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CME MOC

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Troponins in acute coronary syndrome

Alcohol and pneumonia

Rhinosinusitis: Role of imaging

Irritable bowel syndrome-diarrhea

Pictures: Scurvy • Dacryocystitis

Letters: Peripartum depression • Aspirin • DXA screening

COVID-19
Brief perspectives from the front line

COVID-19 coagulopathy: Manifestations, management

Chest imaging in COVID-19

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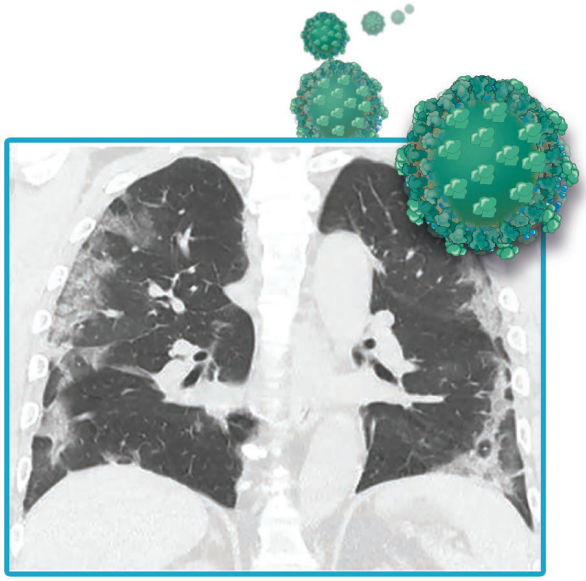

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Table of Contents

CONTINUED ON PAGE 452

Cleveland Clinic

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CONTINUED FROM PAGE 450

A seaworthy nautical tale and a pictured rash

I have correctly diagnosed scurvy several times, missed the diagnosis I do not know how many times, and never treated a patient who had it. This sounds like the beginning of a bad riddle, to which the answer is convoluted. Scurvy, a mimic of vasculitic purpura (pseudovasculitis), has been presented to me at "stump the chump" rounds, although I've never diagnosed or treated it in a patient in front of me, and I'm sure over the years I've missed diagnosing it in patients with early disease caused by chronic malabsorption, unrecognized alcoholism, or voluntary or imposed dietary restrictions.

Elfeki et al, in this issue of the *Journal* (page 478), remind us with striking images that ascorbate, which humans cannot synthesize de novo, is necessary to maintain functional collagen needed for the structural integrity of blood vessels and skin. Patients with scurvy may initially describe fatigue and arthralgias, and may also develop anemia, sometimes with iron deficiency.

Like many clinical disorders, scurvy has an interesting medical history. The discovery of citrus fruit as a cure for scurvy (later determined to contain vitamin C) is oft attributed to Dr. James Lind, a surgeons' mate serving on the *HMS Salisbury* from 1740 to 1747 during the War of the Austrian Succession. He graduated from the University of Edinburgh with an MD in 1748, a year after he retired from the British Navy. His graduation treatise related to venereal disease, likely a clinical expertise honed from years aboard a ship with many ports of call. Lind published his *Treatise of the Scurvy*[1] in 1753. Within this treatise of 450 pages is "the report of Lind's controlled trial comparing six purported treatments for scurvy… rather hidden away and [occupying] just four pages, unmarked by a subheading…"[2] This has been touted as one of the first randomized, controlled, prospective clinical trials, and it resulted in a treatment to cure (with a number needed to treat of 1). Yet it was tucked away in a manuscript that, despite undergoing several printings including translations to French, German, and Italian, had no immediate impact on the practice of the British Navy.

Lind's clinical trial was reasonably well conducted. Although there was no apparent sample size power analysis, 12 sailors suffering from a similar degree of scurvy were selected and isolated to the same quarters and given the same food other than their experimental supplementation. There were 30 to 40 men with scurvy for him to choose from (10% of the crew). "Their cases were as similar as I could have them. They all in general had putrid gums, the spots and lassitude, with weakness of the knees."[3]

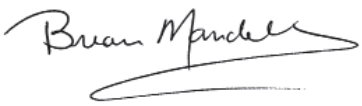
The method of treatment allocation was not clearly stated, but 2 men each were provided 1 of 6 distinct supplements for a planned 14 days: 1.1 L of cider, 25 mL of vitriol (dilute sulfuric acid), 18 mL vinegar 3 times daily, one-half pint of sea water, or 2 oranges and 1 lemon (although apparently the citrus ran out after only 6 days). There was only a historical control group, and there was no defined placebo. There apparently was also no clear scientific hypothesis. Interestingly, there was nautical lore regarding the antiscorbutic properties of oranges dating back to 1498, when Vasco da

doi:10.3949/ccjm.87b.08020

Gama wrote of providing oranges to his sick sailors, and reaffirmed by John Woodall, Surgeon General of the East India Company in 1617.[2]

Despite the data from his randomized trial, there is little evidence that Lind himself was convinced enough by the results to lobby the Admiralty to routinely provide citrus to all ships anticipating protracted sea tours. This practice did not occur until 1795, a year after Lind's death. Lind had apparently suggested that the source of the cure was in the acidity, and limes were initially tried by the Navy (limes were cheaper than lemons, perhaps provided a better group moniker for British sailors, but contained less vitamin C than lemons). Notably, the nutrient value of vitamin C was not recognized until the early 20th century.

Lind's recognized contribution to medical history and evidence-based medicine was an exemplary randomized clinical trial in the absence of a scientific hypothesis, with positive and lasting results, needing only a sample size of 12. Despite the results of this experiment and his future use of lemon juice to treat scurvy in his civilian practice, he wrote regarding the cause of scurvy: "improper diet, air and confinement, the last of which in particular I now judge to be a principal cause… of the scurvy in long voyages at sea."[1]



Brian F. Mandell, MD, PhD
Editor in Chief

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AUGUST

NEUROLOGY UPDATE: A COMPREHENSIVE REVIEW FOR THE CLINICIAN
August 8–9
LIVE STREAM

SEPTEMBER

INTENSIVE REVIEW FOR THE GI BOARDS: LIVE PANEL DISCUSSION AND Q & A
September 16
LIVE STREAM

CLEVELAND CLINIC EPILEPSY UPDATE AND REVIEW COURSE
September 21–24
LIVE STREAM

INTENSIVE REVIEW FOR THE GI BOARDS: INFLAMMATORY BOWEL DISEASE AND SMALL-BOWEL DISEASE PANEL DISCUSSION AND Q & A
September 23
LIVE STREAM

INTENSIVE REVIEW FOR THE GI BOARDS: PANCREAS, BILIARY, ENDOSCOPY PANEL DISCUSSION AND Q & A
September 30
LIVE STREAM

OCTOBER

VIRTUAL NEPHROLOGY UPDATE
October 2
LIVE STREAM

PRACTICAL MANAGEMENT OF STROKE
October 2
LIVE STREAM

STATE-OF-THE-ART ECHOCARDIOGRAPHY 2020
October 2–4
LIVE STREAM

INTENSIVE REVIEW FOR THE GI BOARDS: COLON CANCER, GERD, MOTILITY PANEL DISCUSSION AND Q & A
October 7
LIVE STREAM

INTENSIVE REVIEW OF ENDOCRINOLOGY AND METABOLISM
October 9–11
LIVE STREAM

CARDIOVASCULAR UPDATE FOR THE PRIMARY CARE PROVIDER
October 15–16
LIVE STREAM

ORTHOBIOLOGICS SUMMIT 2020: SCIENCE AND EVIDENCE BEHIND BIOLOGICS IN ORTHOPEDICS
October 17
LIVE STREAM

DECEMBER

A CASE-BASED APPROACH TO MASTERING THE MITRAL VALVE: IMAGING, INNOVATION, INTERVENTION
December 4–5
LIVE STREAM

2021

JANUARY

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
Cleveland, OH

MARCH

PAIN MANAGEMENT SYMPOSIUM
March 27–31
Orlando, FL

APRIL

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

JUNE

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

SEPTEMBER

PRIMARY CARE WOMEN'S HEALTH: ESSENTIALS AND BEYOND
September 9–10
Cleveland, OH

COMPREHENSIVE LIFELONG EXPEDITIOUS CARE OF AORTIC DISEASE
September 17–18
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Perinatal depression

To the Editor: I applaud Drs. Sayres Van Neil and Payne for their article, "Perinatal depression: A review.[1] It brings to light the understated vulnerability of the postpartum period affecting the majority of women worldwide. I would like to clarify 2 points.

The American College of Obstetricians and Gynecologists (ACOG) states that medical care in the "fourth trimester" should include early communication with obstetric providers.[1] In contrast to the review's recommendation for depression screening during the 6-week postpartum visit, ACOG recommends contact with the obstetric provider within 3 weeks of delivery. We, as medical providers, need to normalize and emphasize the importance of early contact, and to acknowledge that postpartum depression and anxiety are common.

Second, your readers include family medicine physicians trained in the full-spectrum primary care of women desiring pregnancy throughout the preconception, peripartum, and postpartum periods. Drs. Sayres Van Niel and Payne allude to primary care physicians, but remark that it is best to refer a woman requiring pharmacologic treatment of a mood disorder during pregnancy or lactation to a psychiatric specialist.

The family medicine physician has an understated position in the care of women with perinatal mood disorders. We often have developed trusted relationships with women prior to their pregnancies. Screening for depression appears to be more successful when a mother shares a medical home with her child, which is common in a family medicine practice setting.[2] Family physicians should be knowledgeable about the benefits and risks of and alternatives to pharmacologic treatment of perinatal mood disorders, and able to address postpartum depression with concrete interventions in up to 92% of newborn visits.[3] Comfort with prescribing antidepressants for nonpregnant populations increases the likelihood that a healthcare provider will screen a woman for perinatal depression.[4]

Postpartum depression is known to affect maternal-infant bonding, breastfeeding success, childhood development, and partner relationships, which can all be addressed by the family physician.[5] Well-trained in treatment of depression and anxiety disorders, the family physician is prepared to be a useful caregiver in the postpartum period, including initiation of pharmacologic treatments if required.

Elise Laflamme, MD
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Lawrence, MA

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doi:10.3949/ccjm.87c.08001

In Reply: We thank Dr. Laflamme for her insightful letter regarding our article.

We wholeheartedly agree that earlier contact with obstetric-care providers, such as during "fourth trimester" contact, is ideal. We also encourage all obstetric providers to screen at least at the 6-week in-person postpartum visit.

Her second point, that family medicine physicians are well-positioned to identify and treat perinatal depression, is also excellent. We agree, and we encourage all family medicine physicians to educate themselves on the basics of psychiatric treatment during pregnancy and lactation.

There is a good deal of misinformation on

the safety of psychiatric medications during pregnancy and lactation, and we recommend that all frontline providers, including internal medicine, family medicine, and OB-GYN physicians, as well as pediatricians, receive education on this topic.

To that end, the International Marcé Society for Perinatal Mental Health is supporting a curriculum in reproductive psychiatry. This ongoing project developed by leaders in reproductive psychiatry aims to educate all frontline providers on these important issues.

With more-complex psychiatric issues during pregnancy or the postpartum period, or when there is a complicated history of prior mental illness, reproductive psychiatrists are available for consultations to primary care providers.

Thank you for this addition to the discussion.

Maureen Sayres Van Niel, MD
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Jennifer L. Payne, MD
The Johns Hopkins University School of Medicine
Baltimore, MD

doi:10.3949/ccjm.87c.08002

DXA after menopause

To the Editor: I want to commend Drs. Tough DeSapri and Brook for their excellent summary on the use of the FRAX tool in assessing the need for dual-energy x-ray absorptiometry (DXA) in postmenopausal women.[1]

A thought experiment that we engage in with our fellows is to take the FRAX tool and calculate the changes in 10-year fracture risk obtained by changing each of the parameters. For example, the patient discussed in the article would have a 10-year risk of a hip fracture of 0.4%. However, if we add 16 years to her age (making her 72 years old), her level of risk is 3.0%, which would justify the use of a medical intervention such as a bisphosphonate. Similarly, her risk increases to 1.3% if she had suffered a previous fracture, and to 0.8% if she had taken a significant amount of glucocorticoids.

Many of us compensate for the lack of quantitation in the FRAX questionnaire by using "fudge factors." For glucocorticoids, we increase the fracture risk by 15% if a patient was on more than 7.5 mg of prednisone for 3 or more months.[2]

One glaring deficiency in the FRAX score is an absence of any reference to diabetes. Type 2 diabetes mellitus is associated with a significant risk of fracture without a significant decrease in bone density.[3] Suggested compensations include adding 10 years to the patient's age or checking "yes" for rheumatoid arthritis when calculating FRAX for a patient with type 2 diabetes mellitus.

The trabecular bone score mentioned by DeSapri and Brook is a way of getting at the issue of bone quality and at least partially corrects the calculation of fracture risk for the diabetic patient. Data entry for the trabecular bone score is now built into the online FRAX tool and can be added after clicking "Calculate." Race also is now available for the US FRAX tool.

Michael Balkin, MD
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doi:10.3949/ccjm.87c.08003

In Reply: Thank you for your commentary on "off-label" use of FRAX to better predict fracture risk for patients (such as those with diabetes or on high-risk medications) who

don't fit neatly into the FRAX algorithm. FRAX does allow for individualized calculation of relative risk of fracture across age and hip bone mineral density. And age may indirectly incorporate risk of falls, as 25% of people over age 65 fall annually.[1]

With the limitations of FRAX, we must recognize that calculation tools must not replace clinical judgment and assessment of fall and fracture risk for our individual patients. Bone mineral density scanning estimates 70% of bone strength, and other factors may influence fracture risk. As Dr. Balkin mentions, the trabecular bone score and also hip geometry (bone strength based on the measurement of proximal femur) may supplement axial bone mineral density testing with central DXA to determine propensity to fracture.[2]

Other technologies are being developed. For example, biomechanical computed tomography uses finite element analysis to provide a virtual stress test of a patient's bone to measure its breaking strength in newtons.

Kristi Tough DeSapri, MD
Cleveland Clinic

Rachel Brook, MD
Cleveland Clinic

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Aspirin for primary prevention

To the Editor: I greatly appreciated the review by Drs. Schenone and Lincoff about aspirin for primary prevention in your May 2020 issue.[1] I wanted to note that the statement in green on page 303, "Statins may dilute the potential benefit of aspirin," conflicts with what I have read regarding statins' ability to improve aspirin resistance.[2]

Moreover, as I interpret a meta-analysis performed by the Antithrombotic Trialists' Collaboration,[3] statins may halve the risk of coronary heart disease, but when aspirin is added, hypothetically the added benefit of the aspirin is marginal, given the increased risk of bleeding. Ultimately it would be the aspirin theoretically diluting the benefit of the statin because of bleeding risk. The authors of the meta-analysis note: "If the risk of occlusive vascular disease is already approximately halved by statins or other measures, then the further absolute benefit of adding aspirin could well be only about half as large as was suggested by these primary prevention trials, but the main bleeding hazards could well remain. In that case, the benefits and hazards of adding long-term aspirin in people without preexisting disease might be of approximately similar magnitude."

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doi:10.3949/ccjm.87c.08005

In Reply: We appreciate the comments made by Dr. Henning about our statement that statins may dilute the benefit of aspirin.[1] She alludes to interesting data on the potential interaction between aspirin and statins from a small study that enrolled patients with coronary artery disease and aspirin resistance (defined as closure time < 186 seconds with Col/Epi cartridges despite a regular aspirin regimen).

In that study, statin therapy was associated with a resolution of in vitro aspirin resistance in up to two-thirds of patients.[2] Notably, however, that study did not assess the impact of this reported interaction on cardiovascular or bleeding outcomes.

Dr. Henning then provides her interpretation of available data proposing that aspirin therapy would dilute the benefit of statin therapy rather than vice versa. We respectfully disagree with this interpretation. The statement in our review that "statins may dilute the benefit of aspirin" refers to the impact of statin therapy on the risk-benefit profile of aspirin on cardiovascular and bleeding outcomes, rather than to drug-drug interactions.

Our statement is also supported by evidence that the relative risk reduction in atherosclerotic cardiovascular events provided by aspirin is about the same across different levels of risk, and thus the absolute risk reduction by aspirin is primarily dictated by the baseline risk of the patient.[3] As the risk of cardiovascular events is reduced by guideline-directed statin therapy, the absolute risk reduction of cardiovascular events provided by aspirin is also reduced by the same magnitude with no anticipated change in the bleeding hazard. Thus, the number needed to treat to prevent 1 cardiovascular event when aspirin is prescribed as add-on therapy to a guideline-directed statin regimen would be expected to increase compared with an aspirin regimen without a statin, while the number needed to harm would likely remain the same. As a consequence, one could expect a dilution of the net overall benefit of aspirin (absolute risk reduction in cardiovascular events minus absolute increase in bleeding risk) reported by initial primary prevention trials, when statins were infrequently used, compared with aspirin added to a background regimen of statin. This has been hypothesized to be a potential reason for the dissipation of benefit in the contemporary aspirin primary prevention trials.[4]

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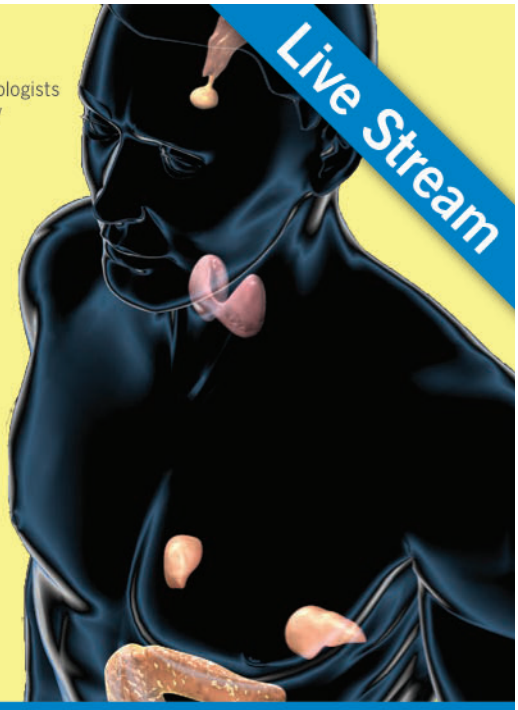

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Coagulopathy in COVID-19: Manifestations and management

ABSTRACT

Severe COVID-19 illness is associated with intense inflammation, leading to high rates of thrombotic complications that increase morbidity and mortality. Markedly elevated levels of D-dimer with normal fibrinogen levels are the hallmark laboratory findings of severe COVID-19–associated coagulopathy. Prophylaxis against venous thromboembolism is paramount for all hospitalized patients, with more aggressive prophylaxis and screening recommended for patients with D-dimer levels above 3.0 µg/mL. Point-of-care ultrasonography is the imaging method of choice for patients at high risk, as it entails minimal risk of exposing providers to the virus.

KEY POINTS

We recommend measuring D-dimer, fibrinogen, prothrombin time, international normalized ratio, and activated partial thromboplastin time every 48 hours in hospitalized patients with COVID-19.

Prophylaxis against venous thromboembolism is recommended for all COVID-19 patients on admission, using low-molecular-weight heparin, unfractionated heparin for those in renal failure, or fondaparinux for those with heparin-induced thrombocytopenia, even in the setting of thrombocytopenia as long as the platelet count is above 25×10^9/L.

Patients with D-dimer levels 3.0 µg/mL or higher should undergo screening with point-of-care ultrasonography and receive more intensive prophylaxis.

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COVID-19–ASSOCIATED COAGULOPATHY (CAC) and disseminated intravascular coagulation are common in COVID-19 and are associated with severe illness and death.[1–3] Critically ill patients without other risk factors for thrombosis can experience various thrombotic events, including microvascular thrombosis, venous and pulmonary thromboembolism, and acute arterial thrombosis.[4]

This article discusses clinical manifestations of CAC, associated laboratory and histologic findings, recent evidence elucidating pathophysiologic mechanisms, and the way we manage it at Cleveland Clinic.

A HIGHLY THROMBOTIC STATE

The clinical presentation of CAC is that of a highly thrombotic state. Shared anecdotal experience from a variety of sources indicates that catheter-associated thrombosis and clotting of vascular access catheters are especially common problems. The need for catheter replacement and dialysis circuits that involve frequent interruption of continuous renal replacement therapy are other high-risk settings.

Two recent studies support the clinical impression that COVID-19 is highly thrombotic. Cui et al[5] reported a 25% incidence of deep vein thrombosis in patients with severe coronavirus pneumonia. Klok et al[4] found a 31% combined incidence of deep vein thrombosis, pulmonary embolism, and arterial thrombosis in critically ill patients with coronavirus. Of these events, 81% were pulmonary thromboembolic.

