New EoE Guidelines Provide Insights

BY MICHELE G. SULLIVAN
Elsevier Global Medical News

New clinical guidelines for eosinophilic esophagitis characterize the disorder as a chronic immune- and antigen-mediated disease.

The updated consensus recommendations, which constitute the first update since 2007, also suggest that eosinophilic esophagitis (EoE) is truly only on the rise in both adults and children, although no one really knows why, according to Dr. Chris Liacouras, first author of the paper. The guidelines also suggest for the first time that the disease may have a genetic underpinning – an abnormality in chromosome 5.

In addition to a genetic predisposition, an increase in food allergies may be at the root of the growing incidence, Dr. Liacouras said in an interview. “This disease is exploding, and many of us believe that foods are responsible but we don’t know exactly how,” said Dr. Liacouras, professor of pediatrics at the University of Pennsylvania, Philadelphia, and codirector of the Center for Pediatric Eosinophilic Disorders at the Children’s Hospital of Philadelphia. “In the 1950s and 60s, we were pretty much eating the same kinds of foods that we do today, and the genetics were there, although still unknown. There is something different going on – maybe something in the way foods are processed,” although there are no data yet to support that theory.

Of course, he added, physicians are also “getting better at looking for EoE and identifying it when we see it.”

The paper, published in the Journal of Allergy and Clinical Immunology, combines the diagnostic, treatment, and research recommendations of 33 pediatric and adult gastroenterologists, immunologists, and allergists (J. Allergy Clin. Immunol. 2011;128:3-20.e6). “The big thing that we are excited about is that this is one of the critical advances in how we treat this disease,” Dr. Liacouras said.

See Guidelines • page 30

Colonoscopy Screening Interval Often Too Short

Repeat exam done before 7 years in 46%.

BY JANE ANDERSON
Elsevier Global Medical News

Nearly half of all Medicare beneficiaries undergo screening colonoscopies more frequently than current guidelines recommend, a large study has found. And another study on colorectal cancer screening showed that clinicians could better target use of the fecal occult blood test.

Together, those findings published in the Archives of Internal Medicine suggest that “there is much room for improvement in the way we measure proper utilization of screening colonoscopy, ensure adequate follow-up, and evaluate net benefit among those who screen positive,” Dr. Patrick G. O’Malley, chief of internal medicine at Walter Reed Army Medical Center, Washington, noted in an accompanying editorial (Arch. Intern. Med. 2011 [doi:10.1001/archinternmed.2011.198]).

See Colonoscopy • page 16

Irradiation Effective in Gastric Lymphoma

BY SARA FREEMAN
Elsevier Global Medical News

LONDON – Low-dose irradiation of the stomach in patients with gastric MALT lymphoma absent or independent of infection by Helicobacter pylori is associated with a 93% disease control rate after 10 years. Presented by Dr. Joachim Yahalom, a radiation oncologist at Memorial Sloan-Kettering Cancer Center in New York, these long-term study findings highlight the high disease-control rates that can be obtained using low-dose involved field radiotherapy (IFRT).

Low-dose IFRT has now become a standard of care in the United States, although approaches still vary in Europe, he reported at the European Society for Therapeutic Radiation Oncology Anniversary Conference. The latest guidelines set by the National Comprehensive Cancer Network on non-Hodgkin’s lymphomas—which includes gastric MALT (mucosa-associated lymphoid tissue) lymphoma—recommend

See Irradiation • page 30
EDITORIAL

Reflections on the First 5 Years Of GI & Hepatology News

Our content is accurate, fair, and fresh, based on recent scientific presentations and publications.

Senior journalists and editors frequently refer to three great principles in providing news: be accurate, be fair, and be open minded. As the first Editor-in-Chief of GI & Hepatology News, I have tried to honor these principles, beginning with our inaugural issue in January 2007.

I quickly learned that monthly publication of GI & Hepatology News, the official newspaper of the AGA Institute, was more of a complex business than I imagined when I took the helm in the winter of 2006. I have had to make thousands of decisions in choosing the content of the newspaper since that time, and I sent many more thousands of emails in the process, but those three principles have been remarkably reliable beacons.

Now, as my 5-year term comes to an end, this issue of the newspaper will be the last one under my full stewardship. For me, this has been a wonderful experience. From readership surveys and from many personal communications, I am extremely pleased to know that GI & Hepatology News is widely read, often front page to back, by AGA members and the general community of gastroenterologists and hepatologists around the world.

In this digital age, information rains down upon us in torrents, often raw, biased, and – relevant to our specialty – indigestible. The concept we fostered is a monthly newspaper with content that is fresh, based on recent scientific presentations and publications. Stories are reviewed for accuracy by the editorial staff and by the speakers and authors involved. The facts are then vetted by our Editorial Board, supplemented as needed by experts from the AGA. Associate Editors and expert consultants often provide commentary and perspective, which gives stories balance and highlights their importance.

Most newspaper readers look at front page stories first, so I put particular effort into deciding which stories to place on the front page, and hope readers will be enticed to look further inside.

In addition to news stories with expert commentaries and editorials, we have added features aimed at practicing clinicians, including “Clinical Challenges and Images” from Gastroenterology, and “Practice Management Toolbox” adapted from Clinical Gastroenterology and Hepatology. Expanded DDW coverage has included summaries submitted by session moderators of the AGA Postgraduate Course, and from AGA President-Elect Plenary Session speakers.

While many readers are forward to receiving the monthly print copy of GI & Hepatology News. The newspaper nowadays depends completely on print distribution. Thus an interactive digital version of the newspaper is available on the AGA website (www.gastro.org/gihepnews), and we have recently added video links to some stories.

Advertisements are the economic lifeblood of newspapers, and I am very happy to state that our ad sales have been strong. However, we remain intent on avoiding commercial bias in our pages. I believe this rigid rule is another feature of our success, which sets us apart, and is recognized by our readers as an important aspect of our content.

IN THIS DIGITAL AGE, INFORMATION RAINS DOWN UPON US IN TORRENTS, OFTEN RAW, BIASED, AND – RELEVANT TO OUR SPECIALTY – INDIGESTIBLE.

I have many to thank, starting with my incredibly strong, extraordinary Associate Editors: Maria T. Abreu, M.D., AGAF; David A. Brenner, M.D.; Robert S. Brown Jr., M.D., M.P.H., AGAF; Douglas K. Rex, M.D., AGAF, Stuart J. Spechler, M.D., AGAF, and Timothy C. Wang, M.D., AGAF.

I am also grateful to the Editors of Gastroenterology, Anil K. Rustgi, M.D., AGAF, and his successor M. Bishr Omary, M.D., Ph.D., and the Editor of Clinical Gastroenterology and Hepatology, C. Mel Wilcox, M.D., for supplying summaries of key stories from their current publications with editorial commentaries. My unbounded gratitude to the AGA Institute Staff: particularly Managing Editor Brook A. Simpson for her never-ending ability to manage an ever-increasing number of items. She is absolutely thrilled that the new Editor-in-Chief will be Colin W. Howden, M.D., AGAF.

Dr. Howden has been a regular expert reviewer for stories in GI & Hepatology News, and has provided several superb editorials and commentaries. He has assembled a remarkable Board of Editors, and has the vision and editorial skills to lead the newspaper to new heights. It will be my great pleasure to assist in a smooth transition.

—-Charles J. Lightdale, M.D., AGAF, is Professor of Clinical Medicine at Columbia University College of Physicians and Surgeons, New York, and Director of Clinical Research in the Division of Digestive and Liver Disease, Department of Medicine, New York Presbyterian Hospital/Columbia University Medical Center.

GI & Hepatology News
GI & Hepatology News is the official newspaper of the American Gastroenterological Association (AGA) Institute and provides the gastroenterologist with timely and relevant news and commentary about clinical developments and about the impact of health care policy and content. For information about GI & Hepatology News, please call 973-290-8245 or e-mail change@elsevier.com.

AGA Institute News Group
AGA Institute News Group is a division of International Medical News Group, Inc., 973-290-8200, AGAinstitute@elsevier.com.
SUPREP® BOWEL PREP KIT
(sodium sulfate, potassium sulfate and magnesium sulfate)
Oral Solution
(17.5g/3.13g/1.6g) per 6 ounces

Important Safety Information
SUPREP® Bowel Prep Kit is an osmotic laxative indicated for cleansing of the colon as a preparation for colonoscopy in adults. Most common adverse reactions (>2%) are overall discomfort, abdominal distention, abdominal pain, nausea, vomiting and headache.

Use is contraindicated in the following conditions: gastrointestinal (GI) obstruction, bowel perforation, toxic colitis and toxic megacolon, gastric retention, ileus, known allergies to components of the kit. Use caution when prescribing for patients with a history of seizures, arrhythmias, impaired gag reflex, regurgitation or aspiration, severe active ulcerative colitis, impaired renal function or patients taking medications that may affect renal function or electrolytes. Use can cause temporary elevations in uric acid. Uric acid fluctuations in patients with gout may precipitate an acute flare. Administration of osmotic laxative products may produce mucosal aphthous ulcerations, and there have been reports of more serious cases of ischemic colitis requiring hospitalization. Patients with impaired water handling who experience severe vomiting should be closely monitored including measurement of electrolytes. Advise all patients to hydrate adequately before, during, and after use. Each bottle must be diluted with water to a final volume of 16 ounces and ingestion of additional water as recommended is important to patient tolerance.

Please see brief summary of Prescribing Information on adjacent page.
Study Supports Link Between PPI Use and Hip Fracture

BY CAROLINE HELWICK
Elsevier Global Medical News

CHICAGO – Regular use of proton pump inhibitors is associated with an elevated risk of hip fracture, even after adjustment for important lifestyle factors, according to the findings of a prospective evaluation from the Nurses’ Health Study.

The association was most striking for women with a history of smoking, observed Dr. Hamed Khalili of Massachusetts General Hospital, Boston.

The Food and Drug Association recently issued an advisory regarding a potential link between PPIs and fractures. While acid-suppressing medications have been hypothesized to increase the risk of osteoporotic fractures, studies examining this association have not been consistent. Most of these analyses have been based on retrospective studies of small populations and have not controlled for important dietary and lifestyle confounders, and they have ascertained PPI use only at a single time point, Dr. Khalili said.

The current study aimed to collect more definitive data by prospectively examining the relationship between chronic PPI use and incident hip fracture among 79,899 postmenopausal women enrolled in the Nurses’ Health Study. Dr. Khalili explained at the annual Digestive Disease Week.

“We found that longer duration of use was associated with increased risk, and the strongest risk was confined to individuals with a history of smoking. … Our findings support the recent decision of the FDA to revise labeling of PPIs to incorporate concerns about a possible increase in the risk of fractures,” Dr. Khalili said.

In 1982, participants in the Nurses’ Health Study were first asked to report all previous fractures and were queried biennially about new fractures. Among the nearly 80,000 subjects with 565,786 person-years of follow-up, there were 893 incident hip fractures over 8 years. PPI use was reported by 7% of participants in 2000 and by 19% of participants in 2008.

Regular use of PPIs was associated with increases in fracture risk of 35%-45% when adjusted for age, calcium intake, and body mass index. The fully adjusted hazard ratio was 1.37, Dr. Khalili reported.

Current smoking status stood out as a significant effect modifier. Women who were current or past smokers and who regularly took a PPI had a 51% increased risk for fracture. In contrast, women who never smoked had only a 6% increased risk, “almost equal to women who never used PPIs,” he noted.

Longer duration of PPI use was associated with greater risk. Compared with never-users, those with 2 years of use had an increase in risk of 36% in the multivariate analysis. The increase was 42% after 4 years of use and 54% when PPIs were used for 6 years or longer (P less than 0.001), he said.

The investigators adjusted for multiple other risk factors, including physical activity, alcohol intake, total daily calcium and vitamin D intake, history of osteoporosis, and use of hormone replacement therapy, bisphosphonates, and thiazides. “This did not materially alter this association,” he noted.

When PPIs were discontinued, the risks declined. Two or more years after discontinuation, the increase in risk of hip fracture was just 9%-10%, he noted.

“The strengths of our study are that it offers detailed, prospectively collected and validated information on PPI use and other risk factors. We had a high response rate, and the participants are educated health professionals,” he said.

But the study lacks information about PPI use prior to 2000, and it lacks specific information about brand and dose of PPI. “It’s not clear whether this is generalizable to other populations.”

The study, however, is in line with other reports of an association, and adds weight to the recommendation that clinicians carefully monitor the need for postmenopausal women to continue long-term on PPIs, especially among those who smoke.

Response from the audience was robust, with one attendee noting, “This is truly excellent work,” and another calling the study “impressive.”

Dr. Khalili reported having no relevant conflicts of interest.
COMMENTARY

Another Bad Break for the PPIs?

The possible association between proton pump inhibitor use and an increased risk of certain fractures (most notably, of the hip) remains controversial. Evidence linking PPI use with fractures has largely come from retrospective, observational studies that have generally reported low levels of risk. These do not, therefore, prove a causal association and should be considered hypothesis-generating.

There have been some inconsistent findings among previous studies on this topic; notably, some studies failed to demonstrate a duration-response effect. In other words, they did not find that prolonged PPI use conveyed a greater risk of fracture than short-term use.

Furthermore, the U.S.-based study by Dr. Corley and colleagues suggested that the risk related to PPI use was only apparent in patients who had other identifiable risk factors for fracture.

A recent, high-quality meta-analysis of observational studies reported a pooled odds ratio of 1.23 (95% confidence interval, 1.14 to 1.31) for hip fracture in association with PPI use – also with no evidence for a duration-response effect.

The 23% increase in risk in the meta-analysis is similar to that reported by Dr. Khalili and colleagues at DDW 2011 (see accompanying article on page 4). In their study of female nurses who were followed prospectively, they reported an adjusted, multivariate hazard ratio (HR) of 1.36 (95% CI, 1.13 to 1.63). Intriguingly, the hazard ratio was only statistically significant among women with a history of smoking (HR 1.51; 95% CI, 1.20 to 1.91). No significant risk was apparent among women who had never smoked (HR 1.06; 95% CI, 0.77 to 1.46).

Since smoking has been linked to osteoporosis, the recent findings of Khalili et al. are consistent with those of Corley et al.; thus PPIs may only be a risk factor for fracture among patients who are already at increased risk.

We should always review the indication(s) for the continued use of medicines, including PPIs, and particularly in our older patients. PPI use should be discontinued in those with no identifiable need for it.

However, the benefits of PPI treatment greatly outweigh the theoretical risks in our patients who have a valid indication. In those patients, the PPI should be given in the lowest effective dose and only continued for as long as the requirement exists. (The same is, of course, true for all medicines.)

The AGA Technical Review on GERD has concluded that PPI treatment per se does not necessitate any extraordinary measures regarding bone mineral density monitoring and calcium and vitamin D supplementation.

References

Medication Adherence Abysmal in Pediatric IBD

BY PATRICE WENDLING
Elsevier Global Medical News

Adherence to oral inflammatory bowel disease medications is very low in children ages 8-18 years, a new study has shown.

The study of 80 patients with inflammatory bowel disease (IBD) found that 26%-12% of patients were taking less than one-third of their prescribed medications and that just one-third of patients were taking their medications 80% of the time, a standard measure of adherence, lead author Dr. Neal LeLeiko said at the annual Digestive Disease Week.

Although adherence was cut almost in half among older adolescents, it was particularly striking that younger children, for whom adults are presumably controlling the distribution of medications, only got their medications 66% of the time.

The clinical implications of these findings about treatment management are profound, as clinicians may attribute flares to either worsening disease or poor treatment response, rather than to missed medications, said Dr. LeLeiko, director of pediatric gastroenterology, nutrition and liver diseases at Hasbro Children’s Hospital and professor of medicine at Brown University in Providence, R.I.

“Clinical correlations suggest a significant potential for alterations in treatment to be based on substantially incorrect impressions of current therapy,” he said.

Dr. LeLeiko and his colleagues used electronic pill caps (TrackCap), pill counts, pharmacy renewal records, and serum levels to evaluate adherence in 40 patients with newly diagnosed IBD and 40 patients with previously diagnosed IBD. Emotional and behavioral functions were measured using the Children’s Depression Inventory (CDI), Child Behavior Checklist (CBCL), and Perceived Stress Scale. Participants were also required to be co-enrolled in an active pediatric biological IBD registry.

The investigators defined adherence as opening the computerized TrackCap the number of times expected based on the prescription documented in the patient medical record, which Dr. LeLeiko acknowledges does not guarantee that the patient actually took the medicine.

Adherence rates ranged from 0% to 97%, with overall average adherence rates of 53% for 5-aminosalicylic acid (5-ASA) and 48% for 6-mercaptopurine (6-MP), he said.

Adherence to 5-ASA was higher among patients with ulcerative colitis than among those with Crohn’s disease (63% vs. 50%), but this difference did not reach statistical significance.

Adherence rates did not vary between one versus two medications, or whether patients were newly diagnosed or had the disease for a year or more. Boys and girls performed equally.

Adherence, however, was significantly correlated with age (P = .03), Dr. LeLeiko said. Patients aged 14 and older took significantly less 5-ASA than those ages 11-13 years or those 11 and under (38% vs. 62% vs. 67%, respectively). The same was true for use of 6-MP (29% vs. 58% vs. 61%).

Contrary to conventional thinking, adherence was not significantly correlated with severity of pain or whether blood was present in the stool at baseline, Dr. LeLeiko said. Disease location (right side only, versus upper colon and left-side impaction) also did not make a difference.

However, adherence was significantly related to patient behavior and mood. Adherence to the IBD medications was significantly lower (21%) in those among those who scored higher for behavior problems on the CBCL, versus adherence of 56% for patients who scored within normal limits on the CBCL. A similar pattern was found for depressive symptoms on the CDI, in that children with more depressive symptoms had lower adherence (31%) compared with those who scored within normal limits for depressive symptoms (62% adherence).

