MAYO CLINIC

Clinical Update

Current Trends in the Practice of Medicine

Vol. 27, No. 5, 2011

Endoscopic Ultrasound: New Diagnostic and Therapeutic Applications

INSIDE THIS ISSUE

Endoscopic ultrasound (EUS) was originally developed to detect pancreatic tumors in the earliest, most treatable stages. Today, EUS remains the primary method for evaluating and staging pancreatic cancer and has emerged as a valuable tool for assessing people at high risk for the disease. In the past few years, however, the role of EUS has expanded well beyond its use in diagnostic imaging.

One of the most important and widely used new applications is EUS-guided fine-needle aspiration (EUS-FNA) cytology. EUS-guided biopsies allow minimally invasive sampling of tissue from tumors and lymph nodes not easily accessible by other methods.

According to Mayo Clinic gastroenterologists, EUS-FNA has significantly changed not only the staging and management of gastrointestinal tract tumors but also the mediastinal staging of lung cancer. Although EUS is thought of as a tool for assessing cancers of the digestive system, it is now arguably one of the preferred methods for the preoperative assessment of non–small cell lung cancer, replacing invasive procedures such as mediastinoscopy and thoracoscopy.

A definitive trial performed by researchers at Mayo Clinic in Florida showed that a combination of EUS-FNA and endobronchial ultrasound-guided FNA can provide nearly complete staging of the mediastinum and is significantly better than previously available methods.

Points to Remember

- Endoscopic ultrasound (EUS) remains the primary method for evaluating and staging pancreatic cancer and has emerged as a valuable tool for assessing people at high risk for the disease.
- The role of EUS has expanded well beyond its use in diagnostic imaging. This includes EUS-guided staging and management of gastrointestinal tract tumors and the mediastinal staging of lung cancer.
- EUS has also evolved into a promising therapeutic tool, guiding the imaging and drainage of cysts in the pancreas and drainage of abscesses in the abdomen, chest, and pelvis.

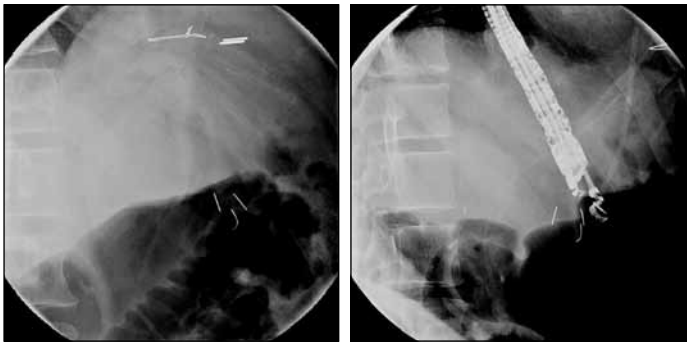

Figure. *Endoscopic ultrasound-guided placement of fiducial markers in the pancreas of a patient undergoing radiation therapy.*

Expanding Diagnostic Possibilities

In the mid-1990s, EUS-guided biopsies, coupled with advances in molecular biology, led to the development of biomarker-based diagnoses. Since then, biomarkers have played an integral role in distinguishing premalignant or malignant pancreatic cysts from benign ones—historically a difficult and unreliable process. Now, analysis of cyst fluid proteins collected by EUS-FNA, along with cytology and imaging tests, may help determine which cysts require surgical intervention.

Molecular testing for tumor markers and genetic mutations can also help guide therapy.

Some genetic biomarkers are predictive of how certain people will respond to particular therapies. Mayo researchers have done a great deal of work in this area, and it has been very helpful for a subset of patients.

Therapeutic EUS

More recently, EUS has evolved from an increasingly sophisticated diagnostic tool into a promising therapeutic one. So far, the most widely available and successful intervention has been pancreatic pseudocyst drainage. EUS guidance allows cysts to be imaged and drained without the risks and potential complications of other methods of cyst puncture.

EUS has also been used to drain abscesses in the abdomen, chest, and pelvis, and EUS-guided cholangiopancreatography is an option when endoscopic retrograde cholangiopancreatography fails or is not possible. Recently, a number of new systems have become available that increase the technical feasibility and convenience of these and other therapeutic procedures, including gallbladder drainage and, potentially, nonsurgical removal of gallstones under EUS guidance.

