MAYO CLINIC

Clinical Update

Current Trends in the Practice of Medicine

Vol. 27, No. 1, 2011

INSIDE THIS ISSUE

The Thyroid Nodule Clinic

The Challenge

Most thyroid nodules—about 95%—are entirely benign. However, identifying the occasional thyroid cancer requires careful evaluation of every nodule found, using a combination of clinical assessment, neck palpation, ultrasound imaging (Figure 1), and, in many cases, analysis of a biopsy specimen (Figure 2, see page 2).

Sometimes, thyroid nodules are noticed by the patient or a family member or are discovered during a routine physical examination. They rarely cause symptoms, unless they are large enough to interfere with swallowing. Thyroid cancer can invade and damage the recurrent laryngeal nerve, causing hoarseness. Such invasion and damage are infrequent, however. Most nodules are incidental discoveries, and now many more such nodules are discovered because of the increased use of imaging performed for other reasons, including carotid ultrasonography, neck or chest computed tomography, magnetic resonance imaging, and even positron emission tomography.

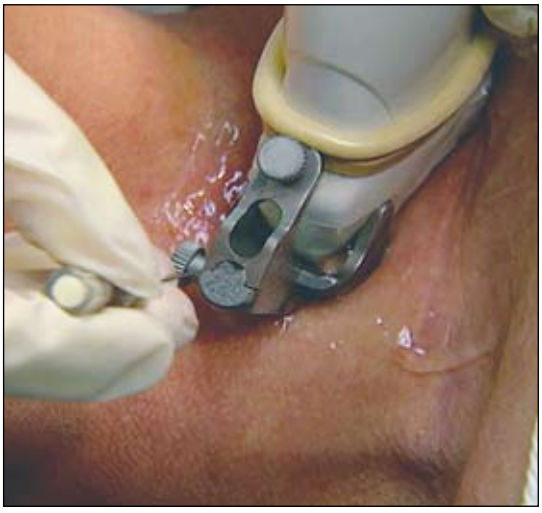


Figure 1. *Ultrasound-guided fine-needle aspiration of a thyroid nodule.*

Points to Remember

- Thyroid nodules are common, with palpable nodules found in 4% to 7% of the adult US population and solitary or multiple nodules found at much higher rates during ultrasonographic screening.
- Early diagnosis improves the likelihood that a cancer can be discovered while still contained within the thyroid gland and amenable to surgery.
- Mayo Clinic endocrinologists opened the Thyroid Nodule Clinic in 2009, providing coordinated care, a thorough assessment, and a definitive diagnosis completed at a single visit.

Early and prompt diagnosis improves the likelihood that a cancer can be discovered while still contained within the thyroid gland and amenable to surgery. Once soft tissue invasion has occurred or lymph nodes are extensively involved, the chance of surgical cure drops substantially and there is a much higher incidence of metastatic spread of these late-stage cancers. Prompt diagnosis is also important for the patient because the finding of a nodule often raises fears about cancer and a delay in diagnosis fuels the concern and anxiety.

The most recent set of guidelines from the American Thyroid Association specifies that the evaluation of a thyroid nodule should include clinical assessment to determine the number, size, and location of all nodules within the gland; measurement of serum thyrotropin (TSH) to exclude hyperthyroidism; ultrasonography to assess the nodule for features of malignancy; and fine-needle

aspiration (FNA) of nodules that meet the appropriate size and ultrasound criteria. However, not every nodule needs to be biopsied, so the clinical scenario and ultrasound features are important in selecting the appropriate nodule for biopsy.

Mayo Clinic endocrinologists opened the Thyroid Nodule Clinic in 2009 to streamline this evaluation and provide a coordinated approach that meets the needs of patients with thyroid nodules. The Thyroid Nodule Clinic provides a 1-stop thyroid nodule evaluation that includes a focused clinical assessment, ultrasound evaluation, and FNA—all typically performed within a 60-minute appointment at a single visit. The ultrasound allows Mayo staff to select both palpable and impalpable nodules for biopsy and target the most suspicious nodule, which is not always the largest nodule. Using ultrasound guidance for those biopsies, Mayo Clinic endocrinologists typically perform more than 600 biopsies per year and expect a clear diagnosis in more that 95% of cases at the first attempt.