To illustrate the potential impact of medication adherence on treatment management, Dr. LeLeiko highlighted the case of a 14-year-old boy with ulcerative colitis who was hospitalized in October and subsequently prescribed prednisone and 5-ASA. The boy did well until he began to complain of fatigue in March. Clinicians questioned whether his steroids had been tapered too abruptly and opted to increase his steroids and start 6-MP. Lab values showed reason for concern, and they noted in his chart that they were considering immunomodulators and biologic agents.

Medication adherence had dropped off posthospitalization, rose to around 66% in March when the boy was unwell, but dropped off again in May when he began to feel better.

Interestingly, when asked about his adherence practices, the boy strongly agreed with the statement that “I understand what I am supposed to do to care for my illness” and was neutral about the statement that “Sometimes I can’t remember everything I am supposed to do about my illness.”

“Adherence cannot be summarized by simply quoting one rate of adherence,” Dr. LeLeiko said. “Adherence is a complex behavior that will likely alter therapy choice and outcomes.”

When asked during a discussion of the study whether the patients’ awareness of being monitored may have affected adherence patterns, Dr. LeLeiko replied that it could, but that one would assume it would only improve the numbers.

Other attendees asked what clinicians should do to improve adherence in pediatric patients. Dr. LeLeiko said it is not clear which method is best for achieving this, but the data show that “practice as usual” change.

“T

This study by LeLeiko and colleagues highlights a concept that more effective. The responsibility can’t all rest with parents or doctors, and we have to remember that parents of children with chronic illness have to ask their teenagers to do many things, not just take pills. Call-back systems and reminders such as text messages may be necessary. It is time to stop lamencing the obvious, and instead develop cool solutions.

MARI A T. ABREU, M.D., AGAF, is Professor of Medicine and Chief, Division of Gastroenterology, University of Miami Miller School of Medicine.

Emmet B. Keeffe, M.D., 1942-2011

iPho

The important issue here is that we need to embrace technology.

Session co-chair Dr. Sandra C. Kim, a pediatric gastroenterologist with the University of North Carolina in Chapel Hill, said in an interview that “It’s not a matter of physicians not taking the time doing everything they can to educate their patients. I think now it’s understanding the psyche of the families and the teenagers themselves … and really emphasizing the principles of self-management.

“This is where as physicians we do well partnering with other colleagues, whether it be educators or the teens themselves.”

Dr. Kim also expressed concern regarding how the low adherence rates measured in relatively high-functioning families in the study — would extrapolate to the rest of the population that does not have the same resources. Households in the study were upper middle class (income more than $71,000), college-educated, and employed, and were largely two-parent families.

Dr. LeLeiko disclosed grant/research support and other financial relationships with Astra-Zeneca, Centocor, and Pro- metheus Laboratories. His co-authors disclosed no conflicts.

To view a video about this study, scan this QR code with your mobile device. Don’t have a QR reader? Get one at mobiletag.com/en/download.php. Or to view the video online, go to http://tiny.cc/gshpw.

Charles J. Lightdale, M.D., AGAF, Editor-in-Chief, GI & Hepatology News

Emmet B. Keeffe, M.D., AGAF, was Professor of Medicine, Chief of Hepatology, and Co-Director of the Liver Transplant Program at Stanford University Medical Center. Remembered for his warmth, generosity, and indomitable spirit, he gave selflessly to the AGA, and is well known to the readers of this newspaper for his frequent and thoughtful contributions. An In Memoriam article will appear in the November issue of Gastroenterology.

An online discussion board has been created where AGA members can leave notes in memory of Dr. Keeffe. AGA plans to compile the notes and share them with the Keeffe family. To make a comment, go to www.gastro.org, click on “Community” then “Discussion Forums.” After logging in, go to the forum titled “In Memory of Emmet B. Keeffe, M.D.”

It is with great sadness that we report the unexpected loss of Emmet B. Keeffe, M.D., AGAF, on August 8, 2011.

Dr. Keeffe was President of the AGA from 2004 to 2005. The shape of his career and research interests were beautifully detailed at the time of his election in a colorful biography published in Gastroenterology, which can be accessed at http://tiny.cc/kul224 (Gastroenterology 2004;126:1454-60).

Dr. Keeffe was Professor of Medicine, Chief of Hepatology, and Co-Director of the Liver Transplant Program at Stanford University Medical Center. Remembered for his warmth, generosity, and indomitable spirit, he gave selflessly to the AGA, and is well known to the readers of this newspaper for his frequent and thoughtful contributions. An In Memoriam article will appear in the November issue of Gastroenterology.

An online discussion board has been created where AGA members can leave notes in memory of Dr. Keeffe. AGA plans to compile the notes and share them with the Keeffe family. To make a comment, go to www.gastro.org, click on “Community” then “Discussion Forums.” After logging in, go to the forum titled “In Memory of Emmet B. Keeffe, M.D.”

■ ■ ■ ■ ■
Complete the Picture of Relief

Breakthrough Heartburn

Complement PPI therapy
Recommend the power of TUMS® Ultra

- Double the neutralizing power per tablet vs. regular strength
- No antacid goes to work faster
- No known PPI interactions
- 400mg elemental calcium per tablet

Goes to work fast to complement PPI therapy
NAC Fails in Pediatric Non-Acetaminophen ALF

CHICAGO – Intravenous N-acetylcysteine had no significant benefit in treating children with acute liver failure that was not caused by acute acetaminophen toxicity, based on a 7-year, multicenter, randomized trial presented at the annual Digestive Disease Week. Administration of N-acetylcysteine, or NAC, has increasingly become part of the standard treatment for liver failure of various causes, said Dr. Robert H. Squires Jr., clinical director, division of pediatric gastroenterology, Children’s Hospital of Pittsburgh, and professor of pediatrics, University of Pittsburgh.

And although research has indicated that NAC improves outcomes in adults with non-acetaminophen acute liver failure, data on use of this treatment in children are limited, he said.

In this study, the primary outcome measure of 1-year survival was not significantly different between the treatment and placebo groups (P = .20). The cumulative probabilities of survival at 1 year were 0.73 (73%) in the NAC-treated group and 0.82 (82%) in the placebo group.

Not only did the treatment show no benefit, but children in the NAC group fared worse than those who received placebo, Dr. Squires noted.

In an interview, Dr. Robert S. Brown Jr., AGAF, said, “This study is very important, as it contradicts [previous] findings in the adult population. However, it is important to be sure that acetaminophen has not played a role in the acute liver failure, as NAC is critical in that situation.” Dr. Brown is the Frank Cardile professor of medicine and surgery and chief of the Center for Liver Disease and Transplantation at Columbia University College of Physicians and Surgeons, New York.

A total of 92 children aged 0-17 years with acute liver failure not related to acetaminophen received a continuous intravenous infusion of NAC (150 mg/kg per day), and 92 children received a placebo solution. The patients were treated for up to 7 days. All the children were enrolled in the Pediatric Acute Liver Failure Study Group.

Secondary outcomes included survival without liver transplantation, length of ICU stay, length of hospital stay, organ system failure, and maximum hepatic encephalopathy score.

The cumulative probability of survival without liver transplant was significantly lower in the NAC group compared with the placebo group overall (P = .04), and in the subset of NAC-treated children younger than 2 years compared with placebo children younger than 2 years (P = .03).

None of the other secondary outcome measures were significantly different between the groups. Baseline demographics were similar for the two groups, although the NAC group had a higher percentage of patients with metabolic disease etiologies, the researchers noted. Exclusion criteria included previous NAC exposure, pregnancy, sepsis, malignancy, intractable hypotension, or signs of cerebral herniation.

“These results do not support broad use of NAC in pediatric acute liver failure [not related to acetaminophen], and emphasize the importance of conducting prospective pediatric drug trials, regardless of results in adults,” Dr. Squires said.

Our triple mission enriches and enlightens care for people with digestive disorders.

UPMC’s Digestive Diseases Center stresses an intimate interaction between discovery, teaching, and clinical care. Our researchers stress translational work, focusing their investigations on real clinical problems and guiding their projects with invaluable feedback from clinicians and patients. In a period of declining CME enrollment, our innovative use of electronic teaching methods has allowed our educational programs to expand. And strong clinical programs in routine to complex pancreatic disease, small-bowel transplantation, colon cancer, immunotherapy, liver disease, and visceral pain all contribute to a synergy in which research, teaching, and clinical practice enlighten and enrich each other.

Bringing together the perspectives of innovative physicians and researchers in order to deliver revolutionary treatments for complex diseases is what we clearly do best...from the patient’s perspective.

To learn more, visit UPMCPhysicianResources.com.

Affiliated with the University of Pittsburgh School of Medicine, UPMC is ranked among the nation’s best hospitals by U.S. News & World Report.
**Clinical Challenges and Images**

**What's Your Diagnosis?**

A 22-year-old man presented with melena and bright red rectal blood loss. He had a 14-year history of persistent microscopic anemia with recurrent episodes of melena and bright red rectal blood loss. The lowest hemoglobin level recorded was 2.7 mmol/L. Over the years, he had repeated gastroscopies and colonoscopies as well as a radionuclide scan for Meckel’s diverticulum, a small bowel follow-through study, a double-contrast barium enema, an abdominal computed tomography (CT) scan, and a TC-99m erythrocyte scintigraphy, but none of this testing revealed the source of bleeding. Recent mesenteric angiography failed to show arteriovenous malformations, contrast extravasation, or blushes of contrast medium. Recurrent stool examinations were negative for parasites and bacteria.

At presentation, physical examination was unremarkable except for blood on rectal examination. Vital signs were within normal limits. Laboratory results were hemoglobin, 7.0 mmol/L (normal, 8.6-10.5 mmol/L); hematocrit 0.34% (normal, 0.40%-0.50%); and mean corpuscular volume, 92 fL (normal, 80-100 fL). Gastroscopy was again unremarkable. Colonoscopy showed blood in the entire colon and distal ileum without a bleeding focus. An abnormality of the jejunum was suspected. A radionuclide scan for Meckel’s diverticulum was not repeated. A double-balloon enteroscopy was performed using both a transanal and transoral approach to acquire endoscopic access to the entire small intestine. No abnormalities were found via the transoral approach over the entire visible length of the duodenum and jejunum.

The results of transanal examination are shown in figure A. Figure B shows results from supine abdominal radiographs after endoscopic administration of a radiological contrast agent. What is the most likely diagnosis?

*The diagnosis appears on page 14.*

---

**Natalizumab Labeling Changed**

The Food and Drug Administration has updated the natalizumab (Tysabri) label to include new information about the risk for progressive multifocal leukoencephalopathy (PML) associated with use of the drug, which is approved to treat multiple sclerosis and Crohn’s disease.

The previous label warned that using an immunosuppressive drug at the same time as Tysabri may raise the risk of developing PML. The label now warns that taking an immunosuppressive drug at any point prior to taking Tysabri increases the risk for PML. The immunosuppressive drugs include mitoxantrone, azathioprine, methotrexate, cyclophosphamide, and mycophenolate. The updated label also includes a new table listing rates of PML by the number of Tysabri infusions.

–Sherry Boschert
Combination Therapy Works Long Term in Biliary Cirrhosis

BY DENISE NAPOLI
Elsevier Global Medical News

Combination therapy consisting of ursodiol and either methotrexate or colchicine for primary biliary cirrhosis showed long-term effectiveness, lasting up to 20 years, wrote Dr. John Leung and his colleagues in the September issue of Clinical Gastroenterology and Hepatology.

Dr. Leung, of the department of gastroenterology at Tufts Medical Center, Boston, and his colleagues studied 29 consecutive primary biliary cirrhosis patients, a chronically progressive disease thought to have an autoimmune etiology. The patients were originally part of an 85-patient, double-blind, prospective, randomized controlled trial comparing colchicine and methotrexate from 1988 to 2000, with ursodiol (ursodeoxycholic acid) added to that regimen 3 years after study initiation.

The patients examined in the current study had completed all 10 years of follow-up in the original trial. At completion, "the randomization code was broken and these 29 patients were treated according to their clinical response, personal preference, and tolerance to therapy."

They were then followed for an additional 9-13 years, either at the authors’ institution (21 patients) or via telephone calls and e-mail correspondence with referring physicians. All patients except one were female, and the median age at the end of the initial 10-year randomized controlled trial (RCT) was 59 years.

According to the authors, of the 29 patients followed for 20 years, "Twenty-one patients are alive and well. Of these, 19 have normal tests of liver function and no signs of portal hypertension."

The outcomes were then analyzed by specific treatment regimen. Of the 11 patients on methotrexate plus ursodiol, "two died of causes unrelated to liver disease at the age of 79 and 70, and 9 are alive and well," reported the authors. All nine of these patients were reported to have normal serum liver enzymes, transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, and bilirubin.

Additionally, albumin levels remained normal in eight patients; the ninth patient entered the initial trial 20 years ago with stage III biliary cirrhosis and now has a slightly decreased albumin level of 3.3 g/dL, along with portal hypertension and nonbleeding, grade 2 varices. This patient remains asymptomatic, however. Another patient receiving this regimen also developed grade 2 esophageal varices, also without bleeding.

There were 18 patients in the colchicine plus ursodiol group, and 12 were alive and well at the end of follow-up, reported the investigators. Of the remaining six, "three died of liver-unrelated causes at the age of 73, 76 and 76 respectively," wrote the authors. "They had normal biochemical tests and two had small esophageal varices at the end of the RCT."

Two patients with elevated liver enzymes at the end of the RCT underwent liver transplant; a third developed varices but was not a candidate for transplant, and died of pneumonia.

Overall, the investigators reported no treatment-related adverse events at the conclusion of follow-up.

"The results of this current study provide further evidence that combination therapy with [ursodiol], colchicine and [methotrexate] is durable and improves the natural history of primary biliary cirrhosis in a subset of primary biliary cirrhosis patients, including some who had historically advanced liver disease at diagnosis," concluded the authors.

And while the investigators conceded that it is impossible to determine whether the benefits were because of ursodiol, combination therapy, methotrexate, or colchicine alone, the observations that liver function remained normal for 10 additional years and that very few patients developed portal hypertension suggests that combination therapy may have been effective.

DR. WILCOX

Dr. Leung and his colleagues declared no outside funding for this study and no personal conflicts of interest.
Trial Supports Addition of Telaprevir for HCV Genotype 2

BY DENISE NAPOLI
Elsevier Global Medical News

Adding telaprevir to the standard regimen of peginterferon-alpha and ribavirin reduced the time needed to attain decreased viral loads in genotype 2 hepatitis C virus infection, reported Dr. Graham R. Foster and his colleagues in the September issue of Gastroenterology.

The drug was less effective in patients with genotype 3 hepatitis C virus (HCV), in the first study to assess use of telaprevir for treating these strains. Dr. Foster, of Queen Mary University of London, and colleagues looked at treatment-naive patients with HCV genotypes 2 and 3 (23 and 26 participants, respectively).

Pregnancy and ribavirin decreased viral loads

Patients received either telaprevir monotherapy (750 mg every 8 hours), telaprevir plus peginterferon-alpha (180 mcg/mg) and ribavirin (400 mg twice daily), or placebo plus peginterferon/ribavirin for 15 days, followed by the standard peginterferon/ribavirin regimen for 22 or 24 weeks. On day 8 of treatment, the proportion of patients with undetectable HCV RNA was 0% in the telaprevir monotherapy group, 20% in the telaprevir plus peginterferon/ribavirin group, and 0% in the peginterferon/ribavirin-only cohort. By day 15, the proportions were 0%, 40% (2 of 5 patients), and 22% (2 of 9 patients), respectively.

The median times to undetectable HCV RNA were 31, 12, and 43 days in the telaprevir monotherapy group, the telaprevir plus peginterferon/ribavirin group, and the peginterferon/ribavirin-only group. Moreover, the proportions of patients with a sustained virologic response (SVR) defined as undetectable HCV RNA at end of treatment and 24 weeks post-treatment were 0%, 40%, and 22% for the respective groups, respectively. Like in the previous studies, the SVR rates were 50% (4/8), 67% (6/9), and 44% (4/9), respectively.

The most frequently reported adverse events were flulike illnesses and pruritis. Of specific concern was a serious adverse event of pancreatitis in one patient. The pancreatitis was considered related to the study medication, in this case, peginterferon/ribavirin. Based on the efficacy shown among treatment-naive patients, “the potential of telaprevir-based triple combination therapy in patients with HCV genotype 2 who have not responded to peginterferon/ribavirin should be explored,” said the authors.

And while the drug’s poor performance among genotype 3 patients makes it “unlikely to have major clinical utility in this patient subpopulation, … for treatment-naive patients with genotype 2 HCV, studies to examine a shortened duration of therapy that includes telaprevir should be considered.”

The study was sponsored by Janssen Pharmaceuticals and Vertex Pharmaceuticals. Several authors had financial relationships with multiple pharmaceutical companies, including Janssen and Vertex. Two investigators were also employees of Tibotec or Janssen.
AGA Members Called On to Support Research

T he National Institutes of Health has long been the premier supporter of biomedical research. However, since 2003, the NIH budget has grown at an annual rate of 1.6%, well below the 2.9% national growth rate of biomedical research, according to the Congressional Research Service. This essential decline in funding is hampering advances across medicine, including the gastrointestinal field.

In 2011, the NIH budget was cut by 1%, avoiding a proposed 5% cut. While the federal budget negotiations are still unclear, NIH is likely to suffer significant budget cuts. Young researchers must have a viable future in academic medicine to ensure a continued pipeline in biomedical research. Thus support from the AGA Research Foundation is critical to ensuring the future of the great advancements we have enjoyed over the last 40 years in gastroenterology and hepatology. The AGA Research Foundation helps to fill the NIH funding gap by supporting young researchers in the field.

