

# CLEVELAND CLINIC JOURNAL OF MEDICINE

**Ordering tests:  
A question of balance**

**Granules on the buccal mucosa**

**Ignore e-cigarettes  
at your patient's peril**

**Should 'daily labs' be a quality  
priority in hospital medicine?**

**Stewardship of laboratory testing:  
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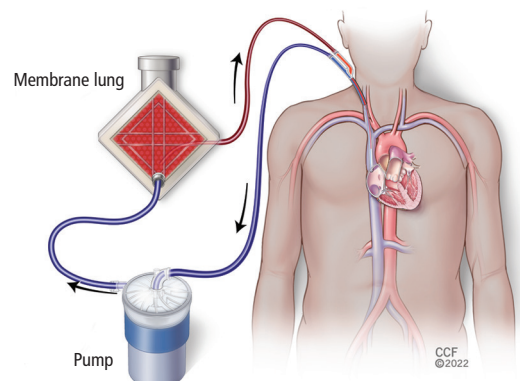
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**Gastroesophageal reflux disease:  
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**Nonalcoholic fatty liver disease:  
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**On the horizon: Extracorporeal  
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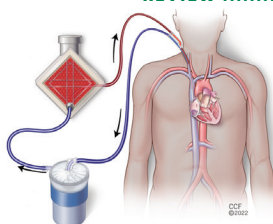
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## Test ordering: Balancing the good for the many with the good for the one

This issue of the *Journal* includes 3 articles on how we order clinical tests. One article relates to screening and treating patients with asymptomatic bacteriuria.<sup>1</sup> The authors review data that generally argue against treating asymptomatic bacteriuria, with its untoward financial ramifications, the potential to increase the prevalence of antibiotic resistance, and the risk of iatrogenic antibiotic-associated complications. The authors persuasively discuss why the frequent practice of treating asymptomatic genitourinary bacterial colonization is unlikely to provide clinical benefit to the patient in all but a few special circumstances. The concern with unnecessary treatment is magnified given the still common utilization of quinolone antibiotics for urinary tract infections.

These underlying issues resemble those encountered when considering antibiotic treatment in patients with acute upper respiratory infection. Although these patients are symptomatic, current evidence indicates that most have a viral not a bacterial infection, and thus are not likely to benefit in the long run from a course of antibiotics. However, antibacterial therapy may offer modest short-term benefit to some,<sup>2</sup> and I confess utilizing them occasionally in select patients (and at times for myself). And there is the rub: Will even selective usage of antibiotics for this condition accumulate to represent too-frequent utilization and thus contribute to the development of antibiotic resistance in the patient and in the community? How do we balance the possible and usually modest immediate good for 1 person against the potential long-term harm for many? Hopefully, this can be accomplished by exercising conservative and justifiable clinical judgment, not by always taking the path of least resistance, which is often prescribing an antibiotic to an expectant, cajoling (and paying) patient.

The other 2 articles in this issue present different perspectives on balancing the advantages and disadvantages of a daily standing order for basic laboratory tests for patients in the hospital.<sup>3,4</sup> Here, the focus is only partly on the patient. Murphy and Schram<sup>3</sup> argue that there is more hype and postulating than actual data demonstrating patient detriment from excess blood draws, and that ordering standing tests takes some of the stress off the attending medical teams. They also argue that the rationale for some institutional and regulatory policies and procedures has blurred the line between quality clinical care and quality fiduciary stewardship. Each added “quality” initiative likely adds to the clinicians’ workload and to the time spent away from delivering clinical care as they shift their focus to designing and monitoring these initiatives. During a time when increased attention needs to be devoted to clinician well-being, Murphy and Schram wonder if focusing on the ordering of daily tests is effort well spent.

Reddy and Henricks<sup>4</sup> counter this with the clinical laboratory and institutional perspective on the not trivial cost-savings that can be accrued by reducing what is often wasted testing—and they raise the important point of the need to inculcate a culture of financial and clinical stewardship into clinical healthcare delivery at every reasonable opportunity.

I can understand both sides of this discussion. Analogous to the time-honored algorithmic approach in trauma medicine, when there is a lot going on for the inpatient and medical team, it may not be unreasonable to place a standing order for daily or alternate-day laboratory tests to monitor values that might be unpredictably changing due to the effects of illness or therapy in



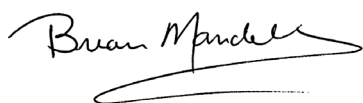
order to ensure that changes are not missed due to oversight in ordering. We have an expectation for regularly scheduled measurement of vital signs for most inpatients. On the other hand, in the patient not on anticoagulant therapy or needing significant transfusions and fluid replacement, there is little need to be checking coagulation parameters on a regular basis. Finding an abnormality does not mandate additional testing or reaction—clinical judgment must be utilized. There are important practice and fiduciary challenges, but not necessarily clinical quality-related issues. All are important and warrant our attention, but the purpose of attending to them should be clear to all.

I, like many of you, live a related underlying issue every day as I confront the electronic medical record with a patient in front of me. There seems to be a minimally accepted myth that including endless, templated, reiterated information (only some of it accurate) in each note will enhance the *quality* of patient care. But will noting yet again my 78-year-old patient's family history of coronary disease and personal history of Bell palsy help me manage his tophaceous gout and post-MI heart failure, or will it instead just bolster the billable moment? This more "complete" visit note does not add quality care to his visit with me. But it does add time and frustration for both the clinician and patient, both in writing and in reading prior notes.

Stressors and expectations continue to pile up on individual clinicians and can be measured by counting our keyboard clicks at the terminals and the time and clicks spent answering additional patient questions in our inbox that we didn't have time to address in person. Compromises need to be made and, hopefully, they can be thoughtful ones that accommodate all constituents. As Ashton discussed several years ago,<sup>5</sup> with attentiveness much can be done to streamline our time spent in clinical documentation.

As a tumultuous 2022 comes to a close, we all realize that public health, socioeconomic, and political situations that have challenged and divided us remain. We can hope and contribute our individual efforts to try to smooth the edges of our lives as they touch others. Although there is much beyond our individual control, we are in unique professional positions to have a positive impact on the lives of our patients and their families. But we need also to focus some energy on protecting our own well-being within the health systems where we work. We can't help others fully if we don't take care of ourselves.

I want to publicly express my personal thanks to all those people who touch the production of the *Journal* in so many ways. Many individuals are listed on our masthead, and there are others who serve invaluable roles. I remind our readers that behind the apparently seamless publication of each monthly issue, there are real people comprising our editorial and production teams. To their credit, and as testimony to their superb professional skills and undaunted attitudes, the many challenges that they have faced this past year have been invisible to those outside of our (virtual) offices. Thank you!



Brian F. Mandell, MD, PhD  
Editor in Chief

1. **Kendall EK, Mauer Y.** Does my patient need to be screened or treated for a urinary tract infection? *Cleve Clin J Med* 2022; 89(12):695–698. doi:10.3949/ccjm.89a.21121
2. **Sng WJ, Wang DY.** Efficacy and side effects of antibiotics in the treatment of acute rhinosinusitis: a systematic review. *Rhinology* 2015; 53(1):3–9. doi:10.4193/Rhino13.225
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4. **Reddy AJ, Henricks WH.** Laboratory stewardship should be a priority in every hospital. *Cleve Clin J Med* 2022; 89(12):691–692. doi:10.3949/ccjm.89a.22068
5. **Ashton M.** Getting rid of stupid stuff. *N Engl J Med* 2018; 379(19):1789–1791. doi:10.1056/NEJMp1809698

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BEST OF RADIATION ONCOLOGY  
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SHAPING THE MANAGEMENT  
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THE BEST OF SAN ANTONIO BREAST CANCER  
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Hollywood, FL

## FEBRUARY

VALVE DISEASE, STRUCTURAL  
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BREAST CANCER UPDATE:  
REVIEW OF BREAST CANCER SYMPOSIA  
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ADVANCES IN CONGENITAL HEART DISEASE  
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BASIC AND CLINICAL IMMUNOLOGY  
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Scottsdale, AZ

## MARCH

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March 27  
Cleveland, OH

COMPREHENSIVE CARE  
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March 31–April 1  
Chicago, IL

## APRIL

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## MAY

BIOLOGIC THERAPIES SUMMIT X  
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PEDIATRIC BOARD REVIEW  
August 27–September 1  
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COMPREHENSIVE, LIFELONG, EXPEDITIOUS  
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September 22–23  
Cleveland, OH



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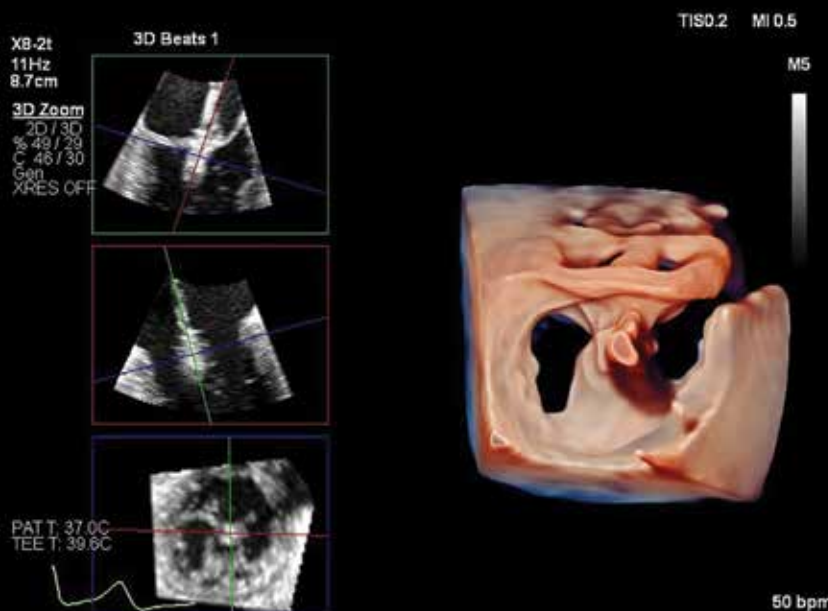
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# Asymptomatic granules on the buccal mucosa

**A**N OTHERWISE HEALTHY 35-YEAR-OLD man was referred to the dentistry and oral surgery department with asymptomatic granules on the buccal mucosa. Intraoral examination showed multiple small, white to yellow papules on both sides of the buccal mucosa (**Figure 1**). Extraoral examination showed no significant abnormalities. A clinical diagnosis of Fordyce spots was made.

## ■ FORDYCE SPOTS: PREVALENCE AND KEY FEATURES

Fordyce spots are ectopic sebaceous glands on the oral and genital mucosa and are considered a normal variant.<sup>1,2</sup> In the oral cavity, the spots often present on the buccal mucosa, the vermillion border of the upper lip, and the retromolar region. The estimated prevalence of Fordyce spots is 0.5% to 6.6%.<sup>3</sup> No genetic and geographic differences have been reported. They are mostly found in male adults or people with oily skin types, and the incidence increases with age, predominantly in the elderly.<sup>1,4</sup>

Fordyce spots appear as multiple, small, slightly elevated, whitish to yellowish papules measuring 0.2 mm to 2 mm in diameter,<sup>1,4</sup> and they cannot be removed by scraping. In most patients, Fordyce spots are asymptomatic, but some patients feel a rough mucosal sensation.<sup>2</sup>

The pathogenesis of Fordyce granules remains poorly understood,<sup>4</sup> and no association between Fordyce spots and specific drugs has been reported.



**Figure 1.** The patient presented with multiple, small, white to yellow papules on the buccal mucosa (left buccal mucosa shown here).

According to a cross-sectional prospective study, hyperlipidemia has been associated with a high density of granules,<sup>5</sup> and a case series showed the presence of Fordyce spots in patients with hereditary nonpolypoid colonic adenomatous polyposis syndrome.<sup>6</sup>

The lesions are often misdiagnosed as a fungal infection or oral lichen planus.<sup>2</sup> No treatment is required except for cosmetic reasons.<sup>1,4</sup>

## DISCLOSURES

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

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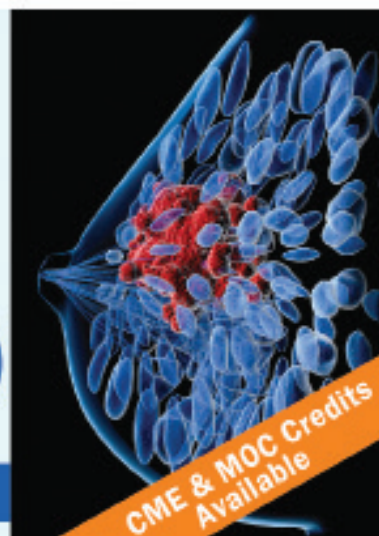
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# Ignore e-cigarettes at your patient's peril

**C**IGARETTE SMOKING is the leading cause of preventable deaths, with more than 1 billion tobacco smokers worldwide.<sup>1,2</sup> This number has remained stagnant since 2007<sup>1</sup> despite extensive public health efforts and the availability of several smoking cessation medications.<sup>1,2</sup> Pharmacotherapies such as nicotine replacement therapy (NRT), varenicline, and bupropion in combination with behavioral therapies are helpful but do not work for all smokers.<sup>3</sup> In fact, long-term abstinence rates are modest for each attempt to quit.<sup>3</sup> Quitting is especially hard for smokers with high levels of nicotine dependence.<sup>3</sup> These subgroups are overrepresented by disadvantaged populations who carry a disproportionate burden of tobacco-related pathology.<sup>1</sup>

As a tool to decrease morbidity and mortality associated with smoking, several countries have endorsed electronic cigarettes (also known as e-cigarettes, vapes, vaporization devices, and electronic nicotine delivery systems) as a therapeutic tool to help refractory smokers to quit or to switch to a less harmful way of using nicotine.<sup>4-10</sup> These devices are used for the inhalation of vapor through a mouthpiece and may use disposable pods or cartridges or refillable tank systems.<sup>4-10</sup> They may be single-use or rechargeable and can be used with or without nicotine (or other drugs).<sup>4-11</sup> E-cigarettes produce an aerosol by heating a solution that usually contains nicotine and volatile organic compounds, and may also contain flavorings.<sup>4-11</sup>

Proponents of e-cigarettes view them as a harm-reduction strategy for refractory smokers.<sup>4-11</sup> Recent guidelines from the National Institute for Health and Clinical Excellence in the United Kingdom support the use of e-cigarettes for smoking cessation, and the

country is considering them as medications.<sup>4,12</sup> In Australia, patients who failed conventional therapies may leave their doctor's office with an e-cigarette prescription.<sup>5</sup>

Last year, the US Food and Drug Administration (FDA) authorized marketing of the Vuse Solo electronic nicotine delivery system products,<sup>6</sup> owing to the premise that the products exposed trial participants to fewer harmful constituents compared with combustible cigarettes (eg, nitrosamine, benzene) by switching to use of these products only.<sup>6</sup> However, the FDA authorization is not considered approval for clinical use but rather for use as a consumer product. Similarly, the US Preventive Services Task Force found insufficient evidence to endorse e-cigarettes for smoking cessation.<sup>2</sup>

While US doctors remain wary of e-cigarettes and seldom discuss them with their patients,<sup>2,5</sup> their popularity remains high among smokers.<sup>5</sup> They mimic the hand-to-mouth movements of combustible cigarettes, have futuristic designs, and come in several attractive flavors.<sup>7-10,13</sup> In a systematic literature review, young e-cigarette users endorsed them as a safer option than combustible cigarettes and viewed them as an effective cessation aid.<sup>13</sup> As patients are already using these products, rather than dismissing use of e-cigarettes, we must provide accurate information to inquiring patients.

## ■ EVIDENCE

A meta-analysis of 38 studies found that the odds of quitting cigarettes were 28% lower in those who used e-cigarettes compared with controls.<sup>7</sup> They determined that e-cigarettes were associated with significantly less quitting among smokers.<sup>7</sup> However, a meta-analysis from Canada disputed these conclu-



sions.<sup>8</sup> The Canadian investigators reported a positive relationship between e-cigarettes and smoking cessation for some smokers.<sup>8</sup> In an effort to reconcile these findings, a Cochrane review evaluated the effects of e-cigarettes to help smokers achieve long-term abstinence.<sup>9</sup> The analysis included 56 studies (N = 12,804), 29 of which were randomized controlled trials (RCTs). The researchers found evidence of moderate certainty that e-cigarettes with nicotine increase quit rates compared with e-cigarettes without nicotine and NRT for at least 6 months. The incidence of adverse effects was low across studies. Mild adverse effects were more common in persons randomized to nicotine e-cigarettes. These side effects included transient mouth and throat irritation, headache, cough, and nausea. However, the Cochrane review did not include the newest versions of e-cigarettes (eg, pod-based devices), which may have higher nicotine concentrations.<sup>9</sup>

E-cigarettes are rapidly evolving, and nicotine concentrations and additives continue to change. For example, the cartridges for one of the more popular pod devices (JUUL brand) come in 3% and 5% nicotine strength and produce higher blood concentrations of nicotine than earlier devices or combustible cigarettes.<sup>14-16</sup> This higher concentration of nicotine could potentially provide better relief from cravings, particularly in severely nicotine-dependent individuals. However, the higher concentration, speed of delivery, and more rapid absorption also increase the potential for addiction to the product.<sup>16</sup>

Overall, the evidence for e-cigarette use for smoking cessation appears mixed.<sup>7</sup> While RCTs indicate a positive effect of e-cigarettes on quit rates, observational studies did not.<sup>7</sup> Patients participating in RCTs often exhibit high levels of motivation to quit, whereas the general population shows varying levels of motivation. Altogether, this research suggests that e-cigarettes seem to work for smoking cessation under optimal conditions but not as well in naturalistic settings.<sup>10</sup> So, what should we tell our patients?

