mg daily was started, and a good response to the glucocorticoid met the Damiani criteria for the diagnosis of relapsing polychondritis.[3] Intravenous cyclophosphamide was added for the life-threatening airway complication and was then switched to methotrexate for maintenance therapy.

RELAPSING POLYCHONDRITIS: KEY FEATURES

Relapsing polychondritis is a systemic inflammatory disease of hyaline cartilage. Up to one-third of patients develop it in association with systemic autoimmune diseases. It may precede, coexist with, or follow vasculitis, autoimmune disorders (eg, rheumatoid arthritis, systemic lupus erythematosus), or malignancies such as solid tumors, lymphoma, and myelodysplastic syndrome in older individuals.[4]

The common manifestation is auricular chondritis.[5] Only 10% of patients with relapsing polychondritis have respiratory symptoms at presentation, but 50% eventually develop airway problems, which carry a poor prognosis and are major causes of morbidity and death.[4]

Calcification of laryngeal cartilage and patchy calcification of the tracheobronchial wall on CT was reported in a case of relapsing polychondritis within 6 months of onset.[6] Diffuse thickening of the tracheal wall and calcification with sparing of the posterior cartilaginous portion on CT is highly typical of relapsing polychondritis.[2]

Airway involvement in relapsing polychondritis should be suspected in patients with audible stridor, and in such cases calcification of tracheal cartilage on neck radiography may aid early diagnosis.

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***Address**: Mitsuyo Kinjo, MD, MPH, Division of Rheumatology, Department of Internal Medicine, Okinawa Chubu Hospital, 281 Miyazato, Uruma City, Okinawa, 904-2293, Japan; kinjomitsuyo@gmail.com*

Jolan Dupont, MD
Gerontology and Geriatrics, Department of Public Health and Primary Care, KU Leuven; Department of Geriatric Medicine, University Hospitals Leuven; Centre for Metabolic Bone Diseases, University Hospitals Leuven, Leuven, Belgium

Michaël R. Laurent, MD, PhD
Gerontology and Geriatrics, Department of Public Health and Primary Care, KU Leuven; Centre for Metabolic Bone Diseases, University Hospitals Leuven; Department of Geriatric Medicine, Imelda Hospital, Bonheiden, Belgium

Lenore Dedeyne, MSc
Gerontology and Geriatrics, Department of Public Health and Primary Care, KU Leuven, Leuven, Belgium

Frank P. Luyten, MD, PhD
Centre for Metabolic Bone Diseases, University Hospitals Leuven; Skeletal Biology and Tissue Engineering Centre, Department of Development and Regeneration, KU Leuven, Leuven, Belgium

Evelien Gielen, MD, PhD
Gerontology and Geriatrics, Department of Public Health and Primary Care, KU Leuven; Department of Geriatric Medicine, University Hospitals Leuven; Centre for Metabolic Bone Diseases, University Hospitals Leuven, Leuven, Belgium

Marian Dejaeger, MD, PhD
Gerontology and Geriatrics, Department of Public Health and Primary Care, KU Leuven; Department of Geriatric Medicine, University Hospitals Leuven; Centre for Metabolic Bone Diseases, University Hospitals Leuven, Leuven, Belgium

Vertebral fractures after denosumab cessation

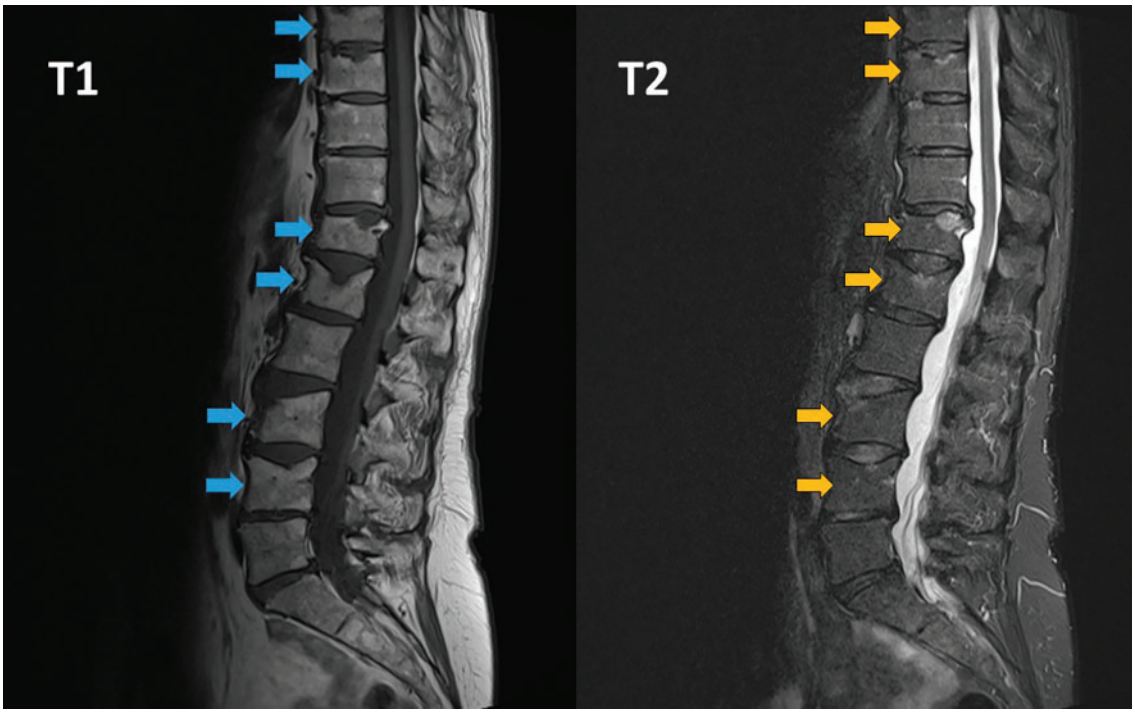

Figure 1. T1-weighted magnetic resonance imaging (left) indicated vertebral fractures of T8, T9, T12, L1, L3, and L4 (arrows). T2-weighting (right) showed bone marrow edema (arrows).

She had a 6-month history of lumbar and dorsal back pain, initially suspected to be facet arthrosis; physical therapy brought no improvement

A 63-year-old woman presented to the outpatient metabolic bone disease clinic with a 6-month history of lumbar and dorsal back pain. Initially, facet arthrosis was suspected and physical therapy suggested.

See related editorial, page 339

Physical therapy for 1 month brought no improvement in her pain. Lumbar radiography was performed, which showed a vertebral fracture at T12. Magnetic resonance imaging (MRI) of the thoracic and lumbar spine (**Figure 1**) revealed vertebral fractures at T6, T7, T8, T9, T12, L1, L3, and L4. T2-weighted MRI revealed bone marrow edema, which suggested that all fractures were recent.

The patient had a history of postmenopausal osteoporosis without prior fractures, treated with subcutaneous denosumab injections every 6 months for 5 years. Ten months before the onset of her first symptoms and 16 months before diagnosis of vertebral fractures,

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denosumab was stopped for a "drug holiday" after 5 years.

There was no imaging available from before the start of denosumab, although computed tomography done for kidney stones 9 months after denosumab cessation showed no lumbar vertebral fractures (thoracic spine not visible on these images). Moreover, her beta-C-terminal telopeptide concentration—a marker of bone turnover—was 852 ng/L (reference range 104–1,008 ng/L) at the time of MRI and diagnosis of vertebral fractures. These findings suggested recent rebound-associated vertebral fractures after denosumab cessation.

REBOUND-ASSOCIATED VERTEBRAL FRACTURE

Denosumab is a commonly used antiresorptive that increases bone mineral density and reduces the risk of vertebral, nonvertebral, and hip fractures in postmenopausal osteoporosis. It has a reversible effect, and after denosumab cessation, bone turnover markers transiently rebound above baseline levels.[1]

A 2018 post hoc analysis of data from the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial on study participants who discontinued denosumab suggested that the rate of vertebral fracture increased after denosumab cessation to a level comparable with that in untreated patients,[2] a phenomenon often described as rebound-associated vertebral fracture.[3–10] In patients who subsequently developed fractures, there was a significant increase in the number of those sustaining multiple vertebral fractures, with previous vertebral fracture being the main risk factor.[2]

Most rebound-associated vertebral fractures occur 2 to 10 months after the effect of the last dose is depleted,[2,3] as in our patient's case.

There is no optimal management protocol for denosumab cessation based on evidence from randomized controlled trials. Based on current knowledge, it is recommended not to stop denosumab without considering alternative treatments (eg, a potent bisphosphonate) in order to prevent rapid loss of bone mineral density and a potential rebound in vertebral fracture risk.[2,11,12] Our patient was treated with zoledronate intravenously immediately after diagnosis of the fractures. At most recent follow-up, she has suffered no additional fractures.

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***Address**: Jolan Dupont, MD, Department of Geriatric Medicine, University Hospitals Leuven, Herestraat 49, PO Box 7003, 3000 Leuven, Belgium; Jolan.dupont@uzleuven.be*

EDITORIAL

Chad L. Deal, MD
Department of Rheumatic and Immunologic Disease,
Center for Osteoporosis and Metabolic Bone Diseases,
Orthopedic and Rheumatologic Institute,
Cleveland Clinic

Denosumab cessation

Physicians and patients have become accustomed to a drug holiday with osteoporosis therapy. The American Society for Bone and Mineral Research has published recommendations for long-term bisphosphonate treatment,[1] in which they suggested that after 5 years of oral or 3 years of intravenous bisphosphonate treatment, one should consider reassessing fracture risk.

See related article, page 337

In women who have no factors that place them at high risk for fracture (hip T score less than −2.5, FRAX score indicating high fracture risk, previous fracture, or fracture on therapy), a holiday should be considered. For patients at high risk, continuing for up to 10 years of oral and 6 years of intravenous bisphosphonate should be considered. But a holiday is not forever. Therapy often needs to be restarted, especially if bone density declines or a fracture occurs.

A holiday is suggested since long-term use of bisphosphonates has been associated with atypical femoral fractures, and higher doses and longer duration of use have been associated with osteonecrosis of the jaw.

However, in the case of bisphosphonates, a holiday is "administrative." Although administration of the drug is stopped, these drugs have a long half-life in bone, and their pharmacologic effects continue for years after discontinuation, depending on the drug and duration of treatment.[2] This prolonged effect after discontinuation is not the case with other therapies for osteoporosis, including the parathyroid hormone analogues abaloparatide and teriparatide, estrogens, estrogen agonists-antagonists (eg, raloxifene), romosozumab, and denosumab.

Dr. Deal has disclosed consulting, membership on advisory committees or review panels, and teaching and speaking for Amgen.

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RAPID BONE LOSS AFTER DENOSUMAB IS STOPPED

Romosozumab is a humanized monoclonal antibody against sclerostin, a cytokine in the Wnt signaling pathway that inhibits bone formation, and denosumab is a fully human monoclonal antibody against RANK-ligand, a cytokine necessary for osteoclast formation and function. Unlike bisphosphonates, which bind avidly to hydroxyapatite and have a long half-life in bone, the effect of these 2 monoclonal antibodies is transient.

In phase 2 trials of denosumab, the gain in bone mass with 2 years of treatment was completely lost after 1 year off therapy.[3] Markers of bone resorption increased after denosumab discontinuation to levels higher than baseline, suggesting a hyperresorptive state. McClung et al[4] found that bone mineral density in the lumbar spine had increased 16.8% after 8 years of denosumab therapy but declined 6.7% in the first year after stopping.

A bisphosphonate holiday is not forever: therapy often needs to be restarted

Some have described the dramatic decline in bone mass as if bone were a "spring"—ie, when pressure is released, the material wants to rebound to the pretreatment state. Finite element analysis, a measure of bone strength, was shown to increase with denosumab treatment in the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial.[5]

MULTIPLE VERTEBRAL FRACTURES

In this issue, Dupont et al[6] report on a patient who experienced "rebound-associated" vertebral fractures after denosumab cessation.

Brown et al[7] analyzed 327 patients from the FREEDOM trial who discontinued denosumab after 2 to 5 doses and were followed for up to 24 months (median 0.8 years). Com-

pared with 470 patients who discontinued placebo, there was no difference in overall fracture rate, 13.5 per 100 patient-years for placebo vs 9.7 for denosumab-treated patients; for vertebral fractures, the rate was 9.3 per 100 patient-years for placebo vs 5.6 for denosumab patients.[7] Limitations of this analysis were the short follow-up period and initiation of other therapies in 42% of placebo and 28% of denosumab recipients.

Case reports of patients experiencing multiple vertebral fractures after denosumab discontinuation have subsequently been published.[8] However, these reports could not assess the change in vertebral fracture risk with discontinuation without a matched placebo control.

Cummings et al[9] analyzed the risk of new or worsening vertebral fractures after denosumab discontinuation in FREEDOM (3 years) and the FREEDOM extension trial (up to 7 additional years). In the 1,001 patients who discontinued denosumab, the vertebral fracture rate increased from 1.2 to 7.1 per 100 patient-years in the year after discontinuation. This fracture rate was similar to that in patients in the placebo group of the trial, suggesting a rapid return to a fracture rate as if on no therapy (n = 470, 8.5 per 100 patient-years). Although the overall fracture rate was not different, the proportion with 2 or more fractures (ie, multiple vertebral fractures) was 60.7% in patients who discontinued denosumab vs 38.7% in patients who discontinued placebo (P = .049). The odds ratio for developing multiple vertebral fractures was 3.9 (95% confidence interval [CI] 2.1–7.2) in those with prior vertebral fractures (either before or during the trial), 1.6 (CI 1.3–1.1) with each additional year off treatment, and 1.2 (CI 1.1–1.3) per 1% decline in annual total hip bone mineral density. There were no differences in nonvertebral fractures with discontinuation.[9]

Fracture risk increases rapidly after stopping denosumab; we must track patients who miss scheduled injections

Multiple vertebral fractures were not reported with discontinuation of alendronate in the FLEX (Fraction Intervention Trial Long-term Extension) study (5 years of alendronate, then 5 years of placebo), or with discontinuation of zoledronate in the HORIZON-PFT (Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly–Pivotal Fracture Trial) (3 years of zoledronate, then 3 years of placebo).[10] Discontinuation of bisphosphonates was not associated with rapid bone loss or with rapid increases in markers of bone resorption.

