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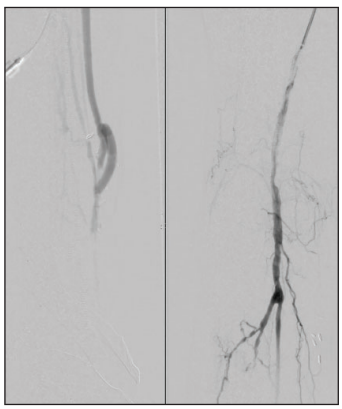

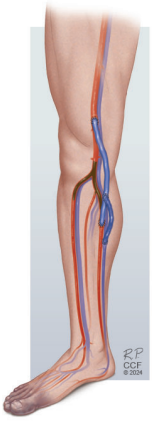

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Table of Contents

CONTINUED ON PAGE 648

Upcoming Features

- Myocardial infarction without obstructive coronary artery disease: Current management strategies
- Hypoglycemia after bariatric surgery: Management updates

CONTINUED FROM PAGE 647

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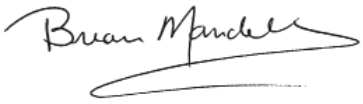
It's time for a little history of medicine—introducing a new feature in CCJM

In this issue of the *Journal*, we introduce a new feature. Adam Brown, MD, a rheumatologist at Cleveland Clinic, will periodically present an editorial related to an article in the same issue. Addressed affectionately in our editorial office as "Adam's angle," his editorials will explore somewhat tangentially the history of a topic related to the article.

In our current issue, Adam writes on an aspect of a Clinical Picture article that depicts a patient with skin manifestations of endocarditis in whom the diagnosis was confirmed after positive blood cultures led to cardiac imaging, emphasizing the importance of blood cultures in confirming the diagnosis.[1] In "The history of blood cultures: From the research laboratory to the bedside," Adam traces the not-straightforward evolution of this now fundamental laboratory test.[2] He describes how, in the process of blood cultures becoming a routinely available laboratory test, their development benefitted from an interesting family relationship in the research laboratory. Adam also notes that until blood cultures became available, the pathobiology of endocarditis as an infection could only be hypothesized. Osler's earlier postulated concept of endocarditis as an infection was validated when the presence of bacteremia was demonstrated in patients with clinically suspected endocarditis, and the specialty of infectious disease was off and running.

Adam is a member of our editorial board and an associate program director of the Rheumatology Fellowship Program at Cleveland Clinic. For those of you who are fans of medical podcasts, his *Rheuminations* podcast often includes his self-described "medical mysteries and other ripping yarns."

I enjoy learning about how researchers and clinicians with only rudimentary tools, diligence, curiosity, and superb reasoning skills at their disposal were able to initially define principles of disease and human physiology that we now accept as common knowledge. I hope you will also.



Brian F. Mandell, MD, PhD
Editor in Chief

1. **Aykent B, Yilmaz O.** Skin manifestations in a patient with acute bacterial infective endocarditis. Clev Clin J Med 2024; 91(11):657–659. doi:10.3949/ccjm.91a.24066
2. **Brown A.** The history of blood cultures: From the research laboratory to the bedside. Clev Clin J Med 2024; 91(11):661–663. doi:10.3949/ccjm.91a.24091

doi:10.3949/ccjm.91b.11024

CME MOC

2024

NOVEMBER

CLEVELAND CLINIC CANCER CONFERENCE: INNOVATIONS IN MULTIDISCIPLINARY CARE
November 1–3
Hollywood, FL

GASTROENTEROLOGY UPDATE: CONTROVERSIES, INNOVATIONS, RESEARCH
November 2
Warrensville Heights, OH

ADVANCING CARDIOVASCULAR CARE
November 8
Columbus, OH

FUTURE OF STROKE CARE: STROKE AND CEREBROVASCULAR DISEASE CONFERENCE
November 9–10
Hollywood, FL, and
Hybrid (Encore)

DIMENSIONS IN CARDIAC CARE
November 10–12
Cleveland, OH

CALCIUM DAY
November 13
Cleveland, OH

PRIMARY CARE +: UPDATES IN PRIMARY CARE, WOMEN'S HEALTH, AND BEHAVIORAL MEDICINE
November 13–16
Beachwood, OH

COMPREHENSIVE NEUROTOXIN COURSE FOR NEUROLOGICAL CONDITIONS
November 16–17
Cleveland, OH

PHYSICIAN ADVISOR SYMPOSIUM
November 20
Live stream

DECEMBER

CASE-BASED MANAGEMENT OF TRICUSPID AND MITRAL VALVE DISEASE
December 6–7
New York, NY

2025

JANUARY

MULTIDISCIPLINARY COLORECTAL ONCOLOGY COURSE
January 10
Cleveland, OH

PULMONARY HYPERTENSION SUMMIT
January 16–17
Hollywood, FL

ASH REVIEW
January 17
Cleveland, OH

BEST OF SAN ANTONIO BREAST CANCER SYMPOSIUM
January 18
Hollywood, FL

MULTISPECIALTY PATHOLOGY SYMPOSIUM
January 24–26
Las Vegas, NV

CENTER FOR EXCELLENCE IN COACHING AND MENTORING: COACHING AND MENTORING ESSENTIALS FOR HEALTHCARE PROFESSIONALS
January 28
Live stream

FEBRUARY

INTERNATIONAL COLORECTAL DISEASE SYMPOSIUM
February 13–15
Fort Lauderdale, FL

WOMEN AND HEART DISEASE: UNIQUE RISKS, RECOGNITION AND MANAGEMENT
February 14
Live stream

PAIN MANAGEMENT SYMPOSIUM
February 15–19
Orlando, FL

MARCH

STRUCTURAL VALVE IMAGING SUMMIT
March 6–9
Hollywood, FL

CLEVELAND CLINIC GUT INSIGHTS: EXPLORING THE LATEST IN GASTROENTEROLOGY
March 17–18
Hollywood, FL

APRIL

UPDATES IN PRIMARY IMMUNODEFICIENCY
April 4–5
Cleveland, OH, and Live stream

WELLNESS AND PREVENTIVE MEDICINE CONFERENCE
April 11
Beachwood, OH, and Live stream

NEPHROLOGY UPDATE
April 23–25
Cleveland, OH

INNOVATIONS IN NEUROSCIENCE
April 25
Avon, OH

ULTRASOUND COURSE: INTEGRATING POCUS INTO YOUR PRACTICE
April 30–May 3
Cleveland, OH

MAY

VASCULITIS 2025: ADVANCES AND CONTROVERSIES IN VASCULITIS
May 8
Cleveland, OH, and Live stream

BIOLOGIC THERAPIES SUMMIT
May 9–10
Cleveland, OH

PRIDE IN PRACTICE: STRATEGIES FOR LGBTQ+ INCLUSIVITY
May 30
Beachwood, OH

HEART OF THE CITY: CLEVELAND CLINIC HVTI CARDIOVASCULAR SYMPOSIUM
May 31
Hollywood, FL

JUNE

EXPANDING THE FRONTIERS OF CONTEMPORARY HEART FAILURE CARE: FROM ACUTE TO CHRONIC
June 6–7
Cleveland, OH

INTENSIVE REVIEW OF INTERNAL MEDICINE
June 9–13
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Basar Aykent, MD
Department of Internal Medicine, Division of Nephrology, Istanbul Sisli Hamidiye Etfal Training and Research Hospital, Istanbul, Turkey

Ozlem Yilmaz, MD
Department of Internal Medicine, Division of Geriatrics, Istanbul Training and Research Hospital, Istanbul, Turkey

Skin manifestations in a patient with acute bacterial infective endocarditis

Figure 1. Petechiae clustered on the tip of the nose.

A 50-year-old woman with end-stage renal disease caused by secondary amyloidosis resulting from familial Mediterranean fever had been receiving routine hemodialysis for 9 years when her arteriovenous fistula became ineffective. Efforts to create another fistula were unsuccessful, and a tunneled dialysis catheter was placed.

See related article, page 661

During a standard hemodialysis session about 5 months later, she experienced the onset of rigors, accompanied by the appearance of painless, inflamed purpuric lesions, which developed into petechiae. The petechiae were located on the nose, with a cluster at the tip of the nose, and on the legs (**Figure 1**). Painless, erythematous hemorrhagic lesions (Janeway lesions) and ecchymotic areas were observed on the dorsum of the hands and feet, palmar surfaces, ankles, and anterior tibial surfaces, and there were palpable purpura on the legs and painful Osler nodes on the fingers (**Figure 2** and **Figure 3**).

The patient was admitted to the hospital. On examination, her temperature was 38.5°C (101.3°F).

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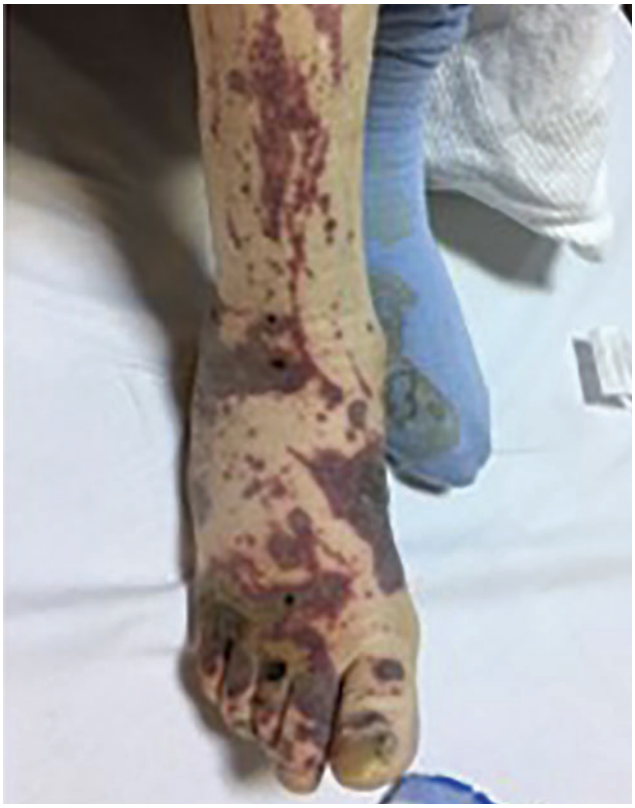

Figure 2. Painless erythematous and hemorrhagic purpura and ecchymotic areas on the anterior surface of the ankle and shin.

A new grade 3 systolic murmur not previously present was detected over the aorta. Laboratory testing showed a neutrophilic leukocytosis (white blood cell count 23 × 10^9/L [reference range 4–11], neutrophils 11 × 10^9/L [1.5–8.0]).

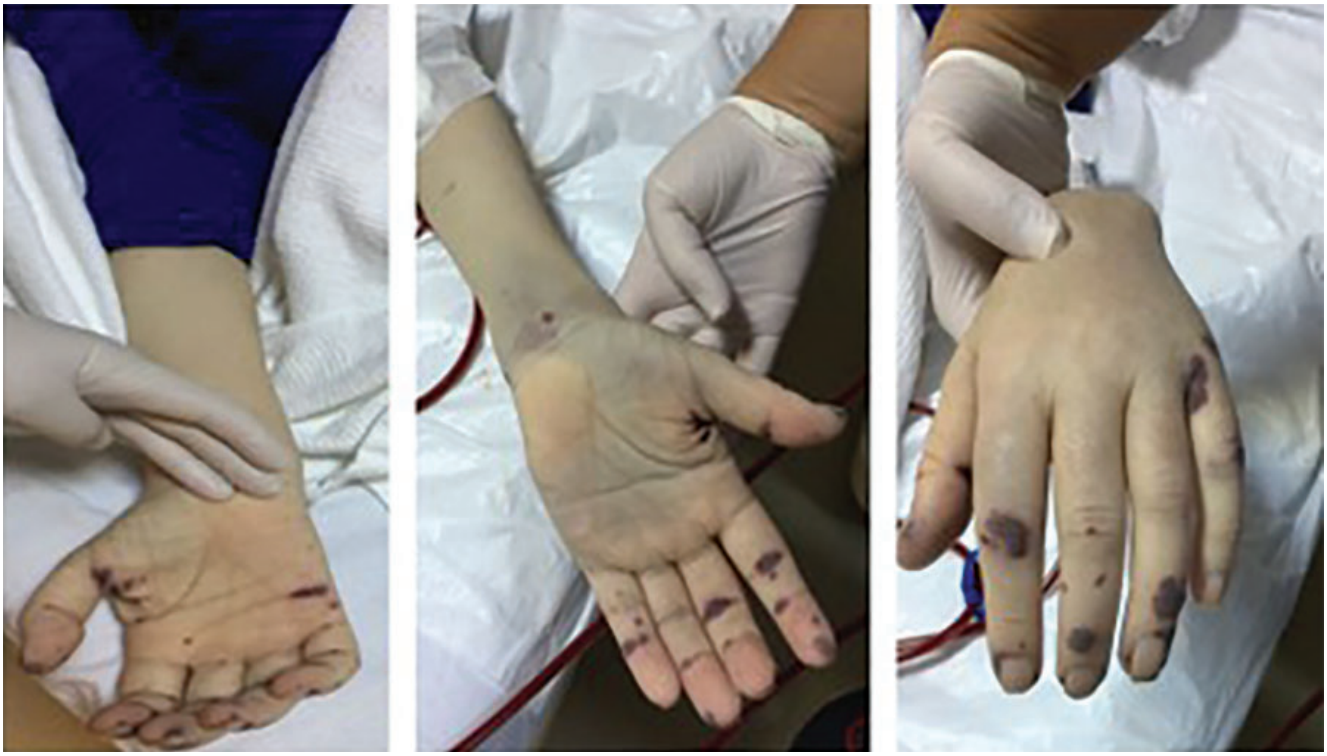

Figure 3. Janeway lesions and ecchymotic areas on the palms and dorsum of the patient's hands. Finger lesions, or Osler nodes, are typically painful.

Blood cultures were obtained from the peripheral veins and catheter at 2-hour intervals, and vancomycin and ceftazidime were started empirically to cover likely causes of catheter-associated bacteremia. After 3 days of antibiotic therapy, the fever persisted, the patient developed severe headache, confusion, and lethargy, and her clinical condition deteriorated further. Diffusion-weighted magnetic resonance imaging of the brain showed diffusion restriction, areas of edema, and sharply defined bright areas in the white matter. A preliminary diagnosis of septic embolism was made.

Infective endocarditis due to metastatic catheter infection was suspected given the skin findings, newly developed systolic murmur, and catheter infection resistant to antibiotic treatment. Blood cultures grew methicillin-resistant *Staphylococcus aureus*, and treatment was changed according to the antibiogram results. Transesophageal echocardiogram showed a 2 × 2-cm mobile vegetation in the aortic valve.

The patient was diagnosed with acute bacterial infective endocarditis. She developed heart failure and cerebral septic embolism during follow-up and passed away in the second week after diagnosis.

SKIN MANIFESTATIONS OF INFECTIVE ENDOCARDITIS

This patient was diagnosed with acute bacterial infective endocarditis after exhibiting signs such as persistent fever, aortic murmur, and skin lesions including Janeway lesions and Osler nodes, classic skin manifestations of endocarditis.[1] Our patient had 2 major criteria for the diagnosis of infective endocarditis (presence of a lesion compatible with endocarditis on echocardiography, growth of microorganisms compatible with infective endocarditis, such as *S aureus*, in 2 blood cultures) and 3 minor criteria (condition that predisposes to infective endocarditis [hemodialysis catheter], fever > 38°C [100.4°F], vascular phenomena [septic cerebral infarction, Janeway lesions]).[2]

Janeway lesions are *painless* erythematous or hemorrhagic lesions found on the palms and soles, while Osler nodes are *painful* petechial lesions found on the fingers and toes.[3] Janeway lesions are more common in acute bacterial endocarditis, and Osler nodes are more often seen in subacute endocarditis.[1,3]

The palpable purpura on the patient's legs were more consistent with a vasculitis process, likely secondary to the increased immune complex activation

and deposition occurring in infectious endocarditis.[4] The cause of Osler nodes and Janeway lesions in endocarditis remains controversial, as studies have reported different histologic findings and both positive and negative results on lesion culture.[1,3] These differences may reflect the timing of biopsy, with earlier biopsy showing septic emboli with microabscess formation and later biopsy showing an inflammatory response to the microabscess and negative culture.[1]

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DISCLOSURES

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Address: Ozlem Yilmaz, MD, Department of Internal Medicine, Division of Geriatrics, Istanbul Training and Research Hospital, 34390 Istanbul, Turkey; dr.ozlemyilmaz@hotmail.com

ADAM J. BROWN, MD, Associate Editor

Adam J. Brown, MD
Department of Rheumatologic and Immunologic Disease, Cleveland Clinic, Cleveland, OH; Clinical Instructor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

The history of blood cultures: From the research laboratory to the bedside

"In order to study the characters of any species of bacterium it is necessary to have it growing apart from every other species. . . . When we have succeeded in separating it, and have got it to grow on a medium which suits it, we are said to have obtained a pure culture."
Dr. Robert Muir, pathologist, *Manual of Bacteriology*, 1897[1]

The case of endocarditis presented in this issue of *Cleveland Clinic Journal of Medicine* highlights the heterogeneity of the cutaneous manifestations of this disease, as well as the importance of blood cultures in making the diagnosis.[2] A patient develops a fever, blood cultures are done, and *Staphylococcus aureus* grows. Next step is to check an echocardiogram to find the source of the bacteremia and, lo and behold, vegetations are found and the boxes of the Duke criteria for endocarditis are checked (2 major criteria). The patient had multiple rashes consistent with endocarditis, but what cemented the diagnosis was the blood culture leading to the echocardiography findings.

