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**Presentation summaries in:**

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**Comprehensive Reports on the Latest Advances in Gastroenterology and Hepatology from:**

## 2013 Advances in Inflammatory Bowel Diseases

December 12-14, 2013
Hollywood, Florida

## 64th Annual Meeting of the American Association for the Study of the Liver

November 1-5, 2013
Washington, DC

## American College of Gastroenterology 2013 Annual Scientific Meeting

October 11-16, 2013
San Diego, California

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# THE GASTRO & HEP REPORT

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# Presentations in IBS

## Rifaximin and Neomycin Improves Constipation in IBS

Methane on the breath in persons with irritable bowel syndrome with constipation (C-IBS) is a "chicken or the egg" situation. C-IBS is associated with methane in the breath, but does reduction of methane in the breath or alteration of methanogenic gut flora alleviate C-IBS?

This question was explored in a presentation by Mark Pimentel of Cedars Sinai Medical Center in Los Angeles, California, at the American College of Gastroenterology 2013 Annual Scientific Meeting (Abstract P1689). In his comparison of neomycin alone and rifaximin plus neomycin in patients with methane-positive C-IBS, the combination was superior for alleviating constipation. Furthermore, eradication of methane in the neomycin/rifaximin group was associated with improvement in constipation.

To arrive at this conclusion, the investigators recruited consecutive patients (18 to 65 years old, Rome III criteria) with C-IBS. All subjects presented for a lactulose breath test after a 12-hour fast; only those with a methane level greater than 3 ppm on at least one breath sample were enrolled. Subjects then completed a stool diary, questionnaire (100 point visual analog scale [VAS] scale for bloating, abdominal pain, constipation, diarrhea, and straining) and a 2-week run-in phase. Study participants were randomized to receive either neomycin at a dosage of 500 mg twice daily plus placebo or neomycin plus rifaximin at a dosage of 550 mg tid for 14 days in a double-blind fashion. Questionnaires were repeated weekly during treatment and for 4 weeks thereafter. On the last week of follow-up, the stool diary was repeated.

A total of 32 subjects were randomized; 17 received neomycin/placebo and 15 received neomycin/rifaximin. Baseline characteristics were similar between both groups. By the second week of treatment, the constipation VAS score was significantly less severe in the neomycin/rifaximin group (30.7±30.7) than the neomycin/placebo group (57.9±25.0; $P$=.011). The same was true for bloating (VAS scores of 45.1±33.3 and 65.1±25.9 for combination and monotherapy groups, respectively; $P$=.045). Constipation remained significantly improved even 3 weeks after the end of treatment with neomycin/rifaximin ($P$<.05). Durable improvement was also seen regarding bloating and straining.

In the neomycin/rifaximin group, eradication of breath methane (≤3 ppm) was associated with a reduction in the severity of constipation (26.6±19.0). Persons with persistent methane in their breath remained severely constipated (67.2±32.1; $P$=.041).

## Fecal Microbiota Transplantation Yields Favorable Outcomes for Patients with IBS

Intestinal microbiota are being increasingly implicated as a cause of many disorders, including IBS. Fecal microbiota transplantation (FMT) restores fecal microbiome diversity and offers impressive cure rates in patients with refractory *Clostridium difficile* infection. It appears that FMT offers similar benefit to patients with IBS. David Pinn of Montefiore Medical Center in the Bronx, New York, shared his findings at the American College of Gastroenterology 2013 Annual Scientific Meeting (Abstract P1688).

Dr Pinn and colleagues conducted a follow-up study of FMT in 13 patients who had IBS that was unresponsive to dietary modification, probiotics, antibiotics, and/or antidepressants. Patients were, on average, 45 years old and had been experiencing IBS for an average of 73 months (range 12 to 180 months). Nine (64%) patients had IBS with diarrhea (IBS-D), 3 (21%) had IBS with constipation (IBS-C), and 1 had mixed IBS (IBS-M). Eleven patients (79%) received FMT once, and 2 patients had it 2 and 3 times, respectively.

Patients completed a 41-point questionnaire before and approximately 11 months after FMT. The questionnaire was designed to quantitate the severity of abdominal pain, bloating, flatus, and dyspepsia (0 to 3, signifying none to severe), diarrhea (normal [0] to 3, 1-2 to >4 bowel movements/day), constipation (normal [0] to 3, >4 to <2 bowel movements/week), and global well-being (3 to 1, signifying poor to good).

Parameters changed during the study, as shown in the **Table**. In 9 patients with IBS-D, the pre-FMT score was 1.89 and post-FMT mean score was 0.78. Of the 3 patients with IBS-C, mean pre-FMT score was 1.33, and post-FMT mean score was 0.33. The 1 patient with IBS-M and had improvement in diarrhea and constipation after FMT. Three (23%) patients reported no improvement.

Before FMT, global well-being was reported as "good" in 0 patients, "acceptable" in 4 (30%), and "poor" in 9 (69%) (mean score: 2.69). After FMT, global well-being was "good" in 3 patients (23%), "acceptable" in 6 (46%), and "poor" in 4 (30%) (mean score: 1.92).

FMT resolved or improved symptoms in 70% of study participants who had refractory IBS. The improvements were as follows: abdominal pain (72%), bowel habits (69%), dyspepsia (67%), bloating (50%), flatus (42%), and quality of life (46%).

**Table.** Effect of Fecal Microbiota Transplantation on Symptoms (N=13)

| Parameter | Before FMT, n (%) | After FMT, n (%) |
|---|---|---|
| Abdominal pain | 11 (79)<br>Mean score: 2.55 | Resolution 3 (27)<br>Improvement 5 (46)<br>No change 3 (27)<br>Mean score: 1.45 |
| Bloating | 12 (80)<br>Mean score: 2.25 | Resolution 2 (17)<br>Improvement 4 (33)<br>No change 6 (50)<br>Mean score: 1.42 |
| Flatus | 12 (92)<br>Mean score: 2.4 | Resolution 2 (17)<br>Improvement 4 (33)<br>No change 6 (50)<br>Mean score: 1.42 |
| Dyspepsia | 6 (43)<br>Mean score: 1.83 | Resolution 2 (33.3)<br>Improvement 2 (33.3)<br>No change 2 (33.3)<br>Mean score: 1.17 |

FMT, fecal microbiota transplantation.

## Linaclotide Provides Moderate Improvement in IBS-C Symptoms and Quality of Life

A comprehensive literature review confirmed findings of recent randomized control trials suggesting that linaclotide is moderately effective in the management of IBS-C. The meta-analysis was conducted by Dileep Atluri of the University Hospitals of Cleveland in Cleveland, Ohio, and colleagues and reported at the American College of Gastroenterology 2013 Annual Scientific Meeting (Abstract P1095).

Databases searched included the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, SCOPUS, Cumulative Index to Nursing and Allied Health Literature, and gastroenterology conference proceedings and abstracts. Content in the meta-analysis included randomized controlled trials of at least 12 weeks that compared linaclotide with placebo in adult patients with IBS-C.

A total of 110 citations were identified. Of these, 3 randomized controlled trials, representing a total of 1773 patients, met the inclusion criteria. The pooled findings showed that, compared with placebo, linaclotide was superior to placebo in achieving adequate IBS symptom relief (RR=0.73; 95% CI, 0.65-0.82). The most common adverse event was diarrhea; incidence of diarrhea leading to discontinuation of therapy were significantly higher among patients receiving linaclotide compared with those receiving placebo (RR=14.75; 95% CI, 4.04-53.81).

Dr Atluri conceded that the paucity of available studies and the highly selective patient population of the studies examined limits generalizability of the findings but that the study results suggest that linaclotide may exert moderate efficacy in patients with IBS-C. He concluded that further studies with longer treatment periods are needed to confirm the efficacy and safety of linaclotide.

In a separate presentation, also delivered at the American College of Gastroenterology 2013 Annual Scientific Meeting (Abstracts P1096), Dr Atluri provided evidence that linaclotide not only improves IBS-C symptoms, but is moderately effective at improving quality of life (QOL).

Dr Atluri and colleagues systematically reviewed the available literature and conducted a meta-analysis to evaluate the efficacy of linaclotide for improving IBS-QOL in patients with IBS-C. Again, content included randomized controlled trials of at least 12 weeks that compared linaclotide with placebo in adult patients with IBS-C. The trials also had to use the IBS-QOL measure, a validated, self-reported, 34-item scale that specifically measures the impact of IBS and associated treatments. Studies were independently assessed by 2 investigators.

Of 110 identified citations, 3 registered clinical trials enrolling 1659 patients met the inclusion criteria. The meta-analysis revealed that, compared with placebo, more patients taking linaclotide achieved clinically meaningful improvement in QOL (RR=0.78; 95% CI, 0.72-0.86).

Dr Atluri, again, noted that relatively few studies were available at the time of this analysis. All the included studies were performed in tertiary care settings with highly selective patient cohorts, and, thus, results may not be generalizable.

## Anti-Vinculin Antibodies Show Presence of IBS

Many cases of IBS begin in the aftermath of acute gastritis. This may be related to neuropathic fallout that results in small intestinal bacterial overgrowth (SIBO). Cytolethal distending toxin B produced by bacteria known to cause gastroenteritis plays a key role in this process through both molecular mimicry and the formation of auto-antibodies to vinculin, a cell migration and adherence protein found predominantly on nerves and epithelium. Now, it appears that anti-vinculin antibodies are elevated in persons with IBS compared with persons without IBS.

Mark Pimentel, of Cedars Sinai Medical Center in Los Angeles, California, presented findings at the American College of Gastroenterology 2013 Annual Scientific Meeting (Abstract P8). Dr Pimentel and colleagues designed a study that would allow them to assess patients with anti-vinculin antibodies as a predictor of IBS compared with healthy persons and those with IBD. Study participants (18 to 65 years old) with Rome-positive IBS were recruited from Cedars Sinai Medical Center in Los Angeles and Beth Israel Deaconess Medical Center in Boston. Participants were excluded if they had concomitant

gastrointestinal (GI) disease or previous GI surgery, adhesions, unstable thyroid disease, diabetes, or HIV. Healthy controls were recruited based on results of a GI symptom questionnaire; all had to score less than 10 for bloating, diarrhea, abdominal pain, and constipation, inclusive on a 0 to 100 VAS. Subjects with IBD were recruited from an expert tertiary care medical center. Patients with Crohn's disease or ulcerative colitis were excluded if they had a history of biologic therapy and were currently taking prednisone. In all, the study evaluated 165 patients with IBS, 30 with IBD, and 26 healthy controls. Demographics were similar between both groups.