IF DENOSUMAB MUST BE STOPPED

Since fracture risk increases rapidly after denosumab discontinuation and multiple vertebral fractures occur with greater frequency, it is important to track patients who miss their scheduled injections. Further, if patients must discontinue denosumab (eg, because of adverse effects), another osteoporosis medication should be initiated to prevent bone loss and prevent fracture.

In the DAPS study (Denosumab Adherence Preference Satisfaction), 115 of 126 patients randomized to denosumab for 12 months were transitioned to alendronate for 12 months; 15.9%, 7.6%, and 21.7% lost bone mineral density in the lumbar spine, total hip, and femoral neck, respectively.[11]

In 6 patients who discontinued denosumab after 7 years and received 1 dose of zoledronate, bone mineral density declined in both the lumbar spine and hip at 18 to 23 months after infusion.[12] Bone mineral density remained significantly higher than baseline in the lumbar spine but declined to pretreatment levels in the hip. The authors suggested that more than 1 dose of zoledronate might be more effective for preventing bone loss.

The timing of administration of zoledronate may be important. Data suggest that if bone turnover is very low, bisphosphonate binding to bone may be reduced, and this lessens its efficacy in preventing bone loss. The ZOLARMAB trial (Treatment With Zoledronic Acid Subsequent to Denosumab in Osteoporosis, clinicaltrials.gov identifier NCT03087851) has enrolled 60 patients in 3 arms, ie, receiving a dose of zoledronate at either 6 or 9 months after denosumab discontinuation, or when a marker of bone resorption rises above a prespecified level. A second dose of zoledronate is given in patients who have a decline in bone mineral density or an increase in a marker of bone resorption. Results are expected in 2020 or 2021.

Given the risks associated with discontin-

uation, should we continue to prescribe denosumab? The answer is that denosumab clearly has a place in therapy for patients at high risk of fracture. Bisphosphonates are not recommended if the glomerular filtration rate is less than 35 mL/min/1.73 m^2. Since denosumab is excreted by the reticuloendothelial system and not the kidney, it is preferred in patients with chronic kidney disease.

Many patients do not tolerate oral bisphosphonates because of gastrointestinal adverse effects or bone pain. With bisphosphonate therapy, increases in bone mass occur in the first 3 years of therapy, after which no further increases occur. Denosumab is unique in that increases in bone mass continue through 10 years of treatment. Analysis of the FREEDOM extension showed that the incidence of nonvertebral fractures was lower with higher total hip T scores achieved with treatment.[13] For these reasons denosumab will continue to have an important place in the treatment of patients with low bone mass. For those who must discontinue denosumab, a bisphosphonate is recommended. More information is needed on oral or intravenous bisphosphonate therapy and the appropriate timing of therapy after denosumab discontinuation.

CONSIDERATIONS DURING THE COVID-19 PANDEMIC

As a result of the current COVID-19 pandemic, there is a higher likelihood that patients will miss scheduled denosumab treatments. Many patients are appropriately wary about coming for an appointment, so it is incumbent on providers to make patients understand the risks of discontinuation.

Many assisted-living facilities and nursing homes do not want residents to go to "routine" heathcare visits. Whenever possible, we should encourage these facilities to administer denosumab to their residents and make financial considerations secondary. If a family member is a healthcare provider, an attempt should be made to have the drug administered at home, if possible.

We should go the extra mile to make sure our patients get appropriate treatment. If all else fails, an oral bisphosphonate should be started, and denosumab can be resumed at a later date.

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***Address**: Chad L. Deal, MD, Department of Rheumatic and Immunologic Disease, A50, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; dealc@ccf.org*

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Douglas Nguyen, MD
Department of Gastroenterology and Hepatology, University of California Irvine, Orange, CA

ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Is it safe to continue biologic agents during surgery in patients with inflammatory bowel disease?

A: Patients with inflammatory bowel disease who are taking monoclonal antibodies against tumor necrosis factor alpha (TNF), interleukins 12 and 23, or integrin can continue taking them around the time of surgery, but small-molecule drugs such as tofacitinib should be withheld.

Inflammatory bowel disease encompasses Crohn disease and ulcerative colitis, and biologic drugs now play an integral role in the treatment of both. Biologic therapy is supplanting thiopurines as the main treatment for inflammatory bowel disease, leading to debate regarding how these drugs should be managed preoperatively in patients undergoing surgery, due to concern for increased risk of postoperative complications.

BIOLOGIC AGENTS

Anti-TNF drugs

The most studied of the biologics with respect to perioperative management have been the anti-TNF drugs, namely:

- **Infliximab and biosimilars** such as infliximabs axxq, dyyb, abda, and qbtx
- **Adalimumab and biosimilars** such as adalimumabs bwwd, afzb, adaz, adbm, bwwd, and atto
- **Certolizumab**.

Studies of anti-TNF drugs

While several meta-analyses have attempted to clarify the effect of these drugs on postoperative outcomes, the results have been conflicting.

Billioud et al,[1] in a meta-analysis, concluded that preoperative anti-TNF use slightly increases overall postoperative complications in patients with inflammatory bowel disease, and particularly infectious complications in patients with Crohn disease.

Ali et al,[2] in another meta-anlysis, also found a higher risk of complications in patients with Crohn disease receiving preoperative anti-TNF agents (and corticosteroids).

Narula et al[3] and **Yang et al**[4] performed meta-analyses demonstrating similar results, both reporting higher rates of total, infectious, and noninfectious postoperative complications in patients with Crohn disease who received infliximab within 30 days before surgery.

Although these studies suggest that anti-TNF therapy should be discontinued before surgery, other studies did not detect a higher risk of infectious complications with anti-TNF therapy.

Xu et al,[5] in a 2019 meta-analysis, found no significant difference in the rates of overall, major, minor, infectious, noninfectious, surgical, and medical complications between 1,407 patients with Crohn disease treated preoperatively with infliximab and 4,589 patients who were not.

Yang et al[6] analyzed 13 studies with a total of 2,933 patients with ulcerative colitis receiving infliximab. They similarly found no correlation between infliximab therapy and postoperative morbidity.

Rosenfeld et al[7] reported results similar to those of Yang et al, but in patients with Crohn disease.

Most of the studies included in these meta-analyses were retrospective, were performed at single centers, and had significant heteroge-

Monocloncal antibodies can be continued, but small-molecule drugs should be withheld

Dr. Nguyen has disclosed teaching and speaking for Abbvie Pharmaceuticals and Janssen Pharmaceuticals.

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neity and small sample sizes. They also varied significantly in confounding variables that were not controlled for such as concomitant medical therapy. Steroid use, in particular, is known to increase the risk of infectious complications in patients with ulcerative colitis or Crohn disease in the perioperative period.[8,9]

The Postoperative Infection in Inflammatory Bowel Disease (PUCCINI) trial[10] was perhaps the best study to date to examine postoperative infectious complications in patients with Crohn disease or ulcerative colitis who had been treated preoperatively with anti-TNF drugs. It prospectively enrolled 955 patients undergoing abdominal surgery, of whom 382 had been treated with anti-TNFs preoperatively and 573 had not. Serum anti-TNF levels were measured preoperatively and reported as either detectable or undetectable.

The investigators found no significant increases in any infection (19.4% vs 20.2%, *P* = .80) or surgical site infections (12.3% vs 12.7%, *P* = .92) in the anti-TNF recipients compared with nonrecipients. Further, detectable serum anti-TNF levels were not associated with higher rates of any infection.[10]

As the first large prospective study of its kind, the PUCCINI trial is currently the best source of information on the preoperative management of anti-TNF therapy in inflammatory bowel disease patients undergoing abdominal surgery.

The PUCCINI trial is currently the best source of information on preoperative management of anti-TNF therapy

Ustekinumab

Ustekinumab, a monoclonal antibody targeting interleukins 12 and 23, was approved in 2016 for use in Crohn disease, though it was previously used off-label for patients for whom anti-TNF therapy failed. After induction, ustekinumab maintenance therapy is given every 8 weeks.

In a multicenter Canadian study[11] comparing preoperative anti-TNF use and preoperative ustekinumab use in patients with Crohn disease undergoing abdominal surgery, there were no significant differences in postoperative complications, length of hospital stay, or mortality rates.

These results were mirrored in a US study of 44 ustekinumab-treated patients and 169 anti-TNF-treated patients undergoing major abdominal surgery. There was no difference in postoperative surgical site infection rates or hospital readmission rates between the 2 cohorts.[12]

Anti-integrin antibodies

Vedolizumab and natalizumab are the most widely used anti-integrin antibodies. The former is a gut-specific antibody that selectively inhibits lymphocyte trafficking and inflammatory response in the gastrointestinal tract. It is given every 8 weeks after induction but can be dosed as often as every 4 weeks in patients with severe disease or those who lose response to initial treatment.[13]

Studies of anti-integrin antibodies

Law et al[14] conducted a meta-analysis comparing 5 studies with 307 patients receiving vedolizumab, 490 patients receiving anti-TNF drugs, and 535 patients not receiving biologic agents. The analysis revealed no significant difference in rates of overall postoperative complications or infectious complications between those on vedolizumab and either those on anti-TNF agents or those with no biologic exposure.

Yung et al[15] recently performed another meta-analysis of 4 studies in 1,080 patients with Crohn disease or ulcerative colitis, who had vedolizumab exposure, anti-TNF exposure, or no exposure to biologics. The ulcerative colitis patients with vedolizumab exposure did have a significantly lower overall postoperative complication rate compared with those with anti-TNF exposure. However, there were no other significant differences in infectious, surgical site, or major complications in those with either ulcerative colitis or Crohn disease between vedolizumab and anti-TNF or vedolizumab and no biologics. Likewise, there were no significant differences in the rates of additional surgery for complications.[15]

SMALL-MOLECULE DRUGS

Tofacitinib, a JAK inhibitor

Tofacitinib, approved in May 2018, is one of the newest medications for moderate to severe ulcerative colitis. This small molecule is a Janus kinase (JAK) inhibitor that is taken orally twice a day. It has been approved for use in rheumatoid arthritis since 2012.[16]

As tofacitinib is a recent addition to inflammatory bowel disease therapy, there are limited data assessing its perioperative use. Current guidelines from the American College of Rheumatology (ACR) and the American Association of Hip and Knee Surgeons (AAHKS) recommend holding tofacitinib starting 7 days before total knee or total hip surgery due to increased risk of infectious complications. It can be resumed as early as 14 days after surgery.[17]

OUR RECOMMENDATIONS

Biologics

In summary, to date, several single-center retrospective reviews, prospective studies, and meta-analyses exploring postoperative complications in inflammatory bowel disease patients on anti-TNF therapy have demonstrated mixed results. However, nearly all of the earlier studies had notable weaknesses, including marked heterogeneity among studies in meta-analyses and lack of controlled variables. On the contrary, the landmark PUCCINI trial has emerged as the most instrumental study of preoperative anti-TNF therapy in patients with inflammatory bowel disease, owing to its robust study design and high power. Given the compelling results of the PUCCINI trial, in addition to several negative studies examining vedolizumab and ustekinumab, we recommend that all biologic therapy be continued preoperatively in both Crohn disease and ulcerative colitis patients.

However, biologic therapy does not need to be continued preoperatively in all cases. For instance, in patients with stricturing Crohn disease undergoing intestinal resection with no plans for biologic therapy postoperatively, preoperative biologic therapy may not be warranted.

As demonstrated by the PUCCINI trial, there is no benefit in measuring serum anti-TNF levels preoperatively. Further, drug levels of other biologic agents have yet to be studied, and thus in the absence of any supporting data, its practice should not be adopted.

The above recommendations pertain to intra-abdominal surgeries only, as only these surgeries were included in the referenced studies.

Small molecules

With respect to tofacitinib, in the absence of any data examining its perioperative use in inflammatory bowel disease patients, our recommendation reflects the 2017 ACR/AAHKS guidelines based on evidence from prior studies in patients with rheumatic diseases. These guidelines reflect the markedly short half-life of tofacitinib, which is 3.2 hours.[16] Therefore, we recommend holding the medication 7 days before surgery and resuming as early as 14 days after surgery. It should be noted, however, that for urgent or emergent situations, we would *not* delay surgery due to any biologic or small molecule therapy. The increased risk of postoperative complications, if even present, does not outweigh the risks of delaying surgery.

Selective JAK inhibitors, namely filgotinib, upadacitinib, and peficitinib, have shown promising preliminary results in clinical trials and may soon be approved for treating inflammatory bowel disease. Because these drugs are so new, their influence on operative outcomes at this time is unknown.

Our recommendations differ from those included in the 2017 professional society guidelines,[17] which recommend holding all biologic medications as close to 1 dosing cycle as possible before all elective procedures. The deviation of our recommendations from these guidelines is due to the recent emergence of groundbreaking studies such as the PUCCINI trial which have allayed fears of increased risks of postoperative complications with biologic use in inflammatory bowel disease patients.

Biologic therapy does not need to be continued preoperatively in all cases

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***Address**: Zain Moosvi, MD, Department of Internal Medicine, University of California Irvine, 101 The City Drive S, Orange, CA 92868; zmoosvi@uci.edu*

Constantine Tsigrelis, MD
Department of Infectious Disease, Cleveland Clinic;
Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

CME MOC

TAKE-HOME POINTS FROM LECTURES BY CLEVELAND CLINIC AND VISITING FACULTY

Recurrent *Clostridioides difficile* infection: Recognition, management, prevention

ABSTRACT

Clostridioides difficile infection (CDI) is the most common cause of diarrhea in hospitalized patients and results in substantial morbidity, mortality, and costs. Its clinical management, primarily with antibiotics, is often complicated by recurrent episodes. These recurrent CDI episodes are thought to be caused by antibiotic disruption of colonic microbiota and usually occur within 4 weeks of completing antibiotic therapy. The risk of recurrent CDI increases after the first episode, creating a need for management strategies to diagnose, treat, and prevent these complications.

KEY POINTS

- Diagnostic testing for CDI should be performed only in symptomatic patients.
- Diagnosis is based on unexplained diarrhea and a positive *C difficile* assay.
- The goal of therapy for recurrent CDI is to allow the normal colonic microbiota to restore itself.
- Fecal microbiota transplantation has shown efficacy for treating recurrent CDI.
- Antimicrobial stewardship and infection prevention are key strategies for preventing CDI.

