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Abdominal pain without physical findings is not always without physical cause

Should every patient with an unprovoked VTE have a hypercoagulable workup?

Stop the clot: When is laboratory evaluation for thrombophilia warranted?

Mesenteric ischemia: Recognizing an uncommon disorder and distinguishing among its causes

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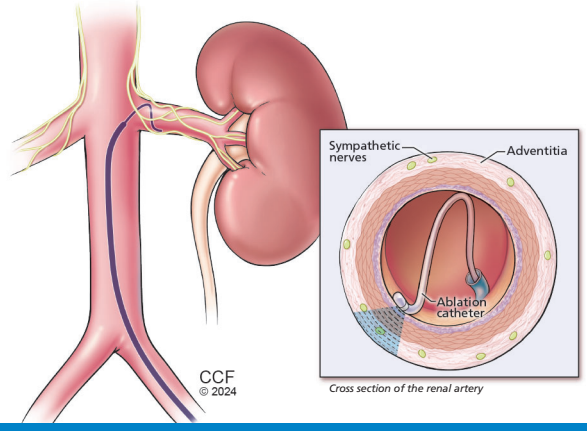

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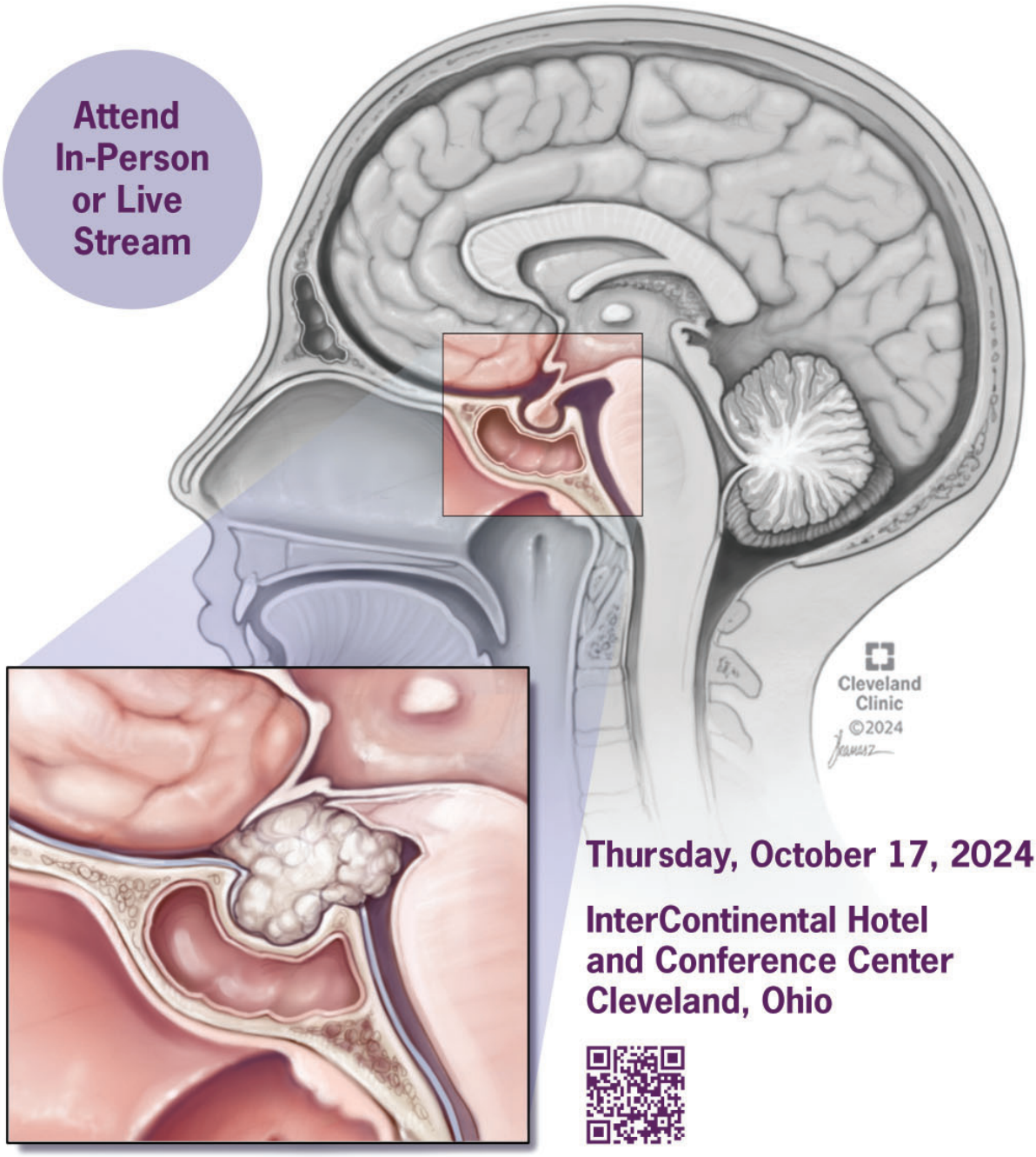

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Abdominal pain without physical findings is not always without physical cause

The first real clinical book (distinct from the usual textbook) I recall reading on a regular basis was *Early Diagnosis of the Acute Abdomen*[1] by Sir Vincent Zachary Cope, MS, MD. The original text was written in 1921, and there are now more than 20 editions with updates. Apparently, I was not alone in my appreciation.

I recall first using Cope's *Early Diagnosis* as a medical student while on my third-year general surgery rotation. I've given away copies to trainees and then purchased newer editions, which I referred to frequently when I was "moonlighting" in the emergency department. Since then, I have used it occasionally, such as when attending on a general medicine inpatient service or when faced with patients experiencing confusing abdominal symptoms. Books like this inspire my respect for those clinical diagnosticians able to separate the *wheat* from the *chaff* in the medical history and physical examination and propose a clinical diagnosis that can then be confirmed using appropriate testing and interventions. But what about clinical scenarios when the physical examination is not helpful?

Given the limitations of diagnostic testing available at the time *Early Diagnosis* was first published, Cope, and other authors since,[2] emphasized the need for high clinical suspicion in the appropriate clinical setting in order to make the diagnosis of mesenteric ischemia. The classic presentation of *acute* mesenteric ischemia is often described as severe and sudden pain out of proportion to physical examination findings. Thus, especially in stoic or perceived histrionic patients, the diagnosis can easily be delayed or missed entirely. As discussed by Wu and Nanjundappa[3] in this issue of the *Journal*, a shared etiologic factor for many patients with acute mesenteric ischemia is the presence of atherosclerotic cardiovascular disease, which translates into this condition being more prevalent in older patients. There are, however, uncommon clinical conditions that can cause acute bowel ischemia in younger patients as well,[4] posing a diagnostic challenge in a young patient with abdominal pain out of proportion to laboratory abnormalities or findings on physical examination that raises the red flag for "drug-seeking behavior" in emergency rooms. It takes vigilance, clinical adroitness, and often some luck to make the correct early diagnosis before bowel infarction occurs when the patient presents with localized abdominal pain, rebound tenderness, a rising lactate level and anion gap, and a dropping bicarbonate. I am always wary of the "drug-seeking behavior" label, particularly in the acute setting.

Chronic mesenteric ischemia can be even more difficult to diagnose. It can progress insidiously. Patients may present with months (or longer) of chronic abdominal pain, also with the relative absence of abdominal physical findings. In older patients, chronic mesenteric ischemia often results from progressing atherosclerotic disease, but in younger patients it could be due to systemic inflammatory vascular disease, hypercoagulable disorders, or noninflammatory syndromes that can cause extrinsic occlusion of the mesenteric vessels. The last of these 3 includes retroperitoneal fibrosis and the difficult-to-diagnose median arcuate ligament syndrome.[5] Patients with chronic occlusive disease may experience postprandial abdominal cramping (abdominal angina) and with discussion

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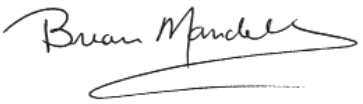
may describe food avoidance and resultant weight loss. These last 2 symptoms are characteristic but not specific, as they also can be strikingly apparent in patients with gastroparesis, gastric cancer, and eosinophilic esophagitis.

The symptoms, laboratory findings, and physical examination of patients with undiagnosed mesenteric ischemia in the real world can be vague and unenlightening. But the sooner the diagnosis is considered and vascular imaging is obtained, the sooner appropriate management decisions can be made. The brief review in this issue[3] is worth reading as a reminder of this serious clinical entity, which is characterized by a disconnect between the patient's symptoms and the physical examination—a disconnect that, when not recognized, can contribute to a catastrophic outcome.



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BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Should every patient with an unprovoked venous thromboembolism have a hypercoagulable workup?

A: The decision to order a hypercoagulable workup for a patient with an unprovoked venous thromboembolism (VTE) must be individualized based on the patient's clinical picture, medical history, and family history. This medical decision remains controversial, as no clear guidelines in the United States have been established on this topic. Testing patients with an unprovoked VTE may lead to excessive medical costs, but when done methodically, hypercoagulable studies may yield valuable results. Ultimately, the decision to test is made on a case-by-case basis.

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UNPROVOKED VTE

VTE most commonly presents either as a deep vein thrombosis or pulmonary embolism. VTE is considered provoked if the patient has a temporary or a permanent risk factor. If there are no identifiable risk factors, then it is considered an unprovoked VTE.[1]

VTEs are diagnosed with a combination of clinical findings and imaging results. Treatment focuses on resolving active thromboses and preventing recurrence. This is achieved with oral factor Xa inhibitors taken for at least 3 months. Moreover, the American College of Chest Physicians recommends extended-duration anticoagulation for select patients with provoked VTEs and most, if not all, patients with unprovoked VTEs.[2] The American Society of Hematology even recommends indefinite anticoagulation for recurrent VTE as long as the patient can tolerate the anticoagulants.[3] Of note, oral vitamin K antagonists (ie, warfarin) are preferred anticoagulants for patients diagnosed with antiphospholipid syndrome.[2,3]

Treatment is started whether the VTE is provoked or unprovoked. First-time provoked VTEs do not require further workup. On the other hand, unprovoked VTEs may require a hypercoagulable workup.

THE HYPERCOAGULABLE WORKUP

Multiple studies in various hospital settings and locations have highlighted the number of inappropriate hypercoagulable tests ordered. One study showed that up to 55% of Medicare patients with provoked VTE received a hypercoagulable workup.[4] These studies pointed to various knowledge gaps and a lack of consistent guidelines as potential causes for inappropriate testing.[5–7] What to test, when to test, and who to test are important questions to consider.

The hypercoagulable workup most often includes 5 tests for inherited thrombophilia: factor V Leiden, prothrombin G20210A mutation, protein C deficiency, protein S deficiency, and antithrombin III deficiency.[8] Tests necessary to diagnose antiphospholipid syndrome might be ordered in certain clinical scenarios; these tests include the lupus anticoagulant functional assay (eg, dilute Russell's viper venom test, patient plasma correction tests), anti-beta-2-glycoprotein 1 antibody (immunoglobulin [Ig] M, IgG), and anticardiolipin antibody (IgM, IgG). One test that should be ordered

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sparingly is the methylene tetrahydrofolate reductase (*MTHFR*) gene test, as several studies have shown that *MTHFR* polymorphisms may not be risk factors for VTE.[9–11]

The ideal time to test patients depends on the nature of the test. For instance, factor V Leiden and prothrombin G20210A mutation are genetic tests, so these may be ordered any time. On the other hand, protein C deficiency, protein S deficiency, and antithrombin III deficiency lead to anticoagulant protein deficiencies during the acute phase of an illness, so testing at that time may lead to unreliable test results.[12] Another factor to consider is whether patients are currently taking anticoagulants. For example, oral factor Xa inhibitors may lead to false-positive lupus anticoagulant assays. Patients should be off oral factor Xa inhibitors for at least 2 to 3 days before testing, and those on a vitamin K antagonist should have therapy held for at least 2 weeks.[8] When testing to diagnose antiphospholipid syndrome, 2 sets of tests must be ordered 12 weeks apart.[8]

A patient with a personal history of recurrent VTE, a family history of VTE, or both may benefit from a hypercoagulable workup. On the other hand, patients with thromboses in the arterial circulation and unusual venous sites (ie, Budd-Chiari, cerebral venous thrombosis) may benefit from an antiphospholipid syndrome workup as this may affect the choice of oral anticoagulants. Patients younger than 45 who develop VTE may benefit from a hypercoagulable and antiphospholipid syndrome workups.[4,8]

POTENTIAL BENEFITS OF TESTING

Hereditary thrombophilias have not been shown to increase the risk of recurrent unprovoked VTEs.[13] Thus, the results of a hypercoagulable workup may only be relevant in select patients.[14] However, there may still be reasons why a patient with an unprovoked VTE should get a hypercoagulable workup.

First, testing allows clinicians to provide guideline-directed recommendations to patients. As noted above, if the hypercoagulable workup results are positive, the American Society of Hematology recommends indefinite use of oral factor Xa inhibitors while tolerated.

Second, some patients are simply curious as to what caused their unprovoked VTE.

Third, a patient may want to know about inherited conditions that could affect their offspring. People with thrombophilias are at an increased risk of developing VTE, which is compounded by taking combined oral contraceptives.[15] Patients found to have thrombophilia could be advised against using combined oral contraceptives.

Finally, doing a hypercoagulable workup may facilitate prevention of flight-related VTE through "flight prophylaxis."[16] A literature review from 2018 on this topic highlighted the Long Flights Thrombosis (LONFLIT)-3 study, which showed that taking low-molecular-weight heparin 2 to 4 hours before departure drastically reduced the risk of VTE.[16] At that time, there were no studies demonstrating the role of oral factor Xa inhibitors in preventing flight-related VTE.

CONCLUSION

In patients with an initial provoked VTE, a hypercoagulable workup is not necessary. Patients who develop clots at unusual sites and are younger than 45 may benefit from an antiphospholipid syndrome workup. Left in the middle are patients with unprovoked VTEs. For these patients, clinicians must take an individualized approach that considers personal and family history to determine the appropriateness of a hypercoagulable workup. Knowing the nuances around testing may increase the value of this workup. A retrospective analysis showed that implementing local guidelines on thrombophilia testing reduced healthcare costs and improved patient care.[17] Establishing consensus guidelines in the United States may optimize the value of these tests further. Along these lines, the National Institute for Health and Care Excellence in England and Wales recommends thrombophilia testing for patients with an unprovoked VTE if it is recurrent or if there is a family history of VTE.[18] Other than these suggestions, a readily available medical calculator that incorporates multiple factors may be helpful in guiding a clinician on when to order a hypercoagulable workup for a patient with an unprovoked VTE.

