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To prophylax or not to prophylax for endocarditis: Still a question

On the surface, the question does not seem complicated. Infective endocarditis (IE) is a bad disease. In most published case series, viridans streptococci of presumed oral origin are the second most common causative bacterial agents (Staphylococcus is the most common), invasive dental procedures release these and other bacteria into the bloodstream, and well-tolerated, inexpensive oral antibiotics such as amoxicillin are effective therapy. Thus, it “makes sense” to prophylax with antibiotics before an invasive dental procedure.

Many guidelines have been written about this over the past half-century. They have evolved in some ways to be simpler (a shorter oral antibiotic course), but in some ways to be more complex (basing the need for prophylaxis on specific patient risk factors). Currently, there is no uniformity among guidelines worldwide, even though they are based on the same available published data. As with many practice guidelines and recommendations, what would seem to “make sense” may not be fully supported or refuted with robust data sufficient to meet the rules of each guideline-writing committee.

In this issue of the Journal, McCartney et al have synthesized the available information into pragmatic recommendations on the prevention of IE and prosthetic joint infections related to dental procedures.

The question of prophylaxis, simply addressed, is one of risks and benefits. What are the risks and costs of a single dose of antibiotic for the individual patient and to society, and how much IE can be prevented by antibiotic prophylaxis? At least in the United States, decisions like this have medicolegal implications and are not exempt from attribution of culpability if adverse outcomes occur, but I don’t intend to discuss that facet of the decision process here.

IE, unrelated to medical or nonmedical intravenous manipulations, is an uncommon condition, and not all episodes are caused by bacteria of oral origin. Hence, there are no great prospective randomized controlled trials to assist guideline-writing committees. The authors of a 2023 systematic review of the literature found a single cohort study that met their criteria and opined that the evidence supporting or discouraging antibiotic prophylaxis before dental procedures to prevent IE is “very low.”

While there is and should be concern regarding any unnecessary antibiotic use, the likelihood of a significant adverse outcome attributable to a single dose of amoxicillin seems low, assuming patients are asked about any history of a significant allergic reaction. Yet the cumulative effect of multiple doses over time in a population is likely incalculable.

There are clinically intriguing aspects of the ongoing dialogue that begin with learning more about the biology of the oral microbiome and about bacteremia resulting from dental procedures and daily gum trauma, as well as from indirect data accumulated mainly from observational studies evaluating antibiotic prophylaxis and IE.

Questions persist as to how to react to the data regarding bacteremia after infrequently performed invasive dental procedures vs bacteremia associated with normal dental hygiene such as

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daily toothbrushing. In an interesting temporal evaluation of bacteremia after a single routine brushing, single dental extraction with amoxicillin prophylaxis, or single extraction without antibiotic, there was no huge clinical difference in the occurrence and persistence of bacteremia with strains known to be associated with IE. The incidence of bacteremia was 23%, 33%, and 60% in the toothbrushing, dental extraction with amoxicillin, and dental extraction without antibiotic groups, respectively. Notably, the duration of bacteremia was less than 20 minutes in greater than 90% of the 290 study volunteers, and only 2% of the brushing group and 5% of the extraction without antibiotic group had ongoing low-level blood culture growth at 60 minutes.

Considering that people with good dental hygiene generally brush twice daily, the cumulative exposure to oral bacteria in the bloodstream from routine dental care is numerically far more likely to be associated with IE than invasive procedures including extractions. The risk is even greater in those with suboptimal dental health. Patients with poor dental hygiene may brush and floss less frequently, but the degree of bacteremia is greater with each brushing in those with more plaque and periodontal disease. Doing the arithmetic, it is surprising that there is not a higher prevalence of IE in the general population. We have more to learn regarding the successful clearance of bacteria from the bloodstream and why those protective mechanisms occasionally fail.

Given the above complexities and the dearth of hard data showing a benefit of prophylaxis, the UK guidelines in 2008 and subsequent Swedish guidelines in 2012 did not recommend antibiotic prophylaxis before invasive dental procedures, even for patients deemed at high risk for IE. Vähäsarja et al6 conducted a cohort study analysis to see if there was an increase in IE after the change in the Swedish guidelines: the authors noted a 40% reduction in antibiotic prescriptions written by dentists, but no significant increase in IE. There are multiple caveats to consider when interpreting this analysis, and a study of similar design in England7 performed after the UK guidelines rescinded the recommendation for prophylaxis, did report an increased incidence in IE in high-risk patients.

So what seems simple is apparently not. Nor in this case is the definition of what “makes sense.”

Brian F. Mandell, MD, PhD
Editor in Chief

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Cleveland, OH, and live stream

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September 22–23  
Cleveland, OH

**WAKE UP TO SLEEP DISORDERS 2023: A CLEVELAND CLINIC SLEEP DISORDERS CENTER UPDATE**  
September 23–24  
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**OHIO OCULAR ONCOLOGY SYMPOSIUM**  
September 23–24  
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**MULTIPLE MYELOMA SCREENING: EARLY DETECTION OF A RARE BLOOD DISEASE**  
September 25  
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**THE PREVENTION AND MANAGEMENT OF CARDIOVASCULAR DISEASE: A CONTEMPORARY UPDATE**  
October 12–13  
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**INTENSIVE REVIEW OF ENDOCRINOLOGY AND METABOLISM**  
October 13–15  
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**HEADACHE TREATMENT: HITTING A HOME RUN WITH PATIENTS**  
October 14  
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October 19–20  
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**RESTORING NEUROLOGICAL FUNCTION: THE CROSSROADS OF NEUROLOGY, PSYCHIATRY, AND NEUROSURGERY**  
October 27  
Cleveland, OH

**UTILIZING ARTIFICIAL INTELLIGENCE IN THE PREVENTION AND MANAGEMENT OF CARDIOVASCULAR DISEASE: APPLICATIONS, BENEFITS, AND CHALLENGES**  
October 27–28  
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November 3  
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November 4  
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Beachwood, OH

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November 10–12  
Beachwood, OH

**CONTEMPORARY MULTIDISCIPLINARY CARE OF THE HEAD AND NECK CANCER PATIENT: UPDATES ON THE INNOVATIVE APPROACHES TO HEAD AND NECK CANCER TREATMENT**  
November 17  
Cleveland, OH

**MULTIPLE MYELOMA SCREENING: EARLY DETECTION OF A RARE BLOOD DISEASE**  
November 17  
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Computed tomography of the head

To the Editor: While I agree with Dr. Muth and colleagues1 that computed tomography (CT) of the head is overused, the claim that it only rarely reveals a contributing process in patients with delirium is at odds with the available evidence. A recent systematic review and meta-analysis including 21,500 patients in 46 studies reported a diagnostic yield of 13% for head CT in hospitalized patients with delirium, suggesting that this test can provide valuable information in selected patients. In addition to the authors’ framework, 2 additional steps should guide the use of head CT: first, individualizing the differential diagnosis, and second, risk-stratification using pretest probability. Applying these steps to the case in their article, consideration of cerebrovascular accident is warranted given the patient’s advanced age and the fact that delirium occurs in approximately 25% of patients with acute stroke.3 However, other features allow us to predict that head CT will have low diagnostic yield. First, the case does not mention focal neurologic deficits, which if present would increase the pretest probability of cerebrovascular accident when using tools like the National Institutes of Health stroke scale as the authors suggest. Second, the occurrence of delirium on hospital day 4 suggests exposure to other causes of delirium more common than acute stroke.4

The presence of focal neurologic deficits in patients with delirium increases the diagnostic yield of head CT from 13% to 19% in medical inpatients.2 If physical examination in this case was without evidence of focal neurologic deficits, then the pretest probability of cerebrovascular accident is low, and neuroimaging may not be necessary. However, in the presence of these deficits, head CT would be justified. In sum, we shouldn’t throw the baby out with the bathwater: the diagnostic yield of even an overused test can be maximized with tailored, probabilistic reasoning.

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REFERENCES
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In Reply: We thank Dr. Ganatra for his comments regarding our 1-Minute Consult.1 In particular, he has brought to our attention recent research concerning the use and utility of computed tomography (CT) in delirium and altered mental status.2 His suggestion to individualize the differential diagnosis and use pretest probabilities to stratify risk is valid, and we fully agree with it. A crucial distinction, however, is that the study cited by Dr. Ganatra included both hospitalized patients and patients in the emergency department, whereas the study we cited and our patient case included only hospitalized patients. The diagnostic yield in emergency department patients may not be generalizable to already-hospitalized patients because these settings have different acuity levels. In fact, head imaging in the emergency department reveals an intracranial process in 14% to 39% of cases, which appears to differ significantly from the yield of CT in hospitalized patients.3

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REFERENCES
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Severe skin rashes

To the Editor: In the June issue, Jaroenpuntaruk et al1 described the early diagnosis and management of severe drug eruptions. We have several suggestions for this review.

Marcantonio ER.

Severe skin rashes

To the Editor: In the June issue, Jaroenpuntaruk et al1 described the early diagnosis and management of severe drug eruptions. We have several suggestions for this review.

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doi:10.3949/ccjm.90c.08001

Severe skin rashes

To the Editor: In the June issue, Jaroenpuntaruk et al1 described the early diagnosis and management of severe drug eruptions. We have several suggestions for this review.

REFERENCES

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First, the subtypes of severe drug eruptions usually include Stevens-Johnson syndrome/toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis (AGEP), but not drug-induced vasculitis.\(^2^,^3\) As noted in the article, drug-induced vasculitis is usually a small-vessel vasculitis and is limited to cutaneous vasculitis and arthralgia. Severe multiple-organ involvement is rare.

The authors also pointed out that skin biopsy is the gold standard for diagnosing severe drug eruptions. It is certainly not the gold standard, although pathology plays a role in the diagnosis and differential diagnosis of drug eruptions. Pathologic clues of drug eruptions include apoptotic keratinocytes, eosinophils within the inflammatory infiltrate, papillary edema, and vascular changes. However, these are nonspecific. The diagnosis of severe drug eruptions lacks specific tests and relies on a comprehensive analysis of the clinical presentation, history, and laboratory findings.\(^2^,^3\)

Finally, it is inappropriate to recommend dermoscopy for AGEP due to a lack of valid evidence. Only 1 case report has mentioned that dermoscopy could help visualize pustules and was useful in distinguishing AGEP from morbilliform drug eruption.\(^4\) It is not difficult to observe pustules with the naked eye in most cases. Furthermore, dermoscopy does not distinguish AGEP from other pustular skin conditions such as pustular psoriasis, subcorneal pustulosis, and pustular vasculitis. Dermoscopy is of limited value in the diagnosis and grouping of drug eruptions.

Identification of a potential culprit drug is complicated by the fact that patients usually use several drugs simultaneously. Patch testing is a safe and practical technique. The utility of testing may vary on the specific drug and the subtypes of drug eruptions.\(^5\) Neither the prick test nor the intradermal test is sensitive than the prick test, and an oral drug-provocation test is prohibited due to the risk of relapse.\(^2\)

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REFERENCES

In Reply: We thank Drs. Zhang, Wu, and Chen for their interest in our article and their helpful points. We agree that many cases of drug-induced vasculitis are self-limited. But without early recognition, while rare, some cases can present as severe multi-organ involvement.\(^1\) We also agree that a comprehensive analysis of the clinical presentation, history, and laboratory findings is important for diagnosing the etiology of a drug rash. While not all severe skin rashes require biopsy, for the 4 diagnoses we reviewed, when there is initial diagnostic uncertainty, we believe skin biopsy is usually a helpful best next step.

Finally, we agree that acute generalized exanthematous pustulosis is primarily diagnosed with clinical, laboratory, and sometimes histologic criteria, often with the support of the European Study of Severe Cutaneous Adverse Reactions diagnostic score. Dermoscopy may help in early stages of disease, although we certainly agree this would be just 1 small part of the diagnostic evaluation.\(^2\)

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REFERENCES

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‘Kissing tonsils’ and splenic infarction from infectious mononucleosis

A 36-year-old man presented to the emergency department with severe pain in the left upper quadrant. This was preceded by 10 days of nonproductive cough, sore throat, and fever. His female partner had experienced similar symptoms starting 2 days prior to his symptom onset.

Physical examination was significant for erythematous swollen tonsils with white exudates, bilateral tender cervical lymphadenopathy, and left upper quadrant tenderness. The tonsils were touching (ie, “kissing”) (Figure 1). There was no stridor or wheezing, but the patient had difficulty swallowing and tolerating oral secretions.

Laboratory studies showed a leukocytosis of 26 × 10⁹/L (reference range 4.0–11.0), with 56% lymphocytes and 11% atypical lymphocytes. Aminotransferases were elevated, with an aspartate aminotransferase 71 U/L (7–30), alanine aminotransferase 92 U/L (11–30), and alkaline phosphatase 119 U/L (16–100). Computed tomography (CT) of the abdomen showed splenomegaly with multiple acute-appearing splenic infarcts visualized as large, wedge-shaped peripheral areas of non-enhancement (arrows).

A heterophile antibody (“monospot”) test was positive, consistent with acute Epstein-Barr virus mononucleosis. Throat culture later grew beta-hemolytic group C streptococci, which was thought to represent colonization. Given the approximation of the tonsils and difficulty swallowing and tolerating secretions, steroids were initiated, and he was transferred to the intensive care unit for monitoring. He was discharged on hospital day 6 with 5 days of dexamethasone, and 8 weeks later his symptoms had resolved.
KISSING TONSILS

DIFFERENTIAL DIAGNOSIS OF TONSILLAR ENLARGEMENT

The differential diagnosis in cases of bilateral tonsillar enlargement in adults includes infection with groups A, C, and G streptococci, Fusobacterium necrophorum, Neisseria gonorrhoeae, Corynebacterium diphtheriae, Toxoplasma gondii, and viral pathogens including Epstein-Barr virus, cytomegalovirus, adenovirus, herpes simplex virus type 1, human herpesvirus type 5, measles, rubella, human immunodeficiency virus, and hepatitis A virus. Other causes of tonsillar enlargement include malignancy, notably squamous cell carcinoma or lymphoma, although these are less likely to present in the acute setting and are usually unilateral. Peritonsillar abscess should be considered, but it is also less likely to have bilateral involvement.

