TICKING TIME BOMBS

New options for interventional brain aneurysm treatment

ALSO:
Global Outreach
Breast Cancer Pathology
Diabetes Drug
ERCP Pancreatitis
Plasmapheresis is used, along with IV medications, to desensitize patients before transplant.

TRANSPLANT

Making a match

Kidney desensitization program readies challenging patients for organ transplant

Kidneys are in high demand. Of the 3,000 people listed for organ transplant in Michigan, more than 2,400 are waiting for kidneys.

The odds of getting a transplant are even tougher when a patient is sensitized — as about 30 percent of patients are — often from a previous transplant, pregnancy or transfusions. Sensitized patients have high amounts of antibodies in their blood that not only make a match difficult, but also increase the odds that a kidney transplant will fail.

The University of Michigan Transplant Center is the only center in Michigan that offers kidney desensitization, a process that removes unwanted antibodies from the bloodstream using IV medications and plasmapheresis. Desensitization can be performed in patients with potential living donors against whom they have antibodies or are blood type incompatible, or patients who are waiting for a deceased donor transplant.

“Sensitization is more common in part because we are doing so many more retransplants,” says Randall Sung, M.D., associate professor of surgery at the U-M Medical School. Sung leads U-M’s kidney transplant program, along with Millie Samaniego, M.D., professor of nephrology, who also leads the desensitization program.

U-M also has a single-center paired donation program that can identify other possible living donors. “So if we have a specific donor in mind, we can reduce antibodies against that donor or possibly against another donor in the paired donor pool. For patients on the waitlist, desensitization doesn’t have to be 100 percent complete, since there are many possible donors,” says Sung.

Sung and Samaniego say that desensitization is often successful and could be applied to many more patients in need of a transplant. “We have state-of-the-art facilities that can characterize antibodies and antibody levels, along with a willingness to treat patients who are at higher risk,” says Sung.

WATCH For more information on the kidney transplant program, including a video about U-M computer software that aids in matching kidney donations to hard-to-match recipients, see Colleagues in Care Online at med.umich.edu/cic

TECHNOLOGY

At your fingertips

The popularity of Apple’s iPad tablet computer has extended to the hospital setting for patients, families and physicians. For example, rather than flip through a magazine, families in surgical waiting areas at the U-M Cardiovascular Center are now invited to borrow an iPad to listen to music, play games or surf the Internet.

The devices are also used by anesthesiology residents to access reference materials, monitor patients and perform administrative tasks such as room and surgical scheduling.

When resident Adam Jenkins, M.D., is rushing to a code, the first thing he reaches for is his iPad.

“Using my iPad I can access Risk Watch, which lets me look up the patient in distress on my way to the code and gain valuable information about him or her before I even arrive,” Jenkins says.

He is among the first group of residents to work in a paperless environment, with all essentials needed for education, patient care and department functions available at his fingertips through the iPad.

2 Colleagues in Care

On the cover: Aditya Pandey, M.D., along with three colleagues, leads an interdisciplinary team of cerebrovascular specialists who treat hundreds of patients with aneurysms and other cerebrovascular conditions each year.
How it works

Veo is not a new type of machine but a new way of processing data, explains Jeff Fessler, Ph.D., a U-M professor in the departments of Electrical Engineering, Computer Science, Radiology and Biomedical Engineering. Using a technique called Model-based Iterative Reconstruction, the technology employs sophisticated algorithms to squeeze more information out of the existing X-ray data.

“It uses a less idealized model of the data collected by a CT scanner, so we need less radiation to make a good picture,” says Fessler, whose research group has been collaborating with GE on the project for about a decade. “But these more accurate models require more computation.”

While conventional CT images can be processed almost instantaneously, Veo can produce about two scans per hour. This eliminates the technology as an option for patients with urgent or emergent conditions who require immediate results.

Still, the wait is much better than a few years ago, when it would take days to process such massive amounts of data.

CT images created using Veo look a little less sharp than standard CT images but still give enough detail for accurate diagnosis. This image shows a dark spot on a patient’s liver, indicative of cancer.
The University of Michigan Health System is teaming up with one of India’s top academic medical programs to collaborate on trauma care research and foster the exchange of medical personnel and ideas.

The alliance with the All India Institute of Medical Sciences (AIIMS) marks the first such partnership between academic medical programs in the United States and India around trauma care, says trauma surgeon Krishnan Raghavendran, M.D., an associate professor of surgery in the Division of Acute Care Surgery at the U-M Medical School.

