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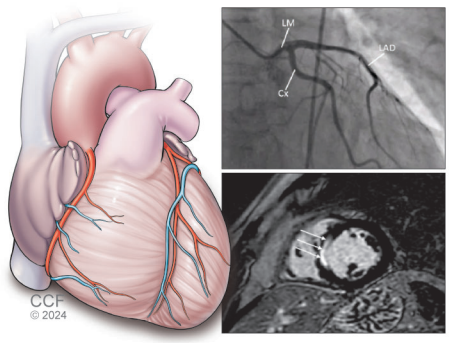

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The causes of vascular insufficiency and Hickam vs Ockham

Two articles in this issue of the *Journal* address the pathobiology of vascular insufficiency. Although the target organs are different in the 2 patients presented, skin and heart, the diagnostic implications have similarities.

Buda et al[1] discuss the evaluation of a 53-year-old patient with myocardial injury and acute myocardial infarction diagnosed by the clinical history and time course of troponin level changes. Elkin and McGervey[2] discuss a 74-year-old patient with discoloration of her feet, foot ulcers, and purple toes. Buda et al's patient had a long-standing history of human immunodeficiency virus infection managed with ongoing antiretroviral therapy, and, despite the myocardial infarction, no obstructive epicardial coronary obstruction was demonstrated on initial coronary angiography. Elkin and McGervey's patient with symptomatic ischemic changes on examination of her feet had a history of Raynaud phenomenon, polycythemia vera, previously treated breast and thyroid carcinomas, deep vein thrombosis, and hypertension.

The success of acute and chronic management strategies for both of these patients depends, in part, on the correct recognition and reversal of the dominant factor(s) contributing to their myocardial and soft-tissue ischemia. In academic exercises such as the clinicopathologic conference, the discussant reasons her or his way through the details of the patient's disease course and proposes a unifying diagnosis. The "diagnostic test" is then presented, which will support or refute the proffered diagnosis.

On teaching rounds and in the clinic one-on-one with a new patient, we pursue a similar mental exercise, hoping to arrive upon a dominant diagnosis. We do this while, as seasoned clinicians, fully realizing that for most of our older adult patients there is rarely just 1 pathologic actor on stage. If indeed there were no obstructing coronary lesions present, did the retroviral infection contribute to low-grade coronary inflammation, metabolic dysregulation, or microvascular obstruction in this 53-year-old man? In the woman with ulcers and purple toes, did prior carcinomas and therapy contribute to endothelial damage, is the history of venous thromboembolism relevant to her current apparent arterial disease, what is the contributory role of the polycythemia vera, and what of the history of Raynaud phenomenon? In other words, is our ingrained reflexive search for a single explanatory diagnosis always reasonable and warranted—or is it truly "just" an academic intellectual exercise?

When reflecting on the landscape of my patients, I don't believe it is a futile exercise. The effort forces us to consider the possibility of a single pathway to expression of the dominant clinical problem(s) at hand. But I also recognize that, for many patients, there is not a single diagnostic explanation for their entire clinical scenario. This got me thinking about Occam's razor,[3] which states that the single unifying diagnosis is the *best*, and Hickam's dictum,[4] stating that there may be several contributing diagnoses. And down the Internet greased rabbit hole I went.

Occam's razor, although embraced by William Osler and expressed by many medical educators since as "diagnostic parsimony," is not originally a medical construct. The original concept likely

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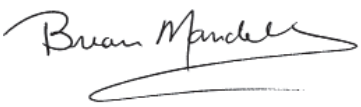
was born from Aristotle, who felt that the simplest explanation for a complex problem was likely the best. William of Occam (or Ockham; 1285–1348), a philosopher who was charged, presumably for other reasons, with heresy by the papal court,[5] popularized Aristotle's concept of simplicity and avoidance of excessive assumptions: "Plurality must not be posited without necessity."[6] It has ultimately made it into our medical aphorisms as, "When explaining a complex set of symptoms, a single diagnosis is better than invoking 2 or more unrelated ones." The reality of course, in other than 9-year-olds, is that the biologic canvas is rarely blank, and there are often confounding, if not impactful, clinical contributors to the expression of what has been termed the "end-point diagnosis."[7]

Hence, the counter to Occam's razor is expressed as Hickam's dictum. This has been attributed to Dr. John Bamber Hickam (1914–1970), who was a well-recognized cardiopulmonary physiologist, chair of the Department of Medicine at Indiana University, and medical educator.[8] I have not been able to find in print his folksy aphorism, but many authors have attributed this to him*: "A patient can have as many diseases as he damn well pleases." As an admonition to avoid premature diagnostic closure, this is a linchpin concept in the application of evidence-based medicine to the patient in front of us. Its applicability has recently been evaluated in a review of published case reports.[4] Its invocation should not stand in the way of attempting to piece together multiple components of a given patient's clinical picture with a single explanation—if that can be done with minimal assumptions and limited stretching of statistical likelihood. Plus, it is satisfying when we can do it.



Brian F. Mandell, MD, PhD
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*If anyone has an actual citation attributing that phrase to Dr. Hickam, please let me know.

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Diabetic retinopathy: Screening, prevention, and treatment

To the Editor: I read with great interest the review on diabetic retinopathy by Dr. Chong and colleagues[1] published in the August 2024 issue of the *Journal*. The article rightly emphasizes the pivotal role of primary care physicians in managing diabetic retinopathy through early detection and referrals. However, there are additional facets of diabetes care that deserve attention to further reduce the growing burden of this disease.

The authors emphasize the importance of glycemic control in preventing diabetic retinopathy. The article, however, could further explore the impact of new therapies, such as sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists, which have shown promise in managing diabetes but have complex interactions with diabetic retinopathy.[2] Recent studies have highlighted potential early worsening of retinopathy when rapid glycemic control is achieved using these agents.[3] Further discussion of this phenomenon could provide clinicians with a more nuanced understanding of the risks and benefits of sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists.

The section on artificial intelligence in diabetic retinopathy screening could be expanded regarding the limitations of artificial intelligence tools. While systems that use artificial intelligence to identify diabetic retinopathy are promising, concerns about lower specificity and inappropriate referrals are noted in other reviews.[4] A broader discussion of these limitations, as well as practical solutions, would aid in implementing such systems in clinical practice.

In summary, the authors have skillfully compiled important information on diabetic retinopathy, providing valuable guidance for clinicians treating patients with diabetes. Their thorough coverage of screening, prevention, and treatment offers critical insights. I commend their work and look forward to future updates and discussions on advancing management strategies and applying these insights in everyday clinical practice.

Ashley Lim, Medical Student
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doi:10.3949/ccjm.91c.12001

In Reply: We thank Ashley Lim for the comments on our review article.[1] We are pleased that readers are interested in our review and appreciate the opportunity to discuss any concerns raised in the letter.

We agree that new therapies such as glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter 2 inhibitors have significant value in achieving glycemic control to prevent diabetic retinopathy, and that GLP-1 receptor agonists have complex and unclear effects on the risk for diabetic retinopathy. Yet, several studies reported findings showing that sodium-glucose cotransporter 2 inhibitors are either not associated with a significantly increased risk of diabetic retinopathy or may even be linked to a significantly reduced risk, findings that seem to support their safety.[2–6]

However, as we discuss in the "Glucagon-like peptide-1 receptor agonists, rapid HbA1c reduction, and retinopathy" section of our review,[1] there is mixed evidence on the effect of GLP-1 receptor agonists on the risk of diabetic retinopathy, with some meta-analyses and trials reporting an increased risk[7–13] and others reporting no significant association between GLP-1 receptor agonists and risk for diabetic retinopathy or diabetic retinopathy progression.[14–18] Consistent with the findings of Wai et al,[19] the studies cited in our review that reported an increased risk of diabetic retinopathy observed an early rise in risk from 3 months to 3 years after patients started a GLP-1 receptor agonist.[11]

Because of the mixed results in the literature, further investigations on treatment methods that can drastically reduce hemoglobin A1c, such as specific types of GLP-1 receptor agonists, other pharmacologic therapies, and bariatric surgery, are necessary to elucidate the mechanism of potential early worsening of diabetic retinopathy and safe management of this complication of diabetes.

In clinical practice, it is important for clinicians to follow the American Diabetes Association screening recommendations[20] for diabetic retinopathy and to consider referring patients to an ophthalmologist to assess retinopathy status when prescribing GLP-1 receptor agonists.

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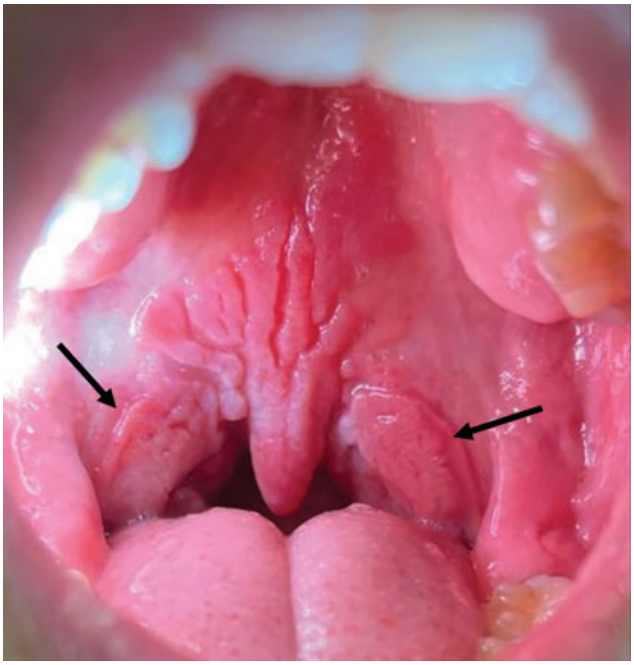

Figure 1. Oral condylomata lata of secondary syphilis (black arrows).

A 22-year-old man presented to the otolaryngology clinic with a 3-month history of painless oral lumps and intermittent sore throat. He had no significant medical history, was sexually active with other men, and was otherwise well.

Physical examination revealed diffuse edema of the oropharynx and nontender, well-demarcated mucosal patches on the soft palate, including the uvula and both palatoglossal arches (**Figure 1**). Examination of the entire body revealed no evidence of rash, lymphadenopathy, or anogenital lesions.

Biopsy of the soft-palate lesion showed intense acute and chronic inflammation, with large numbers of spirochaetal organisms within the surface epithelium (**Figure 2**). Screening tests for human immunodeficiency virus, *Chlamydia trachomatis*, and *Neisseria gonorrhoeae* were negative. However, a rapid plasma reagin test was positive (titer 1:256).

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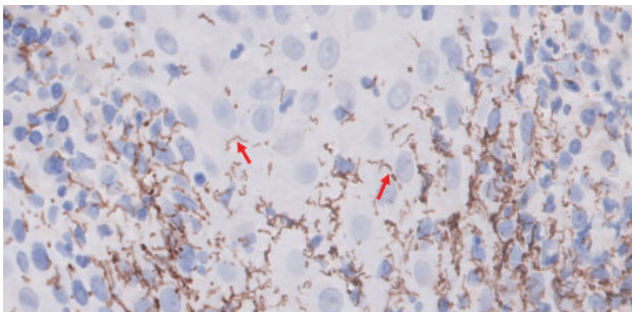

Figure 2. High-power image (1,000 × original magnification) of immunohistochemistry staining positive for *Treponema pallidum* showing numerous long, thin, spirally coiled organisms stained brown (red arrows) within the surface epithelium.

The patient's clinical findings were consistent with oral condylomata lata of secondary syphilis. He was subsequently treated with 1 dose of intramuscular benzylpenicillin, with full resolution of the oral lesions within 2 weeks.

ORAL MANIFESTATIONS OF SYPHILIS

Syphilis is a sexually transmitted infectious disease caused by *Treponema pallidum*. The incidence of primary and secondary syphilis has been increasing in the United States and worldwide in recent years.[1,2]

Oral manifestations of syphilis may occur in all 4 stages of the infection—primary, secondary, latent, and tertiary—but are most common in the secondary stage.[2] The occurrence, however, of purely oral lesions, such as in this case, is a rarely reported entity.[3]

The clinical presentation and histology of oral lesions differ depending on the stage of syphilis. In primary syphilis, a single painless oral chancre is characteristic. Chancres are generally asymptomatic and

present as a single ulcerated, erythematous lesion at the site of inoculation.[2]

Without adequate treatment, about one-quarter of primary infections will progress to secondary syphilis within 4 to 6 weeks after the appearance of the primary lesion.[4] Immunohistochemistry confirms the diagnosis and demonstrates numerous spiral-shaped spirochetes that infiltrate the epithelium.[1] Oropharyngeal manifestations in secondary syphilis are typically multiple, reflecting the hematogenous dissemination of the microorganism. These include highly infectious macules, papules, and ulcers, with patients often presenting with pharyngitis, tonsillitis, and laryngitis and nonspecific systemic symptoms such as malaise and fatigue.[2] Condylomata lata, a classic finding in secondary syphilis, are firm, moist, gray or white papules most often found in the anogenital region. They are infrequently reported in the oral cavity.[5]

Without treatment, the infection progresses to a latent phase in which the clinical signs of secondary disease resolve but patients retain positive serology.[2] It is generally an asymptomatic phase, although patients may experience mucocutaneous lesions.

A portion of infections will then progress over time to late or tertiary disease. The tertiary phase of infection may manifest in the mucus membranes with oral syphilitic gummas. These generally have a necrotic base and can be associated with destruction of the hard and soft tissue, including palatal perforation.[1,4] Gummas that affect the tongue can cause diffuse atrophy, termed "luetic glossitis."[1]

These varied oropharyngeal presentations are often one of the first signs of infection. Because some patients with undiagnosed syphilis may present only with oral lesions, early recognition of oropharyngeal condylomata lata with serologic confirmation should allow for definitive diagnosis and treatment, which may eliminate the need for biopsy if the lesions respond to treatment.

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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: How do I manage my patients with thyrotoxicosis until they see the endocrinologist?

A nonpregnant adult patient presented with progressive anxiety, heat intolerance, and palpitations. Thyroid-stimulating hormone was suppressed at less than 0.01 mIU/mL (reference range 0.5–4.0). Repeat testing showed thyroid-stimulating hormone again at less than 0.01 mIU/mL, with free thyroxine (T4) about 2 times the upper limit of normal at 2.98 ng/dL (0.8–1.8). I diagnosed the patient with thyrotoxicosis and placed a referral to endocrinology, but the patient will not be seen for about 8 weeks and is worried about progressively feeling worse. What steps can be taken in the meantime?

A: For a patient with symptomatic thyrotoxicosis, the first step is a referral to endocrinology, but there can be a long wait time. In the interim, a primary care physician can initiate beta-blockers promptly for symptomatic relief, obtain radioactive iodine uptake and scan if true hyperthyroidism is suspected, and, if high uptake is noted, start an antithyroid drug.

TOO FEW ENDOCRINOLOGISTS

Symptomatic hyperthyroidism is a common problem, affecting approximately 1% of the population.[1] Many primary care physicians would promptly and appropriately refer their patient with thyrotoxicosis to an endocrinologist. However, in an era of widespread and worsening physician shortages, endocrinologists are in short supply and high demand.[2] Wait times of several weeks to even months are common. Meanwhile, the patient is symptomatic. But the primary care physician can do a lot, both diagnostically and therapeutically, until care is established with the endocrinologist.

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STEPS THAT CAN BE TAKEN WHILE AWAITING ENDOCRINOLOGY REFERRAL

1. Determine whether the patient has true hyperthyroidism or excess thyroid hormone due to another cause

This distinction is important, as true hyperthyroidism, ie, increased endogenous thyroid hormone production, is unlikely to resolve spontaneously and should respond to thyroid-directed therapy like thionamides (methimazole and propylthiouracil), radioactive iodine ablation, or thyroidectomy. However, thyroid-directed therapy is unnecessary, ineffective, and potentially harmful for other forms of thyrotoxicosis such as thyroiditis (in which preformed thyroid hormone is released from an inflamed thyroid) or exogenous sources of thyroid hormone.

Exogenous thyrotoxicosis may not require specific testing. This is most obvious when the patient is known to be taking levothyroxine or other thyroid hormone preparations. Surreptitious or accidental exposure, often from weight loss or other health supplements, requires a higher index of suspicion.[3] Patients should be queried about all nonprescription supplements. The main treatment for exogenous thyrotoxicosis is to reduce or eliminate the source of thyroid hormone.

For all remaining patients, the most informative approach is to distinguish true hyperthyroidism (high uptake in the thyroid) from other forms of thyrotoxicosis (low uptake in the thyroid). The gold standard test is really 2 tests in 1: a radioactive iodine uptake study and scan. The "uptake" portion measures the percentage of administered iodine 123 that is present in the thyroid, typically 24 hours after administration. Accompanying nuclear medicine scintigraphy, or gamma scan, images

taken at the 24-hour mark can allow the clinician to visually differentiate between high-uptake states such as Graves disease (diffuse, symmetric uptake), single autonomous nodule (large single focus of concentrated iodine 123), or autonomous multinodular gland (patchy and scattered uptake throughout the thyroid).

Technetium 99m pertechnetate scintigraphy, which measures technetium trapped in the thyroid at approximately 20 minutes, is a quicker test that can be considered if the clinical situation (eg, the thyroid physical examination or prior thyroid imaging) suggests a single toxic adenoma or toxic multinodular goiter.[4]

These tests are ordered through radiology or nuclear medicine.

Importantly, symptomatic treatment (see step 2 below) can be started before radiotracer testing is performed. Thyroid-specific treatment (see step 3 below) should be deferred until after radiotracer testing is done to avoid skewing results. An additional pitfall of using radiotracers is that patients with a significant iodine exposure, such as iodinated contrast in the past several weeks or amiodarone use in the past several months, will have falsely low uptake of either iodine 123 or technetium. Finally, breastfeeding and especially pregnancy are contraindications to radiotracers.[5]

A classic presentation of Graves disease, the most common cause of endogenous hyperthyroidism, can be diagnosed without imaging. With symmetric goiter, recent-onset orbitopathy, and moderate or severe hyperthyroidism, other etiologies of thyrotoxicosis are unlikely. The diagnosis can be confirmed with elevated serum levels of thyroid-stimulating immunoglobulins.[4]

2. Provide symptomatic relief for all forms of thyrotoxicosis

Outpatients with adrenergic symptoms of thyrotoxicosis, such as palpitations, tremors, and anxiety, often desire prompt relief. Oral beta-blockers, such as propranolol or atenolol, can be prescribed without affecting subsequent testing. The usual considerations apply—for example, patients at risk of bronchospasm, such as those with asthma, present a relative contraindication to the use of beta-blockers.[1] Attention must also be paid to pretreatment and posttreatment heart rates and blood pressures, as beta-blockers can lower both.

