

# Digestive Diseases Update

Gastroenterology and Hepatology News

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## Mayo Initiates Multifaceted Microbiome Program

In June 2012, the National Institutes of Health (NIH) published results of its Human Microbiome Project, a 5-year analysis of the microbiomes of more than 200 healthy people. The project, which identified between 81 and 99 percent of microorganismal genera in healthy adults, is the most ambitious survey of the human microbiome to date, providing a reference for future studies investigating the role of the microbiome in human disease.

Heidi Nelson, MD, director of Mayo Clinic's Microbiome Program, notes that the NIH project and studies like it represent an unprecedented shift in thinking about the microbes that inhabit the human body. "Historically we've only thought of pathogens, but we now know through sequencing that bacteria cohabit with us—and encode 100 times more unique



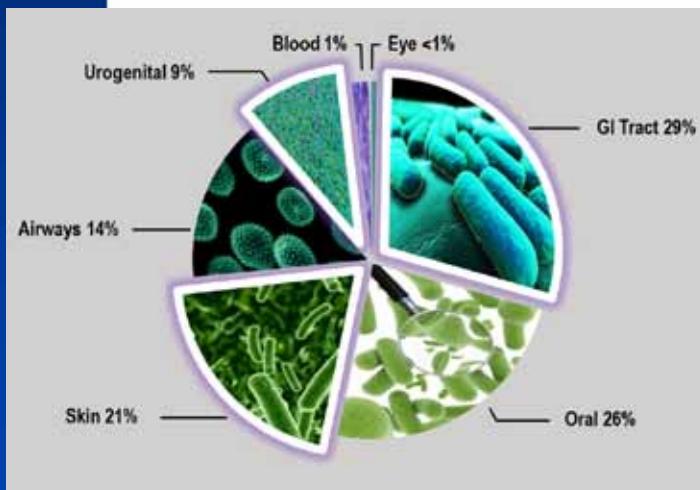
Heidi Nelson, MD

genes than our own genome. So we're developing a microbiome program that allows us to understand not only how bacteria cause disease, but also how they maintain health."

Mayo's Microbiome Program is housed within the Center for Individualized Medicine, which provides infrastructure and resources for researchers interested in studying the role of microbes in a broad range of diseases (Figure). Gastrointestinal (GI) disorders under investigation include celiac disease, inflammatory bowel disease, irritable bowel syndrome (IBS), esophageal reflux and esophageal cancer, *Clostridium difficile* infection, colorectal cancer, and liver and biliary tract diseases.

IBS specialist Purna C. Kashyap, MBBS, points out that changes in microbial ecology have been implicated throughout the GI tract, so it makes sense to investigate them all. "Mayo is very proactive in looking at the role of the microbiota in GI diseases," he says. "We have a number of specialty clinics run by people committed to microbiome research."

That research includes replicating human disease in animal models. To facilitate studies involving the transfer of human gut microbiota to mice, Dr Kashyap is establishing a state-of-the-art, germfree mouse facility at Mayo Clinic in Rochester, Minnesota.



**Figure.** Mayo Clinic is developing a robust, multi-disciplinary microbiome program, with a majority of research focused on the gastrointestinal tract.



Purna C. Kashyap, MBBS

Other researchers are comparing the composition of gut microbial communities in people with and without GI disorders. The aim is to better understand how shifts in microbial populations cause disease and to determine whether restoring homeostasis can improve health.

Dr Kashyap says, "The data are starting to show that there are ways to remedy harmful effects resulting from changes in gut microbes. For example, we have developed a highly successful fecal transplant program at Mayo Clinic in Minnesota for recurring *C difficile* infection. By correcting the underlying disturbance in gut microbiology, we've seen life-altering outcomes in our patients."

The fecal transplant program at Mayo Clinic in Arizona has had equally successful outcomes." (For more information, please see [www.mayo-clinic.org/medicalprofs/fecal-transplants-ddue1012.html](http://www.mayo-clinic.org/medicalprofs/fecal-transplants-ddue1012.html).) A fecal transplant program is also currently in development at Mayo Clinic in Florida.