Several studies have examined EUS-guided ablation of pancreatic cystic neoplasms using ethanol or chemotherapeutic agents such as paclitaxel. Study results show that this method—which avoids surgery and the expense, inconvenience, and potential risks of long-term monitoring—is moderately effective and durable, although longer follow-up is needed.

EUS is also increasingly seen as a safe and effective method for placing fiducial markers in patients undergoing radiation therapy for pancreatic cancer (Figure). Fiducials are small metallic seeds typically made with gold coils. Placed inside a tumor, they reduce organ motion errors, allowing for more precise targeting of tumors and minimizing harm to healthy tissue. EUS-guided fiducial placement is used at Mayo Clinic for both standard radiotherapy and proton therapy and is applicable to all patients with pancreatic cancer. Radioactive seeds can also be implanted in pancreatic neoplasms under EUS guidance.

Enhanced Recovery Pathway: Rethinking Pre- and Postoperative Surgical Care for Colorectal Patients

A decade ago, minimal access procedures radically changed the practice of colorectal surgery. Smaller incisions shortened recovery times, reduced the risk of infection, and decreased trauma and scarring. Today, the field is undergoing another transformation with the growing acceptance of enhanced recovery pathway (ERP), an innovative, multidisciplinary approach to surgical care.

ERP is an evidence-based, multimodal program that seeks to reduce postoperative stress responses and organ dysfunction so that patients recover more quickly, easily, and naturally (Figure 1). According to Mayo Clinic colorectal surgeons, it also overturns decades of established medical practice. Many standard interventions for colon surgery do not necessarily benefit patients, yet they remain in use. Enhanced recovery programs focus on novel practices shown to improve outcomes and quality of care (Figure 2 on page 4).

Feeding vs Fasting

One of the tenets of ERP is that improving the health of patients before surgery results in a faster, less traumatic recovery. For this reason, ERP avoids traditional preoperative fasting and bowel cleansing.

Contrary to standard practice, ERP also allows patients to eat and drink shortly after surgery. Fluid intake begins in the recovery room. Most people eat a small meal that evening and consume a protein-enriched drink the next morning. Mayo Clinic experience has shown that eating does not increase vomiting or paralytic ileus after bowel surgery. Rather, it seems to improve gut function.

In addition, drains and nasogastric tubes are not routinely used, and urinary catheters are promptly removed after 24 hours. These measures not only reduce the incidence of urinary tract infections but also encourage early ambulation, which begins the evening of surgery and is another cornerstone of ERP.

Fewer Opiates and Fluids

Perhaps the most notable issues differentiating enhanced recovery from standard practice involve pain and fluid management. ERP emphasizes both optimal pain control and rapid

healing. Before surgery, patients receive antinausea medication, ibuprofen, and acetaminophen to reduce nausea and preemptively treat pain. Patients are also assessed for a 24-hour spinal anesthetic. Postoperative pain management includes short-term, low-dose oral opioids and regularly scheduled anti-inflammatories.

One of the defining characteristics of ERP is the limited use of intravenous narcotics, a critical factor in speeding the return of normal intestinal function and encouraging early ambulation. By the time patients leave the recovery room, they do not need intravenous medications. Because patients are eating, oral pain medications can be administered. Oral medications have fewer adverse effects and provide more sustained pain control.

Avoiding fluid overload is another key component of ERP. The goal, both during and after surgery, is to maintain the patient's normal fluid balance (euvolemia) and avoid excess sodium (salt) intake. When euvolemic status is maintained, patients gain less than 1 pound (0.5 kg) of fluid, and this is associated with faster recovery of overall function.