Because of the coordinated assessment provided through the Thyroid Nodule Clinic, FNA results are typically available within 2 hours, so the patient usually receives a definitive result of the entire assessment within 4 hours. Patients with a benign nodule can be reassured, and those with a malignant or suspicious nodule can be offered an appropriate surgical referral, often within 24 hours. Mayo Clinic endocrinologists believe that the Thyroid Nodule Clinic improves the care they provide for these patients, while lowering costs, improving efficiency, and providing a better service to referring physicians.

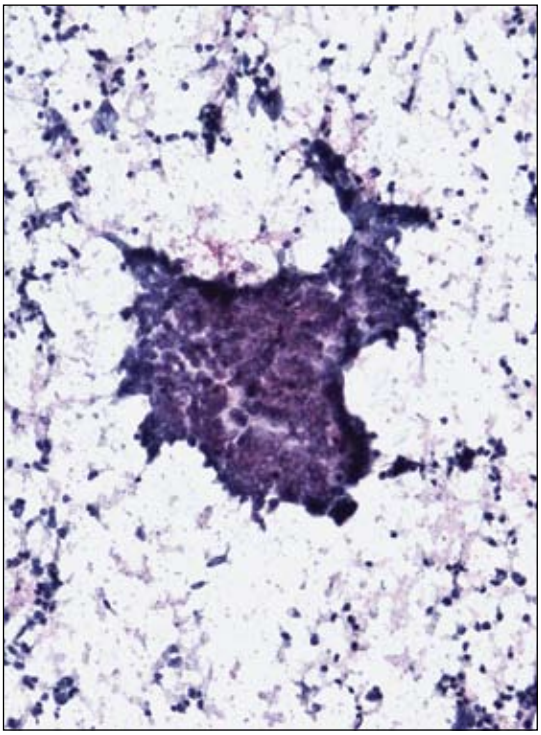


Figure 2. *Thyroid cytology of a specimen of papillary thyroid carcinoma showing papillary architecture and nuclear enlargement with crowding of classic papillary thyroid cancer (Papanicolaou stain, original magnification ×100).*

Perspectives on the Continuing Evolution of Therapy for Atrial Fibrillation

Scope of the Problem

Atrial fibrillation (AF) remains the leading arrhythmia in North America, both in numbers of patients affected and the frequency of accompanying sequelae. The prevalence continues to increase, despite progress in the treatment of contributing factors. Although 1% of individuals in their 60s may have AF, the prevalence increases to 10% to 12% in individuals older than 80 years. Currently 2.5 million Americans have AF, but with the aging population and improved cardiovascular survival, this number may increase to 5 million or 6 million by the year 2050.

In most patients, AF is initially paroxysmal; other patients, particularly those with underlying heart disease, may have more persistent or even chronic AF. Nevertheless, the previously held belief that most paroxysmal AF ultimately progresses to a chronic form has been questioned. Recent studies have suggested that progression occurs in only 20% to 40% of patients over the course of 3 to 5 years, although longer-term data are lacking.

Drug Therapy for AF

Because of stroke risk, most patients require some form of antithrombotic therapy in the form of aspirin, warfarin, or dabigatran. Those patients with no risk factors may completely forgo antithrombotic therapy, while recently published guidelines suggest that therapy with

aspirin alone is adequate in patients at low risk with a CHADS score less than 1. Patients with several risk factors (age >75 years, hypertension, diabetes, prior stroke or transient ischemic attack, left ventricular dysfunction) are at higher risk, necessitating anticoagulation therapy with warfarin.