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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Stop the clot: When is laboratory evaluation for thrombophilia warranted?

On discovering that a patient has an arterial or venous thrombosis, 2 important questions should be considered. First, is a thrombophilia evaluation warranted? Second, if a thrombophilia evaluation is warranted, when should it be conducted? There is tremendous practice variation in this area, which may be a consequence of multiple societies publishing slightly different guidelines and inadequate evidence to guide clinical decisions. In particular, there is a dearth of robust literature to guide clinical practice decisions for patients with an unprovoked thrombotic event. In this issue, Tan et al[1] review the available evidence to guide case-by-case decision-making on the need for a hypercoagulable workup after an unprovoked venous thromboembolism (VTE).

See related article, page 531

INSUFFICIENT EVIDENCE TO SUPPORT ROUTINE TESTING, BUT . . .

The American Society of Hematology guidelines[2] published in 2023 suggest not routinely conducting thrombophilia testing in patients with an unprovoked VTE, noting that the evidence available to support routine testing is weak. However, the estimated relative risk for VTE recurrence is based on the average recurrence incidence across all types of thrombophilia, and the rarity of some of these conditions limits the generalizability of this recommendation. As such, the American Society of Hematology guidelines acknowledge that testing may be considered in cases of unprovoked VTE where the results could influence the anticoagulation duration, and also note that the presence of permanent thrombotic risk factors may dictate the overall duration of anticoagulation.[2]

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Testing for causes of arterial thrombosis

In contrast to VTE, arterial thrombosis has more serious consequences and typically involves end-organ damage, almost always due to atheroembolic events. As with venous thrombosis, routine testing after an index arterial thrombosis event may not be indicated. Nevertheless, for thrombosis in a younger patient without an apparent cause, thrombophilia testing may be reasonable, especially when a family history is established.

A common cause of arterial thrombosis is antiphospholipid syndrome, especially in patients with autoimmune conditions or women with recurrent miscarriage. When considering treatment options for thrombosis in patients with antiphospholipid syndrome, data now convincingly show the superiority of vitamin K antagonists compared with oral factor Xa inhibitors, because factor Xa inhibitors have a higher likelihood of breakthrough arterial thrombosis.[3] In such cases, limited thrombophilia panel testing for anti-beta-2-glycoprotein 1 antibody, anticardiolipin antibody, and lupus anticoagulant may be reasonable because the impact on appropriate treatment is clear.[2]

Paroxysmal nocturnal hemoglobinuria is another serious cause of arterial thrombosis to consider, especially when hepatic venous outflow obstruction or anemia with hematuria is present. It is diagnosed by flow cytometry at most institutions.[4]

Type II (autoimmune) heparin-induced thrombocytopenia should be considered in patients treated with unfractionated heparin or low-molecular-weight heparin who, after starting anticoagulation therapy, experience a precipitous decline in circulating platelets with coinciding venous or arterial thrombosis (which often manifests as ischemic stroke and purpura on skin examination).[5]

Provoked events

Theoretically, with a provoked thrombotic event, it would be reasonable to assume that a future thrombotic event would not occur once the provoking factor has been resolved. However, a higher rate of recurrence has been noted in patients with an index VTE event that occurred in relation to a transient risk factor (eg, trauma with fractures, acute illness, pregnancy or puerperium, hormonal contraceptive use) compared with the general population.[6] In such circumstances, the risk of recurrence and, in turn, the duration of anticoagulation are determined by the severity and persistence of the risk factor. Accordingly, extended-duration anticoagulation is needed in patients with active cancer or a hereditary thrombophilia that would lead to a persistent thrombotic risk. For patients with a limited, transient risk for thrombosis, anticoagulation can be discontinued, typically after 3 to 6 months, or after shared decision-making with the patient on the risks and benefits of continued anticoagulation. Thus, if the family history is suggestive, thrombophilia testing may be warranted to determine whether a homozygous factor V Leiden mutation or homozygous prothrombin G20210A mutation is present, as these mutations constitute a permanent risk for thrombosis, even after successful treatment with anticoagulation.[6]

Optimal timing of testing is uncertain

Unfortunately, the optimal timing for evaluation for these diagnoses is difficult to determine, and active treatment with anticoagulation leads to both false-positive and false-negative results in some thrombophilia tests. The presence of acute thrombosis may also limit the interpretation of the test results.

A CASE-BY-CASE APPROACH

In summary, available evidence does not support routine testing for underlying thrombophilia after a thrombotic event, especially hereditary thrombophilia, given the rarity of these conditions. Establishing the presence of thrombotic illnesses and temporally associated risk factors in first-degree relatives is critical during the initial evaluation, but the benefits of testing for an underlying genetic thrombophilia must be discussed with each patient. As Tan et al[1] correctly highlight, patients often want to know the underlying cause of the thrombotic event, as this may dictate perceived restrictions from certain activities (contact sports, family planning, planned dietary interventions), and it may also determine the overall duration of anticoagulation therapy. Regardless, further well-designed studies are needed to better inform existing recommendations. Such studies could also potentially identify patients who would benefit from thrombophilia testing and provide further guidance on using laboratory testing more judiciously.

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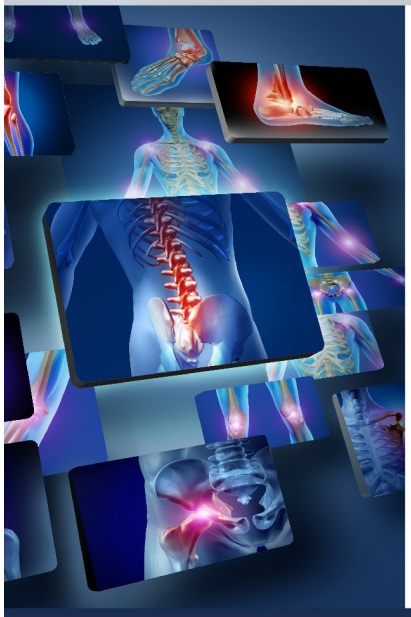

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ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Should my patients with hypertension be referred for renal denervation?

A: Maybe. Select patients should be referred after informed and shared decision-making.

Patients with treatment-resistant hypertension or intolerance to further medication adjustments may be suitable candidates for renal denervation, as it demonstrates a blood pressure (BP)-lowering effect of 5 to 7 mm Hg, comparable to the effect of adding another antihypertensive agent (**Figure 1**).[1–5] Two renal denervation systems—ultrasound and radiofrequency based—are currently approved by the US Food and Drug Administration.[6,7] The European Society of Hypertension updated guidelines[8] state that renal denervation is a consideration for true treatment-resistant hypertension and for patients with drug intolerances and an estimated glomerular filtration rate (eGFR) greater than 40 mL/minute/1.73 m^2.

SETTING EXPECTATIONS, RULING OUT PSEUDORESISTANCE

It is important to discuss with patients that renal denervation serves as an additional option in the antihypertensive arsenal, but it does not cure hypertension. Discussions to set realistic expectations surrounding BP reduction should be had with the patient specifically regarding the need to continue diet and lifestyle modifications and most of their current pharmacotherapy. The importance of shared decision-making is highlighted in these guidelines.

Of note, apparent treatment-resistant hypertension is defined as uncontrolled BP (daytime mean systolic BP ≥ 135 mm Hg) while taking at least 3 optimally dosed (or maximally tolerated) antihypertensive agents, including a diuretic, or controlled hypertension requiring 4 or more medications.[9] When a patient presents with apparent treatment-resistant hypertension, it is critical to rule out pseudoresistance, as these patients may not require any further intervention. White coat hypertension or white coat effect (higher BP in office than at home) is ruled out by evaluating out-of-office BP control. Other contributors to pseudoresistance include improper BP measurement, suboptimal pharmacotherapy, and medication nonadherence.

TREATMENT ADHERENCE

In the **SYMPATHY** (Renal Sympathetic Denervation as a New Treatment for Therapy Resistant Hypertension) trial,[10] investigators assessed renal denervation vs usual care and medication adherence. Physicians and participants were unaware of the adherence assessment, circumventing the Hawthorne effect. Eighty percent of patients were not adherent to the prescribed regimen, with fewer medications detected than prescribed; on average, 2 medications were detected in blood or urine samples as opposed to the 4 prescribed.[10] Ruzicka et al[9] assessed treatment adherence via directly observed therapy in patients with apparent treatment-resistant hypertension. Resistant hypertension resolved in 30% of patients.

Medication nonadherence can be quite challenging, particularly in patients with treatment-resistant hypertension, as pill burden, complex regimens, comorbid conditions, and medication side effects can all contribute. Tools to assess adherence include prescription fill rates and measuring medication concentration in the blood or urine. While not an exclusion for renal denervation, obtaining this information better informs the shared decision-making process. Interestingly enough, simply

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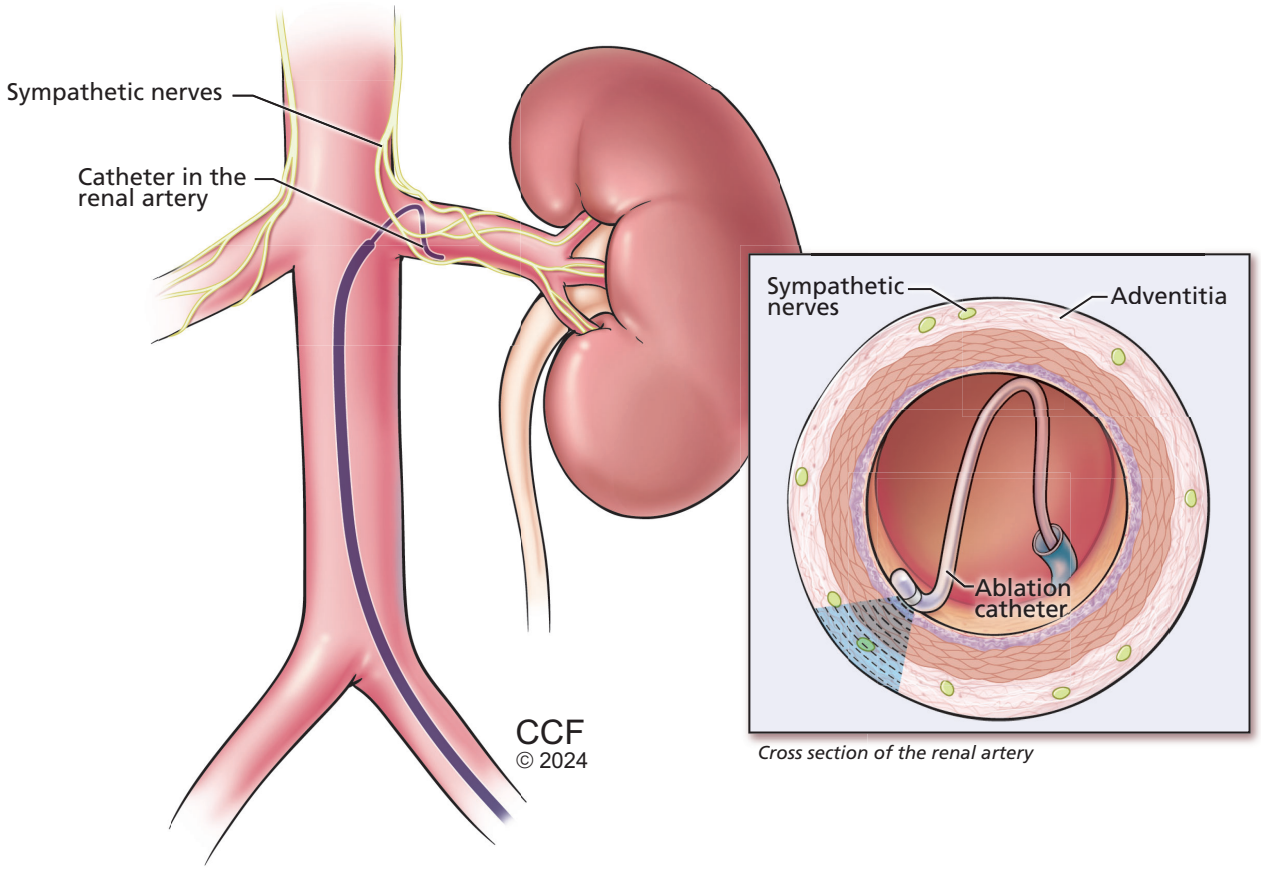

Figure 1. Renal denervation

informing patients of detected nonadherence can lead to behavioral changes (in up to 80% of patients)[11] and reduce BP by up to 46/26 mm Hg.[12] Other strategies such as streamlining the regimen, incorporating combination medications, and engaging in dialogue with the patient to understand potential causes of nonadherence—like side effects or cost concerns—are great starting points to attempt to improve adherence.

SCENARIO 1: APPARENT TREATMENT-RESISTANT HYPERTENSION

A 60-year-old female presents for hypertension follow-up. Although she is on 4 optimally dosed agents (angiotensin-converting enzyme inhibitor, calcium channel blocker, chlorthalidone, and spironolactone), her systolic BP continues to be greater than 140 mm Hg. The physician considers referral for renal denervation.

The history of renal denervation traces back to 1953, when splanchnicectomy (surgical removal of splanchnic nerves) was introduced as a treatment for severe primary hypertension and was shown to be very effective in treating hypertension.[13] However, this procedure became obsolete because of significant morbidity, including severe orthostatic hypotension, urinary and fecal incontinence, and erectile dysfunction.

Renal denervation decreases sympathetic nervous signaling between the central nervous system and the kidneys, considered one of many mediators of hypertension and treatment-resistant hypertension.[14] Numerous early non-sham-controlled trials of renal denervation demonstrated large BP reductions.[15] However, **SYMPLICITY HTN-3** (Renal Denervation in Patients With Uncontrolled Hypertension),[16] the first pivotal randomized sham-controlled trial, did not meet its primary efficacy end point at 6 months, thereby dampening enthusiasm for this technology. Much has been written about the efficacy results of the SYMPLICITY HTN-3 trial, including critiques of the study design, use of confounding medications, and inconsistent procedural techniques.[17] A post hoc analysis derived from patient cohorts showed that there

were no significant differences in BP changes between the denervation and sham control group for patients on vasodilators or aldosterone antagonists, although there was a trend for greater change in office systolic BP in patients in the renal denervation group who were receiving beta-blockers and calcium-channel blockers.[18]

Evidence for efficacy

Subsequent randomized sham-controlled trials[5,19] addressed these shortcomings and produced compelling evidence supporting the efficacy of renal denervation to lower BP. These seminal trials demonstrated noteworthy, albeit not dramatic, BP reduction in patients with uncontrolled hypertension.