### ■ CLINICAL IMPLICATIONS

Smoking remains epidemiologically and clinically significant, particularly in vulnerable populations.<sup>1-3</sup> Clearly, the best advice for smokers is to abstain completely and use FDA-approved medications with behavioral therapies.<sup>2</sup> As clinicians, we need to ascertain the patient's readiness to quit and receptivity to standard therapies.<sup>2</sup> Unfortunately, such strategies may not be acceptable for all smokers. Refractory

smokers may turn to e-cigarettes regardless of physician views.<sup>5</sup> They may use e-cigarettes to quit, to switch to what they consider to be a less harmful alternative, or to complement combustible cigarettes ("dual use").<sup>13</sup>

There is some evidence that e-cigarettes may help some smokers quit and may appear as a less harmful option for those who do not want to quit.<sup>9,10</sup> However, the patient needs to know that the FDA has not approved clinical use of e-cigarettes for smoking cessation, and that the newest e-cigarettes (eg, pod-based devices) have not been as extensively studied and often deliver higher nicotine concentrations, increasing the severity of dependence.<sup>15</sup> Similarly, dual use of combustible cigarettes and e-cigarettes is associated with higher cardiovascular risk than when either is used independently and thus is not advisable.<sup>17,18</sup> Currently, there are no data on long-term health effects of e-cigarettes.<sup>4</sup> Available research suggests that e-cigarette products appear less hazardous than the chemicals released by combustible cigarettes, but this is an evolving issue requiring further research.<sup>4-11</sup>

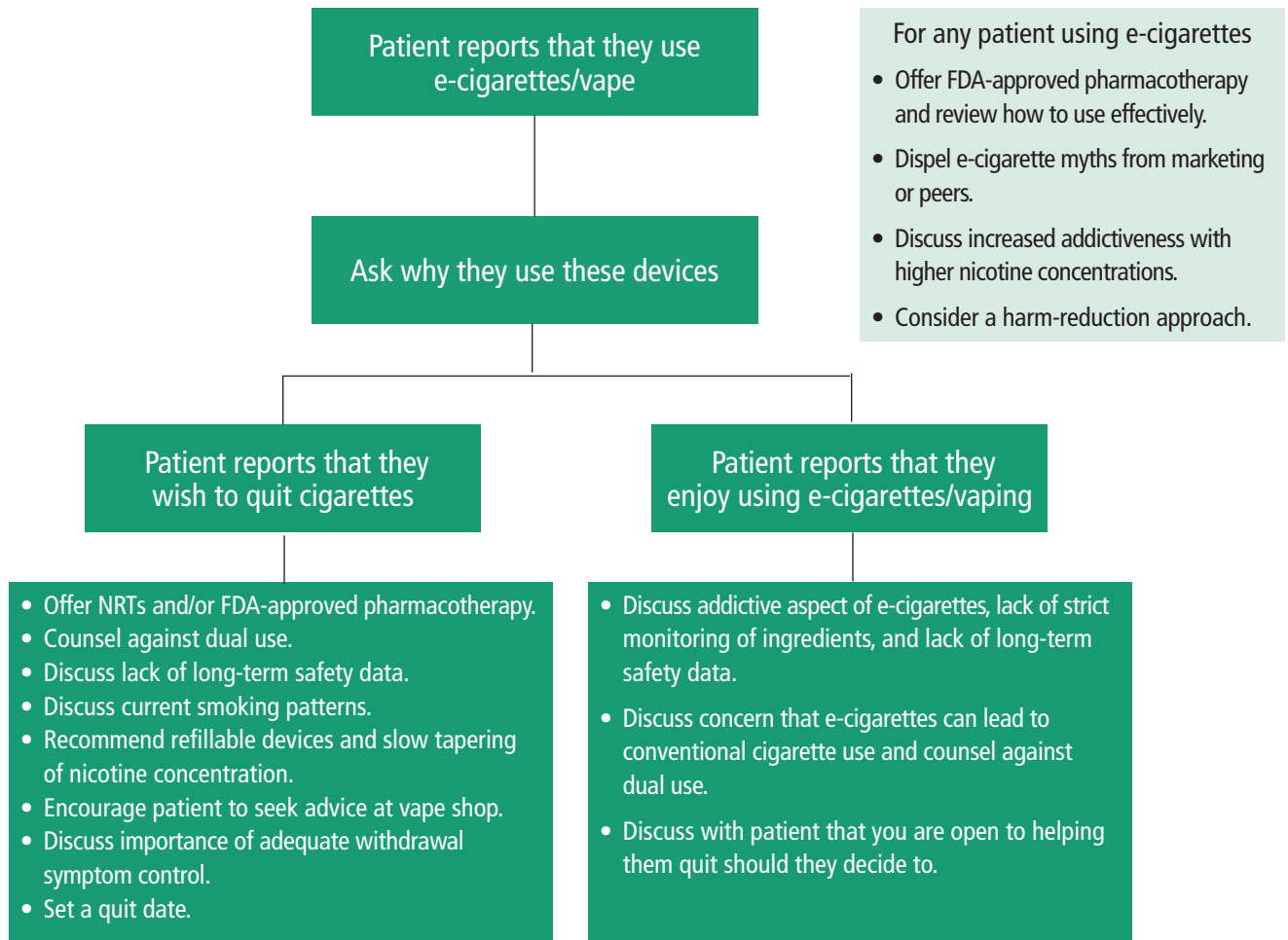
### ■ WHAT PHYSICIANS CAN DO

If a patient is already using e-cigarettes, it is up to the physician to discuss risks and benefits of these devices and provide options with better-established safety profiles of FDA-approved NRT modalities and pharmacotherapy<sup>2</sup> (**Figure 1**). Refusing to broach the subject leaves the patient vulnerable to e-cigarette marketing.<sup>6,13</sup> Clinicians should discuss the risks of dual use as well as the higher concentration of nicotine in pod devices and how it increases the potential for addiction.<sup>16-18</sup>

If the patient chooses to continue to use e-cigarettes, clinicians should advise the patient regarding the following:

- E-cigarettes are not licensed medications, and long-term risks are not known. However, they may appear to be less harmful than combustible cigarettes.<sup>4</sup> Do not engage in dual use, but rather switch completely to e-cigarettes.<sup>4</sup>
- Refillable devices are more likely to help patients quit, as they allow for gradual tapering of the nicotine concentration.<sup>12,19</sup>
- Vape shops may assist patients in identifying the appropriate nicotine concentration to start at based on what is available for each device and how much they smoke.<sup>12,19</sup> It is important that patients receive enough nicotine to overcome withdrawal symptoms.<sup>12,19</sup>





**Figure 1.** How to approach patients regarding e-cigarette use.

FDA = US Food and Drug Administration; NRT= nicotine replacement therapy

- Vape shops may also help patients identify the appropriate device for them.<sup>12,19</sup> It is also important to discuss patient goals. Do they want to replace cigarettes, decrease nicotine intake, or quit smoking altogether?<sup>4</sup>
- Finally, how long would the patient use the device if quitting is their goal?<sup>4</sup> It is important to note that initially there will likely be a trial-and-error phase until the patient finds a nicotine concentration that controls withdrawal symptoms.<sup>12</sup> Patients must use the device for long enough that they are able to quit combustible cigarettes completely.<sup>4</sup> Patients must be actively followed and progress assessed as they attempt to cut down. Clinicians

should also continue to keep an eye for short- and long-term issues resulting from e-cigarette use.

As clinicians, we must provide education on the risks of e-cigarettes and dual use and help patients transition to less harmful options after failing other smoking cessation therapies. With a lack of clear evidence, conflicting public health guidelines, and predatory marketing from e-cigarette companies, it is our duty as clinicians to educate ourselves and help patients make the best choices for their health. ■

## ■ DISCLOSURES

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

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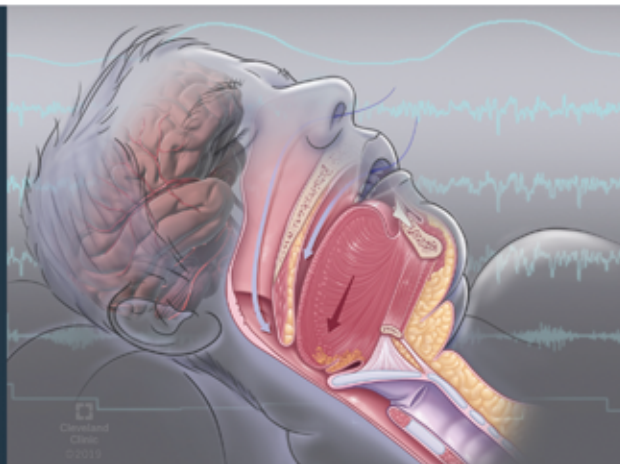
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# Should ‘daily labs’ be a quality priority in hospital medicine?

“Daily labs,” the repetitive ordering of complete blood cell counts (CBCs) and serum electrolyte panels (SEPs) in stable hospitalized patients, is a well-known low-value practice in hospital medicine. Daily lab utilization is often cited as a contributor to an array of harms such as iatrogenic anemia, wasteful spending, and an unpleasant experience for patients. However, a closer look at the evidence reveals that unnecessary daily labs are only a minor contributor to anemia and healthcare costs for most inpatients, while their effect on the patient experience has not been definitively established.

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*See related editorial, page 691*

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An accurate understanding of the magnitude of harm resulting from inappropriate daily labs is relevant in the context of quality improvement (QI), where the objective is to pursue interventions that support institutional priorities and achieve a favorable balance of expected benefit to resource investment.

## ■ RELEVANCE TO QUALITY IMPROVEMENT

Ordering daily CBCs and SEPs, including basic metabolic panels, renal function panels, and comprehensive metabolic panels, is a common practice in the inpatient setting. While these tests are high-yield, low-cost, and play a central role in clinical decision-making, they are also likely to be ordered on a recurring basis without a clear indication. Several studies estimate an inappropriate usage rate of about 25% to 30%.<sup>1</sup> Unnecessary CBC and SEP utilization gained heightened awareness when it was called out by the Society of Hospital Medicine (SHM) in its “Choosing Wisely” list as a common wasteful clinical practice in the hospital setting.<sup>2</sup>

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But there is an important difference between identifying a wasteful clinical practice and assessing its suitability as a QI target. Discussion of even minor problems may be appropriate in educational settings to foster a value-conscious culture among trainees.<sup>3</sup> However, more discernment is needed when an institution considers devoting resources to a clinical QI intervention. The QI community has long recognized the importance of prioritizing change-initiatives based at least partially on their projected impact on institutional priorities.<sup>4</sup>

The concept of QI prioritization is highly relevant to daily labs. While literature on inappropriate daily labs cites a broad range of potential harms to justify intervention, the magnitude of purported harm is often unaddressed or discussed incompletely. In this commentary, we show that the consequences of daily labs may be less pronounced than is commonly suggested. This has implications for what types of daily lab interventions are prioritized by hospitals and the broader hospital medicine community and may guide the evaluation of other QI initiatives.

## ■ IATROGENIC ANEMIA: IDENTIFY PATIENTS AT RISK

Excessive phlebotomy leading to iatrogenic anemia was the chief clinical concern underpinning SHM’s “Choosing Wisely” recommendation to avoid repetitive CBCs and SEPs in stable hospitalized patients.<sup>2,5</sup> The recommendation was based on several studies that associated phlebotomized blood volume with hemoglobin decline in general medicine and critical care patients.<sup>6–8</sup> However, inappropriate daily labs seem to have, at most, a minor role in provoking clinically significant iatrogenic anemia, particularly in general medicine patients.<sup>8</sup>



The following are 2 key points to consider:

**Phlebotomy volume appears to have a modest effect on hemoglobin levels in general medicine patients.** Thavendiranathan et al<sup>8</sup> showed in a widely cited paper that every 100 mL of phlebotomy resulted in a hemoglobin decline of 0.7 g/dL. Given that the mean phlebotomy volume per hospital stay was only 75 mL, an average hospitalization (with length of stay of 5.6 days) saw a hemoglobin decline of about 0.5 g/dL attributable to phlebotomy. This is unlikely to be clinically relevant in most patients. Further, daily labs account for only a portion of overall phlebotomy volume, and inappropriate daily labs represent a smaller portion still. The same study found that 5 days of routine lab orders resulted in 50 mL of phlebotomy volume and a hemoglobin decline of about 0.35 g/dL.<sup>8</sup> The expected hemoglobin drop attributable to wasteful CBCs and SEPs, assuming an inappropriate utilization rate of 25% to 30%, would therefore be estimated to be around 0.1 g/dL over a 5-day hospitalization.<sup>1</sup>

**The clinical relevance of iatrogenic anemia seems isolated to certain patient populations.** In one study, only “severe” hospital-acquired anemia, defined as hematocrit less than 27% with an admission hematocrit higher than 36% to 40%, had a statistically significant association with readmission rates.<sup>9</sup> In this study, the vast majority (85%) of patients with severe hospital-acquired anemia had a major procedure, active hemorrhage, or a hemorrhagic disorder, suggesting an identifiable subset of patients for whom avoidance of unnecessary phlebotomy is most relevant.<sup>9</sup> Adverse effects of iatrogenic anemia have also been established in patients with acute myocardial infarction.<sup>6</sup>

If our goal is to prevent or limit consequential iatrogenic anemia, it may be prudent to identify patients at risk for negative effects of iatrogenic anemia and focus interventions on those patients. This could include patients with active bleeding, bone marrow suppression, or acute myocardial infarction. Unfortunately, these patients may require regular CBCs and SEPs due to clinical instability. Reducing daily lab orders would be most sensible in the context of multifaceted interventions that also target collection tube volume (either by using pediatric tubes or by underfilling standard tubes), bleeding prevention and mitigation, and improved utilization of other laboratory tests.<sup>6,10</sup> Even so, as others have suggested, it is unclear to what extent iatrogenic anemia is preventable.<sup>9</sup>

## ■ WASTEFUL SPENDING: CLARIFY WHO BENEFITS

Purported financial benefits of reducing inappropriate daily labs also feature prominently in the literature on high-value care. These benefits are unintentionally exaggerated in several ways:

**Discussions of daily labs are commonly framed with dramatic statistics** on total healthcare spending without clarifying that laboratory spending—not to mention daily labs specifically—is a minor component of overall healthcare expenditures.<sup>11,12</sup>

**Some studies calculate cost savings based on hospital charges.**<sup>13,14</sup> Charge figures for laboratory tests are readily available, but they are notoriously inflated, are rarely paid in full,<sup>15</sup> and are therefore a poor marker for how many healthcare dollars actually change hands.

**Determining who benefits financially from reduced laboratory utilization is muddled** due to the complexity of US healthcare financing. Not infrequently, it is implied that hospitals or patients are the chief beneficiaries of cost savings resulting from reduced laboratory utilization,<sup>2</sup> but often it is payers who benefit the most.

### Consider fixed costs

Hospitals may in fact be disincentivized to perform less testing because they will be left to cover fixed laboratory costs without payer reimbursement. Even in situations where hospitals bear the full financial responsibility of laboratory testing, such as charity care or reimbursement with fixed payments based on diagnosis-related groups, cost savings are attenuated. This is because most laboratory expenses are fixed costs such as laboratory equipment and staff and not variable costs such as phlebotomy tubes, testing strips, and other consumable materials.<sup>16,17</sup>

“Capacity dynamics” are also unfavorable: an institution may have difficulty realizing savings in laboratory or phlebotomist staffing unless it can shed at least one “full-time equivalent” of testing or phlebotomy. The same rule holds true for laboratory equipment. In fairness, a published intervention noted that the host institution was able to capture new phlebotomist capacity by redirecting some phlebotomist time to the outpatient setting.<sup>18</sup> Also, interventions with potential to reduce phlebotomist or laboratory staff workload may be more highly valued by institutions suffering from staffing shortages.

### Unclear association between daily labs and care ‘cascades’

Healthcare testing “cascades of care” warrant a brief discussion. Cascades of care refer to downstream

healthcare utilization triggered by low-value services. Inpatient daily labs have been cited as a cause of care cascades,<sup>19</sup> but on closer inspection, daily labs are not an ideal example of a cascade-inciting event.

Care cascades characteristically occur when isolated diagnostic tests are ordered in inappropriate situations—for example, when the pretest probability of disease is very low, such as preoperative electrocardiography for low-risk procedures.<sup>20</sup> However, inpatient CBCs and SEPs are not ordered only as diagnostic tests but also to monitor patients' health status. Since the alternative to daily labs in the inpatient setting is usually ordering these tests every other day or several times weekly, any unexpected abnormalities would likely reveal themselves at some point during the hospitalization and would still need to be addressed prior to discharge. Therefore, inpatient daily labs seem to be a low-yield target if the goal is to prevent care cascades.