While relatively rare in the absence of other heart disease, the possibility of an AF contribution to ventricular dysfunction should be considered in patients who have a rapid ventricular response rate and reduced ejection fraction. Establishing appropriate rate control, however, requires some assessment of rate during rest and exertion. While most guidelines recommend that resting rates during AF be less than 90 to 100 bpm, a recent large clinical trial has shown that a resting rate less than 110 bpm is adequate for rate control. During exercise, the heart rate should be maintained at less than 120 bpm.

Restoration of normal sinus rhythm may be the most effective means of rate control. A number of studies have shown the usefulness of membrane-active, antiarrhythmic drug therapy for maintaining sinus rhythm. Approximately 30% to 40% of patients treated with antiarrhythmic therapy achieve control over the course of 1 year of follow-up. These data have been validated by larger comparative clinical trials. Similar results have been reported in studies designed to compare rate and rhythm control therapy. Although an increase in mortality may accompany AF, comparative studies examining the utility of rate vs rhythm control therapy have had disappointing results.

Points to Remember

- Atrial fibrillation (AF) is an increasing burden on the global health care system because of the numbers of patients affected, the impact of stroke, and the cost of both inpatient and outpatient therapy.
- Because of stroke risk, most patients with AF require some form of antithrombotic therapy in the form of aspirin, warfarin, or the newer direct antithrombin agents such as dabigatran.
- A number of observational studies have shown that ablation is of benefit in eliminating AF, reducing its frequency, and improving patients' quality of life.

Nonpharmacologic Therapy for AF

A number of observational studies have shown that AF ablation is of benefit in eliminating AF, reducing its frequency, and improving patients' quality of life (Figure). In most studies, 75% to 85% of patients with paroxysmal AF have been rendered free of this arrhythmia over the course of 1 year of observation. Even in patients with persistent or chronic AF after ablation, the incidence of the arrhythmia is significantly decreased in 10% to 20%.

When Mayo researchers reviewed outcomes of ablation performed at Mayo Clinic, they found (over 2 years of follow-up) that the response to ablation was excellent in more than 75% of patients with paroxysmal AF. Patients with persistent and chronic AF likewise have shown enhanced benefit, although a more aggressive

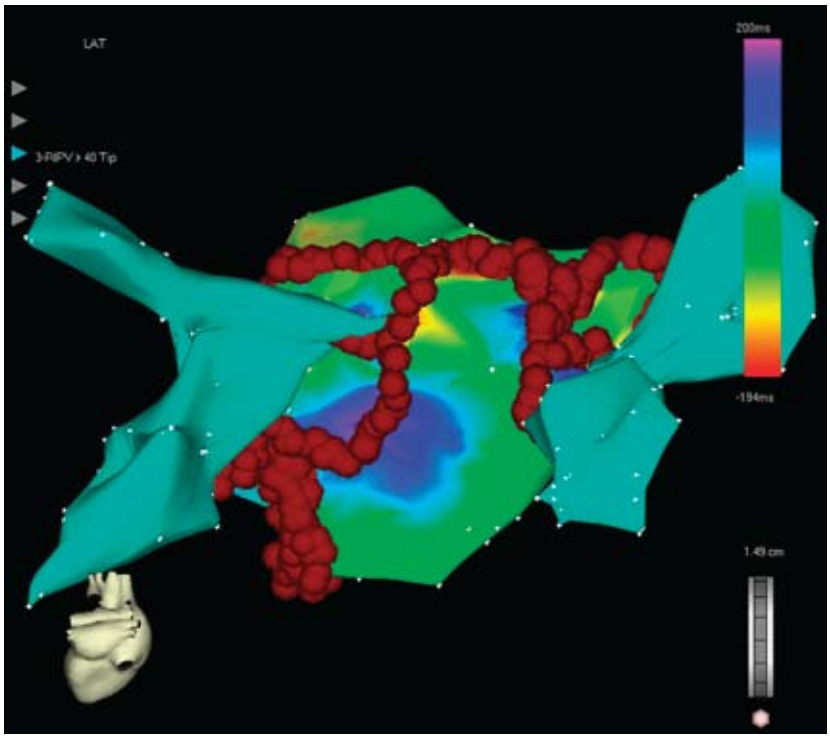


Figure. *Computer-generated map of left atrial activation. Red dots indicate ablation sites.*

