

CLEVELAND CLINIC JOURNAL OF MEDICINE

**Another vaccine article? Yes,
but a different vaccine**

**Spontaneous oral hematomas
on the buccal mucosa**

**Geriatric medicine update:
Alzheimer disease and more**

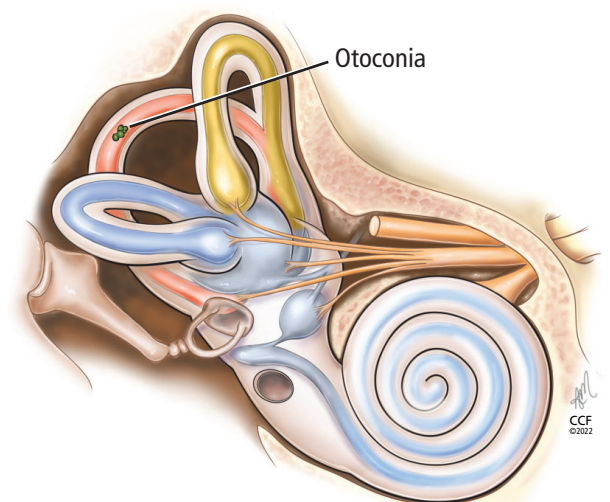
**Hypophosphatemia in a patient
with an eating disorder**

**When should antithrombotic
therapy be resumed after
gastrointestinal bleeding?**

**Update on pneumococcal
vaccination in adults:
Simpler is better**

Reducing the risk of breast cancer

**Benign paroxysmal positional
vertigo: Effective diagnosis
and treatment**



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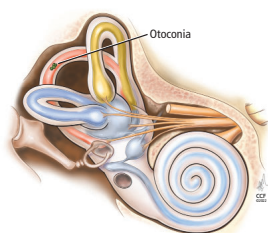
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Another vaccine article? Yes, but a different vaccine

There is a shared weariness in response to discussions of mask-wearing, COVID-19 time warps, and vaccines. Over the past 2 years, most of us got a refresher course on vaccine development and implementation—if we had ever formally been taught or previously thought much about these topics at all. The delivery of mRNA-platformed vaccines to millions of people was a pharmaceutical development and public health tour de force, even if the rollout stutter-stepped at times. We can still do better in terms of total individuals “fully” vaccinated, though we do not yet know the implications of what fully vaccinated means.

COVID-19 vaccine discussions continue. I’ve almost given up on discussions with non-vaxer patients. If they haven’t bought in by now, rational discussion is unlikely to convince them. But I still try with some of my elderly or immunocompromised patients who have been influenced by the conspiracy theories and misinformation promulgated in their family or social circles. I lost enough patients in the early prevaccine days to not go silent into the night. Now, I count it a success if I can convince these at-risk patients to accept appropriate monoclonal antibody prophylactic therapy, or to promise to take a home test if they experience minimal symptoms and alert me if it is positive, and to consider taking antiviral medication.

Questions linger about the COVID-19 vaccines. How long will immunity last? How many boosters constitute full vaccination? Should we trust new vaccines even if they have only been modeled for efficacy? And are we overfocused on the humoral vaccine response?

But my focus here is not on COVID-19 vaccines. As we try to approach social and medical normalcy, it is late autumn, and we are preparing for influenza and pneumonia season. Influenza vaccination remains straightforward. Yearly strain changes in the circulating viruses lead to changes in vaccine composition in an effort to provide appropriate individual and herd protection. I still periodically have to explain to patients why they can’t get the flu from the flu vaccine, but these are not emotionally charged discussions. (As yet, I have heard no concerns about microchips in the flu shots.) There has been even less controversy in the patient community regarding vaccines against streptococcal pneumonia. In the medical community, there has been less controversy but more confusion regarding which pneumococcal vaccine to give when, and to which patient. For that, we have had cheat sheets posted on the wall next to our computer screens.

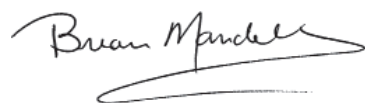
As newer vaccines against *Streptococcus pneumoniae* have arrived, so have confusing recommendations and guidelines for the sequence and timing of administration. And there seems to be limited understanding of the basis for the specific recommendations. In this issue, *Cleveland Clinic Journal of Medicine* deputy editor Craig Nielsen and colleagues summarize the guidelines for administration of pneumococcal vaccines.¹

For decades, we have had the 23-valent pneumococcal polysaccharide vaccine (PPSV23, Pneumovax 23). It is safe and reasonably effective against pneumonia from *S pneumoniae*, but questionably effective against noninvasive infection.² As a T cell-independent immunogen, it provides only a limited immune anamnestic response. The pneumococcal conjugate vaccine (PCV13) was formulated to engage T-cell activation with 13 strain-specific polysaccharide fragments (with overlapping specificity to strains covered by PPSV23) linked to a protein scaffold. Given along with PPSV23, there was a global decline in pneumococcal infections and carriage. The decline in

carriage of *S pneumoniae*, likely the result of PCV13, has resulted in reduced transmission. However, serotypes not covered by PCV13 were still contributing significant morbidity. A newer vaccine (PCV20) covers 7 additional clinically relevant serotypes. This additional coverage was estimated to include about 30% of pneumococcal infections. PCV20 was documented to be safe and to elicit noninferior serotype immunity when compared with PCV13 and PPSV23.³ Interestingly, especially when viewed in the context of concerns about implementation of the newer bivalent COVID-19 vaccine without clinical outcome data, the efficacy comparisons of PCV20 leading to its regulatory acceptance were based not on clinical outcomes but rather on performance in a complicated functional ex vivo opsonization and phagocytosis assay.⁴ Immune efficacy—not a documented reduction in pneumococcal infections—was reported in patients without³ or with⁵ prior pneumococcal vaccination at 1 month after receiving PCV20. Coadministration of PCV20 with quadrivalent influenza vaccine or with an RNA-based SARS-CoV-2 vaccine did not adversely affect any of the immunologic responses.

After approval of the various PCVs, recommendations were offered for their timing of administration based on the methodologic structure of the clinical trials, which indicated additional immunologic benefit to patients receiving more than 1 vaccine. However, it was noted that local injection-site reactions were more common and more bothersome if different vaccines were given in temporal proximity. Nonetheless, it has been proposed that an interval of only 8 weeks, not a full year, can be considered when combining vaccines in patients at high risk for severe pneumococcal infection.⁶

An interesting and unexpected effect of the introduction of the PCVs is an apparent reduction in antibiotic-resistant pneumococcal isolates.⁵ But we still lack data on the long-term clinical efficacy of PCV20 and on the overall efficacy of current immunization practices in patients with disease-associated or iatrogenic immunosuppression. Nonetheless, as Nielsen et al point out in this issue,¹ when it comes to vaccination, simpler is indeed better.



Brian F. Mandell, MD, PhD
Editor in Chief

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2022

NOVEMBER

PRECISION CARE IN LUNG DISEASE
November 3
Cleveland, OH

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November 4
Cleveland, OH

**CURRENT CONCEPTS IN BUPRENORPHINE
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November 5
Live stream

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November 10–11
Beachwood, OH

GASTROENTEROLOGY UPDATE
November 12
Warrensville Heights, OH

DECEMBER

LIVER UPDATE
December 2
Cleveland, OH

MASTERING THE MITRAL VALVE
December 2–3
New York, NY

**SHAPING THE MANAGEMENT
OF PARKINSON DISEASE:
DEBATING THE MOST CONTROVERSIAL
ISSUES AND DISCUSSING THE LATEST
BREAKTHROUGHS**
December 3–4
Lake Tahoe, NV

**A THREAD TO PULL:
UNRAVELING THE COMPLEXITIES
OF MYELOID MALIGNANCIES**
December 9
Live stream

2023

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**THE BEST OF SAN ANTONIO BREAST CANCER
SYMPOSIUM**
January 14
Hollywood, FL

FEBRUARY

**VALVE DISEASE, STRUCTURAL
INTERVENTIONS, AND DIASTOLOGY SUMMIT**
February 2–5
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INHIBITOR-RELATED TOXICITY**
February 9–10
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SUMMIT**
February 16–18
Orlando, FL

**BASIC AND CLINICAL IMMUNOLOGY
FOR THE BUSY CLINICIAN**
February 25–26
Scottsdale, AZ

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**COMPREHENSIVE CARE
FOR THE LIFETIME TREATMENT
OF ADULT CONGENITAL HEART DISEASE**
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MAY

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Spontaneous oral hematoma diagnosed as angina bullosa hemorrhagica

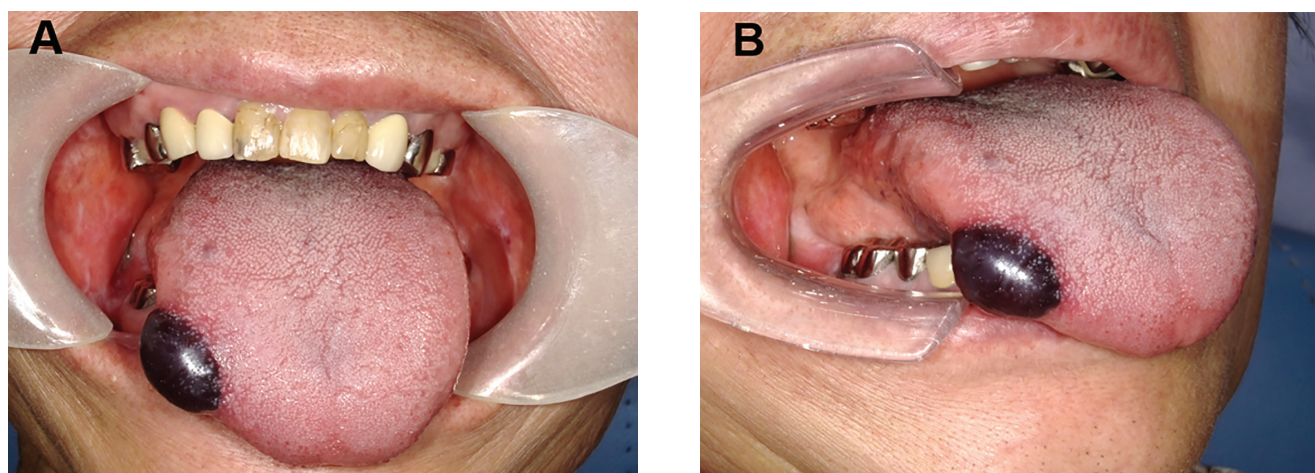


Figure 1. Oral findings at the first visit. (A) Front view. (B) Side view. A well-defined, round, dark purple mass was seen on the right lateral border of the tongue.

A 55-YEAR-OLD WOMAN presented 1 hour after noticing tongue discomfort while eating. On self-examination, she had noticed a rapidly expanding dark purple mass. She had experienced similar episodes previously, but in each case, the mass had ruptured in a day or 2 and healed within a week.

The patient had no significant medical history. On examination, a dark purple mass was noted (**Figure 1**). Results of blood tests were normal, and bleeding diathesis was ruled out. The patient was diagnosed with angina bullosa hemorrhagica and advised that it may recur in other parts of the oral cavity and pharynx, could cause dyspnea if in the pharynx, and caution should be exercised.

After returning home, the patient pressed her

tongue against her teeth; the mass ruptured, and a slightly painful erosion formed that spontaneously healed without scarring after approximately 2 weeks.

■ FEATURES OF ANGINA BULLOSA HEMORRHAGICA

Angina bullosa hemorrhagica is a condition with unknown etiology, in which hemorrhagic blisters (hematomas) spontaneously arise in the oral cavity, regardless of blood abnormalities or systemic diseases.¹ It frequently occurs on the soft palate, buccal mucosa, and tongue, and only rarely on the masticatory mucosa such as the gingiva and hard palate. The lesions predominantly occur in middle-aged and older individuals, and only rarely in children.¹⁻⁵

Angina bullosa hemorrhagica frequently occurs

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during or immediately after ingestion of hard foods and hot beverages, which may result in trauma to the mucous membranes.² Studies have also reported lesions in patients with a history of inhaled corticosteroid use, fragility of blood vessels, diabetes, and hypertension.^{3,5}

The differential diagnosis includes dermatoses that present as mucocutaneous bullous lesions, such as pemphigus vulgaris, mucous membrane pemphigoid, bullous pemphigoid, amyloidosis, acquired epidermolysis bullosa, linear immunoglobulin A dermatosis, herpetiformis dermatitis, and oral bullous lichen planus, as well as hematologic diseases such as leukemia, thrombocytopenia, and von Willebrand disease.^{1,2}

Angina bullosa hemorrhagica is benign and often heals spontaneously, so no specific treatment is required.¹⁻⁵ However, airway obstruction due to hematoma has been reported.⁴ In particular, soft-palate hematomas should be incised and drained to avoid a possible obstruction of the upper aerodigestive tract.^{1,5} In addition, owing to frequent recurrence and unknown etiology, follow-up to avoid misdiagnosis is needed.

DISCLOSURES

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

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REVIEW

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Geriatric update 2022: Preventing Alzheimer disease and more

ABSTRACT

Articles published in 2020 and 2021 contain important research related to preventing Alzheimer dementia; the relationships between frailty, social isolation, and mortality; COVID-19 risks in patients with dementia; hospital-at-home programs; deprescribing antihypertensive drugs; bisphosphonate-related atypical femoral fractures; and cannabis use in older adults.

KEY POINTS

Factors that seem to protect against Alzheimer dementia include aggressive cardiovascular risk-factor modification (best applied at midlife, with diminishing returns after age 75), good sleep, regular physical exercise, cognitively stimulating activities, avoidance of head trauma, and timely intervention for depression—but not aspirin in low daily doses.

Patients with dementia are at increased risk for SARS-CoV-2 infection, and Black patients with dementia are more likely to be infected than White patients with dementia.

Dementia is an independent risk factor for morbidity and mortality in COVID-19.

Deprescribing 1 antihypertensive medication in older adults taking multiple blood pressure medications is not associated with significant changes in blood pressure control.

The risk of atypical femur fractures with bisphosphonate use is much lower than the benefits in fracture reduction.

■ PREVENTIVE HEALTH IN OLDER ADULTS

Ellen is a 65-year-old retiree with hypertension that is well controlled on medications. She takes aspirin and a statin for “good health.” Ellen’s mother has Alzheimer dementia, and Ellen is concerned about her own risk of developing it and asks, “What should I be doing to minimize my risk? Are my medicines helping with this?”

Evidence-based prevention of Alzheimer dementia

Yu et al¹ conducted a large systematic review and meta-analysis grading the evidence for risk factors and preventive measures for Alzheimer dementia. Included in the analysis were 243 prospective observational studies and 153 randomized controlled trials, representing a multiethnic population across 5 continents. Of the patients, 82% were free of dementia at baseline.¹

From analyses of 134 factors came 21 evidence-based recommendations, all carrying levels of evidence of either A (high) or B (intermediate); 19 were strong recommendations while 2 were negative, ie, not recommended. All 21 recommendations are either level A or B, and 19 were rated as strong, with 2 rated not recommended. Of the 19, notable recommendations include weight loss for adults under 65 (with avoidance of weight loss for those over 65), regular physical and cognitive exercise, avoidance of metabolic disease (diabetes, hypertension) via lifestyle, and preservation of restful sleep and mental health. Recommendations also include close cognitive monitoring for patients with diabetes, weight loss in older age, cerebral athero-

sclerosis or microbleeding, orthostatic hypotension, and depression. This meta-analysis concludes recommending against routine use of estrogen replacement in postmenopausal women and acetylcholinesterase inhibitors for prevention of Alzheimer dementia.¹

Protective factors include aggressive cardiovascular risk-factor modification (which seems to have the most impact in midlife, with diminishing returns beyond age 75), good-quality sleep, timely intervention for depression, avoidance of head trauma, regular physical exercise, education in early life, and continuing cognitively stimulating activities.

There is strong support for deprescribing aspirin in adults older than 70 who are taking it for primary prevention

This meta-analysis does not say exactly how much sleep, exercise, and cognitively stimulating activity patients should get. However, the 2019 World Health Organization Risk Reduction of Cognitive Decline and Dementia guidelines² recommend at least 150 minutes of moderate aerobic activity per week and resistance training at least twice per week. Also, studies in the United States have demonstrated a higher risk of dementia in people who slept 5 or fewer hours per night in midlife and early older adulthood, suggesting the optimal duration of sleep for cognitive health is 7 to 8 hours per night.³

Comment. Providers can help patients tailor prevention efforts to their individual needs and stage of life.

Aspirin does not appear to prevent cognitive decline

Ryan et al⁴ published a secondary analysis of the ASPREE (Aspirin in Reducing Events in the Elderly) randomized controlled trial, looking specifically at aspirin use and the development of cognitive impairment. ASPREE⁵ was a 4.7-year, double-blind, placebo-controlled trial in 19,114 healthy community-dwelling adults age 70 and older from the United States and Australia. They were divided into 2 groups, receiving either daily low-dose aspirin (100 mg/day) or placebo. All patients in the aspirin group were newly initiated on low-dose aspirin for the study.