Propranolol may be desirable compared with other beta-blockers, as it alone has been demonstrated to decrease peripheral conversion of T4 to triiodothyronine (T3), at least at high doses (hundreds of milligrams per day).[6] In the outpatient setting, propranolol can be prescribed at doses of 10 to 40 mg, 3 or 4 times daily. Alternatively, a more cardioselective beta-blocker such as atenolol (25–100 mg 1 or 2 times daily) or metoprolol tartrate (25–50 mg 2 or 3 times daily) can be used.[4]

Beta-blocker therapy alone will usually suffice for self-limited causes of thyrotoxicosis such as thyroiditis (including postpartum thyroiditis) or exogenous thyroid hormone (with concomitant reduction or elimination of this exposure).

3. Initiate antithyroid medication for true hyperthyroidism

For patients with true hyperthyroidism awaiting consultation with endocrinology, it is very reasonable to consider oral thionamides such as methimazole or propylthiouracil. These medications directly inhibit thyroid hormone synthesis.[7] This means they will affect thyroid function tests such as thyroid-stimulating hormone and free or total T4 and T3, as well as thyroid uptake and scintigraphy. Hence, as mentioned, ideally they are not initiated until after all diagnostic testing is complete.

Methimazole is typically preferred over propylthiouracil for treatment of nonpregnant adult outpatients because it is dosed less frequently and because of greater concerns for liver toxicity with propylthiouracil.[1] The starting dose depends on the degree of severity of thyrotoxicosis, as determined by both clinical signs and symptoms and biochemical values from laboratory testing. Many guidelines and review articles advocate for basing starting doses on free T4 values[1,4,7]:

- If free T4 levels are 1 to 1.5 times the upper limit of normal: methimazole 5 to 10 mg once daily
- If free T4 levels are 1.5 to 2 times the upper limit of normal: methimazole 10 to 20 mg once daily
- If free T4 levels are greater than or equal to 2 to 3 times the upper limit of normal: methimazole 20 to 40 mg daily in divided doses (eg, 10–20 mg twice daily).

After methimazole is started, thyroid function tests (especially free T4 and either free or total T3) should be repeated every 2 to 6 weeks until euthyroidism is achieved, then every 8 to 12 weeks thereafter, pending endocrinology consultation.[4,7] Assessment of T3 in addition to T4 is necessary, as free T4 may normalize despite persistent T3 toxicosis.[4] Methimazole can be titrated down as thyrotoxicosis improves.[7] Note that thyroid-stimulating hormone may remain suppressed for several months after starting thionamides, so the T4 and T3 assessment is more helpful in the early phase of treatment.

Thionamides can rarely cause hepatotoxicity as well as agranulocytosis or other cytopenias. Rash, affecting

TABLE 1
Recommended initial approach to thyrotoxicosis

Management area	Recommended plan
Diagnostic tests	Thyroid-stimulating hormone, free thyroxine (T4), free or total triiodothyronine (T3), thyroid-stimulating immunoglobulins, radioactive iodine uptake and scan
Symptomatic treatment of all patients (will not affect diagnostic tests)	Propranolol 10–40 mg 3 or 4 times daily *or* Atenolol 25–100 mg 1 or 2 times daily *or* Metoprolol tartrate 25–50 mg 2 or 3 times daily
Thyroid-directed treatment—if any 1 of elevated thyroid-stimulating immunoglobulins *or* high uptake of iodine 123 *or* high uptake of technetium 99m pertechnetate (will affect diagnostic tests) is found	Methimazole dosing based on free T4 levels: 1–1.5 × upper limit: 5–10 mg daily 1.5–2 × upper limit: 10–20 mg daily 2–3 × upper limit: 10–20 mg twice daily

Based on information from references 1,4,6.

6% of treated patients, is the most frequently reported side effect with methimazole.[7] Patients starting methimazole should have a baseline complete blood cell count and liver biochemistry testing to identify any preexisting abnormalities. Methimazole and propylthiouracil should be avoided in patients with a baseline absolute neutrophil count less than 1.0×10^9/L (reference range 1.8–7.7 × 10^9/L) or transaminase levels exceeding 5 times the upper limit of normal.[4]

Serial complete blood cell count and liver biochemistry testing are not necessary, but symptom-driven laboratory testing is recommended.[4] For example, white blood cell count with differential should be measured for any febrile illness or acute pharyngitis, while liver biochemistries should be measured for jaundice, light-colored stool or dark urine, nausea, or new pruritic rash.

THE BOTTOM LINE

Thyrotoxicosis is commonly encountered in primary care. Ideally, a patient diagnosed with thyrotoxicosis will be managed symptomatically with beta-blockers, and then will promptly (perhaps within 2–4 weeks) consult with an endocrinologist for more detailed diagnosis and management. But if the known or suspected wait time for endocrinology consultation is much longer, the astute primary care physician can start beta-blockers promptly for symptomatic relief, obtain radioactive iodine uptake and scan, and, if high uptake is noted, start methimazole.

See **Table 1** for a summarized approach.[1,4,6]

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COMMENTARY

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Matter of the heart: Prioritizing harm reduction in managing infective endocarditis associated with injection drug use

People who inject drugs have a 100-fold higher risk of infective endocarditis compared with the general population.[1] The incidence of injection drug use–associated infective endocarditis (IDU-IE) has increased with the opioid epidemic and growing number of people who inject drugs.[2]

Patients with IDU-IE are typically much younger than patients with infective endocarditis unrelated to IDU (non–IDU-IE),[2] tend to have a lower prevalence of other medical conditions, and achieve similar or better treatment outcomes in the short term, particularly with surgical interventions.[3] However, long-term outcomes are notably poorer compared with non–IDU-IE patients. Those with IDU-IE experience more complex hospital courses, prolonged hospitalizations, higher 30-day readmissions, increased occurrences of reoperation and reinfection, and increased rates of long-term mortality.[3–5]

The American Heart Association recently issued a scientific statement[6] with suggestions and guiding principles for managing IDU-IE. The statement emphasizes the need to treat substance use disorder in conjunction with endocarditis. This stance is endorsed by the American Association for Thoracic Surgery[7] and the American College of Cardiology.[8] We support a multidisciplinary approach that considers how to improve quality of care for IDU-IE from an addiction psychiatry perspective.[9]

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PARENTERAL ANTIMICROBIAL THERAPY: INPATIENT OR OUTPATIENT?

Treatment of infective endocarditis should be customized for each patient. The American Heart Association recommends 6 weeks of parenteral (intravenous or intramuscular) antimicrobial therapy.[6] Once acutely stabilized in the hospital, the patient can be discharged to receive outpatient parenteral antimicrobial therapy through a peripherally inserted central catheter for the remainder of treatment. Peripherally inserted central catheters are the preferred choice for medication administration because their durability allows for long-term access to the bloodstream for frequent drug administrations.[10] Alternative methods may be considered in certain situations, such as shortening the duration of parenteral antibiotic treatment, using long-acting lipoglycopeptide therapy, or switching to oral antibiotics.[6] Each patient is carefully assessed for surgical indications and extracardiac complications during and after their course of antimicrobial therapy.[6]

Despite evidence supporting the effectiveness of outpatient parenteral antimicrobial therapy, patients with IDU-IE receive it at a lower rate than non–IDU-IE patients. There may be concerns about whether IDU-IE patients are good candidates for outpatient therapy—for example, misuse of the peripherally inserted central catheter for self-administration of drugs, treatment nonadherence, challenges related to insurance coverage, and complex psychosocial and legal factors.[10] Nevertheless, extended hospital stays for patients with IDU-IE (often lasting 4 to 6 weeks) can lead to premature patient-directed discharges related

to ongoing addiction, loss of patient autonomy, and conflicts with the healthcare team.[11] Improved communication and rapport between staff and patients will help to prevent premature patient-directed discharges. This includes addressing immediate patient needs such as drug withdrawal and pain and providing concurrent comprehensive addiction and psychiatric treatment.[6]

There is no consensus on using outpatient parenteral antimicrobial therapy for IDU-IE, mainly because of limited clinical data. The American Heart Association recommends it for IDU-IE,[6] but the Infectious Diseases Society of America has expressed concerns about the quality of evidence supporting this approach.[12] These limitations exist because people who inject drugs have been excluded from larger clinical trials[13]; smaller studies demonstrate the safety, effectiveness, and cost benefits of outpatient parenteral therapy for IDU-IE.[10] This lack of consensus and research has affected clinical practice. A recent survey of infectious disease clinicians reported that less than one-third of those who agreed with using outpatient parenteral therapy for IDU-IE had a policy in place at their institutions to guide outpatient parenteral therapy for patients with IDU-IE.[14]

A HARM-REDUCTION APPROACH

Harm reduction is an evidence-based approach that uses interventions aimed at reducing the negative effects of drug-related behaviors without necessarily requiring complete elimination of drug use.[15] An approach based on harm reduction may reassure and encourage people who inject drugs and are reluctant to engage in treatment.

Education and sterile supplies

Patient education on the dangers of sharing needles and other drug-use equipment can help reduce injection-related risk behaviors and lower the likelihood of contracting infections. Providing patients with naloxone kits can further improve their health and safety. Some programs offer sterile needles, syringes, and other supplies to patients, which has proven to be an effective method of reducing blood-borne infections like human immunodeficiency virus and hepatitis C.[16] These initiatives aim to reduce the number of discarded needles and syringes in the community and provide a unique access point for health and social services that may not be readily available to this patient population.[16]

Additional harm-reduction practices include contingency management, which is behavioral therapy where the patient is rewarded (eg, a raffle ticket) for positive change such as a negative drug screen, and supervised consumption sites, which are sterile environments where individuals can use illicit substances under the observation of trained staff, emphasizing overdose prevention.[17]

Better outpatient access

A harm-reduction approach can also help improve outpatient parenteral antimicrobial therapy access for people who inject drugs. An initiative at a tertiary hospital found that people with peripherally inserted central catheters who inject drugs engaged in risky behavior, such as flushing the lines with nonsterile water or injecting drugs into the tubing instead of the port.[18] This led to the development of a comprehensive harm-reduction program that is currently implemented throughout the hospital system. The program provides clear guidance and support to clinical staff when working with people who inject drugs and are being discharged with a peripherally inserted central catheter. It also offers nonjudgmental education on safe injection practices and supplies sterile equipment on patient request.[18]

Specialized assistance: A challenge

Harm reduction also supports medication-assisted treatment or the use of medication alongside behavioral therapy to treat substance use disorders. The most common form of medication-assisted treatment in IDU-IE is medication for opioid use disorder. Some nursing and rehabilitation facilities will not admit patients who have a history of addiction or are prescribed medication for opioid use disorder. This is a challenge for people with IDU-IE who could benefit from a structured environment with specialized assistance or medical observation while completing their antimicrobial treatment. A safety-net hospital in Boston reported that 4 of 10 patients with opioid use disorder were declined admission to facilities.[19] This practice violates the Americans with Disabilities Act, but enforcement is rare and court rulings have had little effect.[19]

ROLE OF ADDICTION SERVICES: INTEGRATED TREATMENT

Complications in IDU-IE often stem from addiction; these include drug-related overdoses, recurrent infections, treatment nonadherence, and poor health-seeking behavior.[8] Although optimal addiction treatment is critical to improve the long-term medical outcomes for these patients,[4] only a small number of hospitals include addiction medicine in their management of IDU-IE.[20]

Medication for opioid use disorder

Optimal addiction treatment includes medications for opioid use disorder: buprenorphine, methadone, and extended-release naltrexone. The American Heart

Association recommends that medications be offered to every IDU-IE patient with opioid use disorder during hospitalization.[6] The choice of opioid use disorder medication should be based on the patient's preferences, addiction treatment history, and availability of medication in the outpatient setting.[21] If patients are already prescribed medication for opioid use disorder, it should not be discontinued during the hospital stay, but it may need to be adjusted.

Medication for opioid use disorder in IDU-IE patients can help to manage drug withdrawal symptoms, cravings, and pain, and it may improve patient engagement and retention. Studies have also shown that initiating medication for opioid use disorder in IDU-IE patients can reduce premature patient discharges.[22] Because premature patient discharges are linked to higher rates of hospital readmissions[23] and mortality,[24] beginning treatment for opioid use disorder could be an effective strategy to enhance patient outcomes, including increasing antibiotic therapy completion.[10]

Multidisciplinary treatment team

Stigma, genetic predisposition, trauma, concurrent psychiatric disorders, social support systems, home environment, education, employment, and legal circumstances all significantly influence the development and perpetuation of addiction. Certain strategies help mitigate these factors:

- Implementing an approach that is comprehensive, nonjudgmental, patient-centric, low-barrier, and centered on harm reduction
- Establishing close posthospitalization follow-up
- Integrating psychiatrists, psychologists, and social workers in IDU-IE care.[25,26]

Several models have been used to integrate addiction treatment into the care of patients with IDU-IE. One involves creating an inpatient multidisciplinary endocarditis team that includes an addictionologist.[9] The team sees all admitted IDU-IE patients and participates in all related meetings. Although the evidence is limited to single-center observational studies, this model has been shown to reduce in-hospital mortality, improve 1-year survival, increase rates of surgery, and decrease time to surgery,[27] as well as reduce the time from admission to addiction consultation and increase initiation of medication for opioid use disorder.[28]

If a multidisciplinary team is unavailable, an option is to establish an inpatient addiction consultation service. This service facilitates initiation of medication for opioid use disorder, improves outpatient addiction follow-up, reduces addiction severity, increases the number of days of abstinence,[29,30] increases the completion of antimicrobial therapy,[20] and decreases short-term mortality.[31]

WHERE TO NOW?

Treating IDU-IE is complex and challenging. Addressing the coexisting addiction is essential to achieve the best long-term outcomes. Despite recommendations from the American Heart Association, American College of Cardiology, and American Association for Thoracic Surgery, many patients with IDU-IE do not receive substance use disorder treatment in conjunction with heart disease treatment. Further research, including experimental and observational studies such as randomized controlled trials, cohort studies, and big data analysis, is needed to encourage clinicians to unlearn and change clinical practices. More qualitative studies are also necessary to determine the attitudes, barriers, and facilitators that can guide clinical practice.

Surgeon and cardiology champions are needed to create urgency and empower their addiction colleagues. Large-scale strategies to reduce stigma must be implemented and explored in hospital settings to improve patient-clinician relationships, reduce patient-directed discharges, and improve patient health-seeking behaviors. Alternatives such as harm-reduction strategies and supervised consumption sites should also be explored. It is essential to understand the social and structural determinants of people who inject drugs in order to identify new prevention strategies that will decrease the incidence of IDU-IE.

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Dr. Cantu-Weinstein has disclosed being an employee of Natera, Inc. and having ownership interest (stock, stock options in a publicly owned company) in Natera, Inc. 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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A 74-year-old woman with purple toes

A 74 YEAR-OLD WOMAN presented to the hospital from the podiatry clinic for evaluation of bilateral foot pain and purple toes. She had a history of Janus kinase (JAK) 2 V617F–positive polycythemia vera, Raynaud syndrome, gastroesophageal reflux disease, prior breast cancer and thyroid cancer, hypertension, and deep vein thrombosis and pulmonary embolism. Her polycythemia vera had been treated with aspirin, which was discontinued due to stomach upset, and hydroxyurea, which was also recently discontinued. She was started on apixaban following her deep vein thrombosis and pulmonary embolism episode and was still taking it at the time she presented.

The patient reported that her symptoms began about 5 months earlier. At that time, she experienced intermittent burning foot pain, worsened by prolonged sitting and standing. She developed painful ulcers on her right hallux, described as "black dots" that expanded, and later developed additional ulcers on her left lateral ankle and right anterior shin. The ulcer on her left ankle was biopsied and found to be consistent with livedoid vasculopathy.

She was started on pentoxifylline and nifedipine, and hydroxyurea was discontinued due to concern that it was contributing to her ulcerations. The ulcers initially improved with wound care. However, about 3 weeks before her current presentation, her toes started to become purple, with persistent "stinging" pain that improved somewhat with warmth and elevation.

PHYSICAL EXAMINATION

On presentation, violaceous discoloration of both feet was noted, with necrotic tissue present distally (**Figure 1**). Her feet were cold to the touch, with palpable dorsalis pedis pulses bilaterally and intact sensation and strength. Cardiac examination was unremarkable, without murmurs, rubs, or gallops. Palpation of her abdomen did not reveal splenomegaly. No joint swelling, erythema, or tenderness to palpation was present.

DIFFERENTIAL DIAGNOSIS

1 What is the most likely diagnosis?

- ☐ Livedoid vasculopathy
- ☐ Critical limb ischemia
- ☐ Microthrombi
- ☐ Erythromelalgia

The differential diagnosis for purple digits is broad. In a hemodynamically stable patient, emergent etiologies include acute limb ischemia, embolic microthrombi, purpura fulminans,[1] and catastrophic antiphospholipid syndrome (APS).[2] Purple digits stem from abnormal blood flow, which can have various causes. These include microembolisms from upstream clots, large aneurysms, peripheral vascular disease, vasospasm, vasculitis and pseudovasculitis, thrombosis or mechanical obstruction, cryoglobulinemia, myeloproliferative syndromes, and hypercoagulability secondary to malignancies or hypercoagulable syndromes.[1,2]

Livedoid vasculopathy, and a "diagnostic time-out"

Livedoid vasculopathy, a thrombotic vasculopathy that is more common in females and presents with lower-extremity ulceration,[3] was initially considered on the differential. However, the presence of abnormal findings of purple toes supporting a competing diagnosis such as microthrombi, diagnostic uncertainty, and unanticipated deviation from the expected ulcer treatment course prompted a "diagnostic time-out"[4,5] to consider whether this patient's presentation represented 1 process related to livedoid vasculopathy or 2 distinct processes.