ASSESSMENT OF TONSILLAR ENLARGEMENT IN INFECTIOUS MONONUCLEOSIS

The typical features of infectious mononucleosis include fever, pharyngitis, lymphadenopathy, and atypical lymphocytosis. Pharyngitis is a relatively common symptom of infectious mononucleosis and is present in an estimated 85% of cases. Pharyngeal inflammation is often accompanied by tonsillar exudates, which usually appear white or gray.

In rare cases, airway compromise secondary to tonsillar edema may occur, and thus it is important to focus on the patient’s ability to swallow. If the patient is not tolerating oral secretions, emergent consultation with an otolaryngologist should be considered. Other causes of tonsillar edema may occur, and thus it is important to present in the acute setting and are usually unilateral. Peritonsillar abscess should be considered, but it is also less likely to have bilateral involvement.

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DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.
Q: Getting to the root of the problem: Should my patient receive antibiotics before dental procedures to prevent infective endocarditis?

A: There has been some confusion within the medical community about antibiotic prophylaxis for specific patient populations before undergoing dental procedures.\(^1\)\(^2\) Guidelines have changed significantly from the original 1955 recommendations that initially included longer antibiotic courses and a more generalized patient population.\(^1\)\(^2\)

Individual risk for infective endocarditis depends on both inherent patient risk factors and procedural risk factors. The American Heart Association,\(^3\) Thornhill et al,\(^1\) and the American Dental Association\(^4\) have provided guidelines and definitions of patient characteristics associated with higher risk of developing infective endocarditis and stratification of various dental procedures:

- Prior history of infective endocarditis
- Prosthetic material used for heart valve repair (including percutaneous valve procedures)
- Unrepaired cyanotic congenital heart disease
- Repaired congenital heart disease in which palliative shunts or conduits were used
- Complete repair or heart transplant with subsequent valvulopathy.\(^1\)\(^3\)\(^4\)

Here, we offer practical points to aid decision-making related to antibiotic prophylaxis for patients and clinicians.

ANTIBIOTIC PROPHYLAXIS AND INFECTIOUS DISEASES

A major aspect of infectious disease practice is to promote antibiotic stewardship for the community at large, which helps to prevent ongoing antibiotic resistance and prevent unnecessary harm to patients from interventions. Infective endocarditis is associated with significant morbidity and mortality; however, given its overall low incidence,\(^1\) randomized controlled clinical trials to study antimicrobial prophylaxis is impractical and unlikely to be completed. Furthermore, it is important to discuss the utility of prophylaxis in patients with prosthetic joints undergoing dental procedures as this has been a controversial topic among clinicians.\(^2\)

If a high-risk patient undergoes an invasive dental procedure, ie, involving gingival or apical manipulation or oral mucosa perforation, it is reasonable to give a single dose of antibiotic prophylaxis 30 to 60 minutes before the invasive dental procedure, usually amoxicillin 2 g. For patients allergic to penicillin, other options include single doses of cephalexin 2 g, doxycycline 100 mg, or azithromycin 500 mg.\(^3\)

Risk classification

A recently published cohort study by Thornhill et al\(^1\) performed risk-stratified, case-crossover analyses of roughly 8 million US patients. It is the only study in recent times to demonstrate that antibiotic prophylaxis in high-risk patients before invasive dental
procedures is successful in decreasing the incidence of infective endocarditis (odds ratio 0.38, P = .002). The study also found a statistically significant temporal relationship between invasive procedures and the subsequent development of infective endocarditis in high-risk patients (odds ratio 2.00, P = .002). Further, they classified patients in need of prophylactic antibiotics according to the type of procedure:

- Invasive: use antibiotic prophylaxis (eg, tooth extraction, oral surgery, scaling)
- Intermediate: possible use of antibiotic prophylaxis (eg, fillings, crowns)
- Noninvasive: antibiotic prophylaxis not necessary (eg, oral examination without gingival-apical manipulation, placement of removable orthodontic appliances ).

This study has limitations. First, the data were obtained from 2000 to 2015 and may not be representative of the current cardiac population given the boom in newer prosthetic valve interventions. Also, there was no microbial identification, which raises the question of another potential cause of infective endocarditis other than the patient's recent dental procedures. Lastly, the study did not capture the population lacking dental insurance, who are more likely to have poor oral hygiene and may have different endocarditis risk profiles.

An interesting aspect seen in this study was the low level of clinician adherence to established guidelines, as approximately one-third of high-risk individuals who underwent invasive dental procedures received antibiotic prophylaxis. Compliance has been a long-standing issue commented on by Wahl in the 1990s, when even cardiologists were roughly 50% compliant with American Heart Association guidelines. In a separate survey, it was shown that dentists were also nonadherent with guidelines and often overprescribed antibiotic prophylaxis owing to medical-legal concerns (24%) and inappropriate classification of high-risk groups, including history of type 2 diabetes (27%), human immunodeficiency virus (18%), and chronic kidney disease (13%).

**MULTIDISCIPLINARY APPROACH**

Currently, a multifactorial approach can be used to decrease the risk of infective endocarditis and includes good oral hygiene and education and counseling of patients to self-monitor.

Oral hygiene

An important modifiable risk factor recognized by the American Heart Association is good oral hygiene, which is believed to be far more important than antibiotic prophylaxis before invasive dental procedures. Routine daily dental care such as toothbrushing has been reported to lead to transient oral bacteremia known to be associated with infective endocarditis, which cumulatively could represent a significant risk over time. Further research has shown that good dental health has been associated with less incidence of this transient bacteremia. Thus, ensuring proper access to and utilization of dental services is another key feature of good oral health. A recent study by the National Center for Health Statistics looked at access to dental insurance in the United States and showed wide variability, with only 50% of adults age 18 to 64 having had dental coverage during the 12-month study period.

**Self-monitoring**

Education and counseling of high-risk patients regarding taking prophylactic antibiotics and monitoring for febrile illnesses after dental procedures is a crucial part of care. For febrile patients, emphasis on the importance of getting blood cultures before systemic antibiotic therapy must be stressed. This can be instrumental in early detection of organisms and early diagnosis and can hopefully lead to rapid de-escalation of therapy, all of which lead to better prognosis for patients.

Additionally, it is important to advise patients to be evaluated by dentistry before advanced cardiac procedures, with the goal of improving oral health and potentially decreasing the risk of infective endocarditis.

**PROSTHETIC JOINT INFECTION: INSUFFICIENT EVIDENCE FOR REGULAR PROPHYLAXIS**

Although it was common in the past for patients with prosthetic joints undergoing invasive dental procedures to receive antibiotic prophylaxis to prevent infection, recent guidelines have shifted away from regular prophylaxis owing to insufficient evidence. In a UK cohort study, Thornhill et al noted no significant temporal association with prosthetic joint infection after invasive dental procedures. A review by Goff et al revealed the pitfalls present in the system of private dentistry, including the lack of awareness by orthopedic surgeons, dentists, and primary care physicians regarding actual infection risk after invasive dental procedures, estimated to be less than 1%. They also described the lack of awareness regarding disadvantages of overprescribing antibiotics leading to patient harm from *Clostridioides difficile* infection and other adverse drug reactions.
TAKE-HOME POINTS

- We understand the extreme caution taken when prescribing prophylactic antibiotics. Currently, there are no reliable data to support prophylaxis of the general joint-replacement population.
- However, for immunocompromised patients, such as those with human immunodeficiency virus, transplant recipients, patients on chemotherapy or those with history of prosthetic joint infections treated surgically, there are conflicting guidelines about antibiotic prophylaxis and further research is warranted.²
- There is convincing evidence currently to prescribe antibiotic prophylaxis to high-risk patients undergoing invasive dental procedures as described.
- It is important to stress that the overall incidence of infective endocarditis after dental procedures is low, and that good oral hygiene, adherence to guidelines, and access to dental care should be at the forefront.
- There is always room to improve on antibiotic stewardship for our patients at large, and we hope that our comments clarify some of the questions that may arise.

REFERENCES


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- Provide patient-appropriate, safe, effective women’s healthcare in special populations including gynecologic and LGBTQ+ and understand limits to access to reproductive health care for all.
- Assess and care for patients with difficult to manage behavioral health disorders including treatment resistant depression, bipolar disorder and adolescent depression using both pharmacologic and non-pharmacologic treatment.
- Identify behavioral and substance addiction in patient care and employ evidence-based recommendations for management, as well as use of toxicology screens to manage risk and abuse.
- Identify indications for injection, risks and benefits and injection of major joints and trigger points including the knee and shoulder, carpal tunnel syndrome and trigger points in patient care.
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A new policy update on breastfeeding: What all clinicians need to know

ABSTRACT

Although the 2022 policy statement on breastfeeding from the American Academy of Pediatrics primarily addresses clinicians caring for pediatric patients, the Academy urges clinicians of all disciplines who may interact with breastfeeding mothers and babies to increase their understanding of breastfeeding and their ability to support this population. Studies published since the 2012 update continue to reinforce the cumulative short-term and long-term infant and maternal health benefits of breastfeeding and human milk consumption.

KEY POINTS

Breastfeeding provides short-term and long-term benefits to mothers and babies.

Exclusive breastfeeding is recommended in the first 6 months and should be supported for 2 years and beyond or as long as desired by the mother and baby.

Breastfeeding support must be individualized to mothers and their infants.

Clinicians should familiarize themselves with resources for determining safety of medications, substances, and imaging.

Clinician advocacy for better support for breastfeeding patients will improve infant and maternal health outcomes and eliminate health disparities.

THE MOST RECENT POLICY STATEMENT ON breastfeeding from the American Academy of Pediatrics (AAP)\(^1\) focuses on enhanced communication with and support for breastfeeding mothers and babies—ie, the breastfeeding dyad—and urges clinicians to increase their understanding of breastfeeding and their ability to support it.

For brevity, this article uses terms such as mother and breastfeeding, but the authors recognize there is terminology that may be preferred over these terms for patients depending on their gender identity and feeding method, such as chestfeeding, breast-milk feeding, lactating parent, and human-milk feeding, and efforts should be made to use the patient’s preferred language in the clinical setting.\(^2\)

WHO IS THE INTENDED AUDIENCE?

The updated guidelines primarily address clinicians caring for pediatric patients, but the recommendations are relevant for any clinician caring for a breastfeeding mother or infant.

WHO WROTE THE GUIDELINES?

The policy update relied on the consensus of the clinical expertise of the AAP Section on Breastfeeding Executive Committee and evidence from recently published peer-reviewed literature. No conflicts of interest were reported.\(^1\)

WHICH RECOMMENDATIONS REMAIN THE SAME?

The update reinforces the importance, duration, and considerations of breastfeeding and
human milk consumption in mothers and newborns. Some of these recommendations remain unchanged from previous AAP guidelines.

**Benefits**

Breastfeeding confers short-term and long-term benefits to mothers and infants that are important to communicate to patients, especially in the prenatal setting. The beneficial effects encompass disease processes that represent most specialties, and clinicians of all disciplines should be aware of them.

For infants, breastfeeding is associated with decreased risk of otitis media, upper and lower respiratory tract infections, asthma, bronchiolitis, necrotizing enterocolitis, atopic dermatitis, celiac disease, gastroenteritis, inflammatory bowel disease, type 1 and type 2 diabetes mellitus, leukemia, childhood obesity, and sudden infant death syndrome. Maternal benefits include lower risk of postpartum hemorrhage, postpartum depression, cardiovascular disease, hypertension, hyperlipidemia, type 2 diabetes, rheumatoid arthritis, endometrial cancer, thyroid cancer, breast cancer, and ovarian cancer.1,3–7

**Duration**

The AAP recommends that infants be breastfed exclusively for 6 months with slow integration of complementary foods, when developmentally appropriate, at about 6 months. Earlier introduction of complementary foods can increase the risk of acute respiratory and diarrheal illnesses.1

**Contraindications**

The policy reiterates known contraindications to breastfeeding, including galactosemia, maternal human T-cell lymphotropic virus type I or II, untreated maternal brucellosis or tuberculosis, and human immunodeficiency virus (HIV) with high viral loads. (Note: A recommendation from the US Department of Health and Human Services published after the AAP guideline allows for breastfeeding in mothers with undetected HIV viral load.3) Infants should not breastfeed from or receive milk from a breast with active herpes lesions, but babies can breastfeed from or receive milk from the unaffected breast.1

**Special considerations**

**Maternal medications.** Most medications are compatible with breastfeeding, and information is readily available. Drugs and Lactation Database (LactMed)9 of the National Library of Medicine and National Institutes of Health can be accessed online at no cost. The book Hale’s Medications and Mother’s Milk 202310 is available through the libraries of many medical institutions. The website InfantRisk Center11 provides information, an app for a small fee, and a free hotline with access to a trained nurse.

Medications with an L5 rating are incompatible with breastfeeding. The L5 rating means that “studies in breastfeeding mothers have demonstrated that there is significant and documented risk to the infant based on human experience…and the risk of using the drug in breastfeeding women clearly outweighs any possible benefit from breastfeeding.”12 Most L5-rated medications are chemotherapeutic agents.10

**Preterm infants.** Additional benefits of breast milk include prevention of respiratory illness and improved neurodevelopmental outcomes in preterm infants.1

**Advocacy and support**

Early clinician intervention to support breastfeeding initiation, duration, and exclusivity leads to longer duration of and compliance with exclusive breastfeeding.13 Hospitals and birth centers should implement maternity care practices to encourage breastfeeding initiation, duration, and exclusivity. Initiating skin-to-skin contact and frequent breastfeeding with support as early as possible maximizes breastfeeding benefits, duration, and compliance. Clinicians are encouraged to assess breastfeeding dyads for challenges and to grow comfortable managing them or, alternatively, to cultivate appropriate referral sources and contacts for patient support.1

**WHAT DIFFERS FROM PRIOR GUIDELINES?**

Since its last update in 2012,14 the AAP made several new recommendations and additions to its breastfeeding policy.