The investigators analyzed serum (enzyme-linked immunosorbent assay [ELISA]) from all participants for the presence of antibodies to human recombinant vinculin. Overall, compared with subjects in the normal control and IBD groups, persons with IBS had significantly greater optical density in the ELISA test for anti-vinculin antibodies. Subjects with a history of acute gastroenteritis had even higher levels of antibodies ($P$<.05). Both centers from which the patients with IBS were recruited had similarly abnormal results ($P$=NS). Assaying for anti-vinculin antibodies is the first diagnostic test for IBS that is based on serum findings related to a pathophysiologic mechanism of IBS (acute gastroenteritis-precipitated molecular mimicry and autoimmunity).

## Patients with IBS-C and Slow Colon Transit Respond Well to Lubiprostone

IBS-C is partially a disorder of altered motility and transit. Lubiprostone is a chloride channel activator that works by increasing fluid secretion in the intestines. A closer look at the effects of lubiprostone in the gut indicate that it also accelerates colonic transit time (CTT) in a subgroup of patients with IBS-C and slow colon transit.

Richard Saad of the University of Michigan in Ann Arbor, Michigan, presented this insight at the American College of Gastroenterology 2013 Annual Scientific Meeting (Abstract P496). The team examined the physiologic effects of lubiprostone in a randomized, double-blind, placebo-controlled study of 49 adults who fulfilled the Rome III criteria for IBS-C. Participants received lubiprostone 24 µg once daily (n=16), lubiprostone 8 µg twice daily (n=17), or placebo (n=16) for 4 weeks. Gastrointestinal motility and transit testing was performed at baseline and in the fourth treatment week, using a wireless motility capsule. The investigators measured gastric emptying time (GET), small bowel transit time (SBTT), CTT, whole gut transit time (WGTT), motility index, and intraluminal pH. The change from mean baseline GET, SBTT, CTT, WGTT, small bowel pH, colon pH, small bowel motility index, and colon motility index was analyzed within each treatment arm using a 2 sample T-test, and using a linear mixed effects model for repeated measures between the 3 treatment arms. Statistical significance was defined as $P$<.05.

Baseline transit, pH, and motility parameters were similar between patients in the different treatment arms, and there were no statistically significant changes in the mean GET, SBTT, CTT, WGTT, small bowel pH, colon pH, small bowel motility index, or colon motility index from baseline. Compared with placebo, there were no statistically significant changes from baseline GET, CTT, SBTT, WGTT, small bowel pH, colon pH, small bowel motility index, or colon motility index in either lubiprostone group.

In a subgroup of 7 patients with IBS-C and delayed baseline CTT, lubiprostone accelerated CTT (placebo did not). In 3 of 4 patients receiving lubiprostone, 8 µg twice daily, CTT accelerated by 21.7 hours. In 2 of these patients receiving lubiprostone, 24 µg once daily, CTT accelerated by an average of 79.5 hours. In contrast, the 1 patient receiving placebo experienced a 27-hour decrease in CTT.

Lubiprostone does not appear to change regional gut transit, luminal pH, or gut motility in IBS-C patients with normal CTT. It does, however, accelerate CTT in a subgroup of patients with slow colon transit.

# Presentations in IBD

## Long-Term Data Support Adalimumab as a Safe, Effective Choice for Patients with Ulcerative Colitis

The safety and efficacy of adalimumab in the treatment of ulcerative colitis was confirmed through an open-label extension study of ULTRA 1 and ULTRA 2. Findings were reported by Jean-Frédéric Colombel of Mt. Sinai Medical Center in New York, New York at the 2013 Advances in Inflammatory Bowel Diseases conference (Abstract P-137). ULTRA 1 and ULTRA 2, two double-blind pivotal trials, tested the effects of adalimumab in adults with ulcerative colitis over a period of 8 to 52 weeks. ULTRA 1 was a randomized, controlled, 8-week induction study with an open-label phase through week 52. ULTRA 2 had a similar design but included induction followed by maintenance, rather than an open-label phase, through week 52.

In ULTRA 1, adalimumab effectively maintained clinical remission in adults with moderate-to-severe ulcerative colitis who were anti-tumor necrosis factor (TNF) therapy-naive and unresponsive to corticosteroids and/or immunosuppressive agents. The results of ULTRA 2 were similarly favorable: adalimumab significantly improved rates of clinical remission, clinical response, and mucosal healing starting at Week 8 and lasting through Week 52. Adalimumab was generally well tolerated; most adverse events were mild or moderate.

The results of open-label extension safety analysis echo these observations. All participants in ULTRA 1, ULTRA 2, and open-label trials had regular safety evaluations. Adverse events were assessed per 100 patient-years of exposure. Event rates were calculated for placebo and adalimumab groups during the double-blind period (up to Week 52) from ULTRA 1 and ULTRA 2, and through April 15, 2012 for any adalimumab exposure.

As of April 15, 2012, a total of 1010 patients had received adalimumab for ulcerative colitis, totaling 2007.4 patient-years of exposure. Dr Colombel noted that the placebo and adalimumab groups had a similar overall rate of adverse events during double-blind treatment. The nature of the adverse events, however, was different. Serious outcomes—infections, ulcerative colitis worsening/flare, and adverse events severe enough to prompt discontinuation of treatment—were more common with placebo. Opportunistic infections, injection site reactions, and hepatic events were more frequent with adalimumab. The rates of adverse events during any adalimumab exposure were consistent with those previously reported for adalimumab and other anti-TNF therapies in the setting of inflammatory bowel disorders. No new safety signals were identified.

## Adalimumab Provides Long-Term Sustained Response in Anti-TNF–Naive Patients with Ulcerative Colitis

To gain insight into sustained response to adalimumab in ulcerative colitis, Subrata Ghosh of the University of Calgary in Calgary, Alberta, Canada and colleagues randomized a group of adults to receive either placebo or adalimumab for 52 weeks as part of the ULTRA 2 study. All the patients had mild-to-moderate ulcerative colitis (Mayo score 6-12; endoscopy subscore 2-3) for 3 months or longer and were failing corticosteroid or immunosuppressive therapy. Previous exposure to anti-TNF therapy did not exclude patients from participating in the analysis. The findings were reported at the 2013 Advances in Inflammatory Bowel Diseases conference (Abstract P-138).

Study participants received adalimumab at loading doses of 160 mg and 80 mg at Weeks 0 and 2, followed by 40 mg every other week starting at Week 4. Patients who responded inadequately could move to open-label adalimumab at a dosage of 40 mg every other week, starting at Week 12.

Patients had endoscopy and full Mayo score determination (using the worst rectal bleeding and stool frequency scores from the previous 3 days) at Weeks 8, 32, and 52. Remission (Mayo score ≤2, no subscore >1), response (Mayo score decrease ≥3 points and ≥30% from baseline, and rectal bleeding subscore ≤1 or decreased by ≥1), and mucosal healing (endoscopy subscore ≤1) were assessed at each point.

The investigators determined the proportion of patients who showed efficacy at all 3 time points. They also examined the data with respect to medication exposure: adalimumab vs placebo, and anti-TNF therapy vs no anti-TNF therapy.

Compared with the placebo group, patients who received adalimumab were significantly more likely to achieve sustained remission, response, and mucosal healing ($P<.01$ for all parameters). Among patients who were anti-TNF–naive, those receiving adalimumab were significantly more likely to achieve the sustained efficacy endpoints than those on placebo ($P<.05$). Although patients who had previous exposure to anti-TNF agents who received adalimumab

had a statistically significant improved sustained response compared with those on placebo ($P$<.05), the extent of improvement for sustained remission and mucosal healing did not reach statistical significance.

## Vedolizumab Effective in Patients with IBD

Vedolizumab, a humanized immunoglobulin G1 monoclonal antibody, reduces inflammation in inflammatory bowel disease (IBD) by exclusively targeting the lymphocyte α4β7 integrin. This interaction prevents gut-homing lymphocytes from binding to mucosal vascular addressin cell adhesion molecule-1 (MAdCAM-1), an immunoglobulin superfamily adhesion molecule that helps direct lymphocytes into Peyer's patches and the intestinal lamina propria.

Data from phase 3 studies, GEMINI 1 and 2 show that vedolizumab has a similar pharmacokinetic profile in both ulcerative colitis and Crohn's disease patient populations. Also, dosing every 4 or 8 weeks maintains serum concentrations at 10 μ/mL or greater, levels that completely saturate the integrin receptors. At the 2013 Advances in Inflammatory Bowel Diseases conference, Maria Rosario of the Hospital Universitario Central de Asturias in Oviedo, Spain discussed the GEMINI studies that led up to these findings (Abstract P-140).

The GEMINI 1 and 2 studies included a 6-week induction phase, during which patients received either vedolizumab, 300 mg IV, or placebo at Weeks 0 and 2. Vedolizumab-treated patients showing a clinical response at Week 6 were randomly assigned to receive vedolizumab, 300 mg IV (intention-to-treat [ITT] population), or placebo every 4 or 8 weeks during the subsequent 46-week maintenance phase. Vedolizumab induction nonresponders (non-ITT population) received open-label vedolizumab every 4 weeks, while patients randomly assigned to placebo during the induction phase continued to receive placebo until week 52. Blood samples collected at predetermined times were analyzed for vedolizumab concentration, pharmacodynamic status (α4β7 [receptor] saturation via MAdCAM-1-Fc binding interference assay), and anti-vedolizumab antibodies. The investigators used descriptive statistics to summarize vedolizumab pharmacokinetic and immunogenicity data, and generated plots of receptor saturation.

Giving vedolizumab at a dose of 300 mg every 4 or 8 weeks produced mean serum concentrations of 10 μg/mL or greater at all time points in patients with ulcerative colitis and Crohn's disease (ITT and non-ITT groups). Complete receptor saturation occurred at Week 6 and was maintained until Week 52 with both 4 and 8 week dosing intervals. Overall, 56 (4%) of 1434 patients tested positive for anti-vedolizumab antibodies at any time during treatment. Thirty-two (10%) of 320 pooled (ulcerative colitis and Crohn's disease, ITT and non-ITT) patients tested positive for anti-vedolizumab antibodies when not taking the drug (Week 66).

Among patients who had an investigator-defined infusion-related reaction, 3 (5%) of 61 tested persistently (at 2 or more consecutive visits) positive for anti-vedolizumab antibodies. Compared with the general study population, patients who tested persistently positive for anti-vedolizumab antibodies generally had lower serum vedolizumab trough concentrations. In the ITT placebo group, patients who received concomitant immunomodulators had a lower rate of anti-vedolizumab antibody positivity (1 [3%] of 32) than those who did not (44 [18%] of 247).

## HBV "Vaccination as Usual" Might be Insufficient for Children with IBD

Almost half of adults and children with IBD have no baseline immunity to hepatitis B virus (HBV), and up to 14% cannot mount an effective immune response after booster vaccination, according to results of a study in children with IBD living in rural West Virginia. Most lacked protective antibodies against HBV—despite being vaccinated during infancy—increasing their risk of infection. Yoram Elitsur of Marshall University Medical Center in Huntington, West Virginia, presented study findings at the 2013 Advances in Inflammatory Bowel Diseases conference (Abstract P-164). Dr Elitsur and colleagues found that 2 doses of HBV vaccination provided protective immunity for most of the study participants even when they were receiving immunosuppressant treatment.

