Successful Liver Transplantation Requires Innovation, Integrated Care

With campuses in Arizona, Florida and Minnesota, Mayo Clinic has the highest volume of liver transplants in the United States and outcomes that are consistently among the best. Mayo’s transplantation practice is based on a commitment to innovation and a strong, multidisciplinary approach to care before, during and after transplantation.

“In the Mayo model, patients are admitted on the hepatology side, but from the beginning, the medical and surgical groups work as a unified team to provide the full continuum of transplantation care,” explains Andrew P. Keaveny, M.D., a hepatologist at Mayo Clinic’s campus in Jacksonville, Florida. “Patients are usually quite sick with multiple medical issues before transplantation and have ongoing medical issues post-transplant, so you very much need a joint approach to managing their care.”

Fast-track model
The Mayo Clinic Transplant Center in Jacksonville is one of the most active in the nation. In 2002, the transplant team there pioneered a fast-track model that sends more than half of patients to the surgical ward after transplantation rather than to the intensive care unit (ICU). This practice, described in the February 2012 issue of *Liver Transplantation*, was shown to provide an appropriate level of care for a subset of transplant recipients without compromising outcomes, while reducing costs. Mayo researchers recently developed an objective, fast-track scoring system that can be adopted by other institutions.
liver transplant programs seeking to adopt a new model of post-transplant care. It appeared in the September 2014 issue of the American Journal of Transplantation.

Living-donor transplantation
Since 2001, the transplant team at Mayo Clinic’s Phoenix campus has performed more than 800 liver transplants, 142 of them by living donation, making Arizona’s living-donor program one of the largest in the western United States. June 2014 data from the Scientific Registry of Transplant Recipients (SRTR) confirms overall one-year patient and graft survival rates of 97.6 and 96.4 percent, respectively — both significantly higher than expected. Three-year survival in patients receiving living-donor grafts is also significantly higher than expected at 100 percent. (See Figure.)

David D. Douglas, M.D., surgical director of the Transplant Center in Phoenix, says the success of Mayo’s approach is apparent in these outcomes. “It is not by chance that all three of the Mayo liver transplant programs have consistently been at the “statistically higher than expected level” in the SRTR reports. Our focus on quality, integrated teams of specialists, and skill and experience translate into excellent outcomes for both donors and recipients,” he says.

Cholangiocarcinoma protocol
Physicians and researchers at Mayo Clinic’s campus in Minnesota helped pioneer preoperative chemoradiotherapy for liver transplant patients and developed a novel therapeutic protocol combining chemoradiation and orthotopic liver transplantation (OLT) for unresectable hilar cholangiocarcinoma or hilar cholangiocarcinoma in the setting of primary sclerosing cholangitis.

Results of a 2008 Mayo Clinic trial published in HPB showed that the protocol achieved significantly lower recurrence and better long-term survival rates than resection, OLT alone or medical treatment. These outcomes were later replicated in a large, multicenter study published in Gastroenterology in 2012. In that study, intent-to-treat survival rates were 68 and 53 percent at two and five years, respectively; post-transplant, recurrence-free survival rates were 78 and 65 percent.

Julie K. Heimbach, M.D., a transplant surgeon at Mayo Clinic’s Minnesota campus and an author of both studies, notes that the cholangiocarcinoma protocol is now the standard of care at transplant centers worldwide, but that stringent selection criteria and a large, established transplantation program are critical for its success.

Hepatitis C regimen
Recently, Mayo Clinic researchers have been at the forefront in using an interferon-free, antiviral regimen for hepatitis C virus (HCV) infection after liver transplantation, consisting of the newly approved direct-acting agents simeprevir and sofosbuvir.

The previous standard of care for post-transplant HCV recurrence — triple therapy with peginterferon, ribavirin, and either telaprevir or boceprevir — had limited effectiveness, significant toxicity and interactions with immunosuppressive medications. It could also induce alloimmune graft injury, thereby reducing patient and graft survival. The new regimen has relatively few side effects, limited drug-drug interactions, and in a large clinical trial at all three Mayo sites, demonstrated a high sustained virologic response rate with just 12 weeks of therapy. Findings were presented at The Liver Meeting 2014 in Boston.

For more information


December 2014 transplant data is available at www.srtr.org.
Genome Sequencing Plays Increasing Role in Pediatric IBD

Over the past two decades, researchers have gained considerable insight into the pathogenesis of inflammatory bowel disease (IBD), which seems to involve complex interactions among genetic predisposition, environmental factors such as diet and microbiome composition, and immune response. The role of genetics, in particular, has received increased attention as new technologies and analytic techniques have been developed, with testing evolving from family-based linkage analysis to genome-wide association studies and, most recently, next-generation sequencing.

