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COVID-19 and thrombocytopenia

Ehlers-Danlos and lightheadedness

Finger tophi and undertreated gout

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Cardiac surveillance in anti-HER2 chemotherapy

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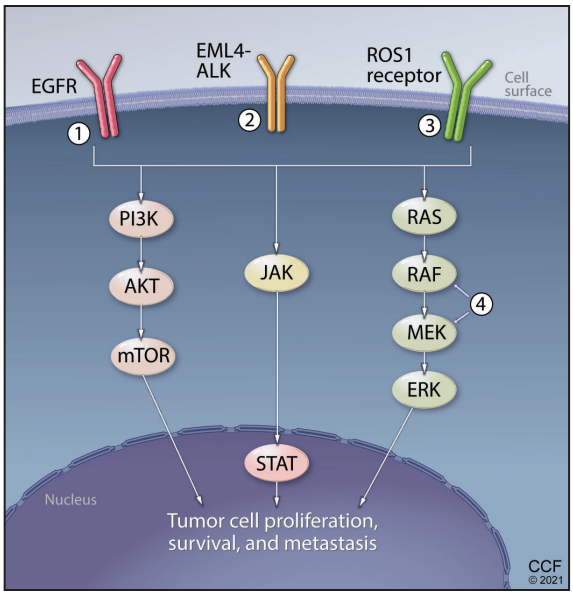

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Implementation Science: A Conversation with David Chambers, DPhil

Tuesday, March 9, Noon-1:30 pm | Virtual

The first session of the **Healthcare Delivery & Implementation Science Center Speaker Series** welcomes **Dr. David Chambers**, a recognized leader in implementation science. Join us for an enlightening conversation and case discussion.

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Why we publish The Clinical Picture

Based on the number of submissions we receive, The Clinical Picture is one of the most popular sections in *CCJM*—and also one of my favorites. Seemingly straightforward in approach, it is the section with our lowest acceptance rate, largely due to the fact that we have specific educational expectations for these pictures and their accompanying stories.

The Clinical Picture section was introduced in the *Journal* in 1997 by my preceding Editor in Chief Dr. John Clough. The very first article in this series was submitted by Dr. Gary Hoffman, who was at the time Chairman of Rheumatology at Cleveland Clinic. Dr. Hoffman, best known for his seminal work in the area of vasculitis, is an astute clinical educator who believes as I do in the power of visual imagery and the value of the clinical examination. His article depicted a patient with undertreated gout.[1]

In an ironic symmetry of content and message, the current issue of the *Journal* contains another Clinical Picture, this one from Drs. Hiroyuki Yano and Mitsuyo Kinjo,[2] that depicts a patient with undertreated gout. They describe exactly the same management challenges Dr. Hoffman discussed 24 years ago.

Gout was extremely common 24 years ago, and is even more so now. These two articles demonstrate that, while clinical findings may be striking enough to be published, they may go unrecognized or underappreciated for their significance and be inadequately addressed in clinical practice.

We do not select images for publication in The Clinical Picture based solely on their uniqueness; in fact, it is often the opposite. We don't generally accept the truly arcane one-of-a-kind image or illustrated unique case report. We look for images that reinforce the value of observation[3] during the physical examination. We look for images that support what Nishigori et al[4] have termed the "hypothesis-driven," and that I have described in lectures and at the bedside as the "directed" physical examination. And when the images prompt us readers to be attentive and influence our clinical behavior when we recognize them in practice, it is a heuristic victory. Sometimes, as with the clinical picture provided by Drs. Yano and Kinjo, the story also provides a powerful message. These are the pictures we look to publish.

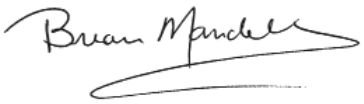
The man described by Drs. Yano and Kinjo[2] suffered recurrent attacks of foot pain several times a year for 10 years, yet gout was apparently not diagnosed and was not treated until he developed chronic kidney disease along with palpable nodules and intradermal papules. Only then was urate-lowering treatment initiated. His attacks diminished, and some tophi regressed, although he never achieved a serum urate level of significantly less than 6.0 mg/dL, which is the generally accepted minimal treatment target for patients with demonstrable tophaceous gout.[5] Although his treatment seemed to be successful as suggested by a decrease in the number of gout flares, it is unlikely that all tophi will resolve with an achieved level of serum urate higher than 6 mg/dL—thus, in the future, flares will likely resume, and further joint and bone damage ensue. This is likely to become an even more significant issue should he require renal transplant.[6]

doi:10.3949/ccjm.88b.02021

Intradermal tophi have been repeatedly described in the literature. With a seeming preference for the cooler extremities, digital and ear locations are common, but diffuse miliary gout is well described.[7,8] Interestingly, unlike in the patient described in this issue, these as well as other types of tophi (particularly those occurring around osteoarthritic finger joints) can be found on examination even before gout flares occur.[9]

To dramatically illustrate the latter point, I attach 2 images of the hands of one of my patients, a 70-year-old international businessman. Despite having tophaceous nodulosis and intradermal tophi to the extent that he could not make a complete fist (**Figure 1**), he had not experienced any flares of arthritis. He had been told "it is only gout" and never received urate-lowering therapy. **Figure 2** shows his hands after 6 months of very aggressive urate-lowering therapy to keep his serum urate level lower than 1 mg/dL. He regained virtually full use of his hands, and the urate-lowering therapy was subsequently changed to maintain a serum urate level of approximately 5 mg/dL.

The teaching points here include that physical findings, once found, should be acted upon when appropriate. We can all benefit from being reminded of the value of looking for less-common findings and reacting to them in the appropriate clinical context. Gout remains a very common and very frequently undertreated clinical condition. A reminder of those facts every quarter-century seems appropriate.



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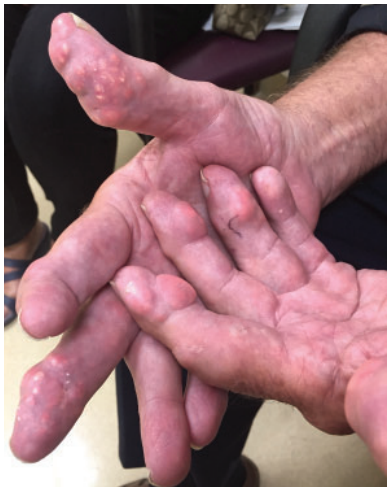

Figure 1. Before treatment.

Figure 2. After treatment.

1. **Hoffman GS**. Perils of nontreatment of hyperuricemia. Cleve Clin J Med 1997; 64(4):215. doi:10.3949/ccjm.64.4.215
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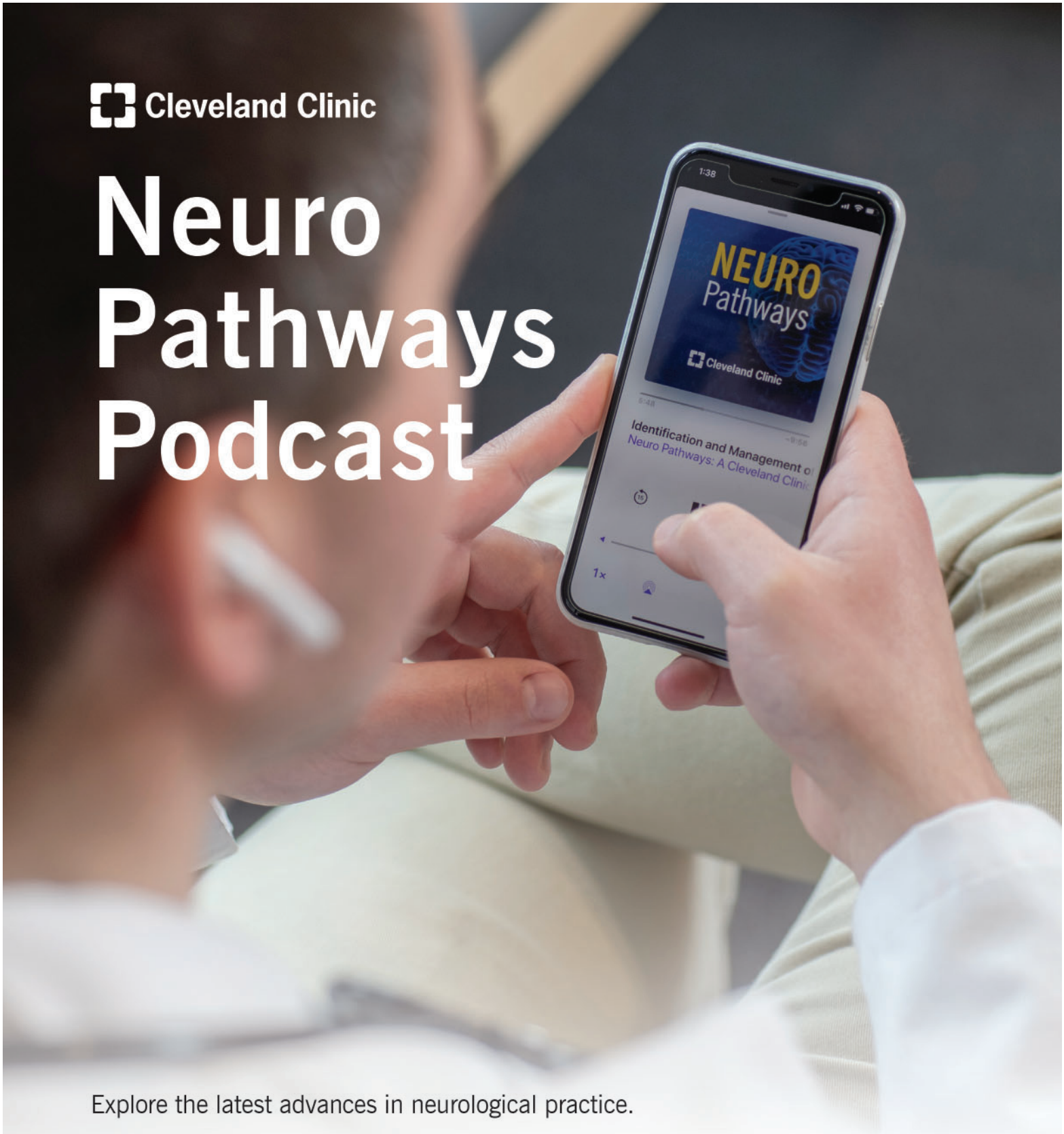

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Cutaneous digital papules

A 51-year-old man presented with cream-colored papules on his fingers. Ten years before, he began to have intermittent attacks of foot pain 2 or 3 times a year. Then, 3 years before this presentation, he developed nodules on both elbows and painless papules on the finger pads of both hands. He received a diagnosis of gout and stage 3b chronic kidney disease, and urate-lowering therapy was initiated at a local clinic. He had had no recurrence of gouty attacks since initiation of this therapy. However, the therapy was not titrated, and he did not reach the serum urate goal. His renal function gradually declined, and he was referred to our hospital.

His medications at the time of presentation included febuxostat 10 mg daily and benzbromarone (a uricosuric not available in the United States) 25 mg daily. He was an executive of a construction company. He said he drank approximately 500 mL of Japanese sake twice a week for the past 30 years. He had no family history of gout.

His vital signs were stable. Physical examination revealed large nodules (7 cm) on both elbows, with similar but smaller lesions on the right lateral malleolus (2 cm) and the right second metatarsophalangeal joint (1 cm), and multiple nontender papules on all fingers, especially the pads (**Figure 1**).

Laboratory testing showed a serum uric acid level of 9.9 mg/dL (reference range 3.7–7.8 mg/dL), blood urea nitrogen 39 mg/dL (8–20 mg/dL), creatinine 2.80 mg/dL (0.65–1.07 mg/dL), and estimated glomerular filtration rate 20.5 mL/min/1.73 m^2.

Radiography of the elbows revealed erosions of the distal humerus and increased nodular soft-tissue density. Aspiration of the nodule on the left elbow revealed needle-shaped crystals exhibiting characteristic negative elongation (birefringence) on compensated polarized light microscopy (**Figure 2**), leading to a diagnosis of tophaceous gout. Febuxostat was increased to 30 mg daily. One year later, he remained free from gouty attacks, with regression of tophi and a uric acid level of 6.6 mg/dL.

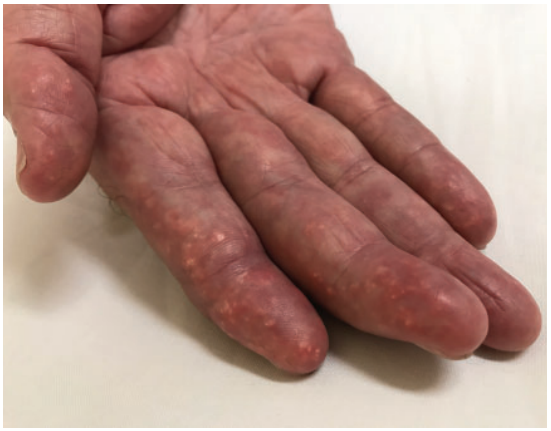

Figure 1. Multiple nontender papules were noted on all fingers.

Tophi in the finger pads is a compelling indication for aggressive urate-lowering therapy

TOPHACEOUS GOUT: KEY FEATURES

Gout, which affects 3.9% of US adults, is a metabolic disease that causes acute inflammatory arthritis, gouty tophi, renal impairment, and kidney stones (calcium oxalate and uric acid nephrolithiasis).[1] Comorbidities such as hypertension, chronic kidney disease, obesity, diabetes mellitus, myocardial infarction, and stroke are common in patients with gout.[2]

Gout has 4 clinical stages; asymptomatic hyperuricemia, acute gouty arthritis, intercritical gout, and advanced tophaceous gout.[3] Gouty tophi typically develop in the fourth stage and present more than 10 years after the first episode of acute gouty arthritis.[2] Tophi

doi:10.3949/ccjm.88a.20063

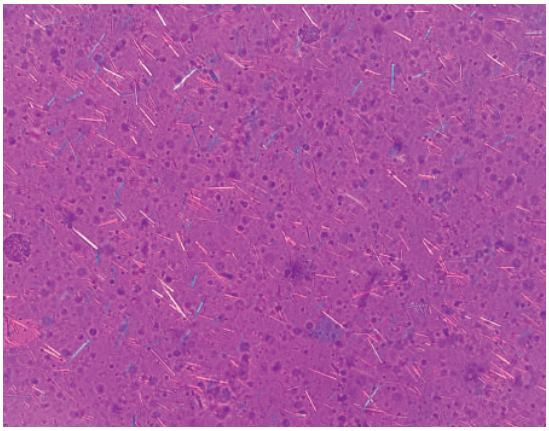

Figure 2. Aspiration of the nodule on the left elbow revealed needle-shaped crystals exhibiting characteristic negative elongation (birefringence) on compensated polarized light microscopy (magnification × 400).

represent a granulomatous inflammatory response triggered by exposure to monosodium urate crystals.[3]

FINGER PAD TOPHI NOT SO UNCOMMON

Tophaceous gout typically presents at articular or periarticular sites, but uric acid crystals may also deposit in extra-articular sites.[4] Finger pad tophi are superficial intradermal collections of monosodium urate. Although thought to be a rare manifestation of advanced gout, they may be overlooked clinically. In a small patient series,[5] finger pad tophaceous deposits were observed in 11 (30.5%) of 36 patients with tophaceous gout.

Risk factors for extra-articular tophi are renal insufficiency, hypertension, long-term use of furosemide, and long duration of disease.[3] The differential diagnosis of papules on finger pulp includes rheumatoid nodule, calcinosis cutis, pyogenic pustules, and fibromatosis.[3,6]

Treatment of gout has four dimensions, ie, urate-lowering therapy (in patients who qualify), flare prophylaxis, flare management, and management of gout-associated comorbidities. Tophi alone are an indication for urate-lowering therapy such as allopurinol, based on the recommendation of the American College of Rheumatology.[7]

TAKE-HOME POINTS

Development of tophi in the finger pads constitutes a compelling indication for aggressive urate-lowering therapy, which may prevent severe degenerative arthritis, secondary infections, and gout-associated comorbidities. We should perform a full physical examination on all gout patients, as tophi can develop in extra-articular locations including the finger pads, helix of the ear, and olecranon bursa.

DISCLOSURES

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

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Pacemaker lead-induced venous thoracic outlet syndrome

A 73-year-old woman came to our office. She had chronic nonvalvular atrial fibrillation, hypertension, systemic lupus erythematosus (in remission), and sick sinus syndrome for which a pacemaker had been implanted 2 years ago. She presented with acute onset of left arm swelling and pain after having taken a domestic airline flight and missing a single dose of her direct oral anticoagulant. She presented to us approximately 10 days after symptom onset.

Examination revealed a blood pressure of 120/78 mm Hg, heart rate 88 beats per minute, and respiratory rate 14 per minute without any distress.

Results of laboratory testing were as follows:

- Hemoglobin 11.1 g/dL (reference range 11.7–15 g/dL)
- Activated partial thromboplastin time 41.5 sec (25–37 sec)
- International normalized ratio 1.3 (0.9–1.1)
- Anticardiolipin antibody less than 9 U/mL (0–11 U/mL).

Duplex ultrasonography of the left upper extremity revealed possible thrombosis or obstruction of the left subclavian vein. She was referred for contrast venography, which revealed a thrombus in the subclavian vein along with venous collaterals (**Figure 1**).

The patient was admitted for ultrasonography-assisted catheter-guided thrombolysis utilizing alteplase along with unfractionated heparin infusion for 24 hours. The next day, she underwent repeat venography, which revealed marked resolution of the thrombus and focal high-grade stenosis of the subclavian vein, which was treated with balloon angioplasty with excellent luminal gain and disappearance of the collaterals.

She continued her oral anticoagulation.