Another major area of investigation is the effect of exogenous and endogenous host factors on microbiota composition.

"The human genome is inherited, but the microbiome is acquired," Dr Kashyap says. "So, we're trying to understand why 1 person has a healthy microbiome and another doesn't. A number of factors, including diet, genetics, and psychosocial stressors, impact the gut microbiota. We need to look at differences in infant feeding, in the way a child is delivered—either vaginally or by cesarean section—and in early exposure to antibiotics to determine if they lead to aberrant microbial populations that contribute to adult-onset disease. For example, obesity is associated with a microbiota that is very efficient at extracting calories from food, but was that microbiota present at birth? These are all questions we're trying to answer, and as the largest patient care center in the area working on the microbiome, we're well positioned to do that."

## Mayo Patients Do Better Than Most Before and After Liver Transplant



Michael R. Charlton, MD

Of the 16,000 people on liver transplant wait lists in the United States, 6,300 undergo transplantation each year and 1,400 others die waiting. Short- and long-term survival statistics and wait list deaths for more than 100 US transplant centers are easily accessible at the Scientific Registry of Transplant Recipients (SRTR) website, [www.srtr.org/who.aspx](http://www.srtr.org/who.aspx).

"Liver transplantation is one of the few areas in medicine where outcomes are closely tracked and measured in a comparable way by the government and other agencies. It's a transparent, objective assessment of center-specific performance that allows patients to make choices that have a major impact on their likelihood of surviving the wait for liver transplantation," notes Michael R. Charlton, MD, of Mayo Clinic in Rochester, Minnesota.

SRTR also reports actual outcomes following liver transplantation for each center in comparison to other programs with similar patients, as well as national averages.

For instance, of 225 adults receiving liver transplants at Mayo Clinic in Minnesota from January 2009 through June 2011, 93.1% were alive at 1 year (Figure). Expected 1-year survival was 89.9% for similar patients at comparable centers. Observed-to-expected survival ratios were even greater at 3 years: 86.7% observed to 80.4% expected.

According to John J. Poterucha, MD, also of Mayo Clinic in Minnesota, "One-month and 1-year survivals are related more to the surgery itself, and after that, a little more to medical care, although you can't really separate the two. Our liver surgeons are excellent. We also have great anesthesiologists and transplant nurses and nonsurgical health care workers who see patients after they leave the hospital. It's a team effort."

Dr Poterucha adds that having the observed survival rate above the expected and national rates provides a benchmark for comparison with other programs.

Comparison is exactly the point of the SRTR data, which, by demonstrating variations among centers, highlight over- and underperforming programs.

### Surviving the Wait List

Dr Charlton emphasizes that survival until the time of transplant is as important as posttransplant survival.

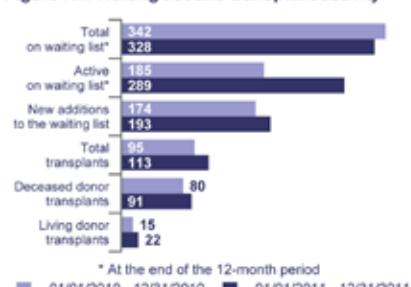
"It's fine to have good outcomes after transplant, but you have to live long enough on the transplant wait list to take advantage of that. Looking at the SRTR data, the wait list mortality rate ranges from 4% to 45% among transplant centers. I'm pleased that the data for Mayo in Minnesota are the best in the country. We have