“Funding from the AGA was fundamental in providing me with the necessary seed money to develop several new lines of investigation,” says Edda Fiebiger, Ph.D., 2008 AGA RSA Recipient. “Especially as a new investigator, grants like the RSA are essential for a positive career development right from the start. Thanks to the generous support from the AGA, my research program is now NIH funded. I do not think that this could have been accomplished without the support I received through the RSA.” Without research, there would be no treatments or diagnostic tests for the myriad of digestive diseases. The young researchers who receive AGA Research Foundation awards will help discover the science on which the practices of tomorrow will be based. Some of the awards already given are being quickly applied by these brilliant recipients to develop diagnostic tests and treatments which will find their way into our doctors’ offices within a few short years.

“It is important to fund researchers trained in GI physiology or gastroenterology who understand the important questions in the field,” remarks Juanita Merchant, M.D., Ph.D., recipient of the 1998 Funderburg Research Award in Gastric Biology Related to Cancer. “Their findings subsequently translate basic discoveries into meaningful therapies.”

“We must continue to fund research in order to improve the care we provide to our patients,” says Dr. LaRusso. “Donations from AGA members to the AGA Research Foundation allow us to fund promising research projects that will impact the lives of all of our patients.”

For more information on how you can advance research within the GI field by making a gift to the AGA Research Foundation or the foundation awards, visit www.gastro.org/foundation or e-mail Stacey Hinton, Director of Development and Foundation Programs at staceyhinton@gastro.org.

Will Debt Ceiling Legislation Hurt GI?

P resident Obama signed legislation to raise the federal debt ceiling, agreed upon by the House and Senate, preventing a government default. The plan increases the debt ceiling by $2.4 trillion, sets discretionary spending caps through 2012, and creates a new legislative committee charged with identifying $1.1 trillion in cuts to reduce the deficit.

The AGA is pleased that Congress finally reached a bipartisan deal on raising the debt ceiling, but is gravely concerned that spending caps will further erode funding for NIH and seriously jeopardize a permanent solution to the broken physician payment formula. Physicians are already facing a 30% cut in Medicare reimbursement, in addition to potential cuts under the Independent Payment Advisory Board (IPAB). The IPAB, charged with making more cuts to providers under Medicare, further thwarts physician participation in the program and patient access to quality care.

The legislation allows the government to borrow into 2013 by increasing the debt limit in two stages. The first increase will raise the debt limit by $900 billion, with the president having immediate access to $400 billion. The additional $500 billion could be blocked by Congressional disapproval, which the president could veto.

The second increase will raise the debt limit by at least $1.2 trillion, also subject to a vote of congressional disapproval, but essentially guarantees an increase, even if Republicans disapprove of the increase, the president could veto the vote, and Republicans lack the two-thirds necessary to override a veto in the Senate.

The agreement caps discretionary spending by roughly $900 billion over the next decade and creates a new legislative committee charged with identifying $1.3 trillion in savings by Nov. 23, 2011. Congress will need to approve the committee’s recommendations and, if they fail, cuts will automatically be triggered, with half coming from Medicare and half coming from defense.

Medicare couldn’t be reduced by more than 2% per year, and the cuts would exempt beneficiaries, leaving providers most vulnerable. Social Security, Medicaid, and veterans’ benefits will be also be exempt from cuts.

The deal provides $17 billion for additional Pell grants (need-based grants to low-income undergraduate and certain postbaccalaureate students to promote access to postsecondary education) through fiscal year 2013, but would bar the student loan program from providing financial incentives to students who repay their loans on time.

The deal also eliminates interest-free grace periods and deferments for most graduate students, which saves $18.1 billion over 10 years, but would jeopardize medical students and researchers.

The AGA will continue to monitor the budget process and its impact on gastroenterology. Look for more updates on the AGA Washington Insider and AGA eDigest.
A Sprinkle of PROTONIX®
(pantoprazole sodium)
For Delayed-Release Oral Suspension
For directions on method of administration please see reverse and Prescribing Information at www.pfizer.com/products.

Indications
- PROTONIX is indicated in adults and pediatric patients five years of age and older for the short-term treatment (up to 8 weeks) in the healing and symptomatic relief of erosive esophagitis. For those adult patients who have not healed after 8 weeks of treatment, an additional 8-week course of PROTONIX may be considered. Safety of treatment beyond 8 weeks in pediatric patients has not been established.
- PROTONIX is indicated for maintenance of healing of erosive esophagitis and reduction in relapse rates of daytime and nighttime heartburn symptoms in adult patients with GERD. Controlled studies did not extend beyond 12 months.

Important Safety Information
- PROTONIX is contraindicated in patients with known hypersensitivity to any component of the formulation or to substituted benzimidazoles.
- Symptomatic response to therapy does not preclude the presence of gastric malignancy.
- Atrophic gastritis has been noted with long-term therapy.
- PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine.
- Hypomagnesemia has been reported rarely with prolonged treatment with PPIs.

- The adverse reaction profiles for PROTONIX Oral Suspension and PROTONIX Delayed-Release Tablets are similar.
- In clinical trials of adult patients, the most frequently reported adverse reactions (>2%) with PROTONIX Delayed-Release Tablets were headache, diarrhea, nausea, abdominal pain, vomiting, flatulence, dizziness, and arthralgia.
- In clinical trials of pediatric patients 1 to 16 years of age, the most frequently reported adverse reactions (>4%) with PROTONIX were URI, headache, fever, diarrhea, vomiting, rash, and abdominal pain.

- Concomitant use of atazanavir or neflunavir and proton pump inhibitors is not recommended.
- Patients treated with PPIs and warfarin concomitantly should be monitored for increases in INR and prothrombin time.
- PROTONIX may interfere with the absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts).
CLINICAL CHALLENGES AND IMAGES

The Diagnosis

Answer to ‘What’s Your Diagnosis?’ on page 9: Meckel’s Diverticulum

The transanal approach showed a 3-cm-long diverticulum located 90 cm proximal to the ileocecal junction (figure C). The diverticulum contained a Forrest II ulcer with a maximum diameter of 1 cm. Endoscopic submucosal dissection of the vesicocele was performed using an Erbe knife, and the diverticulum was removed with an endoscopic ultrasonic dissector. The patient recovered uneventfully, and the pathology report confirmed the diagnosis of Meckel’s diverticulum with a benign hemangioma.

In 10% of adults with overt intestinal bleeding, the bleeding focus remains unresolved after conventional diagnostic evaluation. A Meckel’s diverticulum should always be considered in young adults; it is the most common congenital abnormality of the GI tract, with a prevalence of 2%-3%, and rectal bleeding is the most frequent presentation in adult patients (3). The pathology and clinical picture of this condition are well known, yet the preoperative diagnostic challenge of a complicated Meckel’s diverticulum is often difficult to establish because the symptoms overlap with many disorders. Also, the conventional diagnostic tool, a radiopaque scan for Meckel’s diverticulum, is hampered by low sensitivity (75%).

The double-balloon enteroscopy offers a new perspective to an endoscopic investigation of the small bowel. Through this safe method, 240-270 cm and 120-150 cm of small intestine can be visually examined, respectively, by the transoral and transanal approaches, with an average duration of 75-95 minutes. This case shows the clinical significance of double-balloon enteroscopy for diagnosing unresolved rectal bleeding. Also, the double-balloon enteroscopy allows for endoscopic intervention, which may avoid abdominal surgery in some cases.

References
Antiplatelets Appear Safe When Resecting Small Polyps

BY HEIDI SPLETE
Elsevier Global Medical News

CHICAGO – The rate of postpolypectomy bleeding was less than 1% in clopidogrel patients who continued their medication through the procedure – not significantly higher than that of control patients not taking the antiplatelet drug, investigators reported at the annual Digestive Disease Week.

Current guidelines recommending that patients discontinue antiplatelet medications before an elective colonoscopy are based primarily on expert opinion rather than research studies, said Dr. Linda Feagins of the University of Texas Southwestern Medical Center in Dallas, and her colleagues.

“For our patients, we do not routinely discontinue clopidogrel before colonoscopy because we have judged the cardiovascular risks of that practice to exceed the risks of postpolypectomy bleeding,” Dr. Feagins said.

In this study, Dr. Feagins and her colleagues reviewed data from 118 patients taking clopidogrel at the time of a polypectomy and 1,849 controls not taking clopidogrel. Clopidogrel patients were matched with controls based on age, ethnicity, gender, use of NSAIDs or aspirin, coronary artery disease, diabetes, hypertension, number of polyps removed, size of largest polyp, and polypectomy techniques.

Overall, the frequency of postpolypectomy bleeding was not significantly different between the clopidogrel users and the controls (0.8% vs. 0.3%, respectively). Postpolypectomy bleeding was defined as rectal bleeding within 30 days of polypectomy and repeat colonoscopy confirming bleeding from a polypectomy site. Also, a matched analysis of 111 clopidogrel patients and 111 controls showed no significant difference between the groups in the bleeding rate (0.9% vs. 0.3%, respectively).

The study was limited by its retrospective nature, Dr. Feagins noted, and 85% of the polyps removed in this study were less than 1 cm, suggesting that the results might not apply to polyps 1 cm or larger in size, she said. But the findings also suggest that many clopidogrel patients can safely continue their medications while undergoing polypectomy.

“We speculate that the cardiovascular risks of routinely discontinuing clopidogrel before elective colonoscopy may well exceed any excess risk of postpolypectomy bleeding,” said Dr. Feagins. But more research is needed, and prospective studies are underway, she said.

Dr. Feagins said that she had received grants and/or research support from Centocor.

While the differences between the groups receiving and not receiving clopidogrel are not significant, the authors are correct to point out that significant differences could be seen with more large polyps (because they have higher likelihood of bleeding) and/or larger numbers of polyps. Other fully published work has found that clopidogrel is a risk factor for post-polypectomy bleeding. The decision to stop clopidogrel before colonoscopy or to stop it temporarily after colonoscopy and polypectomy should depend on the cardiovascular risks of stopping the drug (which could be catastrophic and must be taken very seriously), and the estimated risk of bleeding from the polypectomy. Anecdotal data have suggested that clipping the polypectomy site after endoscopic resection of larger polyps may help reduce the risk of delayed bleeding when clopidogrel is continued, which it often must be.

DOUGLAS K. REX, M.D., AGAF, is Distinguished Professor of Medicine at Indiana University, Indianapolis, and Director of Endoscopy at Indiana University Hospital.

PERSPECTIVE

Simple
- Automatic Flow Monitoring
- Simple Push Button Control
- Alphanumeric Data Display
- Available Take Home Kits

Accurate
- Breath Hydrogen Analysis
- Breath Methane Analysis
- Sample Correction
- Upgradable SensorPaks™

Reliable
- Three-Year Warranty
- Solid-State Sensor
- Results In Less Than 50 Sec.
- DataTracker™ Compatible

Breath Tests Help Determine Small Bowel Bacterial Overgrowth and Carbohydrate Malabsorption

LACTOSE SIBO FRUCTOSE

HYDROGEN & METHANE ANALYSIS

QuinTron

Breath Testing Experts Since 1962

USA: 3712 West Pierce St. • Milwaukee, WI 53215 • Toll Free: 1-800-542-4448 (U.S. and Canada)

Europe: via Vico Vigano, 55 • Roma, Italia 00133 • +39-06-4087873

www.QuinTron-USA.com
Screening Interval

Colonoscopy

negative screening result, 46% underwent screening colonoscopy again within 7 years. When broken down by age, 46% of patients aged 75-79 years received repeat colonoscopies within the study period, as did a third of those 80 years and older.

About 57% of the repeat colonoscopies performed during the study period carried a diagnosis that might indicate a legitimate reason for the early exam, and the other 43% did not. Men, patients with comorbidities, and those treated by high-volume colonoscopists or in an office setting received early repeat examinations more often without a clear reason, the researchers found.

The researchers also noted an “inflexion point” at 60 months, where only about 38% of the colonoscopies performed were accompanied by a potentially explanatory diagnosis. “The rapid increase in colonoscopies in the period around 60 months suggests that those might have been routinely scheduled,” the authors wrote.

They also found marked geographic variations, with more than 50% of patients in some regions receiving a repeat exam within 7 years, while fewer than 5% of patients in other areas received repeat exams in that time frame.

Medicare regulations preclude reimbursement for screening colonoscopy within 10 years of a negative screening result, yet only 2% of the claims for nonindicated, early repeat colonoscopies were denied, the researchers found.

In the second study, Dr. Christine E. Kistler of the University of North Carolina at Chapel Hill and her colleagues looked at long-term outcomes following a positive fecal occult blood test (FOBT) in 212 adults aged 70 years and older who were treated at four Veteran Affairs facilities.

They found that 56% of those patients received follow-up colonoscopies, which revealed 34 significant adenomas and 6 cancers. One in 10 patients experienced complications from the colonoscopy or from their cancer treatments (Arch. Intern. Med. 2011 May 9 [doi:10.1001/ archinternmed.2011.206]).

The researchers calculated the net survival benefit from FOBT screening along with the potential burdens, which can include complications from additional testing and/or treatment. Previous trials of FOBT suggest that a person needs a life expectancy of at least 5 years to derive survival benefits from screening; if that person isn’t expected to live 5 years or more, then he or she only risks the potential burdens.

Dr. Kistler and her associates found that 87% of those with the worst life expectancy experienced a negative burden from screening, as did 70% of those with average life expectancy and 65% of those with the best life expectancy. This negative burden could be reduced by better targeting FOBT screening and follow-up to healthy older adults, they said.

The authors of both studies reported no financial conflicts of interest.
Study Suggests HCC Resection Superior to Transplant

ROCA RATON, FLA. – Five-year overall survival in patients with hepatocellular carcinoma was the same whether they were treated by surgical resection or liver transplantation in a new meta-analysis that included the 10 large series that have been reported during the past decade.

This finding constitutes a persuasive argument that resection should be the first-line therapy for patients with hepatocellular carcinoma (HCC), particularly when they have compensated liver function, Dr. Leonidas G. Koniaris said at the annual meeting of the American Surgical Association.

“If you have two treatments, and one costs $750,000 after 5 years and the other therapy costs $40,000, and they have equivalent 5-year survival, the $750,000 therapy should have to prove superiority,” said Dr. Koniaris of the University of Miami.

The meta-analysis included 916 HCC patients treated by surgical resection and 1,176 who underwent hepatic transplantation. The 5-year overall survival rate was 57% in both groups. However, 5-year disease-free survival was significantly better in the transplant group at 39%, versus 23% with resection, he said.

In addition to the meta-analysis, Dr. Koniaris presented a retrospective analysis of the experience at the University of Miami, where close to 3% of all U.S. patients with HCC receive treatment. This study suggested that 5-year outcomes with surgical resection are not just equivalent to those for transplantation, but may actually be superior in certain patient subsets when patients wait-listed for transplant who never receive a donor organ are taken into account in an intent-to-transplant analysis. Such patients have a very poor prognosis, he noted.

The Miami analysis included 416 HCC patients: 109 treated by surgical resection, 270 treated by transplantation, and 37 listed for transplantation who never received a donor organ. Most resections were done within a month of referral. Median time to transplantation was 48 days after listing. Median 5-year overall survival was 53% with resection and 52% in the intent-to-transplant group.

However, in the subset of patients who met the Milan criteria (single tumor less than 5 cm in size or up to three lesions smaller than 3 cm) and who had preserved liver function as reflected by a Model for End-Stage Liver Disease score less than 10, the 5-year overall survival was 63% for resection versus 41% in the intent-to-transplant group (P = 0.03).

The Miami study is a retrospective analysis of nonrandomized patients and hence it has to be considered hypothesis-generating rather than definitive, Dr. Koniaris emphasized. Of note, 74% of the intent-to-transplant group had hepatitis C-related HCC, a relatively poor-prognosis tumor, compared with patients who have large tumors and cannot receive transplant, the conclusion that the outcomes are the same is impossible, due to confounding and selection bias. To compare two therapies applied to two very different groups of patients does not generate reliable answers.

This question can only be answered by randomizing patients who are eligible for both therapies, which is unlikely to be done. At least the investigators should have restricted their analyses to potentially resectable, matched patients in each group.

Robert S. Brown Jr., M.D., AGAF, is the Frank Cardile Professor of Medicine and Surgery and Chief of the Center for Liver Disease and Transplantation at Columbia University College of Physicians and Surgeons, New York.

Although resection may be the best option in some patients and the only viable option in patients who have large tumors and cannot receive transplant, the conclusion that the outcomes are the same is impossible, due to confounding and selection bias. To compare two therapies applied to two very different groups of patients does not generate reliable answers.

This question can only be answered by randomizing patients who are eligible for both therapies, which is unlikely to be done. At least the investigators should have restricted their analyses to potentially resectable, matched patients in each group.
Early TIPS for Ascites Study Seeks to Improve Survival

**BY DR. THOMAS D. BOYER**

The possibility that we can improve the quality and length of life for liver disease patients, without a transplant, is one of the most exciting potential opportunities in our field today. Ascites, the most common complication from cirrhosis, develops in 50% of patients with 10 years. Development of ascites reflects decompensation of the liver and is associated with an increase in morbidity and mortality.

Initially, the ascites is usually controlled easily with diuretics, but as the liver disease worsens, higher and higher doses of diuretics are required to maintain patient comfort. Eventually, diuretic treatment fails and the patient is diagnosed with refractory ascites. The current standard of care for refractory ascites consists of large volume paracentesis (LVP), coupled with an aggressive pharmacotherapy regimen. Transjugular intrahepatic portosystemic shunt (TIPS) therapy is regarded as the last line of defense, a bridge to liver transplantation.

However, these conclusions are based on trials in which bare stents were used to create the TIPS. With covered stents that are now available, better outcomes might be possible. Interventional radiologists and hepatologists have come together in an international trial to determine if TIPS intervention can increase transplant-free survival compared to LVP when performed earlier in the ascitic patient population.