Associate Editor, Adam Brown, MD, discusses an angle related to the article "Skin manifestations in a patient with acute bacterial infective endocarditis" on page 657.

We consider blood cultures to be an essential component of an infectious disease workup, especially in a patient in whom bacterial endocarditis is suspected. It's reasonable to think culturing of blood was adopted rapidly in clinical practice around the time of the microbiology revolution led by Koch, Pasteur, and Lister, but culturing of bacterial organisms was initially a complex and labor-intensive process relegated to the research laboratories across the United States and Europe. It wasn't until endocarditis became a recognized clinical entity in 1885 and the hunt began in earnest to prove the etiology was bacterial that blood cultures were brought to the bedside.

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FROM COMPLEX BEGINNINGS . . .

The *Manual of Bacteriology*, first published in 1897, is a just over 500-page textbook of the knowledge at the time of the rapidly expanding field of microbiology.[1] The textbook walks the reader through the multiple processes for culturing and isolating bacterial organisms, starting with sterilizing of equipment: dry heat in a hot air chamber, wet heat in Koch's steam sterilizer, or a high-pressure steam chamber. Next, the book outlines multiple practices for culturing bacteria with an amalgamation of recipes ranging from ox meat, horse meat, gelatin, agar, blood agar, potatoes, and bread paste.

It took decades of trial and error to develop recipes to create ideal culture media to isolate and grow various organisms. Raw meat was the most popular culture medium, which isn't surprising as bacteria that infect human tissues were the most studied. Many of the bacteria that infect human tissue are also capable of colonizing horse and ox meat. Meat culture had a few negatives, however. For one, the preparation was complex and time consuming.

"It ought to be from an animal recently killed, and should therefore be markedly acid to litmus paper. It must be freed from fat, and finely minced. For each pound of mince add 1000 cc distilled water, and mix thoroughly in a shallow dish. Skim off any fat present, removing the last traces by stoking the surface of the fluid with pieces of filter paper. Set aside in a cool place for twenty-four hours. Place a clean linen cloth over the mouth of a large filter funnel,

and strain the fluid through it into a flask. Pour the minced meat into the cloth, and gathering [sic] up the edges of the cloth in the left hand, squeeze out the juice still held back in the contained meat. Finish this expression by putting the cloth and its contents into a meat press . . . squeeze out the last drops."[1]

Even when prepared correctly, the meat-based culture media presented challenges when used to culture bacteria, as, not surprisingly, meat is opaque and colonies of bacteria could not be observed *growing within*. An advancement in culture technology was the recognition that gelatin could be sterilized and added to the culture mixture to make it clearer and allow the viewer to see bacterial growth *within* the meat culture.

Gelatin was also popular as an additive because it could be purchased ready-made (Gold label from Paris was mentioned in the textbook as being particularly high quality). Challenges with gelatin were noted, however, as at human body temperature—the optimal temperature for growing organisms that affect humans—gelatin is a liquid, making it unstable and potentially leading to a plate full of soupy minced meat.[1]

A substitution for gelatin came from discovering agar's stability and ability to cultivate bacterial organisms. Although agar now is most associated with the thing you made to grow bacteria in your Biology 101 lab, originally agar had nothing to do with bacteriology. *Agar-agar* is a southeast Asian term for seaweed. In the late 1600s it was noted that seaweed and algae when ground and left to dry in the sun turned into a semi-solid jelly and could be used as a food additive.

Agar began to be used in research laboratories in the late 19th century, when Dr. Walther Hesse, then a researcher working in Dr. Robert Koch's laboratory, was having difficulty with the gelatin culture he was applying to the inside of a test tube to grow bacteria, as the gelatin persistently melted in the summertime heat. Legend has it his wife Fanny Hesse, who was working as his unpaid laboratory assistant, suggested using the food additive agar as a culture medium because it is stable at higher temperatures.[3] Not only was agar solid at a wide range of temperatures, but it was also clear and able to grow various bacteria. Agar has been a staple in research and Biology 101 labs ever since.

DIFFERENT MIXTURES FOR DIFFERENT BACTERIA

Not all bacteria, it turns out, are fans of plain, dried-out, pulverized seaweed. Through much trial and error, different additives or formulations of culture media were created to cultivate and isolate certain, more discerning organisms.[1] For example, glycerine broth could be added to cultivate the famously fastidious *Mycobacterium tuberculosis*, whereas glucose could be added for diphtheriae. Pfeiffer influenza bacillus (later recognized to not cause influenza) had a predilection for human or ox blood added to agar plates, inspiring its future name *Haemophilus* (heme-loving) *influenzae*. Even bacteria that had a deep disdain for oxygen could be grown by combining sulfuric acid with pure zinc to create hydrogen, which is then passed over the culture to bind and expel the oxygen and make a comfy anerobic environment for certain organisms.[1] Decades of work, trial, and error led to an assortment of culture media to isolate and grow bacteria in the research laboratory.

BRINGING BLOOD CULTURE TO THE BEDSIDE IN THE PURSUIT OF ENDOCARDITIS

For centuries endocarditis was an enigmatic disease. It is debatable when the first description of endocarditis occurred. Dr. Jean-Nicolas Corvisart in the late 1700s was the first to use the term *vegetation* to describe a lesion on the mitral valve of a patient who died, but there was no clear overarching disease known to cause these valvular changes.[4] Corvisart surmised that the vegetations were caused by syphilis.

Other medical heavyweights had hypotheses about the cause of the vegetations. None other than Dr. René-Théophile Hyacinthe Laënnec, the inventor of the stethoscope, hypothesized that vegetations were caused by thrombus formation.[4]

The "clinical entity" *endocarditis* made its debut on the international stage in 1885 when Dr. William Osler reviewed more than 200 cases of the disease in a Gulstonian lecture series in London.[5] Osler synthesized the data, describing signs and symptoms to look for like fever, joint pain, rash, and splenomegaly. Osler also made the critical observation that a history of valvular abnormalities, such as those resulting from rheumatic fever, predisposes to the development of endocarditis.[4,6] What was the cause? Osler hypothesized it was infectious but couldn't prove it. It would take another 3 decades to prove the infectious etiology of endocarditis.

It wasn't until 1910 that Dr. Hugo Schottmüller cultured viridans streptococci from a patient with endocarditis.[4,7] That same year, Dr. Emanuel Libman, practicing at Mount Sinai in New York City, published a paper with the confident title "The etiology of subacute infective endocarditis," along with Herbert Louis Celler.[8] Libman described 43 patients who died of endocarditis. Blood cultures were done in 36 of these

patients, and "atypical" nonhemolytic streptococci grew in 35.[4]

Libman also reviewed more than 3,000 blood cultures over the preceding 10 years during his studies on the "bacteriology of the blood," recognizing other causes of endocarditis such as *Staphylococcus*.[6] He was particularly inclined to make this discovery, as he had previously worked under the mentorship of Dr. Theodor Escherich in Vienna, a famous pediatrician who first isolated a bacterium from the intestines of multiple children he termed *Bacterium coli commune* and who would later have his name attached to the ever-difficult-to spell *Escherichia coli*. Dr. Escherich was particularly known for his skills of bacterial culture and passed these skills to Dr. Libman.[4]

With blood cultures, Dr. Libman showed the bacterial etiology of infectious endocarditis and how, in the right clinical context, the diagnosis of endocarditis could be made in a living, breathing person. Half a century before the development of echocardiography, blood culture gave us 1 of the 2 major Duke criteria to diagnose infectious endocarditis. Before Dr. Libman's paper, the diagnosis of endocarditis was mostly relegated to the pathologist at autopsy.

CONCLUSION

Culturing and isolating bacteria was a labor-intensive process developed through decades of toil in research laboratories around the globe. The skills Dr. Emanuel Libman attained working directly with Dr. Escherich allowed him to establish the bacterial cause of endocarditis, paving the way for use of bacterial culture in the clinic to help establish the diagnosis of bacteremia and potentially, endocarditis. Once the antibiotic era opened in the 1940s, there was an even greater desire to diagnose bacteremia, as it was recognized that the rapid introduction of antibiotics could reduce the risk of septic shock and death. Techniques for culturing blood improved, becoming less time intensive, and, thankfully for the horse and ox, less reliant on raw meat. In the 1970s automated growth systems were introduced, detecting evidence of bacterial metabolism and division instead of relying on the naked eye of a human.[9]

Blood cultures have become standard practice for evaluating a patient for suspected infection. Next time you're on the hospital wards and you're alerted to fever in a patient with an unknown cause and you go to click the blood culture button, remember the oxen sacrificed, the melted gelatin, and the pursuit of endocarditis that gave us this valuable clinical tool.

DISCLOSURES

Dr. Brown has disclosed consulting and teaching and speaking for Amgen and Chemocentryx.

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Address: *Adam J. Brown, MD, Department of Rheumatologic and Immunologic Disease, A50, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; browna22@ccf.org*

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Primary adrenal insufficiency in adults

To the Editor: I read with keen interest the review article on primary adrenal insufficiency in adults by Drs. Lundholm, Ambalavanan, and Rao.[1] The authors mention that secondary adrenal insufficiency is more common than primary adrenal insufficiency and is most often associated with long-term exogenous steroid use.[1]

The United States is facing an opioid epidemic, with 1 in 10 Americans experiencing chronic pain.[2] Opioids cause adrenal insufficiency by suppressing the hypothalamic-pituitary-adrenal axis. The incidence is reported to be 9% to 29% in patients receiving long-term opiate therapy.[2] Given the widespread use of both legal and illegal opioids, secondary adrenal insufficiency should be considered in patients who present with symptoms of adrenal insufficiency like fatigue, nausea, vomiting, weight loss, and muscle pain.

Anup Katyal, MD
St. Louis, MO

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Vivian Hua, BA
Department of Urology, Cleveland Clinic, Cleveland, OH; Case Western Reserve University School of Medicine, Cleveland, OH

Bradley Roth, BS
Department of Urology, Cleveland Clinic, Cleveland, OH

Andrew Shumaker, MD
Department of Urology, Cleveland Clinic, Cleveland, OH

Raevti Bole, MD
Department of Urology, Cleveland Clinic, Cleveland, OH; Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Petar Bajic, MD
Department of Urology, Cleveland Clinic, Cleveland, OH; Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: What are options for my patients with erectile dysfunction who have an unsatisfactory response to PDE5 inhibitors?

A 68-year-old man with diabetes, hypertension, and hyperlipidemia is experiencing unsatisfactory results with maximum doses of sildenafil (100 mg) and tadalafil (20 mg) for erectile dysfunction. You confirm he is taking his medication as directed. What are the next options for him?

A: Erectile dysfunction (ED), which affects 70% of men over 70 and more than 150 million men worldwide, is defined as a persistent inability to attain or sustain an erection suitable for sexual intercourse.[1] Phosphodiesterase type 5 (PDE5) inhibitors are first-line medical treatment for ED,[1] but up to 40% of patients do not have a satisfactory response to these agents.[2] Alternative therapies for patients who do not respond to PDE5 inhibitors or who experience intolerable side effects from them include intracavernosal injection, vacuum erection devices, and penile prosthesis implantation.

ED MANAGEMENT: GENERAL CONSIDERATIONS

Before medical therapy for ED is tried, it is crucial to address modifiable risk factors, counsel patients on lifestyle modifications, and identify any medications or underlying medical conditions contributing to ED. Risk factors for ED include smoking, obesity, cardiovascular disease, depression, prostate surgery, penile trauma, obstructive sleep apnea, and testosterone deficiency. Lifestyle adjustments such as weight loss, increased cardiovascular exercise, reduced alcohol intake, and quitting smoking can partially alleviate symptoms.[1]

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Also, a thorough history should explore psychological, psychosocial, and relational factors and sexual practices that may be impacting sexual performance, and referral to a sex therapist should be considered.

A diagnosis of ED can indicate the presence of systemic disease or reversible causes like medication side effects or testosterone deficiency (discussed below). When certain medications such as antidepressants or antihypertensives are suspected of contributing to ED,[3] the patient should be advised to talk with the prescribing physician to determine whether alternative medications with better side-effect profiles are available.

Beta-blockers are associated with ED, although the etiology is not well established.[4] Patient awareness or anxiety regarding ED as a potential side effect of beta-blockers may itself contribute to dissatisfaction with erectile function after starting a beta-blocker. While further study is needed, trying an alternative medication for patients on first-generation (propranolol) or second-generation (metoprolol, atenolol) beta-blockers may be considered. In a review of several small studies, Sharp and Gales[5] noted mildly improved or similar sexual function in patients after starting nebivolol, which was attributed to the beta-blocker's ability to stimulate endothelial release of nitric oxide, producing vasoactive effects and potentiating penile erection.

If feasible for the patient, medications like calcium channel blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers can also be explored, as their risk for causing ED is thought to be lower. Thiazide diuretics at high doses have been associated with adverse effects on erectile function

compared with other antihypertensive drugs.[6] However, treatment of hypertension should remain the priority, and it may not be clinically appropriate to adjust antihypertensive medications, particularly without strong evidence to support the use of 1 medication over another.

The evidence regarding a correlation between statin medications and ED risk is conflicting. Some studies suggest that statins have sexual side effects, while others propose that the overall cardiovascular benefit of these medications contributes to improved erectile function.[7] No large-scale randomized controlled trials have established a link between statins and testosterone levels, and cessation of statin therapy or lowering of statin regimens as a means of improving ED is not recommended. Rather, we suggest optimizing well-established contributing factors such as cardiovascular fitness and testosterone levels.

PHOSPHODIESTERASE TYPE 5 INHIBITORS

Despite making lifestyle changes, many patients with ED require PDE5 inhibitors such as sildenafil or tadalafil to improve erectile function. These agents promote erections by increasing nitric oxide levels and blocking the decomposition of cyclic guanosine monophosphate, thereby relaxing the smooth muscle within the corpora cavernosa and increasing blood flow.[1] However, PDE5 inhibitors are efficacious in only 60% to 70% of patients.[2]

When starting PDE5 inhibitors, proper administration should be ensured, as a large proportion of treatment failures with these agents is attributed to incorrect use.[2] Sildenafil should be taken 30 to 60 minutes before intercourse on an empty stomach. The recommended window for taking on-demand tadalafil, which is not impacted by food intake, is 30 to 120 minutes before intercourse, but for optimal effectiveness, it should be taken 60 to 120 minutes before intercourse.[8] Daily low-dose tadalafil (5 mg) may be considered for men who also experience voiding dysfunction due to prostate enlargement or men with mild ED.

Patients taking 5-alpha-reductase inhibitors for benign prostatic hyperplasia who also experience ED and low libido should be referred to a urologist for alternative management strategies such as daily low-dose tadalafil, alpha-blockers, or minimally invasive surgical therapies. In fact, some selective alpha-blockers have been found to preserve or improve erectile function.[9] Combination therapy with daily tadalafil plus on-demand higher-dose tadalafil or sildenafil may be considered.[10]

Before determining that the medication has failed to achieve the desired result, several trials of PDE5 inhibitors with at least 24 hours between doses should be attempted.[11] Additionally, other reversible causes of ED, such as testosterone deficiency, should be assessed. An early morning testosterone level (before 11:00 AM) can identify testosterone deficiency in the presence of symptoms or signs of low testosterone such as low libido, fatigue, and loss of body hair.[10] Testosterone levels less than 300 ng/dL with these accompanying symptoms may warrant treatment with testosterone replacement therapy, which placebo-controlled randomized trials and meta-analyses have demonstrated may help improve erectile function and libido.[10–12] However, patients with ED but no symptoms of testosterone deficiency are less likely to benefit from replacement therapy. Assessment of testosterone deficiency is most valuable in men with borderline response to PDE5 inhibitors and with other signs and symptoms of low testosterone.

Once these avenues have been exhausted, exploring alternative therapies that aid in restoring erectile function should be considered.

OTHER THERAPEUTIC OPTIONS

Therapeutic options beyond PDE5 inhibitors include intracavernosal injection therapy, vacuum erection devices, and penile prostheses.[1,2,11] These alternatives are typically used when the patient does not respond to PDE5 inhibitors or experiences intolerable side effects (eg, headache, flushing, dyspepsia, visual disturbances, backache) from them. Treatment should be based on patient and partner preferences, comorbidities, and current medications.[2] The 2018 American Urological Association guideline on ED[11] emphasizes the importance of shared decision-making between patient and physician. In this process, the physician presents the various treatment options to the patient, and the risks and benefits of each are discussed before the treatment most aligned with patient goals and expectations is determined.

