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Mayo Clinic has offered medical professionals both a quarterly print edition and a monthly online edition of Clinical Update for several years. After conducting research about reading preferences, Mayo is shifting this publication to online issues only.

This will be the final issue of the print edition.

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Combined Organ Transplantation: A Viable Therapeutic Solution for Patients With Dual Vital Organ Failure

Following the reports of the first simultaneous combined heart and kidney transplantation (CHKTx) in 1978 and combined heart and liver transplantation (CHLTx) in 1985, both have become viable therapeutic solutions in the treatment of dual vital organ failure. Since 1987, reports to the United Network for Organ Sharing (UNOS) indicate that CHKTx has been performed in 910 patients through Oct. 31, 2013, and through Oct. 31, 2013, CHLTx was performed in 143 patients at 34 centers (only 15 centers with more than two cases). Through Oct. 31, 2013, combined heart, liver and kidney transplantation was reported in only 13 patients. The Heart Transplantation Program at Mayo Clinic in Rochester, Minn., started in June 1988. More than 500 heart transplantations have been...
performed to date. Included in those transplantations:
• 60 transplants (12 percent) were multiple organ transplants involving the kidney, liver or both
• 30 were CHKTx procedures
• 26 were CHLTx procedures
• 4 were combined heart-liver-kidney transplants

Each of these series represents the largest collection of such procedures performed by a single institution. The frequency of these multiple organ transplants has increased over time: 55 of the 64 procedures have been performed since 2000 (Figure 1). Furthermore, of the 102 patients currently on the heart transplant waiting list:
• 17 are listed for multiple organs
• 12 are listed for combined heart-liver
• 5 are listed for combined heart-kidney

Additionally, combined heart-lung and heart-lung-liver have been performed in a few instances, but are not included in this update.

Overall survival after heart transplantation alone at Mayo Clinic in Rochester since 1988 is 93 percent at one year, 81 percent at five years and 65 percent at 10 years (Figure 2).

Over the same time period, the Mayo outcomes were superior to survival reported by UNOS and the International Society of Heart and Lung Transplantation (ISHLT) at one year (UNOS: 89 percent; ISHLT: 82 percent) and three years (UNOS: 80 percent; ISHLT: 75 percent).

**Combined heart-liver transplantation**

The most common indication for CHLTx is familial amyloidosis (FA), a fatal autosomal dominant disease caused by deposition of an abnormal mutant protein, transthyretin. FA is associated with progressive peripheral and autonomic neuropathy and dysfunction of the cardiac, gastrointestinal and urinary systems. The prognosis for symptomatic cardiac amyloidosis is poor.

The worldwide experience of CHLTx is limited, and fewer than 15 cases have been reported in the literature, of which 11 were performed for FA. The experience at Mayo Clinic in Rochester, 26 CHLTx procedures, exceeds that found in the world literature. FA was the indication for CHLTx in 18 patients, and indications for the
other four CHLTx procedures were hemochromatosis, restrictive cardiomyopathy, congenital heart disease and primary pulmonary hypertension; the last three of these patients had advanced cirrhosis due to chronic congestive heart failure. Median waiting time for patients with FA who underwent CHLTx at Mayo Clinic was 201 days (range, 45 to 443 days). Currently, 12 patients are alive at a mean time of 4.3 years (maximum, 13 years) after CHLTx, and two patients have survived five and eight years after combined heart-liver-kidney transplantation performed for the indication of FA.

One major issue in the long-term follow-up of these patients is progression of peripheral neuropathy, which is part of the clinical spectrum of FA; the extent of neuropathy must be considered during evaluation for CHLTx. Of the 12 late survivors after CHLTx performed for FA at Mayo Clinic, five had evidence of progressive neuropathy. Importantly, survival rates at one month, one year, five years and 10 years after CHLTx were comparable to survival rates after both isolated heart transplant (Figure 3) and isolated liver transplant. Interestingly, freedom from cardiac allograft rejection was significantly higher at 10 years (P = 0.02) after CHLTx (83 percent) compared with that after isolated heart transplant (32 percent).

**Combined heart-kidney transplantation**

Chronic kidney disease following cardiac transplantation is a major source of morbidity and mortality. When patients present with extensive coexisting cardiac and renal disease, the presence of severe, irreversible renal dysfunction is a contraindication for isolated heart transplant. CHKTx has become an accepted treatment option for patients with this challenging clinical scenario. Success has been documented after simultaneous or staged CHKTx. The criteria for consideration of combined organ transplant include a glomerular filtration rate (measured using iothalamate clearance corrected for body surface area) less than 40 mL/min, despite hemodynamic optimization. All 30 CHKTx procedures performed to date at Mayo in Rochester were done as a simultaneous procedure; two were done for FA.