Previous studies comparing TIPS to LVP must be revisited. Conducted in the 1990s and early 2000s, these studies may have failed to consistently demonstrate increased life expectancy for three reasons. First, mostly end-stage patients with refractory ascites were included. Second, neither therapy changes the underlying liver disease, a reason why most therapies, except transplant, have failed to show a survival benefit. Finally, bare metal stents, which had a high failure rate, were the only option for TIPS therapy at the time. This study is being conducted to evaluate whether newer technology like covered stents with a lower failure rate will address this last potential pitfall.

The Early TIPS for Ascites Study is a randomized, multi-center study, sponsored by Gore Medical in collaboration with both hepatologists and interventional radiologists. Given the nature of the TIPS referral pathway, the team approach will lead to better patient care, more coordinated medical management, and improved recruitment. The goal of the study is to determine whether patients with difficult-to-treat ascites benefit most from early TIPS therapy using a covered stent or from continued LVP based on transplant-free survival.

This study has survival as its primary end point, in contrast to previous trials, which looked at control of ascites. There is little question that TIPS is better than LVP in controlling the ascites. But controlled trials show that use of TIPS is associated with more encephalopathy than alternative forms of therapy. What is unclear is the balance of these two factors and the overall impact on survival. This study will also help to answer questions from prior studies that used refractory ascites, because the Early TIPS for Ascites Study protocol allows for enrollment of patients prior to reaching the refractory stage as defined by the International Ascites Club. This is also the first study of its kind in which the Model for End Stage Liver Disease score is used for patient selection and will also be tracked during follow-up as a study end point.

Previous studies comparing TIPS with bare metal stents to LVP in patients with refractory ascites had mixed findings. Yet a recent meta-analysis of these studies found that TIPS patients had significantly longer transplant-free survival than paracentesis patients. A study published last year in the New England Journal of Medicine compared early TIPS intervention with a covered stent to pharmacotherapy/endoscopic band ligation in high-risk vascular bleeding patients, with positive results.

TIPS therapy is a minimally invasive procedure done with closed surgery, as only a small puncture is made in the jugular vein for insertion of the device. A TIPS creates a functional side-to-side portocaval shunt to route blood flow through the damaged liver and into the main blood vessels that carry blood back to the heart. With the TIPS procedure, alternative treatments such as medications and paracentesis for ascites, and endoscopic treatment of varices, may possibly not be needed as often. Some reports have shown significant improvements in TIPS therapy when using a covered stent versus a bare metal stent. Thomas D. Boyer, M.D., is Director of the Arizona Liver Research Institute, Professor of Medicine, and Medical Director of the University Medical Center Liver Transplant Program, University of Arizona College of Medicine, Tucson.

**References**

3. Gastroenterology 2007;131:825-34.

High Carbohydrate Intake Raises Gallbladder Disease Risk in Pregnancy

**BY HEIDI SPLETE**

**Elsvier Global Medical News**

CHICAGO – The risk of gallbladder disease was more than doubled in pregnant women in the top quartile of carbohydrate intake, compared with those in the bottom quartile, in a prospective study of 3,070 pregnant women.

Female gender is a risk factor for gallstones, and pregnancy is an especially high-risk time for gallstone development, Dr. Alexander Wong of the University of Washington, Seattle, said at the annual Digestive Disease Week. “Gallbladder disease is the most common nonobstetrical cause of maternal rehospitalization the first 60 days after delivery,” he said. “Carbohydrate intake has been linked to the risk of gallbladder disease.”

To determine the effect of diet during pregnancy on gallstone formation, Dr. Wong and his colleagues performed ultrasounds on pregnant women during each trimester and at 4-6 weeks post partum. The average age of the women was 25 years, and each had at least two interpretable ultrasounds. Women who had gallstones at the first ultrasound and those with a history of gallstones were excluded. Overall, the cumulative incidence of new gallstones or biliary sludge indicative of gallbladder disease was 10%. Women in the highest quartile of starch consumption were 80% more likely than those in the lowest quartile to show signs of gallbladder disease, and women in the highest quartile of fructose consumption had double the risk, compared with the lowest quartile. Women who formed sludge or stones were more likely to have a higher caffeine and alcohol intake, be of Hispanic ethnicity, the risk, compared with the lowest quartile of fructose intake has been linked to increased maternal rehospitalization. In the previous studies comparing TIPS to LVP, which had a high failure rate, were the only option for TIPS therapy at the time. This study is being conducted to evaluate whether newer technology like covered stents with a lower failure rate will address this last potential pitfall.

The Early TIPS for Ascites Study is a randomized, multi-center study, sponsored by Gore Medical in collaboration with both hepatologists and interventional radiologists. Given the nature of the TIPS referral pathway, the team approach will lead to better patient care, more coordinated medical management, and improved recruitment. The goal of the study is to determine whether patients with difficult-to-treat ascites benefit most from early TIPS therapy using a covered stent or from continued LVP based on transplant-free survival.

This study has survival as its primary end point, in contrast to previous trials, which looked at control of ascites. There is little question that TIPS is better than LVP in controlling the ascites. But controlled trials show that use of TIPS is associated with more encephalopathy than alternative forms of therapy. What is unclear is the balance of these two factors and the overall impact on survival. This study will also help to answer questions from prior studies that used refractory ascites, because the Early TIPS for Ascites Study protocol allows for enrollment of patients prior to reaching the refractory stage as defined by the International Ascites Club. This is also the first study of its kind in which the Model for End Stage Liver Disease score is used for patient selection and will also be tracked during follow-up as a study end point.

Previous studies comparing TIPS with bare metal stents to LVP in patients with refractory ascites had mixed findings. Yet a recent meta-analysis of these studies found that TIPS patients had significantly longer transplant-free survival than paracentesis patients. A study published last year in the New England Journal of Medicine compared early TIPS intervention with a covered stent to pharmacotherapy/endoscopic band ligation in high-risk vascular bleeding patients, with positive results.

TIPS therapy is a minimally invasive procedure done with closed surgery, as only a small puncture is made in the jugular vein for insertion of the device. A TIPS creates a functional side-to-side portocaval shunt to route blood flow through the damaged liver and into the main blood vessels that carry blood back to the heart. With the TIPS procedure, alternative treatments such as medications and paracentesis for ascites, and endoscopic treatment of varices, may possibly not be needed as often. Some reports have shown significant improvements in TIPS therapy when using a covered stent versus a bare metal stent.

As one of the national principal investigators for the Early TIPS for Ascites Study, I believe that the possibility of prolonging patient lives is one of the most exciting new questions in TIPS therapy that we must answer. Most treatments for complications of portal hypertension improve the patient’s condition without affecting survival. We believe that if survival improves in the TIPS cohort, the paradigm for management of cirrhotic ascites might change significantly.

Thomas D. Boyer, M.D., is Director of the Arizona Liver Research Institute, Professor of Medicine, and Medical Director of the University Medical Center Liver Transplant Program, University of Arizona College of Medicine, Tucson.

**References**

3. Gastroenterology 2007;131:825-34.

Chicago – The risk of gallbladder disease was more than doubled in pregnant women in the top quartile of carbohydrate intake, compared with those in the bottom quartile, in a prospective study of 3,070 pregnant women.

Female gender is a risk factor for gallstones, and pregnancy is an especially high-risk time for gallstone development, Dr. Alexander Wong of the University of Washington, Seattle, said at the annual Digestive Disease Week. “Gallbladder disease is the most common nonobstetrical cause of maternal rehospitalization the first 60 days after delivery,” he said. “Carbohydrate intake has been linked to the risk of gallbladder disease.”

To determine the effect of diet during pregnancy on gallstone formation, Dr. Wong and his colleagues performed ultrasounds on pregnant women during each trimester and at 4-6 weeks post partum. The average age of the women was 25 years, and each had at least two interpretable ultrasounds. Women who had gallstones at the first ultrasound and those with a history of gallstones were excluded.

Overall, the cumulative incidence of new gallstones or biliary sludge indicative of gallbladder disease was 10%. Women in the highest quartile of starch consumption were 80% more likely than those in the lowest quartile to show signs of gallbladder disease, and women in the highest quartile of fructose consumption had double the risk, compared with the lowest quartile. Women who formed sludge or stones were more likely to have a higher caffeine and alcohol intake, be of Hispanic ethnicity, and gain less weight during pregnancy. By contrast, the highest quartile of galactose intake was independently associated with a decreased risk of gallbladder disease.

Women with the lowest carbohydrate intake had the greatest weight gain during pregnancy. “We believe that high carbohydrate intake during pregnancy may stimulate even more insulin release, therefore increasing the negative effects of hyperinsulinemia on bile composition,” Dr. Wong said.

“The fructose finding is fairly novel,” added Dr. Ko. “We hypothesize that fructose is metabolized differently than many other carbohydrates.” High fructose intake can cause insulin resistance, which can predispose individuals to gallstone formation, she noted. About the galactose finding she said, “we don’t have a good scientific explanation for why we found that. This is a very preliminary finding that needs further confirmation and explanation.” The results suggest that cutting down on refined, processed carbohydrates during pregnancy might reduce a woman’s risk of gallstones, Dr. Ko noted.

Dr. Ko said she had no relevant financial disclosures.
HalfLytely®
& Bisacodyl tablet
Bowel Prep Kit

PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution and bisacodyl delayed-release tablet

HalfLytely and Bisacodyl Tablet Bowel Prep Kit is a combination of PEG-3350, an osmotic laxative and bisacodyl, a stimulant laxative, indicated for cleansing of the colon as a preparation for colonoscopy in adults. Most common adverse reactions (>3%) are overall discomfort, abdominal fullness, abdominal cramping, nausea, and vomiting. There have been reports of ischemic colitis in patients with use of HalfLytely and 10 mg or 20 mg Bisacodyl Tablets Bowel Prep Kit. Use is contraindicated in the following conditions: gastrointestinal (GI) obstruction, bowel perforation, toxic colitis and toxic megacolon, gastric retention, ileus. Use caution when prescribing for patients with a history of seizures, arrhythmias, impaired gag reflex, regurgitation or aspiration, severe active ulcerative colitis, impaired renal function or patients taking medications that may affect renal function or electrolytes. Patients with impaired water handling who experience severe vomiting should be closely monitored including measurement of electrolytes. Advise all patients to hydrate adequately before, during, and after use.

Please see brief summary of Prescribing Information on adjacent page.
Obese Had Lower Survival 1 Year After Liver Transplant

BY MITCHEL L. ZOLER
Elsevier Global Medical News

PHILADELPHIA – Obesity shortens long-term survival in patients undergoing orthotopic liver transplant, according to a review of 285 patients.

One year out from their orthotopic liver transplants (OLTs), obese transplant recipients (those with a body mass index of 30 kg/m² or greater) had a 75% survival rate, significantly less than the 83% survival rate among nonobese liver transplant patients.

The procedures were performed at the University of Maryland at Baltimore during 2000-2008. Dr. Sameh A. Fayeh reported at the American Transplant Congress.

At 2 years and 5 years after transplantation, survival rates among the obese liver recipients were 67% and 54%, respectively – significantly less than the 79% and 63% survival rates in nonobese patients, said Dr. Fayeh, a transplant surgeon at the University of Maryland.

“I think [obese] patients don’t do well because their continued metabolic derangement, such as diabetes and hypercholesterolemia, affects their survival, but we don’t have proof of this,” he explained.

“It is to be determined whether intensive medical therapy, a rehabilitation program, or bariatric surgery post transplant would improve long-term survival.”

At the University of Maryland, liver transplants generally are not performed in patients with a body mass index greater than 40 kg/m², Dr. Fayeh added.

Obesity had no significant impact on short-term survival. At 1 month after transplant, survival rates were 95% among obese recipients and 97% among the nonobese, a difference that was not statistically significant.

In an interview, Dr. Robert S. Brown Jr., AGAF, said: “This study contradicts prior findings. I think the jury is still out on obesity and OLT, although certainly being obese cannot be good, and we should focus early interventions on limiting post-OLT weight gain.” Dr. Brown is the Frank Cardile professor of medicine and surgery and chief of the Center for Liver Disease and Transplantation at Columbia University College of Physicians and Surgeons, New York.

During the 9-year period that the investigators reviewed, 185 nonobese patients and 100 obese patients underwent an orthotopic liver transplant. About a quarter of the patients were at least 60 years old, about a quarter were African American, and slightly more than two-thirds were men. These and other demographic and clinical factors were similar in the obese and nonobese subgroups.

Early complications occurred at similar rates in the two subgroups, including the incidence of renal failure, mortality during initial hospitalization, and hospital length of stay.

The causes of death during the 5-year follow-up were also similar in the two subgroups. The most common causes of death were sepsis, in about 40% of patients, and graft failure, in about a fifth of the patients in both the obese and nonobese subgroups.

In a multivariable analysis, Dr. Fayen and his associates identified five demographic and clinical features that functioned as independent determinants of mortality. These five factors included use of a liver that came from a deceased donor, which raised the risk for death during follow-up by 2.3-fold, and donor age older than 50 years, which increased mortality risk 2.4-fold.

The other three factors were patient age older than 65, which raised mortality 2.2-fold; cold ischemia time for the transplanted organ exceeding 12 hours, which increased the mortality rate by 80%; and recipient obesity, which raised the mortality risk by 60%.

The American Transplant Congress was sponsored by the American Society of Transplant Surgeons. Dr. Fayeh said he had no disclosures.
While it is generally accepted that altered brain-gut interactions play an important role in the pathophysiology of functional gastrointestinal disorders (Ann. Rev. Med. 2011; 62:181-96), the importance of brain-gut interactions in other chronic disorders, including inflammatory bowel disease, chronic liver disease, and obesity, has received little attention.

This is surprising in view of the tremendous progress being made in the neurosciences, including the influence of peripheral inflammation on central nervous system (CNS) activity, the prominent role of the brain in the regulation of ingestive behavior and in stress neurobiology (Nature Rev. Neurosci. 2011; doi 101088/ nrr3071), and in view of our ability to study the biology of such gut-brain interactions in humans using rapidly evolving, multimodal brain imaging approaches (Nature Rev. Drug Discov. 2006; do1010.1038/nrd 2027).

The Hypersensitive Brain
Functional gastrointestinal (GI) disorders affect up to 15% of the population and have considerable impact on health-related quality of life of affected patients, while treatment options are limited. There is a general consensus that increased perception of physiological and experimental stimuli related to the GI tract plays an important role in many functional GI disorders, in particular those characterized by chronically recurring pain and discomfort, such as irritable bowel syndrome, functional dyspepsia, non-cardiac chest pain, and reflux-negative heartburn.

Equally important, but less well studied, in humans may be brain-gut signaling mechanisms, mediated by the autonomic nervous system, and possibly by the hypothalamic pituitary adrenal (HPA) axis.

Compared to other chronic GI disorders, in which specific gut- and mucosa-related peripheral abnormalities have been well characterized, in functional GI disorders the brain appears to play the dominant role in mediating the symptoms.

Multimodal brain imaging studies have identified both structural and functional alterations of the brain in affected patients (Gastroenterolgy 2011;140:407-11), and some of them are being evaluated as possible biomarkers for these disorders (Gastroenterology 2011;140:1377-9).

The Addicted Brain
Obesity is a major health problem, with up to 35% of adult Americans currently considered obese. In preclinical studies, tremendous progress has been made in the understanding of peripheral, gut-triggered satiety mechanisms as well as in hypothalamic mechanisms regulating ingestive behaviors (Ann. Rev. Psychol. 2008;59:35-92). Meanwhile, the role of higher brain functions in humans, including those related to interoception, and reward mechanisms in the pathophysiology of obesity have largely been ignored.

However, recent breakthroughs in our ability to study the role of the human brain in hedonic aspects of food intake have led to the concept of “food addiction” (Trends in Cog. Sci. 2011;15:37-45). In the normal state, reward-based (hedonic) mechanisms are typically regulated closely by interoceptive feedback from the gut (homeostatic regulation of food intake), but in obesity, this balance appears to be altered, and shifted toward a dominance of hedonic mechanisms with a down-regulation of gut-based feedback systems to the brain.

The Brain in Chronic Inflammation
Despite the extensive preclinical literature demonstrating the effects of peripheral inflammation on the CNS, there is little recognition of the importance of such neuroimmune interactions in human chronic inflammatory diseases affecting the intestine or the liver. Multiple pathways by which peripheral cytokine activation can result in central glia activation have been reported in preclinical studies.

Structural and functional alterations in the human brain associated with peripheral and related central immune activation may play an important role in such common clinical manifestations as fatigue, pain, associated psychiatric comorbidity, and impaired health-related quality of life. Furthermore, chronic psychosocial stress, depression, and anxiety are likely to modulate peripheral immune activity via the autonomic nervous system and the HPA axis.

The Healing Brain
Placebo response rates between 30% and 50% are observed in trials of novel medications in many chronic GI disorders, including functional and inflammatory bowel diseases. While the placebo response has traditionally been viewed as a nuisance in clinical trials, tremendous progress has been made in identifying the neurobiological mechanisms by which the brain can induce clinical remissions in both functional and organic disorders, in response to contextual cues.

Similar salutogenic brain networks are engaged not only in the context of clinical trials, but also by hypnosis, mindfulness meditation, and acupuncture, and probably also by the interactions with a skilled clinician. Electrical or pharmacological vagal stimulation has also been demonstrated to have beneficial effects on inflammation and chronic pain.

Harnessing the brain’s innate general salutogenic mechanisms may be a cost-effective adjuvant strategy to current disease-specific treatments of chronic GI disorders.

Summary and Conclusions
Rapid progress in the neurosciences has largely gone unnoticed by the field of gastroenterology, and few clinicians would implicate the central nervous system as a major component in the pathophysiology of chronic GI disorders other than IBS.