**Benefits**

Research has shown that cumulative breastfeeding time correlates inversely with maternal risk of breast, ovarian, endometrial, and thyroid cancer.15–17 The updated policy addresses the effects of sociodemographic and cultural differences and other disparities on rates of breastfeeding, as well as health outcomes of populations affected by disparities.1

**Duration**

The most publicized part of the update is support for mothers to breastfeed for 2 years and beyond. Previously, the AAP had recommended breastfeeding for at least 1 year. The change was made in response to patients reporting feeling alienated or shamed from breastfeeding longer than 1 year. Neutral,
nonjudgmental language will promote support for breastfeeding mothers and diminish shaming of their infant-feeding decisions.

Inclusive and supportive language is important for lactating mothers, especially those who choose to breastfeed beyond 1 year. Questions such as “Are you still breastfeeding?” rather than “What and how are you feeding your child?” can feel judgmental and lead to feelings of alienation and embarrassment and withholding information. The policy change was also a response to new research concluding additional benefit associated with breastfeeding beyond 1 year. These recommendations align with those of the World Health Organization (WHO) and US Centers for Disease Control and Prevention (CDC).

Contraindications
Suspected or confirmed Ebola virus was added to the list of contraindications to breastfeeding.

Special considerations
The 2022 AAP policy emphasizes the need for clinicians to recognize the impact of various infant and maternal factors on breastfeeding management.

Maternal delayed lactogenesis II, or a delay in the breast milk “coming in” around 72 hours postpartum, affects a special population. Maternal risk factors for delayed lactogenesis include obesity, diabetes mellitus, hypertension, cesarean delivery, and preterm labor. Monitoring the infant’s weight, intake, and output is important, as these infants are at risk for the need of supplementation with formula or donor breast milk. Mothers also need support, as they are at earlier risk of breastfeeding cessation despite the low milk supply being temporary.

Very low birth-weight infants. Mothers of very low birth-weight infants are encouraged to continue to use expressed breast milk to decrease the risks of necrotizing enterocolitis, late-onset sepsis, chronic lung disease, and retinopathy of prematurity in infants. Compared with term infants, late-preterm and early-term infants reportedly have decreased breastfeeding rates, stressing the need for more support for these infants.

Infant hyperbilirubinemia. Increased numbers of breastfeeding sessions per day were associated with lower infant bilirubin concentrations among infants with hyperbilirubinemia. Phototherapy is not an indication for formula supplementation if the baby is hydrated or levels of bilirubin are above exchange transfusion levels. Breast milk jaundice can persist for up to 3 months, and no specific management is needed.

Infants at high risk of peanut allergy. In infants with high risk of peanut allergy (severe eczema or known egg allergy), introducing peanut products as early as 4 to 6 months has been shown to decrease the risk of developing peanut allergies by over 80% at 5 years of age compared to delaying introduction until 12 months. It is recommended that these patients consult a pediatric allergist prior to offering peanut products.

Adoption and surrogacy. Breastfeeding is possible in the case of adoption or surrogacy. It requires the adopting or intended breastfeeding parent to prepare months in advance to offset the lack of typical hormonal changes that occur with pregnancy. Preparation includes taking oral contraceptive therapy and providing stimulation of the breasts every 3 hours with a breast pump.

Prenatal maternal opioid users. It is preferable to breastfeed exclusively and have the mother and newborn sleep in the same room (ie, to “room in”). While this decreases withdrawal symptoms in infants, infants should be closely monitored in inpatient and outpatient settings for withdrawal symptoms.

Marijuana. Although the use of marijuana is discouraged, there are insufficient data to assess the exposure effects on breastfeeding infants.

Smoking cessation. Most nicotine smoking cessation products are safe for breastfeeding mothers to use. Although varenicline can be effective for nicotine smoking cessation, little is known about its safety during lactation, so it is not recommended at this time.

Hepatitis B virus. In mothers known to be hepatitis B surface antigen-positive, their infants should receive the initial dose of the hepatitis B vaccine and hepatitis B immune globulin within 12 hours of birth. However, administration should not delay the initiation of breastfeeding, ideally within the first hour of birth.

Hepatitis C virus. Hepatitis C is detected in mothers who are hepatitis C virus (HCV) antibody-positive, their infants should receive the initial dose of the hepatitis B vaccine and hepatitis B surface antigen-positive, their infants should receive the initial dose of the hepatitis B vaccine and hepatitis B immune globulin within 12 hours of birth. However, administration should not delay the initiation of breastfeeding, ideally within the first hour of birth.

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Hepatitis C virus. Hepatitis C is detected in maternal milk, but transmission is not documented. Breastfeeding is contraindicated only if the nipples are cracked and bleeding.

Mastitis. Mastitis occurs in one-third of postpartum women and is compatible with breastfeeding. The Academy of Breastfeeding Medicine (ABM) published a protocol in 2022 that addresses the clinical spectrum and management of this inflammatory condition. Risk factors include exclusive pumping and hyperlactation. Initial management should include continued physiologic breastfeeding or pumping to comfort rather than to empty completely, ice, ibuprofen, and lymphatic drainage techniques to reduce soft-tissue edema. If no improvement is seen with conservative
DO OTHER SOCIETIES AGREE OR DISAGREE?

The CDC, WHO, ABM, American College of Obstetricians and Gynecologists, American Academy of Family Physicians, United Nations International Children’s Emergency Fund, and Canadian Pediatric Society all make the same duration recommendations as the AAP, including exclusive breastfeeding for the first 6 months of life, followed by slow integration of complementary foods until 1 year, and encouraging breastfeeding for 2 years or longer as mutually desired.24-29

HOW WILL THIS CHANGE DAILY PRACTICE?

The AAP policy update emphasizes the breadth and depth of care needed for the breastfeeding dyad. Mothers at risk of breastfeeding challenges should be identified prenatally by their clinician and be provided appropriate education, counseling, and resources. Those with feeding challenges immediately after delivery warrant close follow-up by their primary care physician and a breastfeeding specialist. Breastfeeding medicine, an emerging specialty, can offer these families an added layer of support and expertise. The challenges mothers and infants face are varied, and the mother-infant dyad should be assessed by a clinician experienced in diagnosing and managing breastfeeding challenges.

Clinicians and other healthcare providers need to be aware of patient populations with lower rates of breastfeeding and develop interventions to ensure easy access to support. Breastfeeding support groups, printed and online educational resources, care coordinators, virtual visits, and a larger geographic presence of lactation consultants and breastfeeding medicine clinicians can ensure improved support. We encourage healthcare institutions to promote a supportive environment for breastfeeding that includes lactation training at all levels of patient-facing healthcare and to create their own evidence-based patient education breastfeeding resources or curate existing resources such as those of the ABM and the Institute for the Advancement of Breastfeeding and Lactation Education.10 Clinicians and patients should be made aware of the health benefits of breastfeeding for mothers and infants and view it as a preventive health measure beyond a nutritional source for infants.

WHEN WOULD THE GUIDELINES NOT APPLY?

The new AAP policy recommendations align with those of other societal and global organizations, such as the WHO and CDC. Guidelines may be difficult to apply to all settings, as access to resources may vary. For example, the benefits of breastfeeding may outweigh the risks for mothers with HIV in resource-constrained countries. In addition, cultural norms surrounding breastfeeding inform many areas of this practice, such as duration, exclusivity, and support. While the guidelines would be difficult to implement in settings with limited public and workplace policies to support...
breastfeeding, there is much work to be done at local and widespread levels to make these new recommendations applicable to all interested dyads.

**REFERENCES**


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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Hoarseness: When to observe and when to refer

ABSTRACT

The terms hoarseness and dysphonia are used interchangeably, and both describe a type of altered vocal quality affecting one-third of patients. While hoarseness may be secondary to benign conditions such as reflux or viral laryngitis, it may suggest benign or malignant vocal-fold pathology. It is important for caregivers to know how to evaluate, treat, and when to refer patients for direct visualization via laryngoscopy. In this article, we review basic laryngeal anatomy and function, symptoms of vocal-fold pathology, and current guidelines from the American Academy of Otolaryngology–Head and Neck Surgery on the diagnosis and treatment of dysphonia, including patient referral.

KEY POINTS

If dysphonia is present for more than 4 weeks or a serious condition is suspected, expedited laryngoscopy is recommended.

Current guidelines note that “alarm symptoms” or red flags such as recent head, neck, or chest surgery or intubation, concomitant respiratory distress or stridor, presence of a neck mass, history of tobacco abuse, or professional use of the voice should prompt escalation of care and referral for direct visualization.

Isolated dysphonia should not be treated with antireflux medication, steroids, or antibiotics.

Patients should undergo laryngoscopy or videostroboscopy before referral for speech therapy.

The terms hoarseness and dysphonia are frequently used interchangeably. However, it is important to clarify that hoarseness is a patient-reported symptom, whereas dysphonia is the perception of altered voice quality noted by the clinician. Dysphonia results when there is a physiologic change to the properties of the vocal folds. This can be secondary to altered muscle tone (neuromuscular), impaired closure and mobility (paresis), increased bulk (e.g., tumor, polyp, cyst), mucosal vibratory changes (e.g., scar, inflammation, edema), or a combination.

In this article, we review basic laryngeal anatomy and function, causes of dysphonia, and current guidelines from the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) on diagnosis and treatment of hoarseness and when to refer patients for specialist evaluation.

HOARSENESS AS A SYMPTOM

Hoarseness, either transient or prolonged, is a common complaint affecting as many as one-third of adults at least once in their lifetime. Unfortunately, only a minority of people seek treatment because they believe it will resolve, they do not know treatment is an option, or physicians do not inquire about perceptible vocal changes. While the majority of hoarseness is caused by benign pathology, up to 3% can be caused by malignant tumors and up to 8% by underlying neurologic disorders. Additionally, benign vocal-fold lesions such as cysts, polyps, and nodules are treatable and are responsible for 10% to
30% of complaints. Thus, the cause of hoarseness cannot be determined without appropriate workup, and definitive treatment cannot be provided until a diagnosis is confirmed. Therefore, it is imperative that clinicians have guidance on how to manage, treat, and refer these patients.

**EVALUATION**

When patients are referred to otolaryngology specialists, flexible laryngoscopy may be performed in the office to directly visualize the larynx to aid in diagnosis and guide treatment (Figure 1). In-office laryngoscopy is a routine otolaryngologic procedure performed with the patient sitting upright and awake, without any sedation. A small, flexible camera is passed through the nasal cavity and advanced through the nasopharynx to view the laryngeal complex from above. It is well tolerated by adults and most children and allows clinicians a direct look at the base of the tongue, hypopharynx, and larynx.

Videostroboscopy uses a similar camera but has a special light mechanism allowing for more detailed visualization of vocal-fold motion and function. However, it is not available in all otolaryngology offices.

**LARYNGEAL ANATOMY**

The laryngeal skeleton consists of 3 unpaired cartilages (thyroid, cricoid, and epiglottic) and 3 paired cartilages (arytenoid, cuneiform, and corniculate). The thyroid cartilage is the largest and houses the vocal folds. From an anterior view, the vocal folds sit approximately midway between the inferior thyroid cartilage margin and the laryngeal prominence or “Adam’s apple” (Figure 2).

The muscles responsible for closing or adducting the vocal folds are the thyroarytenoid, lateral cricoarytenoid, and interarytenoid, and the posterior cricoarytenoid is responsible for opening or abducting the folds. These muscles are all innervated by the recurrent laryngeal nerve. Mobility of the vocal folds resulting in hoarseness can therefore be affected by muscle or nerve dysfunction. While unilateral hypomobility and immobility may result in dysphonia, bilateral hypomobility and immobility can cause critical airway obstruction.
The “false” vocal folds (also called vestibular membrane or vestibular folds) sit superiorly to the “true” vocal folds (also called vocal cords) and are separated by the laryngeal ventricle (Figure 3). The true vocal folds generally protect the airway, modulate airflow and acoustics, and are highly sophisticated anatomic structures that are responsible for phonation. The true vocal folds consist of 3 specialized anatomic layers covering the thyroarytenoid muscle (also called the vocalis muscle): squamous epithelium, superficial lamina propria, intermediate lamina propria, and deep lamina propria. Together, the intermediate and deep lamina propria make up the vocal ligament. The integrity of these layers is important because the vibration of the epithelial layer over the gelatinous layer of the superficial lamina propria produces smooth, clear phonation. Any disruption of these layers by tumor, fibrous nodules, cyst, scar, or muscle atrophy may result in hoarseness.

The laryngeal skeleton is divided into 3 subsections based on the location of the true vocal folds. The area above the true vocal folds is referred to as the supraglottis, the area below the true vocal folds is the subglottis, and the horizontal plane of the true vocal folds is the glottis.

VOCAL-FOLD FUNCTION

The main functions of the larynx are respiration, airway protection, and phonation. It takes great coordination for these mechanisms to synchronize so that patients may breathe, swallow, and phonate simultaneously. For respiration, the vocal folds open via action by the single laryngeal abductor muscle (posterior cricoarytenoid muscle). During expiration, the laryngeal adductor muscles work to pull the vocal folds partially toward the midline and modulate expiratory airflow. The vocal folds protect the airway via multiple complex mechanisms and reflexes (such as coughing or the Valsalva maneuver). During phonation, the vocal folds posture so that they sit in the midline, allowing the folds to vibrate against each other and creating vocalization. The mucosal surface of the folds must line up straight and smooth to create a mucosal wave. Irregularities of the mucosa may cause vibration, leading to dysphonia. The frequency and pitch of the voice may be altered by contraction of the laryngeal muscles at different ratios, causing changes in length and position of the vibrating portion of the vocal folds themselves.

A general understanding of the pathology that may cause dysphonia is helpful to clinicians for properly evaluating patients. The consequence of missing a diagnosis varies greatly depending on the severity and nature of the pathology. For the purpose of this review, we break down the major causes of dysphonia into functional, organic, neurologic, and systemic.