John J. Poterucha, MD

## A. Program Summary

**Figure A1. Waiting list and transplant activity**

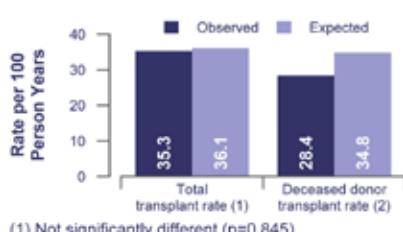


**Table A1. Census of transplant recipients**

Recipients	01/01/2010-12/31/2010	01/01/2011-12/31/2011
Transplanted at this center	95	113
Followed by this center*	974	1,000
...transplanted at this program	955	984
...transplanted elsewhere	19	16

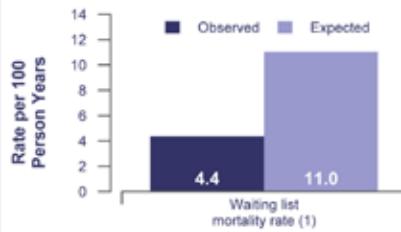
\* Recipients followed are transplant recipients for whom the center has submitted a post-transplant follow-up form for a transplant that took place before the 12-month interval for each column.

**Figure A2. Transplant rates  
01/01/2011 - 12/31/2011**



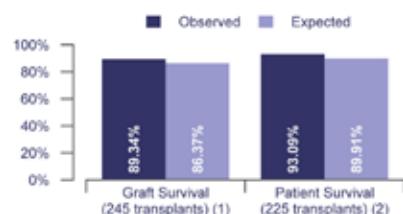
(1) Not significantly different ( $p=0.845$ )  
(2) Not significantly different ( $p=0.052$ )

**Figure A3. Waiting list mortality rates  
01/01/2011 - 12/31/2011**



(1) Statistically lower ( $p<0.01$ )

**Figure A4. First-year adult graft and patient survival: 01/01/2009 - 06/30/2011**



(1) Not significantly different ( $p=0.229$ )  
(2) Not significantly different ( $p=0.184$ )

**Figure A5. First-year pediatric graft and patient survival: 01/01/2009 - 06/30/2011**

This center did not perform any transplants relevant to this figure during 01/01/2009-06/30/2011

The data reported here were prepared by the Scientific Registry of Transplant Recipients (SRTR) under contract with the Health Resources and Services Administration (HRSA).

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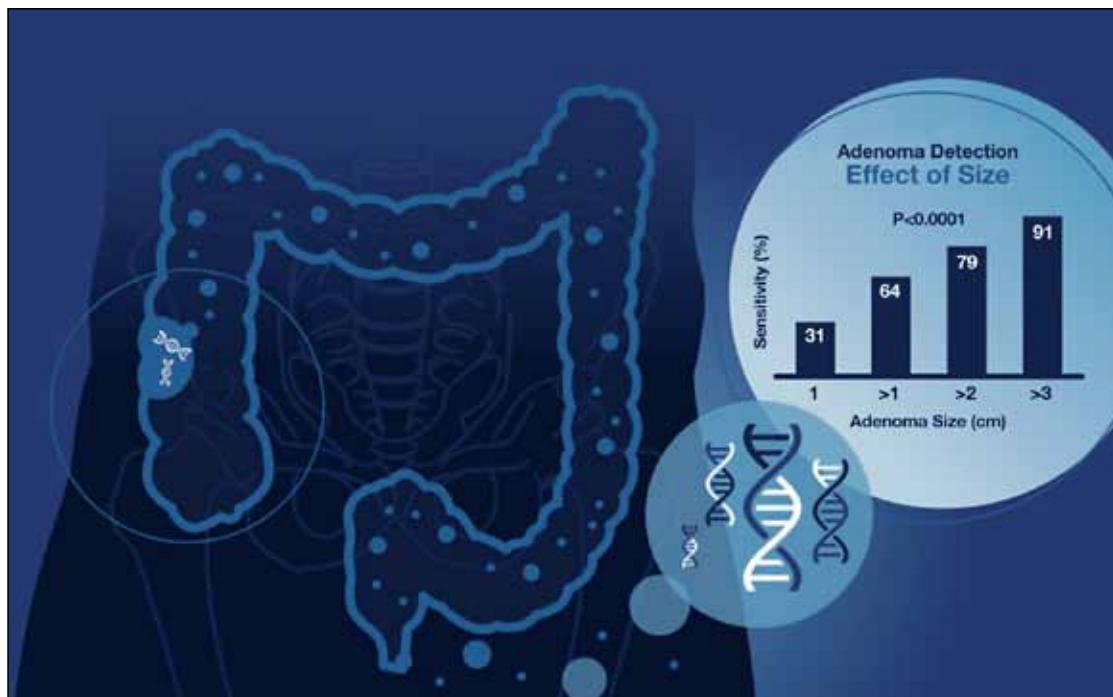
**Figure.** One-year adult patient and graft survival (January 1, 2009-June 30, 2011) and wait list mortality rates (January 1, 2011-December 31, 2011) for Rochester Methodist Hospital, Rochester, Minnesota. Source: Scientific Registry of Transplant Recipients, data released July 12, 2012.