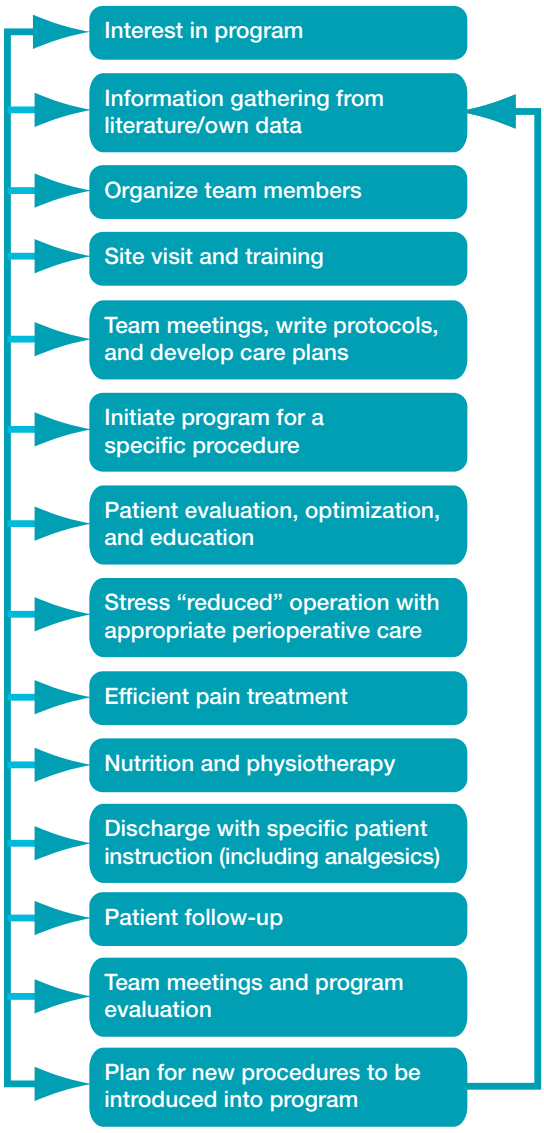

Figure 1. *Implementing an enhanced recovery pathway is a multistage process. A team is involved in the development of care plans and procedures to reduce postoperative stress, implementation of those care plans, patient evaluation and education, and team follow-up and evaluation.*

Adapted from Kehlet H and Wilmore DW. Evidence-Based Surgical Care and the Evolution of Fast-Track Surgery. *Ann Surg.* 2008;248(2):189-98. Used with permission.

Points to Remember

- Enhanced recovery pathway (ERP) is an evidence-based, multimodal program that overturns decades of established medical practice in the care of colorectal surgical patients.
- ERP avoids traditional preoperative fasting and bowel cleansing and, contrary to standard practice, also allows patients to eat and drink shortly after surgery.
- The ERP approach to pain management includes preemptively treating pain and nausea before surgery, avoiding fluid and sodium overload during and after surgery, and limiting the use of intravenous narcotics postoperatively.
- Mayo Clinic colorectal surgeons have noted that benefits associated with ERP include shorter hospital stays, improved outcomes, and fewer long-term complications.

Measurable Benefits

The ability to reduce surgical stress and restore normal function as quickly as possible has profound implications for patients and for health care in general. Enhanced recovery programs have been shown to cut the average hospital stay in half, from 5 or 6 days to just 2 or 3 days, without increasing complications or readmissions. Furthermore, the pathway is associated with a reduction in overall costs.

Research on ERP also shows improved cardiac and pulmonary outcomes, improved muscle function, decreased fatigue, and fewer long-term complications. As important, patients have a better overall experience, with minimal discomfort, a faster return to normal life, and greater