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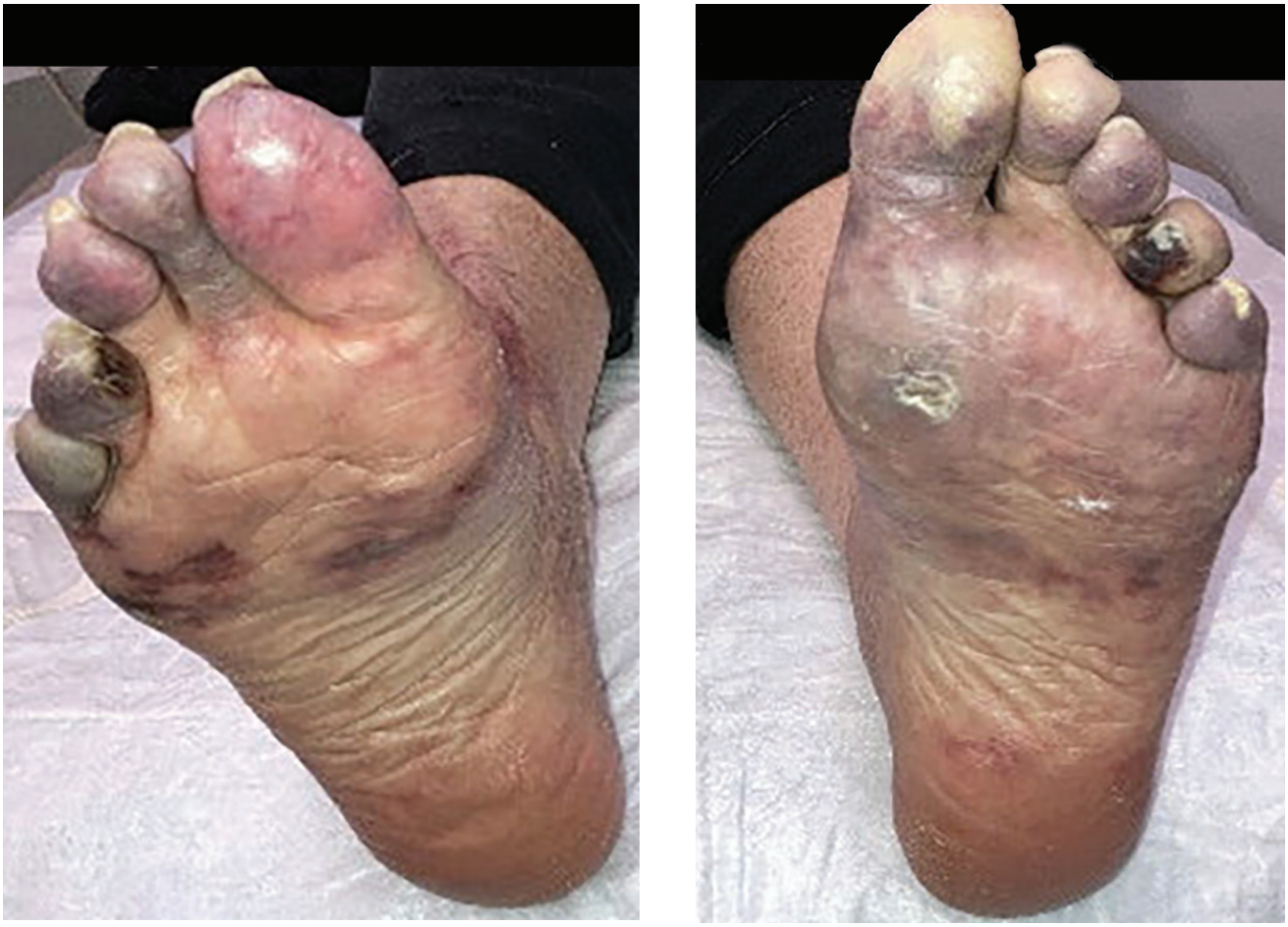

Figure 1. Violaceous discoloration of patient's toes on presentation.

Initially, the patient reported that the symptoms began 5 months previously. However, careful history revealed that her ulcers had been healing with the treatment for her livedoid vasculopathy, and the new symptoms of purple toes developed more recently. While livedoid vasculopathy presents with lower-extremity symptoms and burning, purple toes would be atypical. This prompted consideration of a separate process driving her current presentation or a unifying underlying condition tying these 2 distinct processes together.

Limb ischemia or microthrombi

One of the first branch points in the evaluation of purple digits is the presence or absence of a peripheral pulse. Acute arterial occlusion typically presents with the 5 "Ps": pain, pallor, paresthesia, paralysis, and pulselessness.[6] In this patient, palpable pulses, as well as intact strength and sensation, point away from acute limb ischemia requiring emergent evaluation and treatment. However, palpable pulses do not rule out embolic or thrombotic etiologies. Cholesterol embolization famously produces "blue toe syndrome," and similarly microthrombi, commonly from endocardial vegetations or thrombi, block vessels distal to the dorsalis pedis, leading to ischemia with a palpable pulse. A cardiopulmonary examination can reveal murmurs pointing to endocarditis or valvular abnormalities as a potential source for showering thrombi or vegetations, and a vascular examination can reveal bounding pulses pointing to vascular aneurysms.

Erythromelalgia

Erythromelalgia is a complication of polycythemia vera that is thought to be mediated by a complex interplay of neural and vascular dysfunction involving arteriole-venule shunts[7] and by platelet dysfunction.[8,9] This disorder is marked by episodes of increased temperature, erythema, and burning pain in the extremities, and its symptoms are relieved by cooling of the

TABLE 1
Details of the patient's malignancy history

	T1cN0M0 triple-negative breast cancer	Papillary thyroid carcinoma	Janus kinase V617F–positive polycythemia vera
Diagnosis timing	11 years before current presentation	14 years before current presentation	6 years before current presentation
Medical treatment	Adjuvant chemotherapy (docetaxel and cyclophosphamide)		Aspirin (initially discontinued due to stomach upset), hydroxyurea (discontinued due to leg ulcerations), ruxolitinib
Surgical treatment	Breast-conserving surgery	Total thyroidectomy	
Other treatment			Phlebotomy
Radiation	Radiation to right breast	Radiofrequency ablation	

TNM = tumor, node, metastasis

extremity and limb elevation.[7] Erythromelalgia was considered because the patient had been diagnosed with polycythemia vera but was not taking aspirin, which can improve symptoms or erythromelalgia,[7] and because she reported symptom improvement with leg elevation, suggesting hyperviscosity. She discontinued taking aspirin due to intolerance and was started on apixaban. However, the patient's report of symptom improvement with heat and her cold foot temperature made this diagnosis unlikely.

Other concerns

With concern for small-vessel ischemia, a paraneoplastic vasculitis separate from polycythemia vera–related JAK2-mediated thrombosis was considered, given her history of breast cancer and thyroid cancer (**Table 1**). An autoimmune vasculitis was also considered given her history of Raynaud disease. The patient showed no joint swelling or tenderness, suggesting no autoimmune involvement of the joints, but this did not rule out autoimmune conditions or vasculitis.

Of note, hydroxyurea, a rare cause of both ulceration[10] and livedoid vasculopathy,[11] had been stopped in this patient previously due to concern it was contributing to her leg ulcerations.

CASE CONTINUED: NOTABLE VASCULAR AND LABORATORY TESTING RESULTS

Laboratory test results were notable for hyponatremia to 126 mmol/L (reference range 132–148) and hypokalemia to 3.6 mmol/L (3.7–5.1). A pulse volume recording showing an ankle-brachial index (ie, the systolic blood pressure in the ankle divided by the higher of the systolic pressures in the 2 arms) of 1.08 on the right and 1.02 on the left (1–1.4). A complete blood cell count without differential showed the following:

- White blood cell count 38.27 × 10^9/L (3.7–10.4)
- Hemoglobin 12.9 g/dL (12.3–15.3)
- Platelet count 323 × 10^9/L (150–400).

A differential the next day showed the following: white blood cell count 36 × 10^9/L, with 89% neutrophils (42–75), 4% lymphocytes (16–52), 1% monocytes (1–11), 2% eosinophils (0–7), and 1% basophils (0–4).

A partial workup for thrombophilia had been done when the patient developed lower-extremity ulcers, but full lupus anticoagulant testing was not completed at that time.

2 What aspect of this patient's history or treatment would prevent full lupus anticoagulant testing?

- ☐ Use of a direct oral anticoagulant (DOAC)
- ☐ History of breast cancer
- ☐ Polycythemia vera
- ☐ Use of hydroxyurea

APS is an autoimmune condition in which the presence of antiphospholipid antibodies leads to thrombosis or obstetric complications.[12] Clinical criteria include the presence of arterial, venous, or small-vessel thrombosis or obstetric complications, while laboratory criteria include the presence of antiphospholipid antibodies in plasma, namely lupus anticoagulant, anticardiolipin, or anti–beta-2-glycoprotein 1 antibodies.[12,13]

Full lupus anticoagulant testing could not be completed in this patient because she was taking apixaban.

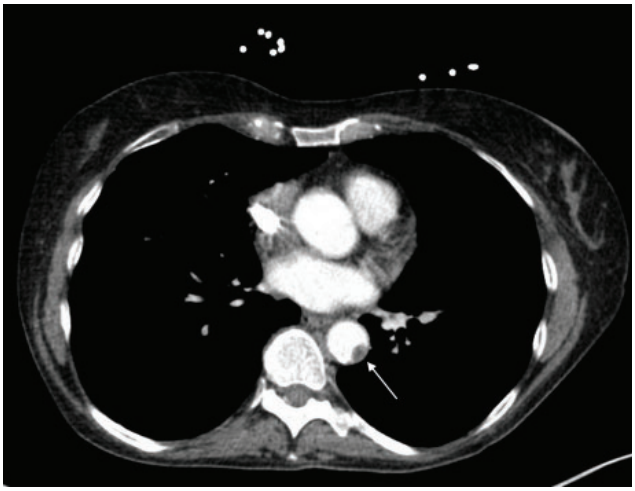

Figure 2. Computed tomography scan showing aortic thrombus.

DOACs can affect APS laboratory assays, causing both false-positive and false-negative lupus anticoagulant findings,[14,15] and different DOACs affect the assays differently.[14] Other anticoagulants can also interfere with testing, but established neutralizers for heparin included in many reagents for the dilute Russell's viper venom time, a common test for lupus anticoagulant, help mitigate this.[14] Several strategies have been proposed to evaluate patients on DOACs for APS, including pausing DOAC, DOAC antagonists, and DOAC removal from the specimen,[14,15] although these are not available in many laboratories.

Apart from guiding the diagnostic workup, her laboratory workup showed significant leukocytosis, hyponatremia, and hypokalemia. The leukocytosis was felt to be reactive, the hyponatremia was likely hypovolemic and improved with fluids, and potassium was repleted.

CASE CONTINUED: FURTHER MANAGEMENT

The partial laboratory workup was negative for anticardiolipin, anti–beta-2-glycoprotein 1 antibodies, and cryoglobulins, and positive for antinuclear antibody (1:640).

With thrombi on the differential, apixaban was discontinued, unfractionated heparin was begun, and an echocardiogram was ordered. Given her history of Raynaud disease and concern for vasoconstriction, nifedipine, which had been started as part of her treatment for livedoid vasculopathy, was continued, and nitroglycerin topical ointment was ordered for treatment of the digital ulcers. To evaluate for neoplastic syndrome, a computed tomography imaging of the chest, abdomen, and pelvis was obtained and showed an 8-mm thrombus (**Figure 2**).

3 What is the most likely location of this patient's thrombus?

- ☐ Bilateral proximal deep veins of the left and right lower extremity
- ☐ Central clot in the inferior vena cava
- ☐ Aorta
- ☐ Carotid artery

The presence of bilateral symptoms from thromboembolic disease implies either bilateral thrombi or a central arterial thromboembolic source. Venous thrombi would propagate towards the heart, not distally. The central arterial source is most commonly the heart, where structural or functional abnormalities can cause clot to form, and thus an echocardiogram is an essential part of the evaluation for arterial thrombi,[16,17] even when, as in this patient, the cardiac examination revealed no murmurs or other abnormalities.

Thrombi within or proximal to the heart can embolize anywhere in the body, while more distal thrombi have fewer potential locations.[17] A thrombus in the carotid arteries would be more likely to embolize to the brain than to the lower extremities.[17] A rare but serious cause of peripheral embolism is mural thrombus in the aorta.[16,18]

THROMBOEMBOLIC DISEASE IN POLYCYTHEMIA VERA

The clinical question now centers on the development of a substantial thrombus in a patient taking apixaban and its management.

The patient was initially started on anticoagulation after she developed a deep vein thrombosis and pulmonary embolism in the setting of polycythemia vera. Thrombosis is a common complication of polycythemia vera, with an estimated incidence of 26% in patients followed for 20 years.[19] Most thrombotic events occur early in the disease course, often preceding diagnosis.[20] Interestingly, this patient's thrombotic event occurred years after her initial polycythemia vera diagnosis. The JAK2 V617F mutation is a strong independent risk factor for thrombosis through multifactorial mechanisms, including overexpression of procoagulant factors and platelet and endothelial cell dysfunction.[21]

There is no clear consensus on the use of vitamin K agonists such as warfarin vs DOACs in patients with polycythemia vera and other myeloproliferative disorders,[19] although there is a greater quantity of evidence

TABLE 2
Details of rheumatology consult clinical reasoning

Clinical feature	Possible rheumatologic etiology	Evidence against rheumatologic etiology
Overall presentation	Lupus erythematosus, systemic sclerosis, other antinuclear antibody spectrum disorders	No inflammatory joint pain, arthritis, serositis, mucositis, or renal involvement No family history of autoimmune disease
Foot ulceration	Raynaud phenomenon	Proximal ulcerations with preserved distal sensation
Rash	Vasculitis	Rash not characteristic of vasculitic etiology, no obvious thickening of large vessels

for vitamin K agonists.[21] The limited number of head-to-head studies comparing vitamin K agonists with DOACs in myeloproliferative disorders show similar outcomes, with some slightly favoring DOACs.[21]

While oral anticoagulation reduces both arterial and venous thrombus risk in patients with polycythemia vera, it is not as protective against arterial thrombus, which is mediated partially by platelet and endothelial dysfunction. Low-dose aspirin is typically used for primary prevention of thrombotic events, including arterial clots, in patients with polycythemia vera.[19] The patient had been taking aspirin before she started apixaban for deep vein thrombosis or pulmonary embolism, at which point it was discontinued because of poor tolerance. It is unclear whether aspirin has an added benefit in patients with polycythemia vera on DOACs or merely increases bleeding risk without significant additional protection from thrombosis.[19,21] Further studies are needed.

This patient potentially had risk factors for thrombosis apart from polycythemia vera. She had undergone a partial workup for APS in the past, but a full workup was needed at this point, especially in the context of her developing thrombosis while taking apixaban.

CASE CONTINUED: RHEUMATOLOGY REFERRAL

The 8-mm thrombus identified on computed tomography was located in the mid-descending thoracic aorta. Similar thrombus was noted in the abdominal aorta close to the bifurcation, and splenic infarcts were noted as well. Echocardiography showed normal systolic and diastolic function and no thrombi or vegetations.

Rheumatology was consulted because of concern for an underlying autoimmune condition, noting the patient's high antinuclear antibody titer, lack of other clinical symptoms of systemic rheumatic disease, negative cryoglobulins, and no clinical or laboratory features of small-vessel vasculitis (**Table 2**). Rheumatology recommended an APS workup, which was positive for lupus anticoagulant. Vascular medicine recommended repeat lupus anticoagulant testing in 12 weeks.

ANTICOAGULATION IN APS

4 What is the preferred anticoagulant agent for APS?

- ☐ DOAC
- ☐ Warfarin
- ☐ Aspirin alone
- ☐ Clopidogrel alone

Two factors in the current presentation could disrupt testing: use of heparin and the presence of active thrombosis. While heparin can be neutralized by specific reagents during lupus anticoagulant testing, heparin levels can exceed the neutralizing ability, and these reagents are not usually present in activated partial thromboplastin time reagents.[14] Thus, results obtained in this clinical context should be interpreted with caution and repeated in the coming weeks, as recommended by vascular medicine.

APS is associated with a characteristic netlike "livedo" rash, which can be further classified into livedo reticularis and livedo racemosa.[22] Both are caused by reduced blood flow, but livedo racemosa is more widely distributed on the trunk and the limbs, is irregular and broken in shape, has abnormal histopathology findings, is always pathologic, and is associated with APS and several other diseases. Although this patient's skin findings were not characteristic of livedo, with violaceous digits rather than a net-like violaceous pattern, her APS adds further evidence for increased thrombotic risk.

In APS, positive lupus anticoagulant is associated with a high risk for thrombosis.[23] The presence of anticardiolipin and anti–beta-2-glycoprotein 1 antibodies may convey additional risk, and some

guidelines define a "high-risk" APS profile as the presence of lupus anticoagulant, presence of double-positive antibodies with or without lupus anticoagulant, triple-positive antibodies, or high antibody titers.[24]

Patients with APS with arterial thrombosis typically are treated more aggressively than those with venous thrombosis.[23] Current data show the risk of arterial thrombosis recurrence is lowest for patients on warfarin in combination with antiplatelet therapy, with some data, including a systematic review of 12 cohort studies and 4 randomized controlled trials, showing that international normalized ratio (INR) targets greater than 3 were associated with a lower risk of recurrence in patients with arterial thrombosis.[25] However, the risk of bleeding with the addition of an antiplatelet agent, oral anticoagulation, or a higher INR target must be weighed against the risk of recurrent arterial thrombosis, especially in the context of studies showing no benefit of high-intensity warfarin in APS for venous thrombus.[23]

The question of vitamin K agonists vs DOACs for APS is more clear-cut than for myeloproliferative disorder, with evidence favoring the former.[19,23] It is important to distinguish between low- and high-risk APS profiles when interpreting studies comparing DOACs vs vitamin K agonists, as some studies showing no differences in venous thrombosis outcomes are limited by underrepresentation of patients with a high-risk APS profile.[24]

Interestingly, in the 2018 Trial on Rivaroxaban in Antiphospholipid Syndrome (TRAPS)[26] comparing warfarin with rivaroxaban in patients with triple-positive APS, recurrent thromboses were seen more often in the rivaroxaban group and were largely arterial. Our patient likely would have been placed on warfarin had her APS diagnosis been established at the time of the initial venous thromboembolism event. Her treatment with apixaban was less protective against future thrombotic events, particularly arterial thrombosis, although it is important to note that the studies done used rivaroxaban, not apixaban. Further, there is a dearth of studies examining use of DOACs specifically for arterial thrombosis in patients with APS.

