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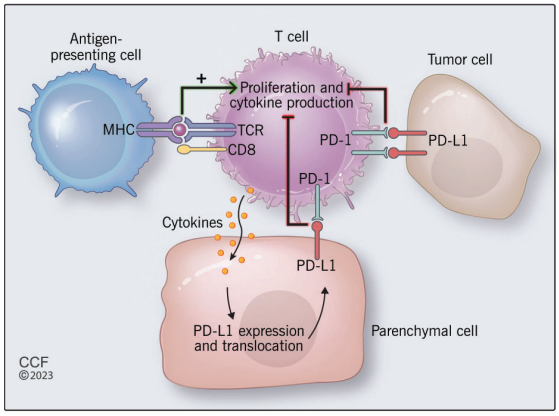

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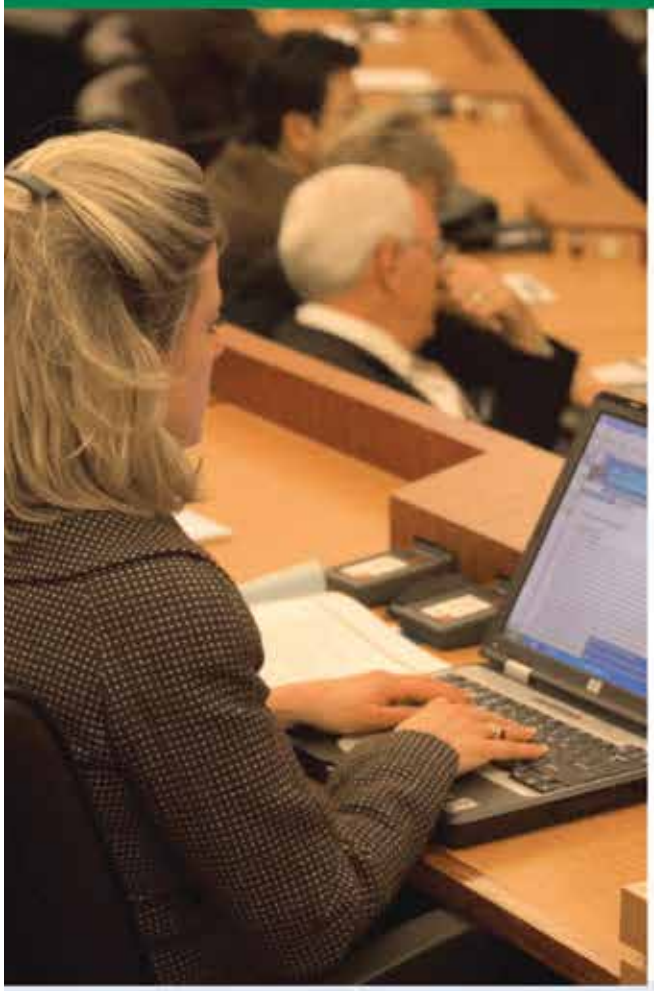

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Aspirin in primary prevention of cardiovascular events: Key questions remain

Are we done with the issue of aspirin (ASA) for primary prevention of cardiovascular (CV) events? Not quite yet. Important questions remain.

ASA for secondary prevention, ie, after an initial CV event, is well entrenched in medical practice,[1] despite the fact that the baseline pharmacotherapy for patients with a CV event is markedly different than it was 2 decades ago. Aggressive lipid-lowering therapy with attention to control of hypertension is now an expectation. It is hard to imagine performing a large-scale placebo-controlled trial to reevaluate the benefit of ASA in secondary prevention.

For ASA as antiplatelet therapy in primary prevention of CV events, as discussed by Mallick et al[2] in this issue of the *Journal*, the published data and guidelines on the limited net value are generally consistent: cardiovascular benefits achieved are small, and the bleeding risks seem higher than many of us assumed.

The studies are seemingly large enough to detect significant benefit even if the "event" rate is low. Assuming that the degree of benefit from ASA in secondary prevention is still robust, and recognizing the caveat that I note above regarding baseline therapy, shouldn't there be net benefit from antiplatelet therapy at preventing type 1 ischemic events? Reasoning in the guidelines for discouraging the general use of ASA as a primary preventive agent comes not only from the limited benefit, but also from the relatively high rate of bleeding in patients on low-dose ASA. Bleeding risk seems to increase with age. In the Dallas Heart Study[3] of 2,191 patients, the likelihood of a bleeding event was increased further in patients who had an increased risk for coronary events as indicated by their coronary artery calcium (CAC) score—the very patients who conceptually might achieve greater benefit from effective prophylaxis.

I wonder if the ultimate risk-benefit ratio of ASA for primary prevention would be sufficiently altered if all patients prescribed ASA were also given high-dose proton pump inhibitor therapy in an effort to reduce gastrointestinal bleeding. But I am more intrigued by trial demographic factors and vascular biology that might have impacted the documented protective response to ASA in the reported studies, and how this can influence how we discuss primary prevention with our patients.

Most large, timed, observational studies excluded patients who were already taking ASA. Thus, patients who had been perceived by their physicians or by themselves to be at higher risk for CV events may not have been enrolled in studies. The US Preventive Services Task Force (USPSTF) recommendations are divided in part on patient age (age increases bleeding risk) with an effort to risk-stratify asymptomatic patients in order to determine which patients would most benefit from a shared decision-making discussion with their physicians. The USPSTF proposed (with limited enthusiasm) an estimated 10% risk of a CV event over 10 years in patients ages 40 to 59, using the American College of Cardiology/American Heart Association (ACC/AHA) assessment of cardiovascular risk,[4] as the trigger for this discussion. Notably, this risk tool does not include family history, markers of inflammation, or advanced coronary imaging. Advanced imaging has been suggested as helpful in further identifying patients who would benefit from primary prevention with ASA.[3]

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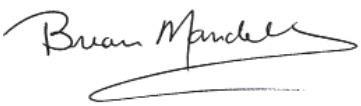
As to vascular biology and the apparent differential effect of ASA in secondary vs primary prevention, might there be fundamental prostanoid-dependent differences in some patients with atherosclerotic (or non-atherosclerotic) disease who develop events and those who don't? I found no evidence for this, but perhaps in patients without advanced disease it takes much longer for the ASA effect to be demonstrated.

The 2022 USPSTF guidelines discourage use of ASA in those over age 60, while the 2019 ACC/AHA guidelines[2] advise patient dialogue in those ages 60 to 70. Both guidelines say to avoid ASA in those over age 70, despite the fact that those patients, even if asymptomatic, would seemingly be more likely to have accumulated significant CV disease and thus would be more likely to benefit from ASA.

While the age-associated increased risk of bleeding must be accounted for, achieving greater reliability in identifying patients at higher risk for CV events would better inform our discussions with patients. I mentioned the use of CAC scoring above, and a recent Danish study of 9,533 asymptomatic patients over age 40 (mean age 60) used coronary computed tomography angiography to demonstrate the presence of nonobstructive coronary artery disease in 36% and obstructive coronary artery disease in 10% of participants.[5] Those with asymptomatic obstructive disease had an 8-fold increase in myocardial infarction. But it remains to be seen if identifying patients with asymptomatic but significant coronary artery disease by CAC scoring, computed tomography angiography, or other modalities will enhance the effective use of ASA (in addition to aggressive statin use). For now, when following the current guidelines, the question of how best to assess CV risk will continue to arise in shared decision-making discussions with our patients.



Brian F. Mandell, MD, PhD
Editor in Chief

1. **Antithrombotic Trialists' Collaboration.** Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002; 324(7329):71–86. doi:10.1136/bmj.324.7329.71
2. **Mallick S, Shroff GR, Linzer M.** Aspirin for primary prevention of cardiovascular disease: what do the current USPSTF guidelines say? Cleve Clin J Med 2023; 90(5):287–291. doi:10.3949/ccjm.90a.22087
3. **Ajufo E, Ayers CR, Vigen R, et al.** Value of coronary artery calcium scanning in association with the net benefit of aspirin in primary prevention of atherosclerotic cardiovascular disease. JAMA Cardiol 2021; 6(2):179–187. doi:10.1001/jamacardio.2020.4939
4. **Goff DC Jr, Lloyd-Jones DM, Bennett G, et al.** 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014; 63(25 Pt B):2935–2959. doi:10.1016/j.jacc.2013.11.005
5. **Fuchs A, Kühl JT, Sigvardsen PE, et al.** Subclinical coronary atherosclerosis and risk for myocardial infarction in a Danish cohort: a prospective observational cohort study. Ann Intern Med 2023; 176(4):433–442. doi:10.7326/M22-3027

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Resistant hypertension: A stepwise approach

To the Editor: I would like to add an important point to the useful review of the diagnosis and treatment of refractory hypertension by Yahr et al[1] in the February issue, specifically the need to evaluate such patients for the possibility of pseudohypertension. It is possible, and in fact does occur, that patients may have both true hypertension and pseudohypertension.

In 1892, Osler described in some patients the persistent palpability of a pulseless radial artery after inflation of the sphygmomanometer cuff to above systolic pressure. Taguchi and Suwangool[2] were the first to describe a patient with pseudohypertension, which they surmised was due to Mönkeberg medical sclerosis. Spence et al[3] described pseudohypertension and the utility of the Osler maneuver in 1979, and this was confirmed by Messerli et al.[4] In the study by Messerli et al, patients who were Osler-positive had falsely elevated blood pressure readings, with a difference of 10 to 54 mm Hg between the cuff pressure and the intra-arterial pressure. These patients had diminished arterial compliance, and the stiffer the artery, the more pronounced the degree of pseudohypertension.

The decreased compressibility or noncompressibility of the brachial artery is due to a combination of intimal calcification, as found in atherosclerosis, and degenerative medial calcifications known as Mönckeberg arteriosclerosis. Mönckeberg medial sclerosis is much more common in patients with diabetes and in patients with chronic kidney disease, as is pseudohypertension. Pseudohypertension is not simply a phenomenon of the discrepancy between blood pressure obtained noninvasively and that obtained intra-arterially. With aging, arteries gradually become less elastic and become larger and stiffer. In such arteries, the reflected wave returns faster and merges with the incident wave in systole. This increases left ventricular afterload and decreases coronary artery blood flow, which leads to left ventricular hypertrophy and increased central blood pressure with attendant untoward physiologic effects.[5] Unfortunately, given that the gold standard for the diagnosis of pseudohypertension requires direct intra-arterial recordings, which is both invasive and impractical, this precludes its use in clinical practice.

Of note, another clue that a patient may have pseudohypertension is the presence of a prominent auscultatory gap (ie, phase 2 of the Korotkoff sounds) when measuring blood pressure.[6] Obviously, this requires that a clinician take the blood pressure with a nonautomated sphygmomanometer. Pulse pressure is a surrogate marker for arterial stiffness, but it alone is inadequate to accurately determine arterial stiffness. Pulse-wave analysis more accurately provides physiologic data on central blood pressure and arterial stiffness but requires significant skill and, again, is impractical in daily practice.[5] The pulse-wave velocity is generally accepted as the simplest noninvasive and reproducible method to assess arterial stiffness.[7] Recently, a high reading of the brachial-ankle pulse-wave velocity was seen to have a positive predictive value for pseudohypertension in elderly patients.[8] There are now available instruments that measure arterial stiffness indirectly by applanation tonometry and pulse-wave analysis. These arterial indices have been shown to have a better prognostic value than the mean arterial pressure or the brachial pulse pressure but have not been incorporated in clinical practice.[5]

I would recommend that any elderly patient diagnosed with hypertension have an Osler maneuver performed. A positive test would suggest the possibility of pseudohypertension. A significant auscultatory gap would reinforce that suspicion, as would the coexistence of diabetes and or chronic kidney disease. The clinician would then uptitrate the dose of the antihypertensive agent or agents in smaller increments than usual, but perhaps more frequently, until either the patient achieves their blood pressure goal or develops any symptoms of orthostatic hypotension. In the elderly, fatigue can also be a symptom or chronic orthostasis. At that point, the dose of antihypertensives would be scaled back to the last dose that was tolerated.

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REFERENCES

1. **Yahr J, Thomas G, Calle J, Taliercio J.** Resistant hypertension: a stepwise approach. Cleve Clin J Med 2023; 90(2):115–125. doi:10.3949/ccjm.90a.22046
2. **Taguchi JT, Suwangool P.** 'Pipe-stem' brachial arteries: a cause of pseudohypertension. JAMA 1974; 228(6):733. pmid:4406262
3. **Spence JD, Sibbald WJ, Cape RD.** Direct, indirect and mean blood pressures in hypertensive patients: the problem of cuff artefact due to arterial wall stiffness, and a partial solution. Clin Invest Med 1979; 2(4):165–173. pmid:549765
4. **Messerli FH, Ventura HO, Amodeo C.** Osler's maneuver and pseudohypertension. N Engl J Med 1985; 312(24):1548–1551. doi:10.1056/NEJM198506133122405
5. **Rafey M.** Beyond office sphygmomanometry: ways to better assess blood pressure. Cleve Clin J Med 2009; 76(11):657–662.
6. **Rao Dayasagar V.** Blood pressure measurement in clinical practice: methods and emerging options. Hypertension J 2019; 5(3):93.

7. **Laurent S, Cockcroft J, Van Bortel L, et al.** Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006; 27(21):2588–2605. doi:10.1093/eurheartj/ehl254
8. **Dai X, Wang H, Fang N.** Prevalence and clinical characteristics of pseudohypertension in elderly patients prepared for coronary artery angiography. Medicine (Baltimore) 2017; 96(48):e8386. doi:10.1097/MD.0000000000008386

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To the Editor: I read with interest the review article by Yahr et al[1] in the February issue, about resistant hypertension. Under the heading "Does the patient have lifestyle factors that raise blood pressure?" there is no mention of stress (chronic or acute crisis) or of psychiatric conditions such as generalized anxiety disorder. In treating the whole patient, these factors should be considered.

An example: a thin 77-year-old White man with no chronic illnesses other than moderate hypertension, well-controlled until 6 months previous to presenting with 180/95 mm Hg pressures (despite adhering to diet and medications), and with a normal lipid profile and normal renal and hepatic function. On questioning, the patient says his spouse was diagnosed with dementia and a movement disorder 8 months before this visit. The patient is the sole caregiver, doing all cooking, cleaning, care related to activities of daily living, and supervision for a "nocturnal wanderer" spouse in her late 70s. He reports 4 to 5 hours of uninterrupted sleep daily.

This is why I think that changes in relationships and environment should be questioned.

Otherwise, an excellent article.

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REFERENCES

1. **Yahr J, Thomas G, Calle J, Taliercio J.** Resistant hypertension: a stepwise approach. Cleve Clin J Med 2023; 90(2):115–125. doi:10.3949/ccjm.90a.22046

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Chondrodermatitis nodularis helicis

A 73-year-old man presented with a mildly tender nonpruritic lesion on his left ear (**Figure 1**) that had been present for 6 months, having first noticed discomfort when sleeping on a firmer pillow on his left side. There was no history of trauma or excessive sun exposure. The patient was periodically picking off the crust, which would always recur. He reported sleeping exclusively on his left side.

Examination revealed a 3-mm lesion on the superior pole of the helix of the ear without erythema. There was a central crust overlaying an ulcerated nodule without discharge or bleeding. The nodule was tender to palpation. Based on the appearance of the lesion and the patient's history of discomfort after changing to a firmer pillow, the lesion was diagnosed as chondrodermatitis nodularis helicis (CNH).

Our patient was advised to avoid putting pressure on the ear and to sleep on the opposite side.

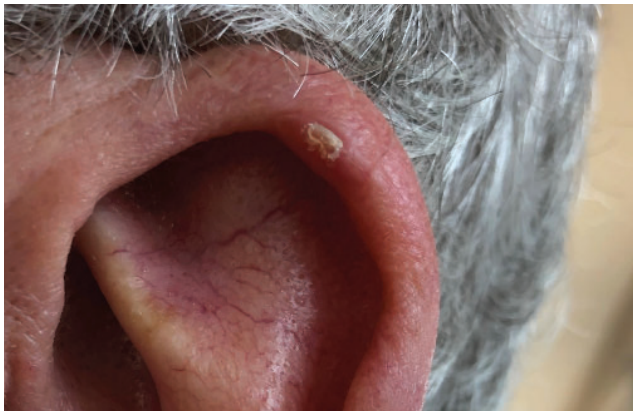

Figure 1. At presentation, the lesion on the helix of the patient's left ear was mildly tender and nonpruritic, with a central crust overlaying an ulcerated nodule.

CHONDRODERMATITIS NODULARIS HELICIS

Classically, CNH is a painful, benign inflammatory nodule or papule on the helix or antihelix of the ear that is tender to touch or pressure.[1,2] Typical lesions are unilateral, 4 to 6 mm in size, and consist of an ulcerated nodule with a central crater. Crusting may or may not be present, and some lesions may have a cystic appearance.

CNH is most common in middle-aged to older fair-skinned men and has a variable male-to-female ratio. The etiology of CNH is multifactorial and can be the result of thinning skin and cartilage seen with aging and with degeneration of cartilage from pressure. CNH can often result in sleep disturbances when patients continue to sleep on the affected side. Involvement of the right side may be more frequent.[3]

The differential diagnosis may include actinic or seborrheic keratosis, basal cell or squamous cell carcinoma, gouty tophi, and keratoacanthoma.[1] Patients are often referred to specialists for biopsy evaluation. However, taking a detailed history, specifically about sleeping patterns, in combination with the location of the lesion should help establish the proper diagnosis. Biopsy should be done when the diagnosis is uncertain, when there is a history of skin cancer or sun-damaged skin, or when the lesion does not respond to noninvasive interventions.

TREATMENTS

As the pathophysiology of CNH is thought to be akin to pressure ulcers, treatment is usually with conservative measures such as pressure avoidance or pressure relief by sleeping on the contralateral side, padding of the ear with sponges or foam, and use of a donut pillow. Clinical response to these interventions can obviate the need for biopsy. Other noninvasive therapies include intralesional steroid injections, topical nitroglycerin gel, cryotherapy, carbon dioxide laser therapy, or photodynamic therapy that uses a light source to improve blood flow.[2,4] Wedge resection

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should be considered when the lesion recurs despite multiple attempts of less invasive interventions.

OUR PATIENT'S CASE CONCLUDED

At follow-up 2 months later, our patient reported significant improvement of symptoms, which further solidified the diagnosis of CNH. The lesion was significantly smaller, and the patient was counseled that CNH can frequently recur and that other treatments may be needed.

REFERENCES

1. **Wagner G, Liefeith J, Sachse MM.** Clinical appearance, differential diagnoses and therapeutical options of chondrodermatitis nodularis chronica helicis Winkler. J Dtsch Dermatol Ges 2011; 9(4):287–291. doi:10.1111/j.1610-0387.2011.07601.x
2. **Salah H, Urso B, Khachemoune A.** Review of the etiopathogenesis and management options of chondrodermatitis nodularis chronica helicis. Cureus 2018; 10(3):e2367. pmid:29805936
3. **Kechichian E, Jabbour S, Haber R, Abdelmassih Y, Tomb R.** Management of chondrodermatitis nodularis helicis: a systematic review and treatment algorithm. Dermatol Surg 2016; 42(10):1125–1134. doi:10.1097/DSS.0000000000000817
4. **Shah S, Fiala KH.** Chondrodermatitis nodularis helicis: a review of current therapies. Dermatol Ther 2017; 30(1):10.1111/dth.12434. doi:10.1111/dth.12434

DISCLOSURES

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Cholesteatoma

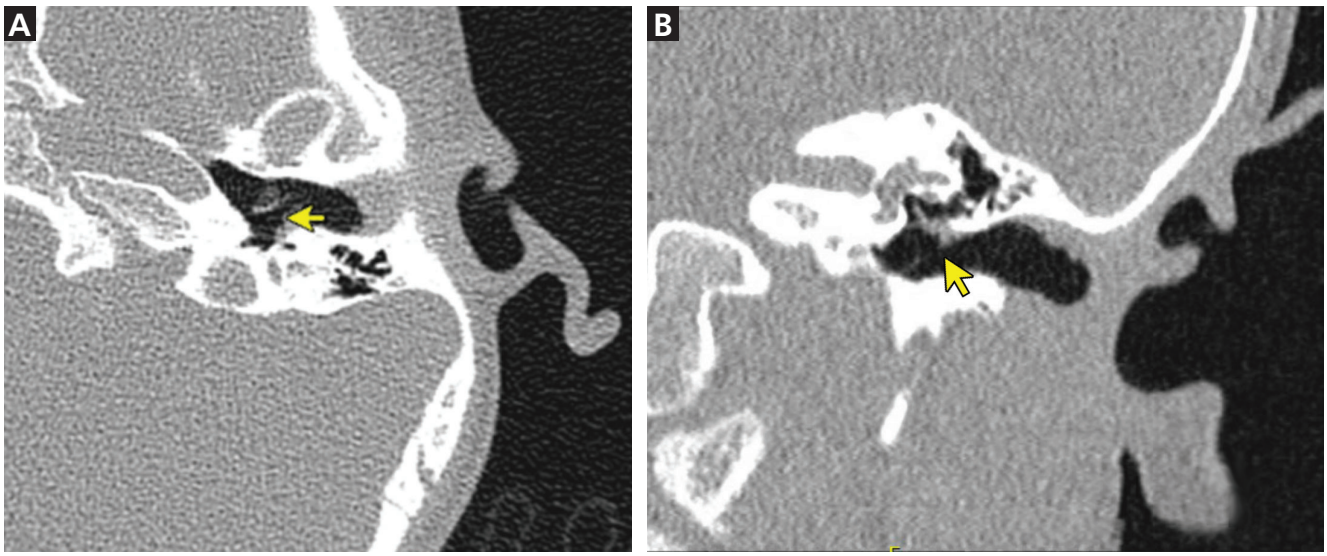

Figure 1. Computed tomography of the patient's temporal bone, without contrast. (A) The axial view shows demineralization and erosion of the incus (arrow), and (B) the coronal view shows soft-tissue extension along the length of the incus (arrow).

After having an abnormal ear examination and a failed hearing screening at her well-child visit with her pediatrician, a 15-year-old female presented for an audiogram, which revealed a left-sided conductive hearing loss. The patient had a history of recurrent acute otitis media of both ears requiring 2 sets of pressure-equalization tubes at ages 2 and 4. There was no family history of hearing loss and no recent history of head or auricular trauma.

Examination in the office was normal on the right side but demonstrated an atelectatic tympanic membrane on the left with a retraction pocket and keratin debris posterosuperiorly. Facial nerve function was intact bilaterally.