Intracavernosal injection

Intracavernosal injection is the direct injection of 1 or more vasoactive medications (eg, alprostadil, papaverine, or phentolamine) into the corpora cavernosa of the penis to promote an erection through local dilation of penile vessels.[11] Intracavernosal injection therapy is efficacious in providing erectile function adequate for sexual intercourse in 53.7% to 100% of patients.[11,13] However, it has higher long-term dropout rates, and its side effects include priapism, ecchymoses, hematoma, penile fibrosis, and penile deformity due to Peyronie disease.[14]

Vacuum erection devices

Vacuum erection devices induce erection by generating negative pressure, which enhances blood flow into the corpora cavernosa, and the erection is maintained with a constricting ring at the base of the penis.[15] Of note, despite initial use of vacuum erection devices for penile rehabilitation after prostatectomy, these devices have not been shown to definitively improve erectile function.[16] Side effects of vacuum erection devices are quite mild but may include discomfort, bruising, numbness, skin irritation, and pain from the constricting ring.[15] Vacuum erection devices are contraindicated in patients with coagulopathies or those taking anticoagulants.[17] Furthermore, combination treatment with PDE5 inhibitors and other accepted therapies such as vacuum erection devices may have greater efficacy than either as monotherapy.[18]

Inflatable penile prosthesis implantation

Another option for patients with ED refractory to more conservative therapies is surgical implantation of an inflatable penile prosthesis.[19] This option has the highest satisfaction rate, and is typically considered after failure of oral therapies in patients who do not desire injection or vacuum erection device therapy.[20] Inflatable penile prosthesis implantation can address penile deformity, making it a particularly advantageous option for patients with ED secondary to Peyronie disease, in whom intracavernosal injection therapy is contraindicated due to the risk of progressive penile scarring and deformity.[1]

Several different prostheses are available, including 2- or 3-piece inflatable penile prostheses or a malleable device.[21] Three-piece inflatable penile prostheses offer the most natural rigidity and flaccidity and are the most commonly implanted penile prostheses in the United States.[1]

Kucuk et al[21] found that patients who underwent inflatable penile prosthesis implantation had greater improvements in their International Index of Erectile Function score than patients who received tadalafil or intracavernosal injection therapy. Partner satisfaction also improved, as both patient and partner Erectile Dysfunction Inventory of Treatment Satisfaction scores were significantly higher with penile prostheses than with other treatment modalities. A multicenter study found that more than 90% of patients who received an inflatable penile prosthesis were able to engage in normal sexual activity following implantation.[22] Potential complications of penile prosthesis implantation include bleeding, infection, erosion, mechanical failure, need for revision surgery, and automatic inflation.[20]

SHOCKWAVE THERAPY

The mechanism of action of low-intensity extracorporeal shockwave therapy (Li-ESWT) in treating ED is unclear. It is hypothesized that extracorporeal shockwaves stimulate expression of endothelial nitric oxide synthase, vascular-endothelial growth factor, and other vascular growth factors, promoting vessel expansion and neovascularization that promote blood flow and erectile function.[23] The Sexual Medicine Society of North America regards Li-ESWT as promising but does not endorse its use beyond research given its novelty.[24] Since the release of this statement, further studies have demonstrated some efficacy of Li-ESWT in men with moderate ED, though an optimal protocol remains to be determined.[25]

It is important to differentiate between Li-ESWT and radial wave therapy, the latter of which uses low-pressure acoustic waves to deliver lower energy with less tissue penetrance compared with Li-ESWT.[26] Direct-to-consumer marketing from men's health clinics often use these 2 terms interchangeably even though a randomized controlled trial found no difference between radial wave therapy and sham therapy for treating ED.[26] The Sexual Medicine Society of North America corroborates this, drawing a distinction between Li-ESWT and radial wave therapy.[24] While regenerative therapies such as Li-ESWT in ED treatment require further investigation, patients should be informed regarding the lack of evidence to support radial wave therapy for ED treatment, particularly as radial wave therapy devices are often promoted as equivalent by health clinics for men.

WHAT NOT TO OFFER

Stem cell therapy was initially proposed to improve erectile function by promoting angiogenesis and tissue healing and reducing scarring, inflammation, and apoptosis.[27] Clinical trials have been limited, and its clinical application is still unknown. Similarly, platelet-rich plasma injections have been studied as an option for ED, but a recent randomized controlled trial found no difference in efficacy between platelet-rich plasma and placebo.[28] Thus, the Sexual Medicine Society of North America's position is that stem cell and platelet-rich plasma therapies should not be used in clinical practice.[24]

CONCLUSION

There are various effective treatment modalities for men who cannot tolerate PDE5 inhibitors or in whom these

agents fail. Treatment choice should take underlying comorbidities into account. Referral to a urologist experienced in sexual dysfunction can ensure that patients choose the option best aligned with their goals and expectations.

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Address: *Vivian Hua, BA, Department of Urology, Q10, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; vxh69@case.edu*

COMMENTARY

Bartolome Burguera, MD, PhD
Chief, Medical Specialty Institute, Cleveland Clinic, Cleveland, OH; Chair, Department of Endocrinology and Metabolism, Cleveland Clinic, Cleveland, OH; Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Marcio L. Griebeler, MD
Department of Endocrinology and Metabolism, Cleveland Clinic, Cleveland, OH; Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

W. Timothy Garvey, MD
Associate Director, Department of Nutrition Sciences and the University of Alabama at Birmingham Diabetes Research Center, University of Alabama at Birmingham, Birmingham AL; Professor, University of Alabama at Birmingham, Birmingham AL

Effective but inaccessible antiobesity medications: A call for sharing responsibility for improving access to evidence-based care

The treatment of obesity is problematic for several reasons. Obesity, obesity complications, and obesity-related diseases are highly prevalent and exact huge social costs. At the same time, we have medications of unprecedented efficacy with lifesaving potential, but these medications remain inaccessible to many patients because of high costs and other factors. This situation is untenable and should be unacceptable to patients, healthcare professionals, and society at large.

THE CONUNDRUM OF OBESITY TREATMENT

Obesity exacts a huge burden of patient suffering and social cost. Obesity affects 42% of US adults,[1] and worldwide its prevalence is rising.[2] Because obesity is a chronic condition, complications and related diseases are also common and are responsible for extensive morbidity and mortality. These include type 2 diabetes, hypertension, dyslipidemia, obstructive sleep apnea, osteoarthritis, cardiovascular disease, and cancer.[3] In 2016, the total cost of chronic diseases attributable to obesity and overweight was $1.72 trillion.[4] As a risk factor, obesity accounts for 47.1% of the total direct and indirect costs of chronic diseases nationwide.[4]

New medications to treat obesity are transformational in terms of efficacy and safety.[5] First-generation obesity medications approved in 2014 or earlier include phentermine, orlistat, phentermine-topiramate extended release, naltrexone-bupropion, and liraglutide. Despite the proven clinical benefit of these drugs, average weight loss is generally less than 6% to 10% in clinical trials.[6]

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Over the past 3 years, regulatory approval has been given to new second-generation medications with mechanisms of action based on agonism of glucagon-like peptide-1 (GLP-1) and other nutrient-regulated hormones. Two such medications, semaglutide and tirzepatide, have achieved weight reductions of up to 20% in phase 3 clinical trials.[5,7] Second-generation medications are more effective in preventing type 2 diabetes and improving lipids, blood pressure, and quality of life. Semaglutide also ameliorates nonalcoholic steatohepatitis and heart failure with preserved ejection fraction, prevents cardiovascular disease events,[8] and slows the rate of the decline in renal function in patients with cardiometabolic disease.[9]

Despite advances, second-generation medications remain unavailable to large numbers of patients. These medications have expensive price tags (approximately $1,000 per month) in the United States.[10] Many healthcare systems, regulatory agencies, and the federal government regard obesity as a lifestyle choice and not a disease, and therefore do not recognize the impact of excess adiposity on health.[11] On the other hand, many insurers and employers who sponsor insurance for their employees regard obesity as a chronic condition that causes comorbidity and increases cost. The consequences of obesity are remote, and it can take years for significant medical issues and costs to materialize. Given the current bankrupting costs of GLP-1 analogs, most insurers are waiting for the price of these medications to drop before treating everyone who meets the broad US Food and Drug Administration (FDA) criteria.

Payers and healthcare systems are unwilling to cover the cost of medications required for long-term

therapy of obesity. This bias runs counter to the scientific basis of obesity as a chronic disease with genetic determinants and pathophysiologic interactions that involve satiety factors and central nervous system feeding centers that generate and sustain excess adiposity.

SHARED RESPONSIBILITIES: A CALL TO ACTION

Since publication of the American Association of Clinical Endocrinology obesity treatment guidelines in 2016,[3] all evidence-based professional guidelines have advocated a complications-centric approach to obesity management and have recommended that obesity medications be available in individualized care plans.

Multiple headwinds prevent patients' full access to recommended evidence-based care, including second-generation medications. Foremost is the problem of bias and stigmatization at all levels, including patients, healthcare professionals, healthcare systems, and society.[12] Internalized bias precludes the patient from acting as a care partner. Bias among medical professionals against obesity as a treatable disease leads to indifferent engagement of patients, and as a result, healthcare systems are disinclined to provide infrastructure and access for coordinated multidisciplinary obesity management programs. At the level of society, bias limits effective health messaging and inhibits the development of an effective built environment and a regulatory environment that can ensure the viability of prepared healthcare systems, the training of enough healthcare professionals, and broad access to care.

It is time to move on from the environment of criticism among patients, physicians, insurance companies, food companies, pharmaceutical companies, and federal agencies to ensure access to comprehensive care and the antiobesity medication armamentarium for patients living with obesity.[13] All stakeholders need to share responsibility and engage in concerted action.

Patients

Every patient deserves to be treated with respect while their disease is appropriately evaluated and the full spectrum of therapeutic options is considered. Patients should be informed and empowered to participate with their healthcare team in the therapeutic plan and should be provided the knowledge and tools they need for long-term success. Given the necessary support and information, patients are responsible for lifestyle modifications that improve nutrition, such as reduced consumption of processed food and increased physical activity. Support should be delivered by an interdisciplinary team that can include physicians and advanced care professionals, as well as dietitians, exercise physiologists, psychologists, and social workers, with availability of referral to sleep specialists, bariatric surgeons, and other specialists as needed. Patients should be encouraged to ask their physicians and other caregivers what evidence-based therapeutic options are available to treat their obesity.

Primary care physicians

Obesity is a chronic condition that requires long-term treatment and follow-up. The patient's primary care physician should seek information regarding current approaches to obesity management and treatment options. Consultation with colleagues who can help address obesity in the context of multidisciplinary care is also advised. Clinicians who are uncomfortable addressing obesity and its complications should refer patients to colleagues who actively treat obesity. For primary care physicians who treat patients with obesity, effective medications should be a readily available therapeutic option, and the clinician should be familiar with the pharmacology, indications, cautions, and potential side effects. Consultation with the patient should include discussion of realistic expectations and potential weight-loss outcomes associated with each medication. Importantly, all healthcare professionals should interact with patients with empathy and respect.

Specialty care

Obesity specialists, endocrinologists, and bariatric surgeons should address the more complicated cases of obesity. Their roles might include coordinating multidisciplinary teams as well as training and consultation for their primary care colleagues. Patients should be referred for bariatric surgical procedures when appropriate, and bariatric surgeons should engage in programs for proper evaluation of patients and have sufficient training and experience to ensure optimal outcomes and follow-up. Given the current price of antiobesity medications, bariatric surgery is more cost-effective.[14] All healthcare professionals should advocate for patients and the need for access to the full spectrum of management options in their healthcare systems, in interacting with payers, and in society at large.

Healthcare systems

Healthcare systems and their leaders should provide the infrastructure for coordinated multidisciplinary care programs over the lifetime of patients who live with obesity, including the full spectrum of evidence-based care and treatment options.[15] They should ensure that patients have access to affordable care and receive it. It is their responsibility to maintain adequately trained

TABLE 1
US list prices (monthly cost) of second-generation antiobesity medications compared with selected other countries

	United States	Spain	Denmark	Netherlands	United Kingdom	Japan	Canada	Dubai
Semaglutide 2.4 mg	$1,349	$314	$343	$296	$233	$69	$388	$326
Tirzepatide 10–15 mg	$1,069	$400	$632	$444	$162	$319	$104	$472

Information based on web searches, direct pharmacy pricing information, and reference 22.

healthcare professionals and support continuing medical education, informatics, and process improvement based on outcomes, together with community-based prevention efforts. Leadership should advocate for affordable medication prices with insurance companies, pharmacy benefit managers, regulators, policymakers, and government agencies.

Employers

A workplace environment that promotes employee health is essential, particularly for managing obesity as a chronic disease. A setting that encourages physical activity, balanced nutrition, and mental wellness can help employees maintain a healthy lifestyle, improve productivity, and decrease absenteeism.

Third-party payers

A limited number of insurance companies and self-insured employers provide coverage for obesity care or antiobesity medications, particularly second-generation medications like GLP-1 receptor agonists. Pharmacy benefit managers are intermediaries between pharmaceutical companies and the healthcare venues. Negotiations between these 2 parties generally increase costs without adding value.[16] About 50 million Americans with obesity could be eligible for insurance coverage for semaglutide,[17] and about 67% have coverage for tirzepatide.[18] Many of these are required to have diabetes for prescriptions to be covered. Each week, US clinicians write more than 500,000 prescriptions for semaglutide and 300,000 for tirzepatide.[18]

In the United States, Medicare Part D does not cover antiobesity medications by statute, and, despite having more flexibility, a minority of state Medicaid programs cover antiobesity drugs, but not second-generation medications.[19] A few weeks after publication of the results of the SELECT (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity) trial,[8] the Centers for Medicare & Medicaid Services (CMS) announced[20] that health plans in the Medicare Part D program will start providing limited antiobesity medication access to patients with obesity and preexisting cardiovascular disease (the good news), but not for obesity per se, which of course is the underlying problem (the bad news). About 3.6 million Medicare beneficiaries (7% overall) had established cardiovascular disease and obesity or overweight in 2020.[21]

The CMS recently began to implement its first round of Medicare drug price negotiations under the Inflation Reduction Act (IRA). The IRA allows for negotiations between CMS and pharmaceutical companies for the cost of medications covered by Medicare Part D to establish the maximum fair price for each drug. It is expected that the IRA will contribute to reduced drug costs for CMS and other payers. However, the negotiations do not consider the disproportionate costs paid by the United States compared with other countries (**Table 1**).[22] Further, the first 10 drugs selected for negotiation do not include any antiobesity medications.[23]

Third-party payers need to find ways to include coverage for all antiobesity medications on behalf of patients. The current system of nontransparent negotiations involving pharmacy benefit managers does not appear to be working for patients living with obesity.

Policymakers

There is a clear need for obesity to be considered as a chronic disease and its treatment covered by all insurance companies and governmental programs. Policies must ensure access and affordable care for obesity. To tackle drug prices, the government recently announced legislative actions in addition to the IRA to lower prescription drug costs. The Treat and Reduce Obesity Act,[24] introduced in the US House of Representatives in 2023, would expand Medicare coverage of intensive behavioral therapy for obesity. The bill also would allow coverage of drugs used to treat obesity under Medicare's prescription drug benefit.

Other measures include overriding the patent for high-priced drugs that have been developed with the help of taxpayer money and letting competitors develop these drugs (known as march-in rights pursuant to the Bayh-Dole Act). Significantly, no federal agency has exercised its right to march in. This development reflects institutional bias against obesity as a chronic disease that fundamentally is recognized only in relation to its complications and related diseases.

Media and health messaging

Obesity has been a trending topic in social media in recent years, particularly since the launch of the more effective second-generation antiobesity medications. Nearly half of the US adult population wants to lose weight,[25] and there is growing awareness of effective recently approved antiobesity medications. Conventional and corporate mass media now more than ever should provide solid, scientifically based information and consult with experts without industry bias. Messaging to promote a culture of wellness, disease prevention, and information regarding obesity as a disease is urgently needed. Importantly, messaging should emphasize the use of antiobesity medications in combination with lifestyle changes to improve health in the context of multidisciplinary medical treatment programs for obesity as a chronic disease.[13]

Pharmaceutical industry

Pharmaceutical and biotechnology companies should be thanked and lauded for developing and earning FDA approval of antiobesity medications. The industry is also responsible for establishing a price structure that allows these medications to be affordable to patients. A fair balance between profits and a pricing scheme that allows patients in need access to antiobesity medications has not been achieved. Given the high costs, the people most in need of antiobesity medications are usually the ones with reduced chances of getting them.

Pharmaceutical companies that produce second-generation antiobesity medications have developed digital health initiatives for patients that include lists of professionals treating obesity and access to online pharmacy services that provide a home-delivery option for antiobesity medications prescribed by their physicians. This measure may reduce some of the burdens that patients and healthcare professionals endure to gain access to antiobesity medications, but it does not solve the cost problem or access for patients without coverage or financial means.

Important disparities in the price of antiobesity medications occur worldwide (**Table 1**).[22] Prices in the United States are significantly higher compared to other high-income countries. The high costs are borne not only directly by individual patients, but also by the societies in which those patients live. It is unacceptable that patients in the United States should pay 10 to 15 times more than patients in other westernized societies.

Disproportionate costs to societies and regions enable drug trafficking. US patients seek antiobesity medications at lower prices in Canada or Mexico for themselves and others. Interestingly, the FDA authorized Florida's drug importation program on January 5, 2024.[26] The FDA may authorize proposals from states or Native American tribes to develop drug importation programs under Section 804 of the Federal Food, Drug, and Cosmetic Act (ie, Section 804 Importation Programs) that allow them to import certain drugs from Canada as long as doing so will provide savings to American consumers and will not present a risk to public health and safety. This seems to be the first step on a path to facilitating importation of certain prescription drugs from Canada.