## ■ PATIENT EXPERIENCE: REDUCE VENIPUNCTURES

Reducing unnecessary daily labs may very well improve the patient hospital experience by decreasing discomfort and improving sleep quality, but there is a gap in the literature as to whether this is truly the case. It is important to note that patient experience related to daily labs is specifically affected by venipuncture.<sup>21</sup> Reducing daily lab orders has the potential to decrease patient discomfort and improve sleep only if the total number of venipunc-

tures is reduced. For example, ordering weekly CBCs but daily SEPs would presumably not result in a meaningful difference in patient discomfort or sleep quality because the total number of venipunctures would remain the same.

## ■ REASONABLE RESOURCES FOR A MODEST PROBLEM

As SHM recommended in their 2013 “Choosing Wisely” list, ordering routine inpatient CBCs and SEPs should be avoided in the presence of “clinical and lab stability.”<sup>22</sup> This recommendation is a helpful principle for clinicians motivated to practice high-value care in the hospital setting. However, demonstrable harms due to unnecessary daily labs are less pronounced than is commonly suggested. This position does not discount efforts to reduce inappropriate utilization of inpatient CBCs and SEPs, but it does have implications for how many resources should be committed to combatting the problem. It is reasonable to conclude that the required resource investment for proposed interventions—as well as the intensity of focus of the hospital medicine community on the problem—should match the modest impact of inappropriate daily labs on outcomes, costs, and the patient experience. ■

## ■ DISCLOSURES

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

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# Laboratory stewardship should be a priority in every hospital

**I**N THEIR COMMENTARY in this issue, Drs. Murphy and Schram<sup>1</sup> state correctly that the overall impact on cost and blood savings from eliminating unnecessary complete blood cell counts (CBCs) and serum electrolyte panels (SEPs) in hospital inpatients is likely to be insignificant over a short hospital stay. The tests are low-cost, and the total aggregate blood volume is also low. And as they note, benefits of reducing daily laboratory tests on patient experience have not been robustly reported in the literature.

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*See related article, page 685*

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## ■ OTHER CONSIDERATIONS

There are other important considerations in this analysis, however, including indirect costs, downstream testing or other workup based on minor abnormalities uncovered during daily testing, patient-care settings other than hospital medicine, and shortages in staff and supplies. Cumulative savings have been documented in several hospital settings—up to \$2 million annually at a single center.<sup>2</sup>

Daily CBCs, SEPs, and coagulation panels are often ordered to monitor general health in the inpatient setting. But minor test abnormalities without clinical findings may lead to additional testing, including more extensive laboratory workup or additional imaging studies. For example, a creatinine elevation above baseline may lead to urine studies, renal ultrasonography, and perhaps even a request for a nephrology consult. In these situations, some may opt to follow a test until it normalizes despite the absence of signs or symptoms, which can lead to additional waste. Data also show that reduced testing does not

lead to missed diagnoses or increased readmissions.<sup>2–4</sup>

Drs. Murphy and Schram maintain that the impact of fewer blood draws on patient experience and the need to reduce phlebotomy visits are not well studied. Subjectively, anyone who has been an inpatient would attest that any needle sticks avoided are welcome in terms of both discomfort and sleep disruption. Further, sleep disruption may have additional downstream effects, such as increased risk of delirium. Although patients may undergo early-morning phlebotomy for additional nondaily testing, many healthcare systems have instituted processes to add on testing to blood that was drawn previously and is stored in the laboratory.

## ■ WASTE WITH BLOOD DRAWS

In the critical care setting, blood is frequently obtained from existing intravenous (IV) lines with significant waste in the blood draw process. Koch et al<sup>5</sup> showed that cardiac surgery patients lose 1 to 2 units of blood to phlebotomy during their hospital stay, mostly due to discard volume (approximately 75%) from the blood draw itself. This adds up, especially when there are blood product shortages. In a hospital medicine patient, blood draws can be performed by a phlebotomist rather than drawn from an existing IV line.

We acknowledge the potential benefit of laboratory technologist and phlebotomist time-savings if both CBCs and SEPs are reduced concomitantly. In fact, this could shift time to other areas of need or even reduce the number of phlebotomists required for morning labs. It could also reduce the burden on bedside nursing staff who may take on these tasks. The need to optimize efficiency of these teams is even more acute in the current labor market. Sav-

ings also include conservation of blood collection tubes, which is relevant because of recent supply chain disruptions.<sup>6</sup>

The impact of targeting just daily CBCs and SEPs may be a small contributor to alleviating healthcare direct costs and waste. But stewardship efforts on these tests, which can be considered low-hanging fruit, can

lead to discussion of how to address more costly tests, as well as how to avoid shotgun approaches to testing for broad differential diagnoses.

### DISCLOSURES

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

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# Q: Does my patient need to be screened or treated for a urinary tract infection?

**A:** Patients with symptoms consistent with urinary tract infection (UTI) do not need to be tested and should be treated.

Patients with classical UTI symptoms that include new or acutely worsening dysuria, urinary frequency, urgency, suprapubic pain, and hematuria, particularly in the absence of vaginal symptoms, can be diagnosed and treated for UTI without the need of urine studies. The probability of UTI is approximately 50% in women with any one of these symptoms and greater than 90% in women with dysuria and frequency without vaginal symptoms.<sup>1</sup>

When patients present with symptoms that are suggestive but not clearly diagnostic of UTI, urine studies should be obtained. Together with symptoms, the presence of bacteria, leukocyte esterase or white blood cells, nitrites, and hemoglobin or red blood cells in the urine support the diagnosis of UTI and its treatment.<sup>2</sup>

Patients with nonspecific findings such as malaise, altered mental status, and cloudy or malodorous urine, should not routinely be evaluated or treated for UTI, unless these acutely occur in patients with spinal cord injury or cognitive disability in which case urine studies are appropriate as the patient is unable to clearly express or experience classic UTI symptoms.<sup>2,3</sup>

Screening and treatment for asymptomatic bacteriuria, or bacteria in the urine without symptoms, should only be done in patients who are pregnant or preparing for a procedure associated with urologic mucosal trauma.<sup>3-5</sup> If a positive urinalysis or culture happens to be obtained in any other patient, anti-

biotics should not be prescribed, as this can lead to possible side effects from treatment, antimicrobial resistance, and undue financial burden.<sup>3,5,6</sup>

## ■ UTI CLASSIFICATIONS

UTI is very common in US adults.<sup>7,8</sup> Prevalence in the overall population is approximately 11%, with increased prevalence (20%) in women over age 65.<sup>7</sup> In the outpatient setting, around 15% of antibiotic prescriptions are for UTI.<sup>8</sup>

UTI refers to the presence of bacteria in the urine combined with symptoms, and UTIs are classified according to the location of bacteria in the urinary tract.<sup>7,9</sup> The term simple cystitis refers to an infection of the lower urinary tract (bladder and urethra), with patients typically presenting with acute or worsening dysuria, urinary frequency and urgency, suprapubic pain, and hematuria.<sup>1,7,9</sup> Complicated UTI, or pyelonephritis, refers to UTI that has extended to the upper urinary tract (ureters and kidneys) and usually presents with symptoms of systemic illness, such as fever, malaise, nausea or vomiting, and new or worsening flank pain.<sup>7,9</sup>

In men presenting with pelvic or perineal pain or voiding difficulties, prostatitis should be considered.<sup>10</sup> Urethritis, typically caused by sexually transmitted pathogens, must be considered in sexually active men presenting with dysuria, pruritus, burning, or discharge at the urethral meatus.<sup>11</sup>

In postmenopausal women, chronic urinary frequency, urgency, or dysuria, especially in combination with vaginal symptoms, should prompt the clinician to consider genitourinary syndrome of menopause as opposed to UTI.<sup>12</sup>



## ■ INTERPRETATION OF URINALYSIS

When a patient presents with atypical urinary symptoms and thus the diagnosis is unclear, urinalysis is recommended (either by dipstick or microscopy).

**Dipstick testing** evaluates for presence of leukocyte esterase, hemoglobin, and nitrites in the urine. Positive leukocyte esterase suggests the presence of pyuria or white blood cells.<sup>13–15</sup> Hemoglobin is suggestive of red blood cells in the urine. Nitrites are highly specific for infection with *Enterobacteriaceae*, the most common organism responsible for UTIs, but because not all bacteria reduce nitrates, a negative test does not exclude infection.<sup>13</sup>

Dipstick urinalysis provides quick semiquantitative results and is usually performed in emergency and ambulatory settings. However, it is dependent on bacterial and cellular concentrations and thus often lacks sensitivity. The presence of nitrates or leukocyte esterase plus hemoglobin, has been shown to have a sensitivity of 77% and specificity of 70% for UTI in female patients, with positive predictive value of 81% and negative predictive value of 65%.<sup>14</sup> The positive predictive value increases to 92% if nitrites plus blood or leukocyte esterase are present. The negative predictive value increases to 73% if all three are negative.<sup>14</sup> In males aged 60 years and older, dipstick findings have been reported to have a positive predictive value of 83% and a negative predictive value of 60%.<sup>15</sup>

**Urine microscopy** examines urinary sediment and can most accurately detect and quantify cells in the urine, as well as identify casts, crystals, and pathogens.<sup>16–18</sup> It can confirm findings on a dipstick or detect abnormalities missed by chemical testing, providing additional clues toward different diagnoses. For example, white blood cell casts are formed in the kidneys and thus suggest pyelonephritis rather than simple cystitis.

**Urine culture** can help guide antibiotic therapy in patients with pyelonephritis or cystitis that has failed empiric therapy, as well as in a number of other settings, such as pregnancy, compromised immunity, urologic abnormalities, presence of an indwelling catheter, stay in an inpatient healthcare facility, recent antibiotic use, or history of prior infection with antibiotic resistant urinary pathogens.<sup>17–20</sup>

## ■ SCREENING FOR ASYMPTOMATIC BACTERIURIA

Asymptomatic bacteriuria is characterized by bacteria in the urine without UTI symptoms, representing bacterial colonization instead of infection and is dis-

tinct from UTI.<sup>4</sup> Thus, the term asymptomatic UTI is incorrect and should be avoided.

Screening for bacteriuria in asymptomatic patients is only recommended if a patient is pregnant (B recommendation, fair evidence) or will undergo a procedure that involves urologic mucosal trauma (strong recommendation, moderate-quality evidence).<sup>3,4</sup> Although urine testing is frequently done for screening purposes in populations such as the elderly, those with indwelling catheters, and during perioperative management, evidence suggests that screening in these populations can lead to harm.<sup>3,5,21</sup> If a positive urine test has been obtained in these populations, the patient should not be treated with antibiotics.<sup>3,5,6,20</sup>

## Infectious Diseases Society of America recommendations

According to the 2019 Infectious Diseases Society of America Asymptomatic Bacteriuria Screening Guidelines,<sup>3</sup> the following populations should be screened:

- Pregnant patients (moderate-quality evidence)
  - Patients undergoing procedures associated with urologic trauma (moderate-quality evidence).
- The following should not be screened:
- Healthy nonpregnant patients (moderate-quality evidence)
  - Patients in long-term care facilities (moderate-quality evidence)
  - Functionally impaired older individuals (low-quality evidence)
  - Patients with diabetes (moderate-quality evidence)
  - Patients with indwelling urethral catheters (low-quality evidence)
  - Patients undergoing elective nonurologic surgery (low-quality evidence)
  - Older patients with altered mental status (very low-quality evidence)
  - Patients with solid-organ transplant other than kidney (moderate-quality evidence)
  - Patients who have received a kidney transplant more than 1 month prior (high-quality evidence)
  - Patients with impaired voiding following spinal cord injury (low-quality evidence).

There is insufficient evidence to recommend for or against screening in the following:

- Patients with high-risk neutropenia (< 100 cells/mm<sup>3</sup>, ≥ 7 days duration following chemotherapy)
- Patients undergoing indwelling catheter removal
- Patients within the first month following kidney transplant.

For older patients without urinary symptoms or systemic signs of infection who present with acute

mental status change, other causes should be assessed first, and supportive treatment is recommended over screening for UTI and subsequent antimicrobial treatment (very low-quality evidence).<sup>3</sup> In a study of emergency room patients age 65 and older, the presence of altered mental status, malaise, or lethargy did not increase probability of bacterial infection.<sup>22</sup>

Currently, there is only anecdotal evidence demonstrating benefit of antibiotic treatment in patients with altered mental status and asymptomatic bacteriuria.<sup>23</sup> In a recent study, antibiotic treatment was administered to 82.7% of 2,733 hospitalized adults (median age, 77 years) with asymptomatic bacteriuria, defined as a positive urine culture without symptoms attributable to UTI.<sup>24</sup> Patients who were older, had altered mental status, or abnormal urinalysis were more likely to receive antibiotics. Antibiotic treatment was not associated with improved clinical outcomes, but rather with 37% longer hospital length of stay.<sup>24</sup>

## ■ HARMS OF TESTING FOR ASYMPTOMATIC BACTERIURIA

Screening asymptomatic patients or those with nonspecific symptoms not consistent with UTI often leads to the discovery of asymptomatic bacteriuria for which treatment is usually not required. Inappropriate screening and treatment of UTI is costly to the individual, healthcare system, and society.<sup>25–27</sup> A US study analyzing preoperative urinalysis data from 2007 to 2017 found that total spending on inappropriate preoperative urinalysis was \$48,675,408, and the estimated cost for antibiotics following inappropriate urinalysis added an additional \$4,854,109.<sup>25</sup>

Improper treatment of asymptomatic bacteriuria can also lead to antibiotic-associated complications,

such as *Clostridioides difficile* infections, ototoxicity, hepatic necrosis, Stevens-Johnson syndrome, anaphylaxis, and increased antibiotic resistance.<sup>5,26</sup> Data from a 2012 US retrospective analysis of female outpatient urine cultures noted *Escherichia coli* antibiotic resistance to ciprofloxacin to be 11.8% among all patients and 29.1% among those age 65 and older. Resistance to trimethoprim-sulfamethoxazole was as high as 22.2% across all age groups and 26.7% in those 65 and older.<sup>27</sup> Rates of resistance are even higher in certain parts of the United States and continue to increase.

## ■ THE BOTTOM LINE

Treatment of UTI is always recommended when patients present with classical UTI urologic symptoms. In this case, urine studies are not needed to establish diagnosis.

Urine studies should be attained when patients present with symptoms that are not clearly diagnostic of UTI. In this case, the presence of bacteria, white or red blood cells in the urine supports treatment.<sup>2</sup>

Patients with nonspecific findings not consistent with UTI should not routinely be evaluated or treated for UTI unless they have mental or physical disability that precludes them from experiencing or expressing urologic symptoms (such as spinal cord injury or mental retardation).<sup>3</sup>

Asymptomatic patients should not be screened for or treated for asymptomatic bacteriuria unless the patient is pregnant or preparing for a procedure associated with urologic mucosal trauma. ■

## ■ DISCLOSURES

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

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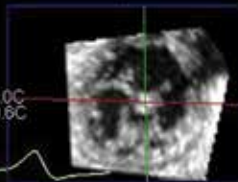
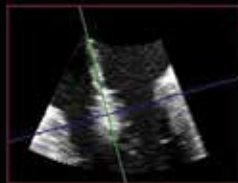
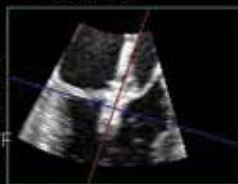
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# Evaluation and management of gastroesophageal reflux disease: A brief look at the updated guidelines

## ABSTRACT

Gastroesophageal reflux disease (GERD) is the most common gastrointestinal disorder seen in primary care offices and is usually managed with proton pump inhibitors (PPIs). The authors present an overview of the updated guidelines from the American College of Gastroenterology, which address the evaluation and management of GERD, including the consequences of long-term PPI therapy and emerging therapies.

## KEY POINTS

If GERD symptoms have resolved with PPIs and the patient has no erosive esophagitis or Barrett esophagus, tapering to the lowest effective dose, intermittent PPI therapy or replacement with a histamine 2 receptor antagonist, and discontinuation when possible should be considered.

Endoscopy is indicated in patients with alarm symptoms such as dysphagia, weight loss, bleeding, vomiting, anemia, chest pain, or refractory symptoms after optimization of PPI therapy.

Surgical options are recommended for patients with objective evidence of GERD and severe reflux esophagitis, large hiatal hernias, or persistent, troublesome GERD symptoms such as regurgitation.

**I**N RESPONSE TO ADVANCES in the diagnostic evaluation and management of gastroesophageal reflux disease (GERD) since previous guidelines were published in 2013,<sup>1</sup> the American College of Gastroenterology (ACG) updated the guidelines in 2022.<sup>2</sup> Here, we offer a brief overview of changes in the outpatient management of GERD outlined in the latest guidelines.

## ■ DIAGNOSTIC AND TREATMENT CHALLENGES

GERD, the result of the reflux of gastric contents into the esophagus,<sup>2</sup> is a diagnosis based on the presence of typical clinical symptoms, characteristic mucosal injury seen on endoscopy, or abnormal esophageal acid exposure demonstrated on a reflux monitoring study. The diagnosis can be challenging because symptoms may overlap with other disorders such as achalasia, eosinophilic esophagitis, or cardiac or pulmonary disease.