CASE CONCLUDED

Vascular medicine recommended an intravenous heparin drip for 72 hours with a target activated partial thromboplastin time of 53 to 78 seconds, with a plan to transition to therapeutic enoxaparin 1 mg/kg twice daily for 4 weeks, followed by a bridge to warfarin with a target INR of 2 to 3 and clopidogrel. The patient's burning bilateral foot pain continued despite the heparin therapy. She underwent aortography with suction thrombectomy of her infrarenal aortic thrombus, after which her pain improved, and she was discharged.

In patients with a descending thoracic aortic thrombus, the initial treatment strategy is typically conservative, with anticoagulation, sometimes antiplatelet agents and, rarely, thrombolytic therapy. Typically, endovascular treatments such as thrombectomy or surgical treatments are used in cases where conservative measures fail, as in this patient, although thrombus size and mobility and diagnostic uncertainty may lead to initially pursuing endovascular or surgical treatment options.[27]

Her hematology team transitioned her polycythemia vera treatment to ruxolitinib, a JAK1-JAK2 inhibitor shown to be superior to standard therapy in controlling hematocrit and symptoms in patients intolerant of hydroxyurea.[28,29]

TAKE-HOME POINTS

- The differential diagnosis for purple toes is broad. A major branch point is the presence or absence of peripheral pulses to rule out critical limb ischemia necessitating urgent evaluation and management.
- Recurrent thrombosis in the setting of anticoagulation necessitates further workup.
- Patients may have multiple risk factors for thrombosis, which may change optimal anticoagulation management.
- The anticoagulation of choice for all patients with APS is warfarin.

DISCLOSURES

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

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REVIEW

CME MOC

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Myocardial infarction with nonobstructive coronary arteries: Current management strategies

ABSTRACT

From 6% to 8% of patients who present with myocardial infarction have no evidence of obstructive coronary artery disease on angiography. This subgroup tends to be younger, and more of them are women. This review highlights a proposed algorithm to identify the underlying cause of myocardial infarction with nonobstructive coronary arteries (MINOCA). We emphasize the need for a collaborative approach in diagnosing and managing MINOCA to improve patient outcomes, advocating for a standardized diagnostic pathway that incorporates cardiac magnetic resonance imaging and comprehensive clinical evaluation to tailor treatments effectively.

KEY POINTS

The diagnosis of myocardial infarction requires a rise or fall in troponin plus other evidence of acute ischemia such as symptoms, electrocardiographic changes, imaging evidence, or a thrombus detected on coronary angiography.

MINOCA is a subtype of myocardial infarction in which there is no significant epicardial stenosis.

MINOCA has multiple potential causes, and additional clinical evaluation and testing are required to determine which one the patient has. However, data are limited regarding subtype-specific treatment and prognosis.

Intracoronary imaging and cardiac magnetic resonance imaging are key tests in the diagnosis of MINOCA.

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A 53-year-old man with a history of human immunodeficiency virus infection, on antiretroviral therapy, was brought to the emergency department by ambulance with acute onset of substernal chest tightness. His initial electrocardiogram showed normal sinus rhythm with borderline inferior-wall ST-segment elevation, which did not, however, meet the criteria for ST-segment elevation myocardial infarction (STEMI) (**Figure 1**). The ST-segment elevation was unchanged on repeat tracing.

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The patient's chest discomfort resolved after he received aspirin, sublingual nitroglycerin, and 4,000 units of intravenous unfractionated heparin. His initial troponin I level was 0.49 ng/mL (upper reference limit 0.030 ng/mL), and it increased to 8.4 ng/mL at 2 hours and 14.7 ng/mL at 6 hours after the initial measurement, which prompted an urgent referral to the cardiac catheterization laboratory.

No obstructive epicardial coronary artery disease (≥ 50% stenosis) or evidence of plaque rupture was noted on initial angiography (**Figure 2**). There was, however, a moderate narrowing in the first septal perforator branch of the left anterior descending artery. Transthoracic echocardiography showed a regional wall-motion abnormality in the mid-anterior and mid-inferior septum.

In view of his symptoms and initial evaluation suggestive of myocardial infarction but without significant stenosis or culprit lesion on

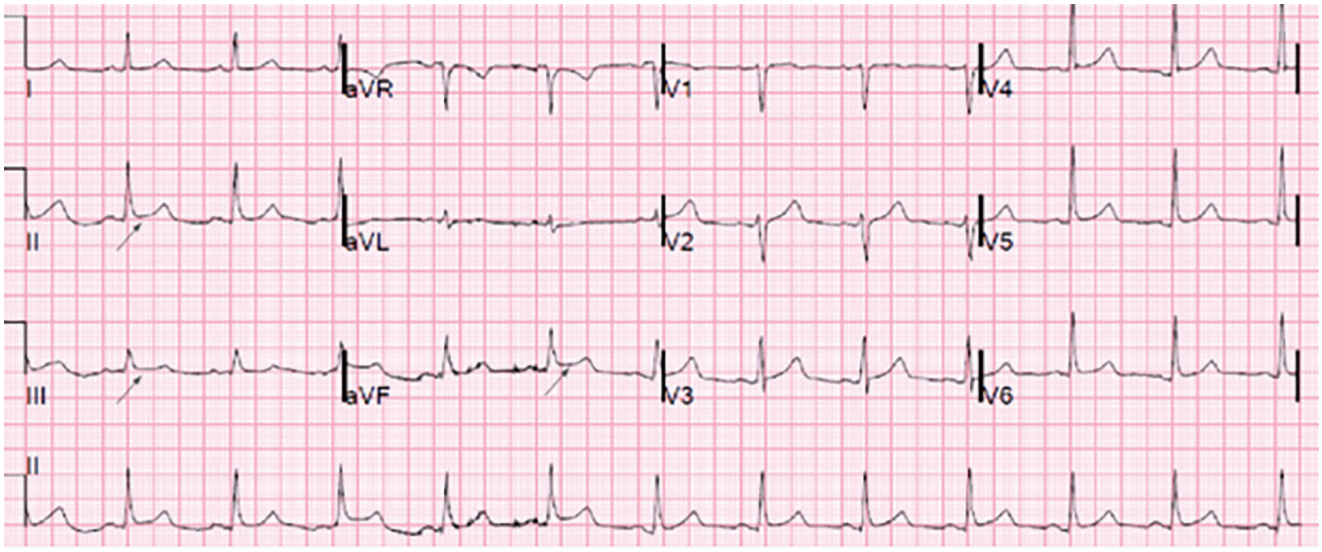

Figure 1. The patient's initial electrocardiogram showing borderline ST-segment elevation, which did not, however, meet the criteria for ST-segment elevation myocardial infarction (ie, ST-segment elevation ≥ 1 mm [0.1 mV] above the baseline in at least 2 contiguous leads [except V_2 and V_3]).

angiography, we gave him a provisional diagnosis of myocardial infarction with nonobstructive coronary arteries (MINOCA).

MYOCARDIAL INFARCTIONS DEFINED AND CLASSIFIED

According to the Fourth Universal Definition of Myocardial Infarction,[1] published in 2018, the diagnosis of myocardial infarction requires myocardial injury and additional evidence of acute myocardial ischemia. Myocardial injury is an umbrella term for all clinical scenarios, regardless of etiology, in which the cardiac troponin level is higher than the 99th percentile upper reference limit. Cardiac troponin I is strongly preferred over troponin T because the former is absent in noncardiac myocytes, so it has higher sensitivity and specificity.

Myocardial infarction is considered acute when there is a rise or fall or both in troponin I, whereas chronic myocardial injury is characterized by elevated cardiac troponin values with variation in troponin values of 20% or less.[1] Thus, myocardial infarction is a subtype of myocardial injury, with rise or fall of troponin I, due to an ischemic etiology, and therefore must be coupled with ischemic symptoms or objective findings on electrocardiography, noninvasive imaging, or cardiac catheterization.

Type 1 vs type 2. The Universal Definition[1] recognizes 5 classes of myocardial infarction. Most type 1 cases result from occlusive or flow-limiting coronary thrombosis after atheromatous plaque rupture or erosion.[2] Type 2 myocardial infarction, in contrast, occurs when myocardial oxygen demand outweighs supply (without plaque rupture), resulting in ischemia. Profound sepsis, significant anemia, or persistent tachyarrhythmia are examples of such supply-demand mismatch.

Type 3 involves sudden cardiac death occurring before cardiac troponin can be measured, and types 4 and 5 are iatrogenic. We won't discuss these further here.

STEMI vs NSTEMI. Depending on the accompanying electrocardiographic changes, myocardial infarctions are also classified as either non-ST segment elevation (NSTEMI) or STEMI. Frequently, STEMI is associated with an acutely and totally occluded artery, whereas NSTEMI is associated with a severe luminal narrowing but with some residual flow. STEMI and NSTEMI are the most common types of type 1 myocardial infarction. While type 2 myocardial infarction is not typically associated with the traditional mechanisms of coronary obstruction seen in type 1 myocardial infarction (where a plaque rupture leads to thrombosis), it can still result in ST-segment elevation on an electrocardiogram.

Obstructive vs MINOCA. Myocardial infarctions can occur without significant epicardial obstructive coronary disease (not clearly type 1 or type 2), a situation termed MINOCA.[3–6] Approximately 6% to 8% of patients presenting with acute myocardial infarction can be classified as having MINOCA.[7]

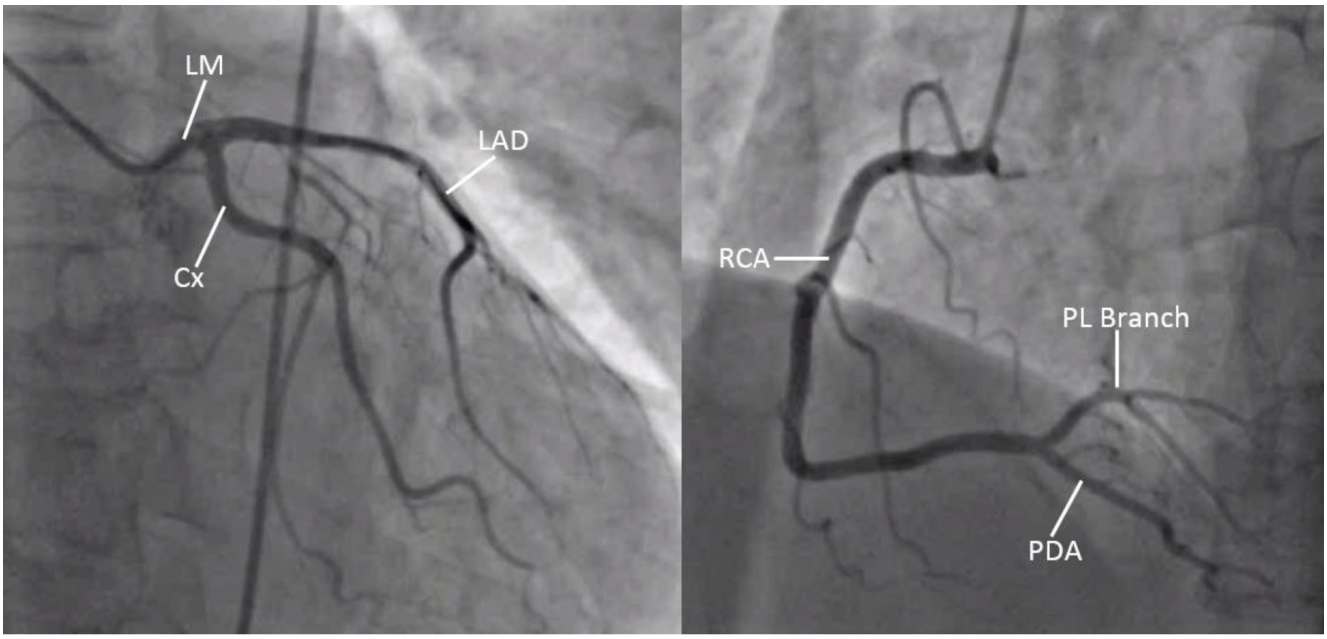

Figure 2. Coronary angiography. On the left, a right anterior oblique caudal view of the left coronary artery, and on the right, a left anterior oblique caudal view of the right coronary artery (RCA), showing no obstructive lesions in the main branches of either.

Cx = circumflex; LAD = left anterior descending; LM = left main; PL = posterolateral; PDA = posterior descending artery

Just as the type 1–vs–type 2 classification scheme has caused confusion among clinicians, as it cannot be directly transposed onto our traditional electrocardiogram-based classification scheme (STEMI vs NSTEMI), MINOCA adds another layer of complexity. In current clinical practice, if coronary angiography doesn't show anything wrong, the evaluation may end there and a patient may be given a variety of diagnoses: NSTEMI, type 2 myocardial infarction, "troponin leak," or no diagnosis, as it is incorrectly presumed that a myocardial infarction cannot occur if the coronary arteries are "clean."

MINOCA AS A CLINICAL CONDITION

To be diagnosed with MINOCA, patients must satisfy the diagnostic criteria for myocardial infarction,[1] and must have no epicardial obstructive disease on coronary angiography. Epicardial obstructive disease refers to lesions with angiographic diameter stenosis of at least 50%, though physiologic assessment is preferred in contemporary practice: the patient has epicardial obstructive disease if the fractional flow reserve is less than or equal to 0.80 and the instantaneous wave-free ratio is less than or equal to 0.89.[8]

Patients are younger and more often female, Black, or Hispanic

Patients with MINOCA are on average younger and more of them are women compared with patients with acute myocardial infarction due to obstructive coronary artery disease.[5,6] In the Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) registry,[9] women were nearly 5 times more likely than men (odds ratio 4.8) to present with MINOCA. Women account for nearly 50% of patients with MINOCA but only 25% of those with myocardial infarction due to obstructive coronary artery disease. Compared with young women presenting with myocardial infarctions due to obstructive coronary artery disease, those with MINOCA were more likely to be premenopausal and less likely to have a history of gestational diabetes.[9]

Patients with MINOCA are also more likely to identify as Black, Hispanic, or Latino.[6,9]

A systematic review[5] found a lower prevalence of dyslipidemia in patients with MINOCA, but other traditional risk factors appear similarly represented. Among young patients presenting with acute myocardial infarction in the VIRGO prospective registry, approximately 11% had MINOCA.[9] Those with

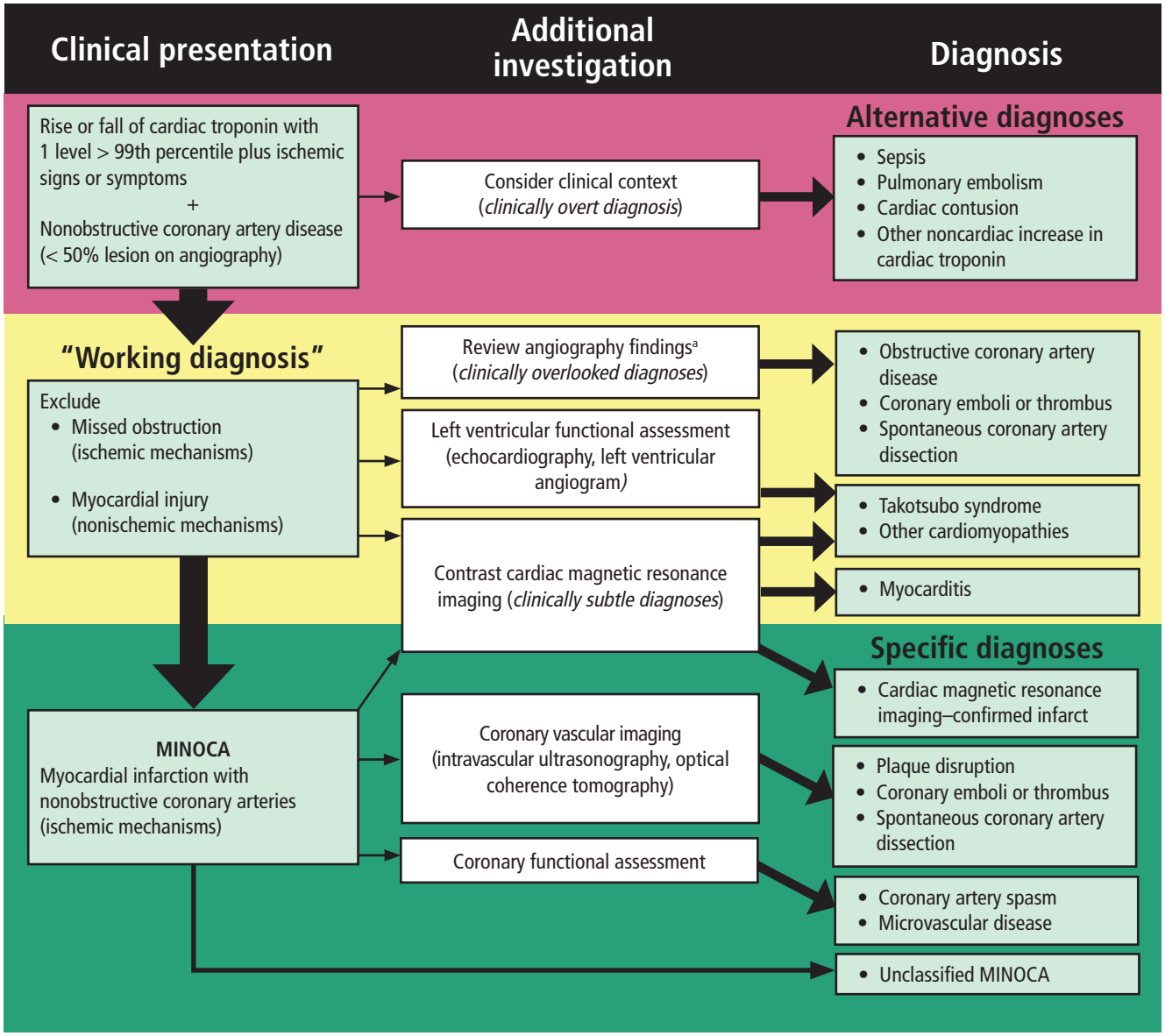

Figure 3. American Heart Association "traffic light" algorithm for the diagnosis of myocardial infarction with nonobstructive coronary arteries (MINOCA). Red excludes nonischemic etiologies, yellow suggests slowing down to evaluate for alternate diagnoses that can mimic MINOCA, and green suggests a confirmed diagnosis of MINOCA.