ablative approach has been required. In those with paroxysmal AF, ablation for the isolation of pulmonary veins may be sufficient, while wider-area circumferential ablation with additional linear ablation or energy delivery directed at the underlying substrate has been required. Additional review demonstrated notable benefit in patients with underlying dilated cardiomyopathies. In many patients, not only was AF eliminated, but a substantial improvement in ejection fraction was observed, particularly in those with nonischemic left ventricular dysfunction.

Clinical Trials

Clarification of Optimal Anticoagulation Through Genetics (COAG) Trial

A randomized, multicenter, double-blind clinical trial to evaluate the efficacy of clinical plus genetic information to guide the initiation of warfarin therapy and to improve anticoagulation control for patients. The protocol includes

- Warfarin therapy for at least 3 months
- Target INR 2-3
- Study enrollment before receiving the first dose
- Follow-up visits at the Gonda 4 Thrombophilia Clinic

For information, contact Nancy Lexvold, RN, at 507-255-7013 or Robert D. McBane, MD, at 507-266-3964

Anatomy vs Physiology-Guided Ablation for Atrial Fibrillation

A study to establish the differential success rate for complete elimination of atrial fibrillation (AF) with combined wide-area circumferential ablation and linear ablation vs combined wide-area circumferential ablation and complex fractionated atrial electrogram (CFAE) ablation. Inclusion criteria are

- History of symptomatic persistent/permanent AF
- Patient recommended for catheter-based, wide-area pulmonary vein isolation
- Available for 13 months of follow-up after ablation

For information, contact Celeste Koestler, RN, or Yong-Mei Cha, MD, at 507-255-2200

Advances in Seizure Prevention and Prediction

The earlier seizure activity is detected, the better the chance of preventing it. For several years, Mayo Clinic neurologists and their neurosurgical colleagues have been working to pinpoint the exact moment and the precise location of seizure generation.

Isolating the Where and When of Microseizures

Three years ago, using microelectrodes 40 microns in diameter, or thinner than a human hair, Mayo Clinic researchers began recording electroencephalographic (EEG) activity from brain regions the size of cortical columns at frequencies beyond the limits of standard EEG recordings. Cortical columns, the smallest functional unit in the cortex, are approximately 300 microns across and contain from 1,000 to 7,500 neurons. In perspective, a typical EEG electrode captures the activity of millions of neurons and hundreds of cortical columns (Figure).

This research revealed that isolated brain regions the size of cortical columns do, indeed, show evidence of seizure activity (microseizures) in humans. The investigators found that microseizures occurred most often in patients with epilepsy but also occurred, although rarely, in control patients without epilepsy. This latter finding demonstrates that pathologic oscillations can occur even in people who do not have epilepsy.

How do microseizures transition to clinical seizures in patients with epilepsy? Mayo Clinic research findings support the hypothesis that in patients with epilepsy, individual microdomains the size of cortical columns generate frequent hypersynchronous discharges, which recruit