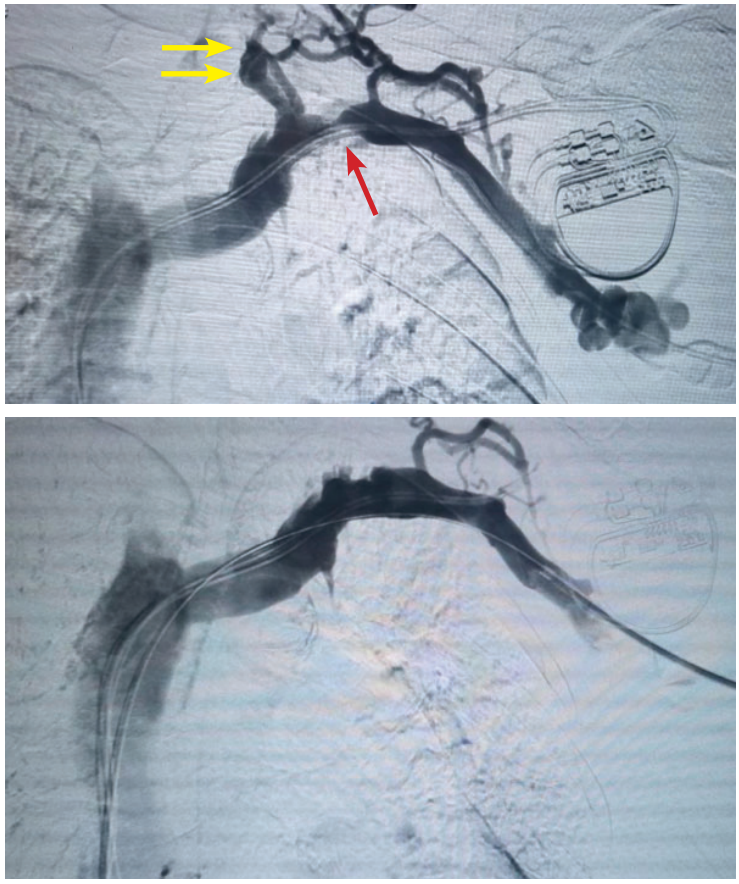

Figure 1. Initial venography (top) depicted a thrombus in the subclavian vein (red arrow) with venous collaterals (yellow arrows). Venography after thrombolysis and angioplasty (bottom) showed reconstitution of the subclavian vein with disappearance of collaterals. Pacemaker leads and catheter are seen in both images.

doi:10.3949/ccjm.88a.20023

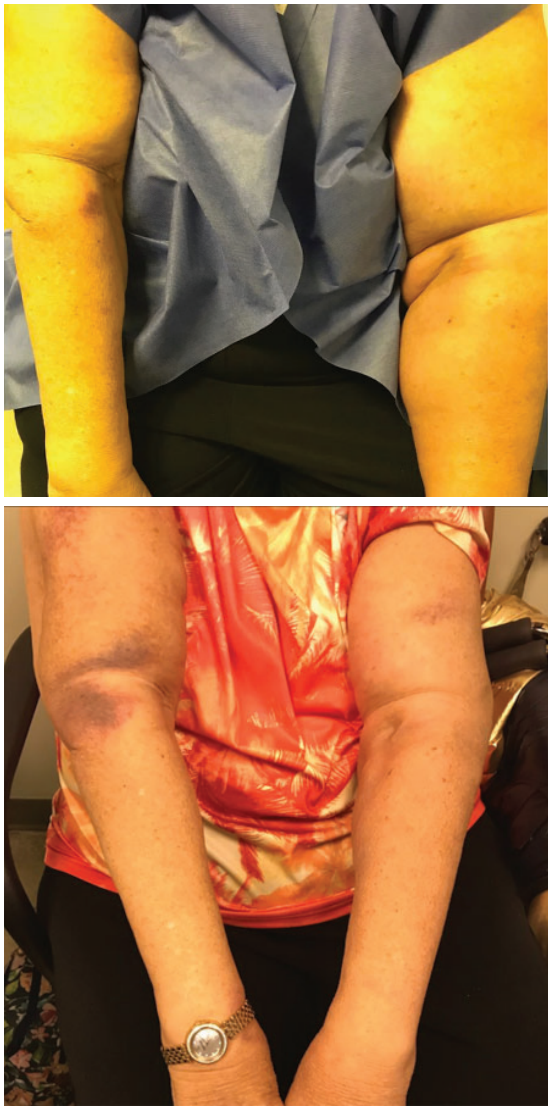

Figure 2. Unilateral left arm swelling at presentation (top) had diminished at 8 weeks after the start of treatment.

Determining the type of venous thoracic outlet syndrome is important, as it influences treatment

At her last follow-up visit, 8 months after her venous stenting, the swelling had diminished substantially (**Figure 2**), and she remained free of symptoms and signs suggestive of venous stent stenosis or occlusion. She has been maintained on anticoagulation.

VENOUS THORACIC OUTLET SYNDROME

Venous thoracic outlet syndrome is the second most common subtype of thoracic outlet syndrome after neurologic thoracic outlet syndrome.[1] It is an uncommon cause of unilateral arm swelling, and needs to be differentiated from deep vein thrombosis involving the brachial or axillary veins.

Venous thoracic outlet syndrome can be primary (from recurrent compression trauma to the subclavian vein from surrounding anatomic structures, leading to thrombosis) or secondary (from pacemaker leads or a hypercoagulable state).[2] Differentiating the types is important and is based on the patient's history, which influences treatment. Primary venous thoracic outlet syndrome affects young people involved in activities requiring strenuous arm use such as tennis and weightlifting, and commonly affects the dominant arm, as opposed to secondary venous thoracic outlet syndrome, which occurs without a predisposing age or occupation.

APPROACHES TO MANAGEMENT

Management of venous thoracic outlet syndrome varies in different institutions, as there are no official guidelines.[1] However, there is a general consensus that primary venous thoracic outlet syndrome, within the first 2 weeks, should be managed by thrombolysis with surgical resection of the first rib. Anticoagulation alone is not the treatment of choice. Angioplasty is indicated in cases with focal venous defects. Secondary venous thoracic outlet syndrome is managed with thrombolysis and anticoagulation, with angioplasty for focal venous disease and removal of the inciting insult when possible, eg, removing the pacemaker lead or changing it to the opposite side. ■

DISCLOSURES

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

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Severe chemical pneumonitis from tetrahydrocannabinol 'vaping' and 'dabbing'

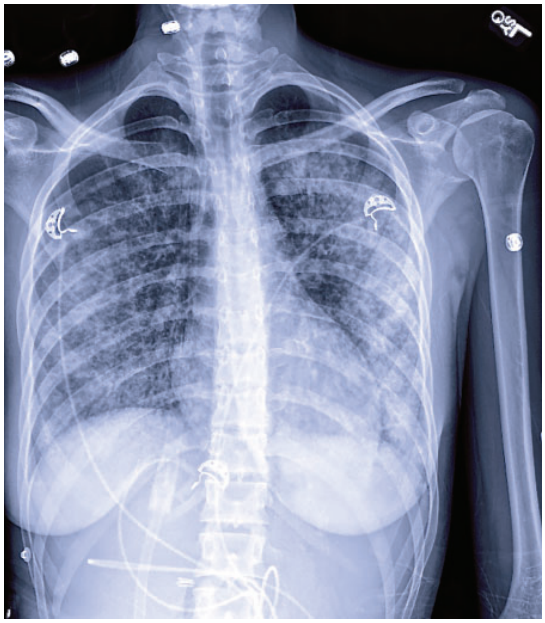

Figure 1. Chest radiograph showing widespread, patchy airspace opacification.

A 19-year-old woman with a history of mild intermittent asthma and regular tetrahydrocannabinol (THC) consumption by "vaping" and "dabbing" (inhaling vaporized, highly concentrated THC oil) presented with several days of fevers, dyspnea, and productive cough. She was febrile, tachycardic, and tachypneic. Laboratory testing revealed an elevated white blood cell count of 15.0 × 10^9/L (reference range 4.4–10.0 × 10^9/L) and a procalcitonin level of 0.3 ng/mL (reference range 0.1–0.5 ng/mL). Her initial chest radiograph was unremarkable.

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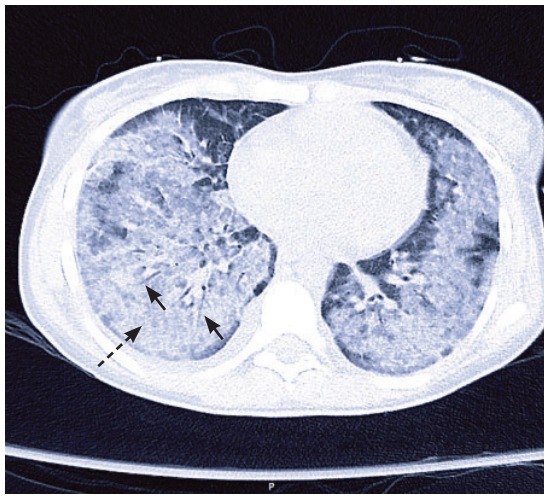

Figure 2. Computed tomography showing bilateral dense consolidation (dashed arrow) with air bronchograms (solid arrows) and peripheral sparing.

She was treated with fluid resuscitation, nebulized albuterol, and antibiotics (ceftriaxone and azithromycin) but developed respiratory failure requiring oxygen by nasal cannula.

A repeat chest radiograph showed central consolidation (alveolar spaces filled with fluid) bilaterally in the midlungs and bases, with progression to widespread, patchy airspace disease (**Figure** 1). Computed tomography revealed bilateral dense consolidation with air bronchograms as well as peripheral sparing (**Figure 2**).

We initiated intravenous corticosteroid therapy and broadened her antibiotic coverage. Her respiratory failure necessitated oxygen supplementation by high-flow nasal cannula, and she was admitted to the intensive care unit.

THC products have been implicated in an outbreak of e-cigarette or vaping product use-associated lung injury (EVALI)

Results from an extensive infectious disease workup were unremarkable, and her antibiotics were discontinued. Her acute lung injury was deemed secondary to chemical pneumonitis from inhalation of aerosolized THC.

After several days of corticosteroid therapy and supportive care, her respiratory status improved. She was counseled on THC cessation, prescribed oral corticosteroids, and discharged with a recommendation to follow up with a pulmonologist.

The patient improved after several days of corticosteroid treatment

AN OUTBREAK OF LUNG INJURY

Among adult marijuana users, 33.7% report multiple methods of use, 19.4% report vaping, and 14.5% report dabbing, according to a 2016 national survey conducted by state health departments.[1] Vaping is inhalation of aerosols produced by electronic cigarettes; dabbing refers to using high heat to vaporize highly concentrated THC in the form of butane hash oil, which is inhaled.

These THC-containing products have been implicated in an outbreak of e-cigarette or vaping product use-associated lung injury (EVALI), with more than 2,800 hospitalized cases and 68 deaths as of February 2020, according to data from the US Centers for Disease Prevention and Control[2]; 82% of the patients had used THC-containing products.

Does vitamin E acetate play a role?

The pathophysiology of EVALI may be mediated in part by vitamin E acetate, which became a popular additive to THC oil, given their comparable viscosities, around the same time as the recent outbreak. Vitamin E acetate is nearly ubiquitous in bronchoalveolar lavage samples taken from case patients but is absent in control groups.[3] Its inhalation may precipitate lung injury by interfering with the ability of pulmonary surfactant to maintain surface tension or by producing ketene, a potentially noxious irritant. In dabbing, the THC product extracted from hash oil using liquid butane (butane hash oil) may degrade into pneumotoxic byproducts at high temperatures.[4]

SUSPECT IT IF PATIENTS REPORT VAPING

Suspect EVALI if patients report vaping or dabbing within 90 days of symptom onset, have pulmonary infiltrates on imaging, and lack evidence of an alternative cause. Patients commonly present with a gradual onset of constitutional, respiratory, or gastrointestinal symptoms.

Laboratory testing may reveal elevations in the white blood cell count, serum inflammatory markers, and aminotransferase levels.[2,5] Infectious disease workup includes evaluation for viral, bacterial, endemic, and opportunistic pathogens, based on patient presentation and geographic prevalence.[5]

Differences from COVID-19 on imaging

Although radiographic findings may be nonspecific, certain imaging features can help differentiate EVALI from other novel lung disorders. Most cases of EVALI show basilar-predominant consolidation and ground-glass opacification that often spares the periphery, with interspersed segments of unaffected parenchyma.[6]

In comparison, the respiratory illness associated with coronavirus disease 2019 (COVID-19) typically causes ground-glass opacification in the acute phase, with subsequent development of septal thickening that may be interlobular (involving septa separating secondary pulmonary lobules) or intralobular (involving septa separating individual acini) and multifocal consolidation. Unlike EVALI, COVID-19 lesions most commonly have a peripheral or subpleural distribution.[7,8]

Despite these distinctions, serologic testing is required to confirm the diagnosis of COVID-19.

SUPPORTIVE CARE, CORTICOSTEROIDS, POSSIBLY ANTIBIOTICS

Management of EVALI focuses primarily on respiratory support, with consideration for empiric corticosteroid and antimicrobial therapy on a case-by-case basis. Significant clinical improvement has been reported with corticosteroid administration, likely due to suppression of the inflammatory response.[5,9]

Patients should be advised to discontinue substance use, and they may require outpatient follow-up.[5]

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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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OUR PEER-REVIEWERS FOR 2020

We thank those who reviewed manuscripts submitted to the *Cleveland Clinic Journal of Medicine* in 2020. Reviewing papers for the *Journal*—both for specialty content and for relevance to our readership—is an arduous task that involves considerable time and effort. Our publication decisions depend in no small part on the timely efforts of reviewers, and we are indebted to them for contributing their expertise this past year.

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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: How should you assess glycemic control if the hemoglobin A1c is inaccurate or uninterpretable?

A: For adult outpatients with type 2 diabetes mellitus, hemoglobin A1c is the standard test used to gauge overall glycemic control during the previous 2 to 3 months and to titrate antidiabetic medications. But hemoglobin A1c does not provide an accurate assessment of frequency or severity of hypoglycemic events. Also, in some instances it may not truly represent glucose control, reflecting an average of high and low blood sugar values, or may not be reportable because of abnormal hemoglobin.

In these situations, an alternative test can be used along with capillary blood glucose testing, which remains the most reliable method of assessing glucose control in the short term. If an alternative test is used, it is important to clearly document it in the chart to reduce confusion, and also to educate the patient to better understand the disease-monitoring process.

HEMOGLOBINOPATHIES CAN INTERFERE WITH HEMOGLOBIN A1c

Many conditions that modify red blood cell production, destruction, or life span can affect the accuracy of hemoglobin A1c measurement (**Table 1**).[1–8]

Hemoglobinopathies can interfere with hemoglobin A1c testing, but this has become less of an issue as more laboratories use high-performance liquid chromatography in routine practice. The National Glycohemoglobin Standardization Program has published a list of commonly used hemoglobin A1c assays and expected interference from hemoglobin variants.[1] If the assay your laboratory uses is affected by these hemoglobin variants, consider other tests to measure long-term glucose control.

Suspect that a hemoglobinopathy or other condition is causing unreliable hemoglobin A1c readings if the hemoglobin A1c value[1–6]:

- Does not correlate with the expected value based on capillary blood glucose readings or laboratory plasma glucose readings
- Is inconsistent with frequently sampled plasma glucose values
- Is greater than 15%
- Changes significantly after the laboratory changes its testing method.

ALTERNATIVE METHODS TO ASSESS LONG-TERM GLYCEMIC CONTROL

Alternative tests to assess glycemic control include capillary blood glucose readings, continuous glucose monitoring, serum fructosamine, glycated albumin, and 1,5-anhydroglucitol.

Capillary blood glucose

Results from capillary blood glucose tests show glucose levels at a specific time and can be taken multiple times during a day. They are useful to identify glucose trends and inform medication adjustments.

This is the most common method to detect hypoglycemia and quantify its severity and frequency. Detecting hypoglycemia is especially important in patients receiving insulin or secretagogues or with other conditions that may predispose them to hypoglycemia. The hemoglobin A1c level can be above goal even if they have hypoglycemia. Capillary blood glucose monitoring relies on patient

Hemoglobin A1c is the standard but it is not perfect; alternatives are available

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TABLE 1

Common clinical conditions that can affect hemoglobin A1c[a]

Clinical condition	Effect on hemoglobin A1c	Mechanism or reason for effect
Asplenia	Increases hemoglobin A1c	Decreased red blood cell (RBC) turnover due to increased RBC life span
Chronic kidney disease	Effects vary based on severity of underlying disease and therapies	**Increased hemoglobin A1c** Carbamyl-hemoglobin production in uremic patients Erythropoietin deficiency **Decreased hemoglobin A1c** Shortened RBC survival Erythropoietin administration Hemodialysis (lowering of urea levels reduces carbamyl-hemoglobin concentration)
Chronic liver disease	Effects vary based on severity of underlying disease and therapies	**Increased hemoglobin A1c** Jaundice (increased glycation reaction in the presence of higher bilirubin concentrations) **Decreased hemoglobin A1c** Increased RBC turnover Antiviral drug therapies may decrease RBC life span
Hemoglobinopathies	Varies with testing method and assay	Multifactorial including anemia and rapid RBC turnover
Hemolytic anemia	Decreases hemoglobin A1c	Reduced RBC total volume Increased RBC destruction shortens RBC life span
Iron deficiency anemia	Increases hemoglobin A1c	Reduced RBC turnover prolongs RBC survival Greater malondialdehyde concentrations increase hemoglobin glycation reactions
Pregnancy	Decreases hemoglobin A1c in first 2 trimesters May increase hemoglobin A1c in third trimester	Increased RBC turnover decreases hemoglobin A1c Increased erythropoietin production decreases hemoglobin A1c Hemodilution decreases hemoglobin A1c
Transfusion	Variable hemoglobin A1c effects	**Increased hemoglobin A1c** Elevated glucose concentration in storage medium **Decreased hemoglobin A1c** Dilutional response
Vitamin B_{12} and folate deficiency anemias	Increases hemoglobin A1c	Reduced RBC turnover prolongs RBC survival

[a]This summation represents most current literature and clinical practice, but should be used as a guide only and should not replace clinical assessment or decision-making.

Based on information in references 1–8.

adherence to checking and recording glucose values several times a day and communicating the results to the care team.

The American Diabetes Association suggests using the estimated average glucose level, as calculated from the hemoglobin A1c, to give patients a reference to compare with the capillary blood glucose values they get at home. The formula is as follows[9]:

Estimated average glucose (mg/dL) = 28.7 × hemoglobin A1c (%) – 46.7

For example if the hemoglobin A1c is 7%, the estimated average glucose value would be 28.7 × 7 – 46.7 = 154 mg/dL. The American Diabetes Association has a conversion calculator on its website.[10]

Continuous glucose monitoring

Continuous glucose monitors measure interstitial glucose levels and are used to assess glucose trends over days to weeks. There are 2 main categories of these monitors: personal and professional.[11,12] Personal monitors are typically worn long-term for patient self-monitoring and come in 2 major types: real-time and intermittently scanned. Health insurance coverage requires specific criteria to be met for approval of either type.

In contrast, a professional continuous glucose monitor, if covered by insurance, is typically used for a shorter time, after which a medical professional retrieves the results. Results are either displayed in real time to the patient or are blinded to the patient.

Personal and professional monitors have shown similar performance qualities. However, both are less reliable for detecting hypoglycemia events than capillary blood glucose readings. In addition, their accuracy depends on reliable sensor placement and avoidance of certain prescribed and over-the-counter medications. Moreover, their use has not been studied in patients with end-stage liver or kidney disease, and they should be used cautiously in patients who have any condition that could affect measurement of interstitial glucose.

Serum fructosamine

Serum fructosamine, a circulating glycated protein (mostly albumin), can be measured to monitor glycemic control when hemoglobin A1c testing is inaccurate. Fructosamine levels provide an estimate of the average blood glucose levels in the preceding 7 to 21 days. This substance can be used to monitor rapid insulin titrations and has been shown to correlate more consistently with continuous glucose monitoring than hemoglobin A1c.[13–15]

Several formulas can be used to estimate the hemoglobin A1c based on the fructosamine level, eg:

Hemoglobin A1c (%) = 0.017 × fructosamine level (µmol/L) + 1.61

By this formula, a fructosamine level of 317 µmol/L converts to a hemoglobin A1c of 7%; a value of 375 µmol/L converts to a hemoglobin A1c of 8%.[16]

However, in patients with conditions associated with altered albumin metabolism, such as nephrotic syndrome, advanced liver disease, or protein-losing enteropathy, the correlation between fructosamine levels and glycemic control may be decreased.[14,15] Some suggest using a correction factor for the general equation, such as multiplying the fructosamine level by 4 and then dividing by the serum albumin level, but this practice has not been widely adopted.[2,15]

Pregnancy is another condition in which fructosamine levels have limited use. In this situation, other tests, such as capillary blood glucose or continuous glucose monitoring, may have better validity and clinical applicability.