The investigators examined the HBV antibody status in 31 children being treated for IBD. The mean age of the patients was 14.5 years; 14 (45%) were girls. Crohn's disease had been diagnosed in 25 (81%) patients) and ulcerative colitis in 6 (19%) patients. Immunomodulator treatments included prednisone, azathioprine, infliximab, and adalimumab. Twenty six (84%) patients were receiving immunosuppressive therapy at the time of analysis.

The investigators retrospectively reviewed the children's charts, looking specifically at levels of hepatitis B surface antigen (HBsAg) and antibody (HBsAb). Patients who were nonimmune for HBV received a booster vaccination series, and their immune status was rechecked. Adequate immune status was defined at an HBV antibody level of more than 10 mIU/mL.

Twenty (65%) patients had no HBV immunity. Of this group, 7 (35%) had been vaccinated for HBV as infants. A booster vaccine was given to 17 (85%) nonimmune children. Of this group, 16 (92%) had an adequate immune response. HBV antibody was present after the booster in 14 children. In 13 (92%) of them, 2 booster doses produced an adequate antibody response.

The investigators urge that children with IBD be carefully assessed for HBV immunity status. Repeat vaccination is recommended to provide full protection for these high-risk patients

## Fecal Microbiota Transplantation Improves Several Parameters in Patients with IBD

Of the various conditions that can contribute to IBD, intestinal dysbiosis is garnering increasing attention. Fecal microbiota transplantation (FMT), involving transplant of stool from healthy donors into the recipient, is well documented to produce impressive cure rates in patients with *Clostridium difficile* infection. A small study in 16 patients, presented by Adam Greenberg of Montefiore Medical Center in Bronx, New York, at the American College of Gastroenterology 2013 Annual Scientific Meeting suggests that FMT has a similar therapeutic benefit in patients with IBD (Abstract P1629).

Dr Greenberg and colleagues followed 16 of 21 patients with refractory IBD who had FMT at Montefiore Medical Center between 2010 and 2012. Patients were asked to complete a questionnaire soliciting pre- and post-FMT data.

Fifty-six percent of patients were adult men. The follow-up period between FMT and data collection averaged 14 months, with a range of 4.5 to 30 months. On average, patients had IBD for 7.5 years before undergoing FMT. Fourteen (87%) patients had ulcerative colitis, and 2 (13%) had Crohn's disease. Initial FMT was by colonoscopy (n=15) or nasojejunal infusion (n=1), followed by self-administered fecal enemas (SAFE) on a tapered to maintenance schedule.

FMT produced improvement in a number of parameters. Frequency of disease flares declined in 10 (63%) of 16 patients and disappeared in 3 (30%) of these 10 patients during an average follow-up period of 21 months (range 8 to 30 months). In 7 (33%) patients, the average number of flares decreased from 10.1 to 2.8 flares per year after FMT. No patient experienced more flares after FMT. Nine patients (56%; 8 ulcerative colitis, 1 Crohn's disease) reported that diarrhea decreased from an average of 8.2 to 3.6 episodes per day after FMT. The remaining 7 (44%) patients noted no change. Of 14 patients (13 ulcerative colitis, 1 Crohn's disease) with rectal bleeding, 4 (29%), 6 (43%), and 3 (21%) reported resolution, decrease, or no change after FMT. One patient (7%) reported that bleeding increased.

Of 11 (69%) patients with abdominal pain, 4 (36%) and 5 (46%) reported that pain improved or resolved, respectively, after FMT. Further, whereas before FMT, 12 (75%) patients had lost weight, after FMT, 8 (67%) patients maintained their weight, and 4 (33%) gained weight.

In addition, FMT reduced the need for concomitant medications. Of the 10 (63%) patients taking oral corticosteroids, 3 (30%) decreased their dosage and 4 (40%) stopped corticosteroid therapy completely. One (25%) in 4 patients was able to discontinue TNF-α inhibitors. The most dramatic improvements following FMT were seen in the 4 patients with ulcerative colitis and concomitant *C difficile* infection. Three patients had been taking corticosteroids and 1 patient had been taking 6-mercaptopurine as maintenance therapy. All patients discontinued maintenance therapy after FMT.

The only adverse event reported after FMT was a transient worsening of abdominal distension in 3 (19%) patients.

## Modified Serologic Testing Algorithm May Work Best in Early IBD

Serologic testing for IBD can be useful in differentiating IBD from other disorders and determining whether the patient has ulcerative colitis or Crohn's disease. Sensitivity and specificity, however, have historically been variable. There is also the question of whether serologic sensitivity and specificity for IBD varies over time, becoming more reliable in persons with long-standing vs recent disease.

Most studies of serologic testing in IBD have involved retrospective analysis. Now, results of a prospective study in patients with recently diagnosed IBD showed that seromarker testing had good sensitivity for identifying clinical IBD, with no age- or sex-dependent differences. Serologic diagnoses and individual antibody positivity appeared to be stable over time, despite early testing and variable testing intervals. Biomarker differentiation between clinical Crohn's disease and ulcerative colitis had low sensitivity but relatively higher specificity.

Eric J. Mao of the Warren Alpert Medical School of Brown University in Providence, Rhode Island reviewed the study methodology and results at the American College of Gastroenterology 2013 Annual Scientific Meeting (Abstract 1678). The investigators prospectively collected serum from a prospective, population-based inception registry of Rhode Island residents with recent clinically confirmed IBD (Crohn's disease, ulcerative colitis, and undetermined IBD). Serum was tested en bloc with Prometheus IBD sgi, and later by Prometheus Laboratories. Forty-two of these patients had independent testing with the same or earlier version of the test. Intervals between testing ranged from 1 to 532 days (mean, 103 days). The team assessed the test's sensitivity for IBD, Crohn's disease, and ulcerative colitis, as well as specificity for Crohn's disease and ulcerative colitis, using the clinical diagnosis as the gold standard. The investigators used McNemar's test to compare biomarker positivity (defined as a value greater than the reference range of the Prometheus test used) and serologic diagnoses between 2 time points.

Of the 408 newly diagnosed IBD cases enrolled in the registry between 2008 and 2012, 367 had serology available

for study. Sensitivity of serologic testing with Prometheus sgi was as follows: 82.7%, IBD; 57.1%, Crohn's disease; and 59.0%, ulcerative colitis. Specificity was 85.9% for Crohn's disease and 79.4% for ulcerative colitis. There were no significant differences in the association between clinical and serologic IBD, Crohn's disease, and ulcerative colitis by gender or across different age groups (0-18, 19-40, 41-60, and >60 years). The low apparent Crohn's disease and ulcerative colitis sensitivity was related to a number of Crohn's disease cases being labeled as ulcerative colitis because of elevated anti-neutrophil cytoplasmic autoantibodies (ANCA) markers or an inconclusive marker pattern for IBD (elevated ANCA and flagellins).

Of patients tested twice, there were no significant changes in serologic diagnoses of IBD, Crohn's disease, and ulcerative colitis, or anti-*Saccharomyces cerevisiae* antibodies (ASCA) immunoglobulin A, ASCA immunoglobulin G, perinuclear ANCA, outer membrane porin C, and bacterial flagellin (CBir1) positivity. Of the 8 clinical IBD-undetermined cases, markers suggested ulcerative colitis in 5, Crohn's disease in 2, and no IBD in 1.

Given that the algorithm used for IBD diagnosis and Crohn's disease/ulcerative colitis differentiation was developed for patients with established IBD, newly diagnosed IBD may require a modified serologic algorithm to optimize sensitivity and specificity.

## High-Dose Infliximab a Possible Answer When Low-dose Is Ineffective in Crohn's Disease

For patients with Crohn's disease who do not respond to treatment with standard dosages of infliximab, high-dose infliximab appears to be safe and effective. Furthermore, higher C-reactive protein levels (CRP) may indicate which patients are most likely to respond to treatment intensification. Steven Hendler of the Icahn School of Medicine at Mount Sinai University in New York, New York, discussed his study at the American College of Gastroenterology 2013 Annual Scientific Meeting (Abstract 1675).

The investigators reviewed electronic medical records of patients with Crohn's disease who received high-dose infliximab (10 mg/kg every 7 weeks to 20 mg/kg every 4 weeks) over 2 years. Criteria reviewed included history, medications, and laboratory data. Safety and efficacy of dose intensification also were analyzed.

Overall, of the 319 patients with Crohn's disease, 87 received high-dose infliximab. Their median age at Crohn's disease diagnosis and initiation of high-dose infliximab were 16.5 and 28.5 years, respectively. Twenty-nine percent failed at least 1 other biologic therapy. Ninety-three percent met criteria for disease activity ranging from moderate/severe to severe/fulminant; of this group, 55% had penetrating disease and 58% had ileocolonic involvement.

The characteristics of high-dose infliximab treatment were as follows: 69% received doses between 10 mg/kg every 7 weeks and 10 mg/kg every 4 weeks; 31% received doses between 15 mg/kg every 8 weeks and 20 mg/kg every 4 weeks. Forty-six percent of patients initiated high-dose infliximab therapy with an immunomodulator. At 4, 24, and 52 weeks of therapy, 20%, 28%, and 18% of patients experienced a full response, and 46%, 30%, and 23% experienced a partial response, respectively.

The investigators also examined CRP levels to see if they correlated with response to infliximab. In a subset of 58 patients receiving high-dose infliximab, CRP was reduced from a median of 21.9 mg/L before treatment, to 4.7 mg/L at around 16.5 weeks after treatment ($P<.001$). Patients who responded fully or partially at 4 weeks had a higher median baseline CRP than those who did not respond (24.9 vs 3.5 mg/L, $P=.04$). The average length of treatment was 30.5 weeks. At the end of follow up (average, 103.5 weeks), 44% of patients remained on high-dose infliximab.

The safety of high-dose infliximab therapy appeared to be consistent with the known adverse effect profile of anti-TNF therapy. There were 11 cases of infection that required hospitalization (7.4 events per 100 patient-years); none were mycobacterial, and 3 were in patients receiving combination immunosuppressant therapy. Melanoma developed in 2 patients, and squamous cell carcinoma of the skin developed in 1. Reasons for discontinuing high-dose infliximab were infection (n=1), infusion reaction (n=2), autoimmune disease (n=2), relocating, insurance coverage (n=16), inadequate response (n=22), and successful de-escalation to a standard treatment dose of infliximab after responding fully to high-density infliximab (n=6).

# Presentations in GERD

## Three Objective Measures Show Concordance in Diagnosis of GERD

Three objective measuring tools are commonly used to confirm the presence of gastroesophageal reflux disease (GERD): the Johnson-DeMeester (JD) scoring system, the DeMeester (D) scoring system, and percent total time pH <4, but are all GERD measurement tests created equal? Could using one test to evaluate a patient yield a different result than using another?