Postoperatively, intensive care unit and hospital stay did not differ significantly between Mayo Clinic’s CHKTx patients and those undergoing isolated heart transplantation. Two early deaths occurred, and late survival for hospital survivors was 100 percent at follow-up extending to five years. Early cardiac allograft dysfunction was present in two patients, but late cardiac allograft function was normal in all patients. Four patients had delayed kidney allograft function, necessitating temporary dialysis, and one of these went on to have permanent graft dysfunction. Survival rates for CHKTx recipients were similar to those achieved after isolated heart transplantation (Figure 4). Similar to the observations after CHLTx, the incidence of cardiac rejection was less frequent after CHKTx than in patients receiving isolated heart transplants. Although the time to first rejection did not differ significantly, one year after transplantation rejection episodes were virtually absent in CHKTx recipients but were still present in isolated heart transplant recipients.

**Summary**

The success of Mayo Clinic’s program is owed to the strong collaboration of a wide multidisciplinary group that participates in preoperative selection and optimization, surgical procedure, postoperative care, and long-term follow-up.

![Survival: IHTx vs CHKTx](image_url)
Found most commonly in patients with lung cancer, breast cancer and melanoma, brain metastases from solid tumors occur in 10 to 30 percent of all adult cancer patients. Signs and symptoms include headache, focal neurological deficit and seizure. Despite significant advances in the detection and treatment of brain metastases, the prognosis for this patient group remains guarded. Left untreated, many patients die not of their primary cancer but of progression of the brain tumor.

Single metastasis to the brain is often treated with surgical resection followed by some type of radiotherapy. The most commonly prescribed treatment options for brain metastases that are surgically inaccessible include symptomatic management with corticosteroids, whole-brain radiotherapy and stereotactic radiosurgery.

Whole-brain radiotherapy (WBRT)
This treatment usually involves 10 to 15 treatments over a period of two to three weeks. Concern about long-term cognitive impairment caused by WBRT may result in lower radiation doses, which can diminish tumor control. If new lesions develop, physicians may be reluctant to repeat WBRT.

Stereotactic radiosurgery (SRS)
Often used in conjunction with WBRT, stereotactic radiosurgery (SRS) allows precise delivery of a high dose of radiation to a defined target with lower toxicity. It can be used to treat multiple lesions in a single session, it doesn’t cause hair loss, and it can be used later to treat new lesions. Additionally, SRS may be more effective against radioresistant tumors and thus it may provide higher tumor-killing potential. Young women with breast cancer that metastasizes to the brain are a good example of the type of patients for whom SRS is particularly beneficial. These patients and other long-term cancer survivors now have access to effective treatment that does not involve side effects associated with WBRT.

In the past, some SRS systems had significant difficulty reaching widely spaced lesions in the brain, thus limiting the number of metastases that could be treated. Prior radiosurgery units rarely allowed the treatment of more than six metastases, and treatment became very complicated if a patient had lesions at opposite ends of the brain. The stereotactic head frame had to be removed and repositioned and the patient re-scanned to reach those targets.

The updated radiosurgery system now available at Mayo Clinic has eliminated those problems, providing neurosurgeons with a new option to offer patients with widely spread metastases to the brain. Using this newer radiosurgery system, Mayo neurosurgeons can treat many brain metastases, including widely dispersed tumors, often in a single 90-minute session.

Mayo is participating in an ongoing National Cancer Institute Radiation Therapy Oncology Group study comparing stereotactic radiosurgery plus whole-brain radiotherapy
The role of luminance in generating common forms of pediatric strabismus and nystagmus is the current focus of a study conducted by the ocular motor physiology laboratory in the Department of Ophthalmology at Mayo Clinic in Rochester, Minn. The study uses video-oculography to noninvasively record eye movements in children with strabismus and nystagmus. Researchers will use the data to investigate the role of fixation versus luminance input to the two eyes in causing strabismus and nystagmus.

Video-oculography can detect positional and velocity changes of the two eyes that cannot be detected on clinical examination. Quantitative analysis of these responses should provide new information about the neurophysiology of these disorders, as well as a means to evaluate and compare treatments.

Three-dimensional eye movement recordings are difficult to obtain in children because these recordings usually necessitate placement of thick contact lenses on the eyes during the test. This 3-D video-oculography system, however, measures horizontal, vertical and torsional eye movements using infrared light in a manner that is noninvasive and more applicable to children.