[a]Consider fractional flow reserve.

Reprinted with permission from Tamis-Holland JE, Jneid H, Reynolds HR, et al. Contemporary diagnosis and management of patients with myocardial infarction in the absence of obstructive coronary artery disease: a scientific statement from the American Heart Association. Circulation 2019; 139(18):e891–e908. doi:10.1161/CIR.0000000000000670. ©2019 American Heart Association, Inc.

MINOCA were more likely to have a hypercoagulable state and more likely to have no traditional cardiac risk factors.

We used to assume that MINOCA had a lower mortality rate than myocardial infarction due to obstructive coronary artery disease, but we can't be sure, as MINOCA was defined and diagnosed in different ways in different studies. Smilowitz et al[6] reported a lower in-hospital mortality rate in patients with MINOCA than in those with myocardial infarction due to coronary artery

disease (1.1% vs 2.9%). However, among young patients (18–55 years) in the VIRGO registry,[9] the 2-month and 12-month mortality rates were similar for both groups.

The European Society of Cardiology issued a guideline paper on MINOCA in 2017,[10] and the American Heart Association (AHA) followed in 2019.[11] The AHA authors formalized and updated the definition of MINOCA in the hope that researchers will consistently use it, which could allow better characterization of the MINOCA population. They also proposed a diagnostic algorithm with the hope that it would lead to more effective management by excluding mimics of MINOCA and consistently identifying underlying etiologies (eg, plaque rupture, spontaneous coronary artery dissection, coronary vasospasm).

Here, we review the AHA guidelines for evaluating patients with MINOCA for the practicing clinician.

NUTS AND BOLTS OF THE AHA STATEMENT

The AHA scientific statement[11] is pertinent to all hospitalized patients with myocardial infarction, although it presumes that everyone has access to imaging, including intravascular ultrasonography, optical coherence tomography, and cardiac magnetic resonance imaging. While the statement is geared toward practicing cardiologists, it is relevant for any hospital-based internist, internal medicine resident, or researcher.

The authors were primarily cardiologists; approximately half were interventional cardiologists, but there was also 1 hematologist and 1 PhD nurse scientist. The document reflects the consensus opinion of the authors and includes a comprehensive literature review, but the authors did not use a more formalized method for preparation such as the Delphi method.

The scientific statement was supported by the AHA, and its authors' potential conflicts of interest are listed at the conclusion of the document. We note, without presumption of conflict, that 3 of the interventional cardiology providers have received consultancy dollars or grant funding from manufacturers of intravascular imaging equipment. We also observe that the recommended diagnostic algorithm strongly prefers newer technologies such as cardiac magnetic resonance imaging and optical coherence tomography, which may not be available at smaller healthcare facilities.

A TRAFFIC-LIGHT ALGORITHM FOR DIAGNOSING MINOCA

The AHA authors[11] point out that MINOCA is a clinical syndrome that results from atherosclerotic and nonatherosclerotic mechanisms. They also emphasize that we lack high-quality, MINOCA-specific clinical studies on which to base therapy recommendations. That said, they propose a 3-step algorithm for diagnosing MINOCA, based on the analogy of a traffic light (**Figure 3**).[11]

Red light: First consider other diagnoses

Faced with a patient who has signs and symptoms suggesting ischemia and a rise in cardiac troponin but whose coronary arteries appear clean on angiography, the first step is to carefully review the clinical history to exclude "overt diagnoses" other than myocardial infarction. Examples include severe sepsis, massive pulmonary embolism, and severe anemia.

In these cases, no further cardiac diagnostic workup is recommended unless there is evidence of ischemia out of proportion to the degree of clinical illness. If there is no alternative diagnosis to explain a troponin elevation, it is reasonable to consider a working diagnosis of MINOCA.

Yellow light: Take a closer look at the angiogram

Once the clinical team reaches a working diagnosis of MINOCA, the next steps are to review the angiogram again and assess left ventricular function with echocardiography or assess the myocardium with cardiac magnetic resonance imaging with gadolinium contrast, or both. An angiographic review may identify epicardial obstructive coronary artery disease that was overlooked on image acquisition or subtle abnormalities, such as distal small-vessel occlusion due to embolism or evidence of spontaneous coronary artery dissection. These findings would replace the working diagnosis of MINOCA with a more specific diagnosis.

We recommend that the referring physician and interventional cardiologist jointly review angiographic images in real time. This strategy allows the referring physician to most effectively transmit clinical history and imaging findings to the interventional cardiologist.

Depending on the findings, the interventional cardiologist can, in turn, decide to take the patient back to the catheterization laboratory for more tests (fractional flow reserve, instantaneous wave-free ratio, intravascular ultrasonography, optical coherence tomography, or coronary functional testing). This blended strategy allows for efficient use of the cardiac catheterization laboratory and avoids repeat invasive testing. Invasive coronary functional testing, as described in the Coronary Microvascular Angina (CorMicA) trial,[12] is becoming more common but is not offered in all cardiac catheterization laboratories. Ideally, all these invasive tests should be done in 1 session so the patient does not have to go back, but this is not always possible.

TABLE 1
Myocardial infarction with nonobstructive coronary arteries (MINOCA): Potential mimics and causes

In a patient with a cardiac troponin level > 99th percentile, a rise or fall of troponin, and objective evidence of ischemia, consider the following:

Mimics (not MINOCA)	Causes of MINOCA
Myocarditis	Coronary microvascular disease
Takotsubo syndrome	Plaque disruption (type 1 myocardial infarction)
Other cardiomyopathies	Supply-demand mismatch (type 2 myocardial infarction without obstruction)
Overlooked obstructive disease: distal or small epicardial vessel occlusions not well visualized on angiography, a positive fractional flow reserve (ie, ≤ 0.80) in a moderate lesion	Spontaneous coronary artery dissection
	Coronary vasospasm
	Thromboembolic disease

Based on information from reference 11.

Left ventricular functional assessment and cardiac magnetic resonance imaging for further characterization of the myocardium, in conjunction with angiographic findings, could similarly replace a MINOCA diagnosis with other mimics such as stress cardiomyopathy (takotsubo syndrome), nonischemic cardiomyopathy, or myocarditis. Mileva et al[13] found that cardiac magnetic resonance imaging resulted in reclassifying 68% of patients with suspected MINOCA as actually having these mimics.

We note that left ventricular angiography (ventriculography), prominent in the AHA clinical algorithm[11] and the earlier European Society of Cardiology paper,[10] is less frequently used because high-quality transthoracic echocardiography and cardiac magnetic resonance imaging are widely available.

Green light: The patient has MINOCA; what is the cause?

If no alternative diagnosis is identified in the red and yellow algorithm steps, we can say the patient has MINOCA. At this point, additional diagnostic testing such as coronary functional assessment can be performed to find the specific underlying etiology for the MINOCA. In this idealized scenario, a thorough clinical history and coronary angiography precede imaging.

We applaud the AHA authors for promulgating a formalized evaluation pathway to search for an underlying etiology of MINOCA in each patient. How often the proposed algorithm will identify an underlying mechanism remains undefined. A clear mechanism of MINOCA was identified in only 25% of cases in the VIRGO registry, although patients did not routinely undergo cardiac magnetic resonance imaging.[9]

Once the diagnosis of MINOCA has been confirmed, subclassification into atherosclerotic or nonatherosclerotic disease can help determine the etiology and the management. As MINOCA is an umbrella term encompassing multiple discrete etiologies (**Table 1**),[11] advanced cardiac imaging is essential in classifying the patient into the appropriate cause, which has important treatment and prognostic implications.

CASE CONTINUED: SEPTAL BRANCH OCCLUSION

Our patient underwent cardiac magnetic resonance imaging, which demonstrated 50% thickness subendocardial enhancement at the mid and basilar anteroseptal wall on delayed imaging after gadolinium was administered, consistent with infarction in the territory of a septal perforator branch of the left anterior descending artery (**Figure 4**).

On further review of the angiographic images with the interventional cardiologist, a moderate stenosis of the proximal portion of the first septal perforator branch was noted. This stenosis was not clearly visualized on orthogonal or cranial views (**Figure 5**). Septal perforator branch occlusions are often caused by an upstream plaque rupture or more distant thromboembolism, such as a left atrial appendage thrombus. We did not think the patient had a ruptured plaque, as he had little plaque elsewhere in his coronary arteries, and a septal perforator branch is infrequently the site of a culprit lesion for an NSTEMI. Intracoronary imaging (optical coherence tomography or

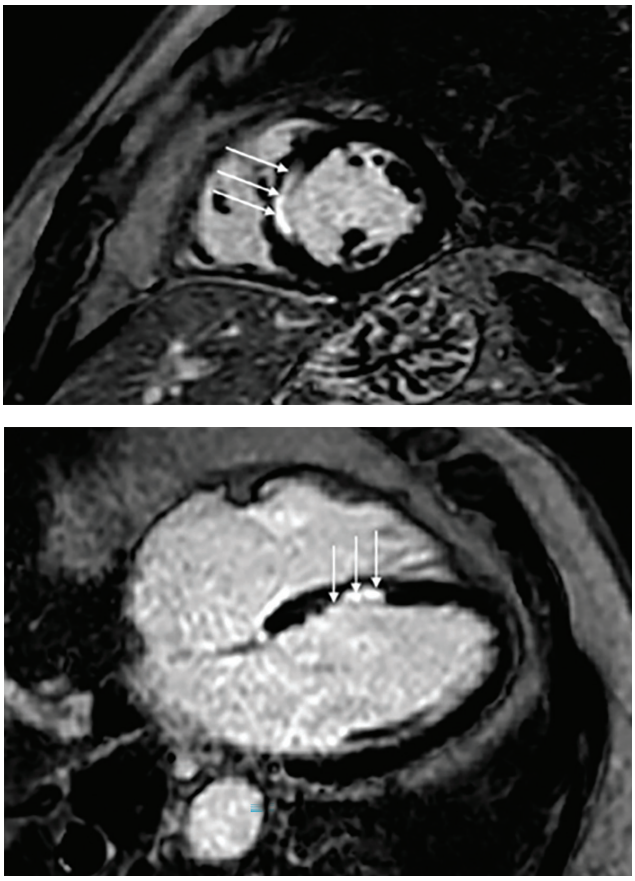

Figure 4. Delayed cardiac magnetic resonance imaging after administration of gadolinium (top, short-axis view; bottom, long-axis view), which demonstrates subendocardial enhancement (scar, white arrows) in the mid-septum amid otherwise normal-appearing left ventricular myocardium (black).

intravascular ultrasonography) is not feasible in such a small-caliber branch.

After close angiographic review and correlation with gadolinium-enhanced cardiac magnetic resonance imaging, the patient's MINOCA was attributed to possible septal branch occlusion and spontaneous recanalization. The patient was treated with dual antiplatelet therapy, an oral beta-blocker, and a high-intensity statin. The patient did well and was discharged on the appropriate therapies.

OUTCOMES BY SUBTYPE UNCERTAIN

Because MINOCA has only recently been defined as a clinical entity, we have little data on long-term outcomes based on MINOCA subtype. Women with

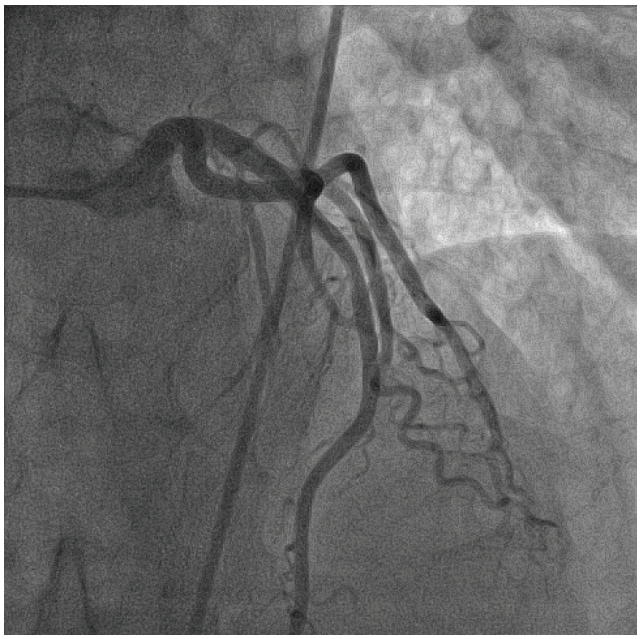

Figure 5. Cardiac magnetic resonance imaging. Anterior-posterior cranial view showing no epicardial obstructive coronary artery disease.

acute myocardial infarction due to spontaneous coronary artery dissection have a higher in-hospital mortality rate than those with acute myocardial infarction alone.[14] The prognostic data from patients with thromboembolic MINOCA are predominantly derived from case reports. Studies of microvascular etiologies are difficult to interpret, as some did not differentiate atherosclerotic microvascular disease from other entities such as takotsubo cardiomyopathy.

As for the mimics of MINOCA, a prospective outcomes registry study showed little excess mortality over up to 10 years of follow-up for patients who were found to have myocarditis by cardiac magnetic resonance imaging, whereas the highest-risk subgroup was patients with cardiomyopathy (a grouping that included stress cardiomyopathy, hypertrophic cardiomyopathy, and dilated cardiomyopathy).[15] Interestingly, cumulative mortality rates among patients with stress (takotsubo) cardiomyopathy were 3 times greater than those with alternative cardiomyopathy diagnoses (infiltrative, restrictive, hypertrophic, and other cardiomyopathies).

Among the patients with a confirmed diagnosis of MINOCA, independent predictors of death include advanced age and ST-segment elevation on presentation.[16] The SWEDEHEART (Swedish Web-system for Enhancement and Development of Evidence-based

care in Heart disease Evaluated According to Recommended Therapies) registry[16] found that independent predictors of major adverse cardiac events and cardiac death in MINOCA patients were similar to those of patients with myocardial infarction from obstructive epicardial coronary artery disease: advanced age, current smoking, diabetes, and reduced left ventricular ejection fraction.

MAJOR CAUSES OF MINOCA

Atherosclerotic cause: plaque disruption

Plaque disruption includes both plaque erosion and plaque rupture.

Plaque erosion is not well understood but is thought to involve apoptosis of endothelial cells secondary to loss of contact with the underlying extracellular matrix.[17] Myocardial infarction after plaque erosion occurs when small thrombi form at the erosion site and subsequently embolize. It can, therefore, present without obstructive epicardial disease (< 50% stenosis) on angiography (MINOCA).

Plaque rupture, in contrast, occurs when there is acute disruption of the fibromuscular cap of the atherosclerotic plaque. In both cases, exposure of the subendothelium to the bloodstream triggers a thrombotic response that can lead to thrombotic coronary occlusion.[17] Complete or near-complete thrombotic occlusion is more likely to be seen with plaque rupture in cases of myocardial infarction due to occluded coronary arteries. Coronary angiography displays the coronary lumen, rather than the vessel itself, and may not detect a small nonocclusive thrombus or thrombosis that has resolved with medical treatment before angiography.

Nonatherosclerotic causes

Spontaneous coronary artery dissection used to be thought to be rare, but it is a relatively common cause of sudden cardiac death and acute myocardial infarction in young women, occurring in 1% to 10% of women with acute coronary syndromes.[14,16–19] Though it can present as MINOCA, the most common presentation is type 1 myocardial infarction, in which there is angiographic evidence of epicardial obstruction. However, many cases may be missed, and therefore the exact prevalence is unknown.[20]

Spontaneous coronary artery dissection can be overlooked on angiography, as the coronary arteries may appear minimally diseased. This is especially true in diffuse and smooth luminal narrowing (type 2 spontaneous coronary artery dissection), caused by an intramural hematoma compressing the lumen.

Vasculopathies and connective tissue disorders may predispose to spontaneous coronary artery dissection, a theory supported by the association between spontaneous coronary artery dissection and fibromuscular dysplasia.[14]

Spontaneous coronary artery dissection should be considered in any case of MINOCA, but it should be higher on the differential in women of childbearing age presenting with acute coronary syndrome and in patients without evident coronary artery plaque.

Coronary vasospasm. Coronary vasospasm can result from exogenous substances such as cocaine, amphetamines, and certain medications (5-fluorouracil, selective serotonin agonists such as sumatriptan) or intrinsic smooth-muscle hyperreactivity. Coronary artery spasm was initially described by Prinzmetal et al[21] in patients with nonobstructive atherosclerotic disease. Classically, transient vasospastic episodes can produce ST elevation, but some episodes can be associated with ST depression. Angina is typical, though frequently not exertional. Prolonged episodes of vasospasm can lead to myocardial ischemia and subsequent MINOCA.

Coronary microvascular disease. Though an in-depth discussion is beyond the scope of this article, coronary microvascular disease (or microvascular dysfunction) is common in patients with MINOCA.[22] Microvascular disease involves arteries less than 0.3 mm in diameter, which are not adequately visualized on coronary angiography. It can manifest as vasospasm, as discussed above, or microvascular angina, which manifests as endothelial dysfunction without observed spasm of the larger vessels. Impaired microvascular function can exacerbate flow restrictions in the epicardial vessels and play an important role in MINOCA.

Cardiac magnetic resonance imaging and positron-emission tomography can help assess for microvascular disease, but the gold standard for diagnosis is functional coronary angiography, as described in the CorMICA trial.[12] If vasospasm or microvascular angina is diagnosed on functional coronary angiography, specific treatment can be given, and noncardiac chest pain can be excluded. Recent European Society of Cardiology guidelines for managing acute coronary syndrome[23] suggest that these tests can be performed at the time of initial angiography if no obstructive coronary artery disease is identified (ie, in MINOCA), but in practice they are not yet widely available. Patients may need to be referred to a tertiary care center or repeat angiography after microvascular dysfunction is suggested on noninvasive imaging.