Computed tomography of the temporal bones demonstrated a left-sided retracted tympanic membrane with soft tissue extending to the long process of the incus, with erosion and demineralization of the ossicle (**Figure 1**). A retraction cholesteatoma was suspected, which is a type of acquired cholesteatoma that develops with trapping of cholesteatoma within a deep retraction of the tympanic membrane.

She was subsequently taken for tympanoplasty with middle ear exploration. Intraoperatively, cholesteatoma was noted involving the incus and significant erosion. The incus was removed, and the stapes suprastructure was found to be uninvolved and was left intact. She underwent ossicular chain reconstruction with a partial ossicular replacement prosthesis after complete removal of the cholesteatoma. Postoperative audiography demonstrated improvement in hearing thresholds.

The patient continued to be followed for cholesteatoma, with no recurrence of the disease. Choles-

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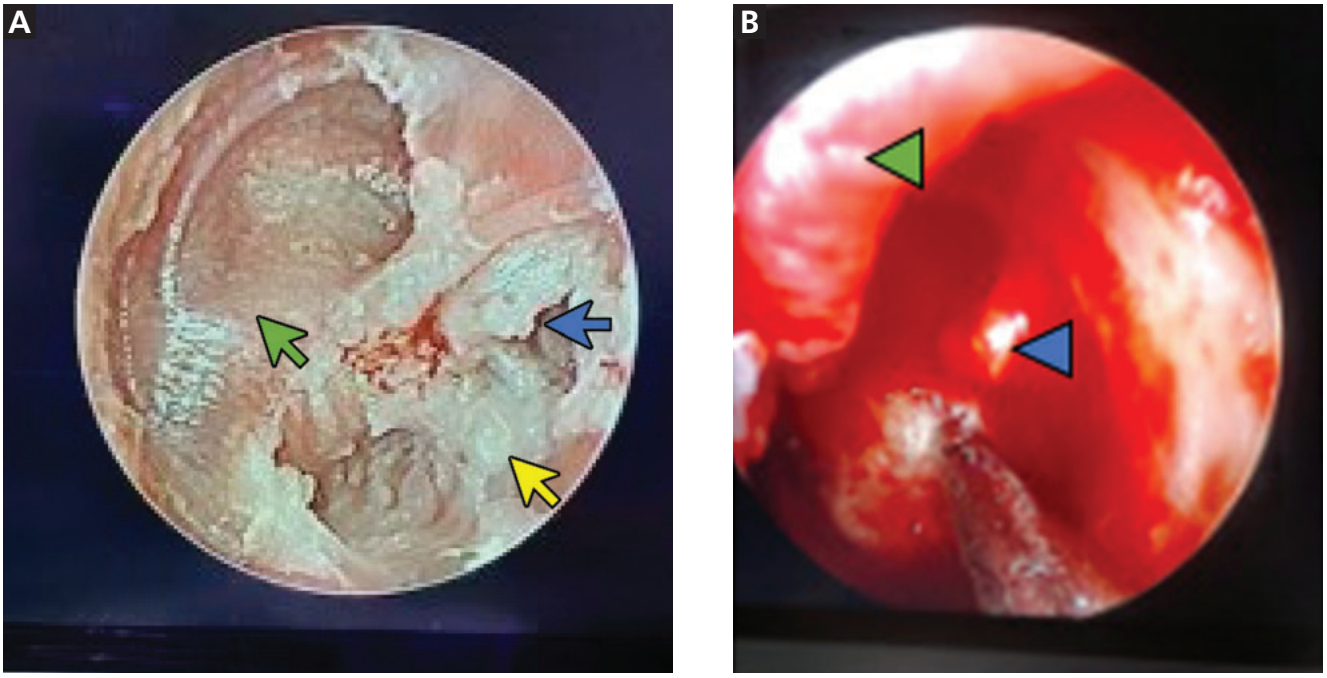

Figure 2. (A) Intraoperative visualization of the patient's retraction cholesteatoma (yellow arrow) prior to removal, with keratin debris in the posterosuperior quadrant (blue arrow). A small remnant of normal tympanic membrane was noted near the annulus anteriorly (green arrow). (B) After elevation of the tympanic membrane (green arrowhead), the lesion was found to have eroded through the tip of the incus (blue arrowhead).

teatomas can recur with an overall disease rate of 4.6% and a residual disease rate of 5.4%,[1] and therefore these patients should be monitored for residual or recurrent disease.

CHOLESTEATOMA: KEY FEATURES

The term cholesteatoma was first used in a case report in 1838 to describe a "tumor" thought to be made of cholesterol and fat (*chole-* for cholesterol, *steat-* for fat, and *-oma* for tumor).[2] This term continues to be used despite the understanding over time that it is instead a progressively enlarging and destructive lesion composed of keratinizing squamous epithelium.[3]

Cholesteatoma is considered congenital when presenting as a white mass behind an intact eardrum in a patient with no history of otitis or previous otologic surgery.[2,3] Acquired cholesteatoma, localized exclusively in the middle ear, affects children and adults and occurs in 3 to 15 per 100,000 children and 9 to 12.6 per 100,000 adults.[2]

Acquired cholesteatoma is often seen in patients with a history of eustachian tube dysfunction, recurrent middle ear infections, or previous otologic surgery,[4] or with a pearly white or yellowish mass behind the tympanic membrane in the middle ear (**Figure 2**).[5] Cholesteatoma may encroach on or erode nearby structures and become secondarily infected, leading to the onset of symptoms as it expands (**Figure 2**).[5] If left untreated, cholesteatoma may erode through the temporal bone or inner ear, where it can cause a perilymphatic fistula, sensorineural hearing loss, vertigo, cerebrospinal fluid leaks, central nervous system infection, or cranial nerve deficits.[5,6]

Hearing loss is a common symptom

Hearing loss is one of the most common symptoms of cholesteatoma. It is predominantly conductive in nature and may be due to otorrhea resulting from secondary infection, chronic inflammation leading to edema and granulation tissue formation, or ossicular erosion.[6] Rarely, cholesteatoma can cause sensorineural hearing loss if it extends to the inner ear.[5,6]

Patients with cholesteatoma may classically present with hearing loss in the setting of an apparent ear infection, abnormal appearance of tympanic membrane and middle ear, or an otherwise normal physical examination. The typical conductive hearing loss that occurs with cholesteatoma must be differentiated from sensorineural hearing loss and other causes of

conductive hearing loss such as trauma, ossicular discontinuity, and otosclerosis.

WHEN TO REFER TO AN OTOLARYNGOLOGIST

Patients with an abnormal examination, a history of recurrent middle ear infections, eustachian tube dysfunction, or previous otologic surgery, or patients with symptoms that fail to improve with treatment should be promptly referred to an otolaryngologist for further evaluation and management.

DISCLOSURES

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REFERENCES

1. **van der Toom HFE, van der Schroeff MP, Pauw RJ.** Single-stage mastoid obliteration in cholesteatoma surgery and recurrent and residual disease rates: a systematic review. JAMA Otolaryngol Head Neck Surg 2018; 144(5):440–446. doi:10.1001/jamaoto.2017.3401
2. **Kuo CL, Shiao AS, Yung M, et al.** Updates and knowledge gaps in cholesteatoma research. Biomed Res Int 2015; 2015:854024. doi:10.1155/2015/854024
3. **Isaacson G.** Diagnosis of pediatric cholesteatoma. Pediatrics 2007; 120(3):603–608. doi:10.1542/peds.2007-0120
4. **McGuire JK, Wasl H, Harris T, Copley GJ, Fagan JJ.** Management of pediatric cholesteatoma based on presentations, complications, and outcomes. Int J Pediatr Otorhinolaryngol 2016; 80:69–73. doi:10.1016/j.ijporl.2015.10.041
5. **Bhutta MF, Williamson IG, Sudhoff HH.** Cholesteatoma. BMJ 2011; 342:d1088. doi:10.1136/bmj.d1088
6. **Rosito LS, Netto LS, Teixeira AR, da Costa SS.** Sensorineural hearing loss in cholesteatoma. Otol Neurotol 2016; 37(3):214–217. doi:10.1097/MAO.0000000000000952

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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Should my elderly hospitalized patient with acute onset of altered mental status undergo stat head CT?

An 82-year-old woman presents to the hospital because of progressively worsening weakness. On hospital day 4, a nurse finds her with severe inattention, disorganized thinking, and an altered level of consciousness. The nurse initiates a rapid response. Computed tomography (CT) of the head without contrast is ordered, which reveals no acute intracranial process. Arterial blood gas measurement reveals respiratory acidosis. The patient is started on bilevel positive end-expiratory pressure ventilation. Repeat arterial blood gas measurement reveals that the acidosis has resolved, and the patient's mental status improves.

A: CT has become an integral tool in patient evaluation. Unfortunately, overreliance may have led to overuse.

In an article commemorating the 50th anniversary of the first CT scan,[1] Dr. Joel Howell reflected on the shift within medicine attributed to the new technology, specifically the ability to detect a lesion that may be contributing to disease. Howell asserted that the challenge of CT is "to determine when finding the lesion can help relieve symptoms and save lives and when it does little to improve the health of the patient."[1]

CT is used to look for intracranial hemorrhage if a patient is receiving anticoagulation. Additionally, it is commonly ordered to rule out a bleed or other intracranial process in hospitalized patients with delirium. However, a retrospective study found that of 220 CT scans performed for acute-onset delirium, only 6 (2.7%) had positive results.[2] This finding raises the question of whether CT is necessary in evaluating delirium, given its cost, radiation exposure, and allocation of a limited resource.

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DIAGNOSIS OF DELIRIUM

Delirium is an acute neurocognitive disorder characterized by sudden changes in attention and cognition. It has been reported to occur in 14% to 56% of hospitalized patients,[3] but it is recognized only 12% to 35% of the time.[4]

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision* (DSM-5-TR) outlines 5 features that characterize delirium: (1) changes in attention and awareness that…(2) develop acutely from a patient's baseline and are… (3) associated with additional changes in cognition… (4) which are not better explained by another preexisting neurocognitive disorder and…(5) can be attributed to a medical condition elicited by history, physical examination, or laboratory data.[5]

There are many clinical methods for assessing delirium, such as asking the patient to count backward from 100 by 7s (serial 7s) or spell "world" backward, in addition to the following:

The Confusion Assessment Method[6] is a practical evidence-based tool to assess delirium at the bedside. Patients exhibiting acute or fluctuating inattentiveness accompanied by either an altered level of consciousness or disorganized thinking would be considered delirious as assessed by this tool.

The 4AT[7] rapid clinical test for delirium is a bedside screening tool that comprises 4 items: an assess-

ment of alertness, separate tests of cognition, and an assessment of changes in mental status.[7]

Electroencephalography. Interestingly, generalized slowing on electroencephalographic monitoring correlates with delirium and may be useful to assess delirium severity.[8]

BEDSIDE CLINICAL ASSESSMENT OF STROKE

Because "time is brain," speed is of the utmost importance when assessing and subsequently treating a potential "brain attack." As mentioned above, although CT is almost reflexively used in the setting of delirium, it rarely reveals a contributing process, suggesting that there is a better way to evaluate our patients.

The National Institutes of Health Stroke Scale (NIHSS) is one of the better known of the many stroke scales. Developed as a research tool to measure outcomes in the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study,[9] over time the scale was truncated and further modified to its present-day version. The original NIHSS had 15 items and assigned a score based on level of consciousness, gaze, visual fields, facial palsy, extremity strength, ataxia, sensation, language, dysarthria, and extinction. Careful assessment of the scale whittled the original 15 items to an essential 11 by eliminating components that were deemed superfluous or poorly reproducible.

The modified NIHSS has been found to be both reliable (ie, different observers will calculate the same score for the same patient) and valid (ie, it correlates with both stroke volumes and clinical outcomes),[10] and it is clinically indicated in every "code stroke." However, it does not fully answer the question as to whether a stroke is occurring.

The 2CAN score[11] was developed as a way for clinicians who are not neurologists to recognize and distinguish inpatient strokes from stroke mimics. Recognition of inpatient stroke is challenging considering the confounding medical conditions and many medications given in the hospital. Possible 2CAN scores range from 0 to 6. Patients get 1 point if they have 1 of the following clinical deficits: asymmetric facial droop; asymmetric arm weakness; or slurred speech, inappropriate words, or inability to speak at all. They get 3 points if they have 2 or more of these deficits. In addition, they get 1 point for each of the following: cardiac surgery in the current hospitalization, history of atrial fibrillation, or being in the hospital less than 24 hours. However, the 2CAN score has not accumulated adequate evidence that it can accurately identify in-hospital strokes.[12]

DELIRIUM: LOOKING FOR OTHER CAUSES, WHILE KEEPING STROKE IN MIND

Regardless of whether the possibility of stroke was ruled out by history and physical examination or imaging, the underlying cause of delirium needs to be identified so that proper treatment can be started.

When approaching a patient in a delirious state, physicians can organize their thinking using the following framework[13]:

- **Neurologic causes:** cerebral hypoxia, seizure, traumatic brain injury, intracranial hemorrhage, brain tumor, hydrocephalus, central nervous system vasculitis, immune-mediated encephalitis
- **Toxic causes:** medications, alcohol, recreational drugs, poisons
- **Metabolic causes:** hepatic encephalopathy, uremia, hypoglycemia, hyperosmolality, electrolyte disturbances, vitamin deficiency, hypercarbia, thyroid disease, Cushing syndrome, hypothermia, hyperthermia
- **Infectious causes:** urinary tract infection, pneumonia, sepsis, meningitis, encephalitis, brain abscess
- **Other causes:** insomnia, hypertension, posterior reversible encephalopathy syndrome.

In the case of our 82-year-old patient, the delirium was most likely due to hypercarbia, a metabolic cause.

THE CASE AGAINST IMAGING

While the differential diagnosis for delirium is very broad, only a handful of the diseases are caused by processes that would require imaging. In fact, most treatable causes of delirium lie outside the brain.[14] By applying the framework described above and assessing the patient with a thorough history, focused physical examination, and appropriate testing reflecting the differential diagnosis, the underlying cause of delirium can be established accurately and would not require imaging.

Not only does excessive imaging weaken our diagnostic reasoning, it also delays proper treatment while we wait for the patient's return from the scanner and for the radiologist's report. This delays time to making a proper diagnosis, subsequently delaying treatment, which can increase morbidity in any medical condition, not just delirium. However, the concepts of stroke mimics[15] and "stroke chameleons" or "hidden

strokes"[16] further challenge our diagnostic abilities and require a heightened level of awareness and understanding that certain presentations may prompt neuroimaging on a case-by-case basis.

THE BOTTOM LINE

Since most causes of delirium are extracranial, imaging is not necessary for every hospitalized patient who develops delirium. Once the diagnosis of delirium is confirmed through the diagnostic criteria outlined in the DSM-5-TR or clinical scores such as the Confusion Assessment Method or the 4AT, the possibility of an underlying cerebral bleeding episode or ischemic process can be evaluated using widely adopted clinical scoring tools such as the NIHSS. These tools, accompanied by the clinician's clinical acumen, can obviate the need for CT, allowing the clinician to think through the differential diagnosis of delirium and narrow the range of potential causes for the individual patient. Subsequent tests and therapies can be ordered accordingly.

DISCLOSURES

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

REFERENCES

1. **Howell JD.** The CT scan after 50 years—continuity and change. N Engl J Med 2021; 385(2):104–105. doi:10.1056/NEJMp2033374
2. **Theisen-Toupal J, Breu AC, Mattison ML, Arnaout R.** Diagnostic yield of head computed tomography for the hospitalized medical patient with delirium. J Hosp Med 2014; 9(8):497–501. doi:10.1002/jhm.2198
3. **Siddiqi N, Stockdale R, Britton AM, Holmes J.** Interventions for preventing delirium in hospitalised patients. Cochrane Database Syst Rev 2007; (2):CD005563. doi:10.1002/14651858.CD005563.pub2
4. **Inouye SK, Westendorp RG, Saczynski JS.** Delirium in elderly people. Lancet 2014; 383(9920):911–922. doi:10.1016/S0140-6736(13)60688-1
5. **American Psychiatric Association.** Diagnostic and Statistical Manual of Mental Disorders. 5th Edition, Text Revision. Arlington, VA: American Psychiatric Association; 2022.
6. **Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI.** Clarifying confusion: the Confusion Assessment Method. A new method for detection of delirium. Ann Intern Med 1990; 113(12):941–948. doi:10.7326/0003-4819-113-12-941
7. **Bellelli G, Morandi A, Davis DH, et al.** Validation of the 4AT, a new instrument for rapid delirium screening: a study in 234 hospitalised older people [published correction appears in Age Ageing 2015; 44(1):175]. Age Ageing 2014; 43(4):496–502. doi:10.1093/ageing/afu021
8. **Kimchi EY, Neelagiri A, Whitt W, et al.** Clinical EEG slowing correlates with delirium severity and predicts poor clinical outcomes. Neurology 2019; 93(13):e1260–e1271. doi:10.1212/WNL.0000000000008164
9. **National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group.** Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995; 333(24):1581–1587. doi:10.1056/NEJM199512143332401
10. **Kasner SE.** Clinical interpretation and use of stroke scales. Lancet Neurol 2006; 5(7):603–612. doi:10.1016/S1474-4422(06)70495-1
11. **Chang P, Ruff I, Bergman D, Mendelson S, Prabhakaran S.** Abstract 193: the 2CAN score: a novel inpatient stroke recognition instrument. Stroke 2018; 49(suppl 1):A193. doi:10.1161/str.49.suppl_1.193
12. **Parrino CR, Noles A, Lalla R, et al.** Optimizing the recognition and treatment of in-hospital stroke: evaluation of the 2CAN score. J Stroke Cerebrovasc Dis 2021; 30(10):106032. doi:10.1016/j.jstrokecerebrovasdis.2021.106032
13. **Mansoor AM.** Frameworks for Internal Medicine. Philadelphia, PA: Wolters Kluwer; 2018.
14. **Marcantonio ER.** Delirium in hospitalized older adults. N Engl J Med 2017; 377(15):1456–1466. doi:10.1056/NEJMcp1605501
15. **Libman RB, Wirkowski E, Alvir J, Rao TH.** Conditions that mimic stroke in the emergency department. Implications for acute stroke trials. Arch Neurol 1995; 52(11):1119–1122. doi:10.1001/archneur.1995.00540350113023
16. **Dupre CM, Libman R, Dupre SI, Katz JM, Rybinnik I, Kwiatkowski T.** Stroke chameleons. J Stroke Cerebrovasc Dis 2014; 23(2):374–378. doi:10.1016/j.jstrokecerebrovasdis.2013.07.015

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Aspirin for primary prevention of cardiovascular disease: What do the current USPSTF guidelines say?

ABSTRACT

The 2022 US Preventive Services Task Force (USPSTF) recommendation notes that the decision to initiate daily aspirin therapy for primary prevention of cardiovascular disease (CVD) should be made on a case-by-case basis for adults ages 40 to 59 with a 10% or greater 10-year CVD risk. The recommendation applies to those without signs or symptoms of clinically evident CVD who are not at an increased risk of bleeding. Clinicians are encouraged to use their judgment in weighing the risks and benefits of aspirin therapy, while taking patient preference into account for patients ages 40 to 60.

KEY POINTS

To calculate the 10-year CVD risk, clinicians are referred to the American College of Cardiology/American Heart Association pooled cohort equation, which uses the variables age, sex, blood pressure, lipids, diabetes mellitus, and tobacco use, but not family history.

For patients age 60 or older, the USPSTF now advises against initiating aspirin therapy as there is a lack of net benefit and as risk of harm may outweigh benefit.

The USPSTF guidelines are based on evidence from 13 studies that suggest that aspirin provides a small benefit for select patients ages 40 to 59, and no net benefit (with potential for harm) for patients age 60 or older.

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The 2022 US Preventive Services Task Force (USPSTF) recommendation statement on the role of aspirin (acetylsalicylic acid, ASA) in primary prevention of cardiovascular disease (CVD)[1] replaces the previous 2016 statement.[2] The update notes that the decision to initiate daily ASA therapy for primary prevention of CVD should be made on a case-by-case basis for adults ages 40 to 59 with a 10% or greater 10-year CVD risk (grade C recommendation, ie, small net benefit for select patients based on individual circumstances).[1] These recommendations apply to those without signs or symptoms of clinically evident CVD who are not at an increased risk of bleeding.

Clinicians are encouraged to use judgment in weighing the risks and benefits of ASA, while taking patient preference into account for patients between ages 40 and 60. When calculating the 10-year CVD risk, clinicians are referred to the American College of Cardiology (ACC)/American Heart Association (AHA) pooled cohort equations (PCE) used in the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk[3] that include age, sex, blood pressure, lipids, diabetes mellitus, and tobacco use, but importantly do not include family history. For patients age 60 or older, the USPSTF now advises against initiating ASA (grade D recommendation, ie, either there is no net benefit, or harm outweighs benefit).[1]

In summary, the 2022 USPSTF recommendation statement, based on evidence from 13 studies, suggests that ASA provides a small

TABLE 1
Summary of 3 large trials on daily aspirin therapy for primary prevention

Trial	Population	Findings
ASCEND[4]	15,480 patients with diabetes and no prior CVD history	Therapy resulted in a 12% reduction in myocardial infarction and ischemic stroke Therapy resulted in a 30% increased risk for a major bleeding event, especially prominent in patients age 60 or older
ARRIVE[5]	12,546 patients with mean 17% 10-year CVD risk	No significant benefit in CVD prevention with therapy compared with placebo Twofold increase in gastrointestinal bleeding seen in aspirin therapy group
ASPREE[6,7]	19,114 patients, average age 74	Therapy provided no benefit in preventing first nonfatal cardiovascular event or death Therapy showed a 30% increased risk of major nonfatal hemorrhage, particularly in upper-gastrointestinal bleeds and intracranial hemorrhage

ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; CVD = cardiovascular disease

benefit for select patients ages 40 to 59 and no net benefit (with potential for harm) for patients age 60 or older.

WHAT IS DIFFERENT FROM PRIOR GUIDELINES?