Results of a prospective study show a strong agreement (kappa 0.903) between the JD and D scores in classifying a 24-hour pH test as normal or abnormal. Furthermore, both scoring systems correlate significantly with percent total time pH <4. Physicians can reliably and confidently use any of these methods if a patient has GERD.

Ryan Kwok of Walter Reed National Military Medical Center in Bethesda, Maryland, presented his study at the American College of Gastroenterology 2013 Annual Scientific Meeting (Abstract P21). Kwok and a team of investigators retrospectively studied 160 patients (average age 46 years) who had 24-hour pH testing for GERD. All patients had abstained from proton pump inhibitors for at least 1 week before the test.

For each 24-hour pH study, the investigators calculated both JD and D composite scores, using the following parameters: percent total time pH <4, percent upright time pH <4, percent supine time pH <4, total number of reflux episodes, number of reflux episodes of greater than 5 minutes duration, and time of longest reflux episode. Scores of greater than 22.0 and greater than 14.7 constituted abnormal JD and D scores, respectively. The investigators compared the JD and D scores with respect to their ability to detect acid reflux expressed as the percent total time pH <4, using a normal threshold of 4.5%.

The JD and D composite scores (R2 0.961; *P* <.001) correlated significantly. They agreed for classifying normal vs abnormal results in 96% of the studies (153/160); in these studies, 102 results were normal and 51 were abnormal by both scoring systems (kappa 0.903; *P*=.000). The JD and D scores also correlated significantly with percent total reflux (R2=0.793 and R2=0.919, respectively), percent upright reflux (R2=0.380 and R2=0.564), and percent supine reflux (R2=0.789 and R2=0.628). Disagreement, which occurred in 7 (4%) of 160 studies, was primarily related to differences in upright reflux in which the JD score was normal (range 16.9 to 20.5) and the D score was abnormal (range 14.9 to 18.5). Using a value of 4.5% for the normal threshold of total percent time acid reflux, the JD and D scores misclassified 19 (12%) and 12 (8%) of patients (*P*=.257), respectively.

## Sleep Position Matters in Reducing Nighttime Gastroesophageal Reflux

Several mechanical interventions have been tested to reduce gastroesophageal reflux that occurs during sleep. These include sleeping on a wedge-shaped support, elevating the head of the bed, and sleeping supine, left side down. Using a sleep device that maintains the patient in a left lateral position with head and torso elevated can prevent gastroesophageal reflux. This finding and others were presented by Erik B. Person of the Medical University of South Carolina in Charleston, South Carolina, at the American College of Gastroenterology 2013 Annual Scientific Meeting (Abstract P47).

The sleep device tested in this randomized controlled trial consisted of a 2-piece inclined base and body pillow that maintains a patient in a lateral position while elevating his or her head and torso. Dr Person and colleagues pursued their hunch that using this sleep device to maintain a fixed position on the left side with the head and torso raised would significantly reduce recumbent gastroesophageal reflux.

Twenty healthy volunteers participated in this study. Each person had 4, 6-hour impedance-pH tests. After placement of a reflux probe, each participant returned home, ate a standardized meal (1350 kcal, 58 g fat), and reclined in 1 of 4 randomly assigned positions: sleep device, right side down; sleep device, left side down; wedge-shaped support, any position; and flat, any position. A wireless position monitor documented position during each study. The investigators blindly calculated the number of reflux episodes and esophageal acid exposure for 6-hour periods. Position monitor data were used to compare the assigned with the actual position.

The patients who slept sleep with the device left side down fared significantly better than others. They had less esophageal acid exposure over 6 hours (mean 0.46%) compared with sleeping flat (3.46%, *P*<.05), with wedge-shaped support (3.59%, *P*<.01) or with the sleep device right side down (4.59%, *P*<.001). They had significantly fewer reflux episodes (mean 5.55) over 6 hours than those who slept with the sleep device right side down (mean 13.23, *P*<.05). Patients assigned to the sleep device, left side down averaged 83% of the first 2 hours and 61% of 6 hours in their assigned position. Those assigned to the sleep

device, right side down spent 72% of the first 2 hours and 53% of 6 hours in their assigned position. Patients sleeping with wedge-shaped support and flat averaged significantly more time supine than those sleeping right- or left-side down ($P$ <.05) over 6 hours.

The sleep device effectively maintained sleepers in the recumbent horizontal position. It dramatically reduced recumbent esophageal acid exposure in patients who slept left side down, but did not help persons who slept right side down.

## Consider Predictors of Response When Opting for Topical Corticosteroids in Eosinophilic Esophagitis

Topical corticosteroids are given first-line status for eosinophilic esophagitis (EoE) despite randomized controlled studies showing only modest efficacy for inducing histologic remission. If there were a way to predict who might and might not benefit from corticosteroids, these agents could be used more selectively. Investigators exploring this discovered that persons least likely to respond to topical corticosteroids are adults who have longitudinal furrows on endoscopy, undergo dilation, and present with no food impactions.

At the American College of Gastroenterology 2013 Annual Scientific Meeting, Fouad Moawad of Walter Reed National Military Medical Center in Bethesda, Maryland, described the study (Abstract P1204). Data from 2 prospective studies and an EoE registry were examined. Seventy-five patients with EoE (age range, 2 to 64 years; average age, 33 years) received an 8-week course of either swallowed fluticasone or viscous budesonide. Response was defined as less than 5 eosinophils per high-powered field (eos/hpf) in both mid-proximal and distal esophageal biopsies. Nonresponse was defined as greater than 5 eos/hpf in the proximal and/or distal esophagus. Demographic, clinical, endoscopic, and histologic features were examined.

The results showed a higher response rate to topical corticosteroids in children compared with adults (60% vs 33%; $P$=.047). Response rates were similar between males and females (33% vs 58%) and between medications (38% fluticasone vs 36% budesonide). Peak proximal (49±50 vs 55±48) and distal eosinophil (71±81 vs 82±86) counts were similar between responders and nonresponders. Response rates to other parameters are listed in the **Table**. Differentiation of response to topical corticosteroids was most associated with age, food impaction, absence of endoscopic furrows, and lack of need for dilation.

In multivariate logistic regression, the independent predictors of nonresponse to topical corticosteroids were adult age (odds ratio [OR] 5.13; $P$=.048), absence of food impaction (OR 0.116; $P$=.005), presence of furrows (OR 8.24; $P$=.006), and dilation (OR 6.30; $P$=.023). The investigators recommend either increasing the dosage of corticosteroids or using an alternate form of treatment, such as dietary elimination, in these patients.

**Table.** Incidence of Response vs Nonresponse to Corticosteroids in Eosinophilic Esophagitis

| Parameter | Responder, % | Nonresponder, % | $P$ value |
|---|---|---|---|
| Age, <18 years | 60 | 40 | .047 |
| Age, >18 years | 33 | 67 | .047 |
| Food impaction | 43 | 21 | .047 |
| Dysphagia | 86 | 85 | .943 |
| Heartburn | 29 | 21 | .474 |
| Endoscopic furrows | 64 | 87 | .019 |
| Endoscopic rings | 54 | 62 | .489 |
| Endoscopic white plaques | 21 | 36 | .181 |
| Dilation | 18 | 43 | .028 |

## Calcium and Multivitamins May Reduce the Risk of Barrett Esophagus in Men with GERD

Barrett esophagus is a complication of GERD that is a precursor to esophageal adenocarcinoma. Limited information suggests that calcium and some vitamins can be protective against certain malignancies. Results of a retrospective review of veterans' records, however, suggest that taking calcium and multivitamins reduces the potential for Barrett esophagus. These findings were presented by Aaron Goldberg of the Phoenix Veterans Affairs Medical Center in Phoenix, Arizona, at the American College of Gastroenterology 2013 Annual Scientific Meeting (Abstract P1201).

Dr Goldberg and an investigative team compared the medical records of 250 patients with biopsy-confirmed Barrett esophagus and 250 controls who had acid-peptic symptoms but no endoscopic Barrett esophagus. The all-male study population was chosen from the Phoenix Veterans Affairs Hospital. Medication histories were reviewed to identify patients who were taking calcium or multivitamins before endoscopy.

The investigators applied logistic and linear regression to determine outcome predictors. They discovered that mean age at diagnosis was significantly older in the Barrett esophagus population compared with controls (61 vs 57 years; $P$<.001). Mean body mass index (BMI) did not differ significantly between groups (28.7 vs 28.9, respectively). On multivariate analysis, independently significant risk factors for Barrett esophagus were the use of calcium (OR

0.467; *P*=.036), multivitamins (OR 0.349; *P*<.001), and age at diagnosis (OR 1.041/year; *P*<.001). Age at diagnosis was associated with prolonged duration of Barrett esophagus (0.06 cm/year, *P*=.006).

The investigators hypothesize that multivitamins might reduce the risk of Barrett esophagus through an antioxidant effect. Calcium might offer protection by binding bile acids and fatty acids, reducing their proliferative effect on epithelial cells. Prospective studies of this relationship are needed.

## Preprandial and Total Reflux Episodes Correlate in Prolonged Impedance Studies

Prolonged multichannel impedance studies can be uncomfortable for patients because of reflux. Would reducing preprandial reflux reduce total reflux frequency during testing and help make impedance studies more comfortable? According to Heather Barton of the Medical University of South Carolina in Charleston, South Carolina, the answer is yes. The study was presented at the American College of Gastroenterology 2013 Annual Scientific Meeting (Abstract P17).

The researchers analyzed a total of 158 24-hour impedance and pH studies from a prospectively maintained database of patients with symptomatic reflux. Patients with previous esophageal surgery and with low distal baseline impedance were excluded from review. Preprandial reflux, defined as any reflux episode occurring before the first meal, was compared with the total number of reflux episodes during the study. All reflux episodes were calculated as a frequency per minute, to account for differences in time before first meal and total study length. The team also noted the correlation between symptoms and medical treatment.

Of the 158 study participants, there was a correlation coefficient of 0.57 between preprandial and total reflux frequency. The median number of preprandial reflux episodes per minute was 0.39 (mean of 0.74 and a standard deviation of 0.98). The median number of total reflux episodes per minute was 0.031 (mean of 0.035 and a standard deviation of 0.02513). Thus, there was moderate correlation between preprandial reflux and total reflux frequency.

These data suggest that shortening the prolonged multichannel intraluminal impedance studies could make the test more comfortable for the patient. This could broaden the suitability of the test to include more patients.