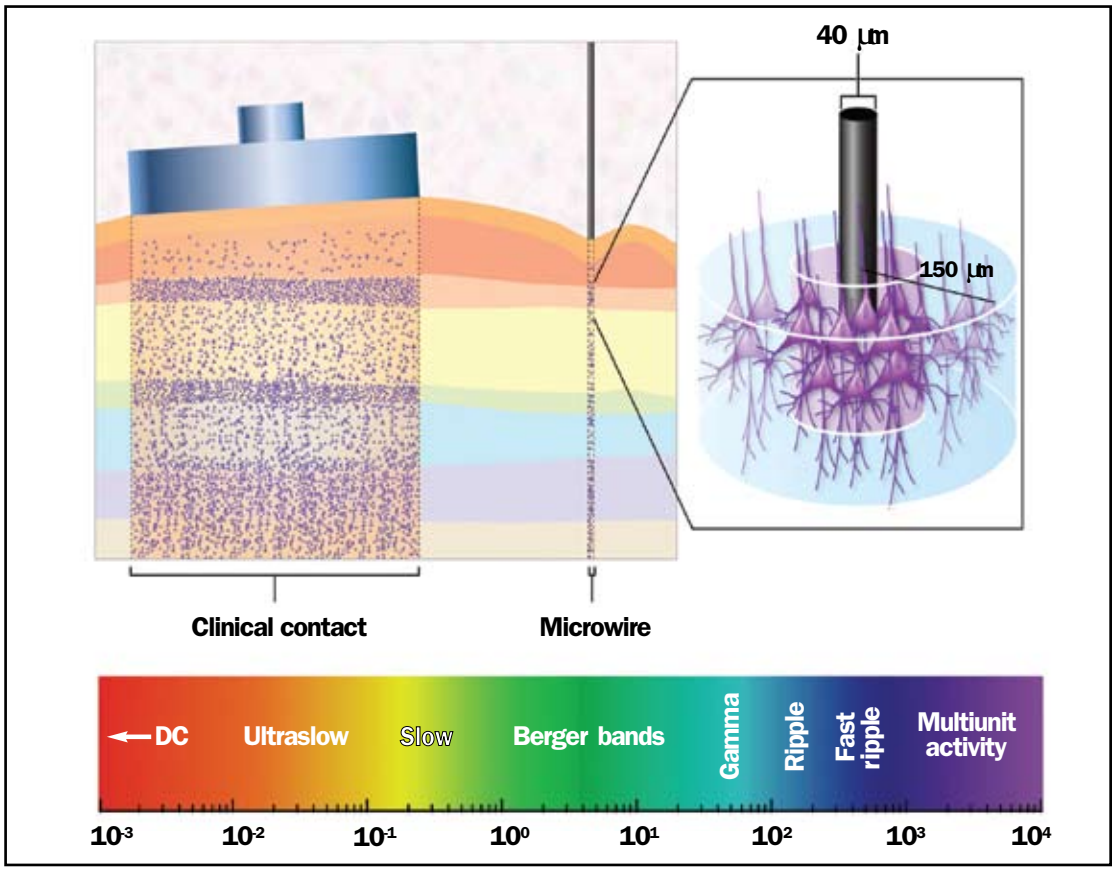


Figure. *Top, The large volume sampled by the millimeter-scale clinical electrode (about 1 million neurons) vs a 0.04-mm microwire. The cortex is organized into columns of neuronal clusters about 0.03 to 0.6 mm in diameter (cortical columns, about 7,500 neurons). Bottom, The frequency range of neuronal network oscillations.*

other columns of neurons. Similar, noncolumnar groupings of neurons have been identified in the rat hippocampus by researchers at UCLA and are known as pathologically interconnected neuron (PIN) clusters. These PIN clusters can be considered microdomains of epileptogenesis or seizure initiation. When a critical volume of microdomain activity is reached, a large-scale seizure is generated. This explanation can be referred to as the sick column hypothesis.

Clinical EEG recordings do not probe the spatial and temporal scales of microdomain activity, which makes early detection difficult. This hypothesis may explain why some patients do not respond to first-generation responsive stimulation devices designed to detect and abort seizures.