While the brain continues to be viewed primarily as the organ concerned with psychological processes, extensive preclinical and a growing body of clinical evidence supports a crucial role of the CNS as the key homeostatic regulator of health and disease. Recognizing and understanding this important role is likely to have major influence on more cost-effective treatments for several chronic GI disorders.

By Dr. Emeran A. Mayer

AGA Digestive Health Outcomes Registry™
AGA Digestive Health Outcomes Registry™

Outcomes-Driven Quality for GI Care
Helping you to:
- Improve patient outcomes.
- Enhance practice efficiencies and profitability.
- Evaluate care of patient populations.
- Demonstrate value to payors, purchasers and patients.

AGA Registry Now Offers Direct Data Submission from EMRs
Integration options include:
- Off-the-shelf reporting with gMed’s gGastro v4
- Customized integration with any EMR system

Don’t have an EMR system? The registry has an easy-to-use web-based interface and sampling methodology to ease data entry time.

Initial clinical areas: IBD and colorectal cancer prevention — Additional clinical areas are in development.

For more information, visit www.AGARegistry.org.

AGA INSTITUTE
G. Mayer, M.D., is Professor of Medicine, Physiology & Psychiatry, and Director, Oppenheimer Family Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA.
The Road to Personalized Therapy for BD

By Dr. Stephen R. Targan

The spectacular evolution of scientific technology over the last decade is accelerating the progress toward personalized medicine for patients with inflammatory bowel diseases (IBD). This progress has been largely a function of improved genetic approaches, however, to realize the goal of individualized therapy for IBD, much remains to be learned about the biologic mechanisms that underlie the varying clinical and subclinical expressions of disease. Free movement of information between genetic and biologic research and across animal and human investigation will allow us to progress most quickly toward our goal.

To date, 71 genetic loci have been associated with Crohn’s disease (CD) and 49 with ulcerative colitis (UC), with many being relevant to both. This verifies a longstanding hypothesis that UC and CD are heterogeneous diseases and that there are subgroups of IBD that share major biologic pathways, and others defined by unique disease-related pathways. It remains to be seen whether these subgroups are determined by individual genes, or whether several gene variants come together to generate unique clinical phenotypes.

Bridging the Gap Between IBD Genomics and Development of Treatment Algorithms

Multiple analytic techniques can be used to stratify subsets of IBD and predict natural history and outcomes. A Genome Wide Association Study (GWAS) compares the entire genome between study populations. The first GWAS performed on the UC population was published in PLoS Medicine in 2007, and these studies have identified related gene groups, but GWAS using larger numbers of patients and additional single nucleotide polymorphisms (SNPs), combined with clinical or biologic sub-type variables, have identified 120 loci associated with IBD. In addition, multiple biomarkers have been associated with different forms of IBD and provide information on the host-environmental interface.

Finally, mucosal gene expression approaches are used to define host-environmental interactions at the level of the mucosa. The following examples show how these approaches together serve to focus the generation of analytical models for further investigation of the inflammatory response and to guide hypotheses for in vitro studies of biologic processes.

In this scenario, a subgroup of patients with UC responds to treatment with the anti-TNF monoclonal antibody, infliximab. Using a UC GWAS, risk and protective SNPs of the IL23R gene were found to be associated with infliximab response. It was also found that risk variants were associated with response, whereas protective variants were associated with no response.

By using GWAS techniques in a refined UC population, we are able to identify variants related to medically refractory UC. We also showed that certain patterns of SNPs and increasing numbers of SNPs are related to a more aggressive time-frame from diagnosis to the need for surgery.

Bio-marker analysis of a cohort of UC patients being treated with infliximab showed that patients in this cohort with the serologic marker pANCA, known to be associated with subtypes of IBD, responded differently. We are able to compare these subgroups to patients without pANCA. Using an expression array to evaluate mucosal gene expression, it was shown that low expression of mRNA from a certain set of genes was associated with response to infliximab, and high expression was associated with lack of response.

Combination of such approaches and variables can be used to generate a model demonstrating that an increased number of risk factors differentiate those patients who do not respond to infliximab from those patients in whom infliximab leads to remission. Importantly, these techniques may well begin to explain differential response results in clinical trials and potentially may be used to identify targets in the nonresponsive population.

Two-Way Translation of IBD Genomic Data to Identify Therapeutic Targets: Man to Mouse, and Back to Man

At present, human genomic discovery is informing animal model investigations, which in turn inform our research to further characterize the mechanisms underlying biologic and clinical manifestations in subgroups of patients with IBD. By analyzing genes and variants identified by GWAS according to their roles in the cellular mechanisms of mucosal inflammation, relationships between genes and their products emerge that may not have been considered previously.

For example, sorting genes by function demonstrated that not only flora of the microbiome, but also viral infections are required for disease expression. Norovirus has been shown to interact with a specific gene mutation essential for altering Paneth cell structure and function in a mouse model of Crohn’s disease. In humans, CD patients with the same genetic abnormality also found to have intestinal changes in their Paneth cell structure and function.

In addition, recent GWAS findings showed that variants of a risk gene, PUTF2, are related to norovirus infectivity. This knowledge gained from mouse studies can be translated to human findings.

Will Genomic Research Allow Us to Alter Natural History?

The natural history of CD is characterized by progression of severity including features of fibrostenotic and penetrating disease, which begs the question of whether there are CD severity genes that can be targeted to alter this natural history.

We have shown that a variant of the TNFSF15 gene is associated with CD in all ethnic groups, with higher expression of the TNFSF15 gene product, the pro-inflammatory cytokine TL1A, and with the need for surgery in a subset of patients with CD. To define the underlying genetic and biologic basis for these findings, we developed mouse models engineered to replicate constitutive over expression of TL1A.

In each model, mice developed long strictures in the small intestine, in addition to multiple strictures in the colon. These results show that the product of TNFSF15 determines a pattern of fibrostenosis consistent with what is seen in CD, and thus is potentially a target for the development of therapy that might alter disease natural history.

Achieving personalized medicine for patients with IBD hinges on rapid in-depth analysis of specific genetic variants to determine functionally causative SNPs. This information will lead to biologically and clinically characterized phenotypically distinct subsets of disease, with specific algorithms for treatment.

Stephan Targan, M.D., AGAF, is Director, Division of Gastroenterology; Director, Cedars-Sinai Inflammatory Bowel and Immunobiology Research Institute; and Director, Cedars-Sinai Inflammatory Bowel Disease Center, Los Angeles, Calif.

Update on Colorectal Cancer Screening

By Dr. Dawn Provencal

This discussion will focus on recommendations for colorectal cancer screening. In the United States, Europe, and Asia, first, the average-risk population refers to those who are asymptomatic, and without a personal history of colorectal adenoma, adenomatous polyps, or inflammatory bowel disease or any history of a first-degree relative with CRC.

The impact of CRC is felt worldwide. It is the second leading cause of cancer death in the United States (CA Cancer J. Clin. 2009;59:225-49). In the European Union, it is the second leading cause of cancer death among men and women (http://ec.europa.eu/dgs/health_and_consumer_policy/communication/communication_2001/health_0905_02_en.pdf). And in Asia, the incidence of CRC is increasing rapidly (Gut 2008;57:1166-76).

However, cancer and cancer deaths can be reduced through screening. CRC screening tests fall into two broad categories: passive and active. In identifying cancer, including the stool tests such as fecal occult blood testing (FOBT), fecal immunochemical testing (FIT), and stool DNA (sDNA), and those that are effective at detecting both cancer and premalignant adenomatous polyps. The latter include the structural exams such as colonoscopy, double-contrast barium enema, and computerized tomographic colonography (Gastroenterology 2008;134:1570-95).

The guiding principles of screening in different countries are the same. In the United States, the first trial of FOBT showing reduced mortality from CRC was not published until 1993. Colonoscopy was introduced as a screening method in the 1990s but was not recommended by the USMSTF for screening until 1997, and became a covered Medicare benefit in 2001 (Am J Gastroenterol. 2010;105:1633-5).

Prior to reviewing the evidence for CRC screening, it is worthwhile to consider that, in the United States, mortality from CRC began to fall around 1980, before any widespread use or recommendation of screening. In fact, the first trial of FOBT showing reduced mortality from CRC was published until 1993. Colonoscopy was introduced as a screening method in the 1990s but was not recommended by the USMSTF for screening until 1997, and became a covered Medicare benefit in 2001 (Am J Gastroenterol. 2010;105:1633-5).

The evidence for the different screening modalities Continued on following page
Recent Advances in Endoscopic Ultrasound

A primary indication for endoscopic ultrasound has always been the local staging of GI cancer. However, this role is fading due to improvements in MRI, CT, and PET scanning, as well as the application of neoadjuvant chemoradiotherapy.

Endoscopic ultrasound (EUS) may regain favor for cancer staging if effective EUS contrast agents are developed – these hold promise for improving the detection of distant metastases, particularly in the liver. For cancer staging, a principal advantage of EUS is its ability to detect and sample lymph nodes. EUS is far superior to all modalities in the detection of lymph nodes, and this advantage over radiology will endure for the foreseeable future.

EUS also plays an important role in evaluation of the pancreas. It is the best modality for structural assessment of the pancreas, particularly when looking for early chronic pancreatitis. Comparative studies with function testing and ERCP have been performed, but most importantly, correlations have been drawn between EUS findings and histology. Additionally, the finding of a normal pancreas by EUS is almost certainly indicative that the gland is normal.

Over the last 5 years, most endosonographers are seeing a significant increase in the number of patients referred for evaluation of pancreatic cysts. There is much speculation about why this is occurring, and the reasons include an increased incidence of mucinous cysts (particularly intraductal papillary mucinous neoplasm, or IPMN), and also the routine use of MRI, or rapid, complete scanning through the pancreas. Gastrointestinal or transduodenal route, has been more widespread, and most major medical centers now provide EUS as a service and are capable of offering training. Inevitably, there will be improvements in the technology, which should further advance the use of this technique.

References
4. Gastroendoscopie Research and Information Center; Epidemiology, Division of Gastroenterology and Hepatology, Digestive Disease Center, Medical University of South Carolina, Charleston.

Continued from previous page

ranges from randomized controlled trials to case-control studies and cost-effectiveness analyses. The strongest evidence for the efficacy of screening comes from randomized controlled trials of FOBT and flexible sigmoidoscopy. Studies of FOBT in the United States, United Kingdom, and Denmark showed up to a 33% reduction in CRC mortality in people who were screened annually and a 15%-18% reduction in mortality for biennial screening (N. Engl. J. Med. 1993;328:1365-71, Lancet 1996;348:1472-7, Lancet 1996;348:1467-71).

The evidence for flexible sigmoidoscopy includes a randomized population trial conducted in the United Kingdom showing that one-time screening with flexible sigmoidoscopy reduced death from colorectal cancer by 31% (Lancet 2010;375:1624-33).

And the evidence for colonoscopy comes from a meta-analysis of the FOBT and flexible sigmoidoscopy research, in which patients with a positive result underwent colonoscopy. In addition, in populations undergoing colonoscopy, there have been comparisons of cancer incidence to expected cancer incidence. Some have shown a reduction in cancer cases, while others have not (N. Engl. J. Med. 1993;328:1365-71, Clin. Gastro. Hep. 2009;7:710-15, Gastroenterology 2005;129:34-41). More recently, a population-based case-control study using administrative claims data showed a 37% reduction in death from CRC in those who underwent colonoscopy.

In summary, the data suggest that there are multiple methods to screen for CRC. In fact, the ability of these methods to reduce death from CRC is about the same, with a 33% reduction in death with FOBT (N. Engl. J. Med. 1993;328:1365-71), a 31% reduction with flexible sigmoidoscopy (Lancet 2010;375:1624-33), and a 37% reduction in death with colonoscopy. In 2011, we may be at the point of screening equipoise or equipoise. Randomized controlled trials of colonoscopy compared to FIT and compared to usual care in Europe are ongoing and may provide additional information on the benefits of using the alternative strategies (http://clinicaltrials.gov/ct2/show/NCT00906997, http://clinicaltrials.gov/ct2/show/NCT00883792).

In the United States, the national colonoscopy study comparing colonoscopy with or without surveillance to FOBT will provide data on the reduction in cancer incidence (http://clinicaltrials.gov/ct2/show/NCT001020118?term=Zauber&rank=1). The newly funded VA Cooperative Study, CSP 577, will compare screening colonoscopy with FIT in 50,000 veterans over a 10-year period and will examine the impact on death from colorectal cancer.

These screening trials may provide definitive evidence about the superiority of one screening strategy compared to another. However, while we wait for their results, the evidence suggests that the alternative screening strategies may be about equal in their ability to prevent death from colorectal cancer.

So, in our efforts to increase screening rates in 2011, there are roles for provider recommendations for screening and individual preferences for screening modalities, as well as an opportunity to improve the uptake of colorectal cancer screening with shared decision making.

Dawn Provenzale, M.D., M.S., is Director, Durham Epidemiologic Research and Information Center; Director, GI Outcomes Research Group, Duke University; and Professor, Division of Gastroenterology, Duke University, Durham, N.C.
Hepatitis C in Minority Populations

About 3.2 million people in the United States are chronically infected with hepatitis C virus (HCV), the leading cause of cirrhosis and hepatocellular carcinoma and the leading indication for liver transplant. HCV prevalence is highest in minorities, especially black men, but blacks have poorer response to peginterferon/ribavirin than whites. VIRAT-IEP-C, a study of black and white patients with genotype 1 HCV treated with peginterferon alfa-2a, found lower sustained virologic response (SVR) rates in blacks compared to whites (28% vs 52%) (Gastroenterology 2006;131:470-7). Blacks also have lower SVR to peginterferon alfa-2b, and lower SVR when infected with HCV genotypes 2 and 3.

The impact of Hispanic ethnicity on HCV treatment response is largely unknown. The LATINO study found significantly lower SVR (34%) to peginterferon/ribavirin in white Hispanics with HCV genotype 1 compared to non-Hispanic whites (49%) (N. Engl. J. Med. 2009;360:257-67). However, the LATINO results may not be generalizable, because inclusion/exclusion criteria were narrow; and investigators did not measure insulin resistance, which is linked to lower SVR and is prevalent in Hispanics. One mechanism for poorer response of blacks and possibly Hispanics to peginterferon/ribavirin was elucidated recently. Genome-wide association studies in HCV-infected patients uncovered single nucleotide polymorphisms in IL28B (IFN-gamma-3 gene) that are strongly associated with race and SVR.

The favorable IL28B CC genotype occurs in highest frequency in East Asians and whites (and is associated with SVR above 80%), intermediate frequency in Hispanics, and lowest frequency in blacks (SVR 53%). In contrast, the unfavorable TT genotype is most frequent in blacks, and is associated with an SVR of 12%. Investigators estimate that variable frequency of the IL28B C-allele explains half the racial differences in SVR to peginterferon/ribavirin.

We have entered a new era of HCV therapy with the recent approval of two direct-acting antiviral (DAA) drugs, boceprevir and telaprevir. DAA use was linked to increased side effects, but DAA/peginterferon/ribavirin significantly improved SVR in patients with HCV genotype 1, and shortened treatment in many patients. Data on DAA use in minorities is limited, but promising. In every trial, addition of the DAA improved the SVR for all ethnic groups. In ADVANCE, SVR in the telaprevir/peginterferon/ribavirin arms (69%-75%) was significantly higher than the peginterferon/ribavirin arm (44%) (N. Engl. J. Med. 2011;364:1195-206). Among 159 blacks (14.4% of patients), SVR was 42%-53% in boceprevir/peginterferon/ribavirin arms compared to 23% in the peginterferon/ribavirin arm. In each DAA trial, blacks had lower SVR than whites, but the number of blacks was small, and statistical comparison between blacks and non-blacks was not performed.

The impact of the IL28B genotype on responsiveness to the DAA arm is unknown. Data from DAA trials suggest that IL28B genotype is a stronger predictor of response than race. However, the strongest predictor of response is receiving DAA. Triple therapy with DAA/peginterferon/ribavirin improves SVR for all ethnicities and IL28B genotypes, narrowing the SVR gap between groups. Accordingly, the relative importance of the IL28B genotype may diminish, but further studies are needed to determine its role in HCV treatment paradigms.

As DAA enter the marketplace, several unresolved issues relevant to minority populations remain. The impact of IL28B, race/ethnicity, and other host factors on treatment responsiveness must be explored in well-designed trials with larger representation of minorities. Innovative strategies are needed to improve minority recruitment into these trials, and care must be taken to ensure that minority patients with hepatitis C have equal access to DAA.

Andrea Ewing Reid, M.D., M.P.H., is Program Director, Gastroenterology Training, Gastroenterology, Hepatology and Nutrition Section, Washington DC VA Medical Center.
Biopsy for Celiac Disease Before Restricting Diet

BY MICHELE G. SULLIVAN
Elsevier Global Medical News

SAN DIEGO – An intestinal biopsy is almost always necessary to confirm celiac disease, and is a must before committing a patient to the only treatment that is effective—a lifelong gluten-free diet.

Sticking to such a restricted diet is difficult and expensive, Dr. Sheila Crowe, AGAF, said at the annual meeting of the American College of Physicians. “A lifelong gluten-free diet sounds simple, unless you’re the patient. ... Eating out is very difficult, especially for children and teens who face a lot of peer pressure.”

“And eating gluten-free at home is expensive. Studies in the United States, Canada, and the United Kingdom confirm that a lifelong diet of gluten-free foods costs about three times more than a normal diet,” said Dr. Crowe, then of the University of Virginia in Charlottesville and currently professor of medicine and director of research, division of gastroenterology, University of California, San Diego.

Because treating celiac disease requires this lifelong commitment, a positive serologic test isn’t enough to rule it in, she said. Nor are any of the available immunologic tests, including the most widely used—tissue transglutaminase IgA (tTG IgA)—that are specific enough to replace intestinal biopsy as the sole method for reliably diagnosing celiac disease.