SUBSTANDARD PRACTICES WITH POTENTIAL HARM

Lack of access to care and the high price of antiobesity medications have given rise to practices that are not in the best interest of patients. Counterfeit or compounded semaglutide or tirzepatide, largely produced by unregulated facilities, has been found in up to 16 countries and has been linked to severe hypoglycemia, seizures, and thrombosis.[27] Neither the ingredients contained in these compounded preparations nor the quality or concentration of the approved medication being emulated can be known for certain. Our patients deserve better.

Another substandard practice is the online availability of obesity medicine prescriptions without adequate assessment of the patient's health status and evaluation for the presence and severity of obesity complications and related diseases.[28] At best, prescriptions are provided to patients by licensed healthcare professionals who never see or examine the patient, but rather rely on self-report information collected remotely from the patient. Patients are not evaluated regarding the impact of adiposity on health. They are given prescriptions without the physical and historical data and standard clinical laboratory results required for optimal treatment decisions and long-term follow up—standard recommendations in all evidence-based treatment guidelines produced by professional organizations. This is inconsistent with treatment of obesity as

a chronic disease. Again, patients deserve better. Both the American Association of Clinical Endocrinology[29] and the European Association for the Study of Obesity[30] have endorsed the diagnostic term *adiposity-based chronic disease* to formalize a complications-centric approach to care directed at improving the health of patients by preventing or treating complications responsible for morbidity and mortality.

As substantiated in treatment guidelines, obesity medications need to be provided by a knowledgeable interdisciplinary team trained in obesity care. Second-generation antiobesity medications are powerful and can lead to excessive weight loss beyond the level that achieves goals for improved health. A significant percentage of this weight loss is muscle mass. Patients need to be actively followed over time by professionals engaged in continuity of care to optimize outcomes, treat or prevent adverse events, preserve and minimize loss of muscle and bone mass, and manage nutrition, psychological disorders, and subspecialty referrals.

CLOSING THOUGHTS

We have medications of unprecedented efficacy and safety for treatment of obesity- and adiposity-based chronic disease that can be lifesaving and can improve health and quality of life. These antiobesity medications need to be used long term, with very frequent weight regain if discontinued. Yet, many patients lack access to these medications and to venues for comprehensive care. Further, healthcare systems in some countries cannot sustain the high cost of second-generation antiobesity drugs for patients who need them. An informed, concerted effort and assumption of shared responsibilities among all stakeholders are needed to realize the far-ranging and transformative benefits of second-generation obesity medications.

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Address: *Bartolome Burguera, MD, PhD, Medical Specialty Institute, F20, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; burgueb@ccf.org*

COMMENTARY

Rahul Aggarwal, MD
Heart and Vascular Center, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Ron Blankstein, MD
Heart and Vascular Center, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Deepak L. Bhatt, MD, MPH, MBA
Director, Mount Sinai Fuster Heart Hospital, New York, NY; Dr. Valentin Fuster Professor of Cardiovascular Medicine, Icahn School of Medicine at Mount Sinai, New York, NY; Member, Writing Committee, 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain

The PRECISE trial: How should patients with chest pain be tested?

Patients who present with chest pain pose a dilemma. As clinicians, we do not want to miss true cases of obstructive coronary artery disease, but chest pain is a nonspecific symptom and many patients with chest pain have no cardiac disease. We cannot take every patient with chest pain to the catheterization laboratory for the gold-standard test, coronary angiography—there are not enough catheterization labs in the world, it would be prohibitively expensive, and we might harm more patients than we help. Therefore, we apply clinical judgment and noninvasive cardiac tests to decide who goes to the catheterization lab.

Clinical guidelines recommend noninvasive cardiac testing in patients who have an intermediate or high pretest probability of having obstructive coronary artery disease and, conversely, say it is reasonable to *not* test patients who are at low risk of it.[1,2]

Determining that a patient is at low risk is challenging, but several scoring systems have been devised. As the latest example, and most relevant to our discussion here, the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE)[3] investigators retrospectively analyzed data from a clinical trial (more about this below) and developed a "minimal risk score" for patients who are having chest pain, to identify those who are actually at low cardiac risk and don't need to undergo cardiac testing.This score is based on 10 clinical variables: age, sex, race or ethnicity, hypertension, hyperlipidemia, diabetes, smoking history, family history of coronary artery disease, unrelated symptoms with physical or mental stress, and high-density lipoprotein cholesterol level.[3] The score assigns a probability of being at minimal cardiac risk, with higher scores indicating lower risk. In the development cohort, the decile with the lowest risk had a mean probability of no risk of 0.54, and 65.6% had normal computed tomography (CT) angiography.[3] The risk score's performance for discrimination was modest, with a C statistic of 0.730, though this was in the cohort in which the risk score was developed and so may overestimate performance. Validation studies did suggest the score could be combined with clinical judgment to help identify patients with low cardiac risk.[4,5] A study also suggested that the risk score overestimated the probability of patients being low risk, indicating that the score assigned them a higher probability of safety than actually observed.[6] As such, studies to evaluate the safety of its use, such as the Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization (PRECISE) trial[7] (further discussion to follow), provide important information on the clinical safety of the risk score.

Another issue in evaluation of chest pain is which noninvasive test to use: the options are functional (stress) testing or anatomic testing with CT angiography, depending on the clinical situation.[1,8,9] CT can also be used to measure the fractional flow reserve, which is a measurement of the flow in distal segments of the coronary artery relative to maximal flow in proximal segments. When used in patients undergoing CT angiography, the addition of CT fractional flow reserve can decrease the rate of unnecessary cardiac catheterizations.[10]

The PRECISE trial[7] sought to answer 2 questions:

- Could the PROMISE minimal risk score identify individuals with symptoms suggesting coronary artery disease who actually were at low risk and could safely forego testing?
- Could a strategy of CT angiography with selective measurement of CT-based fractional flow reserve be beneficial compared with standard testing?

PRECISE DESIGN: USUAL VS 'PRECISION' TESTING

PRECISE was conducted in patients with stable symptoms that suggested coronary artery disease but who did

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TABLE 1
PRECISE trial at a glance

	Precision strategy (n = 1,057)	Usual-testing strategy (n = 1,046)
Intervention	Risk stratification using PROMISE minimal risk score: if score was > 0.46, then further testing was deferred unless patients had known vascular calcifications or atherosclerosis Cardiac testing with CT angiography: if 30% to 90% stenosis was present, then CT fractional flow reserve was added	Physician-guided decision-making: options included deferred testing, stress testing, or cardiac catheterization
Patients who had cardiac testing, n (%)	883 (83.5)[a]	978 (93.5)[a]
Initial cardiac testing, %		
CT angiography	48	< 1
CT angiography + CT fractional flow reserve	31	< 1
Cardiac catheterization	< 1	10
Single-photon emission computed tomography-positron emission tomography	2	32
Stress echocardiography	2	30
Treadmill electrocardiography	1	11
Stress cardiac magnetic resonance imaging	< 1	10
No test	16	7
Patients who had cardiac catheterization, n (%)	135 (12.8)[a]	177 (16.9)[a]
Patients with primary composite endpoint (death, nonfatal myocardial infarction, or cardiac catheterization without obstructive coronary artery disease), n (%)	44 (4.2)[a]	118 (11.3)[a]
Death or nonfatal myocardial infarction	18 (1.7)	12 (1.1)
Cardiac catheterization without obstructive coronary artery disease	27 (2.6)[a]	107 (10.2)[a]
Patients who had revascularization, n (%)	97 (9.2)[a]	54 (5.2)[a]

[a]Statistically significant difference.

CT = computed tomography; PRECISE = Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization; PROMISE = Prospective Multicenter Imaging Study for Evaluation of Chest Pain

Based on information from reference 7.

not have a history of it. Those with contraindications to CT angiography or who had been tested for coronary artery disease within the past year were excluded.[7]

Patients were randomized in a 1-to-1 ratio to either a usual testing strategy—a standard cardiac diagnostic approach based on the clinician's judgment, with options including deferred testing, functional testing, or cardiac catheterization—or to a "precision strategy" (**Table 1**).[7]

Patients in the precision strategy group were first evaluated for cardiac risk by the PROMISE minimal risk score.[3] Patients at low risk (defined as a score > 0.46) were deferred from subsequent cardiac testing unless they had atherosclerosis on prior imaging such as chest CT, in which case they underwent CT angiography anyway, as did patients with higher-risk (lower PROMISE scores). Patients with 30% to 90% stenosis on CT angiography also underwent CT fractional

flow reserve testing to assist in the decision whether to proceed with cardiac catheterization.[7] Of note, the chest pain guideline suggests selectively measuring CT fractional flow reserve in patients who have 40% to 90% stenosis—a slightly more stringent threshold.[1]

The primary composite outcome was death or nonfatal myocardial infarction within 1 year or needless cardiac catheterization, ie, that found no trace of obstructive coronary artery disease.

PRECISE FINDINGS

The PRECISE trial enrolled 2,103 patients in North America and Europe.[7] The mean age was 58 years, about half of the patients were women, and about 85% identified as non-Hispanic White. The primary presenting complaint, present in about 80% of the cohort, was chest pain; 10% of the patients had dyspnea on exertion.

Fewer patients in the precision-testing group compared with the usual-testing group underwent subsequent testing (83.5% vs 93.5%, $P < .001$) (**Table 1**).[7] A total of 20.2% of the patients in the precision group were determined to be at minimal risk by the PROMISE minimal risk score, though only 64.4% of these patients were actually deferred from testing. In the usual-testing group, 32% of the patients underwent nuclear stress testing, 30% underwent stress echocardiography, 11% underwent exercise electrocardiography, 10% underwent stress cardiac magnetic resonance imaging, 10% underwent cardiac catheterization, and 7% had no further testing.

The precision-testing group had a lower rate of the primary composite outcome (4.2% vs 11.3%, unadjusted hazard ratio [HR] 0.35, 95% confidence interval [CI] 0.25–0.50). However, the difference was primarily driven by fewer unnecessary cardiac catheterizations (2.6% vs 10.2%, HR 0.24, 95% CI 0.16–0.36). By 1 year, 18 patients (1.7%) in the precision-testing group had died or had a nonfatal myocardial infarction, compared with 12 patients (1.1%) in the usual-testing group, but the difference was not statistically significant (HR 1.52, 95% CI 0.73–3.15).[7]

Also at 1 year, more patients in the precision group (vs usual testing) were using antiplatelet medications (35.7% vs 27.1%, $P < .001$) and cholesterol-lowering medications (50.0% vs 41.8%, $P < .001$).[7]

IMPLICATIONS

In the PRECISE trial, patients who underwent testing according to the precision strategy were less likely to undergo unnecessary cardiac catheterizations than those with a usual testing strategy. The rates of death or nonfatal myocardial infarction were not statistically significantly different between the precision- and usual-testing groups; however, the study was not powered to detect differences in these clinical outcomes over a 1-year period, as evidenced by low event rates. Indeed, prior studies that demonstrated a benefit of more aggressive preventive therapies in terms of preventing death or myocardial infarction required longer follow-up and more patients.[9] Though the clinical outcomes (death or nonfatal myocardial infarction) and the efficiency outcome (unnecessary cardiac catheterization) were combined into a single outcome, the results were driven by the reduction in unnecessary cardiac catheterizations.

The original PROMISE trial compared functional stress testing (electrocardiography- or imaging-based) and anatomic testing with CT angiography and found no significant difference in cardiovascular outcomes with either approach, although the composite outcome used in PROMISE also included hospitalization for unstable angina and procedural complications. Nevertheless, more patients in the CT angiography group went on to undergo cardiac catheterization, and fewer of them did so unnecessarily, indicating that they had a lower rate of cardiac catheterization without obstructive coronary artery disease.[8]

Notably, the Scottish Computed Tomography of the Heart (SCOT-HEART) trial,[9] which randomized patients with stable chest pain to standard care vs standard care and CT angiography, observed a higher rate of cardiac catheterizations initially but not by 5 years with CT angiography.

Because PROMISE indicated potentially higher rates of cardiac catheterization in those undergoing CT angiography, the use of fractional flow reserve as part of the precision strategy may provide a way to decrease unnecessary cardiac catheterizations among patients with stable cardiac symptoms who undergo CT angiography. PRECISE provides evidence that using this strategy with CT angiography can help identify patients with low cardiac risk who can safely be deferred from subsequent testing and provide clinical parity with a typical physician-driven risk stratification approach.

PROMISE MINIMAL RISK SCORE

Almost one-third of the patients in the precision- strategy group who were identified as being at low risk still underwent CT angiography. Presumably, their physicians used clinical judgment to identify patients who were incorrectly categorized as being at low risk, though some of these patients may have been stratified as higher

risk based on vascular calcifications or atherosclerosis on imaging or by having worrisome symptoms. A prespecified secondary analysis of PRECISE demonstrated that 96% of those who underwent subsequent testing despite being at low risk by the PROMISE minimal risk score had negative testing for obstructive coronary artery disease or ischemia.[11]

These findings highlight challenges that are inherent to using risk scores that are aimed to reduce testing. Notably, physicians who are interested in pursuing testing will often do so, even when advised that such testing can be deferred. Similarly, a registry-based analysis showed that 17% of patients referred for cardiac catheterization were actually at low risk based on the PROMISE minimal risk score, suggesting that too many people are undergoing cardiac catheterization.[4]

IS THE PRECISION STRATEGY SAFE?

An important question is the safety of the precision strategy compared with the usual strategy. The rate of death or nonfatal myocardial infarction was not statistically significantly different between the 2 groups, although at 1 year there was a numerically higher rate of these clinical outcomes in the precision-strategy group (1.7% vs 1.1%, HR 1.52, 95% CI 0.73–3.15).[7] These were attributed to periprocedural myocardial infarctions and type 2 myocardial infarction events. The event rates were low, so determining whether there is a real difference will require further study and monitoring. If anything, one might expect that the precision strategy would have resulted in a lower rate of death or nonfatal myocardial infarction, as prior studies have shown that the use of CT angiography is associated with a reduction in such events.[9,12] Overall, the precision strategy appears safe, but long-term monitoring will be needed.

IS ANATOMIC TESTING SUPERIOR TO FUNCTIONAL TESTING?

When interpreting the PRECISE trial, physicians need to account for the trial having 2 separate interventions that were randomized.

The first intervention was the risk-stratification approach. The usual-testing group was managed exclusively according to their physicians' clinical judgment as to whether they needed subsequent testing, whereas the precision group was managed using the PROMISE minimal risk score, vascular calcifications, atherosclerosis on prior imaging, and clinical judgment.

The second intervention was the type of testing. The usual-testing group underwent functional testing, with options for a variety of testing modalities, or cardiac catheterization. The precision group underwent anatomic testing with CT angiography, followed by selective use of CT fractional flow reserve.

Thus, it is difficult to directly compare the impact of CT angiography vs usual testing. Because the design tested 2 different strategies, it is unclear how each intervention contributed to the improvements in reducing unnecessary cardiac catheterizations.

Understanding the impact of measuring CT fractional flow reserve on the results is also important. PROMISE did not use CT fractional flow reserve in the original study, though a retrospective study observed that it improved the identification of those at risk for adverse cardiovascular outcomes.[13] CT fractional flow reserve has been shown in several registries to identify patients at low risk who can safely forego testing.[14–16]

OPTIMIZING MEDICAL THERAPY

Significantly more patients in the precision-testing group were prescribed antiplatelet and lipid-lowering drugs. Similar findings were observed in SCOT-HEART.[9] This is important, as optimal medical therapy improves cardiac outcomes.[17,18]

A reason that more patients got these needed drugs may be that they underwent CT angiography. Earlier studies also found higher rates of medical therapy after CT angiography.[19] Why would this be? First, CT angiography can detect nonobstructive plaque, which would prompt the physician to prescribe medical therapy.[19,20] Also, with CT angiography, patients can see the plaque for themselves on the images and therefore may be more motivated to adhere to medical therapy, and physicians may be better able to risk-stratify patients and also to educate patients about their risk.[21]

Additional studies are needed to understand how the use of CT angiography can lead to meaningful improvements in cardiovascular outcomes by increasing the use of medical therapies. Importantly, PROMISE and SCOT-HEART were trials that did not provide much guidance to physicians (or patients) with respect to how to intensify medical therapy. In fact, these trials were conducted before we had robust data on the importance of treating nonobstructive plaque. In contrast, reporting the amount of plaque and specific management recommendations based on these findings are now standards of care.[22]

PRECISE WAS PROMISING

PRECISE demonstrated that incorporating the PROMISE minimal risk score in evaluating patients

with worrisome symptoms, along with CT angiography with selective measuring of CT fractional flow reserve, can be an effective strategy to approach evaluation for coronary artery disease and minimize unnecessary cardiac catheterizations. PRECISE was not powered to evaluate the rates of death or myocardial infarction, so monitoring these events will be important. Further studies comparing CT angiography with functional testing are required to better define the benefits of CT fractional flow reserve in avoiding unnecessary cardiac catheterizations—and to test the benefits of CT angiography imaging in guiding medical therapy—but the PRECISE results are very promising.

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Dr. Aggarwal has disclosed serving as a research collaborator for Amarin, Lexicon, and Novartis; receiving research funding support from Bristol Meyers Squibb-Pfizer Alliance; serving as a research principal investigator for Bristol Meyers Squibb-Pfizer Alliance; and prior consulting for Lexicon.

Dr. Blankstein has disclosed consulting for Amgen, Caristo, HeartFlow, Novartis, and Star Therapeutics; conducting institutional research for Amgen; serving as research principal investigator for Nanox AI; and serving as research site principal investigator for Novartis.

