Whether to use steroids to treat alcoholic hepatitis remains controversial.

Andrew K. Burroughs, FRCP, FMedSci; Ashwani Singal, MD, MS; and Vijay Shah, MD, share their thoughts on treatment options.

THE DEBATE STARTS ON PAGE 4
In this issue

RECIPE FOR DISASTER?

Whether to use steroids to treat alcoholic hepatitis remains controversial.

Andrew K. Burroughs, FRCP, FMedSci; Ashwani Singal, MD, MS; and Vijay Shah, MD, share their thoughts on treatment options.

Management Issues of Liver Disease in Pregnancy
Arjmand Mufti, MD, MRCP, and Nancy Reau, MD

Avoiding and Managing the Risks of Endoscopy
Peter B. Cotton, MD, FASGE

Genetic Testing for Hereditary Pancreatic Disease
David C. Whitcomb, MD, PhD

Recertification — Here We Go Again
Kelvin Hornbuckle, MD, AGAF, and F. Taylor Wootton III, MD, AGAF

Credentialing Issues: New Technologies and Techniques
Rajeev Jain, MD, AGAF

Social Media “KUDOS”:
How to Be Ethical in the Digital Wild West
Dan O’Connor, PhD

Obesity and Gastrointestinal Disease: A Worldwide Problem
Peter R. Holt, MD, AGAF

AGA PERSPECTIVES DEPARTMENTS
Classifieds
Editors’ Picks

AGA Perspectives
Vol. 8, No. 6 | December 2012/January 2013

Management Issues of Liver Disease in Pregnancy
Arjmand Mufti, MD, MRCP, and Nancy Reau, MD

Avoiding and Managing the Risks of Endoscopy
Peter B. Cotton, MD, FASGE

Genetic Testing for Hereditary Pancreatic Disease
David C. Whitcomb, MD, PhD

Recertification — Here We Go Again
Kelvin Hornbuckle, MD, AGAF, and F. Taylor Wootton III, MD, AGAF

Credentialing Issues: New Technologies and Techniques
Rajeev Jain, MD, AGAF

Social Media “KUDOS”:
How to Be Ethical in the Digital Wild West
Dan O’Connor, PhD

Obesity and Gastrointestinal Disease: A Worldwide Problem
Peter R. Holt, MD, AGAF

AGA PERSPECTIVES DEPARTMENTS
Classifieds
Editors’ Picks

AGA Perspectives Editor
Sheila E. Crowe, MD, AGAF

AGA Institute Governing Board
Loren Laine, MD, AGAF
Anil K. Rustgi, MD, AGAF
J. Sumner Bell III, MD, AGAF
Nicholas F. LaRusso, MD, AGAF
Vincent W. Yang, MD, PhD
Helen M. Shields, MD, AGAF
John I. Allen, MD, MBA, AGAF
J. Sumner Bell III, MD, AGAF
Sheila E. Crowe, MD, AGAF
Helen M. Shields, MD, AGAF
Vincent W. Yang, MD, PhD

Committee Chairs
Anil K. Rustgi, MD, AGAF
John M. Inadomi, MD, AGAF
Timothy C. Wang, MD, AGAF
Maria T. Abreu, MD, AGAF
Dawn Provenzale, MD, AGAF

Editorial Staff
Alissa J. Cruz
Managing Editor
Aaron R. White
Senior Editorial Director
Matthew A. Nickols
Graphic Designer
Jessica W. Duncan
VP of Communications

Carla H. Ginsburg, MD, MPH, AGAF
PUBLIC AFFAIRS & ADVOCACY COMMITTEE
Sheila E. Crowe, MD, AGAF
PUBLICATIONS COMMITTEE
Timothy C. Wang, MD, AGAF
RESEARCH POLICY COMMITTEE
Maria T. Abreu, MD, AGAF
UNDERSERVED MINORITIES COMMITTEE
Dawn Provenzale, MD, AGAF
WOMEN’S COMMITTEE

Funding for AGA Perspectives is provided by Takeda Pharmaceuticals North America, Inc.
To end 2012 and start the new year, our point/counterpoint experts debate a long-standing controversy: whether corticosteroids are safe and effective therapy for alcoholic hepatitis. I can recall this being discussed when I was a GI fellow. Andrew Burroughs argues that steroids are indeed indicated while Vijay Shah and Ashwani Singal take the position that there are better therapies, which are safer than steroids. Also in this issue, Arjmand Mufti and Nancy Reau provide another perspective on liver disorders: those occurring in pregnant women. Their article presents a very helpful classification and approach to the variety of liver conditions that can occur during pregnancy.

Peter Cotton shares his wisdom on avoiding and managing the risks of endoscopy, while David Whitcomb discusses the role of genetic testing in the evaluation of acute and chronic pancreatic diseases. In this issue’s International Corner, Peter Holt examines the growing worldwide problem of obesity and its impact on GI and liver diseases, including malignancies of the digestive system.