In Cleveland Clinic intensive care units, we are finding that point-of-care ultrasonography (POCUS) detects deep vein thrombosis at a rate of 25% to 30%, similar to rates

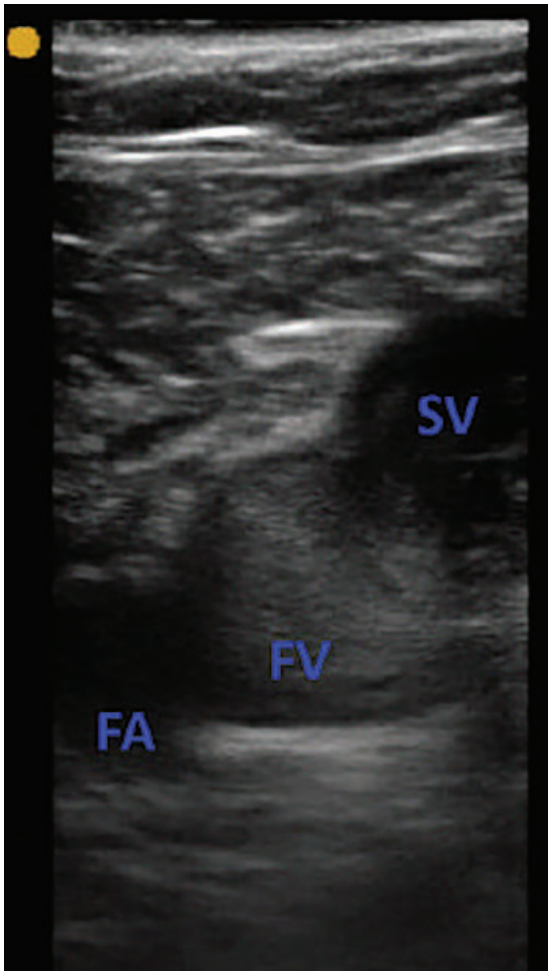

Figure 1. A short-axis view of the femoral vein (FV) and the femoral artery (FA) at the site of the saphenous vein (SV) inflow. Amorphous echogenicity in the femoral vein, greater than that of the adjacent femoral artery, is suggestive of slow venous flow. The vein was fully compressible, ruling out deep vein thrombosis at the site.

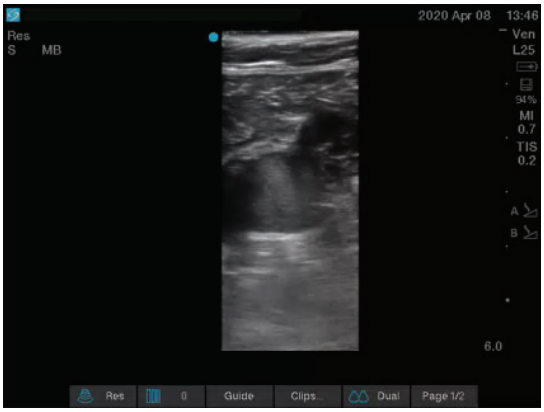

Figure 2. Another short-axis view of the femoral vein (center) and the femoral artery (bottom right) at the site of the saphenous vein inflow (top right). Swirling pattern of high echogenicity suggests low-flow state.

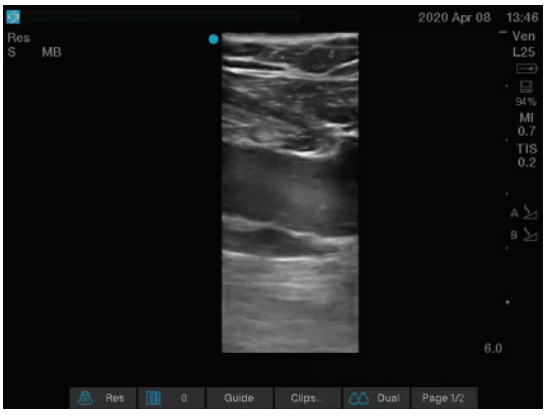

Figure 3. Long-axis view of the femoral vein, with spontaneous echogenicity and slow flow.

The clinical presentation of CAC is that of a highly prothrombotic state

in these studies. Another frequent finding is "slow venous flow." This pattern, described as amorphous echogenicity in major veins, has been associated with a higher subsequent risk of deep vein thrombosis (**Figures 1–3**).[6]

LABORATORY FINDINGS: ELEVATED D-DIMER

The characteristic laboratory findings of CAC (ie, dramatically elevated levels of D-dimer and fibrin degradation products) indicate a highly thrombotic state with high fibrin turnover. However, other markers of disseminated intravascular coagulation remain relatively unchanged.[7] The prothrombin time and activated partial thromboplastin time are only mildly prolonged, if at all, and platelet counts are usually normal or only mildly low (100–150 × 10^9/L).[8–10]

Elevated D-dimer levels on presentation with COVID-19 are associated with more severe disease. Levels of 0.5 µg/mL or higher were found in 59.6%% of patients with severe disease vs 43.2% of those with mild disease.[3] High levels also correlated with the need for intensive care[11] and with death.

In a multivariable regression analysis of 191 patients, Zhou et al[1] reported that the risk of death was more than 18 times higher (odds ratio 18.42, 95% confidence interval 2.64–128.55) for patients admitted with a D-dimer level greater than 1 µg/mL vs less than 0.5 µg/mL. Cui et al[5] reported that D-dimer levels also correlated with risk of venous thromboembolism: a level of 3.0 µg/mL had a sensitivity of 70.0%, specificity of 96.7%, and positive predictive value of 87.5%. Maatman et al[12] reported that standard prophylaxis against venous thromboembolism failed in 29 of 109 patients in the intensive care unit, and of those in whom it failed, all had D-dimer levels greater than 3.0 µg/mL.

Other measures of coagulopathy also predictive

Other indicators of coagulopathy have also been studied in COVID-19 and found to be associated with increased risk.

Prothrombin time, activated partial thromboplastin time. Klok et al[4] did not report D-dimer levels, but found coagulopathy (ie, prolongation of prothrombin time of > 3 seconds or of activated thromboplastin time > 5 seconds) to be an independent risk factor for thrombosis.

Antiphospholipid antibodies. Zhang et al[13] reported that 3 patients with CAC and lower-extremity ischemia had antiphospholipid antibodies (anticardiolipin immunoglobulin A [IgA], anti-beta-2 glycoprotein 1 IgA and IgG) but not lupus anticoagulant. Helms et al,[14] in a multicenter study of 150 patients with COVID-19 in intensive care units in France, found a remarkably high rate of positivity for lupus anticoagulant: 50 of 57 patients (87.7%) among those tested for further evaluation for an elevated activated partial thromboplastin time.

Disseminated intravascular coagulation score. Tang et al[10] found that progression of coagulopathy to overt disseminated intravascular coagulation (defined by the International Society on Thrombosis and Haemostasis as a disseminated intravascular coagulation score ≥ 5 points; the score is based on platelet count, D-dimer level, fibrinogen level, and prolongation of the prothrombin time) predicted a poor prognosis, occurring in 71.4% of all nonsurvivors vs 0.6% of survivors.

Progressive consumptive coagulopathy. Declining levels of antithrombin III, a rise in prothrombin time and activated partial thromboplastin time, and dramatic further increase of D-dimer (> 15.0 µg/mL) appear to indicate severe and progressive disease, developing late in the disease course (day 10 to 14) of nonsurvivors. Fibrinogen levels, which are elevated in the initial phase, drop late in the course of disease in nonsurvivors and may signal impending death.[10]

Low platelet count. Lippi et al,[8] in a meta-analysis of 9 studies with 1,779 patients with COVID-19, examined thrombocytopenia as a marker of disease severity. Thrombocytopenia at presentation was associated with an increased risk of severe disease and death, with a weighted mean difference of 31 × 10^9/L in the platelet count between those with severe and nonsevere disease. The authors noted great heterogeneity among studies, with reported rates of thrombocytopenia in severe disease ranging from 4% to 57.7%.

SEVERE LUNG DAMAGE FROM INFLAMMATION, THROMBOSIS

Histopathologic studies reveal diffuse alveolar damage with profound inflammation, thrombosis, and thrombotic microangiopathy of small vessels and capillaries of the lung. Also noted have been megakaryocytes within pulmonary capillaries with nuclear hyperchromasia and atypia, as well as neutrophils partially degenerated and entrapped in fibers (suggesting neutrophil extracellular traps).[15] An autopsy series of 11 patients showed thrombosis of small and midsized pulmonary arteries in all patients.[16]

Elevated D-dimer levels on presentation correlate with disease severity

Endothelial cell injury and diffuse microvascular thrombosis suggestive of thrombotic microangiopathy have also been reported in extrapulmonary organs, which may explain the acute onset of multiorgan failure without an otherwise obvious etiology.[17]

PATHOPHYSIOLOGY: INFLAMMATION PROMOTES THROMBOSIS

CAC is likely multifactorial, and patients with COVID-19 share many of the classic risk factors for venous thromboembolism seen in adult respiratory distress syndrome from other causes, such as immobility, large vascular-ac-

cess catheters, and systemic inflammation.

The hallmark of COVID-19 is profound inflammation, described as "cytokine storm," characterized by high levels of interleukin 1 (IL-1), IL-6, tumor necrosis factor, and other inflammatory cytokines.[11] Inflammation promotes thrombosis through various mechanisms, including activation of endothelial cells, platelets, monocytes, and the tissue factor-factor VIIa pathway, and by altering fibrinolysis and natural anticoagulant pathways (eg, through changes in levels of thrombomodulin, proteins C and S, and tissue-factor-pathway inhibitor).[18,19] Intense inflammation with thrombosis of pulmonary vessels is also seen in adult respiratory distress syndrome of other etiologies.[20] It remains to be seen if these findings represent a distinct phenotype unique to COVID-19 or are a general indicator of the severity of inflammation with COVID-19.

Serum proteomic profiling of patients with severe acute respiratory syndrome (SARS) identified an N-terminal fragment of complement C3C-alpha (a central component of the complement pathway) as a sensitive biomarker of early SARS.[21] Murine models of SARS and Middle East respiratory syndrome (MERS) have shown that complement activation is a major contributor to lung injury and other organ failure. Complement inhibition in these models reduced organ damage and inflammation.[22,23] Complement inhibition has been suggested as a treatment for COVID-19, but clinical data are not yet available.[24]

Inflammation promotes thrombosis through various mechanisms

One mechanism of microvascular thrombosis that may be specific to COVID-19 is the virus's affinity for angiotensin-converting enzyme 2, which is expressed on alveolar epithelial type II cells and various extrapulmonary tissues, including endothelial cells. Endothelial cell activation may be a unique mechanism of COVID-19-mediated microvascular injury, thrombosis, and subsequent multisystem organ failure.[25,26]

The rate of 87.7% positivity for lupus anticoagulant in patients with COVID-19 reported by Helms et al[14] is striking and needs to be verified, but it supports the idea that endothelial injury is a key mechanism of multiorgan failure and coagulopathy in this disease. The "two-hit" model of thrombosis associated with antiphospholipid syndrome proposes that after a first-hit injury to the endothelium, antiphospholipid antibodies potentiate thrombus formation as a second hit.[27] Activation of the contact system due to increased vascular permeability and thrombotic microangiopathy warrant further exploration.[28]

OUR MANAGEMENT APPROACH

Currently, CAC is managed largely on the basis of case reports and anecdotal experience; controlled studies are urgently needed to better guide care. Management strategies vary greatly among institutions and are likely to change as we learn more about this novel disease.

The approach outlined here describes the Cleveland Clinic consensus based on available information. It tries to balance the risk and benefits of empiric therapy, while minimizing the use of resources (eg, personal protective equipment) and exposure of caregivers to COVID-19.

Monitor D-dimer, fibrinogen, prothrombin time, activated partial thromboplastin time

In view of the characteristic laboratory findings of CAC described above, we monitor D-dimer, fibrinogen, prothrombin time-international normalized ratio, and activated partial thromboplastin time every 48 hours. We define a D-dimer level of at least 6 times the upper limit of normal (3.0 µg/mL fibrinogen equivalent units [FEU]) as high risk.[5,10]

Because antiphospholipid antibodies, including lupus anticoagulant, have been reported in COVID-19, we recommend testing for these if the activated partial thromboplastin time is spontaneously elevated, and we prefer the use of anti-Xa assays to monitor anticoagulation. Anti-Xa assays however, may be affected by high levels of bilirubin (> 6.6 mg/dL) or triglycerides (> 360 mg/dL),[29] which are often elevated in patients with COVID-19 and cytokine storm. Triglyceride levels should therefore be monitored routinely and considered as a possible source of error in patients on anticoagulation who are difficult to maintain within the therapeutic target range.

A hypercoagulable pattern on viscoelastic testing (thromboelastography or rotational thromboelastometry), with faster time to clot formation, rapid clot propagation, and increased clot strength, has been described in several publications.[12,30] However, no evidence

exists on how to best use this information to guide therapy. In line with current guidance from the American Society of Hematology and the International Society on Thrombosis and Haemostasis, we do not routinely use viscoelastic testing to assess hypercoagulability.[31]

Imaging: Use POCUS

To limit caregiver exposure, we minimize formal bedside vascular studies and sending the patient out of the intensive care unit for computed tomographic angiography. We rely heavily on POCUS to assess for evidence of venous thromboembolism. This is in line with recent National Institutes of Health guidance,[32,33] which cites a lack of evidence supporting routine screening examinations but highlights the value of POCUS in the hands of experienced clinicians. POCUS should be bundled with other care (for example, ultrasonography-guided vascular access) to minimize the use of personal protective equipment and caregiver exposure to COVID-19.

Patients at high risk (D-dimer > 3.0 µg/mL FEU) are assessed for deep vein thrombosis using a 3-point compression POCUS examination of both lower extremities. A POCUS deep vein thrombosis examination and echocardiography are also recommended for any patient with sudden cardiopulmonary decline that cannot be explained by an alternative etiology.

A positive POCUS examination for deep vein thrombosis is highly specific and does not need to be confirmed by formal vascular ultrasonography.[34] On the other hand, given the high incidence of pulmonary embolism described, confirmatory studies (ie, formal vascular ultrasonography or computed tomographic angiography) are warranted if the patient has contraindications to empiric anticoagulation and the clinical suspicion of venous thromboembolism is high despite negative POCUS, or if POCUS is not available.

Prophylactic heparin for most

Specific data on the management of CAC are extremely limited, but heparin seems to be the obvious response to such a hypercoagulable process.

In addition to its antithrombotic effect, heparin may have anti-inflammatory, anticomplement,[35] and direct antiviral effects that may be beneficial in COVID-19. Heparin inhibits neutrophil activation, binds inflammatory cytokines, and reduces endothelial activation.[36] Experimental models have also shown that heparin directly binds to SARS-CoV spike protein, the viral anchor site, thereby blocking viral entry into the cell.[37] While promising, these effects have yet to be demonstrated clinically.

Tang et al[38] reported on 449 patients with severe COVID-19 in whom the overall mortality rate was no different (29.7% vs 30.3%, *P* = .910) between those who received heparin (94 patients on low-molecular-weight heparin, 5 patients on unfractionated heparin; prophylactic doses) and those who did not. But among patients with a D-dimer level of more than 6 times the upper limit of normal (> 3.0 µg/mL), heparin recipients had a significantly lower mortality rate than nonrecipients (32.8% vs 52.4%, *P* = .017). The authors concluded that heparin lowers mortality rates in patients with severe COVID-19 and cited a Chinese consensus statement recommending anticoagulation in severe COVID-19. We emphasize that this study retrospectively compared heparin prophylaxis with no prophylaxis.

Full anticoagulation for some?

A late drop in fibrinogen levels may signal impending death

Some evidence indicates that elevated D-dimer levels may predict higher risk of venous thromboembolism despite standard prophylaxis. In a study of 240 critically ill patients with COVID-19, Maatman et al[12] reported a 28% rate of venous thromboembolism in patients receiving standard prophylaxis. Elevated D-dimer (> 2.6 µg/mL) predicted venous thromboembolism with a sensitivity of 89.7%. The authors concluded that standard prophylactic anticoagulant doses may be insufficient to prevent venous thromboembolism in high-risk patients.

Paranjpe et al,[39] in an observational report of 2,773 patients with COVID-19 admitted to a single institution in New York, found that those treated with full anticoagulation (786 patients, 28%) had a similar mortality rate (22.5%) vs those treated with prophylaxis only (22.8%). But among mechanically ventilated patients, in-hospital mortality was 29.1% for those treated with anticoagulation vs 62.7% for patients who did not receive anticoagulation. Despite this dramatic reduction of mortality, the authors advise caution in ap-

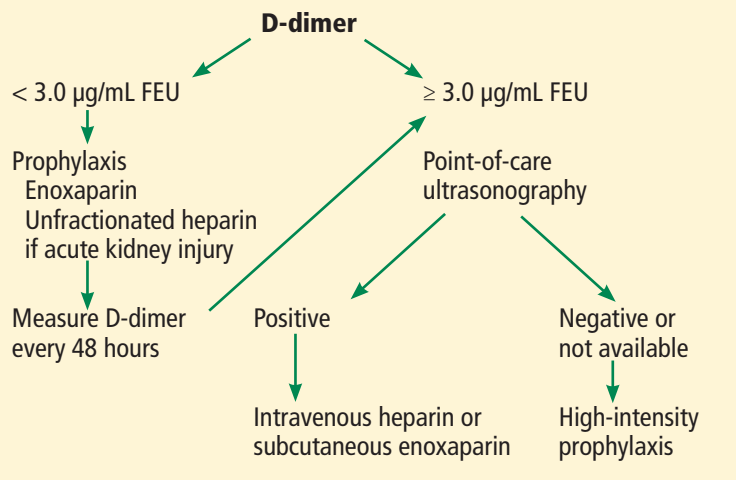

Figure 4. Algorithm for preventing and treating COVID-19-associated coagulopathy.
FEU = fibrinogen equivalent units

plying these findings, given the serious limitations of the report, ie, its observational nature and lack of information on illness severity and indications for anticoagulation.

Taken together, this limited evidence confirms that prophylaxis against venous thromboembolism in critically ill COVID-19 patients is associated with improved outcomes, and there may be a role for full anticoagulation.

A positive POCUS for DVT is highly specific and does not require confirmation

Given the limitations of the studies thus far, it remains unclear if higher prophylactic doses or full anticoagulation offer a benefit beyond standard prophylactic dosing, and which patients may benefit without suffering more bleeding complications.

Thrombolysis has also been suggested for patients whose condition deteriorates despite anticoagulation. Three patients with persistent severe hypoxia and markedly elevated D-dimer showed improvement in oxygenation after being given low-dose tissue plasminogen activator. But despite initial improvement and no reported adverse effects, the ultimate outcome was poor: the improvement was long-lasting in 1 patient but transient in the other 2, and 1 patient died.[40]

Recommendations

Given this lack of evidence, the National Institutes of Health, American Society of Hematology, and International Society on Thrombosis and Haemostasis currently do not recommend treatment beyond standard prophylaxis except for an established indication. The two societies strongly recommend prophylaxis against deep vein thrombosis in all patients on admission, using low-molecular-weight heparin (or unfractionated heparin in those with renal failure, or fondaparinux in those with heparin-induced thrombocytopenia). They stress that prophylaxis should be continued even in the setting of thrombocytopenia so long as the platelet count is higher than 25×10^9/L.[31,41]

Our current approach is based on POCUS screening for venous thromboembolism and intensified prophylaxis in high-risk patients (**Figure 4, Table 1**). We divide patients into 3 categories:

- **Category 1:** D-dimer less than 3.0 µg/mL FEU and no evidence of venous thromboembolism. Patients receive standard prophylaxis and are monitored using serial D-dimer testing.
- **Category 2:** D-dimer 3.0 µg/mL FEU or higher, POCUS-negative. Patients receive intensified deep vein thrombosis prophylaxis.
- **Category 3:** Confirmed thrombosis. Patients receive full anticoagulation.

If the clinical suspicion of venous thromboembolism is high and the patient has no contraindication to anticoagulation, full anticoagulation should be initiated empirically if POCUS or confirmatory tests are not immediately available.

Continuous renal replacement therapy

Given the high rate of clotting in dialysis circuits, all patients on continuous renal replacement therapy receive unfractionated heparin at a rate of 500 U per hour. If ongoing clotting is observed, we increase systemic heparin to bring the activated partial thromboplastin time into the target range according to an acute coronary syndrome nomogram. The target activated partial thromboplastin time is 49 to 67 seconds, and the goal anti-factor Xa level is 0.2 to 0.5 IU/mL, but these may be adjusted if clotting continues despite systemic heparin.