The original ASPREE trial found no difference in disability-free survival and an increased risk of intracerebral hemorrhage in the aspirin group.⁵ The secondary analysis by Ryan et al was done to test the hypothesis that aspirin for cardiovascular primary prevention could reduce the risk of cognitive impairment.⁴

All patients underwent cognitive screening with the Modified Mini-Mental State Examination at enrollment and every other year starting at year 1 by trained study staff. In response to any of 4 cognitive “triggers”—a positive screening test, report of memory concerns, new formal dementia diagnosis, or a new prescription for an acetylcholinesterase inhibitor—they then underwent brain imaging, laboratory tests, and review of clinical notes from their providers. All this information was reviewed by a blinded panel of dementia specialists, and each case was adjudicated as being either probable Alzheimer dementia, possible Alzheimer dementia, mild cognitive impairment, or other cognitive decline or change.

There was no difference in the incidence of Alzheimer dementia, mild cognitive impairment, or other cognitive decline between those taking low-dose aspirin or placebo at 7 years of follow-up.⁴ Although longer follow-up may have captured more cases of cognitive impairment, we believe that 7 years should have been sufficient to see a difference in cognitive outcomes. Subgroup analyses based on demographics and comorbid conditions also showed no difference in any cognitive outcomes. However, the absolute incidences of dementia and mild cognitive impairment in this cohort were lower than had previously been reported in other observational studies.

Comment. This study demonstrated that low-dose daily aspirin does not affect the risk of Alzheimer dementia, mild cognitive impairment, or other cognitive decline. These results are in line with those of other randomized controlled trials and meta-analyses.^{6,7} Previous observational studies suggested that low-dose aspirin had a protective effect, but randomized controlled trials have not borne this out. Coupled with the original ASPREE results showing that aspirin did not prolong disability-free survival and led to a higher rate of major hemorrhage than with placebo, there is strong support for deprescribing aspirin in adults over age 70 who are taking it for primary prevention.

Statins for primary prevention: Time needed to treat

Yourman et al⁸ performed a meta-analysis of 8 studies and 65,383 participants from the original major studies of statins for primary prevention of major adverse cardiovascular events (MACEs), extracting data on how long it takes to see a benefit in adults ages 50 to 75. It is well established that statins prevent MACE in this age group, but the time to benefit was not known. Time to specific absolute risk reduction was obtained from statistical simulations.

This was independent of low-density lipoprotein cholesterol levels achieved.

The time needed to prevent 1 MACE in 100 patients treated with a statin was 2.5 years, varying across individual study populations. The time needed to prevent 1 MACE in 200 people was 1.3 years, and for 500 people it was 0.8 years. The benefit of statin therapy increased with longer follow-up: for 100 people treated with a statin for primary prevention, 0.3 MACEs were prevented at 1 year, 1.3 at 3 years, and 2.5 by 5 years. Statins did not affect all-cause mortality rates.⁸

Comment. This study provides important information to help guide discussions on the risks and benefits of statin therapy for primary prevention. For those with frailty or life-limiting conditions in midlife to later life, the lag time to benefit from statins for primary prevention may not support their use.

What does this mean for Ellen?

Ellen's use of medications to control her blood pressure and prevent cardiovascular disease in midlife helps reduce her risk of Alzheimer dementia. Incorporating more exercise and mentally stimulating activities into her routine and maintaining good sleep and mental health would further reduce her risk. She is an excellent candidate for aspirin deprescribing to reduce her risk of bleeding, since it has no impact on her risk of developing Alzheimer dementia later in life.

■ SOCIAL ISOLATION, LONELINESS, AND THE COVID-19 PANDEMIC

Esther is an 87-year-old African American woman with dementia who lives in assisted living. During the first 6 months of the COVID-19 pandemic, her daughter was not allowed to visit her at all. The assisted living facility had 2 outbreaks of the virus, and Esther became much more withdrawn. Her daughter notes, "She's just a shell of herself. So many of her friends have died this year, and it seems like her community and people with dementia have been affected much more." What have been the consequences of COVID-19 pandemic on older adults?

Many older adults experienced 2 pandemics: the disease itself, and the social isolation due to the lockdowns and shelter-in-place orders imposed to control the spread of the virus. This was particularly true of older adults in long-term care settings and those with dementia.

Social isolation during shelter-in-place orders

Kotwal et al⁹ examined the impact of social isolation

and loneliness in older adults during shelter-in-place orders in a longitudinal study in San Francisco, CA. The researchers telephoned the participants (patients in an academic medical center outpatient and home-based geriatrics setting and at 2 community sites) every 2 weeks from March 2020 to June 2020 and administered a survey.

Loneliness was measured by asking participants if their loneliness was "worse," "about the same," or "better" due to COVID-19, and was graded in severity using the validated 3-item UCLA Loneliness Scale (range 0–6 points; 3+ categorized as high loneliness). Social support was measured using the Modified Duke Social Support Index social interaction subscale (range 0–17; with 6 or less categorized as socially isolated).⁹ This scale measures the number of local contacts a person feels close to or can depend on, the frequency of participation in community activities in the past week, and the frequency of social interaction by telephone, video, internet, or in person.

Many older adults experienced 2 pandemics: the disease itself, and the social isolation due to lockdowns and shelter-in-place orders to control spread of the virus

The researchers reached 151 community-dwelling older adults, with an overall response rate of 40%.⁹ Their mean age was 75, 65% were female, 8% were Black, and 8% were Asian. Overall, 64% of participants lived alone, and many had significant functional impairment, with 50% reporting hearing or vision impairment and 26% reporting difficulty bathing.

The most common form of social interaction was by telephone, with 43% of participants reporting daily telephone socialization. In contrast, there was much less video-based or Internet-based socializing, with 46% of participants reporting no video-based socialization at all and 26% reporting no Internet-based socializing.⁹

Overall, 40% of older adults had social isolation and few social interactions, and 54% had worsened loneliness due to the pandemic. Notably, loneliness levels remained stable or improved from March to June 2020. This suggests resilience and an ability to adapt in many older adults. However, a notable subset experienced persistent or worsened loneliness over time. In these participants, loneliness was strongly associated with worsening of depression and anxiety and worries about coronavirus and general health.

Combined effects of frailty and social isolation or loneliness

Frailty is a well-known predictor of death in older adults, and loneliness itself is associated with increased morbidity and mortality. But what if you have both?

Hoogendijk et al¹⁰ examined the combined impact of frailty and loneliness or social isolation on mortality as part of the larger Longitudinal Aging Study in Amsterdam, The Netherlands. This cohort study followed 1,427 community-dwelling adults age 65 and older for 22 years (1995–2017). Frailty was measured with the Fried criteria: weight loss, low grip-strength, exhaustion, slow gait-speed, and low physical activity. The respondents completed a medical interview with questions about loneliness and social isolation.

The overall prevalence of frailty was 13%.¹⁰ There was substantial overlap between frailty, loneliness, and social isolation, though 43% of the sample had none of these conditions. However, 5.9% of respondents were frail and lonely, and 6.2% were frail and socially isolated.

As expected, older adults who were frail had a higher risk of death than people without any of the conditions (hazard ratio range 1.40–1.48, $P < .01$ in 2 different analyses). However, frailty combined with loneliness or social isolation conferred the highest risk of death. In those who were frail and lonely, the hazard ratio was 1.83 (95% confidence interval 1.42–2.37); for those who were frail and socially isolated it was 1.77 (95% confidence interval 1.36–2.30) compared with people without any of these conditions.¹⁰

Comment. This study demonstrated that frailty by itself is associated with increased mortality risk, and frailty in combination with either loneliness or low social support further increases mortality. This is a call to action for extra attention and interventions in this vulnerable group of older adults, including outreach to reduce social isolation.

COVID-19 and dementia

The toll of the COVID-19 pandemic on older adults has been devastating, but it has been catastrophic on those with dementia. There are many reasons why the risk of COVID-19 would be different for people with dementia, including difficulty complying with preventive measures such as hand-washing, mask-wearing, and social distancing, due to cognitive impairment. Many older adults with dementia live in high-risk settings such as assisted living or memory care facilities or have visiting home health workers, and thus are at greater risk of exposure to the virus. Additionally, many people with dementia require hands-on care for

their essential activities of daily living such as bathing, in which social distancing is impossible.

Wang et al¹¹ sought to document if people with dementia are at higher risk of contracting COVID-19 and to quantify that increased risk. Additionally, they examined risk of adverse outcomes and death due to COVID-19 in people with dementia and examined disparities by age, sex, and race.

This case-control study, conducted in August 2020, used de-identified, standardized electronic health record data from the IBM Watson Health Explorys database, which includes data from 61 million adult patients (20% of the US population), 360 hospitals, and 317,000 providers across all 50 US states. Cases and controls were identified as of August 21, 2020, which was the first wave of the pandemic, before vaccines were developed. From this large database, they identified 1 million patients with dementia, 15,770 with COVID-19, and 810 with both dementia and COVID-19.¹¹

Patients with dementia had a significantly higher risk of COVID-19 compared with people without dementia (adjusted odds ratio 2.00, 95% confidence interval 1.94–2.06, $P < .001$), after accounting for age, sex, race, comorbidities, or having a nursing home stay. Strikingly, there was a significant racial disparity, with Black patients with dementia more likely to have COVID-19 than White patients with dementia (adjusted odds ratio 2.86, 95% confidence interval 2.67–3.062, $P < .001$).¹¹

The risks of morbidity and death with COVID-19 were also increased in patients with dementia. In patients with COVID-19 and dementia, 59% were hospitalized, compared with 23% of COVID-19 patients without dementia ($P < .001$). The rate of hospitalization was also higher in Black patients (73%) than in Whites (54%; $P < .01$). The 6-month mortality rate for patients with COVID-19 and dementia was 21%, compared with 4.8% ($P < .001$) in those without dementia.¹¹

This study demonstrates that patients with dementia have substantially higher risks of contracting COVID-19 and dying of it. Of note, this study was conducted in August 2020, before any COVID vaccine was available. While the current widespread availability of vaccines may temper the high mortality rate somewhat, differential rates of vaccination by race may still lead to disparities in severe illness and mortality from COVID. Additionally, the current variants of the SARS-CoV-2 virus are more easily transmissible, even among vaccinated individuals.

Comment. This study highlights the need for public health level solutions to improve dementia care, address racial disparities, and ensure equitable access to vaccines in both the general population and in long-term care settings to reduce the risk in vulnerable older adults with dementia.

What does this mean for Esther?

The great toll of the pandemic that Esther's daughter noticed is real. People with dementia, such as Esther and others in her assisted living facility, had much higher risks of contracting COVID-19 and dying of it than those without dementia. Getting vaccinated, including getting booster doses, is the best way for Esther to reduce her risk of getting severely ill or dying from COVID-19.

■ SHIFTING HEALTH CARE TO THE HOME

Robert is an 83-year-old man who was admitted to the hospital for community-acquired pneumonia. Before his hospitalization, he could walk with a cane. After several days in the hospital, he was having difficulty with transfers and was discharged to a rehabilitation facility. He reports feeling depressed after being unable to see his family for almost 1 month due to COVID-19 visitation restrictions and wishes he could have received his care at home. Could his hospital and postacute rehabilitation care have been provided in the home?

Hospitalized older adults are at risk of functional decline and complications such as delirium, falls, incontinence, and pressure ulcers.¹² The COVID-19 pandemic has accelerated the shift of healthcare services away from the hospital and other healthcare settings to the home, driven by patient and family desire for in-home care, the expansion of telehealth, and changes in reimbursement.

In November 2020, the Centers for Medicare & Medicaid Services implemented a waiver program that reimburses home-hospital services at the same rate as in-hospital services, leading to an increase in hospital-at-home programs.¹³ The waiver is in effect for the duration of the COVID-19 public health emergency. A bipartisan bill has been introduced in both the US Senate and the House of Representatives that, if passed, would extend the acute hospital care at home waiver.¹⁴

Hospital at home

Levine et al¹⁵ conducted a randomized controlled trial comparing hospital-level care at home and traditional hospital care. The primary outcome was the cost of the acute care episode.

Eligible participants were age 18 or older, lived within the catchment area, had capacity to consent, and had a primary diagnosis of one of several prespecified conditions, including any infection or exacerbation of congestive heart failure, asthma, or chronic obstructive pulmonary disease. Exclusion criteria were residing in a nursing home, high risk for clinical deterioration, need for advanced imaging or procedure, need for routine administration of controlled substances, or need for the assistance of more than 1 person to reach the bedside commode.¹⁵

They enrolled 91 patients, with a median age of 80 in the home group and a median age of 72 in the hospital group. Participants in the home group received at least 1 daily physician visit and 2 daily registered nurse visits, along with additional visits or services as needed (eg, home health aide, physical therapy). Participants in the control group received usual care in the hospital.

Acute inpatient-level care can be safely provided in the home at lower cost, with better patient outcomes and lower readmission rates

The adjusted mean cost of the acute care episode was 38% lower in the home group than in the hospital group ($P < .001$). The home patients underwent less imaging (14% of patients vs 44%), they had fewer laboratory orders per admission (3 vs 15), and they had fewer consultations (2% of patients vs 31%). None of the home patients were transferred back to the hospital during the acute care episode. Home patients had lower 30-day readmission rates (7% vs 23%). Home patients were less sedentary (12% vs 23% of the day) and spent a lower percentage of the day lying down (18% vs 55%).¹⁵

In a qualitative evaluation of the study, home patients described better continuity of care, positive experiences with technology, and more factors promoting healing, including environmental comfort, better sleep, and more physical activity.¹⁶

A limitation of this study was that it was stopped early by the supporting institution to increase the capacity of their home hospital program after interim positive results, resulting in a smaller sample size and limited ability to assess secondary outcomes. The study was conducted with a small number of home physicians at 2 sites within a single healthcare system, which may limit its generalizability. Another notable limitation of the study was that 63% of eli-

gible patients did not enroll in it, largely because the patient or family declined to participate.¹⁶ This differs from other hospital-at-home studies, in which the acceptance rates were over 60%.^{17,18}

Saenger et al¹⁹ evaluated reasons patients agreed or declined to participate in a hospital-at-home program. In their study, 66.7% accepted hospital-at-home care, and those who accepted were older and more likely to be female and have Medicaid or dual-eligible status. Reasons for accepting hospital-at-home care included being more comfortable at home (78%), liking having family around (41%), and being able to do things at home (36%). Of those who declined hospital-at-home care, 35% did not give a specific reason, 15% preferred to receive care in the hospital, and 13% were concerned that hospital-at-home care would be insufficient to meet their care needs.¹⁹

Comments. The randomized controlled trial by Levine et al¹⁵ adds to the growing literature demonstrating that acute inpatient-level care can be safely provided in the home at lower cost with better patient outcomes, including lower readmission rates. Previous studies have shown higher patient and family satisfaction with hospital-at-home, lower rates of delirium, and fewer admissions to skilled nursing facilities after hospitalization.^{17,18,20}

Post-acute rehabilitation at home

Augustine et al²¹ conducted a single-arm retrospective review of patients participating in a rehabilitation-at-home program. Their intervention was a 30-day bundle including an active phase of home-based medical and rehabilitation services typically delivered in a skilled nursing facility and a transitional phase of care coordination. Primary outcome measures were functional mobility and global function. There were 237 participants, with a 89% rate of acceptance and a mean age of 84.2

Average length of stay in the active phase was 14.2 days, and 55% of patients fully or almost fully met their highest functional goal. The hospital readmission rate was 20% within 30 days. Notably, 87.3% of participants were still living at home at 30 days.²¹

The most significant limitation of this study was that it was a single-arm study and did not directly compare rehabilitation at home with postacute skilled nursing facility or home healthcare, although as noted the readmission and mortality rates were comparable.

Comment. This study showed that rehabilitation at home is feasible and desired by patients, but further studies are necessary to evaluate quality outcomes and cost.

What does this mean for Robert?

Robert would have qualified for hospital at home with his diagnosis of community-acquired pneumonia, receiving his care in his home and not being separated from his family. He would have been less likely to require skilled nursing facility placement for rehabilitation.

Although there are an increasing number of hospital-at-home programs, they are not available in all areas. As of September 30, 2022, Centers for Medicare & Medicaid Services has approved 256 hospitals in 37 states to provide acute hospital care at home under the waiver.²²

MEDICATIONS AND OLDER ADULTS

An 81-year-old woman with hypertension and osteoarthritis presents to establish care. She was recently hospitalized due to a hip fracture, which she feels occurred because she was light-headed. Her son is with her and is concerned about his mother's medication regimen, which includes lisinopril, amlodipine, hydrochlorothiazide, rosuvastatin, and acetaminophen with oxycodone. He also asks about whether she should take bone-strengthening medications because of the hip fracture, but the patient has expressed unwillingness in the past due to the risk of the femur fractures she has read about in the news.

Deprescribing antihypertensive drugs

Sheppard et al,²³ in a British study in adults age 80 or older who were taking more than 1 antihypertensive medication, found that eliminating 1 medication did not substantially change the target mean systolic blood pressure less than 150 mm Hg after 12 weeks of follow-up. The study excluded those with a history of heart failure due to left ventricular dysfunction, myocardial infarction, or stroke in the preceding 12 months, secondary hypertension, or inability to consent. The study included 569 participants (48.5% women, mean age 84.8), chosen by their primary care providers as likely able to benefit from deprescribing.