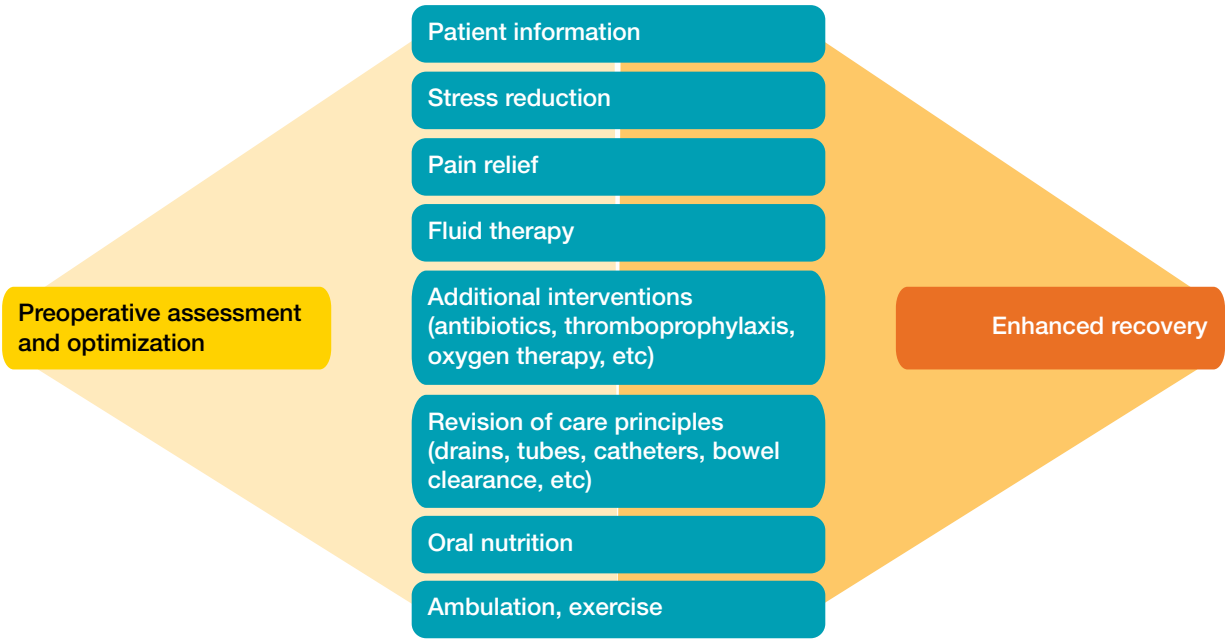

Figure 2. *Enhanced recovery pathway is an evidence-based, multimodal program that seeks to reduce postoperative stress responses and organ dysfunction so that patients recover more quickly, easily, and naturally.*

Adapted from Kehlet H and Wilmore DW. Evidence-Based Surgical Care and the Evolution of Fast-Track Surgery. *Ann Surg.* 2008;248(2):189-98. Used with permission.

independence and participation in their care.

First pioneered 15 years ago, in Denmark, ERP has been used successfully at Mayo Clinic in Rochester, Minnesota, since November 2009. The improvement in patient rehabilitation has been well documented. ERP is a data-driven program at Mayo Clinic, where staff continually evaluate patient care, looking for ways to restore the body to health as soon as possible.

PREVAIL Trial Extends Eligibility for Left Atrial Occlusion Devices in Atrial Fibrillation

Because of the long-term disability and mortality associated with stroke, it remains perhaps the most feared medical event for adult patients. In the United States alone, approximately 800,000 strokes occur per year, the majority of which are first occurrences. Stroke is the third leading cause of death and the leading cause of disability in the United States and accounts for up to $75 billion of health care.

Atrial fibrillation (AF) is a major risk factor for stroke; patients with this arrhythmia have an approximately 5-fold higher risk of stroke. The relationship between increasing age, the increasing incidence of AF, and the increasing rate of stroke has been well documented. Antithrombotic therapy with warfarin (and more recently dabigatran) has been the

Points to Remember

- The PROTECT AF trial confirmed the hypothesis that the left atrial appendage is responsible for the majority of strokes in patients with nonvalvular atrial fibrillation.
- The results of the trial documented that placement of a left atrial occlusion device is noninferior to long-term warfarin therapy for stroke prevention, systemic embolization, and mortality.
- The PREVAIL trial will extend the PROTECT AF trial to a wider range of patients.

cornerstone of stroke prevention in patients with AF, but issues such as bleeding, individual variability in response to drug dosing, and need for laboratory testing have led to its underutilization.