Proton pump inhibitors (PPIs) are still the medical treatment of choice for GERD. Although a PPI trial is used as a diagnostic “test” in patients with the typical symptoms of heartburn and regurgitation, the sensitivity of this approach is only 80% and the specificity 74%.<sup>3</sup> Also, up to 45% of patients treated with PPIs may continue to have symptoms.<sup>4</sup> These patients are designated as having refractory GERD, defined as persistent symptoms despite 8 weeks of twice-daily PPI therapy. In these patients, continued reflux is the cause of the

symptoms in only 21%, with the rest having reflux hypersensitivity or functional heartburn.<sup>5</sup>

Extraesophageal symptoms such as cough, asthma, laryngitis, and throat-clearing have been attributed to GERD. Laryngopharyngeal reflux is defined as the retrograde flow of stomach content to the larynx and pharynx that comes into contact with the upper aerodigestive tract. Evaluation by an ear, nose, and throat, allergy, or pulmonary specialist can be considered to rule out non-GERD causes of the symptoms. Finally, antireflux surgery can be considered in severe cases of erosive esophagitis or large hiatal hernia.<sup>2</sup>

## ■ WHO WROTE THE GUIDELINES?

The original ACG guidelines for the evaluation and management of GERD, published in 1995, were updated in 1999, 2005, and 2013. The 2022 guidelines provide updated evidence-based recommendations. They are structured in the format of statements that are clinically relevant in GERD. The authors developed PICO (patient-population, intervention, comparison, and outcomes) questions and performed an extensive literature search for each question with assistance from a research librarian. The GRADE system (Grading of Recommendations, Assessment, Development, and Evaluation)<sup>6</sup> was used to assess the quality of evidence for each statement.

## ■ WHAT ARE THE MAIN RECOMMENDATIONS?

The updated ACG guidelines include the following recommendations:

- Adult patients with classic GERD symptoms of heartburn and regurgitation without alarm symptoms such as dysphagia, weight loss, bleeding, vomiting, anemia, and chest pain can be treated with an 8-week empiric trial of a PPI taken once daily before meals. An upper age limit is not specified.
- Endoscopy is indicated in patients with alarm symptoms or refractory symptoms after optimization of PPI therapy.
- Reflux testing with a wireless telemetry capsule attached to the esophageal mucosa during endoscopy or transnasal catheter is considered in patients with suspected GERD and normal endoscopy, extraesophageal GERD symptoms, or refractory GERD.
- PPIs continue to be the mainstay of medical treatment. For patients with GERD whose symptoms have resolved and who do not have erosive esophagitis or Barrett esophagus, tapering the PPI to the lowest effective dose, replacement with intermittent PPI therapy or a histamine 2 receptor antagonist, and, when possible, discontinuation should be considered.

onist, and, when possible, discontinuation should be considered.

- Long-term PPI therapy or antireflux surgery is recommended for patients with Los Angeles classification grade C esophagitis (erosions extending over mucosal folds, but over less than three-quarters of the circumference) or grade D esophagitis (confluent erosions extending over more than three-quarters of the circumference).<sup>7</sup>
- Surgical options are recommended for patients with objective evidence of GERD who have severe reflux esophagitis (Los Angeles grade C or D), large hiatal hernias, or persistent, troublesome GERD symptoms such as regurgitation.<sup>7</sup> The treatment is fundoplication, in which the lower esophageal sphincter is strengthened by wrapping the fundus of the stomach around the esophagus in the abdomen. Roux-en-Y gastric bypass is an option to treat GERD in patients with obesity who are candidates for this procedure.
- Transoral incisionless fundoplication (TIF), the endoscopic creation of a gastric fundal wrap with plication, and magnetic sphincter augmentation (MSA), the laparoscopic insertion of a flexible ring of interlinked magnetic beads to augment the weak lower esophageal sphincter, can be alternatives in patients with troublesome regurgitation or heartburn who do not wish to undergo fundoplication and who do not have severe reflux esophagitis or large hiatal hernia.

## ■ WHAT IS THE EXPECTED CLINICAL IMPACT?

The updated ACG guidelines provide a streamlined approach to the management of the myriad presentations of GERD and the indications for use of emerging nonmedical therapies such as TIF and MSA.

Prior guidelines were ambiguous regarding the step-up approach vs the step-down approach in the medical treatment of GERD. The current recommendation is to start PPI therapy when a clinical diagnosis of GERD is made, then to proceed with diagnostic testing if there is no response, or to cut down to the lowest effective dose if there is a complete response.

As discussed in the updated guidelines, another issue in the past was concern about adverse effects with long-term PPI use as reported in observational studies.<sup>2</sup> However, 2 randomized clinical trials published since the last guidelines provide reassuring evidence about the safety of chronic PPI use.<sup>8,9</sup>

AspECT (A Phase III, Randomized, Study of Aspirin and Esomeprazole Chemoprevention in Barrett's

Metaplasia)<sup>8</sup> randomized 2,557 patients with Barrett esophagus to low- or high-dose esomeprazole (20 mg vs 80 mg), with or without aspirin (300 mg or 325 mg), in a 2 × 2 factorial design with a median follow-up period of 8.9 years.<sup>8</sup> Treatment-related serious adverse events were reported in 1% of patients, with no differences between low-dose and high-dose PPI therapy.

In the COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulation Strategies),<sup>9</sup> 17,598 patients being treated with rivaroxaban and aspirin, rivaroxaban alone, or aspirin alone were randomized to receive pantoprazole 40 mg daily or placebo and were followed for 3 years.<sup>9</sup> No significant differences in side effects were noted between PPI and the placebo group except for a trend toward increased risk of enteric infections. However, it is difficult to exclude if PPIs confer any increased risk of these adverse events because they are infrequent, and the study duration may not have been long enough for some adverse events to develop.

Therefore, based on these studies, PPIs are safe for long-term use, especially in patients with erosive esophagitis, Barrett esophagus, esophageal stricture, eosinophilic esophagitis, and PPI-dependent GERD. In addition, potassium-competitive acid blockers are exciting potential new agents for pharmacologic treatment of GERD as they are not purported to have PPI-associated adverse events.

## ■ WHAT IS DIFFERENT FROM PRIOR GUIDELINES?

The updated guidelines differ from previous versions on the following points:

- In the evaluation of GERD refractory to PPI therapy, endoscopy should be performed off PPI therapy for 2 to 4 weeks. Prior guidelines did not recommend cessation of PPI therapy before endoscopy.
- In patients with partial or no relief from PPI therapy with no previous evaluation or in those with extraesophageal symptoms and normal endoscopy, pH testing to detect acid reflux should be performed off PPI therapy.
- In patients with objective evidence of GERD who have refractory symptoms, pH impedance on PPI should be performed to detect the amount of reflux (acidic, weakly acidic, or nonacidic).
- Salivary pepsin testing or oropharyngeal or pharyngeal pH testing is not recommended for the evaluation of laryngopharyngeal reflux symptoms.
- If patients do not respond to a PPI, they can be switched to a different PPI. For patients who have not responded to the new PPI, more than one switch to a different PPI cannot be supported.

- Regarding possible patient concerns about long-term PPI therapy, the current guidelines suggest advising patients that high-quality studies have found that PPIs do not significantly increase the risk of pneumonia, stomach cancer, osteoporosis-related bone fractures, chronic kidney disease, nutritional deficiencies, heart attacks, strokes, dementia, and early death, and that the benefits of PPI therapy far outweigh the risks.
- TIF and MSA may be considered as alternative therapies for refractory GERD.

## ■ DO OTHER SOCIETIES AGREE OR DISAGREE?

The latest recommendations made by the American Gastroenterological Association (AGA) in its 2022 AGA Clinical Practice Update,<sup>10</sup> though almost entirely in concordance with the 2022 ACG guideline, includes the following additional recommendations:

For patients with functional heartburn or reflux hypersensitivity, pharmacologic neuromodulation, referral to a behavioral therapist for hypnotherapy, cognitive behavioral therapy, diaphragmatic breathing, and relaxation strategies, or both, should be offered.

The AGA Clinical Practice Update also recommends Roux-en-Y gastric bypass as an effective primary antireflux intervention in patients with obesity and as a salvage option in nonobese patients, whereas the 2022 ACG guidelines recommend Roux-en-Y gastric bypass only for patients with obesity.<sup>10</sup>

Regarding the role of endoscopy in the management of GERD, the 2015 guidelines of the American Society for Gastrointestinal Endoscopy<sup>11</sup> are largely in concordance with the 2022 ACG guidelines, except that they list the antireflux Stretta procedure (delivery of radiofrequency energy to lower esophageal sphincter) alongside TIF as a potential endoluminal GERD therapy for select patients. The 2022 ACG guidelines do not recommend it in view of cumulative evidence suggesting lack of efficacy.<sup>2</sup>

## ■ HOW WILL THIS CHANGE DAILY PRACTICE?

Even though PPIs are the preferred initial therapy for GERD, a sizable proportion of patients continue to have symptoms. For these patients, it is common practice to try different PPIs without investigating for objective evidence of GERD. Also, PPIs are often prescribed in patients with cough, asthma, or laryngitis on the presumption that it represents extraesophageal GERD, even in the absence of typical GERD symptoms. In these patients, reflux testing should be performed before starting PPI therapy, and esophageal

manometry should be done to rule out motility disorders such as achalasia. If the evaluation shows no evidence of abnormal reflux, PPIs should be stopped. For patients found to have reflux hypersensitivity or functional heartburn, a pain modulator such as a tricyclic antidepressant or selective serotonin reuptake inhibitor may be considered.

If a patient with no alarm symptoms and a good response to a PPI stops the drug after several months and has a relapse of symptoms, PPI therapy is often resumed without further evaluation. For such patients, the updated guidelines recommend endoscopy to identify severe disease necessitating indefinite PPI therapy (eg, erosive esophagitis, Barrett esophagus) and alternative diagnoses (eg, eosinophilic esophagitis).

## ■ WHEN WOULD THE GUIDELINES NOT APPLY?

The 2022 ACG guidelines recommend endoscopic evaluation in patients who have symptoms refractory to PPI therapy or who have a relapse of symptoms after cessation of PPI therapy. This may not apply in certain conditions such as pregnancy or severe cardiopulmonary disease, where endoscopic evaluation may be associated with unacceptable risk. Conversely, endoscopy is indicated even in patients with well-controlled GERD symptoms if they have multiple risk factors for Barrett esophagus such as age over 50, White ethnicity, male

sex, smoking, obesity, or a positive family history.<sup>12</sup>

Also, diagnostic testing for GERD such as endoscopy and reflux monitoring is sometimes indicated in asymptomatic patients.<sup>13,14</sup> For example, before lung transplant, a routine evaluation with reflux monitoring and esophageal manometry is indicated, as untreated GERD may contribute to graft failure.<sup>13</sup> Another group of asymptomatic patients who may benefit from diagnostic testing for GERD are those awaiting bariatric surgery such as sleeve gastrectomy, as this procedure may be associated with worsening of GERD postoperatively.<sup>14</sup>

It is also worthwhile to note that manometry and reflux evaluation are not available in all healthcare settings, and patients may need referral to a tertiary care center for evaluation.

Lastly, the 2022 ACG guidelines also do not mention the on-demand use of histamine-2 receptor antagonists as solo therapy in patients with intermittent symptoms. Randomized controlled trials have demonstrated that standard-dose histamine-2 receptor antagonists are more effective than placebo at relieving heartburn in cases of GERD, with symptomatic relief reported in 60% of cases.<sup>15</sup> ■

## ■ DISCLOSURES

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

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# A 60-year-old man with prostate cancer and embolic strokes

**A** 60-YEAR-OLD MAN WITH stage IV prostate cancer arrived at the emergency department 45 minutes after suddenly losing the ability to speak.

He had received his cancer diagnosis 12 years earlier. At that time, the tumor was still confined to the prostate, and he had undergone prostatectomy followed by adjuvant radiation and leuprolide treatment to block testosterone production. He did well for about 8 years, but then was found to have multiple bone metastases, consistent with stage IVB. His treatment was changed to leuprorelin, abiraterone (an agent that blocks the cytochrome P450 enzyme CYP17 expressed in tumor cells, thereby inhibiting androgen biosynthesis), and prednisone.

His prostate-specific antigen level had been rapidly rising: it had been 60 ng/mL 2 months ago, rising to 200 ng/mL 2 weeks ago. His oncologist had planned to start the immunologic agent sipuleucel-T, which is thought to work through antigen-presenting cells to stimulate a T-cell immune response targeted against prostatic acid phosphatase, which is highly expressed in most prostate cancer cells.<sup>1</sup> However, this treatment had not yet been started.

He had no history of heart valve disease, arrhythmias, coagulopathy, or bleeding diathesis and was not receiving anticoagulation or antiplatelet therapy.

## ■ INITIAL EXAMINATION AND STUDIES

The patient's blood pressure was 198/101 mm Hg, pulse 94 beats per minute, respiratory rate 22 per minute, and temperature 98.6°F (37.0°C). He was alert but unable to follow commands.

On neurologic examination, he had right-sided neglect (ie, he did not respond to stimuli on the right side of his body) and global receptive and expressive

aphasia (ie, he could not speak, and he did not seem to understand us when we spoke to him). He could move all 4 limbs spontaneously without limb drift. The deep tendon reflexes in the upper and lower limbs were 1+ on a scale of 0 (completely absent) to 4+ (clonus) and symmetric. Babinski reflexes were not present. His score on the 42-point National Institutes of Health Stroke Scale was 15, indicating he was having a moderate stroke.

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## The patient underwent thrombectomy, which restored perfusion completely...and his aphasia and dysarthria resolved toward the end of hospital day 1

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His heart rhythm was regular without gallops, murmurs, or rubs. The rest of the examination was normal.

Laboratory testing showed anemia, thrombocytopenia, elevated prothrombin time, and elevated alkaline phosphatase and troponin levels (**Table 1**).

Computed tomography (CT) performed according to stroke protocol showed an acute thrombus in the M2 and M3 segments of the left middle cerebral artery and a subacute infarct in the right parieto-occipital area (**Figure 1**). The patient underwent thrombectomy, which restored perfusion completely (Thrombolysis in Cerebral Infarction [TICI] grade 3), and his aphasia and dysarthria resolved toward the end of hospital day 1.

Transthoracic echocardiography indicated that his ejection fraction, wall motion, and heart valves were normal, and he had no intracardiac clots or shunts.

## ■ DAY 2: ANOTHER STROKE, ON THE OTHER SIDE

However, on hospital day 2, new signs appeared. The left side of his face was drooping, his left upper extrem-

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TABLE 1  
The patient’s laboratory findings

Test	Hospital day 1	Hospital day 2	Hospital day 3	Reference range
Hemoglobin (g/dL)	9.4	7.9	7.5	13.5–17.5
Hematocrit (%)	29.0%	23.7%	21%	38.8%–50%
Platelet count (× 10 <sup>3</sup> /L)	137	110	77	150–450
Prothrombin time (seconds)	13.6	17.5	24.1	9.5–11.6
International normalized ratio	1.19	1.53	2.14	0.9–1.2
Activated partial thromboplastin time (seconds)	33.7	38.1	38	23–29
Fibrinogen (g/L)	1.49	1.19	0.77	2.33–4.96
D-dimer (ng/mL)	36,881	38,136	33,603	220–740
Alkaline phosphatase (IU/L)	253	—	—	40–150
Troponin I (ng/mL)	1.75	—	—	0–0.4
C-reactive protein (mg/dL)	—	2.7	—	< 0.5

ity was weak (his strength was graded 2 on a scale of 5 in the hand, 3 in the forearm, and 4 in the arm), with increased reflexes (2+) in the biceps, brachioradialis, and triceps, and he now had left-sided neglect with right-gaze preference—the opposite of the day before. His heart was still in sinus rhythm and remained so throughout his stay in the hospital.

Repeat CT now showed an acute thrombus in the right M1 segment, and he underwent a second thrombectomy, which restored perfusion (TICI grade 3). The retrieved thrombus had a gelatinous appearance, inconsistent with typical hematologic emboli. Magnetic resonance imaging, done after the procedure, showed new infarcts in the right frontal lobe and left occipital lobe.

The rapid succession of strokes involving different vascular territories suggested a thromboembolic phenomenon. Consultants in neurology, cardiology, and hematology-oncology together agreed it would have been pointless to start anticoagulation, in view of the patient’s poor prognosis due to prostate cancer.