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CLOSTRIDIOIDES (formerly *Clostridium*) *difficile)* is an anaerobic spore-forming bacillus that colonizes the intestinal tract in patients whose normal gut microbiota is disrupted by antibiotic therapy.[1] C *difficile* produces 2 major toxins—toxins A and B—that cause intestinal mucosal injury, diarrhea, and colitis, and in some cases, fulminant infection leading to shock, ileus, and toxic megacolon.[2] C *difficile* infection (CDI) recurs in up to one-quarter or more of treated patients, complicating its management.

In the United States, C *difficile* is a common hospital-acquired infection, affecting about 500,000 patients annually, causing up to 30,000 deaths, and incurring inpatient costs of nearly $5 billion.[2–4] This article reviews the current standards for diagnosing and treating CDI and discusses strategies for managing and preventing recurrent disease.

Diagnosis requires unexplained new-onset diarrhea and a positive *C difficile* assay

DIAGNOSIS

The current standard for diagnosis of CDI requires both unexplained new diarrhea and a positive result on a C *difficile* assay.[2,5] Guidelines recommend laboratory testing for C *difficile* only in patients who have symptoms, defined as unexplained new onset of 3 or more unformed stools per day. Also, practitioners need to rule out use of a laxative (eg, polyethylene glycol) in the preceding 48 hours or a history of chronic diarrhea with no change in symptoms. **Table 1** lists laboratory assays for detecting C *difficile* toxin or organism.[2,5]

Colonization vs infection: Is it important?

C *difficile* **colonization** is the existence of the organism or toxin in the stool of patients who do not have unexplained new diarrhea. C *difficile* **infection** is the existence of the organism

TABLE 1

Diagnostic tests for *Clostridioides difficile*

Test	Characteristics	Sensitivity, specificity
Organism detection assays		
Nucleic acid amplification tests (eg, polymerase chain reaction)	Detects toxin gene (ie, organism) but not toxins	High sensitivity Low to moderate specificity
Glutamate dehydrogenase	*C difficile* common antigen	High sensitivity Low specificity
Toxigenic *C difficile* culture	Growth of *C difficile* organism Testing not readily available Slow turnaround time	High sensitivity Low specificity
Toxin detection assays		
Enzyme immunoassay	Detects free toxins	Low sensitivity Moderate specificity
Cell culture cytotoxicity neutralization assay	Detects free toxins Lacks standardization Slow turnaround time	High sensitivity High specificity, if optimized

Information from McDonald et al, reference 2.

Laboratory testing cannot distinguish between asymptomatic *C difficile* colonization and symptomatic CDI

or toxin in patients with unexplained new diarrhea. Laboratory testing cannot distinguish between asymptomatic C *difficile* colonization and symptomatic CDI.

The prevalence of asymptomatic C *difficile* stool colonization varies from 3% to 26% in adult hospitalized patients to 5% to 7% in elderly patients in long-term care facilities. In asymptomatic adults without any recent healthcare exposure, the prevalence is less than 2%.[2]

A patient presenting with no diarrhea, a positive polymerase chain reaction (PCR) test, and a negative enzyme immunoassay (EIA) test likely has C *difficile* colonization. However, a patient can have a positive EIA result without symptoms, so the best approach is to carefully assess the patient for unexplained new-onset diarrhea.

Institutional policies will determine which CDI tests are used. If the policy is to test *only* stool specimens from patients with unexplained and new onset of at least 3 unformed stools in 24 hours, one has the following options[2]:

- Order a nucleic acid amplification test (NAAT) alone (eg, PCR)
  or
- Order a stool toxin test as part of a multistep algorithm:
  1) NAAT plus toxin test, or
  2) Glutamate dehydrogenase (GDH) plus toxin test, or
  3) GDH plus toxin test, arbitrated by NAAT.

If the facility does not have a policy to submit stool specimens for CDI testing only from patients who have unexplained new-onset diarrhea, a NAAT (eg, PCR) test alone is not recommended because it increases the chance of detecting colonization. Instead, the recommendation is to perform a stool toxin test as part of a multistep algorithm:

1) NAAT plus toxin test, or
2) GDH plus toxin test, or
3) GDH plus toxin test, arbitrated by NAAT

In addition, repeat C *difficile* testing is not recommended to evaluate for cure in patients whose symptoms have improved or resolved.

That is because C *difficile* can continue to be shed in stools for more than 1 month, even after a patient's symptoms have resolved.[6] This is important because treatment of asymptomatic C *difficile* carriers with either metronidazole or vancomycin has not been shown to be beneficial, and vancomycin can prolong C *difficile* colonization or increase the risk of acquiring a new C *difficile* strain.[7]

TREATMENT OF A FIRST EPISODE

The first step in treating CDI is to stop the inciting antibiotic therapy as soon as possible. Antiperistaltic therapy should be avoided, especially if the patient is not receiving antibiotics for CDI.[2,8] Additionally, empiric anti-C *difficile* therapy is not recommended unless a substantial delay in C *difficile* testing results is anticipated or the patient has fulminant CDI.

Treatment of initial episodes of CDI, as outlined in clinical practice guidelines from the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA),[2] is based on the severity of disease.

Nonsevere cases are defined as those in which the white blood cell count remains less than or equal to 15.0×10^9/L and the serum creatinine level is less than 1.5 mg/dL. In such cases, there are 3 options for treatment:

- Vancomycin 125 mg by mouth 4 times a day for 10 days
- Fidaxomicin 200 mg by mouth twice a day for 10 days (more about this agent below)
- Metronidazole 500 mg by mouth 3 times a day for 10 days (if access to vancomycin or fidaxomicin is limited).

The first 2 options carry strong recommendations based on high levels of evidence, whereas the third has a weak recommendation based on a high level of evidence.[2]

Severe cases are those in which the white blood cell count is 15.0×10^9/L or higher or the serum creatinine level is higher than 1.5 mg/dL. There are 2 treatment options:

- Vancomycin 125 mg by mouth 4 times a day for 10 days
- Fidaxomicin 200 mg by mouth twice a day for 10 days.

These options carry strong recommendations based on high levels of evidence.[2]

Fulminant cases are characterized by hypotension, shock, ileus, or toxic megacolon. Treatment is with vancomycin 500 mg by mouth or nasogastric tube 4 times a day, plus metronidazole 500 mg intravenously every 8 hours, especially if the patient has ileus. In addition, if the patient has ileus, one can consider rectal installation of vancomycin 500 mg.[2]

Oral vancomycin therapy for fulminant CDI carries a strong recommendation based on a moderate level of evidence; intravenous metronidazole carries a strong recommendation based on a moderate level of evidence, and rectal vancomycin carries a weak recommendation based on a low level of evidence.[2]

With respect to other therapies for fulminant CDI, there are limited data regarding the use of fidaxomicin. Patients with life-threatening or fulminant CDI or toxic megacolon were excluded from clinical trials evaluating fidaxomicin.[9,10] Additionally, there are limited data on the use of fecal microbiota transplantation (FMT) for fulminant CDI.[2]

RECURRENT CDI

A major clinical challenge is recurrent CDI, which usually occurs within 4 weeks after completion of anti-C *difficile* therapy. The risk of recurrence increases with each episode[11,12]:

- Up to 20% to 25% after the first CDI episode
- Up to 40% to 45% after the second CDI episode
- More than 60% to 65% after 3 or more CDI episodes.

It is recommended that patients with CDI be counseled regarding the risk of recurrence. If a patient's diarrhea initially improves, but the patient subsequently develops new-onset or worsening diarrhea after CDI treatment is completed, the recommendation is to submit a stool sample for CDI testing to evaluate for recurrent CDI. However, in the absence of new-onset or worsening diarrhea, repeat testing for CDI is not recommended to avoid the detection of asymptomatic C *difficile* colonization (see "Colonization vs infection," earlier).

Stop the inciting antibiotic as soon as possible to avoid increasing the risk of recurrent CDI

TREATMENT OF RECURRENT CDI

C *difficile* infection is thought to primarily result from disruption of colonic microbiota

C difficile infection

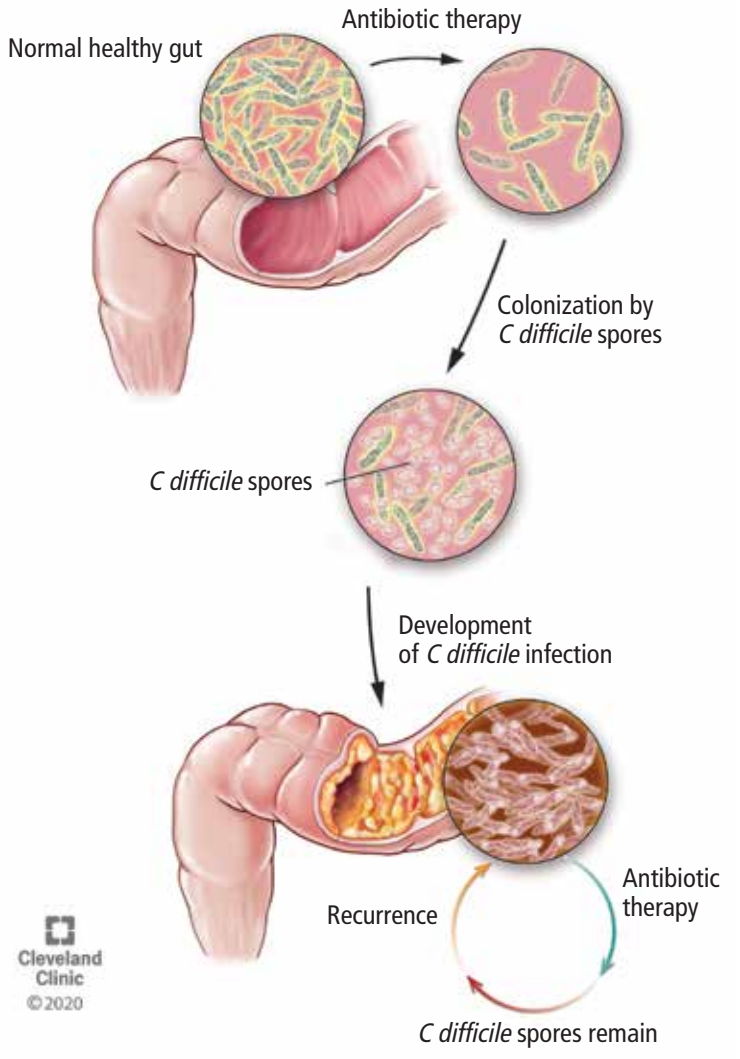

Figure 1. Antibiotic therapy can paradoxically lead to recurrent *Clostridioides difficile* infection by disrupting the normal colonic microbiota.

(**Figure 1**). Therefore, the primary goal of therapy for recurrent CDI is to allow the normal colonic microbiota to restore itself.[11,12] Contributing to the difficulty of treating recurrent CDI is the ability of C *difficile* to transform from a vegetative gram-positive bacillus form, which is susceptible to killing by anti-C *difficile* therapy, to a spore form (**Figure 2**) that is resistant to anti-C *difficile* therapy and most other measures except hypochlorite-based solutions (ie, bleach). Antitoxin immune response may also be a factor in recurrent CDI.[12]

Treatment of recurrent CDI, according to the IDSA and SHEA guidelines,[2] is based on the episode number of CDI, with nonsevere disease and severe disease being treated similarly.

A first recurrence (ie, a second episode), whether severe or nonsevere, has 3 options:

- Vancomycin, 125 mg orally 4 times a day for 10 days (if metronidazole was used for the initial episode)
- Vancomycin in a tapered and pulsed regimen (rather than a second standard 10-day vancomycin course), such as 125 mg orally 4 times per day for 10 to 14 days, then twice a day for 7 days, then once a day for 7 days, then every 2 or 3 days for 2 to 8 weeks
- Fidaxomicin 200 mg orally 2 times per day for 10 days (if vancomycin was used for the initial episode).

All 3 options carry weak recommendations, the first 2 based on low-quality evidence and the third based on moderate-quality evidence.

Oral vancomycin may be administered as a tapered and pulsed regimen. Tapering entails decreasing the dosage stepwise over a period of time to allow the normal colonic microbiota to restore itself. The pulsed regimen at the end of therapy entails dosing vancomycin every 2 to 3 days over a period of time to allow the treatment-resistant spore forms of C *difficile* to convert to the vegetative forms that are susceptible to killing by oral vancomycin.

A second recurrence, whether severe or nonsevere, has 4 options:

- Vancomycin in a tapered and pulsed regimen
- Vancomycin 125 mg 4 times a day by mouth for 10 days followed by rifaximin for 20 days
- Fidaxomicin 200 mg orally 2 times a day for 10 days
- Fecal microbiota transplantation (more about this below).

Although the first 3 options carry weak recommendations based on low levels of evidence, fecal microbiota transplantation carries a strong recommendation based on a moderate level of evidence.[2]

FIDAXOMICIN

Fidaxomicin is a macrocyclic antibiotic that inhibits RNA synthesis. C *difficile* resistance or reduced susceptibility to fidaxomicin is rare,

and it has no cross-resistance with rifamycin antibiotics. Like vancomycin, it is poorly absorbed. It exerts its activity in the gastrointestinal tract and has high fecal concentrations.[13,14]

Fidaxomicin is active against gram-positive anaerobes such as *C difficile* and *Peptostreptococcus* species, with variable activity against aerobic gram-positive cocci such as viridans streptococci and enterococci. However, it is less active against other anaerobic gram-positive bacilli such as *Lactobacillus* species, poorly active against anaerobic gram-negative bacilli (eg, *Bacteroides* species), and resistant to some *Clostridium* species (eg, *C clostridioforme*, *C innocuum*) that are key components of the normal colonic microbiota.[13,14] Therefore, fidaxomicin should have a relatively lower impact on the normal colonic microbiota than therapies such as oral vancomycin.