Duration of anticoagulation

Anticoagulation should be continued for 6 weeks for catheter-associated thrombosis and for at least 3 months for venous thromboembolism. Convalescent patients with persistently elevated D-dimer (greater than twice the upper limit of normal) may benefit from extended prophylaxis or treatment.[42,43]

TABLE 1

Cleveland Clinic approach to anticoagulation prophylaxis and management in COVID-19

	Category 1 D-dimer < 3.0 µg/mL FEU Standard prophylaxis	**Category 2** D-dimer ≥ 3.0 µg/mL FEU High-intensity prophylaxis	**Category 3** Confirmed VTE Full anticoagulation
Standard	Enoxaparin 40 mg subcutaneously every 24 hours	Enoxaparin 40 mg subcutaneously every 12 hours	IV heparin per DVT/PE nomogram or enoxaparin 1 mg/kg subcutaneously every 12 hours
Renal failure	**CrCl 10–30 mL/min:** Enoxaparin 30 mg subcutaneously every 24 hours **CrCl < 10 mL/min or AKI[a]:** Unfractionated heparin 5,000 U subcutaneously every 12 hours **CRRT:** Unfractionated heparin 500 U/hour through circuit **Circuit clotting:** IV heparin per ACS nomogram[a]	**CrCl < 30 mL/min or AKI:** Enoxaparin 40 mg subcutaneously every 24 hours **CrCl < 10 mL/min or AKI[a]:** Unfractionated heparin 7,500 U subcutaneously every 12 hours **CRRT:** Unfractionated heparin 500 U/hour through circuit **Circuit clotting:** IV heparin per ACS nomogram[a]	IV heparin per DVT/VTE nomogram
Obesity			
Standard	**> 100 kg:** Enoxaparin 40 mg subcutaneously every 12 hours **> 120 kg:** Enoxaparin 60 mg subcutaneously every 12 hours	**> 100 kg:** Enoxaparin 60 mg subcutaneously every 12 hours **> 120 kg:** Enoxaparin 80 mg subcutaneously every 12 hours	IV heparin per DVT/PE nomogram or Enoxaparin 1 mg/kg subcutaneously every 12 hours, up to 150 mg Above 150 kg use unfractionated heparin
Renal failure CrCl < 30 mL/min or AKI[b]	≤ **120 kg:** 7,500 U every 12 hours **> 120 kg:** 10,000 U every 12 hours **CRRT:** 500 U/h through circuit **Circuit clotting:** IV heparin per ACS nomogram[a]	≤ **120 kg:** 7,500 U every 8 hours **> 120 kg:** 10,000 U every 8 hours **CRRT:** 500 U/h through circuit **Circuit clotting:** IV heparin per ACS nomogram[a]	IV heparin per DVT/PE nomogram

[a]IV heparin ACS nomogram: initial dose 60-U/kg bolus, then 12 U/kg/hour; target aPTT 49–67 seconds; target heparin anti-Xa 0.2–0.5 units/mL.
[b]AKI definition: doubling of creatinine in 48 hours or anuria.
ACS = acute coronary syndrome; AKI = acute kidney injury; aPTT = activated partial thromboplastin time; CrCl = creatinine clearance; CRRT = continuous renal replacement therapy; DVT = deep vein thrombosis; FEU = fibrinogen equivalent units; IV = intravenous; PE = pulmonary embolism; VTE = venous thromboembolism

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Thoracic imaging in COVID-19

ABSTRACT

The typical findings of COVID-19 on chest radiography and computed tomography (CT) include bilateral, multifocal parenchymal opacities (ground-glass opacities with or without consolidation, and "crazy paving"). In most cases, the opacities are predominantly in the peripheral and lower lung zones, and several have rounded morphology. However, these imaging findings are not pathognomonic for COVID-19 pneumonia and can be seen in other viral and bacterial infections, as well as with noninfectious causes such as drug toxicity and connective tissue disease. Most radiology professional organizations and societies recommend against routine screening CT to diagnose or exclude COVID-19.

KEY POINTS

Chest radiography is considered an appropriate initial imaging diagnostic test for most patients with lower respiratory tract infection, including those suspected of having COVID-19. However, it is neither sensitive nor specific.

CT features of COVID-19 pneumonia are not pathognomonic. Hence, when making the diagnosis, CT findings must be integrated with the clinical presentation, exposure history, prevalence of COVID-19 in the community, and personal risk factors.

A normal result on chest CT cannot exclude the diagnosis of COVID-19, especially early after the onset of symptoms.

Professional societies have issued guidelines on imaging in COVID-19, and the field continues to evolve.

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THE LUNGS are the most common site of infection in COVID-19, and progression to respiratory failure is the most common cause of death. In this brief summary we describe the role of thoracic imaging in COVID-19.

CHEST RADIOGRAPHY IN COVID-19

Chest radiography is considered an appropriate initial imaging diagnostic test for most patients with lower respiratory tract infection, including those suspected of having COVID-19. The radiographic abnormalities in COVID-19 mirror those on computed tomography (CT), demonstrating bilateral, peripheral, and mid-lower-lung-zone-predominant consolidation (**Figure 1**).[1] However, in patients who have a high pretest probability of COVID-19, atypical findings such as diffuse interstitial changes or unilateral focal consolidation (**Figure 2**) should not dissuade the radiologist from suspecting an infection, including COVID-19, as a possible diagnosis.

In patients with progressive disease, the density and extent of parenchymal changes typically increase over time (**Figure 3**). The severity of chest radiographic findings peaks 10 to 12 days after the onset of symptoms.[1]

Unfortunately, most bacterial pneumonias also present as consolidation, and it is difficult to distinguish them from viral infections on chest radiography. The subtleties of rounded morphology and "crazy paving" associated with COVID-19 can only be appreciated on CT and not on plain chest radiographs. Cavitation within an airspace consolidation likely suggests a superadded infection.

Moreover, chest radiography has a high false-negative rate, especially in the early stage of infection, and should not be used as a screening tool to rule out COVID-19. In fact, baseline radiography has a lower sensitivity (69%)

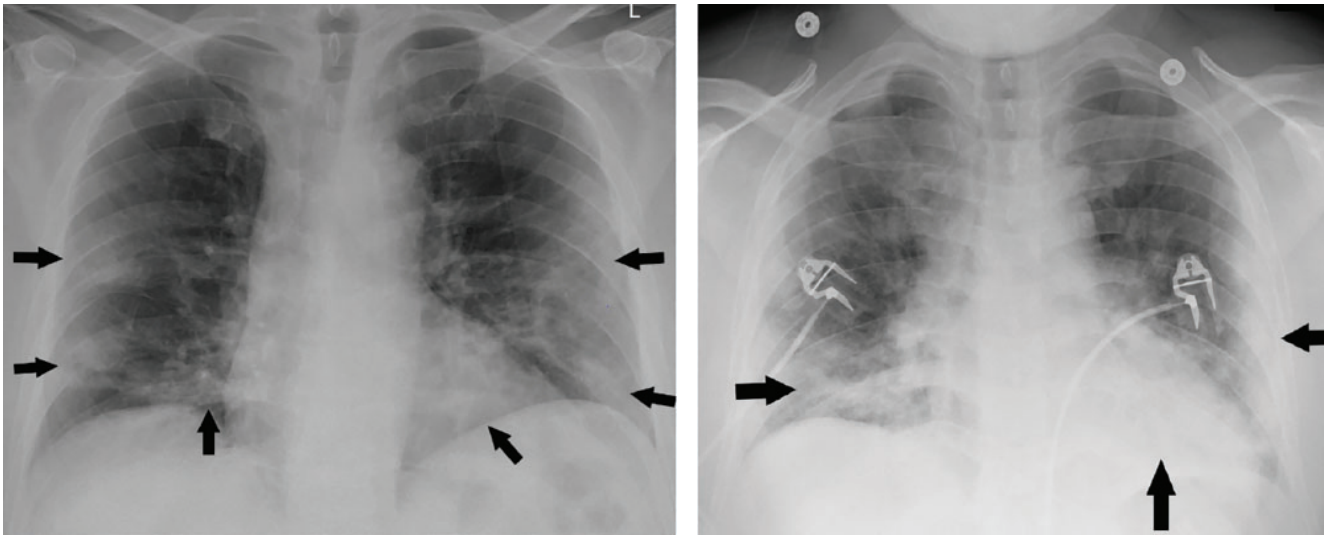

Figure 1. Portable chest radiographs of a patients with COVID-19 demonstrating classic bilateral, multifocal peripheral airspace opacities in the mid-lower-lung zones.

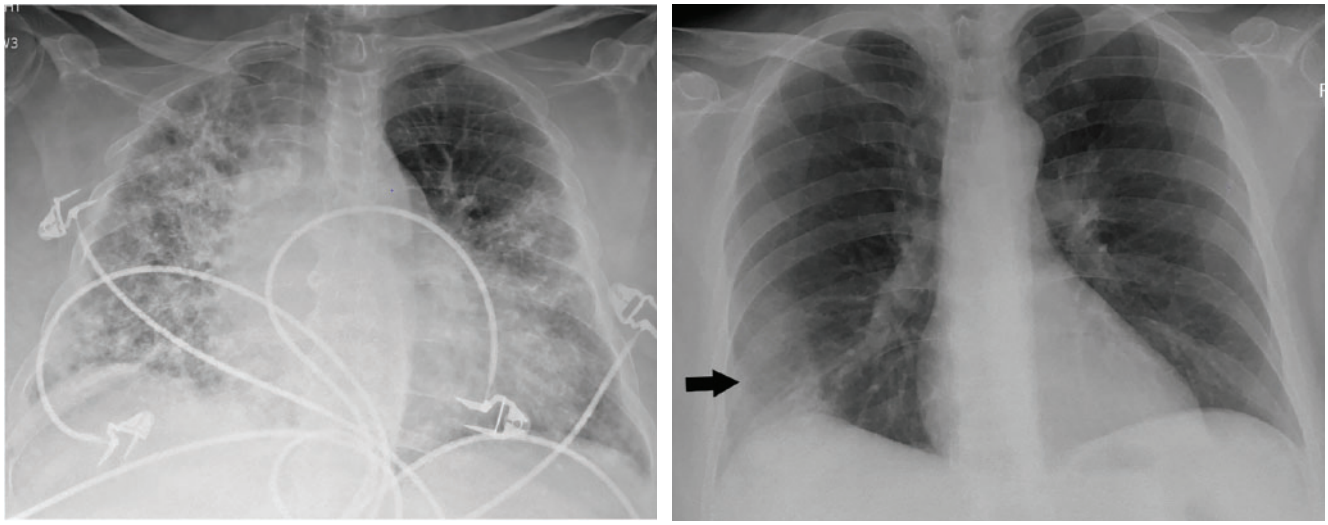

Figure 2. Portable chest radiographs of patients with COVID-19 demonstrating atypical features of diffuse bilateral interstitial changes (A) and unilateral consolidation (B).

than initial reverse transcriptase polymerase chain reaction (RT-PCR) testing (91%).[1]

RADIOGRAPHY 'THROUGH GLASS' TO AVOID SPREADING THE VIRUS

During the pandemic, our hospital (as well as many others in the United States) has employed a method of obtaining portable radiographs in cases of confirmed or suspected COVID-19 through the glass wall of the patient's room in the intensive care unit and in the emergency department. With some minor technical modifications, the chest radiographs taken "through glass" are comparable to those obtained by the standard method (**Figure 4**). This technique has the potential to reduce the consumption of personal protective equipment by radiology technicians and to reduce the risk of machine contamination.[2]

COMPUTED TOMOGRAPHY IN COVID-19

Features of COVID-19 pneumonia on CT are not pathognomonic and are similar to those

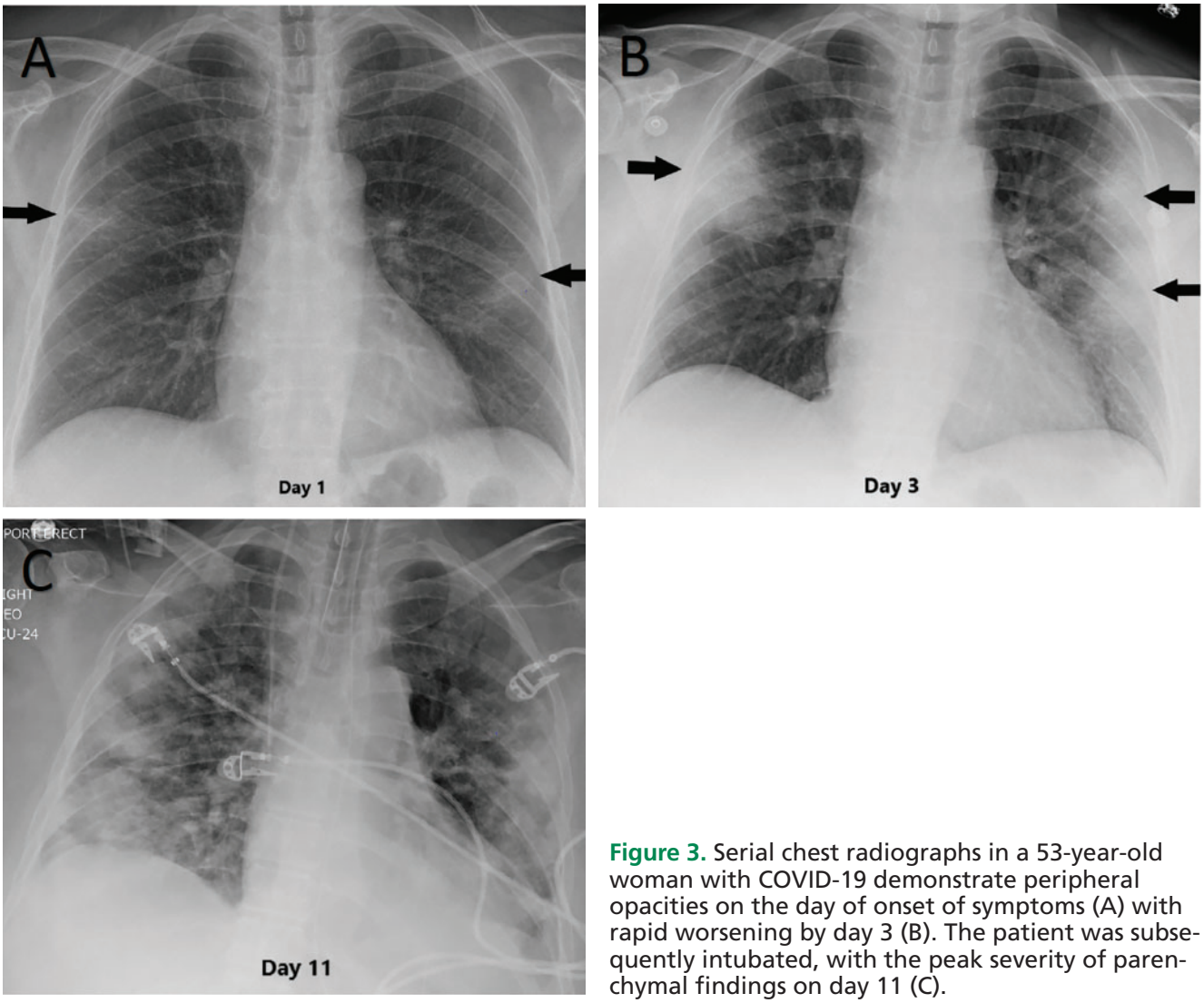

Figure 3. Serial chest radiographs in a 53-year-old woman with COVID-19 demonstrate peripheral opacities on the day of onset of symptoms (A) with rapid worsening by day 3 (B). The patient was subsequently intubated, with the peak severity of parenchymal findings on day 11 (C).

of pneumonia caused by other coronaviruses such as SARS and MERS, as well as other bacterial and viral infections, most notably influenza pneumonia. Moreover, noninfectious etiologies such as drug toxicities and connective tissue disease may produce similar imaging findings. Hence, integration of the clinical presentation, exposure history, prevalence of COVID-19 in the community, and personal risk factors are of paramount importance in suspecting and making the diagnosis.

The most characteristic CT findings of COVID-19 pneumonia are ground-glass opacities with or without consolidation and superimposed interlobular septal thickening (crazy-paving appearance). A reverse halo (central ground-glass opacities with an interrupted peripheral rim of consolidation) has also been described, especially in the later stages of the disease. These lung opacities are frequently bilateral, multilobar, posterior, peripheral, and basilar in distribution and often rounded in morphology (**Figure 5**).[3–9]

Over time, the ground-glass opacities may worsen, with progressive consolidation and more lobes involved. The severity of the CT findings peaks 10 to 12 days after the onset of symptoms.[5] A subset of hospitalized patients with COVID-19 (16.1% in one series) develop extensive lung disease with acute respiratory distress syndrome (ARDS).[10] **Table 1** summarizes the CT findings in the different

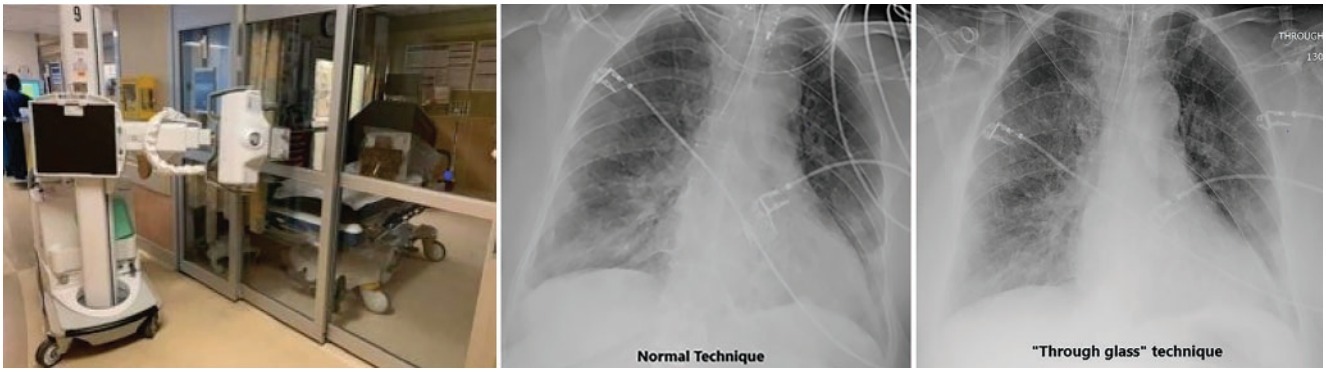

Figure 4. (Left) Setup for obtaining chest radiographs through the glass wall of the room of a patient with suspected or confirmed COVID-19. (Middle) A radiograph obtained in the conventional manner. (Right) A radiograph obtained through the glass.

Chest radiography is considered an appropriate initial diagnostic imaging test for most patients

stages of COVID-19, including recovery (**Figure 6**).[5,11–14]

Gattinoni et al[15] describe 2 different phenotypes in patients with COVID-19: type L, characterized by **l**ow elastance, **l**ow ventilation-to-perfusion ratio, **l**ow lung weight, low recruitability, and CT findings of subpleural opacities; and type H, characterized by **h**igh elastance, **h**igh ventilation-to-perfusion ratio, **h**igh lung weight, **h**igh recruitability, and CT findings of ARDS. Understanding the different pathophysiology is crucial for appropriate patient management.

Thrombotic complications (pulmonary embolism, deep vein thrombosis, ischemic cerebrovascular accident, and myocardial infarction) have emerged as important sequelae that contribute to morbidity and mortality in COVID-19 patients. There is an increased incidence of pulmonary embolism in patients with confirmed COVID-19 disease (**Figure 7**), with rates ranging from 23% to 37% in the recent literature.[16–18] One of the studies[19] showed that body mass index greater than 30 kg/m^2, increase in D-dimer greater than 6 µg/mL, and history of hypertension or prior pulmonary embolism were associated with increased risk of pulmonary embolism in COVID-19.

Twenty percent of COVID-19 patients may have coexistent infections complicating the characterization of imaging observations.[20] Hence, the radiologist has to determine whether or not these findings are part of the same process or are unrelated.[20]

As with most other viral pneumonias, features not typically seen in COVID-19 include pleural effusion, lymphadenopathy, cavitation, and small discreet nodules (including centrilobular or tree-in-bud opacities).[21,22]

THE RADIOLOGICAL SOCIETY OF NORTH AMERICA CONSENSUS STATEMENT

The Radiological Society of North America (RSNA) published a consensus statement in March 2020 on standardized reporting of CT findings related to COVID-19. It had several goals, including to reduce uncertainty and variability in reporting findings potentially attributable to COVID-19, and to enhance the referring providers' understanding of common radiographic findings.[23]

Typical features, according to the RSNA report, are lower-lobe-predominant, peripheral-predominant, multiple, bilateral foci of rounded ground-glass opacities with or without crazy paving, peripheral consolidation, and a reverse halo perilobular pattern (seen later in the disease).

Indeterminate features are absence of typical features and the presence of multifocal, diffuse, perihilar, or unilateral ground-glass opacities with or without consolidation, lacking a specific distribution and that are nonrounded or nonperipheral. Another: few very small ground-glass opacities with a nonrounded and nonperipheral distribution.