“A positive tTG test is not enough to place a person on this lifelong treatment without confirmation from an intestinal biopsy,” she said. “This is especially important for children, because of the higher likelihood of false negatives in that group and the impact of a lifelong dietary restriction.”

tTG IgA has a very high sensitivity and specificity, but it isn’t perfect, Dr. Crowe said. “If you have a patient with clinical symptoms and the tTG comes back negative, there is still a 10% chance that’s a false negative. Another scenario could be a patient who has an autoimmune disease or a relative with celiac, and is experiencing celiac symptoms. If the tTG came back negative on that person, I would still do an endoscopy.”

The only exception is a patient with celiac symptoms who already has biopsy-proven dermatitis herpetiformis, with the classic immunofluorescent IgA deposits at the dermal-epidermal junction. “If you biopsy these patients, the intestine will show the changes associated with celiac disease every time,” Dr. Crowe said.

With AGA Mobile Tools, you can:

» View AGA guidelines on preferred approaches to specific medical problems or issues, helping you stay current and provide optimal patient care.

» Get the latest peer-reviewed journal articles from Gastroenterology and Clinical Gastroenterology and Hepatology.

» View hot topics in news and policy — a great way to keep abreast of what’s happening in the field.

» Learn about research funding opportunities in academic medicine and more.

With AGA Mobile Tools, you can:

• View AGA guidelines on preferred approaches to specific medical problems or issues, helping you stay current and provide optimal patient care.

• Get the latest peer-reviewed journal articles from Gastroenterology and Clinical Gastroenterology and Hepatology.

• View hot topics in news and policy — a great way to keep abreast of what’s happening in the field.

• Learn about research funding opportunities in academic medicine and more.

With AGA Mobile Tools, you can:

• View AGA guidelines on preferred approaches to specific medical problems or issues, helping you stay current and provide optimal patient care.

• Get the latest peer-reviewed journal articles from Gastroenterology and Clinical Gastroenterology and Hepatology.

• View hot topics in news and policy — a great way to keep abreast of what’s happening in the field.

• Learn about research funding opportunities in academic medicine and more.

With AGA Mobile Tools, you can:

• View AGA guidelines on preferred approaches to specific medical problems or issues, helping you stay current and provide optimal patient care.

• Get the latest peer-reviewed journal articles from Gastroenterology and Clinical Gastroenterology and Hepatology.

• View hot topics in news and policy — a great way to keep abreast of what’s happening in the field.

• Learn about research funding opportunities in academic medicine and more.
Bariatric Surgery Now ‘Safer Than Appendectomy’

BY MITCHEL L. ZOLER
Elsevier Global Medical News

ORLANDO – Bariatric surgery achieved an unprecedented level of safety through 2009, as surgeons in the United States mastered the laparoscopic gastric bypass approach and offered patients gastric banding or gastropasty.

These findings were based on data that were collected on more than 100,000 U.S. patients treated at academic medical centers during 2002-2009.

This recent era also ushered in a new list of risk factors for in-hospital mortality in patients who underwent bariatric surgery, including two modifiable risk factors: diabetes and the type of surgery used. Dr. Brian R. Smith said at the annual meeting of the American Society for Metabolic and Bariatric Surgery.

“We [found] preoperative factors that predict mortality. We can’t change patient age, sex, or insurance type, but we can better manage their diabetes preoperatively, and we can change the type of surgery they receive” to minimize their risk, said Dr. Smith, who is a surgeon at the University of California, Irvine, and chief of general surgery at the Veterans Affairs Healthcare System in Long Beach, Calif.

“Bariatric surgery is now statistically safer than appendectomy. Probably the most significant factor is that surgeons have gotten better with the laparoscopic approach; we got over the learning curve,” he said in an interview.

Dr. Smith and his associates reviewed information on 105,287 patients who underwent bariatric surgery during 2002-2009 at hospitals that contribute data to the University HealthSystem Consortium, a database of about 160 U.S. academic medical centers and affiliated hospitals.

During that period, bariatric surgery volume ranged from about 10,000 cases in 2002 to about 16,000 in 2009. Through 2003, open gastric bypass was most commonly being done, and starting in 2004 surgeons also began reporting the use of laparoscopic gastric bypass and gastric banding.

By 2005, about 60% of the roughly 13,000 bariatric procedures that year involved laparoscopic bypass, with open bypass reduced to less than 20% of the total.

During 2009, nearly 70% of the bariatric procedures performed at hospitals in the consortium were laparoscopic bypasses, about a quarter were banding or gastropasty, and only about 6% of the cases involved open bypass, Dr. Smith said.

Concurrent with this shift in the type of bariatric surgery performed came a striking drop in in-hospital mortality. In 2002, the rate was four deaths per 1,000 patients. Over the following 7 years, mortality steadily fell and reached a new low of 0.6 deaths per 1,000 patients in 2009, Dr. Smith reported. (See box, next page). “It’s a remarkable achievement—an American surgical success story,” commented Dr. John M. Morton, who is the director of bariatric surgery at Stanford (Calif.) University.

Dr. Morton attributed the sharp decline in mortality to the rapid switch from open to laparoscopic gastric bypass, the focus starting in 2004 on treatment of bariatric surgery patients at designated centers of excellence, improved clinical pathways, and better patient selection.

“We consistently see mortality rates of 0.1%, 0.3%, tops. That makes bariatric surgery as safe as laparoscopic cholecystectomy and hip replacement,” he said in an interview.

Dr. Smith agreed that the rapid drop in the number of open gastric bypass procedures starting in 2005 and their replacement by laparoscopic procedures played a major role in the fall in patient mortality during the mid-2000s.

The more than 100,000 patients that were reviewed by Dr. Smith included 17% who were older than 60 years. About 80% of them were women and about 73% were white. The prevalence of hypertension was 56%, 30% had diabetes, and 22% had hyperlipidemia. Two-thirds of the patients had private medical insurance coverage.

A multivariate analysis identified six factors that were linked with an increased mortality risk: age older than 60 years, male sex, Medicare coverage, diabetes,
open surgery, and gastric bypass surgery. Diabetes had not previously been identified as a mortality risk in published analyses, and the new list did not include hypertension, which had been a risk factor in prior analyses.

On the basis of these factors, Dr. Smith and his associates developed a mortality risk-scoring formula that assigned one point for each of four risk factors—male sex, Medicare insurance, open surgery, and gastric bypass — and 0.5 points for each of the other two factors, age 60 years or older and diabetes.

After assigning these point values to the patients in the database, they found that patients with a risk score of 3.5 or greater had a sevenfold increased risk of in-hospital mortality, compared with patients with a score of zero or 0.5.

Dr. Smith said that he had no disclosures. Dr. Morton said that he has received an educational grant from Ethicon Endo-Surgery, and he has received honoraria from and served on the scientific advisory board of Vybrant.

To view a video about this study, scan this QR code with your mobile device. Don’t have a QR reader? Get one at mobiling.com/en/download.php. Or to view the video online, go to tiny.cc/9uech.

**DEXILANT works to effectively maintain EE healing and heartburn relief**

**DEXILANT 30 mg provides effective maintenance of EE healing**

62% of patients remained healed over 6 months with DEXILANT 30 mg (n=125) vs 14% with placebo (n=119; p<0.00001). Study primary endpoint.

Results of a 6-month, multicenter, double-blind, placebo-controlled, randomized study of patients who had endoscopically documented erosive esophagitis (EE) treated with DEXILANT for 4 weeks, maintaining healing of EE and relief of heartburn for up to 8 weeks, and treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD) for 4 weeks.

Conclusions of comparative efficacy cannot be drawn from this information.

**Indications**

DEXILANT is indicated for healing all grades of erosive esophagitis (EE) for up to 8 weeks, maintaining healing of EE and relief of heartburn for up to 6 months, and treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD) for 4 weeks.

**Important Safety Information**

DEXILANT is contraindicated in patients with known hypersensitivity to any component of the formulation. Hypersensitivity and anaphylaxis have been reported with DEXILANT use. Symptomatic response with DEXILANT does not preclude the presence of gastric malignancy. Long-term and multiple daily doses of PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Hypomagnesemia has been reported rarely with prolonged treatment with PPIs. Most commonly reported adverse reactions were diarrhea (4.8%), abdominal pain (4.0%), nausea (2.9%), upper respiratory tract infection (1.9%), vomiting (1.6%), and flatulence (1.6%). Do not co-administer atazanavir with DEXILANT because atazanavir systemic concentrations may be substantially decreased. DEXILANT may interfere with absorption of drugs for which gastric pH is important for bioavailability (e.g., amoxicillin, etravirine, delavirdine, iron salts, ketoconazole). Patients taking concomitant warfarin may require monitoring for increases in international normalized ratio (INR) and prothrombin time. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Concomitant tacrolimus use may increase tacrolimus whole blood concentrations.

Please see adjacent brief summary of prescribing information for DEXILANT.

**Note:** Rates based on data for 105,287 patients. Source: Dr. Smith
**BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION**

DEXILANT (dexlansoprazole) delayed-release capsules for oral use

**INDICATIONS AND USAGE**

DEXILANT is indicated for:

**Gastroesophageal Reflux Disease (GERD)**
- Treatment of GERD symptoms (heartburn and acid reflux) for up to 8 weeks
- Maintenance treatment of GERD for up to 6 months
- Treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD) for 4 weeks.

**CONTRAINDICATIONS**

DEXILANT is contraindicated in patients with known hypersensitivity to any component of the formulation. Hypersensitivity and anaphylaxis have been reported with DEXILANT use [see Adverse Reactions].

**WARNINGS AND PRECAUTIONS**

**Gastroesophageal Reflux Disease (GERD)**
- Symptomatic response with DEXILANT does not preclude the presence of gastric malignancy.
- Bone Fracture
- Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines [see Adverse Reactions].

**Hypomagnesemia**
- Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with lansoprazole. In controlled trials, the most common adverse reaction leading to discontinuation of the drug was hypomagnesemia requiring magnesium replacement and discontinuation of the PPI.

**For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically [see Adverse Reactions].**

**ADVERSE REACTIONS**

**Clinical Trials Experience**
- Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The rates observed in the clinical trials of DEXILANT are presented in Table 2.

In controlled studies of DEXILANT, 11% of patients were aged 65 years and over. No overall differences in safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

**GI Hepatic Tests**
- The most common adverse reactions (≥10%) observed in clinical trials of a drug cannot be directly compared to rates observed in practice. Rates observed in the clinical trials of a drug cannot be directly compared to rates observed in practice. The rates observed in the clinical trials of DEXILANT are presented in Table 2.

**Infections and Infestations**
- Postmarketing Experience

**Differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.**

**Blood and Lymphatic System Disorders**
- DEXILANT is indicated for:
- Treatment of GERD symptoms (heartburn and acid reflux) for up to 8 weeks
- Maintenance treatment of GERD for up to 6 months
- Treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD) for 4 weeks.

**Drug Interactions**
- Drug-drug interactions of DEXILANT with warfarin or INR monitoring
- Concomitant administration of dexlansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP3A4.

**Use in Specific Populations**
- Pregnancy
- Therapeutic Effects

**Pediatric Use**
- Safety and effectiveness of DEXILANT in pediatric patients (less than 18 years of age) have not been established.

**Geriatric Use**
- In clinical studies of DEXILANT, 11% of patients were aged 65 years and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.
Renal Impairment
No dosage adjustment of DEXILANT is necessary in patients with renal impairment. The pharmacokinetics of dexlansoprazole in patients with renal impairment are not expected to be altered since dexlansoprazole is extensively metabolized in the liver to inactive metabolites, and no parent drug is recovered in the urine following an oral dose of dexlansoprazole.

Hepatic Impairment
No dosage adjustment for DEXILANT is necessary for patients with mild hepatic impairment (Child-Pugh Class A). DEXILANT 30 mg should be considered for patients with moderate hepatic impairment (Child-Pugh Class B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C).

OVERDOSAGE
There have been no reports of significant overdose of DEXILANT. Multiple doses of DEXILANT 120 mg and a single dose of DEXILANT 300 mg did not result in death or other severe adverse events. However, serious adverse events of hypertension have been reported in association with twice daily doses of DEXILANT 60 mg. Non-serious adverse reactions observed with twice daily doses of DEXILANT 60 mg include hot flashes, confusion, oropharyngeal pain, and weight loss. Dexlansoprazole is not expected to be removed from the circulation by hemodialysis. If an overdose occurs, treatment should be symptomatic and supportive.

CLINICAL PHARMACOLOGY
Pharmacodynamics
Serum Gastrin Effects
The effect of DEXILANT on serum gastrin concentrations was evaluated in approximately 3460 patients in clinical trials up to 8 weeks and in 1023 patients for up to 6 to 12 months. The mean fasting gastrin concentrations increased from baseline during treatment with DEXILANT 30 mg and 60 mg doses. In patients treated for more than 6 months, mean serum gastrin levels increased during approximately the first 3 months of treatment and were stable for the remainder of treatment. Mean serum gastrin levels returned to pre-treatment levels within one month of discontinuation of treatment.

Enterochromaffin-like Cell (ECL) Effects
There were no reports of ECL cell hyperplasia in gastric biopsy specimens obtained from 603 patients treated with DEXILANT 30 mg, 60 mg or 90 mg for up to 12 months. During lifetime exposure of rats dosed daily with up to 150 mg per kg per day of lansoprazole, marked hypergastrinemia was observed followed by ECL cell proliferation and formation of carcinoid tumors, especially in female rats (see Nonclinical Toxicology).

Effect on Cardiac Repolarization
A study was conducted to assess the potential of DEXILANT to prolong the QT/QT interval in healthy adult subjects. DEXILANT doses of 90 mg or 300 mg did not delay cardiac repolarization compared to placebo. The positive control (metoloxacin) produced statistically significantly greater mean maximum and time-averaged QT/QT intervals compared to placebo.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
The carcinogenic potential of dexlansoprazole was assessed using lansoprazole studies. In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with lansoprazole at doses of 5 to 150 mg per kg per day, about 1 to 40 times the exposure of humans based on BSA) exceeded the ranges of historical controls for this strain of mice. Lansoprazole treatment increased the incidence of liver tumors (hepatocellular adenoma and hepatocellular carcinoma). In rats, lansoprazole also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In male rats, lansoprazole produced a dose-related increase in testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15 to 600 mg per kg per day (10 to 80 times the recommended human dose of lansoprazole 30 mg per kg) was not increased. Lansoprazole produced dose-related gastric ECL cell hyperplasia and ECL cell carcinoids in both male and female rats (see Clinical Pharmacology).

In rats, lansoprazole also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In male rats, lansoprazole produced a dose-related increase in testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15 to 600 mg per kg per day (10 to 80 times the recommended human dose of lansoprazole based on BSA) exceeded the low background incidence (range = 1.4% to 10%) for this strain of rat. In a 24-month carcinogenicity study, CD-1 mice were treated orally with lansoprazole doses of 15 to 600 mg per kg per day, 2 to 80 times the recommended human dose of lansoprazole based on BSA. Lansoprazole produced a dose-related incidence of gastric ECL cell hyperplasia. It also produced an increased incidence of liver tumors (hepatocellular adenoma plus carcinoma). The tumor incidences in male mice treated with 300 and 600 mg lansoprazole per kg per day (40 to 80 times the recommended human lansoprazole dose based on BSA) and female mice treated with 150 to 600 mg lansoprazole per kg per day (20 to 80 times the recommended human lansoprazole dose based on BSA) exceeded the range of background incidences in historical controls for this strain of mice. Lansoprazole treatment produced adenoma of retinal testis in male mice receiving 75 to 600 mg per kg per day (10 to 80 times the recommended human lansoprazole dose based on BSA).

A 26-week p53 (+/-) transgenic mouse carcinogenicity study of lansoprazole was not positive. Lansoprazole was positive in the Ames test and in the in vitro human lymphocyte chromosomal aberration assay. Lansoprazole was not genotoxic in the in vivo rat hepatocyte unscheduled DNA synthesis (UDS) test, the in vivo mouse micronucleus test or the rat bone marrow cell chromosomal aberration test. Dexlansoprazole was positive in the Ames test and in the in vitro chromosomal aberration test using Chinese hamster lung cells. Dexlansoprazole was negative in the in vivo mouse micronucleus test.

The potential effects of dexlansoprazole on fertility and reproductive performance were assessed using lansoprazole studies. Lansoprazole at oral doses up to 150 mg per kg per day (40 times the recommended human lansoprazole dose based on BSA) was found to have no effect on fertility and reproductive performance of male and female rats.

PATIENT COUNSELING INFORMATION
To ensure the safe and effective use of DEXILANT, this information and instructions provided in the FDA-approved Patient Information Leaflet should be discussed with the patient. Inform the patient to watch for signs of an allergic reaction as these could be serious and may require that DEXILANT be discontinued.

Advise the patient to immediately report and seek care for any cardiovascular or neurological symptoms including palpitations, dizziness, seizures, and letany as these may be signs of hypomagnesemia (see Warnings and Precautions).

Advis the patient to tell their health care provider if they take azaMXANZ, tazarotene, warfarin and drugs that are affected by gastric pH changes (see Drug Interactions).

Advis the patient to follow the dosing instructions in the Patient Information Leaflet and inform the patient that:
- DEXILANT is available as a delayed release capsule.
- DEXILANT may be taken without regard to food.
- DEXILANT should be swallowed whole.
- Alternatively, DEXILANT capsules can be administrated as follows:
  - Open capsule.
  - Sprinkle intact granules on one tablespoon of applesauce.
  - Swallow immediately. Granules should not be chewed.
  - Do not store for later use.

References:

DEXILANT and DEXILANT (with design) are trademarks of Takeda Pharmaceuticals North America, Inc., registered in the U.S. Patent and Trademark Office. All other trademark names are the property of their respective owners.