But does it decrease the risk of recurrent CDI? In 2 randomized double-blind clinical trials comparing vancomycin with fidaxomicin,[9,10] the clinical cure rates, defined as resolution of diarrhea 2 days after completing therapy, were similar. However, significantly fewer fidaxomicin-treated patients developed recurrent CDI. Louie and colleagues[9] reported that 15.4% of patients developed recurrent CDI within 4 weeks of stopping fidaxomicin compared with 25.3% of patients who were treated with oral vancomycin (P = .005; absolute risk reduction = 9.9%; number needed to treat [NNT] = 10; relative risk reduction = 39.1%). Cornely and colleagues[10] reported similar results, with 12.7% of fidaxomicin-treated patients developing recurrent CDI within 4 weeks compared with 26.9% of vancomycin-treated patients (P = .0002; absolute risk reduction = 14.2%; NNT = 7; relative risk reduction 52.7%). Recurrent CDI was similar in the fidaxomicin and vancomycin groups among patients with the NAP1/BI/027 strain of *C difficile* (ie, North American pulsed-field gel electrophoresis type 1, restriction endonuclease analysis pattern BI, PCR ribotype designation 027), an epidemic strain of *C difficile* which emerged in the early 2000s.[8] In contrast, recurrent CDI was lower with fidaxomicin compared with vancomycin among patients with non-NAP1/BI/027 strains of *C difficile* (7.8% vs 25.5%, respectively, in Louie et al[9] and 9.2% vs 27.4% in Cornely et al[10]).

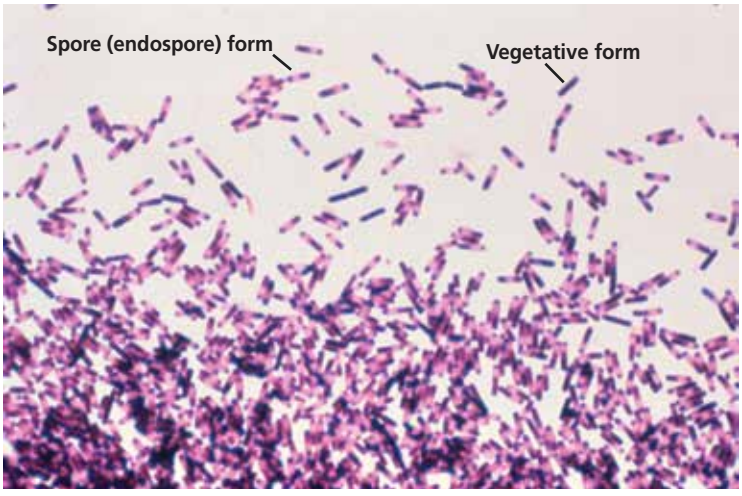

Figure 2. Photomicrograph showing the presence of *Clostridioides difficile* bacteria, many of which have assumed an endospore morphology. This is from a blood agar impression smear incubated for 72 hours anaerobically.

From the US Centers for Disease Control and Prevention, Dr. Gilda Jones; Public Domain; Available at: https://phil.cdc.gov/phil/details.asp?pid=3876

The NAP1/BI/027 strain of *C difficile* was the most prevalent strain of *C difficile* in the United States as far back as 2013.[4] However, the prevalence of this strain has decreased over time both in healthcare-associated *C difficile* isolates (from 21% in 2012 to 15% in 2017) and in community-associated *C difficile* isolates (from 17% in 2012 to 6% in 2017), with the NAP1/BI/027 strain still being the most prevalent healthcare-associated strain in 2017, but no longer the most prevalent community-associated strain.[4]

Fidaxomicin is expensive and may require prior authorization

Fidaxomicin is expensive, costing up to $4,500 for a 10-day course.[15] In my experience, more insurance plans are covering fidaxomicin, but it is advised that before prescribing fidaxomicin, clinicians need to check whether the plan requires prior authorization and whether the patient can afford the copay.

BEZLOTOXUMAB, A NEWER AGENT

Poor antitoxin immune response may also play a role in recurrent CDI.[11] Bezlotoxumab, an immunotherapeutic agent, received Food and Drug Administration (FDA) approval for prevention of recurrent CDI in October 2016. Efficacy was based on a large clinical trial—MODIFY I and II—that enrolled 2,655 adults with primary or recurrent CDI.[16] All were re-

ceiving standard-of-care anti-*C difficile* therapy. Investigators randomized the participants to either bezlotoxumab alone, actoxumab plus bezlotoxumab, or placebo. Actoxumab alone was given in MODIFY I but was discontinued after a planned interim analysis. Bezlotoxumab is a human monoclonal antibody against *C difficile* toxin B. Actoxumab is a human monoclonal antibody against *C difficile* toxin A. The primary end point was recurrent CDI during 12 weeks of follow-up, defined as a new episode of CDI after the initial clinical cure.

Results showed similar initial cure rates in the pooled data set (ie, MODIFY I + II) with bezlotoxumab (80%) and placebo (80%); however, actoxumab plus bezlotoxumab had a significantly lower initial cure rate (73%) than either placebo (P = .0014) or bezlotoxumab alone (P = .0021). The initial cure rate with actoxumab alone (in MODIFY I) (73%) was also significantly lower than placebo (83%; P = .0028).

Sustained cure rates (without recurrent infection) at 12 weeks in the pooled data set were higher with bezlotoxumab (64%) than placebo (54%; P = .0001). Actoxumab plus bezlotoxumab showed no difference in the sustained cure rate (58%) compared with placebo (P = .0851) and a lower sustained cure rate compared with bezlotoxumab alone (P = .0273). Sustained cure with actoxumab alone (in MODIFY I) (47%) was lower than with placebo (55%) (P = .0449).

Bezlotoxumab was approved after the guidelines were written

Recurrent CDI in the pooled data set was lower with bezlotoxumab (17%) and actoxumab plus bezlotoxumab (15%) than with placebo (27%; P < .0001). Recurrent CDI with actoxumab alone (in MODIFY I) (26%) was not different than with placebo (28%; P = .6364).

In summary, bezlotoxumab plus standard-of-care was more effective than standard-of-care alone in reducing the rate of recurrent CDI. Of note, compared with fidaxomicin in the trials discussed above, bezlotoxumab showed a similar absolute risk reduction (10.1%), number needed to treat (10), and relative risk reduction (37.9%) of recurrent CDI. In contrast, actoxumab alone or in combination with bezlotoxumab was inferior to placebo for the initial cure of CDI, and adding actoxumab to bezlotoxumab did not improve the efficacy of bezlotoxumab in reducing the rate of recurrent CDI.

Cost is a concern. Bezlotoxumab is expensive, costing approximately $4,500 per patient course.[15] An editorial accompanying the MODIFY I and II trials suggested that bezlotoxumab use may vary depending on an analysis of cost versus the decrease in CDI recurrence risk compared with other options.[17] Cost-effectiveness analyses have since been performed with conflicting conclusions. One study financed by the manufacturer found bezlotoxumab plus standard care (metronidazole, vancomycin, or fidaxomicin) was cost-effective versus placebo plus standard care for primary or recurrent CDI.[18] In contrast, Lam et al[15] conducted a cost-effectiveness analysis specifically in patients with a first recurrence of CDI and concluded that vancomycin was the most cost-effective regimen for treating a first CDI recurrence. Fidaxomicin had higher quality-adjusted life years but at a cost higher than what was considered cost effective. Lastly, bezlotoxumab plus vancomycin was associated with a higher cost than fidaxomicin alone with an incremental decrease in quality-adjusted life years. The 2018 IDSA-SHEA clinical practice guidelines for CDI noted that bezlotoxumab received FDA approval after the guidelines were written and will be covered in subsequent guideline updates.[2]

FECAL MICROBIOTA TRANSPLANTATION

As discussed above, CDI is thought to primarily result from disruption of the normal colonic microbiota and can recur with many bouts over months or years despite standard therapies. The normal colonic microbiota is composed of a large and diverse community of microbes that resist colonization by new microbes (eg, *C difficile*), resulting in "colonization resistance."[19–21] Antibiotics kill normal colonic microbiota and impair "colonization resistance," and impairment may last up to 4 weeks or longer.

FMT is the reintroduction of normal colonic microbiota from donor feces (**Figure 3**). It can be administered by the upper route (eg, nasogastric or nasoduodenal tube, esophagogastroduodenoscopy, or capsules) or the lower route (eg, colonoscopy, sigmoidoscopy, or enema). The source of stool for FMT is through human donors, either from donors that are

known to the patient (eg, spouse, partner, friend) or from a prescreened volunteer donor pool (ie, stool bank).

To provide guidance for FMT, including indications, donor choice, donor exclusion criteria, donor testing, recipient exclusion criteria, and a protocol for performing FMT, the American Gastroenterological Association convened an expert work group that published guidelines in 2011[20] and updated them in 2015.[22] Recommended indications for FMT for patients with recurrent or relapsing CDI include at least 3 episodes of mild to moderate CDI and failure of a 6- to 8-week vancomycin taper, or at least 2 episodes of severe CDI resulting in hospitalization and associated with significant morbidity.

The American College of Gastroenterology published guidelines in 2013 that recommended considering FMT after 3 CDI recurrences (ie, 4 episodes) and receipt of a pulsed vancomycin regimen.[23] Clinical practice guidelines from IDSA and SHEA from 2018 recommended offering FMT only after patients have been diagnosed with at least 3 CDI episodes (ie, at least 2 recurrences) treated with appropriate anti-*C difficile* therapy.[2]

FMT is not FDA-approved, but its use is subject to FDA regulation. Also, there was concern that applying investigational new drug requirements would make FMT unavailable for patients. In July 2013, the FDA issued a *Guidance for Industry* statement noting that published data suggest FMT may be an effective therapy for management of refractory CDI, but that the FDA intends to exercise enforcement discretion regarding investigational new drug requirements for use of FMT for CDI not responsive to standard therapies. Practitioners who recommend FMT must obtain informed consent from patients, which includes a discussion of its investigational status and its potential risks.[24]

Evidence supporting FMT efficacy

Before 2013, most of the published data on FMT use to treat recurrent CDI were from case reports. In a systematic review by Drekonja et al[25] that included 480 patients treated with FMT for recurrent CDI from 21 case-series studies, FMT had an overall 85% cure rate (defined as resolution of symptoms without recurrent CDI). The method of administration made a difference. Colonoscopic administration produced the highest resolution rate at 90%, followed by enema administration at 78% and upper-gastrointestinal administration at 77%. Although these cases show FMT has substantial success in recurrent CDI, it is relatively low-level evidence. In other reports, FMT administered orally via capsule has had variable success rates, ranging from 70% to 88%.[26–29]

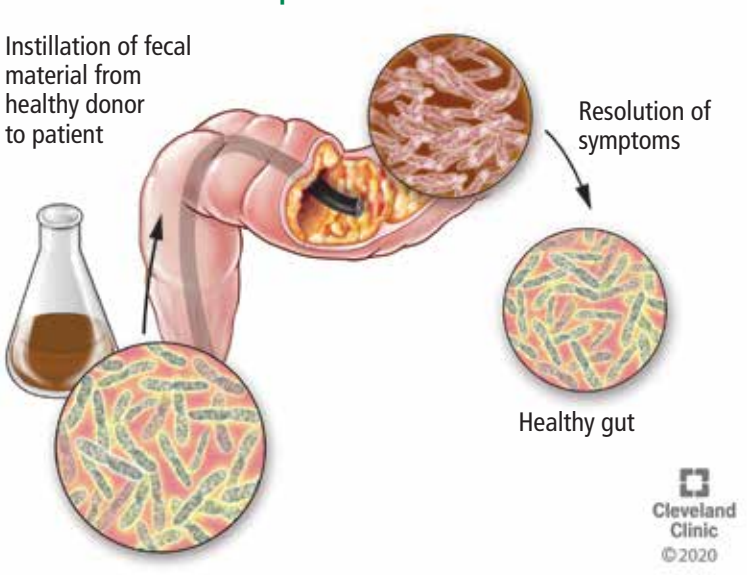

Figure 3. Fecal microbiota transplantation involves instilling fecal material from a healthy donor to restore the normal intestinal flora.

Fecal transplantation is not FDA-approved, but it is subject to FDA regulation

Clinical trials have shown similar efficacy of FMT for recurrent CDI. van Nood and colleagues[30] compared FMT delivered by nasoduodenal tube vs oral vancomycin. The FMT recipients had 81% cure without recurrent CDI within 10 weeks after the first FMT and 94% after 2 FMTs compared with 31% cure for vancomycin ($P < .001$). Cammarota and colleagues[31] compared FMT administered by colonoscopy vs oral vancomycin given in a pulsed regimen over at least 3 weeks. They reported cure rates without recurrent CDI within 10 weeks of 65% after the first FMT and 90% after additional FMT procedures (ranging from 2 to 4 procedures) compared with 26% for vancomycin recipients ($P < .0001$).

In 2016, in a randomized, double-blind, placebo-controlled clinical trial by Kelly et

al,[32] patients with 3 or more CDI recurrences received either FMT from a volunteer stool donor or a placebo composed of the patient's own stool. Both were administered by colonoscopy. All patients had received oral vancomycin for at least 10 days and continued it until 2 to 3 days before the FMT. The cure rate without recurrent CDI within 8 weeks was 91% after first FMT and 100% after second. Interestingly, the autologous FMT was successful 63% of the time, although the cure rate for donor FMT (91%) was significantly higher (P = .042). All patients who received an autologous FMT and developed recurrent CDI were then treated with a donor FMT, with a 100% success rate.

An open-label trial by Hota et al[33] in 2017 compared FMT by enema vs oral vancomycin delivered in a tapered and pulsed regimen over 6 weeks. The cure rates without recurrent CDI within 4 months after FMT were surprisingly low—44% for FMT and 58% for vancomycin—and not consistent with the other published trials.

FMT normalizes microbial diversity

The normal colonic microbiota is primarily composed of Firmicutes and Bacteroidetes

The human microbiota, defined as the total collection of microorganisms within a community, is composed of an estimated 90 trillion microorganisms. Each body site (eg, colon, small bowel, oral cavity, skin) in the healthy human microbiota has a distinct microbial composition. The normal colonic microbiota is a highly diverse microbial community with 2 predominant bacterial phyla in healthy individuals, primarily composed of Firmicutes (approximately 50%) and Bacteroidetes (approximately 30%).[21] Firmicutes include genera such as *Clostridium*, *Lactobacillus*, *Streptococcus*, *Faecalibacterium*, and *Ruminococcus*. Bacteroidetes are dominated by the genus *Bacteroides*. Less than 5% of the colonic microbiota are composed of Proteobacteria, which includes Enterobacteriaceae such as *Escherichia coli* and *Klebsiella* species.[21] The desirable mix is more Firmicutes and Bacteroidetes and fewer Proteobacteria.