## Lower Esophageal Sphincter Electrical Stimulation Effective for Refractory GERD

Interim results of an international, multicenter trial, presented at the American College of Gastroenterology 2013 Annual Scientific Meeting by Peter Siersema of the University Medical Center in Utrecht, The Netherlands, suggest that lower esophageal sphincter electrical stimulation therapy (LES-EST) is effective for GERD (Abstract 2). To date, 25 patients with GERD have been enrolled and received LES-EST implants, although 1 patient was discontinued due to a small bowel trocar perforation that occurred during the implant procedure. Eligible patients are those partially responsive to proton pump inhibitor (PPI) therapy with an off-PPI GERD health-related quality of life (HRQL) score of greater than 20 and a greater than 5-point improvement in HRQL score while on a PPI. Other eligibility requirements are an LES end-expiratory pressure greater than 5 mmHg, an esophageal pH less than 4 for more than 5% of a 24-hour period, a hiatal hernia smaller than 3 cm, and esophagitis.

Of the remaining 24 patients currently in the study, 20 have completed their 3-month evaluation, and of these, 17 have completed their 6-month evaluation. A significant improvement in GERD-HRQL scores compared with baseline was seen at both 3 and 6 months. Fifteen (88%) of the patients evaluated at 6 months reported being able to discontinue PPI medication. Most adverse events that occurred were nonserious, and no stimulation-related gastrointestinal adverse events or sensations were reported.

# Presentations in Endoscopy

## POEM Offers an Edge for Patients with Achalasia

Endoscopic treatments for achalasia include peroral endoscopic myotomy (POEM), botulinum toxin injection, and balloon dilation. Although these are well-established treatments, there has yet to be comparison studies of them; however, Enqiang Linghu of the Chinese PLA General Hospital in Beijing, China, presented the results of a randomized comparison between the 3 treatments at the American College of Gastroenterology 2013 Annual Scientific Meeting (Abstract 28). In this study, POEM offered more symptom remission than botulinum toxin injection and balloon dilation, at no greater risk of complications.

The investigators randomized 45 patients equally into the 3 treatment groups. During POEM, only the inner circular muscle was incised. Patients treated with botulinum toxin injection received a single treatment of 100 units delivered as 4 injections of 25 units each into the quadrants of the muscularis propria at the level of lower esophageal sphincter (LES). Balloon dilation was performed once with a Rigiflex pneumatic dilation balloon of 30 mm diameter, gradually inflated to maximum pressure (up to 12 lbs per square inch) and maintained for 60 seconds under direct endoscopic vision.

The investigators compared and documented outcomes at 1 year. The primary outcome was symptom remission. Secondary outcomes were complications, lower esophageal sphincter pressure (LESP), and maximum esophageal width by barium swallow. Symptom remission was defined as a reduction to no more than 3 in the Eckardt score.

Endoscopic treatments were successful in all 45 patients; follow-up was successful in 93.3% at 1 year after treatment. Symptom remission rate was 100% in the POEM group, 64.3% in the balloon dilation group, and 5.4% in the botulinum toxin injection group. Complication rate was 20.0% in the POEM group, 6.7% in the balloon dilation group, and 0% in the botulinum toxin injection group, with no statistical difference found between the 3 groups. LESP and maximum esophageal width were similar before and 3 months after treatment in all study participants.

## Evidence Mounts for POEM Over Heller Myotomy

POEM is the first natural orifice transluminal endoscopic surgery (NOTES) procedure that appears poised to replace its surgical counterpart, Heller myotomy. Results of a 4-year prospective series of patients followed for an average of 12.5 months supports this prognostication. POEM is safe and effective even in patients with severe achalasia. These promising results were discussed by Stavros N. Stavropoulos of Winthrop University Hospital–Columbia University in Roslyn, New York, at the American College of Gastroenterology 2013 Annual Scientific Meeting (Abstract 29).

The prospective Institutional Review Board study is the largest single-operator series performed by a gastroenterologist worldwide and included 66 patients with achalasia and no contraindication to POEM who were treated between 2009 and 2013. The mean age of the 66 patients who received POEM was 52 years (range, 18-93), with 11% being older than 80 years. Forty-two percent had prior treatment, including pneumatic dilation (n=4), suboptimal balloon dilation (n=10), botulinum toxin injection (n=11), and Heller myotomy (n=3). The mean esophageal diameter was 5.3 cm (range, 2.1-13.5 cm). Eight patients had stage III disease (6-8 cm), and 12 had Stage IV (>8 cm/sigmoidization). Seventeen (26%) patients had severe comorbidities (American Society of Anesthesiology Class III).

The primary study outcome was a decrease in the Eckardt score to 3. Secondary outcomes were adverse events, post-POEM LES pressure, reflux symptoms, a pH study, and timed barium swallow.

Clinical success was achieved by 97% (64/66), 96% (54/56), 96% (47/49), and 93% (27/29) of patients at a minimum follow-up of 1, 3, 6, and 12 months, respectively. Among the patients who had clinical success, 56 had significant decreases in Eckardt score (7.9 to 0.2; $P<.0001$) and LES pressure (42.5-15.4 mmHg; $P<.0001$). In 22 of 26 and 25 of 26 patients, the team observed 100% and greater than 50% emptying at 5 minutes on timed barium swallow, respectively. Two early patients had treatment failure (score >3) and underwent salvage pneumatic dilation with excellent sustained results (score=1).

No patients experienced any significant adverse events, death, aborted POEM or conversion, ICU hospitalization, prolonged (>5 days) hospital stay, POEM-related readmission, surgery or interventional radiology, or blood transfusion. Minor technical adverse events included mucosal flap injury in 18 (27%) patients, pneumoperitoneum requiring needle decompression in 7 patients (10%), and small pneumothorax in 1 (1.5%) patient, which was related to inadvertent air insufflation managed conservatively without a chest tube. Reflux symptoms were absent in 58% of patients. They occurred

rarely, daily, and a few times weekly in 27%, 11%, and 4%, respectively, and were well controlled medically. On follow-up esophagogastroduodenoscopy (EGD), 10 (30%) of 33 patients had erosive esophagitis, while 12 (36%) of 33, including the 10 patients with erosive esophagitis, had a positive pH study.

At a mean follow-up of over a year, POEM remained safe and effective even in significant numbers of patients with severe achalasia (stage III/IV), advanced age, severe comorbidities, and previous failed treatment. On objective tests, GERD appeared to be at least as common as it is after Heller myotomy with fundoplication.

## Fuse Colonoscopy Shortens Surveillance and Improves Detection of Adenomas

Despite being the widely accepted gold standard for detecting gastrointestinal (GI) adenomas, colonoscopy can miss interval cancers. It is not a stretch to postulate that some of these oversights could be related to the design of the colonoscope itself—traditional forward-viewing colonoscopes (TFV) provide only a 170º view of the colon. A new tool, the Fuse (Full Spectrum Endoscope) 1C colonoscope, provides a 330º view of the colon. Evidence from a multicenter, international study of screening-age (50 years) patients indicates that, compared with standard colonoscopy, Fuse 1C colonoscopy provides more accurate surveillance intervals and is significantly better at detecting adenomas.

Douglas K. Rex of Indiana University Medical Center in Indianapolis, Indiana, provided details at the American College of Gastroenterology 2013 Annual Scientific Meeting (Abstract 14). A group of 185 patients, ages 18 to 70, underwent tandem colonoscopy with both a TFV and a Fuse 1C colonoscope. Each patient was assigned the tests in random order, but the same endoscopist performed both. Surveillance intervals were observed as per recommended guidelines. Indications for testing were as follows: screening (55.7%), diagnosis (24.9%), and surveillance (19.5%). Among the subgroup of study participants who were age 50 years, 147 completed back-to-back colonoscopies. The investigators reported surveillance interval results from the overall group and cancer detection findings in the group of persons age 50 years.

When TFV was performed first, Fuse shortened the surveillance interval from 5 to 10 years to 3 years in 4 patients, from 10 years to 5 to 10 years in another 4 patients (no adenoma found by TFV and 1 to 2 small adenomas found by Fuse), and from 10 to 3 years in 1 patient (Fuse found a large adenoma). When Fuse was performed first, TFV never shortened the surveillance interval.

Among the total 67 persons who had TFV first, 23 adenomas were detected by TFV and 17 by Fuse, for a miss rate of 42.5% by TFV. In the 80 patients who had Fuse first, Fuse detected 58 adenomas and TFV detected 5, for a miss rate of 7.9% ($P<.0001$). When TFV was performed first, Fuse found adenomas in 5 patients who had no adenomas by TFV. When Fuse was performed first, TFV never found an adenoma that Fuse had not also discovered.

Fuse colonoscopy shortened surveillance intervals in 9 (60%) of 15 examinations in which TFV missed adenomas and in 9 (10.3%) of 88 overall examinations in which TFV was used first. This included 5 persons with TFV-negative examinations. TFV did not change any intervals when Fuse 1C was done first. In the 50 year-old group, the adenoma miss rate was lower for Fuse 1C than TFV.

## Colonoscopy Validated as Colorectal Cancer Screening Tool

Colonoscopy has become the preferred colorectal cancer (CRC) screening option in the United States, where guidelines recommend repeating colonoscopy in 10 years after a negative index colonoscopy. However, there are no randomized controlled trials documenting the efficacy of colonoscopy, and observational studies examining the impact of colonoscopy on the incidence of CRC produce variable estimates. Now, results of a meta-analysis of observational studies presented at the American College of Gastroenterology 2013 Annual Scientific Meeting (Abstract 13) confirm that colonoscopy is the best screening tool for CRC. Larissa Fujii of the Mayo Clinic in Rochester, Minnesota provided the study details.

The team performed a systematic review and meta-analysis of observational cohort studies (MEDLINE, EMBASE, Web of Science) to determine the pooled annual incidence of CRC occurring in average-risk patients after a negative index (no polyps or CRC) colonoscopy. The investigators abstracted data on the number of interval CRCs, the number of patients at risk, and mean follow-up. They calculated the pooled incidence rate of CRC (per 1000 patient-years) and risk ratio, and evaluated what factors might cause variable estimates of colonoscopy efficacy.

In all, 15 independent cohort studies were identified, involving patients who were an average age of 60.5 years and were followed for 1.6 to 11.2 years. The pooled incidence of CRC after a negative index colonoscopy was 0.5 per 1000 patient years (95% CI 0.1/1000 to 0.86/1000 patient years), equivalent to a 0.05% annual risk. Subgroup analysis revealed stable incidence rates across population- and hospital-based studies. The estimated 5- and 10-year CRC risk of 0.25% and 0.5% compared favorably with the observed 5- and 10-year CRC risk of 0.6% and 1.5%, respectively (average-risk, CRC-free, 60-year-old adult based on 2000 to 2002 surveillance, epidemiology, and end results estimates). On pooled analysis of 4 studies reporting a standardized incidence

ratio, a negative colonoscopy was associated with a 57% lower risk of CRC (OR 0.43; 95% CI 0.22-0.86), similar to the inferred estimates.

Based on this analysis, the pooled annual incidence of CRC after a negative index colonoscopy is 0.05%, which is significantly lower than the observed CRC risk in the general population that does not undergo colonoscopy. This supports the effectiveness of colonoscopy as a screening tool, and validates its use in CRC prevention programs.