a demonstrably unique ability to take care of patients before, during, and after transplant."

Moreover, organ availability does not necessarily correlate with wait list death.

"Some centers with high organ availability have 5 times the number of wait list deaths as centers with poor access to organs. One of the reasons we have fewer wait list deaths is that we have a vibrant living donor program—one of the largest in the country. Having a successful living donor program is a huge advantage, but

we really have the whole package, including easy access to our transplant clinics and hospital teams; if patients feel they need to be seen, we see them straight away. Program-specific practices for when a patient first arrives in hospital or clinic really make a difference, too. Ultimately, it's important to remember that the best access to organs doesn't mean the best survival. You can have a lot of planes on the runway, but that doesn't mean you can fly them all well."



**Figure.** Detection rates for stool DNA test increase with polyp size and progression risk.

## Stool DNA Highly Accurate for Colorectal Cancer and Large Adenomas



David A. Ahlquist, MD

Although current screening efforts have reduced colorectal cancer (CRC) incidence and mortality rate, CRC continues to be the second leading cause of cancer death in the United States. In the rest of the world, incidence rates are rising sharply.

"We have a mandate to improve effectiveness of screening by better use of existing tools and by creating better tools," says David A. Ahlquist, MD, of Mayo Clinic in Rochester, Minnesota. "If one had to start all over, the ideal screening test would be noninvasive and affordable; would require no bowel prep, medication restriction, or diet change; and would detect neoplasms on both sides of the colorectum with high accuracy."

A new multimarker test for stool DNA (sDNA) developed by Mayo Clinic in collaboration with Exact Sciences Corp of Madison, Wisconsin, meets those requirements. No special preparation or restrictions are needed, and it can be performed on mailed-in samples, eliminating the need for an office visit. It has also proved highly accurate at detecting premalignant polyps and early-stage CRC.

The sDNA test is an automated assay for tumor-specific DNA changes, including methylated *BMP3* and *NDRG4*, a mutant form of *KRAS*, the  $\beta$ -actin gene, and hemoglobin. In 3 blinded case-control studies, each involving more than 1,000 patients, that have been published or presented in the past year, detection rates for the

critical screening targets were remarkably high. Sensitivity for CRC has been 85% to 98%; for high-grade dysplasia, 82%; for adenomas greater than 1 cm, 64%; and for serrated polyps greater than 1 cm, 60%.

Detection rates increase with polyp size and progression risk (Figure). Sensitivity was 64% for both adenomatous and serrated polyps greater than 1 cm, 77% for those greater than 2 cm, and 92% for polyps larger than 4 cm. Of critical importance, detection is not affected by location or stage.

Dr Ahlquist says that cumulative sensitivity can approach 100% after a few checks if the test is applied programmatically every 3 years. "The point sensitivity of the Pap test for precancerous dysplasia is about 50%, yet the Pap test has nearly eliminated cervical cancer in women who are regularly screened. The point sensitivity of the sDNA test is better than that of the Pap. Our hope is that sDNA tests will help eradicate colon cancer, if regularly applied over time," he says.