Coronary thromboembolic disease. Coronary thromboembolism can result in MINOCA if partial or complete lysis occurs before angiography. Embolism

can arise from a remote location, such as the left atrial appendage in the setting of atrial fibrillation, or it could result from downstream embolization in acute coronary syndrome. Anecdotally, "local" embolism is more likely to resolve with medical therapy than "remote" thrombi, given the lack of thrombin cross-linking in the former. Coronary thrombi or emboli—as with any other cause of MINOCA—can occur in the presence or absence of acquired or inherited hypercoagulable states.

CLINICAL WORKUP OF MINOCA: WHAT'S NEW?

A diagnostic algorithm. We endorse the AHA traffic light algorithm for the diagnosis of MINOCA (**Figure 3**).[11] In this paradigm, red excludes nonischemic etiologies, yellow suggests slowing down to evaluate for alternate diagnoses that can mimic MINOCA, and green suggests a confirmed diagnosis of MINOCA. If there is no emergent or urgent indication for coronary angiography, we suggest carefully considering the clinical picture to exclude common but nonischemic causes of troponin elevation, such as sepsis, end-stage renal disease, cardiac contusion in the setting of trauma, and pulmonary embolism.

If acute myocardial infarction remains the most likely diagnosis, it is reasonable to proceed to coronary angiography. For patients without at least 50% epicardial coronary artery stenosis, it is important to review the coronary angiography with the interventional cardiologist to exclude overlooked disease, namely distal small-vessel obstructive disease, spontaneous coronary artery dissection, and coronary emboli or thrombus (yellow section of **Figure 3**).

Intracoronary imaging with intravascular ultrasonography or optical coherence tomography should be considered in patients with MINOCA and less than 50% stenosis on coronary angiography. Intravascular ultrasonography can often identify plaque rupture and atherosclerosis.

In one study, plaque rupture or erosion was diagnosed by intravascular ultrasonography in 16 (42%) of 42 women with MINOCA.[24] Several other studies reported that plaque rupture is visualized on intravascular ultrasonography in roughly one-third of patients with MINOCA.[3,4] The number of patients with MINOCA who have plaque erosion is unknown, as intravascular ultrasonography does not reliably detect it.[24,25] Further, plaque erosion is more common in women and younger patients, consistent with the overall demographics of MINOCA.[26]

Optical coherence tomography is not available in all centers, but it has superior spatial resolution and can be used to evaluate patients for plaque erosion. Although they can be helpful, intravascular ultrasonography and optical coherence tomography are used sparingly to diagnose spontaneous coronary artery dissection, as they may propagate the dissection.[27,28]

Invasive functional assessment of the epicardial vessels by measuring the instantaneous wave-free ratio or fractional flow reserve can be helpful in determining physiologically significant disease that may be overlooked on angiography alone.[11]

Stress imaging. If angiography is completed without physiologic assessment using fractional flow reserve or instantaneous wave-free ratio (or functional coronary angiography), ischemia can be detected on functional stress testing using nuclear (single-photon emission computed tomography, positron-emission tomography) or magnetic resonance stress imaging. Stress cardiac magnetic resonance imaging can be helpful in reaching a specific diagnosis. Alternatively, positron-emission tomography with computed tomography can detect ischemia and allows for the assessment of microvascular function using the myocardial blood flow ratio.[11]

Cardiac magnetic resonance imaging. If a careful review of the coronary angiography films and adjunctive intracoronary imaging are not revealing, cardiac magnetic resonance imaging is a key diagnostic tool. It is the imaging modality of choice for MINOCA in both the European[10] and the AHA guidelines.[11] It can provide evidence to support a diagnosis of (type 1) myocardial infarction, as in our patient, or an alternate diagnosis, such as myocarditis, takotsubo syndrome, or cardiomyopathy. On the other hand, it has multiple barriers to routine use, including availability, cost, potential increased hospital length of stay, patient discomfort due to claustrophobia, and inability to use gadolinium in patients with impaired renal function.

Early studies of cardiac magnetic resonance imaging in MINOCA suggested it has a lower diagnostic yield if troponin levels are lower.[29] The European Society of Cardiology position paper[10] on MINOCA suggests it has a low diagnostic yield when the troponin is less than 100 times the upper limit of normal. A report by Dastidar et al[30] suggests that definitive diagnosis can be achieved after cardiac magnetic resonance imaging in three-quarters of MINOCA cases. We would expect that the diagnostic yield may be lower in a less-selected patient population or if patients with lower-level troponin elevation are routinely included—the mean troponin elevation was 14 times the upper limit of normal in the subset with normal cardiac magnetic resonance imaging compared with 48 times the upper limit of normal in the MINOCA diagnosis group.[30]

Provocative testing for vasospasm. The diagnosis of vasospastic MINOCA requires a demonstration of coronary artery spasm with provocative testing.[31] For patients presenting with chronic, episodic, nonexertional angina, in whom coronary artery spasm is considered likely and evaluation has been unrevealing, provocative testing may be appropriate. The safety of intracoronary acetylcholine has been demonstrated in stable patients, with death and major adverse cardiac event rates no higher than those of coronary angiography.[13,14,16] Typically, diagnosis relies on clinical assessment and electrocardiographic findings (standard or ambulatory monitoring), with provocation tests only occasionally done.

Empiric treatment of presumed vasospastic MINOCA with calcium-channel blockers or long-acting nitrates is low-risk. It has been shown to reduce the recurrence of symptoms.[32]

Coagulation studies. In patients with unprovoked coronary thromboembolism and MINOCA, without evidence of paroxysmal atrial fibrillation, evaluation for a hypercoagulable state can be considered in conjunction with a hematologist in the outpatient setting.

TREATMENT

As MINOCA is a recently recognized clinical syndrome that occurs secondary to disparate underlying diagnoses, the evidence to support specific treatments for it is both limited and heterogeneous. Treatment of all patients with MINOCA should include and emphasize lifestyle management, especially in those with diffuse nonobstructive atherosclerosis (< 50%), microvascular disease, or a supply-demand mismatch.

Most cases of MINOCA are due to causes that are common, and therefore, guideline-directed therapies for secondary prevention of atherosclerotic cardiovascular disease may be indicated. Among patients with MINOCA enrolled in the SWEDEHEART registry,[16] treatment with statins and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers was associated with a reduction in major adverse cardiac events during a 4-year follow-up. There was a trend toward improved outcomes in patients treated with beta-blockers, which did not reach statistical significance. The use of dual antiplatelet therapy was not associated with improved outcomes.

That said, medical therapies should be tailored to the underlying etiology. For example, patients with diffuse nonobstructive disease or microvascular disease are more likely to benefit from statin therapy, whereas its routine use is not recommended in patients with spontaneous coronary artery dissection. In patients with spontaneous coronary artery dissection, a conservative approach is recommended to avoid instrumentation of the artery and propagating the dissection plane. The use of calcium channel blockers in those with coronary spasm has been shown to reduce symptoms, and there is evidence that anticoagulation may be appropriate for the prevention of thromboembolic disease.[12,33,34]

We hope that with a standardized diagnostic pathway that regularly includes cardiac magnetic resonance imaging, as suggested by the AHA scientific statement,[11] most patients with MINOCA will receive a specific diagnosis to guide therapy. Routine assessment may provide a specific diagnosis in many cases of MINOCA, and we may be able to avoid unnecessary treatments in up to three-quarters of cases. Moreover, patients with a normal cardiac magnetic resonance imaging result may not require any medical therapy. Collaborative studies of MINOCA and other less-common cardiac diseases, including spontaneous coronary artery dissection and stress cardiomyopathy, may be able to identify a more homogeneous patient population to define optimal treatment strategies.

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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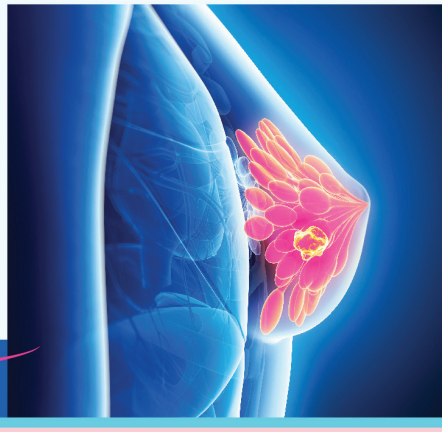

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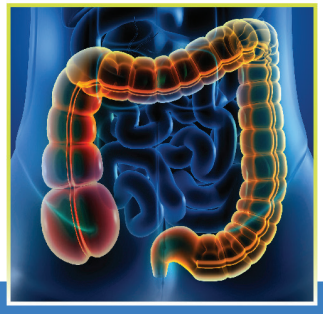

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The diagnostic dilemma of myocardial infarction without obstructive coronary artery disease: Advanced imaging to the rescue!

Myocardial infarction with nonobstructive coronary arteries (MINOCA) was first documented more than 70 years ago based on autopsy data describing myocardial necrosis in the absence of obstructive epicardial coronary disease.[1]

See related article, page 743

MINOCA accounts for approximately 5% to 15% of all myocardial infarctions, yet it remains underappreciated and often misdiagnosed, leading to gaps in appropriate management and treatment.[2] In 2019, the American Heart Association (AHA) published a scientific statement[3] specifically addressing this issue, offering a comprehensive framework for diagnosing and managing patients who experience myocardial infarction without significant coronary artery obstruction.

In this issue of the *Journal*, Buda et al[4] provide a critical appraisal and a clinical workflow perspective of the AHA statement. Their article is clinician-friendly and aims to simplify the algorithm outlined in the AHA statement while explaining the significance of each of its components. They critique some of the content of the statement, emphasizing that many of the advanced imaging techniques advocated by the AHA algorithm are not readily available in smaller medical centers. While the AHA authors seem to consider practicing cardiologists as the primary audience, Buda et al aim to bring the workup of MINOCA to the internist or hospitalist, who are often confronted with these patients.

doi:10.3949/ccjm.91a.24106

We agree with the authors of both the AHA statement[3] and this review article[4] that a thorough understanding of the definition and causes of MINOCA and its diagnosis is crucial in contemporary practice, particularly with the advent of high-sensitivity troponin assays and multimodality imaging techniques.

INVASIVE VS NONINVASIVE IMAGING

As highlighted by Buda et al,[4] MINOCA disproportionately affects women of childbearing age who do not have the traditional risk factors for atherosclerotic cardiovascular disease. The authors appropriately advocate for a comprehensive and holistic patient assessment to rule out alternative and competing diagnoses. Once MINOCA is established as the working diagnosis, they recommend a cardiac-focused workup, including transthoracic echocardiography, cardiac magnetic resonance imaging (MRI), coronary angiography, or combinations of these tests.

Realistically, to diagnose MINOCA, one must confirm there are no epicardial obstructive coronary lesions, which can only be done by performing invasive angiography or coronary computed tomography (CT) angiography. Because these patients have evidence of myonecrosis (elevated troponin), most clinicians and workflow patterns would steer them toward invasive angiography. While it is noted that cardiac MRI and transthoracic echocardiography are done before angiography in routine clinical settings, urgent or emergent coronary angiography often takes precedence during episodes of acute coronary syndrome, as most

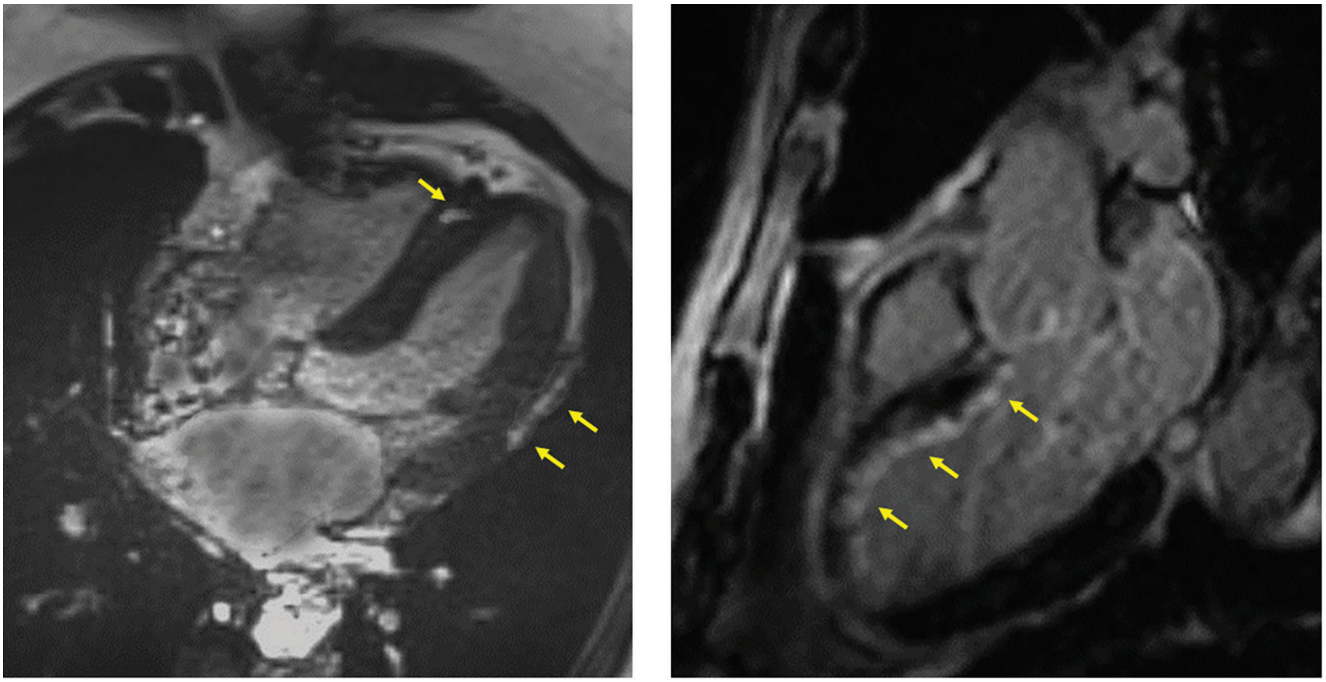

Figure 1. Cardiac magnetic resonance imaging can reliably distinguish between myocarditis and coronary ischemic events in patients presenting with myocardial infarction with nonobstructive coronary arteries. Left panel, gadolinium enhancement (arrows) in the middle of the myocardium in the septum and below the epicardium in the lateral wall is a distribution pattern consistent with inflammatory disease or myocarditis. Right panel, enhancement (arrows) beneath the endocardium along the anterior septum and the anterior apex is a distribution consistent with an acute coronary injury likely originating from disease of the left anterior descending artery.

institutions have well-established protocols for activating the catheterization laboratory but lack algorithms for urgent noninvasive imaging.

MINOCA IS A WORKING DIAGNOSIS THAT NEEDS TO BE NARROWED DOWN

The authors agree with the AHA statement that MINOCA is a working diagnosis that needs to be refined or narrowed down to a specific etiology to initiate appropriate treatment. They classify the causes of MINOCA into atherosclerotic conditions, such as plaque disruption, and nonatherosclerotic conditions, including spontaneous coronary artery dissection, coronary thromboembolism, and coronary vasospasm.

Although we appreciate the concept of keeping it simple and using available resources, clinching the specific etiology of MINOCA frequently requires advanced techniques beyond angiography. The most fruitful of them are cardiac MRI performed in a timely manner, intravascular imaging performed in a timely manner, and assessment of microvascular and vasospastic disorders of the coronary arteries.

CARDIAC MRI CAN POINT TO ETIOLOGY

Buda et al[4] agree that cardiac MRI is quite helpful in defining the etiology of MINOCA. They argue that it should precede invasive testing, which is a valid argument, with exceptions that we discussed earlier.

The advantage of MRI over simpler cardiac imaging modalities such as echocardiography is that it provides insight into the site and distribution of myocardial injury, as defined by late gadolinium enhancement, myocardial edema, or both (**Figure 1**). The distribution of such injury can point to its etiology: epicardial or midmyocardial enhancement is likely caused by myocarditis, whereas ischemic injury is always subendocardial and frequently follows a specific regional anatomic pattern. That pattern can also help in selecting the targets of intracoronary imaging and interrogation when invasive testing ensues.