## Radiofrequency Ablation or Cryotherapy for Barrett Esophagus with Dysplasia?

Barrett esophagus is a major precursor of esophageal adenocarcinoma, a disorder that is becoming more common in the United States. The bridge between the 2 disorders is dysplasia, a premalignant lesion and precursor of esophageal adenocarcinoma that lies within the Barrett mucosa. Dysplasia can be treated in several ways, leaving physicians to consider which treatment might be best for their patients. Results from a comparison study show that radiofrequency ablation (RFA) and cryotherapy are equally effective for decreasing the surface area of Barrett epithelium and eradicating intestinal metaplasia and dysplasia.

Faisal Sheikh of the North Shore Long Island Jewish Hospital in Manhasset, New York, presented his study at the American College of Gastroenterology 2013 Annual Scientific Meeting (Abstract P9). Dr Sheikh and his colleagues reviewed procedure reports, pathology, and visit notes from 40 patients with Barrett esophagus who were treated with either RFA or cryotherapy at a community practice. The team specifically examined each patient's information regarding the number of treatments, length of the initial tongue, presence or absence of dysplasia and intestinal metaplasia, decrease in surface area, resolution of mucosal tongue, and Prague classification.

Of the 40 patients included in the review, 27 had been treated with RFA and 13 with cryotherapy. All 40 patients successfully lost dysplasia and surface area of the Barrett's epithelium. Findings are summarized in the **Table**. Of the 27 patients treated with RFA, 2 patients had very mild stenosis and there was 1 episode of vocal cord trauma related to anesthesia. Of the 13 patients treated with cryotherapy, 1 patient had a clinically significant GI bleed that required intervention.

**Table.** Comparison of Radiofrequency Ablation and Cryotherapy in Barrett Esophagus

| | RFA (n=27) | Cryotherapy (n=13) |
|---|---|---|
| Number of treatments needed | 3.3 | 3.15 |
| Starting length of Barrett esophagus | 4.48 cm | 3.15 cm |
| Loss of intestinal metaplasia (histologic evidence) | 12 (44.4%) | 6 (46.1%) |
| Resolution of mucosal tongue | 18 (66.7%) | 8 (61.5%) |

RFA, radiofrequency ablation.

Given the increasing incidence of esophageal adenocarcinoma, randomized prospective studies should be considered to further evaluate the effectiveness of the available treatment modalities.

## Endoscopy Confirmed Effective in Resolution of Barrett High-Grade Dysplasia

Patients with Barrett high-grade dysplasia (HGD) and intramucosal cancer (intramucosal cancer) have a number of endoscopic options: endoscopic mucosal resection (endoscopic mucosal resection), RFA, cryotherapy, and argon plasma coagulation (APC)/band ligation. Although these are highly effective for eradicating dysplasia in most patients, persons who are older and who do not receive RFA are more likely to have small areas of residual Barrett esophagus that can progress to HGD or cancer. RFA, with or without endoscopic mucosal resection, and younger age predict complete eradication of Barrett esophagus.

Prashanthi N. Thota of the Cleveland Clinic shared insights into predictors of response to endoscopy at the American College of Gastroenterology 2013 Annual Scientific Meeting (Abstract P3). Dr Thota and colleagues reviewed a prospectively collected database of patients who underwent endoscopic therapy for HGD or intramucosal cancer from 2006 to 2011. Patients who underwent endoscopic mucosal resection only were excluded. Variables such as age, race, gender, BMI, alcohol use, smoking, diabetes, hypertension, hyperlipidemia, and medication use were analyzed. Endoscopic data included length of the Barrett segment, hiatal hernia size, number of endoscopies, and biopsy results.

Among 118 patients reviewed, 60 patients had RFA and 58 had cryotherapy. There were differences between the groups. Compared with patients who had RFA, patients who had received cryotherapy were older and more likely to have never ingested alcohol; they also received more treatment sessions for a longer duration (Table). Patients with RFA were more likely to have complete eradication of dysplasia (100% vs 90%; $P$=.012). There were no other significant differences between the 2 groups.

Barrett HGD was completely eradicated in 72 (61%) patients, and was present without dysplasia in 40 (33.8 %) patients. In 6 (5%) patients, HGD persisted or progressed to cancer. Persons who had complete eradication of metaplasia were treated longer (months 32.8± 20 vs

23.3±18.8; *P*=.011) and had more follow-up (months 36.8±21.5 vs 25.9±18.7; *P*=.006). There were no other significant differences. After adjusting for all variables, patients who had RFA vs cryotherapy had a threefold higher chance that metaplasia would be eradicated (OR 2.9, 95% CI 1.1,7.7; *P*= .031). In addition, for every 1 month increase in the EGD follow-up time, the odds of complete metaplasia eradication (OR 1.04, 95% CI 1.01, 1.07; *P*= .002) increased by 4%. Younger age was positively associated with eradication of metaplasia/dysplasia (66.7± 10.6 vs 75.8±9.3 years; *P*=.042). Endoscopic mucosal resection and RFA were associated with eradication of metaplasia/dysplasia, while cryotherapy and APC/band ligation were less effective. These findings support the high efficacy of endoscopic therapy for eradicating Barrett HGD and intramucosal cancer.

## Addition of ROSE Unnecessary When Using EUS-FNB in the Diagnosis of Nonpancreatic Adenocarcinoma

Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is highly effective for detecting and evaluating pancreatic lesions and adenocarcinoma but offers poor diagnostic accuracy in nonpancreatic adenocarcinoma. Since histologic evaluation is often needed to fully assess nonpancreatic lesions, would it be possible to forgo EUS-FNA and rapid on-site cytology evaluation (ROSE) during the workup and only evaluate nonpancreatic lesions with EUS-fine needle biopsy (FNB) alone?

Rajesh N. Keswani and his colleagues at Northwestern University in Chicago, Illinois tackled this issue and presented their findings at the American College of Gastroenterology 2103 Annual Scientific Meeting (Abstract 31). They found that EUS-FNB without ROSE offers high diagnostic accuracy for evaluating lesions that are likely to require histologic evaluation. Adding EUS-FNA and ROSE to the workup consumed time and resources without improving diagnostic accuracy.

The investigation was a retrospective cohort analysis of persons who underwent EUS sampling of nonpancreatic adenocarcinomas over 28 months (February 2011 to May 2013) following the introduction of a new core biopsy needle (EchoTip ProCore, Cook Endoscopy, Winston-Salem, North Carolina). Lesions included lymphadenopathy or retroperitoneal/mediastinal mass (LRMM), subepithelial mass, non-adenocarcinoma pancreas, or gastrointestinal wall thickening. Two cohorts were compared: patients who had EUS-FNB without EUS-FNA or ROSE (EUS-FNB group) and patients who had EUS-FNA with ROSE and, if needed, EUS-FNB (EUS-FNA/B group). The primary study outcome was diagnostic accuracy, defined as the percentage of total cases where an accurate cytologic or histologic diagnosis was achieved. The secondary outcome was total procedure time.

**Table.** Diagnostic Accuracy of EUSFNB vs EUS-FNA/B,* %, range

| Criteria | EUS-FNB (n=43) | EUS-FNA/B (n=53) |
|---|---|---|
| Overall diagnostic accuracy | 83.7 (72.7-94.7) | 84.9 (75.3-94.5) |
| LRMM | 100 | 92.6 (85.6-99.7) |
| Subepithelial mass | 81.0 (69.2-92.7) | 70.6 (58.3-82.9) |
| Nonpancreatic lesions | 84.2 (73.3-95.1) | 84.4 (74.6-94.2) |

*95% confidence interval.

EUS-FNB, endoscopic ultrasound-guided fine-needle biopsy; EUS-FNA/B, endoscopic ultrasound-guided fine-needle aspiration + rapid on-site cytology±EUS-FNB; LRMM, lymphadenopathy or retroperitoneal/mediastinal mass.

The investigators examined a total of 96 lesions (43 EUS-FNB, 53 EUS-FNA/B). In the EUS-FNB cohort, subepithelial mass (48.8%) and LRMM (20.0%) were the first and second most common indications. In EUS-FNA/B group, LRMM (50.9%) and subepithelial mass (26.4%) were the first and second most common indications. Mean lesion size was similar between both groups (23.8 mm EUS-FNB, 27.6 mm EUS-FNA/B; *P*=.35). In the EUS-FNA/B group, a median of a 4 (±1.4) EUS-FNA passes were performed before either ending the procedure or performing EUS-FNB. In 9 (17%) patients, a diagnosis was obtained by EUS-FNA alone.

Results showed that overall diagnostic accuracy was similar between the EUS-FNB and EUS-FNA/B groups (83.7% vs 84.9%, *P*=NS) (**Table**). In the subgroup of subepithelial mass lesions, diagnostic accuracy remained similar in the EUS-FNB and EUS-FNA/B groups (81.0% vs 70.6%; *P*=.7). In cases involving only a single needle size, diagnostic accuracy was numerically greater with a 19-gauge needle (93.3%, n=15) compared with a 22- or 25-gauge needle (78.6%, n=14 and 71.4%, n=7, respectively). EUS-FNB procedures were significantly shorter than those in the EUS-FNA/B group (58.4 min vs 73.5 min, *P*<.0001). Considering these findings, EUS-FNB without ROSE may be the optimal technique for diagnosing lesions other than pancreatic adenocarcinoma.

# Presentations in Hepatology

## Novel Interferon- and Ribavirin-Free Regimen Results in SVR12 Rates of Over 90% in HCV Genotype 1b Infection

A novel interferon- and ribavirin-free regimen comprised of ABT-450, a protease inhibitor boosted by ritonavir, and ABT-267, an nonstructural 5A inhibitor, resulted in SVR12 in more than 90% of patients infected with genotype 1b hepatitis C virus (HCV), according to findings from an open-label phase 2 PEARL-1 study presented at both the American College of Gastroenterology 2013 Annual Scientific Meeting and the 64th annual meeting of the American Association for the Study of the Liver by Eric Lawitz founder of The Liver Institute of South Texas and Medical Director of the institute's affiliate, Alamo Medical Research (Abstract 75). The ongoing PEARL-1 trial was designed to investigate whether the combination of ABT-450 and ABT-267 can achieve high cure rates in patients with HCV genotype 1b infection. The findings reported by Dr Lawitz evaluated the safety and efficacy of the 2-drug regimen in 82 patients with HCV genotype 1b. Of these 82 patients included in the study, 42 were noncirrhotic, treatment-naive, and infected with HCV genotype 1b. The remaining 40 patients were infected with HCV genotype 1b and were null-responders to pegylated interferon/ribavirin therapy.

All patients received 12 weeks of treatment with ABT-450 (150 mg once daily), along with 100 mg of ritonavir to maintain high serum levels of ABT-450, plus ABT-267 (25 mg once daily). The primary outcome of the study was the proportion of patients achieving SVR12, while secondary outcomes included on-treatment virologic failure, posttreatment relapse, and SVR4. Safety analyses evaluated adverse events occurring in more than 10% of patients, serious adverse events, adverse events resulting in discontinuation or interruption of treatment, and clinically significant abnormal laboratory findings.