Atypical features are absence of typical or indeterminate features and the presence of isolated lobar or segmental consolidation without ground-glass opacities, discrete small nodules (centrilobular, tree-in-bud), lung cavitation, or smooth interlobular septal thicken-

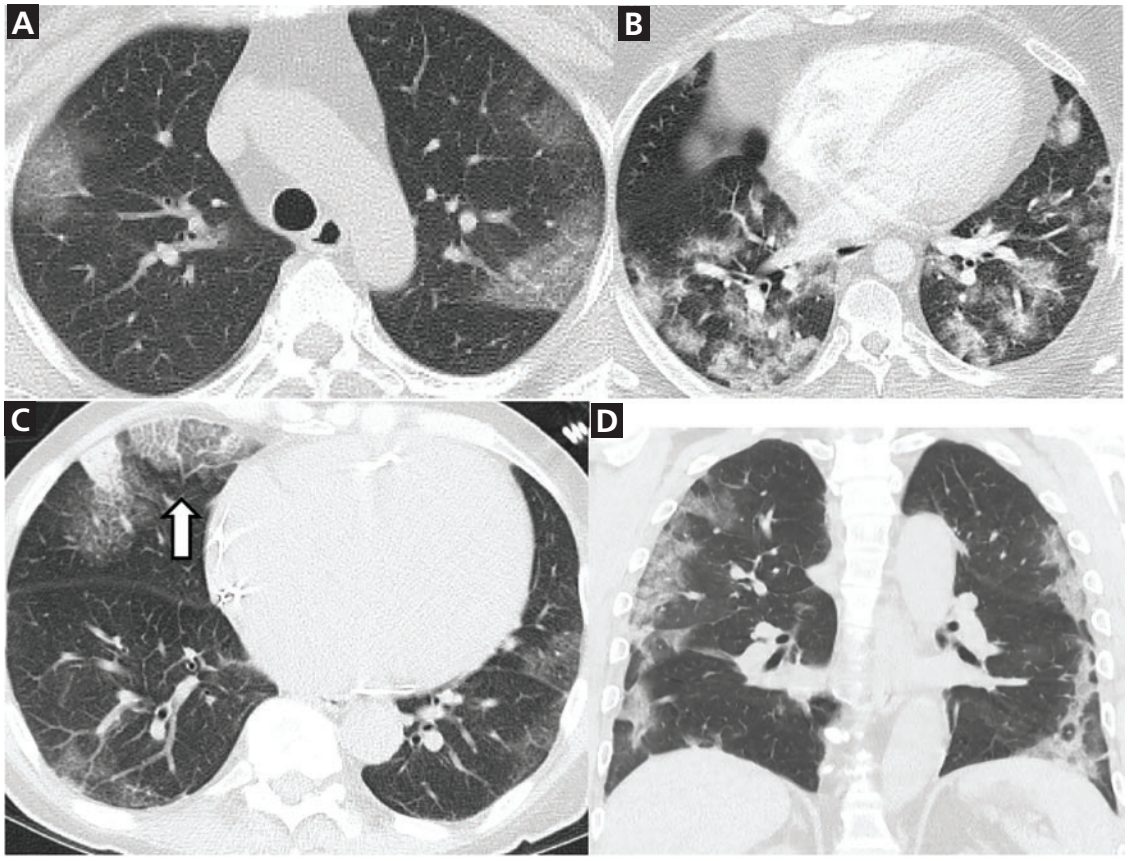

Figure 5. Typical computed tomographic features of COVID-19. Unenhanced axial images of the lungs of 4 different patients with COVID-19 demonstrate bilateral, multifocal, peripheral ground-glass opacities, and consolidation, most with rounded morphology. "Crazy paving" (ground-glass opacities with superimposed interlobular septal thickening and intralobular lines) is seen in (C) (white arrow).

ing with pleural effusion.

Caveats. The statement advises including cautionary language in radiographic reports. If typical features of COVID-19 are present, for example, the statement advises mentioning that other processes can also cause a similar imaging pattern. If indeterminate features are seen, the statement points out that these features are nonspecific. Even if no findings are present to indicate pneumonia, it notes that CT may be negative in the early stages of COVID-19.

ROLE OF CT IN COVID-19

The sensitivity of chest CT in detecting COVID-19 pneumonia has been reported to be 97%, the specificity 25% to 56%, and the accuracy 68% to 72%.[9,21,24,25] CT findings may be negative in 20% to 25% of patients early in the course of the disease. Hence, a normal chest CT scan cannot exclude the diagnosis of COVID-19, especially early after the onset of symptoms.[25] CT has been reported to become abnormal in more than 95% of cases after 5 to 6 days of infection.

The available literature suggests that CT imaging may be helpful in early detection of pneumonia in patients in whom COVID-19 is strongly suspected but who have an initial false-negative RT-PCR screening test.[21,26,27]

Chest radiography has a high false-negative rate, especially in the early stage of infection

CURRENT RECOMMENDATIONS

Most radiology professional organizations and societies as well as the US Centers for Disease Control and Prevention currently recommend against performing routine screening CT to diagnose or exclude COVID-19.[23,28]

TABLE 1

Stages of COVID-19 on chest CT

Early stage (0–2 days)

Approximately 50% of patients have negative chest CT

The remaining have ground-glass opacities (44%) and consolidation (17%), more often unilateral

The less pulmonary consolidation identified on CT, the greater the probability of initial negative reverse transcriptase polymerase chain reaction results[11]

Intermediate stage (3–5 days)

9% of patients have negative chest CT

88% have ground-glass opacities with or without crazy paving (a sign of progression or peak stage), and 55% have consolidation (bilateral in 76%, peripheral in distribution in 64% with rounded morphology)[12]

Late phase (6–12 days)

Most patients have positive CT findings

Progressive consolidation, evolving linear consolidation, and organizing pneumonia

Reverse-halo appearance (a sign of healing or evolving lesion)[12]

Ground-glass opacities in 88% with or without crazy paving

Severe phase

Massive pulmonary consolidation and "white lungs"

Recovery phase

Parenchymal abnormalities resolve with residual linear opacities (**Figure 6**)

Based on information from references 5 and 11–14.

CT is commonly indicated for hospitalized, symptomatic patients with worsening respiratory status or in patients with moderate to severe features of COVID-19 regardless of the COVID-19 test results.[23,28] The societies also suggest that hospitals consider deploying portable radiography units in ambulatory care facilities for use when chest radiographs are considered medically necessary. The surfaces of these machines can be easily cleaned, avoiding the need to bring patients into radiography rooms.

FLEISCHNER SOCIETY STATEMENT

In a multinational consensus statement, the Fleischner Society states that in a resource-constrained environment (in which personal protective equipment or COVID-19 testing may not be available), imaging is indicated for medical triage of patients with suspected COVID-19 who present with moderate to severe clinical features and a high pretest probability of the disease.[28]

The report further states that imaging is not routinely indicated as a screening test for COVID-19 in patients without symptoms, nor for patients with mild features of COVID-19 unless they are at risk for disease progression. Imaging is indicated for patients with moderate to severe features of COVID-19 regardless of the COVID-19 test results, and for patients with COVID-19 and evidence of worsening respiratory status. In a resource-constrained environment where access to CT is limited, chest radiography may be preferred for patients with COVID-19 unless features of respiratory worsening warrant the use of CT.

Daily chest radiographs are not indicated in stable intubated patients with COVID-19. CT is indicated in patients with functional impairment or hypoxemia after recovery from COVID-19. And COVID-19 testing is indicated in patients incidentally found to have findings suggestive of COVID-19 on a CT scan.[28]

All patients undergoing imaging should be masked.[29] Appropriate infection-control procedures should be followed before scanning subsequent patients.[23]

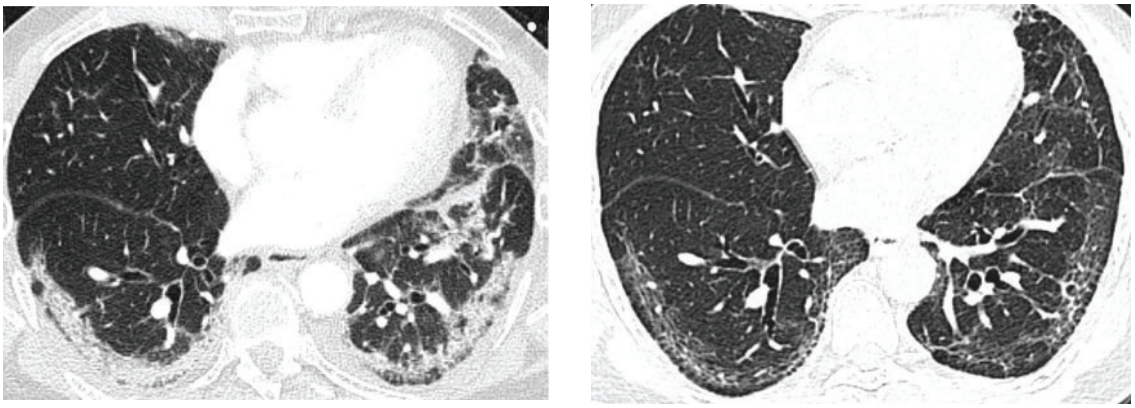

Figure 6. CT scans in a 73-year-old man with COVID-19 demonstrate resolution of subpleural consolidation with residual reticular and fibrotic changes.

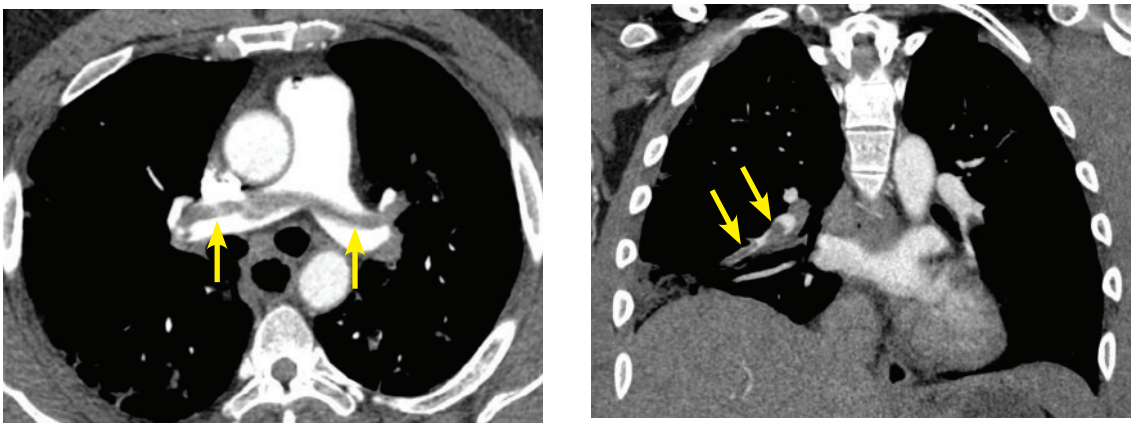

Figure 7. CT images of 2 different patients with COVID-19 demonstrating pulmonary embolism.

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CORRECTION

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

The article in the June 2020 issue by Wu S, Coombs DM, Gurunian R (Liposuction: Concepts, safety, and techniques in body-contouring surgery. Cleve Clin J Med 2020: 87 (6); 367–375; doi: 10.3949/ccjm.87a.19097) contained an omission. The article included photographs of 2 nude patients. The male patient's genitals were covered, while the female patient's were not. The photographs have been modified accordingly in the online version of the article. We apologize for this oversight.

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Acute dacryocystitis

A 57-year-old woman presented with swelling, pain, and redness over the left eye for the past 2 days. She reported no history of trauma or fever. Examination revealed a diffuse, tender, warm swelling over the left medial canthus with purulent discharge at the inferior punctum, conjunctival injection, and swelling of the eyelids (**Figure 1**). A diagnosis of acute dacryocystitis with preseptal cellulitis was made, and she was started on intravenous amoxicillin-clavulanic acid, analgesics, and topical heat application. Endoscopic intranasal drainage of the sac was performed. She recovered completely and was asymptomatic at follow-up 2 months later.

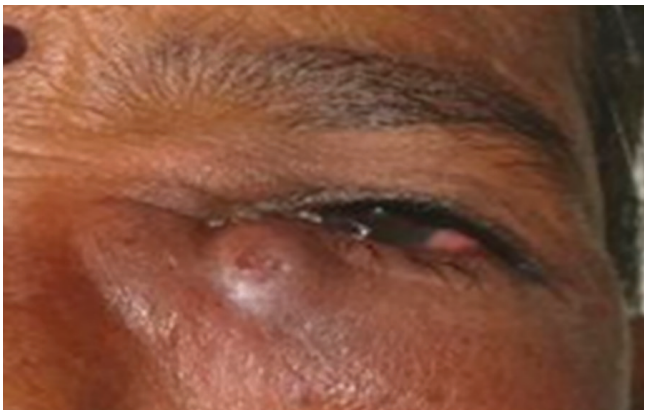

Figure 1. Diffuse swelling of the left medial canthus and eyelids.

ACUTE DACRYOCYSTITIS

Acute dacryocystitis is inflammation of the lacrimal sac. Common implicated causative organisms are *Staphylococcus* species, beta-hemolytic streptococci, pneumococci, and *Haemophilus influenzae*.[1] Its pathogenesis is related to blockage of the nasolacrimal duct, which is either primary or secondary to trauma, infection, neoplasm, or an intranasal pathology such as deviated nasal septum or rhinitis.[1] The obstruction results in stasis of secretions in the sac, leading to infection.

Patients present with the sudden onset of redness, swelling, and pain in the medial part of the orbit. Extension of the swelling around the eye and conjunctival injection implies the development of preseptal cellulitis.[2] Complications, more commonly occurring in children, include eyelid necrosis, orbital cellulitis, orbital abscess, and vision loss.[2] Proptosis, pain with moving the eye, and ophthalmoplegia suggest orbital cellulitis.

The differential diagnosis includes acute ethmoid sinusitis, lacrimal sac or sinonasal tumor, and infected sebaceous cyst. Diagnosis is aided by contrast-enhanced computed tomography, which helps define the extent of infection, differentiates between preseptal and orbital cellulitis, and detects associated pathology in the sinuses and surrounding structures. However, imaging was not necessary in this patient because her clinical symptoms and signs confirmed the diagnosis.

Treatment includes antibiotics (eg, amoxicillin, ciprofloxacin, clindamycin) and drainage of the abscess. The route of administration of antibiotic depends on the severity of the infection, with an intravenous route preferred in the presence of complications.

Traditionally, dacryocystorhinostomy is delayed until after the acute phase is over. But studies have shown that early endoscopic dacryocystorhinostomy is safe and reduces the duration of cellulitis.[3]

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Scurvy: Old, but still relevant

A patient with alcohol use disorder presented with fatigue, dyspnea, and bruising

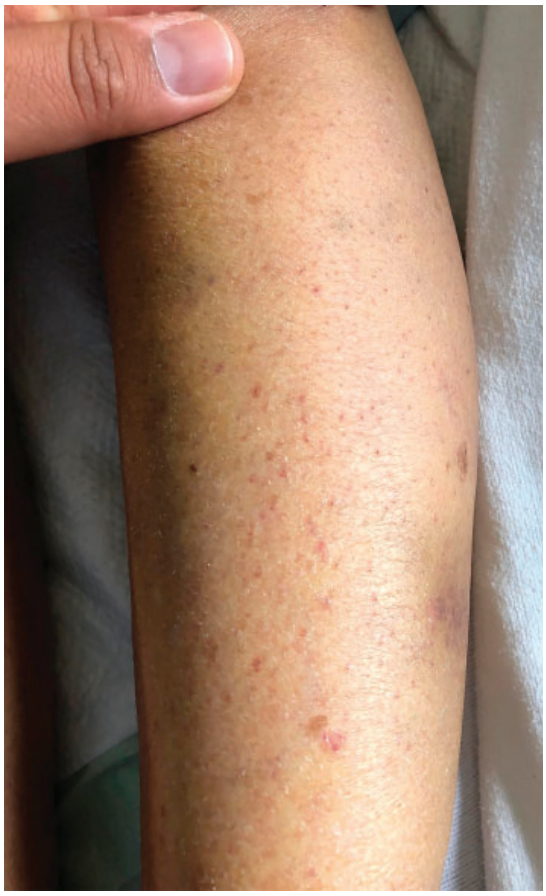

Figure 1. Perifollicular hemorrhage involving the anterior aspect of the lower left leg.

A 54-year-old woman with alcohol use disorder presented to the emergency department with a 3-week history of progressively worsening fatigue, dyspnea on exertion, and easy bruising. She initially noticed a fingertip-size bruise on the right thigh that rapidly enlarged to involve both thighs, calves, and ankles.

She reported poor appetite, substantial weight loss, and inadequate nutrition with intentional avoidance of vegetables, fruits, and red meat for over a year. She had no history of causes of bruising, including use of oral anticoagulants or antiplatelet medications.

She appeared malnourished and frail. Her body weight was 94 lb. Physical examination revealed a cutaneous perifollicular hemorrhage, petechiae, and a large area of ecchymosis involving the thighs, calves, and ankles that was notably tender to palpation (**Figures 1–3**).

Laboratory testing results were significant for a hemoglobin concentration of 6.2 g/dL (reference range 12–16), mean corpuscular volume 84.5 (81–98), serum iron 14 µg/dL (37–145), iron saturation 5% (20%–50%), ferritin 90 ng/mL (13–150), soluble transferrin receptor–ferritin index 1.73 (> 1.4 has more than 90% sensitivity and specificity for the diagnosis of iron deficiency anemia), thiamine 47 nmol/L (70–180), 25-hydroxyvitamin D 15 ng/mL (> 30), and vitamin C less than 0.1 mg/dL (0.4–2). Platelet count, coagulation studies, and vitamin B_{12} and folate levels were normal. Fecal occult blood testing was negative. A clinical diagnosis of scurvy was established based on the history of a severely restricted diet, low serum vitamin C level, and resolution of physical findings after initiating oral vitamin C replacement.

High-dose oral vitamin C was administered and a vitamin C-rich diet was prescribed, leading to resolution of her symptoms and physical findings within 10 weeks. Iron, thiamine, and vitamin D were also supplemented.

THE CHANGING FACE OF THE SCURVY PATIENT

Scurvy, described as early as 1500 BCE,[1] results from severe dietary deficiency of L-ascorbic acid (vitamin C), a cofactor that humans must acquire from exogenous resources, primarily from

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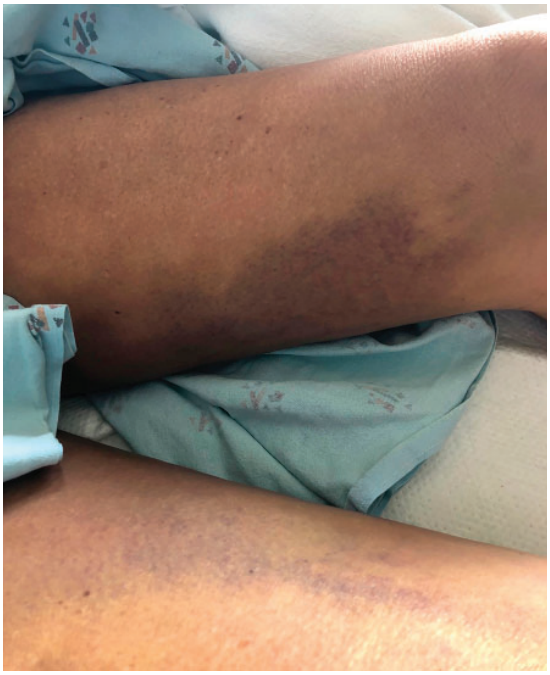

Figure 2. Ecchymosis involving the medial aspect of both thighs.

fruits and vegetables. It is well documented in the literature that sailors who spent months at sea could avoid scurvy by consuming a diet rich in vegetables and fruits.[2]

Ascorbic acid is a cofactor for lysyl hydroxylase, an enzyme essential in hydroxylation of proline and lysine residues in the cross-link formation of collagen. It is also essential for iron absorption. In its absence, assembly of the collagen triple helix is incomplete, rendering collagen-dependent structures such as blood vessels unstable, leading to hemorrhagic manifestations and poor wound healing.[3]

Scurvy is now only rarely encountered in the United States. Risk factors include alcohol use disorder, malnutrition, malabsorption, cigarette use, and psychiatric disorders. Signs and symptoms tend to manifest when the body's vitamin C stores drop below 300 mg. This can occur within as few as 1 to 3 months of absence of vitamin C from the diet.[4]

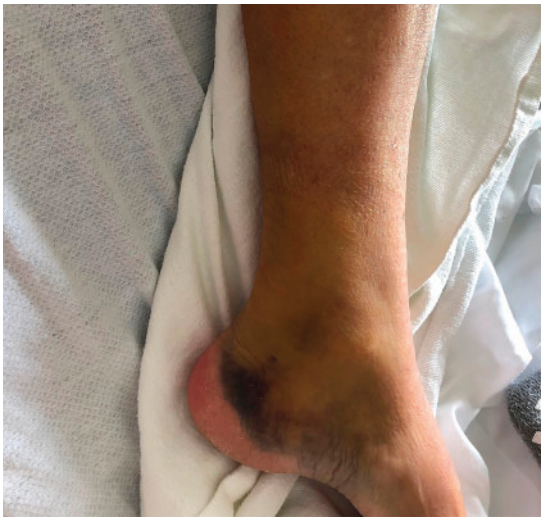

Figure 3. Atraumatic ecchymosis involving the left ankle area.

Clinical manifestations of scurvy can be divided into an early phase, characterized by nonspecific symptoms such as fatigue, malaise, and loss of appetite, and a late phase, with impaired wound healing, gingival bleeding, lower-extremity petechiae, and ecchymosis, along with symptoms secondary to tissue hemorrhage including bone pain and pseudoparalysis.[5]

The diagnosis of scurvy is primarily based on the history and physical examination,[6] and is confirmed with undetectable vitamin C serum levels. Iron deficiency anemia and multivitamin deficiency often occur concurrently. Clinicians should have a high index of suspicion for scurvy in the patient with alcohol use disorder who presents with poor nutritional history, extensive bruising, and iron deficiency anemia. ■

Her signs and symptoms resolved within 10 weeks of vitamin C therapy

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ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Should we monitor troponin up to peak value when evaluating for acute coronary syndrome?