Left atrial appendage occlusion devices are being tested as an alternative to antithrombotic therapy for patients with nonvalvular AF. To date, a single randomized trial has been completed. Only 1 device was tested in that trial (Watchman; Atritech, Inc, Plymouth, Minnesota) (Figure). The Embolic Protection in Patients With Atrial Fibrillation (PROTECT AF) trial randomized patients with nonvalvular AF at risk for stroke (a CHADS2 score ≥1) either to device implantation or to conventional therapy with warfarin. To qualify for enrollment in the study, patients had to be able to receive warfarin. In the device group, patients were treated with warfarin for 45 days on the basis of the assumption that by the end of 45 days, the device would have become fully endothelialized. These patients then received aspirin and clopidogrel for 6 months and then aspirin alone. Both primary efficacy and primary safety end points were used with a noninferiority design. The efficacy end point was a composite of all-cause death, stroke or thromboembolism, and major bleeding.

The PROTECT AF trial substantiated the hypothesis that the left atrial appendage was responsible for the majority of strokes in patients with nonvalvular AF and documented that device placement is noninferior to long-term warfarin therapy for stroke prevention, systemic embolization, and mortality. There was an early safety hazard in the device group, with increased perioperative events, mainly pericardial effusion. In addition, a small number of perioperative strokes occurred, usually the result of air embolism during the procedure. Subsequent to completion of the study, a continued access protocol was initiated, which documented continued efficacy of the device and a reduction in procedural complications, the latter of which was achieved by improved operator experience and implantation techniques and equipment design modifications.

Risks associated with invasive procedures, while infrequent, account for a potential early safety hazard. The risk-benefit ratio of this early safety hazard with the device needs to be compared with the long-term potential for adverse effects with antithrombotic therapy in the consideration of specific therapeutic strategies for each individual patient.

Another trial (PREVAIL) with a similar design using this specific device has been initiated. Mayo Clinic is participating in this 50-site randomized trial that will enroll up to 475 patients. Patients must have nonvalvular AF, be eligible for warfarin therapy, and have a CHADS2 score of 2 or more. Randomization will be 2:1 to receive the device vs warfarin-only therapy. The primary end point is a composite of hemorrhagic stroke, ischemic stroke, systemic embolism, and cardiovascular or unexplained death. This follow-on trial will attempt to confirm the improved safety results seen in the continued access protocol and document the safety and efficacy results when new centers and implanting physicians are added.

For additional information about enrolling patients in PREVAIL, please call 507-255-8354.

Figure. *The Watchman left atrial appendage system has a self-expanding nitinol frame structure with fixation barbs, and a permeable polyester fabric covers the atrial face of the device.*

Adapted from Fountain RB, Holmes DR, Chandrasekaran K, et al. The PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic PROTECTion in Patients With Atrial Fibrillation) Trial. *Am Heart J.* 2006;151(5):956-61. Used with permission.

American Heart Association Updates CPR Guidelines

About 50 years ago, the American Heart Association (AHA) published guidelines for performing cardiopulmonary resuscitation (CPR) in response to sudden cardiac arrest. Because most cardiac arrests occur outside the hospital, the goal of these guidelines is to prepare rescuers to deliver a rapid, effective response.

Although the use of CPR has made an impact, most experts agree there is still room for improvement. According to the AHA, many victims of out-of-hospital sudden cardiac arrest do not receive any bystander CPR, and when they do, the quality of compressions is usually inadequate. In 2010, the AHA published updated guidelines for CPR and emergency cardiac care (ECC) in an attempt to address these issues.

According to the AHA, the 2010 guidelines are the product of an international evidence evaluation process that involved hundreds of international resuscitation scientists and