Hemoglobin A1c does not detect hypoglycemic episodes

Glycated albumin

This is an emerging measure that may improve the overall predictive value of glycemic control. The proportion of serum albumin that is glycated provides an estimate of glycemic control in the previous 14 to 21 days. This value is easily converted to an approximate hemoglobin A1c value by dividing by 3. This is more straightforward than converting fructosamine to hemoglobin A1c and may provide better information regarding postprandial glucose values.[17]

However, glycated albumin values may not be reliable in patients with conditions that alter albumin metabolism such as nephrotic syndrome, hypo- or hyperthyroidism, or cirrhosis.[13]

1,5-Anhydroglucitol

1,5-Anhydroglucitol is a dietary polyol that competes with glucose for reabsorption in the renal tubule when circulating glucose concentrations are elevated. Lower circulating serum concentrations of 1,5-anhydroglucitol correspond with increased glycosuria and hyperglycemia within the previous 7 to 14 days.[18,19]

This test is not as reliable in patients with altered renal perfusion, though it provides valuable information in assessing same-day periods of hyperglycemia, particularly glucose values greater than 180 mg/dL. Also, 1,5-anhydroglucitol is not a reliable indicator of glucose control in patients on sodium-glucose cotransporter 2 inhibitors, which increase glycosuria.[20]

EDUCATING PATIENTS AND PROVIDERS ON ALTERNATIVE TESTS

Healthcare providers need to know that hemoglobin A1c does not correlate with capillary or venous blood glucose levels in some situations—otherwise, one might inappropriately escalate or de-escalate therapy. If alternative tests are used because of inaccurate or uninterpretable hemoglobin A1c values, clinicians need to document the clinical rationale. This documentation may prevent a hemoglobin A1c test from being ordered and falsely interpreted.

Many conditions can affect hemoglobin A1c measurements

Patient education is also important. Successful diabetes education efforts have led to widespread recognition of hemoglobin A1c as the standard diagnostic test for monitoring glycemic control. If a different test is used, the practitioner needs to explain the rationale to the patient and provide education on the alternative method. A diabetes educator, clinical pharmacist, or nurse may be able to facilitate this education.

If the patient has an abnormal hemoglobin variant, it should be added to the problem list. Consider adding ICD-10 code D58.2 (abnormal hemoglobin not otherwise specified) or D58 (other hereditary hemolytic anemias). Each facility can consider development and implementation of specific solutions.

Finally, insurance companies and other groups focused on quality metrics need to be informed of the inaccuracy of hemoglobin A1c testing for individual patients. With so many groups transitioning to population health data, a missing or inaccurate hemoglobin A1c test may affect the ability to assess glycemic control across a patient population and could affect assessment of performance measures for individual clinicians and practice groups. If data sets are automatically abstracted, the auditing software can penalize providers for not having tested hemoglobin A1c as a fundamental component of diabetes management.

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Severe thrombocytopenia in a patient with otherwise asymptomatic COVID-19

TABLE 1

The patient's complete blood cell count

Test	Patient's value[a]	Reference range
White blood cell count	7.03 × 10^9/L	3.7–11.0
Red blood cell count	4.46 × 10^{12}/L	3.90–5.20
Hemoglobin	14.4 g/dL	11.5–15.5
Hematocrit	41.2%	36%–46%
Platelet count	**3.0 × 10^9/L**	150–400
Mean corpuscular volume	92.4 fL	80–100
Mean corpuscular hemoglobin	32.3 pG	26.0–34.0
Mean corpuscular hemoglobin concentration	35.0 g/dL	30.5–36.0
Mean platelet volume	11.7 fL	9.0–12.7
Red cell distribution width coefficient of variance	11.9%	11.5%–15.0%
Reticulocytes	84 × 10^9/L 1.9%	18–100 0.4%–2.0%
Neutrophils	4.59 × 10^9/L 65.3%	1.45–7.50 55%–70%
Lymphocytes	1.77 × 10^9/L 25.2%	1.00–4.00 20%–40%
Monocytes	0.57 × 10^9/L **8.1%**	< 0.87 2%–8%
Eosinophils	0.09 × 10^9/L 1.3%	< 0.46 1%–4%
Basophils	< 0.03 × 10^9/L 0.1%	< 0.11 0.5%–1%
Nucleated red blood cells	< 0.01 × 10^9/L 0%	< 0.01 0%

[a]Abnormal results are shown in bold.

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A 35-YEAR-OLD WOMAN with a medical history significant only for recently diagnosed essential hypertension presented to an urgent-care facility with easy bruising, petechiae, and gingival bleeding. She said that she had noticed large ecchymoses from minimal trauma on her upper and lower extremities for the past week, as well as a petechial rash. A complete blood cell count at that time revealed a platelet count of 3.0 × 10^9/L (reference range 150–400 × 10^9/L), and she was told to go to the nearest emergency department.

In the emergency department, repeat testing confirmed that her platelet count was indeed only 3.0 × 10^9/L, while the rest of her complete blood cell count values were unremarkable (**Table 1**). Her blood pressure was 167/104 mm Hg, heart rate 80 beats per minute, respiratory rate 16 breaths per minute, and oxygen saturation 99% on room air.

CAUSES OF THROMBOCYTOPENIA

1 All of the following are possible causes of thrombocytopenia except for which one?

- ☐ Thrombotic thrombocytopenic purpura
- ☐ Disseminated intravascular coagulation
- ☐ Immune thrombocytopenic purpura
- ☐ Glucose-6-phosphate dehydrogenase deficiency
- ☐ Hemolytic uremic syndrome

The causes of thrombocytopenia can be divided into disorders of decreased platelet production and disorders of increased platelet consumption or destruction.

Disorders of decreased production include

TABLE 2

Differential diagnosis for thrombocytopenia

Disease	Thrombocytopenia	Hemolysis[a]	ADAMTS13	PT/PTT	Fibrinogen	D-dimer
Thrombotic thrombocytopenic purpura	Yes	Yes	Low	Normal	Normal	Normal
Hemolytic uremic syndrome	Yes	Yes	Normal	Normal	Normal	Normal
Disseminated intravascular coagulation	Yes	Yes	Normal	Prolonged	Low	High
Immune thrombocytopenic purpura	Yes	No	Normal	Normal	Normal	Normal

[a]Anemia, increased lactate dehydrogenase, decreased haptoglobin, increased reticulocyte count, increased unconjugated bilirubin.
ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; PT/PTT = prothrombin time and partial thromboplastin time

bone marrow diseases, such as myelodysplastic syndromes and aplastic anemia, and liver disease.

Disorders of platelet destruction or consumption include immune thrombocytopenic purpura and hemolytic processes. Thrombocytopenia can also occur during massive fluid resuscitation or blood transfusion without the transfusion of platelets, known as posttransfusion purpura, or during hypersplenism.[1]

Thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura is caused by a genetic or acquired deficiency of ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13).

ADAMTS13 is a protease responsible for cleaving von Willebrand factor during times of high shear stress and resultant platelet adhesion, preventing large von Willebrand factor multimers from accumulating. A deficiency of ADAMTS13 leads to accumulation of large von Willebrand factor multimers that platelets then attach to, leading to widespread microvascular thrombosis.[1,2]

The clinical features seen with thrombotic thrombocytopenic purpura are widespread and may include symptoms of thrombocytopenia and hemolytic anemia; renal dysfunction; neurologic impairment, including headaches, confusion, or even stroke and seizures; gastrointestinal symptoms such as nausea, vomiting, diarrhea, and abdominal pain; and

TABLE 3

The patient's chemistry panel

Test	Patient's value[a]	Reference range
Sodium	141 mmol/L	136–144
Potassium	**3.5 mmol/L**	3.7–5.1
Chloride	105 mmol/L	97–105
Carbon dioxide	25 mmol/L	22–30
Blood urea nitrogen	8 mg/dL	7–21
Creatinine	**0.97 mg/dL**	0.58–0.96
Glucose	**69 mg/dL**	74–99
Total protein	6.9 g/dL	6.3–8.0
Calcium	9.4 mg/dL	8.5–10.2
Total bilirubin	4.1 g/dL	3.9–4.9
Conjugated bilirubin	0.3 mg/dL	0.2–1.3
Alkaline phosphatase	56 U/L	34–123
Alanine aminotransferase	22 U/L	7–38
Aspartate aminotransferase	19 U/L	13–35
Anion gap	11 mmol/L	9–18

[a]Abnormal results are shown in bold.

TABLE 4

The patient's other blood tests

Test	Patient's value[a]	Reference range
Immunoglobulin G	1,120 g/L	717–1,411
Immunoglobulin A	279 g/L	78–391
Immunoglobulin M	123 g/L	53–334
Ferritin	159 ng/mL	14.7–205.1
Interleukin 6	< 2.2 pg/mL	< 6.0
C-creative protein	0.1 mg/L	< 0.9
Creatine kinase	122 U/L	42–196
Troponin T	< 0.010 ng/mL	0.000–0.029
D-dimer	**790 µg/mL**	< 500
Fibrinogen	**440 mg/dL**	200–400
International normalized ratio	1.3	0.9–1.3
Prothrombin time	10.3 s	9.7–13.0
Partial thromboplastin time	25.4 s	23.0–32.4
Haptoglobin	180 mg/dL	81–238
Lactate dehydrogenase	**304 U/L**	135–214
Coombs	Negative	Negative
Hepatitis B surface antigen	Negative	Negative
Hepatitis B surface antibody	**Positive**	Negative
Hepatitis B core antibody, total	Negative	Negative
Hepatitis C antibody 1A	Negative	Negative
HIV1/2 antibodies	Negative	Negative
Syphilis	Nonreactive	Nonreactive

[a]Abnormal results are shown in bold.

fever. Laboratory findings include those typically seen in hemolytic anemia, including low haptoglobin, increased lactate dehydrogenase, and an increased reticulocyte count, as well as thrombocytopenia, schistocytes on peripheral blood smear, and possibly increased creatinine with proteinuria, hematuria, or both.[2]

The PLASMIC score[3] can be used to predict the likelihood of ADAMTS13 deficiency in patients with thrombocytopenia and schistocytes. It is calculated by awarding 1 point for each of the following features, if present:

- Platelet count < 30×10^9/L
- Hemolysis (reticulocyte count > 2.5%, undetectable haptoglobin, or indirect bilirubin > 2 mg/dL)
- No active cancer
- No solid organ or stem cell transplant
- Mean corpuscular volume < 90 fL
- International normalized ratio < 1.5
- Creatinine < 2.0 mg/dL.

Patients with scores of 5 or higher should be empirically treated for thrombotic thrombocytopenic purpura with plasma exchange, as this condition can be life-threatening if untreated.[4]

Disseminated intravascular coagulation

Disseminated intravascular coagulation is a clinical syndrome in which the processes of both coagulation and fibrinolysis are inappropriately activated, leading to bleeding, clotting, or both. The coagulation and fibrinolytic processes may be inappropriately activated during sepsis or in other conditions such as pregnancy or malignancy. Typical laboratory findings include prolonged prothrombin time and partial thromboplastin time, low levels of fibrinogen, increased levels of D-dimer, and findings consistent with microangiopathic hemolytic anemias.[5,6]

Immune thrombocytopenic purpura

Immune thrombocytopenic purpura is an acquired, isolated thrombocytopenia modulated by platelet autoantibodies, with a platelet count less than 100×10^9/L.[7] It is a diagnosis of exclusion, with clinical features of thrombocytopenia ranging from petechiae, mucosal bleeding, and easy bruising to internal bleeding and hemorrhagic stroke. Other than a low platelet count, laboratory data are typically normal.

Primary immune thrombocytopenic purpura is due to production of autoantibodies against platelets, whereas the secondary form can be triggered by many different conditions, including viral illnesses and autoimmune diseases.[7,8]

Glucose-6-phosphate dehydrogenase deficiency

Glucose-6 phosphate dehydrogenase deficiency is an X-linked genetic disorder that can lead to hemolytic anemia after ingestion of certain foods or drugs. Glucose-6 phosphate dehydrogenase is an enzyme that protects red blood cells from oxidative injury, and lack of it renders red blood cells susceptible to oxidative damage. As a result, red blood cells are lysed during times of oxidative stress.[9]

Laboratory data reveal a hemolytic process,

with schistocytes and bite cells on peripheral blood smear, decreased levels of haptoglobin, and increased lactate dehydrogenase. However, platelet counts and coagulation studies are typically unaffected.[10] Therefore, this is the correct answer to the question above.

Hemolytic uremic syndrome

Hemolytic uremic syndrome is a thrombotic microangiopathy that is caused by infection with Shiga toxin-producing *Escherichia coli* and leads to acute kidney injury, hemolytic anemia, and thrombocytopenia. Clinical features typically include abdominal pain and a diarrheal illness, and laboratory data reveals a hemolytic process with increased lactate dehydrogenase and decreased levels of haptoglobin, schistocytes on peripheral blood smear, thrombocytopenia, normal ADAMTS13 levels, normal prothrombin time and partial thromboplastin time, and possibly rising creatinine, hematuria, proteinuria, and hypertension.[11]

The laboratory findings commonly seen in thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, disseminated intravascular coagulation, and immune thrombocytopenic purpura are summarized in **Table 2**.

BACK TO THE PATIENT

The patient's complete blood cell count (**Table 1**), chemistry panel (**Table 3**), and other tests (**Table 4**) excluded other differential diagnostic considerations, including thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, and other hemolytic processes. She had not received any transfusions (which would have suggested posttransfusion purpura), and she had not received any medications commonly associated with drug-induced thrombocytopenic purpura, such as beta-lactam antibiotics. A peripheral blood smear revealed thrombocytopenia and normal-appearing white and red blood cells, indicative of immune thrombocytopenic purpura (**Figure 1**).

CAUSES OF SECONDARY IMMUNE THROMBOCYTOPENIC PURPURA

2 All of the following are causes of secondary immune thrombocytopenic purpura except which one?

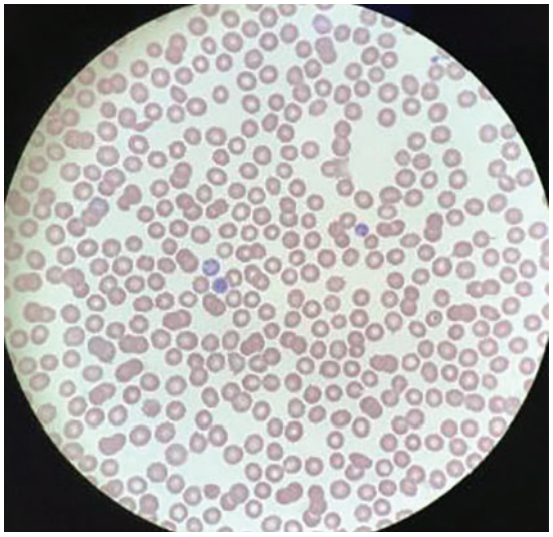

Figure 1. On the patient's peripheral blood smear, no platelets were visible.

- ☐ Human immunodeficiency virus
- ☐ Chronic obstructive pulmonary disease
- ☐ Systemic lupus erythematosus
- ☐ Hepatitis
- ☐ Chronic lymphocytic leukemia

Viral infections are often implicated in secondary immune thrombocytopenia, including hepatitis C, human immunodeficiency virus, many herpesviridae such as Epstein-Barr virus and cytomegalovirus, and others.[12,13] Autoimmune disorders such as systemic lupus erythematosus, rheumatoid arthritis, and hematologic malignancies can be implicated in immune thrombocytopenic purpura as well.

Chronic obstructive pulmonary disease, on the other hand, has not been documented as a cause of secondary immune thrombocytopenic purpura, although it can cause a reactive polycythemia as a result of chronic hypoxia.[14] Therefore chronic obstructive pulmonary disease is the correct answer.

A young woman, seemingly healthy, presents with easy bruising

AN INTERESTING AND TIMELY PLOT TWIST

A nasal swab for SARS-CoV-2—the cause of coronavirus disease 2019 (COVID-19)—was ordered, as is currently standard practice for all of our admitted patients, and her test was positive by polymerase chain reaction assay. The patient said she had no shortness of breath, cough, fevers or chills, diarrhea, anosmia, or dysgeusia on admission or in the past weeks or

TABLE 5

Reported cases of COVID-19-associated immune thrombocytopenic purpura

Case	Presenting symptoms	COVID symptoms present before or on admission?	Hospital day of decrease in platelet count	Initial platelet count (× 10^9/L)	First ITP intervention	Platelet count after first ITP intervention (× 10^9/L)	Second ITP intervention (if applicable)	Platelet count after second ITP intervention (×10^9/L)
Hindilerdin et al[22]	Easy bruising, fatigue, fever, dry cough	Yes	Day 0	10	IVIG 1 g/kg × 2 days	25	Prednisolone 1 mg/kg/day × 10 days	100
Tsao et al[23]	Rash, purple lesions in mouth, bruising	Yes	Day 0	5	IVIG 1 g/kg once	320	N/A	N/A
Artru et al[24]	Dyspnea, fever, cough, asthenia	Yes	Day 4	1	IVIG 0.4 g/kg × 5 days Dexamethasone 40 mg/day × 4 days	30	Dexamethasone 40 mg/day × 4 days	75
Bennett et al[25]	Fever, dyspnea, diarrhea, cough	Yes	Day 0	< 3	IVIG 1g/kg × 2 days	105	N/A	N/A
Levesque et al[26]	Dyspnea, dry cough, fever	Yes	Day 20	23	IVIG 1 g/kg × 2 days Dexamethasone 40 mg × 4 days	< 10	Romiplostim daily × 10 days Vincristine × 1 day Methylprednisolone 500 mg IV × 4 days	178
Murt et al[27]	Petechiae, easy bruising	Yes	Day 0	9	IVIG 2 g/kg × 2 days	54	N/A	N/A
Bomhof et al[28]								
Patient 1	Oral mucosal petechiae, spontaneous skin hematomas	Yes	Day 0	< 3	Platelet transfusion IVIG 1 g/kg × 2 days	47	Dexamethasone	51
Patient 2	Petechiae, bleeding from hemorrhoids, epistaxis	Yes	Day 0	2	Platelet transfusion Dexamethasone 40 mg daily × 4 days	2	IVIG	32
Patient 3	Fever, coughing, dyspnea	Yes	Day 12	3	N/A	N/A	N/A	N/A
Granat et al (current case)	None	N/A	0	3	Platelet transfusion Dexamethasone 40 mg × 1 day	67	Prednisone 1 mg/kg × 4 days	268

ITP = immune thrombocytopenic purpura; IVIG = intravenous immunoglobulin; N/A = not available

months. She did not need supplemental oxygen or intensive care. She said she had been compliant with mask-wearing and social distancing, but she worked for a cleaning company and had been in contact with many people and potentially contaminated surfaces.

In view of the pertinent negative findings described above and the temporal relation-

ship between her symptoms and her positive SARS-CoV-2 test, we concluded that her otherwise-asymptomatic COVID-19 was the trigger for her severe thrombocytopenia.

TREATMENT OF SEVERE SECONDARY IMMUNE THROMBOCYTOPENIA

3 All of the following are treatment options for severe secondary immune thrombocytopenic purpura except which one?

- ☐ Glucocorticoids
- ☐ Intravenous immunoglobulin
- ☐ Rituximab
- ☐ Splenectomy
- ☐ Plasma exchange

First-line treatment for severe secondary immune thrombocytopenia includes glucocorticoids, intravenous immunoglobulin, or both. Both are thought to interfere with destruction of platelets.[15] An additional first-line treatment is anti-D immunoglobulin. Second-line treatments include thrombopoietin receptor agonists, splenectomy, and rituximab.[16]

Plasma exchange is considered a first-line treatment for thrombotic thrombocytopenic purpura and serves to replace the deficient ADAMTS13 molecule. However, it is not typically used to treat immune thrombocytopenic purpura,[16] and therefore this is the correct answer.

BACK TO THE PATIENT

In the emergency department, the patient received 1 dose of dexamethasone 40 mg and 2 units of platelets. She was admitted to the hospital for 2 days, during which she received 2 doses of oral prednisone 1 mg/kg/day. She was discharged home on the third day with instructions to take an additional 2 doses of prednisone 1 mg/kg/day. A repeat complete blood count after she finished her course of steroids, 5 days after her initial presentation, revealed a platelet count of 268 × 10^9/L.