A: No. Once the cardiac troponin concentration is higher than the 99th percentile (the upper reference limit), finding the peak value (before levels start to descend) does not help diagnose the cause of the elevation. Although the peak level has prognostic significance, continuing to follow the level after the initial set of measurements adds cost to the evaluation without providing further insight into cause, and any prognostic information gained would not change the subsequent evaluation or management, which should be driven by guidelines.[1]

See related editorial, page 483

Once troponin is over the 99th percentile, finding the peak value does not aid diagnosis

DEFINITIONS

Standard practice in evaluating for possible acute coronary syndrome includes following serial cardiac troponin levels.

The Fourth Universal Definition of Acute Myocardial Infarction calls cardiac troponin levels above the 99th percentile *myocardial injury*, which is considered acute if the level rises or falls (or both).[2] *Acute myocardial infarction* requires acute myocardial injury plus signs or symptoms of acute myocardial ischemia or other findings. There are 5 types of myocardial infarction; here, we are mainly concerned with type 1 (caused by acute coronary occlusion) and type 2 (caused by an acute imbalance of oxygen supply and demand).

DISTINGUISHING THE CAUSE OF TROPONIN ELEVATION

In the workup of acute coronary syndrome, cardiac troponin levels may be elevated, but keep in mind that they can be elevated in many conditions other than type 1 myocardial infarction.

Type 1 vs type 2 myocardial infarction

Distinguishing type 1 from type 2 acute myocardial infarction is important but challenging. No clinical criteria exist to reliably tell them apart,[3] and unfortunately, cardiac troponin levels (whether initial, peak, or the trend over time) cannot help to do so either.[4] The delta value (ie, the change in cardiac troponin level in a defined time period) has been studied for this purpose; although the absolute change is more reflective of the different types of myocardial infarction than the percent change, neither can reliably distinguish between them.[4,5]

Other causes of troponin elevation

Cardiac troponin levels can be elevated in other conditions that commonly arise in medically complex patients, eg, sepsis, acute stroke, respiratory failure, hypertensive crisis, or with some chemotherapy regimens.[6] In some diseases, such as heart failure and chronic kidney disease, levels may be persistently elevated. Hence, trying to find a peak value in a patient with persistently elevated levels may be futile and is an inappropriate use of this biomarker.

DOES TROPONIN PREDICT ADVERSE EVENTS?

The degree of cardiac troponin elevation in myocardial infarction can indicate the extent of myocardial damage and help predict ad-

Dr. Apple has disclosed membership on advisory committees, review panels, or board of directors for Brava Diagnostics, HyTest, Instrumentation Laboratory, and Siemens.

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verse events.[7,8] Treatment decisions, however, should not be based on degree of elevation alone. Rather, patients should be managed with guideline-directed medical therapies, procedures, and education,[1] regardless of the degree of troponin elevation.

All patients who are diagnosed with acute coronary syndrome with elevated cardiac troponin should undergo echocardiography, which provides prognostic information similar to that of the peak troponin value, obviating the need to follow troponin levels until they peak.[9]

After acute coronary syndrome is diagnosed, and especially if confirmed with angiography, further troponin testing may confuse the clinical picture. Studies have found that although cardiac troponin levels rise after angiography or percutaneous coronary intervention, the increase is not associated with adverse events.[10]

IF SYMPTOMS RECUR

Cardiac troponin levels are often elevated in hospitalized patients experiencing recurrent symptoms after a myocardial infarction.[11] In this situation, the patient should be managed on the basis of ischemic symptoms, echocardiographic changes, and hemodynamic status rather than on the elevated troponin alone. Troponin rises with reinfarction, but for the initial evaluation, monitoring levels to a peak will not lead to differences in management, rendering it unnecessary in this context.

TESTING INCREASES COSTS

Chest pain is one of the most common presentations in the emergency department, and costs run high for its evaluation.[12] After the first set of cardiac troponin levels has been obtained, additional measurements (including prolonged monitoring until a peak occurs) do not add useful or reliable information to the workup or change the treatment plan. Excessive troponin testing also leads to unnecessary cost, increased length of stay, and further blood draws.[13]

Addressing the issue of inappropriate troponin monitoring will help reduce unnecessary resource utilization at both the individual provider and systems levels. Love et al,[14] in a study analyzing electronic medical record requests over 2 months, found that providers overrode a best practice alert (that recommended not conducting unwarranted cardiac troponin testing) 97% of the time. Further education and collaboration between emergency medicine and laboratory medicine physicians and clinical chemists is recommended to help limit overuse and misinterpretation of cardiac troponin testing.[15]

NEW TESTS DO NOT CHANGE THE MESSAGE

New troponin assays are becoming more sensitive; in practice this means that elevated values will likely be detected much sooner. Although these assays are sometimes called "high-sensitivity," their characteristics vary, and what high sensitivity means is not clearly defined in current guidelines.

The potential for overtesting remains if providers continue to follow cardiac troponin levels after the rising or falling pattern has become apparent, particularly when a diagnosis has already been made.

After acute coronary syndrome is diagnosed, further testing may confuse the clinical picture

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EDITORIAL

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Cardiac troponin testing: Goodbye, 'troponinemia'

The way we stratify risk for patients with chest pain suspected to arise from an acute coronary syndrome has rapidly evolved, thanks to higher cardiac troponin assay precision and sensitivity.[1,2] Because fewer than 10% of patients in whom acute coronary syndrome is suspected actually have a myocardial infarction,[3] algorithms using high-sensitivity assays have the potential to improve triage and reduce the costs associated with unnecessary hospital admissions and longer emergency department observation. The 2019 Fourth Universal Definition of Myocardial Infarction recommends using high-sensitivity cardiac troponin assays and has proposed criteria for further classifying patients with myocardial injury vs infarction.[4]

See related article, page 480

In this issue, Anderson and colleagues[5] advocate against continuing to measure serial cardiac troponin levels after the diagnosis of acute coronary syndrome is established. Doing so lacks clinical utility and results in significant waste without improving patient care. We wholeheartedly agree with their plea.

The COMPASS-MI project (Calculation of Myocardial Infarction Risk Probabilities to Manage Patients With Suspicion of Myocardial Infarction)[6] examined cardiovascular risk assessment based on cardiac troponin concentration, change in troponin level, and timing of resampling. Patients deemed to be at high risk based on their troponin level and absolute change during serial sampling had a significantly higher incidence of myocardial infarction and death. Of note, this determination was made using a 2-sample strategy, with the second sample obtained either early (45–120 minutes) or late (> 120–210 minutes) after the baseline sample.

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THREE CLINICAL BUCKETS

Measuring cardiac troponin twice (at baseline and then either 1 hour or 3 hours later, using a high-sensitivity assay) enables clinicians to place most patients with chest pain into 1 of 3 clinical "buckets."

Not acute coronary syndrome. Most patients fall into this category, having normal troponin levels, no increase in troponin level, and no other criteria for acute coronary syndrome. With the diagnosis ruled out, they can be safely discharged from the emergency department with minimal risk of acute ischemic complications or death. However, it is critical that other life-threatening causes of chest pain such as acute aortic dissection, pulmonary embolism, and pneumothorax be considered before this determination is made.

Any troponin elevation is prognostically important, regardless of the etiology

Definite acute coronary syndrome. At the other extreme, a minority of patients present with either established ST-elevation myocardial infarction on electrocardiography or marked elevations in troponin, which rules them in for significant acute myocardial injury. The higher the troponin level, the more likely ischemia or myocarditis is the cause of the chest pain, and admission would be warranted regardless of underlying mechanism.

Possible acute coronary syndrome. The challenge for a clinician is when troponin levels are in the intermediate range and the cause and nature of the elevation are uncertain. In particular, is the cause type 1 myocar-

dial infarction (due to arterial occlusion), or is it type 2 (due to supply-demand mismatch), and is it an acute or a chronic injury? And the optimal strategy for further evaluation is not well defined.

Sometimes trivialized with the terms "troponinemia" or "troponinitis," troponin elevation that is not obviously associated with a diagnosis should not be dismissed as clinically irrelevant. To establish a diagnosis and determine further care, the clinical presentation and troponin findings must be integrated, and a judgment on the mechanism of myocardial injury must be made. However, further serial troponin testing is unlikely to benefit this group.

The High-STEACS trial (High-Sensitivity Troponin in the Evaluation of Patients With Suspected Acute Coronary Syndrome)[7] assessed whether implementing high-sensitivity cardiac troponin testing and the recommendations of the Universal Definition of Myocardial Infarction led to changes in investigation, treatment, and outcomes in patients stratified according to the proposed diagnostic classification. The strategy led to increases in the diagnosis of type 1 myocardial infarction, type 2 myocardial infarction, and acute and chronic myocardial injury. Unfortunately, although the strategy "identified patients at high risk of cardiovascular and noncardiovascular events [it was] not associated with consistent increases in treatment or improved outcomes."[7] The investigators concluded by calling for trials of secondary prevention to determine whether this risk is modifiable in patients without type 1 myocardial infarction.

In conclusion, a 2-sample algorithm for high-sensitivity cardiac troponin testing is a powerful and rapidly evolving tool for determining risk of future cardiovascular events and all-cause mortality. It has introduced an important shift not only in understanding the degree and trend of troponin elevation, but also in acknowledging that any elevation is prognostically important regardless of the etiology. Dismissing troponin elevations as "troponinemia" no longer appears to be a viable strategy, and appropriate attention is needed to best assess cardiovascular and noncardiovascular risk. ■

Dismissing elevations as 'troponinemia' is no longer a viable strategy

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Rhinosinusitis and the role of imaging

ABSTRACT

Acute, uncomplicated rhinosinusitis is a clinical diagnosis. Imaging should only be used in the case of complicated sinus infections, recurrent or chronic sinus disease, or in surgical planning. The authors discuss key features of complicated and uncomplicated rhinosinusitis, management, and recommendations on the use of imaging in diagnosis.

KEY POINTS

When not clinically indicated, imaging increases healthcare costs and may expose patients to radiation and intravenous contrast unnecessarily.

Imaging in the setting of acute uncomplicated rhinosinusitis has not been shown to change clinical outcomes.

Computed tomography without contrast enhancement is the gold standard for sinus imaging when complications of rhinosinusitis are suspected.

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A 31-YEAR-OLD WOMAN presents to the outpatient clinic for evaluation of 2 weeks of nasal congestion and drainage, headache, and facial pressure. Her symptoms were mild at onset and seemed to improve over a few days, but then again worsened, and she has developed purulent nasal discharge. She is a smoker.

On clinical examination, she is afebrile, with mucosal edema and turbinate hypertrophy seen on anterior rhinoscopy. Based on her clinical presentation, she is suspected to have acute bacterial rhinosinusitis. Is imaging necessary to confirm this diagnosis?

RHINOSINUSITIS: AN OVERVIEW

Rhinosinusitis, the symptomatic inflammation of the nasal cavity and sinuses,[1] can be divided into rhinitis and sinusitis, yet the two terms are often combined because the nasal mucosa and sinus mucosa are often inflamed synchronously.[2] It is one of the most commonly treated conditions in ambulatory care, but the presentation is often similar to that of other upper respiratory tract infections, and accurate diagnosis is difficult.[3] Symptoms commonly include nasal drainage, nasal obstruction, and facial pain or pressure. Other symptoms can include fever, headache, cough, ear pain or pressure, and anosmia.[4]

The diagnosis is generally based on symptoms and their duration.[1] Acute rhinosinusitis is defined as up to 4 weeks of purulent nasal drainage accompanied by "nasal obstruction, facial pain-pressure-fullness, or both."[1] In most cases, symptoms resolve in 7 to 10 days. Rhinosinusitis is subacute if symptoms persist beyond 4 weeks and less than 12 weeks, and chronic when symptoms last more than 12 weeks with objective evidence of mucosal inflammation

TABLE 1

Rhinosinusitis: Types and features

	Clinical features	Acute vs chronic	Complications
Viral	Symptoms improve Duration < 10 days		
Bacterial	Symptoms persist > 10 days "Double sickening": symptoms improve, then worsen High fever, then worsening symptoms	Acute: < 4 weeks Subacute: 4–12 weeks Chronic: > 12 weeks Recurrent: 4 or more episodes	Uncomplicated: contained in nasal cavity and sinuses Complicated: spread to orbit, nervous system, surrounding structures
Fungal	Seen in immunosuppression, chronic steroid use, diabetes mellitus	Acute: < 4 weeks Chronic: > 4 weeks	Noninvasive: contained within sinuses Invasive: spread beyond sinuses
Allergic	Predominance of sneezing, rhinorrhea, nasal congestion and itching		Chronic rhinosinusitis

visualized endoscopically or radiographically. Chronic rhinosinusitis may present with or without nasal polyps.[1]

Recurrent rhinosinusitis is defined as 4 or more episodes of acute rhinosinusitis per year with no symptoms between episodes.[1]

INFECTIOUS VS NONINFECTIOUS

Rhinosinusitis is generally a clinical diagnosis

Rhinosinusitis can be infectious or noninfectious. Infectious rhinosinusitis is classified as viral, bacterial, or fungal (**Table 1**).

Viral rhinosinusitis

Viral infection is the most common cause of rhinosinusitis and is diagnosed clinically when symptoms are present for less than 10 days and do not worsen.[3]

Bacterial rhinosinusitis

Bacterial infections are estimated to account for only 0.5% to 2% of rhinosinusitis cases. The gold standard for the diagnosis of bacterial sinusitis is a bacterial culture of the paranasal sinus cavity obtained by direct sinus aspiration.[5]

Bacterial infection is suspected when symptoms are present for longer than 10 days without signs of clinical improvement, follow a biphasic pattern and initially improve but worsen after 5 to 6 days (referred to as "double sickening"), or are severe and include fever with temperature higher than 39°C (102°F),[3] purulent nasal discharge, or facial pain lasting more than 3 to 4 days.[5,6]

No single symptom is diagnostic of bacterial rhinosinusitis. It is estimated that purulent nasal secretions carry a sensitivity of 0.77 and a specificity of 0.54, double sickening a sensitivity of 0.74 and specificity of 0.41, and nasal congestion or obstruction a sensitivity of 0.83 and specificity of 0.24.[7] In patients with all 3 symptoms of nasal discharge, nasal obstruction, and facial pain persisting longer than 10 days, only 40% to 50% have true bacterial sinusitis.[8]

C-reactive protein testing has been used in addition to signs and symptoms to increase the accuracy of predicting acute bacterial sinusitis, but this has yet to be prospectively validated.[7]

Fungal rhinosinusitis

Fungal rhinosinusitis refers to a wide variety of conditions that can present acutely in severely immunocompromised patients, or chronically in patients with mild immunosuppressive states such as diabetes mellitus or chronic corticosteroid use.[9] It is categorized as acute (less than 4 weeks) or chronic (greater than 4 weeks), and as noninvasive or invasive.

Noninvasive fungal infection includes fungal colonization, fungus ball, and allergic fungal rhinosinusitis.[10] Invasive fungal infections spread beyond the sinuses to involve bone, organs, or other structures.[11]

Infection needs to be distinguished from

fungal colonization, encountered in patients with anatomic abnormalities such as nasal polyps.[9] Fungal infections are also thought to have a role in the development of chronic rhinosinusitis.[10]

Noninfectious rhinosinusitis

Allergic rhinitis—an immune-mediated inflammatory response of the nasal mucous membranes after inhalation of allergens—may be seasonal, perennial, or episodic based on the exposure pattern to the triggering allergen.[12] It is distinguished from infectious rhinosinusitis by the presence and predominance of sneezing, rhinorrhea, nasal congestion, and nasal itching. It is estimated to cause 30% of cases of acute maxillary rhinosinusitis.[2]

In allergic rhinosinusitis, purulent nasal drainage is not typically present, and patients do not have facial pain or pressure.[13]

Migraine headache may also be associated with symptoms of rhinosinusitis, including sinus pressure, sinus pain, nasal congestion, runny nose, watery eyes, and itchy nose. In one study, 88% of patients self-diagnosed or physician-diagnosed with sinus headaches also fulfilled the International Headache Society criteria for migraine with or without aura.[14]

Complications of infectious rhinosinusitis

When rhinosinusitis spreads beyond the nasal cavity and sinuses to involve the orbit, nervous system, or other surrounding structures,[15] complications can include preseptal or orbital cellulitis, abscess formation, meningitis, cavernous sinus thrombosis, and osteomyelitis. Although complications are uncommon, occurring in only 1 in 1,000 cases,[3] they can be life-threatening.[16]

Ocular involvement should be suspected when patients present with ocular pain, eyelid swelling, pain with eye movements, visual changes, or displacement of the globe.[17]

Signs of central nervous system involvement, such as meningitis or intracranial abscess, include altered mental status, headache, nausea, vomiting, and fever.[15] Involvement of the cavernous sinus should be suspected when palsy of cranial nerve III (oculomotor), IV (trochlear), or VI (abducens) is noted.[17]

Patients who present with these symptoms should be promptly evaluated for complicated infections.[15]

MANAGEMENT: GENERAL APPROACHES

When patients present with symptoms of acute rhinosinusitis believed to be uncomplicated based on review of history, observation is recommended for a period of 7 to 10 days,[1,5] with symptomatic treatment including analgesics, intranasal glucocorticoids, intranasal saline irrigation, decongestants, and antihistamines.[1,3,5] Analgesics including acetaminophen and nonsteroidal anti-inflammatory drugs are useful for relief of pain and fever.[3] Intranasal corticosteroids are useful for reducing inflammation of nasal mucosa, thereby facilitating sinus drainage.[1,5]

Glucocorticoids

A 2013 Cochrane review found that patients who received intranasal glucocorticoids were more likely to experience symptomatic improvement compared with placebo, and higher doses brought more symptom relief.[18]

Nasal irrigation

Nasal saline irrigation has been shown to improve mucociliary clearance, but evidence of effectiveness is limited. One randomized controlled trial found that daily use of hypertonic nasal saline irrigation decreased nasal symptoms, but another study found no difference when no symptomatic treatment was compared with a combination of nasal saline irrigation, topical decongestants, and intranasal steroids.[1,3]

Nasal saline irrigation can improve mucociliary clearance, but evidence of effectiveness is limited

Decongestants

Decongestants, including oral and topical forms, are also options for symptom relief in rhinosinusitis. However, oral decongestants are not recommended due to a lack of clinical trials that have studied their effectiveness in acute sinusitis.[3,5]

Xylometazoline nasal spray, a topical decongestant, was shown in 2 small studies to be effective at reducing congestion of sinus and nasal mucosa on imaging studies.[3]

Decongestants should be used with caution and for no longer than 3 to 5 consecutive days to prevent the development of rebound congestion.[1]

Antihistamines

Antihistamines are not recommended for the treatment of acute rhinosinusitis, as there are

no studies to support their effectiveness, and they may worsen congestion by causing excessive dryness of nasal mucosa.[1]

Antimicrobials

Evidence for the use of antimicrobials in acute bacterial sinusitis is weak due to a lack of standardization in diagnosis and duration of symptoms. In addition, 65% of patients thought to have acute bacterial rhinosinusitis treated with placebo improve spontaneously.[5]

Prescribing antibiotics is appropriate in cases of persistent and worsening symptoms. The Infectious Diseases Society of America (IDSA) recommends starting with amoxicillin and clavulanate when the clinical diagnosis of acute bacterial rhinosinusitis is made, and then monitoring for signs of improvement or worsening for 48 to 72 hours after initiation of treatment.[5] In contrast, the American Academy of Otolaryngology–Head and Neck Surgery suggests either antibiotics or a 7-day observation period ("watchful waiting"), with initiation of antibiotics if symptoms worsen or fail to improve during that time.[1]

The addition of clavulanate is recommended to improve the coverage of beta lactamase-producing *Haemophilus influenzae* and *Moraxella catarrhalis*.[3,5] If patients initially treated with amoxicillin with clavulanate do not demonstrate improvement, it is recommended to change antibiotics to either high-dose amoxicillin plus clavulanate, doxycycline, a respiratory fluoroquinolone such as moxifloxacin or levofloxacin, or a dual treatment of clindamycin plus a third-generation oral cephalosporin.[3,5]

Even with findings such as air fluid levels, plain radiography cannot distinguish viral from bacterial infection and so is not recommended

Symptomatic treatments may also be prescribed as adjuncts to antibiotic therapy. The IDSA recommends nasal saline irrigation and intranasal glucocorticoids for acute bacterial rhinosinusitis. Decongestants and antihistamines are not recommended.[5]

In certain cases, consultation with a specialist should be sought. Patients with immunocompromised states, obstructive anatomic defects, recurrent sinusitis, fungal sinusitis, or suspected neoplasm should be evaluated by a specialist. Patients with severe symptoms such as persistent fever with temperature greater than 39°C (102°F), altered mental status, suspected ocular complications such as orbital cellulitis or intraorbital abscess, cavernous sinus thrombosis, or suspected neurologic complications such as meningitis or intracranial abscess should be referred to a specialist.[3] Otolaryngology referral is appropriate for patients who have persistent symptoms despite initial treatment, patients with recurrent or chronic sinusitis, or in patients in whom anatomic abnormalities are suspected.[2] Referral to ophthalmology or neurology for suspected serious ocular or central nervous system involvement may be warranted.