In **RADIANCE-HTN TRIO** (A Study of the ReCor Medical Paradise System in Clinical Hypertension-Resistance to Triple Medication Pill),[5] ultrasound-based renal denervation was compared with a sham procedure in patients with uncontrolled BP despite 3 or more antihypertensive medications. Renal denervation reduced daytime ambulatory BP more than the sham procedure: –8.0 mm Hg (interquartile range –16.4 to 0) vs –3.0 (interquartile range –10.3 to 1.8). The median between-group difference was –4.5 mm Hg (95% confidence interval [CI] –8.5 to –0.3, adjusted P = .022). The median between-group difference in patients with complete ambulatory BP data was –5.8 mm Hg (95% CI –9.7 to –1.6, adjusted P = .0051).[5]

The randomized, single-blind, sham-controlled **SPYRAL HTN-ON MED** (Global Clinical Study of Renal Denervation With the Symplicity Spyral Multi-electrode Renal Denervation System in Patients With Uncontrolled Hypertension on Standard Medical Therapy) expansion trial[19] evaluated radiofrequency-based renal denervation in patients with uncontrolled hypertension. The study enrolled 467 patients from multiple countries, 80 of whom were randomized to undergo renal denervation or the sham procedure. At 36 months, the ambulatory systolic BP reduction was –18.7 mm Hg (standard deviation [SD] 12.4) for the renal denervation group (n = 30) and –8.6 mm Hg (SD 14.6) for the sham control group (n = 32), with an adjusted treatment difference of –10.0 mm Hg (95% CI –16.6 to –3.3, P = .0039). Treatment differences between the renal denervation group and sham control group at 36 months were as follows:

- –5.9 mm Hg (95% CI –10.1 to –1.8, P = .0055) for mean ambulatory diastolic BP
- –11.0 mm Hg (95% CI –19.8 to –2.1, P = .016) for morning systolic BP
- –11.8 mm Hg (95% CI –19.0 to –4.7, P = .0017) for night-time systolic BP.

TABLE 1
Patient characteristics for potential treatment with renal denervation

Exclusion criteria
White coat hypertension
Secondary hypertension
Renovascular hypertension
Primary aldosteronism
Hyperthyroidism
Pheochromocytoma
Cushing syndrome
Coarctation of the aorta
Isolated systolic hypertension
Pregnancy
Estimated glomerular filtration rate < 30 mL/minute/1.73 m^2
Inadequate renal artery anatomy
Characteristics of potential candidates
Treatment-resistant hypertension
Multiple medication intolerances
Medication adherence difficulty

Safety evidence

Safety concerns surrounding renal denervation are worth addressing. Theoretical concerns include damage to the renal artery from the applied energy, resulting in dissection or de novo stenosis, and contrast-associated nephropathy causing eGFR decline.[20,21] Currently, there are no safety signals noted in these trials within the constraints of the populations studied (eGFR > 40 mL/minute/1.73 m^2). Longer-term data from **Global SYMPLICITY** (Global Prospective Registry for Sympathetic Renal Denervation in Selected Indications Through 3 Years)[3] showed overall reassuring eGFR trends, and new renal artery stenosis (> 70% diameter stenosis) occurred in only 3 (0.1%) of 2,112 patients at risk over a 1-year follow-up period and 4 (0.3%) of 1,345 at risk over 3 years. Notably, the US Food and Drug Administration Circulatory System Devices Panel in August 2023 voted unanimously that both ultrasound-based (Paradise Ultrasound system) and radiofrequency-based (Symplicity Spyral System) renal denervation technologies are safe.[6,7]

When deciding whether to proceed with renal denervation in patients like the one in scenario 1, clinicians must provide careful education, set realistic expectations, and explore alternative options. Also, renal denervation should only be considered after ruling out pseudoresistance. Patients considering renal denervation must understand that potential BP reduction from denervation is most likely equivalent

to that of an additional antihypertensive agent. Aside from having a higher baseline BP and heart rate, no other factors that predict response to renal denervation therapy have been identified.[4] Also, there are no head-to-head trials comparing renal denervation and additional pharmacologic interventions.

SCENARIO 2: INTOLERANCE TO BP MEDICATIONS

A 36-year-old female seeks a second opinion regarding the management of hypertension. Diagnosed with hypertension 2 years ago, she has tried multiple medications with poor tolerance owing to allergic reactions or side effects. Her BP remains uncontrolled, and renal denervation is being considered.

Patients with multiple drug intolerances are candidates for renal denervation. **RADIANCE HTN SOLO** (A Study of the ReCor Medical Paradise System in Clinical Hypertension)[1] examined the use of ultrasound energy–based renal denervation in adult patients age 18 to 75 with hypertension while off antihypertensive therapy. Patients who underwent renal denervation had a greater reduction in daytime ambulatory systolic BP compared with those who had the sham procedure: –8.5 mm Hg (SD 9.3) vs –2.2 mm Hg (SD 10.0). The difference between groups was –6.3 mm Hg (95% CI –9.4 to –3.1, $P = .0001$).[1]

RADIANCE II (A Study of the Recor Medical Paradise System in Stage II Hypertension)[22] further evaluated renal denervation in a similar population of adults with previously uncontrolled hypertension on up to 2 antihypertensive medications. The procedure was performed after a 4-week medication washout. Daytime ambulatory systolic BP was significantly reduced with renal denervation (mean –7.9 mm Hg [SD 11.6]) vs sham procedure (mean –1.8 mm Hg [SD 9.5]), with an adjusted difference between groups of –6.3 mm Hg (95% CI –9.3 to –3.2, $P < .001$). The BP-lowering effect of renal denervation was consistent throughout the 24-hour circadian cycle.[22]

Similar results were achieved in the **SPYRAL HTN-OFF MED** (Global Clinical Study of Renal Denervation With the Symplicity Spyral Multi-electrode Renal Denervation System in Patients With Uncontrolled Hypertension in the Absence of Antihypertensive Medications) cohort[2] in which patients with hypertension not on any antihypertensive medications achieved a significant drop in BP with renal denervation vs sham, with a difference of –3.9 mm Hg for 24-hour systolic BP and –6.5 mm Hg for in-office systolic BP.

A patient-level pooled analysis of RADIANCE-HTN SOLO, RADIANCE-HTN TRIO, and RADIANCE II revealed that the BP-lowering effect of ultrasound-based renal denervation was consistent across the spectrum of hypertension severity.[4] BP reduction effects were shown to be sustained after 3 years in the Global SYMPLICITY registry,[3] with the largest BP drop in the subgroups with more severe hypertension. The data illustrate that renal denervation is a reasonable and effective alternative for patients who cannot tolerate or are unable to take medications, even if they do not meet the criteria for true treatment-resistant hypertension.

It is important to note that secondary forms of hypertension represent a contraindication for renal denervation. Before referring the 36-year-old patient in scenario 2 for renal denervation, an in-depth evaluation for secondary causes should be completed. Hypertension treatment in the setting of an underlying secondary cause should be tailored to the underlying pathology. Whether there is a supportive role for renal denervation in select cases is yet to be seen.

Table 1 lists exclusion criteria and characteristics of patients for whom treatment with renal denervation could be appropriate.

THE BOTTOM LINE

Recent studies have demonstrated the efficacy and safety of catheter-based renal artery denervation with radiofrequency or ultrasound energy in reducing blood pressure across the hypertension spectrum, with multiple trials suggesting a significant and sustained reduction in BP. In some studies, BP reduction was sustained for up to 36 months after renal denervation. More data are needed to determine whether attenuating the renal sympathetic nervous system offers end-organ protection beyond BP reduction. Renal denervation may be offered as an alternative or adjunct to pharmacotherapy in patients with apparent treatment-resistant hypertension, multidrug intolerance, or nonadherence. Shared decision-making, including establishing realistic expectations regarding lowering BP, is crucial before proceeding with renal denervation.

DISCLOSURES

Dr Laffin has disclosed being an advisor or review panel participant for research for Arrowhead, AstraZeneca Pharmaceuticals, Crisper Therapeutics, Gordy Health, and LucidAct Health; teaching and speaking for Cardiometabolic Health Congress; Executive Committee member of SURMOUNT MMO Trial for Eli Lilly; consulting for Idorsia Pharmaceuticals Ltd and Medtronic; Executive Committee member in phase 2 trials for Mineralys Therapeutics; and past research relationship with Amgen. Dr Ziada has disclosed teaching and speaking for Abbott Vascular. Dr. Nanjundappa has disclosed teaching and speaking for Abbott, Medtronic, and Phillips Healthcare, consulting for Argon and Phillips Healthcare, and ownership interest (stock, stock options in a publicly owned company) for Zoll. Dr Mehdi has disclosed being an advisor or review panel participant for Fresenius, teaching and speaking for GlaxoSmithKline, and past teaching and speaking for AstraZeneca. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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Mesenteric ischemia: Recognizing an uncommon disorder and distinguishing among its causes

ABSTRACT

Mesenteric ischemia occurs because of inadequate intestinal blood flow. Its severity depends on the vessels involved and whether collateral blood vessels are available to prevent malperfusion. Mesenteric ischemia is an uncommon cause of abdominal pain, but it is associated with high mortality and often poses a diagnostic challenge to clinicians because its symptoms are nonspecific. Early recognition and treatment are imperative to improve patient outcomes.

KEY POINTS

- Mesenteric ischemia is classified into acute or chronic subtypes according to the timing of vessel occlusion and onset of symptoms.
- Diagnosis requires a high index of suspicion with focused evaluation.
- Early recognition and intervention are key to preventing morbidity and mortality.

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Mesenteric ischemia is an uncommon cause of abdominal pain that occurs from inadequate intestinal blood flow. It is associated with high mortality owing to the challenge of diagnosis. Mesenteric ischemia is classified as acute or chronic based on the timing of vessel occlusion and onset of symptoms. Early recognition and treatment are imperative to improve patient outcomes. This article reviews key features of common and uncommon causes of mesenteric ischemia.

MESENTERIC CIRCULATION

The mesenteric circulation is a complex vascular network supplied by 3 primary vessels: the celiac artery, superior mesenteric artery (SMA), and inferior mesenteric artery. The celiac artery perfuses the gastric, splenic, and hepatic organs, as well as the intestines through the gastroduodenal artery; the SMA supplies the midgut organs from the duodenal papillae to the proximal two-thirds of the colon; and the inferior mesenteric artery perfuses the distal one-third of the transverse colon, descending colon, and proximal two-thirds of the rectum. The celiac artery and SMA are primarily connected through the pancreaticoduodenal arcades, and the SMA and inferior mesenteric artery are connected by the marginal artery of Drummond and the arc of Riolan. Such collateral pathways ensure that the intestines are protected from transient periods of malperfusion.

TABLE 1
Causes and clinical features of acute mesenteric ischemia

Cause	Incidence (%)	Clinical features	Risk factors
Arterial embolism	49	Acute, severe abdominal pain Peritonitis Bloody bowel movements	Atrial fibrillation Left ventricular dysfunction Aortic atherosclerosis Endocarditis
Arterial thrombosis	29	Postprandial pain Weight loss Food aversion	Atherosclerosis (acute-on-chronic mesenteric ischemia) Abdominal trauma Dissection Vasculitis
Nonocclusive mesenteric ischemia	20	Peritonitis Sepsis	Critical illness Vasoconstrictive medications
Venous thrombosis	10	Vague, colicky abdominal pain	Surgery Inflammatory bowel disease Cirrhosis Sepsis Malignancy Hypercoagulability

Based on information from references 6 and 8.

TYPES OF MESENTERIC ISCHEMIA

Mesenteric ischemia can be classified as acute or chronic according to the timing of blood flow compromise and symptom onset. Acute mesenteric ischemia is a potentially fatal vascular emergency characterized by sudden intestinal hypoperfusion after abrupt obstruction of arterial or venous blood flow.[1] Symptoms of acute mesenteric ischemia are typically profound owing to a lack of available collateral blood vessels. Chronic mesenteric ischemia refers to episodic intestinal hypoperfusion caused by multivessel stenosis or occlusion, usually due to atherosclerosis. Symptomatic patients typically present with abdominal angina, characterized by postprandial pain, weight loss, and food aversion.[2–4]

ACUTE MESENTERIC ISCHEMIA: CLINICAL RECOGNITION

Acute mesenteric ischemia is uncommon, accounting for less than 1.5% of all emergency department visits for abdominal pain, but its overall mortality exceeds 60%, owing to complications of intestinal infarction and sepsis.[5–7] Clinical presentation varies depending on the underlying pathologic process (**Table 1**).[6,8] The classic clinical presentation involves severe abdominal pain that is "out of proportion" to the physical examination.[7] However, patients may present with atypical symptoms such as nausea, vomiting, and diarrhea, or complications such as peritonitis or sepsis, which often contribute to diagnostic delay.[6,7]

The nonspecific nature of symptoms makes it difficult to differentiate acute mesenteric ischemia from other intra-abdominal pathologies such as acute cholecystitis, pancreatitis, and small-bowel obstruction. A high index of suspicion is critical to making the diagnosis and restoring blood flow, thereby improving patient outcomes. Morbidity depends on how long the vessel has been occluded and whether collateral circulation is present. Patients who present with sepsis are more likely to have poorer outcomes.[7]

CAUSES OF ACUTE MESENTERIC ISCHEMIA

Mesenteric arterial occlusion from embolism or thrombosis is the most common cause of acute mesenteric ischemia (49% and 29%, respectively), followed by nonocclusive mesenteric ischemia (20%–22%) from splanchnic hypoperfusion and vasoconstriction and venous thrombosis (10%).[6,8]

Arterial embolism

Acute arterial embolism causing partial or complete occlusion of the vessel lumen accounts for most (49%) cases of acute mesenteric ischemia.[8] The SMA is often affected owing to its large diameter and oblique take-off

angle, with most emboli lodging distal to the origin of the middle colic artery.[9,10] Most emboli originate from an intracardiac source of thrombus, such as the left atrium in atrial tachyarrhythmia or left ventricle in cardiomyopathy or myocardial ischemia.[11,12] Less commonly, atheroembolism or thromboembolism originates from a proximal aortic segment.[13] Rarely, mesenteric artery embolism has been described as a sequela of infective or nonbacterial thrombotic endocarditis.[14,15]

The symptoms of embolic mesenteric artery occlusion are usually acute and dramatic because of a lack of collateral blood vessels. The typical patient is older, and women are more likely to be affected.[9] Abdominal pain is the predominant symptom in 50% to 80% of patients and may be poorly localized.[16] Nausea, vomiting, or diarrhea are observed in approximately 50% of patients.[16] As bowel infarction develops, signs of peritonitis such as abdominal rebound and guarding may be seen on examination. Bloody bowel movements are uncommon until advanced stages of ischemia, and only one-third of patients present with the classic triad of abdominal pain, fever, and bloody stools.[2] Clinicians should be aware of more atypical presentations, such as mental status change in patients age 65 or older.[17]

Risk factors that should raise suspicion for acute arterial occlusion include history of cardiac arrhythmia, valvular disease, recent myocardial infarction, or aortic atherosclerosis. Roughly one-third of patients report a prior embolic event, and approximately 50% have a history of atrial fibrillation.[7]

Computed tomography angiography is 82% to 96% sensitive and 94% specific in the diagnosis of acute mesenteric ischemia and can additionally indicate a proximal source of embolus.[12,18] Evaluation of these patients should also include prompt echocardiography. Select patients may benefit from ambulatory cardiac monitoring at a later time.