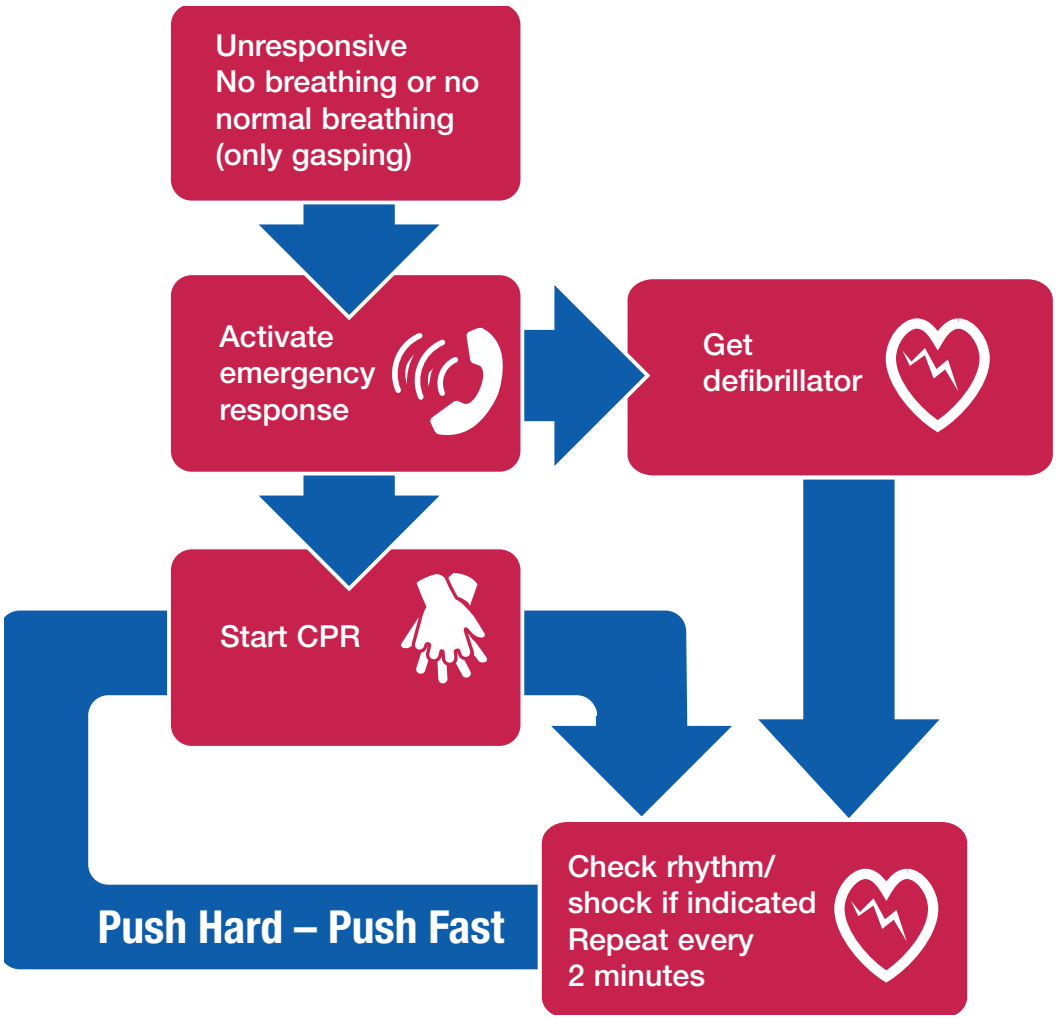

Figure. *Basic Life Support algorithm for performing cardiopulmonary resuscitation (CPR).*

Adapted from Travers AH, Rea TD, Bobrow BJ, et al. 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science. Part 4: CPR Overview. *Circulation*. 2010;122(18 Suppl 3):S676-84. Used with permission.

experts who assessed, discussed, and debated thousands of peer-reviewed publications. A Mayo Clinic anesthesiologist played a key role in the 2010 guidelines development process. The summary that follows highlights some of the major issues in the 2010 AHA Guidelines for CPR and ECC that affect all rescuers, whether they are health care providers or lay rescuers.

Altering the CPR Sequence to C-A-B

Untrained or lay rescuers have been shown to spend too much unproductive time trying to confirm the need to do CPR. Establishing an airway and doing rescue breathing are also very difficult and most often ineffective when untrained rescuers are involved. Previous AHA guidelines told rescuers to assess responsiveness, call for help, open the airway, check for breathing, give 2 breaths, and check for a pulse before beginning compressions. Because the most urgent immediate need is to compress the chest and move blood, the new AHA guidelines now simplify the response by recommending that compressions should begin immediately if the victim is unresponsive and not breathing or is breathing abnormally (gasping for breaths).