FUNCTIONAL CAUSES OF DYSPHONIA

Functional dysphonia is the alteration of vocal quality in the absence of anatomic or neurologic dysfunction. It is relatively common and present in 10% to 40% of patients referred to multidisciplinary voice clinics. It is predominantly seen in women and typically follows...
symptoms of upper respiratory infection. Stress, emotion, and psychologic conflict tend to exacerbate symptoms. Muscle tension dysphonia is the preferred term owing to presumed dysregulation of laryngeal muscle tension caused by either intrinsic or extrinsic laryngeal muscles. Laryngoscopic examination often reveals a “squeezing” or hyperfunction of the laryngeal complex. These patients are best treated with voice therapy with a voice-focused speech language pathologist.

ORGANIC CAUSES OF DYSPHONIA

Acute and chronic laryngitis
Acute laryngitis causes up to 40% of complaints of hoarseness, lasts up to 2 weeks, and most commonly is viral in origin. Alternatively, chronic laryngitis is long-standing and can have several causes, such as reflux, exposure to nicotine and noxious inhalants or inhaled corticosteroids, excessive alcohol or caffeine intake, and bacterial or fungal infection. The most common symptoms of chronic laryngitis overlap with other conditions and include dysphonia, pain, globus, cough, throat-clearing, and dysphagia. Treatment includes avoidance of causative factors and treatment of underlying infectious or inflammatory conditions.

Benign vocal-fold lesions
Vocal-fold nodules are bilateral fibrous swellings along the junction of the medial edge of the anterior and middle third of the true vocal folds. They act like calluses and prevent the propagation of a smooth mucosal wave, resulting in dysphonia. They are secondary to functional voice disorders and vocal abuse or misuse; 80% of patients will recover with voice therapy alone, while those with recalcitrant lesions may require surgical excision.

Polyps and cysts also occur at the medial edge of the true vocal folds but are unilateral tissue proliferations that disrupt the mucosal wave and result in dysphonia. Unlike nodules, they typically do not resolve with therapy and do require surgical excision.

Papillomas. Recurring respiratory papillomatosis is caused by human papillomavirus and leads to respiratory papillomas, which are exophytic lesions that grow along the laryngeal and sometimes tracheobronchial mucosa. When they disrupt vocal-fold vibration, they cause dysphonia and may also lead to airway obstruction. They are generally benign but rarely can have malignant transformation. The disease course can vary greatly and may stabilize in some patients, while progressing to severe obstructive disease requiring frequent excision in others. Treatment is surgical excision, with a limited role for topical and systemic therapy. Rosenberg et al showed a therapeutic advantage after human papillomavirus vaccination in patients with recurring respiratory papillomatosis, with vaccination resulting in fewer surgical procedures required and greater surgery-free intervals. Therefore, the AAO-HNS has published a position statement supporting vaccination for all patients ages 9 to 45.

Scar or sulcus vocalis is a furrow of the epithelium parallel to the vocal-fold edge, dampening the mucosal wave and decreasing pliability. Vocal-fold scars are similar but associated with deposition of fibrous tissue that deposits between the mucosal layer and the deeper muscular layer, causing stiffness of the vocal folds and resulting in dysphonia, vocal fatigue, and increased vocal effort. These conditions may be congenital or caused by vocal trauma, misuse, or surgery.

Reinke edema is also referred to as polypoid constrictis and involves swelling of the true vocal folds owing to accumulation of fluid within the potential space between the superficial lamina propria and the vocal ligaments (also called the Reinke space). The fluid accumulation is due to subepithelial hypervascularity, leading to vascular permeability and the disruption of collagen deposition. Reinke edema is almost exclusively caused by smoking, but vocal abuse or laryngopharyngeal reflux may also play a role. Primary treatment is smoking cessation, treating reflux, and voice therapy. Severe obstructive Reinke edema may require surgery after these conservative treatments.

Malignant or premalignant vocal-fold lesions
Two-thirds of laryngeal cancer is located on the true vocal folds (glottic cancer). Squamous cell carcinoma accounts for over 90% of these cancers, and the earliest symptom is generally hoarseness. Because of this, 24% to 30% of glottic tumors are diagnosed in the early T1 stage, at which point the chances of local and distant metastases are extremely low, and 5-year survival is nearly 100%. Treatment for early-stage glottic carcinoma is either transoral microsurgical resection or radiation therapy.

If early symptoms are ignored and tumors present at later stages (T3 and T4), more radical resection or multimodality treatments are required, and 5-year survival is much lower. Premalignant changes on the vocal folds may appear as keratotic lesions referred to as leukoplakia or as hypervascular, angiogenic-like lesions. Surgical pathology is necessary to provide definitive diagnoses.

Atrophy. Presbylarynx involves atrophy of the true vocal folds secondary to the natural physiologic
aging process. As muscles and mucus-producing cells atrophy, the true vocal folds bow and prevent complete glottic closure. This leads to glottic insufficiency (where air escapes during attempted closure) and increases the surface viscosity of the mucus. These changes result in a hoarse, breathy, weak, or strained voice.

Presbylarynx is present in up to 25% of patients over age 65. Initial treatment is voice therapy, but procedures to improve glottic competence are also an option. Bowing and atrophy are not exclusive to elderly patients and can also be seen in patients who have experienced significant weight loss or general debility.

**NEUROLOGIC CAUSES OF DYSPHONIA**

**Paresis or paralysis.** A large spectrum of vocal-fold hypomobility exists. Complete immobility is generally referred to as paralysis whereas hypomobility is referred to as paresis. Resulting dysphonia is from incomplete glottic closure or irregular vocal-fold motion. The most common cause of vocal-fold paralysis is iatrogenic owing to surgery or trauma along the course of the recurrent laryngeal nerve. Surgeries that frequently risk the integrity of the nerve include thyroidectomy and parathyroid, carotid, cardiac, thoracic, and cervical spine surgery.

A new vocal-fold paresis may also be a symptom of compression of the recurrent laryngeal nerve by a tumor such as thyroid or lung carcinoma. In 2% to 41% of cases, the cause of paresis cannot be identified and is termed idiopathic. Approximately 39% of unilateral idiopathic cases recover partial or complete motion, and 52% experience complete vocal recovery. If paresis persists past 12 months, recovery is unlikely. Initial treatment for paresis or paralysis is voice therapy or augmentation and medialization. Temporary measures (injection augmentation with filler materials) to procedurally medialize the true vocal folds are often employed to improve voice, airway protection, and cough strength. However, after 12 months of paresis, more permanent surgical procedures (such as type I thyroplasty or reinnervation) may be considered.

**Spasmodic dysphonia** is a dystonia affecting the laryngeal muscles and has 2 different subtypes, adductor and abductor. Adductor spasmodic dysphonia is more common (90% of cases) and presents with a pressed, creaky voice caused by the vocal folds inappropriately pushing closed against each other. Conversely, abductor spasmodic dysphonia is more rare (10% of cases) and causes breathy voice breaks owing to the vocal folds inappropriately opening during phonation. Spasmodic dysphonia is treated with injection of botulinum toxin into the affected muscles to weaken them and improve stability of the voice.

**Vocal tremor** is an involuntary rhythmic contraction of the laryngeal musculature resulting in dysphonia. Essential tremor is a generalized neurologic condition that may affect several structures (eg, hands, limbs, head) or specific structures in isolation, such as musculature impacting the voice. Essential vocal tremor is the most common type of vocal tremor and is predominantly found in females (90.6%), with an average onset age of 70. It first presents as increased vocal effort but eventually progresses to obvious and disruptive fluctuations in the frequency and amplitude of phonation. Vocal tremor is difficult to treat, and there are currently no management guidelines. Some proposed treatment strategies include pharmacologic management, botulinum toxin injection, vocal-fold augmentation, and deep brain stimulation.

**Other central and peripheral neurologic disorders.** Parkinson disease is caused by degeneration of dopaminergic neurons of the substantia nigra, resulting in a movement disorder. Symptoms manifest as resting tremor, bradykinesia, rigidity, and loss of coordination, with 70% to 89% of patients experiencing dysphonia with disease progression. Patients with Parkinson disease generally have difficulty initiating and controlling their rate of speech, and the voice is often described as tremulous, breathy, soft, monopitch, or harsh. Laryngoscopy will generally show decreased sensation, bowing of the true vocal folds, glottic insufficiency, and slowed vibration.

Parkinson disease is pharmacologically treated with levodopa. Unfortunately, there is no strong evidence that levodopa improves phonation, and other treatment strategies are generally employed. Voice therapy with a specific modality called the Lee Silverman Voice Treatment program is highly effective in Parkinson disease patients and is only performed by specially trained speech language pathologists. Other procedural interventions such as vocal-fold augmentation (“plumping” up the vocal folds by injecting temporary filler materials into them) can also be employed to help increase volume and strength of phonation.

Other neurologic disorders that can result in dysphonia include myasthenia gravis and Eaton-Lambert disease. Therefore, when clinicians evaluate patients with dysphonia, it is vital to perform a thorough neurologic examination and keep a broad differential diagnosis in mind.
HOARSENESS

■ SYSTEMIC CAUSES OF DYSPHONIA

Systemic diseases such as amyloidosis, rheumatoid arthritis, lupus, granulomatosis with polyangiitis (Wegner granulomatosis), sarcoidosis, tuberculosis, and several others may manifest with laryngeal pathology, leading to hoarseness. Treatment requires a multidisciplinary approach to treat the underlying disease process while also observing and managing laryngeal manifestations. Esophageal reflux can also cause backflow of refluxate into the larynx, resulting in irritation, laryngitis, and hoarseness.2

■ AAO-HNS 2018 GUIDELINES ON HOARSENESS AND DYSPHONIA

Who created them and how are they determined?
The original guidelines were put forth by the AAO-HNS in 200919 and updated in 2018.1 The Academy has a well-established system for creating guidelines that involves a systematic literature search with review by an expert committee. The information is then used to create key action statements with associated strengths of recommendation: strong recommendation, recommendation, option, recommendation against, and strong recommendation against.20 The current guidelines have 13 key action statements.1

Main recommendations
The AAO-HNS has published key action statements and recommends the following to clinicians to identify and manage dysphonia1:

- Obtain a thorough history and perform a physical examination for possible causes.
- “Alarm symptoms” or red flags should prompt escalation of care and referral for direct visualization, including recent head, neck, or chest surgery or intubation, concomitant respiratory distress or stridor, presence of a neck mass, history of tobacco abuse, or professional use of the voice (eg, singer, teacher, politician).
- Referral for laryngoscopy should be considered and is recommended if dysphonia is present for more than 4 weeks or if a serious condition is suspected. However, laryngoscopy can be considered an option if dysphonia is present at any time for any duration, although discretion for referral is left to the clinician.
- Imaging of any kind should not be routinely performed before laryngoscopy if the only complaint and finding at examination is dysphonia.
- There is a recommendation against pharmacologic management with antireflux medications or steroids in the setting of isolated dysphonia.
- There is a strong recommendation against antibiotic treatment for dysphonia.
- Patients should also undergo laryngoscopy before speech therapy referrals; for pathology amendable to therapy, patients should be appropriately referred to speech therapy.
- Surgery should be offered to patients with amendable lesions, such as benign vocal fold lesions that do not respond to therapy, glottic insufficiency, or malignancy.
- For patients with dystonia or spasmodic dysphonia, botulinum toxin injections should be offered in an attempt to weaken the targeted musculature and improve vocal quality.
- Clinicians should provide patients with information on preventive measures and should document and follow patient dysphonia outcomes.

Changes from previous guidelines
It is important to note that the 2018 guidelines1 are updated and vary from the previous 2009 guidelines.19 Changes include the following:

- A major change from 2009 is the addition of a recommendation for expedited referral and escalation of care when alarm symptoms or red flags such as recent head, neck, or chest surgery or intubation, concomitant respiratory distress or stridor, presence of a neck mass, history of tobacco abuse, or professional use of the voice are present.20 New guidelines recommend clinicians wait no longer than 4 weeks1 (old guidelines recommended 3 months19) for hoarseness improvement or resolution before referral for direct visualization.
- Previous guidelines gave clinicians the option to treat chronic laryngitis with a trial of reflux therapy without direct visualization. However, it is important to note that the new guidelines recommend against antireflux medications in isolated dysphonia suspected to be caused by reflux without direct visualization.
- Prior guidelines did not recommend that clinicians should track outcomes. The present guidelines recommend that changes to quality of life, resolution, improvement, or worsening of symptoms should be documented.

How will the guidelines impact the way clinicians practice?
One purpose of these guidelines is to avoid delayed diagnosis of treatable benign lesions, systemic diseases, and early malignancies with an aim to impact the order in which clinicians evaluate and treat
hoarseness. Further, pharmacologic management and imaging should not take place before direct visualization. This helps avoid unnecessary costs and complications associated with drug therapy and imaging. The guidelines also serve to appropriately funnel patients to speech therapy, which may not be a typical part of the clinician’s treatment algorithm.

### TAKE-HOME MESSAGES

While the terms hoarseness and dysphonia may be used interchangeably, hoarseness is a patient-reported symptom while dysphonia is diagnosed by a clinician as altered vocal quality. Hoarseness guidelines from the AAO-HNS assist clinicians in treatment and referral of patients. It is important to recognize that vocal fold pathology can range from benign to malignant, and that ignoring unresolved hoarseness or treating it with inappropriate pharmacotherapy can decrease quality of life or increase the risk of morbidity and mortality when associated with more serious conditions. Referral for direct visualization with laryngoscopy should be prompted by the noted red flags, 4 weeks of unresolved dysphonia, or any suspicion for underlying disease.

### DISCLOSURES

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

### REFERENCES

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Evaluating troponin elevation in patients with chronic kidney disease and suspected acute coronary syndrome

ABSTRACT

Many patients with chronic kidney disease have chronically elevated cardiac troponin levels, and if they present with symptoms suggesting an acute coronary syndrome, it is often difficult to determine if this is the correct diagnosis. This article briefly reviews the major challenges in diagnosing acute coronary syndrome in patients with chronic kidney disease, describes the mechanisms and prognostic significance of troponin elevation in chronic kidney disease, and provides a diagnostic algorithm to risk-stratify patients with chronic kidney disease who have troponin elevation and suspected acute coronary syndrome.

KEY POINTS

Clinicians should use troponin measurements judiciously within a suggestive clinical context and, even more than in the general population, rely on serial testing in light of the high prevalence of elevated baseline troponin levels in patients with chronic kidney disease, even in the absence of acute coronary syndrome.