Participants were randomized to the 1-drug reduction arm or to usual care. An algorithm for the order of reduction was provided (first calcium channel blockers, then angiotensin-converting enzyme inhibitors, then thiazide diuretics), but the practitioner was not bound by the algorithm. If a beta-blocker or alpha-blocker was to be eliminated, the suggestion was to reduce it gradually.

Sixty-six percent of participants were able to complete this unblinded prospective study. At baseline, the mean systolic blood pressure was 129.4 mm Hg in the reduction group and 130.5 mm Hg in the usu-

al-care group. At the end of 12 weeks, this had risen to 133.7 mm Hg in the reduction group and 130.8 mm Hg in the usual-care group ($P = .005$), but without clear clinical significance. As for the primary outcome, 86.4% of the patients in the reduction group and 87.7% of those in the usual-care group still had blood pressure lower than 150 mm Hg; the difference was not statistically significant.²³

The study length was short, and the authors emphasized that this was a noninferiority trial in a very old population and that long-term outcomes should be analyzed in future studies.²³

Bisphosphonates and risk of atypical femur fracture

Clinicians and patients are often concerned about the risk of atypical fractures associated with the use of bisphosphonates.

Black et al²⁴ used data from patients enrolled in Kaiser Permanente of Southern California to determine the rate of atypical femur fractures in women who used bisphosphonates for any length of time between January 1, 2007, and November 30, 2017. The database included 196,129 women. They discovered 277 atypical femur fractures, for an overall rate of 0.0014%. Exposure ranged from 3 months to over 8 years.

The highest atypical femoral fracture rate (13.1 per 10,000 patient-years) was in those who took a bisphosphonate for more than 8 years. Of those who took bisphosphonates between 5 and 8 years, the rate was 6.04 per 10,000 patient-years. Asian women were at a higher risk than White women (5.95 vs 1.09 per 10,000 patient-years), although the risk was still low. The risk of atypical femur fracture decreased precipitously at 3 months after discontinuation and remained low thereafter.²⁴

This study showed that the absolute risk of atypical femur fracture was very low compared with reductions

in the risk of hip and other fractures with initial bisphosphonate treatment. As the authors pointed out, “Among Whites, the number of fractures prevented for each fracture type far outweighed bisphosphonate-associated atypical fractures at all time points. For example, after 3 years, there were 2 bisphosphonate-associated atypical fractures as compared with 149 hip fractures prevented and 541 clinical fractures prevented.”²⁴

Cannabis use in older adults

Yang et al²⁵ asked all patients age 65 and older presenting to a geriatrics clinic at the University of California-San Diego during 1 week in 2019 to complete an anonymous survey on personal marijuana use, both tetrahydrocannabinol (THC) and cannabidiol (CBD) products.

They found a 15% rate of use (83 of 568 respondents), with 50 respondents stating that they started as an older adult. Forty-six percent reported CBD use only. The remainder either did not know what they were using, used only THC, or used both THC and CBD. Reasons for use included pain, insomnia, and anxiety. The most common side effect ($n = 5$) was dizziness. Three people stated that no one knew about their use, and 34 said that their healthcare provider knew.²⁵

Maxwell et al²⁶ report similar trends from the Behavioral Risk Factor Surveillance System in the United States. They advise researchers and clinicians to be more attentive to potential cannabis use in older adults and call for clinical trials to study the effects on this population.

DISCLOSURES

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

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SYMPTOMS TO DIAGNOSIS

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Hypophosphatemia in a patient with an eating disorder

A 32-YEAR-OLD WOMAN PRESENTED to the emergency department for hypophosphatemia. She had a history of an eating disorder and had recently started treatment at an inpatient eating disorder treatment center. There, her electrolyte levels were screened routinely. She had visited the emergency department twice within the previous 3 weeks because of hypophosphatemia as low as 1.0 mg/dL (reference range 2.5–4.5). On both occasions, this laboratory finding had been detected with screening at her care facility, and she had been discharged from the emergency room following phosphorus repletion.

On this presentation, her only symptoms were mild fatigue, poor short-term memory, and 1 week of intermittent diarrhea that began only after she started taking oral potassium phosphate 500 mg 3 times daily. She described memory difficulty over 1 to 2 weeks, noting trouble with concentration and feeling “hazy.” She had a history of bulimia nervosa, but no recent vomiting or laxative or diuretic use.

MEDICAL HISTORY

Her medical history included iron deficiency anemia thought to be secondary to heavy menses. Two months earlier, blood testing had shown the following results:

- Hemoglobin 10.8 g/dL (reference range 11.5–15.7)
- Mean corpuscular volume 79 fL (80–100)
- Red blood cell distribution width of 14.5% (11.5–14.5%)
- Normal white blood cell and platelet counts
- Ferritin 12.3 ng/mL (13.0–150.0).

The patient had not tolerated oral iron due to gastrointestinal side effects and had received intravenous ferric carboxymaltose 3 weeks and 1 week prior

to presentation. Her only medication was oral potassium phosphate 500 mg 3 times daily, which had been started after her second emergency department visit. She had no notable family history of kidney problems or gastrointestinal disease.

ELECTROLYTE ABNORMALITIES

1 Which of the following is not a common electrolyte abnormality associated with vomiting and bulimia nervosa?

- ☐ Hypokalemia
- ☐ Hypophosphatemia
- ☐ Hyponatremia
- ☐ Hypernatremia

Recurrent vomiting associated with bulimia nervosa leads to loss of stomach acid, composed primarily of hydrochloric acid. Its loss leads to increased serum pH and hypochloremia. Hypochloremia in turn blocks renal bicarbonate excretion by inhibiting the activity of the bicarbonate-chloride exchange channel present in the collecting duct epithelium, causing increased serum bicarbonate and metabolic alkalosis.¹ In response to the elevated serum bicarbonate, hydrogen shifts to the vascular space to buffer the bicarbonate, and there is a subsequent intracellular shift of potassium to balance the electrochemical gradient.^{2,3} Hypokalemia can result.

Hypernatremia would be an unexpected electrolyte abnormality associated with vomiting and bulimia nervosa. Gastrointestinal losses such as vomiting and diarrhea commonly lead to a hypovolemic hypotonic hyponatremia due to extrarenal losses of sodium and subsequent water reabsorption.⁴ Therefore, hyponatremia would be a more typical finding than hypernatremia.

■ REFEEDING SYNDROME

Refeeding syndrome can result in hypophosphatemia and hypokalemia, and patients with bulimia are at increased risk of this condition. Refeeding syndrome is marked by varying electrolyte and metabolic abnormalities after the reintroduction of food, either orally or via artificial nutrition, after an extended period of low intake.⁵ There is no universal definition of refeeding syndrome, making it difficult to diagnose or study.⁶

A person with malnutrition needs energy to maintain essential cellular functions, so the body uses stores of phosphate found mainly in bone and soft tissue to generate adenosine triphosphate.⁷ With the reintroduction of food in an energy-depleted state, the accompanying increase in insulin leads to intracellular shifting of both potassium and phosphorus in the setting of total body electrolyte depletion.⁵ This precipitated drop in phosphorus can result in clinical manifestations of refeeding syndrome, such as respiratory distress from muscular dysfunction, and hypotension and arrhythmias from cardiac dysfunction.⁵ The drop in phosphorus can also cause decreased production of 2,3-diphosphoglycerate, leading to tighter oxygen affinity by hemoglobin and ultimately to tissue hypoxia.⁵ Thus, the clinical manifestations of severe hypophosphatemia can include sequelae from depletion of adenosine triphosphate and tissue hypoxia, with metabolic encephalopathy, cardiac arrhythmias, respiratory muscle weakness, proximal myopathy, rare cases of rhabdomyolysis, and hemolytic anemia.^{5,6}

■ LOSING PHOSPHORUS

On arrival at the emergency department, the patient's blood pressure was 119/74 mm Hg, her heart rate was 74 beats per minute, and her body mass index was 24 kg/m². She had no muscle weakness or tenderness, her cardiac examination was normal with no extra heart sounds or signs of heart failure, and she had normal respiratory effort. Neurologically, she was alert and oriented, with no paralysis or paresthesia, but she reported impaired ability to recall recent events without overt confusion.

Her phosphorus level was still low at 1.6 mg/dL, but her potassium, bicarbonate, calcium, magnesium, and creatinine levels were normal. A complete blood cell count showed normal white blood cell and platelet counts. The hemoglobin was 11.1 g/dL with a mean corpuscular volume of 81.2 fL and a red blood cell distribution width of 17.2%.

The patient was given 45 mmol of intravenous sodium phosphate and admitted to the internal medicine floor. Glucose was not administered.

2 Where is most phosphorus reabsorbed by the kidney?

- ☐ Proximal convoluted tubule
- ☐ Loop of Henle
- ☐ Collecting duct
- ☐ Distal collecting duct

Phosphorus is unique among clinically relevant electrolytes in that nearly all reabsorption occurs in the proximal convoluted tubule alone.⁸ This aspect of renal phosphate handling has two significant clinical applications:

- Commonly used medications that act in other parts of the nephron, such as loop or thiazide diuretics, do not cause phosphorus dysregulation
- Proximal tubular dysfunction leading to hypophosphatemia usually manifests as Fanconi syndrome, which results in a recognizable set of other electrolyte and urinary changes such as a nonanion gap metabolic acidosis, hypouricemia, mild proteinuria, glucosuria, and hypokalemia.

■ LOW PHOSPHORUS DESPITE REPLETION

The patient's history of an eating disorder initially suggested a diagnosis of refeeding syndrome leading to hypophosphatemia. She was put on a phosphorus-rich diet with aggressive repletion of phosphorus. On the date of admission, she received 150 mL of oral phosphorus solution and 45 mmol of intravenous sodium phosphate. The following day, she received 60 mL of oral phosphorus solution and 18 mmol of intravenous potassium phosphate. On the third day, she received 30 mmol of intravenous sodium phosphate and 18 mmol of intravenous potassium phosphate.

Phosphorus repletion must be done with caution, particularly when given intravenously. Intravenous phosphorus can precipitate with calcium, leading to hypocalcemia, arrhythmias, and calcium-phosphate crystal formation in the kidneys. Therefore, repletion in this patient involved a combination of oral and intravenous routes with twice-daily monitoring to avoid overrepletion. General guidelines for oral repletion of hypophosphatemia above 1 mg/dL are to give 1,000 to 2,000 mg per day divided into 3 doses.⁹ The maximum recommended regimen for intravenous phosphate repletion for patients with normal calcium levels and renal function is 0.64 mmol/kg of elemental phosphorus given over 6 to 8 hours.⁹

Repeat phosphorus levels remained low, between 1.6 and 2 mg/dL, despite ongoing repletion. Urinalysis did not show proteinuria or glucosuria. There was less concern about fasting or postprandial phosphorus level changes because patients with normal renal function have a maximal postprandial increase of 5% at 3 hours after eating.¹⁰ While insulin drives intracellular shifting of phosphorus in the postprandial state, patients without renal impairment can balance phosphorus to prevent large swings in serum phosphorus levels. In patients with chronic kidney disease, serum phosphorus level changes are more pronounced, with phosphorus levels decreasing about 7% postprandially.¹⁰

■ MEDICATION AND HYPOPHOSPHATEMIA

3 Which of the following medications is not associated with renal phosphorus wasting?

- ☐ Cisplatin
- ☐ Spironolactone
- ☐ Acetazolamide
- ☐ Intravenous iron

Spironolactone acts in the collecting duct where phosphorus is not significantly reabsorbed, so it is not associated with renal phosphorus wasting. Since most phosphorus is absorbed in the proximal tubule, acetazolamide has a large phosphaturic effect.⁷ Its phosphaturic effect is thought to be linked to either a direct effect on the reabsorption of phosphorus in the distal tubule, or more likely via the inhibition of carbonic anhydrase, causing lowered cotransport of sodium and phosphate in the proximal tubule.⁷ Cisplatin can cause a proximal tubular injury, leading to phosphorus wasting.¹¹ Intravenous iron can cause phosphorus wasting. Hypophosphatemia is more associated with the ferric carboxymaltose formulation.¹²

In our patient, the absence of proteinuria or glucosuria argued against proximal tubular dysfunction. The term Fanconi syndrome denotes general dysfunction of the proximal tubule, which leads to urinary loss of several key molecules, including phosphorus, amino acids, glucose, and bicarbonate.¹³ While proteinuria in Fanconi syndrome is generally minimal, the detection of glucosuria is a key early diagnostic clue.¹³ Causes of Fanconi syndrome in adults include exposure to certain heavy metal, some forms of monoclonal gammopathy, and Sjögren syndrome.¹³ Medications that can lead to proximal tubule dysfunction include cisplatin, antiretrovirals such as tenofovir, and carbonic hydrase inhibitors such as acetazolamide and topiramate.¹³ The main features of proximal tubule

dysfunction that are most readily identifiable via laboratory workup are aminoaciduria and glucosuria, both of which were absent in this patient.¹³

■ CLOSING IN ON THE CAUSE

At this point, the hypophosphatemia had been present for almost a month, dating back to the patient's first presentation to the emergency department, and had been refractory to repletion.

In general, hypophosphatemia may be due to decreased intestinal absorption of phosphorus, diarrhea leading to phosphorus loss, internal redistribution of phosphorus (as in refeeding syndrome), and renal phosphorus loss. While the patient had a history of an eating disorder, she reported good recent oral intake without abuse of laxatives and without diarrhea to cause intestinal losses of phosphorus. Refeeding syndrome causing phosphorus redistribution had been considered initially, but her phosphorus levels remained low despite repletion.

To evaluate for renal phosphorus wasting, a 24-hour urine phosphorus excretion measurement was done. Under normal conditions, the kidney should be able to decrease phosphorus excretion significantly in response to low serum levels, so an elevated urinary phosphorus level would be unexpected with prolonged hypophosphatemia.¹⁴ The fractional excretion of phosphorus was 45% to 70% (normal is less than 20%). Additional test results included a normal 25-hydroxyvitamin D, a normal parathyroid hormone, a low activated vitamin D of 17.9 pg/mL (reference range 18–78), and a normal fibroblast growth factor 23 (FGF-23).

4 What is the most likely cause of the patient's renal phosphorus wasting?

- ☐ Primary hyperparathyroidism
- ☐ Nutritional vitamin D deficiency
- ☐ Type 2 renal tubular acidosis
- ☐ Intravenous iron-induced renal phosphorus wasting
- ☐ FGF-23–secreting tumor

The combination of recent administration of intravenous iron and elevated urine phosphorus excretion makes intravenous iron-induced hypophosphatemia the most likely diagnosis. Intravenous iron-induced hypophosphatemia results from the interaction between iron and FGF-23,^{7,12} a peptide that plays an important role in renal phosphorus handling. FGF-23 is expressed primarily by osteocytes and inhibits reabsorption of phosphorus in the proximal tubule.¹⁵

In the setting of hypophosphatemia, FGF-23 is downregulated to reduce phosphorus excretion and ameliorate serum phosphorus levels. As a rare side effect, intravenous iron can block the degradation of FGF-23, leading to increased serum FGF-23 levels. In that setting, FGF-23 then inhibits renal phosphorus reabsorption.⁸

In our patient, the normal level of FGF-23 is unexpected in the setting of low serum phosphorus and supports the diagnosis of intravenous iron-induced renal phosphorus wasting. FGF-23 also inhibits 1- α -hydroxylase expression in the kidney, leading to lower levels of activated vitamin D as seen in this patient. The low activated vitamin D levels also support intravenous iron as the culprit and can lead to a secondary elevation in parathyroid hormone that can cause phosphorus wasting.¹⁵

Primary hyperparathyroidism can decrease renal absorption of phosphorus while increasing reabsorption of calcium, but the patient's calcium and parathyroid hormone levels were normal, making this diagnosis unlikely.⁸ Vitamin D deficiency can lead to less effective phosphorus reabsorption, as activated vitamin D assists in proximal tubule reuptake of phosphorus. But the patient's 25-hydroxyvitamin D levels were normal, so a nutritional deficiency was unlikely.⁸ A type 2 or proximal renal tubular acidosis resulting from Fanconi syndrome would lead to increased excretion of phosphorus since, as noted, the proximal tubule is the main site of phosphorus reabsorption. While all causes of Fanconi syndrome present with a type 2 renal tubular acidosis, some causes of type 2 renal tubular acidosis such as familial and some sporadic forms are not associated with Fanconi syndrome.¹⁶ The patient's urinalysis did not suggest other signs of a proximal tubulopathy such as glucosuria or proteinuria, and no acidosis was present.