©2011 Takeda Pharmaceuticals North America, Inc.
LPO 07152 3111 Printed in U.S.A.
few times where both pediatric and adult specialists are working together as one group,” Dr. Liacouras said.

“In addition, disagreements in the literature suggest that patients seem to be presenting with more advanced disease since the 2007 report was released,” he said. “The natural history of the disease also remains controversial.”

In addition, Adult gastroenterologists have only recently recognized EoE while pediatric gastroenterologists have appreciated this disease (by biopsy) since the late 1990s. Before 1995, we never saw this degree of rings and strictures (in children),” he added.

The defining aspects of the new diagnostic criteria include histology results from multiple esophageal biopsies coupled with clinical findings. “The problem, especially for adults, has been that many gastroenterologists expect the pathologist to make the diagnosis,” Dr. Liacouras said. “[Pathologists] can only describe what they’re seeing; the clinician has to combine the patient’s clinical findings and history with the degree of esophageal eosinophilia to make an accurate diagnosis.”

According to the guidelines, “With few exceptions, 15 eosinophils per high-power field is considered a minimum threshold for a diagnosis of EoE.” Other histopathologic findings may include basal cell hyperplasia, dilated intracellular spaces, and lamina propria fibrosis isolated to the esophagus. Because of the disease’s exclusive location in the esophagus, proton pump inhibitors are most often used initially as a way to rule out EoE.

“You want to be sure that acid reflux disease is not causing this problem. If the patient responds to a proton pump inhibitor, they may have ‘PPI-responsive esophageal eosinophilia’ but they do not have EoE,” said Dr. Liacouras. The symptoms include gastroesophageal reflux, heartburn, abdominal pain, and swallowing problems. Dysphagia and food impaction are the most common presenting symptoms in adolescents and adults. Patients typically experience bleeding problems. Patients with EoE often also present with other manifestations of atopic disorders—food allergy, asthma, eczema, chronic rhinitis, and environmental allergies, the guidelines note.

Skin prick and patch testing are effective supplemental diagnostic tools, but they are not perfect, Dr. Liacouras said. “This disease is not an anaphylactic event or an immediate hypersensitivity reaction; this is why it’s hard to use allergy testing as a diagnostic tool.”

Treatment recommendations have evolved since 2007. For both adults and children, topical steroids have been shown to be effective. These include steroids such as fluticasone, used with a spacer and swallowed instead of inhaled. Since the 2007 guideline, there’s also an oral viscous suspension of budesonide mixed in sucrose,” Dr. Liacouras said.

“Equally effective is the elimination of typical allergy-inducing foods. In children, many studies have shown that the removal of foods significantly improves both the symptoms and abnormal histology of EoE. Similar findings have begun to be reported in adults. Currently, biologics have not been adequately studied, and have not been proven impactful in this disorder,” he added. Because of the chronicity of the disease, both children and adults require lifelong therapy.

Eosophageal disease provides relief to some patients, but unless there are high-grade esophageal strictures, it’s reasonable to try medical or dietary therapy first, the authors wrote. Because of an increased risk of perforation, the guidelines advise physicians to use “a more conservative and careful approach” for EoE patients, compared with those who have other, more benign conditions.

The authors also call for future studies to identify EoE subgroups, further investigate the disease’s genetic underpinning, and study the role of allergy testing. Pediatric and adult specialists should time their joint efforts to improve diagnostic criteria and determine the optimal therapy.

“The joint effort of pediatric and adult clinical and basic scientists in a variety of subspecialties has been paramount in the rapid understanding of this disease process,” the paper said. “It is critical that leaders [in basic science, gastroenterology, pathology, and allergy and immunology] continue to work together and undertake studies on the natural history, pathophysiology, biomarkers, diagnosis, and therapeutic approaches, not only to increase the scientific and clinical knowledge of EoE but also to improve the lives of children and adults affected by the disease.”

Gastric MALT Lymphoma

Irradiation • from page 1

BY KERRI WACHTER

Eluciver Global Medical News

BOSTON – Gastric bypass surgery appears to be associated with increased fracture risk over the long term. Other fractures were not assessed for many years, and therefore we may be missing some of those effects,” said Dr. Kennel.

Dr. Kennel noted that most of the patients who underwent gastric bypass procedure used for bariatric surgery between 1985 and 2004 at the Mayo Clinic. The average age of the bariatric surgery patients was 44 years and most were female. A total of 79 patients experienced 132 fractures. Bariatric surgery patients had an increased risk of fracture at nearly all of the skeletal sites studied, not just in weight-bearing bones.

The higher rate of fractures following bariatric surgery suggests that structural and biochemical changes in bone that are observed after bariatric surgery are clinically important. Clinicians should discuss bone health with patients who have undergone or are considering bariatric surgery,” he said. Dr. Kennel noted that he and his coinvestigators have no significant financial relationships to report.
High Dietary Fat Linked to Esophageal Cancer

No association was found between fat consumption and diagnosis of Barrett’s esophagus.

BY RICHARD HYER
Elsevier Global Medical News

CHICAGO – Total dietary fats and saturated fatty acids were found to be positively associated with esophageal adenocarcinoma, but not with Barrett’s esophagus, in a prospective cohort study reported at the annual Digestive Disease Week.

“The role of fats may therefore be important in the change from metaplasia into neoplasia,” said principal investigator Dr. Max Yates, who is with the Norfolk and Norwich (England) University Hospital. “Dietary fats and saturated fats should therefore be measured in future etiological studies of adenocarcinoma.”

The study was intended to evaluate the role of dietary fat in the etiology of Barrett’s esophagus and esophageal adenocarcinoma. Barrett’s esophagus is characterized by metaplastic change in the cells of the lower esophagus, Dr. Yates said, and is recognized as a risk factor for esophageal adenocarcinoma.

A prospective cohort study design was selected, because the alternative case-control designs are subject to recall bias and selection bias, which can then lead to inaccuracies in the dietary information, he said.

The cohort was recruited from the EPIC (European Prospective Investigation into Cancer and Nutrition) Norfolk County database. The EPIC study overall has recruited more than 500,000 participants in 10 countries, and the EPIC-Norfolk cohort consists of 23,790 participants (aged 45-74 years) from rural, suburban, and inner-city areas.

There were three groups in the study: 3,667 randomly selected controls, 100 cases of Barrett’s esophagus, and 61 cases of esophageal adenocarcinoma. Controls were about the same age as were patients with Barrett’s esophagus (median, 59-60 years at recruitment), whereas those with esophageal adenocarcinoma were about 7 years older (median, 67 years). More than 80% of both groups were male. In this prospective cohort, the median age at diagnosis was 67 years for the Barrett’s patients and 73 years for the esophageal adenocarcinoma patients.

With the help of a nutritionist at study enrollment, participants began a 7-day food diary, which is “the most accurate, validated form of pragmatic nutritional assessment in large-scale epidemiological studies,” said Dr. Yates.

Patients recorded all food and beverages consumed, along with brands, portion sizes, and recipes. The diaries were coded using the DINER (Data Into Nutrients for Epidemiological Research) program.

Quintiles of dietary fat intake were generated, and hazard ratios were estimated using Cox regression analysis adjusted for age, sex, body mass index, smoking, alcohol use, and total energy intake.

The study population was divided into quintiles of dietary fat intake, and no association was found between total dietary fat intake and the diagnosis of Barrett’s esophagus. However, for esophageal adenocarcinoma, a stepwise increase in risk was observed across all quintiles of fat intake.

“The fifth (highest) quintile has just under four times greater risk, compared to the lowest,” said Dr. Yates, noting that this finding nevertheless did not quite reach statistical significance. However, he pointed out, the trend from one quintile to the next was 50%, and this was statistically significant with a hazard ratio of 1.50 (95% confidence interval, 1.05-2.14; P = .03).

The results were similar for saturated fats. No association was found between dietary saturated fat intake and a diagnosis of Barrett’s esophagus.

However, there was an increased risk for esophageal adenocarcinoma with greater saturated fat intake. “The fifth (highest) quintile had around three times greater risk, compared to the lowest,” said Dr. Yates. The trend, or average increase between quintiles, was statistically significant (HR, 1.35; 95% CI, 1.01-1.85; P = .04).

Dr. Yates concluded that total fats and saturated fatty acids were positively associated with esophageal adenocarcinoma, but not with Barrett’s esophagus.

“This has been demonstrated for the first time using food diaries, in a prospective cohort,” he said, adding that fats may play a role in the transition of tissue from metaplasia to neoplasia.

The study is ongoing, with a goal of assessing many different dietary factors, to determine whether they are involved in the development of this type of cancer.

The study was funded by Cancer Research UK and the U.K. Medical Research Council. Dr. Yates stated that he had no relevant financial disclosures.

Oncology for the GI
Horizons for the Future

October 14 & 15, 2011
The Westin Georgetown
Washington, DC
Hotel Reservation Deadline: Sept. 21
Pre-registration Deadline: Oct. 7

Don’t miss this one-of-a-kind conference that will review the interplay between genetics and patient management for a variety of GI malignancies.

Attention GI Fellows! Register at a reduced rate. Complimentary registration and monetary prizes for fellows who present outstanding abstracts for poster presentation.

Earn up to 14.25 AMA PRA Category 1 Credits™.

Register online at www.gilearn.org/freston.
Wake Forest Baptist Health

Hepatologist, Non-transplant
Department of Medicine, Gastroenterology
Seeking exceptional BC/BE Hepatologist to join us at Wake Forest Baptist Health, located in Winston-Salem, NC.
• MD
• Associate Professor level
• Gastroenterology and Hepatology Fellowship Trained
• Successful record of clinical excellence; research experience with evidence of independent funding; leadership; and a strong interest in graduate medical education
• North Carolina licensure or eligible

Selected candidate will serve as the Director of Hepatology and build a preeminent Hepatology program of the highest quality with balanced excellence in patient care, research and education. The Digestive Health Center at Wake offers the region’s most experienced experts in digestive diseases and the most advanced equipment and procedures to diagnose and treat gastrointestinal diseases. AA/EO employer.

Interested candidates send CV to
Monica Kiger
(336)716-0532 - telephone; (336) 716-5139 - fax
mkiger@wakehealth.edu
http://www.wakehealth.edu/HR/Faculty/Physician-and-Faculty-Careers.htm

Have questions on classifieds? Call Andrea LaMonica
(914) 381-0569 • (800) 381-0569 for more information.

Hepatologist

Minneapolis/St. Paul, Minnesota

Are you searching for an exciting, rewarding metropolitan practice with a competitive benefits and comp package, paid malpractice, and great colleagues? HealthPartners Medical Group (HPMG) is a successful multispecialty physician practice headquartered in Minneapolis/St. Paul, Minnesota and neighboring western Wisconsin. Our growing GI team has an excellent practice opportunity for a BC/BE gastroenterologist with Hepatology fellowship training or practice experience to care for our growing Hepatology patient base at nationally recognized Regions Hospital and our state-of-the-art Digestive Care Center in St. Paul.

Apply at www.healthpartners.jobs, forward your CV and cover letter to Lori.M.Fake@healthpartners.com, or call 800-472-4695 Ext EO.

HealthPartners Medical Group
healthpartners.com

Sanford Health Fargo is currently seeking BC/BE Gastroenterologists. Excellent productivity based opportunity - 60% endoscopy and 40% out-patient. Seven endoscopy suites just steps from the clinic. Hospital consults only; 100% hospitalist coverage. ERCP & EUS skills are desirable but not required. Call 1:8. Opportunity exists to teach medical students and Internal Medicine residents. Offering a competitive compensation plan with two years guaranteed salary plus incentives and a comprehensive benefits package. Willing to sponsor physicians with H1B or J1 visas.

Fargo, North Dakota, a diverse metropolitan community of 190,000, offers exceptional K-12 and higher education systems, world-class healthcare, affordable housing, low cost of living and a myriad of cultural and entertainment opportunities. The only things lacking are traffic jams and high crime rates. Visit www.fmchamber.com & www.fargo.k12.nd.us to learn more or contact:

Jean Keller, Physician Recruiter
Sanford Physician Placement
Phone: (701) 280-4853
Email: Jean.Keller@sanfordhealth.org
www.sanfordhealth.org
AA/EEO

MAINE: RIVERSIDE URBAN CENTER


NEW HAMPSHIRE

Hospital salaried position. State of the art endoscopy suite. Opportunity for Hepatology, ERCP Potential for EUS, manometry, and endoscopic GERO procedures. Service area of 90,000. Salary income guarantee, incentive plan, full benefits, sign on bonus, educational loan repayment. 4 day work week. 6 week vacation. CME. Beautiful New England town offers traditional outdoor venues, from snowboarding and skiing to year round tennis, swimming, horseback riding and Community Theater. Interstate drive to Boston and Montreal. No state income or sales tax. J-1 invited to inquire. Contact Lianne Harris, Health Search New England; 207-886-5680; Lharris@nehs.net

Project HOPE
Give.

WAKE FOREST BAPTIST HEALTH

Gastroenterology Opportunities (General and Hepatology)
Springfield, Illinois

The Department of Internal Medicine, Divisions of Gastroenterology & Hepatology at Southern Illinois University seeks additional Gastroenterologist/Hepatologist for its growing Division. Interested candidates should be board certified in Internal Medicine, and board eligible in Gastroenterology. Positions can accommodate general GI candidates, especially with an interest in inflammatory bowel disease or hepatology. Currently, the Division is led by Russell D. Yang, MD, PhD and consists of six gastroenterologists and two nurse practitioners. In this position, you will be involved with patient care and the teaching of medical students and residents. A faculty appointment is available at the Assistant or Associate Professor Level based upon experience and track record. Opportunities for basic and clinical research are available and encouraged.

To learn more, contact Beth Briggs at 800-678-7858 or via email ebriggs@ckjsearch.com.

Sanford Health News Rates
GI & Hepatology News Rates

4 Column Classified Ads

From 1” to 12” Sizes from 1/48th of a page to a full page

or contact: Andrea LaMonica
(800) 381-0569 or fax your ad to: (914) 381-0573

Email ad to: a.lamonica@elsevier.com

Elsevier
60 Columbus Road, Building B
Morristown, NJ 07960
Link Between PPI Use and *C. difficile* Inconsistent

**BY PATRICE WENDLING**

*Elsevier Global Medical News*

CHICAGO — The effect of proton pump inhibitors on *Clostridium difficile* infection was neither strong nor consistent in a longitudinal hospital cohort of 61,834 patients.

Previously conducted case-control studies reported that PPIs were associated with a two- to threefold increase in the risk of *C. difficile* infection (CDI), but these latest findings suggest that the impact of PPIs may be overstated, Dr. Kyung Sup Hong said, at the annual Digestive Disease Week.

In his study, CDI incidence per 1,000 person-years was 3.5 in patients receiving PPIs for less than 3 months (group 1), 7.4 in those on PPIs for 3 months but less than 1 year, (group 2), and 4.5 in those on PPIs for at least 1 year (group 3).

In logistic regression analysis that adjusted for PPI exposure, age, comorbid conditions, and daily PPI use in the previous 8 weeks, the association between PPI duration and CDI was significant, increasing from an odds ratio of 1 in group 1 (reference) to 2.59 in group 2 (P value less than .001), and to 2.17 in group 3 (P less than .01), Dr. Hong said.

Notably, the use of antibiotics in the previous 8 weeks significantly and markedly increased the risk of *C. difficile* infection to a very high odds ratio of 41.7 (P less than .01).

In a Cox proportional hazard model that further adjusted for the interval from PPI initiation to CDI attack or last follow-up, however, the association between PPI use and CDI was significant only for group 2 (hazard ratio 1.94, P less than .001) and not group 3 (HR 1.2, P = .25), said Dr. Hong of Seoul (South Korea) National University.

“We conclude that PPIs’ impact on CDI is neither strong nor consistent; therefore, PPIs seem to be an important confounder rather than a cause of CDI,” he said.

A recent study among hospital discharges (Arch. Intern. Med. 2010;170:784-90) reported a dose-response effect with acid suppression and the risk of CDI, but Dr. Hong noted that it provided no information about medications before admission.

In that study, the risk of CDI on or after the third hospital day increased from 0.3% in nonusers of acid suppressors to 0.6% in those receiving histamine, receptor antagonist therapy, to 0.9% in those receiving daily PPI and one 1.4% in those receiving more-frequent PPI therapy.

Dr. Hong and his colleagues aimed to evaluate the effect of PPI treatment duration on CDI development among all adults older than age 20 years who visited the Seoul National University Hospital and took a prescription PPI from January 2005 to December 2009.

Among the 61,834 patients, there were 534 CDI cases, of which 5 were identified with endoscopy only, and the remaining 529 were diagnosed via positive results on a *C. difficile* toxin assay.

CDI was reported in 319 of the 50,534 (6.3%) patients in group 1; 176 of the 9,112 (1.94%) patients in group 2; and 18 of the 2,178 (0.74%) patients in group 3.

The average follow-up time from the first PPI prescription until the last visit was 22 months, 32 months, and 47 months, respectively.

Patients infected with *C. difficile* were significantly older than those without, in the age range 20 to 92 years.

**PERSPECTIVE**

This study addresses an important topic, especially as the rates of *C. difficile* infection are on the rise, with corresponding major public health and health economics implications. In this study of hospital-based cases, the association between use of proton pump inhibitors and *C. difficile* infection was evident for shorter but not longer durations of PPI use.

Interpreting studies of the association between PPI use and *C. difficile* infection is complex.

On the whole, PPI users tend to represent a sicker patient population and are thus more predisposed to infection with *C. difficile*, irrespective of their PPI use. The authors adjusted for comorbidities; however, there are frequently unmeasured confounders representing poorer health that cannot be fully accounted for using traditional statistical methods.