HEMATOLOGIC COMPLICATIONS OF COVID-19

The thrombotic complications of COVID-19 have been well documented.[17–20] Thrombocytopenia can occur with COVID-19 by various mechanisms, including disseminated intravascular coagulation and sepsis.[21]

In addition, there have been multiple case reports of COVID-19–induced severe secondary thrombocytopenia (**Table 5**).[22–28] The patients all had typical symptoms of COVID-19 such as cough, fever, or shortness of breath. The timing of thrombocytopenia varied, with some patients developing it early in their hospital course and others developing it days after admission. All patients, excluding 1 who died shortly after developing thrombocytopenia, were treated with intravenous immunoglobulin, corticosteroids, or both, with hematologic recovery in all reported cases. To our knowledge, however, ours is the first documented case of a SARS-CoV-2–positive patient presenting with symptomatic severe thrombocytopenia but no COVID-19 symptoms.

This patient's experience further reveals that SARS-CoV-2 can cause severe secondary immune thrombocytopenia, and is unique in showing that thrombocytopenia can be the sole presenting disorder in COVID-19. Hematologic monitoring of COVID-19 patients is becoming increasingly important, especially with respect to hypercoagulable complications,[29] but attention must also be directed to platelet counts. Conversely, patients presenting with isolated thrombocytopenia should be screened for SARS-CoV-2 infection. ■

Her platelet count: 3 × 10^9/L (reference range 150–400)

DISCLOSURES

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

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A 21-year-old woman with Ehlers-Danlos syndrome and persistent lightheadedness

A 21-year-old woman presents with positional lightheadedness when going from supine to sitting or standing, which is associated with prominent heart palpitations without any overt syncope. She has experienced the symptoms for several years, but the frequency has progressively increased from a few times a month to many times a day. Also, she has a history of unexplained gastrointestinal symptoms including bloating, nausea, and cramping.

Her medical history includes diagnoses of hypermobile (type 3) Ehlers-Danlos syndrome and autoimmune-mediated hypothyroidism, for which she takes oral levothyroxine daily. She had been smoking 1 pack of cigarettes per day for the past 3 years but stopped 2 months ago. She denies using alcohol or recreational drugs.

PHYSICAL EXAMINATION

Sitting, her blood pressure is 106/66 mm Hg and her pulse is 87 beats per minute and regular. Three minutes after standing, these values are 91/69 mm Hg and 115 beats per minute. Her respiratory rate is 16 breaths per minute, and her oral temperature is 36.8 °C (98.3 °F).

She has no thyromegaly or carotid bruits. On auscultation, her lungs are clear and heart sounds are normal without any murmur. Her abdomen is soft and nontender to palpation. Her extremities are warm, without edema, and have equal, palpable peripheral pulses. The neurologic examination is normal. The musculoskeletal examination is significant for global hypermobility in her joints.

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PREVIOUS TEST RESULTS

An electrocardiogram a few months before her visit showed normal sinus rhythm, and a transthoracic echocardiogram showed normal cardiac chamber dimensions and biventricular systolic function, a normal mitral valve with trivial regurgitation, and normal ascending aorta dimensions. A 30-day cardiovascular event monitor recorded numerous symptomatic episodes of palpitations and lightheadedness, all of which were associated with sinus tachycardia of varying rates. Her thyroid-stimulating hormone level is 1.91 mIU/L (reference range 0.47–4.68 mIU/L).

For several years, a 21-year-old woman has had lightheadedness upon standing, and it is getting worse

WHAT'S CAUSING HER LIGHTHEADEDNESS?

1 Which of the following is the most likely cause of this patient's symptoms?

- ☐ Postural orthostatic tachycardia syndrome (POTS)
- ☐ Orthostatic hypotension
- ☐ Inappropriate sinus tachycardia
- ☐ Atrial or ventricular arrhythmia

Our patient has nonspecific symptoms, so the differential diagnosis is broad and could include any of those disorders.

Postural orthostatic tachycardia syndrome

POTS is commonly characterized by an exaggerated heart rate response without significant orthostatic hypotension in the absence of re-

versible causes such as medications, anemia, or thyroid dysfunction.[1] It occurs predominantly in women of childbearing age (ages 15–50).

Presenting symptoms are usually nonspecific, such as lightheadedness, blurred vision, palpitations, headache, and nausea.[2] The syndrome can be associated with several other diseases, including hypermobile Ehlers-Danlos syndrome, an inherited collagen disorder characterized by joint hypermobility. Because of this association, any patient with hypermobile Ehlers-Danlos syndrome and with nonspecific symptoms should be assessed for POTS.

Studies suggest that there is a higher prevalence of POTS in patients with hypermobile Ehlers-Danlos syndrome and that patients with POTS start to experience symptoms at an earlier age if they have a hypermobility syndrome.[3–6] Rowe et al[3] were the first to report an association between POTS and a joint hypermobility syndrome, in 1999. Wallman et al[4] found that the hypermobile Ehlers-Danlos syndrome is more prevalent in patients with POTS (18%) than in the general population (0.02%). Gazit et al[5] reported that 21 of 27 patients with the syndrome had abnormal autonomic manifestations, such as POTS, orthostatic hypotension, or uncategorized orthostatic intolerance. Kanjwal et al[6] found that POTS tends to present at an earlier age in patients with a hypermobile syndrome.

POTS symptoms are usually nonspecific: lightheadedness, blurred vision, palpitations, headache, and nausea

The difference between patients with POTS and hypermobile Ehlers-Danlos syndrome vs those with POTS related to other causes is unclear. However, patients with the syndrome use more healthcare resources, including practitioner evaluations for chronic pain and medications, than those without the syndrome.[7]

This patient's young age, symptoms, and diagnosis of hypermobile Ehlers-Danlos syndrome raise suspicion of POTS and make it the most likely diagnosis. However, POTS can be self-limited or follow a relapsing-remitting pattern over several years, which can make it difficult to diagnose.

Orthostatic hypotension

The classic orthostatic hypotension symptom is a significant drop in blood pressure when standing up from sitting or lying down. The consensus definition is a fall in systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of at least 10 mm Hg within 3 minutes of standing. Orthostatic hypotension can be symptomatic or asymptomatic. It has a higher prevalence in patients over age 70 and is usually associated with other disorders such as diabetes mellitus, Parkinson disease, pure autonomic failure, and multiple system atrophy.[8–10]

This patient's lack of orthostatic blood pressure drop, young age, and absence of associated comorbidities makes this diagnosis less likely.

Inappropriate sinus tachycardia

This syndrome is defined as sinus tachycardia of more than 100 beats per minute at rest with a mean 24-hour heart rate of more than 90 beats per minute that is not due to primary causes. It is often associated with distressing palpitation symptoms.

Inappropriate sinus tachycardia is induced by both physiologic and emotional stresses; however, POTS is induced only by orthostasis. Use of a 24-Holter monitor can confirm inappropriate sinus tachycardia.

Although there may be an overlap between POTS and inappropriate sinus tachycardia, the latter is not likely in this patient because her resting heart rate was not more than 100 beats per minute, a diagnostic requirement of the syndrome.

Atrial or ventricular arrhythmia

Atrial or ventricular arrhythmias can cause syncope or near-syncope. These are broad categories that can include ventricular tachycardia, sinoatrial node dysfunction, atrioventricular node block, and atrial arrhythmias such as supraventricular tachycardia, fibrillation, or flutter.

This patient had normal sinus rhythm, and her 30-day event monitor showed no arrhythmias, making an atrial or ventricular cardiac arrhythmia unlikely.

WHAT ABOUT HER EHLERS-DANLOS SYNDROME?

2 What is the inheritance pattern of hypermobile Ehlers-Danlos syndrome?

- ☐ Autosomal dominant
- ☐ Autosomal recessive
- ☐ X-linked dominant

Autosomal dominant

Although the gene or genes responsible for this syndrome have not been identified, it appears to follow an autosomal dominant pattern of inheritance.[11]

Autosomal recessive

Other clinical subtypes of the Ehlers-Danlos syndrome, including classic, cardiac-valvular, dermatosparaxis, kyphoscoliotic, spondylodysplastic, and musculocontractural, follow an autosomal recessive pattern of inheritance; however, the hypermobile Ehlers-Danlos syndrome subtype does not.[12]

X-linked dominant

None of the clinical subtypes follow an X-linked dominant inheritance in the 2017 diagnostic criteria. The X-linked Ehlers-Danlos syndrome with muscle hematoma is no longer included in the syndrome spectrum.[12]

BACKGROUND ON EHLERS-DANLOS SYNDROME CLASSIFICATIONS

Hypermobile is only 1 category of Ehlers-Danlos syndrome, albeit the most common. In the late 1960s, the Ehlers-Danlos syndrome was classified into 5 distinct subtypes.[13,14] In 1986, an international workshop held in Berlin on classification (nosology) of inherited connective tissue diseases identified 11 subtypes of Ehlers-Danlos syndrome based on the inheritance patterns and phenotypic presentation.[15] A significant portion of their diagnostic criteria was based on subjective assessment and, thus, is not very reliable.

Improved understanding of the molecular basis for Ehlers-Danlos syndrome led to the 1997 Villefranche revised nosology, which classified the syndrome into 6 subtypes.[16] The major diagnostic criteria for the hypermobile Ehlers-Danlos syndrome subtype were generalized joint hypermobility and skin involvement. Minor diagnostic criteria included recurring joint dislocations, chronic joint or limb pain, and a positive family history. Joint hypermobility should be assessed using the Beighton scoring system, with hypermobility defined as a score of 5 of 9 or greater.[16]

Date of her diagnosis important

This patient was evaluated by a rheumatologist in 2016, found to have a 7 of 9 Beighton score, and diagnosed with hypermobile Ehlers-Danlos syndrome based on the Villefranche nosology criteria. In 2017, the International Consortium published new diagnostic criteria for Ehlers-Danlos syndrome that identified 13 unique subtypes.[12] These criteria include extra-articular features and more strict diagnostic criteria for the hypermobile Ehlers-Danlos syndrome.

In a recent study by Miller et al[17] that looked at the prevalence of hypermobile Ehlers-Danlos syndrome in patients with POTS, only 19 (56%) of 32 patients who self-reported a hypermobile Ehlers-Danlos syndrome diagnosis met the 2017 diagnostic criteria. Therefore, it is always important to confirm a self-reported diagnosis using the new criteria.

We know that this patient was diagnosed according to the Villefranche criteria, but we don't know whether the diagnosis was updated using the 2017 criteria. That may not matter, because the new criteria have been criticized for being too restrictive. McGillis et al[18] reported that the 2017 diagnostic criteria leave many highly symptomatic patients without a diagnosis. Further, the newest diagnostic criteria have not been validated and, thus, require refinement to improve their diagnostic accuracy.

CASE CONTINUED: DIAGNOSING POTS

Comorbidities usually associated with hypermobile Ehlers-Danlos syndrome include chronic pain, gastrointestinal dysfunction,[19] orthostatic intolerance, and POTS.[20] Voermans et al[21] reported that 29 (73%) of 40 patients with Ehlers-Danlos syndrome had myalgia continuously or frequently after exercise.

Our patient has gastrointestinal symptoms including bloating, nausea, and cramping. She also has chronic generalized pain that has required multiple emergency department visits. At this point, POTS is still the most likely diagnosis of her lightheadedness.

Comorbidities associated with hypermobile Ehlers-Danlos syndrome: chronic pain, gastrointestinal dysfunction, orthostatic intolerance, and POTS

3 Which of the following is the most appropriate test to diagnose POTS?

- ☐ Tilt-table testing
- ☐ 24-hour ambulatory blood pressure recording
- ☐ Plasma norepinephrine measurement

Tilt-table testing

The correct answer is tilt-table testing. The diagnostic criteria for POTS include at least 3 months of symptoms that increase on standing and improve when lying down, plus either a heart rate increase of more than 30 beats per minute or a sustained heart rate of at least 120 beats per minute, and a nonsignificant drop in blood pressure (< 20/10 mm Hg).[22] Children and adolescents can have a slightly higher physiologic range and require a heart rate increase of more than 40 beats per minute for the diagnosis.[1] Tilt-table testing is the definitive test, as it is done in a controlled setting with few variables that may alter the accuracy of results.[23]

24-hour ambulatory blood pressure recording

A 24-hour ambulatory blood pressure recording is not the correct test, as it would not be helpful in the evaluation of POTS. In order to diagnose POTS, we need a diagnostic test that evaluates changes in heart rate and blood pressure in both the supine and upright positions in a controlled setting—like the tilt-table test.

Plasma norepinephrine measurement

A hyperadrenergic variant form of POTS has been defined as an increase in plasma norepinephrine levels at rest and on standing (serum norepinephrine level ≥ 600 pg/mL). This would not be the initial test for evaluating patients with suspected POTS because the sensitivity and specificity of this test are not clear for POTS.

She experienced gradual improvement in her symptoms and quality of life

Back to the patient

Our patient underwent tilt-table testing. Her baseline heart rate was 84 beats per minute in sinus rhythm and her blood pressure was 114/74 mm Hg. She was then moved to a 70% tilt position. Immediate upright vital signs were heart rate 113 beats per minute and blood pressure 105/77 mm Hg. She was kept in the head-up tilt position for a total of 30 minutes. During this time, vital signs were monitored every 1 minute. The patient reported symptoms of lightheadedness, extreme fatigue, difficulty catching breath, and weakness during this 30-minute period. Her heart rate ranged from a low of 106 beats per minute and a high of 152 beats per minute. It increased to 120 beats per minute at 3 minutes upright and stayed 120 to 150 beats per minute for the remainder of upright positioning. She had no significant fall in blood pressure during tilting. After resuming the supine position, the patient had immediate recovery of heart rate at 86 beats per minute with blood pressure of 109/64 mm Hg. In addition, all her symptoms resolved. Therefore, our patient had a positive tilt-table test for POTS.

MANAGING POTS

4 Which of the following is the most appropriate initial step in managing POTS for this patient?

- ☐ Nonpharmacologic treatment and lifestyle modifications
- ☐ Start a beta-blocker
- ☐ Start midodrine
- ☐ Start pyridostigmine

Nonpharmacologic treatment and lifestyle modifications

Nonpharmacologic treatment should be used first.[1] Management should aim at withdrawing medications that might worsen POTS, avoiding dehydration, increasing fluid intake (up to 2 L per day), increasing daily salt intake (up to 3–5 g), wearing waist-high compression stockings to decrease venous pooling, and engaging in aerobic and some resistance exercises involving the legs and abdomen.[1,6]

Pharmacologic therapy

Usually, multiple approaches are needed to treat patients with POTS. Several medications are used off-label, including fludrocortisone, beta-blockers, midodrine, clonidine, methyldopa, and pyridostigmine. The choice of therapy should be based on clinical expertise and patient tolerance or response.

We counseled our patient about lifestyle modifications and gradually started her on fludrocortisone, a beta-blocker in a low dose, and pyridostigmine. She experienced gradual improvement in her symptoms and quality of life.

DISCLOSURES

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

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Reversal of direct oral anticoagulants: Highlights from the Anticoagulation Forum guideline

ABSTRACT

The 2019 guideline from the Anticoagulation Forum provides clear instructions on how to use 2 agents for reversing the effects of direct oral anticoagulants (DOACs): idarucizumab for dabigatran-associated bleeding and andexanet alfa for bleeding associated with rivaroxaban and apixaban. The guideline also discusses off-label use of andexanet alfa for bleeding associated with edoxaban and betrixaban and the use of hemostatic agents such as activated prothrombin complex concentrate and 4-factor prothrombin complex concentrate. Lastly, it offers approaches for building and managing stewardship programs at the health system level.

KEY POINTS

- DOACs offer many advantages over warfarin.
- The number of patients treated with DOACs is increasing, as are rates of major and life-threatening DOAC-associated bleeding.
- Clear guidelines for the reversal of DOAC-associated bleeding are needed.
- Reversal agents are now commercially available and have demonstrated their ability to reverse the effects of DOACs.
- These agents are expensive and pose some thrombotic risk—thus the need for comprehensive reversal guidelines.

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Direct oral anticoagulants (DOACs) include dabigatran, which is a direct thrombin (factor IIa) inhibitor, and 4 direct factor Xa inhibitors: rivaroxaban, apixaban, edoxaban, and betrixaban. These agents have a number of approved indications, including prevention of systemic embolization and stroke in patients with nonvalvular atrial fibrillation, preventing and treating venous thromboembolism, and secondary prevention of arterial ischemic conditions in chronic coronary arterial disease and peripheral artery disease (**Table 1**).

Many clinical trials have shown DOACs to be noninferior to warfarin, and they offer many advantages over warfarin. They are associated with less intracranial bleeding, do not require routine blood monitoring, have fewer dietary and drug interactions, and have predictable pharmacokinetics with rapid onset of action.[1–3] Because they have short half-lives, they do not need bridging (ie, substitution of a shorter-acting agent) before surgical procedures for which anticoagulation must be interrupted, thereby significantly simplifying periprocedural planning.[4,5]

Since the number of patients treated with DOACs is increasing, major and life-threatening DOAC-associated bleeding has also been on the rise.

ANTICOAGULATION FORUM GUIDELINE

A 2019 guideline from the Anticoagulation Forum[6] provides clear instructions on how to manage DOAC-associated bleeding.

TABLE 1

Approved indications for direct oral anticoagulants

	Nonvalvular atrial fibrillation	Treatment of deep vein thrombosis or pulmonary embolism	Prevention of deep vein thrombosis in total knee replacement	Prevention of deep vein thrombosis in total hip replacement	Prevention of deep vein thrombosis in medically ill	Coronary artery disease or peripheral artery disease
Apixaban	Yes	Yes	Yes	Yes	No	No
Betrixaban	No	No	No	No	Yes	No
Dabigatran	Yes	Yes	No	Yes	No	No
Edoxaban	Yes	Yes	No	No	No	No
Rivaroxaban	Yes	Yes	Yes	Yes	No	Yes

Intended audience for the guideline

General practice, hematology, anticoagulation clinics, emergency, cardiovascular, surgical, and intensive care providers.

Authors of the guideline

The authors of the guideline are associated with the Anticoagulation Forum (acforum.org) and are recognized experts in the field. Conflicts of interest were disclosed when present.

Process used for writing the guideline

The unanimous consensus of all authors was determined for each question addressed. The authors conducted a PubMed search related to each key question by prioritizing studies involving patient-reported bleeding, thromboembolism, and mortality. In addition, they reviewed supplemental material of studies cited, US Food and Drug Administration (FDA) package inserts, and www.clinicaltrials.gov and also manually reviewed references.

MAIN RECOMMENDATIONS OF THE GUIDELINES

Available reversal agents

Two FDA-approved target-specific reversal agents are now commercially available.

Idarucizumab is a humanized monoclonal antidabigatran antibody fragment approved for reversing dabigatran-associated bleeding.[7]

Andexanet alfa is a modified recombinant inactive form of human factor Xa that binds to and blocks the effects of factor Xa inhibitors. It is approved for reversal of apixaban and rivaroxaban in cases of bleeding.[8] However, its use to reverse the effects of edoxaban and betrixaban is currently off-label, as larger studies are still needed to determine its efficacy and safety for this use.

Off-label use of hemostatic agents. The guideline also includes suggestions for off-label use of hemostatic agents such as activated prothrombin complex concentrate (APCC) for dabigatran-associated bleeding[8] and 4-factor prothrombin complex concentrate (4FPCC) for direct factor Xa inhibitor-associated bleeding.[9,10]

APCC contains a balanced ratio of the zymogen forms of factors II, VII, IX, and X (which are procoagulants); protein C (an anticoagulant); and tissue factor pathway inhibitor, cofactors V and VIII, and protein S.[9] In a prospective study,[10] it was associated with good hemostasis and no thromboembolic events.