Dr. Bhatt has disclosed the following: Advisory Board: Boehringer Ingelheim, Cardax, CellProthera, Cereno Scientific, Elsevier, Janssen, Level Ex, Merck, Myokardia, NirvaMed, Novartis, Novo Nordisk, PLx Pharma, PhaseBio, Stasys; Ownership interest (stock, stock options in a publicly owned company): AngioWave, Bristol-Myers Squibb, DRS. 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Address: *Deepak L. Bhatt, MD, MPH, MBA, Director, Mount Sinai Fuster Heart Hospital and Dr. Valentin Fuster Professor of Cardiovascular Medicine, Icahn School of Medicine at Mount Sinai, 1 Gustave Levy Place, Box 1030, New York, NY 10029; DLBhattMD@post.Harvard.edu*

GREGORY W. RUTECKI, MD, Section Editor

Fachreza Aryo Damara, MD
Department of Vascular Surgery, Cleveland Clinic, Cleveland, OH

Khaled I. Alnahhal, MD
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Hassan Dehaini, MD
Department of Vascular Surgery, Cleveland Clinic, Cleveland, OH

Georgeanne Botek, DPM
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Lee Kirksey, MD, MBA
Vice Chairman, Department of Vascular Surgery, Cleveland Clinic, Cleveland, OH; Clinical Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

A man with chronic limb-threatening ischemia and no revascularization options: Can we save his foot?

A 60-YEAR-OLD BLACK MAN presented to our clinic with ischemic pain at rest in the right foot and dry gangrene of the forefoot and big toe (**Figure 1**).

The patient had an extensive medical history that included the following:

- Multivessel coronary artery disease, for which he had undergone coronary artery bypass grafting 1 year previously
- Chronic limb-threatening ischemia in the left leg, for which he had undergone a left popliteal-to-dorsalis pedis artery bypass
- Type 2 diabetes mellitus
- Hyperlipidemia
- Hypertension
- Smoking (he had quit 8 years previously after a 12.5-pack-year history)
- A remote history of alcoholism.

He also had end-stage kidney disease. He had received a kidney transplant 10 years before the current presentation but was back on dialysis because of transplant failure. He was still taking prednisone and tacrolimus.

He was also taking warfarin 2.5 mg, aspirin 81 mg, atorvastatin 80 mg, and insulin injections. He was not on any oral antidiabetic medications.

INITIAL EVALUATION

On initial physical examination, his right foot was edematous with extensive dry-appearing gangrene of the big toe, while the forefoot was relatively spared (**Figure 1**). We could feel no pedal pulses, the ankle-brachial and toe-brachial indices were low (see below), and pulse-volume waveform recordings demonstrated moderate dampening at the ankle and severe dampening at the level of the metatarsals and digits.

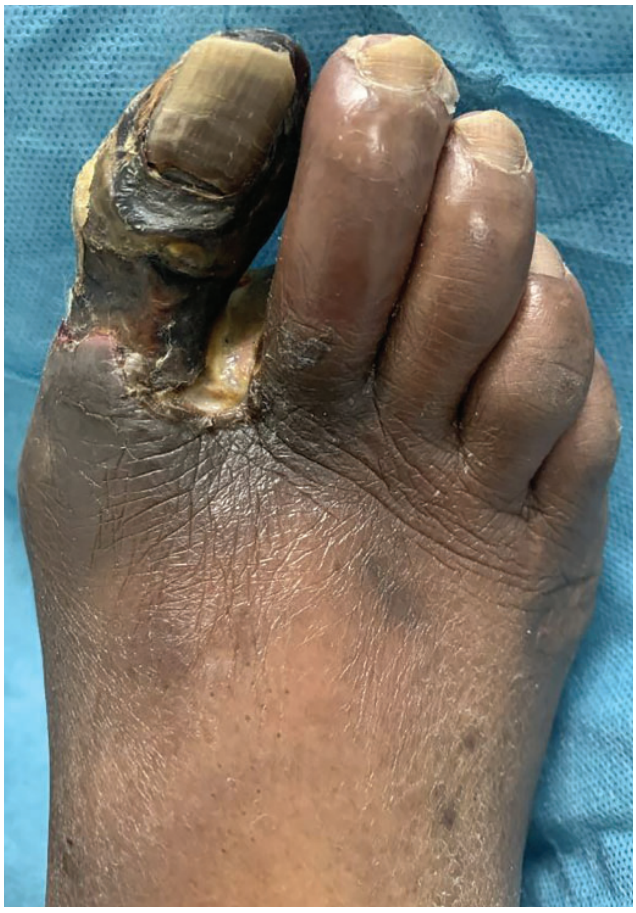

Figure 1. At presentation, the patient had dry gangrene of the right hallux and an interdigital ulcer.

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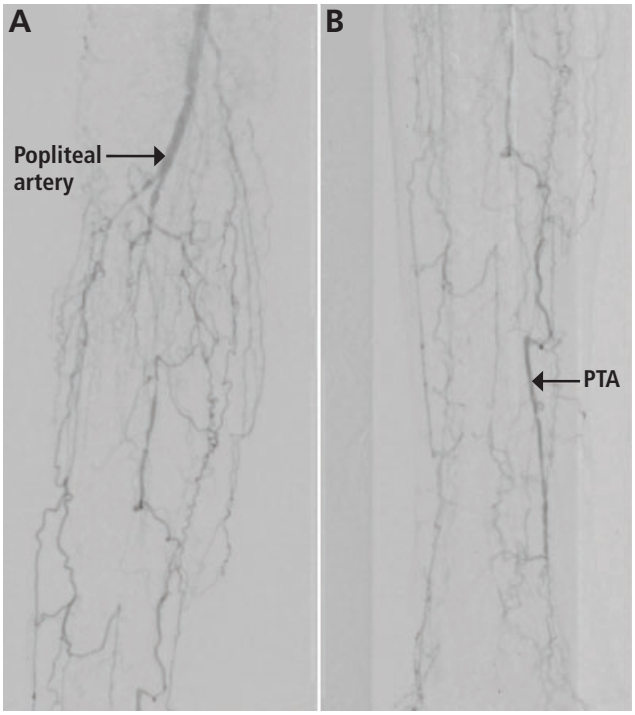

Figure 2. Preoperative angiogram showing the patient's (A) patent popliteal artery and (B) occluded posterior tibial artery (PTA).

Notable laboratory and noninvasive vascular results at presentation

- Resting right ankle-brachial index (ie, the systolic blood pressure in the ankle divided by the higher of the systolic pressures in the 2 arms) 0.51, compared with 0.64 1 month before (reference range 1.0–1.4)
- Resting right toe-brachial index 0 (> 0.65)
- Right wound, ischemia, and foot infection (WIfI) stage 4 (W-2, I-3, fI-0; more about this below)[1]
- Hemoglobin concentration 11.0 g/dL (13–17 g/dL)
- Mean corpuscular volume 84.2 fL (80–100 fL)
- Mean corpuscular hemoglobin 25.3 pg (26–34 pg)
- Mean corpuscular hemoglobin concentration 30.1 g/dL (30.5–36.0 g/dL)
- Red blood cell distribution width-coefficient of variation 18.7% (11.5%–15.0%)
- Serum creatinine 3.25 mg/dL (0.73–1.22 mg/dL)
- Blood urea nitrogen 25 mg/dL (9–24 mg/dL)
- Hemoglobin A1c 6.1% (4.3%–5.6%)
- Low-density lipoprotein cholesterol (LDL-C) 80 mg/dL (< 100 mg/dL)

Computed tomography angiography was performed and later supplemented with catheter-based angiography to evaluate the arteries in his leg. The right superficial femoral artery had moderate focal stenosis, and there was severe infrapopliteal disease, with multilevel stenosis of the tibioperoneal trunk and total occlusion of the anterior tibial, posterior tibial, and peroneal arteries, all relatively close to their respective origins (**Figure 2**). Importantly, there was a short segment of the posterior tibial artery with a relatively normal vessel caliber that was reconstituted by collaterals at the supramalleolar level of the calf. No named vessels were identifiable distal to the malleolus.

Over the next month, the pain worsened, and the gangrenous toe became infected (fI-1) and needed to be amputated. A multidisciplinary team was convened to discuss the surgical options, consisting of specialists in internal medicine, cardiology, vascular surgery, podiatry, interventional cardiology, interventional and diagnostic radiology, and vascular medicine.

PERIPHERAL ARTERY DISEASE IS LINKED TO CARDIOVASCULAR DISEASE

1 For the moment, let's put aside what needs to be done for the patient's leg and think about his cardiovascular risk. Which of the following steps would be appropriate to improve it?

- ☐ Perform echocardiography
- ☐ Perform coronary angiography
- ☐ Intensify his lipid-lowering therapy
- ☐ Intensify his glycemic control

Patients with peripheral artery disease are at risk of concomitant atherosclerotic disease in other vascular beds, including the heart and brain. In a 2008 report of the Reduction of Atherothrombosis for Continued Health (REACH) registry,[2] for example, about half of patients with peripheral artery disease also had coronary artery disease.This percentage is even higher in patients with chronic limb-threatening ischemia.

Further, the risk of major adverse cardiovascular events is significantly higher in patients with polyvascular disease. In the REACH registry, patients with symptomatic peripheral artery disease with polyvascular disease taking standard medications had rates of cardiovascular death, myocardial infarction, or stroke of 4.7% at 1 year and 9.1% at 2 years, and the rate of limb events was 5.7% at 2 years.[3] The 3-year incidence rates of cardiovascular death, myocardial infarction, stroke, and repeat hospitalization were all significantly higher in those with polyvascular disease compared with those with involvement of a single vascular bed.[4]

This increased risk persists in more recent trials. In the placebo group of the 2017 FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial,[5] the 3-year risk of major adverse cardiac events was about 17.4% in patients with peripheral artery disease with polyvascular bed involvement compared with 10% in those with peripheral artery disease alone.

Echocardiography and coronary angiography would not be indicated at this time, however. Despite the elevated risks, screening for coronary disease is not currently recommended in patients who have no coronary symptoms.[6] This is because all patients with peripheral artery disease should receive intensive medical management. Further, we have no data to suggest that performing coronary revascularization before noncardiac arterial revascularization improves the cardiovascular outcomes of patients who have no coronary symptoms.

Intensive glycemic control can improve outcomes in patients with chronic limb-threatening ischemia. However, this patient's hemoglobin A1c is already well controlled at 6.1%.[7]

More-intense lipid-lowering therapy should be considered for this patient. He has polyvascular atherosclerotic disease, prior cardiovascular events, and chronic limb-threatening ischemia. His LDL-C level of 80 mg/dL at presentation is within the reference range for the general population, but for someone with his history it should be lower—he is still at "very high risk" for recurrent events and therefore would benefit from adding an adjunctive agent such as ezetimibe, a proprotein convertase subtilisin/kexin type 9 inhibitor, or both if needed, with a target LDL-C level lower than 55 mg/dL.[8,9] Just before his intervention, our patient's LDL-C was 34 mg/dL, with no adjunctive agents.

OTHER RISK FACTORS FOR PERIPHERAL ARTERY DISEASE

Many other factors pertinent to our patient affect the risk and outcomes of peripheral artery disease, including social and economic determinants of health and modifiable risk factors. The most significant risk factors involved in this patient's presentation, management, and recovery were diabetes mellitus and chronic kidney disease. Furthermore, Black people, as evidenced in our patient, have been shown to be at higher risk for chronic limb-threatening ischemia and undergoing amputations.[10] This is due to unequal access to care and socioeconomic inequalities that contribute to inadequate management of the aforementioned risk factors.

Diabetes mellitus is an independent risk factor for amputation due to infection and peripheral neuropathy, the latter of which results in diabetic ulcers and foot deformities.[11] Concomitant peripheral artery disease amplifies such risk by impairing arterial inflow and wound healing. Patients with peripheral artery disease with diabetes mellitus are more likely to develop chronic limb-threatening ischemia and undergo amputation compared with their counterparts without diabetes.[12] Those patients are further burdened with higher mortality rates at a significantly younger age compared with patients with peripheral artery disease who do not have diabetes.[12]

Chronic kidney disease. The prevalence of peripheral artery disease is higher in patients with chronic kidney disease than in the general population, and its prevalence increases with increasing severity of the kidney disease.[13] Furthermore, the severity of peripheral artery disease correlates with the severity of chronic kidney disease.[14] Chronic kidney disease is also a factor in the outcomes of peripheral artery disease and revascularization procedures; it independently increases the risk of death and limb loss after revascularization, particularly in patients with end-stage kidney disease.[15–17]

HOW SHOULD WE MANAGE HIS LIMB ISCHEMIA?

2 Which of the following is the best option for managing our patient's peripheral vascular disease at this point?

- ☐ Amputation of his foot
- ☐ Open arterial bypass surgery
- ☐ Endovascular arterial revascularization
- ☐ Deep venous arterialization

Global guidelines on management of chronic limb-threatening ischemia call for assessing 3 factors when considering revascularization procedures: the patient's cardiovascular risk (to determine whether they can undergo surgery without suffering a major adverse cardiovascular event), the stage of the peripheral vascular disease (limb staging, to determine whether they need to undergo surgery), and the anatomic pattern of disease (to determine whether and how surgery can be done).[18]

Preoperative cardiovascular risk stratification

Perioperative cardiac risks with peripheral vascular disease surgery are determined by patient-related factors and the type of surgery.

Patients undergoing peripheral artery revascularization are at moderate to high risk of perioperative adverse cardiac events such as nonfatal myocardial infarction or cardiac death.[19] In the National Surgical Quality Improvement Program study, major adverse cardiac events occurred in 2.0% of 2,155 patients undergoing lower-extremity bypasses to treat claudication symptoms only, and in 1.0% of 1,770 patients undergoing infrainguinal endovascular interventions.[20] In another study, the rate of cardiac complications was higher in 580 patients with chronic limb-threatening ischemia, ranging from 1.3% to 2.1% for acute myocardial infarction and 3.0% to 3.8% for perioperative mortality.[21] Therefore, it is imperative to address any potential reversible risk factors.

Perioperative cardiac risk evaluation begins with a focused cardiovascular history and physical examination. It is also reasonable to obtain an electrocardiogram for most patients. Any unexplained cardiovascular symptoms (eg, dyspnea, chest pain, or syncope), abnormal examination findings (eg, new murmur, jugular venous distension, or pedal edema), or worrisome electrocardiographic abnormalities (eg, advanced conduction disease, newly diagnosed pathologic Q waves) may warrant additional investigations that may include chest radiographs, echocardiography, or ischemia testing.

If nothing worrisome is noted, several risk assessment tools can be used to estimate the patient's perioperative risk of major adverse cardiac events, such as the revised cardiac risk index, the National Surgical Quality Improvement Program risk calculator, and the Vascular Study Group cardiac risk index.[22] However, most patients will be at intermediate to high risk. Routinely measuring cardiac biomarkers (high-sensitivity troponin T and N-terminal pro-B-type natriuretic peptide) can also provide additional prognostic information in patients without symptoms undergoing intermediate- or high-risk surgery, and is recommended by the European guidelines,[23] but not by the American guidelines.[24]

For patients who cannot exercise at more than 4 metabolic equivalents—and most patients with chronic limb-threatening ischemia cannot—it is reasonable to consider a pharmacologic stress test (nuclear vs echocardiogram) before any intermediate- or high-risk procedures. Evidence of moderate- to large-territory ischemia or severely depressed left ventricular ejection fraction may warrant coronary angiography before the procedure.

Of note, while routine coronary revascularization has never been shown to improve perioperative cardiovascular outcomes, decisions about revascularization are made on a case-by-case basis based on standard revascularization guidelines.[25] Higher-risk lesions such as multivessel coronary disease or left main disease will need additional considerations based on the risks of delaying coronary vs peripheral artery intervention. A team-based multidisciplinary approach is critical to achieving good patient outcomes.[26]

Despite our patient's significant history of cardiovascular disease, electrocardiography indicated left axis deviation but no pathologic Q waves. Echocardiography revealed normal left ventricular systolic function with an ejection fraction of 65% ± 5% (2-dimensional biplane) and no valvular dysfunction. A cardiac stress test was unremarkable with normal ST-segment response, and angina was not provoked. A cardiac nuclear stress test demonstrated normal perfusion with a reduced ejection fraction of 45%. Thus, we decided he could proceed with his surgery.[10]

Limb staging

Limb staging uses the "WIfI" classification system,[1] which assigns up to 3 points each for the wound (W), ischemia (I), and foot infection (fI). The patient's right limb had a gangrenous digit (W-2), severe ischemia (I-3), and mild infection (fI-1), consistent with WIfI stage 4, the highest. This means he was at high risk of amputation unless we attempted to revascularize his foot.

The anatomic pattern

Thus, our patient needed surgery to save his foot, and he was able to undergo surgery from a cardiac standpoint. But could we actually do anything for him?

Our patient had multilevel occlusive disease. He had only moderate stenosis of the superficial femoral artery stenosis that was less than 10 cm and no significant disease in the popliteal artery. However, the tibioperoneal trunk was severely narrowed, all 3 infrapopliteal vessels were chronically occluded and severely calcified, and there was no inframalleolar target artery crossing the ankle into the foot.