Raghavendran was part of a delegation from U-M that traveled to New Delhi in late February to discuss the venture. The group — which also included Steven Kunkel, Ph.D., senior associate dean for research, and Kevin Chung, M.D., M.S., assistant dean for instructional faculty and associate director of Global REACH — toured the Jai Prakash Narayan Trauma Center at AIIMS and met with high-ranking government officials, including the minister of Health and Family Welfare, the director general of Health Services and members of the National Disaster Management Authority.

**A MONUMENTAL PROBLEM**

Both sides have much to gain, Raghavendran explains. India has grown rapidly in recent decades, but its medical infrastructure hasn’t kept pace with its increasingly packed highways and byways. Motor vehicle crashes kill more than 150,000 people in India each year, compared with 33,000 in the United States, a country with far more cars and far fewer people. According to the Indian trauma center’s web site, someone dies in a traffic accident every two minutes, with two out of five patients perishing because treatment could not be provided in time.

“It’s a monumental problem and we’re eager to help AIIMS and the government of India develop a network of more than 140 trauma centers around the country,” Raghavendran says. “U-M is verified as a Level 1 Pediatric and Adult Trauma Center and a Burn Center by the American College of Surgeons. We’re bringing a lot of experience and proven protocols to the table, along with a very robust program of basic and clinical science research.”

Michael W. Mulholland, M.D., Ph.D., chair of the Department of Surgery and Frederick A. Coller Distinguished Professor of Surgery, says there’s no need for India to go through the same growing pains as the United States did when building a national trauma system.

“We’re hoping to help them accelerate that process,” Mulholland says. “At the same time, India is more than three times as populous as the U.S. and sees a different mix of cases than we see, which presents a great opportunity for research collaboration.”
India’s medical infrastructure has not kept pace with its growth, and motor vehicle crashes now kill more than 150,000 people in India each year.

“...India develop a network of more than 140 trauma centers around the country.”

Krishnan Raghavendran, M.D.

A FULFILLING MISSION

The alliance helps fulfill U-M’s mission to facilitate health research, education and collaboration with global partners for the benefit of communities worldwide. Along with potential training opportunities for medical students, residents, nurses and doctors in both hemispheres, there are hopes of one day establishing a joint institute for trauma research.

Already, Raghavendran says, U-M has recommended that trauma centers in India adopt protocols to help prevent pneumonia in patients on ventilators and to reduce antibiotic resistance by more narrowly targeting antibiotic use in patients.

“Both sides are very excited about the potential opportunities that may develop from this collaboration,” he adds.

REACH OUT Learn more about Global REACH, U-M’s international health research, education and collaboration program at globalreach.med.umich.edu

From maternal health in Ghana, to hepatitis in China, to adrenal cancer in Brazil, the U-M Medical School has stepped up its efforts to partner with health professionals and researchers overseas and improve health for all.

This emphasis on global outreach and impact includes a joint institute with the Peking University Health Science Center in Beijing, training programs for medical students from Africa and a new fellowship program for current and recent medical graduates to do research in one of six developing nations.

Other partnerships have been forged with the University of Sao Paulo, Brazil, and the University of Ghana as platforms for a broad range of collaboration.

U-M medical students can now elect to follow a Global Health and Disparities Path of Excellence as a part of their curriculum, as well as electing to spend part of their fourth year abroad at any of 21 institutions from Ireland and India to Panama and Ecuador. Students and faculty from all over the world come to Ann Arbor as visiting medical scholars to meet and collaborate with American clinicians, educators and researchers.

These experiences are helping U-M tackle health issues worldwide. And as more people from all over the world travel to the United States or move here permanently, the lessons learned will also help improve care in our own nation.
For patients, being diagnosed with a brain aneurysm can feel like they’ve been told they have a ticking time bomb in their head. A rupture could occur at any time, and their odds of surviving the resulting subarachnoid hemorrhage with good functionality are approximately 50 percent.

Recent advances in treating intracranial aneurysms and other cerebrovascular conditions have made it possible to defuse many of these “bombs” before they cause irreparable harm. Both open surgical and endovascular approaches, and the neuroimaging to guide them, have improved in the last decade.

But until recently, some patients with especially large, deep or complex aneurysms have still been deemed inoperable. Now, teams at the University of Michigan Health System and other top centers can offer a broad range of approaches to fill aneurysms or divert blood flow from entering them.
MAKING THE INOPERABLE OPERABLE

The newest is a first-of-its-kind stent-like option called the Pipeline Embolization Device.