■ CAUSES OF EMBOLIC STROKE

1 Of the following, which is the most common cause of cardioembolic stroke?

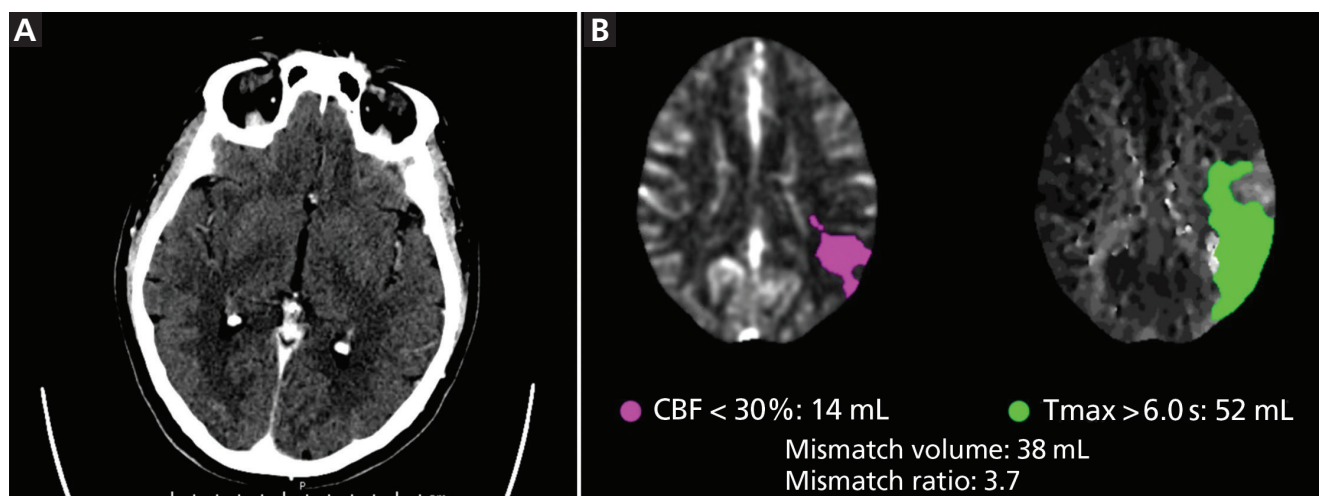
- ☐ Bacterial endocarditis
- ☐ Advanced heart failure
- ☐ Atrial fibrillation
- ☐ Right-to-left cardiac shunt

Stroke is classified as either hemorrhagic or ischemic, with ischemic stroke more common. Cardioembolic stroke is a subcategory of ischemic stroke.

Atrial fibrillation is common and is becoming more so. Estimates of its prevalence vary widely, but Colilla et al<sup>2</sup> project that it will affect 12.1 million people in the United States by 2030. Owing to its high prevalence, it is the most common cause of cardioembolic stroke and may account for 15% of all strokes in the United States.<sup>3</sup>

In fact, atrial fibrillation may be causing even more strokes than we think. Recent studies suggest that undiagnosed paroxysmal atrial fibrillation accounts for a significant proportion of the 30% of strokes that are classified as embolic stroke of undetermined source.<sup>4</sup> In this situation, patients may be experiencing episodes of atrial fibrillation, but not in the clinic or hospital. Implantable cardiac devices such as pacemakers and loop recorders have made it easier to diagnose paroxysmal atrial fibrillation and have helped establish that episodes of atrial fibrillation lasting at least 6 minutes increase the risk of stroke 2.5-fold for the subsequent 2.5 years.<sup>5</sup>

Advanced heart failure and recent myocardial infarction increase the risk of stroke 3-fold.<sup>6</sup> The mechanism seems to be regional stasis due to wall-motion abnormalities associated with these 2 conditions and the hypercoagulable condition resulting from the inflammatory process triggered by transmural infarcts, leading to clots forming in the left ventricle.<sup>4</sup> In addition, many patients with either of these conditions



**Figure 1.** (A) Initial noncontrast computed tomography (CT) shows no gross abnormalities. (B) The mismatch perfusion CT image shows abnormal perfusion in the left middle cerebral artery, inferior division distribution (CBF = cerebral blood flow; Tmax = time to maximum).

undergo percutaneous coronary angiography for diagnosis and treatment, which can rupture an aortic arch atheroma.<sup>4</sup> Cardiac sources should be considered particularly in those under age 45 even without clinical evidence of advanced heart failure.

**Bacterial endocarditis** increases the risk of embolic stroke dramatically. Merkler et al<sup>7</sup> reported that 2,275 (13%) of 17,926 patients with infective endocarditis had strokes in the year surrounding the diagnosis, with more than an 80-fold increase in risk in the first month compared with baseline.

**Right-to-left shunt** can allow venous thromboemboli to paradoxically enter the atrial arterial circulation and cause strokes. Although about one-fourth of adults have a patent foramen ovale, it does not appear to be a strong risk factor for stroke, except possibly in patients under age 50.<sup>4</sup>

Other causes of cardioembolic stroke include mechanical prosthetic heart valves, dilated cardiomyopathy, regional left ventricular akinesis, atrial myxoma, and rheumatic heart disease. Noncardiac causes of embolic stroke include aortic arch atheroma, carotid plaque, and, most relevant to our patient, malignancy.

### Cancer as a cause of stroke

Cancer is a major cause of embolic stroke.<sup>8–10</sup> About 10% to 15% of all patients admitted to a stroke service also had cancer, and for some, stroke was the initial symptom of cancer.<sup>8–10</sup> In one study, the odds ratio of having undiagnosed cancer when an arterial thromboembolic event occurs was 1.69 (95% confidence inter-

val 1.63–1.76).<sup>10</sup> Although all types of stroke are seen in patients with cancer, embolic stroke of undetermined source accounts for about half of all ischemic strokes.<sup>8</sup>

The association of cancer with thromboembolic events, both arterial and venous, is not a new finding. Professor Armand Trousseau made the first observations of this phenomenon in the 1860s.<sup>11</sup>

The risk of stroke is particularly high in the year before cancer is diagnosed, the first 6 months after the diagnosis, and when cancers metastasize to distant sites.<sup>8</sup> Neoplasias frequently associated with stroke include leukemias, lymphomas, and cancers of the lung, breast, pancreas, colon, rectum, kidneys, and prostate.<sup>8,9</sup>

**Multiple mechanisms** explain the association between cancer and stroke.<sup>8,9</sup>

Cancer cells invading the vascular system can trigger the coagulation cascade, activate platelets, or both.<sup>9</sup>

Some tumors are highly active in terms of protein production. Mucin in particular, which prostate cancer frequently produces, can mimic coagulation factors or make the plasma more viscous, triggering the coagulation cascade.<sup>9</sup>

Tumors can also mechanically compress large vessels, leading to blood stasis and clotting.<sup>9</sup>

Neutrophil activity and platelet activity are both increased in cancer, leading to platelet aggregation and coagulation cascade activation.<sup>8</sup>

Certain chemotherapies such as methotrexate, asparaginase, and cisplatin and cancer-supportive therapies such as colony-stimulating factors also increase the risk of stroke.<sup>9</sup> Radiation may accelerate the process of atherosclerosis.<sup>8</sup>



TABLE 2  
International Society of Thrombosis and Hemostasis scoring system for disseminated intravascular coagulopathy

	Points
<b>Platelet count</b>	
> 100 × 10 <sup>9</sup> /L	0
50–100 × 10 <sup>9</sup> /L	1
< 50 × 10 <sup>9</sup> /L	2
<b>D-dimer level</b>	
No change	0
Moderate increase	1
Strong increase	2
<b>Prothrombin time</b>	
≤ 3 seconds	0
> 3 to 6 seconds	1
> 6 seconds	2
<b>Fibrinogen level</b>	
> 1 g/L	0
≤ 1 g/L	1
<b>Sum of points</b>	
< 5: not suggestive of overt DIC (repeat in 1 to 2 days)	
≥ 5: suggestive of overt DIC (repeat daily)	

DIC = disseminated intravascular coagulopathy  
Based on information in reference 15.

Systemic thrombotic microangiopathy, which was first observed in autopsy studies, is another mechanism.<sup>9</sup>

DAY 3: BLEEDING

Hospital day 3 saw new trouble for our patient: mild bleeding from the nose and frank bleeding in the urine, the latter requiring placement of a 3-way Foley catheter with continuous bladder irrigation. He had not received any anticoagulation or antiplatelet therapy.

And another new sign was a holosystolic murmur (graded 2 on a scale of 6), loudest over the apex and increasing with expiration, indicating new mitral regurgitation. Cardiac telemetry still showed sinus rhythm.

Table 1 shows pertinent laboratory results obtained on that day. No schistocytes were seen on preliminary review of a peripheral smear specimen obtained on day 2 or on the final report of the smear, which was received on day 9.

DISSEMINATED INTRAVASCULAR COAGULOPATHY

Which of the following is the most common laboratory abnormality in disseminated intravascular coagulopathy (DIC)?

- ☐ Thrombocytopenia
- ☐ Low fibrinogen level
- ☐ Prolonged prothrombin time
- ☐ Elevated D-dimers

DIC is systemic activation of the coagulation system.<sup>9,12,13</sup> Whether the insult that triggers it is an inflammatory process due to cancer, trauma, infection, or an autoimmune condition, the result is an imbalance between thrombus formation and thrombolysis that ultimately leads to consumption and exhaustion of these factors.<sup>12–14</sup> Up to 15% of patients with cancer or major trauma and up to 40% of patients with sepsis (due to gram-negative rods in particular) present with DIC.<sup>13,14</sup>

DIC associated with malignancies is thought to be caused by tumor cells expressing procoagulant factors such as cysteine protease, which has factor X-activating properties.<sup>13</sup> Also, mucin production, which is increased in prostate cancer, appears to play a role by increasing plasma viscosity.<sup>9</sup> Almost all patients with advanced malignancies experience a procoagulant state that places them at risk for DIC.<sup>13</sup>

One of the major challenges in clinical practice is that DIC is frequently a subclinical condition, and no single symptom, finding, or test value confirms the diagnosis.<sup>12,13</sup> Most patients who present with symptoms have widespread clotting resulting in various degrees of organ damage.<sup>13</sup>

Highly vascularized organs such as the liver, kidneys, spleen, lungs, and brain are more susceptible to occlusion of the microvasculature caused by the fibrin deposits.<sup>12–14</sup> However, as coagulation factors and platelets are used up, a minority of patients experience bleeding as the predominant manifestation.<sup>13,14</sup>

Varied laboratory findings in DIC

No single test is diagnostic of DIC because, although each of them is highly sensitive, they lack specificity.<sup>12</sup>

**Thrombocytopenia** or a rapidly falling platelet count is seen in 98% of patients with DIC.<sup>12</sup> Thus, it is the correct answer choice above. Extremely low platelet counts increase the risk of bleeding between 4-fold and 5-fold.<sup>12</sup> However, half of patients have platelet counts higher than 50 × 10<sup>9</sup>/L—ie, low, but not extremely low.<sup>12</sup>

Prothrombin times and activated partial thromboplastin times are prolonged in about half of patients.

Fibrinogen levels remain normal or even elevated in half of patients with DIC, because it is an acute-phase reactant.<sup>12</sup>

The International Society of Thrombosis and Hemostasis scoring system incorporates prothrombin time, platelet count, and D-dimer and fibrinogen levels (Table 2).<sup>15</sup> It has a sensitivity and specificity of 95%, and high scores strongly correlate with risk of death.<sup>12,15,16</sup>

### DIC management

In general, DIC must be managed by correcting the underlying inflammatory process. In our patient, who had stage IVB prostate cancer, the underlying inflammatory state was irreversible. Treatment for DIC associated with malignancy includes supportive treatment with platelet transfusion (aiming at a platelet count higher than  $30$  to  $50 \times 10^9/L$ ), fresh frozen plasma, and fibrinogen concentrate (guided by the fibrinogen concentration in the patient's plasma). The use of heparin does not have enough data to support it.<sup>14</sup>

### ■ A NEW MITRAL VEGETATION, MULTIPLE INFARCTS

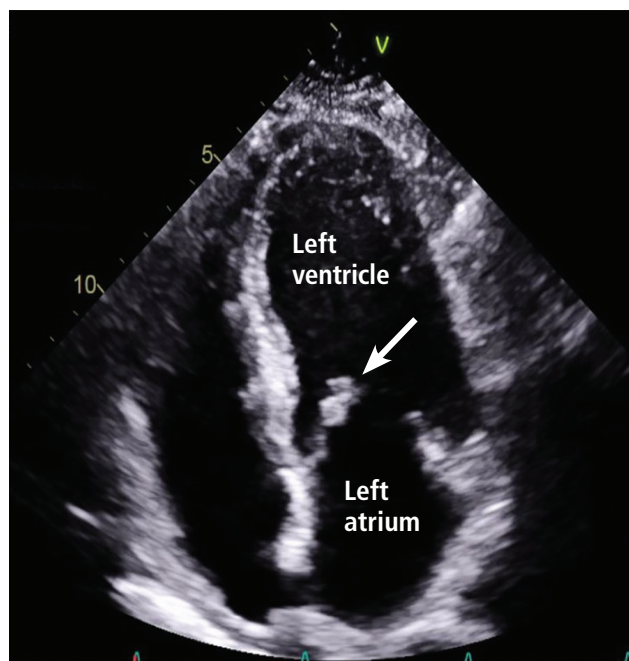
In our patient, repeat echocardiography showed a new mobile mass measuring  $0.6$  by  $0.8$  cm on the anterior mitral leaflet, causing moderate regurgitation (Figure 2).

The patient had no physical findings to suggest bacterial endocarditis. Furthermore, 2 sets of blood cultures were obtained, and they remained negative. The opinion of cardiology and infectious disease physicians was that the patient had nonbacterial thrombotic endocarditis.

CT of the chest, abdomen, and pelvis revealed infarcts in the kidneys and spleen and multifocal osseous metastases in the pelvis and several vertebrae. The cardiology and hematology-oncology consultants agreed that the multiple infarcts involving the kidneys and spleen were consistent with DIC.

Because the patient's hemoglobin level was low and falling, he was given a blood transfusion, and his fibrinogen level was monitored with the intention of giving him cryoprecipitate if the level dropped below  $100$  mg/dL. Unfortunately, his hematologic values did not improve (Table 2),<sup>15</sup> and he became increasingly tachypneic, with persistent epistaxis requiring intubation to protect his airway.

He had intermittent episodes of supraventricular tachycardia and suffered an anterior myocardial infarction with pulmonary edema (Killip class III).



**Figure 2.** Transthoracic echocardiography showed a new mitral valve vegetation (arrow) on the apical four-chamber view.

Further, new neurologic signs arose, prompting repeat CT of the head, which showed hemorrhagic transformation of the subacute strokes.

The patient did not have an advance directive in place before his admission. However, he did sign a medical power of attorney form during the hospital stay naming a family member to make surrogate decisions for him if he lacked capacity to make them. The decision was made with this family member and the rest of the family to move to comfort care. The patient died shortly thereafter.

### ■ NONBACTERIAL THROMBOTIC ENDOCARDITIS

**3** What is the most common cause of noninfectious endocarditis?

- ☐ Systemic lupus erythematosus
- ☐ Congenital valve abnormalities
- ☐ Malignancy
- ☐ Blood culture-negative endocarditis

**Malignancy** is the cause of 78% to 80% of cases of nonbacterial thrombotic endocarditis, mostly cancers of the pancreas, lungs, or stomach and adenocarcinomas of unknown origin.<sup>17,18</sup> However, the literature is limited to 2 autopsy series.<sup>17,18</sup> Deppisch and Fayemi,<sup>17</sup> in a 1976 autopsy study of 65 patients with nonbac-

terial thrombotic endocarditis, reported that adenocarcinoma was the most common histologic type of cancer associated with this condition, and 18.5% had findings suggestive of DIC. As mentioned previously, prostate cancer produces proteins such as mucin that create a hypercoagulable state.<sup>13</sup>

The mitral valve is affected in about two-thirds of patients, while the aortic valve is involved in one-fourth, and both valves are compromised in a minority of cases.<sup>17,18</sup> Compared with the vegetations in bacterial endocarditis, those of nonbacterial thrombotic endocarditis are more friable and more likely to become dislodged.<sup>19</sup> Thus, patients with nonbacterial thrombotic endocarditis are more likely to experience systemic embolization to the brain, spleen, and kidneys. For instance, embolic strokes occurred in 27% of patients (8 of 30) with nonbacterial thrombotic endocarditis in 1 series,<sup>20</sup> compared with 21% (25 of 133) with bacterial endocarditis in another series.<sup>21</sup>

In our patient, the acute presentation of mitral regurgitation was consistent with nonbacterial thrombotic endocarditis.

**Blood culture-negative endocarditis** is not the same as nonbacterial thrombotic endocarditis. Blood cultures can remain negative in 2% to 40% of all cases of endocarditis.<sup>22</sup> Negative blood cultures can result from giving antibiotics before blood samples for cultures are obtained or from infection with fastidious organisms such as *Bartonella* and *Mycoplasma*.<sup>22</sup>

Molecular techniques such as polymerase chain reaction are increasingly being used in diagnosing blood culture-negative endocarditis.<sup>22</sup>

**Systemic lupus erythematosus and antiphospholipid syndrome** are other causes of nonbacterial thrombotic endocarditis.<sup>19,23,24</sup> About 11% of patients with lupus have evidence of nonbacterial thrombotic endocarditis or Libman-Sacks endocarditis, a form of nonbacterial thrombotic endocarditis seen in lupus. The mechanisms causing the valve damage, which eventually lead to formation of a vegetation, include deposition of immunoglobulins and complement factors in the case of lupus and formation of antibodies against the phospholipids of the endothelium in the case of antiphospholipid syndrome.<sup>19</sup> In patients with lupus, the risk of nonbacterial thrombotic endocarditis is correlated with the duration of the lupus and is associated with the presence of antiphospholipid syndrome, although the latter is not necessary.<sup>19</sup>

**Congenital valvular abnormalities** such as a bicuspid aortic valve are a risk factor for bacterial endocarditis but not for nonbacterial thrombotic endocarditis.<sup>25</sup> The endothelial damage caused by the congenital defect and subsequent turbulence facilitates adhesion of bacteria whenever an organism reaches the bloodstream.<sup>25</sup>

## DISCLOSURES

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# On the horizon: Extracorporeal carbon dioxide removal

## ABSTRACT

Extracorporeal carbon dioxide removal (ECCO<sub>2</sub>R) uses mechanical systems to treat hypercapnic respiratory failure. Its utility has been investigated in acute respiratory distress syndrome (ARDS), acute exacerbations of chronic obstructive pulmonary disease (COPD), and status asthmaticus, and as a bridge to lung transplant. In this review, we discuss how it works, why it should help, and current evidence supporting its use.