IMAGING OPTIONS

Rhinosinusitis is a clinical diagnosis. Imaging is reserved for cases of complicated rhinosinusitis, recurrent sinusitis, chronic rhinosinusitis, and immunocompromised patients.[4] Imaging findings do not always correlate with symptoms. It is estimated that 3% to 40% of asymptomatic patients may have sinus abnormalities on computed tomography (CT). Thus, imaging should corroborate the presenting signs and symptoms.[19] Indications for imaging are based on the classification of rhinosinusitis[19] (**Figure 1**).

Plain radiography

Plain radiography can detect mucosal thickening, air fluid levels, opacification of the sinuses, anatomic variants, and foreign bodies,[3] but it has poor sensitivity and specificity for sinus disease and thus is not usually recommended.[20]

Computed tomography

CT of the sinuses has become the gold standard for sinus imaging in the case of complicated sinus disease because of improved visualization of sinus anatomy.[4]

Cone-beam CT, a technique that creates 3-dimensional images of bony and soft-tissue structures of the face, is used primarily in dental imaging to evaluate the structures of the face, nasal cavity, and sinuses.[21] It may be useful in the assessment of odontogenic sinusitis and maxillary sinus involvement.[19]

Magnetic resonance imaging

Magnetic resonance imaging (MRI) with and without intravenous contrast may be used to evaluate sinus disease, but it is not often the first imaging test performed.

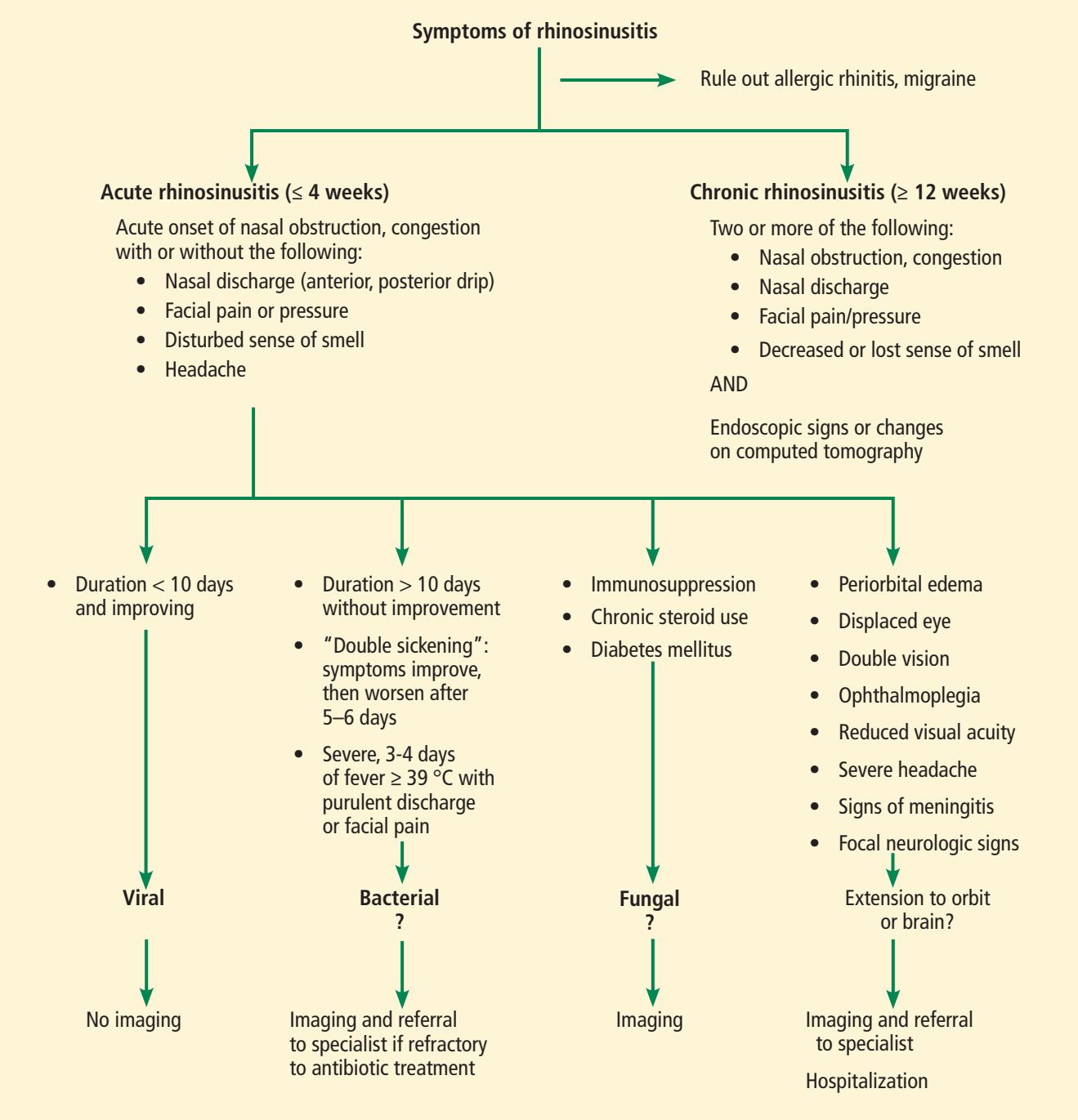

Figure 1. Approach to imaging in rhinosinusitis.

IMAGING IN ACUTE UNCOMPLICATED VIRAL OR BACTERIAL RHINOSINUSITIS

Referring back to our case of the 31-year-old woman, she presented with signs and symptoms consistent with acute, uncomplicated, likely bacterial rhinosinusitis, based on the duration of symptoms and double sickening. Acute, uncomplicated bacterial or viral rhinosinusitis is a clinical diagnosis, and patients who meet diagnostic criteria for uncomplicated rhinosinusitis should not undergo imaging.[4,19,22,23]

Plain radiography in acute uncomplicated bacterial rhinosinusitis carries a sensitivity of

76% and a specificity of 79%.[20] But even in the presence of positive findings such as air fluid levels, plain radiography cannot distinguish between viral and bacterial infections and therefore is not recommended.[3]

In one study, CT of the nasal passages and sinuses performed in otherwise healthy patients who presented with "common cold" symptoms revealed a high prevalence of meatal and sinus findings, including occlusion of the ethmoid infundibulum in 77% of patients, abnormalities of one or both maxillary sinuses in 87%, and ethmoid sinus abnormalities in 65% of patients. On repeat CT 2 weeks later, these findings had resolved or clearly improved in 79% of patients without antibiotic treatment.[24] Thus, CT and MRI are not useful in the context of uncomplicated sinusitis. In addition, CT exposes patients to unnecessary radiation.[4] When complications of rhinosinusitis or spread of infection are suspected, imaging can be considered.[25]

IMAGING IN ACUTE COMPLICATED VIRAL OR BACTERIAL RHINOSINUSITIS

In patients with suspected rhinosinusitis who present with symptoms indicating spread of infection beyond the sinuses and nasal cavity, imaging may be performed for diagnostic purposes.[15]

Findings on CT that suggest sinusitis include thickened mucosa, air fluid levels, and opacification of the sinuses

CT without contrast enhancement is the gold standard of sinus imaging and often the first test performed when complications of rhinosinusitis are suspected, as it affords the best delineation of bone and allows for visualization of bony integrity and erosion. Findings on CT suggestive of sinusitis include thickened mucosa (> 4 mm), air fluid levels, and opacification of the sinuses.[25]

MRI may be indicated when complications such as aggressive intracranial or intraorbital spread of infection or cavernous sinus thrombosis is suspected, and for definition of soft-tissue masses.[19] T1-weighted MRI is recommended to evaluate abscess or extension of infection past the sinuses, and T2-weighted MRI can differentiate inflammatory mucosa from soft-tissue masses. Contrast-enhanced MRI is recommended if cavernous sinus thrombosis is suspected.

When complications involving the orbit or cranium are suspected, the American College of Radiology recommends CT with contrast enhancement or MRI without contrast for evaluation.[19] While the American College of Radiology notes that intravenous contrast is generally not needed, IDSA guidelines recommend contrast-enhanced CT with axial and coronal views in the case of suspected complications.[5]

IMAGING IN RECURRENT ACUTE OR CHRONIC RHINOSINUSITIS

Recurrent acute rhinosinusitis is defined as 4 or more episodes of acute rhinosinusitis per year, with no symptoms of rhinosinusitis between episodes. Chronic rhinosinusitis is symptom duration of more than 12 weeks with objective evidence of mucosal inflammation visualized endoscopically or radiographically.[1] In either case, and in cases of sinonasal polyposis, imaging is warranted for evaluation and operative planning if surgery is warranted.[19]

Noncontrast CT is indicated as part of the workup before any surgical intervention, as it provides the best preoperative information, including delineation of complex anatomy, and may even be used intraoperatively to guide surgery. MRI is not first-line due to lack of bony detail. Cone-beam CT is useful in the assessment of odontogenic sinusitis and maxillary sinus involvement.[19] Plain radiography may reveal foreign bodies or assist in diagnosing anatomic variants, but is not used clinically due to the superiority of CT.

In patients with a history of recurrent or chronic sinusitis who have had imaging in the past, in the absence of new symptoms, imaging does not provide further information and findings often remain unchanged. Repeat imaging is not necessary unless clinical signs or symptoms have changed.[5]

IMAGING IN FUNGAL SINUSITIS

Depending on the type of fungal infection suspected, imaging may be warranted.[19] For saprophytic fungal infestations, which are frequently asymptomatic, the diagnosis is made clinically, and no imaging is required for diagnosis.

Fungus ball, another noninvasive fungal presentation, may be evaluated with CT of

the sinuses or panoramic dental imaging; it appears as hyperattenuated material filling a single sinus.

Allergic fungal rhinosinusitis is the most common form of fungal sinus disease and is evaluated with CT or MRI. Classic findings on CT include the "double-density" sign caused by thick fungal mucin surrounded by hyperplastic mucosa. MRI with T1 and T2 weighting can be used to support the diagnosis.

When invasive acute or chronic fungal infection is suspected, contrast-enhanced CT or contrast-enhanced MRI can be used to visualize the sinuses, brain, and orbits.[9] CT findings of invasive infection can include hypoattenuating mucosal thickening over the affected sinus and nasal cavity, bony erosion, and findings extending beyond the sinus and nasal cavities. MRI is time-consuming to obtain yet favorable for evaluating intracranial and intraorbital spread.[10]

IMAGING IN ALLERGIC RHINITIS

Imaging is not routinely recommended in patients who present with symptoms of allergic rhinitis. When patients present with symptoms of rhinosinusitis (as opposed to rhinitis, which affects only the nasal cavity), signs of complicated infections, signs of neoplasm, or persistence of symptoms and chronic rhinosinusitis, imaging may be warranted. As in the case of complicated rhinosinusitis, CT without contrast is typically the first imaging test recommended.[12]

THE BOTTOM LINE

Acute, uncomplicated rhinosinusitis remains a clinical diagnosis. Imaging should only be used in the case of complicated sinus infections, recurrent or chronic sinus disease, or in the case of surgical planning.[25] Yet imaging is still frequently performed despite these recommendations.[4]

Imaging when not clinically indicated is associated with increased healthcare costs and unnecessary exposure to radiation and, in some cases, intravenous contrast material.[4] Imaging in the setting of acute uncomplicated rhinosinusitis has not been proven to change clinical outcomes.[26] Clinical judgment to carefully select patients who are appropriate for imaging, as well as selecting low-dose radiation options when available, are ways to minimize imaging utilization.

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REVIEW

CME MOC

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Pneumonia and alcohol use disorder: Implications for treatment

ABSTRACT

Patients with alcohol use disorder (AUD) are at higher risk of pneumonia and of poor outcomes. This article reviews the etiology of pneumonia in patients with AUD, its impact on mortality and resource utilization, and its implications for treatment.

KEY POINTS

Contrary to common belief, pneumonia due to *Klebsiella pneumoniae* or other gram-negative organisms is not more common among patients with AUD than in the general population.

Pneumonia patients with AUD have a higher prevalence of *Streptococcus pneumoniae* infection than other pneumonia patients.

Broad-spectrum antibiotics to empirically cover gram-negative organisms are not necessary for patients with AUD unless other risk factors are present, such as hospitalization in the past 90 days or previous infection with a resistant gram-negative organism.

Hospitalized patients should be monitored for signs of alcohol withdrawal syndrome, which is a key contributor to increased morbidity and mortality.

All adults with AUD should be given pneumococcal vaccine.

Dr. Deshpande has disclosed membership on advisory committees or review panels for Ferring Pharmaceuticals.

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Alcohol consumption is a risk factor for community-acquired pneumonia and for poorer outcomes of community-acquired pneumonia. In theory and according to conventional wisdom, patients with community-acquired pneumonia who are heavy drinkers should be at greater risk of infection with gram-negative organisms such as *Klebsiella pneumoniae*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* than nondrinkers, but clinical studies do not bear this out. However, patients who are heavy drinkers are at greater risk of infection with *Streptococcus pneumoniae*, a gram-positive organism.

In this article, we review the pathophysiologic and epidemiologic evidence regarding the organisms responsible for pneumonia in patients who drink. We also examine the impact of drinking on mortality and resource utilization.

PNEUMONIA AND ALCOHOL USE DISORDER ARE COMMON

Community-acquired pneumonia is the most common cause of death due to infectious disease.[1] Its severity is influenced by patient factors such as age, sex, immune status, smoking, and comorbidities.[2]

Alcohol use disorder (AUD) affects about 6% of the adult population in the United States.[3] It is common among patients hospitalized for pneumonia,[4] and there is a strong and consistent relationship between AUD and risk of community-acquired pneumonia.[5]

Although strictly speaking, AUD is a psychiatric diagnosis, we will use the term to describe heavy alcohol consumption in general.

ALCOHOL IMPAIRS HOST DEFENSES

Alcohol consumption contributes to development of pneumonia in a number of ways, altering the body's flora and impairing defensive mechanisms along the entire length of the respiratory tract.

Chronic alcohol intake contributes to malnutrition, which further leads to breakdown of local protective barriers in the respiratory tract.[6] It alters the oropharyngeal flora, facilitating colonization by gram-negative organisms in the oral cavity.

Alcohol blunts mental function and suppresses cough and gag reflexes, thus increasing the risk of aspiration.[7,8] It decreases mucociliary clearance,[9] impairing both innate and acquired immunity.[10] It decreases phagocytic function of the alveolar macrophages, reduces the production of chemokines, and blunts chemotaxis of neutrophils.[11] Impaired recruitment of neutrophils suppresses pulmonary clearance of bacteria.[10] Alcohol also lowers the granulocyte and lymphocyte counts.[12–14]

By impairing host defense mechanisms, alcohol increases susceptibility to a wide range of pathogens: gram-positive, gram-negative, aerobic, anaerobic, mycobacterial, fungal, and viral.[10] The combination of virulent pathogens and weakened host defenses is thought to contribute to the severity and poor outcomes of pneumonia in patients with AUD.[2,10]

Alcohol alters the body's flora and impairs defense mechanisms in the respiratory tract

SEVERE DISEASE, POOR OUTCOMES

Alcohol also adversely affects other organ systems required to support an immune response. Comorbidities associated with AUD include liver disease and cirrhosis, diabetes, hypertension, coronary artery disease, cardiomyopathy, heart failure, dementia, psychiatric disorders, kidney disorders, and cancers.[15] As a result, pneumonia in patients with AUD is characterized by worse symptoms, more complications, greater likelihood of developing resistant pathogens, and poorer outcomes.[2,10]

AUD has traditionally been associated with higher age-adjusted mortality rates[16,17] and greater resource utilization, including intensive care, mechanical ventilation, longer stay, and higher cost.[2,4,18,19] There are several potential explanations.

First, patients with AUD have a more severe presentation, often with bilateral or multilobar pneumonia[16] necessitating mechanical ventilation. Alcohol is also a major contributor to malnutrition,[6] which results in immune suppression,[6,7,10,20] with a direct toxic effect on lung health.[21,22]

Second, patients with AUD frequently have comorbid illnesses, including liver, kidney, and cardiac disorders,[15] which could complicate the pneumonia.

Lastly, abstinence can precipitate alcohol withdrawal syndrome, which may increase length of stay and risk of death.[23,24]

Epidemiologic evidence for higher mortality rates in AUD

In the early 1900s, Capps and Coleman[17] found a direct relationship between alcohol intake and higher mortality rates in patients with pneumonia. With the advent of antibiotics, however, the impact of alcohol on mortality diminished.[4] In a 1990 meta-analysis of 127 studies, Fine et al[25] found that alcohol use was not associated with mortality in patients with pneumonia, and in a prospective study, Mortensen et al[26] found no association between AUD and pneumonia-related mortality.

Patients with AUD also tend to be more likely to need intensive care. de Roux et al[2] and Saitz et al[4] attributed this to a direct toxic effect of alcohol, but they did not consider alcohol withdrawal syndrome. Taking this factor into account, the increase in intensive care unit transfers appears limited to patients with alcohol withdrawal syndrome, implying that there is no contribution from a direct toxic effect.[18]

Similarly, many studies have found an association between AUD and greater length of stay, leading to greater hospital cost.[2,4,16,18] Lack of social support and homelessness might contribute to a longer hospital stay. However, the increased length of stay was also limited to patients with alcohol withdrawal syndrome,[18] making it unlikely that social determinants of health contributed to the increased length of stay.

GRAM-NEGATIVE ORGANISMS: WEAK EVIDENCE FOR TREATMENT

Because the pathogen is unknown at the time of diagnosis in most patients with pneumonia, including those with AUD, treatment is

TABLE 1

Recommended treatment for pneumonia

Setting	Patients with risk factors for resistant gram-negative organisms	Patients without risk factors
Outpatient	A respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin), or A beta-lactam (high-dose amoxicillin or amoxicillin-clavulanate, or ceftriaxone, cefpodoxime, cefuroxime) plus a macrolide (azithromycin, clarithromycin, or erythromycin) Doxycycline can be an alternative to a macrolide	A macrolide (azithromycin, clarithromycin, or erythromycin), or Doxycycline, or Amoxicillin
Inpatient, not in intensive care	An antipneumococcal, antipseudomonal beta-lactam (eg, piperacillin-tazobactam) plus either ciprofloxacin or levofloxacin, or An antipneumococcal, antipseudomonal beta-lactam plus an aminoglycoside and azithromycin, or An antipneumococcal, antipseudomonal beta-lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone For penicillin-allergic patients, substitute aztreonam for the beta-lactam	A respiratory fluoroquinolone, or A beta-lactam (cefotaxime, ceftriaxone, ampicillin, or ertapenem) plus a macrolide Doxycycline can be an alternative to macrolide A respiratory fluoroquinolone should be used for penicillin-allergic patients
Intensive care	An antipneumococcal, antipseudomonal beta-lactam plus either ciprofloxacin or levofloxacin, or An antipneumococcal, antipseudomonal beta-lactam plus an aminoglycoside and azithromycin, or An antipneumococcal, antipseudomonal beta-lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone For penicillin-allergic patients, substitute aztreonam for the beta-lactam	A beta-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin or a fluoroquinolone For penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam

Based on information in references 1, 27, and 28.

primarily empiric. To be effective, the choice of antibiotic should be informed by an understanding of the most common microorganisms.

Guidelines for the treatment of community-acquired pneumonia from the Infectious Diseases Society of America (IDSA) recognize alcoholism as a major risk factor for infection with *P aeruginosa* and other gram-negative organisms.[1,27,28]

In inpatients, recommended empiric therapy for patients at risk of resistant infections (**Table 1**)[1,27,28] includes broad-spectrum antibiotics with activity against resistant gram-negative organisms (eg, antipneumococcal, antipseudomonal beta-lactam antibiotics, respiratory fluoroquinolones, and aminoglycosides).

However, despite long-held beliefs about the etiology of pneumonia in patients with AUD, the evidence cited in the 2007 guideline[27] in support of this recommendation is weak.

In theory, gram-negative organisms should be more common

Due to poor dental hygiene, AUD patients are more susceptible to periodontal disease and dental caries, which provide a hospitable environment for anaerobes, increasing their concentration among the oral flora.[29] Anaer-

TABLE 2

Studies finding a higher prevalence of oropharyngeal colonization with gram-negative organisms in people with alcohol use disorder

Study	Population	Findings
Dao et al,[32] 2014	613 men, rural Vietnam	*Klebsiella pneumoniae* was the most common gram-negative organism, isolated in the nasopharynx in 28% *K pneumoniae* was found in 23% of light drinkers, 30% of moderate drinkers, and 34% of heavy drinkers Weekly alcohol consumption was associated with *K pneumoniae* oropharyngeal carriage (OR 1.7; 95% CI 1.04–2.8)
Mackowiak et al,[31] 1978	124 people with AUD and 84 controls, Dallas, TX	Colonization with gram-negative bacilli in 35% of those with AUD vs 18% of controls Of those with AUD who had gram-negative colonization, 33% had *Enterobacter* species and 23% had *Escherichia coli*
Fuxench-Lopez et al,[33] 1978	34 with AUD and 28 controls, Puerto Rico	Gram-negative colonization in 59% of those with AUD and 14% of controls Among AUD samples, *K pneumoniae* accounted for 40% of the pharyngeal secretions and 76% of the isolates were in the *Klebsiella-Enterobacter* group of organisms
Golin et al,[34] 1998	58 with AUD and 59 controls, Brazil	Gram-negative organisms in 49% of those with AUD and 40% of controls Anaerobic microbes were present in 85% of those with AUD vs 31% of controls

AUD = alcohol use disorder

obes are important pathogens in aspiration pneumonia in patients with AUD.[30]

Alcohol also induces changes in the defense mechanisms of the upper respiratory tract. Inability of the host to block the attachment of the microorganisms by coating them with specific immunoglobulin A or nonspecific glycoproteins[31] allows gram-negative organisms to adhere to the mucosal surface more easily, while impairment of leukocyte function also favors gram-negative colonization.