Arterial thrombosis

Mesenteric artery thrombosis accounts for 25% to 30% of acute mesenteric ischemia events.[6] A majority occur at the origin of the SMA or celiac arteries in patients with preexisting atherosclerotic disease.

Acute thrombosis of a stenotic vessel results in symptoms like those of acute mesenteric embolism, also referred to as acute-on-chronic mesenteric ischemia.[19] In some cases, however, progression from stenosis to occlusion and bowel infarction may be insidious owing to the ability of extensive collaterals to maintain gut viability.[20] This often leads to delays in seeking medical care. Many patients report prodromal symptoms of postprandial pain, weight loss, or food aversion suggestive of chronic mesenteric ischemia.[19] Acute abdominal pain in a patient who has a history of such symptoms should raise suspicion for acute mesenteric artery thrombosis.

Less commonly, mesenteric artery thrombosis may occur from vessel injury following abdominal trauma or dissection or an underlying hypercoagulable state from infection or malignancy.[21] Hereditary or acquired thrombophilia are rare causes of mesenteric artery thrombosis. Vasculitis, typically of small to medium vessels, can infrequently result in acute mesenteric ischemia by way of arterial occlusion or vasospasm.[22,23]

Nonocclusive ischemia

Nonocclusive mesenteric ischemia accounts for approximately 20% of acute mesenteric ischemia cases and has an in-hospital mortality of up to 50%.[6,9,24] This form of mesenteric ischemia occurs in the setting of low blood flow states, such as low cardiac output, hypovolemia, or septic shock, leading to splanchnic arterial vasoconstriction, intestinal hypoxia, and necrosis.[25] The extent of ischemic injury is dependent on the number of vessels affected, collateral circulation available, and duration of hypoperfusion.

Nonocclusive mesenteric ischemia is typically seen in patients with severe preexisting disease such as heart failure, aortic insufficiency, and renal impairment, or in patients who are critically ill and receiving vasoconstrictive medications.[25] Symptoms may be absent, as these patients are usually intubated and sedated, and diagnosis is often further delayed by other overshadowing conditions such as hypovolemia and hypotension. As a result, the diagnosis may not be established until complications such as peritonitis or sepsis have developed.[26] Unexplained clinical deterioration with biomarkers of tissue ischemia should raise suspicion for nonocclusive mesenteric ischemia.[27] Computed tomography angiography is used for initial screening and to exclude other causes of acute mesenteric ischemia, and the diagnosis is confirmed on catheter-directed angiography or surgical exploration.[28]

Treatment is focused on hemodynamic support and correcting the underlying cause. Transcatheter infusion of vasodilators such as papaverine and nitroglycerin may be used to relieve mesenteric vasoconstriction in cases where bowel necrosis has not occurred, and laparotomy is indicated when acute peritoneal signs are present.[24]

Venous thrombosis

Mesenteric venous thrombosis is the least common cause of acute mesenteric ischemia, accounting for 10% of cases, with the superior mesenteric vein affected in approximately 95% of cases.[6,29] Other factors that

can impact blood flow include inflammation caused by pancreatitis, inflammatory bowel disease, infection, or trauma including surgery.[2,30] Malignancy is present in up to 16% of patients diagnosed with acute mesenteric venous thrombosis.[29] Cirrhosis and hereditary or acquired thrombophilia can also increase the risk for mesenteric venous thrombosis.[30] Approximately 20% of cases are idiopathic.[2,30]

Mean age at presentation is 40 to 60 years, and mesenteric venous thrombosis is slightly more common in men.[31] The severity of ischemic symptoms depends on the timing of thrombotic occlusion, with acute thrombotic venous occlusion resulting in more profound symptoms because collateral circulation has not developed. Patients may describe middle abdominal pain that is vague and colicky. The onset of pain is usually less abrupt than with acute arterial mesenteric ischemia, and patients typically present with nausea, vomiting, diarrhea, and abdominal cramping. Approximately 75% of patients have symptoms for at least 48 hours before seeking medical attention, and up to 29% of patients are hemodynamically unstable on presentation.[31]

Computed tomography with and without oral contrast is an appropriate initial screening test, and computed tomography or magnetic resonance angiography may be pursued if the initial computed tomography is nondiagnostic and clinical suspicion remains high.[2,30] Doppler ultrasonography is highly specific but less sensitive for mesenteric venous thrombosis, and assessment of the smaller vessels is limited.[29] All patients should be assessed for history of malignancy, liver disease, and recent surgery. Anticoagulation is recommended in cases of acute mesenteric venous thrombosis; the duration of anticoagulation is 6 months or longer depending on the underlying cause.[29]

CAUSES OF CHRONIC MESENTERIC ISCHEMIA

Chronic mesenteric ischemia describes intermittent or continuous intestinal hypoperfusion caused by occlusive disease of the mesenteric vessels. Most cases of chronic mesenteric ischemia are due to atherosclerosis. Less common causes include fibromuscular dysplasia, vasculitis, and retroperitoneal fibrosis.

Atherosclerosis

More than 90% of cases of chronic mesenteric ischemia result from atherosclerotic disease affecting the proximal segments of the visceral vessels.[4,9] Risk factors include smoking, hypertension, diabetes, and the presence of atherosclerosis in other arterial beds. Most patients with chronic mesenteric ischemia are female.[3] The reason is not entirely clear but appears to be related to more acutely angulated mesenteric vessels in women compared with men.[32]

Mesenteric artery stenosis is common, with postmortem and duplex ultrasonography studies reporting an overall prevalence of 6% to 29% and as high as 67% in patients older than 80.[4] Despite this, clinical manifestations of chronic mesenteric ischemia are rare because extensive collateral vessels develop over time, protecting against visceral malperfusion. Because of these collateral networks, symptoms and the need for revascularization are often delayed until at least 2 of the mesenteric vessels are stenosed.[33] The likelihood of mesenteric artery stenosis progressing to symptomatic chronic mesenteric ischemia is higher in multivessel disease.[4] In a retrospective analysis of 77 patients with asymptomatic SMA stenosis, patients with stenosis of 2 or more mesenteric vessels had a higher incidence of chronic mesenteric ischemia compared with patients with single-vessel disease (15.1% vs 0%).[34] Approximately 20% to 50% of cases of symptomatic chronic mesenteric ischemia will progress to acute mesenteric ischemia, or acute-on-chronic mesenteric ischemia.[35]

More than 70% of patients with symptomatic chronic mesenteric ischemia report abdominal angina, a postprandial abdominal pain often described as dull and crampy that usually begins within 30 minutes of eating and lasts 1 to 2 hours.[4] As abdominal pain progresses over time, many patients turn to adaptive eating patterns, eating smaller portions or, in advanced cases, avoiding food (ie, food fear).[35] Weight loss is a key feature and is present in more than 60% of patients.[4,34] Less typical symptoms include nausea, vomiting, diarrhea, or constipation.[36]

Physical examination is often nonspecific but may reveal signs of malnutrition or cachexia. An abdominal bruit may be present; however, the classic triad of abdominal bruit, postprandial pain, and weight loss is present in only approximately 22% of cases.[4]

The nonspecific nature of symptoms makes it challenging to differentiate chronic mesenteric ischemia from common abdominal pathologies such as gallstone disease and peptic ulcer disease. Again, a high index of suspicion is crucial to promptly establish the diagnosis. A careful patient history should aim to identify patients with atherosclerotic risk factors and those reporting weight loss. The diagnosis is further supported by radiographic findings of high-grade stenosis or occlusion of at least 2 mesenteric vessels. Computed tomography angiography is recommended as the initial study of choice for mesenteric ischemia by the Society for Vascular Surgery, American College of Radiology, and European Society of Vascular Surgery, with close to

100% sensitivity. However, duplex ultrasonography is an effective, low-cost alternative that is more than 90% sensitive and specific in detecting high-grade stenosis.[37]

Fibromuscular dysplasia

Rarely, chronic mesenteric ischemia has been reported as a complication of fibromuscular dysplasia, a nonatherosclerotic, noninflammatory disorder leading to stenosis, aneurysm, dissection, or occlusion of arteries that predominantly occurs in young and middle-aged women.[38] The US Registry for Fibromuscular Dysplasia reported mesenteric involvement in 15.1% of cases; however, symptoms of mesenteric ischemia were rare (1.3%).[39,40]

Symptomatic patients present with severe abdominal pain or signs of acute arterial dissection.[41,42] Because fibromuscular dysplasia can affect nearly any vascular bed, many patients will have multivessel involvement, which can result in other signs and symptoms, including pulsatile tinnitus and hypertension.

The classic angiographic appearance of beading (medial fibroplasia) or focal stenosis (intimal fibroplasia) supports the diagnosis.[39] Histopathology has shown proliferation of the arterial smooth muscle cells and destruction of elastic fibers.[41]

Vasculitis

Mesenteric ischemia is a rare but severe, life-threatening manifestation of systemic vasculitis.[43] Chronic inflammation can cause arterial wall thickening leading to stenosis or occlusion, or can weaken the arterial media and lead to aneurysm formation.[44] Gastrointestinal involvement is mostly seen in vasculitis affecting the medium and large arteries, such as polyarteritis nodosa, giant cell arteritis, and Takayasu arteritis.[43] Cases of mesenteric vasculitis have also been reported in patients with systemic lupus erythematosus and Behçet disease.[45,46] Inflammatory markers may be elevated but can be nonspecific. Further serologic testing is often necessary, including a viral hepatitis panel, antineutrophil cytoplasmic antibodies, and antinuclear antibodies. Diagnosing the underlying condition is important, as these patients may require immunosuppression in addition to other therapies for ischemia.

Retroperitoneal fibrosis

Retroperitoneal fibrosis is a rare inflammatory disease of the retroperitoneum that occurs predominantly in middle-aged men. The fibrosis characteristically encases the infrarenal abdominal aorta and iliac arteries, and may compress visceral vessels, resulting in ischemia.[47,48] More than 50% of cases are idiopathic; other causes include malignancy and infection.[49]

Patients typically present with dull abdominal or low back pain. Other symptoms include diarrhea, weight loss, jaundice, and leg swelling. Renal impairment resulting from ureteral obstruction is seen in up to 25% of cases.[50] Diagnosis is made based on a high index of suspicion and computed tomography and magnetic resonance imaging showing retroperitoneal perivascular soft-tissue masses.

CONCLUSION

Mesenteric ischemia remains a diagnostic challenge to many clinicians because it is uncommon and its symptoms are nonspecific. Early recognition and focused evaluation are crucial for timely diagnosis and prevention of catastrophic complications.

DISCLOSURES

Dr. Wu reports no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest. Dr. Nanjundappa has disclosed teaching and speaking for Abbott, Medtronic, and Phillips Healthcare, consulting for Argon and Phillips Healthcare, and ownership interest (stock, stock options in a publicly owned company) for Zoll.

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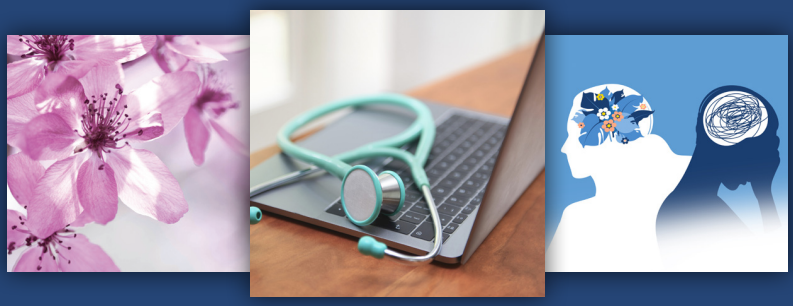

REVIEW

CME MOC

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Primary adrenal insufficiency in adults: When to suspect, how to diagnose and manage

ABSTRACT

Primary adrenal insufficiency is rare but serious; it puts patients at risk of acute decompensation and adrenal crisis due to insufficient cortisol and aldosterone production. Further, its diagnosis is often delayed, or it is mistaken for secondary adrenal insufficiency, which can have life-threatening consequences. Early recognition and appropriate treatment can greatly improve patient outcomes and quality of life.

KEY POINTS

- Unlike secondary adrenal insufficiency, primary adrenal insufficiency requires lifelong replacement of both glucocorticoids and mineralocorticoids, most commonly hydrocortisone and fludrocortisone.
- The first step in diagnosing adrenal insufficiency in general is to measure the early-morning cortisol level, looking for a low value. If the result is indeterminate, the next step is to do a cosyntropin stimulation test.
- To confirm the diagnosis of primary adrenal insufficiency specifically, one should measure the adrenocorticotropic hormone level, ideally concurrently with an early morning cortisol level, looking for a high value.
- To ensure adherence with lifelong steroid therapy and avoid adrenal crises, patients need adequate and ongoing education about the benefits and side effects of this treatment.

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Untreated primary adrenal insufficiency is life-threatening because patients can present with sudden decompensation and severe illness, such as adrenal crisis. Yet, the diagnosis is often significantly delayed, or it is misdiagnosed as secondary adrenal insufficiency. Unlike secondary adrenal insufficiency, therapy for primary adrenal insufficiency must include both glucocorticoid and mineralocorticoid replacement. It is important for clinicians to recognize, treat, and adequately counsel affected patients to improve patient adherence and outcomes.

PRIMARY VS SECONDARY ADRENAL INSUFFICIENCY

Adrenal insufficiency is a heterogeneous group of conditions in which there is a deficit of the main adrenal stress hormone, cortisol. When confronted with a patient who has adrenal insufficiency, it is critical to distinguish whether the insufficiency is primary or secondary because the workup and treatment differ fundamentally.