In a head-to-head comparison, sDNA also proved far superior to a plasma test for methylated septicin 9 (SEPT9), identifying 82% of adenomas ranging from 1 to 5 cm compared with 14% detected with SEPT9. sDNA identified patients with curable-stage CRC with 90% sensitivity, whereas SEPT9 had 50% sensitivity. False-positive results were 7% and 27%, respectively, between the 2 tests.

"Our findings are entirely consistent with the biology of marker release," Dr Ahlquist says. "Cancerous and precancerous cells are shed into the stool and detected by the sDNA test long before tumors progress to invade the bloodstream for detection by plasma SEPT9 screening. Biology favors the stool test; I am very confident about that."

Unlike colonoscopy and fecal blood testing, the sDNA test is not an operator-dependent evaluation; it is a standardized automated procedure with results interpreted by a computer. The test is also performed less frequently than fecal blood testing—the most commonly used noninvasive option—thereby providing more opportunities for increasing compliance and reducing costs.

## Release Date and Future Directions

An optimized sDNA assay recently underwent a study involving more than 12,000 patients across multiple centers in the United States and Canada. Data from that study will be reviewed by the US Food and Drug Administration early in 2013, and if approved, the test will become available shortly thereafter. Because of its developmental role, Mayo Clinic will be one of the first medical centers to offer it.

Mayo researchers are also actively involved in developing other applications for the sDNA testing, including the detection of cancer and precancerous lesions in patients with inflammatory bowel disease and of cancers and precancers above the colon.

"We are actively pursuing development of a single test that will someday screen the entire gastrointestinal tract," Dr Ahlquist says.

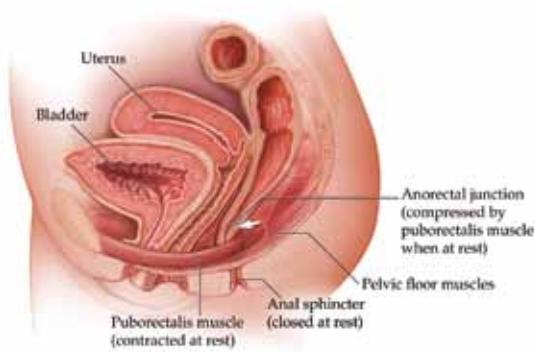
## Beyond Biofeedback: A Comprehensive Program for Pelvic Floor Constipation

As many as 50% of people with chronic constipation have pelvic floor dyssynergia (PFD)—impaired relaxation and coordination of pelvic floor and abdominal muscles during evacuation. Straining and a feeling of incomplete elimination are common symptoms, but because slow-slow-transit constipation and dyssynergia can overlap, some patients may also present with also present with other symptoms (e.g., bloating).

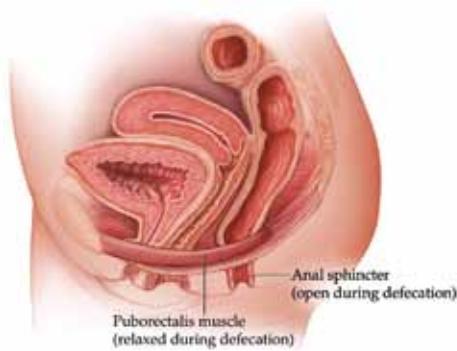
A thorough history and careful digital examination are key components in diagnosing PFD. The diagnosis can be confirmed by anorectal manometry with balloon expulsion and, in some cases, traditional proctography or dynamic magnetic resonance imaging defecography to visualize pathologic pelvic floor motion, sphincter anatomy, and greater detail of surrounding structures.