In reviewing the USPSTF guidelines from 2016,[2] the authors carefully reviewed 11 randomized controlled trials, but only 2 were of good quality. While there was a statistically significant benefit in the meta-analysis regarding nonfatal myocardial infarction, the heterogeneity of the studies was high. There was no statistically significant impact on CVD mortality, nonfatal ischemic stroke, or all-cause mortality. Based on the best evidence at the time, in 2016 the USPSTF gave a stronger recommendation for ASA use in younger patients, suggesting initiating low-dose ASA for primary prevention of CVD in adults ages 50 to 59 with a 10% or greater 10-year CVD risk, if risk for bleeding was not increased (grade B recommendation, ie, moderate certainty of overall benefit).[2] Patients ages 40 to 49 were not included in the 2016 guidelines.

The 2016 guidelines also recommended shared decision-making for individuals ages 60 to 70 with high cardiovascular risk and low risk of bleeding, and "indeterminate" recommendations for those younger than 50 or older than 70.[2]

The 2022 USPSTF guidelines incorporate 3 more recent large, randomized trials[4–7] (all published in 2018) that convincingly showed either minimal or no benefit in terms of ASA use and reduced ischemic events, with a large relative risk of bleeding in all 3 trials (**Table 1**).[1] Thirteen randomized control trials that investigated ASA in primary CVD prevention were included in a recent meta-analysis[8] comprising more than 160,000 participants.

While ASA use showed an absolute risk reduction of 0.38% (number needed to treat of 265) in nonfatal myocardial infarction and ischemic stroke in patients with no history of CVD, there was no significant reduction in cardiovascular or all-cause mortality.[9] The meta-analysis had a large number of participants under age 50 and over age 70, unique compared with prior trials. The benefit of ASA was similar across age groups. However, the risk associated with bleeding was significantly higher in patients age 60 and older.[1] Thus, the risks were felt to outweigh the potential benefits.

Overall, the 2022 USPSTF guidelines are substantially different from the previous guidelines in terms of clinical actions recommended, age ranges for the impacted population, and grades of recommendation.

DO OTHER SOCIETIES AGREE OR DISAGREE?

The 2019 ACC/AHA guidelines[10] for ASA use in primary prevention differ slightly from the 2016 and 2022 USPSTF guidelines, recommending individualized approaches in those ages 40 to 70 with a "higher risk" for cardiovascular disease, and against ASA use for primary prevention in those over age 70. There was no explicit 10-year CVD risk threshold above

TABLE 2
A comparison of the 2022 USPSTF and 2019 ACC/AHA guidelines for daily aspirin use for primary prevention, by age

	Age 40 to 60	Age 60 to 70	Age > 70
USPSTF 2022[1]	Individualize for risk > 10% for CVD events using pooled cohort equation (grade C)	No aspirin (grade D)	No aspirin (grade D)
ACC/AHA 2019[10]	Individualize for higher risk patients (COR IIb/LOE A)	Individualize for higher risk patients (COR IIb/LOE A)	No aspirin (COR III/LOE B-R)

ACC = American College of Cardiology; AHA = American Heart Association; COR = class of recommendation; COR IIb/LOE A = high-quality evidence showing treatment may be reasonable, but effectiveness is not well established; COR III/LOE B-R = moderate-quality evidence showed no benefit and potential harm; CVD = cardiovascular disease; grade C = small benefit in select patients; grade D = no net benefit or harm outweighs benefit; LOE = level of evidence

which one should consider initiating ASA therapy for those ages 40 to 70. **Table 2** highlights differences between the 2019 ACC/AHA guidelines and the 2022 USPSTF recommendations.[1,10]

HOW WILL THIS CHANGE DAILY PRACTICE?

Heart disease and stroke remain the leading causes of mortality in the United States, accounting for over 1 in 4 deaths. Individuals ages 40 to 59 with no history of CVD should be assessed for CVD risk factors using the ACC/AHA pooled cohort equation[3] (also referred to as the atherosclerotic CVD [ASCVD] risk estimator) and initiated on ASA only on an individual basis if benefit is judged to exceed risk.

Recent trials (**Table 1**)[1,4–7] brought to light the significantly increased risk of bleeding associated with ASA that was not previously recognized. Therefore, assessment of bleeding risk should be a strong consideration in deciding whether to initiate ASA. The ACC notes numerous clinical circumstances related to potential bleeding risks where they suggest avoiding ASA, including gastrointestinal bleeding history, peptic ulcer disease, use of nonsteroidal anti-inflammatory drugs, steroids, anticoagulants, age over 70, thrombocytopenia, and coagulopathies.[10] Unfortunately, there is no available validated calculator in the United States to assess bleeding risk in aspirin use for patients.

A prospective cohort study in New Zealand developed the Predicting Risk of Death in Cardiac Disease Tool (PREDICT), a web-based prognostic bleeding risk model to estimate absolute bleeding harm of ASA in the context of primary prevention of CVD.[11] This study has certain measures that are not available in the United States (eg, deprivation, a measure of social determinants that would need to be recalibrated) and has considerable complexity to assess 5-year risk of CVD events and major bleeding, including numerous variables: eg, age, sex, ethnicity, socioeconomic deprivation, smoking, diabetes, family history of coronary artery disease, cancer history, liver or renal disease, peptic ulcer disease, prior bleeding, alcohol use, chronic pancreatitis, systolic blood pressure, hyperlipidemia, and use of nonsteroidal anti-inflammatory drugs, steroids, or serotonin reuptake inhibitors.[11] While PREDICT is not validated for clinical use in the United States, the variables can likely be used by clinicians in shared decision-making to qualitatively assess bleeding risk for patients ages 40 to 59.

In summary, both sets of guidelines (USPSTF[1] and ACC/AHA[10]) confirm avoiding ASA use in patients age 70 or older, while the 2022 USPSTF guidelines now recommend against using ASA in all patients over age 60. USPSTF recommends customizing the decision for those ages 40 to 60 with a 10% or greater 10-year CVD risk, while AHA/ACC recommends customizing in higher-risk patients ages 40 to 70. Both guidelines will likely lead to an increased recognition of bleeding risk with ASA, and we anticipate a marked reduction in ASA use for primary prevention of CVD, particularly in older age groups. The meta-analysis from 2022[8] suggests that for patients older than 60, the risk of bleeding outweighs the small benefit ASA may have on CVD prevention.

For this reason, our recommendation aligns with the 2022 USPSTF guidelines to not initiate ASA therapy for patients age 60 or older. It is possible that the future iteration of the AHA/ACC guidelines may also assume this stance, as the trials used for the meta-analysis were not available in 2019. Clinicians

will still wish to customize their decision regarding when to initiate ASA therapy for individuals ages 40 to 59 with a 10% or greater 10-year CVD risk.

Quantitative risk estimators should be used in conjunction with many other factors to guide management.[3] In addition to the PCE, we recommend taking additional risk factors into account to guide decisions. The 2019 ACC/AHA guideline[10] on primary prevention of cardiovascular disease provides an in-depth analysis of risk-increasing factors that can guide the clinician-patient risk discussion, and risks of bleeding have been described in detail above.

WHEN WOULD THE GUIDELINES NOT APPLY?

The ACC/AHA ASCVD risk estimator has been validated in non-Hispanic White and non-Hispanic African American individuals, leading to uncertainty regarding evaluation in other racial and ethnic groups.[3] Recently, Gomez et al[12] highlighted increased and unique cardiovascular risk in Hispanic and Latinx cohorts, suggesting that they should be included in shared decision-making discussions regarding primary prevention of CVD. The ACC/AHA PCE also tend to underpredict CVD risk in individuals of lower socioeconomic status and individuals with chronic inflammatory diseases. Further studies are needed to determine increased risk and tools to help quantify risk in these groups.

Additionally, patients with the genetic condition familial hypercholesterolemia (FH) have increased risk for early and premature ASCVD events.[13,14] Although homozygous FH is relatively uncommon and can present in childhood, heterozygous FH is a common condition affecting nearly 1 in every 220 individuals globally.[13] FH is typically diagnosed based on family history of hypercholesterolemia, clinical examination findings, early-onset ASCVD, and elevated levels of low-density lipoprotein cholesterol.[13,14] Based on the ACC/AHA guidelines, risk calculators are not applicable to the FH population, who are generally treated aggressively with medications to lower low-density lipoprotein levels. In this high-risk population, lipid experts generally recommend ASA for primary prevention.[14] But considering recent evidence, future studies should reevaluate its role in primary prevention in those over age 60.

Other risk factors to consider in individualizing risk assessment include a family history of coronary artery disease,[15] chronic kidney disease, and chronic inflammatory conditions,[16] which can accelerate atherosclerosis. Certain genotypes associated with elevated lipoprotein(a) are also associated with higher CVD risk,[17] but the ability to use genomics to quantify that risk is still under investigation.

Some groups have studied the role of coronary artery calcium (CAC) in identifying individuals who are more likely to benefit from ASA for primary prevention. Cainzos-Achirica et al[18] concluded that CAC may be superior to the PCE to inform personalized allocation of ASA in primary prevention. Similarly, Miedema et al[19] have shown that those with a CAC score of 100 or higher had a favorable risk-benefit ratio with ASA use, whereas those with a CAC score of 0 had net harm from ASA use.[19] The risk of radiation should be especially discussed with women of childbearing age, and CAC scoring should be avoided in pregnant women. In patients for whom the risk-benefit assessment and shared decision-making are equivocal, CAC could serve as a mechanism to guide clinical practice.

DISCLOSURES

Dr. Linzer reports research as principal investigator for American Board of Internal Medicine and United Healthcare, and consulting for Harvard. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

REFERENCES

1. **US Preventive Services Task Force, Davidson KW, Barry MJ, et al.** Aspirin use to prevent cardiovascular disease: US Preventive Services Task Force recommendation statement. JAMA 2022; 327(16): 1577–1584. doi:10.1001/jama.2022.4983
2. **Bibbins-Domingo K; US Preventive Services Task Force.** Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: US Preventive Services Task Force recommendation statement. Ann Intern Med 2016; 164(12):836–845. doi:10.7326/M16-0577
3. **Goff DC Jr, Lloyd-Jones DM, Bennett G, et al.** 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published correction appears in J Am Coll Cardiol 2014; 63(25 Pt B):3026]. J Am Coll Cardiol 2014; 63(25 Pt B):2935–2959. doi:10.1016/j.jacc.2013.11.005
4. **ASCEND Study Collaborative Group, Bowman L, Mafham M, et al.** Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med 2018; 379(16):1529–1539. doi:10.1056/NEJMoa1804988
5. **Gaziano JM, Brotons C, Coppolecchia R, et al.** Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. Lancet 2018; 392(10152):1036–1046. doi:10.1016/S0140-6736(18)31924-X
6. **McNeil JJ, Woods RL, Nelson MR, et al.** Effect of aspirin on disability-free survival in the healthy elderly. N Engl J Med 2018; 379(16):1499–1508. doi:10.1056/NEJMoa1800722
7. **McNeil JJ, Wolfe R, Woods RL, et al.** Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. N Engl J Med 2018; 379(16):1509–1518. doi:10.1056/NEJMoa1805819

8. **Guirguis-Blake JM, Evans CV, Perdue LA, Bean SI, Senger CA.** Aspirin use to prevent cardiovascular disease and colorectal cancer updated evidence report and systematic review for the US Preventive Services Task Force. JAMA 2022; 327(16):1585–1597. doi:10.1001/jama.2022.3337
9. **Barry AR, Semchuk WM, Thompson A, LeBras MH, Koshman SL.** Use of low-dose acetylsalicylic acid for cardiovascular disease prevention: a practical, stepwise approach for pharmacists. Can Pharm J (Ott) 2020; 153(3):153–160. doi:10.1177/1715163520909137
10. **Arnett DK, Blumenthal RS, Albert MA, et al.** 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in Circulation 2019; 140(11):e649–e650] [published correction appears in Circulation 2020; 141(4):e60] [published correction appears in Circulation 2020; 141(16):e774]. Circulation 2019; 140(11):e596–e646. doi:10.1161/CIR.0000000000000678
11. **Selak V, Jackson R, Poppe K, et al.** Predicting bleeding risk to guide aspirin use for the primary prevention of cardiovascular disease: a cohort study. Ann Intern Med 2019; 170(6):357–368. doi:10.7326/M18-2808
12. **Gomez S, Blumer V, Rodriguez F.** Unique cardiovascular disease risk factors in Hispanic individuals. Curr Cardiovasc Risk Rep 2022; 16(7):53–61. doi:10.1007/s12170-022-00692-0
13. **McGowan MP, Hosseini Dehkordi SH, Moriarty PM, Duell PB.** Diagnosis and treatment of heterozygous familial hypercholesterolemia. J Am Heart Assoc 2019; 8(24):e013225. doi:10.1161/JAHA.119.013225
14. **Goldberg AC, Hopkins PN, Toth PP, et al.** Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol 2011; 5(suppl 3):S1–S8. doi:10.1016/j.jacl.2011.04.003
15. **Colantonio LD, Richman JS, Carson AP, et al.** Performance of the atherosclerotic cardiovascular disease pooled cohort risk equations by social deprivation status. J Am Heart Assoc 2017; 6(3):e005676. doi:10.1161/JAHA.117.005676
16. **Crowson CS, Gabriel SE, Semb AG, et al.** Rheumatoid arthritis-specific cardiovascular risk scores are not superior to general risk scores: a validation analysis of patients from seven countries. Rheumatology (Oxford) 2017; 56(7):1102–1110. doi:10.1093/rheumatology/kex038
17. **Kronenberg F, Mora S, Stroes ESG, et al.** Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. Eur Heart J 2022; 43(39):3925–3946. doi:10.1093/eurheartj/ehac361
18. **Cainzos-Achirica M, Miedema MD, McEvoy JW, et al.** Coronary artery calcium for personalized allocation of aspirin in primary prevention of cardiovascular disease in 2019: the MESA study (multi-ethnic study of atherosclerosis). Circulation 2020; 141(19):1541–1553. doi:10.1161/CIRCULATIONAHA.119.045010
19. **Miedema MD, Duprez DA, Misialek JR, et al.** Use of coronary artery calcium testing to guide aspirin utilization for primary prevention: estimates from the multi-ethnic study of atherosclerosis. Circ Cardiovasc Qual Outcomes 2014; 7(3):453–460. doi:10.1161/CIRCOUTCOMES.113.000690

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BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: What is the optimal approach to infiltration and extravasation of nonchemotherapy medications?

A: The immediate response to leakage of intravenous (IV) medications is warm or cold compression and assessment of severity. If the severity is grade 3 or above,[1] an antidote is needed and must be identified quickly. The antidote depends on the type of medication that has leaked.

In general, hyaluronidase is the antidote of choice for nonvesicant agents, but other agents include topical nitroglycerin, phentolamine, terbutaline, and sodium thiosulfate. These agents work by vasodilating to clear the drug from the area and neutralizing the harmful irritants.

IMPORTANT DISTINCTIONS: TERMINOLOGY

An review of terminology is helpful when discussing leakage of IV fluids.

A vesicant is an agent capable of causing tissue damage when escaped from the intended vascular pathway into surrounding tissue.

An irritant or nonvesicant is an agent that causes discomfort including, aching, tightness, and phlebitis with or without inflammation, but does not typically cause tissue necrosis.

Infiltration is leakage of a nonvesicant solution into the surrounding tissue. It is a relatively common occurrence and can cause redness, swelling, and pain or discomfort but does not cause tissue necrosis.

Extravasation is leakage of vesicant fluid out of a blood vessel into surrounding tissue. It can cause more damage than infiltration of nonvesicant solutions and can lead to blistering, tissue ischemia, and necrosis. In extreme cases, surgical debridement, skin-grafting, or even amputation may be required.

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In this article, we will use the terms extravasation and extravasated for any IV infusion-related leakage.

THE PROBLEM

The frequency of extravasation in adults is between 0.1% and 6%.[2] Some suggest the incidence is decreasing thanks to improved infusion procedure, early recognition of drug leakage, and training.[2]

The consequences of fluid leakage from a vessel into surrounding tissue vary depending on the agent being dispensed. Awareness of these agents and their potential consequences will enhance the likelihood of prompt recognition and treatment.

IMMEDIATE INTERVENTIONS

The following immediate interventions are recommended to prevent complications:

- Stop administration of fluid
- Disconnect the IV tubing, but leave the catheter or needle in place to facilitate aspiration of fluid from the extravasation site and, if indicated, administration of an antidote
- Do not flush the line
- Remove the catheter or needle if an antidote will not be administered into the extravasation site
- If an antidote is indicated, inject it through the catheter to ensure delivery to the extravasation site, then remove the catheter
- Elevate the site and apply warm or cold compresses.

Thermal compression and massage

Thermal compression improves patient outcomes.[3] Cooling with ice packs aids in vasocontriction, theoretically restricts spread of the drug, and decreases

TABLE 1
Grading the severity of extravasation damage

Grade	Presentation	Treatment
1	Minimal swelling, pain at infusion site	Stop infusion Remove cannula and tapes Elevate
2	Pain at infusion site, mild swelling, no skin-blanching, minimal redness, normal capillary refill time	Stop infusion Remove cannula and tapes Elevate
3	Pain at infusion site, swelling, skin-blanching with or without redness at the infusion site, sluggish capillary refill time, normal or decreased perfusion, hard to flush cannula	Stop infusion Leave cannula until reviewed by a doctor Photograph injury if this will not delay treatment Provider to commence irrigation procedure within 1 hour of extravasation by irrigating affected area using saline or appropriate antidote Apply nonocclusive dressing as advised Elevate limb Consider plastic surgery team consult Nursing staff to continue to observe the site hourly for the first 24 hours to monitor for adverse effects Provider should review the site 1–2 hours after antidote to assess effectiveness, and reviewed again in 24 hours
4	Pain at infusion site, marked swelling, skin-blanching, coolness, reduced capillary refill time, decreased perfusion, with or without arterial occlusion, with or without blistering	Stop infusion Leave cannula until reviewed by clinician Photograph injury if this will not delay treatment Commence irrigation procedure within 1 hour of extravasation by irrigating affected area using saline or appropriate antidote Apply nonocclusive dressing as advised Elevate limb Refer to plastic surgery team Nursing staff to continue to observe the site hourly for the first 24 hours to monitor for adverse effects Review the site 1–2 hours after antidote to assess effectiveness, and review again in 24 hours

Based on information in references 5 and 6.

pain and inflammation in the area. Warming the affected area with dry heat promotes vasodilation and increases blood flow, enhancing dispersion of the vesicant agent and decreasing accumulation of the drug in the localized tissue.

The standard of care and recommended application schedule for both warming and cooling is 15 to 20 minutes 4 times daily for 24 to 48 hours.[2] Some guidelines suggest up to 6 times daily for 1 or more days.[2]

Physical massage may aid in the dispersal of extravasated drugs. To monitor and document the leakage, a surgical felt pen is used to gently draw an outline on the skin of the affected area.

GAUGING THE SEVERITY, SELECTING AN ANTIDOTE

Many patients with extravasation experience erythema, edema, ulceration, stinging, burning, pain, tissue-sloughing, and even necrosis. A severity of grade 3 or greater, which requires an antidote, is characterized by pain, swelling, sluggish capillary refill time, normal or decreased perfusion, and other symptoms (**Table 1**).[1,4–6]

Treatment differs depending on the extravasated medication, and the selection process may be complex. In general, hyaluronidase is the antidote of choice for nonvesicant agents. Other antidotes include topical

TABLE 2
Current antidotes for intravenous extravasation

Antidote	Mechanism and use	Preparation	Administration
Sodium thiosulfate[5–7]	Neutralizes reactive species and reduces formation of hydroxyl radicals that can cause tissue injury Used as first line for most vesicants	From 25% sodium thiosulfate solution: mix 1.6 mL with 8.4 mL sterile water for injection From 10% sodium thiosulfate solution: mix 4 mL with 6 mL sterile water for injection	Use 2 mL of the prepared solution for each 1 mg of drug extravasated
Hyaluronidase[7]	Hydrolyzes hyaluronic acid in connective tissue, possibly leading to dilution and diffusion of extravasated drug Used as first line for most vesicants	To obtain a 15-unit/mL concentration, mix 0.1 mL (of 150 units/mL) with 0.9 mL of 0.9% sodium chloride in 1-mL syringe Usually dosed as 15 to 25 units intradermally over 5 injections	Ideally administer within 1 hour of the event
Phentolamine[5,7]	Alpha-adrenergic antagonist that promotes vasodilation and capillary blood flow Used as preferred agent for vasopressors	5 to 10 mg in 10 to 20 mL of 0.9% sodium chloride	Administer within 12 to 13 hours of the injury
Nitroglycerin topical[5,7]	Increases nitric oxide, promoting vasodilation Used for vasopressors (alternative to phentolamine	2% ointment: A half-inch of ointment equals 7.5 mg of nitroglycerin 5-mg/day transdermal patch	1-inch strip applied to site of ischemia; can re-dose every 8 hours as necessary 1 patch daily
Terbutaline[5,7]	Alpha-adrenergic agonist that promotes vasodilation and capillary blood flow Used for vasopressors (alternative to phentolamine)	1 mg in 10 mL of 0.9% sodium chloride	Inject locally across symptomatic sites

nitroglycerin, phentolamine, terbutaline, and sodium thiosulfate. Their vasodilating effects clear the drug from the affected area and neutralize harmful irritants that cause discomfort (aching, tightness, and phlebitis with or without inflammation) but typically not tissue necrosis. The treatment varies depending on the medication involved and the grade of severity (**Tables 2 and 3**).[1–8]

CONTRAST MEDIA EXTRAVASATION

Extravasation of IV-administered iodine-based and gadolinium-based contrast media can cause serious tissue damage, including necrosis. While the incidence of contrast media extravasation is relatively low (between 0.1% and 0.9%),[9–11] factors associated with increased risk of contrast extravasation include use of iodine-based contrast (as opposed to gadolinium contrast), use of automatic power injectors, high injection rates, patient-related factors (older age, female sex, cachexia, IV drug use, inpatient status), venous access site (dorsum of hand), and small-gauge needles (less than 22-gauge).[9,12] Use of high-osmolar and high-viscosity contrast media increases the risk of extravasation. Prewarming the contrast agent to 37°C (98.6°F) lowers the viscosity and, in turn, the probability of extravasation.[9]

The clinical presentation of contrast extravasation resembles that of other vesicant drug extravasations and can include local pain, tenderness, swelling, redness, itching, and skin tightness. In more severe