Because troponin assays vary in diagnostic accuracy, clinicians should be familiar with the characteristics of the local assay used at their institution.

In addition to troponin levels, clinicians should integrate presenting symptoms, traditional risk factors, electrocardiographic changes, and echocardiographic findings.

Troponin elevations pose a dilemma in patients with chronic kidney disease. Cardiovascular disease accounts for about half of deaths in patients with chronic kidney disease, making it the leading cause of death in this high-risk group.1,2 Acute coronary syndrome is diagnosed on the basis of a combination of symptoms, changes on electrocardiography, and a typical rise and fall in cardiac troponin I and cardiac troponin T levels. An increase in cardiac troponin beyond the 99th percentile (the upper reference limit) is clinically relevant, and peak troponin levels inform a risk-based strategy. However, the high prevalence of chronically elevated cardiac troponin in chronic kidney disease makes a biomarker-based diagnosis of acute coronary syndrome challenging.

No validated cutoff values of troponin specific to patients with chronic kidney disease are available. Hence, isolated measurements are difficult to interpret, especially when baseline levels are not known on presentation. Any acute kidney injury in which the serum creatinine level increases by 40% to 60% may result in a 20% rise in cardiac troponin, followed by a subsequent fall during the recovery phase of the kidney injury, mimicking the pattern seen in acute coronary syndrome.3

The influence of dialysis on troponin levels remains controversial due to paucity of data on the confounding effects of sample timing and type of dialysis.4 A small observational study of patients without known heart disease who were about to begin dialysis found that those
with asymptomatic multivessel coronary artery disease already had higher cardiac troponin levels.\textsuperscript{5}

Adding to the diagnostic uncertainty, the presenting symptoms of acute coronary syndrome are more commonly atypical (eg, isolated dyspnea) in patients with chronic kidney disease,\textsuperscript{4} and are often misattributed to nonischemic phenomena such as interdialytic volume overload or intradialytic fluid shifts. When patients with chronic kidney disease do experience an acute coronary syndrome, the prevalence of chest pain (the typical pathognomonic symptom) is inversely related to the patient’s stage of chronic kidney disease, as low as 40\% in those with advanced disease.\textsuperscript{7}

In addition, many patients with chronic kidney disease have abnormal ST-T patterns on electrocardiography even in the absence of acute coronary syndrome, and these may be due to electrolyte abnormalities, left ventricular hypertrophy, and conduction abnormalities, making acute coronary syndrome even more difficult to recognize.\textsuperscript{4}

\section{INCREASED RELEASE AND DECREASED CLEARANCE}

Troponin levels can be elevated in chronic kidney disease as a result of increased release by injured myocytes, decreased clearance by the failing kidneys, or both.

Emphasis was traditionally placed on decreased clearance, as troponin fragments that would normally be excreted by the kidneys would accumulate in patients with decreased glomerular filtration.\textsuperscript{8} However, numerous factors specific to chronic kidney disease contribute to chronic myocardial injury, resulting in an ongoing source of cardiac troponin. These include coronary microvascular disease, left ventricular hypertrophy, hypoperfusion related to hypotension or anemia, and cardiotoxic uremic toxins.\textsuperscript{8}

Notably, regenerating skeletal muscle reverts back to expressing embryonic forms of cardiac troponin T, but not cardiac troponin I, in response to an increased catabolic state in chronic kidney disease.\textsuperscript{9}

\section{TROPONIN IS AN IMPORTANT PROGNOSTIC FACTOR}

The Acute Catheterization and Urgent Intervention Triage Strategy trial randomized 13,819 patients at moderate and high risk with non-ST-elevation myocardial infarction to different antithrombotic regimens and an early invasive strategy.\textsuperscript{10} Of these patients, 2,179 had established chronic kidney disease, and in this group, those with cardiac troponin elevation had higher rates of death or myocardial infarction at 30 days (hazard ratio 2.05) and at 1 year (hazard ratio 1.72). However, the absolute level of baseline elevation did not add further prognostic precision, likely because of the numerous confounding factors specific to chronic kidney disease.\textsuperscript{10}

In a large multicenter prospective trial in patients with low estimated glomerular filtration rates and suspected acute coronary syndrome, troponin I levels higher than the 99th percentile (in this study, 16 ng/L in women or 34 ng/L in men, measured by high-sensitivity assay) accurately identified those at high risk for acute coronary syndrome or cardiac death within 1 year, whereas patients with levels lower than 5 ng/L were at low risk.\textsuperscript{11}

\section{STEPWISE APPROACH TO THE DIAGNOSIS}

Physicians should measure cardiac troponin levels within the appropriate clinical context and, even more so in patients with chronic kidney disease, commit to serial testing, given the low positive predictive value of individual samples if the baseline level is unknown. The following are important considerations.

\section{Follow serial cardiac troponin levels}

For patients with chronic kidney disease and signs that suggest acute coronary syndrome, we recommend tracking the rise and fall of cardiac troponin levels over the 3 hours after presentation with high-sensitivity assays, or over 6 hours with conventional assays, or up to 9 hours in those with end-stage renal disease, rather than documenting a single value (or a rapid change over a 1-hour period), which is in line with national guidelines.\textsuperscript{12,13}

Gunsolus et al\textsuperscript{14} found that serial troponin I measurements over 3 to 6 hours, using a 99th percentile cutoff (16 ng/L in women and 34 ng/L in men), had a sensitivity for myocardial infarction of at least 95\% in patients presenting to the emergency department with symptoms suggesting ischemia, across the spectrum of chronic kidney disease, including dialysis patients. However, the specificity decreased with decreasing renal function.

Baseline levels may help contextualize new elevations in the absence of significant kidney function changes. Patient characteristics (eg, sex) can affect high-sensitivity troponin values. However, no prospective trials of longitudinal cardiac troponin assessment have been done to justify baseline testing in patients with chronic kidney disease, especially given the lack of clear guidelines on the need for further testing in the presence of asymptomatic troponin elevations.
Troponin assays are not all the same

High-sensitivity troponin assays should be preferred because they have shown greater accuracy, especially when applied serially, given their lower coefficient of variation. However, high-sensitivity troponin assays are not all the same (Table 1). Even assays from the same manufacturer may not be interchangeable because manufacturers continually make changes to antibodies and calibration materials. Therefore, it is imperative that clinicians familiarize themselves with their institution’s current assay.

Although guidelines do not specify a preferred assay, troponin I has been observed to be less affected than troponin T by renal dysfunction and more specific for myocardial injury in patients with chronic kidney disease. In fact, experimental data suggest that cross-reactivity with fetal cardiac troponin T isoforms re-expressed in diseased or regenerating skeletal muscle may contribute to elevated cardiac troponin T levels in patients with chronic kidney disease without symptoms. In contrast, cardiac troponin I has never been found to be expressed in skeletal muscle at any point during development or in adverse muscular dystrophy.

Threshold for diagnosis

For patients with chronic kidney disease whose baseline troponin levels are already above the 99th percentile, a 20% rise on serial measurements is indicative of an ongoing myocardial injury and would be a
reasonable threshold change for a suspected diagnosis of acute coronary syndrome.\textsuperscript{13}

When initial levels are only mildly elevated (eg, high-sensitivity troponin T < 20 ng/L), any absolute change greater than 5 or 10 ng/L should raise concern for acute coronary syndrome. In fact, several studies have reported small absolute changes in troponin in patients with acute coronary syndrome,\textsuperscript{26–30} possibly as a result of plaque rupture occurring days before clinical presentation, when troponin samples are taken during the plateau phase of troponin release. Therefore, symptom duration should inform the significance of small troponin changes in patients with chronic kidney disease with suspected acute coronary syndrome.

**Chronic kidney disease vs acute kidney injury**

Kidney injury, defined as an estimated glomerular filtration rate less than 60 mL/min/1.73 m\textsuperscript{2} or an albumin-creatinine ratio 3 mg/mmol or higher, should be considered chronic only if it has been present for at least 3 months before presentation. Acute kidney injury in the setting of acute coronary syndrome is relatively common and has different diagnostic consequences compared with stable chronic kidney disease.

**A proposed workup algorithm**

A workup algorithm is shown in Figure 1. Briefly, one should use clinical judgment, integrating coronary artery disease risk factors, high-risk symptoms, typical electrocardiographic changes, and echocardiographic findings, which affect the predictive value of cardiac troponin testing and help to determine the likely mechanism of myocardial injury. The numerous possible nonischemic causes of cardiac troponin elevation should be entertained early in the differential diagnosis.

Regardless of the frequent atypical presenting symptoms often misattributed to noncardiac causes, a newly reduced ejection fraction accompanied by regional wall-motion abnormalities is highly suspicious for acute coronary syndrome.

**New ST-segment elevation**

Electrocardiographic evidence of new ST-segment elevation together with a compelling acute coronary syndrome presentation should prompt catheterization laboratory activation irrespective of the troponin level. Broad, asymmetrically peaked (“hyperacute”) T waves or loss of precordial T-wave balance may be seen in the early stages of ST-segment elevation myocardial infarction (STEMI). Also, keep in mind other common STEMI equivalents (eg, biphasic T waves)\textsuperscript{31} and the possibility that coronary artery occlusion may fail to result in electrocardiographic findings that meet STEMI criteria (ie, subtle STEMI). In the latter case, a formula based on 4 electrocardiographic variables has been proposed to assist clinicians.\textsuperscript{32}

In contrast, careful comparison of electrocardiographic patterns and troponin levels with earlier baseline values (or serial monitoring, if those are unavailable) would help identify patients with non-ST-segment elevation myocardial infarction (NSTEMI). Current guidelines advocate for an early invasive strategy in unselected patients with high-risk NSTEMI (eg, hemodynamic or electrical instability), but patients with moderate and severe chronic kidney disease were underrepresented in landmark trials. This is important, since delaying angiography may be desirable for 2 reasons in highly selected patients with chronic kidney disease with NSTEMI. First, optimal medical therapy may allow the plaque to stabilize and mitigate the thrombus burden. Second, it would enable preprocedural optimization of hemodynamically unstable patients, administration of intravenous fluid to minimize postprocedural acute kidney injury, or both.

A 2009 analysis of 23,262 patients with chronic kidney disease with NSTEMI in the Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies registry\textsuperscript{33} showed a 1-year survival advantage in patients with mild to moderate chronic kidney disease undergoing an early invasive strategy, but no apparent benefit among those with severe chronic kidney disease. The theoretical benefits of an early invasive strategy were possibly outweighed by the higher procedural risks in patients with stage 4 or 5 chronic kidney disease. Notably, the outdated definition of early invasive strategy (ie, angiography and possible revascularization within 14 days of admission, whereas now it means within 24 hours of admission) and the use of old-generation stents would limit its generalizability to current practice.

Along the same lines, a propensity-matched analysis published in 2022\textsuperscript{34} found no significant reduction in mortality rates with an early invasive strategy in patients with an estimated glomerular filtration rate less than 45 mL/min/1.73 m\textsuperscript{2}.

Lacking randomized studies specifically in patients with chronic kidney disease, the available data would justify an immediate invasive strategy (ie, within 2 hours) only in patients with chronic kidney disease with high-risk NSTEMI features (eg, hemodynamic...
Consider nonischemic etiologies:
- Pulmonary (e.g., pulmonary embolism, pulmonary hypertension, acute respiratory distress syndrome)
- Cardiac (acute decompensated heart failure, myocarditis, tachyarrhythmia)
- Others (sepsis, cerebrovascular accident, gastrointestinal bleeding, thrombotic thrombocytopenic purpura, cardiopulmonary resuscitation, rhabdomyolysis, cardiotoxic drugs)

Chest pain:
- At rest or with minimal exertion
- Crescendo pattern > 10 minutes in duration
- Not resolving with rest or sublingual nitroglycerin
- ± Anginal equivalents (e.g., dyspnea on exertion or diaphoresis)
- ± New regional wall-motion abnormality or reduced left ventricular ejection fraction

Acute coronary syndrome
- Not suspected
- ST-segment elevation ≥ 1 mm in 2 contiguous leads with reciprocal ST depression or new left bundle branch block with positive Sgarbossa criteria

> 20% change in troponin upon serial testing over 3–6 hours (or up to 9 hours in end-stage kidney disease)

Acute coronary syndrome not suspected

Non-ST-segment elevation myocardial infarction suspected
- Dynamic horizontal or downsloping ST depressions ≥ 1 mm
- ± T-wave inversions ≥ 1 mm

High-risk non-ST-elevation myocardial infarction features
- Refractory angina despite intensive medical therapy
- Evidence of heart failure (new or worse)
- Hemodynamic instability
- Sustained ventricular arrhythmia

Acute coronary syndrome not suspected

Estimated glomerular filtration rate (eGFR)
- ≥ 45 mL/min/1.73 m² or eGFR < 45 mL/min/1.73 m² with high-risk GRACE score (> 140)

Immediate invasive strategy (within 2 hours)

Delayed invasive strategy (within 72 hours)

Early invasive strategy (within 24 hours)

Immediate invasive strategy

Activate catheterization laboratory for suspected ST-segment elevation myocardial infarction

Figure 1. Diagnostic evaluation of elevated troponin in patients with chronic kidney disease and suspected acute coronary syndrome.

GRACE = Global Registry of Acute Coronary Events; TIMI = Thrombolysis in Myocardial Infarction
or electrical instability), and an early invasive strategy (ie, within 24 hours) in patients with NSTEMI and chronic kidney disease stage 2 or 3a (Figure 1).

Conventional risk scores—eg, GRACE (Global Registry of Acute Coronary Events) or TIMI (Thrombolysis in Myocardial Infarction) score—should guide the need for an early invasive strategy in non-high-risk NSTEMI patients with chronic kidney disease stages 3b through 5, who would otherwise be at higher than average risk for periprocedural complications. While the change in troponin level is critical in diagnosing acute coronary syndrome, initial abnormal biomarker status recorded at presentation should be used for prognostication with the GRACE or TIMI score.35

**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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Unilateral green pleural effusion in a 22-year-old woman

A 22-year-old medical student presented with dyspnea while walking to class. She reported slowly progressive dyspnea, fatigue, and reduced exercise tolerance over 6 months in addition to chills, night sweats, palpitations, and a weight loss of 5 pounds that she initially attributed to stress. She denied cough, chest pain, abdominal pain, nausea, and vomiting, and reported no changes in her menses or diet over several months.