Primary adrenal insufficiency stems from a problem in the adrenal gland itself, and there are deficits of hormones produced at multiple layers of the adrenal cortex: mineralocorticoids from the zona glomerulosa, glucocorticoids from the zona fasciculata, and the sex hormones dehydroepiandrosterone (DHEA), sulfated DHEA (DHEA-S), and androstenedione from the zona reticularis. Therefore, patients with primary adrenal insufficiency require both glucocorticoid and mineralocorticoid

supplementation to survive. Primary adrenal insufficiency is relatively rare, with a prevalence of approximately 100 to 140 per million people in western countries, and it disproportionately affects women between ages 30 and 50.[1–3]

Primary adrenal insufficiency was first described in 1855 by Thomas Addison.[4] He initially dubbed the condition "melasma suprarenale," but it became known as "Addison's disease." Although Addison discovered his eponymous condition by studying a series of patients with adrenal tuberculosis, today the term is used to refer to primary adrenal insufficiency from any etiology (see *Causes of primary adrenal insufficiency,* below).

Secondary adrenal insufficiency is characterized by inadequate adrenocorticotropic hormone secretion stemming from a problem in the pituitary gland or hypothalamus (the latter is sometimes called "tertiary adrenal insufficiency") or from suppression of the hypothalamic-pituitary-adrenal axis, most often associated with chronic exogenous steroid use. Adrenocorticotropic hormone is necessary for cortisol and adrenal androgen generation. However, production of the mineralocorticoid aldosterone is unaffected, since it is predominantly and independently regulated by the renin-angiotensin-aldosterone system. Thus, patients with secondary adrenal insufficiency need only glucocorticoid replacement. Secondary adrenal insufficiency is more common than primary, affecting 150 to 280 per million people.[2,3]

DIAGNOSIS IS OFTEN DELAYED

It takes a high degree of clinical suspicion to recognize and treat primary adrenal insufficiency promptly. Affected patients have higher rates of adrenal crisis and death than those with other forms of adrenal insufficiency, as they have life-threatening deficiencies in both cortisol and aldosterone.[5] The insidious and nonspecific symptoms of primary adrenal insufficiency are often misattributed to psychiatric or gastrointestinal disease.[6] Even once adrenal insufficiency is recognized, primary adrenal insufficiency is often mistaken for secondary, as the latter is roughly 2 to 3 times more prevalent.[1–3] No surprise, then, that observational studies have found an average delay of 3 to 6 months before primary adrenal insufficiency is identified, which can be life-threatening for patients.[6,7]

While many patients with primary adrenal insufficiency ultimately establish care with an endocrinologist, most initially present to clinicians in primary care, emergency medicine, hospital medicine, or other medical specialties. Therefore, it is relevant to review an approach to the diagnosis, workup, and management of primary adrenal insufficiency in adults for these medical audiences.

WHEN TO SUSPECT PRIMARY ADRENAL INSUFFICIENCY

Many of the features of primary adrenal insufficiency are nonspecific and overlap with those of adrenal insufficiency from any cause, eg, fatigue, nausea, anorexia, abdominal pain, weight loss, hypotension, hypovolemia with postural dizziness, hyponatremia, and unexplained hypoglycemia. These symptoms may range from mild to life-threatening and may be masked until times of significant stress or illness. Suspect adrenal crisis in any patient who presents with shock out of proportion to the severity of his or her illness, possibly associated with otherwise-unexplained confusion, lethargy, fever, vomiting, or dehydration.

When looking for clinical features to distinguish primary from secondary adrenal insufficiency, consider 2 key factors:[8]

Symptoms of aldosterone deficiency. Without sufficient mineralocorticoid production, patients with primary adrenal insufficiency are more prone to significant hypovolemia and hyperkalemia, with more frequent symptoms of salt craving than those with secondary adrenal insufficiency.

Signs of adrenocorticotropic hormone excess. Alpha melanocyte-stimulating hormone is a byproduct of adrenocorticotropic hormone breakdown, and it has pigmentary action at the melanocortin 1 receptor in melanocytes in skin and mucosa.[8] Therefore, in primary adrenal insufficiency, excess adrenocorticotropic hormone secretion can lead to skin hyperpigmentation that resembles a long-lasting suntan.

BIOCHEMICAL EVALUATION

Biochemical evaluation is key to confirming a diagnosis of adrenal insufficiency from any cause.

Low early morning cortisol

First, there must be evidence of low serum cortisol at its daily peak, around 8 AM. Random cortisol checks, no matter how low, cannot reliably make a diagnosis of adrenal insufficiency. The recommended timing is based on an expected diurnal variation during a normal sleep-wake cycle.

Patients with significantly altered sleep schedules (eg, night shift workers) should have their cortisol levels checked at whatever time they routinely wake up after maintaining a consistent sleep pattern for a

few weeks. Cortisol interpretation becomes even more difficult in hospitalized patients, particularly in the intensive care unit, in part due to sleep disruptions and acute stress associated with illness.[9,10] As a result, there are no recognized cortisol cutoff values for diagnosing adrenal insufficiency in this setting.

Outside the intensive care unit, a morning cortisol value lower than 3 µg/dL in the absence of cortisol-binding globulin deficiency is consistent with adrenal insufficiency and does not require further testing if symptoms are consistent with this diagnosis. Meanwhile, a cortisol value above 13 to 18 µg/dL (depending on the assay used) excludes adrenal insufficiency.[11,12]

There are other common complicating factors to consider when interpreting early morning cortisol levels:

Variations in binding globulin and albumin. The cortisol assay measures total cortisol, which includes both free (active) hormone and bound hormone (80% to 90% is bound to cortisol-binding globulin and 10% to 15% is bound to albumin, leaving only 5% to 10% of cortisol active in free circulation). Oral contraceptive pills and other estrogen compounds can increase cortisol-binding globulin and inflate total cortisol levels. Conversely, total cortisol levels are falsely low when albumin levels are below the normal range. In these cases, especially when the albumin level is less than 2.5 g/dL, the free cortisol assay should be used instead.[13] However, delay in getting free cortisol results can limit their clinical usefulness in urgent situations.

Exogenous steroid therapy. Cortisol levels are not reliable if patients are receiving exogenous steroids, as these can both decrease the measured cortisol by suppressing the hypothalamic-pituitary-adrenal axis and, conversely, increase the measured cortisol if the assay detects the exogenous steroid. We recommend waiting until the steroid has cleared the system, generally about 24 hours depending on the steroid's duration of action, before testing cortisol levels in these patients.

For patients with indeterminate early morning cortisol values, one should proceed with further testing.

Cosyntropin stimulation test

If the cortisol value is indeterminate, the next step in confirming a diagnosis of adrenal insufficiency from any cause is to perform a cosyntropin stimulation test. Cosyntropin is a synthetic peptide consisting of the first 24 amino acids of the natural adrenocorticotropic hormone molecule.

To perform the test, 250 µg of cosyntropin is given intramuscularly or intravenously, and cortisol levels are checked at baseline, 30, and 60 minutes.[1] If both the 30- and 60-minute values are below the laboratory's threshold, the patient has adrenal insufficiency. The test can be done at any time of day but is often done in the morning so that the baseline level meaningfully reflects the daily peak cortisol. It can also be performed using free cortisol levels if the serum albumin level is below the normal range.

Cosyntropin stimulation testing can be done even if the patient is receiving dexamethasone, as this exogenous steroid does not falsely increase the cortisol assay. For this reason, the cosyntropin stimulation test is the main method used to assess residual adrenal function in patients who require uninterrupted steroid therapy. The cutoff for diagnosis varies (< 12.6 vs < 18.0 µg/dL) depending on the cortisol assay used.[1]

A cortisol value exceeding the cutoff at any time point during stimulation testing can be used to exclude adrenal insufficiency. One exception is that stimulated cortisol values can be falsely normal in acute secondary adrenal insufficiency, and this should be suspected in the setting of recent pituitary trauma or surgery.

DHEA-S testing

Recently, researchers have been looking at the value of DHEA-S testing, as this hormone has a long half-life and does not have diurnal variation. One method involves calculating the DHEA-S ratio by dividing the DHEA-S level by the lower limit of an age- and sex-specific reference range. Charoensri et al reported that a DHEA-S ratio greater than 1.78 was 100% sensitive for ruling out adrenal insufficiency.[14] Additionally, Suresh et al reported that a DHEA-S level less than 25 µg/dL confirms adrenal insufficiency, while a level greater than 100 µg/dL excludes it, with good sensitivity and specificity.[15] If the DHEA-S level is between 25 and 100 µg/dL, ie, indeterminate, the next step would be cosyntropin stimulation testing.

Other tests and findings

Other tests for adrenal insufficiency such as the metyrapone stimulation test, the low-dose cosyntropin stimulation test, or the insulin tolerance test can be used but should be performed and interpreted with the assistance of an endocrinologist.[16]

Once a diagnosis of adrenal insufficiency is made, glucocorticoid therapy should be initiated without delay. Even if results are not back, if clinical suspicion for adrenal insufficiency is high, steroids should be started once laboratory samples are drawn.

Additional testing may be needed to distinguish between primary and secondary adrenal insufficiency. It is a common misconception that the cosyntropin stimulation test necessarily diagnoses primary

TABLE 1
Congenital and inborn causes of primary adrenal insufficiency

Category and cause		Key features[a]
Congenital adrenal hyperplasia[1]	21-Hydroxylase deficiency	Most common subtype Classic variant causes deficiency of both cortisol and aldosterone Can also cause virilization in females due to accumulation of dehydroepiandrosterone metabolites
	11-Beta-hydroxylase deficiency	Accumulation of aldosterone precursor 11-deoxycorticosterone results in hypertension and hypokalemia
	3-Beta-hydroxylase deficiency	Lack of dehydroepiandrosterone conversion to testosterone causes ambiguous genitalia in boys
Other enzymatic abnormality[17]	Aldosterone synthase deficiency	Isolated mineralocorticoid deficiency
	Deficiency of P450 side-chain cleavage enzyme	Slows the rate-limiting step in cortisol synthesis
ACTH resistance[23]	Familial glucocorticoid deficiency type 1	Tall stature, isolated deficiency of glucocorticoids, and generally normal aldosterone production
	3A (Allgrove, AAA) syndrome	Achalasia, Addison disease, alacrimia, *AAAS* gene mutation
Adrenoleuko dystrophy[23]	Accumulation of very long chain fatty acid in adrenal cortex	Inhibited response to ACTH; X-linked recessive disorder associated with neurologic deficits that predominantly affects males and typically presents in adolescence
Congenital adrenal dysgenesis[1]	Congenital but can also be secondary to ACTH deficiency	Hypotrophy of adrenal cortex, adrenal insufficiency, hypogonadism, especially in males due to reduction in adrenal androgens
Others (rare)[1,17,23]	Wolman disease	Lysosomal acid lipase deficiency that results in accumulation of fat and diffuse punctate adrenal calcification causing adrenal insufficiency Very poor prognosis
	Abetalipoproteinemia	Fat malabsorption results in lack of cholesterol to make steroids
	Mitochondrial disorders	External ophthalmoplegia, retinal degeneration, cardiac conduction defects

[a]Not all listed primary adrenal conditions necessarily present with both glucocorticoid and mineralocorticoid deficiency.

AAA = achalasia, Addison disease, alacrimia; ACTH = adrenocorticotropic hormone

disease; even in secondary disease the adrenal gland has a slow, suboptimal response to synthetic exogenous adrenocorticotropic hormone due to a chronic lack of endogenous stimulus. The adrenocorticotropic hormone level is the most reliable way to differentiate primary from secondary adrenal insufficiency. Ideally it should be measured concurrently with an early morning cortisol. Adrenocorticotropic hormone levels greater than 2 times the upper limit of normal at any time of day are consistent with a diagnosis of primary adrenal insufficiency.[1]

Additional laboratory findings that can increase suspicion for a diagnosis of primary adrenal insufficiency include elevated renin, low aldosterone, low sodium, and high potassium.[1]

Once primary adrenal insufficiency has been diagnosed, the next step is to identify the cause.

CAUSES OF PRIMARY ADRENAL INSUFFICIENCY

Autoimmune destruction of the adrenal gland is the most common cause of primary adrenal insufficiency in the western world, responsible for up to 90% of cases.

TABLE 2
Acquired causes of primary adrenal insufficiency

Category and cause		Key features[a]
Autoimmune (most common)	Sporadic (from affected 21-hydroxylase enzyme)	40% of autoimmune cases,[12] common in patients age 30–50[25]
	Autoimmune polyglandular syndrome type 1[b]	Hypoparathyroidism, chronic mucocutaneous candidiasis, Addison disease, other autoimmune diseases such as pernicious anemia, alopecia (5% to 10%)[17]
	Autoimmune polyglandular syndrome type 2[b]	Autoimmune thyroid disease, type 1 diabetes, vitiligo, premature gonadal failure (60%)[17]
Infection	Tuberculosis	Most common cause in countries where tuberculosis is prevalent An extra-adrenal primary lesion is usually present Antitubercular medications do not reverse destruction[18]
	Disseminated histoplasmosis, paracoccidioidomycosis, human immunodeficiency virus or acquired immunodeficiency syndrome, cytomegalovirus, tertiary syphilis	Extremely rare, extra-adrenal manifestations are seen first
Injury	Bilateral adrenal hemorrhage due to sepsis	Classically with disseminated meningococcemia, but can also occur with *Pseudomonas aeruginosa, Streptococcus pneumoniae,* or *Staphylococcus aureus* sepsis[19]
	Bilateral adrenal hemorrhage due to anticoagulation	Rarely occurs with systemic anticoagulation Usually within the first 2 weeks of therapy[20]
	Infarction due to antiphospholipid antibody syndrome	Bilateral venous thrombosis Affects more men than women Antibodies target lipid-rich cells in the adrenal gland[21]
	Physical trauma	
Metastases	In decreasing order: lung, breast, melanoma, stomach[22]	Adrenal glands are prone to metastasis due to relatively rich blood supply Mere presence of metastasis does not cause adrenal insufficiency; severe destruction (> 90%) of the adrenal cortex is necessary
Acquired adrenal dysgenesis	Secondary to adrenocorticotropic hormone deficiency; can also be congenital	Hypotrophy of adrenal cortex, adrenal insufficiency, hypogonadism, especially in males due to reduction in adrenal androgens[1]
Iatrogenic	Surgical bilateral adrenalectomy	Usually performed in the setting of Cushing disease or bilateral pheochromocytoma
	Drugs	See **Table 3**
Infiltrative	Hemochromatosis, sarcoidosis, amyloidosis	Extensive infiltration of adrenal cortex results in dense fibrosis and deficiency of cortisol and aldosterone[24]

[a]Not all listed primary adrenal conditions necessarily present with both glucocorticoid and mineralocorticoid deficiency.
[b]From major histocompatibility complex class II mutations plus environmental triggers such as mental stress, viral infections, drugs.