**Noninvasive examinations**

During the 10- to 15-minute examination, the patient is seated comfortably and merely looks straight ahead. The patient wears a lightweight (about 20 ounces) rubber mask, much like a scuba mask. The inside of the mask contains an infrared light source and two video cameras off to the side. The cameras measure the positions of the two eyes as the patient looks in different directions. The only risks to the patient include a temporary feeling on the face and red marks from wearing the mask.

The 3-D video-oculography device records eye position at 250 hertz and is considered minimal risk for use in children and adults. Because the system works in the infrared wavelengths, it is capable of recording in either light or dark. The video camera records horizontal and vertical eye movements and also the torsional position (the degree of twisting) of the eyes in each position of gaze.

This torsional measurement is critical to establishing which neural pathways are commanding the eyes to behave normally or abnormally during eye movement. This information helps ophthalmologists determine which muscles and nerve centers are affected within the brain, which can help direct surgical treatment with unprecedented precision. It will also provide measurement of the position and eye velocity of the eyes to determine whether a given surgery is effective for nystagmus.

Some forms of pediatric strabismus, such as intermittent exotropia and dissociated vertical divergence, are modulated by luminance.

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**Points to remember**

- Infrared video-oculography is unique in its ability to measure binocular eye position in total darkness. Because it is noninvasive, video-oculography can be used in children.
- Mayo Clinic is conducting a study using video-oculography to noninvasively determine horizontal, vertical and torsional eye position and provide detailed quantitative information regarding changes in eye position under different stimulus conditions.
- Infrared video-oculography is also useful in documenting other neurological forms of nystagmus and determining the efficacy of different forms of treatment.

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Mayo is also participating in a study examining the role of using SRS to treat the tumor cavity after surgical resection to once again try to obviate any potential long-term side effects of whole-brain radiotherapy.
The Center for Sleep Medicine at Mayo Clinic in Rochester, Minn., has a comprehensive, multidisciplinary practice treating children and adults. With a strong clinical focus, the center has consultants with experience diagnosing and treating sleep disorders ranging from the rare to the well-known. After initial clinical evaluation, patients may be referred for polysomnography in the center’s 24-bed sleep lab.

The center’s 22 consultants include neurologists, psychiatrists, pediatricians and pulmonologists. The neurologists who treat adults at the center specialize in sleep medicine. Although Mayo’s sleep medicine specialists treat the full spectrum of sleep disorders, such as obstructive and central sleep apnea, additional areas of expertise include management issues in restless legs syndrome, rapid eye movement (REM) sleep behavior disorder and narcolepsy.

**Broad Experience and Active Research Guide Mayo’s Sleep Medicine Practice**

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**Restless legs syndrome**

Mayo Clinic has a national reputation in treatment for and research on restless legs syndrome, also known as Willis-Ekbom disease. This is the most common sleep-related movement disorder seen at Mayo. Sleep disorders specialists at Mayo have experience in the management of complex cases of restless legs syndrome, including many patients with treatment-related problems, in which there have been drug failures and drug side effects.

Although therapies, notably dopamine agonists, are available to treat restless legs syndrome, managing the condition remains difficult. The results of a recent Mayo study of the long-term effects of treatment with the dopamine agonist pramipexole (Mirapex) suggest that the drug’s efficacy decreases over time, leading to increased dosages and adjunct therapies. According to an article in the December 2012 issue of *Sleep Medicine*, augmentation developed in 42 percent of patients in the Mayo study over a mean follow-up period of eight years. Side effects, including daytime sleepiness and impulse control disorders, were reported by 74 percent of study participants.

For patients who experience difficulties with dopamine agonists, Mayo sleep disorder specialists have experience prescribing alternatives, including gabapentin (Neurontin), pregabalin (Lyrica) and opioids. Iron supplements may be prescribed for patients with iron deficiency, which has been associated with restless legs syndrome.
REM sleep behavior disorder

REM sleep behavior disorder (RBD) is a parasomnia characterized by dream-enactment behavior and abnormal motor activity during REM sleep. RBD has been considered rare, but recent Mayo Clinic research suggests the incidence may be higher than previously thought, particularly in men older than age 70. Mayo sleep specialists have a large experience with RBD.