## KEY POINTS

While ECCO<sub>2</sub>R may help facilitate low tidal volume ventilation in ARDS, evidence that it improves the survival rate is as yet wanting.

Similarly, although this therapy appears promising in other indications, evidence is still sparse.

The risks associated with ECCO<sub>2</sub>R, including hemorrhage, must be weighed against its purported clinical benefits.

At this time, the use of ECCO<sub>2</sub>R, promising as it is, should be explored within the confines of clinical research with a view to improving its safety and efficacy.

EXTRACORPOREAL CARBON DIOXIDE removal (ECCO<sub>2</sub>R) is similar to extracorporeal membrane oxygenation (ECMO) in that it involves shunting blood through a membrane device. But unlike ECMO, it does not provide significant oxygenation. The primary purpose is to remove carbon dioxide. Compared with ECMO, ECCO<sub>2</sub>R can be used with lower blood flow rates and smaller cannulas.<sup>1</sup> It may also be less expensive and easier to implement.

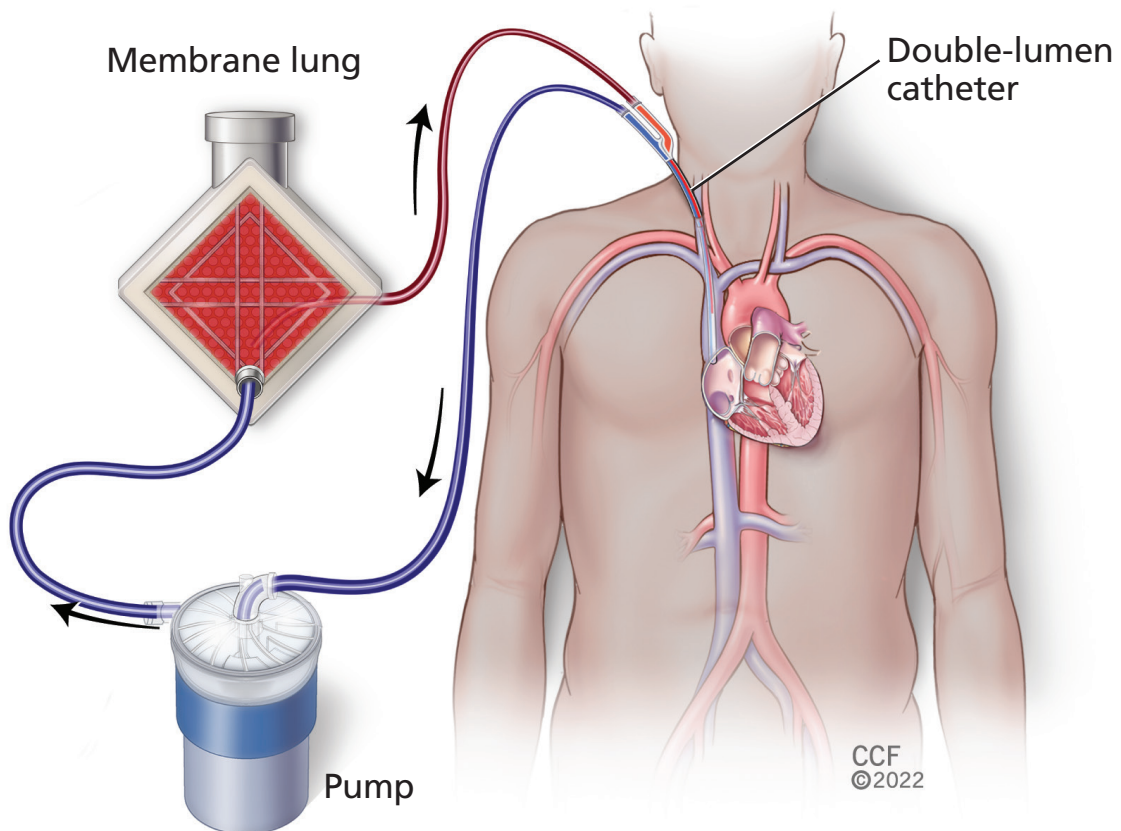
ECCO<sub>2</sub>R has been studied in various pulmonary diseases, eg, acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD),<sup>2</sup> and asthma,<sup>3</sup> and as a bridge to lung transplant.<sup>4</sup> Currently, only one ECCO<sub>2</sub>R device is approved by the US Food and Drug Administration, for use of up to 5 days.

As use of ECCO<sub>2</sub>R becomes more widespread, physicians will need to get more familiar with it. Extracorporeal life support technologies such as ECMO and ECCO<sub>2</sub>R require highly specialized training and technology.<sup>5</sup> The Extracorporeal Life Support Organization currently lists 351 ECMO-certified centers in the United States.<sup>6</sup>

This article, a primer for clinicians, provides an overview of ECCO<sub>2</sub>R including the rationale for its use, how it works, and evidence of its benefits.

## ■ WHY REMOVE CARBON DIOXIDE?

Hypercapnia and ensuing acidosis have detrimental effects on multiple body systems. Hypercapnia decreases myocardial contractility and increases pulmonary vasoconstriction, which could worsen right ventricular after-



**Figure 1.** Basic venovenous extracorporeal carbon dioxide removal circuit.

load, perpetuating right ventricular failure.<sup>7</sup> Hypercapnic acidemia may also contribute to lung injury by increasing production of nitric oxide. But on the other hand, it mitigates lung injury by decreasing reactive oxygen species, ie, superoxides. Theoretical benefits of ECCO<sub>2</sub>R include the following:

**Avoiding barotrauma.** Normally, we get rid of carbon dioxide by breathing it out, and for a patient on a ventilator, to get rid of more carbon dioxide, we would have to turn up the tidal volume, the ventilation rate, or both. But increasing the tidal volume can cause barotrauma. ECCO<sub>2</sub>R allows us to keep the tidal volume low.

**Slightly better oxygenation.** As the arterial partial pressure of carbon dioxide goes down, the partial pressure of oxygen in the alveoli should go up according to the alveolar gas equation—whereby, basically, the alveolar partial pressure of oxygen equals the fraction of inspired oxygen minus the partial pressure of carbon dioxide. Also, ECCO<sub>2</sub>R, by correcting hypercapnia, allows the ventilation strategy to focus on oxygenation.<sup>8</sup>

## CARBON DIOXIDE PHYSIOLOGY

Carbon dioxide is the product of metabolism within mitochondria.<sup>9</sup> With the help of the enzyme carbonic anhydrase, mostly in red blood cells, it combines with water to form carbonic acid, which dissociates into bicarbonate and hydrogen ions. All of these reactions are reversible, and although there is far more bicarbonate than dissolved carbon dioxide circulating in the blood, bicarbonate can rapidly be converted back to carbon dioxide as the latter is removed from the blood through breathing, maintaining the partial pressure of carbon dioxide.

Carbon dioxide is transported in the blood both dissolved in plasma and bound to hemoglobin, but the blood's carrying capacity for carbon dioxide is not limited by the hemoglobin concentration and binding capacity, as it is for oxygen. Compared with oxygen, carbon dioxide is more soluble and diffusible in the blood and has a linear hemoglobin dissociation curve that keeps going up, whereas that of oxygen reaches a plateau.

TABLE 1

### Differences between extracorporeal carbon dioxide removal (ECCO<sub>2</sub>R) and extracorporeal membrane oxygenation (ECMO)

	ECCO <sub>2</sub> R			ECMO	
	Respiratory dialysis	Membrane lung		Venovenous	Venoarterial
Conditions treated	Hypercapnic respiratory failure	Hypercapnic respiratory failure	Hypercapnic respiratory failure	Hypercapnic respiratory failure Hypoxemic respiratory failure	Hypercapnic respiratory failure Hypoxemic respiratory failure Cardiac failure
Circuit	VS → ML → VS	VS → ML → VS	AS → ML → VS	VS → MO → VS	VS → MO → AS
Flow rates	0.25–0.5 L/min	0.5–5 L/min	0.5–5 L/min	2–6 L/min	2–6 L/min
Pros	Uses current dialysis catheters	Single-catheter options	Pumpless	Oxygenation and CO <sub>2</sub> removal	Oxygenation and CO <sub>2</sub> removal Cardiac support
Cons	CO <sub>2</sub> removal only	CO <sub>2</sub> removal only	CO <sub>2</sub> removal only Mean arterial pressure > 65 mm Hg required	Increased surgical complexity	

AS = arterial system; CO<sub>2</sub> = carbon dioxide; ML = membrane lung; MO = membrane oxygenator; VS = venous system

Given these differences in transport and dissociation physiology, carbon dioxide removal is more effective than oxygen delivery at lower blood-flows.

#### ■ ECCO<sub>2</sub>R SYSTEMS

The typical ECCO<sub>2</sub>R setup (**Figure 1**) has 3 essential parts: the catheter or catheters, the membrane “lung,” and a pump (depending on the system) to circulate the blood.<sup>1</sup> Because the equipment continues to evolve and get more complicated, the Extracorporeal Life Support Organization<sup>10</sup> has developed standardized nomenclature to describe ECCO<sub>2</sub>R systems based on catheter function (drainage, reinfusion, or both), access site, size, and tip placement.

ECCO<sub>2</sub>R systems are frequently classified as either venovenous or arteriovenous. Venovenous systems take blood from a vein and return it to a vein, sometimes the same vein. A pump generates the necessary flow, allowing cannulation through low-pressure venous vessels, often with a single, dual-lumen, bicaval catheter (**Figure 1**). Arteriovenous systems usually use 2 single-lumen cannulas, which take blood from an artery and return it to a vein, with the arterial pressure driving blood flow. Such pumpless systems, while caus-

ing less blood trauma, require adequate cardiac output and larger cannulas to maintain adequate blood flow.

ECCO<sub>2</sub>R systems typically operate at lower flow rates than ECMO systems, as low as 250 mL/minute in combined ECCO<sub>2</sub>R-hemodialysis systems.<sup>11</sup>

**Table 1** compares key features of ECCO<sub>2</sub>R and ECMO systems.

#### ■ CARBON DIOXIDE REMOVAL MECHANISMS

ECCO<sub>2</sub>R systems use 2 main methods to remove carbon dioxide from blood.<sup>12</sup>

**The membrane lung technique**, the more common method, directly removes dissolved carbon dioxide by diffusion. Blood is circulated through microscopic channels on one side of a membrane, while gas without any carbon dioxide in it (the “sweep” gas) flows on the other side, generating a gradient so that the carbon dioxide diffuses across out of blood into this column of moving air. Other factors affecting carbon dioxide removal include the oxygen concentration in the sweep gas, the surface area of the membrane, and the rate of blood flow.

**The respiratory dialysis technique** removes carbon dioxide indirectly by removing bicarbonate ions

by hemodialysis. By itself, this would make acidemia worse because it leaves the acidic hydrogen ions in place while removing the basic bicarbonate ions.<sup>13</sup> To counter this deleterious effect, hydroxide and tris(hydroxy-methyl)aminomethane need to be infused, which can lead to hemolysis and arrhythmias. However, a 2020 study in pigs demonstrated the feasibility of this method by using a low-bicarbonate dialysate and avoiding blood acidification.<sup>14</sup>

Bicarbonate removal through ultrafiltration rather than hemodialysis has also been studied and can perform at lower blood flow rates than hemodialysis.<sup>15</sup>

## ■ ACUTE RESPIRATORY DISTRESS SYNDROME

About 10% of patients in intensive care units and 20% to 25% of patients on mechanical ventilators are there because they have ARDS.<sup>16</sup> It is a heterogeneous syndrome caused by a dysregulated inflammatory response resulting in damage to the interface between the capillary endothelium and alveolar epithelium. This in turn leads to increased capillary permeability, noncardiogenic pulmonary edema, and decreased lung compliance.

A low-tidal-volume strategy is the cornerstone of ARDS management. Setting the ventilator to a lower tidal volume improves survival outcomes by reducing ventilator-induced lung injury, but it also leads to hypercapnia due to decreased alveolar ventilation. ECCO<sub>2</sub>R has undergone trials to see if it can alleviate this effect and permit low-tidal-volume ventilation (4–6 mL/kg predicted body weight) or even ultralow-tidal-volume ventilation (< 4 mL/kg predicted body weight).

While interest in using ECCO<sub>2</sub>R in ARDS dates back to the 1980s, investigation is ongoing.

**The Xtravent study** (Extrapulmonary Interventional Ventilatory Support in Severe Acute Respiratory Distress Syndrome),<sup>17</sup> in 2013, compared ultralow-tidal-volume ventilation (about 3 mL/kg) plus ECCO<sub>2</sub>R vs about 6 mL/kg without ECCO<sub>2</sub>R in 79 patients with ARDS. Neither the number of ventilation-free days nor the mortality rate differed between the 2 treatment groups.

**The SUPERNOVA trial** (Strategy of Ultra-Protective Lung Ventilation with Extracorporeal CO<sub>2</sub> Removal for new-Onset Moderate to Severe ARDS),<sup>18</sup> in 2019, tested the feasibility of ECCO<sub>2</sub>R in maintaining ultralow tidal volume (4 mL/kg) in 95 patients with ARDS, 33 of whom were treated with a lower-powered carbon dioxide extraction machine and 62 with a higher-powered machine. Combining both groups,

ultralow-tidal-volume ventilation was obtained by 24 hours in 82% of patients (64% with the low-powered machines and 92% with the high-powered machines,  $P < .001$ ), with tidal volume, respiratory rate, minute ventilation, plateau pressure, and driving pressure significantly lower than at baseline; 69 patients (62%) survived to hospital discharge.<sup>19</sup>

**The REST trial** (Protective Ventilation With Veno-venous Lung Assist in Respiratory Failure),<sup>20</sup> in 2021, found no statistically significant reduction in mortality at 90 days. A concern with this trial is that patients were recruited based on severity of hypoxemia rather than ARDS criteria, which only 60% met at enrollment. A significant number of patients may not have exhibited conventional ARDS physiologic patterns, such as increased alveolar dead-space fraction and decreased respiratory system compliance. Studies have shown that these 2 factors, rather than severity of hypoxemia, may be better entry criteria in ECCO<sub>2</sub>R studies.<sup>21</sup> Also, the trial was stopped early due to futility and thus may have lacked power to detect a clinically important difference in mortality.

**Acute respiratory distress syndrome due to COVID-19** ARDS due to COVID-19 can progress to hypercapnic respiratory failure,<sup>22</sup> and ECCO<sub>2</sub>R has been used in this situation as well.

**Akkanti et al**<sup>23</sup> reported that respiratory acidemia improved in 29 patients with its use, with peak effect within 24 hours. However, only 11 patients (38%) survived to hospital discharge. This high mortality rate (62%) is comparable to that in COVID-19 patients on ECMO (37% to 59%, worsening over time).<sup>24</sup>

**Allescher et al**<sup>25</sup> studied the use of the Advanced Organ Support system (ADVOS), a combined ECCO<sub>2</sub>R-renal replacement-liver support system, in COVID-19 patients with mild to moderate ARDS. Multiple laboratory values improved (creatinine, blood urea nitrogen, pH, bicarbonate), but the in-hospital mortality rate was still 55%.

## ■ ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is defined by chronic inflammation of the airways, pulmonary parenchyma, and vasculature.<sup>26</sup> Its natural course includes episodes of acute deterioration (exacerbations), with a reported intensive care unit mortality rate of 25% in patients needing mechanical ventilation in 1 large study.<sup>27</sup> ECCO<sub>2</sub>R has been investigated in this population to see if it can help patients avoid needing mechanical ventilation.



Kluge et al,<sup>28</sup> in a retrospective study, reported that 19 of 21 patients for whom noninvasive ventilation had failed were able to avoid intubation by receiving ECCO<sub>2</sub>R.

Burki et al,<sup>29</sup> in a pilot study in 20 patients in 2013, found that a venovenous device provided clinically useful levels of carbon dioxide removal, significantly lowering the partial pressure of arterial carbon dioxide and raising the pH.

Del Sorbo et al<sup>30</sup> found a lower risk for intubation when bilevel positive airway pressure and ECCO<sub>2</sub>R were used together instead of bilevel positive airway pressure alone. In addition, the hospital mortality rate was lower in the ECCO<sub>2</sub>R group.

The ECLAIR study<sup>31</sup> (Extracorporeal Lung Assist to Avoid Intubation in Patients Failing NIV for Hypercapnic ARF) found that 14 of 25 patients with acute COPD exacerbation for whom noninvasive ventilation failed were able to avoid intubation with ECCO<sub>2</sub>R.