Delivered via endovascular technique, it is placed within the parent vessel across the aneurysmal opening. But unlike a stent, the fine-mesh Pipeline diverts blood flow away from the aneurysm into the parent vessel. This allows the vessel wall to remodel itself over time and completely clot off the aneurysm. It was approved last year by the FDA for large or giant wide-necked brain aneurysms arising on the internal carotid artery.

“This allows us to treat patients who had no other option,” says Aditya Pandey, M.D., a U-M assistant professor of neurosurgery and member of the U-M Cerebrovascular Disease team. “It’s a promising new technology, but durability will be determined with long-term usage.”

The team gives referring physicians direct access to one of the four attending physicians 24 hours a day, every day of the year.

Pandey and his colleagues B. Gregory Thompson, M.D., Joseph Gemmete, M.D., and Neeraj Chaudhary, M.D., M.R.C.S., F.R.C.R., lead an interdisciplinary team of cerebrovascular specialists who evaluate and treat hundreds of patients with aneurysms and cerebrovascular conditions each year.

Imaging studies such as contrast-enhanced MRI, MRI angiography, CT angiography or catheter-based cerebral angiography can confirm aneurysms. The next challenge is to determine the best treatment approach for the particular patient.

“We truly have an armamentarium at our disposal — a wide range of treatments to offer,” Pandey says.

A LIQUID CURE

Unruptured intracranial aneurysms usually do not cause symptoms, but in certain circumstances they can cause severe headaches or even stroke-like symptoms (weakness, numbness, speech difficulty and visual disturbance). But once an aneurysm has ruptured, most patients describe their symptom as the worst headache of their life. Many also experience photophobia, blurred or double vision, stiff neck, nausea and vomiting.

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As many referring physicians realize, UM’s hospitals and operating rooms are often at or near full capacity due to an ever-growing demand for care of all types. The recent opening of a new UM facility for children’s, women’s and bone marrow transplant care has helped create new capacity, as have efforts to create observation units for adult patients.

Now, the UM Health System has embarked on a new $163 million project to expand and realign adult inpatient care, adding 120 new beds and eight operating rooms by the end of 2014.

The project will convert the former Mott and Women’s Hospital building into an adult hospital with a major emphasis on clinical neurosciences: imaging, surgical and inpatient care for patients with disorders affecting any part of the nervous system and cranial base.

The move of these services out of University Hospital will allow other services to expand and realign for a better patient experience.

Even as the project is going on, UMHS will be making more physical and operational changes to increase capacity and optimize the experience for patients and referring physicians.
The U-M cerebrovascular team recently published data showing that patients can be successfully treated with coils, even when the anatomy around their aneurysm is complex or located deep in the brain, using a special delivery system called the Penumbra catheter.

Another recently published U-M study showed that the team’s ability to use both CT imaging and digital subtraction angiography during an endovascular procedure greatly enhances treatment compared with traditional imaging.

At the same time, U-M is participating in national research on the genetic roots of aneurysm formation, studying families with multiple members who have intracranial aneurysms to determine which genes might increase the chance of formation and rupture.

In addition, the team is currently evaluating mechanisms of injury to the brain once the aneurysm has ruptured, and will be initiating a trial to evaluate the role of certain medications in protecting the brain from aneurysmal bleeding.

RESEARCH For more information on these studies, including full citations, visit Colleagues in Care Online at med.umich.edu/cic

options that we can choose from to suit the individual,” says Thompson, the J.E. McGillicuddy Professor of Neurosurgery and Radiology, a neurosurgeon trained in both microsurgery and minimally invasive interventional neuroradiology techniques.

One option is a liquid called Onyx HD-500, which can be deployed through a catheter to fill the aneurysm sac. A balloon catheter is first threaded into the vessel that has the aneurysm, and then it is positioned to completely bridge the neck of the bulge. Next, the liquid is delivered into the aneurysm’s open space through a second catheter that rides along with the balloon catheter. Onyx HD-500 hardens instantaneously, completely obliterating the aneurysm.

The U-M team also offers both open surgical clipping options and endovascular placement of coils to fill aneurysms and prevent rupture. Specialized stents to support and seal off coil-filled aneurysms have been available for the last six years at U-M.

MORE OPTIONS MEAN MORE ACCESS

A specially constructed “hybrid suite” for neurointerventional care at U-M allows the patient to have dual imaging modalities during elective and emergent care. This is especially important for stroke patients who need both an angiogram and a CT of the head to be performed quickly for endovascular intervention.