Genome-wide association studies have identified at least 163 genetic loci containing susceptibility genes for Crohn’s disease, ulcerative colitis, or both. A major disadvantage of these studies, however, is that they are more likely to detect common variants than rare ones—a problem that can be remedied by exome sequencing, which can identify rare, highly damaging variants associated with familial forms of early- or very early-onset IBD (VEO-IBD).

At Mayo Clinic, a unique collaboration between pediatric gastroenterology and the Center for Individualized Medicine (CIM) offers young patients the opportunity for deep sequencing of DNA and in most cases exome sequencing to try to identify the genetic basis of their symptoms as well as a therapeutic strategy to treat them.

**VEO-IBD: A case study**

Children with very early-onset IBD (children younger than ages 6 to 10 years) usually have more-extensive inflammation (pancolitis) at time of diagnosis and more medically refractory disease than teens or adults do. In many cases, they have a more definable primary immunodeficiency that exhibits features similar to IBD. Unlike typical IBD inheritance, which is polygenic, early-onset forms may involve a single, very rare genetic allele.

Michael C. Stephens, M.D., a pediatric gastroenterologist at Mayo Clinic’s campus in Rochester, Minnesota, describes the case of a now 17-year-old patient who has had severe symptoms of IBD since infancy and is currently being treated in the pediatric gastroenterology-individualized medicine program.

Dr. Stephens explains: “He is about the size of a 10-year-old because inflammation and malabsorption have stunted his growth. In addition to gastrointestinal symptoms, he has arthritis, eye inflammation, and thyroid and skin manifestations. When he first came to us, we performed exome sequencing and discovered several possible candidate genes. We then met with the Genomic Odyssey Board, which is composed of genetics experts, researchers and counselors from all three Mayo campuses, to determine if any of the genetic mutations were medically actionable. The one that seemed most important was an LPS-responsive beige-like anchor (LRBA) gene mutation that affected protein expression. In talking to our colleagues across the country, we learned that less than 20 patients are known to have had problems with that gene. We also realized that the fusion protein abatacept, which is not a conventional therapy for either Crohn’s disease or ulcerative colitis, might be helpful in this case. Several other patients with LRBA disorders had been treated with abatacept and had significant improvement. There were also existing data about the use of this drug in other immunodeficiencies that resulted in autoimmune enteropathy.”

After two months of abatacept, the patient has shown some response, which is measured both by a reduction in inflammation markers and clinical improvement, including weight gain and reduced severity of arthritis and ophthalmic symptoms. “Although early, we are optimistic; no other therapy has generated such improvement in this patient,” Dr. Stephens says.

Mayo Clinic researchers are also looking for medically actionable novel genes in a family with three generations affected by IBD. “The data are just coming back, and again, it looks like just one gene,” Dr. Stephens says. “One of our goals is to use the integration across pediatric and adult GI as well as the CIM to provide a comprehensive multidisciplinary program for families with multiple affected members. The family could come to Mayo and have adult and pediatric specialists collaboratively build a treatment strategy. Where appropriate, this will utilize the genetic resources of the CIM, and the family will hopefully leave with a treatment plan specifically designed for them and their type of IBD.”

**Microbiome research**

Dr. Stephens has been actively involved in an international effort to identify better ways to stratify patients with IBD, with a focus on factors that predict more-severe disease. A recent publication from this group found a marked increase in Enterobacteriaceae, Pasteurellaceae, Veillonellaceae and Fusobacteriaceae.
The incidence of *Clostridium difficile* infection (CDI) has risen sharply over the last two decades, with 500,000 cases reported in the United States in 2010 alone. Multiple relapses are also increasingly common, with up to 25 percent of patients experiencing at least one recurrence of disease two to four weeks after completing standard antibiotic therapy. Recurrence rates rise with each subsequent episode, and as many as 40 percent of patients are likely to relapse after the second episode and 65 percent or more after a third episode.

CDI can occur without antibiotic exposure, but it mainly results from antibiotic-induced dysbiosis — disruption of the microbial composition of the gut and its ability to resist colonization by *C. difficile*. Traditional therapy for relapsing CDI — usually oral metronidazole and vancomycin — has limited success because it fails to correct a disordered microbiome and may contribute to further dysbiosis. (See Figure.)

Fecal microbiota transplantation (FMT), on the other hand, which is increasingly recognized as a safe and effective intervention for patients with recurrent CDI, restores microbial homeostasis and has proved far superior to vancomycin. It is not yet a first line therapy, however, and is typically only considered in patients who have had three or more documented cases of CDI or two CDI-related hospitalizations and failed a long vancomycin taper.

FMT for recurrent CDI is available at all Mayo Clinic sites, where a variety of *C. difficile* and microbiome studies are also underway.