Azzi et al,<sup>32</sup> in a 2021 study, similarly examined ECCO<sub>2</sub>R use in patients who were at risk of noninvasive ventilation failure; 85% of the patients (22 of 26) avoided intubation. Complications in this study included major bleeding in 7 (20%) of the ECCO<sub>2</sub>R recipients, which was, however, less than in earlier studies,<sup>31</sup> despite a higher body mass index than in the control group (30 vs 25 kg/m<sup>2</sup>).

## ■ STATUS ASTHMATICUS

Asthma is a chronic inflammatory disorder of the airways, defined by variable and at least partially reversible airflow obstruction due to bronchial hyperresponsiveness to a variety of triggers.<sup>33</sup> As in COPD, the natural course is marked by exacerbations with episodes of acute respiratory distress caused by increases in airway swelling, secretions, and muscle constriction. The most extreme form is called status asthmaticus. These exacerbations are the reason for many intensive care unit admissions, with many patients requiring intubation (61% in 1 series).<sup>34,35</sup>

Tiruvoipati et al<sup>36</sup> used ECCO<sub>2</sub>R to treat 15 patients with acute or acute-on-chronic respiratory failure of various etiologies, including 2 with acute asthma exacerbation that required mechanical ventilation. In these 2 patients, the partial pressure of arterial carbon dioxide returned to near-normal levels within 6 hours, and both were discharged alive from the hospital.

Bromberger et al<sup>37</sup> applied ECCO<sub>2</sub>R in 26 intubated patients with status asthmaticus, whose arterial blood pH and arterial partial pressure of carbon dioxide improved, allowing for lowering of

inflation pressures on the ventilator. Additionally, the use of vasopressors was significantly decreased after ECCO<sub>2</sub>R initiation. Twenty patients were extubated while on ECCO<sub>2</sub>R, and all survived to hospital discharge.

While more research is required to see if ECCO<sub>2</sub>R can lower the mortality rate in this population, extracorporeal life support in asthma patients is associated with higher survival rates than in patients with other indications for extracorporeal life support,<sup>38</sup> and we hope this benefit may extend to ECCO<sub>2</sub>R. ECCO<sub>2</sub>R is not currently approved for this status asthmaticus.

## ■ A BRIDGE TO LUNG TRANSPLANT

Many patients with end-stage lung disease experience an acute decline in respiratory status while waiting for a transplant.<sup>39,40</sup> This can necessitate a bridging strategy with ECMO or ECCO<sub>2</sub>R. In such patients, “awake” ECMO (ie, with the patient awake, on ECMO, not on a ventilator) has been shown to have more favorable outcomes compared with mechanical ventilation.<sup>41</sup> Given that ECCO<sub>2</sub>R has smaller cannula sizes, easier insertion techniques, and lower flow rates than ECMO, it may be a better method for awake bridging<sup>42</sup> in those with primary hypercapnic respiratory failure, including those waiting for a repeat lung transplant.<sup>43</sup>

Benazzo et al<sup>44</sup> reported on 120 patients bridged with extracorporeal life support from 1998 to 2017, of whom 26 received ECCO<sub>2</sub>R.

Fischer et al<sup>40</sup> reported on arteriovenous ECCO<sub>2</sub>R in 12 patients with end-stage lung disease of various causes with ventilation-refractory severe hypercapnia and respiratory acidosis awaiting lung transplant. Ten patients underwent transplant, despite positive blood cultures in 7, use of mechanical ventilation, and need for extracorporeal life support, all of which are contraindications to lung transplant in some centers.

## ■ COMPLICATIONS

ECCO<sub>2</sub>R has been associated with various complications. The complex interplay between the patient’s sera and the artificial materials used in any extracorporeal device can lead to systemic inflammation by activating coagulation factors, platelets, leukocytes, and complement.<sup>3</sup>

Hemorrhage is common and can be catheter-related or at other sites such as the stomach, lungs, or brain. Doyle and Hunt<sup>45</sup> estimated an incidence of severe hemorrhage of nearly 40% in patients on ECMO, and the use of systemic anticoagulation alone

does not seem to be associated with bleeding risk.

**Hemolysis** has been reported in 2% to 11%,<sup>3</sup> with post hoc analysis of the SUPERNOVA data noting higher rates of hemolysis and bleeding in patients on low-flow than on high-flow systems.<sup>18</sup>

**Limb ischemia** can occur in 4% to 10% but is encountered more with arterial than with venous catheterization,<sup>12</sup> and it is of less concern in single-site venous cannulations.

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**Thrombocytopenia** has been reported in patients on ECCO2R in rates ranging from 2% to 13%.<sup>18,20</sup> ■

## DISCLOSURES

Dr. Lund has disclosed consulting for ALung Technologies. Tracy Dill has disclosed employment with ALung Technologies. Dr. Duggal has disclosed work as advisor or review panel participant and principal or co-investigator of funded research for ALung Technologies. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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# Is your patient at risk for NAFLD?

## ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) affects approximately 37% of US adults. The progression from nonalcoholic fatty liver with no inflammation to steatohepatitis with inflammation and progressive fibrosis is associated with substantial morbidity and mortality. The epidemic of NAFLD requires that primary care providers recognize at-risk patients and screen them. The authors review identifying individuals at risk, treatment options founded on lifestyle modification, and when to consider referring patients to a hepatologist.

## KEY POINTS

Screen for NAFLD in patients with diabetes, those with 2 or more metabolic risk factors, or those with fatty liver on imaging.

The Fibrosis-4 score is a noninvasive tool using age, aspartate aminotransferase and alanine aminotransferase values, and platelet count to identify patients at risk for fibrosis.

Vibration-controlled transient elastography measures liver stiffness and helps determine the presence and severity of fibrosis.

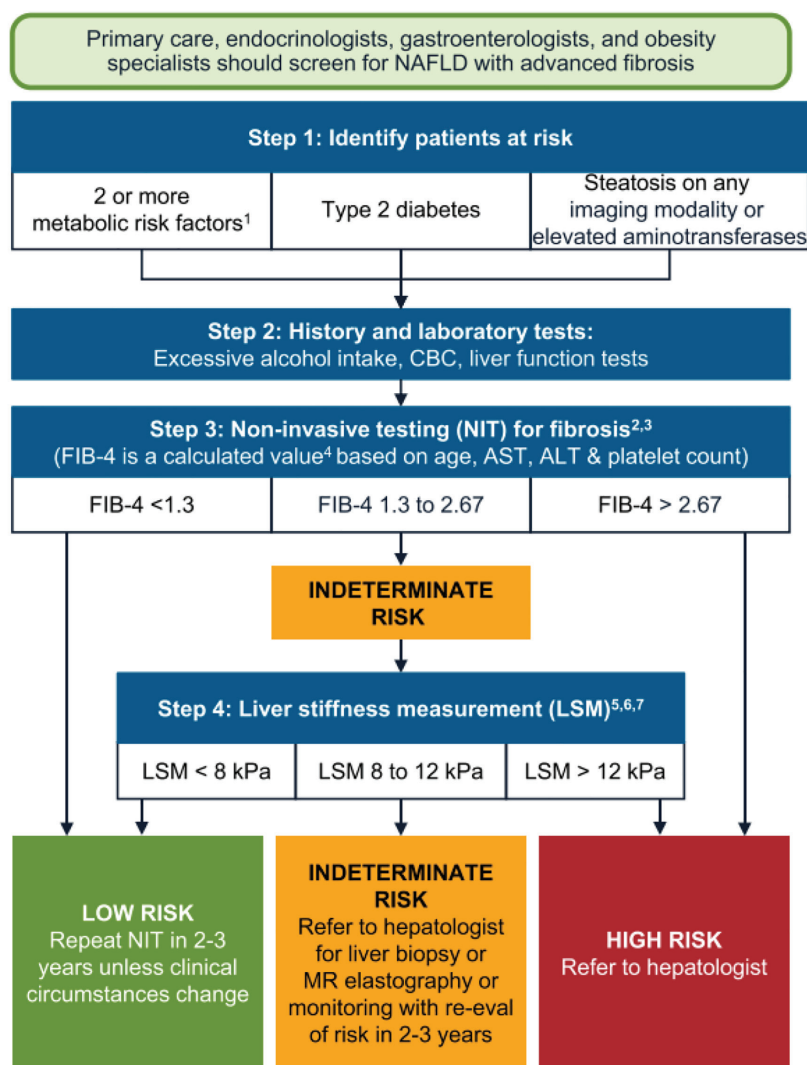
Intensive lifestyle modification with a calorie-restricted Mediterranean diet, exercise, and weight loss is the mainstay of treatment for NAFLD.

**N**ONALCOHOLIC FATTY LIVER DISEASE (NAFLD) is the most prevalent chronic liver disease in the world, affecting 25% of the world population.<sup>1</sup> NAFLD includes nonalcoholic fatty liver (NAFL), which is fatty liver without inflammation or liver damage, and nonalcoholic steatohepatitis (NASH), which is fatty liver with inflammation or liver damage, or both. In the United States alone, NAFLD affects approximately 37% of the population,<sup>2</sup> and the increasing incidence in the setting of obesity and the metabolic syndrome epidemic is expected to have a considerable impact on the development of cirrhosis, complications of liver disease, and liver cancer.<sup>1</sup> NASH cirrhosis is now the leading indication for liver transplant in women, patients over age 54, and Medicare recipients.<sup>3</sup> Patients with NAFLD are at increased risk for cardiometabolic diseases and malignancy, hence the benefit of early recognition.<sup>4</sup>

The challenge is to identify patients who have NASH and predict which patients are at the highest risk for developing fibrosis. Obesity, metabolic syndrome, and type 2 diabetes are the main risk factors for NAFLD, but the presence of other conditions such as genetic factors, sleep apnea, polycystic ovarian syndrome, and hypothyroidism also appear to play a role.<sup>5</sup>

Primary care providers (PCPs) play a central role in identifying patients with NAFLD and NASH, yet gaps in knowledge may inhibit the diagnosis and management of the disease. NASH and advanced fibrosis often remain undiagnosed in the primary care setting until signs and symptoms of advanced liver disease are present. To address this need, the American Gastroenterological Association (AGA), in collaboration with other professional societies, published clinical care pathways to provide guidance to providers in screening, diagnosis, and management of NAFLD (**Figures 1 and 2**).<sup>2</sup>





**Figure 1.** Screening patients for NAFLD with advanced fibrosis.

<sup>1</sup>Metabolic risk factors: central obesity, high triglycerides, low high-density lipoprotein cholesterol, hypertension, prediabetes, or insulin resistance.

<sup>2</sup>For patients 65+, use FIB-4 < 2.0 as the lower cutoff. Higher cutoff does not change.

<sup>3</sup>Other NITs derived from routine laboratories can be used instead of FIB-4.

<sup>4</sup>Many online FIB-4 calculators are available such as <https://www.mdcalc.com/calc/2200/fibrosis-4-fib-4-index-liver-fibrosis>.

<sup>5</sup>Ultrasonography acceptable if vibration-controlled transient elastography (VCTE, FibroScan) is unavailable. Consider referral to hepatologist for patients with hepatic steatosis on ultrasonography who are indeterminate or high risk based on FIB-4.

<sup>6</sup>LSM values are for VCTE (FibroScan). Other techniques such as bidimensional shear-wave elastography or point shear-wave elastography can also be used to measure LSM. Proprietary commercially available blood NITs may be considered for patients considered indeterminate or high risk based on FIB-4 or APRI (aspartate aminotransferase-to-platelet ratio index), or where LSM is unavailable.

<sup>7</sup>Eddowes et al (Gastroenterology 2019; 156[6]:1717–1730.) used 8.2 and 12.1 kPa as cutoffs for LSM using VCTE. Validation of simple (rounded) cutoffs reported by Papatheodoridi et al (J Hepatol 2021; 74[5]:1109–1116.).

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood cell count; MR = magnetic resonance; NAFLD = nonalcoholic fatty liver disease

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	<b>LOW RISK</b> FIB-4 < 1.3 or LSM < 8 kPa or liver biopsy F0-F1	<b>INDETERMINATE RISK</b> FIB-4 1.3 - 2.67 and/or LSM 8 - 12 kPa and liver biopsy not available	<b>HIGH RISK<sup>1</sup></b> FIB-4 > 2.67 or LSM > 12 kPa or liver biopsy F2-F4
	Management by PCP, dietitian, endocrinologist, cardiologist, others	Management by hepatologist with multidisciplinary team (PCP, dietitian, endocrinologist, cardiologist, others)	
Lifestyle intervention <sup>2</sup>	Yes	Yes	Yes
Weight loss recommended if overweight or obese <sup>3</sup>	Yes	Yes	Yes
	May benefit from structured weight loss programs, anti-obesity medications, bariatric surgery	Greater need for structured weight loss programs, anti-obesity medications, bariatric surgery	Strong need for structured weight loss programs, anti-obesity medications, bariatric surgery
Pharmacotherapy for NASH	Not recommended	Yes <sup>4, 5, 6</sup>	Yes <sup>4, 5, 6, 7</sup>
CVD risk reduction <sup>8</sup>	Yes	Yes	Yes
Diabetes care	Standard of care	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)

**Figure 2.** Management of NAFLD and NASH.

<sup>1</sup>Patients with stage F4 or cirrhosis (based on biopsy, LSM values based on vibration-controlled transient elastography [VCTE, FibroScan] or > 5.0 kPa on MRE) should undergo hepatocellular carcinoma surveillance. Varices screening is recommended if LSM > 20 kPa or platelet count of < 150,000/mm<sup>3</sup>.

<sup>2</sup>All patients require regular physical activity, healthy diet, avoid excess alcohol intake.

<sup>3</sup>Weight loss recommended for cardiometabolic benefit and reversal of steatosis. Greater weight loss is often associated with more benefit, such as reversal of steatohepatitis (usually with weight loss ≥ 7%) or fibrosis (usually with weight loss ≥ 10%).

<sup>4</sup>Individualize based on further workup and efforts to confirm the diagnosis of NASH. Liver biopsy provides helpful information and should be considered when there is a diagnostic doubt, such as in patients with indeterminate, unreliable, or conflicting noninvasive assessments or as part of phase 2 or 3 clinical trials.

<sup>5</sup>No pharmacologic agent is FDA-approved for the treatment of NASH. Patients with type 2 diabetes may benefit from some diabetes medications, such as pioglitazone (Sanyal et al, N Engl J Med 2010; 362:1675–1685; Bril et al, Diabetes Care 2019; 42:1481–1488; Aithal et al, Gastroenterology 2008; 135:1176–1184; Cusi et al, Ann Intern Med 2016; 165:305–315; Belfort et al, N Engl J Med 2006; 355:2297–2307) and some GLP-1 RAs (Armstrong et al, Lancet 2016; 387:679–690; Newsome et al, N Engl J Med 2021; 384:1113–1124) that have reported histologic improvement in randomized controlled trials in patients with NASH, either with or without diabetes. Among GLP-1 RAs, semaglutide has the strongest evidence of liver histologic benefit (Newsome et al, N Engl J Med 2021; 384:1113–1124).

<sup>6</sup>Vitamin E improves steatohepatitis in patients with NASH without diabetes (Sanyal et al, N Engl J Med 2010; 362:1675–1685), with less evidence in patients with type 2 diabetes (Bril et al, Diabetes Care 2019; 42:1481–1488).

<sup>7</sup>Pharmacotherapy in patients with NASH cirrhosis is very limited and should be avoided until more data become available.

<sup>8</sup>Statins can be used safely in patients with steatohepatitis and liver fibrosis. Avoid in patients with decompensated cirrhosis.

CVD = cardiovascular disease; FDA = US Food and Drug Administration; GLP-1 RAs = glucagon-like peptide-1 receptor agonists; LSM = liver stiffness measurement; MRE = Magnetic resonance elastography; NASH = nonalcoholic steatohepatitis; PCP = primary care provider

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TABLE 1  
NAFLD spectrum and classification

	NAFL	Early NASH	Fibrotic NASH	Advanced fibrosis	Cirrhosis
Fibrosis stage	No fibrosis	F0–F1 (no or mild fibrosis)	≥ F2 (significant fibrosis)	≥ F3 (advanced fibrosis)	F4
Histologic features	≥ 5% steatosis	≥ 5% steatosis and inflammation with hepatocyte injury (ballooning)	≥ 5% steatosis and inflammation with hepatocyte injury	≥ 5% steatosis and inflammation with hepatocyte injury	Bridging fibrosis
Weight loss needed for improvement, % of total	≥ 5%	≥ 7%	≥ 10%	≥ 10%	Not applicable <sup>a</sup>

<sup>a</sup>Some cases of reversal of F4 cirrhosis were observed with significant weight loss, such as with bariatric surgery.<sup>10</sup>

NAFL = nonalcoholic fatty liver; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis

Data from references 7–10.

■ NAFLD AND NASH DEFINED

NAFLD encompasses a wide spectrum of conditions, ranging from simple fat infiltration in the liver (NAFL, also called hepatic steatosis), to fatty liver with inflammation (NASH), and to the development of advanced fibrosis that may progress to cirrhosis, decompensated liver disease, and hepatocellular carcinoma.