Her medical history was significant for iron deficiency anemia owing to menorrhagia, which was resolved, and well-controlled gastroesophageal reflux disease. She confirmed compliance with her prescription medications of iron tablets and proton pump inhibitors and denied use of nonsteroidal anti-inflammatory drugs. She had undergone oral surgery in childhood, and her family history was significant for medulloblastoma in her brother, prostate cancer in her grandfather, and unknown cancer in her grandmother. Socially, she drank 2 alcoholic drinks on the weekends and denied smoking cigarettes or vaping. On examination, her vital signs included the following:

- Heart rate 130 beats per minute
- Temperature 39.1°C (102.4°F)
- Oxygen saturation 94% on room air
- Respiratory rate 18 breaths per minute
- Blood pressure 128/68 mm Hg.

Significant physical examination findings were pallor, reduced breath sounds on the right hemithorax associated with dullness to percussion, and lack of egophony. She had palpable lymphadenopathy in her axillae bilaterally. The remaining clinical examination was unremarkable, with laboratory testing results as follows:

- White blood cell count 12.0 × 10^9/L (reference range 4.5–11.0)
- Hemoglobin 13.5 g/dL (12.1–15.1)
- Platelet count 630 × 10^9/L (150–450)
- Lactate dehydrogenase 279 IU/L (105–333)
- C-reactive protein 275 mg/dL (< 10).

Liver enzymes, renal function, and coagulation studies were within reference ranges. A workup for infectious disease—including urinalysis, urinary antigens for pneumonia, blood cultures, respiratory culture, gram stain, and viral panel testing—was unremarkable.

**IMAGING FINDINGS**

Her chest radiograph (Figure 1) was concerning for unilateral right pleural effusion in addition to a widened mediastinum. Lung fields were otherwise normal. Computed tomography of the chest (Figure 2)
GREEN PLEURAL EFFUSION

confirmed ill-defined bulky mediastinal and bilateral perihilar masses and bilateral axillary lymphadenopathy. The right mainstem and right distal bronchi were narrowed owing to extrinsic compression caused by the masses, with corresponding atelectasis of the right upper and middle lobes. A large right pleural effusion was seen. No filling defect was detected, ruling out pulmonary embolism. The lung parenchyma was otherwise normal without evidence of ground-glass opacities, consolidation, nodules, cysts, or septal thickening.

**DIFFERENTIAL DIAGNOSES**

1. What is the most likely cause of this patient’s unilateral pleural effusion?

   □ Heart failure
   □ Infection
   □ Malignancy
   □ Lymphangioleiomyomatosis
   □ Hepatic hydrothorax
   □ Chylothorax

   The patient presented with a history of chronic dyspnea associated with mild weight loss and “B symptoms,” ie, night sweats, fever, and weight loss, suggesting lymphoma. She lacked chest pain, lower extremity edema, or paroxysmal nocturnal dyspnea and did not smoke cigarettes or indulge in excessive alcohol use. While having no personal risk factors for malignancy, she did have a significant family history.

   The most likely cause of the unilateral pleural effusion in this patient would be malignancy owing to the slowly progressive dyspnea, B symptoms, and the presence of mediastinal masses. She lacked physical findings to suggest heart failure. The screen for infectious disease was negative, and imaging findings were inconsistent with infection or lymphangioleiomyomatosis. She did not have preceding trauma, chest surgery, history of congenital syndromes, or abnormal nails on her hands or feet to suggest chylothorax. Furthermore, liver enzyme tests were normal, making the presence of hepatic hydrothorax less likely. **Table 1** summarizes key features of common causes of pleural effusions.

   Performing thoracentesis would be the most appropriate next step. This procedure would not only alleviate her dyspnea but also allow sampling of the pleural fluid for diagnostic purposes. Common laboratory tests performed on pleural effusion fluid are listed in **Table 2**. Dichotomization of pleural effusions into transudative or exudative subtypes utilizing the Light criteria is a key step in narrowing the differential diagnosis. Common causes of transudative effusions include heart failure, hepatic hydrothorax, nephrotic syndrome, or pulmonary embolism. Exudative pleural effusions are seen in infections, malignancies, autoimmune conditions, and pancreatitis to name a few. Light criteria analysis of pleural fluid has 99% sensitivity and 96% accuracy to identify exudative effusion.

   The patient underwent lung ultrasonography to assess the safety of performing thoracentesis and secondarily to determine the site of needle insertion. Thoracentesis resulted in the drainage of 1,500 mL of green-hued, thin, nonviscous pleural fluid (**Figure 3**). It was lymphocytic and exudative by the Light criteria. Bilirubin and triglyceride analysis of the pleural fluid was done due to its green color. It revealed a bilirubin count of 0.6 mg/dL, a pleural fluid-serum bilirubin ratio of 1, and a triglyceride of 30 mg/dL. Culture and Gram stain were negative. Cytopathology was concerning for the presence of atypical lymphocytes. Given the presence of widespread lymphadenopathy on imaging, there was concern for hematopoietic malignancy.

   2. What was the cause of green pleural effusion?

   □ Biliothorax
   □ Chylothorax
   □ Empyema
   □ Malignancy
The most common cause of green pleural fluid is biliothorax. Most often seen following trauma or surgery, the green color is a consequence of biliary leakage intraperitoneally. Biliary fluid may seep into the pleural space via diaphragmatic pores, leading to the accumulation and development of pleural effusion. The exact
mechanism of green pleural fluid in other diseases such as empyema, chylothorax, and malignancy is less well understood. It has been theorized that green pigments are produced by bacteria in empyema. Some authors have suggested that an increase in pleural fluid viscosity owing to excess pleural fluid protein and cellularity may cause the green color in chylothorax and malignant pleural effusions.

In our patient, the pleural fluid-serum bilirubin ratio of 1, along with a low pleural fluid bilirubin level, ruled out biliothorax. Additionally, she had no recent abdominal surgeries or trauma to cause biliary leak. As her triglyceride level was less than 110 mg/dL, chylothorax was unlikely. Culture data from pleural fluid analysis were unrevealing. Malignancy is the most likely cause of green pleural effusion in this patient as it was exudative and lymphocytic in nature.

What are the next steps in view of the lymphadenopathy and abnormal cytology of the pleural fluid?

- Repeat thoracentesis for serial cytopathologic assessment
- Pleural biopsy

The diagnostic yield for malignancy on pleural fluid cytology is low, between 40% and 60%. Additional sampling of pleural fluid increases sensitivity by 27%, beyond which there is no improvement in the diagnostic yield with subsequent procedures. The type of malignancy also influences the diagnostic yield of cytologic analysis of pleural fluid. Generally, the highest yield is for adenocarcinomas—including lung, ovarian, breast, and pancreatic—and is much lower for head and neck cancers, sarcomas, renal, and lymphomas. For hematopoietic malignancies like lymphoma, the diagnostic yield of pleural fluid cytology is between 22.2% and 94.1%. Thus, repeating thoracentesis would not be the appropriate next step in this case.

Blind pleural biopsy is commonly used worldwide, specifically in the diagnostic algorithm for tuberculous pleural effusion. The diagnostic yield of pleural biopsy for malignancy is low, akin to that of pleural fluid analysis. Imaging-assisted thoracoscopic
pleural biopsy has a much higher diagnostic yield for malignancy but it is not routinely performed owing to cost and the requirement for a specially trained surgeon or pulmonologist. 1 Although a cohort study of 34 patients reported a superior diagnostic yield of pleural biopsy compared with pleural fluid analysis for the diagnosis of lymphoma, pleural involvement in lymphoma is usually part of a systemic manifestation and is only rarely the primary source.

The gold standard technique for diagnosing malignant lymphomas is excisional lymph node biopsy. 30 The lymph node is removed in its entirety by a surgeon to allow for complete histologic examination of the lymph node architecture. Based on the findings, provisions for other tests such as flow cytometry and molecular genetic testing can be made. 30,31

Some criticisms of excisional lymph node biopsy relate to its invasive nature and higher rate of bleeding and infection. However, if the lymph nodes are superficial, it is an excellent diagnostic test. Core needle biopsy and fine-needle aspiration are minimally invasive procedures. Core needle biopsy uses a wider needle than fine-needle aspiration, thus a larger tissue sample may be obtained. 32,33 Core needle biopsy has a much higher diagnostic yield than fine-needle aspiration and is more common. 34 Studies have demonstrated that fine-needle aspiration has a diagnostic yield as low as 29%, and only 2% when correlated with findings of excisional lymph node biopsy. 35,36 Thus, fine-needle aspiration overall has a low yield and is inferior to core needle biopsy and excisional lymph node biopsy. 36 Even though core needle biopsy is gaining popularity, a recent large-scale study of lymphoma patients found excisional lymph node biopsy to have superior diagnostic yield compared with core needle biopsy. There was an increased risk of a nondefinite diagnosis with core needle biopsy. 37 In this case, the presence of multiple superficial axillary lymph nodes—coupled with a patient with a low-risk profile to undergo general anesthesia—argues for the use of excisional lymph node biopsy as the most appropriate diagnostic test.

In our patient, pathologic analysis of the excisional lymph node biopsy confirmed the diagnosis of lymphocyte-rich Hodgkin lymphoma. Figure 4 illustrates the complete distortion of the usual lymph node architecture owing to the presence of atypical polymorphous infiltrates. Hematoxylin and eosin staining (Figure 5) revealed numerous large and atypical lymphocytes characterized by large-sized, irregular, and multilobed nuclei. The nucleoli ranged from single to multiple. Some mummified cells were identified, with condensed cytoplasm and pyknotic eosinophilic or basophilic nuclei. The cells were morphologically compatible with Hodgkin and Reed-Sternberg cell morphology. By immunohistochemistry, the cells of interest were positive for PAX5 (weak), CD30, and CD15 stains, and negative for CD3, CD20, CD45, CD43, CD2, and LK1. Flow cytometry showed no phenotypic evidence of non-Hodgkin lymphoma.
GREEN PLEURAL EFFUSION

STAGING

To determine the stage of classic Hodgkin lymphoma, our patient underwent positron emission tomography, which revealed mediastinal, pericardial, hilar, axillary, and subpectoral lymphadenopathy with extension of hypermetabolic activity into the central spinal canal at level T5 of the spine. Thus, she was diagnosed with stage IV classic Hodgkin lymphoma owing to the involvement of multiregional lymphoid tissue above and below the diaphragm, in addition to extranodal tissue of the axial spine.

TREATMENT

A chemotherapy regimen of doxorubicin, vincristine, dacarbazine, and brentuximab was initiated. The patient lacked neurologic symptoms and signs to suggest spinal stenosis or cauda equina syndrome. Thus, the T5 lesion was monitored without the initiation of steroids or radiation therapy. Her dyspnea had improved following thoracentesis, but she experienced intermittent central chest pain, which was attributed to the mediastinal mass effect. After the initiation of chemotherapy, she reported the resolution of her symptoms. She was discharged home with outpatient oncology follow-up.

PLEURAL EFFUSIONS IN HODGKIN LYMPHOMA

Pleural effusions are seen at presentation in patients with lower stages of Hodgkin lymphoma, with rates ranging from 10% to 30%.38,39 When present, these effusions are usually associated with poor survival, warranting the initiation of aggressive up-front therapy.38,39 The pleural effusions in Hodgkin lymphoma are typically exudative, lymphocytic, and serosanguinous in nature.40 A jelly-like consistency of pleural fluid is associated with mesothelioma.41 Chylothorax has often been associated with lymphoma owing to the obstruction of the lymphatic vessels or the thoracic duct by the tumor or bulky lymphadenopathy.40,42 Chylothoraces are usually white or milky in appearance. The color of effusions in Hodgkin lymphoma can vary from serous to bloody. The color of the pleural fluid has no correlation with prognosis.43 Black pleural fluids have been reported in malignancy and chronic hemothorax owing to the abundance of hemosiderin-laden macrophages.

Our patient’s case illustrates a novel presentation of green-colored unilateral pleural effusion associated with classic Hodgkin lymphoma. A comprehensive history and physical examination allow the clinician to narrow the differential diagnoses in the hopes of obtaining high-yield tests to shorten the time it takes to arrive at the true diagnosis and expedite treatment. Laboratory analysis of pleural fluid and its characterization by color and viscosity play crucial parts in the diagnostic algorithm for the etiology of pleural effusions. As illustrated in this case, a systematic and algorithmic approach to the management of pleural effusion is vital.

TAKE-HOME POINTS

• New-onset pleural effusion must be evaluated by analysis of the pleural fluid for diagnostic purposes.
• Prior to thoracentesis, an adequate amount of pleural fluid must be present. The safety of the procedure can be confirmed with lung ultrasonography.
• Thoracentesis may function as a therapeutic tool to alleviate dyspnea.
• Meticulous visual inspection to characterize the color and viscosity, in addition to laboratory analysis of pleural fluid including the utilization of the Light criteria, is paramount to determine the etiology of the pleural effusion as it may necessitate additional testing of the pleural fluid.
• Excisional lymph node biopsy is the gold standard test for the diagnosis of lymphoma.

Acknowledgment: We thank Carmen Fullmer, MS, for her assistance and support in preparing this manuscript.

DISCLOSURES

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


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Late complications after allogeneic hematopoietic cell transplant: What primary care physicians can do

ABSTRACT

Survivors of allogeneic hematopoietic cell transplant (HCT) face the risk of many serious complications in the long term, which primary care physicians play an integral role in recognizing and treating. In this review, the authors summarize the most common complications that primary care physicians see after HCT recipients return to their care: chronic graft-vs-host disease; cardiovascular, metabolic, endocrine, rheumatologic, orthopedic, infectious, neurologic, and cognitive complications; secondary malignancies; psychiatric disorders; and impairments in quality of life and sexual health. Also discussed are health maintenance and screening recommendations for this patient population.