SVR12 was achieved in 36 (90%) of the null responders and 40 (95.2%) of the treatment-naive patients. SVR4 rates were 100% among treatment-naive patients and 88% among prior null responders. There were no virologic failures in the treatment-naive group, but 4 virologic failures occurred among null responders: 1 viral breakthrough during treatment, after an initial treatment response, and 3 posttreatment virologic relapses.

The treatment regimen was generally well tolerated, with no discontinuations related to adverse events or laboratory abnormalities. However, 2 patients were lost to follow-up and another 2 temporarily interrupted the study drug due to adverse events.

On the basis of these results, Dr Lawitz concluded that ABT-450, boosted by ritonavir, plus ABT-267 for 12 weeks was generally well tolerated and provided high response rates in treatment-naive patients and prior null responders infected with HCV genotype 1b.

## Studies Confirm Efficacy of Simeprevir in Difficult-to-Treat HCV Genotype 1 Subpopulations

The efficacy of simeprevir, which was approved for use in combination with pegylated interferon and ribavirin in November 2013, was confirmed in a number of trials presented at the 64th annual meeting of the American Association for the Study of the Liver. Included were results of the phase 3 PROMISE study of prior relapsers and the phase 3 QUEST-1 and QUEST-2 trials of treatment-naive patients with genotype 1 HCV infection.

The PROMISE study evaluated simeprevir plus pegylated interferon and ribavirin in patients infected with HCV genotype 1 who previously experienced a relapse after prior treatment with pegylated interferon-based therapy. The analysis, presented by Xavier Forns, of the Liver Unit of the Hospital Clinic of Barcelona in Spain, focused on safety and efficacy outcomes in difficult-to-cure patient subgroups, such as those with the IL28B TT genotype, a METAVIR score of F4, or HCV genotype 1a with baseline Q80K polymorphism (Abstract 1092).

A total of 394 patients who had received interferon-based therapy for at least 24 weeks and relapsed within 1 year were randomly assigned in a 2:1 ratio to receive simeprevir (150 mg QD) or placebo, in addition to pegylated interferon plus ribavirin, for 12 weeks. Patients in the control group continued to receive pegylated interferon plus ribavirin for an additional 36 weeks, while patients in the experimental group received pegylated interferon plus ribavirin for an additional 12 or 36 weeks, depending on response.

SVR12 was achieved in 65% of patients with the IL28B TT genotype, 74% of patients with a METAVIR score of F4, and 70% of patients with genotype 1a HCV who were treated with simeprevir plus pegylated interferon and ribavirin compared with 19%, 26%, and 28% of patients, respectively, who were taking placebo plus pegylated interferon and ribavirin. Among patients with the genotype 1a Q80K polymorphism at baseline, 47% of patients treated with simeprevir plus pegylated interferon and ribavirin

achieved SVR12, compared with 30% of patients treated with placebo plus pegylated interferon and ribavirin.

Findings of the QUEST-1 and QUEST-2 trials were reported during a poster session by Ira M. Jacobson, MD, of the Weill Cornell Medical College in New York City (Abstract 1122). In QUEST-1, simeprevir 150 mg once daily plus peginterferon/ribavirin (n=264) was compared with placebo plus peginterferon/ribavirin (n=130) in treatment-naive patients with HCV genotype 1 infection. Patients received simeprevir or placebo for the first 12 weeks of peginterferon/ribavirin therapy. In the QUEST-2 trial, patients were randomly assigned in a 2:1 ratio to receive either simeprevir 150 mg once daily plus peginterferon (alpha-2a or alpha-2b) for 12 weeks followed by peginterferon/ribavirin alone for 12 weeks or placebo plus peginterferon (alpha-2a or alpha-2b) and ribavirin for 12 weeks followed by peginterferon/ribavirin alone for an additional 36 weeks. In both trials, the treatment duration was 24 weeks for patients in the simeprevir arm who had an HCV RNA load of less than 25 IU/mL at Week 4 and an undetectable HCV RNA load at Week 12. Treatment duration was 48 weeks in all other patients.

Eighty percent of treatment-naive patients given simeprevir in combination with pegylated interferon and ribavirin in both QUEST-1 and QUEST-2 achieved the primary endpoint of SVR12 compared with 50% of patients treated with placebo plus pegylated interferon and ribavirin. The analysis, which included patients considered difficult to treat, found that 61% of patients who had the IL28B TT genotype, 60% of patients with a METAVIR score of F4, and 75% of patients infected with genotype 1a HCV treated with simeprevir combined with pegylated interferon and ribavirin achieved SVR12 compared with 21%, 34%, and 47% of patients taking placebo plus pegylated interferon and ribavirin, respectively. Among patients with the genotype 1a Q80K polymorphism at baseline, 58% of patients treated with simeprevir combined with pegylated interferon and ribavirin achieved SVR12 compared with 52% of patients treated with placebo in combination with pegylated interferon and ribavirin, but the difference was not statistically significant.

## Study Confirms Utility of Transient Elastography in Diagnosing Cirrhosis

Transient elastography (FibroScan), a noninvasive tool for measuring liver stiffness in patients with hepatic fibrosis, greatly enhances clinical assessment of liver cirrhosis, reported Naveen Gara, of the Georgetown University Washington Hospital Center Liver Diseases Branch of the National Institute of Health in Washington DC. The results of the study, presented at the 64th annual meeting of the American Association for the Study of the Liver, confirm the usefulness of transient elastography in the diagnosis of cirrhosis in patients with chronic liver disease (Abstract 1461).

The degree of hepatic fibrosis correlates with disease severity in patients with chronic HCV infection and is directly related to the outcome of the disease. Although liver biopsy is considered the gold standard for assessing fibrosis, it is invasive. Dr Gara and colleagues' study evaluated the usefulness of transient elastography as an adjunct to clinical judgment in the assessment of liver fibrosis.

The study compared the accuracy of clinical acumen, with or without the use of transient elastography, with liver biopsy to determine fibrosis stage. Over a period of 18 months, a total of 98 consecutive patients with chronic HCV infection who were scheduled to undergo liver biopsy were enrolled. The mean age of the patients was 54 years. Fifty-six percent of the patients were male, 56% were white, and 72% were infected with HCV genotype 1.

Each patient was interviewed and examined independently by a junior and senior hepatologist who made an assessment of fibrosis severity as 0 (mild, Ishak 0-2), 1 (moderate, Ishak 3-4), or 2 (severe, Ishak 5-6). Transient elastography was then performed with the examiners being blinded to each other's results. The initial estimate of liver fibrosis could then be revised, based on the results. At the end of the study, all clinical and laboratory data were given to an expert hepatologist for assessment of liver fibrosis as 0, 1, or 2. The expert hepatologist was then given the transient elastography scores from both examiners and asked to reassess fibrosis stage.

Eighty-four patients were included in the final analysis; 14 were excluded due to cancelled biopsy, failed transient elastography examination, or both. On initial clinical assessment, the kappa coefficient between the junior hepatologist and biopsy stage was 0.48, which improved to 0.62 after transient elastography. Results for the senior hepatologist were 0.61 before and 0.58 after transient elastography. The initial kappa for the reviewing hepatologist was 0.53, which improved to 0.63 after transient elastography. Diagnosis of cirrhosis was correct by clinical assessment in 73% to 82% of cases and 91% to 100% after transient elastography.

Transient elastography correctly identified all cases of cirrhosis, and interoperator correlation for transient elastography was 0.85, reported Dr Gara. Although clinical assessment of cirrhosis was excellent, it varied according to the level of experience of the examining physician.

## Sofosbuvir plus Ribavirin Yields 90% Sustained Viral Response Rate in Treatment-Naive Patients with Genotype 3 HCV Infection

A 24-week course of ribavirin plus sofosbuvir resulted in a sustained viral response at 12 weeks (SVR12) in over 90%

of treatment-naive patients with genotype 3 HCV infection treated in the phase 3 VALENCE trial. The dual regimen of sofosbuvir and ribavirin also yielded high SVR rates in treatment-experienced patients with genotype 3 HCV without cirrhosis and in patients with genotype 2 HCV after 12 weeks of treatment. The findings were reported at the 64th annual meeting of the American Association for the Study of the Liver.

To assess the safety and efficacy of sofosbuvir plus ribavirin administered for 12 or 24 weeks, Stefan Zeuzem, MD, of the Department of Medicine at Johann Wolfgang Goethe University, Frankfurt, Germany, and colleagues conducted a randomized controlled trial at a number of centers throughout Europe (Abstract 1085). In the initial study, over 300 treatment-naive or treatment-experienced patients infected with HCV genotype 2 or 3 were randomized in a 4:1 ratio to receive sofosbuvir (400 mg/day) plus ribavirin (1000 or 1200 mg/day) or placebo for 12 weeks. The trial was subsequently amended to extend treatment duration to 24 weeks for patients with hard-to-treat genotype 3 infection because emerging data suggested that a longer treatment course might be of benefit.

Of the 419 patients included in the analysis, 73 were infected with genotype 2 HCV, 261 with genotype 3 HCV (including 11 treated for 12 weeks before the protocol change), and 85 patients with genotype 2 or genotype 3 HCV who received placebo before the protocol change. About 60% of the participants were men, and the median age of the study participants was 60 years. About one-third of the patients had the favorable IL28B CC gene variant and about 20% had liver cirrhosis. Approximately 60% of the participants had been treated previously for HCV but were either null responders or prior relapsers.

A high percentage of patients responded to treatment in both arms; SVR12 was achieved after 12 weeks of treatment in 68 (93%) of the 73 patients infected with genotype 2 HCV. Of 250 patients with genotype 3 HCV, 212 (85%) obtained SVR12 following 24 weeks of treatment. Patients with genotype 2 HCV infection had high response rates with 12 weeks of sofosbuvir/ribavirin regardless of previous treatment or cirrhosis status. SVR12 rates were 97% for treatment-naive patients without cirrhosis, 100% for treatment-naive patients with cirrhosis, 91% for treatment-experienced patients without cirrhosis, and 88% for treatment-experienced patients with cirrhosis.

Results were somewhat less impressive for patients infected with genotype 3 HCV. However, high SVR12 rates (92% and 94% for patients with and without cirrhosis, respectively) were achieved in treatment-naive patients. These rates fell to 87% for treatment-experienced patients without cirrhosis and 60% for treatment-experienced cirrhotic patients.

These findings added weight to the approval of sofosbuvir plus ribavirin for the treatment of genotype 2 (12 weeks treatment) and genotype 3 (24 weeks of treatment) HCV infection, which occurred this past December 2013. Sofosbuvir in combination with ribavirin and peginterferon alpha also was approved for treatment of genotype 1 HCV at this time.