In a large single-center series of 719 patients with suspected acute coronary syndrome and nonobstructive coronary arteries,[5] the MRI-based diagnosis was myocardial infarction in 26%, myocarditis in 26%, stress cardiomyopathy in 12%, and other cardiomyopathy

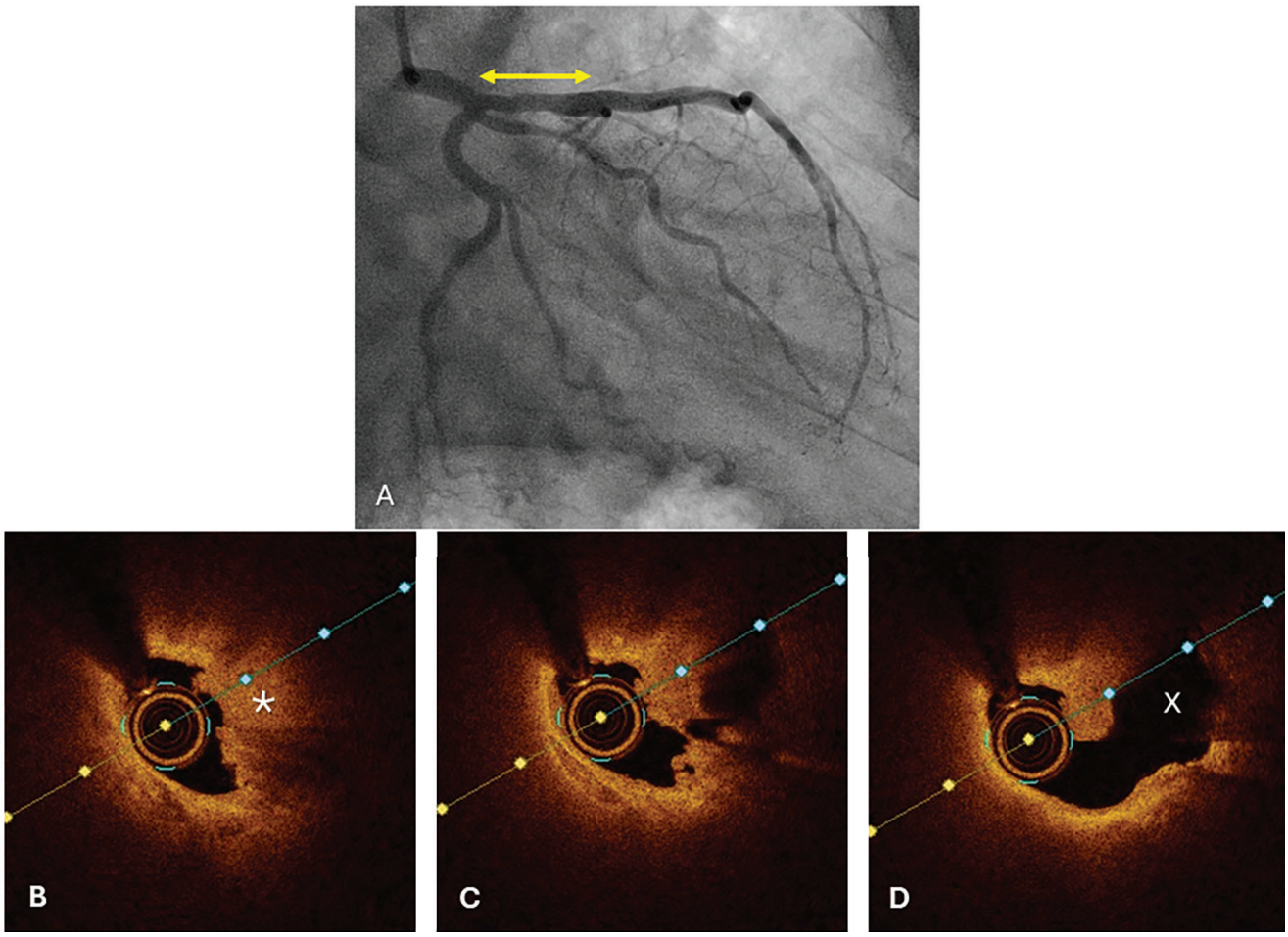

Figure 2. Optical coherence tomography can define the underlying pathophysiology of the coronary event in myocardial infarction with nonobstructive coronary arteries. (A) Relatively mild angiographic disease of the proximal left anterior descending artery (arrow) in a patient with acute chest pain, abnormal biomarkers, and anterior T-wave inversions. (B) Optical coherence tomography demonstrates significant luminal narrowing and intraluminal thrombosis (asterisk). In that frame, the thrombus is shielding underlying plaque structure, but a few millimeters distally (C), the thrombus is still apparent and there is a disruption of the underlying intima. (D) Further distally, some thrombus is adherent, and there is an ulcer crater (X) after release of plaque content downstream.

in 10%; the remaining 26% had normal or nonspecific scans. Importantly, imaging within 14 days of the event was an independent predictor of reaching a diagnosis, as late gadolinium enhancement and edema fade over time.

ADVANTAGES OF INVASIVE ANGIOGRAPHY AND INTRAVASCULAR IMAGING

As mentioned above, angiography is an essential step in diagnosing MINOCA. Invasive angiography has some advantages over CT angiography, which is typically done in more stable patients rather than ones presenting with abnormal cardiac biomarkers. In addition, CT angiography may lack the resolution to identify subtle plaque disruptions such as erosion. And spontaneous coronary artery dissection, which typically affects smaller and tortuous vessels, is difficult to diagnose with certainty on CT angiography.

Invasive angiography also lets you perform intracoronary imaging with either intravascular ultrasonography or optical coherence tomography. Atherosclerotic plaque disruption can result in more typical obstructive lesions and acute coronary syndromes, but in MINOCA, such disruption may be too subtle to define angiographically. Intracoronary imaging is

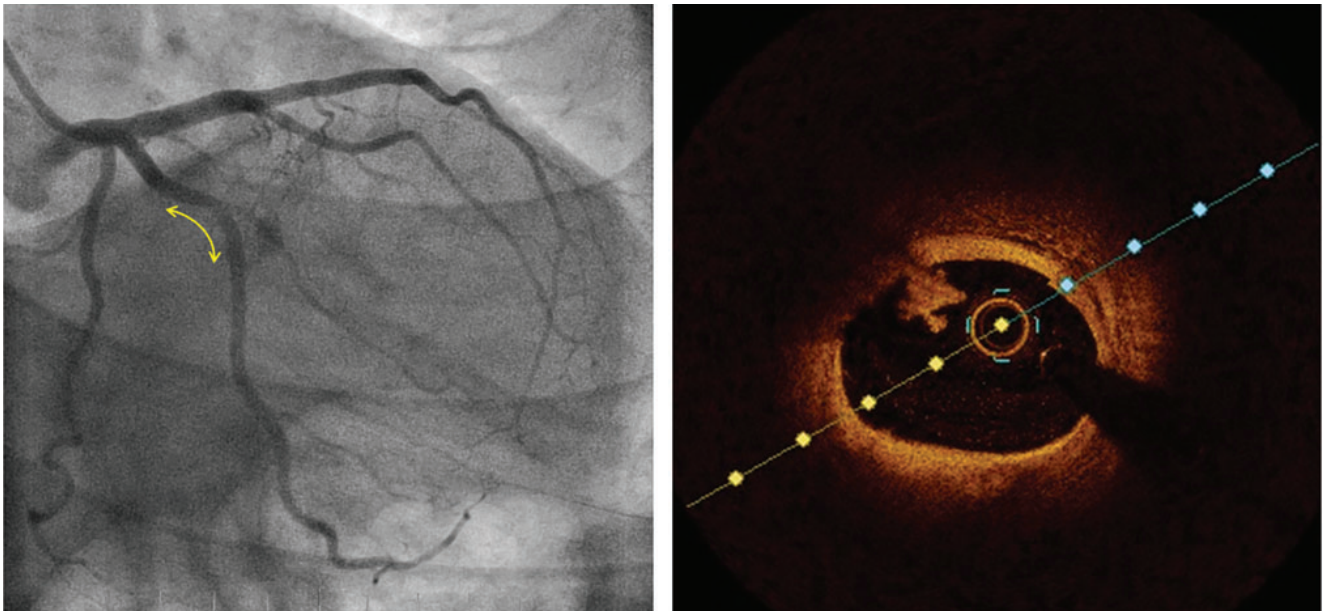

Figure 3. Optical coherence tomography can define subtle findings beyond the resolution of angiography. In the left panel, angiography in a patient with myocardial infarction with nonobstructive coronary arteries shows minimal haziness in the proximal circumflex artery (arrow). In the right panel, optical coherence tomography demonstrates a small thrombus with intact underlying plaque, representing plaque erosion.

crucial in identifying plaque rupture, plaque erosion, or eruptive calcified nodules—the 3 major pathways leading to myonecrosis.

While Buda et al[4] say that intravascular ultrasonography may be good enough and that optical coherence tomography is not readily available in many institutions, these modalities are not equivalent. Optical coherence tomography has much higher resolution, about 10-fold that of intravascular ultrasonography, thus providing a fair chance of detecting any form of plaque disruption with higher sensitivity and specificity (**Figure 2, Figure 3**). Additionally, optical coherence tomography is much more suited to define intraluminal thrombosis compared with intravascular ultrasonography, as the echo density of an adherent or layered thrombus is frequently indistinguishable from that of a heterogeneous plaque.

But anatomic evidence of plaque disruption may change over time. A small thrombus on top of an eroded plaque, or an even larger thrombus resulting from plaque rupture, will embolize downstream or be eliminated by intrinsic fibrinolytic mechanisms. Therefore, intracoronary imaging should be considered in the acute phase, ideally at the time of the initial angiogram, to maximize the chances of identifying culprit anatomic findings.

BEYOND IMAGING: TESTING FOR VASOSPASM AND MICROVASCULAR DYSFUNCTION

Although coronary vasospasm is not necessarily associated with obstructive lesions, it is essentially caused by coronary endothelial dysfunction and commonly associated with a degree of atherosclerosis. Non–endothelial-dependent coronary microvascular dysfunction is another important category of coronary disease that is not necessarily associated with obstructive lesions, but is a form of coronary disease nonetheless. In fact, microvascular dysfunction is grossly underdiagnosed and associated with major adverse cardiovascular events and worse medium- and long-term prognosis.[6–8]

The search for causes of MINOCA should include a detailed assessment of microvascular disorders with their various endotypes.[9] Endothelial-dependent vasomotor disorders can be assessed using intracoronary acetylcholine provocation (**Figure 4**). Clinicians may elect to postpone provocative testing until after the acute phase, but unfortunately that requires an additional invasive procedure because there are no well-established noninvasive tests for coronary spasm.

Testing for non–endothelial-dependent microvascular dysfunction involves assessing coronary flow reserve and microvascular resistance. This can be done

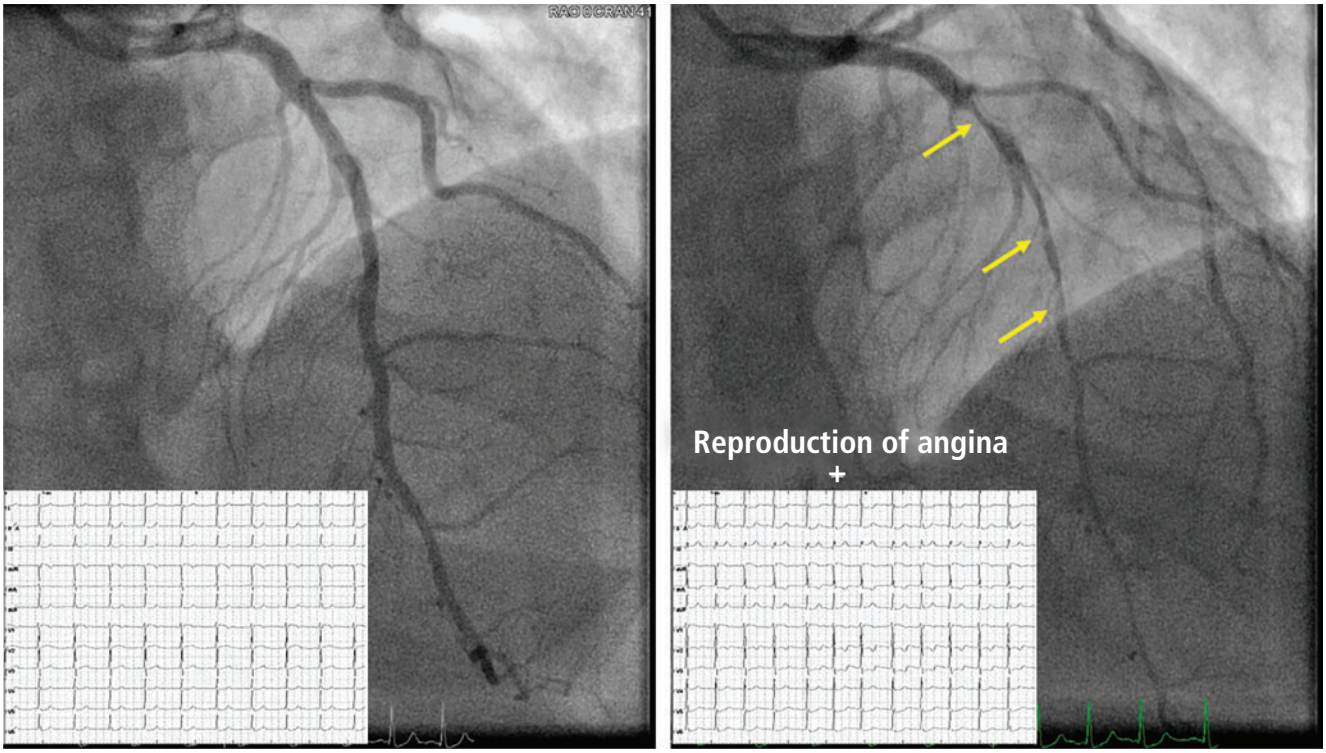

Figure 4. Provocative acetylcholine testing for coronary spasm. In the left panel, a young female patient with a long history of smoking presenting with myocardial infarction with nonobstructive coronary arteries has mild luminal irregularities in the left anterior descending artery. The right panel shows that intracoronary injection of escalating doses of acetylcholine provokes anginal symptoms, ST depression in precordial leads, and epicardial spasm in the mid segment of the anterior descending artery (arrows). Calcium channel blockers, nitrates, or both can be used to control spasm and vasospastic angina, and aggressive risk factor control is also needed.

in the catheterization laboratory using bolus or continuous thermodilution—injecting or infusing saline that is colder than body temperature.[10] The resulting changes in pressure and temperature in the coronary arteries are used to calculate the coronary flow at rest; then hyperemia is induced using intravenous adenosine or intracoronary saline infusion, flow is measured again, and from these numbers coronary flow reserve is calculated. The pressure and temperature changes are also integrated to calculate microvascular resistance, independent of the impact of epicardial disease, if any (**Figure 5**).

Positron-emission tomography to measure myocardial blood flow during stress is a well-established, noninvasive tool for evaluating coronary microvascular dysfunction. While not mentioned by Buda et al,[4] it can be considered in the diagnostic process of more-stable MINOCA patients as it has diagnostic and prognostic relevance.[11]

TREATMENT SHOULD BE INDIVIDUALIZED

Patients with MINOCA are a highly heterogeneous group, and their management should be tailored to the individual rather than a one-size-fits-all approach. The diagnosis of myocarditis or stress cardiomyopathy leads to an entirely different treatment algorithm than an ischemic etiology, whether epicardial or microvascular.

The authors[4] propose treating patients with presumed coronary vasospasm using calcium channel blockers or nitrates without prior diagnostic testing, arguing that this treatment carries minimal risk. However, both American[3] and European[12] guidelines for management of chest pain recommend testing for coronary vasospasm and microvascular dysfunction before initiating treatment. Randomized trials in MINOCA patients demonstrated that treatment based on the specific endotype of microvascular disorder is superior to empiric treatment in terms of symptom relief and improvement of quality of life.[13] Even experienced

Figure 5. Microvascular testing using thermodilution for assessment of coronary flow reserve (CFR). A patient presenting with myocardial infarction with nonobstructive coronary arteries and giving a history of exertional angina has no evidence of obstructive lesions. Thermodilution assessment based on transit time at rest and with hyperemia reveals abnormally low CFR and a high index of microcirculatory resistance (IMR; abnormal values in red box). Microvascular angina is diagnosed, and the patient can be treated with beta-blockers and ranolazine in addition to risk factor management.

FFR = fractional flow reserve; Pd = pressure measured distal to the stenosis; Pa = aortic pressure; RRR = resistive reserve ratio

cardiologists frequently miss the true endotype based on clinical assessment and nonspecific tests.[14]

NOVEL TOOLS ARE IMPROVING DIAGNOSIS AND TREATMENT

MINOCA is an umbrella term that encompasses a number of disparate diagnoses. It is important to consider the spectrum of differential diagnoses until a true coronary etiology can be identified. Advances in cardiac and coronary imaging and physiologic assessment now allow for a thorough and accurate workup, which underlie the appropriate therapy and outcome. While clinical assessment and basic tests are irreplacable, novel tools have undeniably improved the yield of MINOCA workups and targeted therapies.

DISCLOSURES

Dr. Ziada has disclosed teaching and speaking for Abbott Vascular. Dr. Zghyer reports no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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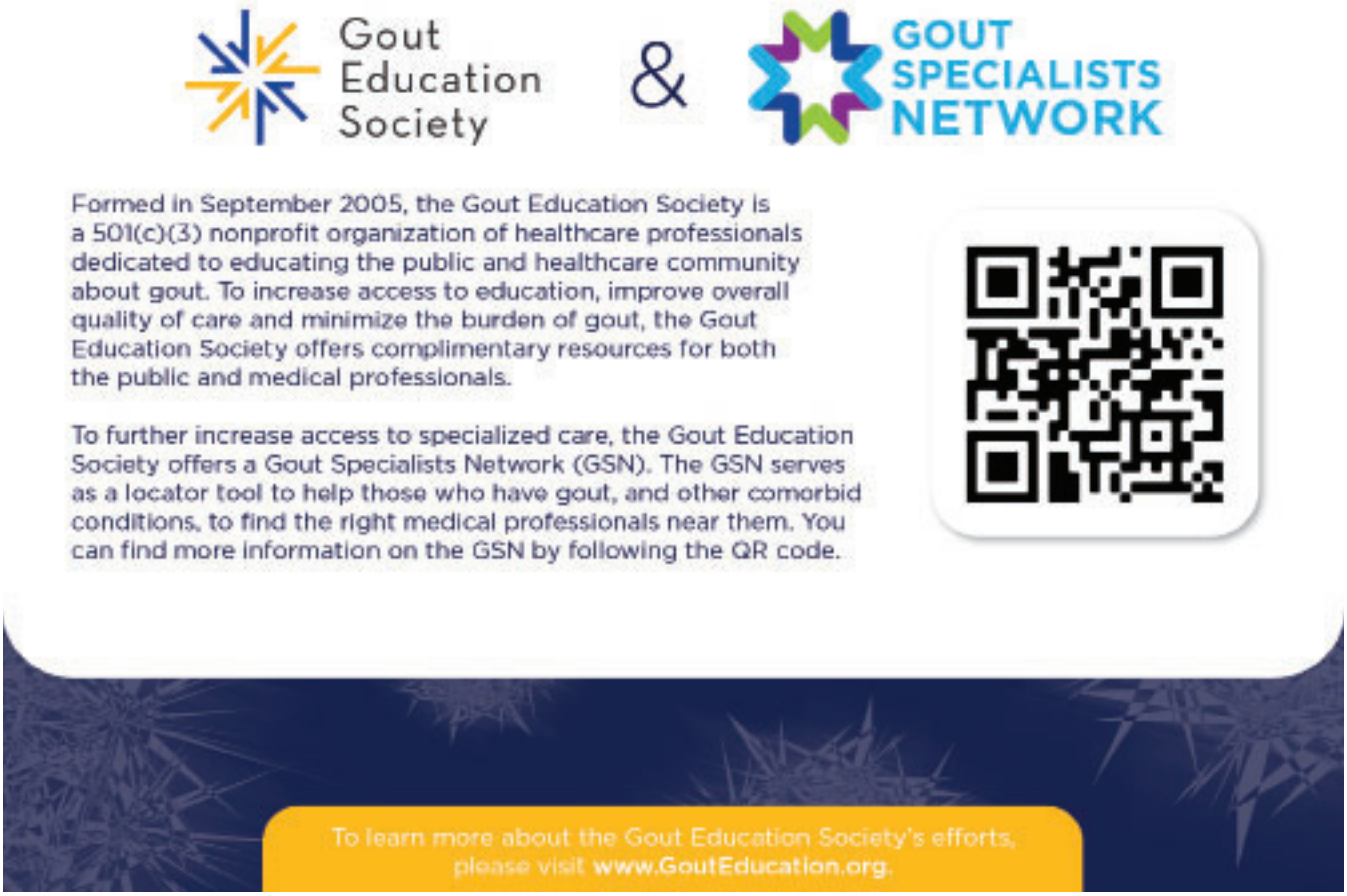

REVIEW

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Managing urogenital tract disorders: 10 urology pearls for primary care physicians

ABSTRACT

Primary care physicians frequently encounter patients with urogenital diseases. These 10 evidence-based pearls will help physicians to refine the care they provide, avoid some common missteps, and more quickly determine when a referral is appropriate.