FGF-23-secreting tumors are very rare with fewer than 1,000 cases reported in the literature.¹⁷ These tumors typically present at age 40 to 45 and are usually of mesenchymal origin.¹⁷ FGF-23-secreting tumors can lead to renal phosphorus wasting via increased circulating levels of FGF-23 and the mechanisms listed above. More apparent symptoms of weight loss, bone pain, and fractures occur later in the disease process, but in this case an FGF-23-secreting tumor is less likely given the rarity of the condition, the younger age of the patient, and the recent usage of intravenous iron.¹⁷ When there is concern about an FGF-23-secreting tumor, positron emission tomography with a somatostatin receptor-targeting radiotracer such as gallium-68 can help localize a tumor.¹⁸

■ DIAGNOSIS REACHED

The patient was diagnosed with intravenous iron-induced hypophosphatemia given her recent history of intravenous iron infusions, persistently low phosphorus, high fractional excretion of phosphorus, and inappropriately normal FGF-23 levels. Intravenous iron-induced hypophosphatemia is most commonly associated with ferric carboxymaltose administration but may be seen less commonly with iron polymaltose and saccharated iron oxide formulations.¹⁹ Other risk factors for hypophosphatemia from intravenous iron include higher baseline renal function, lower body weight, and iron deficiency anemia caused by uterine bleeding.²⁰ Chronic kidney disease decreases the amount of filtered phosphorus, lowering the amount available to be excreted in the urine and blunting the phosphaturic side effect of high FGF-23. Therefore, patients with lower creatinine levels may be at higher risk of the side effect.¹⁷

Lower body weight has also been associated with a higher risk of developing hypophosphatemia from intravenous iron. Intravenous iron formulations are administered in fixed doses, so people with lower body weight experience a larger dose-response effect as they receive a relatively higher dose of iron.¹⁷

Intravenous iron-induced hypophosphatemia typically occurs within the first 14 days after an injection of iron, as intact FGF-23 is maximal during that time.²¹ Ferric carboxymaltose has been shown to cause persistent hypophosphatemia with a median time to resolution of 84 days.²² The mechanism by which ferric carboxymaltose and other iron formulations inhibit the cleavage of FGF-23 has not yet been discovered, making it difficult to elucidate the cause of the prolonged duration of hypophosphatemia.²³

In FGF-23-mediated hypophosphatemia, treatment includes repletion of phosphorus and correction of the inhibited vitamin D activation through calcitriol supplementation.²⁴ There are currently no therapies to alter the actions of FGF-23 on the kidney.²⁴ Repletion of phosphorus is recommended until normalization of serum levels through serial monitoring.

■ OUTCOME

After several days of phosphorus replacement, calcitriol, and a high-phosphorus diet, our patient's serum phosphorus finally rose to the normal range. Given the risk of acute phosphate nephropathy and renal failure associated with intravenous phosphorus, her renal function was monitored and stayed normal throughout the duration of inpatient treatment.²⁴ Because of

the severity of her hypophosphatemia and continued renal loss of phosphorus, a peripherally inserted central catheter was placed. She was discharged on twice-daily infusions of 30 mmol sodium phosphorus, 1,000 mg of oral phosphorus 4 times daily, and calcitriol. Two weeks later, with ongoing normal phosphorus levels, intravenous phosphorus infusions were stopped. Her oral phosphorus dosing continued over a slow taper for 4 months before finally normalizing off treatment. She has since remained off phosphorus supplements.

TAKE-HOME POINTS

- Refeeding syndrome has no universally accepted definition, screening tools, or assessment criteria, making diagnosis, management, and risk evaluation difficult.
- Bulimia nervosa is associated with several potentially severe electrolyte abnormalities, with varying symptoms related to each one. Associated hypophosphatemia is generally short-lived and treatable with replacement therapy.

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1-MINUTE CONSULT

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BRIEF
ANSWERS
TO SPECIFIC
CLINICAL
QUESTIONS

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Q: When should antithrombotic therapy be resumed after gastrointestinal bleeding?

A: RESTARTING ANTITHROMBOTIC THERAPY is recommended when indicated in patients after gastrointestinal bleeding, such as those with acute coronary syndromes or atrial fibrillation, or following percutaneous intervention.¹ However, the timing is critical, as premature re-initiation can lead to recurrent bleeding, and delayed re-initiation can increase risk of thromboembolic events.

Antithrombotic therapy decreases unfavorable outcomes secondary to underlying etiology.¹ The timing of re-initiating therapy after gastrointestinal bleeding warrants an individualized approach. The plan may be modified after consideration of factors related to the bleeding event, thromboembolic risk, and patient comorbidities.¹

■ MAGNITUDE OF THE PROBLEM

In the United States, antiplatelet and oral anticoagulant (OAC) therapy has increased considerably, from 29.5% in 2011 to 68.0% in 2017 with a sizeable contribution from increased use of novel OACs (non-vitamin K OACs) from 0.1% in 2011 to 43.5% in 2017.² Antiplatelet use has also increased, but use of clopidogrel decreased from 100% to 65% by the end of 2011 and leveled off thereafter.³ In 2013, clopidogrel still remained the most prescribed OAC, and ticagrelor had replaced a substantial portion of prasugrel.³ Use of the combination of an OAC and single antiplatelet drug (dual therapy) increased from 14.8% in 2011 to 36.3% in 2017, and use of an OAC with dual antiplatelet therapy (triple therapy) increased from 14.6% in 2011 to 31.6% in 2017.²

Bleeding commonly complicates antithrombotic

therapy. The reported incidence of bleeding associated with OAC therapy varies from 10 to 17 and 2 to 5 per 100 patient years for all bleeding complications and for major bleeding complications, respectively, depending on patient characteristics and underlying diseases.^{1,4-6} Numerous trials—eg, Management of Atherothrombosis With Clopidogrel in High-Risk Patients (MATCH),⁷ Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA),⁸ and Secondary Prevention of Small Subcortical Strokes Trial (SPS3)⁹ have shown increased risk of early bleeding with dual antiplatelet therapy compared with either separate regimen.¹⁰ Furthermore, triple therapy is associated with higher bleeding risk compared with dual therapy despite similar rates of all-cause mortality.¹¹

■ RISKS AND BENEFITS OF RESTARTING THERAPY

Although resumption of anticoagulant therapy after gastrointestinal bleeding is associated with increased risk of recurrent bleeding, it is also associated with significant decrease in thromboembolic events and all-cause mortality.¹² A number of clinical trials^{7,8,13-15} have compared agents for ideal therapy. The WOEST trial (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting?)^{13,14} reported that dual therapy caused fewer bleeding events than triple therapy, with no excess ischemic events or trade-off in efficacy.

Among OACs, novel OACs were associated with fewer bleeding events compared with vitamin K antagonists (eg, warfarin, acenocoumarol) and were as effective; hence, direct-acting OACs (eg, apixaban, dabigatran, edoxaban, rivaroxaban) are the preferred

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agents.¹³ Furthermore, current evidence also favors re-initiating antithrombotic therapy after gastrointestinal bleeding as it leads to better mortality outcomes.¹⁶ Of the P2Y₁₂ receptor inhibitors commonly used (clopidogrel, ticlopidine, ticagrelor, prasugrel, and cangrelor), clopidogrel is preferred as it is effective and has the lowest bleeding risk, followed by ticagrelor.¹³

■ TOOLS FOR DECISION-MAKING

The HAS-BLED scoring is a useful tool that has been validated for predicting bleeding risk in patients who require OACs, particularly those with atrial fibrillation or flutter.¹⁷ Points are given for hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratio (INR), age over 65, use of medications that predispose to bleeding, and consumption of alcohol. A score of 3 or higher indicates a high risk of bleeding ($\geq 5.8\%$ per year).¹³ Other scoring systems (eg, Glasgow-Blatchford,¹⁸ Rockall¹⁹) are available and may guide decision-making in specific situations.

■ TRIVIAL AND MILD BLEEDING

For trivial bleeding, antithrombotic therapy may be continued without interruption.^{20–22} For patients with mild bleeding (needing medical attention without hospital stay), dual antiplatelet therapy may be continued, but re-evaluation of the duration of therapy or switching from a stronger (eg, ticagrelor or prasugrel) to a weaker agent (clopidogrel) should be considered.^{20–22} For patients on triple therapy, de-escalating to dual therapy may be considered.^{13,20} Patients on vitamin K antagonists may be advised to postpone the next dose until the INR is less than 2.^{21,23,24} Patients on novel OAC therapy may be asked to skip one dose.²⁰

■ MODERATE BLEEDING

Moderate bleeding is defined by a hemoglobin drop of 3.2 g/dL or bleeding that requires hospitalization in a patient who is otherwise hemodynamically stable.^{21,22} For moderate bleeding, interrupting dual antiplatelet therapy and switching to a single agent, preferably a P2Y₁₂ inhibitor (eg, clopidogrel, ticagrelor) is recommended, especially in upper gastrointestinal bleeding.^{20,21,25} Dual antiplatelet therapy may be re-initiated within 3 days after gastrointestinal bleeding has stopped, but the duration of therapy may be shortened, and switching from a stronger to a weaker agent should be considered.^{20,21,25}

If using OACs, therapy should be discontinued

and vitamin K antagonists therapy should be reversed until gastrointestinal bleeding stops, unless very high thromboembolic risk is present: eg, mechanical heart valve, cardiac assist device, or a CHA₂DS₂-VASc (congestive heart failure, hypertension, age ≥ 75 , diabetes mellitus, stroke/transient ischemic attack–vascular disease, age 65–74, female sex) score of 4 or higher.^{21–23} In patients on dabigatran, activated charcoal may be used if the last dose of novel OAC is within 2 to 4 hours.²¹ OAC therapy should be re-initiated within 1 week of gastrointestinal bleeding with a direct-acting OAC at the minimum possible dose, or with a vitamin K antagonist with a target INR of 2 to 2.5.^{20,21} If the patient was on triple therapy, de-escalate to dual therapy.^{13,20–22}

■ SEVERE BLEEDING

Severe bleeding is characterized by more than a 4.8-g/dL drop in hemoglobin requiring hospitalization in a patient otherwise hemodynamically stable.²¹ In these patients, all recommendations stated for moderate bleeding may apply; however, all antithrombotic medications should be discontinued if bleeding persists despite treatment.^{20,21} The need for antiplatelets should be re-evaluated. If needed, the duration of therapy should be shortened and a weaker agent used.^{21,22}

If the patient was on OACs, stopping and reversing therapy is indicated unless there is a high risk of thromboembolic events.^{21,22} The preferred reversal agent for vitamin K antagonists is a prothrombin complex concentrate.^{21,23,26,27} Additionally, the guideline recommends against the use of prothrombin complex concentrates for novel OAC reversal (very low certainty of evidence).^{21,26,27} In patients on dabigatran, reversal may be done with idarucizumab, which acts in under 5 minutes.^{20–24,28}

Therapy with OACs should be re-initiated, only if indicated, within 1 week of gastrointestinal bleeding, with a direct-acting OAC starting at the minimum dose or a vitamin K antagonist with a target INR of 2 to 2.5.^{20–22} If the patient was on triple therapy, de-escalating to dual therapy may be considered.^{13,20,21} If the patient is on dual therapy, consider discontinuation if safe.^{20,21}

■ LIFE-THREATENING BLEEDING

In cases of life-threatening bleeding, all antithrombotic therapy should be discontinued immediately.^{20,21} If using OAC therapy, discontinue and reverse immediately.^{20,21} Re-initiation of antiplatelets in life-threatening bleeding requires additional evaluation with endoscopy and assessment of patient risk factors.^{20–22,24}

If a decision is made to restart antiplatelet therapy, a P2Y12 inhibitor should be used, especially in upper gastrointestinal bleeding. If restarting OAC therapy, low-dose apixaban is preferred.²⁰

TAKE-HOME MESSAGES

- Use an individualized approach to re-initiate anti-thrombotic therapy after gastrointestinal bleeding.
- For trivial and mild bleeding, an OAC and anti-platelet drug may be continued with adjustments in the regimen.
- When using antiplatelets for moderate or severe bleeding, periodically re-evaluate the need for these agents. If indicated, re-initiate within 3 days after gastrointestinal bleeding has stopped. However, the duration of therapy may be shortened, and switching from a stronger to weaker agent should be considered. Dual antiplatelet therapy may be switched to a single agent, preferably a

P2Y12 inhibitor.

- When using OAC drugs for moderate or severe bleeding, therapy should be re-initiated within 1 week of gastrointestinal bleeding with a direct-acting OAC, starting at the minimum dose, and with vitamin K antagonists with a target INR of 2 to 2.5. If the patient was on triple therapy, de-escalate to dual therapy.
- For life-threatening bleeding, all therapy should be stopped immediately and reversed. After endoscopic evaluation and assessment of patient risk factors, if a decision is made to re-initiate therapy with an OAC, low-dose apixaban is preferred. If restarting antiplatelet therapy, a P2Y12 inhibitor is preferred.

DISCLOSURES

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

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Update on pneumococcal vaccination in adults: Simpler is better

ABSTRACT

Recommendations for pneumococcal vaccination in adults have been updated in the hopes not only of preventing more cases of invasive pneumococcal disease but also of making the recommendations simpler and easier to follow.

KEY POINTS

Adults age 65 and older at average risk who have not yet received any pneumococcal conjugate vaccine should receive either 1 dose of 20-valent pneumococcal conjugate vaccine (PCV20), or 1 dose of 15-valent pneumococcal conjugate vaccine (PCV15) followed at least 1 year later by 1 dose of 23-valent pneumococcal polysaccharide vaccine (PPSV23).

The same recommendation applies to those age 19 through 64 at higher risk who have not yet received any pneumococcal conjugate vaccine.

Adults who previously received PCV13 should receive PPSV23 according to previous recommendations of the Advisory Committee on Immunization Practices, but PCV20 can be used in place of PPSV23 if the latter is hard to obtain.

Adults who previously received only PPSV23 may receive 1 dose of PCV20 or PCV15 at least 1 year after their last PPSV23 dose.

RECOMMENDATIONS FOR PNEUMOCOCCAL vaccination in adults have evolved as newer vaccines with different antigens have become available and the incidence of disease has fallen. This article summarizes the 2022 guidelines from the Advisory Committee on Immunization Practices (ACIP) of the US Centers for Disease Control and Prevention (CDC).^{1,2}

■ HOW THE RECOMMENDATIONS EVOLVED

Recommendations for pneumococcal vaccination in adults go back 25 years:

1997: Give 1 dose of the 23-valent pneumococcal polysaccharide vaccine (PPSV23) to adults at average risk age 65 and older.^{3,4}

2012: Give both the 13-valent pneumococcal conjugate vaccine (PCV13) and PPSV23 to adults with immunocompromising and other medical conditions that place them at higher risk of invasive pneumococcal disease.^{5,6}

2014: Expanded indications for PCV13—give it, along with PPSV23, to all adults age 65 and older.⁷

2019: Another layer of complexity—do not automatically give PCV13 to adults age 65 and older, but use a process of shared clinical decision-making to help determine who should get it in addition to the PPSV23 vaccine.^{8,9} The evolution of these guidelines over a relatively short time seemed to create a level of complexity around practice implementation and patient understanding.

2022: The ACIP revises the guidelines in the hopes not only of preventing more cases

TABLE 1

Recommendations for the initial pneumococcal vaccination in adults who have not yet received a pneumococcal conjugate vaccine

Age	19 to 64	65 and older
No risk factors ^a	None	PCV20 alone or PCV15, then PPSV23 in 1 year ^b
With risk factors	PCV20 alone or PCV15, then PPSV23 in 1 year	PCV20 alone or PCV15, then PPSV23 in 1 year

^aRisk factors include immunodeficiency, iatrogenic immunosuppression, solid-organ transplant recipient, generalized malignancy, Hodgkin disease, leukemia, lymphoma, multiple myeloma, hemoglobinopathies, asplenia, cerebrospinal fluid leak, cochlear implant, human immunodeficiency virus infection, diabetes, alcoholism, tobacco use, and other chronic diseases (heart, kidney, liver, lung).

^bIn patients with a cochlear implant, cerebrospinal fluid leak, or immunocompromising condition, an interval of 8 weeks between PCV15 and PPSV23 can be considered instead of an interval of at least 1 year.

PCV15 = 15-valent pneumococcal conjugate vaccine; PCV20 = 20-valent pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine

of pneumococcal disease but also of simplifying the recommendations and thereby making them easier to implement.¹

THE NEW RECOMMENDATIONS

The new recommendations^{1,2} revolve around 3 vaccines and 2 dosing schedules: 15-valent pneumococcal conjugate vaccine (PCV15) in series with PPSV23, and 20-valent pneumococcal conjugate vaccine (PCV20).

Adults who have not received a pneumococcal conjugate vaccine previously

Give 1 dose of PCV20 alone, or give 1 dose of PCV15 now and give PPSV23 at least 1 year later to:

- Patients age 65 and older at average risk of invasive pneumococcal disease
- Patients age 19 to 64 at higher risk (Table 1).

No additional doses beyond the initial doses are recommended at this time.

Adults who previously received PCV13

These patients should receive PPSV23 as previously recommended by the ACIP. The benefit of getting PCV15 or PCV20 after getting PCV13 has not been evaluated. Guidance essentially remains unchanged from before this current revision.

This being said, PCV20 can be used in place of PPSV23 if the latter is hard to obtain. If patients receive PCV20 or PCV15 plus PPSV23, such that they are transitioned to the new recommendations, no additional doses at age 65 are necessary.^{1,2}

Adults who previously received PPSV23 only

Patients may receive 1 dose of PCV20 or PCV15 at least 1 year after their last PPSV23 dose. No additional doses of any pneumococcal vaccine are necessary after PCV20 or PCV15.^{1,2}

Patients with a cochlear implant, cerebrospinal fluid leak, or immunocompromising condition

An interval of 8 weeks between PCV15 and PPSV23 can be considered instead of an interval of at least 1 year. Patients can also receive a single dose of PCV20.^{1,2}

RATIONALE FOR THE CHANGE

The incidence of pneumococcal disease (pneumococcal pneumonia and meningitis) has been steadily decreasing over the past 20 years, ever since PCV7 vaccination was started in children in 2000, and has been declining further with the introduction of PCV13 in 2010.^{1,8} These reductions are thought to be predominantly from indirect effects on pneumococcal transmission through herd immunity.