**FMT at Mayo Clinic’s campus in Florida**

Maria I. Vazquez Roque, M.D., a gastroenterologist at Mayo Clinic’s campus in Jacksonville, Florida, observes that the Food and Drug Administration (FDA) initially proposed requiring investigational new drug (IND) status for FMT procedures. That stance would have denied access to the procedure for many, if not most, patients and was later changed. For the time being, the FDA exercises enforced discretion.

“The IND would have been too cumbersome and expensive, but once that changed, we were able to start performing the procedure,” she says. “We have completed nine FMTs since January 2014, with a 100 percent success rate and no recurrences. We have a nurse who contacts patients at one week and at one, three and six months, so we have good data about relapses. In terms of recovery, what we see is that within one or two days, people are starting to feel better. Patients who are on suppressive doses of vancomycin are able to discontinue it. It’s thrilling what a difference FMT makes. For some, there is an initial yuck factor, but in my experience, once it’s known how much this is helping patients and how appreciative they are, that goes away.”

**FMT at Mayo Clinic’s campus in Arizona**

Since 2011, approximately 125 FMTs have been performed at Mayo Clinic’s campus in Phoenix, with an approximate 90 percent success rate. A retrospective analysis of Arizona’s initial experience, which appeared in the August 2013 issue of *Mayo Clinic Proceedings*, found the procedure safe, highly effective and relatively simple to implement.

“Overall, we remain very impressed with the usefulness of FMT in treating multiple recurrences and refractory cases of *C. difficile* infection and continue to receive many referrals, both locally and from around the country,” says John K. DiBaise, M.D., a gastroenterologist at Mayo’s Phoenix campus. “We aren’t using frozen specimens but have gone to using standard donors, which has reduced patient costs and the
efficiency of getting the procedure completed. Another thing that sets our program apart is the team approach, which includes members from infectious diseases, gastroenterology and endoscopy, with a nurse coordinator facilitating all aspects of the procedure.”

Researchers in Arizona and at Mayo Clinic’s campus in Rochester, Minnesota, are retrospectively evaluating the effect of FMT on CDI patients with concomitant inflammatory bowel disease (IBD) and prospectively analyzing recipient quality of life and satisfaction with the procedure. Other studies are in the preliminary stages, including an investigation into the use of FMT to decolonize vancomycin-resistant enterococcus in the gut and planning studies to evaluate FMT in the setting of IBD, irritable bowel syndrome and other conditions.

**FMT at Mayo Clinic’s campus in Minnesota**

Physicians at Mayo Clinic’s campus in Rochester, Minnesota, have performed about 180 FMTs — mainly using specimens from standard volunteer donors — with an overall 90 percent success rate. Frozen stored donor samples are now also being used to make scheduling FMT more convenient and decrease uncertainty of donor availability. The campus has a dedicated CDI clinic serving patients with first-time infections as well as recurring and complicated CDI.

“The clinic is staffed by experienced physicians and a team of study coordinators, nurses, lab technicians and microbiome researchers who have a special interest in C. difficile,” says Sahil Khanna, MBBS, who co-directs the clinic. “In addition to managing patients with CDI, we are doing research on engraftment of gut bacteria within the colon after FMT and are part of clinical trials to evaluate newer modalities for FMT, including enema and capsule-based forms.”

**For more information**


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**Clostridium difficile infection (CDI)**

- Best example of disease resulting from alteration of the gut microbiome
- Gram-positive, anaerobic, spore-forming
- Two large toxins: A and B
- Binary toxin: NAP1/027/BI strain: North American Pulsed Field type 1 (NAP1), restriction endonuclease-analysis (REA) type BI, or polymerase chain reaction ribotype 027


**Figure.** CDI mainly results from antibiotic-induced dysbiosis.
Interferon-Free HCV Regimens Balance Benefits, Costs

In early 2013, the standard of care for patients with hepatitis C virus (HCV) genotype 1 was pegylated interferon (peginterferon) plus ribavirin plus an NS3A/4A protease inhibitor such as boceprevir or telaprevir. Although an improvement over peginterferon-ribavirin regimens, triple therapies still required treatment durations of nearly a year, had significant side effects and contraindications, and needed the unpopular and troublesome backbone of interferon.

Less than a year later, the course of HCV treatment changed radically with the approval of sofosbuvir and simeprevir — oral, direct-acting antiviral agents that provided substantially higher virologic response rates with less toxicity and shorter treatment durations than boceprevir and telaprevir, all without the use of interferon. On the new regimens, even patients who had relapsed with prior interferon-based therapy appeared to have sustained virologic response (SVR) rates similar to treatment-naive patients.