As a result, the pharynx of patients with AUD may be colonized with gram-negative organisms, which might predispose to gram-negative pnemonia.[31–33] Indeed, studies in which swabs of the oropharynx of patients with AUD were compared with those of controls without AUD found higher prevalences of gram-negative organisms, in particular *K pneumoniae* (**Table 2**).[31–34]

Aspiration of commensal oropharyngeal bacteria

Alcohol is a potent inhibitor of the central nervous system and depresses the cough reflex.[10] In addition, loss of consciousness and vomiting due to alcohol intoxication is one of the most common reasons for aspiration.[35] Aspiration of oropharyngeal bacteria including anaerobic ones such as *Fusobacterium nucleatum*, *Bacteroides melaninogenicus*, and *Bacteroides fragilis* could result in a wide variety of lung infections ranging from simple pneumonitis to necrotizing pneumonia, lung abscesses, and empyema.[36]

CLINICAL STUDIES OF ALCOHOL AND ORGANISMS

Because pneumonia remains a clinical diagnosis and the causative organism is not known in most patients, there is always some uncertain-

TABLE 3

Prevalence of gram-negative organisms in pneumonia patients with or without alcohol use disorder

Study	No. of patients, location	Gram-negative organisms	With AUD	Without AUD	Gram-positive organisms	With AUD	Without AUD
Fernández-Solá et al,[16] 1995	50, Barcelona	Gram-negative bacilli	19%	0[a]	*Streptococcus pneumoniae*	6%	6%
Marik,[39] 2000	148, United States and Canada	*Pseudomonas aeruginosa* and *Acinetobacter* species	22%	5%[a]			
Arancibia et al,[38] 2002	559, Barcelona	Gram-negative bacilli	11%	11%			
Paganin et al,[37] 2004	112, Réunion Island	*Klebsiella pneumoniae*	30%	10%[a]			
Saitz et al,[4] 1997	23,198, Massachusetts	*Haemophilus influenzae* Gram-negative bacilli	5% 2.5%	3.5%[a] 4%	*S pneumoniae* *Staphylococcus sp.*	15% 3%	6%[a] 2%
de Roux et al,[2] 2006	1,347, Europe	Gram-negative bacilli *Pseudomonas aeruginosa* *H influenzae*	9% 5% 2%	11% 3% 4%	*S pneumoniae*	27%	16%[a]
Gupta et al,[18] 2019	137,496, United States	*Escherichia coli* *K pneumoniae* *P aeruginosa*	7% 6% 1%	10%[a] 7%[a] 1%	*S pneumoniae* *Staphylococcus aureus*	6% 4%	2%[a] 3%

[a]Statistically significant ($P < .05$).
AUD = alcohol use disorder

ty in treating it. The cause might be a virus or it could be a bacteria that can't be cultured. When an organism is present it is most often *Staphylococcus* or *Streptococcus* spp.

A number of retrospective and prospective studies have examined the association between AUD and types of organisms (**Table 3**).[2,4,16,18,37–39] In total, nearly 6,000 patients with AUD were compared with nearly 160,000 patients without AUD. However, we could find no studies of the impact of AUD on the ability to isolate specific pathogens.

Gram-negative organisms

In support of the association between AUD and gram-negative infections, the IDSA guideline cites 2 studies, one by Paganin et al[37] and the other by Arancibia et al.[38]

Paganin et al[37] performed a prospective study at a tertiary hospital on Réunion Island in the Indian Ocean in the 1990s. Among 112 patients with community-acquired pneumonia admitted to the intensive care unit, those with *K pneumoniae* were more likely than those with pneumonia due to other pathogens to abuse alcohol (84% vs 56%, $P < .001$).

Arancibia et al[38] prospectively studied 559 patients hospitalized in Barcelona, Spain. Interestingly, their findings do not support the assertion in the guideline—the prevalence of gram-negative bacteria was the same (13%) in patients with or without AUD.

Fernández-Solá et al,[16] in a retrospective study of patients with community-acquired pneumonia in an emergency department also in Barcelona, found that gram-negative bacilli were present in 3 of 16 patients with AUD and 0 of 34 patients without AUD.

Another retrospective study,[39] in 148 patients with septic shock, 23 of whom had

AUD, found that *Pseudomonas* and *Acinetobacter* were more common in patients with AUD than in those without AUD (22% vs 5%, $P = .01$).

In contrast, 2 prospective[2,38] and 2 retrospective[4,18] studies, including nearly 6,000 patients with AUD and more than 150,000 without AUD, found no association between AUD and gram-negative infections.[18] In fact, the largest study found that gram-negative infections were *less* common in patients with AUD.[18]

The reason for these discrepancies is unclear. It may be related to differing populations, due either to region—it has been suggested that *Klebsiella* is associated with AUD around the Indian Ocean in particular—or patient factors that have evolved over time.[40] Patients with pneumonia are generally sicker now than they were 30 years ago, with more comorbidities that may predispose them to gram-negative infections.

Streptococcus pneumoniae is more common in AUD

By impairing host defenses, alcohol increases susceptibility to a wide range of pathogens

S pneumoniae has long been known as a common cause of community-acquired pneumonia.[27] Several studies (**Table 3**)[2,4,16,18] have confirmed that it is more common among patients with AUD than those without AUD.

In a large retrospective study conducted almost 25 years ago, Saitz et al[4] found that of 23,198 patients who were admitted to hospitals in Massachusetts with a principal diagnosis of pneumonia, 824 (4%) had AUD. *S pneumoniae* was present in 15% of patients with AUD compared with 6% in those without AUD ($P < .0001$).

In a prospective study conducted in Europe, de Roux et al[2] also found that *S pneumoniae* was significantly associated with pneumonia in patients with AUD (27% vs 16%, $P = .005$).

In the largest and most recent study, Gupta et al[18] found that *S pneumoniae* was present in 6% of pneumonia patients with AUD compared with 2% of patients without AUD ($P < .0001$).

With the advent of pneumococcal vaccine 2 decades ago and the recommendation for vaccination in high-risk AUD patients, the incidence of *S pneumoniae* pneumonia was expected to drop. Instead, the percent of pneumonia cases that were due to *S pneumoniae* pneumonia in the most recent study was higher than in studies conducted more than 20 years ago.[2,4,18] This was particularly true for patients with AUD, which suggests failure to follow vaccination guidelines in this population.

Less-common organisms

***Mycobacterium tuberculosis*.** A meta-analysis by Lönnroth et al[41] found that compared with the general population, the risk of pulmonary tuberculosis is substantially higher in people with AUD (pooled effect size 2.94, 95% CI 1.89–4.59). In patients with tuberculosis, excessive alcohol consumption is also a risk factor for more extensive disease, hospitalization, and death.[10] Also, patients with tuberculosis who have AUD tend to have recurrent hospitalizations and thus greater resource utilization.[42]

However, baseline rates of tuberculosis in the United States are low, and patients with AUD should not be immediately suspected of having it unless they have other risk factors such as immunocompromised status, close contact with patients with tuberculosis, or occupational risk.[43]

Pneumocystis jirovecii (formerly called *P carinii*) is a common cause of pneumonia in immunocompromised patients. Because patients with AUD have depressed cell-mediated immunity, they are in theory susceptible to it,[13] but we found only 1 case report of *P jirovecii* pneumonia in a human immunodeficiency virus-negative patient with AUD.[44]

IMPLICATIONS FOR TREATMENT

When they come to the hospital with pneumonia, patients with AUD are often empirically treated with broad-spectrum antimicrobials of different classes to cover resistant gram-negative and gram-positive organisms.[2,16,18,26,45] The IDSA guidelines support this approach. In addition, the more severe presentation of pneumonia in this population may influence physicians to choose broader coverage.

However, despite sound theoretical reasons that patients with AUD should be at risk for gram-negative infections, the epidemiologic data do not support this association. If anything, patients with AUD are at lower risk of gram-negative infections. This is important

because broader-spectrum antibiotics may put patients at higher risk of acute kidney injury, *Clostridioides difficile* infection, and future antimicrobial resistance. Quinolones in particular have been the subject of recent concern regarding hypoglycemia and cognitive disturbances, including delirium.

AUD is a risk factor for *S pneumoniae* and perhaps invasive infections. All recommended regimens for community-acquired pneumonia provide adequate coverage for *S pneumoniae*, and should have fewer side effects than broader-spectrum agents. Patients with AUD should therefore receive the same empirical therapy as other patients with community-acquired pneumonia unless they also have other risk factors for resistant infections such as hospitalization in the past 90 days or previous infection with a resistant gram-negative organism.

If a patient with AUD does not respond to initial treatment, clinicians should consider less-common causes of pneumonia, including resistant gram-negative organisms, anaerobes, *M tuberculosis*, and *P jirovecii*.

Abstinence from alcohol during hospitalization can lead to alcohol withdrawal syndrome, especially when a patient's alcohol use is not known to the treating physician. Delirium tremens, seizures, and hallucinations increase the risk of adverse outcomes in alcohol withdrawal syndrome.[23,24] Prompt recognition and management of alcohol withdrawal syndrome can improve outcomes and may help reduce resource utilization.

Pneumococcal vaccination is recommended for all patients with AUD. For those between the ages of 19 and 65 years, only the 23-valent pneumococcal polysaccharide vaccine (PPSV23) is recommended. Because widespread use of the 13-valent pneumococcal conjugate vaccine (PCV13) in children has markedly reduced the prevalence of those strains included in the vaccine, sequential use of PCV13 plus PPSV23 is reserved for patients at very high risk, including those with chronic kidney disease or immunocompromised status, and is now optional for patients older than 65 years.[46] Shared decision-making is recommended in this age group, and alcohol use may be considered a risk factor. Although there is little harm in receiving PCV13, it is costly and offers limited benefit. Because patients with AUD may neglect self-care and lack a primary care provider, vaccination prior to discharge is a reasonable strategy to prevent future pneumonias.

SUMMARY

Despite pathophysiologic theories for why patients with AUD should be at increased risk for resistant gram-negative infections, a number of prospective and retrospective studies demonstrate that they are at increased risk for *S pneumoniae* but not resistant gram-negative infections. Patients with AUD also tend to use more medical resources, primarily because of alcohol-related comorbidities and alcohol withdrawal syndrome. Unless other risk factors for drug-resistant organisms are present, patients with AUD should receive guideline-recommended empirical therapy for community-acquired pneumonia, with attention to early signs of alcohol withdrawal syndrome.

Abstinence from alcohol during hospitalization can lead to alcohol withdrawal syndrome

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CME MOC

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Irritable bowel syndrome with diarrhea: Treatment is a work in progress

ABSTRACT

Irritable bowel syndrome (IBS) is a heterogeneous functional disease with a high prevalence and significant impact on quality of life. Traditionally understood as a pure disorder of brain-gut interaction, it is increasingly clear that IBS encompasses diverse pathologies, some of which involve objective alterations of intestinal structure, function, and the microbiome. IBS is subclassified as diarrhea, constipation, or mixed type based on the most prominent stool form. We review the diagnosis and management of the diarrheal type through a pathophysiologic lens, with attention to recent developments that can inform a mechanistically based targeted approach to treatment.

KEY POINTS

IBS is classified as IBS-diarrhea when at least 25% of bowel movements on symptomatic days are type 6 or 7 on the Bristol Stool Scale.

New research suggests that IBS has diverse pathologies that include intestinal inflammation, postinfectious sequelae that increase intestinal permeability, food sensitivities, microbiome alterations, and bile acid malabsorption.

Therapies are increasingly being targeted at one or more of these pathologies, leading to the availability of new treatments such as probiotics, bile acid sequestrants, and the low-FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet.

First-line therapies still include antidiarrheals, regular exercise, psychological therapy, and the traditional IBS diet.

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Irritable bowel syndrome (IBS) remains a clinical diagnosis, and its treatment is still mostly empiric and focused on relieving symptoms. That said, our understanding of its mechanisms is progressing, and treatments are increasingly targeted to the etiology in the individual patient.

A FUNCTIONAL DISEASE

IBS is a functional disease characterized by chronic intermittent abdominal pain and altered bowel habits.[1] Patients may also experience postprandial or stress-related abdominal bloating and sensation of incomplete emptying.[2] Comorbid dyspepsia, mood disorder, chronic migraines, interstitial cystitis, and fibromyalgia are common.[2]

The estimated national prevalence is 10% to 12%,[3] although some estimates are as high as 21%.[1] There is a well-documented 3:1 female predominance.[2] This disorder accounts for 25% to 50% of all gastroenterology referrals nationwide, and its healthcare burden exceeds $20 billion annually.[4]

Irritable bowel syndrome has 3 subtypes:

IBS-diarrhea (IBS-D) is diagnosed when at least 25% of bowel movements on symptomatic days are type 6 (mushy consistency without clear edges) or type 7 (completely liquid without solid substance) on the Bristol Stool Scale[5,6]

IBS-constipation (IBS-C) is diagnosed when 25% of bowel movements are type 1 (hard and lumpy) or type 2 (sausage-like and lumpy).

IBS-mixed (IBS-M) is diagnosed when both criteria are fulfilled.

About one-third of patients fall into each subtype.[3] This review focuses on the diagnosis and management of IBS-D.

TABLE 1

Diagnoses to consider before irritable bowel syndrome-diarrhea

- Inflammatory bowel disease
- Food intolerance or sensitivity
- Small intestinal bacterial overgrowth
- Bile acid diarrhea
- Pancreatic exocrine deficiency
- Medication side effects
- Functional diarrhea
- Colon cancer
- Chronic parasitic infection
- Microscopic colitis
- Thyroid disease
- Celiac disease

TABLE 2

Alarm signs and symptoms

- Age over 50
- Gastrointestinal bleeding
- Anemia
- Fever
- Night sweats
- Unintentional weight loss
- Family history of organic gastrointestinal disease

Other symptoms that should alert provider to consider another diagnosis

- Nocturnal symptoms
- Symptoms that persist when fasting
- Low fecal osmotic gap (fecal osmotic gap = 290 mOsm/kg) – 2 × (stool Na + stool K); a low gap (< 50 mOsm/kg) suggests a secretory cause of diarrhea such as microscopic colitis. Patients with IBS would be expected to have a normal gap.

DIAGNOSIS

Endoscopy is not recommended in patients who meet Rome IV criteria unless they have alarm signs or laboratory abnormalities

The most widely accepted set of diagnostic criteria for IBS is Rome IV,[2] ie, recurrent abdominal pain at least 1 day per week in the last 3 months that is (at least 2 of the following required):

- Related to defecation
- Associated with a change in stool frequency
- Associated with a change in stool form.

A validation study of the Rome IV criteria was performed at 9 sites in 3 countries and showed a 62% sensitivity and 97% specificity, although patients with inflammatory bowel disease, celiac disease, and diabetes were excluded.[7] The gold standard was normal findings on endoscopy and a physician diagnosis of IBS, which carries inherent subjectivity that detracts from the veracity of these statistics. The Rome IV criteria are not able to differentiate IBS from other causes of lower gastrointestinal symptoms, especially those not visible on endoscopy.

When evaluating patients who meet Rome IV criteria, many other disorders must be considered (**Table 1**). We also advise against limiting IBS diagnosis to patients with abdominal "pain." All therapies approved by the US Food and Drug Administration for IBS have been studied on the basis of earlier Rome criteria, which also included patients with abdominal "discomfort."

In the past, the exclusion of other causes of IBS symptoms centered around endoscopic workup to exclude inflammatory bowel disease. Now, endoscopy is not recommended in patients who meet Rome IV criteria unless they have alarm signs (**Table 2**) or laboratory abnormalities because the odds of finding inflammatory bowel disease, celiac disease, colon cancer, or microscopic colitis in this setting are negligible (**Figure 1**).[3]

In the absence of alarm signs, laboratory tests such as fecal calprotectin (reference range < 40 µg/g) are considered sufficient to effectively exclude inflammatory bowel disease.[1,3] Alternatively, some recommend serum C-reactive protein (< 0.5 mg/dL)[3] and fecal lactoferrin (< 7 µg/g).[8]

Routine screening for celiac disease is recommended by some guidelines,[3,8] based on a meta-analysis that reported a nearly 10-fold higher prevalence than in the general population.[9] However, a more recent observational study showed a 0.41% prevalence in both IBS-

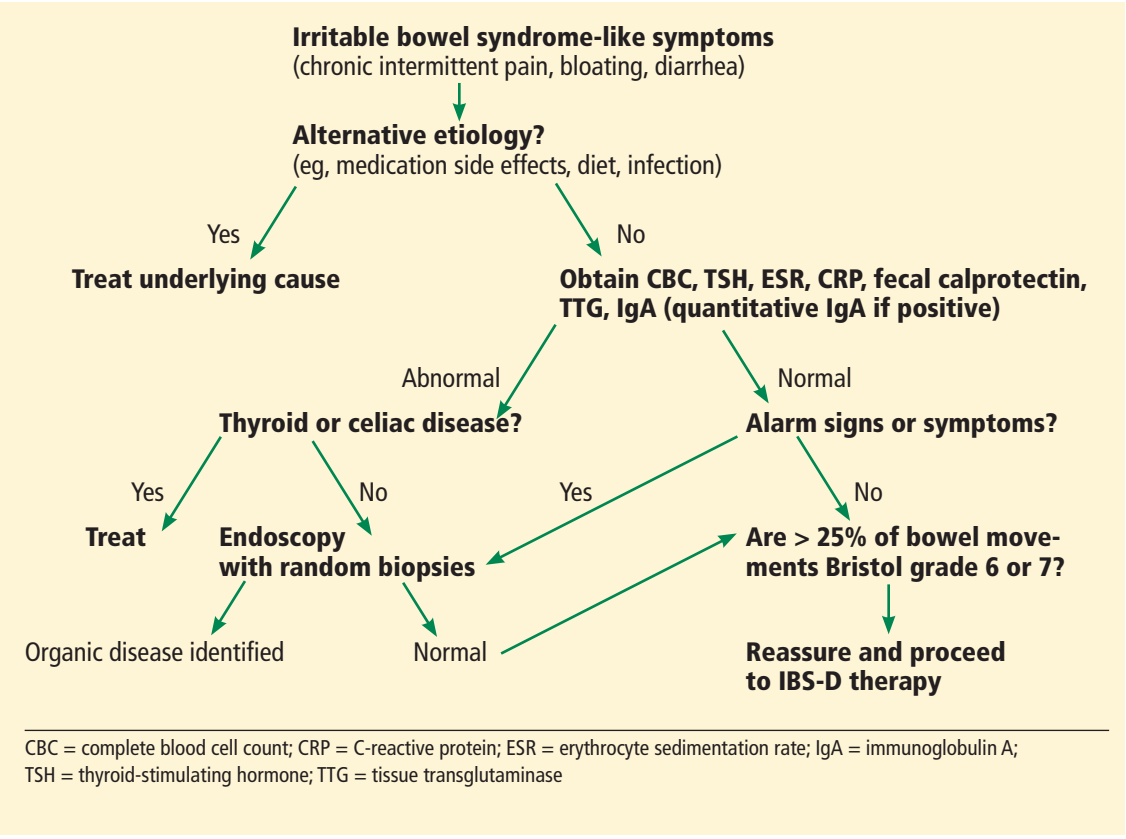

Figure 1. Algorithm for diagnosing irritable bowel syndrome-diarrhea (IBS-D).

D and the general population.[10]

Any patient with suspected IBS undergoing screening colonoscopy should have random biopsies of the right and left colon to rule out microscopic colitis.[1]

MANAGEMENT

Management of IBS-D should be targeted to its underlying etiology. However, in the absence of a clear understanding of the mechanisms that produce symptoms, treatments have traditionally focused on symptom relief, namely, antidiarrheals.

Antidiarrheal therapy

Loperamide, the best studied antidiarrheal, is a synthetic opioid that slows intestinal motility and increases absorption of water and electrolytes, leading to firmer and less frequent stools.[11] In several older studies reinforced by a meta-analysis, loperamide improved diarrhea in patients with IBS-D, but it had little effect on other symptoms such as abdominal pain.[11]

Many clinicians choose loperamide as a first-line therapy for IBS-D due to availability, low cost, and minimal adverse effects at low doses.

Many clinicians choose loperamide as a first-line therapy for IBS-D

Soluble fiber supplements such as psyllium that act as stool bulking agents are recommended by recent guidelines for the management of IBS.[3] Although their use in IBS-D may be counterintuitive, these supplements may improve stool consistency. However, their use in IBS-D specifically has not been adequately studied.