In 2021, the US Food and Drug Administration licensed the PCV15 and PCV20 vaccines for all adults over age 65 and for adults age 19 to 64 with risk factors for invasive pneumococcal disease. The 2 additional serotypes covered by PCV15 cause an additional 15% of cases of invasive pneumococcal disease, and the 7 additional serotypes included in PCV20 cause an additional 27% of cases beyond those covered by PCV13.¹ We anticipate that the introduction of the PCV15 and PCV20 will lead to further reductions in

the incidence of pneumococcal disease.

The safety and efficacy of both PCV15 and PCV20 were evaluated in multiple randomized controlled trials, and no significant adverse events or deaths were noted with either vaccine. The most commonly reported side effects included injection site reactions, fatigue, myalgias, arthralgias, and headache.

CONTINUED EVOLUTION

The 2022 ACIP recommendations^{1,2} continue the evolution of the pneumococcal vaccine guidelines over the past 25 years. Like all new recommendations, they may take some time to implement in clinical practice.

The guidelines are most straightforward in adults who have not yet received any pneumococcal vaccine. They are a little more complicated for those who have

partially completed their vaccination series and those with immunocompromising or underlying conditions. For these groups, the new guidelines are still similar to the earlier iterations of the guidelines, but they do allow for a transition to a simpler approach.

The CDC has a mobile app, *PneumoRecs VaxAdvisor*, to help physicians and other providers determine which pneumococcal vaccines are recommended for their individual patients: <https://www.cdc.gov/vaccines/vpd/pneumo/hcp/pneumoapp.html>.

In the end, we hope the ACIP's attempt to simplify regimens across age and risk groups will improve vaccination compliance in our patients.

DISCLOSURES

Dr. Tan has disclosed teaching and speaking for Pfizer. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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Reducing the risk of breast cancer

ABSTRACT

Breast cancer remains the most common female malignancy in the United States. Reducing this cancer burden involves identification of high-risk individuals and personalized risk management. Because coronary artery disease remains the primary cause of death for women, any intervention to reduce breast cancer risk must be weighed against comorbidities and interventions affecting cardiovascular risk reduction. For select women at increased risk for breast cancer, preventive medication can greatly decrease risk and is vastly underutilized. Women's health clinicians are poised to evaluate risk, promote breast cancer risk reduction, and manage overall health.

KEY POINTS

Patients with atypical hyperplasia (ductal or lobular) or lobular carcinoma in situ greatly benefit from risk-reducing medication.

Benefits of risk-reducing medication likely outweigh risks if the 5-year risk estimate is 3% or greater with the Gail model, or if the 10-year risk is 5% or greater with the Tyrer-Cuzick model.

Carriers of genetic or likely pathogenic variants who are predisposed to estrogen-receptor–positive breast cancers should consider preventive medication.

Cardiovascular risk and risk reduction as it relates to hormonal manipulation must weigh into decision-making.

Obesity management and alcohol reduction are critical in all patients.

ONE IN 8 WOMEN (13%) will develop breast cancer in her lifetime, at a median age of 62.¹ We aim to help practitioners identify patients at risk, understand options for risk reduction, and determine when the benefits of risk-reducing medications outweigh the risks. High-risk individuals include those with hereditary cancer syndromes, adverse genomic profiles, personal or family history of breast cancer, or benign high-risk lesions, and cancer survivors who underwent therapeutic irradiation as part of prior treatment before age 30.²⁻⁴ In some scenarios, absolute risks are well defined, and in others, risk modeling can support decision-making.^{2,3}

The pillars of breast cancer risk management include enhanced surveillance with contrast-enhanced magnetic resonance imaging (MRI), risk-reducing endocrine therapy, and risk-reducing surgery.³ Enhanced surveillance is recommended for patients meeting certain criteria. A discussion of risk-reducing surgery is advised for those with pathogenic variants (PVs) or likely pathogenic variants (LPVs) in highly penetrant genes (*BRCA1*, *BRCA2*, *PALB2*, *CDH1*, *TP53*, *STK11*, and *PTEN*) and is considered for those with a compelling family history or a history of therapeutic thoracic radiation before age 30.⁵ Discussing preventive medication in patients predisposed to estrogen-receptor–positive (ER+) breast cancers is clinically indicated, and a solid understanding of risk assessment and risk reduction is critical for the primary care provider to decrease morbidity and mortality. Four medications are recommended for breast cancer prevention: tamoxifen, raloxifene, exemestane, and anastrozole.⁶

We review here the approach to risk assessment, specific agents used in risk reduction, patient selection, and timing of therapy within a framework for personalized risk management.

TABLE 1
Guidelines to evaluate for hereditary breast cancer

- Age 50 or younger
- Ovarian cancer (at any age)
- Triple-negative breast cancer (at any age)
- Male breast cancer (at any age)
- Multiple primary breast cancers
- Pancreatic cancer
- Metastatic prostate cancer
- Three or more diagnoses of breast cancer in the patient or a close blood relative
- Two or more close (first-degree) relatives with breast or prostate cancer at any age
- To aid in treatment decisions using poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors in patients with metastatic or very-high-risk breast cancer
- Lobular breast cancer with a personal or family history of diffuse gastric cancer
- Ashkenazi Jewish ancestry
- Finding of a mutation in somatic tumor testing
- A patient without a cancer diagnosis but with a first-, second-, or third-degree relative meeting the above criteria: Exceptions: 1) If patient is eligible for PARP inhibitors; 2) If patient meets testing criteria based only on pancreatic cancer or metastatic prostate cancer, the affected relative must be a first-degree relative

Based on information in references 5, 7, and 8.

IDENTIFYING THOSE AT HEREDITARY RISK

Identified germline PVs or LPVs in genes associated with hereditary breast cancer account for 5% to 10% of breast cancer cases.¹ The National Comprehensive Cancer Network (NCCN), the United States Preventive Services Task Force (USPSTF), and other organizations recommend that primary care providers assess family history to identify those at hereditary risk, ideally by age 30 (Table 1).^{5,7,8} It is most important to identify patients with increased hereditary risk as breast cancers occur more frequently and at a much younger age.⁹ Historically, few patients met early eligibility criteria for genetic testing. Over time, however, guidelines have broadened, reflecting emerging evidence that germline PVs and LPVs are more common than previously believed. In a study of more than 4,100 patients in 2 large obstetrics-gynecology practices, 23.8% met criteria for genetic testing.¹⁰ Another recent study of underserved patients at an urban academic medical center also found that 24.4% of patients met USPSTF criteria for genetic counseling.¹¹ It is not uncommon for patients needing genetic counseling to present to a generalist's practice.

Genetic testing refers to clinical-grade next-generation multigene panel sequencing of highly penetrant

and moderately penetrant genes causal in hereditary breast cancer.⁴ These genes are inherited in an autosomal dominant fashion: only 1 copy of the malfunctioning gene need be inherited to exhibit the syndrome. As testing becomes more common, practitioners must understand how to interpret results. And as data have matured, estimates of risk and recommendations for management of carriers of PVs or LPVs in breast cancer predisposition genes have been refined by national cancer organizations such as NCCN.⁵

For example, a negative result must be interpreted based on what is known in the patient's family. If the patient is a "true negative" for a known highly penetrant PV, that person returns to a population-level risk estimate (eg, that of average women). True negatives for moderate-risk genes, uninformative negatives (a negative result in a patient or family member of that patient), and patients with "variants of uncertain significance" (considered to be clinically negative) default to the use of mathematical risk modeling for risk estimation and management.

Multifactorial risk models have been developed to inform practitioners about eligibility for enhanced surveillance with contrast-enhanced MRI and to guide discussions with patients about preventive medication.² The development of breast cancer in families with moderate-risk genes and in families where there is "clustering" but no identified genetic mutation may be influenced by other factors that modulate an individual's risk, so a negative test for a moderately penetrant familial variant does not negate possible risk.^{2,12}

Common genetic variants called single nucleotide polymorphisms, in combination, may explain up to 18% of familial clustering.^{1,13} The polygenic risk score (a weighted sum of these breast cancer-associated single nucleotide polymorphisms) may further refine risk estimates in both carriers and noncarriers of PVs or LPVs. This genomic contribution to risk assessment will be further discussed.

PREVENTIVE MEDICATION IN GENE CARRIERS

For patients with PVs or LPVs in breast cancer predisposition genes, there are evidence-based risk-management guidelines.⁵ Risk-reducing salpingo-oophorectomy (RRSO) is recommended in *BRCA1* carriers between ages 35 and 40 and in *BRCA2* carriers between ages 40 and 45.⁵ Consequences of early surgical menopause include an increased risk of cardiovascular disease, accelerated bone loss, dementia, and increased overall mortality.¹⁴ Additionally, many women suffer from severe vasomotor symptoms, sleep

TABLE 2
An overview of tumor pathology in hereditary breast cancer

Gene with pathogenic variant	Estrogen-receptor–positive tumor	Estrogen-receptor–negative tumor	Triple-negative tumor
<i>BRCA1</i>	Increasingly positive after age 50	+++ particularly before age 50	+++ particularly before age 50
<i>BRCA2</i>	++	Over-representation, ^a but still primarily estrogen-receptor–positive	Over-representation, ^a but still primarily estrogen-receptor–positive
<i>PALB2</i>	++	Over-representation, ^a but still primarily estrogen-receptor–positive	Over-representation, ^a but still primarily estrogen-receptor–positive
<i>ATM</i>	+++		
<i>CHEK2</i>	+++		
<i>CDH1</i>	+++		
<i>TP53</i>	+++		
<i>BARD1</i>		+++	+++
<i>RAD51C</i>		+++	+++
<i>RAD51D</i>		+++	+++

^aEstrogen receptor tumors are more common than in the general population but are still not the predominant type of tumor pathology.

+ = relative prevalence

disturbance, fatigue, anxiety, depression, urogenital changes, and sexual dysfunction.¹⁴ Thus, systemic hormone therapy is recommended unless otherwise contraindicated for *BRCA1/2* PV and LPV carriers undergoing early RRSO until the age when natural menopause would have occurred (approximately age 50), and generally precludes the use of preventive agents.^{15–17} Studies suggest that undergoing RRSO before age 50 is associated with a decrease in breast cancer risk, all-cause mortality, and breast cancer mortality, particularly in those with *BRCA2* PVs or LPVs. This breast cancer risk reduction is not mitigated by postmenopausal hormonal therapy.^{15,18}

Cardiovascular risk

While previous American Heart Association guidelines noted that early menopause increases cardiovascular disease risk, it is now recognized that coronary heart disease risk accelerates in average-risk women during the menopause transition and after menopause.¹⁹ Literature suggests that menopausal hormone therapy in women ages 50 to 59 is associated with improved cardiovascular morbidity and all-cause mortality (in healthy average-risk women).^{19,20} Additionally, the Women's Health Initiative studied the

administration of conjugated equine estrogen, with more than 20 years of follow up (in average risk women randomized to estrogen or placebo), and showed that use of conjugated equine estrogen in postmenopausal women with prior hysterectomy was significantly associated with a lower risk of breast cancer incidence and mortality.²¹ Although this finding cannot be extrapolated to “previvors” (unaffected gene carriers) with early surgical menopause, the data are provocative and should be discussed with patients at the time that hormone use would typically be discontinued.

Preventive endocrine therapy

Germline PV and LPV carriers predisposed to ER+ breast cancers may benefit from preventive endocrine therapy. In a study of more than 50,000 breast cancer patients, tumor pathology was associated with known breast cancer predisposition genes.^{22–26} ER+ tumors are commonly seen in patients with pathogenic or likely pathogenic variants in *BRCA1* (after age 50), *BRCA2*, *PALB2*, *ATM*, *CHEK2*, *CDH1*, and *TP53*. Estrogen-receptor–negative (ER–) or triple-negative breast cancers are more common in patients with PVs and LPVs in *BRCA1* under age 50 and in patients with *BARD1*, *RAD51C*, and *RAD51D* (Table 2).

Follow-up studies will determine the effectiveness of preventive endocrine therapy in patients with hereditary cancer syndromes, but the medication will most likely be effective in patients prone to ER+ disease, given the mechanism of action of these medications. Data from the Breast Cancer Prevention Trial of the National Surgical Adjuvant Breast and Bowel Project suggested that tamoxifen reduced breast cancer risk by 62% in *BRCA2* carriers (risk ratio [RR] 0.38; 95% confidence interval [CI] 0.06–1.56) but not in *BRCA1* carriers (RR 1.67; 95% CI 0.32–10.07).²⁷ However, these were very small numbers, and results did not meet statistical significance. Of the 288 women who developed breast cancer among the more than 13,000 in the study, only 8 had *BRCA1* PVs or LPVs, and 11 had *BRCA2* PVs or LPVs.²⁷ There are no published data in other gene PV and LPV carrier groups.

The most important factors influencing risk in patients without germline PVs or LPVs are family history, atypical benign breast lesions, and extreme breast density

RISK MODELING

In noncarriers of PVs or LPVs, in patients with variants of uncertain significance, or in untested patients with a family history or other risk factors, risk can be estimated using models. Short-term thresholds have been suggested at which the benefits of preventive therapy likely outweigh the risks; risks for coronary artery disease and venous thromboembolism must also be considered.³

The most important factors influencing risk are family history, atypical benign breast lesions, and extreme breast density. Breast density is a term that describes the relative amounts of glandular and fibrous connective tissue vs fatty tissue seen on a mammogram.^{28,29} Women with heterogeneously dense tissue (approximately 40% of women) and women with extremely dense tissue (approximately 7% of women) are considered to be mammographically “dense.”²⁹ Women with extremely dense breast tissue are at increased risk of breast cancer, and detection is more difficult with mammography alone.³⁰

Tyrer-Cuzick, CanRisk, and Gail models

Some risk models (eg, Tyrer-Cuzick, CanRisk) incorporate first-, second-, and third-degree relatives, family size, and genetic testing in their risk estimation.

^{31,32} Breast density, postmenopausal hormone use, lobular carcinoma in situ (LCIS), and polygenic risk score are also incorporated into the Tyrer-Cuzick and CanRisk models. The Tyrer-Cuzick model uses the *BRCA* status of tested family members, and the CanRisk model has recently been updated to incorporate the effects of *PALB2*, *CHEK2*, and *ATM* PVs and LPVs as well. It also incorporates lifestyle factors and disease pathology and predicts both breast and ovarian cancer risk.^{31,32}

The modified Gail model, also known as the Breast Cancer Risk Assessment model (<http://bcrisk-tool.cancer.gov>) is clinically the most commonly used model, validated in women age 35 and older. It involves 8 questions and provides estimates of 5-year and lifetime risk. However, it does not apply to women with a history of LCIS, incorporates only first-degree relatives, and does not take into account age at diagnosis, paternal history, anthropomorphic or lifestyle factors, genetic testing, or breast density. If a woman has an estimated 5-year risk of developing breast cancer of at least 1.66% using the Gail model, risk-reducing medication might be discussed, though the threshold at which the benefits outweigh the risk is felt to be 3% or greater.^{6,33–35}

The Tyrer-Cuzick model (<http://www.ems-trials.org/riskevaluator/>) takes more time to complete but is manageable in a busy clinic and provides estimates of short-term and lifetime risk. The CanRisk model (<http://www.canrisk.org>) is comprehensive but would likely need to be done outside of a routine clinical visit.

An international validation study with long-term follow-up comparing the models showed that models that include a multigenerational family history have better ability to predict risk.³⁶ The USPSTF suggests that if the 5-year estimated risk using the Gail model is 3% or greater, the benefit of preventive medication likely outweighs the risks in the absence of contraindications.⁷ The American Society of Clinical Oncology recommends a threshold of 5% or greater using the 10-year risk estimate from the Tyrer-Cuzick model.³⁷

MAMMOGRAPHIC DENSITY, BENIGN ATYPICAL LESIONS, AND THERAPEUTIC CHEST IRRADIATION

Density

Although breast density is an important independent risk factor for breast cancer,³⁸ no recommendations currently exist for the use of preventive medication based solely on density. Discussion of

TABLE 3
Medications used for breast cancer risk reduction: A brief summary of clinical trials

Trial	N	Eligibility	HR ^a	HR ^b	NNT
NSABP P-1 5-year trial Tamoxifen 20 mg vs placebo ³³	13,388	Pre- and post-menopausal; Gail model-estimated 5-year risk $\geq 1.66\%$	0.51	0.14 for AH; 0.44 for LCIS	22
IBIS-1 5-year trial Tamoxifen 20 mg vs placebo ⁴⁸	7,154	Pre- and post-menopausal; 50% on hormone-replacement therapy	0.75; with long-term follow-up 0.71	Not stated	Not stated
STAR P-2 5-year trial Tamoxifen 20 mg vs raloxifene 60 mg ^{34,50}	19,747	Postmenopausal	Equal at 5 years; with long-term follow-up; raloxifene = 0.62	Equal	Not stated (about 22)
MAP.3 3-year trial Exemestane 25 mg, exemestane 25 mg plus celecoxib, vs placebo ⁴⁶	4,560	Postmenopausal	0.35	0.36 (for AH/LCIS combined)	26 at 5 years
IBIS II 5-year trial Anastrozole 1 mg vs placebo ⁴⁷	3,864	Postmenopausal	0.47	0.31 (for AH/LCIS combined)	29 ^c
Low-dose tamoxifen 3-year trial Tamoxifen 5 mg vs placebo ⁴⁹	500	Pre- and post-menopausal; included patients with ductal carcinoma in situ	0.48	Not stated	22

^aFor reduction in invasive breast cancer.