Given the advanced limb stage and lack of a pedal or plantar target artery, our patient had no options for distal arterial bypass. Criteria of no-option anatomy are "desert" foot, defined as no patent pedal arteries, or inadequate venous conduit for bypass due to severe calcification or long-segment occlusion.[27] This challenging situation occurs in up to 20% of patients with chronic limb-threatening ischemia.

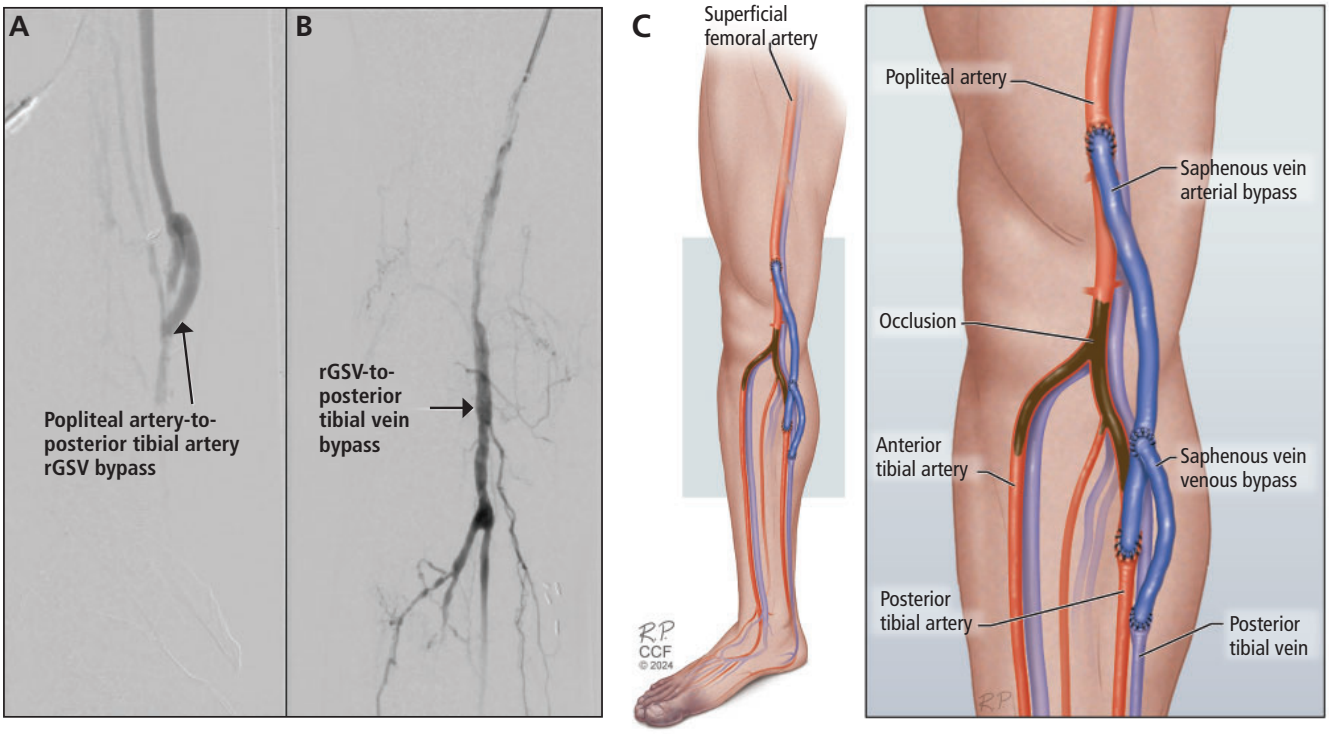

Figure 3. (A) Angiogram of popliteal-to-posterior tibial artery bypass using a reversed greater saphenous vein (rGSV) graft. (B) Venogram of rGSV-to-posterior tibial vein bypass. (C) A drawing shows deep venous arterialization of the posterior tibial vein.

THE PATIENT WANTS TO KEEP HIS FOOT

Our patient was at extremely high risk of losing his foot if we did nothing, and with no arteries available for revascularization, amputation might have been a reasonable option at this point. However, after a comprehensive discussion with the patient and his wife, he adamantly declined this option. Therefore, we decided to explore other revascularization options.

Currently, there are no guidelines or adequate data comparing the relative efficacy of alternative treatments for patients with no-option anatomy, but one of them is deep venous arterialization.

DEEP VENOUS ARTERIALIZATION: AN OPTION WHEN THERE IS NO OPTION

Deep venous arterialization is an option in cases in which no inframalleolar target artery path is available for conventional revascularization, as in our patient. It involves directing arterial blood flow to a deep vein via a conduit such as an autogenous vein graft (**Figure 3**).

This procedure can be performed using an open approach, a percutaneous approach, or a novel hybrid approach, but we expect that newer specialized endovascular devices will lead to wider use of less-invasive approaches. In our patient, open bypass was selected as the planned first stage in view of his anatomic occlusive pattern. Open tibial artery bypass with an autogenous conduit has demonstrated superior patency compared with endovascular tibial intervention.

Acceptable outcomes have been described for both the open and percutaneous approach; however, no direct randomized comparisons have been performed for these techniques. A literature review from 2020 showed that the open approach had better patency rates; however, few studies directly compared the open and percutaneous procedures, making it hard to make evidence-based clinical decisions.[28] Possible reasons for better patency rates with open bypass surgery are the ability to directly ligate perforating veins and reverse the vein to eliminate significant flow disruption from the residual obliterated venous valve, which can cause early graft failure.[29,30]

Outcomes of deep venous arterialization

Published patency rates of deep venous arterialization for chronic limb-threatening ischemia are 44% to 88% at 1 year with the open approach, 29% to 40% at 6 months with the endovascular approach, and 6.9% at

1 year with the hybrid approach.[31–33] Major amputation rates range from 0% to 70% with the open approach, 0% to 28.5% with the endovascular approach, and 23% to 31% with the hybrid approach.[28]

These comparisons are limited by the paucity of studies, their retrospective nature, and their substantially heterogeneous populations. Nevertheless, given the current evidence, open deep vein arterialization is an option with acceptable efficacy for patients in whom major amputation would be the only other option.

Techniques of deep venous arterialization

LimFlow is a novel endovascular system that uses an arterial and a venous catheter, which are placed under ultrasonography guidance to obtain better alignment, crossing, and retrieval of the wire, after which stent grafts are deployed.[33] A multicenter trial (Percutaneous Deep Vein Arterialization for the Treatment of Late-Stage Chronic Limb-Threatening Ischemia [PROMISE II]) of this system is underway in 20 sites across the United States with a goal of enrolling 100 participants. Preliminary 6-month results in 105 patients were promising, with an amputation-free survival rate of 66%, significantly exceeding the target endpoint of 54%. Furthermore, the limb salvage rate was 76%, the survival rate was 87%, and the wound healing rate was 76%.[34]

In centers where the commercially manufactured device is not available or reimbursed, off-the-shelf items can be used as an alternative approach. Several techniques have been described in performing off-the-shelf techniques—the arteriovenous spear technique, the venous arterialization simplified technique, and use of a penetration wire or reentry device.

The arteriovenous spear technique is performed by simultaneously puncturing the tibial artery and vein under duplex ultrasonography visualization.[35] This technique does not require a snare or balloon for vessel wall penetration. The limitation of this technique is it relies heavily on the technical skill in the puncturing process.

The venous arterialization simplified technique uses an overlapping inflated balloon and snare catheter to insert a needle under a fluoroscopic view.[36] However, small, tortuous, and calcified vessels, particularly in below-the-ankle arteries, make it more challenging to pass the snare catheter. A study in 18 patients in Japan assessed 12-month outcomes using the combination of arteriovenous spear technique and the venous arterialization simplified technique.[37] The technical success rate was 88.9%, the limb salvage rate was 72.2%, and the amputation-free survival rate at 12 months was 49.4%.

The use of a reentry device or penetration wire with a heavy tip is limited by the difficulty of penetrating the vessel wall if it is heavily calcified. The alternative step is to use a posterior tibial artery balloon to expand the target punctured vessel. In a case series of 14 patients who underwent the procedure with intravascular ultrasonography guidance, the technical success rate was 100%, the median time of primary patency was 8 months, and the limb salvage rate was 78% within 2 years of follow-up.[38]

CASE CONTINUED: SURGERY AND POSTOPERATIVE COURSE

We performed open deep venous arterialization, using the greater saphenous vein as a graft to link the popliteal artery, the posterior tibial artery, and the posterior vein by end-to-side anastomosis and ligating all the side branches to the posterior tibial vein (**Figure 3**). In a subsequent procedure, we performed endovascular vein valve lysis of the tibial and plantar venous arch to complete the pedal revascularization.

A pulse was palpable in the bypass graft at the end of the procedure. Postoperative imaging showed the bypasses were patent and outflow to the foot via the arterialized deep venous and plantar arch system was significantly improved. The patient tolerated the procedure well and recovered appropriately.

ANTITHROMBOTIC REGIMENS

3 What is the recommended postoperative antithrombotic regimen for this patient?

- ☐ Rivaroxaban 2.5 mg twice a day with aspirin
- ☐ Full-dose anticoagulation therapy alone
- ☐ Warfarin (target international normalized ratio 2.5) with an antiplatelet agent
- ☐ Aspirin or clopidogrel alone

After arterial bypass, we need to consider the risk of thrombosis in both the bypass target vessel (taking into account its caliber and quality) and the conduit used (autogenous vs prosthetic). In this patient, the runoff was deemed "disadvantaged" as a result of both size and caliber. For this reason, long-term anticoagulation (warfarin or an oral antithrombotic) is indicated.[39] Our patient was discharged home taking warfarin (with a target international normalized ratio of 2.5), and continued to take aspirin 81 mg once daily.

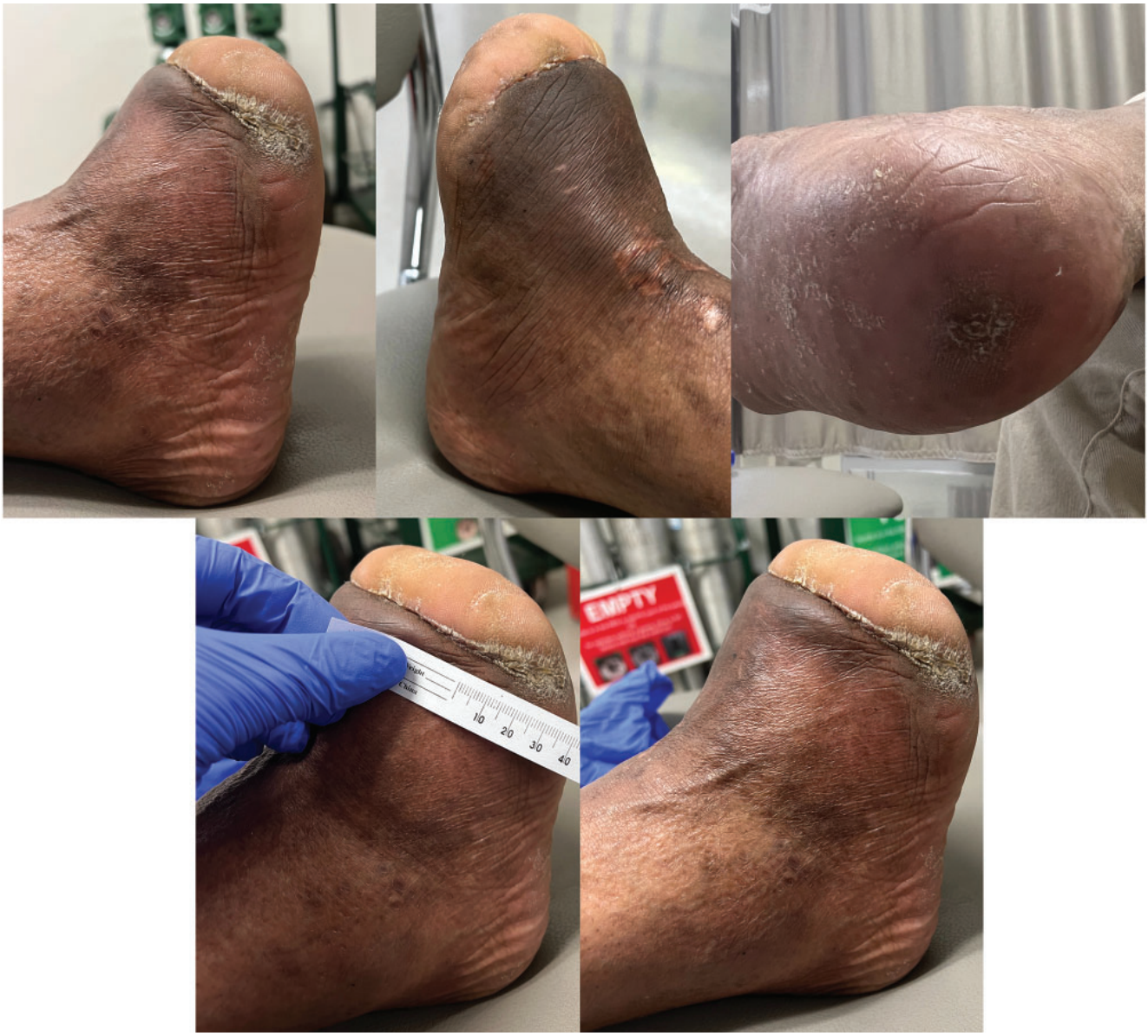

Figure 4. Healed right foot 2.5 years after surgery.

There are data to support the use of rivaroxaban 2.5 mg twice a day along with aspirin 81 mg for patients with peripheral artery disease after lower limb revascularization, but rivaroxaban is contraindicated in patients with advanced renal disease.[40–42] The COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial[43] compared the postoperative use of rivaroxaban (with or without aspirin) vs aspirin alone in patients with stable atherosclerotic disease. Those who were on rivaroxaban had fewer cerebrovascular and cardiovascular events with comparable major bleeding complications.

Similar findings were reported in the subsequent VOYAGER PAD (Vascular Outcomes Study of ASA Along With Rivaroxaban in Endovascular or Surgical Limb Revascularization for Peripheral Artery Disease) trial,[44] which compared rivaroxaban with aspirin and aspirin alone following lower-limb revascularization. Compared with those on aspirin alone, patients taking rivaroxaban 2.5 mg twice daily along with aspirin had significantly lower rates of major

adverse cardiovascular events (myocardial infarction, ischemic stroke, death) and lower-limb events (acute limb ischemia, major amputation) (15.5% vs 17.8%; *P* = .009). The risk of major bleeding was similar between the 2 groups as assessed by the Thrombolysis in Myocardial Infarction grading system (*P* = .07); however, it was higher with rivaroxaban and aspirin than with aspirin alone according to the International Society on Thrombosis and Haemostasis grading system (*P* = .007).

CASE CONCLUDED

At the patient's first follow-up visit, his right ankle-brachial index had improved from 0.51 previously to 0.73, with normal pulse-volume waveforms at the ankle. Chronic *Pseudomonas* osteomyelitis, diagnosed by microbiological testing of tissue and bone, hindered wound healing, necessitating a transmetatarsal amputation. Six weeks after surgery, the patient underwent catheter-based intervention of the venous system to obliterate valve structures and augment outflow. His ischemic pain had resolved, and the amputation site had healed.

Two years after surgery, the patient was doing well, his pulse-volume recordings were unchanged, and the arterial bypass and deep venous system were still patent (**Figure 4**). He is ambulatory in diabetic shoe wear. He is currently off antibiotics and is maintained on appropriate blood-thinning medications.

This case shows that deep venous arterialization can be a viable revascularization option for high-risk patients with advanced chronic limb-threatening ischemia and a "no-option" anatomic arterial occlusive pattern. As with all patients who have undergone revascularization for chronic limb-threatening ischemia, close surveillance with primary-assisted procedures can play a role in prolonging patency. Additionally, a multidisciplinary approach and patient-centered care are crucial to achieving favorable outcomes in limb-threatened patients with advanced disease. This includes thorough preoperative preparation, selecting the appropriate surgical intervention, and optimal postoperative medical therapy.

TAKE-HOME POINTS

- The aim of treating chronic limb-threatening ischemia is to restore blood flow to the region of tissue loss to permit complete wound healing and to return the patient to ambulatory status. In this patient population, the WIfI classification stratifies the risk of amputation and the potential benefit of revascularization.
- The finding of peripheral artery disease represents an opportunity to initiate and optimize guideline-directed medical therapy and reduce the patient's risk of major cardiovascular and cerebrovascular events.
- Revascularization may be accomplished by open bypass surgery or catheter-based intervention depending on multiple factors, such as the presence of rest pain or tissue loss, medical comorbidity profile, the presence of saphenous vein conduit, and the anatomic distribution of the arterial occlusive process.
- Patients in whom conventional arterial bypass or endovascular revascularization is not technically feasible have what is referred to as a "no-option" arterial occlusive anatomic pattern. For those patients, major limb amputation at a below-the-knee level is the only plausible option by conventional management strategies.
- In selected cases, deep venous arterialization can be a viable last-resort option for revascularization for those with advanced chronic limb-threatening ischemia and a "no-option" anatomic pattern before considering major amputation. Clinical research is ongoing to help define the patient profile with the greatest benefit relative to risk.
- Primary patency and amputation rates vary following open, endovascular, and hybrid deep venous arterialization.
- A multidisciplinary approach and patient-centered care are crucial to achieving favorable outcomes in limb-threatened patients with advanced disease. The interdisciplinary approach is necessary in preoperative preparation, selection of the appropriate revascularization strategy, and optimal postoperative medical therapy.