### Pelvic Floor Retraining

Biofeedback is the treatment of choice for pelvic floor constipation, with some studies showing improvement in up to 70% of patients. Although many centers are familiar with retraining techniques to improve pelvic floor dysfunction in patients with fecal incontinence, very few have the expertise needed to teach patients with constipation how to appropriately coordinate



Amy E. Foxx-Orenstein, DO



**Figure.** Puborectalis muscle at rest and during defecation.

abdominal and pelvic floor muscles during defecation.

At Mayo Clinic, the schedule for biofeedback training varies across centers. In Rochester, Minn., patients receive a two-week intensive pelvic floor retraining program in which they learn and practice these techniques. Many patients who have not responded to pelvic floor retraining elsewhere will improve with this program. In Arizona, biofeedback is incorporated into a comprehensive bowel management program.

"Our program is not centered solely on biofeedback," she explains. "Our goal is to improve symptoms and, to the best of our ability, restore normal bowel function. And that requires a multifaceted approach."

The first step is a constipation education class jointly conducted by a dietitian and a nurse educator. Patients are referred to the class by a physician and learn general techniques for managing their condition.

"The class gives people an understanding of the process and a greater awareness of why things don't work," Dr Foxx-Orenstein says.

Patients also meet individually with a dedicated nurse educator who provides a focused session on bowel management techniques. Central to the process is a daily regimen that combines an evening dose of fiber supplement with a morning routine of mild physical activity; a hot, preferably caffeinated beverage; and, possibly, a fiber cereal followed by another cup of a hot beverage—all within 45 minutes of

waking. "This routine augments early-morning high-amplitude peristaltic contractions by incorporating multiple stimulators," Dr Foxx-Orenstein says.

The regimen, designed for all types of constipation, is fine-tuned for PFD. Some patients do not need fiber; others need stimulant or osmotic laxatives.

"The program changes over time as patients make small advancements, but some bowel management techniques are useful for everyone," explains Dr Foxx-Orenstein.

Once patients with pelvic floor constipation have these basic tools, they begin biofeedback training, which provides auditory and visual feedback to help retrain the pelvic floor and relax the anal sphincter. Patients also learn to identify internal sensations associated with relaxation and long-term skills and exercises for use at home.

Because pelvic floor dysfunction is often associated with sexual or physical abuse and other psychological stressors, psychological counseling is a standard component of the evaluation process.

"This is a multidisciplinary approach to a complex problem," says Dr Foxx-Orenstein. "It is not simple, and it takes a combined approach to make it truly successful. In some, the improvement is minor, but there is improvement. In others, it can be life-changing." She adds, "We invite other institutions to come learn what our techniques are and how we interact with patients, with the hope this approach can become more common and widespread."

## Physician Update

An e-mail newsletter and a physician video blog. Visit [www.mayoclinic.org/medicalprofs](http://www.mayoclinic.org/medicalprofs) for more details.

The screenshot shows the 'Patient Care' section of the newsletter. It includes a heading 'Enteroscopy improves diagnosis and management of IBD' with a brief summary and a link to 'Read More'. Another section, 'Research', discusses 'NOTES hybrids and scopes show promise' and 'Split-dose bowel prep improves colonoscopy quality and outcomes'. The 'Education' section highlights 'Advancements in Technology and Understanding of Esophageal Diseases' and 'Mayo Clinic Gastroenterology & Hepatology 2013'.

# Treatment for Relapsing Autoimmune Pancreatitis Still Uncertain

Autoimmune pancreatitis (AIP) is the pancreatic manifestation of a multiorgan syndrome called *immunoglobulin G4-related disease (IgG4-RD)*, which can affect various organs, including the bile ducts, salivary glands, kidneys, lungs, and lymph nodes. Although associated with specific histologic, clinical, and morphologic findings, AIP remains difficult to distinguish from pancreatic cancer. Maintaining remission and treating recurrences have proved equally challenging.

Administration of an oral corticosteroid is the standard treatment for AIP. Most patients show marked improvement in clinical symptoms 2 to 4 weeks after starting corticosteroid therapy, but 30% to 50% have a relapse after stopping treatment or during treatment tapering.