Clonazepam (Klonopin) has been the most common first line treatment for RBD. But the medication’s possible side effects — which include cognitive impairment, dizziness and unsteadiness — are of particular concern in elderly patients. A recent Mayo study compared longitudinal outcomes for RBD treated with clonazepam and melatonin. According to an article in the March 2013 issue of Sleep Medicine, study results indicated that although both treatments reduced RBD behaviors and injuries, melatonin-treated patients reported fewer adverse effects. Often Mayo specialists begin treatment of RBD patients with melatonin and then move to clonazepam if it isn’t effective.

Mayo physicians have also been at the forefront of research linking RBD to neurodegenerative disorders. A recent collaborative study with researchers from the University of Minnesota, updating research begun in the 1990s, reported that the vast majority (81 percent) of men initially diagnosed with idiopathic RBD developed a parkinsonian disorder or dementia. The mean interval from onset of RBD to emergence of the neurodegenerative disorder was 14 years, with the range extending to 29 years. Unfortunately, at this point there are no medications that can prevent that progression from occurring, but this predisposed group will be an excellent model for testing such drugs as soon as they become available.

Narcolepsy

Narcolepsy has been studied and treated at Mayo Clinic since at least the 1930s. Mayo researchers completed one of the first epidemiologic studies of the disease, defining its prevalence and incidence. As with other sleep disorders, Mayo physicians have experience treating complex cases of narcolepsy. A range of stimulant medications is available, and the major challenge is establishing a dose that is effective while minimizing adverse side effects. In an article published in the June 2005 issue of Sleep, a Mayo study demonstrated a significantly higher occurrence of psychosis, substance misuse and psychiatric hospitalizations in patients with narcolepsy who used high-dose stimulant therapy compared with those using standard doses. Mayo physicians also have experience with the range of selective serotonin reuptake inhibitors and norepinephrine reuptake inhibitors prescribed for cataplexy, as well as sodium oxybate, which helps improve nighttime sleep and may help with daytime sleepiness. Research on the progression of narcolepsy is yielding intriguing results that may ultimately improve treatment.

For more information


Points to remember

• Mayo Clinic’s comprehensive, multidisciplinary team of experienced sleep medicine specialists treat the full spectrum of sleep disorders, including obstructive and central sleep apnea. Areas of expertise also include management of restless legs syndrome, REM sleep behavior disorder and narcolepsy.

• For a current listing of Mayo Clinic’s ongoing clinical trials related to sleep disorders, go to www.mayo.edu/research/clinical-trials.
Education Opportunities

25th Annual Clinical Reviews — A Family Medicine and Internal Medicine Update
Four-day review features medical updates and management strategies for various diseases via lectures, Q-and-A panel discussions, a unique interactive format that allows for immediate audience participation, breakout sessions and Meet the Preceptor luncheons for one-on-one interaction with faculty. For more information or to register, call 480-301-4580, email mca.cme@mayo.edu or visit www.mayo.edu/cme.

ENT for the Primary Care Provider
April 11, 2014, in Rochester, Minn.
This course provides some key factors in identifying and treating a number of common ear, nose and throat (ENT) disorders as well as when referral to an otolaryngologist should be considered. This year’s symposium features a choice between two breakout sessions: “Hands-on training in the diagnosis and treatment of benign paroxysmal positional vertigo” or “Pediatric ENT emergencies: What needs action now or later?” For more information or to register, call 800-323-2688 (toll-free), email cme@mayo.edu or visit www.mayo.edu/cme.

21st Annual Nicotine Dependence Conference
April 14-16, 2014, in Rochester, Minn.
This course will spend an entire morning on e-cigarettes, including sharing information about the science, misinformation and regulatory issues surrounding these products. There will be a panel discussion as well, so bring your questions! The role of social media will be explored, and we will discuss both the art and science of medicine when it comes to treating tobacco dependence. For more information or to register, call 800-323-2688 (toll-free), email cme@mayo.edu or visit www.mayo.edu/cme.

35th Annual Practice of Internal Medicine
May 5-9, 2014, in Rochester, Minn.
Celebrating its 35th consecutive year, this is a postgraduate course designed to provide general internists, internist-subspecialists, family medicine physicians and other primary care professionals with a state-of-the-art update in internal medicine. Lectures, panel presentations and concurrent workshops are presented by specialists from the Mayo Clinic faculty. The topics represent some of the most common problems encountered in clinical practice, including the management of a variety of medical issues seen in areas of gastroenterology, infectious diseases, general internal medicine, rheumatology, geriatrics, emergency medicine, pulmonary, endocrinology, cardiology, neurology and women’s health. For more information or to register, call 800-323-2688 (toll-free), email cme@mayo.edu or visit www.mayo.edu/cme.

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