KEY POINTS

Patients who undergo allogeneic HCT have complex problems, their comorbidities may wax and wane, and their care requires careful coordination between the primary care physician, transplant physician, and primary oncologist.

Primary care physicians should monitor for complications, assisting with the management of the potential sequelae.

Primary care physicians are also important in managing underlying chronic conditions and in routine health screening and maintenance.

Allogeneic hematopoietic cell transplant (HCT) is a potentially curative therapy for many malignant and nonmalignant conditions. The procedure itself is managed by a multidisciplinary hematology-oncology team, but optimal long-term care of transplant recipients, who can have potentially complex problems, relies on close collaboration with the primary care physician (PCP).

For the first 100 days or so after transplant, patients typically follow up with their transplant providers weekly. Afterward, most patients see their transplant team less frequently, and many return to their referring or primary oncologist and local PCP teams for long-term management (Figure 1), although the posttransplant course can vary from patient to patient and from center to center. In addition, many patients travel long distances to receive their transplant at an academic medical center, and as a result they may be more likely to resume routine care with their local oncologist or PCP before day 100.

Below, we summarize the most common complications that PCPs may see after HCT recipients return to their care. These include chronic graft-vs-host disease; cardiovascular, metabolic, endocrine, rheumatologic, orthopedic, infectious, neurologic, and cognitive complications; secondary malignancies; psychiatric disorders; and impairments in quality of life and sexual health. We also highlight health maintenance and screening recommendations.
Thanks to advances in HCT techniques and technology, including preventing and managing graft-vs-host disease and posttransplant infections, long-term survival rates have increased.1 An analysis of nearly 40,000 allogeneic HCT recipients found that the nonrelapse mortality rate in the first year after the procedure decreased from 24.4% in the 1990s to 9.5% in the years 2013 through 2016.2 But as more patients are living longer, many long-term complications and chronic conditions are becoming more prevalent.

The pathogenesis of post-HCT late effects is likely influenced by several factors. Transplant-specific factors include endothelial injury and DNA damage induced by chemotherapy and radiation; graft-vs-host disease; immunosuppressive treatment and subsequent gonadal and hormonal dysfunction; chronic inflammation; and the new development of cardiovascular risk factors. In addition, defective T-cell immunity may allow oncogenic viruses to reactivate and may also contribute to the development of subsequent malignancies. Patient risk factors such as age, genetic susceptibility, lifestyle, and health behaviors all contribute to the accelerated processes of late effects.

Historically, allogeneic HCT was performed to enable patients to receive high doses of myeloablative chemotherapy and radiotherapy to eradicate tumor cells. The transplant was done with the goal of re-establishing normal hematopoietic and immune function, as normal cells were damaged along with the tumor cells by the chemotherapy and radiotherapy. However, we now believe that the donor cells also provide an immune benefit and likely help cure malignant diseases by a graft-vs-tumor effect.2

The most common indications for allogeneic HCT are acute myeloid leukemia, acute lymphoblastic leukemia, lymphomas, myelodysplastic syndrome, and myeloproliferative disorders.2 Once a patient is deemed to be a candidate for allogeneic HCT—a decision that is outside the scope of this article—they are admitted to the hospital for approximately 30 days, during which they receive conditioning chemotherapy and then, on “day 0,” the infusion of allogeneic cells. They are then monitored for engraftment, potential infections, toxicities, and adequate nutrition.

Graft-vs-host disease, which can be acute or chronic, occurs after allogeneic HCT when nonidentical donor immune cells (the graft) attack those of the recipient (the host), causing inflammation, fibrosis, and potential end-organ damage. Chronic graft-vs-host disease occurs in 30% to 50% of allogeneic HCT recipients (the incidence varies with a number of factors and has been increasing over time),3 and apart from relapse, it is the leading cause of late morbidity and death in this group.3,4

The median time from transplant to the onset of chronic graft-vs-host disease is about 5 months, but it can occur at any time.5 The distinction between acute and chronic graft-vs-host disease was previously based on the timing of the onset of symptoms (before or after day 100). However, clinical and pathologic features are now more commonly used to distinguish between the two.6,7

A National Institutes of Health consensus
group now recognizes the categories of “classic acute,” “classic chronic,” “de novo late acute,” “recurrent late acute,” “persistent late acute,” and “chronic overlap” graft-vs-host disease.\textsuperscript{6,7}

The most commonly affected organs are the skin, liver, gastrointestinal tract, and lungs, but nearly any organ system can be affected and most patients have organ involvement at the time of diagnosis.\textsuperscript{8} Common signs and symptoms are listed in Table 1.\textsuperscript{9}

Chronic graft-vs-host disease requires systemic immunosuppressive therapy for a long time (median of 2 to 3.5 years). Corticosteroids are the mainstay, typically in high doses, eg, prednisone 0.5 to 1 mg/kg/day or the equivalent.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Chronic graft-vs-host disease: Common findings, questions to ask the patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organs affected</td>
<td>Common findings</td>
</tr>
<tr>
<td>Skin</td>
<td>Poikiloderma: erythema</td>
</tr>
<tr>
<td></td>
<td>Sclerotic features: thickened skin</td>
</tr>
<tr>
<td></td>
<td>Lichen planus-like features: purple polygonal plaques</td>
</tr>
<tr>
<td></td>
<td>Lichen sclerosus-like features: wrinkled, atrophic plaques</td>
</tr>
<tr>
<td></td>
<td>Morphea-like features: small, red or purple patches with white center</td>
</tr>
<tr>
<td></td>
<td>Dryness</td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
</tr>
<tr>
<td></td>
<td>Hypopigmentation or hyperpigmentation</td>
</tr>
<tr>
<td>Mouth</td>
<td>Lichen planus-like changes: lacy white patches</td>
</tr>
<tr>
<td></td>
<td>Xerostomia (dry mouth)</td>
</tr>
<tr>
<td></td>
<td>Gingivitis: swelling, redness, bleeding, or pain of the gums</td>
</tr>
<tr>
<td></td>
<td>Mouth ulcers</td>
</tr>
<tr>
<td></td>
<td>Mucosal atrophy</td>
</tr>
<tr>
<td></td>
<td>Mucosal pseudomembranes</td>
</tr>
<tr>
<td></td>
<td>Mucoceles: painless mucus-filled cysts</td>
</tr>
<tr>
<td>Eyes</td>
<td>Dry, gritty, painful eyes</td>
</tr>
<tr>
<td></td>
<td>Photophobia</td>
</tr>
<tr>
<td></td>
<td>Periorbital hyperpigmentation</td>
</tr>
<tr>
<td>Liver</td>
<td>Jaundice</td>
</tr>
<tr>
<td></td>
<td>Total bilirubin, alkaline phosphatase, and alanine aminotransferase levels &gt; 2 times the upper limit of normal</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Anorexia</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
</tr>
<tr>
<td></td>
<td>Weight loss</td>
</tr>
<tr>
<td></td>
<td>Dysphagia</td>
</tr>
<tr>
<td>Lungs</td>
<td>Cough</td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
</tr>
<tr>
<td>Muscles and joints</td>
<td>Joint swelling</td>
</tr>
<tr>
<td></td>
<td>Joint stiffness</td>
</tr>
<tr>
<td></td>
<td>Muscle cramps</td>
</tr>
<tr>
<td></td>
<td>Arthralgias</td>
</tr>
<tr>
<td></td>
<td>Arthritis</td>
</tr>
<tr>
<td>Genitalia</td>
<td>In women: vaginal dryness, pruritus, dyspareunia, lower urinary tract symptoms</td>
</tr>
<tr>
<td></td>
<td>In men: burning, phimosis</td>
</tr>
</tbody>
</table>

Based on information in reference 9.
What PCPs can do: Conduct a thorough physical examination, ask targeted questions about the most common presenting signs of chronic graft-vs-host disease, and order routine laboratory tests such as a comprehensive metabolic panel (Table 1). If there is any suspicion of chronic graft-vs-host disease, the PCP should promptly communicate with the patient’s transplant physician. Early recognition of the signs and symptoms is necessary for prompt treatment and has the potential to halt progression to more severe and morbid phenotypes.

While the transplant physician should manage the treatment of chronic graft-vs-host disease, the PCP should help manage the complications of long-term corticosteroid therapy (Table 2). These complications can be recognized by performing routine physical examinations, by monitoring weight, blood glucose levels, electrolytes, and blood pressure, and by inquiring about bone, muscle, gastrointestinal, and psychiatric symptoms.

<table>
<thead>
<tr>
<th>CARDIOVASCULAR AND METABOLIC COMPLICATIONS</th>
</tr>
</thead>
</table>
| Allogeneic HCT recipients are at increased risk of long-term cardiovascular complications. Several studies found the risk of cardiovascular death to be 2.3-fold to 3.7-fold higher in HCT recipients than in the general population.11 Armenian et al reported that 10 years after HCT the cumulative incidence of hypertension was 37.7%, diabetes 18.1%, and hyperlipidemia 46.7%.12 Metabolic syndrome, defined by obesity or increased waist circumference, dyslipidemia, hypertension, and hyperglycemia or insulin resistance, develops in as many as 49% of HCT recipients.11 The risk of cardiovascular events and death is significantly higher in patients who meet the criteria for metabolic syndrome than in those who do not. Additional risk factors for cardiovascular disease in HCT recipients include cumulative exposure to cardiotoxic chemotherapy (eg, anthracyclines), chest radiation before HCT, and decreased cardiac function before HCT.

What PCPs can do: Vigilantly screen for and treat hypertension, diabetes, and hyperlipidemia. Several transplant societies have specific guidelines (Table 3).11–13 Although many of the recommendations are similar to those for the general population, HCT recipients should be screened soon after transplant.
ENDOCRINE COMPLICATIONS

Thyroid dysfunction
Subclinical and overt hypothyroidism are both complications of allogeneic HCT and may be common after radiation to the neck, mediastinum, or total body.

What PCPs can do: Monitor thyroid function annually in all HCT recipients irrespective of risk factors, and repeat testing as needed based on reported symptoms.14

Gonadal failure and infertility
Gonadal failure after allogeneic HCT is common and can be caused by radiation damage to the hypothalamus-pituitary axis, damage to the gonads from chemotherapy or radiation, or both.

In general, the ovaries are more sensitive to radiation and chemotherapy than the testes, and almost all female allogeneic HCT recipients over age 12 who receive myeloablative conditioning develop premature ovarian insufficiency.15,16 Hypogonadism can also lead to dyspareunia and resultant poorer quality of life. Estrogen replacement therapy is often used to treat symptoms of estrogen deficiency, including vasomotor and urogenital symptoms, and can prevent bone loss associated with menopause. Although it may increase the risk of venous thromboembolism, this is rare in patients under age 60.17 It may also increase the risk of endometrial cancer.

Most men have normal testosterone levels after HCT, although many eventually become infertile. Testosterone levels should be measured if the patient develops symptoms such as erectile dysfunction or decreased libido.18 Testosterone replacement therapy can be used to treat symptoms related to testosterone deficiency,17 although it increases the risk of prostate cancer.

What PCPs can do: Assess symptoms of hormone deficiency, discuss replacement therapy and its risks, and, in patients receiving hormone replacement therapy, offer routine screening for complications (eg, prostate-specific antigen testing).

Osteopenia and osteoporosis
Bone loss and subsequent fragility fractures can cause significant long-term morbidity for allogeneic HCT recipients. While fragility fractures may occur later, bone loss can start within the first 6 to 12 months after transplant.19 Around half of HCT recipients develop osteopenia within 4 to 6 years, and the incidence of osteoporosis is approximately 20% after 2 years.20 The 2 most common causes of bone loss after allogeneic HCT are hypogonadism and corticosteroid treatment for graft-vs-host disease.16

What PCPs can do: Because bone loss starts early after transplant, recommend dual-energy x-ray absorptiometry within the first year.

Bisphosphonates are the mainstay of treatment for patients with low bone density and should be considered in patients with established osteopenia or osteoporosis or patients at high risk of bone loss, such as those receiving long-term glucocorticoid therapy for chronic graft-vs-host disease.

Before starting patients on bisphosphonate therapy, vitamin D levels should be measured and patients should receive adequate vitamin D supplementation. Also, because of the risk of jaw osteonecrosis, patients

<table>
<thead>
<tr>
<th>Complications</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Moderate exercise 150 minutes per week</td>
</tr>
<tr>
<td></td>
<td>Tobacco cessation counseling</td>
</tr>
<tr>
<td></td>
<td>Maintain a healthy weight</td>
</tr>
<tr>
<td></td>
<td>Eat a healthy diet</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Screen with hemoglobin A1c or fasting plasma glucose 3 months after transplant for patients at high risk (on corticosteroids)</td>
</tr>
<tr>
<td></td>
<td>Repeat every 6 months if elevated</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Check a fasting lipid panel 3 months after transplant</td>
</tr>
<tr>
<td></td>
<td>Repeat evaluation every 3 to 6 months for patients at high risk (on sirolimus, calcineurin inhibitors, or corticosteroids)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Check blood pressure at every visit at least annually for all patients, regardless of age or other risk factors</td>
</tr>
</tbody>
</table>

Based on information in references 11–13.
HEMATOPOIETIC CELL TRANSPLANT

should undergo a dental examination before starting bisphosphonate therapy. While the optimal duration of treatment has yet to be elucidated, long-term use of bisphosphonates (ie, beyond 5 years) may lead to subtrochanteric fractures.18 Patients should also be advised to engage in regular weight-bearing activity, follow a healthy diet, and avoid tobacco and alcohol.16

**INFECTIOUS COMPLICATIONS**

Allogeneic HCT recipients are at risk of numerous infectious complications. The type of complication depends on the time from transplant and the engraftment status. Allogeneic HCT recipients lose their immunity posttransplant and must receive all their vaccinations again—ie, vaccinations given during childhood and those given during adulthood. Immunocompetency increases with time from transplant. Typically, patients can safely receive routine vaccinations again between 3 and 12 months posttransplant (Table 4).21–24 Because many patients are still on immunosuppressive therapy or treatment for chronic graft-vs-host disease, it is imperative that they receive routine vaccinations to prevent infection from communicable diseases. Most inactivated vaccines can be given between 3 and 6 months after transplant, whereas live vaccines such as varicella and measles-mumps-rubella must be delayed until 2 years after transplant. COVID-19 vaccinations can be safely given 3 months posttransplant, whereas the inactivated influenza vaccine should be given 6 months posttransplant. If there is an influenza outbreak, the influenza vaccine can be given at 4 months posttransplant and a second dose can be considered.22

**What PCPs can do:** While many patients receive their vaccinations from their transplant physicians, PCPs are also able to vaccinate these patients if necessary. There are many nuances to vaccinating this vulnerable population that are outside the scope of this review, but we suggest communicating with the transplant team or primary oncologist if questions arise.