Patients with recurrent CDI are known to have abnormal colonic microbiota, and FMT has been shown to normalize microbial diversity. In an FMT clinical trial by Kelly et al,[32] fecal microbiome analysis (ie, total genes and gene products such as RNA and proteins produced by resident microbial communities) was performed at least 5 days before and 2 to 8 weeks after FMT. Before FMT, patient samples showed marked dysbiosis and lower diversity with more Proteobacteria and fewer Firmicutes and Bacteroidetes compared with donor samples. After FMT, patient samples showed normalization of the fecal microbiota.

The FMT clinical trial by van Nood and colleagues[30] found similar results. Before FMT, fecal microbial diversity was low. After FMT, microbial diversity was similar to that of donor stools with 2- to 4-fold more Bacteroidetes and clostridium clusters IV and XIVa and up to 100-fold less Proteobacteria.

Similar changes in the fecal microbiome were seen in a clinical trial comparing vancomycin with fidaxomicin.[14] Vancomycin led to a decrease in *Bacteroides/Prevotella* and Firmicutes group organisms, whereas fidaxomicin appeared to spare those groups.

Adverse effects of FMT

Adverse effects related to FMT may include the following[34,35]:

- Transmission of infectious agents to the patient from the donor feces
- Complications from the FMT delivery procedure
- Long-term adverse effects related to the new colonic microbiota.

The human intestinal microbiota participates in a number of processes including maturation and continued education of the host immune response; regulation of intestinal endocrine functions and neurologic signaling; energy biogenesis; biosynthesis of vitamins and neurotransmitters; metabolism of bile salt;, and reaction to or modification of certain drugs.[36] The long-term impact of FMT on the development of illnesses such as metabolic syndrome and immune disorders is unknown. Screening donors for various diseases can help minimize these potential effects.[34,35]

Several reports of transmission of infectious agents from donor stool by FMT have been reported. In June 2019, the FDA published a safety alert on the transmission of extended-spectrum beta-lactamase (ESBL)-producing *E coli* after FMT in 2 immunocompromised patients. One patient died.

The stools, which came from a single donor, were not tested for these organisms before the FMT.[37] As a result, the FDA instituted requirements for stool donor screening questions regarding those with or at high risk for colonization with multidrug-resistant organisms (MDRO), and required that donor stool be tested for, at a minimum, ESBL-producing *E coli*, vancomycin-resistant enterococci (VRE), carbapenem-resistant Enterobacteriaceae, and methicillin-resistant *Staphylococcus aureus*. Additionally, the informed consent process for FMT should describe the risk of MDRO transmission and invasive infection and the measures implemented for donor screening and stool testing.[38]

Further information about these 2 patients was subsequently published.[39] One of the patients had liver cirrhosis and was enrolled in a trial of FMT oral capsules to treat refractory hepatic encephalopathy. The other patient had undergone an allogeneic hematopoietic-cell transplant and was enrolled in a trial of FMT oral capsules before and after the cell transplant. He developed neutropenia and fever on day 5 after stem cell infusion and was found to have ESBL-*E coli* bacteremia. He died 2 days later from severe sepsis.

In March 2020, the FDA published another safety alert regarding the suspected transmission of enteropathogenic *E coli* (EPEC) and Shigatoxin-producing *E coli* (STEC) from FMT products supplied by a stool bank and used to treat recurrent CDI.[40] Two patients developed EPEC infection after receiving an FMT product prepared from stools from 2 different donors. Four patients developed STEC infection after receiving an FMT product prepared from a stool from a single donor. Four of the 6 patients required hospitalization, but none died. Additionally, there were 2 patients who died after receiving an FMT product manufactured from the donor associated with the 4 STEC infections. Both of these patients developed diarrhea after the FMT, but their stools were not tested for STEC. For one of the patients who died, the stool used to manufacture the FMT product was positive for STEC, but it is not known if STEC infection contributed to the patient's death. For the other patient who died, the stool used to manufacture the FMT product administered was negative for STEC, and the FDA did not suspect that the STEC was transmitted by this FMT product to this patient.[41] In April 2020, the FDA recommended additional protections for FMT use, including testing donor stools by nucleic acid amplification tests for EPEC and STEC and excluding any stools testing positive.[42]

PROBIOTICS

Probiotics are preparations of viable microorganisms consumed by the patient. Studies have been conducted, but there are insufficient data to recommend probiotics for primary prevention of CDI.

The rationale for this conclusion is based on a Cochrane Review published in 2017 that evaluated the efficacy of probiotics for preventing C *difficile*-associated diarrhea (CDAD).[43] Note that C *difficile* infection (CDI) was previously referred to as CDAD and there are clinical trials published using both terms. The CDI term was introduced in guidelines from IDSA and SHEA in 2010,[2] and from the American College of Gastroenterology in 2013,[23] and publications began using it. The authors of the Cochrane Review[43] separated CDAD and CDI in their outcome groups and found that probiotics were effective only in preventing CDAD in patients whose baseline CDAD risk was greater than 5% (N = 2,454 in 13 trials; moderate certainty evidence). If the baseline CDAD risk was 0% to 2% (N = 5,845 patients in 15 trials; moderate certainty evidence) or 3% to 5% (N = 373 in 3 trials; low certainty evidence), probiotics had no effect on CDAD rates. Probiotics were also not effective in preventing CDI (N = 1,214 in 15 trials; moderate certainty evidence).

Routine use of probiotics for inpatients on antibiotics for primary prevention of CDI is not recommended

Based on these meta-analysis findings and that typical CDI incidence rates are about 3% or less, even during outbreaks, in hospitalized patients age 65 or older on antibiotics with a length of stay greater than 2 days,[2] routine use of probiotics for inpatients on antibiotics for primary prevention of CDI is not recommended.[2,23]

PRIMARY AND SECONDARY CDI PROPHYLAXIS

For patients who are on antibiotics to treat an infection other than CDI (eg, pneumonia),

during or shortly after CDI treatment, the IDSA and SHEA CDI guidelines do not recommend extending the length of CDI treatment beyond the recommended duration or restarting CDI treatment shortly after completion of CDI therapy (ie, "secondary" CDI prophylaxis), due to insufficient data.[2] The authors suggest that if a decision is made to institute secondary CDI prophylaxis, practitioners should consider low doses of vancomycin (eg, 125 mg once daily) or fidaxomicin (eg, 200 mg once daily) while the patient is on systemic antibiotics.[2]

For patients considered at high risk for developing CDI but who do not have active or recent CDI, administration of "primary" CDI prophylaxis (ie, administering anti-*C difficile* therapy to prevent CDI) is not recommended. In a randomized nonblinded trial comparing vancomycin (125 mg once daily) in patients receiving systemic antibiotics versus no prophylaxis, there was a lower risk of developing hospital-onset CDI (0% vs 12%, respectively; $P = .03$) with vancomycin prophylaxis; however, an analysis of the development of CDI after hospital discharge was limited by loss of follow-up.[44] In a randomized double-blind placebo-controlled trial in patients undergoing hematopoietic stem cell transplant, fidaxomicin (200 mg once daily) treatment was not different from placebo for the primary composite end point of "prophylaxis failure" (28.6% vs 30.8% with placebo, $P = .278$).[45] In a prespecified sensitivity analysis restricted to confirmed CDAD independent of missing data, CDAD was lower with fidaxomicin compared with placebo (4.3% vs 10.7%, $P = .0014$); however, only 64% of subjects in each treatment group completed study treatment and follow-up.[45]

Patient rooms and environmental surfaces should be disinfected with a hypochlorite solution

One of the principal concerns with CDI prophylaxis is that anti-*C difficile* therapies disrupt the normal colonic microbiota. Whether this affects CDI recurrence in the long term or increases the risk of colonization with multidrug-resistant bacteria is unknown. Vancomycin with a prolonged taper was shown in an animal model study to persistently disrupt the colonic microbiota, including a significant decrease in Firmicutes and increase in Proteobacteria, as well as to decrease colonization resistance to *C difficile* and vancomycin-resistant enterococci.[46] Fidaxomicin did not lead to disruption in colonization resistance. In another animal model study, vancomycin markedly disrupted the microbiota and led to prolonged loss of colonization resistance to *C difficile*, vancomycin-resistant enterococci, carbapenem-resistant *Klebsiella pneumoniae*, and *E coli*. Metronidazole had a more transient effect than vancomycin.[47]

Strategies for CDI prevention

There are 2 core strategies for preventing CDI: antibiotic stewardship, by implementing a program to optimize the use of antibiotics and minimize disruption of normal colonic microbiota, and infection prevention, by adhering to practices that block the spread and acquisition of the *C difficile* organism.

Optimize use of antibiotics

- Use antibiotics only when needed.
- Use narrow-spectrum antibiotics if possible. If the patient does not have a documented infection and lacks signs of sepsis, and if deemed appropriate by the treating clinician, consider waiting for culture testing results and then target the organism.
- Change from a broad-spectrum to a narrow-spectrum antibiotic as soon as possible.
- Use the shortest possible treatment duration. The risk of developing CDI increases with longer antibiotic durations, with patients receiving more than 7 days of antibiotics having the highest risk.[48]

Block the spread and acquisition of the *C difficile* organism

C difficile is an obligate anaerobe able to survive and spread in the environment by conversion to spore form (**Figure 2**). Of note, *C difficile* is not part of normal colonic microbiota. *C difficile* spores can be transmitted from colonized patients to other patients either by healthcare workers (eg, on the hands) or from contaminated hospital environmental surfaces or equipment. These spores may then be ingested by noncolonized patients, survive exposure to the acidic environment of the stomach, and colonize the colonic lumen.

In a study published in 1989, McFarland et al[49] found that of 399 patients admitted to a medical ward with negative admission *C difficile* rectal swab cultures, 83 (21%) acquired *C difficile* during their hospitalization. The patients were tested for *C difficile* every 3 days.

In addition, environmental cultures were collected during the study, and 62 of 216 (29%) samples were positive. These included the bedrail, commode, floor, call button, windowsill, toilet, dialysis machine, sink, slipper bottoms, and nasogastric alimentation preparation. The frequency of positive environmental cultures was greater for patients with diarrhea (49%) than for asymptomatic carriers (29%). Further, C *difficile* cultures were taken from the hands of healthcare workers before and after interaction with patients whose cultures were positive, and 20 of 34 (59%) hand cultures were positive for C *difficile*.[49]

Their findings emphasize the importance of blocking the spread of C *difficile* by physically washing away the spores with soap and water and by wearing gloves and gowns to prevent contact with the spores. Moreover, patient rooms and environmental surfaces should be disinfected with a hypochlorite-based solution (ie, bleach). This recommendation includes disinfection of equipment, such as blood pressure cuffs, thermometers, stethoscopes, and pen lights. If disposable equipment is not an option, then confine equipment to a single patient with CDI. Of course, all equipment shared between patients should be cleaned and disinfected between uses.

Other strategies to prevent C *difficile* include placing infected patients in a private room and using contact precautions while waiting for culture results. Encourage patients to wash their hands, especially before eating, as well as to shower or bed bathe to reduce the burden of spores on their skin.

TAKE-HOME POINTS

- Submit stool specimens for CDI testing only from patients with unexplained or new onset of at least 3 unformed stools in 24 hours.
- Do not treat patients who have asymptomatic C *difficile* carriage (ie, colonization); therapy has not been shown to be beneficial and can prolong C *difficile* colonization.
- For patients with CDI, stop the inciting antibiotic as soon as possible.
- For the first CDI episode, use vancomycin or fidaxomicin; metronidazole is only used as a third-line agent for nonsevere disease.
- For the second CDI episode, use vancomycin, vancomycin tapered and pulsed, or fidaxomicin.
- For a third CDI episode or more, use vancomycin tapered and pulsed, or vancomycin then rifaximin, or fidaxomicin, or fecal microbiota transplant.
- Fecal microbiota transplantation is associated with resolution of recurrent CDI, but its role in initial CDI episodes and fulminant CDI is not established.
- If considering bezlotoxumab therapy, assess the cost vs the recurrence risk compared with other options.
- To prevent CDI, optimize antibiotic use to minimize disruption of normal colonic microbiota, and physically block the spread and acquisition of the C *difficile* organism.

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***Address**: Constantine Tsigrelis, MD, Department of Infectious Disease, G21, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; tsigrec@ccf.org*

REVIEW

CME MOC

Jeana Cost, LPC, CEDS
ACUTE at Denver Health, Denver, CO;
Eating Recovery Center, Denver, CO

Mori J. Krantz, MD
Department of Medicine, University of Colorado School of Medicine, Aurora, CO

Philip S. Mehler, MD, FACP, FAED
Founder, ACUTE at Denver Health, Denver, CO;
Eating Recovery Center, Denver, CO; Professor, Department of Medicine, University of Colorado School of Medicine, Aurora, CO

Medical complications of anorexia nervosa

ABSTRACT

Anorexia nervosa is a mental illness characterized by self-starvation, marked weight loss, and malnutrition. As the illness worsens, numerous medical complications develop throughout the body. Some of these resolve with effective nutritional rehabilitation and weight gain, whereas others can lead to permanent damage.

KEY POINTS

The structural cardiac hallmark of this disease is myocardial atrophy characterized by a reduction in left ventricular mass index and volume, which commonly results in mitral valve prolapse.

Most female patients are amenorrheic and have low estrogen levels because they have reverted to a prepubertal state; male patients have low testosterone levels.

Marked loss of bone mineral density occurs, which can lead to early osteopenia and osteoporosis, even in adolescent patients, and this loss may be permanent.

Pulmonary complications include spontaneous pneumothorax, pneumomediastinum, and aspiration pneumonia.

Patients may also have generalized brain atrophy, damaged gray and white matter, and cognitive deficits that persist after treatment.

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Anorexia nervosa (AN) is a common mental illness characterized by self-starvation, excessive weight loss, and malnutrition. Unlike in most other mental health disorders, in which physical health may be completely normal, compromised physical health is inextricably connected with this illness. Multiple concomitant medical complications occur throughout the body and become more pronounced as the severity of the illness increases. This review discusses these complications, many of which resolve with effective nutritional therapy and weight gain. Others can lead to permanent damage.