Update on Implanted Devices to Detect and Abort Epileptic Seizures

Two new implantable epilepsy devices that use electrical stimulation are undergoing multicenter trials for treatment of medically refractory epilepsy. One device uses electrical stimulation of the anterior nucleus of the thalamus to modulate the brain activity and prevent seizures. Another device under investigation is the responsive neurostimulator system. Initial

Points to Remember

- Mayo Clinic neurologists and neurosurgeons have been working to pinpoint the exact moment and the precise location of seizure generation.
- The recent discovery that seizurelike events can occur in pathologic microdomains (ie, microseizures) in humans adds to a growing body of evidence that seizures may begin before they are evident on clinical recording systems and well before patients have symptoms.
- Initial results from 2 pivotal multicenter trials have demonstrated the efficacy and safety of implantable epilepsy devices that use electrical stimulation for reducing seizure frequency in patients with medically intractable partial epilepsy.

results from these 2 pivotal multicenter trials have demonstrated the efficacy and safety of these devices.

Predicting Seizures: Devices on the Horizon

Not knowing when a seizure will occur is one of the most debilitating aspects of epilepsy. Patients may have only 4 or 5 seizures a month, each lasting a few minutes. But those few minutes mean they can't drive, and they may be afraid to go out in public for fear of having a seizure, which can lead to social isolation.

The recent discovery that seizurelike events can occur in pathologic microdomains (ie, microseizures) in humans adds to a growing body of evidence that seizures may begin before they are evident clinically. In the future, devices may be able to provide patients with warnings that a seizure is about to occur or, possibly, to prevent a seizure.

Future Applications

The future of seizure prevention rests on understanding the mechanisms underlying seizure generation. As knowledge in these areas advances, future clinical applications include improvements in epilepsy surgery and the devices delivering neurostimulation and the possible development of algorithms that identify periods of increased probability of seizures.

Childhood Fractures: When to Worry

Childhood bone fractures are common and often cause concern for patients, parents, and clinicians. Understanding the typical timing and types of fractures is helpful when deciding who needs further evaluation for potential underlying disease. The rate of fractures increases substantially during puberty for both boys and girls, but to a greater degree for boys. The peak incidence of fractures in girls occurs around 10 to 12 years of age and in boys around 13 to 15 years of age. Forearm fractures are by far the most common type of fracture during childhood (Figure 1). However, vertebral compression fractures are distinctly uncommon in children and should always be a cause for concern and additional evaluation (Figure 2).

Children with 1 or 2 traumatic fractures are unlikely to have an identifiable disorder and do not routinely require further evaluation. Obtaining a detailed history about the circumstances surrounding a fracture is important in determining the level of concern. Multiple fractures, atypical fractures (such as vertebral compression fractures), low-trauma fractures, and a family history of metabolic bone disease are all red flags that should prompt further investigation. Children with inflammatory bowel disease, celiac disease, chronic glucocorticoid exposure, neuromuscular disorders, and others (Box) warrant special attention to optimize bone health, since they are at increased risk for low bone density. A family history of frequent fractures should prompt consider-

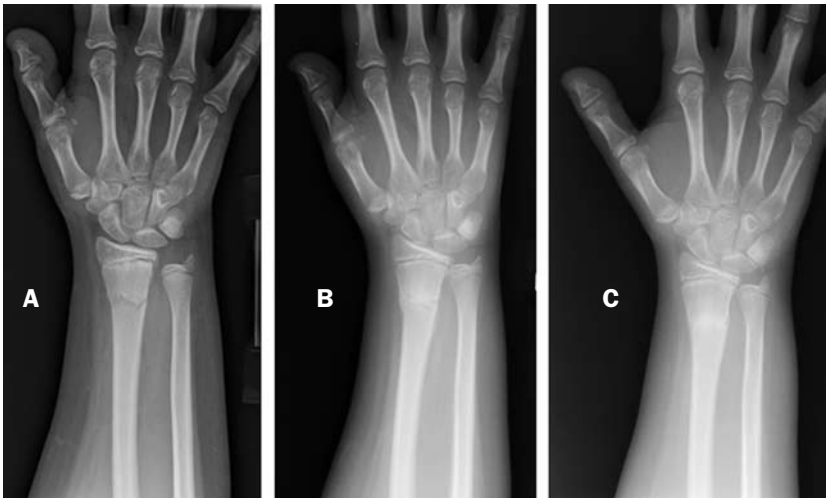


Figure 1. *Trauma-related fracture of the distal radius. A, Radius shortly after injury. B and C, Subsequent normal bone healing.*