“Sofosbuvir is a very effective NS5B nucleoside polymerase inhibitor with a clean side effect profile and few drug-drug interactions. It really revolutionized treatment for HCV and led the drive toward elimination of interferon in management of this virus,” says Hugo E. Vargas, M.D., director of hepatology and vice chair of Gastroenterology and Hepatology at Mayo Clinic’s Phoenix campus.

Simeprevir is a once-daily, HCV N53/4A protease inhibitor with a more favorable side effect profile than others in its class. In November 2014, the Food and Drug Administration (FDA) approved simeprevir in combination with sofosbuvir as an all-oral, interferon- and ribavirin-free treatment option for genotype 1 chronic hepatitis in adults.

Data supporting the regimen are based on results of the COSMOS study, a phase 2 clinical trial that looked at the safety and efficacy of combined sofosbuvir and simeprevir, with or without ribavirin, for 12 or 24 weeks. Study results were published in the November 2014 issue of The Lancet. Cohorts included genotype 1 infected treatment-naive and treatment-experienced patients with compensated liver disease. The treatment response in both cohorts was high, with an overall SVR of 92 percent. In the advanced cirrhosis group, the response rates remained equally high, regardless of the use of ribavirin or treatment duration.

Still, as other, perhaps superior, agents are approved, sofosbuvir plus simeprevir is unlikely to remain the preferred interferon-free regi-
Interdisciplinary Collaboration Crucial for CRC Management

Management of patients with colorectal cancer (CRC) is a multifaceted process, requiring breadth and depth across many disciplines. Mayo Clinic’s long and rich history of interdisciplinary collaboration and cooperation is the foundation of the CRC program on all three Mayo Clinic campuses.

“We understand the disease differently because we work cohesively, are integrated in how we work and think, and have maintained joint research projects and practice-related standards, algorithms and work flows — all of which are consistent and of the highest quality,” explains Heidi Nelson, M.D., a colorectal surgeon and researcher at Mayo Clinic’s campus in Rochester, Minnesota.

CRC management begins with accurate diagnosis and imaging, extends through high-quality surgery, advanced adjuvant therapies and genetic profiling, and ends with translational research. Mayo Clinic physicians have made — and continue to make — contributions in each of these areas.

Cologuard
In October 2014, the Food and Drug Administration approved Cologuard, a noninvasive, multtarget stool DNA screening test for colorectal cancer. Co-developed by Mayo Clinic and Exact Sciences, Cologuard is an automated assay for tumor-specific DNA changes, including aberrant methylated BMP3 and NDRG4, a mutant form of KRAS, β-actin, and hemoglobin.

In the large, pivotal trial that led to its approval, sensitivity of Cologuard for CRC was 92.3 percent overall and 94 percent for the earliest and most curable cancer stages — on a par with colonoscopy. But unlike colonoscopy, Cologuard requires no bowel prep, office visit, or dietary or medication restrictions.

Screening and genetic testing
In the initial screening for Lynch syndrome, the most common hereditary colon cancer disorder, tumor tissue is evaluated through molecular microsatellite instability or immunohistochemistry (IHC) testing. IHC testing, commonly used at Mayo Clinic, is about 95 percent accurate, identifying in most people the MMR gene in which either a germline mutation or somatic alteration that silences gene expression occurs.

Until recently, this analysis was performed using Sanger sequencing at a cost of around $1,000 per gene. But in April 2013, Mayo Clinic introduced a hereditary colon cancer multigene panel that uses next-generation sequencing and array comparative genomic hybridization to evaluate for germline mutations in 17 genes associated with CRC development. The panel, which is relatively inexpensive, provides a comprehensive evaluation for hereditary colon cancer in high-risk patients and can also serve as a second-tier test when previous targeted gene analysis is negative.

Surgical excellence
“We are performing more and more laparoscopic and robotic surgeries and trying to disturb physiology less and less,” Dr. Nelson says. “Robotics is definitely evolving here. We believe it is important to work on advancing any platform that will benefit patients in the long term. As long as it’s done in a responsible manner and causes no harm, we keep pushing the envelope.

Results have been reviewed and reported since the first surgeries were performed at Mayo Clinic, and local failure rates have always been in the single digits — 5 to 9 percent. That’s an outstanding result.”

Proton beam therapy
Construction of proton radiotherapy facilities is underway at Mayo Clinic campuses in Minnesota and Arizona. Each will use intensity-modulated proton beam therapy with pencil scanning, an advance over most proton therapy
Translational research

Mayo researchers are actively engaged in identifying novel mutations for CRC and were involved in a recent international association study that found a significantly increased cancer risk in people with genetic variation on chromosome 4q32.2. Results of the study appeared in the November 2014 issue of Carcinogenesis. “The goal is to translate advances in medical genetics into diagnostic tests that can be used every day. At Mayo, we are always looking for translational opportunities,” Dr. Nelson says.

For more information