Similar problems have been encountered in observational studies of PPI use and the potential interaction with *Clostridium difficile*. I think the jury is still out as to whether PPIs can be blamed for contributing to increased rates of *C. difficile* infection.

**JULIAN ABRAMS, M.D., M.S., is an Assistant Professor of Clinical Medicine, Department of Medicine, Columbia University College of Physicians & Surgeons. He has no relevant disclosures.**

Mutations Linked to Barrett’s, Esophageal Adenocarcinoma

**BY MARY ANN MOON**

*Elsevier Global Medical News*

Researchers have identified germline mutations in three genes that appear to be associated with Barrett’s esophagus and esophageal adenocarcinoma, according to a report in JAMA.

The mutations, however, only accounted for a small proportion, 11%, of cases of Barrett’s esophagus (BE) and esophageal adenocarcinoma (EAC) in this study. Mutations in the MSR1 gene accounted for 7% of cases, and mutations in either ASCC1 or CTHRC1 accounted for approximately 2% each, said Mohammed Orloff, Ph.D., of the Genomic Medicine Institute and Taussig Cancer Institute at the Cleveland Clinic, and his associates.

Most cases of BE and EAC are thought to be sporadic rather than inherited, but in the past few decades clustering of cases in families has been observed, supporting the existence of predisposition genes as well, the authors explained.

“The discovery of germline mutations in a gene or genes that predispose to BE/EAC may have ramifications regarding cancer risk assessment, genetic counseling, premorbid diagnosis, and targeted surveillance and management, and also [may] add to the fundamental understanding of the pathophysiology of sporadic BE and EAC,” they wrote.

Over the course of 5 years, the investigators performed a series of genetic studies that led to their discovery of these three germline mutations.

They began by recruiting 298 adults with histologically proven Barrett’s esophagus and/or esophageal adenocarcinoma and/or polyps as families with two or more cases of these disorders, from 16 academic and community hospitals and clinics across the United States.

They found and genotyped 21 pairs of siblings in which both siblings were affected and 11 pairs of siblings in which only one sibling was affected. The researchers identified what appeared to be significant genomic regions in these subjects, then validated these “potentially interesting” regions and performed fine mapping in a separate series of 176 patients with BE and/or EAC.

Further analysis revealed that 200 ancestry-matched population control subjects, Dr. Orloff and his associates said. Only white patients of northern or western European descent were included.

The investigators integrated these results with publicly available data on somatic gene expression derived from 19 other affected patients to develop a list of 12 biologically plausible candidate genes to be scanned in more detail for germline mutations. This analysis showed that three candidate genes were significantly associated with BE or EAC (P less than .001).

The genes were MSR1 (macrophage scavenger receptor 1), ASCC1 (activating signal cointegrator 1 complex subunit 1), and CTHRC1 (collagen triple-helix repeat-containing 1).

A similar mutational analysis performed in a separate series of 58 cases obtained from outpatient endoscopy clinics confirmed these results.

“These three genes together accounted for 11% of our cases, reflecting what is normally considered a moderate- to high-penetration genetic load for a disease,” Dr. Orloff and associates wrote.

No mutations of these three genes were found in a pooled group of 264 control subjects.

“MSR1, on chromosome 8p22, encodes the class A macrophage scavenger receptor, which is macrophage-specific trimeric integral membrane glycoproteins implicated in many macrophage-associated, hormonal, and pathological processes including inflammation, innate and adaptive immunity, oxidative stress, and apoptosis,” the investigators noted.

ASCC1 is thought to link inflammatory pathways to tumor suppression pathways. CTHRC1 is expressed in tissue repair processes; it may play a role in the host response to GERD and may predispose carriers to having decreased sphincter tone in the lower esophagus.

In summary, germline mutations in MSR1, ASCC1, and CTHRC1 in patients with BE/EAC appear physiologically relevant to these disorders, encoding proteins involved in apoptosis, innate immunity, polarity, and mobility that affect inflammatory and [other] pathways,” Dr. Orloff and associates wrote.

Larger studies are needed to determine whether genotyping to hunt for mutations in these genes and their variants would be useful in assessing people’s risk of developing BE or EAC, as well as in diagnosing the cancer earlier, when it is more responsive to treatment, the researchers said.

This study was funded in part by the M. Frank and Margaret Domiter Rudy Endowment of the Cleveland Clinic Taussig Cancer Institute and by grants from the National Cancer Institute and National Institutes of Health. No relevant financial conflicts of interest were reported.
Content from this column was originally published in the “Practice Management: Opportunities and Challenges” section of Clinical Gastroenterology and Hepatology. “Practice Management Toolbox” provides key information and resources necessary for facing the unique challenges of today’s clinical practices.

Resources for Practical Application: To view additional resources about this topic and to access our coding corner, visit www.cgjournal.org/content/practice_management.

Health care has become a full-fledged industry, representing a significant proportion of the national economy. Yet the failure of this industry to control costs, or at least show improved outcomes for patients, has caused providers, suppliers, and payers to become targets of increasing frustration from the rest of society. As costs spiral to unsustainable levels, players outside the health system, namely from the business community, are weighing in with their own perspectives on the crisis and how to fix it. One approach that has been gaining significant traction is value-based purchasing, a business management concept already used in many other industries.

Value-Based Health Care The application of value-based purchasing to the U.S. health care system has been most fully articulated by M.E. Porter1 and Elizabeth Teisberg, business school professors at Harvard University and the University of Seattle. They essentially aim to restore the standard rules of economics to the health care market. Put simpistically, an open market makes in- tentional manipulation of costs on the part of providers much easier. Essentially, an open market makes it possible for unscrupulous providers to charge high fees to patients with private insurance.

In a value-based system, providers compete based on the measured outcomes of their patients. Those providers with the best outcomes will capture more business. Rather than trying to find new ways to maximize profit by shifting costs, providers will focus their attention on providing the most cost-effective care for their patients. A competitive system based on results will be much more effective in improving cost-effectiveness than the current model of trying to second-guess physicians’ decisions and constraining patients’ choices.

Results Are Assessed for Specific Illnesses Over the Full Cycle of Care As described, value in health care is assessed from the patient’s perspective. The patient is concerned with achieving the best overall outcome for a specific medical condition, and over the full cycle of care. The current system is fragmented by physician specialty and the specific procedures performed. A value-based model envisions established protocols to be the standard for a condition, and if not available, to identify and perform the most cost-effective care on patients. A value-based system also envisions ACCREDITATION STANDARDs to be developed and validated true outcomes and governance central to the development and implementation of the vision described. But given the identified issue, intervention is made to address the problem, and additional data are collected to confirm improvement. As these organizations continue to participate in the accreditation process, they are expected to develop increasing sophistication in performing continuous quality-improvement activities.

Ultimately, accredited AECs will need to measure actual endoscopy results, such as adenoma detection rates. Once such results are provided in a meaningful way for prospective patients, value will increase dramatically. This is viewed as a critical step toward a value-based vision of health care delivery. And other payers. The measurement and reporting of outcome measures will soon be mandatory. AECs that proactively refine their measurement capabilities through data collection and continuous quality-improvement processes will enjoy significant advantages.

Today, value-based health care may sound like just another catchy buzzword. Certainly, the evolution of health care in the United States may not conform exactly to the vision described. But given the proven external forces at work on our industry, it is certain that gastroenterologists and other providers increasingly will be forced to show that their services provide real value to patients. Accreditation is, and will be, an important mechanism to promote AECs in this value-based system.

References

Lawrence S. Kim, M.D., FACG, AGAF, medical officer, medical affairs, AGA Institute and other organizations are working to develop and validate true outcomes and governance central to the development and implementation of the vision described. But given the identified issue, intervention is made to address the problem, and additional data are collected to confirm improvement.

As these organizations continue to participate in the accreditation process, they are expected to develop increasing sophistication in performing continuous quality-improvement activities.

Ultimately, accredited AECs will need to measure actual endoscopy results, such as adenoma detection rates. Once such results are provided in a meaningful way for prospective patients, value will increase dramatically. This is viewed as a critical step toward a value-based vision of health care delivery. And other payers. The measurement and reporting of outcome measures will soon be mandatory. AECs that proactively refine their measurement capabilities through data collection and continuous quality-improvement processes will enjoy significant advantages.

Today, value-based health care may sound like just another catchy buzzword. Certainly, the evolution of health care in the United States may not conform exactly to the vision described. But given the proven external forces at work on our industry, it is certain that gastroenterologists and other providers increasingly will be forced to show that their services provide real value to patients. Accreditation is, and will be, an important mechanism to promote AECs in this value-based system.

References

Lawrence S. Kim, M.D., FACG, AGAF, medical officer, medical affairs, AGA Institute and other organizations are working to develop and validate true outcomes and governance central to the development and implementation of the vision described. But given the identified issue, intervention is made to address the problem, and additional data are collected to confirm improvement.

As these organizations continue to participate in the accreditation process, they are expected to develop increasing sophistication in performing continuous quality-improvement activities.

Ultimately, accredited AECs will need to measure actual endoscopy results, such as adenoma detection rates. Once such results are provided in a meaningful way for prospective patients, value will increase dramatically. This is viewed as a critical step toward a value-based vision of health care delivery. And other payers. The measurement and reporting of outcome measures will soon be mandatory. AECs that proactively refine their measurement capabilities through data collection and continuous quality-improvement processes will enjoy significant advantages.

Today, value-based health care may sound like just another catchy buzzword. Certainly, the evolution of health care in the United States may not conform exactly to the vision described. But given the proven external forces at work on our industry, it is certain that gastroenterologists and other providers increasingly will be forced to show that their services provide real value to patients. Accreditation is, and will be, an important mechanism to promote AECs in this value-based system.

References

Lawrence S. Kim, M.D., FACG, AGAF, medical officer, medical affairs, AGA Institute and other organizations are working to develop and validate true outcomes and governance central to the development and implementation of the vision described. But given the identified issue, intervention is made to address the problem, and additional data are collected to confirm improvement.

As these organizations continue to participate in the accreditation process, they are expected to develop increasing sophistication in performing continuous quality-improvement activities. Ultimately, accredited AECs will need to measure actual endoscopy results, such as adenoma detection rates. Once such results are provided in a meaningful way for prospective patients, value will increase dramatically. This is viewed as a critical step toward a value-based vision of health care delivery. And other payers. The measurement and reporting of outcome measures will soon be mandatory. AECs that proactively refine their measurement capabilities through data collection and continuous quality-improvement processes will enjoy significant advantages.

Today, value-based health care may sound like just another catchy buzzword. Certainly, the evolution of health care in the United States may not conform exactly to the vision described. But given the proven external forces at work on our industry, it is certain that gastroenterologists and other providers increasingly will be forced to show that their services provide real value to patients. Accreditation is, and will be, an important mechanism to promote AECs in this value-based system.

References

Lawrence S. Kim, M.D., FACG, AGAF, medical officer, medical affairs, AGA Institute and other organizations are working to develop and validate true outcomes and governance central to the development and implementation of the vision described. But given the identified issue, intervention is made to address the problem, and additional data are collected to confirm improvement.

As these organizations continue to participate in the accreditation process, they are expected to develop increasing sophistication in performing continuous quality-improvement activities. Ultimately, accredited AECs will need to measure actual endoscopy results, such as adenoma detection rates. Once such results are provided in a meaningful way for prospective patients, value will increase dramatically. This is viewed as a critical step toward a value-based vision of health care delivery. And other payers. The measurement and reporting of outcome measures will soon be mandatory. AECs that proactively refine their measurement capabilities through data collection and continuous quality-improvement processes will enjoy significant advantages.

Today, value-based health care may sound like just another catchy buzzword. Certainly, the evolution of health care in the United States may not conform exactly to the vision described. But given the proven external forces at work on our industry, it is certain that gastroenterologists and other providers increasingly will be forced to show that their services provide real value to patients. Accreditation is, and will be, an important mechanism to promote AECs in this value-based system.
The following adverse reactions, presented by body system, were reported infrequently (less than 1%) by LIALDA-treated ulcerative colitis patients in the three long-term maintenance trials (maintenance phases of these trials):

**Cardiac Disorders:** tachycardia

**Skin and Subcutaneous Tissue Disorders:** acne, alopecia, pruritis, urticaria

**Gastrointestinal Disorders:** colitis, flatulence, nausea, pancreatitis, rectal polyp, vomiting

**Nervous System Disorders:** dizziness

**Respiratory, Thoracic and Mediastinal Disorders:** pharyngolaryngeal pain

**General Adverse and Adverse Drug Reactions Site Disorders:** asthenia, pyrexia

**Ear and Labyrinth Disorders:** ear pain

Postmarketing Experience

In addition to the adverse reactions reported above in clinical trials involving LIALDA, the adverse reactions listed below have been identified voluntarily from post-approval use of LIALDA and other mesalamine-containing products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Cardiac Disorders:**
- tachycardia

**Skin and Subcutaneous Tissue Disorders:**
- acne, alopecia, pruritis, urticaria

**Gastrointestinal Disorders:**
- colitis, flatulence, nausea, pancreatitis, rectal polyp, vomiting

**Nervous System Disorders:**
- dizziness

**Respiratory, Thoracic and Mediastinal Disorders:**
- pharyngolaryngeal pain

**General Adverse and Adverse Drug Reactions Site Disorders:**
- asthenia, pyrexia

**Ear and Labyrinth Disorders:**
- ear pain

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B. Reproduction studies with mesalamine have been performed in rats at doses up to 1000 mg/kg/day (2.3 times the maximum recommended human dose based on a body surface area comparison) and in rabbits at doses up to 500 mg/kg/day (2.9 times the maximum recommended human dose based on a body surface area comparison) and have revealed no evidence of impaired fertility or harm to the fetus due to mesalamine. These studies are not necessarily predictive of human response, this drug should be used during pregnancy only if clearly needed. Mesalamine is known to cross the placental barrier.

Nursing Mothers

Low concentrations of mesalamine and higher concentrations of 5'-n-acyl metabolite have been detected in human breast milk. The clinical significance of this has not been determined and there is limited experience of nursing women using mesalamine. Caution should be exercised if LIALDA is administered to a nursing woman.

Pediatric Use

Safety and effectivness of LIALDA in pediatric patients have not been established.

Geriatric Use

Reports from uncontrolled clinical studies and postmarketing reporting systems suggested a higher incidence of blood dyscrasias, i.e., neutropenia and pancytopenia in patients who were 65 years or older who were taking mesalamine-containing products such as LIALDA. Caution should be taken to closely monitor blood cell counts during mesalamine therapy.

Clinical trials of LIALDA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Systemic exposures are increased in elderly subjects. [see Clinical Pharmacology in the Prescribing Information].

OVERDOSAGE

LIALDA is an aminosalicylate, and symptoms of salicylate toxicity may include tinnitus, vertigo, headache, confusion, drowsiness, sweating, seizures, hyperventilation, dyspnea, vomiting, and diarrhea. Severe intoxication may lead to suppression of electrolyte balance and blood pH, hyperthermia, dehydration, and end organ damage.

There is no specific known antidote for mesalamine overdose; however, conventional therapy for toxicity may be beneficial in the event of acute overdosage. Fluid and electrolyte imbalance should be corrected by the administration of appropriate intravenous therapy. Adequate renal function should be maintained.
Now approved to maintain remission of ulcerative colitis

**Indication**

Lialda® is indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis and for the maintenance of remission of ulcerative colitis.

**Important Safety Information**

- Lialda is contraindicated in patients with known hypersensitivity to salicylates or aminosalicylates or to any of the ingredients of Lialda.
- Renal impairment, including minimal change nephropathy, acute and chronic interstitial nephritis, and, rarely, renal failure, has been reported with products such as Lialda that contain mesalamine or are converted to mesalamine. It is recommended that patients have an evaluation of renal function prior to initiating use of Lialda and periodically while on therapy. Exercise caution when using Lialda in patients with known renal dysfunction or a history of renal disease.
- Mesalamine has been associated with an acute intolerance syndrome (3% of patients in clinical trials with mesalamine or sulfasalazine) that may be difficult to distinguish from an exacerbation of ulcerative colitis. Symptoms include cramping, acute abdominal pain and bloody diarrhea, and sometimes fever, headache, and rash. Observe patients closely for worsening of these symptoms while on treatment. If acute intolerance syndrome is suspected, promptly discontinue treatment with Lialda.
- Some patients who have experienced a hypersensitivity reaction to sulfasalazine may have a similar reaction to Lialda or compounds that contain or are converted to mesalamine. Mesalamine-induced cardiac hypersensitivity reactions (myocarditis and pericarditis) have been reported with Lialda and other mesalamine-containing medications. Caution should be taken when prescribing Lialda to patients with conditions predisposing them to the development of myocarditis or pericarditis.
- There have been reports of hepatic failure in patients with pre-existing liver disease who have been administered mesalamine. Caution should be exercised when administering Lialda to patients with liver disease.
- Pyloric stenosis or other organic or functional obstruction in the upper gastrointestinal tract may cause prolonged gastric retention of Lialda, which would delay mesalamine release in the colon.
- In clinical trials, the most common adverse reactions (incidence ≥2%) were ulcerative colitis, headache, flatulence, liver function test abnormality, and abdominal pain. Pancreatitis occurred in <1% of patients and in some cases resulted in discontinuation of therapy with Lialda.
- The concurrent use of mesalamine with known nephrotoxic agents, including non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of renal reactions. The concurrent use of mesalamine with azathioprine or 6-mercaptopurine can increase the potential for blood disorders.
- Safety and effectiveness of Lialda in pediatric patients have not been established.

**Updated Prescribing Information**

Please see the updated Brief Summary of Full Prescribing Information on adjacent page which includes new safety and dosing information for Lialda.

hcp.lialda.com

Lialda® is a registered trademark of Shire LLC.

©2011 Shire US Inc., Wayne, PA 19087      LIA-02559      07/11