**NEUROLOGIC AND COGNITIVE COMPLICATIONS**

Central nervous system complications are common after allogeneic HCT and vary widely in incidence (ranging from 3% to 44%), severity, and etiology.25 These complications can be infectious, metabolic, cerebrovascular, and cognitive.

**Cerebrovascular disease**

Data indicate a 0.6-fold to 5.6-fold increased risk of cerebrovascular disease in HCT recipients.26 Possible causes include an increased prevalence of risk factors including diabetes, hyperlipidemia, and hypertension; inflammatory changes from chronic graft-vs-host disease; and medication toxicities.26 PCPs must be cognizant of this risk and manage cardiovascular risk factors appropriately (see “Cardiovascular and metabolic complications,” above).

---

**TABLE 4**

**Recommended vaccination schedule after allogeneic hematopoietic cell transplant**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Time posttransplant to initiate vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-valent pneumococcal conjugate (PCV20)</td>
<td>3 months</td>
</tr>
<tr>
<td>Tetanus-diphtheria</td>
<td>≥ 6 months</td>
</tr>
<tr>
<td>Acellular pertussis</td>
<td>≥ 6 months</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em> type B</td>
<td>3 months</td>
</tr>
<tr>
<td>Meningococcal disease</td>
<td>≥ 6 months</td>
</tr>
<tr>
<td>Inactivated polio</td>
<td>6–12 months</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>≥ 6 months</td>
</tr>
<tr>
<td>Inactivated influenza</td>
<td>≥ 6 months</td>
</tr>
<tr>
<td>Measles-mumps-rubella</td>
<td>≥ 24 months</td>
</tr>
<tr>
<td>Varicella</td>
<td>≥ 24 months</td>
</tr>
<tr>
<td>Human papillomavirus</td>
<td>6–12 months</td>
</tr>
<tr>
<td>COVID-19</td>
<td>3 months</td>
</tr>
</tbody>
</table>

Based on information in references 21–24.
Neurocognitive dysfunction

Neurocognitive dysfunction is the complication most likely to be encountered by PCPs in the outpatient setting. A retrospective study from 2018 found that 35.7% of allogeneic HCT recipients displayed global cognitive dysfunction at 3 years posttransplant. Transplant-associated risk factors for cognitive dysfunction include high-dose chemotherapy, total body irradiation, and graft-vs-host disease, whereas patient-associated risk factors include older age, male sex, and lower pre-transplant education, income, and cognitive reserve. The most common symptoms were loss of verbal recall, loss of fluency, and deficits in executive functions.

**What PCPs can do:** Transplant physicians do not routinely monitor for neurocognitive dysfunction, so the PCP plays a key role in diagnosis. It is important that PCPs be aware of the risk, assess cognitive function at least annually, and relay concerns to the transplant physician.

### PSYCHIATRIC DISORDERS AND IMPAIRMENTS IN QUALITY OF LIFE

Depression, anxiety, posttraumatic stress disorder, and other impairments in quality of life are common but often underrecognized and undertreated after allogeneic HCT.

**Depression and anxiety**

A retrospective study found that 15% of allogeneic HCT survivors experienced symptoms of depression and 14% had anxiety. These symptoms may increase rather than abate as time passes, as patients must also learn to cope with changes in their domestic roles, employment, and financial situations. In the same study, 81% of survivors reported fatigue that led to a reduction in physical activity, worsened quality of life, and depression. Decreased exercise tolerance is also related to decreased quality of life and disability in HCT recipients. Chronic graft-vs-host disease and continued immunosuppression are also associated with worse quality of life and depression.

The Patient Health Questionnaire 2 can be used to screen patients for depression and then, if warranted, the Patient Health Questionnaire 9 can be used to diagnose major depressive disorder.

**Posttraumatic stress disorder**

Patients who undergo allogeneic HCT are also at risk for developing posttraumatic stress disorder (PTSD). Patients admitted for allogeneic HCT undergo prolonged and sometimes socially isolating hospitalizations, which can lead to healthcare-associated PTSD. Fenech et al reported that 39 (18.9%) of 206 HCT recipients had clinically significant symptoms of PTSD at 6 months posttransplant, and risk factors included baseline psychological distress, lack of social support, and reduced physical activity. The primary care PTSD criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, known as PC-PTSD-5, can be used for screening.

**What PCPs can do:** Assess for psychological symptoms at least annually, and communicate with the transplant physician and mental health professionals if there is concern for the aforementioned disorders.

### SEXUAL HEALTH

HCT recipients are at risk of disturbances to their sexual health due to genital chronic graft-vs-host disease, hypogonadism, and other causes.

In women, genital chronic graft-vs-host disease can present as lichen sclerosus-like skin changes or vaginal scarring and stenosis and lead to symptoms such as dryness, burning, dyspareunia, bleeding, abnormal discharge, pruritus, and lower urinary tract symptoms. In men, genital chronic graft-vs-host disease may present as lichen sclerosus-like skin changes, phimosis, balanitis, posthitis, erectile dysfunction, burning, or dyspareunia.

While genital chronic graft-vs-host disease can lead to sexual dysfunction in both men and women, it is also important to consider additional causes such as anxiety, depression, and hypogonadism, as discussed above.

**What PCPs can do:** Help recognize and diagnose impairments to sexual health. If there is concern for genital chronic graft-vs-host disease or other causes of sexual dysfunction, refer the patient to their transplant physician, gynecologist, or urologist.

### SUBSEQUENT MALIGNANCIES

Subsequent malignancies account for 5% to 10% of late deaths in allogeneic HCT recipients and include solid malignancies, hematologic malignancies, and posttransplant lymphoproliferative disorders. The most common oncologic complication in HCT recipients is a subsequent solid malignancy. Secondary hematologic malignancies and posttransplant lymphoproliferative disorder occur much less frequently.

**Solid malignancies**

After allogeneic HCT, recipients are at higher risk of developing solid malignancies than the general population. The reported cumulative incidence of solid cancers
after allogeneic HCT ranges from 1.2% to 1.6% at 5 years, 2.2% to 6.15% at 10 years, and 3.8% to 14.9% at 15 years.36

What PCPs can do: Screen for cancer (Table 5),18,36–42 and communicate with the transplant physician and primary oncologist if there are questions regarding screening in the setting of specific risk factors. Equally important is to tell transplant recipients to refrain from smoking and drinking alcohol and to routinely wear sunscreen to protect against malignancy.

Hematologic malignancies

Hematologic malignancies are the most common indication for allogeneic HCT. Thus, relapsed disease can be challenging to distinguish from a subsequent hema-

<table>
<thead>
<tr>
<th>TABLE 5</th>
<th>Screening for solid tumors in allogeneic hematopoietic cell transplant recipients vs the general population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General population</strong></td>
<td><strong>Allogeneic transplant recipients</strong></td>
</tr>
<tr>
<td><strong>Skin cancers</strong></td>
<td>Routine screening not recommended</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Breast cancer</strong></td>
<td>Yearly mammogram beginning at age 45&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Head and neck cancer</strong></td>
<td>Routine screening not recommended</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Colorectal cancer</strong></td>
<td>Colonoscopy every 10 years beginning at age 45&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Esophageal cancer</strong></td>
<td>Routine screening not recommended</td>
</tr>
<tr>
<td><strong>Thyroid cancer</strong></td>
<td>Routine screening not recommended</td>
</tr>
<tr>
<td><strong>Lung cancer</strong></td>
<td>Annual low-dose computed tomography for high-risk cigarette smokers beginning at age 50&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td><strong>Prostate cancer</strong></td>
<td>Discuss prostate-specific antigen screening at age 50</td>
</tr>
<tr>
<td><strong>Cervical cancer</strong></td>
<td>Papanicolaou smear every 3 years beginning at age 25&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Patients at high risk may require earlier or more frequent screening.
<sup>b</sup>Patients at high risk, including those with inflammatory bowel disease (Crohn disease or ulcerative colitis), family history of colorectal cancer, or a genetic syndrome, may require earlier or more frequent screening.
<sup>c</sup>Current smokers or those who quit within the past 15 years with a 20-pack-year history.
<sup>d</sup>Starting at age 30—cotesting with human papillomavirus every 5 years or Papanicolaou testing alone every 3 years. Discontinue at age 65 if certain criteria are met.
<sup>e</sup>Cotesting preferred, but cytology-only acceptable. If cytology-only is done, if 3 consecutive tests are negative, can increase the interval to every 3 years. If initial cotesting with human papillomavirus is done and negative, can increase interval to every 3 years. Continue past age 65.

Based on information in references 18 and 36–42.
tologic malignancy such as acute myeloid leukemia or myelodysplastic syndrome, although reported rates of subsequent hematologic malignancies are generally low. Secondary hematologic malignancies are thought to result from oncogenic transformation of normal donor cells in the transplant recipient, as opposed to those after autologous HCT, in which malignancy likely arises from the cryopreserved autograft. Symptoms may those after autologous HCT, in which malignancy likely result from oncogenic transformation of normal lymphadenopathy, dysfunction of the involved organs, and compression of surrounding structures. Symptoms may usually occur in the setting of prolonged immunosuppression after HCT. Extranodal masses are common, and other manifestations may include constitutional symptoms (eg, fevers, chills, weight loss, night sweats), lymphadenopathy, dysfunction of the involved organs, and compression of surrounding structures. Symptoms may typically occur in the setting of prolonged immunosuppression after HCT. Extranodal masses are common, and other manifestations may include constitutional symptoms (eg, fevers, chills, weight loss, night sweats), lymphadenopathy, dysfunction of the involved organs, and compression of surrounding structures. Symptoms may usually occur in the setting of prolonged immunosuppression after HCT. Extranodal masses are common, and other manifestations may include constitutional symptoms (eg, fevers, chills, weight loss, night sweats), lymphadenopathy, dysfunction of the involved organs, and compression of surrounding structures. Symptoms may usually occur in the setting of prolonged immunosuppression after HCT. Extranodal masses are common, and other manifestations may include constitutional symptoms (eg, fevers, chills, weight loss, night sweats), lymphadenopathy, dysfunction of the involved organs, and compression of surrounding structures.

Posttransplant lymphoproliferative disorder

Posttransplant lymphoproliferative disorder is a group of lymphoid disorders, usually B cell in origin, that typically occur after allogeneic HCT. Extramedullary masses are common, and other manifestations may include constitutional symptoms (eg, fevers, chills, weight loss, night sweats), lymphadenopathy, dysfunction of the involved organs, and compression of surrounding structures. Posttransplant lymphoproliferative disorder is a group of lymphoid disorders, usually B cell in origin, that typically occur after allogeneic HCT. Extramedullary masses are common, and other manifestations may include constitutional symptoms (eg, fevers, chills, weight loss, night sweats), lymphadenopathy, dysfunction of the involved organs, and compression of surrounding structures. Posttransplant lymphoproliferative disorder is a group of lymphoid disorders, usually B cell in origin, that typically occur after allogeneic HCT. Extramedullary masses are common, and other manifestations may include constitutional symptoms (eg, fevers, chills, weight loss, night sweats), lymphadenopathy, dysfunction of the involved organs, and compression of surrounding structures. Posttransplant lymphoproliferative disorder is a group of lymphoid disorders, usually B cell in origin, that typically occur after allogeneic HCT. Extramedullary masses are common, and other manifestations may include constitutional symptoms (eg, fevers, chills, weight loss, night sweats), lymphadenopathy, dysfunction of the involved organs, and compression of surrounding structures. Posttransplant lymphoproliferative disorder is a group of lymphoid disorders, usually B cell in origin, that typically occur after allogeneic HCT. Extramedullary masses are common, and other manifestations may include constitutional symptoms (eg, fevers, chills, weight loss, night sweats), lymphadenopathy, dysfunction of the involved organs, and compression of surrounding structures.

What PCPs can do: Be aware of this rare yet serious complication and refer patients who may display any new symptoms to their transplant physicians.

IT TAKES A PARTNERSHIP

The care of HCT recipients is complex and requires a partnership between the transplant physician, primary oncologist, and PCP. Understanding and awareness of the various late-onset complications that can arise after allogeneic HCT are extremely valuable, as the PCP is often the first to detect, investigate, and manage them. It is of equal importance that the PCP communicate any concerns with the patient’s transplant physician, primary oncologist, or both.

Although transplant recipients are a special patient population, many of the late-onset complications that they face are within the scope of typical primary care practice. Members of the primary care team, including advanced practice practitioners, nurses, and medical assistants, are often the first to recognize late complications and, owing to their expertise, are also best suited to aid in their management.

There are several known challenges. A survey of PCPs found that more than half of the respondents reported a gap in knowledge regarding the unique screening and prevention guidelines for HCT survivors. Acknowledging this deficit, we hope that this review article serves as a resource for PCPs as they care for this vulnerable population.

In summary, the PCP plays an integral role in screening for and managing chronic coexisting conditions. While the recommendations above are primarily based on consensus, and are not exclusively based on evidence for each specific organ system, PCPs are in a position to help prevent many posttransplant complications. PCPs are uniquely qualified to alter the trajectory of patients after allogeneic HCT, and their importance should not be underestimated.

REFERENCES


DISCLOSURES

Dr. Hamilton has disclosed the following: DSMB member with Angiocrine; advisor or review panel participant with Equillium, Incyte, NKarta, and Sanofi; consulting for Incyte; and teaching and speaking for Pfizer and Therakos. 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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