TABLE 3
Drugs that can cause primary adrenal insufficiency

Drug[a]	Use	Mechanism of primary adrenal insufficiency
Mitotane	Adrenolytic adrenocortical carcinoma therapy	Damages adrenal cortex through free radical generation, blocks cortisol production, and alters peripheral conversion of steroids[27]
Etomidate	Anesthetic	Etomidate and metyrapone inhibit 11-beta-hydroxylase and decrease endogenous cortisol synthesis[28,29]
Metyrapone, mifepristone	Cushing syndrome therapy	Mifepristone in high doses blocks the glucocorticoid receptor[28]
Ketoconazole	Antifungal	Inhibits several adrenal enzymes responsible for androgen and cortisol synthesis such as cholesterol side chain cleavage enzyme, 17-alpha-hydroxylase, 11-beta-hydroxylase, and aldosterone synthase[28]
Levoketoconazole	Cushing syndrome therapy	
Rifampicin	Antitubercular	Induce CYP3A4, promote rapid cortisol clearance from the blood[17]
Phenytoin	Antiseizure	
Immune checkpoint inhibitors: ipilimumab (CTLA-4), nivolumab (PD-1), pembrolizumab (PD-1)	Malignancy therapy, most often melanoma	Can cause adrenal antibodies, resulting in destruction of cortex[30,31] Can also be associated with secondary adrenal insufficiency through hypophysitis
Abiraterone	Prostate cancer therapy	Selectively and irreversibly inhibits 17-alpha-hydroxylase/C17,20-lyase to cause androgen and glucocorticoid deficiency[32]

[a]Not all listed medications causing primary adrenal insufficiency necessarily present with both glucocorticoid and mineralocorticoid deficiency.
PD-1 = programmed cell death protein 1; CTLA-4 = cytotoxic T-lymphocyte–associated protein 4.

Based on information from references 1,17,23,27–32.

Other causes include infections (eg, tuberculosis), adrenal hemorrhage or infarction, metastases, surgical resection, and congenital conditions.[17–24] Drug-induced primary adrenal insufficiency is also emerging. Congenital and inborn causes of primary adrenal insufficiency are listed in **Table 1**,[1,17,23] and acquired causes are listed in **Table 2**.[1,12,17–22,24,25]

Drug-induced primary adrenal insufficiency is on the rise

Drug-induced primary adrenal insufficiency is rapidly increasing in incidence. While mitotane and etomidate have long been known to cause adrenal dysfunction, the advent of immune checkpoint inhibitors and other medications to treat cancer and immune diseases has increased the incidence of iatrogenic adrenal disease. Recognizing adrenal insufficiency in such patients can be challenging, as the symptoms frequently overlap with those of the disease that required the use of that medication in the first place.

A 2022 study of reports received by the US Food and Drug Administration found 56 drugs suspected of causing primary or secondary adrenal insufficiency.[26] The most common medications that cause primary adrenal insufficiency are listed in **Table 3**.[1,17,23,27–32] Some of these drugs can induce primary adrenal insufficiency by suppressing the adrenal enzyme cascade, while others can induce adrenal antibodies, directly harm the adrenal cortex, or induce cortisol metabolism.

Practical approach to finding the cause of primary adrenal insufficiency

After excluding clear iatrogenic causes with a patient history and medication list, a stepwise approach is recommended for finding the cause of primary adrenal insufficiency.[1]

21-Hydroxylase antibody testing. Since most cases are autoimmune, the recommended workup begins with 21-hydroxylase antibodies. Imaging is not necessary and is relatively nonspecific for a diagnosis of autoimmune primary adrenal insufficiency but may show small atrophic adrenal glands.

When autoimmune disease is identified, it is important to consider other autoimmune diseases that can be associated with primary adrenal insufficiency such as thyroid disease, type 1 diabetes, pernicious anemia, and

celiac disease. The most common patterns are autoimmune polyglandular syndromes 1 and 2. With a sensitivity of approximately 90%, a negative 21-hydroxylase antibody test does not necessarily exclude autoimmune disease in cases with a high clinical suspicion in the absence of another identifiable cause.[2,33]

Computed tomography. If 21-hydroxylase antibody testing is unremarkable, a computed tomography scan of the adrenal glands is recommended. Generally, more than 90% of both adrenal cortices must be damaged before the signs and symptoms of primary adrenal insufficiency manifest.[12] Computed tomography is done to look for any overt adrenal infiltration, infection, hemorrhage, malignancy, or injury. A positive result will require further investigation based on the clinical history, physical examination, and suspected cause. For example, QuantiFERON testing should be considered for those at risk for tuberculosis, which remains the second leading cause of primary adrenal insufficiency worldwide.[18]

17-Hydroxyprogesterone level. Though other causes of primary adrenal insufficiency are rare, if patients do not have antibodies or computed tomography findings, screening for congenital adrenal hyperplasia is recommended by measuring the 17-hydroxyprogesterone level, looking for elevated values.

Very-long-chain fatty acids. In adolescent male patients, consider screening for adrenoleukodystrophy by looking for elevated levels of very-long-chain fatty acids.

Other rare genetic conditions can be tested for based on the patient's phenotype and comorbidities, with the guidance of an expert in genetics. If all workup is unrevealing, then primary adrenal insufficiency is considered idiopathic.

HOW TO TREAT PRIMARY ADRENAL INSUFFICIENCY

The general approach to treating primary adrenal insufficiency of any etiology is physiologic replacement of necessary glucocorticoids and mineralocorticoids. These medications must be started promptly upon diagnosis, which often occurs in primary care or the hospital. Adherence to medical therapy must be emphasized to prevent serious illness. Further medication titration, surveillance, and consideration of nonessential androgen replacement should take place with an endocrine specialist if available.

Glucocorticoid replacement with hydrocortisone

The starting dose of hydrocortisone is 15 to 25 mg per day (approximately 8–15 mg/m^2 per day by body surface area) divided into 2 or 3 doses, given that hydrocortisone is cleared in approximately 8 hours.[1] To mimic the physiologic diurnal variation in cortisol, the recommended dose is higher (10–15 mg) in the morning and lower (5–10 mg) in the afternoon, 6 to 8 hours later. The body's natural glucocorticoid production is low during sleep, but an evening dose (2.5–5 mg) can be considered in patients who feel symptoms of adrenal insufficiency overnight.

Newer, modified-release hydrocortisone formulations contain both immediate- and sustained-release components and are taken once daily. This improves medication adherence and is thought to better match physiologic cortisol variability. Initial randomized controlled trials demonstrated improvements in weight, glucose tolerance, blood pressure, and quality of life with modified-release hydrocortisone.[34,35] These formulations are not widely used yet and are undergoing ongoing study.

Other glucocorticoid medications. Prednisone and prednisolone (3–5 mg/day) are 4 times more potent than hydrocortisone and can be taken once daily. While there is no significant medical evidence that one steroid formulation is better than another, hydrocortisone is easier to titrate to avoid the consequences of excessive long-term steroid exposure.[36] The risks of long-term excess steroid exposure are even higher with dexamethasone, which is 20 times more potent than hydrocortisone. Forss et al[37] surveyed 1,245 patients with adrenal insufficiency worldwide and reported that 75% were receiving hydrocortisone, 11% were on prednisone or prednisolone, 6% were on cortisone acetate, 4% were on dexamethasone, and the rest were on other drugs.

Once therapy has begun, laboratory cortisol levels are no longer useful for guiding dose adjustment. Instead, the need for glucocorticoid titration is determined by clinical response. Fatigue, nausea, weakness, anorexia, weight loss, hypoglycemia, hypotension, or the occurrence of an adrenal crisis suggest inadequate glucocorticoid replacement, and the dose should be increased. Cushingoid features (round facies, purplish striae, easy bruising, dorsocervical fat pad, central obesity), weight gain, fatigue, proximal muscle weakness, bone loss, hypertension, hyperglycemia, and an increased infection rate are evidence of cortisol excess. Fear or evidence of these symptoms is a common reason for steroid nonadherence.[38]

Both excess and suboptimal glucocorticoid therapy cause clear harms. Thus, providers should monitor for early symptoms and work with patients to aim for the lowest replacement steroid dose that is sufficient.

Mineralocorticoid replacement

The starting dose of mineralocorticoid replacement is fludrocortisone 50 to 100 µg daily, titrated to a range of 50 to 300 µg daily.[39] Clinical features are used to assess the adequacy of therapy. Patients should be asked about salt craving or dizziness and screened for orthostatic hypotension and laboratory abnormalities such as hyperkalemia or hyperreninemia, which suggest mineralocorticoid underreplacement.

Conversely, signs of volume overload such as hypertension or hypokalemia and hyporeninemia can be a clue for overreplacement. Patients who develop hypertension while on fludrocortisone can decrease the dose but should not stop fludrocortisone therapy altogether. Other antihypertensive agents can be started for additional blood pressure control when the lowest fludrocortisone dose is already in use.

Some glucocorticoids at high doses (hydrocortisone > 20 mg and prednisone or prednisolone > 50 mg) can act at the mineralocorticoid receptor with approximate equivalent strength as fludrocortisone 100 µg.[40] Fludrocortisone can be held in these circumstances but must be promptly resumed when glucocorticoid doses are lowered below these thresholds. In contrast, dexamethasone does not have any appreciable mineralocorticoid effect despite its strong potency as a glucocorticoid.

Androgen replacement

Unlike glucocorticoid and mineralocorticoid replacement, androgen replacement is nonessential, and not everyone with primary adrenal insufficiency needs it. Men with primary adrenal insufficiency do not require adrenal androgen replacement because they have adequate sources of DHEA, DHEA-S, and testosterone produced by the testes.

In premenopausal women, however, DHEA and DHEA-S are the main circulating androgens and are produced predominantly in the adrenal gland, with only a minor contribution from the ovaries. Physiologic levels are highest in young women and taper off above age 30. Therefore, the ideal candidate for DHEA treatment is a young woman with primary adrenal insufficiency who is experiencing symptoms of low libido, fatigue, and depression, in the absence of a clear alternative cause.[1,41]

The starting dose of DHEA is 25 mg daily, which can be increased to 50 mg daily.[1,42] To assess dose adequacy, blood DHEA-S levels should be checked 3 months after dose changes and then yearly, aiming for a mid-normal DHEA-S level on a day that the DHEA replacement is held. DHEA supplementation should only be continued if there is a significant improvement in symptoms of depression, energy, or libido. Treatment is done on a 6-month trial basis, and therapy is stopped if there are no clear enduring benefits. Positive effects of treatment may also be self-limited to a few months, even at an appropriate dose. Symptoms of hirsutism, acne, or oily skin can result from DHEA therapy and suggest overreplacement.

Lifesaving considerations

Lifelong glucocorticoid and mineralocorticoid replacement is essential for all patients with primary adrenal insufficiency. The consequences of missed steroid doses may be as mild as fatigue, or as severe as shock and adrenal crisis. Each year, an alarming 8% of patients with primary adrenal insufficiency experience an adrenal crisis requiring hospital treatment.[43] More than half of adrenal crises develop in the setting of vomiting or diarrhea.[43]

A functional adrenal gland naturally produces higher levels of cortisol in response to stress, but patients with primary adrenal insufficiency cannot mount this same response, as they are dependent on exogenous cortisol. To simulate this adrenal stress response, patients are instructed to double their glucocorticoid dosing ("stress-dose steroids") if they are having intercurrent illnesses such as diarrhea, vomiting, upper respiratory infection, fever, or significant stress. Patients are advised to use stress-dose steroids for 2 to 4 days.[44] If a longer course is necessary, then they are instructed to contact their provider to discuss next steps with the goal of avoiding excessive glucocorticoid exposure. Hospitalized patients with prolonged illness may require longer durations of stress dosing but should be tapered back to their replacement dosage once medically stable.

To reduce avoidable hospitalizations and deaths, it is crucial that patients have ready access to their medications. All patients should keep extra pills available in their car, purse, or luggage, or with nearby friends and family so that they always have medication on hand. An intramuscular glucocorticoid injection kit (such as hydrocortisone 100-mg injection with needle and syringe, which has both glucocorticoid and mineralocorticoid effect) should be prescribed and kept at home if a patient is ever unable to take oral medication. Those who are closest to the patient should be trained to use the parenteral injection kit as needed. If a kit is unavailable, patients should go to an emergency department for prompt steroid treatment. In the event of unconsciousness, medical alert notification (such as a bracelet, necklace, badge, or card) can be lifesaving as it notifies emergency providers to give steroids and fluids.

Typical treatment of suspected adrenal crisis in the emergency department consists of 100 mg of hydrocortisone either intravenously or intramuscularly, followed by a liter of normal saline over 60 minutes.[45] Additional parenteral steroid doses should be given 3 or 4 times per day until the patient is able to restart oral therapy.

Patients with primary adrenal insufficiency and their families must be counseled and periodically reminded of all these interventions to ensure their steroid therapy is adequate and uninterrupted. Patient education is key to avoid overt adrenal insufficiency and adrenal crises. Nonadherence is a significant problem; in a survey of 81 patients in Europe, 85% reported a degree of nonadherence, and many were dissatisfied with the information they had received from their providers.[38] Only by understanding the rationale that underlies the evaluation and management of primary adrenal insufficiency can providers recognize and treat this disease, increase patient adherence, and lower the risks of adrenal crises and death.

DISCLOSURES

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

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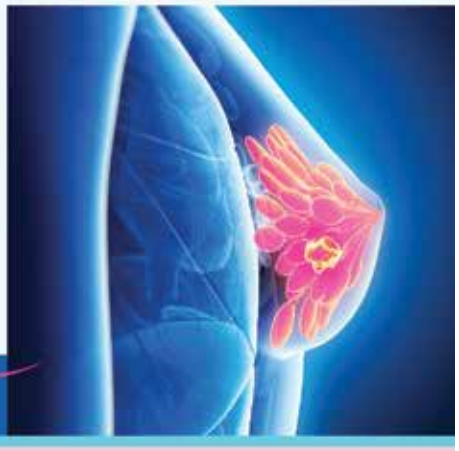

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COMMENTARY

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Vaccine hesitancy in the time of COVID: How to manage a public health threat

As of May 11, 2024, only 15% of US children and 22% of US adults had received the updated 2023–2024 COVID-19 vaccine (42% of those 75 and older). Similarly, only 54% of children, 48% of adults, and 78% of adults age 75 and older had received the updated influenza vaccine, while 23% of adults 60 or older had received a respiratory syncytial virus (RSV) shot.[1] In contrast, immunization rates for standard childhood vaccinations remain in the range of 90% for those born in 2019 and 2020.[2]

These numbers are below the targets, especially for COVID-19 vaccination. The 3 COVID-19 vaccines available and authorized for use in the United States are safe and effective and have highly favorable risk-benefit profiles. They are relatively easy to obtain, and the Centers for Disease Control and Prevention has issued clear recommendations for using them. And so it is frustrating for many healthcare professionals to repeatedly see patients who refuse to be vaccinated.