^bFor reduction in invasive breast cancer in patients with AH and LCIS.

^cTo prevent 1 cancer in 7 years of follow-up, 36 women would need to be treated.

AH = atypical hyperplasia; HR = hazard ratio; IBIS = International Breast Cancer Intervention Study; LCIS = lobular carcinoma in situ; MAP = Mammary Prevention trial; NNT = number needed to treat; NSABP = National Surgical Adjuvant Breast and Bowel Project; STAR = Study of Tamoxifen and Raloxifene

supplemental imaging is warranted, particularly in high-risk patients.

Atypical lesions

In women with benign atypical biopsy lesions and in women with LCIS, preventive therapy is highly recommended. Atypical ductal hyperplasia (ADH) or atypical lobular hyperplasia (ALH) confers an approximately 30% risk of breast cancer at 25 years of follow up.^{39–41} LCIS is associated with a risk of approximately 2% per year.⁴² The risk increases if ADH, ALH, or

LCIS is detected in younger women and if more tissue is involved (measured as the number of terminal duct lobular units involved).³⁹

Chest irradiation

Therapeutic thoracic radiation in a patient under age 30 (eg, to treat Hodgkin lymphoma) results in a breast cancer risk exceeding 35% by age 50⁴³ and may be associated with a higher mortality risk.⁴⁴ A study examining low-dose tamoxifen (5 mg daily for 2 years) demonstrated reduction in established biomarkers of

risk (mammographic density and serum insulin-like growth factor-1 levels) in these patients.⁴⁵

■ PREVENTIVE AGENTS

Table 3^{33,34,46–50} summarizes trials of 4 medications used for breast cancer risk reduction: tamoxifen, raloxifene, exemestane, and anastrozole. In breast cancer treatment trials,^{33,34,46–52} tamoxifen and the aromatase inhibitors prevented not only breast cancer recurrence, but also contralateral disease. Raloxifene had been shown in osteoporosis trials to reduce breast cancer risk.⁵² Thus, these agents were selected for randomized trials of primary reduction of breast cancer risk. The following section will review the medications, results of relevant clinical trials, and side effects. The clinical trials were all randomized and double-blind, and all except the Study of Tamoxifen and Raloxifene were placebo-controlled.⁵⁰ Although breast cancer rates decreased overall with the use of these medications,^{33,34,46,47} no decrease in mortality has been demonstrated to date.

The protective effects of risk-reducing agents persist at least 10 years after stopping the medication

Selective estrogen receptor modulators: Tamoxifen and raloxifene

Selective estrogen receptor modulators (SERMs) are a class of drug that acts on the estrogen receptor with action that varies by tissue, selectively inhibiting or stimulating estrogen-like action. Contraindications to SERMs include a history of deep vein thrombosis or pulmonary embolism, thrombotic stroke, retinal vein thrombosis, transient ischemic attack, or known inherited clotting predisposition. They should not be used while pregnant or breastfeeding or with concurrent use of warfarin or estrogen.⁵³ Other considerations include the presence of independent risk factors for thromboembolic disease (advancing age, obesity, smoking),⁵⁴ migraine with aura (due to concern for stroke),⁵⁵ and use of an unreliable birth control method along with use of tamoxifen.⁵³ Given the increased risk of thromboembolic disease with SERMs, it is imperative that women be assessed for personal and familial risks for this potential complication.

Tamoxifen was approved in 1998 by the US Food and Drug Administration (FDA) for breast cancer risk

reduction following results of the National Surgical Adjuvant Breast and Bowel Project P-1 study.³³ The study showed an approximate 50% reduction in invasive and noninvasive breast cancer in premenopausal and postmenopausal women, and a greater reduction in women with atypical hyperplasia or LCIS.³³

The study randomized 13,388 women at increased risk of breast cancer to receive tamoxifen 20 mg daily for 5 years or placebo.³³ Women were considered at increased risk of breast cancer if they were age 60 or older, were age 35 to 59 with a 5-year risk of 1.66% or higher (using the Gail model), or had a history of LCIS.³³ A reduction in rate of fractures of the hip, radius (Colles fracture), and spine was observed in the tamoxifen arm, and no effect was noted on the rate of ischemic heart disease. There was an increased risk of endometrial cancer (5.4 per 1,000 women in the placebo group, and 13 per 1,000 women in the tamoxifen group at 66 months).³³

There were 18 pulmonary emboli in the tamoxifen group vs 6 in the placebo group (RR 3.01; 95% CI 1.15–9.27).³³ The average annual rate of deep vein thrombosis was 1.34 vs 0.84 per 1,000 women in the tamoxifen vs placebo-treated groups (RR 1.60; 95% CI 0.91–2.86), which reached statistical significance only in women age 50 and older.³³

The rate of cataract formation in women who were cataract-free at randomization was 21.72 per 1,000 in the placebo group and 24.82 per 1,000 in the tamoxifen group (RR 1.14; 95% CI 1.01–1.29).³³

In healthy premenopausal women, there was no statistically significantly increased risk of serious side effects with tamoxifen, and it was generally well tolerated.³³ Vasomotor symptoms were common in both the tamoxifen and control groups but more common in the tamoxifen group, and the drug was associated with vaginal discharge.³³ Benefits have been shown to persist for at least 10 years after stopping the medication.⁴⁸

The recommended duration of tamoxifen therapy for risk reduction is 5 years.^{6,7,37} Another option for patients with ADH, ALH, or LCIS is “low-dose” tamoxifen.³⁷ A 2019 study from Italy cited a 50% risk reduction with the use of 5 mg daily for 3 years in this population.⁴⁹ As 5-mg tablets are not available in the United States, an alternate regimen is 10 mg every other day. The efficacy of low-dose tamoxifen seems to be greater, however, in postmenopausal women.⁵⁵

Raloxifene (also FDA-approved for osteoporosis prevention) was FDA-approved for breast cancer risk reduction in September 2007 after the publication of results from the National Surgical Adjuvant Breast

and Bowel Project Study of Tamoxifen and Raloxifene P-2 trial.^{34,56} The Study of Tamoxifen and Raloxifene randomized 19,747 postmenopausal women with a mean age of 58.5 and a mean Gail model-estimated 5-year breast cancer risk of 4.03% to either tamoxifen 20 mg or raloxifene 60 mg daily for 5 years.³⁴ There were 36 cases of uterine cancer with tamoxifen and 23 with raloxifene (RR 0.62; 95% CI 0.35–1.08), and cumulative uterine cancer incidence rates through 7 years were 14.7 per 1,000 for tamoxifen and 8.1 per 1,000 for raloxifene ($P = .07$). Thromboembolic events were less common with raloxifene (RR 0.70; 95% CI 0.54–0.91), and no differences were found for ischemic heart disease or stroke. There were also fewer cataracts (RR 0.79; 95% CI 0.68–0.92). Osteoporotic fractures and death were similar in the 2 groups. Tamoxifen and raloxifene had equivalent effects in reducing the risk of invasive breast cancer in all examined subgroups, including women with a history of atypical hyperplasia and LCIS, who had the highest annual rates of developing breast cancer. Tolerance was similar.³⁴

At a mean follow-up of 81 months, raloxifene retained 76% of the effectiveness of tamoxifen (with a 38% reduction in breast cancer risk) with less endometrial cancer risk (RR = 0.55; 95% CI 0.36–0.83; $P = .003$).⁵⁰ The superiority of tamoxifen in reducing risk comes with significant costs in postmenopausal women: more endometrial cancers, hysterectomies for benign disease, thromboembolic events, and cataracts, particularly for women over age 65, who have a higher risk of adverse events with tamoxifen.⁵⁷

Aromatase inhibitors: Exemestane and anastrozole

Aromatase catalyzes the aromatization of androgen precursors such as testosterone, producing estrogen. Aromatase inhibitors are taken to block the production of estrogen. While neither exemestane nor anastrozole is FDA-approved for breast cancer risk reduction, both are recommended by NCCN, USPSTF, and the American Society of Clinical Oncology.^{6,7,37} Aromatase inhibitors can reduce bone density, necessitating monitoring.

Exemestane. In the study by Goss et al of exemestane for breast cancer prevention in postmenopausal women,⁴⁶ 4,560 postmenopausal women with a median age of 62.5 and a median Gail-estimated 5-year risk of 2.3% were randomly assigned to daily exemestane 25 mg, exemestane 25 mg plus celecoxib, or placebo.⁴⁶ At a median follow-up of 35 months, there was a 65% relative reduction in the annual incidence of breast cancer with exemestane. There were no significant

differences between the 2 treatment groups in terms of skeletal fractures, cardiovascular events, other cancers, or treatment-related deaths. No serious toxic effects and only minimal changes in health-related quality of life were noted. Exemestane also reduced the risk of ductal carcinoma in situ, LCIS, ADH, and ALH, suggesting possible further reductions in invasive cancers during long-term follow-up.⁴⁶

Anastrozole. In the International Breast Cancer Intervention Study II trial,⁴⁷ 3,864 postmenopausal women ages 40 to 70 from 18 countries were randomized to receive anastrozole 1 mg daily or placebo for 5 years.⁴⁷ There was a 53% reduction in breast cancer with the use of anastrozole (hazard ratio 0.47; 95% CI 0.32–0.68; $P < .0001$). Musculoskeletal adverse events (including carpal tunnel syndrome and joint stiffness) and vasomotor symptoms were reported in more women in the anastrozole group ($P < .0001$). Dry eyes, vaginal dryness, and hypertension were also significantly increased. Overall adherence was 75%, and after a median follow-up of 131 months, a 49% reduction in risk persisted, with no excess fractures, other cancers, cardiovascular disease, or death.⁵⁸

■ OBESITY AND BREAST CANCER

Obesity and physical inactivity have been shown to have a major impact on outcomes in both breast cancer and cardiovascular disease, and all patients should be counseled on diet and lifestyle, including alcohol in moderation or not at all.^{59,60}

The mechanisms by which obesity increases breast cancer risk are complex, but achieving and maintaining ideal body weight appears to be critical

Defined as a body mass index of at least 30 kg/m², obesity has a major impact across the breast cancer continuum, including an increased risk of postmenopausal and triple-negative breast cancers, delay in diagnosis, increased complications from surgery and radiation, and decreased survival.⁵⁹ The high prevalence of obesity is a major public health concern for all Americans and disproportionately affects Black women, with a recent study showing more than 55% obesity.⁶⁰

In the Women's Health Initiative Dietary Modification randomized trial (N = 48,835),²¹ triple-negative breast cancer cases were significantly reduced

in the low-fat diet arm (defined as 24.3% of energy). Body weight was also significantly reduced, and there was a significant reduction in deaths from breast cancer ($P = .02$).²¹ The mechanisms by which obesity increases breast cancer risk are complex, and it is not yet known whether the low-fat diet or weight loss resulted in mortality reduction, but the importance of achieving and maintaining ideal body weight appears to be critical.

■ IMPACT OF THE POLYGENIC RISK SCORE

The polygenic risk score has been shown to improve the discriminatory accuracy of risk modeling in validation cohorts,⁶¹ and it has also been shown to sub-stratify risk in carriers of genetic PVs and LPVs and in high-risk noncarriers.⁶² Clinically, it was recently shown to influence the uptake of risk-reducing medication in a cohort of women at high risk for breast cancer.⁶³ The polygenic risk score has strong potential to refine clinical breast cancer risk assessment and to assist in prevention counseling of women at increased risk. More study is needed.

■ KEYS TO SUCCESSFUL RISK MANAGEMENT

A comprehensive approach to breast cancer risk management includes personalized risk assessment with consideration of comorbidities and patient goals.

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Patient selection, clear communication of risks and benefits, and appropriate timing are the keys to successful management as noted in these take-home points.

- Informed practitioners are needed to care for specified high-risk patients and to educate patients about the risks and benefits of risk modification.
- Prevention strategies should involve identification of patients at risk for hereditary breast cancer, as early intervention is critical.
- Preventive medication is extremely effective in patients with benign atypical lesions.
- Short-term risk thresholds can inform discussions regarding risk-reducing medication.
- The epidemic of obesity, inactivity, and alcohol consumption must be addressed in the United States to reduce burden of disease.^{60,64}
- The polygenic risk score can be used to further sub-stratify risk estimates, aiding women in clinical decision-making.^{61–63}
- Potential cardioprotective effects of hormonal therapy in early postmenopause must be considered in shared decision-making with patients, as well as noting cardiovascular and venous thromboembolic risk factors.

■ DISCLOSURES

Dr. Pederson has disclosed consulting for Myriad Genetics. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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REVIEW

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Benign paroxysmal positional vertigo: Effective diagnosis and treatment

ABSTRACT

Benign paroxysmal positional vertigo (BPPV), caused by wayward crystals ("rocks") in the semicircular canals of the inner ear, is the most common cause of brief symptoms of vertigo secondary to head and body movements. Diagnosing and treating it are simple to do in the medical office. This article reviews the differential diagnosis for patients presenting with dizziness and vertigo, the pathophysiology of BPPV, how to diagnose it using maneuvers to elicit symptoms and nystagmus, how to interpret the nystagmus pattern to determine where the rocks are, and how to treat it using different maneuvers to reposition ("roll") the rocks back where they belong.

KEY POINTS

BPPV symptoms typically last seconds to minutes and are not associated with hearing loss or other neurologic signs or symptoms.

Dizziness or vertigo when lying down or changing positions is a strong predictor of BPPV. The condition is easily diagnosed with the Dix-Hallpike and supine roll maneuvers.

Treatment can be done by a general practitioner or by a specialist in vestibular rehabilitation or vestibular audiology. If repositioning maneuvers do not relieve the symptoms, a full workup, including radiographic imaging and a vestibular test battery, should be considered.

DIZZINESS IS A COMMON complaint that can affect people of all ages: roughly 15% of American adults report a balance or dizziness problem.¹ It is the reason for many emergency room visits, secondary to benign conditions (eg, vestibular conditions, migraine, psychogenic conditions) and serious conditions (eg, stroke, inflammatory central nervous system disease, intracranial tumor, or hemorrhage).

Unfortunately, balance disorders are often difficult to diagnose and manage, owing in part to the subjective symptoms and the complexity of the neurologic, cardiovascular, metabolic, toxic, vestibular, and psychiatric conditions that can cause them. The symptoms can also be similar to those of life-threatening conditions, making the diagnostic workup challenging.

This article provides an update on benign paroxysmal positional vertigo (BPPV), a common balance disorder, and how to distinguish it from other causes of dizziness, vertigo, and imbalance with easy position-changing maneuvers. We also discuss how best to treat it, also with position-changing maneuvers.

■ DIZZINESS VS VERTIGO

Patients use the term *dizziness* to describe several different sensations, but medically speaking it is different from vertigo. Dizziness is any distortion of the sensation of where one is within a space, whereas vertigo is a false sensation of movement, specifically rotation or spinning.²

A thorough case history can differentiate between these sensations and point to a cause.

TABLE 1
Symptoms and temporal pattern of common disorders of dizziness

Disorder	Symptoms	Temporal pattern
Benign paroxysmal positional vertigo (BPPV)	Head or body movement-provoked vertigo	Episodic; seconds to minutes; can have delayed latency in symptoms or fatigue of symptoms upon repeat movement
Cervical vertigo	Dizziness, imbalance or lightheadedness with neck pain or changes in neck position	Episodic; minutes to hours
Menière disease	Vertigo with fluctuating hearing loss, aural fullness, and tinnitus	Spontaneous onset; episodic; 20 minutes to 24 hours
Vestibular neuritis	Vertigo without auditory symptoms, followed by head movement-provoked symptoms	Sudden onset; 1–3 days
Labyrinthitis	Vertigo with auditory symptoms, followed by head movement-provoked symptoms	Sudden onset; several days
Acoustic neuroma or vestibular schwannoma	Imbalance with brief episodes of dizziness; auditory symptoms; occasional neurologic symptoms	Gradual onset; progressive and continuous
Superior canal dehiscence	Autophony, disequilibrium, positional vertigo, and pressure- or sound-induced symptoms of vertigo	Episodic; seconds to minutes
Perilymphatic fistula	Pressure- or sound-induced symptoms of vertigo, imbalance	Sudden onset; episodic; seconds to minutes
Vascular event (anterioinferior cerebellar artery or posterioinferior cerebellar artery stroke)	Vestibular crisis event: vertigo with associated hearing loss and other neurologic symptoms and signs followed by head movement-provoked symptoms	Sudden onset; lasting 1–3 days

Based on information in references 3 and 4.

Questions should focus on the following:

- Quality of symptoms, such as vertigo, oscillopsia (the illusion that objects are moving back and forth), general imbalance, or lightheadedness
- Time course of symptoms, such as speed of onset, duration, the circumstance of onset, time since the initial episode, and frequency of episodes
- Associated factors, such as migraine or changes in vision, hearing, or breathing
- Exacerbating and relieving factors, such as head or body movements, closing or opening the eyes, looking in one direction or another, entering or leaving a busy visual field, coughing, sneezing, or loud sounds
- Other pertinent medical history, such as issues with vision, disabilities of the lower extremities,

medications that can cause dizziness, diabetes, neuropathy, cerebrovascular disease, stroke, neck pain, seizures, hypertension, cardiac problems, or ototoxicity.