NAFL is defined by the presence of at least 5% of fat infiltration in the liver without hepatocellular injury and in the absence of other etiologic factors such as alcohol, drugs, and other chronic liver diseases. NASH involves at least 5% steatosis and inflammation with hepatocyte injury (ballooning), with or without fibrosis.<sup>6</sup>

Liver fibrosis is classified as stages F0–F4, as follows:

- Stage F0–F1 (early NASH, no or mild fibrosis)
- Stage F2 or higher (fibrotic NASH)
- Stage F3 or higher (advanced fibrosis)
- Stage F4 (cirrhosis) (Table 1).<sup>7–10</sup>

In US adults with NAFLD, 25% will progress to NASH and 25% of patients with NASH will develop cirrhosis.<sup>11</sup> Based on findings by Younossi et al as cited by Diehl and Day,<sup>11</sup> liver fibrosis at the time of diagnosis is advanced in 25% of patients. It is estimated that liver fibrosis progresses by 1 stage per decade, but the rate of progression or regression varies considerably by individual.<sup>11</sup>

Patients with NAFLD have an increased overall mortality, and there is a clear association between stages of fibrosis and liver-related mortality. However,

cardiovascular disease is the primary cause of death, reflecting the burden of metabolic derangement of NAFLD.<sup>6</sup>

Factors that drive progression of NAFLD include alcohol consumption and the presence of commonly associated comorbidities such as obesity, hypertension, dyslipidemia, diabetes and insulin resistance, hypothyroidism, polycystic ovarian syndrome, and obstructive sleep apnea.<sup>1</sup>

There is no consensus on the threshold of alcohol consumption that differentiates alcohol-related liver disease from NAFLD. According to Sanyal et al as cited by Cotter and Rinella,<sup>1</sup> a common cutoff for substantial alcohol intake leading to exclusion in NASH clinical trials is more than 21 drinks weekly for men and more than 14 drinks weekly for women. The National Institute on Alcohol Abuse and Alcoholism as cited by Cotter and Rinella<sup>1</sup> defines a standard drink as containing 14 g of alcohol.

The effect of alcohol on NAFLD progression is difficult to assess because of inaccurate reporting of alcohol consumption and genetic differences in susceptibility to alcohol-related liver injury. It is best to assume that there is no safe amount of alcohol consumption for patients with NAFLD.<sup>1</sup> Given the lack of precise definition of significant alcohol consumption in patients suspected of having NAFLD, the concept of the term “metabolic dysfunction-associated fatty liver disease” (MAFLD) has been proposed.<sup>12,13</sup> MAFLD, which encompasses the previously discussed definition of NAFLD, is more inclusive than NAFLD as it does not exclude exces-

sive alcohol usage in its definition.<sup>12</sup>

It is worth noting that contrary to other liver diseases in which hepatocellular carcinoma (HCC) develops from cirrhosis, patients with NAFLD may develop HCC without the presence of cirrhosis. In a population-based study of medical records from 26 major integrated US healthcare systems, out of 392,000 NAFLD patients identified, 1,110 had a diagnosis of HCC, and of those, 170 (15.3%) did not have cirrhosis. Risk factors for development of HCC in the noncirrhotic patients were identified as older male sex, smoking history, diabetes, and elevated alanine aminotransferase.<sup>14</sup>

Patients with NAFLD who are diagnosed with HCC are typically older with higher extrahepatic comorbidities and a lower prevalence of cirrhosis than patients with HCC due to viral or alcohol-related liver pathology. The occurrence of HCC in the absence of liver cirrhosis poses a challenge for surveillance.<sup>15</sup> Liver fibrosis progresses over time and typically remains asymptomatic until patients present with decompensated cirrhosis or are diagnosed with HCC, at which time the opportunity for curative treatment decreases.<sup>16,17</sup>

## ■ SCREENING

In a primary care setting, NASH and advanced fibrosis are often undiagnosed until signs and symptoms of advanced liver disease are present. As such, PCPs are on the front line of identifying patients with NAFLD and stratifying patients at risk for developing advanced fibrosis in order to provide optimal management and referral. Different screening algorithms have been proposed to facilitate the delivery of care to patients and to optimize appropriate referrals to hepatology.<sup>18–21</sup> The AGA recommends screening for NAFLD with fibrosis (**Figure 1**)<sup>2</sup> in patients with the following:

- 2 or more metabolic risk factors (central obesity, triglycerides  $\geq 150$  mg/dL, high-density lipoprotein  $< 40$  mg/dL in men or  $< 50$  mg/dL in women, hypertension, prediabetes)
- Type 2 diabetes mellitus
- Incidental findings of fatty liver or elevated liver enzymes.

Screening for these high-risk individuals should include assessment for excessive alcohol use ( $> 21$  drinks/week for men,  $> 14$  drinks/week for women) and basic laboratory studies, including complete blood cell count and liver enzymes.<sup>2</sup>

While NAFLD often presents with abnormal

liver enzyme levels, the levels may be normal even in patients with advanced fibrosis. In a systematic review and meta-analysis of 4,084 patients, the alanine aminotransferase was normal in 25% of patients with NAFLD and 19% of patients with NASH.<sup>22</sup> The initial assessment of elevated liver enzymes starts with the exclusion of alternative or coexisting causes of liver or biliary diseases. This is best achieved by obtaining a detailed alcohol-intake history, evaluating for clinical signs of advanced liver disease, testing for hepatitis C, and consideration of testing for hepatitis B, autoantibodies (antinuclear, antimitochondrial, anti-smooth muscle), ferritin, immunoglobulins, and alpha-1 antitrypsin. Liver imaging to evaluate for mass lesions should also be performed.<sup>2</sup>

## ■ DIAGNOSIS

Fatty liver is typically detected on imaging studies such as ultrasonography or other advanced imaging. There is no laboratory test or imaging study that can conclusively diagnose NASH. The gold standard for NASH diagnosis and differentiation from NAFL is liver biopsy, the utility of which is limited due to invasiveness, risk of complications, patient acceptability, sampling variability, and cost.

Given these limitations and the high prevalence of NAFLD, it is important for PCPs to feel comfortable using noninvasive tools to assess for NASH, advanced fibrosis, and cirrhosis.<sup>23</sup> Noninvasive testing includes the use of serum biomarkers and imaging studies.

### Scoring systems

Scoring systems that utilize simple clinical and laboratory variables to assess the likelihood of advanced liver fibrosis include the Aspartate Transaminase Platelet Ratio Index, the NAFLD Fibrosis Score, and the Fibrosis-4 (FIB-4) score.<sup>23</sup> The FIB-4 score utilizes age, platelet count, aspartate aminotransferase, and alanine aminotransferase for evaluation of advanced fibrosis. It has been validated in patients with hepatitis C and human immunodeficiency virus coinfection to assess the need for biopsy and has more recently been used in patients with NAFLD.<sup>24</sup> In a study of 541 adults with NAFLD, a FIB-4 cutoff score of 1.3 or less had a 90% negative predictive value, while a cutoff of at least 2.67 conferred an 80% positive predictive value for advanced fibrosis.<sup>25</sup>

### Imaging

Ultrasonography is more effective at detecting ste-



atosis in patients with moderate to severe steatosis (greater than 20% to 30%) but less effective in patients with mild steatosis (< 20%).<sup>7</sup> Therefore, it is important to stratify a patient's risk of steatosis even if the ultrasound does not show steatosis.

Liver elastography can be used with both ultrasonography and magnetic resonance imaging. Transient elastography with the FibroScan device uses pulse-echo ultrasound waves to evaluate liver stiffness as an indirect indicator of the presence or absence of advanced fibrosis and steatosis. It can be used in most patients, except in those with severe obesity. Magnetic resonance elastography is very sensitive at diagnosing steatosis and fibrosis, but it is expensive and not widely available.<sup>23</sup>

### Other approaches to risk stratification

Noninvasive markers for advanced fibrosis and the development of novel pharmacologic agents that affect natural progression of advanced fibrosis<sup>26,27</sup> present an opportunity for PCPs to identify patients at high risk. Although there is no preferred approach to risk stratification, the guiding principle is to rule out advanced fibrosis using simple, noninvasive technology such as FIB-4 scoring, followed by transient elastography in patients at intermediate or high risk. Currently, FIB-4 scoring is one of the best noninvasive biomarkers, and its performance is enhanced by combining it with elastography in a sequential manner. The combination was found to be cost-effective in addition to providing high diagnostic accuracy,<sup>18,28</sup> and it represents an opportunity for PCPs to develop a partnership with a gastroenterology or hepatology practice and avoid unnecessary referrals.

## MANAGEMENT OF NAFLD AND NASH: LIFESTYLE MODIFICATION

Intensive lifestyle modification including weight loss, diet, and exercise is the first-line intervention and the only approved therapeutic approach for treating NAFLD. Given the considerable challenges of lifestyle modifications, a multidisciplinary team approach that includes a physician, dietitian, psychologist, and exercise physiologist is optimal. When a multidisciplinary team is not available, physician guidance can affect outcomes, as several studies have shown that physicians play an important role in motivating patients to lose weight with diet and exercise recommendations. They can also provide regular follow-up care.<sup>29</sup>

**Figure 2<sup>2</sup>** is a clinical care pathway for the management of NAFLD and NASH by risk of fibrosis.

### Weight loss goals

Weight loss of 5% or more of total weight can decrease liver steatosis, loss of 7% or more can lead to resolution of NASH, and loss of 10% or more can lead to fibrosis regression or lack of progression (**Table 1**).<sup>7-10</sup> In a prospective study of 293 patients with histologically defined NASH encouraged to follow lifestyle modification for weight loss over 52 weeks, there was resolution of NASH in 90% and regression of fibrosis in 45% of patients who lost 10% or more of their baseline body weight.<sup>30</sup>

In order to achieve substantial weight loss, daily calories should not exceed 1,200 kcal for women and 1,500 kcal for men. A low-calorie diet should be prescribed, even for patients with lean NAFLD (body mass index  $\leq 25$  kg/m<sup>2</sup> in non-Asian or  $\leq 23$  kg/m<sup>2</sup> in Asian patients), targeting a weight loss of 3% to 5%, given the histologic benefits for steatosis and NASH.<sup>8</sup>

### Weight loss medications

Antiobesity medications, ideally in the setting of a structured weight-loss program, should be considered in the appropriate patients. A detailed discussion of antiobesity medications is beyond the scope of this article, but glucagon-like peptide-1 (GLP-1) agonists such as liraglutide or semaglutide may be good options,<sup>31,32</sup> as discussed below (see "Drug therapy.")

### Diet

Most experts recommend the Mediterranean diet for patients with NAFLD. This diet is rich in olive oil, fish, nuts, whole grains, fruits, and vegetables. It has shown superiority in long-term weight loss compared with low-fat diets and improves metabolic derangement and steatosis even without weight loss.<sup>33</sup> Refined carbohydrates and alcohol should be avoided. Intake of refined carbohydrates is linked to increased systemic inflammation, which worsens NAFLD.<sup>34</sup>

Patient acceptance of dietary intervention is challenging because of habits, culture, and ethnicity,<sup>35</sup> but it is important to implement strategies to avoid relapse of weight gain. Ideally, dietary intervention is applied to the entire household to improve adherence. Lifestyle intervention is less effective in resolving NASH in elderly patients, patients with type 2 diabetes, and patients with more severe histologic activity on liver biopsy.<sup>29</sup>

### Exercise

Exercise, even without weight loss, can lead to a 20% to 30% reduction of intrahepatic lipids.<sup>29</sup> This occurs through various pathways, including improved peripheral insulin resistance and a decrease in delivery of fatty acids to the liver.<sup>36</sup> A behavioral assess-

ment for eating disorders and underlying psychiatric disorders such as depression can be valuable. Barriers to engagement in exercise should be evaluated, with practical solutions discussed with the patient.<sup>34</sup>

## ■ SURGICAL AND PHARMACOLOGIC OPTIONS

### Bariatric procedures

Bariatric surgery or, more appropriately, metabolic surgery,<sup>37</sup> has been shown to substantially improve NASH in patients with obesity as reported in a prospective study of 109 patients, in which 70 patients (85%) had resolution of NASH after bariatric surgery.<sup>9</sup> In a recent retrospective analysis of 196 patients who underwent bariatric surgery, active steatohepatitis was successfully reversed with 70% of patients showing fibrosis regression of 1 or more stages, but advanced fibrosis persisted in 47% of patients.<sup>10</sup> Endoscopic bariatric procedures (eg, intragastric balloon, transpyloric shuttle, gastric reduction or plication, duodenojejunal bypass liner, and dual-path enteral bypass magnets) have also been effective in NAFLD by both weight loss-dependent and weight loss-independent pathways.<sup>38</sup>

### Drug therapy

No medications for the treatment of NAFLD have been approved by the US Food and Drug Administration (FDA), but many pharmacologic agents are being evaluated for the treatment of NASH.<sup>39</sup> The mainstay of treatment for NAFLD remains weight loss, exercise, and treating metabolic comorbidities such as diabetes and dyslipidemia. Management of comorbidities presents PCPs with an opportunity to prescribe medications that may have a positive effect on reducing fibrosis, such as pioglitazone, GLP-1 receptor agonists, and sodium-glucose co-transporter-2 inhibitors.

**Pioglitazone** has been shown to improve insulin sensitivity, lower liver enzyme levels, and reduce NASH regardless of the presence of type 2 diabetes, but there are many adverse effects including weight gain.<sup>6,26</sup> Pioglitazone 30 mg once daily improves hepatic steatosis and inflammation, but 45 mg once daily is needed to improve fibrosis.<sup>26</sup> Given the improvement on liver histology, the American Association for the Study of Liver Diseases practice guidelines indicate that pioglitazone may be used in patients with biopsy-proven NASH. However, the risks and benefits should be considered and discussed with patients before initiation of therapy.<sup>6</sup>

**GLP-1 receptor agonists** liraglutide and sema-

glutide are currently being studied as treatment for NASH. The results appear promising, with improvement of liver enzyme levels, liver histology, and insulin resistance, but additional studies are needed to evaluate routine use for treatment of NASH.<sup>31,32</sup> Although these 2 medications are not yet FDA-approved for the treatment of NASH, they could be considered for treatment of diabetes or obesity in patients with NAFLD, as both medications have FDA indications for diabetes and obesity.

**Sodium-glucose cotransporter 2 inhibitors** are currently being studied in NAFLD. Trials include the Effect of Empagliflozin on Liver Fat in Patients With Type 2 Diabetes and nonalcoholic Fatty Liver Disease trial<sup>40</sup> and the Dapagliflozin Efficacy and Action in NASH study.<sup>41</sup> Early results indicate that empagliflozin and dapagliflozin reduce steatosis in patients with type 2 diabetes,<sup>41,42</sup> and dapagliflozin may also reduce liver fibrosis. However, this finding was only seen in patients with substantial liver fibrosis, and it is not clear if weight loss due to the medication caused the improvement.<sup>41</sup>

**Metformin** has been shown to improve insulin resistance and lower liver enzymes in patients with NAFLD.<sup>43,44</sup> However, it does not improve histology.<sup>45</sup> In a meta-analysis of 4 high-quality randomized controlled trials, Musso et al<sup>46</sup> found no improvement in liver enzymes or histology in individuals with NASH treated with metformin plus lifestyle intervention compared with those treated with lifestyle intervention alone—independent of dose, treatment duration, or presence of diabetes. Because metformin has not been shown to improve fibrosis, the American Association for the Study of Liver Diseases does not recommend this medication for the treatment of NASH.<sup>6</sup>

### Vitamin E, coffee, and herbals

In patients without diabetes, vitamin E 800 IU daily has been shown to improve NASH but does not have a considerable effect on fibrosis.<sup>47</sup>

Moderate caffeine intake has been associated with a lower risk of all-cause mortality as evidenced in an analysis of a large group of adults in the National Health and Nutrition Examination Survey 1999 to 2014.<sup>48</sup> A recent meta-analysis of 11 epidemiologic studies showed that regular coffee consumption has a favorable effect on NAFLD<sup>49</sup>: individuals who drink coffee regularly had a 23% decreased risk of development of NAFLD compared with those who did not regularly drink coffee. Individuals with established NAFLD who drank coffee daily had a 32% reduced risk of developing fibrosis. Setiawan et al and Wadhawan et al as cited in Hayat et al<sup>49</sup> reported that drinking more than 2 cups of coffee a day

was associated with a lower risk of liver fibrosis, cirrhosis, and hepatocellular carcinoma. The proposed mechanism for this decrease in liver injury associated with drinking coffee is the antioxidant effects of caffeine, as well as several other components found in coffee.<sup>49</sup>

Silymarin, an extract of milk thistle, was reported to reduce fibrosis without improvement in steatosis or inflammation, though larger studies are needed.<sup>50</sup> Resveratrol, a chemical found in red wine, may in conjunction with lifestyle modification improve inflammation in patients with NAFLD, though the benefits in NASH are inconsistent.<sup>51</sup>

## CONCLUSION

In this era of a global epidemic of NAFLD, PCPs play an essential role in identifying patients with NAFLD

and in screening them for advanced fibrosis using noninvasive techniques. The screening and management algorithms proposed by the AGA provide an opportunity to develop partnerships with gastroenterology or hepatology practices and avoid unnecessary referrals. There is no FDA-approved pharmacotherapy for NASH. Intensive lifestyle modification to manage weight, diet, and physical activity is the only approved therapy. ■

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