Below, we review the history of vaccine hesitancy, what we do and do not know about the currently available COVID-19 vaccines, and ways for clinicians to help patients decide whether to be vaccinated against COVID-19.

VACCINE HESITANCY IS NOT NEW

Vaccine hesitancy did not start with the COVID-19 pandemic.[3] Skepticism regarding the value of vaccination dates to the ancient practice of variolation (intradermal insertion of material from smallpox blisters, which minimized the impact of any subsequent natural smallpox infection), which became popular in Europe and the American colonies in the 18th century. For example, in Boston in 1721, Dr. Zabdiel Boylston began performing variolation (which he learned from an enslaved African person) in an attempt to stem an epidemic of smallpox. He was supported in this practice by royal governor Samuel Shute and theologian Cotton Mather—and opposed by local patriots that included a young printer's apprentice named Benjamin Franklin. Dr. Boylston had to go into hiding, and Reverend Mather's house was firebombed.[4] Things did not change much in the 19th century when variolation was replaced with cowpox (vaccinia) as the first vaccine (**Figure 1**).

The 1853 British Compulsory Vaccination Act, requiring smallpox vaccination for infants, was met with fierce and at times violent resistance by the working class, who saw it as the latest oppressive move by the ruling class to exert control over their bodies. This resistance was only enhanced by the fact that those who refused to have their children vaccinated were severely fined or thrown into jail under harsh conditions.[3,5]

Similarly, antivaccination sentiments in the United States at the end of the 19th century were also initially a reaction to mandatory vaccination laws. Of note, the Supreme Court at that time ruled that such laws were constitutional if they were necessary to ensure public safety.[6] The clear decreases in morbidity and mortality from smallpox and polio following large-scale vaccination campaigns led to a general acceptance of the safety and efficacy of vaccines.

A number of events over the past 75 years has led to public concerns about vaccine safety and efficacy. As is often the case, the full story took longer to emerge.[3] Among these events were the following:

- Inadequate inactivation of polio vaccine, leading to tens of thousands of cases of polio and 10 deaths (*This happened in 1955, and this vaccine is no longer used.*)

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Figure 1. "The Cow Pock—or—the Wonderful Effects of the New Inoculation" by cartoon satirist James Gillray, June 12, 1802. Portrays a scene from the Smallpox and Inoculation Hospital at St. Pancras of people taking the shape of cows after being inoculated with vaccinia by Edward Jenner.

Reproduced from Library of Congress. http://hdl.loc.gov/loc.pnp/ds.14062.

- Contamination of polio vaccines with SV40 virus (*But no clinical consequences of SV40 contamination were found.*)
- A 1-in-100,000-person increase in cases of Guillain-Barré syndrome during the 1976 influenza vaccination campaign (*The risk of Guillain-Barré syndrome following influenza vaccination is currently closer to 1 excess case in 1 million, which is lower than the risk following influenza infection.*)
- Neurologic complications from diphtheria-tetanus-pertussis vaccine (*The risks were determined to be extremely low, and a decrease in vaccination in the United Kingdom led to a significant outbreak of pertussis.*)
- Claims of autism in association with the measles-mumps-rubella vaccine. (*The article reporting this association was found to be flawed and retracted by the publisher [*The Lancet*]. Financial ties were revealed between the primary author of that article and attorneys pursuing legal action against vaccine manufacturers.*[7])

Along with *selfie* and *CRISPR*, the term *vaccine hesitancy* first appeared in the English language in 2002 (www.merriam-webster.com/time-traveler/2001). It was initially included in the Oxford English Dictionary in 2006 and is defined there as hesitancy, reluctance, or refusal to have oneself or one's children vaccinated against an infectious disease or diseases. *Vaccine resistance* describes an extreme form in which people are not merely unsure but are actually opposed to vaccination. Complacency, inconvenience in accessing vaccines, and lack of confidence are key factors underlying vaccine hesitancy.

VACCINE HESITANCY AS A THREAT TO HEALTH

Vaccination has had a substantial positive impact on both individual health and public health, but its gains are compromised by vaccine hesitancy. In 2019, the World Health Organization identified vaccine hesitancy as 1 of the top 10 threats to global health.[8] They noted that vaccination currently prevents 2 to 3 million deaths a year and that an additional 1.5 million deaths could be prevented if vaccination rates were higher.

Successes of vaccination campaigns

At the level of individual health, vaccines have decreased morbidity and mortality from a variety of infectious diseases both by reducing the risk of new infection and by minimizing the impact of infection in individuals who become infected despite vaccination. Notable successes include vaccines against measles, diphtheria, varicella zoster (which causes chicken pox and shingles), and human papillomavirus (which causes cervical dysplasia and cancer).

As for public health, vaccinations can decrease the spread of infection and the burden on the healthcare system. Vaccination campaigns have eradicated smallpox, are closing in on eradicating polio, and have "eliminated" measles in the United States, at least for the time being. (In this context, "elimination" means no endemic measles transmission for at least 1 year in the presence of a well-performing surveillance system.)

Measles deserves special mention. While vaccination rates for measles-mumps-rubella and polio remain high overall, there are pockets where decreasing rates of vaccination have led to recent outbreaks of measles. Worldwide cases of measles surged by 30% in 2019, which was attributed, at least in part, to vaccine hesitancy.[8] In the United States, the "eliminated" status of measles is at risk, with 159 cases reported in the first 6 months of 2024 (**Figure 2**).[9] At the same time, the vaccination rate among kindergartners has declined, from 95.2% during the 2019–2020 school year to 93.1% in the 2022–2023 school year.[9] Recent trends—an increase in the number of cases and declines in immunization rates—indicate that gains can be vulnerable and depend upon ongoing public health efforts to maintain high rates of acceptance of the measles-mumps-rubella vaccine.

Varicella zoster. In addition to reducing the incidence of childhood infectious diseases, several vaccines also prevent some of the long-term consequences of infections. For example, the childhood varicella-zoster vaccine decreases the risk of shingles later in life, and the human papillomavirus vaccine given at ages 9 to 26 years decreases the risk of cervical dysplasia and cancer. The 2-dose varicella-zoster childhood vaccine in the United States (typically given in combination with measles-mumps-rubella) has led to approximately a 90% decline in the incidence of diagnosed infections, hospitalizations, and death due to varicella zoster.[10] And in multiple studies, people who were vaccinated in childhood had about a 50% lower incidence of shingles later in life.[10]

Human papillomavirus. Even more striking, in cancer prevention, women who received the quadrivalent human papillomavirus vaccine before age 17 were approximately 90% less likely to develop invasive cervical cancer later in life, and those who received it between ages 17 and 30 were about 50% less likely.[11] A Cochrane review of 26 randomized controlled trials with 73,428 participants found that women age 15 to 25 years, negative for any high-risk human papillomavirus subtype at study entry, who received the vaccine had a 63% lower risk of precancerous lesions, with a number needed to vaccinate of 55.[12]

COVID-19 vaccines are effective, but degree of efficacy is hard to determine in 2024

The 3 COVID-19 vaccines available in the United States—the Pfizer-BioNTech (Comirnaty) and Moderna (Spikevax) mRNA vaccines and the Novavax (NVX-CoV2373) adjuvanted protein vaccine—have also shown similar impressive degrees of efficacy (**Figure 3**).[13–19] In the pivotal phase 3 studies that led to the emergency use authorizations for these vaccines, they decreased the incidence of severe disease by 90% to 100% (**Table 1**).[15–17]

Unfortunately, it is difficult to precisely ascertain their current efficacy, and in turn to provide precise information to the public about their efficacy at this time. This is because the circulating variant is different (Alpha vs Omicron KP.3) and the preexisting level of host immunity to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; either from prior infection or vaccination) in the general population is different as well.

While some vaccines confer lifelong protection (particularly the live virus vaccines such as vaccinia), the COVID-19 vaccines probably do not, and periodic booster immunizations are recommended. Currently available data suggest that serum antibody levels decline faster with the mRNA vaccines than with the protein vaccines.[20] However, for most vaccines, memory B cells and T cells (which mount an immune response on reexposure) may persist for considerably longer than plasma antibodies. This is an area of current study.

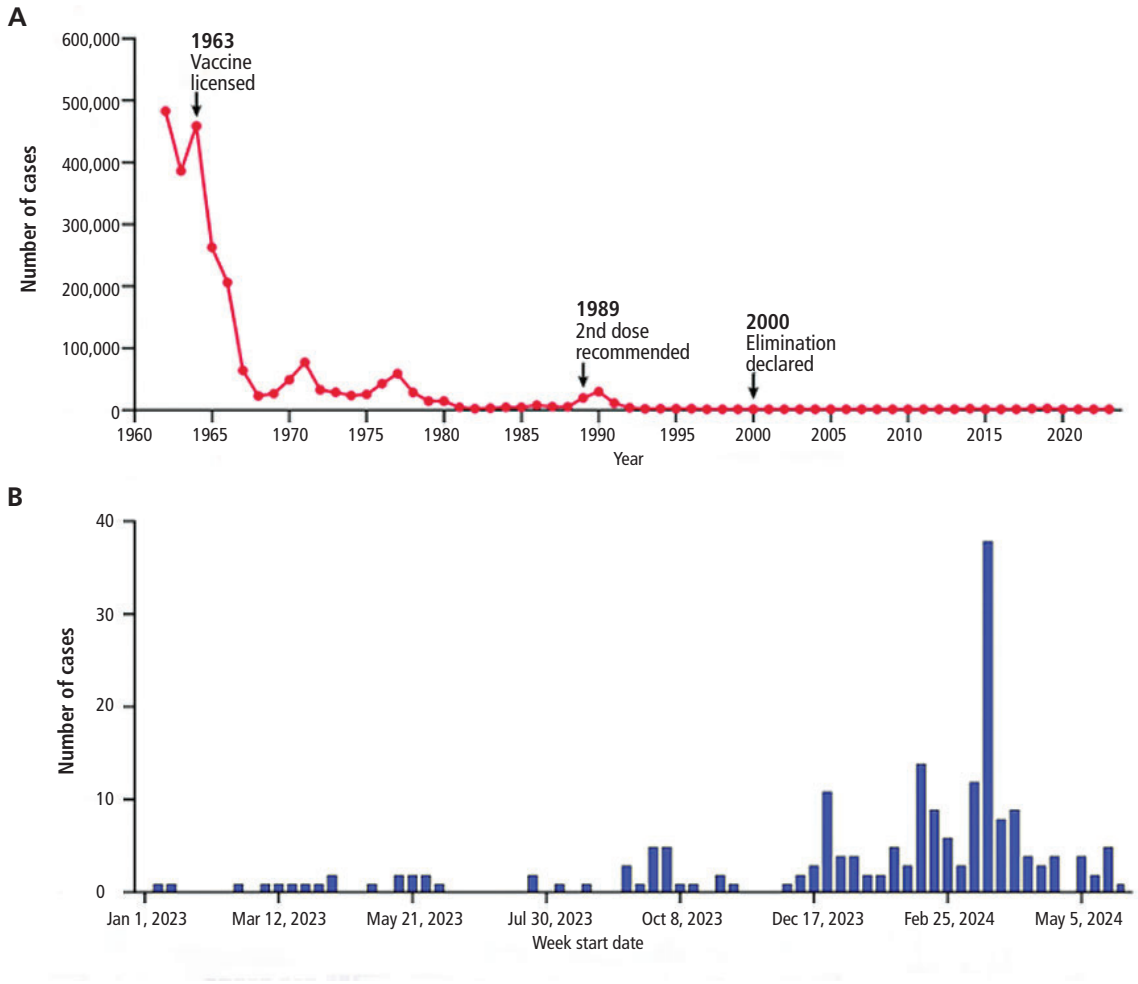

Figure 2. Measles cases in the United States (A) 1962 to 2023 and (B) January 2023 to March 2024.

Adapted from reference 9.

One thing we can say with assurance, however, is rates of serious adverse events are very low with these vaccines, with similar rates in the placebo and vaccine groups in the pivotal studies (**Table 1**).[15–17]

Complicating any meaningful discussion about the current efficacy of the COVID-19 vaccines, the estimates, other than those derived from the pivotal phase 3 studies, vary widely in both the scientific and lay literature. Some of these differences are due to different definitions of efficacy being used, eg, rates of overall infection vs rates of symptomatic infection vs rates of serious illness or death.

Other differences derive from the different methodologies used. These range from the gold standard of a randomized, double-blind controlled trial to the more convenient use of observational cohorts. These latter studies are often referred to as "real-world evidence"[21,22] and typically compare outcomes between people who have or have not been vaccinated. While they control for a variety of known and measured variables as best they can, they remain confounded by unrecognized variables. For example, people who elect to be vaccinated and get booster shots probably differ in ways we do not measure (such as degree of risk-taking behaviors) from those who do not. Those differences might influence the relative risk of exposure to SARS-CoV-2—for example, people who are opposed to social distancing and masking are more likely to be opposed to vaccination.[23]

Thus, it is hard to draw a firm conclusion about the current level of efficacy of these vaccines. It is fair to say that they are effective, but the magnitude of that efficacy is not clear.