4FPCC, which contains factors II, VII, IX, and X; proteins C and S; antithrombin III; and human albumin, can be considered for reversing direct factor Xa inhibitor-associated bleeding. However, in 2 studies,[11,12] 4FPCC

A 2019 guideline provides clear instructions on how to manage DOAC-associated bleeding

TABLE 2

When to give high vs low dose andexanet alfa infusion

Drug	Last dose	Time from last dose: < 8 hours or unknown	Time from last dose: ≥ 8 hours
Apixaban	≤ 5 mg	Low dose[a]	Low dose
	> 5 mg or unknown	High dose[b]	Low dose
Rivaroxaban	≤ 10 mg	Low dose	Low dose
	>10 mg or unknown	High dose	Low dose

[a]Low dose: 400 mg intravenous bolus at a target rate of 30 mg/minute, followed by 4 mg/minute for up to 120 minutes.
[b]High dose: 800 mg intravenous bolus at a target rate of 30 mg/minute, followed by 8 mg/minute for up to 120 minutes.

The Joint Commission will require healthcare systems to have protocols for managing DOAC-related bleeding

was associated with ischemic stroke and thromboembolic events. Therefore, caution is needed when using this agent.

Supportive care should be considered in all cases of bleeding associated with DOACs. This includes stopping the DOAC, applying local hemostasis, transfusing red blood cells and platelets, and volume resuscitation.

Indications for reversal agents

The guideline does not recommend routinely using reversal agents for DOAC overdose, but strongly recommends using them only in cases of the following:

- Life-threatening bleeding
- Bleeding into critical organs
- Other major bleeding not controlled with maximal support measures (stopping the anticoagulant or other medications that prolong bleeding, compression or procedures to stop the bleeding at the bleeding site, volume resuscitation, or transfusion)
- Concerns or reasonable expectation that there is a clinically relevant plasma DOAC level
- Urgent invasive procedures in DOAC-treated patients, including cardiac, vascular, and neurosurgical emergency surgeries that need to be performed to save limbs, organs, or the life of the patient.[13]

Dosage

The guideline recommends the following in cases of major bleeding or to reverse anticoagulation for urgent procedures:

If the patient is taking dabigatran, give idarucizumab 5 g intravenously. If idarucizumab is not available, the alternative is APCC 50 units/kg intravenously (off-label use).

If taking rivaroxaban in doses of 10 mg or less or if the last dose of rivaroxaban was taken 8 or more hours ago, initiate andexanet alfa in a low dose, ie, 400 mg intravenous bolus at a target rate of 30 mg/minute followed by continuous infusion at 4 mg/minute for up to 120 minutes.

If the amount or time of the last dose is unknown or if it was more than 10 mg less than 8 hours ago, initiate high-dose andexanet alfa, ie, 800 mg intravenous bolus at a rate of 30 mg/minute followed by continuous infusion at 8 mg/minute for up to 120 minutes. If andexanet alfa is not available, the recommended alternative is 4FPCC 2,000 units intravenously (**Table 2**).

If taking apixaban in doses of 5 mg or less or if the last dose of apixaban was taken 8 or more hours ago, initiate low-dose andexanet alfa (400 mg intravenous bolus at a target rate of 30 mg/minute followed by continuous infusion at 4 mg/minute for up to 120 minutes). If the time or amount is unknown or the last dose was more than 5 mg and less than 8 hours ago, initiate high-dose andexanet alfa (800 mg intravenous bolus at a rate of 30 mg/minute followed by continuous infusion at 8 mg/minute for up to 120 minutes) (**Table 2**). If andexanet alfa is not available, the recommended alternative treatment is 4FPCC 2,000 units intravenously.

If taking edoxaban or bextrixaban, give andexanet alfa 800 mg intravenous bolus followed by continuous infusion of 8 mg/minute for up to 120 minute (off-label use) or 4FPCC 2,000 units intravenously (**Table 3**).

Concerns

The specific reversal agents that are available for dabigatran and anti-Xa inhibitors are of clear clinical benefit, as outlined above. However, the Anticoagulation Forum guideline expresses concern over the high cost of DOAC reversal agents, which may limit their availability. In addition, there is a risk of thrombosis associated with 4FPCC and andexanet alfa. Arterial and venous thrombosis, myocardial infarction,

TABLE 3

Reversal agents for dabigatran-, edoxaban- and betrixaban-related major bleeding or a required urgent procedure

DOAC	Reversal agent dosing
Dabigatran	Idarucizumab 5 g intravenously (IV) If idarucizumab is not available, the alternative treatment recommended is activated prothrombin complex concentrate 50 units/kg IV (off-label use)
Edoxaban, betrixaban	Andexanet alfa 800 mg IV bolus at 30 mg/minute followed by continuous infusion of 8 mg/minute for up to 120 minutes (off-label use) or 4-factor prothrombin complex concentrate 2,000 units IV

ischemic stroke, cardiac arrest or sudden death were observed within 3 to 30 days post administration of 4FCC[11] and andexanet alfa[8] (median time to the first event was 7 days).

With idarucizumab treatment, rates of thrombotic events (venous thromboembolism, ischemic stroke, myocardial infarction, and systemic embolism) were 4.8% at 30 days and 6.8% at 90 days. However, the study reported that events at 30 days may have been caused by the low level of restarting anticoagulation treatment. Thrombotic events at 90 days were likely associated with the underlying prothrombotic medical conditions rather than idarucizumab treatment.[7]

With APPC treatment, there were no thrombotic events reported.[10] However, postmarketing surveillance reported thromboembolic events especially after high doses and in patients with thromboembolic risk factors.[14]

Therefore, the benefit of reversing anticoagulation therapy must be carefully weighed against the risk of thromboembolic events. Proper anticoagulation should be resumed once the risk of thromboembolism outweighs the risk of bleeding. The patient should be monitored for possible thromboembolic events during and after the administration of a reversal agent.

Stewardship programs

Finally, the guideline authors recommend that health systems focus on building a stewardship program to address challenging DOAC reversal cases appropriately. Most of the potential challenges can be placed into the categories of acquisition and cost, operational logistics, and appropriate utilizations. A stewardship team dedicated to developing, implementing, and maintaining system-wide processes and protocols pertaining to optimal utilization of DOAC reversal agents has been shown to be effective in overcoming these challenges.

DIFFERENCES WITH EARLIER GUIDELINES, AND EXPECTED CLINICAL IMPACT

The Anticoagulation Forum guideline provides a rational, systematic, clinical approach for treating DOAC-associated bleeding with idarucizumab and andexanet alfa. Before it was published, 2 pivotal guidelines discussed anticoagulant reversal strategies, 1 from the American College of Cardiology in 2017[4] and the other from the European Heart Rhythm Association in 2018.[13]

In 2 studies, 4FPCC was associated with ischemic stroke and thromboembolic events

Newer agent. These two guidelines were published before the FDA approved andexanet alfa and therefore did not contain comprehensive dosing information and recommendations on using it in reversing the effects of DOACs. Despite this difference, they offer valuable clinical information that supplements the Anticoagulation Forum guideline.

Laboratory tests. The American College of Cardiology paper,[4] which covered all oral anticoagulants, including warfarin, discussed using various laboratory tests to determine the anticoagulant levels. These laboratory tests included:

- Dilute thrombin time, ecarin clotting time, or ecarin chromogenic assay. A prolonged time or elevated assay suggests possible dabigatran overdose.

TABLE 4

Dosing of antifibrinolytic agents

Tranexamic acid	1–1.5 g orally every 8–12 hours for duration of bleeding
	10-20 mg/kg intravenous (IV) bolus followed by 10 mg/kg IV every 6–8 hours for major bleeding, hemophilic bleeding, or after major trauma
	Longer intervals for renal insufficiency
Epsilon-aminocaproic acid	3 g orally 3–4 times per day
	2 g IV every 6 hours or 1 g IV every hour, depending on the urgency
Desmopressin	0.3 µg/kg subcutaneously
	0.3 µg/kg IV in 50 mL of normal saline over 15–30 minutes

Information from reference 17.

- Chromogenic anti-Xa assay. Absence of chromogenic anti-Xa activity indicates a possible absence of clinically relevant apixaban, rivaroxaban, or edoxaban levels.
- Activated partial thromboplastin time. Prolonged time suggests a possible overdose.
- Prothrombin time. Prolonged prothrombin time suggests a possible overdose of apixaban, rivaroxaban, or edoxaban.

Special populations. The European Heart Rhythm Association's guideline[13] contained important clinical information on the use of DOACs in special patient populations such as fragile and older patients, patients with extreme body weights, and patients with epilepsy and malignancy.

Other agents. Additionally, unlike the US guidelines, the European guideline[13] supports diuresis with intravenous fluids for dabigatran overdose and antifibrinolytic agents in the setting of non–life-threatening major bleeding.

Hospital protocols. As DOACs become more widely prescribed, health systems will need to establish comprehensive evidence-based practice guidelines in anticoagulation management that includes reversal strategies. As of July 1, 2019, The Joint Commission on Accreditation of Healthcare Organizations will require health systems to have approved evidence-based practice protocols for the reversal of anticoagulation and the management of bleeding events related to each anticoagulant medication.[15] The Anticoagulation Forum guideline will serve as a valuable tool for meeting the Joint Commission's National Patient Safety Goal for anticoagulant therapy (NPSG.03.05.01).

Antifibrinolytic agents have advantages such as low cost, availability, and low risk of thrombosis

OTHER SOCIETIES' RECOMMENDATIONS

Antifibrinolytic agents

In view of concerns about costs and side effects associated with reversal agents, some experts suggest using antifibrinolytic agents such as tranexamic acid and epsilon-aminocaproic acid for major bleeding (including life-threatening bleeding) and less serious bleeding with other comorbidities.[16] The use of antifibrinolytic agents was also recommended by the 2018 European Heart Rhythm Association guideline[13] and by *UpToDate*.[17] The advantages of these agents are their lower cost and ready availability, with minimal risk of thrombosis.

In addition to these agents, desmopressin can be used in settings of impaired platelet function associated with uremia or antiplatelet agents.[15] Dosing of desmopressin is 0.3 µg/kg subcutaneously, or intravenously in 50 mL of normal saline over 15 to 30 minutes (**Table 4**).[17] Only 2 doses are recommended due to concerns for tachyphylaxis and hyponatremia.[15]

A limitation of antifibrolytic agents is the lack of good quality clinical studies. However, a multicenter randomized clinical trial is currently enrolling patients to evaluate tranexamic acid for DOAC-associated intracerebral hemorrhage (ClinicalTrials.gov identifier NCT02866838).

There is also promising research on ciraparantag (PER977), which is a universal antidote for direct thrombin factor Xa inhibitors and heparinoids.[18]

SUMMARY

In summary, the Anticoagulation Forum guideline provides clear instructions on the use of 2 reversal agents, idarucizumab and andexanet alfa, for dabigatran-associated bleeding and direct factor Xa inhibitor-associated bleeding, respectively. The guideline also discusses the use of prohemostatic agents such as APPC and 4FPPC if idarucizumab and andexanet alfa are not available. Although it does not discuss the use of antifibrinolytic agents, it offers strategies for establishing and managing anticoagulation stewardship programs at the health system level.

DISCLOSURES

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Oral immunotherapy: The answer to peanut allergy?

ABSTRACT

Peanut and tree-nut allergies have increased dramatically in prevalence, especially in children. Historically, children with food allergies have been treated through strict avoidance of the allergen. Recently, an oral preparation of peanut allergen (Palforzia) was approved for immunotherapy (ie, desensitization) in children 4 to 17 years old. This article reviews oral immunotherapy and its role in children with peanut allergies.

KEY POINTS

Peanut allergy is the most common food allergy in children.

A peanut-allergen powder is the first product approved by the US Food and Drug Administration for the treatment of childhood peanut allergy.

This product is given in a 3-phase oral protocol that gradually increases the dose to desensitize the patient to peanuts.

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Food allergies affect 32 million Americans, including roughly 1 in 13 children or 2 in every average-size American classroom.[1,2] In a recent survey,[3] approximately 38% of 4,075 respondents, both children and adults, reported having at least 1 food-related allergic reaction per year.

Many food allergies are first diagnosed when the patient is a young child. The most common food allergy in children is peanut and tree-nut allergy, estimated to affect 1 million children, and its prevalence more than tripled between 1997 and 2008.[4] Peanut allergy is also the most common cause of severe food-associated anaphylaxis.

Risk factors for peanut allergy include severe atopic dermatitis, egg allergy in infancy, a family history of peanut allergy, and a personal or family history of atopy.[5,6] The higher risk of familial peanut allergy may be in part related to delayed and reluctant introduction of peanuts to siblings of peanut-allergic children. Recent research suggests that delayed introduction of peanut into the diet is linked to higher rates of peanut allergies.[4,7] The Learning Early About Peanut Allergy trial showed that introducing peanuts to children at age 4 to 11 months decreased the risk of developing a peanut allergy in children at high risk.[8] Once patients develop peanut allergy, only 20% to 25% develop tolerance; most maintain their allergy for life.[9]

A NEW TREATMENT OPTION

Treatment of peanut allergy has been largely limited to educating patients and families about ingredient labeling and recommending complete avoidance of peanuts. Anaphylaxis caused by exposure to an allergen requires im-

TABLE 1

Protocol for the peanut-derived oral immunotherapy agent

Phase	Duration	Dosage
Dose-escalation	Single day	5 levels: 0.5, 1, 1.5, 3, and 6 mg; increasing doses every 20–30 minutes
Up-dosing	Months	11 levels: 3, 6, 12, 20, 40, 80, 120, 160, 200, 240, and 300 mg daily; increasing doses at visits every 2 weeks
Maintenance	Months to years	300 mg daily

Adapted from information in reference 15.

mediate treatment with epinephrine.

Oral immunotherapy is an emerging option offered by a limited number of allergists and immunologists. Although this therapy has shown some efficacy for food allergy desensitization, it has been criticized for lacking established protocols, having high rates of adverse reactions, and using grocery store products that may contain variable amounts of the allergenic proteins.[10,11]

In January 2020, the US Food and Drug Administration (FDA) approved a novel peanut-derived oral immunotherapy product for treating childhood peanut allergy: Palforzia (peanut *Arachis hypogaea* allergen powder-dnfp). Containing a powder derived from roasted peanuts packaged in capsules or sachets at varying doses, it is indicated for use in children 4 to 17 years old. The capsule or sachet is not swallowed. Instead, it is opened, and the powder is mixed with applesauce, pudding, or something similar. It is given in dosing phases according to an oral immunotherapy protocol.

GRADUALLY INCREASING DOSES

Oral immunotherapy is based on the concept of desensitization, exposing the patient to gradually increasing doses of a specific allergen to induce tolerance and raise the threshold that triggers a reaction. Over time, this process desensitizes the immune system to the allergen so that the symptoms that occur on exposure are less severe or cease altogether.

Whereas oral immunotherapy uses oral ingestion of antigenic proteins to promote physiologic changes that suppress an allergic response to the antigen, desensitization to other allergens is done by various other routes, including the subcutaneous (the most common example being environmental allergen immunotherapy or "allergy shots"), sublingual, and epicutaneous routes.

Although its mechanisms are not completely understood, oral immunotherapy works primarily through allergen activation of dendritic cells in the gut mucosa, resulting in effector cell modulation. This inhibits immunoglobulin E-dependent mast cell and basophil activation, mitigating the ability of an allergen to elicit an allergic response. During desensitization, T-regulatory cell function is increased while antigen-specific T-helper 2 (Th2) cells become apoptotic and anergic.[12]

A 3-phase protocol

A typical oral immunotherapy protocol[13–15] proceeds in 3 phases: initial dose escalation, up-dosing or buildup, and maintenance **(Table 1)**.[15] Some protocols also use an oral food challenge at the beginning and end of the study, sometimes after a period of avoidance of the study drug.

Treatment of peanut allergy has consisted of education, avoidance, and epinephrine

The dose-escalation phase typically lasts 1 day and starts at a very small, subthreshold dose of the allergen. This dose is increased to the goal dose for that day or the highest dose tolerated without symptoms. Labeling recommendations for the peanut immunotherapy agent are to begin at 0.5 mg and increase the dose every 20 to 30 minutes up to 6 mg **(Table 1)**.[15] This phase requires close patient monitoring in a healthcare facility by a practitioner trained to manage potentially severe allergic reactions, including anaphylaxis. Patients need to be observed for at least 60 minutes after the last dose.

Up-dosing phase. After the dose-escalation phase, patients continue to take the high-

est dose that they achieved, at home, once a day, until the first up-dosing phase appointment. For the peanut-allergen product, this needs to be within 4 days.

At each up-dosing appointment, the patient receives a higher dose and is then observed for reactions. If all goes well, the patient continues to take the higher dose every day at home until the next appointment, typically at 2-week intervals, until the goal dose or the highest tolerated dose is reached. This is the maintenance dose. At this dose, the patient has achieved desensitization and can maintain allergen hyporesponsiveness during regular ingestion of food.

Of importance: patients need to take their medicine every day. Even brief dosing interruptions—just a few days—can result in loss of desensitization, and patients can have a hypersensitivity reaction to a previously tolerated dose of the allergen.

For the peanut oral immunotherapy agent, the up-dosing phase has 11 levels, starting at 3 mg/day and increasing every 2 weeks until the patient reaches 300 mg/day. Each new dose level is administered under supervision at a healthcare facility.

Oral immunotherapy is not a cure for food allergies—it reduces reactivity to peanut

The maintenance phase can go on for months to years, during which the patient continues to take the established maintenance dose every day. The recommended dosage for the peanut-allergen product is 300 mg/day.

Adding a food challenge

If the patient has been in the maintenance phase for a long time and is doing well, a food desensitization challenge may be performed using an age-appropriate, full serving of food. (The gold standard for diagnosing food allergy is a double-blind, placebo-controlled food challenge, but this is rarely done.)

In some protocols, if the patient completes a food challenge without symptoms, the daily maintenance dose is discontinued for 4 to 12 weeks, and another food challenge is performed. If the patient can ingest the food without an adverse reaction, then sustained unresponsiveness has been achieved, meaning the desensitized state is maintained without the need for regular allergen ingestion. The duration of sustained unresponsiveness achieved using the FDA-approved peanut powder product has not been established in clinical trials.

Some patients experience symptoms of a hypersensitivity reaction during the food challenge: eg, they had been tolerating the controlled doses of allergen, but had a reaction to a full meal. These patients are often deemed "bite-proof," meaning they are unlikely to have an allergic reaction to 1 bite of a peanut product or a product contaminated by peanut, but unlike patients who have sustained unresponsiveness, they need to continue their maintenance dosing to sustain their hyporesponsiveness, and they should avoid peanuts in their diet.

WHAT ARE THE EFFICACY AND SAFETY CONCERNS OF ORAL IMMUNOTHERAPY?

Safety and efficacy data for the peanut-allergen agent come from clinical trials that enrolled more than 700 patients who were allergic to peanuts.

In a phase 3 trial,[16] 551 patients ages 4 to 55 with allergic dose-limiting symptoms at 100 mg or less of peanut protein (approximately one-third of a peanut kernel) were randomly assigned to receive the study drug or placebo in an escalating-dose protocol. Most patients (n = 496) were between ages 4 and 17, which reflects the FDA-approved age range.

Once participants reached the final study dose, they underwent a peanut challenge. The study drug recipients could ingest higher doses of peanut protein without dose-limiting symptoms than placebo recipients. The most common adverse reactions during treatment (incidence > 5%) were gastrointestinal, respiratory, and skin symptoms and anaphylactic reactions.[16]

This peanut-derived oral immunotherapy agent, like other forms of oral immunotherapy (which are not FDA-approved), is not appropriate for patients with uncontrolled asthma, eosinophilic esophagitis, or other eosinophilic gastrointestinal disease.