Common vestibular disorders have typical characteristics (Table 1)^{3,4} that are key to quickly narrowing down the cause of symptoms and making appropriate referrals.

■ A COMMON CAUSE OF DIZZINESS AND VERTIGO

BPPV is one of the most common vestibular causes of dizziness. Royle et al⁵ reported that it was the most frequent diagnosis in patients presenting to the emergency department with dizziness. Its prevalence increases with age, and it more often affects people over age 40. It is more common in women than in men.⁶

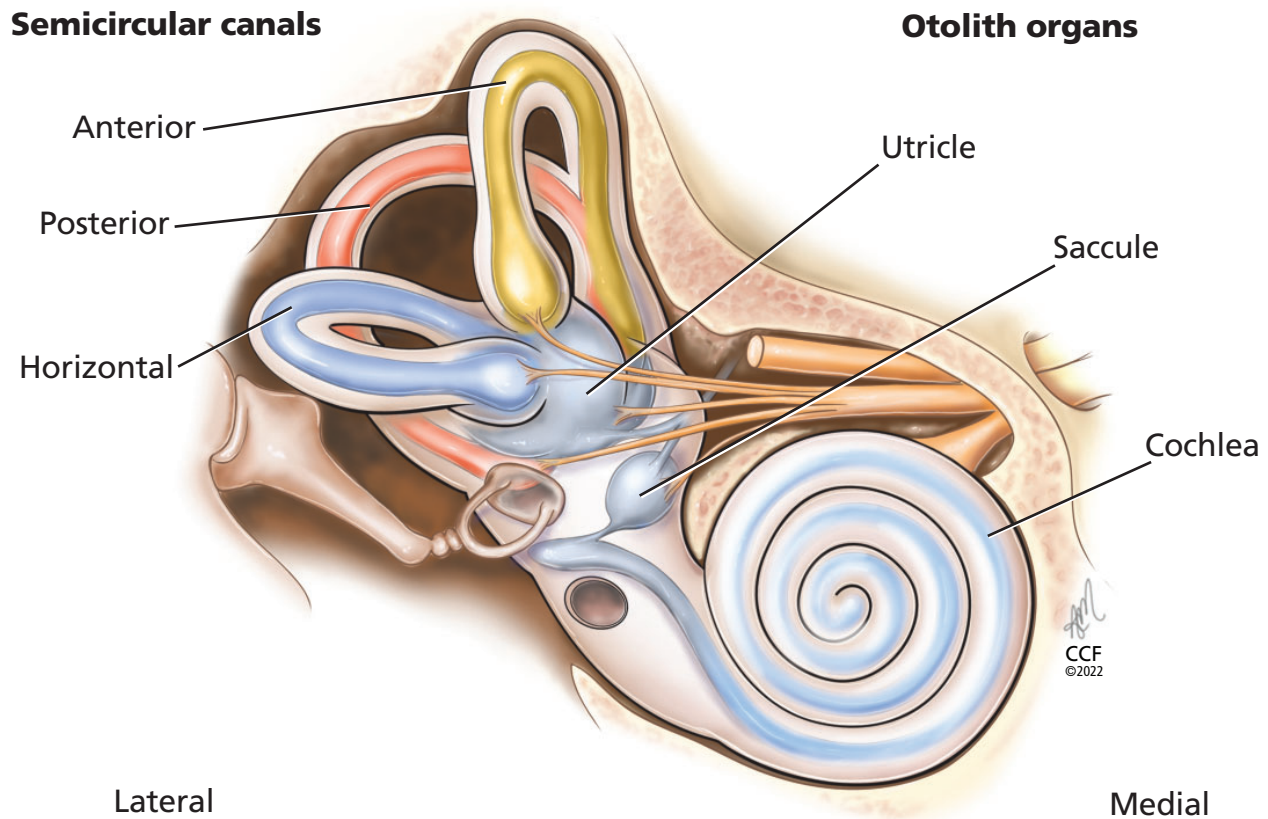


Figure 1. The semicircular canals (anterior, posterior, horizontal) sense angular acceleration, and the otolith organs (saccule, utricle) sense linear acceleration, providing internal cues for orientation of position in space, movement, gaze stabilization, and postural control.

Even though BPPV is common, it often goes unrecognized,⁷ leading to costly and unnecessary diagnostic procedures, referrals, and treatment. Undetected and untreated, BPPV can also lead to poor quality of life and to falls,⁸ the leading cause of injury and trauma-related hospital admissions in older adults.⁹

■ BRIEF EPISODES OF VERTIGO, ASSOCIATED WITH MOVEMENT

BPPV presents as brief episodes of vertigo, typically lasting seconds to minutes and associated with head movement, neck movement, or overall positional changes.¹ Common triggers include:

- Rolling over in bed
- Looking up or down
- Rising from a supine position
- Lying down from a sitting position
- Leaning forward.

There can be a short-lasting latency of seconds between the initial positional change and corresponding symptoms. Patients may also experience nausea or

emesis during an episode and report a general sense of floating or imbalance.

■ CAUSES OF BPPV

Deep within the petrous part of the temporal bone lies the membranous labyrinth, housed within the bony labyrinth (**Figure 1**). The membranous labyrinth is filled with fluid (endolymph) and houses the cochlea and the vestibular structures: the 3 semicircular canals—anterior, posterior, and horizontal (also called lateral)—and the 2 otolith organs (saccule and utricle). The semicircular canals sense angular acceleration, and the otolith organs sense linear acceleration, providing our internal cues for orientation of position in space, movement, gaze stabilization, and postural control.

Body movements cause the fluid in the semicircular canals to move and stimulate cilia on sensory hair cells. This triggers transmission of neural signals to the brain to initiate appropriate reflex responses for the eyes, head, and postural adjustments. These reflexive

TABLE 2
Observed nystagmus patterns based on semicircular canal involvement

Provocative maneuver	Nystagmus direction	Affected canal
Dix-Hallpike	To the affected side and up	Posterior
Dix-Hallpike	To the affected side and down	Anterior
Supine roll, right ear down	Right (geotropic)	Horizontal. The head-turn direction eliciting stronger nystagmus indicates the affected horizontal canal
Supine roll, left ear down	Left (geotropic)	
Supine roll, right ear down	Left (apogeotropic)	Horizontal. The head-turn direction eliciting weaker nystagmus indicates the affected horizontal canal
Supine roll, left ear down	Right (apogeotropic)	

movements allow us to see things clearly when our head and body are in motion and keep us from falling.

The 3 semicircular canals are positioned at 90-degree angles to one another and thus can sense rotation in all directions. The 3 in the right ear are functionally paired with the 3 in the left ear:

- The right horizontal with the left horizontal
- The right anterior with the left posterior
- The right posterior with the left anterior.

Thus, for instance, when turning one's head to look over the right shoulder, the right horizontal semicircular canal is excited and the left horizontal is inhibited.

The utricle and saccule are gravity-sensitive and contain dense crystals called otoconia resting on top of the sensory organs. With linear movements (eg, leaning to the side), the otoconia move, signaling reflexive responses similar to those of the semicircular canals to maintain eye, head, and body equilibrium.

BPPV is caused by free-floating otoconia that have been dislodged from the otolith organs as a result of injury, infection, diabetes, migraine, osteoporosis, prolonged bedrest, or aging.¹⁰ Dislodged otoconia can gather in the semicircular canals. Since each semicircular canal is oriented in a different plane in space, when the dislodged otoconia gather in 1 or more of them, they can be stimulated upon positional changes and cause vertigo and nystagmus.

Most cases of BPPV are either idiopathic or caused by head trauma,¹¹ but it can be a result of other vestibular disorders (eg, Menière disease, labyrinthitis) or central nervous system disorders (eg, migraine, multiple sclerosis).

Recent evidence suggests BPPV has a seasonal aspect, perhaps related to varying vitamin D levels

throughout the year. Otoconia are composed of calcium carbonate and therefore could have risk factors for demineralization, similar to bone. Maia et al¹² analyzed 214 patients diagnosed with idiopathic BPPV in Brazil over 5 years and found that significantly more patients presented in the autumn and winter than in the spring and summer. This suggests that lower vitamin D levels, due to less sunlight, could be contributing to the seasonality of BPPV.

■ DIAGNOSTIC MANEUVERS

BPPV is relatively simple to diagnose and treat. By moving the patient into different positions, observing their eye movements, and asking if they feel like their head is spinning, clinicians can determine which semicircular canal is being stimulated. Otoconia in the posterior semicircular canal account for up to 90% of cases, and otoconia in the horizontal canal account for most of the rest, while involvement of the anterior semicircular canal is relatively rare and is usually due to failed repositioning maneuvers to remove otoconia from the posterior canal.¹³

Nystagmus consists of oscillation of the eyes¹⁴ and can be horizontal (to the side and back), torsional (rotary in nature), or vertical (up or down and back), or a combination of some or all three. The direction and characteristics of the eye movements correspond to the semicircular canal stimulated during positioning (Table 2). The symptoms are brief, often lasting less than 60 seconds.

Dix-Hallpike maneuver

The variants of BPPV affecting the vertical semicircular canals (ie, the posterior and anterior) are

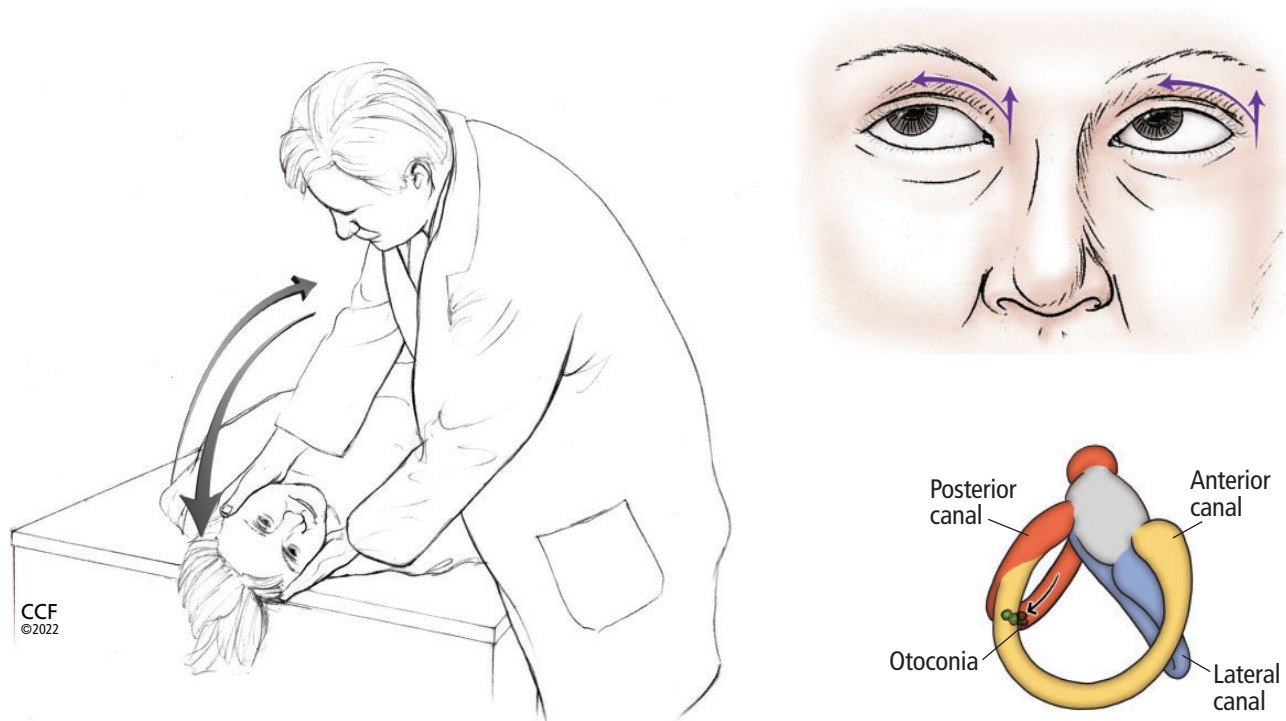


Figure 2. The Dix-Hallpike maneuver to detect otoconia in the posterior or anterior semicircular canals. If the otoconia are suspected to be in the right ear, the patient sits upright with the head turned 45° to the right; if the otoconia are suspected to be in the left ear, the patient turns the head to the left. The clinician then quickly moves the patient into a head-hanging supine position and checks for signs of nystagmus, and the patient reports any symptoms (eg, dizziness, vertigo). After 60 seconds, the patient is returned to a seated position with the head still turned, and the clinician again observes symptoms and signs. During the maneuver, movement of otoconia within the right posterior semicircular canal (in the lower-right image) causes an excitatory response—ie, nystagmus—to the right and up, as the arrows indicate in the upper-right image.

diagnosed by performing the Dix-Hallpike maneuver.¹⁵ This consists of 2 positional changes (sitting to supine, and supine to sitting) with the patient's head turned 45° (**Figure 2**).¹⁶ When the patient is moved from the sitting to the supine position, the clinician may observe the excitatory eye movement pattern of the canal with the otoconia, with horizontal nystagmus toward the involved ear and either of the following:

- Up (if the otoconia are in the posterior canal)
- Down (if they are in the anterior canal).

When the patient moves from supine back to sitting, a reverse nystagmus pattern should be observed, indicating inhibition of the canal with the otoconia, with torsional nystagmus toward the healthy side and either of the following:

- Down (for the posterior canal)

- Up (for the anterior canal).

The maneuver is then repeated with the patient's head turned the other way, ie, to assess both right and left sides.

Supine roll test

The Dix-Hallpike maneuver may not always elicit vertigo and nystagmus in cases of BPPV that are due to otoconia in the horizontal semicircular canal. Therefore, the supine roll test is recommended as the second screening maneuver (**Figure 3**).¹⁶

A positive sign of BPPV during this test is horizontal nystagmus in both the head-right and head-left positions. If the nystagmus is in the same direction that the head is turned, the pattern is called *geotropic*. If it is in the opposite direction, the pattern is called *apogeotropic*.

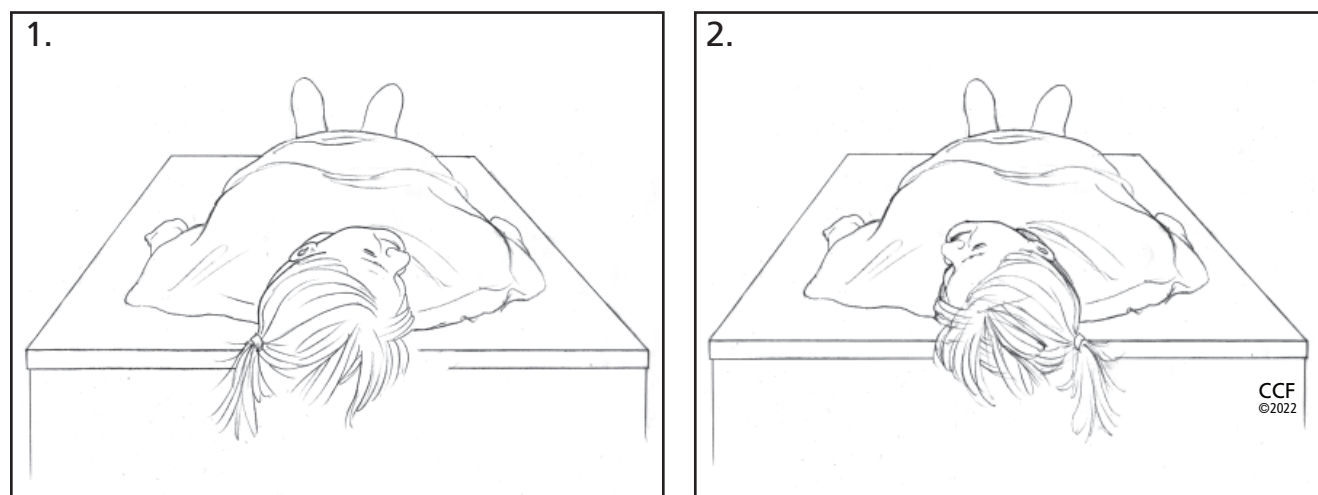


Figure 3. The supine roll test to detect otoconia in the horizontal semicircular canals. (A) With the patient in a supine position, the clinician quickly rotates the patient's head to the right and assesses for horizontal nystagmus and patient symptoms. (B) After 30 to 60 seconds, the clinician quickly rotates the patient's head to the left and again observes for horizontal nystagmus and symptoms. The direction of nystagmus (ie, geotropic vs apogeotropic) with the head-movement changes indicates the involved horizontal canal (Table 2).

Refer when in doubt

Recent clinical practice guidelines outline that proper diagnosis of BPPV is made when both patient-reported symptoms and the appropriate nystagmus pattern are observed during position changes.¹⁷ However, false-negative results can occur. When BPPV is strongly suspected based on history but the Dix-Hallpike and supine roll maneuvers are negative, the patient should be referred to a vestibular therapist or vestibular audiologist for further evaluation.