INCIDENCE AND ETIOLOGY

The peak age of onset is during adolescence. Incidence rates are increasing in both males and females, although the disease primarily affects adolescent girls and young women. Although estimates vary, 1% or more of women may develop AN during their lifetime, and the average duration of the illness is 6 years.[1,2]

AN is the deadliest of all mental illnesses. Mortality rates are as high as 5%,[2] and patients carry a 10-fold increased risk for suicide.[2] About 20% of deaths in patients with AN are the result of suicide.[3]

The etiology of AN is complex, with many genetic, psychological, environmental, and social variables at play. Patients who have a first-degree relative with AN, for example, have a 10-fold greater risk of having the illness themselves.[4] Those with comorbid psychological illnesses such as depression, anxiety, and substance abuse are also at increased risk. A number of factors can trigger or exacerbate this eating disorder and sustain it, including societal and media pressure to appear thin,

diet culture, occupations that require a lean physique (eg, sports, modeling), lack of a support system, and traumatic events (eg, sexual assault, physical abuse, neglect).

EVALUATION

The assessment and diagnosis of AN was updated in the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5).[5] Hallmarks of the illness include intentional caloric restriction resulting in weight loss, intense fear of gaining weight, and body image distortions (ie, believing that they are grotesquely fat, when in fact they are normal or even underweight).

The DSM-5 includes a severity index for evaluating body mass index (BMI), which allows healthcare providers to assess the severity of malnutrition and the proper level of necessary care. The index has 4 categories: mild (BMI > 17 kg/m^2), moderate (16 to 16.99), severe (15 to 15.99), and extreme (< 15).

The DSM-5 also allows professionals to assess for one of two subtypes of the illness. The *restricting type* is associated with the previously mentioned symptoms and behaviors and does not include regular bingeing of food, whereas the *binge-eating/purging type* is marked by bingeing and purging behaviors such as self-induced vomiting or the misuse of diuretics or laxatives, or both. The difference between the latter subtype and bulimia nervosa is that bulimia does not include any weight-loss criteria, and the behaviors are accompanied by a sense of lack of control.

Sinus bradycardia, profound reversible sinus node dysfunction, and orthostatic hypotension are uniformly observed

MEDICAL AND THERAPEUTIC APPROACHES

Treatment options are subject to ongoing debate and a lack of empiric evidence. The patient's medical stability, psychiatric stability, AN severity, age, support system, and duration of illness must be assessed. In the United States, patients have access to levels of care on the spectrum from general outpatient care to acute medical inpatient hospitalization. Therapeutic approaches vary based on age and level of care.

While the most commonly used approach for children and adolescents is family-based therapy, a much wider variety of treatments can be used in adults, such as cognitive remediation therapy, exposure therapy, dialectical behavior therapy, and acceptance and commitment therapy. That no single approach has emerged as the definitive evidence-based optimal treatment further suggests that there are many other factors to consider.[6]

PROGNOSIS

Recovery rates for AN vary considerably. Studies that focused on adolescents report recovery rates from 17.2% to 50%, and those that focused on adults report recovery rates from 13% to 42.9%.[1]

Studies show that while eating disorders themselves are undertreated, a large number of patients receive only partial treatment for other comorbid issues such as depression, anxiety, substance abuse, and medical concerns. Improved recognition and assessment of eating disorder symptoms will lead to effective intervention and treatment and thus benefit the patient.[7]

The rest of this review discusses the medical complications associated with AN.

CARDIAC PROBLEMS

Changes in the structure and function of the heart, autonomic parameters, and cardiac repolarization have been noted in contemporary systematic reviews of AN.[8]

Myocardial atrophy, the structural hallmark of this disease, is characterized by a reduction in left ventricular mass index and an attendant decrease in left ventricular volume.

Mitral valve prolapse is common in AN. Although its mechanism has not been fully elucidated, it is thought to be a consequence of myocardial atrophy and reduced left ventricular chamber size leading to relative valvular laxity even in the absence of myxomatous valve degeneration. This "valvular-ventricular disproportion theory" suggests that either excessive mitral valve tissue or inadequate left ventricular cavity size results in prolapse. Supporting this theory is the observation that prolapse disappears in patients after weight restoration but recurs when patients lose weight again.[9]

In a cohort study,[10] the authors observed mitral valve prolapse in most of their patients with severe AN but found no significant cor-

relation between left ventricular dimension and prolapse. In contrast, a low heart rate had a significant correlation with mitral valve prolapse. Therefore, the cause of prolapse is likely multifactorial and may also be mediated by increased underlying vagal tone and resultant bradycardia.

Pericardial effusion may develop with progressive weight loss but generally remits with weight restoration and concurrent normalization of serum triiodothyronine (T_3) levels.[11]

Sinus bradycardia, profound reversible sinus node dysfunction, and orthostatic hypotension are uniformly observed in patients with severe AN.[12] Electrocardiography may be appropriate depending on the patient's body mass index (BMI). It is unlikely to reveal much if the BMI is higher than 17 kg/m^2, but is likely to show significant bradycardia or other arrhythmia if less than 15. As BMI drops, bradycardia and hypotension become more pronounced.

There are no functional cardiovascular hallmarks diagnostic of AN. However, tissue Doppler indices of diastolic dysfunction (impaired relaxation, ventricular stiffness) are present.[13] Analogously, increased arterial pulse wave velocity, a measure of aortic stiffness, has also been described.[14]

Although studies show that patients with AN have lower exercise capacity, blood pressure, and peak cardiovascular indices (eg, oxygen consumption), actual systolic ventricular function is maintained at peak exercise.[15] This preserved ejection fraction suggests that despite marked caloric restriction, deconditioning, and skeletal muscle atrophy, left ventricular systolic function remains ostensibly preserved.

Sudden cardiac death is often the cause of premature death in patients with AN. Autonomic dysfunction, as measured by reduced heart rate variability, has been described in AN patients, although a consistent pattern has not emerged when evaluated systematically.[16,17] Similarly, delayed repolarization manifested as prolongation of the rate-corrected QT (QTc) interval on 12-lead electrocardiography has been posited as a likely cause. However, this association has been disproved by the single largest electrocardiographic study of AN patients, in which the population mean QTc interval was 417 ms.[18]

Although QTc prolongation and torsade de pointes occur in patients with eating disorders, the data linking QTc prolongation, AN, and risk of sudden death are confounded by the presence of concurrent hypokalemia and medications that block the delayed rectifier potassium ion channel.

Perhaps the most compelling piece of recent research that supports this interpretation is a 10-year population-based cohort study of 430 women with AN and 123 controls in Denmark.[17] Overall, there was no difference in mean QTc interval or risk of prolonged QTc between patients with AN and healthy controls. However, patients with AN had a notably higher risk of a cardiac event (ventricular tachycardia, aborted cardiac arrest, or cardiac arrest) compared with controls (hazard ratio 10.4, 95% confidence interval 2.6–41.6, P = .001), as well as all-cause mortality (hazard ratio 11.2, 95% confidence interval 5.1–24.5, P < .001). This relationship with cardiac events and all-cause mortality was not related to the baseline QTc interval.[17]

Decreased R-wave amplitude on electrocardiography is also commonly noted, though a relationship with major adverse cardiac events has not been demonstrated.

Despite the aforementioned cardiovascular complications observed in AN, an exact mechanism underlying the increased cardiovascular mortality risk in this disorder has not been firmly established. One possibility is subclinical left ventricular systolic dysfunction as manifested by abnormalities in myocardial torsion and global longitudinal systolic strain.[19,20] Another possibility is focal regional fibrosis as a nidus for malignant ventricular arrhythmia, which has been suggested by late gadolinium enhancement on magnetic resonance imaging.[21]

We believe further investigation of subclinical cardiovascular dysfunction and long-term arrhythmia monitoring and larger population-based cohort studies are needed to address the ongoing inordinately high risk of sudden cardiac death in this generally young population.

Gastroparesis and constipation occur, especially as weight loss worsens

GASTROINTESTINAL PROBLEMS

As a direct result of weight loss and malnutrition, gastrointestinal transit time slows.

Gastroparesis and constipation are therefore common in patients with AN, especially as weight loss becomes more severe.[22] If the patient is symptomatic, metoclopramide or a macrolide antibiotic can be prescribed for a short time until some weight gain occurs.

Superior mesenteric artery syndrome occurs in patients with AN as a result of weight loss-induced atrophy of the mesenteric fat pad. Normally, the fat pad tethers the artery and prevents its medial movement, which could compress the third portion of the duodenum as it passes between the superior mesenteric artery and the aorta. Patients with superior mesenteric artery syndrome complain of fullness, nausea, and epigastric pain that begins soon after eating and is relieved by vomiting. The diagnosis is made by an upper gastrointestinal series or abdominal computed tomography.[23] Superior mesenteric artery syndrome is treated with a soft or liquid diet until sufficient weight gain occurs to reconstitute the fat pad.

Diarrhea can occur early in the refeeding process due to small-bowel atrophy and a reduction in the absorptive area. A low level of blood diamine oxidase supports this etiology.[24]

Liver disease. Aminotransferase levels are often elevated in AN. There are two main causes. Early on, before refeeding starts, it is likely caused by apoptosis—programmed hepatocyte cell death triggered by starvation.[25] However, if levels start to abnormally elevate with refeeding, it is more likely to be caused by steatohepatitis, which responds to an alteration in the macro-composition of the diet with a reduction in calories from carbohydrates.[26] Surprisingly, albumin levels are normal even with severe AN.

Functional bowel disorders are common in patients with AN.[27]

The lungs are not immune to the ravages of anorexia nervosa

PULMONARY PROBLEMS

For many years, the lungs were thought to be immune to the ravages of AN. However, we now know that this is not the case.[28]

Spontaneous pneumothorax and pneumomediastinum occur in patients with AN.

Aspiration pneumonia can occur with marked weight loss due to weakening of the pharyngeal muscles and swallowing problems, which can be identified by modified barium swallow studies.

Pulmonary function tests may be abnormal and show an obstructive pattern, but the cause is unknown.

LOW WHITE BLOOD CELL, RED BLOOD CELL, PLATELET COUNTS

Gelatinous marrow transformation occurs as malnutrition worsens. Specifically, serous fat atrophies in the bone marrow, and normal marrow fat is replaced by a thick mucopolysaccharide substance that impedes the egress of precursor cells from the bone marrow.[29,30] This leads to trilinear hypoplasia with leukopenia, anemia, and thrombocytopenia detected in that order of decreasing frequency.[31]

Leukopenia. Interestingly, despite frank neutropenia, patients with AN are not at increased risk of infection, and thus neutropenic precautions are not needed. Similarly, the use of expensive growth factors is not indicated because the marrow reconstitutes quickly with nutritional rehabilitation.

Anemia in AN is typically normocytic, but when the red blood cell indices are abnormal, it is typically macrocytic, although vitamin B_{12} and folate levels are not low.[32] Microcytic anemia is rare and requires additional evaluation.

MULTIPLE ENDOCRINE ABNORMALITIES

Many endocrine abnormalities occur in patients with AN.

Amenorrhea is present in most females, who have low estrogen levels due to reversion to a prepubertal state in the hypothalamic-pituitary axis,[33] and most males have low testosterone. Menses generally resume when approximately 95% of ideal body weight is achieved,[34] although it can take 6 to 9 months for this to occur. Of note, pregnancy can occur even with amenorrhea and is dangerous for the patient and the fetus.

Low leptin levels normalize with weight restoration and nutritional rehabilitation.[35] Leptin levels may correlate with onset of regular menses.

Growth hormone resistance accompanies AN, as do **elevated serum cortisol levels**. Most patients have **euthyroid sick syndrome,** which is self-limited and reverses after nutritional rehabilitation.

Hypoglycemia is most often detected in

patients with more severe forms of the illness and BMIs of less than 15 kg/m^2. Hypoglycemia is a bad prognostic sign, as it portends hepatic failure and an inability to actualize gluconeogenesis and glycogenolysis.[36]

LOSS OF MUSCLE AND BONE

Sarcopenia. Even though patients with AN tend to be young, they have significant sarcopenia and loss of skeletal muscle mass. This in turn causes a dangerous state of weakness and increases the risk of falls in more severely ill patients. These complications are completely reversible with weight gain and physical therapy.

Bone loss. A serious and possibly irreversible complication of AN that correlates with the presence of sarcopenia is the loss of bone mineral density and a proclivity toward early development of osteopenia and osteoporosis, even in adolescent patients.

The etiology of this exuberant loss of bone mineral density is likely multifactorial and includes elevated cortisol levels, low leptin and sex hormone levels, low body weight, and growth hormone resistance.[37] As a result, these patients are often left with a markedly increased risk of fragility fractures, even long after their AN has remitted.[38]

Loss of bone mineral density in patients with AN is different from that in postmenopausal women. In AN, it is not only due to increased resorption but also decreased bone formation. This "uncoupled" state is why the loss of bone mineral density is so marked in AN.[37]

Measuring bone mineral density is very important if the patient has had anorexia nervosa for more than 1 year or amenorrhea for more than 9 or 12 months because there is exuberant and severe loss of bone mineral density. On the other hand, urinary telopeptide levels are not indicated, as one can make the decision to treat osteoporosis on the basis of the DXA results.

Treatment of osteoporosis in AN is controversial. Most agree that osteopenia should be treated by weight restoration and resumption of menses along with adequate intake of calcium and vitamin D. Some experts in the field, however, are more cautiously aggressive with the osteoporosis of AN and have advocated for judicious consideration of medical treatment with bisphosphonates, transdermal estrogen, denosumab, or teriparatide. Currently, the use of denosumab has been described only in case reports. Also, the adverse effects of each of these drug classes, although rare, need to be fully explained to the patient before proceeding to prescribe.

For many years, oral contraceptives were not recommended as a treatment for bone loss due to low efficacy reported in studies in patients with AN. However, a recent cross-sectional study suggests that oral contraceptives may have a very limited role in severe AN.[39]

Bone densitometry should be done every 2 years during the active phases of AN.

NEUROLOGIC SYSTEM: BRAIN ATROPHY

Anorexia nervosa is characterized by marked brain atrophy on brain imaging studies. Particular areas of the brain seem to be preferentially damaged, including both gray and white matter and areas of the insula and thalamus.[40] With weight restoration, these brain-size abnormalities seem to reverse, but there may be ongoing cognitive deficits that persist as a secondary medical complication of AN with permanent adverse sequelae. Brain atrophy may explain the abnormalities in taste, smell, thalamic function, and temperature regulation as well as the overall mental slowness seen in persons with more severe forms of the illness.

A recent cross-sectional study suggested that oral contraceptives may have a very limited role in the treatment of AN-induced osteoporosis

DERMATOLOGIC COMPLICATIONS

Patients with AN can develop a variety of skin conditions, including xerosis, which results in painful, dry, and fissured skin, acrocyanosis, and lanugo hair growth on the sides of the face and along the spine. The hair growth occurs as a result of the body attempting to conserve heat and is not a sign of masculinization.[41] Also seen are brittle hair and nails and unexplained hypercarotenemia, which gives the skin a yellowish appearance.