TABLE 3
Antidotes for nonchemotherapy drug extravasation

Extravasated drug	Classification: vesicant or irritant	Immediate topical treatment	Antidote
Acyclovir[2,5-7]	Irritant or vesicant; alkaline agent (pH 11)	Cooling	Hyaluronidase
Aminophylline[2,4]	Vesicant; alkaline agent (pH 8–10)	Warming	Hyaluronidase
Amiodarone[1,6,8]	Vesicant; acidic agent (pH 3.5–4.5)	Warming	Hyaluronidase
Amphotericin B[4]	Vesicant; acidic agent (pH 5–7)	Cooling	Hyaluronidase; for liposomal, consider flushout instead
Ampicillin[4]	Vesicant; hyperosmolar agent	Warming	Hyaluronidase
Calcium chloride 10%[2,4]	Vesicant; hyperosmolar agent	Warming	Early-onset: hyaluronidase Delayed-onset: sodium thiosulfate
Dantrolene[4]	Vesicant; alkaline agent (pH 9.5–10.3)	Warming	Hyaluronidase
Dextrose 10%–50%[4]	Vesicant; hyperosmolar agent	Warming	Hyaluronidase
Dobutamine[2,4]	Vesicant; vasopressor	Warming	First-line: phentolamine Second-line: terbutaline/topical nitroglycerin
Dopamine[2,4]	Vesicant; vasopressor	Warming	First-line: phentolamine Second-line: terbutaline/topical nitroglycerin
Doxycycline[4]	Vesicant; acidic agent (pH 1.8–3.3)	Warming	Hyaluronidase
Epinephrine[2,4]	Vesicant; vasopressor	Warming	First-line: phentolamine Second-line: terbutaline/topical nitroglycerin
Esmolol[4]	Vesicant; acidic agent (pH 4.5–6.5)	Warming (no literature support)	Hyaluronidase
Etomidate[2,4]	Irritant (rarely vesicant); hyperosmolar agent	Warming (no literature support)	Hyaluronidase
Lorazepam[4]	Vesicant; hyperosmolar agent	Warming (no literature support)	Hyaluronidase
Mannitol 20%[4]	Vesicant; hyperosmolar agent	Warming	Hyaluronidase
Metronidazole[4]	Vesicant; acidic agent (pH 5.5)	Warming (no literature support)	Hyaluronidase
Methylene blue[4]	Vesicant; vasopressor	Warming (no literature support)	First-line: topical nitroglycerin Second-line: phentolamine or terbutaline
Nafcilllin[4]	Vesicant or irritant	Warming	Hyaluronidase
Nitroglycerin[2]	Vesicant; hyperosmolar agent	Warming or cooling	Hyaluronidase
Norepinephrine[2,4]	Vesicant; vasopressor	Warming	First-line: phentolamine Second-line: terbutaline/topical nitroglycerin
Parenteral nutrition[2,4]	Vesicant; hyperosmolar agent	Warming	Hyaluronidase, nitroglycerin
Pentobarbital[4]	Vesicant; alkaline agent (pH 9–10.5)	Warming	Hyaluronidase
Phenobarbital[2,4]	Vesicant; hyperosmolar agent	Warming (no literature support)	Hyaluronidase
Phenylephrine[2,4]	Vesicant; vasopressor	Warming	First-line: phentolamine Second-line: topical nitroglycerin
Phenytoin and fosphenytoin[2,4]	Vesicant; alkaline agent (pH 10–12)	Warming	Hyaluronidase or nitroglycerin
Potassium chloride[2,4]	Irritant; hyperosmolar agent	Warming	Hyaluronidase
Potassium phosphate[6]	Irritant; hyperosmolar agent	Cooling	Hyaluronidase
Sodium bicarbonate 8.4%[2,4]	Vesicant; hyperosmolar agent	Warming	Hyaluronidase
Sodium chloride (> 3%)[2,4]	Vesicant; hyperosmolar agent	Warming	Hyaluronidase
Sodium phosphate[4]	Vesicant; hyperosmolar agent	Warming	Hyaluronidase
Penicillin[4]	Vesicant	Warming (no literature support)	Hyaluronidase
Valproate[4]	Vesicant	Cooling	Hyaluronidase with washout
Vancomycin[4]	Irritant or vesicant; acidic agent	Warming (no literature support)	Hyaluronidase
Vasopressin[4]	Vesicant; vasopressor	Warming	First-line: topical nitroglycerin Second-line: phentolamine or terbutaline

cases or with large-volume, high-osmolarity contrast extravasation, skin-blistering, soft-tissue necrosis, or compartment syndrome can occur.

Treatment requires immediate discontinuation of the infusion, aspiration of contrast if possible, conservative measures such as limb elevation and cooling compresses, and injection of hyaluronic acid. There is no set threshold of extravasate volume at which surgical consultation is warranted. However, it has been suggested that plastic surgery consultation be requested when extravasation volume is greater than 100 to 150 mL.[9,13] Severe symptoms such as ulceration or necrosis may warrant surgical consultation regardless of extravasate volume.

PREVENTION

Focusing on preventive measures will lower the risk of extravasation, promote patient trust, and increase patient satisfaction.[2] Patient engagement is key to prevention. When infusing a vesicant, counsel the patient to immediately report changes in skin color, integrity or firmness, temperature, mobility, sensation, or pain.[2] The vein used for infusion should be a large, intact vessel with good blood flow, specifically a basilic, cephalic, or antebrachial vein. Avoid veins in the hands, dorsum of the foot, any joint space, or antecubital fossa area.[2] Always check for blood backflow to ensure correct catheter positioning.[2] When possible, use of a central venous catheter helps limit drug extravasation.[14]

DISCLOSURES

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

REFERENCES

1. **The Royal Children's Hospital Melbourne.** Clinical guidelines (nursing). Extravasation injury management. https://www.rch.org.au/rchcpg/hospital_clinical_guideline_index/Extravasation_Injury_Management/. Accessed April 11, 2023.
2. **Kim JT, Park JY, Lee HJ, Cheon YJ.** Guidelines for the management of extravasation. J Educ Eval Health Prof 2020; 17:21. doi:10.3352/jeehp.2020.17.21
3. **Roca-Sarsanedas J, Galimany-Masclans J, Regidor-Braojos AM, Falcó-Pegueroles A.** Topical treatment of tissue damage due to extravasation of iodinated contrast using thermal compresses. J Tissue Viability 2022; 31(1):135–141. doi:10.1016/j.jtv.2021.12.0063.
4. **Ong J, Van Gerpen R.** Recommendations for management of noncytotoxic vesicant extravasations. J Infus Nurs 2020; 43(6):319–343. doi:10.1097/NAN.0000000000000392
5. **University of Illinois, Chicago.** What are current recommendations for treatment of drug extravasation? https://dig.pharmacy.uic.edu/faqs/2021-2/february-2021-faqs/what-are-current-recommendations-for-treatment-of-drug-extravasation. Accessed April 11, 2023.
6. **Reynolds PM, MacLaren R, Mueller SW, Fish DN, Kiser TH.** Management of extravasation injuries: a focused evaluation of noncytotoxic medications. Pharmacotherapy 2014; 34(6):617–632. doi:10.1002/phar.1396
7. **Lau BC, Lee NH.** Acyclovir extravasation: case report and review of the literature. Austin J Orthopade & Rheumatol 2016; 3(1):1026. https://austinpublishinggroup.com/orthopedics-rheumatology/fulltext/ajor-v3-id1026.php. Accessed April 11, 2023.
8. **Fox AN, Villanueva R, Miller JL.** Management of amiodarone extravasation with intradermal hyaluronidase. Am J Health Syst Pharm 2017; 74(19):1545–1548. doi:10.2146/ajhp160737
9. **Roditi G, Khan N, van der Molen AJ, et al.** Intravenous contrast medium extravasation: systematic review and updated ESUR Contrast Media Safety Committee guidelines. Eur Radiol 2022; 32(5):3056–3066. doi:10.1007/s00330-021-08433-4
10. **Nicola R, Shaqdan KW, Aran S, Prabhakar AM, Singh AK, Abujudeh HH.** Contrast media extravasation of computed tomography and magnetic resonance imaging: management guidelines for the radiologist. Curr Probl Diagn Radiol 2016; 45(3):161–164. doi:10.1067/j.cpradiol.2015.08.004
11. **Hwang EJ, Shin CI, Choi YH, Park CM.** Frequency, outcome, and risk factors of contrast media extravasation in 142,651 intravenous contrast-enhanced CT scans. Eur Radiol 2018; 28(12):5368–5375. doi:10.1007/s00330-018-5507-y
12. **Heshmatzadeh Behzadi A, Farooq Z, Newhouse JH, Prince MR.** MRI and CT contrast media extravasation: a systematic review. Medicine (Baltimore) 2018; 97(9):e0055. doi:10.1097/MD.0000000000010055
13. **Wang CL, Cohan RH, Ellis JH, Adusumilli S, Dunnick NR.** Frequency, management, and outcome of extravasation of nonionic iodinated contrast medium in 69,657 intravenous injections [published correction appears in Radiology 2015; 274(1):307]. Radiology 2007; 243(1):80–87. doi:10.1148/radiol.2431060554
14. **Loubani OM, Green RS.** A systematic review of extravasation and local tissue injury from administration of vasopressors through peripheral intravenous catheters and central venous catheters. J Crit Care 2015; 30(3):653.e9–653.e6.53E17. doi:10.1016/j.jcrc.2015.01.014

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COMMENTARY

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The perfect storm: An unseasonably early RSV annual epidemic, a severe annual flu epidemic, and a smoldering COVID-19 pandemic

"And now these three remain: faith, hope and love. But the greatest of these is love." 1 Corinthians 13:13

Some seasonal respiratory viruses can assure a perfect storm, as has been the case most recently with an unseasonably early respiratory syncytial virus (RSV) epidemic, a severe annual influenza virus epidemic, and a smoldering coronavirus (COVID-19) pandemic.[1] Much has been discussed since last October about this looming "tridemic" or "triple-demic" of RSV, influenza, and COVID. Given the predominance of these 3 respiratory viruses during the late fall, winter, and early spring, I will henceforth limit my comments to just these 3 viruses, although this by no means implies that other respiratory viruses are of less significance.

The following clinical scenarios are meant to emphasize the overlapping clinical manifestations of respiratory viral infections that make clinical diagnosis challenging.

THREE CLINICAL SCENARIOS

Scenario 1

A 50-year-old male patient who underwent kidney transplantation 10 years prior to presentation developed low-grade fever and nasal congestion on a Friday afternoon, the last week of November 2022, after exposure to an office coworker with similar symptoms. He was up-to-date on COVID vaccine recommendations and the annual influenza vaccine. A single nasopharyngeal swab for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), RSV, and influenza detection by polymerase chain reaction (PCR) was collected, and he was promptly started on oseltamivir. Molnupiravir could not be prescribed without a documented positive PCR test for SARS-CoV-2. His symptoms did not change over the subsequent 12 hours. Once SARS-CoV-2 was confirmed and RSV and influenza were not detected, he was treated with molnupiravir for 5 days starting Saturday morning, and symptoms rapidly improved.

Scenario 2

A 40-year-old, healthy internist developed sudden-onset fever, headache, and cough on a Thursday evening, the second week of December 2022. She had diagnosed multiple patients earlier that week and in the preceding weeks with COVID and influenza. She was up-to-date on COVID vaccine recommendations and the annual influenza vaccine. An astute clinician, she self-diagnosed influenza A, had a nasopharyngeal swab for SARS-CoV-2 and influenza PCR collected, and started taking oseltamivir the same night her symptoms started. Influenza A was detected by PCR, and SARS-CoV-2 was not detected. Her symptoms did not improve until the third day of oseltamivir treatment. She was afebrile without the use of antipyretics by the fourth day of treatment and returned to work after completing 5 days of therapy.

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Scenario 3

A 61-year-old husband and wife developed nasal congestion, cough, and malaise without fever in the third week of November 2022. Both were up-to-date with COVID vaccine recommendations and the annual influenza vaccine. Both completed home rapid antigen-detection tests for SARS-CoV-2 that were negative. Their symptoms slightly improved, and they decided not to cancel their 5-day vacation in sunny Florida the following week around Thanksgiving. The husband's 79-year-old mother joined them on their vacation. Shortly after returning home, she developed similar symptoms. She was up-to-date on COVID vaccine recommendations and annual influenza vaccine. Her home rapid antigen-detection test for SARS-CoV-2 was negative, and a nasopharyngeal swab PCR test did not detect influenza or SARS-CoV-2. Her symptoms lingered for 10 days despite treatment with over-the-counter analgesics, nasal decongestants, and cough suppressants. She completely recovered by the end of the second week of illness.

The first and second patients had PCR-confirmed COVID and influenza A, respectively. No microbiologically confirmed diagnosis was made for the 3 patients in the third clinical scenario, but the epidemiology and clinical course suggest RSV infection.

TRIPLEDEMIC

Outdoor seasonal climate and human behavior impact the seasonality of many respiratory viruses, including SARS-CoV-2,[2] but modern living partially shields us from climate extremes of temperature and humidity.[1] Several respiratory viruses, including RSV, human metapneumovirus, and human coronaviruses (strains 229E, NL63, OC43, HKU1) display biennial variations.[1] Some, such as metapneumovirus, display cyclical subgroup predominance every 1 to 3 years. Seasonality of other respiratory viruses is less evident.

Overlapping of epidemiology and clinical presentation of various respiratory viruses makes clinical diagnosis a matter of statistical probability rather than certainty, particularly in immunocompromised individuals.[3] Immunity following acute infection is short-lived, so repeated infections do occur. Vaccines and specific antiviral agents are available to prevent and treat SARS-CoV-2 infection and influenza. These vaccines prevent severe infections requiring hospitalization but are less successful in preventing mild or asymptomatic infections, prevent exacerbation of underlying lung and heart diseases, and prevent secondary bacterial pneumonia. While natural infections may be more effective than vaccines in preventing a subsequent infection by the same virus,[4] choosing intentional exposure for the purpose of acquiring natural immunity over vaccine-induced immunity should not be condoned, as fatal outcomes can occur in healthy individuals.[5] Vaccines and therapeutics for other respiratory viruses are not currently available.

Behavioral measures successfully applied during the early peak of the COVID pandemic were at least partially successful in reducing infection spread, particularly before preventive vaccines and effective therapeutics became available. Collateral benefit of these behavioral measures was a concomitant reduction in incidence of other respiratory viruses. However, these measures kept us "cocooned," resulting in a current exposure-immunity "debt" or "gap." Inching closer to SARS-CoV-2 infection- and vaccine-induced herd immunity, decreased SARS-CoV-2 virulence, and behavioral restriction fatigue are pushing us out of that cocoon, and hence a greater proportion of the population is more susceptible to other respiratory viruses, including RSV and influenza.

Another collateral damage of the COVID pandemic is decreased uptake (49.4%) of influenza vaccination in adults during the 2021 to 2022 influenza season, a decrease of 0.8% percentage points from the previous influenza season.[6]

RESPIRATORY SYNCYTIAL VIRUS

Chimpanzee coryza agent was discovered in 1956 as a cause of colds in chimpanzees, and was renamed RSV in 1957 after it was identified as the most common cause of pediatric bronchiolitis.[7,8] RSV is currently the most common cause of lower respiratory tract infections (LRTIs).[9] Symptomatic treatment results in recovery in the vast majority of children, but RSV is associated with severe disease in certain high-risk children and adults, resulting in up to an estimated 120,000 hospitalizations and 10,000 deaths annually in older US adults,[9] similar to or surpassing the impact of influenza.[8]

Peak months of seasonal RSV activity typically occur in December or January. However, for the 2022 to 2023 season, an increase in RSV cases began in late August and surged 5-fold by November of 2022,[10] stretching resources and capacity of healthcare facilities that were already grappling with rising cases of COVID and influenza. Although hospitalization from RSV in seniors in the early fall of 2022 was significantly lower than that for children, this was still 10 times higher (about 6 of every 100,000) for that

time in the season than in years before the COVID pandemic.[10]

Because seniors had been appropriately concerned about the spread of the COVID omicron variant and maintained previously adopted preventive public health measures like masks and social distancing, their exposure to children with the RSV infection was delayed. When the population began loosening their adherence to these measures in the fall of 2022, the rate of hospitalization from RSV infection in seniors increased.

RSV Prevention

Palivizumab is the most widely used monoclonal antibody used prophylactically to reduce RSV hospitalizations and protect against severe disease in high-risk infants with a history of premature birth or bronchopulmonary or hemodynamically significant congenital heart disease.[11,12]

A randomized phase 1/2 study with an RSV prefusion F vaccine for maternal immunization showed it was well-tolerated and immunogenic in adults.[11] A randomized, double-blinded, placebo-controlled phase 3 study with the same vaccine evaluated vaccination during pregnancy against medically attended LRTIs in newborn infants and enrolled 7,358 maternal participants and found no safety concerns for both vaccinated mothers and their newborns, with 81.8% and 69.4% vaccine efficacy during the first 3 and 6 months of life, respectively.[13–15] As noted at a national meeting in October 2022, preplanned interim analysis of a phase 3, global, multicenter, randomized, double-blinded, placebo-controlled study with the same vaccine in adults age 60 and older showed 66.7% and 85.7% efficacy against LRTI with 2 or more and 3 or more symptoms, respectively, with no safety concerns.[16] RSV vaccines by 2 other manufacturers have recently been shown to be similarly effective in adults age 60 and older.[17,18] Calculating the number needed to vaccine to prevent 1 case of LRTI with these 3 investigational vaccines ranged from 96 to 385. In February 2023, the US Food and Drug Administration (FDA) Vaccines and Related Biological Products Advisory Committee proposed provisional approval of one of these vaccines in adults age 60 and older[19] and set an action date for August 2023, following the acceptance of the marketing authorization application for this vaccine candidate by the European Medicines Agency under accelerated assessment for both older adult and maternal immunization.[20]

Treatment for the vast majority of cases of RSV LRTIs is supportive, and early therapy with ribavirin and intravenous gamma globulin may be associated with improved survival in immunocompromised persons. Rilematovir (JNJ-53718678), a novel, oral, selective small-molecule RSV fusion protein inhibitor displays very potent antiviral activity and low cytotoxicity against RSV A2 strain and strains from both A and B subtypes.[21] A randomized, dose-varying, placebo-controlled study with this molecule administered once daily for 7 days to 69 healthy adult volunteers inoculated with RSV substantially reduced mean and peak viral load, time to peak viral load, duration of viral shedding, mean overall symptom score, and nasal secretion weight.[22] However, the manufacturer of rilematovir terminated 3 studies in early 2022 in hospitalized pediatric patients, adult outpatients, and patients with hepatic impairment, stating that this decision was not based on safety concerns.

INFLUENZA

Despite a misnomer that the 1918 "Spanish flu" pandemic originated in birds and was transmitted to humans and then to pigs, the first human cases were detected in a soldier's camp in Kansas in March 1918.[23,24] Human influenza A virus was not discovered as a "filterable organism" for another 15 years, until 1933, when an influenza virus was demonstrated by Alphonse Raymond Dochez to be producible in humans.[23] In 1977 at the Armed Forces Institute of Pathology, Taubenberger and Reid[23] sequenced 9 fragments of 1918 influenza viral RNA from 4 of 8 virus gene segments from a US serviceman's preserved lung tissue after he succumbed to "influenza and pneumonia" in September 1918 and from lung tissues of Alaskan Inuit Natives who died from influenza A during the 1918 pandemic, were buried in a mass grave, and frozen in permafrost.[24]

Fast forward to 2022, the influenza A (H3N2) virus circulated earlier than during seasons preceding the COVID pandemic in certain countries in the Southern Hemisphere, such as Chile.[25] Also in Tennessee, the influenza season began earlier than usual, resulting in higher rates of pediatric symptomatic illness and hospitalizations compared with adults and prior seasons.[26] By early December 2022, it became clear that the current influenza season was more severe and associated with 1.6 times more hospitalizations than the highest cumulative rate in the last 13 years.[27] Consequently, the percent fill rate for oseltamivir became almost 15 times higher than it had been in previous years,[28] and the US Department of Health and Human Services through the Administration

for Strategic Preparedness and Response announced at the end of 2022 that they are making additional supplies of oseltamivir to ensure supply for states, territories, and tribes owing to increased demand for the antiviral during this influenza season.[29]

COVID IS NOT GOING ANYWHERE

Human cases of COVID, the coronavirus disease caused by SARS-CoV-2, were first reported in Wuhan, China, in December 2019 and most likely had their ecological reservoir in bats.[30] Because humans do not have much interaction with bats, it is believed that SARS-CoV-2 jumped the species barrier to humans through an intermediate animal host that is more likely to be handled by humans.[30]

On December 30, 2019, Dr. Li Wenliang warned in an online chat group (WeChat) that he had seen a report showing positive test results of SARS in 7 patients.[31,32] However, he did not formally report the outbreak to the authorities at that time and was reprimanded at that time for disrupting public order. On December 26, 2019, Dr. Zhang Jixian, Director of the Respiratory and Critical Care Medicine Department of Hubei Provincial Hospital of Integrated Chinese and Western Medicine, diagnosed a senior couple living in a residential community near that hospital with viral pneumonia. The computed tomography (CT) chest images reminded her of similar CTs in patients she had cared for during the 2003 SARS outbreak, also in Wuhan.[32] After "summoning" the couple's son for "mandatory" chest CT that showed findings similar to his parents' CT, and hospitalization of a fourth patient with similar clinical and CT findings within the next day, and after excluding influenza in all 4 patients, Dr. Jixian reported her concern, and on December 30 at 3:10 pm, the Wuhan Municipal Health and Health Commission issued the official "emergency notice reporting the treatment of pneumonia of unknown cases."[32] Dr. Jixian is thus considered the first physician to report the novel coronavirus before its outbreak.

COVID seasonality in temperate countries is now well established, with data showing that with an increment of 1°C above the average temperature is associated with a reduction of about 61 COVID deaths per million annually.[2] Some findings suggested that COVID transmission is inversely proportional to temperature and absolute humidity.[33] Even though epidemiologic data were consistent with COVID as a seasonal low-temperature infection, seasonality alone was not sufficient to curtail viral transmission to the extent that nonpharmacologic interventions were no longer needed.[34]

In an unprecedented approach to containing the COVID pandemic, the US government provided free COVID home antigen testing kits to any resident who requested. This likely facilitated home testing for many people, possibly allowing for early medical intervention for those who seek care if they test positive. However, there were several drawbacks to the widespread use of home testing:

- Posttest probability depends on pretest probability, and people interpreted results indiscriminately, whether they got tested for asymptomatic screening before family gatherings or for acute illness.
- Sick people with negative tests may not have pursued PCR testing as recommended, mistakenly accepting negative tests as guaranteed "ruleout," even if they remained ill.
- Tests may not have been performed accurately per the manufacturers' instructions.
- Tests may have been used beyond their labeled expiration dates (which was actually recommended by the US government at one point during the pandemic).
- Since reporting results of these home tests was not required, people could have—intentionally or unintentionally—spread the infection to others.