Adverse reactions are a leading reason for stopping oral immunotherapy. In the randomized controlled trial of peanut allergen,[16] 43 (11.6%) of the 362 patients assigned to the active treatment group withdrew because of adverse events. Gastrointestinal disorders

accounted for most of the adverse reaction-related discontinuations. Most discontinuations occur during the escalation or up-dosing phases, with only a few patients withdrawing during the maintenance phase.[15,16]

For those experiencing adverse reactions, the onset was typically rapid (median time 4 minutes after the dose), and symptoms resolved relatively quickly (median time 37 minutes).[15] Thus, careful patient monitoring is crucial during the first hour after dosing. Additionally, dose escalation and up-dosing must be done in a medical setting with medical personnel experienced with oral immunotherapy and treatment of allergic reactions.

Patients should be cautioned that the FDA-approved oral immunotherapy product is not a cure for food allergies; instead, it is intended to reduce their reactivity to peanut. In the initial clinical trials, an exit challenge was included to approximate a real-life scenario of accidental ingestion.

Daily dosing important

Longitudinal studies are under way, with 2-year data from an open-label follow-up study that suggest long-term efficacy of daily treatment with the peanut-derived oral immunotherapy agent.[17] Patients who received daily doses in the study showed greater immunomodulation and higher rates of desensitization that increased over time compared with patients given nondaily dosing. Furthermore, most patients in the daily-dosing groups had lower adverse event rates than those in the nondaily dosing groups.

All forms of oral immunotherapy carry the risk of life-threatening anaphylaxis. Oral immunotherapy has not been studied in pregnant women, and the risks to a fetus are unknown. Anaphylactic reactions could lead to hypotension and potential fetal demise.

Counseling needed

Patients and families must be carefully counseled on the signs and symptoms of anaphylaxis and carry auto-injectable epinephrine at all times. Strict avoidance of allergens, aside from daily oral immunotherapy dosing, is imperative. Illness, physical exertion around dosing, and recent dental work or tooth loss may increase the risk of a reaction.

When identifying candidates for oral immunotherapy, consideration should be given to the capacity of the patient and family to adhere to the safety precautions and dosing regimens. This requires careful discussion of medication compliance, family support, and ability to attend regularly scheduled appointments before initiating treatment. Patients with families who are not highly motivated to incorporate the necessary lifestyle modifications are unlikely to be ideal candidates for therapy.

IMPLEMENTING A PROGRAM: COST, TRAINING, RISKS, LIMITATIONS

Incorporating oral immunotherapy into a clinical practice requires significant resources dedicated to staffing, training, and physical space. Due to the extended course of treatment, a practice interested in implementing oral immunotherapy would need to ensure that adequate clinical support staff are available for preparing materials, administering doses, monitoring, and treating reactions if they occur.

The initial dose-escalation visit can last 5 to 6 hours. During this time, doses are given every 20 minutes, and clinicians monitor and assess the patient's vital signs, making it a time-intensive first day.

Dosing interruptions of only a few days can result in loss of desensitization

Subsequent visits in the up-dosing phase involve preparing materials, administering 1 dose, and monitoring for a minimum of 1 hour. As a clinical practice with oral immunotherapy grows, these subsequent visits would require a structure similar to the established practice of incorporating allergen inhalant immunotherapy in allergy practices, but more allergic reactions are expected with oral immunotherapy.

Providers and clinical support staff should have appropriate training for administering oral immunotherapy and managing allergic reactions. Practices must be equipped with medications needed to treat anaphylaxis, oxygen, and basic resuscitation supplies.

Clinicians who prescribe the FDA-approved product and pharmacies that dispense it are required to register with the FDA Risk Evaluation and Mitigation Strategy program.[18] This ensures that clinical practices admin-

istering oral immunotherapy are adequately prepared to monitor, identify, and treat anaphylaxis.

Given the intensive process, duration, and lifestyle restrictions associated with oral immunotherapy, patients and their families need extensive education before starting treatment. Adequate time is needed for consultations with providers to counsel on the risks, benefits, and limitations of oral immunotherapy. This is a crucial part of optimizing success and safety with oral immunotherapy.

Thus, the cost of oral immunotherapy will include both the fees associated with supplies (ie, drug and materials used for dosing) and the cost of additional provider time, clinical support staff, and physical space to accommodate the frequency and duration of office visits. The list price for Palforzia is about $890 per month ($11,000/year), although the manufacturer has various patient assistance and copay savings programs. This is much more expensive than purchasing grocery store products and using them in published protocols. A cost-effectiveness analysis found that the new product may be cost-effective only under some assumptions.[19]

While peanut-derived oral immunotherapy has been shown to be effective for mitigating allergic reactions to peanut, there are limitations that play a role in determining ideal candidates for treatment. Notably, not all patients may be able to achieve tolerance. Additionally, individuals undergoing oral immunotherapy must continue a daily maintenance dose to maintain hyporesponsiveness, as the duration needed to achieve uniform sustained tolerance is not yet known.

The risk of reactions during oral immunotherapy must also be carefully considered. A recent meta-analysis of 12 oral immunotherapy trials showed a higher frequency of reactions and epinephrine use while undergoing oral immunotherapy compared with food avoidance alone.[11] But this does not take into account the protective effect and better quality of life associated with oral immunotherapy once maintenance dosing has been achieved.[20] Providers, patients, and families must seriously consider the level of resources and commitment required for the success of oral immunotherapy before undertaking this treatment.

AN EXCITING TIME OF EMERGING OPTIONS

Oral immunotherapy with this new product for peanut allergy has challenges and limitations and therefore requires careful consideration from patients, families, and prescribers. However, its approval ushers in an exciting time of emerging therapeutic options for patients with food allergy.

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Cardiac surveillance for anti-HER2 chemotherapy

ABSTRACT

Surveillance of left ventricular function, part of current US Food and Drug Administration recommendations for anti-human epidermal growth factor receptor 2 (anti-HER2) chemotherapy, is based on historical data involving patients who received concomitant anthracycline therapy, a key enhancer of cardiac risk. More recent anti-HER2 treatment data suggest that cardiotoxicity detected by screening is rare and usually benign for patients who do not have cardiovascular risk factors and are not taking an anthracycline. Because of the burden of repetitive echocardiography required for surveillance and the risk of false-positive results, potentially leading to discontinuing lifesaving treatment, we advocate for a more focused cardiac surveillance strategy.

KEY POINTS

Accurate diagnosis of cardiotoxicity is critical, as false-positive results may lead to inappropriate stopping of potentially lifesaving chemotherapy.

We suggest routine serial measurement of left ventricular ejection fraction by echocardiography only for patients who have received anthracyclines or are considered at high cardiac risk.

All patients should be counseled to promptly report relevant symptoms.

For patients who develop clinically significant congestive heart failure, discontinuing anti-HER2 therapy should be strongly considered.

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Anti-human epidermal growth factor receptor 2 (anti-HER2) therapy has been a game-changer for some forms of aggressive breast cancer, drastically reducing mortality rates. The US Food and Drug Administration (FDA) calls for close cardiac surveillance in patients receiving these drugs. But this recommendation is based on an early clinical trial with circumstances that are no longer frequently relevant. As it now stands, this strategy is burdensome, dangerous for patients who are unnecessarily advised to discontinue therapy, and often ignored in practice.

This article discusses what drove the current FDA cardiac surveillance strategy for anti-HER2 therapy and the challenges it poses in practice and clinical research. Results of more recent clinical trials are reviewed, and in light of them, new best practices for anti-HER2 therapy management and cardiac monitoring are proposed.

HER2 EFFECTS, TESTING, AND THERAPY

About 1 in 4 patients with breast cancer has an aggressive tumor that overexpresses a tyrosine kinase receptor protein called human epidermal growth factor receptor 2 (HER2, also known as HER2/neu, CD340, Erbb2, and proto-oncogene Neu). It is encoded by the *ERBB2* oncogene on chromosome 17.[1] Signaling through this receptor promotes cell proliferation and opposes apoptosis; when it is overexpressed, uncontrolled cell growth results.

Patients with breast cancer undergo HER2 testing to assess prognosis and determine candidacy for personalized therapy. Over the past 20 years, agents targeted against HER2 have been developed, contributing to a halving of

TABLE 1

Trials involving anti-HER2 treatment

Study[a]	Year	No. of patients	Duration (years)	Early vs metastatic	Anthracycline	Follow-up (years)	Echocardiography result	LVEF drop (%)	Heart failure incidence (%)	Cardiac death (%)
OHERA[7]	2019	3,733	1	Early	Yes	5	4+	2	3	< 1
KATHERINE[8]	2019	1,486	0.4	Early	No	5	4+	NA	NA	0
NSABP[9]	2017	407	1	Early	Yes	5	4+	1	NA	< 1
HERA[10]	2017	5,099	1–2	Early	No	10	4+	< 1	NA	NA
APHINITY[11]	2017	4,805	1	Early	No	10	5+	NA	< 1	< 1
Dang et al[12]	2016	406	1	Both	No	4	4+	3	< 1	NA
HORG[13]	2015	481	1	Early	No	7	3+	< 1	0	0
CLEOPATRA[14]	2013	804	1	Both	No	3	3+	1	< 1	< 1
NeoSphere[15]	2012	417	0.4	Both	No	2 weeks	3+	< 1	< 1	0
BCIRG-006[16]	2011	3,222	1	Both	Yes	5	7+	14	< 1	0
Slamon et al[6,b]	2001	234	0.8	Metastatic	Yes	> 2	NA	16	27	0

[a]All trials included radiation therapy and were adjudicated.
[b]Pivotal trial leading to stringent US Food and Drug Administration recommendations for cardiac surveillance.
APHINITY = A Study of Pertuzumab in Addition to Chemotherapy and Trastuzumab as Adjuvant Therapy in Participants With Human Epidermal Growth Receptor 2 (HER2)-Positive Primary Breast Cancer; BCIRG = Breast Cancer International Research Group; CLEOPATRA = A Study to Evaluate Pertuzumab + Trastuzumab + Docetaxel vs. Placebo + Trastuzumab + Docetaxel in Previously Untreated HER2-Positive Metastatic Breast Cancer; HER2 = human epidermal growth factor receptor 2; HERA = HERceptin Adjuvant; HORG = Hellenic Oncology Research Group; KATHERINE = A Study of Trastuzumab Emtansine Versus Trastuzumab as Adjuvant Therapy in Patients With HER2-Positive Breast Cancer Who Have Residual Tumor in the Breast or Axillary Lymph Nodes Following Preoperative Therapy; LVEF = left ventricular ejection fraction; NA = not available; NeoSphere = A Study of Pertuzumab in Combination With Herceptin in Patients With HER2 Positive Breast Cancer; NSABP = National Surgical Adjuvant Breast and Bowel Project; OHERA = Observational Study of Cardiac Events in Patients with HER2-Positive EBC Treated with Herceptin

breast cancer mortality rates, in what is widely regarded as a phenomenal success story.[2] Anti-HER2 agents include the following[3,4]:

Monoclonal antibodies, eg, trastuzumab, which targets the extracellular domain of HER2, and pertuzumab, which prevents HER2 receptor homodimerization and heterodimerization, which are necessary for activation

Ado-trastuzumab emtansine, an antibody-drug conjugate

Small-molecule inhibitors that block the HER2 receptor intracellularly, eg, lapatinib, available in oral formulations.

Other targeted anti-HER2 therapies are continually being developed.

CARDIAC ISSUES WITH TRASTUZUMAB DISCOVERED EARLY

Current FDA recommendations regarding the frequency of surveillance of left ventricular function with anti-HER2 therapy are conservatively based on historical data involving patients receiving concomitant anthracycline therapy.[5]

The pivotal trastuzumab randomized controlled trial in patients with metastatic breast cancer, published in 2001, reported a 27% rate of cardiac dysfunction and a 16% rate of New York Heart Association (NYHA) class III or IV heart failure in patients who received trastuzumab with anthracycline chemotherapy.[6] These findings prompted the FDA to issue a stern package-insert warning of cardiomyopathy for anti-HER2 treatments, and recommendations for cardiac surveillance.

Trastuzumab's package insert recommends measuring left ventricular ejection fraction (LVEF) before starting therapy, every 3 months during treatment, and at the completion of therapy. If drug therapy is withheld for cardiotoxicity, studies should be repeated

monthly. Furthermore, after completion of therapy, LVEF should be measured every 6 months for at least 2 years.[5] Thus, a minimum of 9 echocardiograms is recommended for patients undergoing a standard 12-month adjuvant dosing schedule, with an indefinite (and potentially lifelong) number of 3-monthly echocardiograms for those with metastatic disease on continual anti-HER2 therapy.

RECENT DATA PUT RECOMMENDATIONS IN QUESTION

Subsequent clinical trials[7–16] have generally indicated a more favorable cardiac profile (**Table 1**).

The 2007 Herceptin Adjuvant (HERA) trial found a 3% rate of cardiac dysfunction and a 0.6% rate of NYHA III or IV heart failure.[17] A 2019 trial[8] found that only 1.2% of patients discontinued dual therapy because of decreased ejection fraction, while adjudicated cardiac events occurred in less than 1%. The relationship between decreased ejection fraction assessed by cardiac monitoring and the development of clinical heart failure was not discussed.

Current recommendations are conservatively based on historical data

Although the risk of cardiac dysfunction from anti-HER2 therapy now appears low, the FDA package-insert warning and recommendations remain. Extensive cardiac monitoring and echocardiographic testing regimens are still part of the standard protocols of clinical trials involving this drug.[8,11,18,19] In a 2017 trial,[11] up to 13 imaging studies (preferably echocardiograms) were scheduled using the following protocol: at baseline, during treatment (at chemotherapy cycles 2, 6, 10, and 14) and during follow-up (months 3, 6, 12, 18, 24, 36, 48, 60), resulting in a potential total of 19,318 studies for 1,486 patients.

WHAT ACCOUNTS FOR DIFFERENT RESULTS BETWEEN TRIALS?

Several factors may help explain different event rates between clinical trials of the same drug.

Concomitant vs sequential therapy. In early studies, trastuzumab was given concomitantly with an anthracycline and cyclophosphamide. It has since been realized that cardiotoxicity rates are much lower if trastuzumab is given sequentially with other drugs. This is likely the most important explanation of the differences between the early and late anti-HER2 clinical trials.

More surveillance in the drug arm. A 2019 long-term study[20] found a higher rate of cardiotoxicity in patients treated with trastuzumab than in those treated with chemotherapy alone. But LVEF was measured 5 times in the trastuzumab group vs no routine testing in the control group. Because cardiotoxicity is more likely to be revealed if more LVEF measurements are taken, more surveillance usually results in findings in the more tested arm.

Exclusion criteria. Cardiac event rates may be underestimated in clinical trials that exclude high-risk patients who are more likely to experience such events.

Problems of definition. Duplicative, inconsistent, and sometimes contradictory consensus criteria to classify cardiotoxicity can affect event rates. For example, a study participant experiencing an asymptomatic drop in LVEF from 60% to 35% might be reported as having either grade 0 left ventricular dysfunction, grade 1 heart failure, or a grade 3 ejection fraction decrease.[21,22]

Method of event reporting. Variability in reported outcomes data can arise if studies only include adverse events that are "site reported."[23] But this is less relevant for objective findings, such as drop in ejection fraction, which should be documented in the primary data. Ideally, all events, whether or not they are thought to be treatment-related, are reported, with details provided for events that are believed not to be treatment-related.[23]

Findings from screening using surveillance echocardiography would probably not be confused with acute events associated with other temporary or persisting causes of left ventricular dysfunction (eg, sepsis, acute coronary syndrome, acute arrhythmia including atrial fibrillation, takotsubo cardiomyopathy).

PRINCIPLES OF CARDIAC SURVEILLANCE

More than 50 years ago, Wilson[24] wrote about the attributes of an ideal screening test and advised caution: "In theory, screening is admirable, but in practice there are snags; the central idea is simple and may appear deceptively straightforward." Wilson's screening criteria and their applications to surveillance echo-

TABLE 2

Wilson's criteria for an ideal screening test, applied to cardiac surveillance for chemotherapy

Criteria[24]	Surveillance echocardiography for chemotherapy
The condition should be an important health problem	Cardiotoxicity is an important health problem but is detectable by screening only in a minority of patients
The natural history of the condition should be understood	The natural history of cardiotoxicity has been reasonably well studied for established chemotherapy agents such as anti-HER2
There should be a recognizable latent or early symptomatic stage	Left ventricular dysfunction typically relates to acute toxicity and becomes manifest within the first year of exposure. Early recognition is important, because cumulative doses typically compound toxicity
A test should exist that is easy to perform and interpret, and is acceptable, accurate, reliable, sensitive, and specific	Imaging with echocardiography has these qualities but also involves considerable challenges and limitations
An accepted treatment for the disease should exist	Current guideline-directed heart failure management is recognized as treatment for chemotherapy-related cardiomyopathy. Evidence is limited for specific treatments beyond these guidelines, although the subject is under active investigation
Treatment should be more effective if started early	If started early, current guideline-directed heart failure management is considered to be more effective. Early recognition of chemotherapy-related cardiomyopathy is important for preventing additional dose exposures, which typically compound toxicity
There should be a policy on who should be treated	Current guideline-directed heart failure management covers who should be treated
Diagnosis and treatment should be cost-effective	Limited data suggest favorable cost-effectiveness for screening and early treatment, although a more targeted approach can likely significantly improve it
Case-finding should be a continuous process	Case-finding can be a continuous process

cardiography during chemotherapy are presented in **Table 2**.[24]

LVEF WITH ECHOCARDIOGRAPHY IS RECOMMENDED FOR SCREENING

Currently, LVEF is the screening variable of choice.[19] Strain assessment is a nonactionable supportive tool. However, it is the focus of ongoing research and is increasingly being used, especially as it received a formal Current Procedural Terminology code by the US Centers for Medicare and Medicaid for reimbursement to Medicare providers.[25]

Echocardiography is the preferred screening method, although cardiac magnetic resonance imaging is considered to be the gold standard and is advised in selected cases (ie, if echocardiographic images are inadequate or yield equivocal findings). Another option, multigated acquisition radionuclide scanning, is not a first-line test, as it involves radiation and introduces cross-modality error.

BALANCING THERAPY RISKS AND BENEFITS

The *net benefit of therapy* refers to balancing the risks of toxicity with prognosis and available treatment options. Potential cardiotoxicity may be more acceptable in the setting of a cancer with a poor prognosis and few treatment possibilities. On the other hand, cardiotoxicity is less likely to be an acceptable risk

for a later-generation drug in a cancer with multiple existing therapies and a generally good prognosis.

Regarding breast cancer, regimens without an anthracycline have been shown to be as effective as those with an anthracycline, especially for women at low risk of recurrence. Strategies without an anthracycline involve much lower rates of cardiotoxicity, with rates of NYHA class III and IV heart failure being close, if not equal, to those with placebo (0.4% over 5 years or fewer than 1 per 1,000 patients per year).[18] They have also demonstrated improved survival and favorable cardiac safety for metastatic cancer.[26]

Because anti-HER2 treatment is used against a particularly aggressive cancer, decisions regarding interrupting or stopping it based on side effects have especially important implications. Whether such decisions should be made based on a surrogate echocardiographic end point, possibly in the absence of symptoms, needs careful consideration.

CARDIAC MANAGEMENT AND ANTI-HER2 THERAPY

Echocardiography is the preferred screening method, although MRI is considered the gold standard

Anti-HER2 treatment in patients with preexisting cardiac dysfunction has been associated with a worse prognosis and higher rate of symptomatic heart failure compared with patients with preserved ejection fraction at baseline.[27] However, preexisting cardiac dysfunction is a relative rather than an absolute contraindication to starting anti-HER2 treatment. The FDA recommends extreme caution in treating such patients,[5] and a cardiologist should be involved in management.