Points to Remember

- Approximately one-third of children will sustain a fracture by the age of 18 years. Most of these children do not have an underlying metabolic bone disorder that requires evaluation and treatment.
- Multiple fractures, unexplained fractures (especially in infants), atypical fractures (such as vertebral compression fractures), low-trauma fractures, and a family history of metabolic bone disease are all red flags that should prompt further investigation.

Box. Conditions Associated With Low Bone Density or Fractures in Children

- Anorexia nervosa
- Anticonvulsant use
- Dietary calcium deficiency
- Glucocorticoid excess
- Growth hormone deficiency
- Homocystinuria
- Hyperthyroidism
- Hyperparathyroidism
- Idiopathic juvenile osteoporosis
- Immobilization
- Leukemia
- Malabsorption (eg, celiac disease, inflammatory bowel disease)
- Neuromuscular disorders
- Osteogenesis imperfecta
- Osteoporosis pseudoglioma syndrome
- Vitamin D deficiency

ation of inherited conditions, such as osteogenesis imperfecta.

Unexplained fractures, especially in infants, mandate consideration of nonaccidental trauma if an underlying bone disorder is not clearly identified. Poor fracture healing also should raise suspicion of an underlying bone disease. Most fractures in children show radiographic evidence of callus formation by 3 to 6 weeks. By 8 to 12 weeks, most fractures are united radiographically and no longer require any form of external immobilization.

Evaluation

A basic laboratory evaluation includes such tests as serum calcium, phosphorus, creatinine, parathyroid hormone, 25-hydroxyvitamin D, and urine calcium determination. The serum concentration of 25-hydroxyvitamin D is the best test to determine whether adequate vitamin D stores are present. The serum concentration of the active metabolite of vitamin D (1,25-dihydroxyvitamin D) can be variable in children with nutritional vitamin D deficiency (low concentration of 25-hydroxyvitamin D) and is usually not helpful in determining vitamin D status. Growing children have a markedly greater serum alkaline phosphatase concentration than adults, and an appropriate reference range for age and sex should be used. Alkaline phosphatase level will usually be elevated in the context of a recently sustained, healing fracture. Clinical findings supporting a secondary cause of poor bone health (Box) should also guide the evaluation.

Dual-energy x-ray absorptiometry (DXA) is a widely available technique for determining bone density. Children with frequent, low-trauma, or atypical fractures are good candidates for bone density measurement. Children with disorders associated with low bone density, such as inflammatory bowel disease, may also benefit from bone density determination. DXA measurements in children should be performed in centers with experience obtaining and interpreting the scan.

Prevention

Adequate intake of calcium and vitamin D is the foundation of any treatment program to promote bone health. The American Academy of Pediatrics currently recommends that all children receive 400 IU of vitamin D daily, which can be obtained through the diet (mainly milk), supplementation, or both. The optimal amount of vitamin D intake or serum vitamin D concentration for children has not yet been clearly defined. Avoiding excessive caffeine and soda intake should also be advised.

Bisphosphonates may be beneficial in select children with low bone density and fractures. They are not approved by the Food and Drug Administration for use in children and should only be given under the supervision of a clinician experienced with their use in children.

For consultation about childhood fractures and whether further evaluation is needed, please contact the Mayo Clinic Referring Physician Service (see page 8 for contact information).