KEY POINTS

Attributing microscopic hematuria to a patient's use of an antiplatelet or anticoagulation medication—without an appropriate workup—is imprudent. These 2 drug classes can unmask hematuria, sometimes revealing a sinister etiology; an algorithmic evaluation is warranted.

Gross hematuria requires urgent computed tomography urography and urology referral.

Sodium-glucose cotransporter 2 inhibitors are associated with lower urinary tract symptoms and a small but significantly increased risk of urogenital infections.

Prostate-specific antigen reference ranges based on age have been found to increase the detection of more potentially curable tumors in young men and decrease the detection of less advanced tumors in older men, compared with the standard reference range of 4.0 ng/mL.

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PRIMARY CARE PHYSICIANS commonly encounter diseases of the urogenital tract, and this frequency will likely increase as the population ages. Early identification and appropriate management are, of course, necessary to reduce the morbidity and mortality associated with urologic conditions. However, primary care physicians may not always feel optimally positioned for certain aspects of urologic care.

Researchers note that formal urologic education has dropped over the years. In 1956, 99% of all US medical schools required a clinical rotation in urology, but by 2014, only 5% did.[1] A 2022 study of medical students found that only 4 of the 173 respondents (2%) said that their school required a clinical urology rotation. These students (who had an expressed interest in urology) also reported that they had minimal exposure to certain urologic topics, including bladder drainage, erectile dysfunction, and urologic emergencies.[1]

The 10 urology pearls that follow offer evidence-based guidance on issues that primary care physicians are likely to encounter with some frequency in practice. They provide valuable guidance on why physicians should, among other things, advise older men with benign prostatic hyperplasia to avoid certain antihistamines, avoid dismissing the presence of microscopic hematuria in patients taking anticoagulants, and alert patients who are taking sodium-glucose cotransporter 2 (SGLT-2) inhibitors to an increased risk of urogenital infections.

1. Advise older men with benign prostatic hyperplasia to avoid common anticholinergic and sympathomimetic medications to reduce their risk of developing acute urinary retention.

Older men (age > 60 years) are at higher risk for developing acute urinary retention if they have benign prostatic hyperplasia, obstructive urinary symptoms, or poor bladder emptying. With this in mind, it's wise to educate at-risk patients—notably older men with benign prostatic hyperplasia—to avoid certain medications that can cause acute urinary retention.[2]

Specifically, diphenhydramine and chlorpheniramine, over-the counter antihistamines, are potent anticholinergic medications that can cause acute urinary retention.[2,3] Other common over-the-counter medications associated with acute urinary retention include phenylephrine and pseudoephedrine (alpha-receptor agonists), which are commonly found in cold medications. Prescription medications like baclofen, cyclobenzaprine, and tricyclic antidepressants such as amitriptyline have also been implicated in acute urinary retention.[2]

2. Manage acute urinary retention in male patients with benign prostatic hyperplasia by placing a Foley catheter for bladder decompression, starting them on an alpha-1 adrenergic antagonist, and ordering a voiding trial within 1 to 2 weeks.

Men with significant acute urinary retention are unable to pass urine, and this may be accompanied by suprapubic or abdominal discomfort. The most common underlying reason for acute urinary retention is benign prostatic hyperplasia, but it also can be precipitated by infection, inflammatory prostatitis, urethral stricture, or recent initiation of a medication known to cause urinary retention (see Pearl 1).

Bladder decompression is the first step to address acute urinary retention, which is often accomplished by the placement of a Foley catheter. Bladder rest is critical, especially for patients who have high urine volume at the time of initial catheterization, which may indicate detrusor dysfunction.

Medication initiation is an important next step. An alpha-blocker (eg, tamsulosin, alfuzosin, silodosin) is used to address untreated benign prostatic hyperplasia and lower urinary tract symptoms. A 5-alpha reductase inhibitor (eg, finasteride, dutasteride) can also be started with an alpha-blocker as dual therapy, but it can take months to see its maximum effect.

Finally, refer the patient to a urologist so that a voiding trial can be performed in the next 1 to 2 weeks. Prolonged catheterization is usually not beneficial unless you are waiting for a 5-alpha reductase inhibitor to reach maximum effect.

If medications do not restore bladder emptying, clean intermittent catheterization or surgical intervention may be indicated.[4]

3. Investigate—rather than dismiss—the presence of microscopic hematuria in patients taking an antiplatelet or anticoagulation medication.

Microscopic hematuria—red blood cells greater than or equal to 3 per high-power field[5]—is common, but not normal. In young healthy patients, it may be present after vigorous exercise or as a consequence of menstrual contamination of urine. In other patients, it may be a sign of nephrolithiasis or urinary tract infection. But microscopic hematuria may also signal something more sinister. Malignancy in any part of the genitourinary system is in the differential, and attributing hematuria to a patient's use of an antiplatelet or anticoagulation medication without an appropriate workup is imprudent.[5]

A careful history to identify any nonmalignant causes is the first step of the workup, and urinalysis with microscopic analysis will guide the direction of the evaluation. For example, active sediment with the presence of red blood cells or significant protein suggests a renal etiology. A patient with acute onset of unilateral flank or groin pain and hematuria may have nephrolithiasis and should be evaluated with abdominal noncontrast computed tomography imaging (or ultrasonography if patient is pregnant). A patient with pyuria on urinalysis and symptoms suggestive of a urinary tract infection can be treated with antibiotics and a follow-up urinalysis in 4 to 6 weeks.[6]

For patients without an apparent etiology, risk assessment will guide the evaluation.[5]

In low-risk patients (women < 50 years, men < 40 years, never smoker or < 10 pack-years of smoking, and 3–10 red blood cells per high-power field), a urinalysis should be repeated in 6 months. If normal, the workup is complete.

In intermediate-risk patients (women 50–59 years, men 40–59 years, 10–30 pack-years of smoking, and 11–25 red blood cells per high-power field), renal ultrasonography and referral to urology for cystoscopy are indicated.

In high-risk patients (age ≥ 60 years, > 30 pack-years of smoking, > 25 red blood cells per high-power field, or history of gross hematuria), imaging with computed tomography urography, followed by referral to urology for cystoscopy, is recommended.

4. Know the reasons why urology should be contacted urgently. Red or reddish-brown urine does not always require urgent urology referral.

Several things can mimic gross hematuria.[6] For example, hemoglobin is a potent pigment; as little as 1 mL of blood can cause urine to appear grossly bloody. Myoglobin is often reddish-brown in color and may transiently appear in the urine after vigorous exercise. (The urinalysis in this case will be heme positive, but red blood cells will be absent from urine microscopy.) Eating beets and taking certain medications like phenazopyridine can lead to a transient red color change, in the absence of blood or red blood cells, and usually resolves quickly. Porphyria can also cause a color change in the urine, often with a normal urinalysis.[7]

Myoglobinuria with elevated creatine kinase may indicate rhabdomyolysis, a medical emergency. A large amount of myoglobin in the urine can cause acute kidney injury, and these patients are often admitted for vigorous intravenous hydration.

Gross hematuria requires urgent computed tomography urography and urology referral. Blood clots may obstruct the flow of urine and cause urinary retention. In severe cases, a urologist will need to place a large-bore urinary catheter to allow for bladder irrigation or to intervene with cystoscopy and clot evacuation.

5. Blood in the ejaculate is alarming to patients but is almost always benign—consider infection, medical procedures, and even possible parasite encounters during recent travel as potential causes.

Hematospermia, or gross blood in the ejaculate, often resolves on its own. In younger patients, infection is the most common cause.[8] A urinalysis should be obtained to rule out urinary tract infection and, if negative, a sexually transmitted infection workup should be considered. The patient's history will guide the evaluation.

In older patients, hematospermia is usually attributed to a postprocedure sequalae, such as a prostate biopsy or radiation for prostate cancer. In these cases, it is self-limited. A workup for sexual transmitted infections should also be considered in this population if the sexual history warrants it.

Other causes of hematospermia in adults can include malignancy, but the likelihood of cancer is low.[8] Another rare cause of hematospermia is schistosomiasis, which is caused by a parasitic worm found in infected waters. If a patient reports recent travel, ask whether they have traveled to endemic areas, which include sub-Saharan Africa, southeast Asia, and China.[9]

Patients with persistent hematospermia should be referred to a urologist to rule out other more serious causes.

6. Refer to Bosniak grading and American Urological Association guidelines to inform the management of kidney lesions found incidentally on cross-sectional imaging. Many lesions are cysts that require no further evaluation, but some cysts and all solid masses require further imaging.

Cysts are classified using the Bosniak grading system. Category I and II cysts don't require further evaluation, while category IIF through IV cysts require follow-up or intervention. Hyperdense and hemorrhagic cysts are benign (considered a Bosniak II cyst) and do not require further follow-up. All solid masses and Bosniak III to IV cysts require either intervention or long-term follow-up by a urologist.[10–12]

For masses that require serial follow-up, dedicated kidney imaging with computed tomography or magnetic resonance imaging should be used to distinguish benign from more suspicious masses. Vascular lesions, like aneurysms and fistulas, can also be followed serially by computed tomography or magnetic resonance imaging. Ultrasonography is less sensitive for determining malignant potential.

The urologist or radiologist will provide a recommendation for reimaging intervals. Small size at presentation (< 3 cm) and lack of growth or slow growth are favorable prognostic features.[11]

7. Advise patients taking SGLT-2 inhibitors that the medication is associated with lower urinary tract symptoms and a small but significantly increased risk of urogenital infections.

SGLT-2 inhibitors (eg, empagliflozin, dapagliflozin) are an exciting new class of antihyperglycemic medications used to treat patients with type 2 diabetes and have been shown to have positive effects on glycemic control, blood pressure, heart failure, and chronic kidney disease progression. SGLT-2 inhibitors lower serum blood sugar by inducing glycosuria, which causes patients to pass larger amounts of urine or feel that they have to urinate more often. Men may ascribe these symptoms to benign prostatic hyperplasia, but medications for this condition will not mitigate the symptoms.

In addition, glycosuria, coupled with the impaired immunity of diabetes and the moist environment in the urogenital tract, results in an increased risk in mycotic infections.[13] Uncircumcised men have the greatest risk of complications, which include balanitis or phimosis.

Women taking SGLT-2 inhibitors can have a higher risk of cystitis or vaginal yeast infections.

When starting patients on an SGLT-2 inhibitor, be sure to tell them about the risk of infection and the ways that they can mitigate that risk. Tell patients that it's important to clean and dry the genitals and perineum completely after urination. For patients who are uncircumcised, recommend that they retract the foreskin and ensure they dry the area thoroughly. Advise patients to seek medical attention immediately if they notice any symptoms or signs of infection.

8. Refer patients with Peyronie disease, a condition that is not rare, to a urologist if it impairs their ability to have intercourse.

Peyronie disease is an acquired penile deformity that causes a curvature of the penis; in some patients, it can interfere with the ability to have intercourse. As a type of erectile dysfunction, it may be psychologically and physically distressing to the patient. Patients may be reluctant or embarrassed to mention their symptoms to their doctor. Reported rates of incidental diagnosis are as high as 16%.[14] Peyronie disease may be diagnosed incidentally during evaluation for erectile dysfunction.[14]

The diagnosis is usually straightforward after taking a patient history and performing a penile examination. A fibrous plaque can often be palpated along the penile shaft. If the deformity bothers the patient or impairs their ability to have sex, patients can be referred to a urologist to determine whether medical or surgical treatment is warranted. Treatment may include injections with collagenase *Clostridium histolyticum* to break up the plaque or, in more serious cases, surgical correction.[14] If the deformity is minor or does not bother the patient, referral is unnecessary. Home remedies and folklore treatments are unproven and should be avoided.[14]

9. Avoid treating asymptomatic bacteriuria with antibiotics unless the patient falls into 1 of 3 exceptions to the "do not treat" rule.

In almost all instances, patients with asymptomatic bacteriuria (no dysuria, frequency, or urgency) should not be treated for a urinary tract infection, according to the latest guidelines from the Infectious Diseases Society of America.[15] The presence of bacteria in the urine, a positive urine culture (≥ 100,000 colony-forming units/mL), the presence of pyuria (≥ 10 leukocytes in the urine), or leukocyte esterase positivity without any of the above urinary symptoms does not indicate a urinary tract infection.[15] Even with specific sensitivities, empiric or directed antibiotics should not be prescribed. This particularly includes asymptomatic patients with a chronic indwelling Foley catheter (who frequently have bacterial colonization).

There are 3 exceptions to the "do not treat asymptomatic bacteriuria" rule.[15] They are (1) patients who are pregnant, (2) those undergoing a urologic procedure that may induce mucosal bleeding or pyelovenous backflow, and (3) patients who recently received a transplanted kidney (within 30 days of transplant). The transplant nephrologist should be consulted for the last case.

It's also important to be alert to 2 groups that require special attention and a nuanced response.

Patients with a spinal cord injury may have symptoms that differ from the classic genitourinary symptoms of a urinary tract infection. Signs and symptoms in patients with a spinal cord injury who have a urinary tract infection can include fever, malaise, lethargy or sense of unease, or new or worsening urinary incontinence or leaking around the catheter, spasticity, cloudy urine, malodorous urine, back pain, bladder pain, dysuria, or autonomic dysreflexia.[15] In the absence of these signs and symptoms, asymptomatic bacteriuria should not be treated.

Functionally or cognitively impaired older men and women may also present unique challenges as they may not be able to communicate their symptoms. In the community, these patients with pyuria or bacteriuria often receive empiric antibiotics for suspected urinary tract infection. However, the Infectious Diseases Society of America guidelines[15] strongly recommend against starting empiric antibiotic treatment when these patients develop bacteriuria with no localizing genitourinary symptoms or fever in the context of either delirium (acute mental status changes) or a recent fall. Instead, assess for other causes of delirium or the fall and carefully observe the patient.

The guidelines place a high value on avoiding adverse outcomes, such as antimicrobial resistance or *Clostridioides difficile* infection, in this population. Cloudy or malodorous urine as a sign of a urinary tract infection should only be considered as a proxy symptom in patients with spinal cord injury or dementia. In patients who are intact neurologically, urine odor or cloudiness should not be considered as a substitute for traditional symptoms of a urinary tract infection.

A patient who presents with a symptomatic infection with dysuria or other symptoms and has a positive urine culture should receive targeted therapy based on the bacterial sensitivities. In the absence of the stipulated exceptions, asymptomatic bacteriuria with or without pyuria should not be treated with antibiotics.

10. Refine your approach to prostate-specific antigen (PSA) screening by considering age-specific reference ranges, watching for medications that can alter PSA results, and focusing on a PSA value's "velocity" when considering a referral.

PSA screening has a long and complicated history. In 2012, the US Preventive Services Task Force[16] recommended against using PSA-based screening for prostate cancer. This change in strategy corresponded with an increase in the incidence of advanced prostate cancer cases in the years that followed. In 2018, this recommendation was changed back to a C recommendation, meaning that the decision to undergo PSA screening for men age 55 to 69 years should be individualized based on shared decision-making.[17]

Consider age-specific ranges. Historically, a PSA value of greater than 4.0 ng/mL has been used as an indicator for referral to a specialist for further evaluation and possible biopsy. In a study by Partin et al,[18] reference ranges of 0 to 2.5 ng/mL serum PSA (40–49 years); 0 to 3.5 ng/mL (50–59 years); 0 to 4.5 ng/mL (60–69 years); and 0 to 6.5 ng/mL (70–79 years) were defined to detect fewer (potentially insignificant) prostate cancers in older men and more (potentially curable) cancers in younger men. The researchers found that age-specific PSA reference ranges increased the detection of potentially curable tumors in young men and decreased the detection of less advanced tumors in older men compared with the standard reference range of 4.0 ng/mL.

Watch for certain medications. Medications such as 5-alpha reductase inhibitors (finasteride, dutasteride) lower the PSA by 50%. So, if a patient on this medication has a measured PSA of 2.5 ng/mL, the correction would be 5.0 ng/mL, which can be in the abnormal range, depending on screening strategy. Recent sexual activity, urologic procedures, and recent urinary tract infections can also temporarily increase the PSA value. Repeating the testing in 3 to 4 weeks is prudent. Even in the absence of these features, a single elevated value should be repeated.

Another medication issue related to PSA values merits attention. As part of its participation in the American Board of Internal Medicine's Choosing Wisely campaign, the American Urological Association warns against the practice of prescribing antibiotics to decrease initially raised PSA values and to reduce the need for prostate biopsy: "Don't treat an elevated PSA with antibiotics for patients not experiencing other symptoms."[19–21]

Focus on a PSA value's "velocity." The rate of rise or velocity of a PSA value over time can be helpful in determining which patients to refer to a urologist before the level reaches a screening threshold. It is much more concerning to a urologist for a patient to have a steady PSA increase from 1.0 to 3.0 ng/mL over a 1-year span than to have the same 6.0 ng/mL value over several years. Urologists now are using additional testing to determine which patients should undergo a prostate biopsy. These tests include multiparametric prostate magnetic resonance imaging; serum free PSA, bound PSA, or both; and urinary biomarkers.

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Dr. Shirk has disclosed consulting for Ceevra and Procept Biorobotics. Dr. Paige reports no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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