DISCLOSURES

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Address: *Lee Kirksey, MD, MBA, Vice Chairman, Department of Vascular Surgery, F30, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; kirksel@ccf.org*

Rebecca S. Gold, MD, MAS
Acting Instructor, Provisional Chief, Department of Medicine, University of Washington School of Medicine, Seattle, WA; Veterans Administration Puget Sound Healthcare System, Seattle, WA

Meagan Williams, MD
Assistant Professor, Department of General Internal Medicine, Dell Medical School, University of Texas at Austin, Austin, TX

Heather M. Wainstein, MD
Assistant Professor, Department of General Internal Medicine, UT Southwestern Medical Center, Dallas, TX

Cervical cancer screening in high-risk patients: Clinical challenges in primary care

ABSTRACT

The risk of developing cervical cancer is not equal across populations—individual health history, economic, political, and societal factors influence cervical cancer risk. Certain health conditions, including human immunodeficiency virus (HIV) infection, immunosuppression, and history of high-grade cervical dysplasia, are associated with higher cervical cancer risk and warrant distinct screening, surveillance, and management guidelines. It is imperative for clinicians to recognize high-risk groups and apply appropriate corresponding guidelines. However, this can be difficult in practice, as recommendations regularly evolve. This review offers up-to-date guidance in a case-based format on cervical cancer screening, surveillance, and management for high-risk patients.

KEY POINTS

- Cervical cancer screening, surveillance, and management in high-risk populations differ compared with average-risk populations.
- Individuals at increased risk include those with a history of HIV infection, immunosuppression, in utero exposure to diethylstilbestrol, or high-grade cervical dysplasia or human papillomavirus–related lower genital tract cancer, and those who have been underscreened.
- High-risk patients generally require more-intensive screening (ie, every 3 years vs every 5) and screening past age 65.

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Cervical cancer is the fourth most common cancer in women worldwide and a leading cause of cancer deaths in developing parts of the world.[1,2] In resource-rich countries, cervical cancer incidence and mortality are lower due to the availability of screening and human papillomavirus (HPV) vaccination.[1] However, certain populations in the United States have a higher cervical cancer incidence, including individuals who are immunocompromised due to human immunodeficiency virus (HIV) infection[3] or other causes or who are living in communities with higher poverty levels, likely due to limited access to healthcare and screening.[4] Moreover, studies suggest that the proportion of US patients who are up-to-date on cervical cancer screening has decreased in recent years, from 86% in 2005 to 77% in 2019, with the lowest rates in non-White, underinsured, rural, and nonheterosexual women.[5]

Persistent infection with oncogenic high-risk HPV, particularly subtypes 16 and 18, causes almost all cases of cervical cancer.[6,7] Fortunately, the vast majority of cervical HPV infections are transient.[8,9] Risk factors for persistent HPV infection include infection with oncogenic subtypes, older age, immunosuppression, smoking, and possibly other sexually transmitted infections—although it is unclear if this is correlation or causation.[7,10] When cervical HPV infection persists, progression from initial infection to cervical intraepithelial neoplasia (CIN) and finally invasive cancer takes years to decades.[11] Cervical cancer screening can detect

TABLE 1
Cervical cancer screening among average-risk patients

Organization	Recommended screening test and frequency		
2018 US Preventive Services Task Force[13]	**Age < 21 years** No screening	**Age 21–29 years** Cervical cytology (Pap test) every 3 years	**Age 30–65 years** Choose between • Cervical cytology (Pap test) every 3 years, or • Primary HPV testing every 5 years, or • Cotesting every 5 years
2020 American Cancer Society[12]	**Age 25–65 years** Primary HPV testing every 5 years preferred Acceptable alternatives (given access to primary HPV testing may be limited): • Cotesting every 5 years, or • Cervical cytology (Pap test) every 3 years		

HPV = human papillomavirus; Pap = Papanicolaou

precancerous changes, and treatment of these precursors can prevent the development of invasive cancer.[12]

SCREENING FOR AVERAGE-RISK PATIENTS

There are 3 methods generally used for cervical cancer screening:

- Cytology, or Papanicolaou (Pap) test: evaluation of cellular morphology for abnormalities
- Primary HPV testing: detection of DNA from high-risk HPV with genotyping to identify whether HPV-16, HPV-18, or other high-risk genotypes are present; primary HPV testing should be ordered with reflex cytology (performed if the sample is positive for HPV)
- Cotesting: cytology and high-risk HPV testing administered together.

Because cytology alone has lower sensitivity for precancer and cancer than HPV-based testing (ie, primary HPV testing or cotesting),[13] cytology alone should be repeated every 3 years, while HPV-based testing can be repeated every 5 years.[12,13] Primary HPV testing is a more efficient screening method than cotesting but is not universally available. There are currently only 2 US Food and Drug Administration–approved primary HPV tests,[12] so clinicians should ensure an approved assay is used.

Screening recommendations for average-risk individuals vary by professional organization. We typically use either the 2018 US Preventive Services Task Force[13] or 2020 American Cancer Society guidelines[12] (**Table 1**). **Figure 1** provides guidance on how to identify average-risk patients.[14,15] Note that both guidelines recommend following age-specific screening recommendations for all average-risk patients, regardless of HPV-vaccination status or sexual activity.[12,13]

Both the US Preventive Services Task Force and American Cancer Society guidelines note that there is no significant benefit of continuing to screen patients who are older than 65 and have had previous adequate screening with no history of CIN2, CIN3, adenocarcinoma in situ, or invasive cancer (collectively termed CIN2+) in the past 25 years (**Table 2**).[12,13] Patients who have undergone a hysterectomy with removal of the cervix (total hysterectomy) for benign indications with no history of CIN2+ in the past 25 years can also discontinue screening. Patients who have undergone a hysterectomy that retained the cervix (subtotal or supracervical hysterectomy) should continue screening per guidelines for average- or high-risk patients, as clinically appropriate.[12,13]

MANAGEMENT FOR AVERAGE-RISK PATIENTS

For average-risk patients, clinicians should use the 2019 American Society of Colposcopy and Cervical Pathology (ASCCP) risk-based management consensus guidelines[16] to interpret HPV and cytology results and decide on appropriate next steps. ASCCP has created a management guidelines web application (https://app.asccp.org) that is available free of charge and a smartphone application (https://www.asccp.org/mobile-app) available for purchase. These guidelines are based on the principle of "equal management for

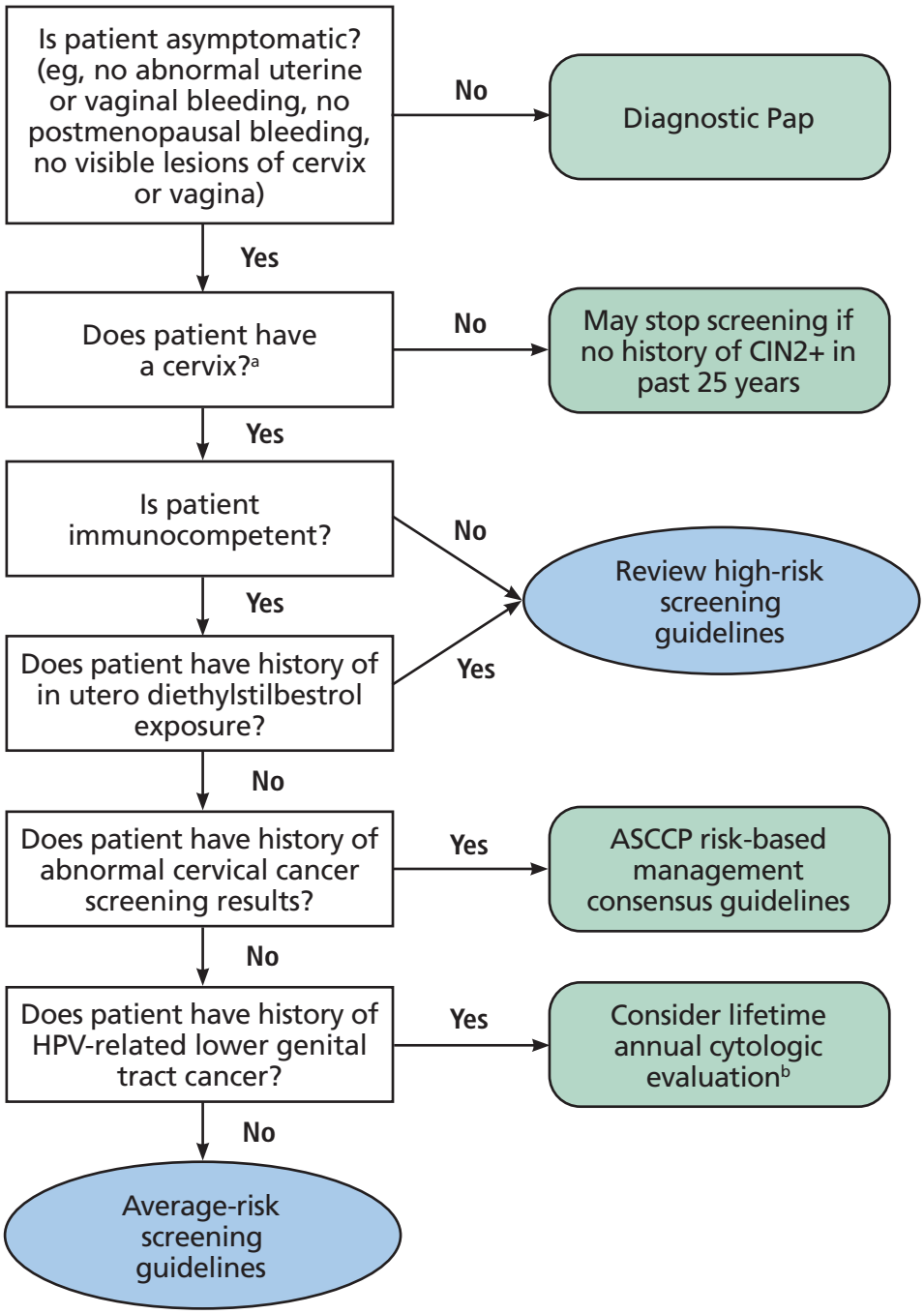

Figure 1. Who can follow average-risk screening guidelines?

[a]For patients who are uncertain if their cervix was removed during a benign hysterectomy, clinicians can review surgical records or perform an examination to determine the presence of the cervix.

[b]Lifetime annual cytologic evaluation based on current Society of Gynecologic Oncology recommendations.[15]

ASCCP = American Society of Colposcopy and Cervical Pathology; CIN2+ = cervical intraepithelial grade 2 or higher; HPV = human papillomavirus; Pap = Papanicolaou

Based on data from reference 14.

TABLE 2
When to stop cervical cancer screening in average-risk patients

Age > 65 years, if…	After hysterectomy, if…
Patient is asymptomatic, and	Total hysterectomy (removal of the cervix) was performed,[a] and
Has no history of CIN2 or worse in the past 25 years, and	Hysterectomy was performed for benign indication, and
Has undergone adequate prior screening: • 3 consecutive negative cytology results in past 10 years with most recent within 3 years, or • 2 consecutive negative HPV test results in past 10 years with most recent within 5 years	There is no history of high-grade precancerous lesion (eg, CIN2 or worse) in the past 25 years or history of HPV-related lower genital tract cancer

[a]Patients who have undergone a hysterectomy and retained the cervix (subtotal or supracervical hysterectomy) should continue screening per guidelines for average- or high-risk screening, as clinically appropriate.
CIN2 = cervical intraepithelial grade 2; HPV = human papillomavirus

Based on information in references 12 and 13.

equal risk" and therefore follow a risk-based rather than a results-based approach to determine management.

Risk is estimated using current screening results and prior screening and colposcopic biopsy results (if known) while considering personal factors such as age and frequency of screening. Decisions are based on whether the immediate risk of CIN3+ (CIN3, adenocarcinoma in situ, or invasive cancer) is 4% or greater. This level of risk requires further management, which typically necessitates the involvement of gynecology or gynecology-oncology for colposcopy or treatment. If the risk is less than 4%, then the tool looks at the 5-year risk of CIN3+ to determine the surveillance interval (eg, repeat screening in 1, 3, or 5 years). These patients can continue to be followed in a primary care setting.[16]

SCREENING AND MANAGEMENT FOR HIGH-RISK PATIENTS: CASE SCENARIOS

The following cases illustrate commonly encountered challenges in screening and managing patients at increased risk for developing cervical cancer.

Case 1

A 35-year-old woman with a history of systemic lupus erythematosus (not currently on medication) presents for an annual examination. Her last Pap test 3 years ago was normal and negative for HPV. She asks if she needs a Pap test. Her physician advises that she can wait another 2 years because she had negative cotesting 3 years ago and is not on immunosuppressive medication.

Case 2

A 45-year-old woman who recently underwent hysterectomy presents for an annual examination. She asks if she needs a Pap test. She reports that her hysterectomy was performed for fibroids and heavy menstrual bleeding. The pathology was benign, and the report confirms the cervix was removed. She mentions having had an abnormal Pap test in her 30s requiring "a procedure" but that subsequent Pap tests were normal. Her physician advises that she does not need further cervical cancer screening because the cervix was removed.

Case 3

A 68-year-old woman with a history of hypertension presents for an annual examination. She recently relocated and is new to the clinic. While reviewing the care gaps in the electronic medical record, which generates alerts based on patient age, the physician notes that they need to discuss breast cancer screening. There is no alert for cervical cancer screening, so the physician assumes that the patient has aged out and does not need anything further at this time.

WHO IS CONSIDERED HIGH-RISK?

Individuals who have a history of HIV, solid organ or hematopoietic stem cell transplant, systemic lupus erythematosus, treatment with immunosuppressive medications, in utero diethylstilbestrol (DES) exposure, high-grade cervical dysplasia, or HPV-related lower genital tract cancer or who have been underscreened or never-screened are all at higher risk for developing invasive cervical cancer.[3,10,15,17,18] As such, there are distinct screening and management recommendations for these individuals.

Cervical cancer screening recommendations for patients who are immunosuppressed but do not have HIV are limited due to a lack of quality evidence.

TABLE 3
Immunosuppressants and immunosuppressive treatments

Calcineurin inhibitors	Cytotoxic agents	mTOR inhibitors	Steroids	Biologics	Monoclonal antibodies
Tacrolimus (Crohn; non-FDA)	Mycophenolate	Sirolimus	Prednisone (IBD; FDA)	Abatacept	Basiliximab
Cyclosporine (UC; non-FDA)	Azathioprine (IBD; non-FDA)	Everolimus	Prednisolone (IBD; FDA)	Adalimumab (IBD; FDA)	Daclizumab
	Leflunomide (Crohn; non-FDA)		Budesonide (IBD; FDA)	Anakinra	Muromonab
	Chlorambucil		Dexamethasone (IBD; FDA)	Apremilast	
	Cyclophosphamide			Certolizumab (Crohn; FDA)	
	Mercaptopurine (IBD; non-FDA)			Etanercept (Crohn; non-FDA)	
	Methotrexate (Crohn; non-FDA)			Golimumab (UC; FDA)	
	Platinum compounds			Infliximab (IBD; FDA)	
	Fluorouracil			Ixekizumab	
	Dactinomycin			Natalizumab (Crohn; FDA; (UC; non-FDA)	
				Rituximab	
				Secukinumab	
				Tocilizumab	
				Ustekinumab (Crohn; FDA)	
				Vedolizumab (IBD; FDA)	

FDA = US Food and Drug Administration; IBD = inflammatory bowel disease; mTOR = mammalian target of rapamycin; UC = ulcerative colitis

Reprinted from Moscicki AB, et al. Guidelines for cervical cancer screening in immunosuppressed women without HIV infection. J Low Genit Tract Dis 2019; 23(2):87–101. doi:10.1097/LGT.0000000000000468 with permission from Wolters Kluwer Health.

Following a detailed literature review, Moscicki et al[17] published guidelines for cervical cancer screening in immunosuppressed women without HIV infection and determined that the following patient populations being treated with immunosuppressive medications (**Table 3**) have a higher risk of developing cervical cancer compared with the general population:[3]

- Solid organ transplant
- Hematopoietic stem cell transplant
- Systemic lupus erythematosus (regardless of treatment status)
- Inflammatory bowel disease or rheumatoid arthritis.

Note that this group found that patients with systemic lupus erythematosus are at increased risk of developing cervical dysplasia and cancer regardless of treatment status.[17] The underlying mechanism for this is unclear but is postulated to stem from increased risk of HPV infection owing to underlying immune dysregulation.[19]

SCREENING AND MANAGEMENT IN HIGH-RISK POPULATIONS

HIV infection

Cervical cancer screening guidelines for individuals living with HIV are well-supported by retrospective and prospective studies.[3,14,16,20,21] Current US Department of Health and Human Services and National Institutes of Health Office of AIDS Research screening and management guidelines for individuals living with HIV are summarized in **Table 4**.[3,16,20,21] Briefly, cervical cancer screening should begin at the time of initial HIV diagnosis but not before age 21. Cytology (Pap test) is the recommended screening method in individuals less than 30 years old and is performed annually for a total of 3 years. If the 3 consecutive Pap tests are normal, then follow-up screening is recommended every 3 years.

Individuals 30 years or older living with HIV should be screened with cytology alone using the approach detailed above or with cotesting every 3 years to continue throughout the individual's lifetime (and not, as in the general population, end at age 65).[3] Primary HPV testing is not approved for use in patients with HIV as it has not been validated in this population.