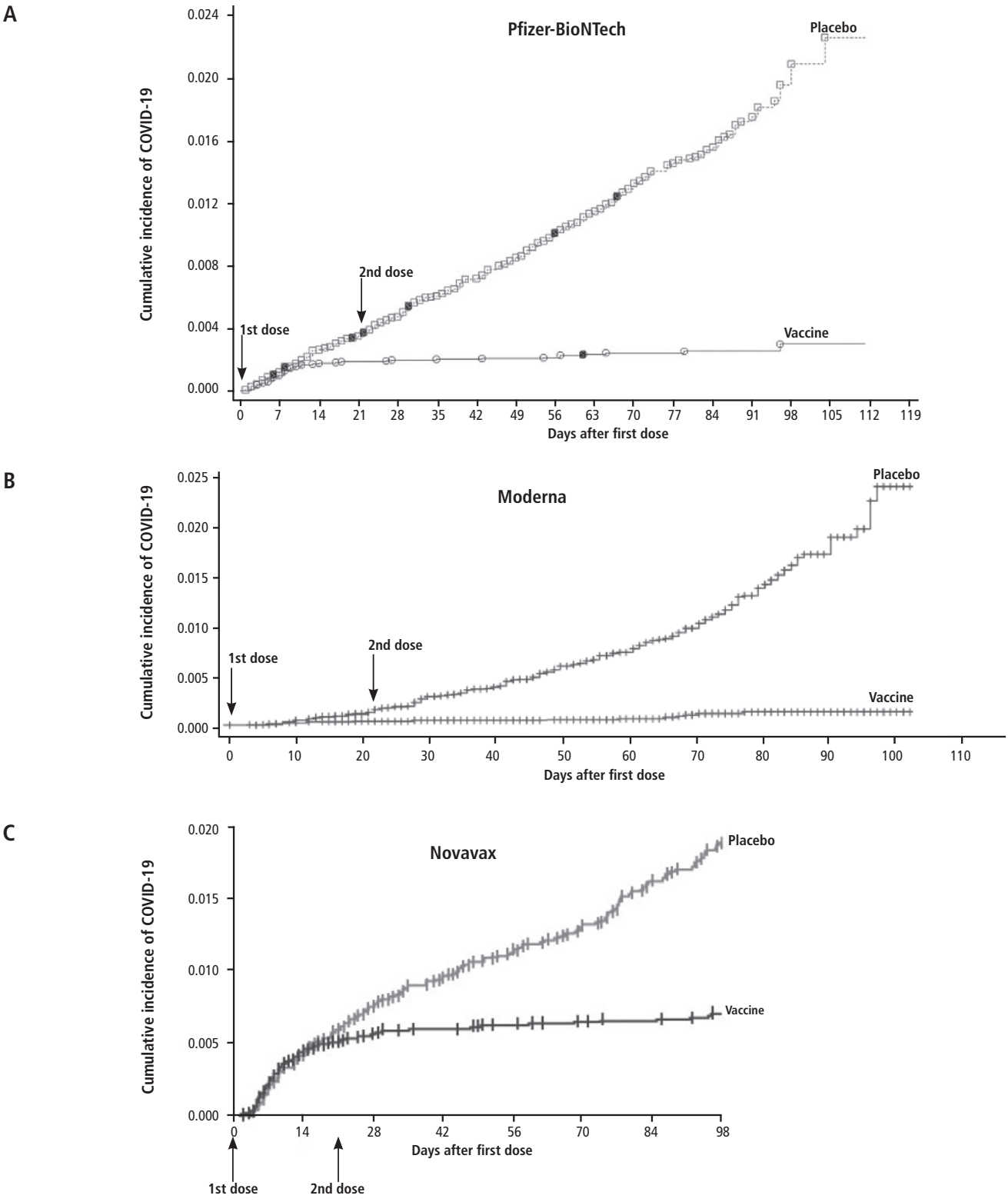

Figure 3. Clinical results from the pivotal studies of the (A) Pfizer-BioNTech, (B) Moderna, and (C) Novavax COVID-19 vaccines.

Adapted from references 14,18,19.

TABLE 1
Efficacy and safety of COVID-19 vaccines

Vaccine	Group	Number of patients	Cases of severe disease[a]	Vaccine efficacy against severe disease (%)[a]	Serious adverse event rates (%)[a,b,c]
Pfizer-BioNTech (Comirnaty)[15]	Vaccine	21,720	1	90	0.6
	Placebo	21,728	9		0.5
Moderna (Spikevax)[16]	Vaccine	15,181	0	100	1.6
	Placebo	15,170	30		1.4
Novavax (NVX-CoV2373)[17]	Vaccine	19,714	0	100	0.6
	Placebo	9,868	4		0.6

[a]The only valid comparisons are between the placebo and vaccine groups for each vaccine due to slightly different reporting criteria.
[b]Slightly different definitions were used in different trials.
[c]As specified in the text, lower-grade adverse events, typically local reactions, were frequent in both the placebo (22%–43%) and vaccine (78%–92%) groups.

Vaccination prevents *severe* COVID-19

The COVID-19 vaccines appear to be most effective in preventing severe disease and death and least effective in preventing infection itself. In other words, an infection in someone who is vaccinated does not mean that the vaccine does not work; the COVID-19 vaccines, like most others, may not prevent infection but do greatly decrease the impact of infection. Data from the Omicron period suggest that vaccination is associated with a 62% decrease in hospitalization and 69% decrease in critical illness during the first 2 months following vaccination, dropping to a 24% decrease in hospitalization and a 50% decrease in critical illness during months 4 to 6.[24,25]

Given the strong, consistent data indicating that the risk of vaccination is low (discussed below), one can conclude that the risk-benefit ratio remains strongly in favor of vaccination. Thus, it is important for the clinician to provide context as to the nature of that benefit, namely protection from severe disease, when making such a statement to a prospective vaccine recipient. It is also worth noting that efficacy decreases with time after the last shot, making a strong case for getting periodic boosters.

To be clear, the discussion on whether to be vaccinated when the vaccines were first available, when there had not yet been widespread exposure to SARS-CoV-2 and the circulating variants were more virulent, was much less nuanced than the situation today. At that time, the data from the randomized controlled trials were current and the mRNA vaccines were shown to be safe and effective—especially from the perspective of preventing death. Appreciating this difference will be critical to an effective response to the next pandemic.

DISCUSS THE PROS AND CONS, BUT DON'T ARGUE WITH PATIENTS

Because we live in an environment of conflicting information, an important key to discussing the risks and benefits of any indicated vaccine with patients is to avoid getting into an adversarial relationship. To start, acknowledge that the patient has the final word on what they elect to do and that your job is to provide them with reliable information on which they can base their decision. Indicate you will provide a clear recommendation based on the available information while at the same time acknowledging that there are still some unknowns.

While suspicion of physicians and hospitals in general is widespread, individuals typically have high confidence in their own clinician, especially if they have a long-standing relationship. A survey commissioned by the American Board of Internal Medicine Foundation carried out from December 2020 through January 2021 concluded that trust in individual clinicians is greater than trust in the healthcare system as a whole;[26] however, trust in physicians decreased during the COVID-19 pandemic and needs to be rebuilt.[26,27]

In discussions about vaccine safety and efficacy, point out that one cannot rely on social media, which typically have no filters or peer review on what is posted. As a consequence, such postings may not be based on evidence or data and may instead be based on politics and beliefs. For example, in the survey cited above, 78% of Democrats said they had confidence in their doctor to administer a COVID-19 vaccine compared with 51% of Republicans.[26]

While the survey did not explore the reasons for these differences, a plausible explanation may be the sources of their information via commercial and social media. Psychologist Dan Ariely of Duke University has coined the term "funnel of misbelief" to describe the way in which rational people may end up with very different views of the world based on their emotions, degree of stress, cognitive biases, personality, and exposure to different types of social forces.[28] When we don't understand what is going on around us (eg, a COVID pandemic), there is a deep psychological need to come up with some narrative, real or imaginary, to explain things.

It is often stated that one is entitled to their own opinions, but not their own facts. While the facts regarding the safety and efficacy of many vaccines, including the COVID-19 vaccines, are clear, the way they are interpreted through a political lens can be confusing. It is the responsibility of the clinician to help the patient identify the facts so that they may reach an informed decision. An approach being studied is the 4-step technique of "empathetic refutation,"[29] in which the clinician:

1. Elicits concern (asking patients to share their thoughts to uncover what they perceive as the underlying facts)
2. Affirms whatever truths are contained in their thoughts
3. Offers a tailored refutation of any misconceptions with facts
4. Provides additional facts in support of vaccination.

It is important to avoid value judgments and instead to listen and support without becoming argumentative. The patient's perspective on the topic may be more related to the degree of emotion with which they approach the issue rather than stemming from disagreement regarding the facts.

In her book *Thinking in Bets*,[30] poker champion Annie Duke notes that people may most easily accept the first thing they hear to be true and that it may take some time to move to a different position. She goes on to note that it is important to communicate one's own degree of uncertainty when discussing controversial issues and frame a discussion moving from acknowledgement of uncertainty to identifying areas of agreement (for example, COVID can cause severe illnesses and death) and from there discussing ways to avoid a bad outcome. In other words, spend time focusing on and agreeing on the problem before moving to potential solutions.

Egregious misinformation has arisen from false claims regarding the danger of vaccines through inaccurate interpretations of the incidence of adverse events that occur following vaccination. An adverse event is any undesirable experience that occurs after a medical product is used in a patient. In this regard, it is important to distinguish between an adverse event that is due to a vaccine vs an adverse event not due to a vaccine occurring in a person who coincidentally received a vaccine.

The cleanest data on adverse events of vaccines come from the randomized placebo-controlled trials that are done early in the testing of a new vaccine (**Table 1**).[15–17] Additional data come from postauthorization and postlicensure reporting to the Vaccine Adverse Event Reporting System (VAERS). The randomized controlled trials allow a clear distinction between events due to the vaccine (seen more frequently in the vaccine than in the placebo group) and those that would have occurred regardless of vaccination (seen at the same frequency in both groups). While not as robust, VAERS data can be particularly valuable in helping to spot a rare vaccine-related adverse event by comparing the incidence of the event in vaccinated individuals vs in the general population.

What are the risks from the COVID-19 vaccines?

After close to 8 million doses of the Janssen (Johnson & Johnson) Ad26 COVID-19 vaccine had been given in the United States, 17 cases of the thrombosis with thrombocytopenia syndrome were reported to the VAERS.[31] This was an approximately 15-fold relative risk, although a small absolute risk, and appeared to be focused in women 18 to 49 years of age. In response, the Centers for Disease Control and Prevention modified its recommendations for use of the Ad26 platform vaccine,[32] and the observation likely played a role in the June 2023 revocation of the US emergency use authorization of this vaccine following a request from Janssen. This example can be used to illustrate some of the steps taken in the United States to monitor even rare vaccine risks and the subsequent actions taken when a new risk is identified.

Some claim that all reported adverse events in vaccine recipients are due to the vaccine. This can be confusing to the public. As noted above, it can be easy to conflate adverse events due to a vaccine with adverse events not due to a vaccine in someone who has received a vaccine. For example, every day most people drink water, but not everyone who got sick on a given day became ill from the water they drank; in some instances that might be true, in other instances not. As noted above, the best way to determine the impact of an intervention is in a randomized placebo-controlled trial, the exact type of trial that led to the authorizations and licensures of the current COVID-19 vaccines.

It is true that these vaccines were developed in record time and initially provided on the basis of emergency use authorization. However, it is important to point out that the study designs, with approximately 30,000 individuals per study and subsequent follow-up for a minimum of 2 years, that led to their formal licensure were comparable to designs of studies done for other licensed vaccines.

For the Moderna RNA vaccine, the frequency of serious adverse events was similar in the placebo and vaccine groups (1.4% vs 1.6%).[16] For the Pfizer-BioNTech vaccine, the frequency of serious adverse events after 1 dose was 0.5% for the placebo group and 0.6% for the vaccine group.[15] For the Novavax vaccine,[17] the frequency of any serious treatment-emergent adverse event was 1.0% for the placebo group and 0.9% for the vaccine group (**Table 1**). While one cannot use these numbers to compare the vaccines to each other, owing to differences in the precise definitions used in the different studies, it is clear that the incidence of serious events was comparable between the placebo and vaccine groups in each study.

As expected, less-serious events, especially local reactions, were more frequent in the vaccine groups than in the placebo groups of the studies. The rates of total local adverse events after the second shot in the placebo and vaccine groups, respectively, were 43% vs 92% for the Moderna vaccine,[16] 12% vs 78% for the Pfizer-BioNTech vaccine,[15] and 22% vs 79% for the Novavax vaccine.[17]

An evidence-based review of the adverse effects of COVID-19 vaccination and intramuscular vaccine administration conducted by the independent National Academies of Science, Engineering and Medicine,[33] released in 2024, concluded that overall the most common side effects associated with COVID-19 vaccines were similar to those of other vaccines, ie, flu-like syndromes and local reactions at the injection sites. The review, however, did note convincing evidence of a causal relationship between the mRNA vaccines and myocarditis. The frequency of these events was too low to be detected in the randomized controlled trials, with the evidence of the association coming from the observational cohort studies and reporting to VAERS—again demonstrating the importance of the different ways safety signals are pursued. Overall, this risk was on the order of 7 in 100,000 in vaccine recipients (compared with a pre-COVID rate of 1 in 100,000), more common in white males ages 16 through 30, more common with the second dose, and rarely seen in individuals over 50. Of note, these rates are considerably lower than the rate of myocarditis following COVID-19 (150 in 100,000), a rate that is at least halved with prior vaccination.[34,35]

The National Academies Review Committee also concluded that there was no relationship between the mRNA vaccines and thrombosis with thrombocytopenia syndrome, infertility, Guillain-Barré syndrome, Bell palsy, or myocardial infarction.[33] In contrast, they did report that there was sufficient evidence to conclude that there is a causal relationship between the Ad26 and ChAd platform COVID-19 vaccines and the thrombosis with thrombocytopenia syndrome and the Guillain-Barré syndrome. Of note, these latter 2 vaccines are not available in the United States.

Thus, while the COVID-19 vaccines available in the United States have some risks, severe adverse effects due to the vaccines are rare and the risks are greatly outweighed by the benefits. In everyday life one takes risks in order to derive benefits.

A RELATIONSHIP BUILT ON TRUST

In discussing vaccines in general and COVID-19 vaccines in particular, it is important to empower patients to be their own advocate while helping them sort through the information, emphasizing what we know and where uncertainty remains. To use an analogy, patients typically trust that high blood pressure is bad and should be managed—including with drugs that have a number of side effects. The medical profession needs to work to develop a similar level of trust in the science behind the licensure of vaccines. For COVID-19 vaccines, it is important for the clinician to provide their patients with an objective view of our current understanding of the safety and efficacy of these vaccines and to employ shared decision-making to maintain a relationship built on trust.

Vaccines have been some of the most effective strategies we have to decrease the morbidity and mortality of many infectious diseases, and they need to remain front and center in dealing with today's infectious disease threats as well as those of tomorrow. By neither overstating nor understating their safety and efficacy we may be able to optimize their value today and in the future.

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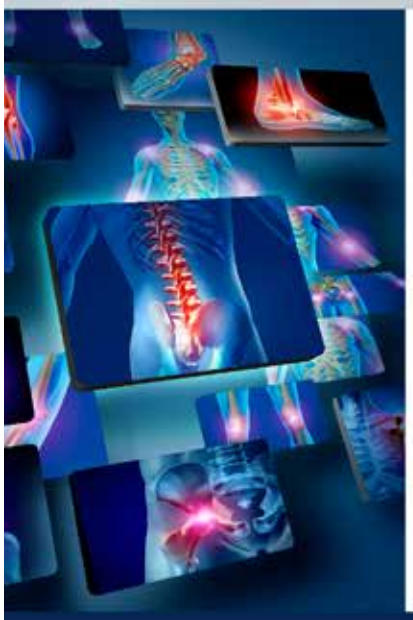

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