For patients who develop clinically significant congestive heart failure, discontinuing anti-HER2 therapy should be strongly considered. For patients without symptoms, treatment-specific LVEF thresholds for stopping medications have been developed, with slightly different recommendations between FDA-approved labeling, clinical trial protocols, and professional society guidelines. Criteria from clinical trials that do not involve anthracycline therapy tend to be a little less stringent because anti-HER2-associated toxicity is considered to be dose-independent, nonapoptotic, and potentially reversible (type 2 cardiotoxicity). In contrast, anthracycline-mediated cardiotoxicity is regarded as type 1 (ie, irreversible and related to cumulative dose).[28]

A commonly used threshold defining cardiotoxicity is a decrease in LVEF of more than 10% to a value below the lower limit of normal. Hussain et al,[29] in a study of 23 patients with asymptomatic LVEF decline who continued trastuzumab, found that 14 patients (61%) tolerated it without a cardiac event, 6 (26%) developed further worsening of LVEF, 1 (4%) developed heart failure, and 2 (9%) died of a possible or probable cardiovascular cause.

Strategies to prevent or attenuate cardiotoxicities include participation in cardio-oncology programs (particularly for symptomatic or high-risk patients being considered for anti-HER2 treatment, including anyone with baseline low LVEF), early recognition of cardiac side effects, active cardiac surveillance, and cardioprotective medical therapy.

INTERPRETING SERIAL TESTING IS A CHALLENGE

Accurate diagnosis of cardiotoxicity is critical, as false-positive results may lead to inappropriate stopping of potentially lifesaving chemotherapy.

Serial echocardiography in patients with cancer can be difficult and measurement variability may be high. Reasons may be technical (eg, concomitant lung disease, high or low body mass, postoperative status) or involve confounding factors (eg, variable hemodynamics, medications, fluid status).[30] Published test-retest variability data have generally been derived between 2 tests rather than multiple tests and conducted under optimized experimental settings in academic centers. Even optimized test-retest variability remains close to echocardiographic thresholds used to define real interval change representative of true cardiotoxicity, especially with multiple tests.

Outside of trial settings, false-positive results are not infrequent. In addition, pre-chemotherapy studies may manifest hyperdynamic function. Teasing out whether serial changes are related to cancer therapy vs comorbid illness (eg, concomitant arrhythmia, ischemia, stress cardiomyopathy, and myocarditis) may be challenging.

Optimizing measurement accuracy

Repeat echocardiographic studies should be performed in as consistent a manner as possible (eg, same equipment, technician, and reporting physician). Multiple ways to measure LVEF should be used, including quality 3-D echocardiography (ideally without contrast for highest reproducibility), the biplane Simpson method (with contrast, if necessary), and visual assessment, with reporting of the best available data.[19] Global longitudinal strain may provide corroborative data when concordant; if discordant, the quality of the data should be reviewed again with particular attention to wall tracking. Ideally, differences between serial tests should be compared to the maximal detectable difference, a value that can be calculated for each echocardiographic laboratory, providing a threshold to distinguish likely test error from real change.[31] For borderline cases, obtaining an experienced second opinion, an early interval repeat study, or an alternative test (eg, cardiac magnetic resonance imaging) should be considered.

Treating chemotherapy-related cardiomyopathy remains a challenge

Applying current guideline-directed heart failure management to chemotherapy-related cardiomyopathy can be particularly challenging. Especially for patients undergoing chemotherapy, titrating levels of beta-blockers and renin-angiotensin system antagonists to optimal dosing is often difficult because of poor tolerability. Outside these guidelines, data to support the use of cardioprotective medical therapy to prevent chemotherapy-related cardiotoxicity are modest at best. Studies are limited by marginal effect size, small patient numbers, and short follow-up.

Should general cardiotoxicity screening be eliminated?

Many have questioned the usefulness of currently proposed cardiac monitoring for patients on anti-HER2 therapy, particularly for those who are asymptomatic, without cardiovascular risk factors, and who have not had concomitant anthracycline therapy.[32] Data assessing the cost-effectiveness of screening strategies for cardiotoxicity are limited.[33] To avoid placing additional financial and time burdens on patients with cancer and their families, some have suggested that simply monitoring patients on clinical parameters alone is best.[26]

Current practice regarding screening for chemotherapy-related cardiomyopathy is a legacy of its mutable historical background. It is overshadowed by variable and conflicting guidelines, with the result that most patients on anti-HER2 treatment actually receive minimal or no cardiac imaging.[34,35] If oncologists are voting with their feet, it appears that recommendations are perceived as promoting overtesting, with a common result being minimal or no testing in actual practice.

A PATH FORWARD

We suggest a more focused cardiac surveillance approach to low-risk, asymptomatic patients receiving anti-HER2 treatment. Routine serial LVEF measurement by echocardiography should be done only if patients have received anthracyclines or are considered to be at high risk (eg, concomitant hypertension, borderline low LVEF). For these patients, studies should be carried out at baseline, post-anthracycline (if appropriate), and every 3 months while on anti-HER2 treatment. Less frequent testing may be justified for patients with metastatic disease who have repeatedly normal LVEF test results. Patients should be informed about potential symptoms of cardiotoxicity and advised to report them promptly. ■

We suggest a more focused cardiac surveillance approach to low-risk, asymptomatic patients receiving anti-HER2 treatment

DISCLOSURES

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REVIEW

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Precision treatment for metastatic non–small cell lung cancer: A conceptual overview

ABSTRACT

Recent developments in precision oncology have increased the complexity of diagnostic and therapeutic decisions. Here, we broadly review the field of precision oncology and discuss common mutational drivers in non–small cell lung cancer (NSCLC) that directly relate to the diagnosis, evaluation, and treatment of patients with metastatic disease.

KEY POINTS

A number of driver alterations (mutations and chromosomal rearrangements) occur in patients with NSCLC.

Mutations in the *EGFR* and *BRAF* genes and rearrangements involving the *ALK* and *ROS1* genes can be targeted with novel agents.

These targeted therapies have demonstrated superior outcomes and far less toxicity compared with traditional cytotoxic chemotherapy in patients with metastatic NSCLC.

Efficiently identifying genetic alterations that can be treated with existing therapies is key to providing best-practice care to all patients.

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In the past few years, targeted therapies have become widely available and have revolutionized the treatment of patients with advanced solid tumors, particularly metastatic non–small cell lung cancer (NSCLC). For patients who have 1 of a select few actionable genetic alterations, phase 3 trials in NSCLC have consistently shown survival benefits associated with targeted agents compared with chemotherapy.[1–3] Large-scale real-world data suggest these targeted therapies are improving survival on a population level.[4]

Targeted therapies are costly, with estimates of cost per quality-adjusted life-year of $150,000 to over $200,000. However, they are also associated with improved quality of life and fewer adverse effects compared with chemotherapy.[3,5–8]

The drugs fall under the expanding umbrella term of "precision oncology," which refers to both the diagnostic method (ie, genomic sequencing) and the treatments prescribed based on the results. Recent advances in genomic sequencing have allowed for efficient and reliable identification of patients who may benefit from precision therapies.

Here, we review precision oncology and the most clinically relevant mutations that can be found among patients with metastatic NSCLC. We further review the diagnostic tests available to clinicians to assess for these mutations. Last, we discuss opportunities to streamline testing in an efficient manner.

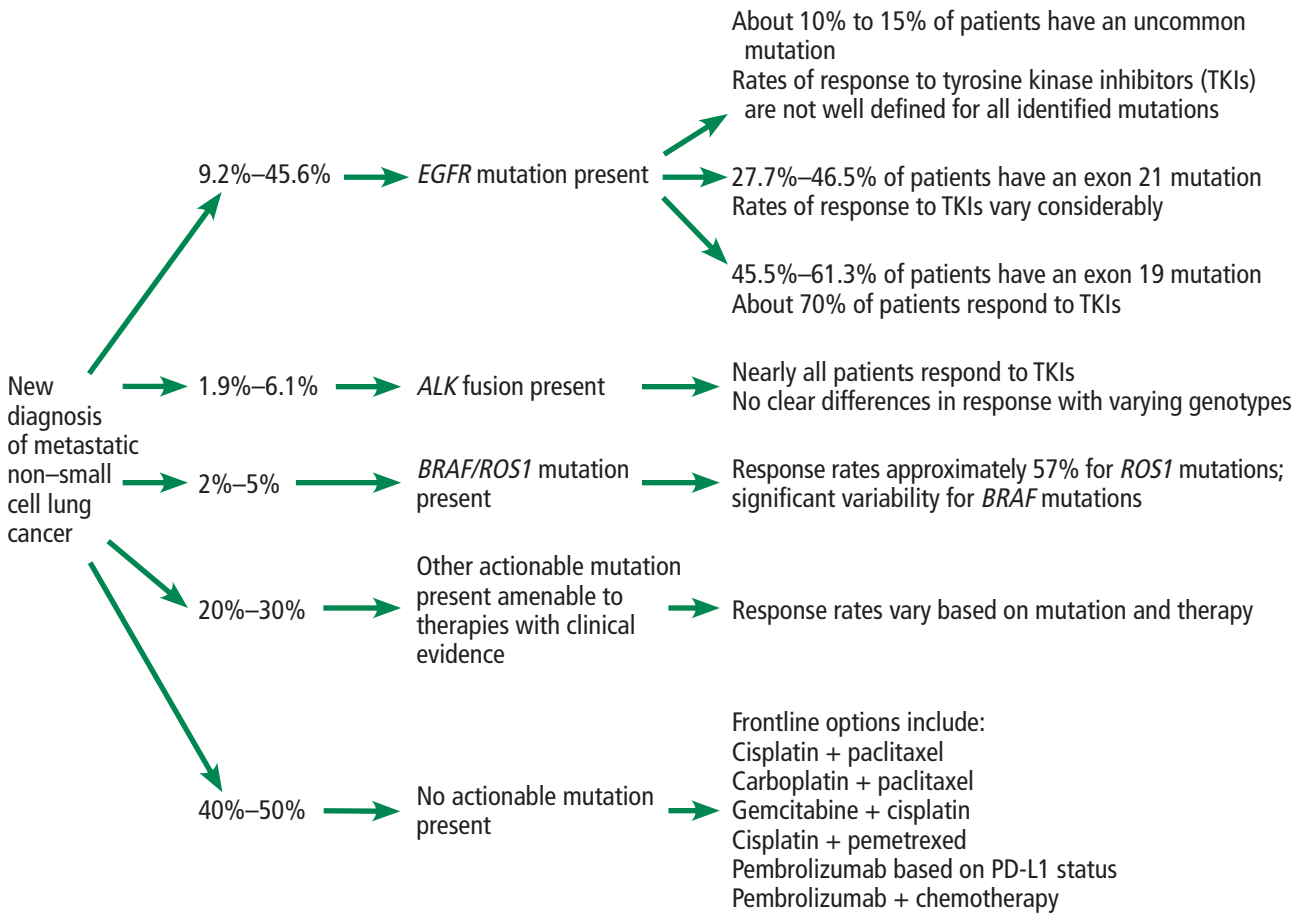


Figure 1. The current paradigm for precision oncology for NSCLC.

PRECISION ONCOLOGY

Advances in the diagnosis and treatment of NSCLC have come to define the paradigm of precision oncology (**Figure 1**). Through remarkable laboratory-based efforts and wide-ranging epidemiologic studies, a significant number of critical genetic alterations that cause cells to grow, divide, and turn cancerous have been discovered.

As opposed to other accompanying and functionally neutral ("passenger") mutations, these specific "driver" mutations are functionally important to the growth of the malignancy.[9] Further investigation into these driver mutations uncovered targeted therapies that provide a line of highly efficacious treatments, significantly improving overall survival for patients with metastatic NSCLC.

These developments have fundamentally altered clinicians' approaches to intervention in NSCLC over the past decade. Additionally, successes achieved in patients with NSCLC have encouraged further research efforts toward expanding the role of precision oncology for patients with other advanced malignancies.

In this review, we do not discuss immunotherapy, which is a general term referring to immune checkpoint inhibitors, namely agents that alter the cytotoxic T-lymphocyte–associated protein 4 and programmed death-ligand 1 pathways. These agents have also vastly reshaped the treatment paradigm for patients with metastatic NSCLC, but specifically have a far greater role in patients who do not have a highly actionable mutation or fusion. The topic of immunotherapy is part of a broader discussion than is possible in this review.

GENETIC ALTERATIONS FOR WHICH THERAPIES ARE APPROVED

Several genetic alterations identified in patients with metastatic NSCLC can currently be targeted with therapies approved by the US Food and Drug Administration (FDA), including mutations in the epidermal growth factor receptor (*EGFR*) and *BRAF* genes and chromosomal rearrangements of the anaplastic lymphoma kinase (*ALK*) and *ROS1* genes. The rates of alterations are shown in **Figures 1** and **2**. The associated targeted therapies for the different alterations are described in **Table 1**[10–22] and **Figure 2**. Definitions and examples of key terms used in this article are given in **Table 2**, while a schematic review of the consequences of various actionable alterations is shown in **Figure 3**.

EGFR mutations

EGFR is a transmembrane tyrosine kinase receptor that operates within signal transduction pathways facilitating cellular growth and apoptosis. In the United States, nearly 20% of patients with NSCLC harbor a pathogenic *EGFR* mutation.[23] Mutations in the *EGFR* gene, which codes for the EGFR receptor, lead to dimerization of receptors. This dimerization causes constitutive activity of the tyrosine kinase associated with the EGFR protein, thereby inducing a hyperproliferative state.

Targeted treatments are directed toward inhibiting either the extracellular receptor or the intracellular tyrosine kinase. Among patients with metastatic NSCLC, efforts to inhibit intracellular tyrosine kinase have been most successful. The following drugs that inhibit EGFR tyrosine kinase are FDA-approved:

- Erlotinib, a first-generation drug
- Gefitinib, a first-generation drug
- Afatinib, a second-generation drug
- Dacomitinib, a second-generation drug
- Osimertinib, a third-generation drug.

A number of mutations can be found within the *EGFR* gene. The variants that are most susceptible to targeted treatments include exon 19 deletions and exon 21 substitutions (L858R). Cancers associated with less common mutations involving exon 18 and 20 may respond to tyrosine kinase inhibitor (TKI)-based therapy, but sensitivity varies by specific mutation and is often lower compared with exon 19 and 21 mutations.

A number of clinical trials have demonstrated marked improvements in overall survival with use of TKIs compared with traditional chemotherapy in patients with an *EGFR* mutation. Later-generation TKIs such as osimertinib not only overcome a common mechanism of resistance, the T790M mutation, but also provide better progression-free and overall survival outcomes than earlier-generation TKIs for all patients with metastatic NSCLC harboring typical pathogenic *EGFR* mutations.[24]

Common adverse effects with TKIs are predominantly cutaneous, namely acneiform rash and dry skin, followed by diarrhea. Rarely, patients may develop interstitial lung disease. This is not an exhaustive list of potential adverse effects and neither are the adverse effect profiles described for the targeted therapies listed for patients harboring actionable alterations in *ALK*, *ROS1*, or *BRAF*.

Actionable alterations among patients with non–small cell lung cancer

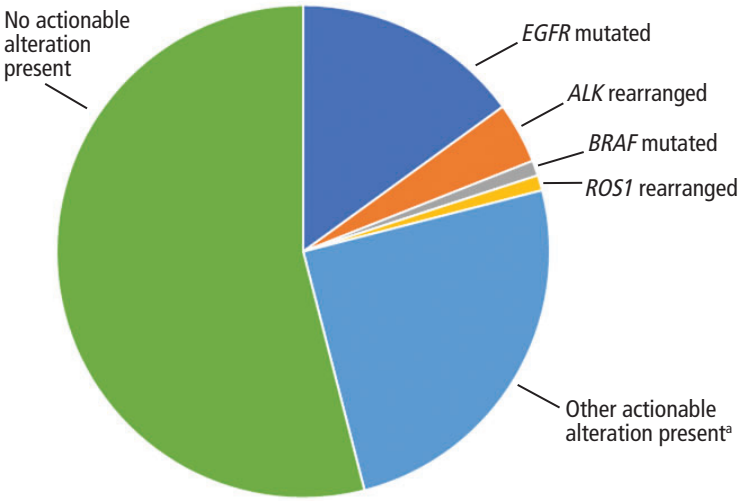


Figure 2. Rates of actionable mutations in patients with non–small cell lung cancer (NSCLC). Of note, NSCLC encompasses about 85% of lung cancers. Compared with smokers, nonsmokers have far higher rates of actionable mutations.

[a]Though another 20% to 30% of patients with NSCLC have some form of actionable alteration, the corresponding targeted agents are not necessarily FDA-approved. Of note, drugs targeting MET and RET have recently been approved for suitable NSCLC candidates.

TABLE 1

Approved targeted therapies for non–small cell lung cancer and their comparative effectiveness

Target	Treatment	Mechanism	Median progression-free survival compared with standard therapy (months)
EGFR	Erlotinib	First-generation endothelial growth factor (EGFR) tyrosine kinase inhibitor (TKI)	9.7 vs 5.2[10] 13.1 vs 4.6[11]
	Gefitinib	First-generation EGFR TKI	9.2 vs 6.3[12] 10.8 vs 5.4[13]
	Afatinib	Second-generation EGFR TKI	11.1 vs 6.9[14]
	Osimertinib	Third-generation EGFR TKI	18.9 vs 10.2[15; a]
ALK	Ceritinib	First-generation ALK/ROS1/HGFR TKI	16.6 vs 8.1[16]
	Crizotinib	First-generation ALK/ROS1/HGFR TKI	10.9 vs 7.0[17]
	Alectinib	Second-generation ALK/ROS1/HGFR TKI	Median not reached[18]
	Brigatinib	Second-generation ALK/ROS1/HGFR TKI	24.0 vs 11.0[19]
ROS1	Crizotinib	First-generation ALK/ROS1/HGFR TKI	17.6[20; b] 15.9[21; b]
	Entrectinib	First-generation ALK/ROS1/HGFR TKI	Trials ongoing
BRAF	Dabrafenib	BRAF V600E serine/threonine kinase inhibitor	14.6[22; c]
	Trametinib	MEK 1/2 Inhibitor	14.6[22; c]

[a] Comparison of third-generation EGFR inhibitor against first- and second-generation agents (gefitinib, erlotinib) as a first-line treatment.
[b] No comparison against alternative therapy in patients with non–small cell lung cancer (NSCLC) with *ROS1* mutations.
[c] No comparison against alternative therapy; treatment applied as combination dabrafenib-trametinib therapy in patients with *BRAF*-positive NSCLC.

Phase 3 trials consistently show marked survival benefits with targeted agents

BRAF mutations

BRAF mutations, commonly associated with melanoma, lead to a mutated serine-threonine kinase in the MAPK kinase pathway. A *BRAF* mutation is the driver oncogene in 1% to 3% of cases of NSCLC.[25]

NSCLC *BRAF* mutations take multiple forms, including the classic V600E form (50%), a G469A form (40%), and a D594G form (11%). Targeted therapies developed to date are primarily effective against the V600E mutation. Specific targeting of MEK1/2 mutations further downstream in the signaling pathway has also demonstrated long-term benefit and has been approved as a treatment option by the FDA.

Currently available and approved therapies for *BRAF*-mutant NSCLC include:

- Dabrafenib, a V600E serine/threonine kinase inhibitor
- Trametinib, a MEK 1/2 inhibitor, used in combination with dabrafenib.

Additional therapies being investigated include a combination of encorafenib with binimetinib, among others.

Common side effects of BRAF and MEK inhibitors include rash, diarrhea, and fever. A wide collection of uncommon adverse effects have been described, including systolic heart failure and retinopathy.