"We've been treating AIP for 10 years. Early on, there was a question of how to treat patients after the initial presentation was treated," says Suresh T. Chari, MD, a principal author of Mayo Clinic's AIP diagnostic criteria known as HISORt (histology, imaging, serology, other organ involvement, and response to steroid therapy).

"Our only guide was what the Japanese were doing, which was to put patients on small doses of steroids for 2 to 3 years," he says. "But long-term steroid treatment, especially for elderly people, is controversial. So we decided we would treat the initial presentation with a 3-month course of tapering steroid therapy and monitor patients closely for relapses. We found that only about half the patients had a relapse. Those who did were treated with another 3-month course of steroids or with a repeat course of steroids and an immunomodulator—either azathioprine or 6-mercaptopurine."

The corticosteroid-immunomodulator combination seemed promising for maintaining remission until patients began to have a relapse while taking it, too.

## An Unexpected Discovery

Then, in 2006, a patient with AIP and IgG4-related sclerosing cholangitis who could not tolerate 6-mercaptopurine had orbital symptoms.

Dr Chari explains, "The ophthalmologist who saw our patient directed us to Dr Thomas Witzig, who was treating orbital pseudolymphoma with rituximab. He suggested that we stain the pancreatic biopsies for CD20, and if there were abundant CD20 positive cells, the disease would respond to rituximab."

The disease did respond. Within a month, the patient's pancreatic and extrapancreatic symptoms disappeared, and his disease remained

in remission for 2 years with maintenance rituximab therapy.

Rituximab, an anti-CD20 antibody targeted to B lymphocytes, is typically used to treat lymphomas, leukemias, transplant rejection, and certain autoimmune disorders, including rheumatoid arthritis. This was the first time it had been used—albeit serendipitously—for AIP. Rituximab eventually proved effective for both induction and maintenance of remission in other AIP patients.

A retrospective comparison of 116 patients with AIP at Mayo Clinic found that during a median follow-up period of 47 months, 52 patients had 76 relapse episodes. Twenty-four patients were treated with a second course of corticosteroids and 27 patients with corticosteroids and an immunomodulator. Relapse-free survival until the second relapse was similar in both groups. Twelve patients who were steroid-intolerant or had immunomodulator-resistant disease were treated with rituximab. Of these patients, 83% had complete remission, with no relapses on maintenance therapy.

Rituximab is not a cure for the disease and has its downsides. It is expensive and not yet approved by the US Food and Drug Administration for use for IgG4-RD. Although the majority of patients tolerate it well, it has a long list of adverse effects, including potentially fatal progressive multifocal leukoencephalopathy. Further, about 40% of patients have a relapse if rituximab is used only for inducing remission without follow-up maintenance therapy.

"We treat AIP with a bottom-up approach, starting with the cheapest drug and working up to the most expensive," Dr Chari says. "Rituximab costs an arm and a leg, so it's not appropriate to say that this is a first-line drug for everybody. It is a lifesaver for some patients who are otherwise hard to treat, but I'm not a fan of using it for everybody. Future studies will help tailor the treatment to the individual needs of the patient."

He adds, "We're starting to see patients whose disease is harder to diagnose and harder to treat. I learn from previous patients and I see patterns that make sense, so I keep trying different things to see if they work. But medicine is just not that straightforward. Once we know for sure there is a path that others can follow, then we can point the way. In the meantime, we can only show where we came from and where we're going."



Suresh T. Chari, MD

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### **Mayo Clinic Gastroenterology and Hepatology 2013**

February 21-24, 2013  
Scottsdale, Arizona

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February 21-24, 2013  
Visit the course webcast website, [www.mayo.edu/cme/gastroenterology-2013S347](http://www.mayo.edu/cme/gastroenterology-2013S347), for system requirements and registration information.

### **Mayo Clinic General Thoracic Surgery Symposium**

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