## Entecavir/Tenofovir Combination Therapy Offers Promise to Patients with Chronic HBV Infection

Adults with chronic hepatitis B virus (CHB) infection face a lifetime of illness that, if untreated, usually progresses to cirrhosis and ends in liver cancer. The goal of treatment for this group is to suppress hepatitis B virus (HBV) replication and protect the liver so patients are spared these outcomes. For most patients, monotherapy is insufficient to eradicate infection. Combination therapy with potent antivirals, however, may provide greater benefit. A Polish study showed that the combination of entecavir and tenofovir disoproxil fumarate (tenofovir) produced virologic response in approximately 75% of patients who had failed prior nucleos(t)ide monotherapy for CHB. No treatment-emergent resistance was observed, and the regimen was well tolerated. Maciej Jablkowski of the Medical University of Lodz in Lodz, Poland, presented these findings during a post session at the 64th annual meeting of the American Association for the Study of the Liver (Abstract 1044).

The study was a phase 3 single-arm, open-label, multicenter evaluation of the efficacy and safety of entecavir and tenofovir combination therapy in 92 patients with CHB who had failed previous treatment with nucleos(t)ide (including lamuvidine) monotherapy. Patients received at least 1 dose of once-daily entecavir, 1 mg, plus tenofovir, 300 mg, for up to 96 weeks, with 24-week follow-up. The primary end point was the proportion of patients with a virologic response (HBV DNA <50 IU/mL) at Week 48. Noncompleters were considered treatment failures. Secondary endpoints included loss and seroconversion of hepatitis B e antigen (HBeAg) and hepatitis B surface antigen (HBsAg), and emergence of resistance mutations during treatment. The investigators performed cumulative assessments of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs).

At week 48, virologic response was achieved by 17 (85%) of 20 patients who previously failed lamuvidine, 37 (77%) of 48 those who previously failed entecavir, and 6 (55%) of 11 patients who previously failed tenofovir. There was no genotypic evidence of treatment-emergent resistance. Twenty-seven patients (29%) experienced at least 1 TEAE, all of which were grade 1/2. Of these, fatigue (10%) and nausea (9%) were most common.

Three patients (3%) experienced 5 SAEs; none were considered related to study treatment. The combination of entecavir and tenofovir was well tolerated.

The combination of potent antivirals with nonoverlapping resistance profiles, such as entecavir and tenofovir, may provide superior antiviral efficacy compared with single agents for the treatment of CHB. More information will unfold as this study continues and additional safety and efficacy analyses are completed.

## Hepatitis B Virus Nonimmunity Prevalent in Children with NAFLD

Obesity is well known to contribute to such high-profile disorders as diabetes and heart disease. Less well known is the connection between obesity and poor serologic response to HBV vaccination. Most children with nonalcoholic fatty liver disease (NAFLD) are obese and are insufficiently immunized against HBV following routine pediatric vaccination, according to Minesh Mehta of the University of Cincinnati in Ohio, who presented findings at the 64th annual meeting of the American Association for the Study of the Liver (Abstract 1228).

Dr Mehta and colleagues retrospectively analyzed clinical data from children with NAFLD, ages 6 to 18 years, who had been prospectively enrolled in an institutional review board-approved pediatric NAFLD registry. Criteria for registry enrollment were chronically elevated liver enzymes and negative exclusionary testing for other causes of steatohepatitis. The team specifically reviewed the database for laboratory data supporting the presence of both HBV surface antibodies (HBsAb) and HBV surface antigen (HBsAg). Children who lacked HBsAb in the setting of negative HBsAg were categorized as hepatitis B nonimmune.

Results of this research showed that 96 (48%) of 200 children had no documented HBsAb serology. Of the 104 subjects with documented HBsAb status, only 29 (28%) had positive HBsAb serology. The remaining 75 children—72%—were HBV-nonimmune. Thus, HBV nonimmunity was prevalent, despite that the participating patients had been treated according to existing guidelines for universal pediatric HBV vaccination.

The findings could be attributed to either an incomplete vaccination series or a diminished immunogenic response to HBV vaccination in the setting of NAFLD, reported Dr Mehta. She and colleagues propose that children with NAFLD should be screened comprehensively for HBV immunogenicity as well as infection. Those who are insufficiently immunized could then receive catch-up or booster vaccinations.

## Nucleos(t)ide Analogs Expand Therapeutic Options for Patients with HBV Infection Posttransplant

For patients with CHB, orthotopic liver transplant (OLT) can interrupt the progression to cirrhosis and liver failure. However, it is by no means a panacea: without HBV prophylaxis or treatment, 75% to 80% of transplant recipients will experience recurrent aggressive HBV infection that threatens survival of both the graft and the patient. Hepatitis B immune globulin (HBIg) in combination with a nucleos(t)ide analog (NS/NT) is an HBV infection prophylactic mainstay for patients requiring OLT. Treatment with HBIg, however, is costly and cumbersome. New evidence supports the efficacy of an alternative option: combination therapy with 2 NS/NT analogs. Study details on this were reported at the 64th annual meeting of the American Association for the Study of the Liver by Saro Khemichian of the University of Southern California in Los Angeles (Abstract 1748). Dr Khemichian and investigators followed 20 patients with CHB who underwent OLT over a 10-year period (from March 2001 until July 2011). Nineteen patients were Asian and 1 was white; 15 were male and 5 were female. The mean age of the patients at the time of treatment conversion was 56.2 years.

All patients received at least 12 months of HBIg and a single NS or NT. Between 12 and 132 months (average, 75.7 months) after OLT, HBIg was discontinued and a second NS or NT was added to the regimen, leaving each patient on NS/NT combination prophylaxis. Every 3 months during combination therapy, patients had HBV DNA and HBsAg assessments. Patients were followed for an average of 17.9 (range 4 to 52) months.

At the time of treatment conversion, all patients had undetectable levels of HBsAg and HBV DNA, but detectable levels of hepatitis B surface antibody (anti-HBs). During follow-up, 19 patients remained negative for HBsAg and HBV DNA. One study participant, who converted to tenofovir once weekly plus reduced-dose lamivudine 125 months after OLT, experienced recurrence. The patient's levels of HBsAg were detectable 7 months postrecurrence, but HBV DNA remained undetectable, and levels of alanine transaminase were normal. This patient had chronic renal failure and required dialysis. In all other study participants, renal function remained unchanged.

These results suggest that combination therapy with NS/NT is a safe and effective alternative to regimens involving HBIg for persons infected with HBV. More studies of NS/NT combination therapy may further support this intervention as a viable option in patients infected with HBV.

# Brief Summary about BreathTek UBT

**Intended Use**

The BreathTek® UBT for *H. pylori* Kit (BreathTek UBT Kit) is intended for use in the qualitative detection of urease associated with *H. pylori* in the human stomach and is indicated as an aid in the initial diagnosis and post-treatment monitoring of *H. pylori* infection in adult patients. The test may be used for monitoring treatment if used at least 4 weeks following completion of therapy. For these purposes, the system utilizes an Infrared Spectrophotometer for the measurement of the ratio of $^{13}CO_2$ to $^{12}CO_2$ in breath samples, in clinical laboratories or point-of-care settings.

The BreathTek UBT Kit is for administration by a health care professional, as prescribed by a physician.

**Warnings and Precautions**

- For in vitro diagnostic use only. The Pranactin®-Citric solution is taken orally as part of the diagnostic procedure and contains Phenylalanine (one of the protein components of Aspartame), 84 mg per dosage unit, and should be used with caution in diabetic patients. (For reference, 12 ounces of typical diet cola soft drinks contain approximately 80 mg of Phenylalanine.)
- A negative result does not rule out the possibility of *H. pylori* infection. False negative results do occur with this procedure. If clinical signs are suggestive of *H. pylori* infection, retest with a new sample or an alternate method.
- False negative test results may be caused by:
  - — Ingestion of proton pump inhibitors (PPIs) within 2 weeks prior to performing the BreathTek UBT. If a negative result is obtained from a patient ingesting a PPI within 2 weeks prior to the BreathTek UBT, it may be a false-negative result and the test should be repeated 2 weeks after discontinuing the PPI treatment. A positive result for a patient on a PPI could be considered positive and be acted upon.
  - — Ingestion of antimicrobials, or bismuth preparations within 2 weeks prior to performing the BreathTek UBT
  - — Premature POST-DOSE breath collection time for a patient with a marginally positive BreathTek UBT result
  - — Post-treatment assessment with the BreathTek UBT less than 4 weeks after completion of treatment for the eradication of *H. pylori*.
- False positive test results may be caused by urease associated with other gastric spiral organisms observed in humans such as *Helicobacter heilmannii* or achlorhydria.
- If particulate matter is visible in the reconstituted Pranactin-Citric solution after thorough mixing, the solution should not be used.
- Patients who are hypersensitive to mannitol, citric acid or Aspartame should avoid taking the drug solution as this drug solution contains these ingredients. Use with caution in patients with difficulty swallowing or who may be at high risk of aspiration due to medical or physical conditions.
- No information is available on use of the Pranactin-Citric solution during pregnancy.

**Adverse Events**

During post-approval use of the BreathTek UBT, the following adverse events have been identified: anaphylactic reaction, hypersensitivity, rash, burning sensation in the stomach, tingling in the skin, vomiting and diarrhea. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to establish a causal relationship to drug exposure.

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Otsuka
Medical Device Division of
Otsuka America Pharmaceutical, Inc.

Urea Breath Test for *H. pylori*
BreathTek®



April 2014 05US14EBP0143

# *H. pylori*
# Easy to find. Hard to kill.

## Antibiotic resistance is approaching 25%, increasing the need for eradication confirmation[1]

The prevalence of *H. pylori* in the United States is estimated between 30% to 40%.[2] Americans born outside the country and those over the age of 50 have an even higher prevalence of *H. pylori* (60% and 50%, respectively).[3,4]

While *H. pylori* is relatively easy to find, it can be difficult to eradicate. As many as 1 in 4 patients fail *H. pylori* eradication therapy.[5,6] In addition, a number of controlled trials indicate significant resistance of *H. pylori* to antibiotics in triple therapy.[1] The data suggest that *H. pylori* resistance is on the rise.[1]

BreathTek® UBT for *H. pylori* is an easy and convenient test to confirm *H. pylori* eradication. BreathTek UBT offers excellent sensitivity (96%) and specificity (96%) in adult patients.[7] BreathTek UBT is a patient-friendly option that may increase compliance. Urea breath test (UBT) methods are recommended by the American College of Gastroenterology over stool testing to confirm *H. pylori* eradication.[1,2,8,9]

Please see BRIEF SUMMARY on adjacent page or visit www.breathtek.com

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**Visit booth 2919 to experience the testing option convenience of BreathTek UBT during Digestive Disease Week, May 3-6.**

Urea Breath Test for *H. pylori*

BreathTek®