The AHA literature states that numerous studies have shown that there is enough oxygen remaining in the blood following cardiac arrest to provide sufficient oxygen to the body for several minutes while the rescuer is doing compressions only. And additional research data show that survival for out-of-hospital adult cardiac arrest is higher when bystanders made some attempt rather than no attempt to provide CPR.

Continued Emphasis on Adequate Rate and Depth of Chest Compressions

Compressions are the most critical part of the CPR sequence in a witnessed cardiac arrest. Interruptions in compressions stop blood

Points to Remember

In 2010, the American Heart Association (AHA) published new guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiac care. The key issues and major changes addressed include the following:

- A simplified universal adult Basic Life Support (BLS) algorithm (Figure).
- A change in sequence from Airway-Breathing-Compression (A-B-C) to Compression-Airway-Breathing (C-A-B) for lone rescuers and use of compression-only rescue for lay rescuers untrained in CPR.
- Continued emphasis on teaching rescuers to deliver chest compressions of adequate rate (at least 100 per minute) and depth (to at least 2 inches [5 cm]).

flow. Given these facts, the new AHA guidelines state that chest compressions should be delivered at a rate of at least 100 per minute and a depth of at least 2 inches (5 cm). Rescuers must also allow complete chest recoil after each compression, minimize interruptions in compressions, and avoid excessive ventilation.

These new guidelines address a couple of limitations presented by the previous guidelines. Despite encouragement to "push hard," rescuers often fail to compress the chest deep enough. Recommending a minimum depth of 2 inches for compression of the adult chest, rather than the range noted in the previous guidelines, will encourage more effective compressions. Reminders to allow for chest recoil between compressions also help prevent creating excessive pressure in the chest cavity, which impairs return of blood to the heart and thus reduces the amount of blood delivered with chest compressions.

In summary, the new guidelines are an attempt to make the performance of CPR simpler and more effective for both lay and trained rescuers. For more details about the new guidelines and the updates to both Basic Life Support and Advanced Cardiac Life Support procedures, see "2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science" in the November 2, 2010, issue of *Circulation* (2010;122[18 Suppl 3]:S639-S946)."

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Education Opportunities

The 85th Annual Clinical Reviews
November 7 - 9, 2011
Mayo Civic Center, Rochester, MN
Clinical Reviews seeks to update physicians on the latest recommendations involving the medical subspecialties important for the primary care physician through a comprehensive program consisting of lectures and panel and roundtable discussions on problems of general interest in various areas of medicine, surgery, and pediatrics relevant to clinical practice.

Geriatric Update for the Primary Care Provider
November 10, 2011
Leighton Auditorium, Siebens Building, Rochester, MN
The Division of Primary Care Internal Medicine offers this 1-day program to provide family practitioners, internists, general practitioners, advanced nurse practitioners and physician assistants with current information on the care of elderly patients, including clinical evaluation, management strategies, and innovative practice models. All topics are selected for their clinical relevance. Time is allocated for questions and discussion.

OB/GYN Clinical Reviews
November 10 - 11, 2011
Kahler Hotel, Rochester, MN
This conference addresses a variety of relevant and controversial topics facing patients and their health care providers today. It includes specific clinical challenges encountered in caring for women of all ages and is applicable to many practice styles and settings. Presentations emphasize obstetrical and gynecologic standards of care and problem solving using current treatment modalities. This program is designed for practicing obstetricians, gynecologists, family practitioners, certified nurse midwives, nurse practitioners, and physician assistants.

Multidisciplinary Update in Breast Disease With Preconference Workshop: Radioactive Seed Localized Breast Surgery
November 16 - 19, 2011
Marriott Sawgrass, Ponte Vedra, FL
This 3-day continuing medical education course will provide a multidisciplinary update in prevention, evaluation, diagnosis, management, and treatment of benign and malignant breast diseases and survivorship issues. The information provided in this course is intended for multiple physician and surgical specialties, including internal medicine, family medicine, oncology, radiology, and breast, general, oncology, and plastic surgery. Other health care professionals with an interest in patient care related to breast diseases will find this course helpful, including physician assistants, nurse practitioners, and nurses.

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