It was not until December 2022 that the National Institutes of Health launched a website for users to anonymously report the result of at-home COVID tests.[35] However, this is merely an option and not mandatory. Granted that antigen test results likely underestimate infection prevalence, I think we missed a golden opportunity to track the results of these home tests to allow better contact-tracing and possibly tackle disease containment. The National Health and Nutrition Examination Survey collects SARS-CoV-2 serology data and self-reported vaccination and disease history among adults.[36] In doing so, they have provided preliminary insights about disease prevalence and vaccine uptake and noted that 43.7% of respondents were possibly asymptomatically infected, and healthy young adults and ethnic minorities may have had less access to testing and unknowingly exposed others, amplifying disparities in infection rates and outcomes.[36]

Frequent SARS-CoV-2 mutations resulting in new variants sweeping the country and the impact of vaccination, infection, and therapy on the incidence and severity of infection[37] have fueled misinformation about viral transmission and complacency toward preventive behaviors, such as "mask fatigue."[38] Data have shown that lifting universal masking mandates in schools resulted in a 5% increase in cases.[39]

The current dominant variant nationwide is XBB.1.5, accounting for half of cases, followed by BQ.1.1, accounting for about a quarter of cases,[40] while the original omicron variant has almost disappeared. Fortunately, these latest variants don't appear to cause more serious disease than their predecessors. Nevertheless, even though the ongoing COVID pandemic in the United States is mostly associated with mild illness, it is certainly not just a nuisance, with 300 to 500 related current daily deaths, which cumulatively exceed severe seasonal influenza epidemic-associated deaths.[41] We also should not forget that influenza and SARS-CoV-2 coinfections occur and can result in more serious illnesses if not promptly recognized and treated.[42]

COVID VACCINES WORK AND WILL BE ADMINISTERED ANNUALLY

Public trust in the almost unprecedented safety and protective efficacy rates of the initial COVID vaccines has been partially dampened after breakthrough infections and reactogenicity data accumulated. However, the majority of scientists and, hopefully, the population believe that these vaccines prevented an unknown number—likely in the millions—of hospitalizations and deaths worldwide.[43] Interim analysis of a prospective observational cohort study conducted at Kaiser Permanente Southern California comparing more than 900,000 individuals age 18 and older who received 2 doses of mRNA-1273 vaccine through June 2021, and who were matched 1:1 to randomly selected unvaccinated individuals followed through September 2021, showed 88.0% vaccine effectiveness against SARS-CoV-2 infection at 0 to < 2 months and 75.5% at 6 to < 8 months.[44]

Studies assessing "booster" doses (admittedly a moving target) of vaccine showed that additional doses conferred additional protection compared with "primary series" (which differs depending on age and underlying diseases) in immunocompetent adults[45] as well as nursing home residents.[46] Those who were not up-to-date with recommended COVID vaccines had a 30% to 50% higher risk for acquiring SARS-CoV-2 infection compared with those who were up-to-date with COVID vaccines.[46]

Natural COVID infection confers some immunity against subsequent infections. While antibody levels wane over time following natural infection or vaccination, data have shown that COVID vaccination confers higher and long-lasting antibody levels, including in pregnant women and cord blood, particularly when natural infections are mild.[47] COVID vaccine correlate of protection has been illusive, but accumulating data support using neutralizing antibodies (which increase after vaccination only) and not anti-spike protein antibodies (which increase after natural infection or vaccination) as the agreed-upon correlate of protection, which would merit its use for near-term decisions about vaccines.[48]

Recent data showed cross-neutralization ability of the omicron-containing bivalent booster vaccine that was introduced in late 2022 against emerging omicron subvariants that are not contained in the vaccine.[49] Early estimates of bivalent mRNA vaccine booster dose are showing vaccine effectiveness in preventing symptomatic infection,[50] COVID-associated emergency department or urgent care encounters, and COVID-associated hospitalizations,[50–52] including infections attributable to omicron BA.5 and XBB/XBB.1.5-related sublineages.[40]

Latest estimates from the World Health Organization show that 4 of 5 people who died from COVID were over age 60, but only 3 in 4 people in that age group completed primary vaccine series.[40] Unfortunately, only about two-thirds of healthcare professionals who received primary COVID vaccines received a booster dose, and only about 80% received influenza vaccination during 2021 to 2022 season.[53] It does not seem probable that we can convince vaccine-skeptical patients to get vaccinated unless we ourselves "walk the talk."

We may finally be getting clarification on what to expect regarding future COVID vaccines instead of the roller coaster we have been riding for the last 3 years and the number of doses of the monovalent vaccine needed to maintain vaccine effectiveness, from 1 to 5 doses to the most recent bivalent vaccine. The FDA Vaccines and Related Biological Products Advisory Committee stated in a briefing document released in January 2023, ahead of a meeting with its vaccine advisors, that their intended approach would be similar to that of the annual influenza vaccination program, with the goal to predict in the spring of 2023 which SARS-CoV-2 strain would be expected to pose the greatest threat in the winter of 2023 to 2024.[54] A vaccine targeting that strain would then be distributed in the fall of 2023, with annual updates to that COVID vaccine expected in each future year. Reducing uncertainty about future vaccines would hopefully improve vaccine uptake.

COVID TREATMENT OPTIONS, SOME ALREADY OBSOLETE

The first SARS-CoV-2 monoclonal antibody, bamlanivimab, received emergency use authorization (EUA) by the FDA in November 2020 for patients with mild COVID-related illness who had certain medical conditions that put them at risk for progression to severe illness, with the intent to prevent emergency department and urgent care visits, hospitalizations, and deaths. Subsequently, other monoclonal antibodies were sequentially developed in what seems like lightning-speed succession to catch up with SARS-CoV-2 mutations and new variants, from casirivimab-imdevimab later on in November 2020, to bamlanivimab-etesevimab in February 2021, to sotrovimab in May 2021, to bebtelovimab in February 2022. In addition, tixagevimab-cilgavimab was authorized by the FDA in December 2021 for pre-exposure prophylaxis for patients who are not expected to mount a protective response to vaccines and are at risk for severe illness if they get infected. SARS-CoV-2 finally outsmarted us, and newer variants became resistant to the last 2 available monoclonal antibodies, bebtelovimab and tixagevimab-cilgavimab, within 10 to 12 months of their EUA, resulting in withdrawal from the market by the FDA in December 2022. We are currently in a "monoclonal antibody void," and we have to manage our patients with other agents currently available on the market.

Our current antiviral armamentarium is limited to intravenous remdesivir, oral nirmatrelvir-ritonavir, and oral molnupiravir.[55–58] Intravenous remdesivir is fully approved by the FDA, while the oral agents received EUA. Retrospectively analyzed data following EUA of oral nirmatrelvir-ritonavir showed 51% lower hospitalization rates in adults within 30 days after diagnosis when prescribed within 5 days of diagnosis, compared with those who were not prescribed this drug.[55] Preliminary disturbing data are showing up to 5% risk of rebound COVID-related illness that may be severe enough to require hospitalization in patients who initially improve with either oral antiviral agent.[56] New mutations conferring resistance to remdesivir have been described,[57] and time will tell to what extent this may impact future effectiveness of SARS-CoV-2 therapeutics. Interim analysis of a randomized, multicenter placebo-controlled phase 3 clinical trial showed that sabizabulin, an oral novel microtubule disruptor that has antiviral as well as anti-inflammatory properties, when administered to hospitalized patients with moderate to severe COVID who were at high risk for acute respiratory distress syndrome and death, resulted in a 25% absolute reduction and a 55% relative reduction in mortality compared with placebo.[58] The study was stopped for efficacy earlier than what had been planned by the independent data-monitoring committee. Data were submitted to the FDA for approval, and more data and analysis were requested.

A phase 3, multicenter, noninferiority, observer-blinded, randomized clinical trial conducted in China during the outbreak of omicron (B.1.1.529) SARS-CoV-2 variant showed that VV116 (an orally bioavailable deuterated remdesivir hydrobromide) was noninferior to nirmatrelvir-ritonavir to alleviate symptoms in adults with mild-to-moderate COVID at high risk for progression to severe disease.[59] The majority of COVID patients do not require hospitalization, and the supply of oral nirmatrelvir-ritonavir, molnupiravir, and intravenous remdesivir clearly falls short of the global demand for outpatient management. If VV116 is approved, it would help fill at least part of the current void for outpatient treatment; and given the familiarity of both healthcare providers and the public with the worldwide successful track record of intravenous remdesivir, VV116 stands a better chance for acceptance and widespread use in patients with mild-to-moderate COVID.

There is no question that we must continue recommending, particularly to our most vulnerable and immunocompromised patients, the COVID preventive and treatment options that are accepted by the majority of scientists,[60] at least until the pandemic is declared over.

THE PANDEMIC AFTER THE PANDEMIC

Worldwide prevalence of long COVID, defined as persistence of symptoms or development of new symptoms more than 4 weeks after initial infection, ranges up to 45%.[61] Even patients with mild COVID are at higher risk compared with uninfected people for persistence of anosmia and dysgeusia during the first 6 months after infection and for persistence of dyspnea and weakness in the second 6 months after infection, regardless of the SARS-CoV-2 variant, but the majority of symptoms resolve within a year.[62] Adults have persistent symptoms early on more than children, and women and men are roughly equally affected. Vaccinated patients with breakthrough infection have a lower risk of persistent symptoms than unvaccinated patients,[63] particularly those pre-

senting with moderate or severe symptoms of acute illness. Some patients who have had one COVID-related infection and subsequently let down their guard regarding preventive measures and compliance with recommended vaccination doses erroneously think they are invincible to reinfection and that there is no potential added protection from subsequent doses of the vaccine. Regardless of vaccination status, data have shown that compared with no reinfection, reinfection increases risk of all-cause mortality, hospitalization, and risk of pulmonary, cardiovascular, hematologic, gastrointestinal, renal, psychological, musculoskeletal, and neurologic sequelae.[5] Also, compared with noninfected controls, cumulative risk increased according to number of reinfections.

LIGHT AT THE END OF THE TUNNEL

Despite the early and potentially looming fear of a "tripledemic," US surveillance data showed a different situation. The earlier and more-severe RSV season declined after peaking during the second week of November 2022, influenza declined after peaking during the first week of December 2022, and the uptick in COVID-related hospitalization after Christmas 2022 was short-lived and nowhere near surges of this pandemic in the last 3 years.[64] Needless to say, the future is unpredictable, with a second peak of RSV commonly occurring in the spring, and with influenza B cases typically peaking in late winter, early spring.

THE BOTTOM LINE

All three viruses—RSV, influenza, and COVID—can cause severe illness requiring hospitalization and can be fatal, whether as a result of severe viral pneumonia or secondary bacterial or fungal pneumonia, or by exacerbation of underlying chronic cardiopulmonary diseases. Despite the presumed absence of human natural immunity to SARS-CoV-2, the lack of current FDA-approved vaccines and treatment options for RSV, and the availability of several vaccines and a handful of antiviral agents active against influenza, I still believe that influenza takes the prize of "worst actor."

Influenza is pervasive

Influenza is unpredictable, pervasive, and endemic in wild birds—which are all around us, and their droppings are unavoidable. Further, human consumption depends on manufacturing and technology and more widespread travel, and with birds in all parts of the world, in one way or another, all of this contributes to annual influenza epidemics. We fully anticipate annual influenza virus antigenic drift(s) accounting for annual epidemics and potential antigenic drift(s) that result in pandemics. Highly pathogenic avian influenza epidemics with potential pandemic spread occur with concerning frequency.[65]

The majority of influenza vaccine production remains the archaic egg-based process. We are annually playing "catch-up," with the Northern Hemisphere targeting predominant influenza serotypes in the Southern Hemisphere during the preceding flu season, and vice versa. Year-round influenza activity near the equator and global warming add to the complexity and shortcomings of this process. Also, half of US influenza vaccine suppliers manufacture their vaccines outside of the United States, making the implementation of quality control measures more challenging.

Although annual influenza vaccination is the most effective prevention, public and healthcare workers' annual influenza vaccine uptake remain suboptimal. Despite multiple decades of influenza vaccine research, ample immunogenicity, and protective efficacy data, public trust in vaccine is both weak and unrealistic (100% protective efficacy and protection from other viral respiratory tract infections should not be expected), and continued myths about inaccurate associations with certain side effects or subsequent disorders persist.

Antiviral agents and resistance

Adamantane resistance among circulating influenza A (H3N2) viruses has rapidly increased over the last 3 decades, becoming universal during the 2005 to 2006 season, and has persisted since then.[66] Therefore, amantadine and rimantadine are no longer recommended. Neuraminidase resistance mutations in seasonal influenza A (H1N1) increased during the 2007 to 2008 influenza season, conferring resistance to oseltamivir, but not zanamivir. Fortunately, the 2009 pandemic influenza A (H1N1) that has since essentially completely replaced the previously circulating seasonal influenza A (H1N1) is susceptible to the neuraminidase inhibitor oseltamivir, the current primary antiviral agent used to treat influenza. Patients who do not respond to the antiviral medications they are receiving may need to have their treatment regimens altered to fit their clinical circumstances.[66]

For additional perspective, in examining and comparing the impact of the 1918 influenza pandemic, the ongoing acquired immunodeficiency syndrome worldwide epidemic that started in 1981, and the cur-

TABLE 1
Comparing 1918 influenza pandemic, AIDS worldwide epidemic, and COVID-19 pandemic

	1918 Influenza A (H1N1) pandemic	AIDS epidemic (cumulative, ongoing since 1981)	COVID pandemic (ongoing)
World population	1.8 billion	7.8 billion	7.8 billion
Number of deaths	50 million	40.1 million	6.9 million
Percent deaths	2.5%	0.5%	0.9%
Duration	2 years	42 years	3 years
Epidemic curve	"W": young adults and extremes of age	Inverted "U": young adults	"U": extremes of age
Number infected	500 million	84 million	670 million
Percent infected	30%	1.1%	8.6%

AIDS = acquired immunodeficiency syndrome

rent COVID pandemic (Table 1), it becomes clear that the 1918 influenza pandemic had the worst outcomes.

DISCLOSURES

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

REFERENCES

1. **Moriyama M, Hugentobler WJ, Iwasaki A.** Seasonality of respiratory viral infections. Annu Rev Virol 2020; 7(1):83–101. doi:10.1146/annurev-virology-012420-022445
2. **D'Amico F, Marmiere M, Righetti B, et al.** COVID-19 seasonality in temperate countries. Environ Res 2022; 206:112614. doi:10.1016/j.envres.2021.112614
3. **Mendoza MA, Motoa G, Raja MA, et al.** Difference between SARS-CoV-2, seasonal coronavirus, influenza, and respiratory syncytial virus infection in solid organ transplant recipients. Transpl Infect Dis 2023; 25(1):e13998. doi:10.1111/tid.13998
4. **COVID-19 Forecasting Team.** Past SARS-CoV-2 infection protection against re-infection: a systematic review and meta-analysis. Lancet 2023; 401(10379):833–842. doi:10.1016/S0140-6736(22)02465-5
5. **Bowe B, Xie Y, Al-Aly Z.** Acute and postacute sequelae associated with SARS-CoV-2 reinfection. Nat Med 2022; 28(11):2398–2405. doi:10.1038/s41591-022-02051-3
6. **Centers for Disease Control and Prevention.** Flu vaccination coverage, United States, 2021–22 influenza season. Updated October 18, 2022. https://www.cdc.gov/flu/fluvaxview/coverage-2022estimates.htm. Accessed April 15, 2023.
7. **Walsh EE, Hall CB.** Respiratory syncytial virus (RSV). In: Bennett JE, Dolin R, Blaser MJ. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 8th ed. Philadelphia, PA: Saunders; 2014:1948–1960.e3.
8. **Falsey AR, Walsh EE.** Respiratory syncytial virus infection in adults. Clin Microbiol Rev 2000; 13(3):371–384. doi:10.1128/CMR.13.3.371
9. **American Lung Association.** RSV in adults. https://www.lung.org/lung-health-diseases/lung-disease-lookup/rsv/rsv-in-adults. Accessed April 15, 2023.
10. **Centers for Disease Control and Prevention.** RSV-NET: Respiratory Syncytial Virus Hospitalization Surveillance Network. https://www.cdc.gov/rsv/research/rsv-net/dashboard.html. Accessed April 15, 2023.
11. **Walsh EE, Falsey AR, Scott DA, et al.** A randomized phase 1/2 study of a respiratory syncytial virus prefusion F vaccine. J Infect Dis 2022; 225(8):1357–1366. doi:10.1093/infdis/jiab612
12. **Sun M, Lai H, Na F, Li S, Qiu X, Tian J, Zhang Z, Ge L.** Monoclonal antibody for the prevention of respiratory syncytial virus in infants and children: a systematic review and network meta-analysis. JAMA Netw Open 2023; 6(2):e230023. doi:10.1001/jamanetworkopen.2023.0023
13. **US National Institutes of Health.** A trial to evaluate the efficacy and safety of RSVpreF in infants born to women vaccinated during pregnancy. ClinicalTrials.gov Identifier: NCT04424316. https://clinicaltrials.gov/ct2/show/NCT04424316. Accessed April 15, 2023.
14. **Pfizer, Inc.** Pfizer announces positive top-line data of phase 3 global maternal immunization trial for its bivalent respiratory syncytial virus (RSV) vaccine candidate. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-positive-top-line-data-phase-3-global. Accessed April 15, 2023.
15. **Kampmann B, Madhi SA, Munjal I, et al.** Bivalent prefusion F vaccine in pregnancy to prevent RSV illness in infants. N Engl J Med 2023; Apr 5. doi:10.1056/NEJMoa2216480
16. **Walsh EE, Polack F, Zareba A, et al.** LB748. Efficacy and safety of bivalent respiratory syncytial virus (RSVpreF) vaccine in older adults, Open Forum Infect Dis 2022; 9(suppl 2):S923.
17. **Papi A, Ison MG, Langley JM, et al.** Respiratory syncytial virus prefusion F protein vaccine in older adults. N Engl J Med 2023; 388(7):595–608. doi:10.1056/NEJMoa2209604
18. **Falsey AR, Williams K, Gymnopoulou E, et al.** Efficacy and safety of an Ad26.RSV.preF-RSV preF protein vaccine in older adults. N Engl J Med 2023; 388(7):609–620. doi:10.1056/NEJMoa2207566
19. **US Food and Drug Administration.** Advisory Committee Meeting. Vaccines and Related Biological Products Advisory Committee February 28–March 1, 2023 meeting announcement https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-february-28-march-1-2023-meeting#event-information Accessed April 15, 2023.
20. **European Medicines Agency.** Opinion of the Paediatric Committee on the agreement of a paediatric investigation plan and a deferral and a waiver: EMEA-002795-PIP01-20. https://www.ema.europa.eu/en/documents/pip-decision/p/0202/2021-ema-decision-10-may-2021-agreement-paediatric-investigation-plan-granting-deferral-granting_en.pdf. Accessed April 15, 2023.
21. **Roymans D, Alnajjar SS, Battles MB, et al.** Therapeutic efficacy of