Patients with HIV are at increased risk for other HPV-associated cancers as well. At the time of cervical cancer screening, the genitalia and perianal region should be carefully examined for visual signs of warts or invasive cancer.[3] If a patient with HIV undergoes a total hysterectomy for benign disease and has no history of CIN2+, then ongoing routine screening for cervical or vaginal cancer is generally not necessary. However, female patients with a history of CIN2+ are at increased risk for vaginal and vulvar cancer and should be followed with an annual vaginal cuff Pap test.[3] Some providers perform more frequent screening or resume screening after hysterectomy for benign

TABLE 4
Cervical cancer screening and management among individuals with HIV

Screening

Age to start	Age to stop	Recommended test and frequency		Rationale
Screening should begin at time of diagnosis but not before age 21	Screening should continue throughout a patient's lifetime (considering life expectancy)[a]	**Age < 30 years** Cytology (Pap test) at baseline, then annually If 3 consecutive Pap tests are normal, then cytology every 3 years (until age 30)	**Age ≥ 30 years** Choose between cytology (Pap test) at baseline, then annually (if not already completed before age 30); if 3 consecutive Pap tests are normal, then cytology every 3 years or cotesting every 3 years	Begin screening at age 21 to provide a 3–5-year window before age 25, when the risk of invasive cervical cancer in patients with HIV exceeds that of the general population[20]; while historically screening was done before age 21, patients rarely develop cervical cancer before age 21[21] In patients age < 30, cotesting is not recommended due to a high prevalence of transient HPV in this age group[3]

Management

Regardless of age, colposcopy is recommended in the following scenarios:
- HPV-positive ASC-US; if HPV testing is not performed, then repeat cytology in 6–12 months is recommended, with colposcopy referral for ASC-US or worse
- All cytology results of low-grade squamous intraepithelial lesion or worse (including ASC-H, atypical glandular cells, adenocarcinoma in situ, and high-grade squamous intraepithelial lesion) regardless of HPV test results (if completed)

[a]If a patient with HIV undergoes a hysterectomy with removal of cervix (total hysterectomy) for benign disease and has no history of cervical intraepithelial neoplasia 2+, then ongoing routine screening for cervical or vaginal cancer is generally not recommended.

ASC-H = atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; ASC-US = atypical squamous cells of undetermined significance; HIV = human immunodeficiency virus; HPV = human papillomavirus; Pap = Papanicolaou

Data from references 3 and 16.

disease if HIV is poorly controlled or begins to progress (eg, rising viral load, falling CD4 level, new opportunistic infection). However, there are no current guidelines around this practice.

Individuals with HIV have a higher risk of CIN3+ with low-grade abnormalities on cytology. As such, regardless of age, colposcopy is recommended for HPV-positive atypical squamous cells of undetermined significance[3,14,21] and all cytology results of low-grade squamous intraepithelial lesion or worse, regardless of HPV test results (if completed).[16] Clinicians can refer to the ASCCP web or mobile application (https://www.asccp.org).[16] In general, treatment for CIN in patients with HIV should be managed according to ASCCP guidelines.[3,16]

Immunosuppressed, no history of HIV

Immunosuppressive therapy. Per ASCCP, patients with a history of solid organ transplant or hematopoietic stem cell transplant, systemic lupus erythematosus (regardless of treatment), and inflammatory bowel disease or rheumatoid arthritis on immunosuppressive therapy should follow the US Department of Health and Human Services screening and management guidelines for individuals with HIV.[3,17] Patients with inflammatory bowel disease or rheumatoid arthritis not on immunosuppressive therapy or patients with type 1 diabetes mellitus should follow screening guidelines for average-risk individuals.[17] Patients who have undergone hematopoietic stem cell transplant and develop genital graft-vs-host disease or chronic genital graft-vs-host disease should resume annual cervical cytology until 3 consecutive normal results or repeat baseline cotesting (if ≥ 30 years).[17]

Transplant. Screening guidelines for transplant patients differ between organizations.[3,17,22–25] The American Society of Transplantation recommends screening with Pap or cotesting every 6 months for the first year after solid organ transplant, then annually indefinitely if the first tests are negative, although this has been noted as a weak recommendation based on low-quality evidence.[23] The American Society of Transplantation suggests changing the frequency back to every 6 months for 1 year following treatment for rejection. These same American Society of Transplantation guidelines also recommend that transplant recipients be screened with

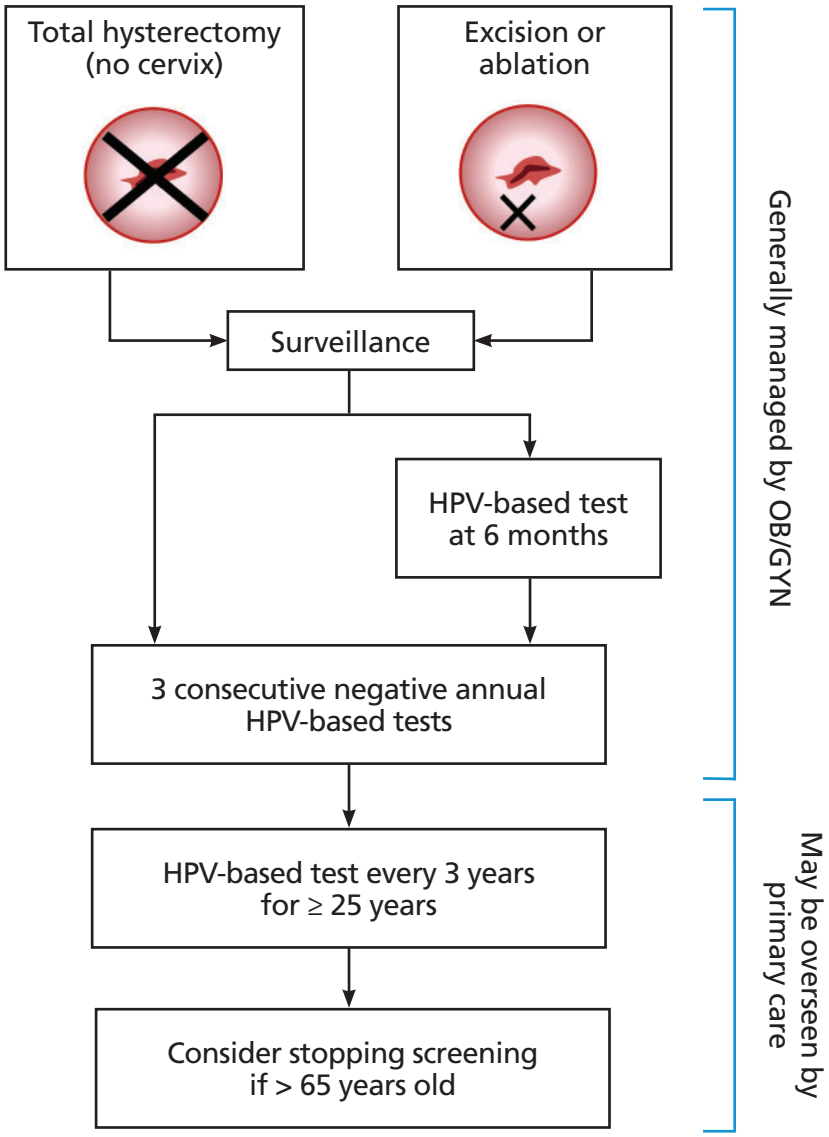

Figure 2. Management and surveillance for patients with a history of high-grade cervical dysplasia (high-grade squamous intraepithelial lesion, cervical intraepithelial 2 or 3, or adenocarcinoma in situ).

HPV = human papillomavirus; OB/GYN = Obstetrics and Gynecology

the same periodicity as women with HIV infection, in keeping with ASCCP and Moscicki et al.[17] A study modeling the application of US Department of Health and Human Services screening intervals for women with HIV to solid organ transplant patients found that more than two-thirds could have safely qualified for extending screening to every 3 years after 3 consecutive annual benign cytologic test results.[24] Further studies are needed among solid organ transplant recipients.

Autoimmune diseases. Notably, there are other groups of patients who are immunosuppressed, not specifically listed above, who may also warrant more intensive screening. For example, Australia's Cancer Council cervical cancer screening guideline[25] recommends considering HPV-based screening every 3 years for patients who are being treated with immunosuppressive therapy for autoimmune diseases such as neuromyelitis optica or sarcoidosis, as well as for patients with congenital immune deficiency. However, there are no definitive recommendations for patients with other autoimmune diseases, as data are limited in these populations. As such, clinicians may consider shared

decision-making for patients on active immunosuppression for autoimmune diseases not specifically considered by current guidelines,[17] as it may be reasonable to follow screening guidelines for individuals with HIV.[3,17]

History of high-grade cervical dysplasia

After a diagnosis with high-grade cytology or histology (ie, high-grade squamous intraepithelial lesion or CIN2, CIN3, or adenocarcinoma in situ), patients require treatment followed by increased short-term and long-term surveillance, based on the 2019 ASCCP risk-based management consensus guidelines.[16] Patients treated with total hysterectomy should undergo 3 annual HPV-based tests (**Figure 2**). Patients treated with excision (eg, cold knife or laser conization, loop electrosurgical excision procedure) or ablation (eg, cryotherapy, carbon dioxide laser or thermal ablation), with the cervix left in place, should also receive HPV-based testing at 6 months, then annual HPV-based testing until 3 consecutive normal HPV-based tests. Then patients can enter long-term surveillance with HPV-based testing every 3 years for a minimum of 25 years, even beyond age 65. Note that these patients should never return to 5-year interval testing.

If a patient reaches 65 years and has completed the recommended 3-year interval screening for 25 years, then clinicians can use shared decision-making to determine the need for continued screening.[16,26–28] Approximately 20% of cervical cancers occur in patients older than 65 years.[16,26,29] Long-term population studies suggest a persistent 2-fold increase in cervical cancer risk after treatment of a histologic high-grade squamous intraepithelial lesion, which continues for at least 25 years and seems to be higher for patients older than 50.[16,27,28] As cervical cancer risk appears to remain above general population levels,[27] continued screening is acceptable, as long as the patient remains in good health. In contrast, discontinuation of screening is recommended if a patient has limited life expectancy.

HIV and cervical dysplasia. Patients with HIV and a history of a high-grade squamous intraepithelial lesion should generally undergo treatment followed by increased short-term and long-term surveillance according to ASCCP guidelines with cotesting, as primary HPV testing is not approved for patients with HIV.[3,16] Surveillance should be continued throughout a patient's lifetime, regardless of treatment choice (ie, even if treated with total hysterectomy).[3] CIN recurs more frequently among patients with HIV,[30] and risk of recurrence may correlate with degree of immunosuppression.[21,30] As such, some clinicians perform more frequent follow-up in patients with HIV, particularly those with poorly controlled disease, although there are no current guidelines for this practice.[3]

History of HPV-related lower genital tract or anal cancer

Patients with HPV-associated invasive lower genital tract cancer (vulvar, vaginal, or cervical cancer) who have successfully undergone primary treatment are still at an increased risk for not only local disease recurrence but also for other HPV-related malignancies.[15] Although the optimal surveillance strategy for these patients has not yet been established, the Society of Gynecologic Oncology[15] recommends close monitoring by gynecologic oncology providers with complete assessment of areas susceptible to HPV-infection, including the vulva, vagina, cervix, and the perianal region, via visual inspection, speculum, bimanual, and rectovaginal examination. Although data are limited, this group also recommends lifetime annual cytologic evaluation of the cervix or vagina if the cervix is removed.

At time of diagnosis with anal cancer, it is recommended that female patients additionally undergo screening for cervical cancer if they are not up to date, given the frequent association between anorectal HPV infection and HPV infection of the cervix.[31] However, there are no specific recommendations for increased frequency of cervical cancer screening in individuals who have completed primary treatment for anal cancer. At present, these individuals can follow screening guidelines for average-risk individuals.[32,33]

DES exposure

Before 1971, millions of people were exposed in utero to DES given to mothers to prevent pregnancy complications.[18] Several adverse outcomes have been linked to this exposure, including increased risk of developing vaginal and cervical clear-cell adenocarcinoma, a rare form of cervical cancer not related to infection with high-risk HPV, as well as precursors of cervical and vaginal cancer (ie, squamous intraepithelial lesions or CIN).[12,18,34] Historically, DES-exposed patients were advised to have annual pelvic examinations with visualization of the cervix and vaginal wall, and collection of cytology specimens from the cervix and all 4 quadrants of the vagina.[35] However, most guidelines do not specifically address screening in patients who were exposed to DES and do not have updated recommendations to reflect the aging DES-exposed population.[12,35] Moreover, there is no specific guidance on the incorporation of HPV-based testing in addition to cytology.

Palpation for focal lesions or areas of abnormal tissue growth is a crucial part of the examination for DES-

exposed patients and may provide the only evidence of clear-cell adenocarcinoma.[36] During inspection, the speculum should be gently rotated as it is withdrawn to fully assess the entire vaginal wall. Colposcopy is no longer recommended as part of routine screening but should be used to follow-up any abnormal cytology.[35] When abnormal cytology is reported, it may be helpful to consult a gynecologist experienced in evaluating DES-exposed patients, when available. There are no clear recommendations for when to stop screening; however, it may be reasonable to continue annual screening as long as the patient would be interested in treatment should cancer be detected.[35]

Inadequate prior screening

The majority of invasive cervical cancer cases occur in individuals who were inadequately screened, never screened, or were unable to complete appropriate follow-up and treatment.[10,12,13] Moreover, in the United States, cervical cancer incidence and mortality are disproportionately high among racial and ethnic minorities (eg, African American, American Indian and Alaska Native, Hispanic, Asian American), sexual and gender minorities, individuals with disabilities, recent immigrants, individuals with low income, the uninsured and underinsured, medically underserved patients, and geographically isolated populations with limited access to care. Targeted outreach to select populations may help address these disparities.

One other promising possible solution is HPV self-sampling.[37] Self-sampling was recently approved by the US Food and Drug Administration for use in the healthcare setting and may help increase screening of women who have traditionally faced barriers to care or have experienced trauma.[12,38,39]

Note that in patients who have never been screened or have rarely been screened (defined by ASCCP as patients who have not undergone screening within the past 5 years) and who are not pregnant and are 25 or older, expedited treatment (ie, treatment without preceding colposcopic biopsy) should be considered for HPV-positive high-grade squamous intraepithelial lesion cytology, regardless of HPV genotype.[16]

When caring for older patients with inadequate prior screening, it may be reasonable to order cotesting to establish a new "baseline" rather than primary HPV testing or cytology alone. Cervical cancer screening should be continued beyond age 65 in patients who have not had adequate prior screening (**Table 2**) or have an unknown screening history.[13] Inadequate screening at younger ages or stopping screening before criteria for cessation have been met are important risk factors for developing cervical cancer at older ages and being diagnosed with more advanced stage disease.[12] In the absence of a history or confirmation of recent adequate negative screening results, clinicians should continue screening patients beyond age 65 if their life expectancy is more than 10 years, at least until criteria for cessation are confirmed or longer, based on shared decision-making.

CASES REVISITED

Case 1

A 35-year-old woman with systemic lupus erythematosus, regardless of treatment status, is at elevated risk for developing invasive cervical cancer and therefore should follow US Department of Health and Human Services screening guidelines for individuals with HIV.[3,17] She should undergo screening with cotesting every 3 years and therefore is due for screening now. Note that cytology alone would also be an option but would require clarifying whether she had previously completed 3 consecutive annual Pap tests with normal results.

Case 2

A 45-year-old woman who has had a hysterectomy should be evaluated for type of hysterectomy performed (ie, with or without removal of cervix) and history of CIN2+ in the past 25 years. Removal of the cervix can be confirmed by reviewing the hysterectomy operative or pathology reports or by examination with speculum and palpation. A history of CIN2+ can be ascertained by reviewing prior pathology reports, or when needed, by eliciting further history on prior procedures, as loop electrosurgical excision procedures or cone procedures are typically performed for higher grade (eg, ≥ CIN2 or high-grade squamous intraepithelial lesion) colposcopic biopsy results.

For this patient, if a history of CIN2+ is confirmed, she will need long-term surveillance with HPV-based testing of the vaginal cuff at 3-year intervals for a minimum of 25 years from date of the loop electrosurgical excision procedure or cone procedure (even if the patient were to turn 65 during that period), even though her cervix has now been removed. Again, note that this patient should never return to screening every 5 years.

Case 3

A 68-year-old woman should be evaluated to determine whether she is at average or high risk for developing cervical cancer (eg, history of immunosuppression or history of CIN2+ in the past 25 years), the presence or absence of a cervix, and adequacy of prior screening. Adequate prior screening for this patient is defined

as 3 consecutive negative cytology screenings or tests in the previous 10 years with the most recent having been within 3 years, or 2 consecutive negative HPV-based tests in the previous 10 years with most recent having been within 5 years. It can be difficult, particularly when patients relocate or transfer from a different healthcare system, to obtain documentation of screening history. However, the physician should attempt to review this history with the patient, send record-release requests, and, in the absence of confirmation, consider continued screening until criteria for cessation of screening are met.

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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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Address: *Rebecca S. Gold, MD, MAS, Department of Medicine, University of Washington, 1660 S Columbian Way, S-123-PCC, Seattle, WA 98108; goldr@uw.edu*

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