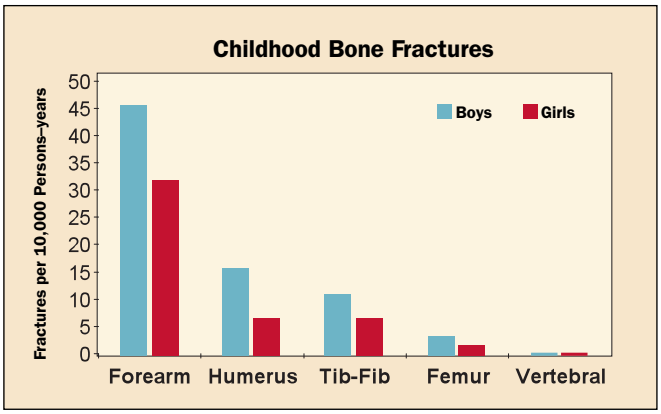


Figure 2. *Incidence of specific fracture types in children. Tib-Fib indicates tibia and/or fibula. Data from Cooper C, Dennison EM, Leufkens HGM, Bishop N, van Staa TP. Epidemiology of childhood fractures in Britain: a study using the general practice research database. J Bone Miner Res. 2004 Dec;19(12):1976-81.*

Mayo Clinic
Clinical Update

Medical Editor:
Scott C. Litin, MD

Editorial Board:
Robert P. Shannon, MD
Douglas M. Peterson, MD

Clinical Update is written for physicians and should be relied upon for medical education purposes only. It does not provide a complete overview of the topics covered and should not replace the independent judgment of a physician about the appropriateness or risks of a procedure for a given patient.

Contact Us

Mayo Clinic welcomes inquires and referrals, and a request to a specific physician is not required to refer a patient.

Arizona
866-629-6362

Florida
800-634-1417

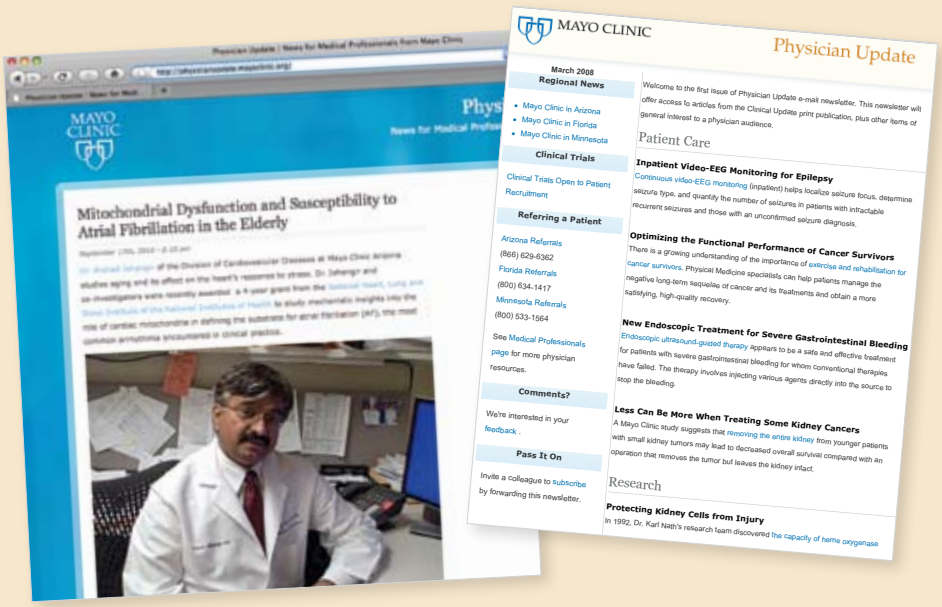
Minnesota
800-533-1564

Resources

mayoclinic.org/medicalprofs

- Clinical trials
- CME
- Grand Rounds
- Scientific videos
- Online referrals

Physician Update



Mayo Clinic has online options for medical professionals

An e-mail newsletter and a physician video blog. Visit **www.mayoclinic.org/medicalprofs** for more details.

MAYO CLINIC | mayoclinic.org

4500 San Pablo Road
Jacksonville, FL 32224

200 First Street SW
Rochester, MN 55905

13400 East Shea Boulevard
Scottsdale, AZ 85259

MC2024-0311