a respiratory syncytial virus fusion inhibitor. Nat Commun 2017; 8(1):167. doi:10.1038/s41467-017-00170-x
22. **Stevens M, Rusch S, DeVincenzo J, et al.** Antiviral activity of oral JNJ-53718678 in healthy adult volunteers challenged with respiratory syncytial virus: a placebo-controlled study. J Infect Dis 2018; 218(5):748–756. doi:10.1093/infdis/jiy227
23. **Taubenberger JK, Hultin JV, Morens DM.** Discovery and characterization of the 1918 pandemic influenza virus in historical context. Antivir Ther 2007; 12(4 Pt B):581–591. pmid:17944266
24. **Centers for Disease Control and Prevention.** The deadliest flu: the complete story of the discovery and reconstruction of the 1918 pandemic virus. Updated December 17, 2019. https://www.cdc.gov/flu/pandemic-resources/reconstruction-1918-virus.html. Accessed April 15, 2023.
25. **Olivares Barraza MF, Fasce RA, Nogareda F, et al.** Influenza incidence and vaccine effectiveness during the southern hemisphere influenza season—Chile, 2022. MMWR Morb Mortal Wkly Rep 2022; 71(43):1353–1358. doi:10.15585/mmwr.mm7143a1
26. **Thomas CM, White EB, Kojima N, et al.** Early and increased influenza activity among children—Tennessee, 2022–23 influenza season. MMWR Morb Mortal Wkly Rep 2023; 72(3):49–54. doi:10.15585/mmwr.mm7203a1
27. **Centers for Disease Control and Prevention.** Weekly US influenza surveillance report. Updated April 14, 2023. https://www.cdc.gov/flu/weekly/index.htm. Accessed April 15, 2023.
28. **GoodRx Health.** Live updates: tracking the RSV, flu, and COVID 'tripledemic.' Updated April 11, 2023. https://www.goodrx.com/healthcare-access/research/flu-season-tracking-tamiflu-fills. Accessed April 15, 2023.
29. **Department of Health and Human Services.** HHS increases access to tamiflu through the strategic national stockpile. Updated December 21, 2022. https://www.hhs.gov/about/news/2022/12/21/hhs-increases-access-to-tamiflu-through-the-strategic-national-stockpile.html. Accessed April 15, 2023.
30. **World Health Organization.** Origin of SARS-CoV-2. https://apps.who.int/iris/bitstream/handle/10665/332197/WHO-2019-nCoV-FAQ-Virus_origin-2020.1-eng.pdf. Accessed April 15, 2023.
31. **Czernin J.** Dr. Li Wenliang and the time of COVID-19. J Nucl Med 2020; 61(5):625. doi:10.2967/jnumed.120.245712
32. **Li X, Cui W, Zhang F.** Who was the first doctor to report the COVID-19 outbreak in Wuhan, China? J Nucl Med 2020; 61(6):782–783. doi:10.2967/jnumed.120.247262
33. **Rayan RA.** Seasonal variation and COVID-19 infection pattern: a gap from evidence to reality. Curr Opin Environ Sci Health 2021; 20:100238. doi:10.1016/j.coesh.2021.100238
34. **Liu X, Huang J, Li C, et al.** The role of seasonality in the spread of COVID-19 pandemic. Environ Res 2021; 195:110874. doi:10.1016/j.envres.2021.110874
35. **CareEvolution, LLC.** Make My Test Count https://makemytestcount.org/. Accessed April 15, 2023.
36. **Akinbami LJ, Kruszon-Moran D, Wang CY, et al.** SARS-CoV-2 serology and self-reported infection among adults—National Health and Nutrition Examination Survey, United States, August 2021–May 2022. MMWR Morb Mortal Wkly Rep 2022; 71(48):1522–1525. doi:10.15585/mmwr.mm7148a4
37. **Wang X, Zein J, Ji X, Lin DY.** Impact of vaccination, prior infection and therapy on omicron infection and mortality [published online ahead of print, 2022 Nov 23]. J Infect Dis 2022; jiac460. doi:10.1093/infdis/jiac460
38. **Czeisler MÉ, Lane RI, Orellana RC, et al.** Perception of local COVID-19 transmission and use of preventive behaviors among adults with recent SARS-CoV-2 infection—Illinois and Michigan, June 1–July 31, 2022. MMWR Morb Mortal Wkly Rep 2022; 71(46):1471–1478. doi:10.15585/mmwr.mm7146a2
39. **Cowger TL, Murray EJ, Clarke J, et al.** Lifting universal masking in schools—COVID-19 Incidence among students and staff. N Engl J Med 2022; 387(21):1935–1946. doi:10.1056/NEJMoa2211029
40. **World Health Organization.** Tracking SARS-CoV-2 variants. https://www.who.int/activities/tracking-SARS-CoV-2-variants. Accessed April 15, 2023.
41. **El-Sadr WM, Vasan A, El-Mohandes A.** Facing the new COVID-19 reality. N Engl J Med 2023; 388(5):385–387. doi:10.1056/NEJMp2213920
42. **Adams K, Tastad KJ, Huang S, et al.** Prevalence of SARS-CoV-2 and influenza coinfection and clinical characteristics among children and adolescents aged < 18 years who were hospitalized or died with influenza—United States, 2021–22 influenza season. MMWR Morb Mortal Wkly Rep 2022; 71(50):1589–1596. doi:10.15585/mmwr.mm7150a4
43. **Fitzpatrick MC, Moghadas SM, Pandey A, Galvani AP; the Commonwealth Fund.** Two years of US COVID-19 vaccines have prevented millions of hospitalizations and deaths. https://www.commonwealthfund.org/blog/2022/two-years-covid-vaccines-prevented-millions-deaths-hospitalizations. Accessed April 15, 2023.
44. **Florea A, Sy LS, Luo Y, et al.** Durability of mRNA-1273 against COVID-19 in the time of delta: interim results from an observational cohort study. PLoS One 2022; 17(4):e0267824. doi:10.1371/journal.pone.0267824
45. **Florea A, Sy LS, Qian L, et al.** Effectiveness of messenger RNA-1273 vaccine booster against coronavirus disease 2019 in immunocompetent adults. Clin Infect Dis 2023; 76(2):252–262. doi:10.1093/cid/ciac785
46. **Dubendris H, Reses HE, Wong E, et al.** Laboratory-confirmed COVID-19 case incidence rates among residents in nursing homes by up-to-date vaccination status—United States, October 10, 2022–January 8, 2023. MMWR Morb Mortal Wkly Rep 2023; 72(4):95–99 doi:10.15585/mmwr.mm7204a3
47. **Otero S, Miller ES, Sunderraj A, et al.** Maternal antibody response and transplacental transfer following severe acute respiratory syndrome coronavirus 2 infection or vaccination in pregnancy. Clin Infect Dis 2023; 76(2):220–228. doi:10.1093/cid/ciac793
48. **Gilbert PB, Donis RO, Koup RA, Fong Y, Plotkin SA, Follmann D.** A COVID-19 milestone attained—a correlate of protection for vaccines. N Engl J Med 2022; 387(24):2203–2206. doi:10.1056/NEJMp2211314
49. **Canaday DH, Oyebanji OA, White EM, et al.** SARS-CoV-2 antibody responses to the ancestral SARS-CoV-2 strain and Omicron BA.1 and BA.4/BA.5 variants in nursing home residents after receipt of bivalent COVID-19 vaccine—Ohio and Rhode Island, September–November 2022. MMWR Morb Mortal Wkly Rep 2023; 72(4):100–106. doi:10.15585/mmwr.mm7204a4
50. **Link-Gelles R, Ciesla AA, Roper LE, et al.** Early estimates of bivalent mRNA booster dose vaccine effectiveness in preventing symptomatic SARS-CoV-2 infection attributable to Omicron BA.5- and XBB/XBB.1.5-related sublineages among immunocompetent adults—increasing community access to testing program, United States, December 2022–January 2023. MMWR Morb Mortal Wkly Rep 2023; 72(5):119–124. doi:10.15585/mmwr.mm7205e1
51. **Tenforde MW, Weber ZA, Natarajan K, et al.** Early estimates of bivalent mRNA vaccine effectiveness in preventing COVID-19-associated emergency department or urgent care encounters and hospitalizations among immunocompetent adults—VISION Network, nine states, September–November 2022. MMWR Morb Mortal Wkly Rep 2022; 71(5152):1616–1624. doi:10.15585/mmwr.mm715152e1
52. **Surie D, DeCuir J, Zhu Y, et al.** Early estimates of bivalent mRNA vaccine effectiveness in preventing COVID-19-associated hospitalization among immunocompetent adults aged ≥ 65 years—IVY Network, 18 states, September 8–November 30, 2022. MMWR Morb Mortal Wkly Rep 2022; 71(5152):1625–1630. doi:10.15585/mmwr.mm715152e2
53. **Razzaghi H, Srivastav A, de Perio MA, Laney AS, Black CL.** Influenza and COVID-19 vaccination coverage among healthcare personnel—United States, 2021–22. MMWR Morb Mortal Wkly Rep 2022; 71(42):1319–1326. doi:10.15585/mmwr.mm7142a2
54. **US Food and Drug Administration.** Vaccines and Related Biological Products Advisory Committee Meeting. January 26, 2023. FDA Briefing Document. Future Vaccination Regimens Addressing COVID-19. https://www.fda.gov/media/164699/download
55. **Shah MM, Joyce B, Plumb ID, et al.** Paxlovid associated with de-

creased hospitalization rate among adults with COVID-19—United States, April–September 2022. MMWR Morb Mortal Wkly Rep 2022; 71(48):1531–1537. doi:10.15585/mmwr.mm7148e2
56. **Wang L, Berger NA, Davis PB, Kaelber DC, Volkow ND, Xu R.** COVID-19 rebound after paxlovid and molnupiravir during January–June 2022. Preprint. medRxiv 2022; 2022.06.21.22276724. Published 2022 Jun 22. doi:10.1101/2022.06.21.22276724
57. **Hogan JI, Duerr R, Dimartino D, et al.** Remdesivir resistance in transplant recipients with persistent coronavirus disease 2019. Clin Infect Dis 2023; 76(2):342–345. doi:10.1093/cid/ciac769
58. **Barnette KG, Gordon MS, Domingo Rodriguez D, et al for the Phase 3 COVID-19 Investigators.** Oral sabizabulin for high-risk, hospitalized adults with COVID-19: interim analysis. N Eng J Med Evid 2022; 1(9). Published July 6, 2022. https://doi.org/10.1056/EVIDoa2200145
59. **Cao Z, Gao W, Bao H, et al.** VV116 versus nirmatrelvir-ritonavir for oral treatment of COVID-19. N Engl J Med 2023; 388(5):406–417. doi:10.1056/NEJMoa2208822
60. **Patel P, Twentyman E, Koumans E, et al.** Information for persons who are immunocompromised regarding prevention and treatment of SARS-CoV-2 infection in the context of currently circulating omicron sublineages—United States, January 2023. MMWR Morb Mortal Wkly Rep 2023; 72(5):128–131. doi:10.15585/mmwr.mm7205e3
61. **O'Mahoney LL, Routen A, Gillies C, et al.** The prevalence and long-term health effects of long COVID among hospitalised and non-hospitalised populations: a systematic review and meta-analysis. EClinicalMedicine 2022; 55:101762. doi:10.1016/j.eclinm.2022.101762
62. **Mizrahi B, Sudry T, Flaks-Manov N, et al.** Long COVID outcomes at one year after mild SARS-CoV-2 infection: nationwide cohort study. BMJ 2023; 380:e072529. doi:10.1136/bmj-2022-072529
63. **Richard SA, Pollett SD, Fries AC, et al.** Persistent COVID-19 symptoms at 6 months after onset and the role of vaccination before or after SARS-CoV-2 infection [published correction appears in JAMA Netw Open 2023; 6(2):e230734]. JAMA Netw Open 2023; 6(1):e2251360. doi:10.1001/jamanetworkopen.2022.51360
64. **Centers for Disease Control and Prevention.** National emergency department visits for COVID-19, influenza, and respiratory syncytial virus. Updated January 17, 2023. https://www.cdc.gov/ncird/surveillance/respiratory-illnesses/index.html. Accessed April 14, 2023.
65. **Nature.** Bird flu 2005: the ongoing story. https://doi.org/10.1038/news050912-1. Accessed April 15, 2023.
66. **Centers for Disease Control and Prevention.** Antiviral drug resistance among influenza viruses. Updated November 3, 2016. https://www.cdc.gov/flu/professionals/antivirals/antiviral-drug-resistance.htm. Accessed April 15, 2023.

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REVIEW

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Endocrinopathies from checkpoint inhibitors: Incidence, outcomes, and management

ABSTRACT

Immune checkpoint inhibitors are used more and more to treat several types of cancer, significantly extending cancer-free survival. However, concerns are growing about their toxic effects, which are many and varied. Endocrinopathies are some of the most frequently reported adverse effects, and thyroid dysfunction is the most common of these. Here, we review the incidence and severity of each immune checkpoint inhibitor-related endocrinopathy, possible factors related to toxicity risk, and principles of management.

KEY POINTS

The US Food and Drug Administration has so far approved 9 immune checkpoint inhibitors, which variously target programmed cell death protein 1, programmed cell death ligand 1, cytotoxic T-lymphocyte–associated protein 4, and lymphocyte activation gene 3.

Checkpoint inhibitor drugs have revolutionized cancer treatment, as they unleash the power of the immune system to destroy cancer cells.

Professional societies have issued guidelines for surveillance and treatment of immune checkpoint inhibitor-associated endocrinopathies.

With time and further research, strategies for predicting, preventing, and treating these toxicities should emerge.

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The discovery of the molecular mechanisms by which cancer cells evade the immune system has brought about a revolution in cancer immunotherapy. In the past, immunotherapy had very limited success, but unmasking these mechanisms paved the way toward the invention of immune checkpoint inhibitors—monoclonal antibodies that block key regulators of the immune system. Cancer cells typically target these regulators, suppressing the immune response against them and thereby helping them evade the immune system.

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Starting with ipilimumab in 2011, the US Food and Drug Administration (FDA) has so far approved 9 immune checkpoint inhibitors that target the following proteins:

- Programmed cell death protein 1 (PD-1, less commonly known as CD279)
- Programmed cell death ligand 1 (PD-L1, also known as CD274)
- Cytotoxic T-lymphocyte–associated protein 4 (CTLA-4, also known as CD152)
- Lymphocyte activation gene 3 (LAG-3).

These drugs have become mainstays in treating a variety of tumors, including those of the lung, esophagus, stomach, colon, liver, kidney, bladder, uterus, and skin.[1] In fact, their efficacy has overtaken that of standard treatments, prolonging survival even in patients with tumors of advanced stage.

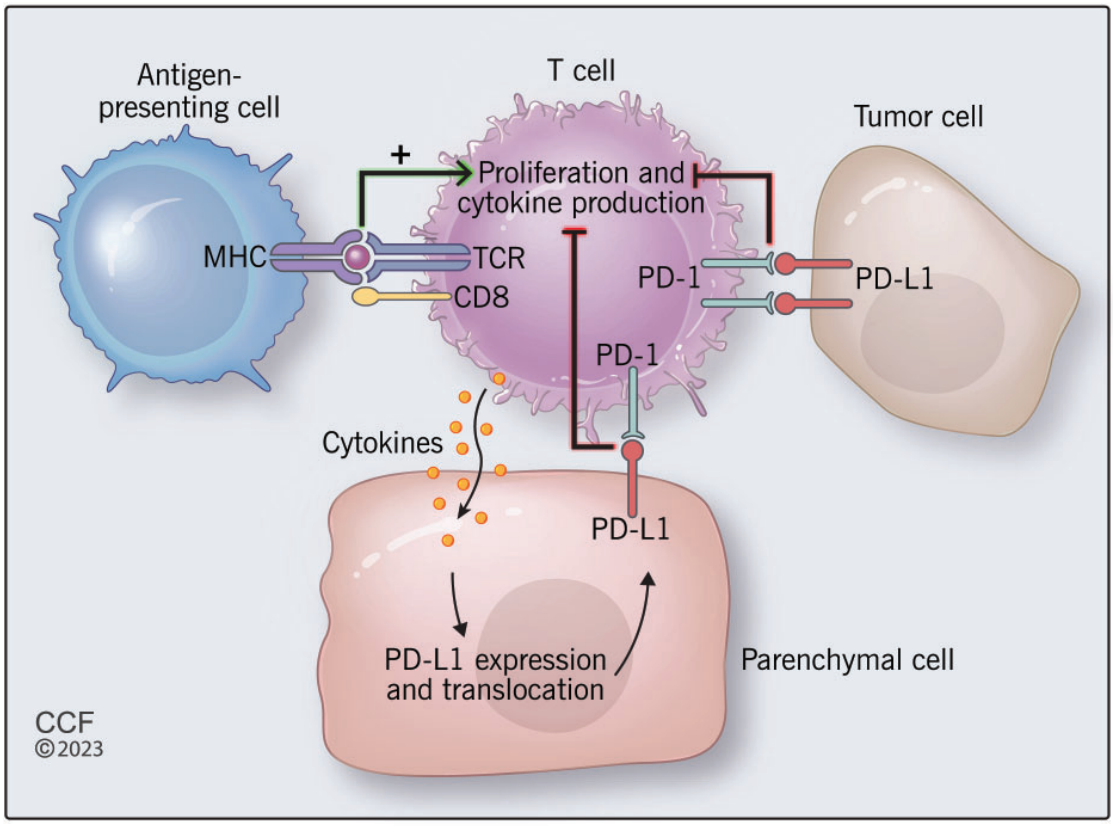

Figure 1. Proposed mechanism of the programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 pathway (PD-L1). (MHC = major histocompatibility complex ; TCR = T-cell receptor.)

Nevertheless, concerns about the immune-related adverse effects of these drugs have been growing.[2] The excessive activation of the immune system by these drugs causes dermatologic, endocrine, gastrointestinal, pulmonary, and other toxicities.[2]

In particular, endocrinopathies occur in roughly 10% of patients who receive immune checkpoint inhibitors.[3] Hypopituitarism, type 1 diabetes mellitus, and thyroid and adrenocortical dysfunction are the most common disorders that checkpoint inhibitors cause, depending on the drug.[4] The severity of these events has prompted researchers to look for adjuncts to minimize the toxicities while maintaining the efficacy of the drugs.[3]

Here, we review the mechanisms of action of the currently approved immune checkpoint inhibitors, the incidence of their associated endocrinopathies, the short-term and long-term outcomes of these adverse effects, and their management based on current guidelines.

MECHANISM OF ACTION OF IMMUNE CHECKPOINT INHIBITORS

The PD-1/PD-L1 pathway

PD-1, a cell-surface protein, was discovered by Ishida and colleagues[5] while studying apoptosis. It is most notably expressed by activated cytotoxic T cells after recognizing non-self antigens presented by major histocompatibility complexes of antigen-presenting cells.[6] The interaction of the T-cell receptor and the major histocompatibility complex results in release of cytokines that trigger expression of PD-L1 by local parenchymal tissue.[7] Parenchymal PD-L1 then binds T-cell PD-1 to transmit an inhibitory signal to the T cell and induce peripheral immune tolerance, so that healthy parenchymal tissue is protected from inflammatory destruction.[6,7]

Tumor cells manipulate this pathway by overexpressing PD-L1, so that T cells become exhausted and apoptosis is inhibited (**Figure 1**).[6] Therefore, blocking either PD-1 or PD-L1 enhances cytotoxic T-cell

TABLE 1
Common Terminology Criteria for Adverse Events (CTCAE)

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Asymptomatic or mild symptoms or change in affected chronic condition from baseline (eg, diabetes mellitus)	Moderate symptoms; limiting age-appropriate instrumental activities of daily living	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care activities of daily living	Life-threatening consequences; urgent intervention indicated	Death

Adapted from reference 18.

activity against PD-L1–expressing cells, including those of both the tumor and the parenchyma.

As of today, 4 PD-1 inhibitors (nivolumab, pembrolizumab, cemiplimab, and dostarlimab) and 3 PD-L1 inhibitors (atezolizumab, avelumab, and durvalumab) have been approved by the FDA.[4]

The CTLA-4 pathway

CTLA-4 is another T-cell surface protein that transmits inhibitory signals when bound by its ligands.[8] It is homologous to T-cell receptor, which, in contrast, transmits stimulatory signals when bound. CTLA-4 binds the T-cell receptor ligands CD80/86 on antigen-presenting cells with greater affinity and avidity than T-cell receptor.[9] Thus, it can outcompete T-cell receptor for its ligands and prevent its downstream stimulatory signal.

While this pathway is not manipulated by tumor cells, blocking CTLA-4 to ease T-cell receptor-CD80/86 binding enhances T-cell activation and cytotoxic activity against tumors.[9] Ipilimumab remains the only FDA-approved CTLA-4 inhibitor to date.[4]

The LAG-3 pathway

The role of the LAG-3 pathway in tumorigenesis has been extensively studied since its discovery more than 30 years ago.[10]

LAG-3 is a transmembrane protein that binds major histocompatibility complex class II, suppressing proliferation and activation of T cells.[10] This protein is also expressed on B cells and therefore has similar regulatory effects on B cells and natural killer cells.[10] Naive T cells express low levels of LAG-3, but tumor antigens cause an increase in activity of LAG-3, leading to T-cell exhaustion.[10]

Inhibiting the LAG-3 pathway restores T-cell function, thereby leading to increased accumulation and effector function on tumor cells.[10] Of note, combining LAG-3 inhibition with PD-1 blockade reduces tumor burden synergistically.[11]

In March 2022, the FDA approved the first human LAG-3 inhibitor (relatlimab), to be used in combination with nivolumab to treat unresectable or metastatic melanoma, based on data from a randomized phase 2 and 3 study.[12]

INCIDENCES OF ENDOCRINE IMMUNE-RELATED ADVERSE EVENTS

Pituitary dysfunction

Hypopituitarism is a rare endocrine disorder that can result from disease of the pituitary gland or the hypothalamus. Hypophysitis, ie, inflammation of the pituitary gland, usually leads to pituitary enlargement[13,14] and has been reported to be a major cause of immune checkpoint inhibitor-mediated hypopituitarism, although some authors use the terms hypopituitarism and hypophysitis interchangeably.[15] As the use of immune checkpoint inhibitors has increased in recent years, so has the incidence of hypophysitis.[13,14]

Immune checkpoint inhibitor-induced hypophysitis affects the anterior pituitary (which secretes follicle-stimulating hormone, luteinizing hormone, adrenocorticotropic hormone, thyroid-stimulating hormone, prolactin, endorphins, and growth hormone) more often than it affects the posterior pituitary (which secretes antidiuretic hormone and oxytocin),[16,17] and most patients have multiple hormonal deficiencies. Barroso-Sousa et al[3] reported in a meta-analysis that 36 (39%) of 92 patients on immune checkpoint inhibitor regimens who developed hypophysitis had symptoms of grade 3 or higher on the Common Terminology Criteria for Adverse Events (CTCAE) scale (**Table 1**).[3,18]

Central hypothyroidism is the most frequent complication, followed by **hypogonadism**. This is distinctive with the CTLA-4 inhibitor ipilimumab, suggesting that CTLA-4 is expressed preferentially by the thyrotropin-secreting and gonadotropin-secreting cells.[16,19]

Central adrenal insufficiency is also common and is concerning, as it can lead to life-threatening adrenal crisis.

Hypoprolactinemia: Prolactin levels are usually low; hyperprolactinemia is uncommon.[17]

Growth hormone deficiency is rare, as the growth hormone axis is usually spared.[14]

Diabetes insipidus is a very rare feature of hypopituitarism.[20]

Risk factors for pituitary dysfunction

Male sex seems to play a role in incidence, with higher rates reported in men.[16,17,21] Although this male predominance may be confounded by the sex discrepancies associated with melanoma (which also occurs more frequently in men, and which is treated with ipilimumab), the rates of hypophysitis still appear to be higher after taking this into account.[16,17] This is in contrast to other etiologies of autoimmune hypophysitis, which are more common in women.[14]

Age is a contributing factor, with people over age 65 having a higher risk.[16,17]

Ipilimumab. Immune checkpoint inhibitor-induced hypophysitis-hypopituitarism is almost exclusively associated with the CTLA-4 inhibitor ipilimumab, and it appears to be the most common endocrinopathy associated with this drug,[14] with incidences in the range of 10% to 15% reported.[16,17] Cumulative dosage or cycle frequency do not appear to affect the incidence significantly.[16]

However, the incidence is significantly higher with nivolumab-ipilimumab combination therapy (about 8%) than with ipilimumab alone (about 4%).[3]

Hypophysitis-hypopituitarism occurs significantly less often with PD-1 inhibitors than with ipilimumab, and the presentations may drastically differ between the 2 drug classes, strongly suggesting independent pathways.[22] For instance, gland enlargement and combined axis dysfunction are more common in those treated with ipilimumab, whereas secondary adrenal insufficiency with subtle gland enlargement is more common with PD-1 inhibitors.[22]

Human leukocyte antigen (HLA)-DR15. Due to the pathogenic nature of immune-related adverse events in general, predisposing HLA variants have been researched as a way to predict adverse outcomes. So far, studies have revealed an association between HLA-DR15 and the development of immune checkpoint inhibitor-induced secondary insufficiency.[23]

Course of hypopituitarism

The median time of onset of hypophysitis-hypopituitarism is 8 to 10 weeks after initiating treatment,[16,17] although this can vary by as much as 4 months.[24] Unlike other forms of autoimmune hypophysitis, it is usually not accompanied by visual disturbances.