TREATMENT MANEUVERS

Once BPPV has been diagnosed, treatment is based on the semicircular canal involved. This involves a series of clinician-guided head and body movements to move the otoconia out of the semicircular canal and back into the utricle, with the assistance of gravity. The process is simple and can be performed on a standard examination chair that can fully recline, or on a table. These maneuvers can often provide immediate and long-lasting relief.¹⁰ In several studies, their effectiveness ranged from roughly 76% to 93%.^{18–20}

Epley maneuver for posterior or anterior canal BPPV

In 1992, Epley²¹ described a series of head and body movements to move otoconia out of the vertical (ie, the posterior and anterior) semicircular canals. The procedure is easy to perform but requires careful atten-

tion to keep the patient's head and body in the proper position throughout the maneuver (Figure 4).¹⁶ Also, the patient's eyes should be monitored throughout each stage of the maneuver to observe the pattern of nystagmus, which should remain consistent with that observed during the Dix-Hallpike or supine roll maneuver. Consistent nystagmus patterns ensure that the clinician has not moved the otoconia to a different semicircular canal rather than the otolith organs.

Semont maneuver, an alternative to the Epley maneuver

The Semont maneuver is a suitable alternative to the Epley maneuver for treating vertical canal BPPV.²² This maneuver requires quickly moving the patient through a series of head and body positions (Figure 5).

As with the Epley maneuver, the clinician should focus on nystagmus patterns throughout the maneuver, which should be consistent with those observed during diagnostic screening (eg, the Dix-Hallpike maneuver).

The log roll maneuver for treating horizontal canal BPPV

As indicated above, properly diagnosing the affected side for horizontal semicircular canal BPPV requires carefully reviewing the nystagmus pattern (geotropic vs apogeotropic) during the supine roll test.

Geotropic horizontal-canal BPPV is more common than apogeotropic.¹⁷ Often, listening to the

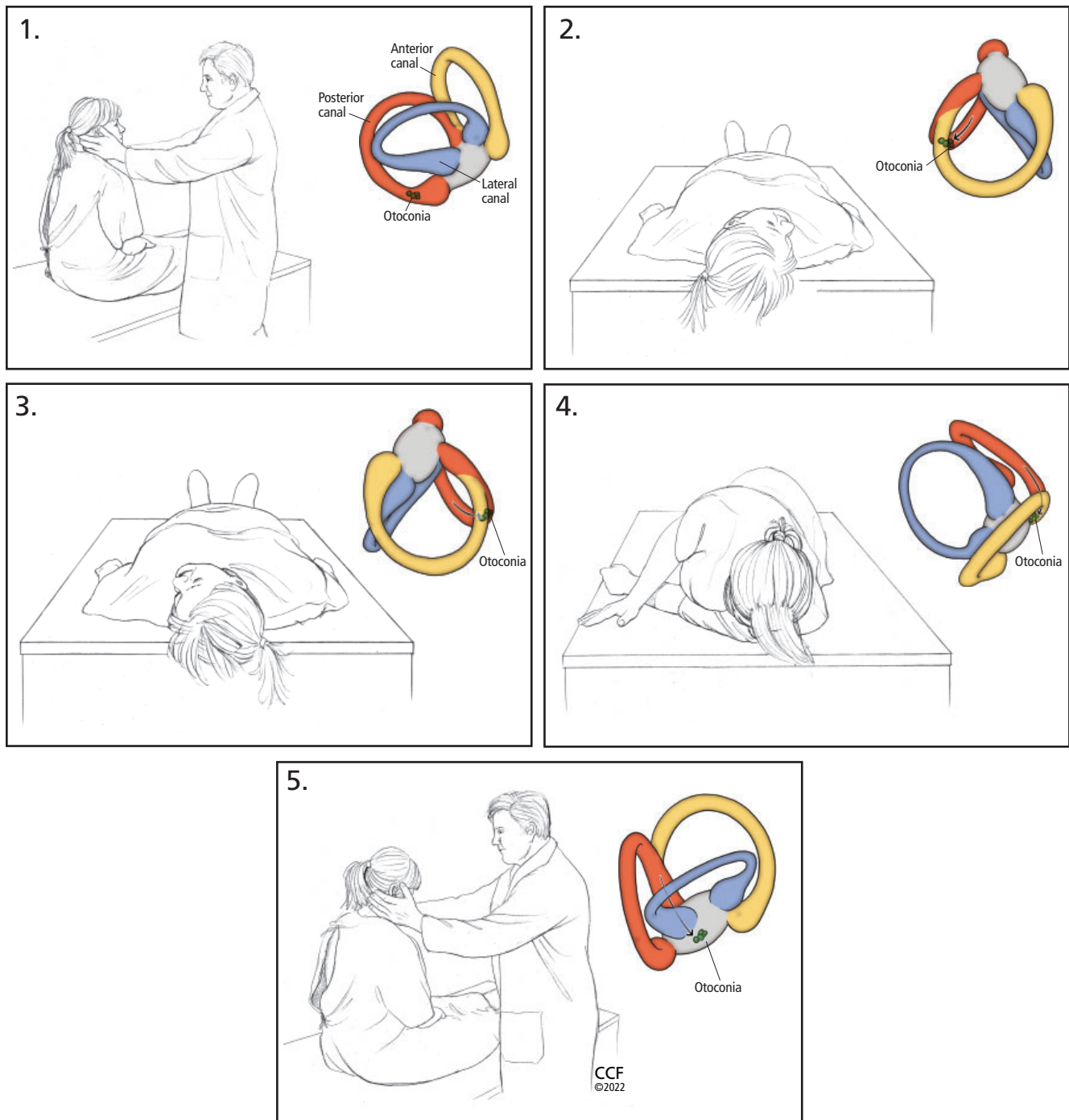


Figure 4. The Epley maneuver to clear otoconia from the posterior or anterior semicircular canals:

1. Place the patient in a seated position on the bed and turn their head 45° toward the ear with the suspected otoconia. The color insets show movement of otoconia.
2. Quickly move the patient to a supine position with head turned and extended downward.
3. Move the patient's head to the other side, being careful to keep it in the correct plane. The final position after turn should be 45° toward the unaffected ear, extended downward.
4. Assist the patient onto the unaffected side with the patient's chin remaining 45° toward the unaffected ear (patient will be looking toward the ground in this position).
5. Finally, help the patient back to a seated position, keeping their head turned over their shoulder.

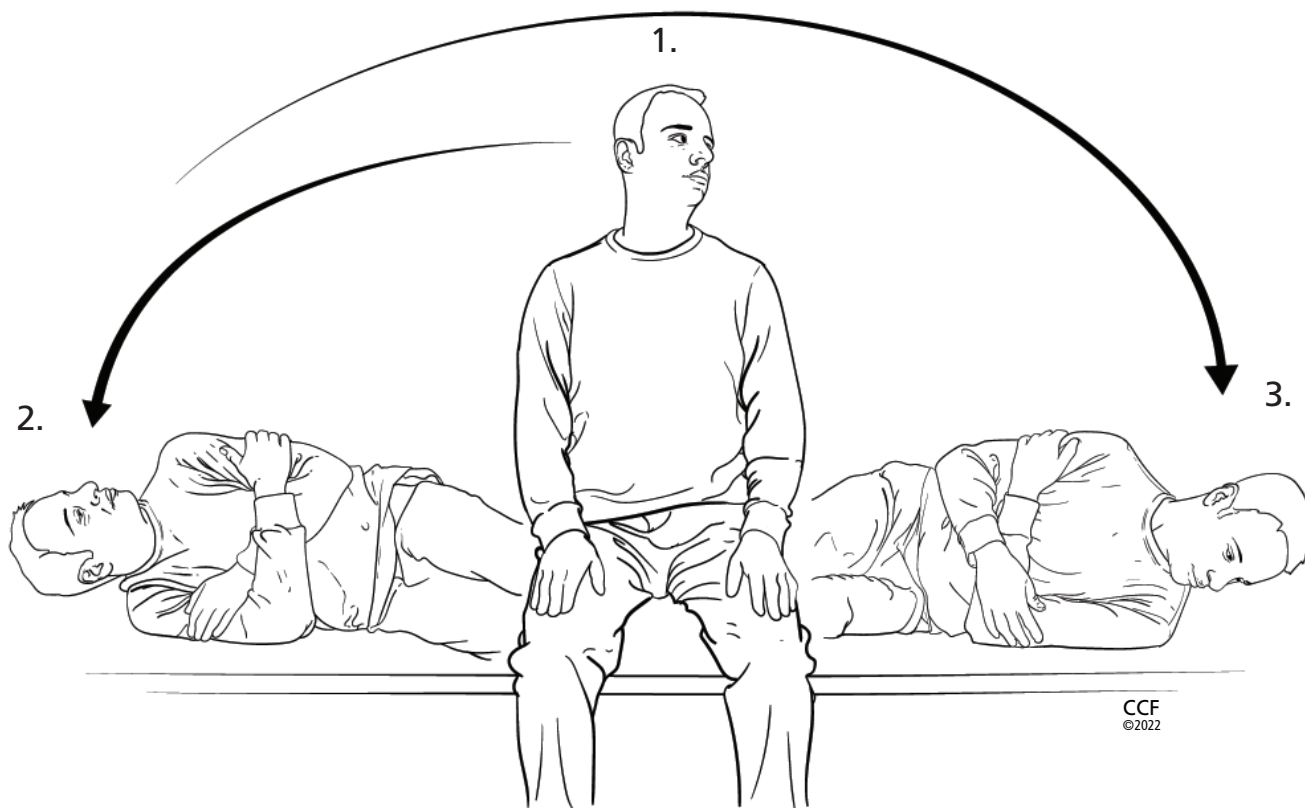


Figure 5. Semont maneuver, an alternative way to clear otoconia from the posterior or anterior canals:

1. Place the patient in a seated position on the bed and turn the head 45° away from the ear with the suspected otoconia in the vertical semicircular canal.
2. Quickly move the patient on their side with the nose facing the ceiling.
3. Quickly move the patient back up and onto their other side with the head in the same 45° angle with the nose facing toward the ground. The examiner then assists the patient to a seated position, keeping the head at 45° away from the ear with suspected vertical semicircular canal benign paroxysmal positional vertigo (BPPV).

Note: The head position described in step 1 is used for posterior semicircular canal BPPV. The patient should turn the head 45° toward the ear with suspected vertical semicircular canal BPPV if the anterior semicircular canal is affected.

patient describe their symptoms and observing the nystagmus patterns help to determine which side is affected and should be treated. Referral to a vestibular specialist is warranted to ensure the correct side and proper treatment. Additionally, many other disorders can present with direction-changing horizontal nystagmus, and thorough evaluation to rule in or rule out BPPV should be made in these cases (see “BPPV care path” below).

Given that geotropic horizontal semicircular canal BPPV is more common than the apogeotropic variant, clinicians can perform the log roll 360° maneuver. If the apogeotropic variant is present, the Gufoni maneuver can be performed.^{4,17} Following

the steps shown in **Figure 6** ensures proper head and body placement for moving the debris out of the affected horizontal canal. It is imperative to support the patient’s head during all movements. The patient should be kept in each position until symptoms and nystagmus stop.

■ BPPV CARE PATH

The following care path is a suggested guideline to evaluate and treat BPPV.¹⁷

1. Determine if the patient’s symptoms of dizziness or vertigo last seconds to minutes in response to position changes. If the patient has acute neurologic or cardiovascular symptoms, consider further workup

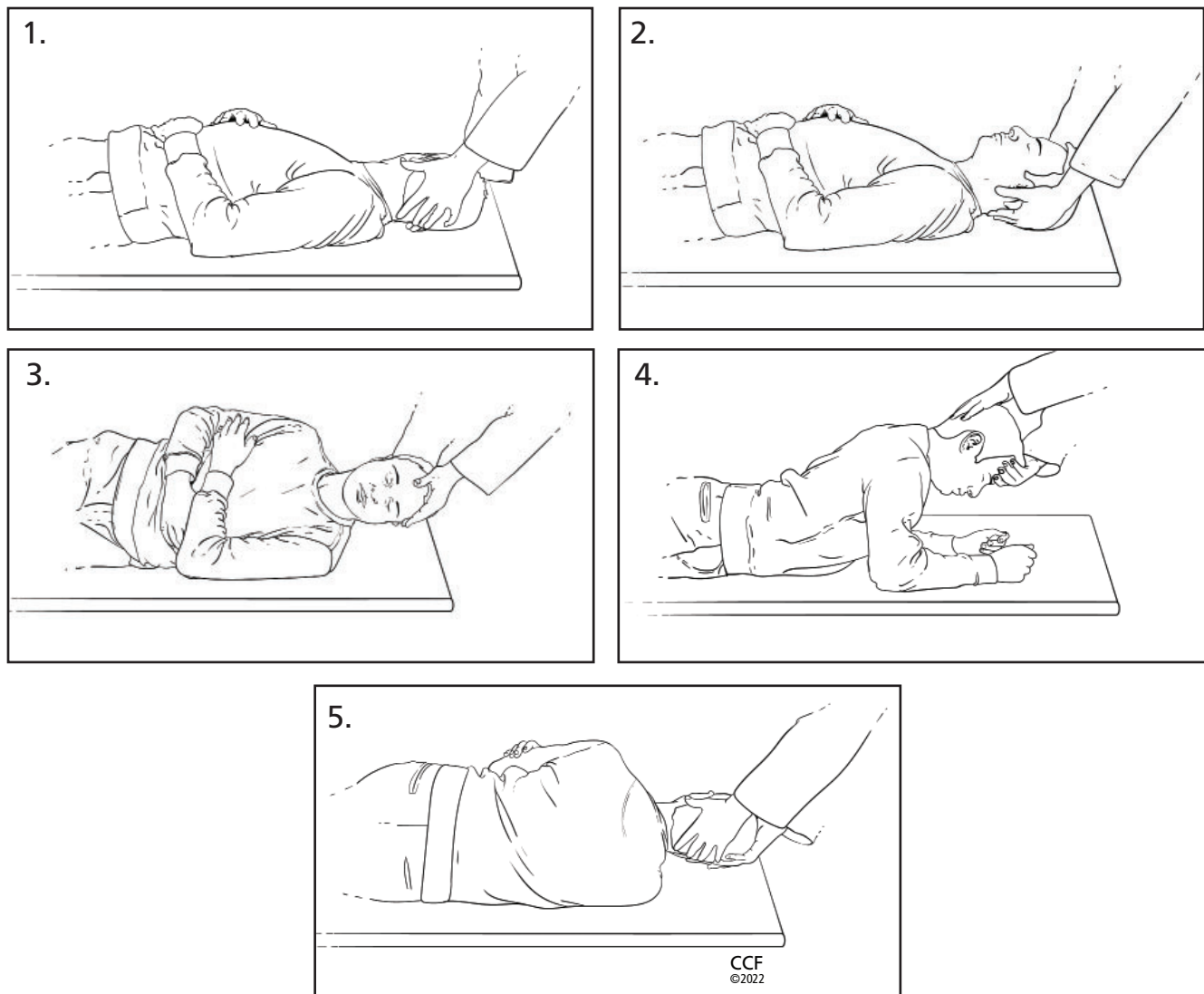


Figure 6. Log roll (360°) maneuver to clear otoconia from the horizontal semicircular canal:

1. Place the patient in the supine position and turn their head 90° toward the ear with the suspected otoconia in the horizontal semicircular canal.
2. Next, turn the patient's head back to center, with the head elevated 30°.
3. Maneuver the patient onto their side (90°) toward the unaffected ear.
4. Move the patient into the prone position with elbows flexed. Note: Sometimes treatment can end in this position (called 270° maneuver).
5. Finally, help the patient back onto their back toward the ear involved, completing a complete 360° rotation.

to rule out stroke or a cardiovascular diagnosis.

2. Take vital signs, including blood pressure.
3. Check medications.
4. Perform cranial nerve examination; look for any nystagmus or disconjugate eye movements.
5. Perform the Dix-Hallpike maneuver and the supine roll maneuver. If these maneuvers elicit symptoms and nystagmus, consider treatment for

BPPV (Table 3) or refer the patient to a vestibular physical therapist or vestibular audiologist to perform the treatment maneuver.

6. If the patient meets diagnostic criteria for BPPV and has no other symptoms or signs suggesting another otologic or neurologic disorder, do not recommend radiographic imaging or formal vestibular testing. If the patient does have separate otologic

TABLE 3

Treatment maneuvers for BPPV, based on location of otoconia

Location	Treatment maneuver
Posterior canal	Epley or Semont
Anterior canal	Epley or Semont
Horizontal canal (geotropic-type nystagmus pattern)	Log roll (360°)

or neurologic indications or a complicated history or if the diagnosis of BPPV is unclear, a full workup should be considered including referral to an ear, nose, and throat specialist, a vestibular audiologist for formal vestibular testing, and a neurologist.

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7. Many patients experience lingering symptoms of imbalance after successful treatment of BPPV. Consider referral to a vestibular rehabilitation program to promote compensation for and habituation to symptoms.
8. Patients may also find it useful to perform particle-repositioning maneuvers at home to help treat recurrent or persistent BPPV. Patients may be provided with handouts on how to perform home treatment or referred to online resources (eg, <https://my.clevelandclinic.org/health/diseases/11858-benign-paroxysmal-positional-vertigo-bppv>).

DISCLOSURES

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