“While the availability of all these options makes it possible to treat more patients than ever before, we are also conscious of the need to evaluate new technologies fully,” says Gemmete, an associate professor of Radiology and Neurosurgery, interventional neuroradiologist and director of U-M’s Neurointerventional Radiology fellowship program. He adds, “Outcome studies do show that morbidity and mortality are comparable between open and endovascular approaches, and length of hospital stay is shorter with the ability to send patients directly home within 24 hours of treatment higher with endovascular care.”

“Here at U-M, our cerebrovascular team treats the whole spectrum of neurovascular diseases — in adults and children, and in brains and spinal cords,” says Chaudhary, an assistant professor of radiology and neurosurgery at U-M and a neurointerventional radiologist.
One and Done

On-site pathology evaluations reduce repeat surgeries

Nearly one in three women who have breast cancer surgery will need to return to the operating room for additional surgery after the tumor is evaluated by a pathologist.

A new service at the University of Michigan Comprehensive Cancer Center cuts that number drastically by having pathologists on-site in the operating suite to assess tumors and lymph nodes immediately after they are removed. Meanwhile, the surgeon and patient remain in the operating room until the results are back, and any additional surgery can be done immediately.

This cut the number of second surgeries needed by 64 percent, to one in every 10 women.

U-M began offering the service about two years ago at its East Ann Arbor Ambulatory Surgery Center, where the majority of its outpatient breast cancer surgeries now occur. A study evaluating 271 patients treated eight months before this program began and 278 treated during the next eight months appears in the American Journal of Surgery.

“The frequent need for second surgeries among patients undergoing breast cancer surgery represents a tremendous burden for patients. Beyond the inconvenience and additional time away from work, additional surgeries can result in worse cosmetic outcomes and increased complication rates,” says lead study author Michael S. Sabel, M.D., associate professor of surgery at the U-M Medical School. “Our experience shows that offering on-site pathology consultation has a substantial impact on quality of care.”

Before the on-site pathology, 25 percent of patients needed a second operation to remove more tissue, compared with 11 percent after the service began. Among patients with positive lymph nodes, 93 percent of them avoided a second surgery with on-site pathology.

Conducting on-site pathology requires frozen section analysis for preserving and evaluating the cells. After this is completed, U-M pathologists then process the tumors for standard fixed tissue testing. The study showed consistent results across both types of analysis.

The study authors also considered new guidelines that suggest fewer women need to have their lymph nodes removed if the sentinel lymph node biopsy is positive. The authors factored in that reduction and still found that intraoperative analysis was highly cost-effective.

“Establishing an intraoperative pathology consultation service is feasible, highly efficient and extremely beneficial to patients and surgeons,” says Sabel. “And it reduces the cost of cancer care.”

RESULTS Get linked to the American Journal of Surgery article, along with information on other clinical studies enrolling patients with breast cancer, at Colleagues in Care Online at med.umich.edu/cic

Our experience shows that offering on-site pathology consultation has a substantial impact on quality of care.

Michael S. Sabel, M.D.

Doctor bio

Michael S. Sabel, M.D., is an associate professor of Surgery in the Division of Surgical Oncology. He is also the director of the University of Michigan Comprehensive Cancer Center Breast Cancer Clinical Outcomes Project and is principal investigator on several clinical trials in breast cancer and melanoma.

Sabel received his medical degree from Temple University School of Medicine in Philadelphia and completed postgraduate training in general surgery at Rush-Presbyterian-St. Luke’s Medical Center in Chicago and fellowships at Roswell Park Cancer Institute in Buffalo, NY. Sabel joined the faculty at the University of Michigan in 2001.
An effective new diabetes drug also reduces incidence of hypoglycemia

Emerging research shows that TAK-875, a new drug for Type 2 diabetes, improves glycemic control and is equally effective as glimepiride but has a significantly lower risk of hypoglycemia. Drugs like TAK-875 that activate the free fatty acid receptor (FFA1) have the potential to help diabetics release more insulin and improve control of blood glucose levels with few side effects.

“In view of the frequent hypoglycemia after treatment with sulfonylureas, the low-risk of hypoglycemia after treatment with TAK-875 suggests that there may be a therapeutic advantage to targeting FFA1 in treating people with Type 2 diabetes,” says researcher Charles Burant, M.D., Ph.D., professor of Internal Medicine and the Robert C. and Veronica Atkins Professor of Metabolism at the U-M Medical School.

Free fatty acid receptor 1 plays a vital role in stimulating and regulating the production of insulin. It works by boosting the release of insulin from pancreatic beta cells when glucose and fatty acids rise in the blood, such as after a meal, which results in a fall in blood glucose levels. TAK-875 is a novel oral medication designed to enhance insulin secretion in a glucose-dependent manner, which means that it has no effect on insulin secretion when glucose levels are normal.