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***Address**: Philip Mehler, MD, FACP, FAED, Denver Health Medical Center, 723 Delaware Street, Pav M, Denver, CO 80204; pmehler@dhha.org*

Shannon Wu, BA
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, Ohio

Demetrius M. Coombs, MD
Resident Physician, Department of Plastic Surgery, Dermatology and Plastic Surgery Institute, Cleveland Clinic, Cleveland, Ohio

Raffi Gurunian, MD, PhD
Staff Surgeon, Department of Plastic Surgery, Dermatology and Plastic Surgery Institute, Cleveland Clinic; Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, Ohio

Liposuction: Concepts, safety, and techniques in body-contouring surgery

ABSTRACT

Liposuction is the second most commonly performed cosmetic surgery in the United States and the most common surgical procedure in patients between the ages of 35 and 64; practitioners of medicine and surgery will undoubtedly encounter these patients in their practice. This brief review discusses the role of liposuction and fat transfer in aesthetic and reconstructive surgery, as well as key considerations, indications, and safety concerns.

KEY POINTS

The most common area for fat removal is between the inframammary fold and gluteal fold—namely, the abdomen, flanks, trochanteric region, lumbar region, and gluteal region.

Liposuction is increasingly being used as an adjunct to enhance other aesthetic procedures such as breast augmentation, cervicoplasty, abdominoplasty, gluteal fat transfer, and body contouring after bariatric surgery.

Gluteal fat transfer, popularly called the "Brazilian butt lift," is an application of liposuction in which large volumes of fat are transferred from an undesirable area, such as the abdomen or inner thighs, to the buttocks.

Noncosmetic indications include management of lipomas, lipedema, and lipodystrophy syndromes.

The most common complication is contour deformity.

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Suction-assisted lipectomy, more commonly known as liposuction, is an outpatient procedure that removes adipose tissue from the subcutaneous space with the goal of achieving a more desirable body contour. It is the second most commonly performed cosmetic surgery in the United States and the most common surgical procedure in patients between the ages of 35 and 64.[1] In 2018, surgeons performed 258,558 liposuction procedures, a 5% increase from 2017.[2] The number of liposuction procedures increased 124% from 1997 to 2015.[3]

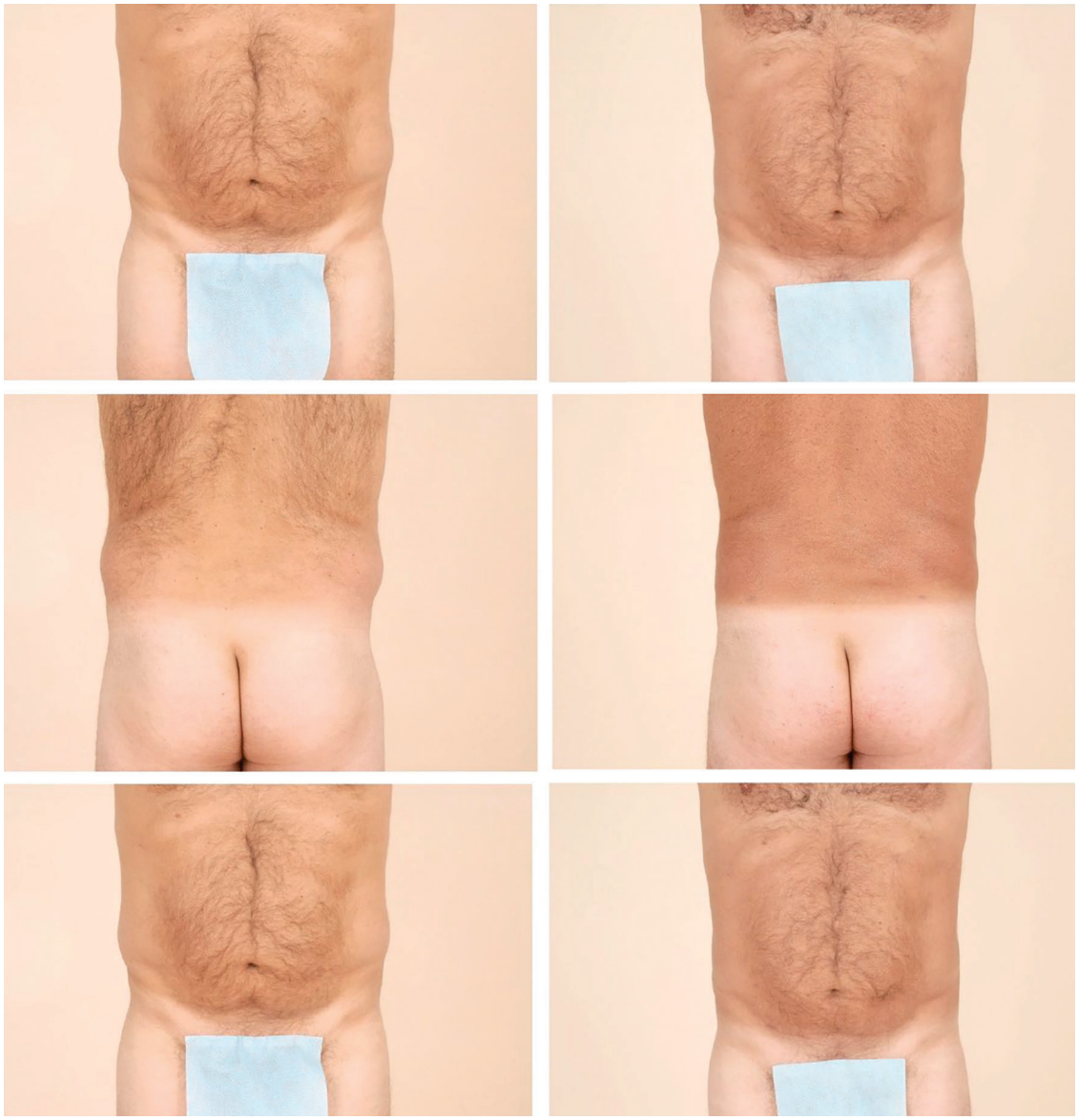
Liposuction is advantageous in that the removal of fat cells limits future deposition of fat in those areas.[4] Ultimately, liposuction allows plastic surgeons to semipermanently redistribute volume in accordance with a patient's ideal, and with lower complication, morbidity, and mortality rates than with other surgical procedures.

In addition to its utility for purely aesthetic purposes, liposuction is an important adjunct in reconstructive surgery, particularly of the breast and face, when harvested fat is autologously reinjected in these tissues. One particular procedure rising in popularity and gaining significant attention in the media is gluteal fat grafting.

This article provides a general overview of liposuction, including its history, current techniques, indications, and safety concerns.

HISTORY

The first attempt at fat removal was by Dujarrier in 1921, who operated on the knees and calves of a dancer. Injury to the femoral artery led to amputation of the leg.[5] In 1964, Schrudde cu-



Ideally, patients have adequate skin elasticity and are within 20% to 30% of their ideal body weight

Figure 1. Left: Preoperative appearance of a 52-year-old man who presented for liposuction of localized adiposity within the abdomen and bilateral flanks. Right: The same patient 6 months later after removal of 1.4 L of adipose tissue.

retted subcutaneous fat from a patient's leg, but observed skin necrosis in 4 of 15 separate patients, in addition to hematoma and seroma.[6]

The era of modern liposuction began in 1975 when Arpad and Fischer pioneered the use of blunt hollow cannulas and suction curettage for liposuction on the outer thighs, but the patients ultimately experienced deforming lymphorrhea.[7] An important milestone was reached in 1977 when Illouz developed the "wet technique," in which injection of hypotonic saline solution and hyaluronidase into adipose tissue before liposuction reduced hemorrhagic risk.[8] This type of hydrodissection, similar to that used today, preserved neurovascular bundles and enlarged the deep adipose layer for easier aspiration.

In 1983, Fournier used syringes instead of mechanical suction for better control of negative pressure.[9] By 1987, Klein had developed the tumescent technique—a type of local anesthesia infiltration that permitted the re-

moval of larger volumes of fat while reducing bleeding.[10] Toledo expanded the use of syringes to include various gauges and sizes for aspiration of adipose tissue in 1988.[11]

In the early 1990s, the development of ultrasonographically guided liposuction by Zocchi expanded the use of liposuction for previously unfavorable, fibrous areas such as the buttocks.[12,13] The development of minimally invasive, laser-assisted liposuction by Apfelberg, also in 1992, prevented destruction of neurovascular structures by cannulas and promoted tissue tightening for an aesthetic result.[14] Recently, the development of power-assisted liposuction has further expanded and improved this procedure, increasing the popularity and use of liposuction.[15]

COSMETIC INDICATIONS

Liposuction is used to achieve body contouring by removing excess fat deposits in undesirable areas of the body. Fat is suctioned from demarcated areas in the body amenable to contouring.

The most common area for fat removal is between the inframammary fold and gluteal fold—namely, the abdomen, flanks, trochanteric region, lumbar region, and gluteal region (**Figure 1**). Other areas of fat removal include the breasts (eg, breast reduction surgery), thighs, and calves.

The site of incision is an important anatomic consideration, and the surgeon should select regions where the surgical scar, although modest, can be hidden by clothing, as well as locations conducive to broad fanning of the cannula during the procedure.

There are 5 zones in which superficial subcutaneous tissues adhere to underlying deep fascia of muscle: the lateral gluteal depression, gluteal crease, distal posterior thigh, midmedial thigh, and inferolateral iliotibial tract. Because these zones define the natural shape of the body, suctioning from these areas increases the risk of contour deformities.[16] Ideally, patients have adequate skin elasticity and are within 20% to 30% of their ideal body weight to achieve desired aesthetic outcomes.[17]

Liposuction is also increasingly being used as an adjunct to enhance other aesthetic procedures such as breast augmentation, cervicoplasty, abdominoplasty, gluteal fat transfer, and body contouring for postsurgical bariatric patients (**Figure 2 and Figure 3**).[18] Liposuction can also be used to promote gender-specific features.[19] In women, the goals of liposuction are to promote shapely contours of the breasts, waist, hip, and buttocks. In men, liposuction aims to achieve upper body dominance, such as removing excess flank adipose tissue ("love handles").

GLUTEAL FAT TRANSFER

Gluteal fat transfer, popularly called the "Brazilian butt lift," is an application of liposuction in which large volumes of fat are transferred from an undesirable area, such as the abdomen or inner thighs, to the buttocks.[20] Fat is first removed by liposuction (the volume of which varies widely and remains largely based upon the patient's preoperative anatomy) and is then used to augment the contour of the buttocks commensurate with the patient's desires and anatomic deficiencies.[21,22]

High-volume fat transfer, defined as a volume greater than 1,000 mL per buttock, has historically been associated with a higher risk of infection at the graft site and seroma formation at the harvested site. Newer evidence suggests high-volume buttock fat transfer may be safe and effective with proper technique.[23] Thus, the contour is improved in both the donor region, such as the waist, and the recipient region.

More than 26,000 gluteal fat transfer procedures were performed in 2018

The popularity of gluteal fat transfer is rapidly increasing due to shifting beauty standards in American culture and attention from celebrity figures. More than 26,000 gluteal fat transfer procedures were performed in 2018, a 16% increase from the previous year, and a 132% increase from 2013.[3,24] However, reports of fatal pulmonary fat embolisms following injury to gluteal veins and an estimated mortality rate of 1 in 3,000 from this procedure warrant continued investigation about its safety and ideal technique.[25]

The Multi-Society Gluteal Fat Grafting Task Force[26] was established to investigate and improve patient safety of this procedure, and current research including anatomic studies as well as educational symposia are ongoing. Risks and alternative methods such as gluteal implants must be discussed with the patient

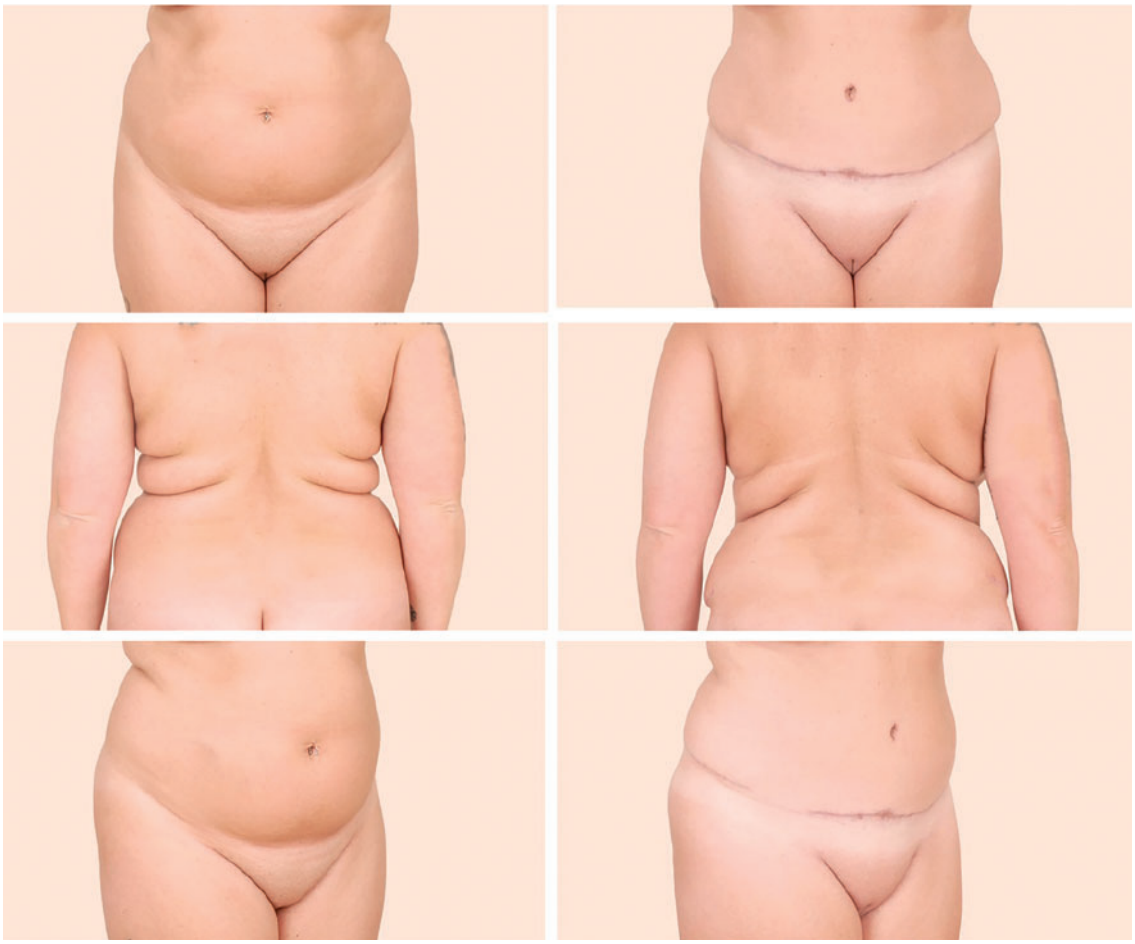


Figure 2. Left: A 38-year-old woman who presented with excess skin and adiposity of the anterior abdomen and excess adipose tissue in the bilateral upper back and hips. Right: The same patient 5 months later after full cosmetic abdominoplasty and liposuction of the bilateral upper back and hip areas (with a total of 2 L of tissue removed), illustrating that these procedures may be combined safely and yield satisfying results.