Pituitary enlargement and hypophysitis usually resolve, but hypopituitarism can persist (with or without steroid treatment) and may be permanent depending on the hormonal axis involved.[24] For example, the thyroid axis may recover in the long term, but recovery of corticotroph cell function is rare. Therefore, quality of life after immune checkpoint inhibitor therapy poses a major issue for patients with secondary adrenal insufficiency.

Thyroid dysfunction

Thyroid dysfunction is the most common endocrine immune-related adverse event associated with immune checkpoint inhibitor therapy. Dysfunction can be in the form of either thyrotoxicosis or hypothyroidism, but the latter is the more common presentation.[13]

Although some authors use the terms *thyrotoxicosis* and *hyperthyroidism* interchangeably, we would like to clarify the definitions. Hyperthyroidism is thyroid hormone overproduction caused by an intrinsic pathological excess in thyroid hormone synthesis and secretion by the thyroid gland, and examples are Graves disease, toxic adenoma, and toxic multinodular goiter. Thyrotoxicosis, however, encompasses all causes of thyroid hormone excess, including hyperthyroidism and pathologies that result in a temporary excess release of thyroid hormone, as we will describe later.

Thyrotoxicosis as the primary presentation is predominantly related to silent or destructive thyroiditis, and in most of these cases, hypothyroidism ensues shortly thereafter (median time 42 days).[14,25] Therefore, many thyrotoxic adverse events may go undetected without close monitoring.[14] For example, in a study by Lee et al[25] of 45 patients who developed thyroid dysfunction after anti-PD-1 monotherapy or combination therapy, thyrotoxicosis was the initial presentation in 78% of patients, although 80% of those patients subsequently developed hypothyroidism.[25] A study by Lu et al[26] showed that only 9.3% of hypothyroidism cases reported to the FDA reporting system manifested with destructive thyroiditis (initially presenting as hyperthyroidism).

Graves disease is also an uncommon presentation of immune checkpoint inhibitor-induced thyrotoxicosis.[13] However, due to inconsistency in reporting, the incidence of Graves disease as an adverse event may be underreported.[13,27]

Barroso-Sousa et al,[3] in a meta-analysis of 38 randomized controlled trials, calculated the overall incidence of hypothyroidism to be 6.6% (95% confidence interaval 5.5%–7.8%) and the incidence of thyrotoxicosis to be 2.9% (95% confidence interval 2.4%–3.7%).[3,14]

Most recently, Lu et al,[26] using data from the US food and Drug Administration Adverse Event Reporting System (FAERS) from 2011 until 2020, reported a much lower incidence of thyroid dysfunction—ie, 2.6%. Of these cases, 62% were hypothyroidism, 22.7% were hyperthyroidism, and 15.3% were reported as thyroiditis without thyroid function information.[26] The authors accounted for this discrepancy as simply due to differences in study design and reporting, as clinical trials typically have closer follow-up and therefore more frequent reporting. Also, the FAERS reporting system may not capture less-severe adverse events. However, recent clinical data strongly suggest that the incidence of immune checkpoint inhibitor-induced thyroiditis and hypothyroidism is increasing,[28,29] which is to be expected given the increased screening and reporting as well as increased use of immune checkpoint inhibitors.

Regarding severity, most of the thyroid-related adverse events are either asymptomatic (subclinical) or cause mild or moderate symptoms (CTCAE grade 1 or 2), with less than 1% leading to severe symptoms, hospitalization, or death (CTCAE grade 3 or higher).[30]

Risk factors for thyroid dysfunction

Women may have a higher risk of thyroid dysfunction than men.[15,26,31,32] An explanation may be related to sex-hormone–mediated immune regulation, or possibly sex-specific autoimmunity.[33]

Elevated body mass index may also be associated with increased risk, earlier onset of symptoms, and overt hyperthyroidism.[15,31]

Advanced age may also increase the risk of severe thyroid dysfunction, leading to increased rates of hospitalization, morbidity, and death.[26]

Tyrosine kinase inhibitor use may also predispose to immunotherapy-related thyroid dysfunction,[30,34] although tyrosine kinase inhibitors can also independently cause thyroid dysfunction.[35]

Biomarkers that may predict thyroid-related adverse events are elevated levels of thyroid-stimulating hormone, thyroid autoantibodies, thyroglobulin, and cytokines.[15,31,36] In addition, Kurimoto et al[36] demonstrated that higher serum levels of interleukin 1-beta, interleukin 2, and granulocyte-macrophage colony-stimulating factor at baseline and early decreases in interleukin 8, granulocyte colony-stimulating factor, and monocyte chemoattractant protein 1 were significantly associated with thyroid dysfunction ($P < .5$).[36]

Agent used. The incidence of thyroid dysfunction strongly depends on the type of agent and whether it is given as monotherapy or combined therapy. For instance, studies by Barroso-Sousa et al[3] and Lu et al[26] clearly demonstrated that the anti-PD-1 class poses the highest risk of thyroid dysfunction. On the other hand, the anti-CTLA-4 agent ipilimumab is associated with the lowest frequency of thyroid dysfunction.

Combination anti-CTLA-4 and anti-PD-1 therapy arguably has the highest risk of thyroid dysfunction. Of note, whereas previous studies consistently reported a higher incidence of thyroid dysfunction with combination anti-CTLA-4–anti-PD-1 therapy than with monotherapy of each class,[3,4] Lu et al recently reported that the incidence of PD-1-related hypothyroidism exceeded that with combination therapy.[26] However, this pattern of more adverse events with combination therapy is not unique to thyroid dysfunction, as discussed above with pituitary dysfunction. Also, higher CTCAE grades of thyroid dysfunction are more frequent with combination therapy.[3,13]

Dose and tumor type are not significantly associated with the incidence of immunotherapy-mediated thyroid dysfunction.[3,13]

Course of thyroid dysfunction

The time of onset of thyroid dysfunction varies greatly, within the first 15 weeks of therapy in most reported cases,[37] but as early as 7 days or as late as 3 years in others.[14] Also, the time to onset is shorter with combined immunotherapy than with monotherapy.[25]

Most cases of hypothyroidism remain permanent and require long-term levothyroxine replacement therapy.[13,14]

Pancreatic endocrine dysfunction, diabetes mellitus

The adverse effects of immune checkpoint inhibitor therapy on pancreatic endocrine function manifest in a similar manner to type 1 diabetes mellitus, with low or undetectable C-peptide and elevated autoantibody levels.[14,38]

TABLE 2
Thyroid dysfunction due to immune checkpoint inhibitors: American Society of Clinical Oncology guideline

Situation	Action
Screening	Thyroid function tests, ie, thyroid-stimulating hormone (TSH) with or without thyroxine (T4) every 4–6 weeks while on therapy
Asymptomatic hypothyroidism (grade 1), TSH > 4.5 and < 10 mIU/L	Monitor thyroid function tests routinely as above Continue immune checkpoint inhibitor
Symptomatic hypothyroidism (grade 2) or TSH persistently > 10 mIU/L	Start levothyroxine (1.6 µg/kg/day if age < 70; 25–50 µg/day if age > 70 or multiple comorbidities); monitor TSH every 6–8 weeks until TSH is at goal, then every 6–12 months unless symptoms change Consider holding immune checkpoint inhibitor until symptoms resolve Consider endocrine consultation for challenging presentation or for hormonal therapy
Severely symptomatic hypothyroidism (grade 3 or 4)	Hold immune checkpoint inhibitor until symptoms resolve Hospital admission usually required Endocrine consultation recommended to assist with rapid hormone replacement Hydrocortisone should be given in the event central hypothyroidism is considered Start on chronic levothyroxine therapy and monitor as above on discharge.
Asymptomatic or mildly symptomatic thyrotoxicosis (grade 1)	Continue immune checkpoint inhibitor Start beta-blocker Monitor TSH and T4 every 2–3 weeks after diagnosis for possible hypothyroidism transition (and treat as for primary hypothyroidism) Consider endocrine consult for persistent thyrotoxicosis (> 6 weeks)
Mildly symptomatic thyrotoxicosis (grade 2)	Consider holding immune checkpoint inhibitor until symptoms improve Consider endocrine consultation Start on beta-blockers Refer to endocrinologist for persistent thyrotoxicosis (> 6 weeks) for additional workup and possible medical thyroid suppression
Severely symptomatic thyrotoxicosis (grade 3 or 4)	Hold immune checkpoint inhibitor until symptoms resolve Endocrine consult for all patients Start on beta-blocker Hospitalization with endocrine consultation to be considered in severe cases to guide medical therapy

Adapted from reference 49.

Incidence rates have been reported to be between 0.2% and 0.9%, with 0.1% being CTCAE grade 3 or higher.[3] However, there are recent reports of a more fulminant course with rapid-onset diabetic ketoacidosis[39,40] associated with a disproportionately normal to mildly elevated hemoglobin A1c.[38,41] Incidence rates are higher with PD-1 inhibitors (nivolumab, pembrolizumab), followed by PD-L1 inhibitors.[38,41] Combination therapy may also increase risk, with a shorter onset of symptoms after initiation of therapy.[38,41]

Akturk et al,[38] in a systematic review and meta-analysis of 71 cases, reported that the mean age of the patients was 61.7 (± 12 years), 55% of cases were in men, and the median time to onset was 49 days (range 5–448 days) after starting treatment. Half of the patients had autoantibodies at presentation, with a higher incidence of diabetic ketoacidosis and more rapid onset of diabetes mellitus than in patients without autoantibodies. An at-risk *DR* or *DQ* allele as present in 85% of patients tested, similar to the rate in childhood-onset diabetes.[38]

In a systematic review, de Filette et al[41] reported comparable results, with similar incidences of diabetic ketoacidosis (71%) and islet autoantibodies (53%). However, fewer patients (65%) had susceptible HLA genotypes. These findings suggest a role of allele

TABLE 3
Hypopituitarism due to immune checkpoint inhibitors: American Society of Clinical Oncology guideline

Situation	Action
Screening and workup	Routine thyroid function tests as outlined in Table 2 If central hypothyroidism is suspected, evaluate morning adrenocorticotropic hormone (ACTH) and cortisol as well as electrolytes ACTH stimulation testing can be falsely negative early in hypophysitis, as adrenal reserve declines slowly after pituitary stimulation is lost
Asymptomatic or mild symptoms (grade 1)	Consider holding immune checkpoint inhibitor until patient is stabilized on hormone replacement Endocrine consultation Initiate hormonal replacement for affected axis Adrenal insufficiency: corticosteroid replacement (hydrocortisone 15–20 mg in divided doses) No adrenal insufficiency: consider lower steroid dosing (average daily dosing over 2 months < 7.5 mg) due to report of reduced survival on higher dosing Initiate other hormone replacement after steroid initiation and only after adrenal insufficiency is corrected, to avoid crisis
Moderate symptoms (grade 2)	Consider holding immune checkpoint inhibitor until the patient is stabilized on hormone replacement Endocrine consultation Consider oral pulse-dose steroid therapy in patients with magnetic resonance imaging evidence of swelling or threatened optic chiasm compression; taper over 1 to 2 weeks, then maintenance steroid therapy Other hormonal replacement therapy as above
Severe symptoms (grade 3 or 4)	Hold immune checkpoint inhibitor until patient is stabilized on hormone replacement Endocrine consultation Hospitalize or refer to emergency department for normal saline (at least 2 L) and monitored free water replacement if the patient has diabetes insipidus Intravenous stress steroids (initial dosing: hydrocortisone 50–100 mg every 6 hours), then oral pulse-dose therapy tapered over 1–2 weeks in patients with magnetic resonance imaging evidence of significant swelling, optic chiasm compression, severe headache, or visual changes Taper stress-dose steroids to oral maintenance dose over 5–7 days Other maintenance therapy as above Patients should have a medical alert device as well as education on stress-dosing for sick days, when to seek medical attention for impending adrenal crisis, and use of emergency steroid injectables

Adapted from reference 49.

screening in patients who may be at risk of immune checkpoint inhibitor-induced diabetes.

As in childhood-onset type 1 diabetes, lifelong insulin therapy is needed, and unlike other immune checkpoint inhibitor endocrinopathies, pancreatic dysfunction does not respond to immunosuppressive therapy.[42]

Adrenal gland dysfunction

Immune checkpoint inhibitor-associated primary adrenal insufficiency is an infrequent manifestation of immune-related adverse events, accounting for less than 2%.

Barroso-Sousa et al,[3] in their meta-analysis and systematic review, reported only 43 cases of any grade primary adrenal insufficiency among 5,831 patients (0.7%), of which 14 (0.3%) were grade 3 or higher. In another study, among 256 patients who received ipilimumab, 2 cases of primary adrenal insufficiency (0.8%) were observed.[43]

Grouthier et al[44] reported that, of a total of 50,108 immune checkpoint inhibitor-associated adverse events (reported using the World Health Organization's pharmacovigilance database of individual case safety reports over a decade), there were 451 cases of primary adrenal insufficiency, of which 45 were "definite" and 406 "possible." A small majority (51.8%) of the cases were in men, with a median age of 66 years. Most patients had received immune checkpoint

TABLE 4
Adrenal dysfunction due to immune checkpoint inhibitors: American Society of Clinical Oncology guideline

Situation	Action
Screening and workup	No screening recommended Workup for suspected adrenal insufficiency includes morning adrenocorticotropic hormone (> 2 times the upper limit of normal), cortisol (< 3 µg/dL), basic metabolic panel, renin, and aldosterone Adrenocorticotropic hormone testing can be considered for indeterminate results Rule out other causes such as infection or metastatic disease
Asymptomatic or mild symptoms (grade 1)	Consider holding the immune checkpoint inhibitor until the patient is stabilized on hormone replacement Endocrine consultation Start hydrocortisone treatment (15–20 mg in divided doses) and titrate to maximum 30 mg/day for residual adrenal insufficiency Most primary adrenal insufficiency cases will also require fludrocortisone (starting dose 0.1–0.5 mg/day) Patients should have a medical alert device as well as education on stress-dosing for sick days, when to seek medical attention for impending adrenal crisis, and use of emergency steroid injectables
Moderate symptoms (grade 2)	Consider holding immune checkpoint inhibitor until the patient is stabilized on hormonal replacement Endocrine consultation Initiate outpatient corticosteroid treatment 2–3 times the maintenance dose (hydrocortisone 30–50 mg/day; prednisone 20 mg/day) to manage acute symptoms and decrease stress dosing after 2 days Initiate fludrocortisone as above Patient education as above
Severe symptoms (grade 3 or 4)	Hold the immune checkpoint inhibitor until the patient is stabilized on hormonal replacement Endocrine consultation For inpatient management, normal saline (at least 2 L) with intravenous stress-dose steroids (initial dosing: hydrocortisone 50–100 mg every 6 hours), then taper to oral maintenance doses over 5–7 days Maintenance therapy as above Patient education as above

Adapted from reference 49.

inhibitor monotherapy (nivolumab 44.3%, pembrolizumab 11.7%, and ipilimumab 23.6%), and 17.9% had received combination therapy. The median time to onset was 120 days (range 6–576).[44]

Immune checkpoint inhibitor-associated primary adrenal insufficiency is associated with significant rates of morbidity (> 90% of cases are severe) and mortality (7.3%). Mortality rates were similar in the subgroups receiving combination therapy vs monotherapy.[44]

Melanoma recurrence may also be a concern, due to persistently elevated adrenocorticotropic hormone and melanocyte-stimulating hormone levels, although no studies to date have fully investigated this theory.[45]

Other endocrinopathies

Primary hypoparathyroidism,[46] lipodystrophy,[47] and polyendocrine syndrome[48] have been reported in case reports, but further characteristics are yet to be determined.

GUIDELINES FOR MANAGING ENDOCRINOPATHIES

The American Society of Clinical Oncology,[49] the National Comprehensive Cancer Network,[50] and the Society of Immunotherapy of Cancer[51] have published practice guidelines on the recognition and management of immune checkpoint inhibitor-related endocrinopathies. The guidelines have similarities, but those of the American Society of Clinical Oncology are the most comprehensive, addressing acute management by CTCAE grade as well as when to consider endocrinology referral for thyroid dysfunction (**Table 2**), hypopituitarism (**Table 3**), adrenal insufficiency (**Table 4**), and diabetes (**Table 5**).[49]

The American Association of Clinical Endocrinology[52] has also published a clinical review on the evaluation and management of immune checkpoint inhibitor-mediated endocrinopathies, which shares a similar approach. However, it recommends a low threshold for endocrinology referral in the event of

TABLE 5
Diabetes due to immune checkpoint inhibitors: American Society of Clinical Oncology guideline

Situation	Action
Screening and workup	Screening glucose at baseline and with each treatment cycle while on therapy and at follow-up visits for at least 6 months Monitor symptoms for hyperglycemia Other laboratory tests include urine or serum ketones (or both), anion gap on a metabolic panel, anti-glutamic acid decarboxylase antibody, anti-islet cell antibodies, C-peptide
Asymptomatic or mild symptoms (grade 1), or type 2 diabetes with fasting glucose < 160 mg/dL and no new evidence of ketoacidosis or pancreatic autoimmunity	Can continue immune checkpoint inhibitor with close clinical follow-up Refer to primary care physician for diabetes management
Moderate symptoms (grade 2), or type 2 diabetes with fasting glucose > 160–250 mg/dL and no new evidence of ketoacidosis or pancreatic autoimmunity	May hold immune checkpoint inhibitor until glucose control is obtained Urgent endocrine consultation for any patient with new-onset checkpoint inhibitor-associated diabetes Initiate insulin Refer to emergency department if unable to initiate therapy or if urgent outpatient specialist evaluation is unavailable
Severe symptoms (grade 3 or 4), or worsening glucose, glucose > 500 mg/dL, ketoacidosis, or other metabolic abnormality	Hold immune checkpoint inhibitor until glucose control is obtained to levels and symptoms similar to grade 1 Admit for diabetic ketoacidosis, volume and electrolyte resuscitation, and insulin initiation Endocrine consultation recommended for all patients Insulin therapy appropriate for all patients

Adapted from reference 49.

any laboratory derangement suggesting endocrine organ dysfunction. This includes thyroid dysfunction, as closer monitoring and further tests for adrenal insufficiency may be warranted.

Generally, unless patients have moderate or severe symptoms (CTCAE grade 3 or 4), immune checkpoint inhibitor therapy can continue throughout the endocrine adverse event. Permanently stopping these drugs is not routinely recommended,[49] as most endocrinopathies are long-term and are treatable. This is unlike other immune-related adverse events (eg, pulmonary toxicities), for which more aggressive temporary or permanent discontinuation is recommended.[49]

Also, unlike in other organ-specific immune-related adverse events, steroids are not routinely recommended except in hypophysitis and primary adrenal insufficiency. High-dose steroids do not improve recovery rates in patients with hypophysitis[53] and have been associated with worse outcomes.[54] Therefore, high-dose steroids are reserved for patients with associated mass-effect symptoms. Similar outcomes have also been shown in patients with immune checkpoint inhibitor-induced diabetes,[42] and steroids are generally avoided.

Dehydroepiandrosterone replacement is controversial. However, deficiency can be tested and treated in women with low libido or energy who are judged to be otherwise well-replaced for other hormonal deficiencies.

The adverse effects of immune checkpoint inhibitors do have an upside: they may predict that the drug is working on the cancer, and the patient can expect prolonged recurrence-free survival.[55] In particular, endocrine immune-related adverse events (particularly thyroid dysfunction) may have the strongest associations with improved clinical outcomes.[56] These correlations therefore further support the consideration of not discontinuing immune checkpoint inhibitor therapy once the adverse events are manageable.

AN EMERGING PICTURE

With the increased use of immune checkpoint inhibitors in cancer treatment, more precise reporting of their extensive endocrine immune-related adverse events is occurring. This will give a clearer picture of the true incidences and characteristics of each endocrinopathy and will help inform further updated guidelines for pretreatment investigations, monitoring, and management. Prolonged routine posttreatment monitoring should also be considered, as some adverse effects can occur many months after discontinuation.

Interspecialist planning and monitoring with endocrinologists and oncologists should also be considered, as this may allow earlier hormone-replacement therapy, as well as immunotherapy de-escalation for those with moderate to severe events.

Primary care physicians should be aware of the need to perform routine screening and surveillance investigations, when to consider endocrinology referral, and when to consider urgent or emergent care referral. Patients should be routinely and extensively counseled on the endocrine adverse effects, including the common signs and symptoms, when to seek urgent care, and the likelihood of indefinite hormonal replacement therapy should these events occur.

Finally, larger prospective studies are needed to answer questions pertaining to risk factors (age, sex, autoimmune markers), interventions to reduce risk of endocrinopathies, and the risk of recurrence after restarting therapy.