In a study published in Lancet, Burant and colleagues randomly assigned 426 patients with Type 2 diabetes who were not achieving adequate glucose control through diet, exercise or metformin treatment to one of five doses of TAK-875, placebo or glimepiride. The primary outcome was change in glycosylated hemoglobin (HbA1c) from the start of the study.

At 12 weeks, all doses of TAK-875 resulted in significant drops in HbA1c compared with a placebo. A similar reduction occurred in patients given glimepiride. At a TAK-875 dose of 25 mg or higher, about twice as many patients (33 percent to 48 percent) reached the American Diabetes Association target HbA1c of less than 7 percent within 12 weeks, compared with a placebo (19 percent), and was similar to glyburide (40 percent).

TAK-875 was generally well-tolerated. The incidence of hypoglycemia was significantly lower for all doses of TAK-875 compared with glimepiride (2 percent versus 19 percent) and was similar to a placebo (2 percent).

Almost one-quarter of patients receiving neuropathy diagnoses — a common comorbidity of diabetes — undergo high-cost, low-yield MRIs, while very few receive low-cost, high-yield glucose tolerance tests, according to research from University of Michigan neurologists.

The research was led by Brian Callaghan, M.D., assistant professor of neurology at U-M, and published in the Archives of Internal Medicine (Jan 2012; 172: 127–132). It found that MRIs were frequently ordered but glucose tolerance tests were not.

“We spend a lot of money to work up a diagnosis of neuropathy. The question is whether that money is well spent,” Callaghan says. “Currently no standard approach to the evaluation of peripheral neuropathy exists. We do a lot of tests that cost a lot of money, and there’s no agreement on what we’re doing.”
The procedure was a success, but after ERCP, 24-year-old Jessica Calcagno experienced abdominal pain that she says was so unbearable she went to the emergency room.

A clinical trial led by gastroenterologists at the University of Michigan shows, for the first time, an effective way for patients like Jessica to avoid post-endoscopic retrograde cholangiopancreatography pancreatitis, a common and painful complication of the GI procedure used to diagnose and treat problems of the bile and pancreatic ducts.

The finding is significant in helping the one in four high-risk patients who develop post-ERCP pancreatitis.

"ERCP is a very important procedure that can provide life-saving interventions for people who need it, although it is considered the most invasive of all the endoscopic procedures and it does have risks associated with it," says lead study author and gastroenterologist B. Joseph Elmunzer, M.D., assistant professor of internal medicine at the U-M Medical School.

According to the study, published in the New England Journal of Medicine, hospitalizations for post-ERCP pancreatitis were dramatically reduced by administering a single dose of the non-steroid anti-inflammatory drug indomethacin.

Indomethacin is believed to inhibit an inflammatory response by the pancreas that can occur after ERCP.

The primary focus of the research was post-ERCP pancreatitis, which was defined as new upper abdominal pain, an elevation in pancreatic enzymes of at least three times the upper limit of the normal range 24 hours after the procedure, and hospitalization for at least two nights.

But according to the study, only 9.2 percent of patients who took indomethacin developed post-ERCP pancreatitis, compared with 16.9 percent of those who took a placebo — a 46 percent drop in relative risk.

"The results of the study were very impressive," Elmunzer says. "We found that indomethacin was highly protective."

The trial ended early after an interim analysis showed clear safety and benefit for the first 600 patients enrolled. The trial is already changing clinical practice.

Calcagno suffered post-ERCP pancreatitis after doctors performed ERCP to find and remove a growth. She was hospitalized for five days because of the complication. At her next ERCP at the U-M’s Division of Gastroenterology, she was given indomethacin.

"Following the procedure, I went home and felt fine. I was a little sore, but that’s standard so it was great," she says. "I have many more ERCP procedures to go through in my life. I feel comforted knowing that I can leave after the procedure and not develop pancreatitis."

The results of the study were very impressive. We found that indomethacin was highly protective.

B. Joseph Elmunzer, M.D.

Only 9.2 percent of patients who took indomethacin developed post-ERCP pancreatitis.

WATCH View a video about post-ERCP pancreatitis, including Jessica’s story, on Colleagues in Care Online at med.umich.edu/cic

STUDY Get links to the New England Journal of Medicine article and a list of current gastroenterology clinical research studies on Colleagues in Care Online at med.umich.edu/cic
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