Fat harvested in liposuction can be used to 'lipofill' in breast reconstruction, burns, and scars

before this procedure. Moreover, as with any aesthetic or reconstructive procedure, the American Society of Plastic Surgeons recommends that patients seek consultation from a board-certified plastic surgeon.

NONCOSMETIC INDICATIONS

Liposuction is also being used for reconstructive purposes, including management of the following disorders:

- Lipomas and angiolipomas, with minimal to no scarring
- Lipedema, in which subcutaneous fat deposition in the lower limbs can interfere with daily activities such as walking; in these patients, liposuction can improve mobility[27]
- Lymphedema, particularly if it is refractory to traditional conservative treatments
- Lipodystrophy syndromes, which are congenital or acquired diseases of fat atrophy; liposuction with autologous fat transfer can replace loss of fat in areas such as the feet or buttocks to relieve physical discomfort[28]
- Cervicodorsal lipodystrophy associated with Cushing syndrome and use of HIV medications[29]
- Gynecomastia in men and macromastia in women, in conjunction with mammoplasty. Additionally, liposuction can be used to:
- Reduce excess fat deposits at surgical sites in obese patients who are undergoing tracheostomy, colostomy, or urostomy procedures

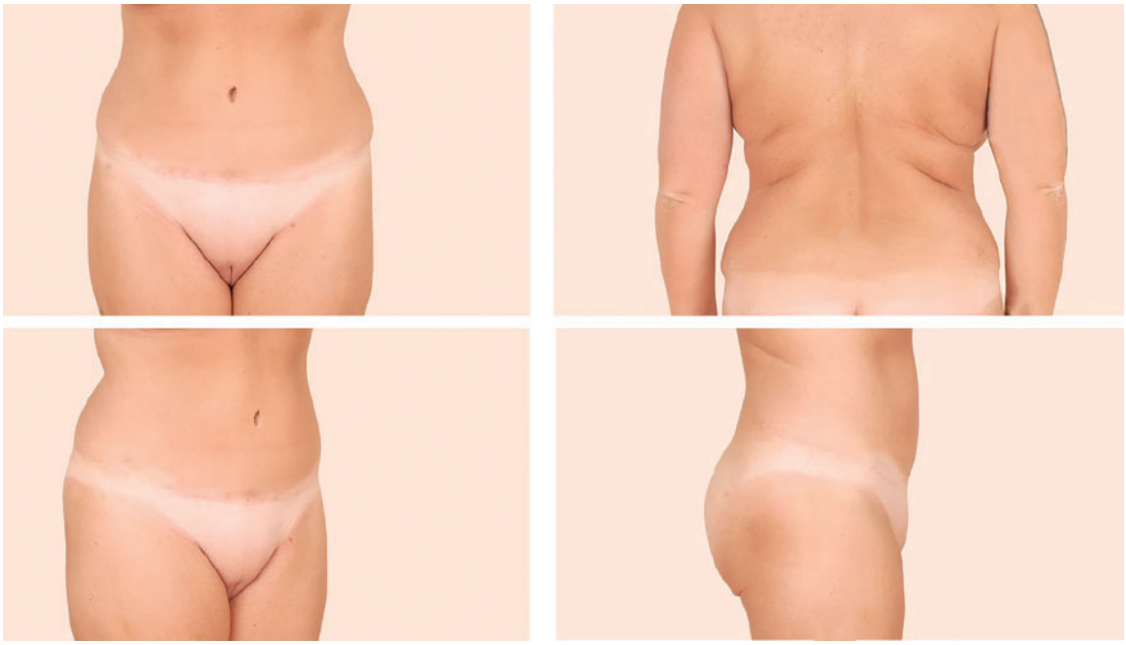


Figure 3. The same patient from Figure 2, now almost 19 months after surgery but having lost weight, demonstrating stable long-term results after abdominoplasty and liposuction. Note the stable improvement in bilateral flank and upper-back adiposity.

- Reduce the amount of subcutaneous fat in flaps created for reconstructive procedures, thereby improving aesthetic results
- Collect harvested fat to "lipofill" in breast reconstruction, burns, and scars because adult adipose-derived stem cells are contained therein.[30]

Although no absolute contraindications exist for liposuction, relative contraindications should be considered during the patient evaluation.[31] Anticoagulants and medications that interfere with lidocaine metabolism should be stopped before liposuction.[32] Poor skin firmness and elasticity in elderly patients would lead to poor skin draping postoperatively and potentially increase patient dissatisfaction.

Further, reasonable expectations must be established, and patients with body dysmorphic disorder may require a psychiatric consultation before surgery. Patients with diabetes mellitus, cardiac disease, and liver disease may need medical clearance before surgery at the discretion of both the surgeon and the facility where the procedure is to take place. Lastly, as has been discussed elsewhere in the surgical literature, poorly controlled diabetes increases the risk of infection.

TECHNIQUES

The most common technique remains the traditional suction-assisted lipectomy (**Table 1**).[33–36] Small-volume liposuction procedures in which a maximum of 1,000 mL of fat is removed can be performed with local anesthesia. Although there is no maximum volume of fat that can be removed in a single setting, the risk for seroma and fluid imbalance increases along with the volume of fat that is removed.

The most common technique is traditional suction-assisted lipectomy

Megaliposuction, a procedure in which an amount greater than 10% of body weight is removed, can be safely performed by an experienced surgeon. Large-volume liposuction procedures should be performed with general anesthesia.[19] Harvested fat may be used for subsequent fat transfer.[19]

The advantages of liposuction are short surgery time (typically under 3 hours, depending on the extent of fat removal) and concomitant procedures. In addition, patients undergoing liposuction have a short recovery period, unobtrusive scars, permanent results, low complication rates, and low morbidity and mortality rates relative to other surgical procedures. Because adipocytes are removed, further storage of fat in those areas is limited,

TABLE 1

Liposuction techniques

Suction-assisted lipectomy
Negative pressure from a syringe applied to a small- volume, blunt-tip suction cannula is used to remove fat.[29] Suctioning from the superficial layer should be avoided to prevent dimpling, hyperpigmentation, and contour irregularities.[19] The superficial fat layer contains vertical fibrous septa, which would result in contour deformities if disrupted; however, exploitation of this anatomy with the liposuction cannula, also known as abdominal etching, has been demonstrated to produce highly defined abdominal aesthetic contours (eg, "6-pack abs").[33]

Ultrasound-assisted lipectomy
Transmitting ultrasound energy to emulsify fat prior to its removal,[34] ultrasonographically assisted lipectomy (UAL) can be advantageous in fibrous areas, such as the back, chest, and upper flank, that are more difficult to target in standard liposuction. UAL has shown marked benefit in treatment of gynecomastia. However, larger incisions are required in UAL and operations require more time. There is an increased risk of thermal injury to subdermal tissues due to the exothermic energy caused by ultrasound.

Laser-assisted lipectomy
Laser-assisted lipectomy (LAL) is performed by inserting a laser fiber via a small incision.[35] Although complications of LAL are rare, 1 study observed a complication rate of 0.93% that included skin burns and a local infection.[36]

Power-assisted lipectomy
Power-assisted lipectomy is performed with an external power source, typically an electric vacuum pump.[35] This technique can be advantageous for large volumes of tissue removal and in densely fibrous areas, as the power assistance reduces operator fatigue.

leading to high patient satisfaction with long-term results.[37]

More research is needed to determine the degree of fat reaccumulation in the treated area and redistribution to nontreated areas.[38,39] As expected, weight gain can still occur, and the patient should be advised to maintain a well-balanced diet and exercise regimen.

RISK FACTORS

Patients with cardiovascular disease, pulmonary disease, diabetes, and vascular disease face a greater risk with this procedure. Tobacco use is a risk factor for surgical complications.[40,41] Ongoing infections before the procedure, particularly near the area of the liposuction site (eg, cellulitis), would require treatment with antibiotics and resolution of infection before surgery. Previous venous thromboembolism, eg, pulmonary embolism, may also increase the risk of surgical complications.

COMPLICATIONS

Complications are relatively uncommon in liposuction and of low risk relative to other procedures.[42] In one study, the overall complication rate was 2.4%.[43] The complication rate was higher (3.5%) when liposuction was combined with other procedures, whereas liposuction as a solitary procedure had a complication rate of only 0.7%.[41] Complications include ecchymosis, edema, surgical site infection, seroma, hematoma, and venous thromboembolism (**Table 2**).[43]

The most common complication of liposuction is contour deformity. As many as 9% of patients may report soft-tissue depressions or elevations, skin panniculus, folds, or wrinkles.[44] Contour deformities can be prevented by using smaller diameter cannulas, avoiding suctioning from superficial layers, employing a "crisscrossing" technique, and allowing slight undercorrection for postoperative fat lysis.[45]

Seroma and hematoma are also rare complications of liposuction.[46] Seromas, which are collections of serous fluid resulting from breakdown of the fibrous tissue network, may develop from initial blind cannula injury to small perforating vessels or lymphatic vessels.[31] Use of progressive tension sutures—primarily a technique to address dead space in surgeries such as abdominoplasty ("tummy-tuck")—has been shown to reduce the rate of seroma from 9% to 2%.[46]

Wound infection is reported in fewer than 3% of inpatient liposuction cases and in approximately 1% in outpatient surgeries.[47] Low infection rates can be attributed to surgeon expertise, proper prophylactic antibiotics, and sterile technique, among other factors. Although uncommon, early-stage wound infections (ie, cellulitis) may develop into more severe sepsis or necrotizing fasciitis—the latter of which is a surgical emergency.[48]

A 2018 study estimated that after liposuction with or without subsequent fat grafting, at least 17 patients have experienced clinically significant fat embolization, or fat embolization syndrome.[49] However, more recent data suggests that worldwide, fatal and nonfatal fat

embolism, particularly after gluteal fat grafting, may exceed 135 cases.[50]

Although fat embolism is rare, its mortality rate of 10% to 15% warrants careful postoperative monitoring for rapid detection and treatment, and it has been reported to occur within 12 to 72 hours after surgery.[50,51] As described, gluteal fat transfer is the only procedure with a higher risk of fatal fat embolism, and is still considered to have the highest mortality rate of any aesthetic procedure.[52]

The incidence of venous thromboembolic events (deep venous thrombosis and pulmonary embolism) after liposuction is low at 0.03%.[53,54] Pulmonary embolism is the most common cause of death after this procedure, which carries an overall mortality rate of 0.01%.[54] Same-day ambulation after liposuction surgery is encouraged to prevent thromboembolic events.

As with any surgical procedure, liposuction causes a transient elevation of acute inflammatory markers (interleukin 6, C-reactive protein), but there is no increased risk of progression to renal disease or chronic inflammation.[55] Some studies suggest that, due to permanent removal of adipocytes, the long-term metabolic benefits of liposuction include improved insulin sensitivity and reduced inflammation. However, more studies are warranted.[56]

Systemic complications that arise weeks to months after surgery include edema, lymphedema, wound dehiscence, hypertrophic scar formation, ecchymosis, and skin laxity. Blind cannula injury can lead to abdominal wall injury, bowel perforation, or vessel injury. Although uncommon, skin devascularization and skin necrosis can occur if the surgeon sutions too closely to the skin undersurface and injures the dermal plexus.[57]

Breast augmentation with autologous fat transfer may lead to fat necrosis that mimics microcalcifications suspicious for breast cancer on mammographic imaging.[58] However, the incidence of these imaging findings is similar to those in patients without fat transfer, and thus, breast augmentation does not hinder detection of breast cancer.

TABLE 2

Complications of liposuction

Short-term complications
Wound infection
Hematoma, seroma
Edema
Ecchymosis
Paresthesia
Fat embolism, pulmonary embolism
Skin necrosis
Long-term complications
Contour deformity
Hyperpigmentation
Hypertrophic scarring
Lymphedema

FUTURE DIRECTIONS

Liposuction can improve body contour and reduce body mass index, and advances are continually being developed. Due to the benefits of long-term weight redistribution, low surgical risk, and short operation time, patients seeking body contour changes will continue to pursue liposuction. The long-term effects on metabolic sequelae such as insulin sensitivity are still being actively researched.[59,60]

Noncosmetic indications are also expanding, particularly fat grafting for breast, facial, and pedal reconstruction.[61] Although liposuction can address a wide variety of needs spanning from cosmetic to reconstructive purposes, the procedure is rarely covered by Medicare or third-party insurance plans, even for issues that cause functional impairment.[62]

Research is being performed in noninvasive body contouring such as cryolipolysis, which may decrease subcutaneous fat deposits while providing dermal tightening with no surgical scars.[63,64] Cryolipolysis (CoolSculpting), deoxycholic acid subcutaneous injection (Kybella), and radiofrequency skin-tightening (Thermage) are nonsurgical volume-reduction and tissue-tightening procedures that address dissatisfaction with body contouring but remain beyond the scope of this manuscript. We mention them for the sake of completeness.

Approximately 1% of outpatient liposuction cases result in wound infection

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***Address**: Raffi Gurunian, MD, PhD, Department of Plastic Surgery, Dermatology and Plastic Surgery Institute, A60, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; gurunir@ccf.org*

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