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REFERENCES

1. **Twomey JD, Zhang B.** Cancer immunotherapy update: FDA-approved checkpoint inhibitors and companion diagnostics. AAPS J 2021; 23(2):39. doi:10.1208/s12248-021-00574-0
2. **Champiat S, Lambotte O, Barreau E, et al.** Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. Ann Oncol 2016; 27(4):559–574. doi:10.1093/annonc/mdv623
3. **Barroso-Sousa R, Barry WT, Garrido-Castro AC, et al.** Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a systematic review and meta-analysis. JAMA Oncol 2018; 4(2):173–182. doi:10.1001/jamaoncol.2017.3064
4. **de Filette J, Andreescu CE, Cools F, Bravenboer B, Velkeniers B.** A systematic review and meta-analysis of endocrine-related adverse events associated with immune checkpoint inhibitors. Horm Metab Res 2019; 51(3):145–156. doi:10.1055/a-0843-3366
5. **Ishida Y, Agata Y, Shibahara K, Honjo T.** Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. EMBO J 1992; 11(11):3887–3895. doi:10.1002/j.1460-2075.1992.tb05481.x
6. **Alsaab HO, Sau S, Alzhrani R, et al.** PD-1 and PD-L1 checkpoint signaling inhibition for cancer immunotherapy: mechanism, combinations, and clinical outcome. Front Pharmacol 2017; 8:561. doi:10.3389/fphar.2017.00561
7. **Mahoney KM, Rennert PD, Freeman GJ.** Combination cancer immunotherapy and new immunomodulatory targets. Nat Rev Drug Discov 2015; 14(8):561–584. doi:10.1038/nrd4591
8. **Walunas TL, Lenschow DJ, Bakker CY, et al.** CTLA-4 can function as a negative regulator of T cell activation. Immunity 1994; 1(5):405–413. doi:10.1016/1074-7613(94)90071-x
9. **Guo Q, Huang F, Goncalves C, Del Rincón SV, Miller WH Jr.** Translation of cancer immunotherapy from the bench to the bedside. Adv Cancer Res 2019; 143:1–62. doi:10.1016/bs.acr.2019.03.001
10. **Grosso JF, Kelleher CC, Harris TJ, et al.** LAG-3 regulates CD8+ T cell accumulation and effector function in murine self- and tumor-tolerance systems. J Clin Invest 2007; 117(11):3383–3392 doi:10.1172/JCI31184
11. **Goding SR, Wilson KA, Xie Y, et al.** Restoring immune function of tumor-specific CD4+ T cells during recurrence of melanoma. J Immunol 2013; 190(9):4899–4909. doi:10.4049/jimmunol.1300271
12. **Tawbi HA, Schadendorf D, Lipson EJ, et al.** Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. N Engl J Med 2022; 386(1):24–34. doi:10.1056/NEJMoa2109970
13. **Stelmachowska-Banas M, Czajka-Oraniec I.** Management of endocrine immune-related adverse events of immune checkpoint inhibitors: an updated review. Endocr Connect 2020; 9(10):R207–R228. doi:10.1530/EC-20-0342
14. **Chang LS, Barroso-Sousa R, Tolaney SM, Hodi FS, Kaiser UB, Min L.** Endocrine toxicity of cancer immunotherapy targeting immune checkpoints. Endocr Rev 2019; 40(1):17–65. doi:10.1210/er.2018-00006
15. **Anderson B, Morganstein DL.** Endocrine toxicity of cancer immunotherapy: clinical challenges. Endocr Connect 2021; 10(3):R116–R124. doi:10.1530/EC-20-0489
16. **Faje AT, Sullivan R, Lawrence D, et al.** Ipilimumab-induced hypophysitis: a detailed longitudinal analysis in a large cohort of patients with metastatic melanoma. J Clin Endocrinol Metab 2014; 99(11):4078–4085. doi:10.1210/jc.2014-2306
17. **Faje A.** Immunotherapy and hypophysitis: clinical presentation, treatment, and biologic insights. Pituitary 2016; 19(1):82–92. doi:10.1007/s11102-015-0671-4
18. **US Department of Health and Human Services National Institutes of Health National Cancer Institute.** Common Terminology Criteria for Adverse Events (CTCAE). Version 5.0, Published November 27, 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_8.5x11.pdf. Accessed April 11, 2023.
19. **Iwama S, De Remigis A, Callahan MK, Slovin SF, Wolchok JD, Caturegli P.** Pituitary expression of CTLA-4 mediates hypophysitis secondary to administration of CTLA-4 blocking antibody. Sci Transl Med 2014; 6(230):230ra45. doi:10.1126/scitranslmed.3008002
20. **Nallapaneni NN, Mourya R, Bhatt VR, Malhotra S, Ganti AK, Tendulkar KK.** Ipilimumab-induced hypophysitis and uveitis in a patient with metastatic melanoma and a history of ipilimumab-induced skin rash. J Natl Compr Canc Netw 2014; 12(8):1077–1081. doi:10.6004/jnccn.2014.0105
21. **Caturegli P, Di Dalmazi G, Lombardi M, et al.** Hypophysitis secondary to cytotoxic T-lymphocyte-associated protein 4 blockade: insights into pathogenesis from an autopsy series. Am J Pathol 2016; 186(12):3225–3235. doi:10.1016/j.ajpath.2016.08.020
22. **Faje A, Reynolds K, Zubiri L, et al.** Hypophysitis secondary to nivolumab and pembrolizumab is a clinical entity distinct from ipilimumab-associated hypophysitis. Eur J Endocrinol 2019; 181(3):211–219. doi:10.1530/EJE-19-0238
23. **Yano S, Ashida K, Sakamoto R, et al.** Human leucocyte antigen DR15, a possible predictive marker for immune checkpoint inhibitor-induced secondary adrenal insufficiency. Eur J Cancer 2020; 130:198–203. doi:10.1016/j.ejca.2020.02.049

24. **Scott ES, Long GV, Guminski A, Clifton-Bligh RJ, Menzies AM, Tsang VH.** The spectrum, incidence, kinetics and management of endocrinopathies with immune checkpoint inhibitors for metastatic melanoma. Eur J Endocrinol 2018; 178(2):173–180. doi:10.1530/EJE-17-0810
25. **Lee H, Hodi FS, Giobbie-Hurder A, et al.** Characterization of thyroid disorders in patients receiving immune checkpoint inhibition therapy. Cancer Immunol Res 2017; 5(12):1133–1140. doi:10.1158/2326-6066.CIR-17-0208
26. **Lu D, Yao J, Yuan G, Gao Y, Zhang J, Guo X.** Immune checkpoint inhibitor-related new-onset thyroid dysfunction: a retrospective analysis using the US FDA adverse event reporting system. Oncologist 2022; 27(2):e126–e132. doi:10.1093/oncolo/oyab043
27. **Tan MH, Iyengar R, Mizokami-Stout K, et al.** Spectrum of immune checkpoint inhibitors-induced endocrinopathies in cancer patients: a scoping review of case reports. Clin Diabetes Endocrinol 2019; 5:1. doi:10.1186/s40842-018-0073-4
28. **Shariff AI, Qamar A, Velez Rivera J, et al.** SAT-414 a single center retrospective analysis and review of endocrinopathies from immune checkpoint inhibitors between 2007 and 2017. J Endocr Soc 2020; 4(suppl 1):SAT–414.
29. **Brody HM, Macherla S, Bulumulle A, Namireddy P, Cherry, CR.** The real-world incidence of immunotherapy-related thyroid dysfunction: a retrospective analysis of a single center's experience over five years. J Clin Onc 2020; 38(suppl 5):98.
30. **Zhan L, Feng HF, Liu HQ, et al.** Immune checkpoint inhibitors-related thyroid dysfunction: epidemiology, clinical presentation, possible pathogenesis, and management. Front Endocrinol (Lausanne) 2021; 12:649863. doi:10.3389/fendo.2021.649863
31. **Pollack R, Ashash A, Cahn A, Rottenberg Y, Stern H, Dresner-Pollak R.** Immune checkpoint inhibitor-induced thyroid dysfunction is associated with higher body mass index. J Clin Endocrinol Metab 2020; 105(10):dgaa458. doi:10.1210/clinem/dgaa458
32. **Zhai Y, Ye X, Hu F, et al.** Endocrine toxicity of immune checkpoint inhibitors: a real-world study leveraging US Food and Drug Administration adverse events reporting system. J Immunother Cancer 2019; 7(1):286. doi:10.1186/s40425-019-0754-2
33. **Triggianese P, Novelli L, Galdiero MR, et al.** Immune checkpoint inhibitors-induced autoimmunity: the impact of gender. Autoimmun Rev 2020; 19(8):102590. doi:10.1016/j.autrev.2020.102590
34. **Sbardella E, Tenuta M, Sirgiovanni G, et al.** Thyroid disorders in programmed death 1 inhibitor-treated patients: is previous therapy with tyrosine kinase inhibitors a predisposing factor? Clin Endocrinol (Oxf) 2020; 92(3):258–265. doi:10.1111/cen.14135
35. **Abdel-Rahman O, Fouad M.** Risk of thyroid dysfunction in patients with solid tumors treated with VEGF receptor tyrosine kinase inhibitors: a critical literature review and meta-analysis. Expert Rev Anticancer Ther 2014; 14(9):1063–1073. doi:10.1586/14737140.2014.929501
36. **Kurimoto C, Inaba H, Ariyasu H, et al.** Predictive and sensitive biomarkers for thyroid dysfunctions during treatment with immune-checkpoint inhibitors. Cancer Sci 2020; 111(5):1468–1477. doi:10.1111/cas.14363
37. **Barroso-Sousa R, Ott PA, Hodi FS, Kaiser UB, Tolaney SM, Min L.** Endocrine dysfunction induced by immune checkpoint inhibitors: practical recommendations for diagnosis and clinical management. Cancer 2018; 124(6):1111–1121. doi:10.1002/cncr.31200
38. **Akturk HK, Kahramangil D, Sarwal A, Hoffecker L, Murad MH, Michels AW.** Immune checkpoint inhibitor-induced type 1 diabetes: a systematic review and meta-analysis. Diabet Med 2019; 36(9): 1075–1081. doi:10.1111/dme.14050
39. **Gaudy C, Clévy C, Monestier S, et al.** Anti-PD1 pembrolizumab can induce exceptional fulminant type 1 diabetes. Diabetes Care 2015; 38(11):e182–e183. doi:10.2337/dc15-1331
40. **Ishikawa K, Shono-Saito T, Yamate T, et al.** A case of fulminant type 1 diabetes mellitus, with a precipitous decrease in pancreatic volume, induced by nivolumab for malignant melanoma: analysis of HLA and CTLA-4 polymorphisms. Eur J Dermatol 2017; 27(2): 184–185. doi:10.1684/ejd.2016.2923
41. **de Filette JMK, Pen JJ, Decoster L, et al.** Immune checkpoint inhibitors and type 1 diabetes mellitus: a case report and systematic review. Eur J Endocrinol 2019; 181(3):363–374. doi:10.1530/EJE-19-0291
42. **Clotman K, Janssens K, Specenier P, Weets I, De Block CEM.** Programmed cell death-1 inhibitor-induced type 1 diabetes mellitus. J Clin Endocrinol Metab 2018; 103(9):3144–3154. doi:10.1210/jc.2018-00728
43. **Ferrari SM, Fallahi P, Elia G, et al.** Autoimmune endocrine dysfunctions associated with cancer immunotherapies. Int J Mol Sci 2019; 20(10):2560. doi:10.3390/ijms20102560
44. **Grouthier V, Lebrun-Vignes B, Moey M, et al.** Immune checkpoint inhibitor-associated primary adrenal insufficiency: WHO VigiBase report analysis. Oncologist 2020; 25(8):696–701. doi:10.1634/theoncologist.2019-0555
45. **Harsch IA.** Hypothesis: does adrenalitis caused by immune checkpoint-inhibitors put melanoma patients at an elevated risk for recurrence? J Immunother Cancer 2019; 7(1):166. doi:10.1186/s40425-019-0651-8
46. **Piranavan P, Li Y, Brown E, Kemp EH, Trivedi N.** Immune checkpoint inhibitor-induced hypoparathyroidism associated with calcium-sensing receptor-activating autoantibodies. J Clin Endocrinol Metab 2019; 104(2):550–556. doi:10.1210/jc.2018-01151
47. **Falcao CK, Cabral MCS, Mota JM, et al.** Acquired lipodystrophy associated with nivolumab in a patient with advanced renal cell carcinoma. J Clin Endocrinol Metab 2019; 104(8):3245–3248. doi:10.1210/jc.2018-02221
48. **Gunjur A, Klein O, Kee D, Cebon J.** Anti-programmed cell death protein 1 (anti-PD1) immunotherapy induced autoimmune polyendocrine syndrome type II (APS-2): a case report and review of the literature. J Immunother Cancer 2019; 7(1):241. doi:10.1186/s40425-019-0713-y
49. **Schneider BJ, Naidoo J, Santomasso BD, et al.** Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update [published correction appears in J Clin Oncol 2022; 40(3):315]. J Clin Oncol 2021; 39(36):4073–4126. doi:10.1200/JCO.21.01440
50. **Thompson JA, Schneider BJ, Brahmer J, et al.** Management of immunotherapy-related toxicities, version 1.2022: NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2022; 20(4):387–405. doi:10.6004/jnccn.2022.0020
51. **Brahmer JR, Abu-Sbeih H, Ascierto PA, et al.** Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. J Immunother Cancer 2021; 9(6):e002435. doi:10.1136/jitc-2021-002435
52. **Yuen KCJ, Samson SL, Bancos I, et al.** American Association of Clinical Endocrinology disease state clinical review: evaluation and management of immune checkpoint inhibitor-mediated endocrinopathies: a practical case-based clinical approach. Endocr Pract 2022; 28(7):719–731. doi:10.1016/j.eprac.2022.04.010
53. **Min L, Hodi FS, Giobbie-Hurder A, et al.** Systemic high-dose corticosteroid treatment does not improve the outcome of ipilimumab-related hypophysitis: a retrospective cohort study. Clin Cancer Res 2015; 21(4):749–755. doi:10.1158/1078-0432.CCR-14-2353
54. **Albarel F, Gaudy C, Castinetti F, et al.** Long-term follow-up of ipilimumab-induced hypophysitis, a common adverse event of the anti-CTLA-4 antibody in melanoma. Eur J Endocrinol 2015; 172(2):195–204. doi:10.1530/EJE-14-0845
55. **Foster CC, Couey MA, Kochanny SE, et al.** Immune-related adverse events are associated with improved response, progression-free survival, and overall survival for patients with head and neck cancer receiving immune checkpoint inhibitors. Cancer 2021; 127(24): 4565–4573. doi:10.1002/cncr.33780
56. **Martini DJ, Goyal S, Liu Y, et al.** Immune-related adverse events as clinical biomarkers in patients with metastatic renal cell carcinoma treated with immune checkpoint inhibitors. Oncologist 2021; 26(10):e1742–e1750. doi:10.1002/onco.13868

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EDITORIAL

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Reincarnating autoimmunity: Immune-related adverse events as new diseases

Oncologists who give immunotherapy today have had to rediscover internal medicine all over again. After immune checkpoint inhibitor therapy has been started, and even after it has been stopped, immune-related adverse events (irAEs) can manifest in any organ at unpredictable times and can replicate any naturally occurring autoimmune disease. But while irAEs can mimic their naturally occurring counterparts, their presentations, the ideal immunosuppressive regimens to control them, and their durations are unique. As such, irAEs are a new class of autoimmune disorders whose optimal diagnosis, management, and treatment remain incompletely discovered and ripe for innovation.

See related article, page 307

A SPECTRUM OF DISORDERS

The clinical spectrum of irAEs is broad. Any organ can be affected, and any naturally occurring autoimmune process can be mimicked by the massive inflammation generated by checkpoint inhibition. Common forms include immune-mediated diarrhea and colitis, inflammatory joint disease, hypothyroidism, and adrenal insufficiency. Unusual forms touch every organ system and range from hair repigmentation to aplastic anemia.[1]

Some irAEs are fatal. Perhaps the best described is the "triple M" syndrome, a highly morbid combination of myocarditis, myositis, and myasthenia gravis.[2] Many phenomena that are likely immune-related have similarities to post-COVID-19 phenomenon, including brain fog, venous thromboembolism,[3] and major adverse cardiovascular events.[4]

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FIRST REPORTED IN 2006

The first report of an irAE was logged in a pharmacovigilance database in 2006,[5] as trials of checkpoint inhibitors got underway. In 2011, the modern era of cancer immunotherapy commenced with the approval of ipilimumab for metastatic melanoma. In 2012, 7 articles were published on irAEs and the first guide to practical management was published by the American Society of Clinical Oncology.[6] Case reports and case series followed, as oncologists and medical subspecialists began to encounter these new disorders in their clinics and hospitals. These new experiences spurred a wave of publications (**Figure 1**), including a review of immune-mediated colitis in this *Journal*.[7] In 2022 alone, 1,424 articles were published on the topic of immune-related adverse events. Since the first article on irAEs was published in 2007,[8] more than 5,000 articles have been published on the clinical sequelae of checkpoint inhibition.

Dr. Kennedy and colleagues, in this issue of the *Journal*, present a welcome summation of endocrine dysfunction associated with checkpoint inhibitor therapy. Their article marches through all the flavors of checkpoint inhibitor-mediated endocrinopathy—the incidence, treatment, and optimal therapy, at least what has been published thus far. Endocrine irEAs are some of the most common long-term chronic sequelae of checkpoint inhibitor therapy.[9]

DIFFICULT QUESTIONS OF RISK VS BENEFIT

Confronting metastatic disease, an oncologist might dismiss the importance of possible endocrine irAEs, believing that permanent hypothyroidism is a relatively small price for inducing remission from stage IV disease. However, in the context of stage II or III

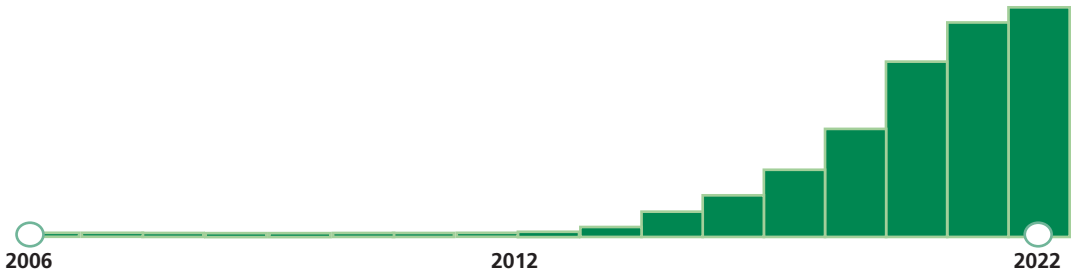

Figure 1. Timeline of articles on PubMed with the search term "immune-related adverse events." More than 5,000 articles have been published since 2006 on a clinical phenomenon that did not exist before the introduction of checkpoint inhibitor therapy for cancer.

cancer, particularly when surgical resection alone has high cure rates (eg, resected stage II melanomas, which have an over 70% cure rate with surgery alone[5] and for which adjuvant anti-PD1 immunotherapy was approved in 2022), the prospect of permanent endocrinopathies makes the risk-vs-benefit calculation difficult for both patients and practitioners when deciding whether to begin a year of checkpoint inhibition.

INSURANCE HAS NOT CAUGHT UP

Despite the enormous medical interest in this new spectrum of clinical entities and despite medical recognition for well over a decade, irAEs do not exist in the medical insurance system: they do not yet have billable International Classification of Diseases codes. Obtaining prior authorization for biologic treatments that are recommended in major national and international guidelines is often challenging due to the nonexistence of appropriate billing codes that match the medical indication. Lack of proper reimbursement and prior authorization for biologic treatments is a significant barrier to optimizing treatment for irAEs and hampers the ability of the medical community to properly measure the medical, financial, and social impacts of this new class of disease.

STAY CURIOUS AND KEEP LEARNING

Every step in discovering the incidence of, inventing diagnostic algorithms for, and learning how to manage irEAs is a stride forward in the necessary and overdue education about the acute and chronic medical consequences of checkpoint inhibitor therapy for clinical practitioners in all disciplines, but most especially internal medicine, emergency medicine, and medical subspecialties. Lessons we have learned and continue to learn from these side effects, reinforced by the lessons from the COVID-19 era, have reminded us all in the medical specialties about the power and pleiotropy of the immune system. In these reincarnations of autoimmunity, we do as we always have done in medicine—constantly and consistently stay curious and renew our medical knowledge and practice. ■

DISCLOSURES

The author reports no relevant financial relationships which, in the context of her contribution, could be perceived as a potential conflict of interest.

REFERENCES

1. **Rivera N, Boada A, Bielsa MI, et al.** Hair repigmentation during immunotherapy treatment with an anti-programmed cell death 1 and anti-programmed cell death ligand 1 agent for lung cancer. JAMA Dermatol 2017; 153(11):1162–1165. doi:10.1001/jamadermatol.2017.2106
2. **Kimura T, Fukushima S, Miyashita A, et al.** Myasthenic crisis and polymyositis induced by one dose of nivolumab. Cancer Sci 2016; 107(7):1055–1058. doi:10.1111/cas.12961
3. **Roopkumar J, Swaidani S, Kim AS, et al.** Increased incidence of venous thromboembolism with cancer immunotherapy. Med (NY) 2021; 2(4):423–434. doi:10.1016/j.medj.2021.02.002
4. **Chitturi KR, Xu J, Araujo-Gutierrez R, et al.** Immune checkpoint inhibitor-related adverse cardiovascular events in patients with lung cancer. JACC CardioOncol 2019; 1(2):182–192. doi:10.1016/j.jaccao.2019.11.013
5. **Bleicher J, Swords DS, Mali ME, et al.** Recurrence patterns in patients with stage II melanoma: the evolving role of routine imaging for surveillance. J Surg Oncol 2020; 122(8):1770–1777. doi:10.1002/jso.26214
6. **Weber JS.** Practical management of immune-related adverse events from immune checkpoint protein antibodies for the oncologist. Am Soc Clin Oncol Educ Book 2012; 174–177. doi:10.14694/EdBook_AM.2012.32.79
7. **Khan F, Funchain P, Bennett A, Hull TL, Shen B.** How should we diagnose and manage checkpoint inhibitor-associated colitis? Cleve Clin J Med 2018; 85(9):679–683. doi:10.3949/ccjm.85a.18020
8. **O'Day SJ, Hamid O, Urba WJ.** Targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4): a novel strategy for the treatment of melanoma and other malignancies. Cancer 2007; 110(12):2614–2627. doi:10.1002/cncr.23086
9. **Patrinely JR Jr, Johnson R, Lawless AR, et al.** Chronic immune-related adverse events following adjuvant anti-PD-1 therapy for high-risk resected melanoma [published correction appears in JAMA Oncol 2021; 7(5):785]. JAMA Oncol 2021; 7(5):744–748. doi:10.1001/jamaoncol.2021.0051

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To read articles as CME activities and claim credit, go to www.ccjm.org, click on the "CME/MOC" menu, and then "Articles." Find the articles that you want to read as CME activities and click on the appropriate links. After reading an article, click on the link to complete the activity. You will be asked to log in to your MyCME account (or to create an account). Upon logging in, select "CME," complete the activity evaluation, and print your certificate.

Call 216-444-2661 or e-mail ccjm@ccf.org with questions.

Maintenance of Certification (MOC) Points

All *Cleveland Clinic Journal of Medicine* CME activities are eligible for ABIM MOC points. Physicians may claim MOC points in addition to CME credit.

Follow the instructions for completing and claiming credit for CME activities.

When you log into your MyCME account, select "CME & MOC" and enter your ABIM identification number and your date of birth. The system will store this information after you enter it the first time.

Complete the quiz and evaluation and print your CME certificate.

May 2023 CME/MOC activity

Estimated time to complete the activity: up to 1 hour

Endocrinopathies from checkpoint inhibitors: Incidence, outcomes, and management

Release date: May 1, 2023
Expiration date: April 30, 2024

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Participants claiming CME credit from this activity may submit the credit hours to the American Osteopathic Association for Category 2 credit.

AMERICAN BOARD OF INTERNAL MEDICINE (ABIM):
Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1.0 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Please Note: To receive MOC you must select the MOC option during the online credit claiming process and complete the required steps. ABIM MOC points will be reported within 30 days of claiming credit.