Therapy targeting the brain-gut axis

Traditionally, IBS has been understood as a disorder of brain-gut interactions manifesting as visceral hypersensitivity.[12] Patients may experience an exaggerated sensory response to intestinal contractions, distention, and perhaps microinflammation[13] due to sensitization of afferent nerves in the gut wall, pre- or postganglionic efferent nerves, or central nerves.[12]

Central nerves, perhaps stimulated by psychosocial stressors, may also contribute to ir-

regular peristalsis.[12] Although studies have not identified a consistent pattern of disordered gastrointestinal peristalsis,[12] a subset of IBS patients have a higher frequency of powerful colonic contractions, called high-amplitude propagating contractions, which typically lead to cramping and urgency.[13,14]

Therapies targeted toward this view of IBS have been used for decades.

Cognitive behavioral therapy is recommended as first-line[4] or second-line therapy.[15] In a large meta-analysis, clinic-administered cognitive behavioral therapy decreased the risk of persisting symptoms compared with placebo (hazard ratio [HR] 0.60).[15]

The benefit of self-administered cognitive behavioral therapy (ie, the patients learn how to perform the techniques on themselves) is less clear. A recent meta-analysis found no significant benefit, although some individual studies have shown that it was useful.[16,17] Efficacy may depend on how this therapy is administered.

A recent meta-analysis reported significant benefit of relaxation therapy (number needed to treat [NNT] = 6), multicomponent psychological therapy (NNT = 4), hypnotherapy (NNT = 5), and dynamic psychotherapy (NNT = 4).[17] Mindfulness meditation, stress management, and cognitive behavioral therapy administered via the internet were not found to significantly reduce the risk of persistent symptoms. The authors noted that all psychological therapies delivered without personal contact between the patient and therapist lacked significant benefit.

Peppermint oil is an underappreciated treatment of IBS

Tricyclic antidepressants can modulate pain and slow gastrointestinal motility through their anticholinergic effects.[17] In a large, recently updated meta-analysis that included a variety of tricyclic antidepressants, the risk of persistent IBS symptoms was lower than that with placebo (HR 0.65, NNT = 4.5).[17] The authors did not suggest a preference for any particular agent of this class.

Selective serotonin reuptake inhibitors can increase gastrointestinal motility via serotonin receptors of the enteric nervous system. Their use should be reserved for constipation-type IBS, although most trials of antidepressant therapy did not differentiate between IBS subtypes.[17] There have been no randomized clinical trials of serotonin-norepinephrine reuptake inhibitors for IBS.[17]

Antispasmodics are thought to decrease symptoms of pain by relaxing gut contractions and slowing motility.[18] They are intended for short-term use, after meals. Their use is limited by anticholinergic side effects, including constipation, but guidelines recommend their use.[3]

A recent meta-analysis of antispasmodic use showed significant improvement in overall IBS symptoms (NNT = 5).[3] Specifically, otilonium (NNT = 5), pinaverium (NNT = 4), hyoscine butylbromide (NNT = 3), dicyclomine (NNT = 4), and drotaverine (NNT = 2) were all found to significantly improve overall symptoms.[3] The overall quality of the data, however, is limited by the age of the trials, with nearly all having occurred 2 to 3 decades ago, with the exception of drotaverine and pinaverium.

Combination therapy with the antispasmodic mebeverine and cognitive behavioral therapy was more effective than mebeverine alone after 3 months in a randomized controlled trial (NNT = 5).[19] However, after 12 months, there was no longer a statistically significant difference between the 2 groups.

Melatonin has been studied as a potential therapy for IBS, given its involvement in the regulation of gastrointestinal motility, nociception, and possible anti-inflammatory properties.[20] Melatonin has been shown to reduce abdominal pain in patients with IBS, but its suitability for IBS-D patients in particular has not yet been studied.[20] It is not among the therapies for IBS-D endorsed by a published guideline.

Peppermint oil is an underappreciated treatment of IBS. It has antispasmodic and anti-inflammatory properties and serotonin 5-HT_3 receptor antagonism that can slow motility and may decrease visceral hypersensitivity.[21] It is used as first-line therapy in Europe due to its minimal adverse side effect profile.[21] A recent meta-analysis of peppermint oil use showed that it significantly improved overall symptoms (NNT = 4).[3]

Care must be taken in prescribing peppermint oil to patients with gastroesophageal reflux disease, however, because peppermint relaxes the gastroesophageal sphincter. This side effect can be limited with a delayed-release

form that has recently been shown to induce a 67% reduction in severe symptoms after 4 weeks of use compared with 35% with placebo (NNT = 3.0).[21]

Serotonin receptor antagonism

Serotonin is an important neurotransmitter in the gut that plays a prominent role in inducing peristalsis, intestinal distention, and contraction and modulating sensation of intestinal stimuli both centrally and peripherally.[22] Patients with IBS-D have been shown to have high postprandial serum levels of serotonin.[23,24]

Alosetron and ondansetron are serotonin 5-HT_3 receptor antagonists that decrease gastrointestinal motility and may modulate pain perception.[24]

Alosetron is a potent and effective therapy for IBS-D, with meta-analysis data showing significant benefit (NNT = 7),[25] but it was withdrawn from the market in 2001 due to reports of ischemic colitis.[26] However, it has recently been reinstituted for compassionate use at a lower dose (0.5 mg twice a day).

Ondansetron is less potent than alosetron, but a recent placebo-controlled randomized crossover study[27] showed that, compared with placebo, it reduced the frequency of stools by 11%, reduced bloating and urgency by 1 day per week, and decreased gut transit time by 10 hours, although it did not decrease abdominal pain, and it had a minimal adverse effect profile.[27] The mean dose of ondansetron was 4 mg daily.

An opioid agonist and antagonist

Eluxadoline is a mu- and kappa-opioid agonist and a delta opioid antagonist. It is thought to regulate gastrointestinal motility, intestinal secretion, and visceral sensation and provide central analgesia.[28]

In pooled data analysis of 2 recent randomized controlled trials involving 2,427 patients, those using eluxadoline had decreased abdominal pain and improvement in stool consistency compared with placebo (NNT = 9).[28] Adverse effects include sphincter of Oddi spasms (0.5%) in patients with previous cholecystectomy, including some that manifested as pancreatitis.[29] This led to a US Food and Drug Administration warning against use of eluxadoline in patients without a gallbladder.[30] The modest degree of benefit, along with the safety profile and cost of eluxadoline, explains why some gastroenterologists prefer other available therapies.

THERAPY TARGETING AN UNDERLYING INTESTINAL ABNORMALITY

Recent developments have suggested novel disease mechanisms that have diversified our understanding of IBS. Five emerging theories of increasing relevance are intestinal inflammation, postinfection, food sensitivity, microbiome alterations, and bile acid malabsorption.[1,2]

Intestinal inflammation

Patients with IBS may have a subtle but abnormal increase in inflammatory cells in the bowel, especially in close proximity to nerves.[31] An increased number of activated mast cells and heightened cytokine production caused by release of serine proteases is one suggested mechanism.[1,2] It is possible that eosinophils also play a role, as they have recently been found in large numbers in the intestines of patients with nonceliac gluten sensitivity, a condition that considerably overlaps with IBS in clinical presentation.[32]

A variety of anti-inflammatory therapies have been used in trials for IBS, mostly with negative results

Based on this theory, a variety of anti-inflammatory therapies has been used in trials for IBS, mostly with negative results.

Prednisolone in moderate daily doses was compared with placebo in postinfectious IBS-D.[33] It lacked benefit, although patients already taking steroids may be at lower risk of developing IBS.[34]

Several 5-aminosalicylic acids have been used in trials as well. A recent meta-analysis of mesalazine found no benefit compared with placebo.[31]

Other anti-inflammatory agents. Encouragingly, though, several recent studies assessed therapies that reduce mast cell activation and its effects, including the mast cell stabilizers cromoglycate and ketotifen, the histamine-1 receptor antagonist ebastine, and the dietary supplements palmitoylethanolamide and polydatin with largely positive results.[35–40]

While promising, these therapies remain controversial, have not yet reached mainstream practice, and have not been endorsed by any major guidelines.

TABLE 3

Proposed diets for irritable bowel syndrome

Traditional IBS diet

Eat small, frequent meals

Reduce gas-producing foods, including:
- Soda
- Juice
- Caffeine
- Beans
- Onions
- Bagels
- Pretzels
- Alcohol
- Wheat
- Certain fruits

Modified NICE diet

Eat small, frequent meals

Limit high-fiber foods

Avoid:
- Alcohol
- Caffeine
- Soda
- Sorbitol

Low-FODMAP diet

Avoid wheat, selected fruits and vegetables, corn syrup, onions

FODMAP = fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; NICE = National Institute for Health and Care Excellence

Elimination of gluten is not recommended for IBS-D

Postinfectious pathophysiology

During acute gastrointestinal infection, there is a transient increase of lymphocytes and neuroendocrine cells in the gastrointestinal tract. These can alter motility through serotonin production and increase intestinal permeability. It is postulated that these abnormalities occasionally persist, leading to IBS,[1,2] as has recently been shown after *Giardia* infection.[41]

This theory is supported by the discovery that patients with IBS have elevated levels of 2 key antibodies in the bacteria-host interaction during acute gastrointestinal illness: anti-CdtB and antivinculin antibodies.[42] In fact, antivinculin antibodies themselves may play a role in the complicated postinfectious pathophysiology, as decreased levels of vinculin can lead to weaker cell-cell adhesion and decrease the integrity of the extracellular matrix, making the intestine more permeable.[43] It may also alter gut motility by binding with actin located near the interstitial cells of Cajal, which help regulate motility.[43]

Glutamate. Until recently, there were no therapies targeted to this mechanism, but a recent small randomized controlled trial of glutamate, a dietary supplement purported to reduce intestinal permeability, showed markedly positive effects compared with placebo in postinfectious IBS (NNT < 2).[44] However, the reproducibility of these results has been questioned,[45] and this therapy is not currently recommended by any guideline.

Food sensitivity

Most patients with IBS believe their symptoms are related to diet.[3,4] Unlike with food allergy, there is no established way to identify specific food sensitivities. In one study, patients with IBS were placed on exclusion diets based on their serum immunoglobulin G (IgG) titers to various food antigens and compared with a sham diet group.[46] There was a significant decrease in symptom severity in the true diet group, especially when those who did not adhere to the diet were excluded (NNT = 2.5).

While encouraging, most of the foods that were excluded were those already known to cause increased symptoms in IBS patients such as wheat, milk, and yeast, perhaps rendering IgG testing unnecessary. This method is not currently used to devise diets for IBS patients.

FODMAPs. Elimination of fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) is recommended by the guidelines.[1] FODMAPs are sugars that ferment in the gut due to inadequate digestion; common ones are lactose, fructose, fructans, and sorbitol. Foods containing FODMAPs include wheat, some fruits and vegetables, corn syrup, and onions.

An initial observational study showed significant symptom improvement in 74% of IBS patients adhering to a low-FODMAP diet.[47] However, this study only included patients with a positive fructose breath test and did not

include a control group.

A subsequent small randomized controlled trial reported a mean 30% decrease in symptom severity with a low-FODMAP diet compared with a typical Australian diet.[48] However, subsequent randomized controlled trials that compared the low-FODMAP diet with a traditional IBS diet,[49] or the modified UK National Institute for Health and Care Excellence (NICE) diet (**Table 3**)[50] showed no difference in efficacy—each diet caused global symptom improvement in approximately 50% of patients. The low-FODMAP diet led to decreased abdominal pain compared with the modified NICE diet. Therefore, while a low-FODMAP diet is recommended by the guidelines,[3] it is also reasonable to prescribe other, simpler diets. Moreover, nonresponders at 4 weeks should discontinue the low-FODMAP diet and start an alternative one. Patients should be encouraged to eat small, healthy meals frequently and exercise.[1]

Conversely, patients who do improve with a low-FODMAP diet after 4 weeks must carefully reintroduce FODMAPs to devise a long-term individualized diet under the guidance of a trained nutritionist.

Lactose. Nearly 40% of IBS patients are estimated to have lactose maldigestion.[2] Some experts recommend excluding lactose even in patients without true lactose intolerance.[2]

Gluten elimination is not recommended.[3] While one randomized controlled trial appeared to show that a gluten-free diet was beneficial in patients with IBS,[51] a subsequent trial showed no benefit in those already on a low-FODMAP diet.[52,53] The earlier study did not differentiate between gluten and fructans, and the symptom improvement was likely related to elimination of the FODMAP fructans rather than gluten.

Microbiome alterations

Some patients with IBS have an altered microbiome composition.[53] Whether this constitutes small intestinal bacterial overgrowth remains controversial.

Part of this controversy is due to a lack of a gold standard diagnostic test for small intestinal bacterial overgrowth itself. Intestinal aspirates are expensive, unreliable, and technically difficult to obtain.[54] The reliability of breath testing is controversial because a variety of substrates can be used, and most tests lack uniform criteria for positivity.[55] Abnormal breath tests are common among IBS patients, ranging from 35% to 84%.[56]

A meta-analysis using case-control studies of patients with IBS and healthy controls showed that the IBS patients were 3 times more likely to have an abnormal breath test.[55] The glucose breath test appears to have the highest specificity for IBS.[55] This has led some to hypothesize that some patients with IBS-like symptoms may truly have small intestinal bacterial overgrowth, or can be treated as such.[55]

However, a study that applied the diagnostic criteria of an abnormal breath test and abnormal jejunal aspirate cultures to IBS patients compared with healthy controls found no difference between the 2 groups.[56] When a lower cutoff for positivity of jejunal aspirates was used, IBS patients had a greater prevalence of positive criteria. This may suggest a milder form of overgrowth-like pathology.

Routine screening of IBS patients for small intestinal bacterial overgrowth is currently not standard practice,[3] but research into targeted therapies that act on the microbiome is ongoing.

Low-FODMAP diet. Responders to the low-FODMAP diet experienced large changes in the composition of their microbiomes.[57] Unfortunately, response to the diet was not predicted by baseline microbiome composition. There is hope that in the future, we will discover properties of patient fecal microbiota that may help predict which IBS patients will respond most to the low-FODMAP diet.[57] Perhaps breath testing will prove effective at predicting response.[47]

Probiotics theoretically replenish the microbiome with certain bacteria, alter gut pH, provide barrier protection and have anti-inflammatory effects.[31,58] Though the quality of data is poor and scattered among various formulations, probiotics are currently recommended for IBS-D, given their minimal risk.[3,58]

Probiotics are currently recommended for IBS-D, given their minimal risk

Rifaximin is an antibiotic that is poorly absorbed, which maximizes its effect on the gastrointestinal tract while minimizing systemic adverse effects. The Targeted, Nonsystemic Antibiotic Rifaximin Gut-Selective Evaluation of Treatment for IBS-D 1 (TAR-

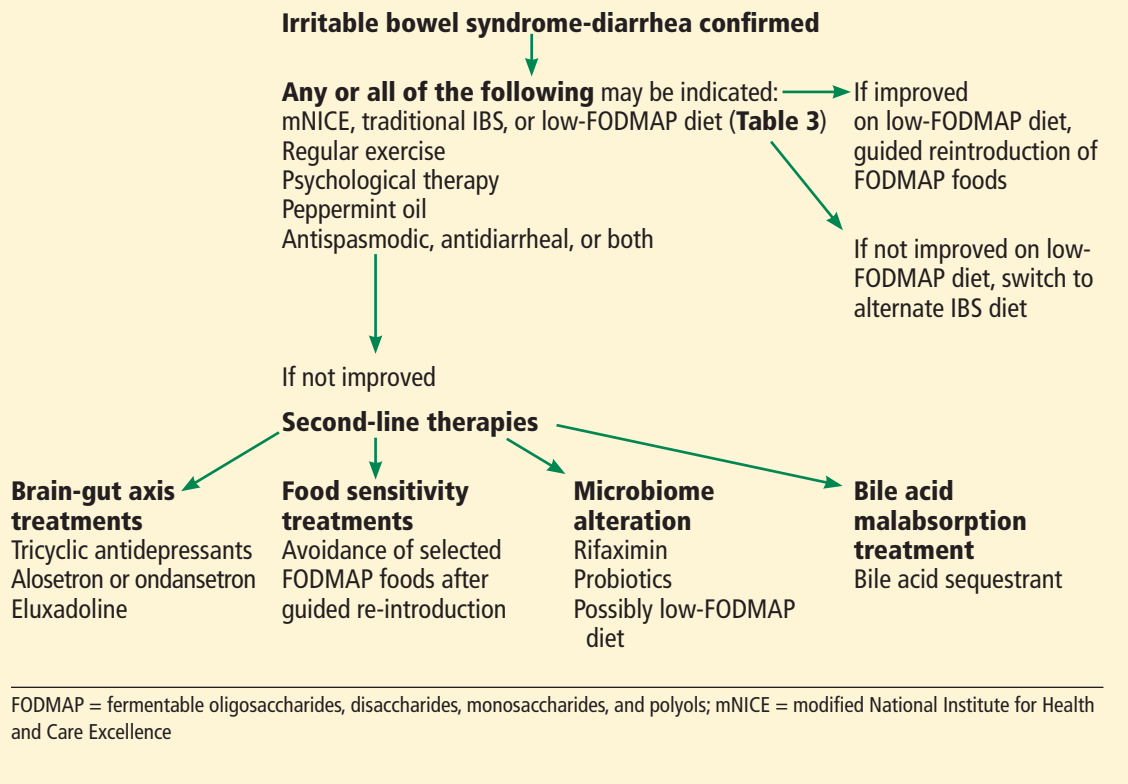

Figure 2. Suggested algorithm for treating irritable bowel syndrome-diarrheal type.

Fecal microbiota transplant is not currently endorsed, but that may change

GET 1) and TARGET 2 controlled trials showed greater adequate relief of IBS-D or IBS-M symptoms (NNT = 10) in patients taking rifaximin compared with placebo with 3 months follow-up.[59] The TARGET 3 study showed that retreatment with rifaximin remains effective if symptoms recur.[60]

While response to rifaximin correlates with improvement in lactulose breath testing,[61] an attempt to predict response to rifaximin using lactulose breath testing was unsuccessful.[61] Rifaximin is currently approved for empiric use in IBS-D.[3]

Fecal microbiota transplant. In a small randomized controlled trial, 65% of patients had significant improvement in their symptoms 3 months after receiving a fecal microbiota transplant (NNT = 4.5).[62] Unfortunately, the benefit above placebo was not sustained at 12 months.

A subsequent meta-analysis showed no overall evidence of benefit from fecal microbiota transplant compared with placebo, although on subgroup analysis, patients who received only single-dose transplants had a modest benefit (NNT = 5). A newly published randomized controlled trial showed a large benefit over placebo.[63]

Fecal microbiota transplant is not currently endorsed by any guideline for IBS-D, but that may change in light of the emerging evidence.

Bile acid malabsorption

Increased amounts of bile in the colon can increase colonic motility, fluid secretion, mucosal permeability, and visceral sensation.[64] Bile acid malabsorption may be present in 30% to 50% of IBS-D patients.[1] Bile acid absorption can be detected by serum tauroselcholic acid (SeHCAT) level, fecal bile acid, serum 7 alpha-hydroxy-4-cholesten-3 (C4), or fibroblast growth factor 19 (FGF19) measurement.

In a recent study, abnormal SeHCAT levels in patients with IBS-D predicted response to treatment with a bile acid sequestrant with impressive accuracy.[65] Unfortunately, SeHCAT testing is not currently available in the United States. Direct measurement of fecal bile acid requires 48-hour stool collection

and a high-fat diet so it may be impractical for many patients.

Serum C4 and FGF19 were evaluated as biomarkers for bile acid malabsorption, both separately[66,67] and more recently in combination,[68] and have been found to have specificity and negative predictive value of approximately 80% but lower sensitivity and positive predictive value.

Abnormal serum C4 levels have previously been shown to predict response to bile acid sequestrant therapy in IBS-D, although in a very small sample.[69] Based on this, some authors have recommended serum C4 and FGF19 as screening tests for bile acid malabsorption in IBS-D patients,[68] but this has not reached mainstream practice and is not currently recommended by any guideline. Expert opinions are mixed regarding empiric use of bile acid sequestrants in IBS-D patients.[8]

TARGETED THERAPY STILL A WORK IN PROGRESS

Irritable bowel syndrome is a heterogeneous disease that is a conglomerate of several pathologic mechanisms and degrees of severity that require individualized management strategies. Diagnosis remains clinical and extends beyond the Rome IV criteria. While the traditional understanding of IBS as a disorder of brain-gut interactions remains true, ongoing research has contributed to an evolving understanding of IBS that includes an increasing number of subtle yet objective microscopic intestinal abnormalities that likely contribute to the pathophysiology of IBS-D.

Therapies are increasingly targeting one or more of these mechanisms, leading to availability of several new treatment options (**Figure 2**). Identifying patients' precise mechanism of disease to enable targeted therapy remains a work in progress, but there is reason to hope this can be achieved in the near future. In the meantime, evidence-based therapy remains empiric, although clinicians are free to adjust the order in which approved therapies are attempted in accordance with their clinical suspicion for the most prominent symptoms or pathophysiology.

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