ALK rearrangements

ALK rearrangements lead to fusion protein products, most commonly involving echinoderm microtubule protein-like 4 (EML4). In the United States, nearly 6% of patients with NSCLC harbor an *ALK* rearrangement.[23] The fusion in these rearrangements connects the ALK protein with exon 20 of the EML4 protein, thereby leading to constitutive activation of the ALK tyrosine kinase. Similar

TABLE 2

Definitions and descriptions of key terms

Precision oncology—An umbrella term underscoring the personalized management of cancer patients. Precision oncology includes both the diagnostic methods required to individualize treatment of each patient's malignancy and the treatments administered based on the results of precision testing thereafter. The diagnostic methods may evaluate protein expression, cytogenetics, and mutations identified within tumor DNA. Examples of precision treatments include targeted therapies and immune checkpoint inhibitors.

Non–small cell lung cancer (NSCLC)—A broad collection of histologic findings identified in patients with lung cancer. Approximately 85% of lung cancers include NSCLC histologic findings, while 15% are small cell lung cancers. The 2 most commonly diagnosed NSCLCs are adenocarcinoma and squamous cell carcinoma. The rate of actionable mutations is far greater in patients with adenocarcinoma than in those with squamous cell carcinoma.

Driver mutation—A genetic alteration that provides a tumor cell with a fundamental growth advantage compared with normal tissue. If a targeted therapy has been discovered and validated among cancer patients harboring a specific driver mutation, the mutation may also be actionable. If a driver mutation has been studied extensively and is related to a better or worse prognosis, the mutation may be clinically relevant regardless of actionability.

Passenger mutation—A mutation discovered within tumor DNA that does not drive tumorigenesis. Patients may have both driver and passenger mutations.

Clinically relevant mutation—Mutations or alterations that may alter the course of treatment for a given patient with a specific cancer. Clinically relevant mutations may be predictive of response to targeted therapies or prognostic for standard treatment approaches.

Actionable mutation or actionable alteration—Genetic mutations or alterations that correlate with response to targeted therapies. Mutations may be within oncogenes, thereby driving tumorigenesis, or tumor suppressor genes, thereby limiting mechanisms that mitigate tumorigenesis. Mutations most frequently correspond with increased or decreased activity of critical proteins. Targeted therapies commonly exert their effects on these specific proteins. On the other hand, cytotoxic chemotherapy often drives mutations in tumor DNA, which encourages cell apoptosis.

Chromosomal rearrangement—A form of genetic alteration in which 2 chromosomes are fused in abnormal combinations. The resulting proteins may drive cellular neoplastic transformation. In patients with NSCLC, rearrangements involving the *ALK* and *ROS1* genes are associated with response to targeted therapies.

Targeted treatment/therapy/agent—Drugs that specifically treat the proteins resulting from actionable genetic alterations. Within the realm of metastatic NSCLC, the most commonly prescribed targeted therapies are tyrosine kinase inhibitors (TKIs), which target the hyperactivity of the epidermal growth factor receptor.

Precision testing—Diagnostic tests conducted on resected tumor samples or tumor DNA collected and centrifuged from the blood of cancer patients that evaluate the potential response to targeted therapies. Protein expression, chromosomal rearrangements, and tumor DNA sequencing may be evaluated by precision testing.

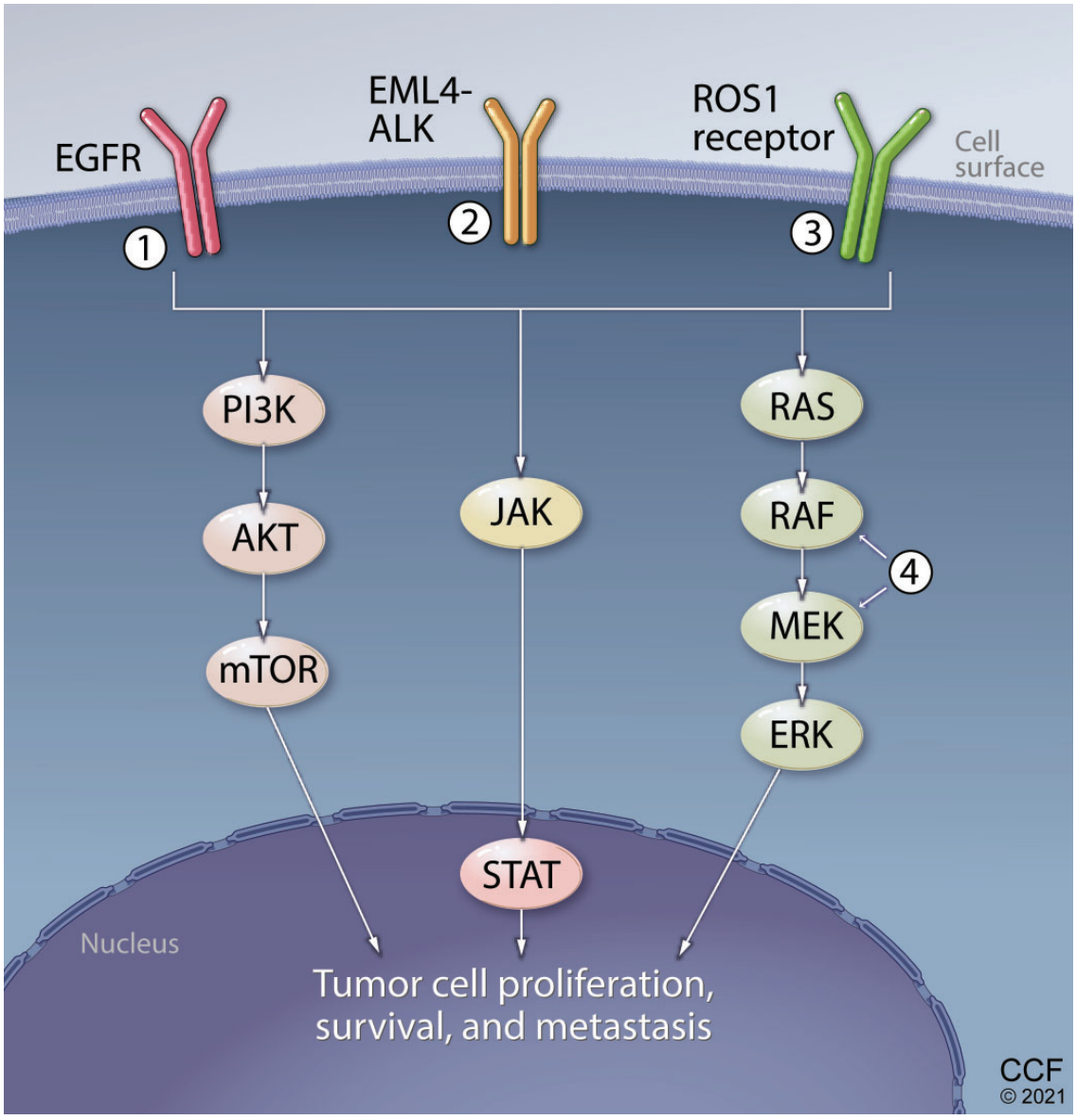
Immunohistochemical (IHC) staining—A technique used by pathologists to visualize antigens (proteins) expressed on tumor cells. Two types of antibodies are used to indicate antigen: one antibody binds to the antigen, and another fluorescently labeled antibody binds to the antigen-antibody complex, thereby confirming the expression of a specific protein.

Fluorescence in situ hybridization (FISH)—Similar to IHC, FISH analysis uses patient tissue samples for a histology-based assay of genetic variants. However, unlike IHC, FISH probes are predicated on complementary binding that can identify specific genetic sequences of interest. Using fluorescently labeled DNA or RNA probes created to reciprocally bind targets of interest, FISH analyses are able to detect the presence of their target sequences, and thus genetic variants, within prepared tissue samples.

Tumor DNA sequencing—A broad term encompassing the various modalities to evaluate tumor DNA for mutations that may be clinically relevant. The DNA findings from a patient's tumor sample are compared with standard databases to confirm the presence of mutations. Tumor DNA sequencing may assess the DNA of certain genes, whole exomes, or the entire genome.

Next-generation sequencing (NGS)—A form of tumor DNA sequencing in which massive amplification of preselected portions of tumor DNA can be evaluated concurrently. Several complementary DNA probes are affixed to comprehensive NGS plates that allow for multiple portions of DNA to be sequenced simultaneously. The data output may be in the form of fluorescence, temperature, or current change, depending on the design of the NGS platform. Given the large volume of data generated concurrently, large-scale automated algorithms are required to process cumulative sequencing information.

Liquid biopsy or plasma genotyping—A form of NGS that is conducted on DNA from dead tumor cells identified in the blood of patients with cancer. Liquid biopsy requires the collection and separation of circulating tumor DNA using advanced centrifuge techniques.



AKT = protein kinase B; ALK = anaplastic lymphoma kinase; BRAF = B-rapidly accelerated fibrosarcoma; EGFR = epidermal growth factor receptor; EML4 = echinoderm microtubule-associated protein-like 4; ERK = extracellular regulated kinase; JAK = Janus kinase; MEK = mitogen-activated protein kinase kinase; mTOR = mechanistic target of rapamycin; PI3K = phosphatidylinositol 3-kinase; RAF = rapidly accelerated fibrosarcoma; RAS = rat sarcoma; ROS1 = reactive oxygen species proto-oncogene 1, receptor tyrosine kinase; STAT = signal transducer and transcription

Figure 3. Pathways of proliferation. Certain key proteins that are abnormally active due to mutations and genetic rearrangements contribute to tumor cell proliferation, survival, and metastasis. Targeted therapies can block these pathways, specifically inhibitors of (1) epidermal growth factor receptor (EGFR), (2) anaplastic lymphoma kinase (ALK), (3) ROS1, (4) BRAF/MEK, and others.

to *EGFR* mutations, the *ALK* rearrangement creates a downstream transduction pathway via the AKT and ERK signaling pathways that encourages growth and discourages apoptosis.

ALK inhibitors have demonstrated excellent outcomes among patients with metastatic *ALK*-rearranged NSCLC.

Common adverse effects with ALK inhibitors include gastrointestinal toxicities. Brady-

cardia, QT prolongation, and interstitial lung disease are possible.

Currently available and approved ALK inhibitors are:

- Crizotinib, a first-generation drug
- Ceritinib, a first-generation drug
- Alectinib, a second-generation drug
- Brigatinib, a second-generation drug
- Lorlatinib, a third-generation drug.

ROS1 rearrangements

Rearrangements of the receptor tyrosine kinase c-ros oncogene 1 (*ROS1*) on chromosome 6 lead to constitutive tyrosine kinase activity, stimulating oncogenic signals through downstream pathways. Importantly, the *ROS1* rearrangements result in a mutant protein form that is structurally very similar to that seen among *ALK* rearrangements. That structural similarity creates cross-sensitivity and cross-reactivity with broad-target tyrosine kinase inhibitors, allowing for use of these targeted therapies in patients with *ROS1* rearrangements in addition to their originally intended targets. Approximately 1% of patients with NSCLC in the United States harbor a *ROS1* rearrangement.

Currently approved therapies include:

- Crizotinib, first-generation
- Entrectinib, first-generation.

Other tyrosine kinase inhibitors in development or recommended as alternative therapies include ceritinib.

Adverse effects are drug-dependent. Targeted agents that concurrently serve as ALK inhibitors, such as crizotinib, share the aforementioned ALK-inhibitor risk profiles. On the other hand, entrectinib is part of a separate collection of drugs that are typically prescribed for patients with neurotrophic tyrosine receptor kinase (NTRK) gene fusions in other solid tumors. Patients receiving these drugs may face a separate group of adverse effects, most commonly fatigue, liver and kidney dysfunction, and myelosuppression.

MET, *RET*, AND OTHERS

In the summer of 2020, the FDA approved treatments for patients harboring alterations in *RET* (selpercatinib and pralsetinib) and *MET* (capmatinib).[26–28]

However, these alterations represent only a fraction of the spectrum of pathogenic alterations in NSCLC; many more are currently being investigated in the laboratory and through clinical research. These include alterations in *KRAS*, *NRAS*, *AKT*, *DDR2*, *HER2 (ERBB2)*, *PIK3CA*, *MEK1*, *PTEN*, and *FGFR*.[29,30]

This list, and our understanding of how these alterations drive tumorigenesis in NSCLC, will continue to expand in the years to come.

TESTS FOR CLINICALLY RELEVANT MUTATIONS

Precision oncology requires equal emphasis on new drugs and identifying the patients most likely to benefit from them. Medical oncologists constantly face decisions about the best diagnostic test and timing of testing for their patients with NSCLC. A thorough understanding of the tests available is therefore critically important to the delivery of the best possible care.

The current diagnostic tests include:

- Immunohistochemical (IHC) staining
- Fluorescence in situ hybridization (FISH)
- Reverse transcriptase polymerase chain reaction (RT-PCR)
- Tissue-based next-generation sequencing (NGS).

The diagnostic accuracy, breadth of mutations, financial cost, and time required for each test vary considerably.

Precision oncology requires equal emphasis on new drugs and identifying the patients most likely to benefit from them

Immunohistochemical staining

IHC staining is a histology-based analytical tool for identifying mutational variants through specialized stains and targeted antibodies to demonstrate the presence or absence of a genetic variant within the tissue sample. It is largely used as a screening tool, given its demonstrated ability to efficiently capture identifiable variants.

Multiple studies have demonstrated sensitivity ranging from 86% to 100% and specificity of 76% to 100% for detecting *ALK* variants, with similar evidence for detecting *EGFR* mutations.[31–35]

The cost of IHC ranges from $33 to $124 and averages $73, making it the cheapest test for mutations.[36] IHC testing for *ALK* is FDA-approved, with FISH used for equivocal cases. For *ROS1*, IHC may be used in screening, but

further FISH, PCR, or NGS testing should be used to confirm positive results and rule out false-positive results.

Because of limited sensitivity in detecting specific *EGFR* mutations, using IHC to determine candidacy for targeted agents against EGFR is discouraged in current guidelines for mutational testing.[37]

Fluorescence in situ hybridization

Similar to IHC, FISH analysis utilizes patient tissue samples for a histology-based assay of genetic variants. However, unlike IHC, FISH probes are predicated on complementary binding that can identify specific genetic sequences of interest. Using fluorescently labeled DNA or RNA probes created to reciprocally bind targets of interest, FISH analyses can detect the presence of their target sequences, and thus genetic variants, within prepared tissue samples.

FISH remains the gold standard for detecting mutant fusion protein variants and is still widely used for this purpose today. The sensitivity ranges between 90.3% and 100% and the specificity between 97.7% and 100% among patients being tested for *ALK* rearrangements.[38,39] Cost of FISH testing averages about $300, and turnaround processing time averages about 2 to 5 days, marginally longer than that of IHC processing.[36]

RT-PCR has the advantage of not requiring a biopsy sample

The most significant drawbacks of FISH testing arise from its limited scope (each test is specific for 1 genetic variant), need for fluorescent microscope workstations, and the qualitative component of its assessment (there may be some ambiguity based on the cutoff point for positive vs negative results).[40]

Reverse transcriptase polymerase chain reaction-based methods

RT-PCR analysis uses unique, labeled DNA probes to identify, amplify, and quantify the levels of specific genetic variants in tissue samples. It has demonstrated efficacy and accuracy as a stand-alone diagnostic tool and in comparison to IHC, FISH, and NGS.[41] Advantages: it can perform multiple simultaneous assessments, it can be done on samples other than biopsy tissue (such as blood), and it is objective—there is no subjective rating of positivity as in IHC and FISH. Its sensitivity for identifying mutational variants ranges from 88% to 100% and its specificity from 94% to 100%.[39,42,43]

While the individual costs of a single RT-PCR assay are difficult to characterize owing to the variability of pricing of reagents, technical labor, and available facilities, multiple studies have demonstrated the cost-effectiveness of RT-PCR testing in comparison to histology-based diagnostic tools.

Tissue-based next-generation sequencing

By identifying the full genetic sequences of targeted areas of the genome, NGS is able to identify both documented and previously undiscovered mutational variants by similar principles of complementary nucleotide binding as RT-PCR, but at a larger scale.[44] This broad applicability allows for interrogation of an ever-expanding library of driver mutations, all at once, with pinpoint accuracy.

Advances in NGS technology over the last several years have driven down overall costs while improving accuracy and ease of application, making economical feasibility a reality. NGS is now commonly used in genetic assessment in advanced NSCLC.[45–47] In its earliest iterations, NGS was demonstrated to have high sensitivity and specificity values by validation studies (95%–99%, with positive predictive value > 99%).[48] More recent studies have assessed these markers of accuracy at 100% for both sensitivity and specificity, establishing NGS as the comparative technique against which other mutation identification processes can be evaluated.[49,50]

However, the estimated cost of targeted gene panel sequencing averages $1,609, with significant variation depending on the size of the panel of mutational targets, preference for whole-exome sequencing ($4,459), or whole-exome plus RNA sequencing ($5,938).[45] In addition, turnaround times for NGS studies are long, with estimates of 13 to 21 days on average in multiple studies.[51]

Plasma genotyping

Plasma genotyping, popularly called "liquid biopsy," a broad collection of screening tests utilizing capture and identification of circulating tumor DNA (ctDNA), has demonstrated incredible promise in its early forms.[52–55] It has significant clinical potential, given its ease of implementation, low risk compared with tis-

sue-dependent screening methods, rapid turnaround time, and ability to perform screening analysis without limitations (eg, amount of tissue collected, need for repeat biopsy). This technology may allow for detection of new actionable mutations, characterization of response to therapy, and identification of mechanisms of resistance to therapy.[56,57] Early assessments have demonstrated some level of agreement between ctDNA assessments and previously confirmed tissue diagnoses, with high levels of individualized variant identification by ctDNA alone.

HOW HAS NEXT-GENERATION SEQUENCING ALTERED TESTING PRACTICES?

Clinicians practicing precision medicine must carefully consider the cost-benefit analysis of this approach and plan their diagnostic and therapeutic course accordingly: What actionable information will result from testing? What testing method will provide maximal utilizable information at the lowest cost? What is the feasibility of implementing a therapy based on that information?

Clinicians can use a wide array of testing procedures that have well-documented clinical efficacy, from histology-based IHC analyses to small-scale quantitative PCR assays. Employing these tests for initial screening, especially in settings with limited access to advanced technologies or ability to follow through on the data they provide, even for a faster stepwise diagnostic approach, could allow clinical oncologists to refine their approach to diagnosis and treatment in the precision medicine era.

NGS technology provides an unparalleled view of the genetic framework of a patient's disease. It allows clinicians and researchers to identify a significant proportion of the full mutational burden of a tumor and uncover the various targets for which therapies can be used. This has created many opportunities for research and clinical investigation of this technology, opening the door for trials exploring the efficacy of a wide range of therapies.

Looking ahead, application of NGS technology to ctDNA isolated from simple blood samples continues to expand the landscape of precision medicine. The potential to identify and exhaustively characterize tumors with rapid, noninvasive diagnostic tools is incredibly appealing. Like NGS technology and the precision oncology movement as a whole, the inherent potential for paradigm-shifting clinical impact will continue to drive interest in this technology.

FUTURE DIRECTIONS FOR RESEARCH AND CLINICAL PRACTICE

As research advances our understanding of the molecular framework of NSCLC, clinicians must stay informed about the latest testing methods and therapies, actionable mutations, and breakthrough approaches. Research into the *EGFR*, *BRAF*, *ALK*, *ROS1*, and other alterations driving disease has unlocked treatments that have changed the course of disease in countless patients. The use of precision medicine in NSCLC will benefit patients for years to come.

Future discussions of the research and therapies surrounding NSCLC will necessarily focus on:

- Discovery of new driver mutations
- New therapies that target these currently unidentified mutations
- Advances in currently developed therapies
- Results of clinical trials and bench research currently in progress
- Expansion and streamlining of the testing procedures used for variant identification (ie, genomic sequencing).

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

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