While many of us might not worry about credentialing in day-to-day practice, the article on the issues associated with credentialing of new technologies by Rajeev Jain is interesting and timely as new technologies are being developed and introduced into practice. Another timely perspective comes from Dan O’Connor, who discusses the emerging ethics of social media. Kelvin Hornbuckle and F. Taylor Wootton provide their perspective on the American Board of Internal Medicine (ABIM) GI maintenance of certification (MOC) process and make the plea that cost and time efficiency are taken into account when considering the recertification process for busy GI practitioners. AGA Perspectives will report on the planned updates for the ABIM MOC process later in 2013.

I join Mark Donowitz in asking AGA members to contribute to the AGA Research Foundation, which supports young investigators at a time when NIH funding and other sources of research support have declined. In this issue, two young scientists — Adam Bass and Ashwin Ananthakrishnan — who were recipients of the 2012 Funderberg Award and the 2011 AGA Research Scholar Award (RSA), respectively, are featured. Having received an AGA RSA as a young investigator, I can attest to the importance of receiving AGA support, as this played a major role in my development as a clinician scientist. I hope that our readers will consider contributing to the AGA Research Foundation at the end of this year to support GI research. Visit www.gastro.org/aga-foundation/contribute to make a donation.

With best wishes for the 2013 new year,

Sheila E. Crowe, MD, AGAF
EDITOR
RECIPE FOR DISASTER?

Whether to use steroids to treat alcoholic hepatitis remains controversial.
Hepatologists and gastroenterologists with a special interest in liver disease deal with a fair share of medical emergencies related to liver disease. Amongst these, the acutely jaundiced patient in whom a quick abdominal ultrasound examination has excluded biliary obstruction remains a challenge, not so much for diagnosis, but in management. The history and serological markers usually confirm the initial clinical suspicion, including a diagnosis of acute alcoholic hepatitis. However, alcoholic hepatitis is different compared to other diagnoses. If there is no improvement (either spontaneously or following specific therapy such as antiviral agents), there is the chance of liver transplantation; this is not so for alcoholic hepatitis. Prolonged abstention is required in order to be placed on a waiting list for liver transplantation in most health-care systems. The alcoholic hepatitis patient has usually misused alcohol up to, or close to, the time of admission, and is usually very sick, jaundiced — often with renal dysfunction, some ascites (but not always) — confused (maybe with incipient or concomitant alcohol withdrawal symptoms), and sometimes with infection, all at presentation. Clinicians dealing with such patients know the prognosis is poor.

I, as others, grade the severity of alcoholic hepatitis to gauge prognosis. Will Maddrey was the first to do this routinely, and his discriminant function (DF) is still in use today. Interestingly, this publication concerned the threshold of severity of alcoholic hepatitis, which was a DF of 32 or more, at which corticosteroids are avoid corticosteroids: Despite recommendations from professional GI societies to use corticosteroids as the first-line treatment for severe alcoholic hepatitis, the topic remains controversial. This is evidenced from the results of a recent survey of practicing gastroenterologists and hepatologists where less than half of respondents chose corticosteroids for treating severe alcoholic hepatitis despite societal guidelines. Indeed, the practice patterns of the authors gravitate away from corticosteroid use in alcoholic hepatitis as well. Arguments against the use of corticosteroids in treating alcoholic hepatitis include the limited subgroups that benefit, potential for infectious complications during treatment, non-response in a significant proportion of patients, and availability of safer options.

Alcohol abstinence along with nutritional supplementation to correct associated malnutrition remains the supportive care cornerstone for improving the long-term outcome of patients with alcoholic liver disease. The role for pharmaco-therapy is murkier. The major arguments against corticosteroids in this disease relate to the limited subgroups of patients for whom treatment is applicable and the adverse effects associated with therapy. Contraindications for use of corticosteroids and/or patient subgroups that were excluded in previous corticosteroid-based randomized controlled trials include...
Even if I were to concede that the answer as to whether corticosteroids are of benefit is not known, I would still prescribe corticosteroids.

CONTINUED FROM PAGE 5

should be administered. Whether to give corticosteroids is still debated now, 30 years later! The prognosis of alcoholic hepatitis from more than 30 years ago may well have been worse than it is today, and perhaps the DF threshold is too low. However, over the years, several trials have shown that without steroids, about 35 percent of patients with a DF of 32 or more die within 28 days.2 Despite this terrible prognosis, these patients are not eligible for liver transplantation.

What then is the alternative? What can I as the responsible clinician do to help my patient? Is there a specific treatment? Yes, corticosteroids are a specific treatment. Am I convinced survival chances are increased by their use? I am, based on the best evidence I believe to be available, i.e., the meta-analysis based on individual patient data from the better quality trials evaluating severe alcoholic hepatitis.3 However, a previous Cochrane standard meta-analysis of randomized trials,2 which held a lower level of evidence methodologically, suggested no survival benefit. Though this analysis included evaluation of some poor quality trials, it still found a favorable trend in severe alcoholic hepatitis.

Even if I were to concede that the answer as to whether corticosteroids are of benefit is not known, I would still prescribe corticosteroids. No evaluation has shown harm, and there is nothing else which has documented benefit, except a single trial of pentoxyphylline, that has not been subsequently confirmed. However, I perform a transjugular liver biopsy4 to confirm the diagnosis, as decompensated alcoholic cirrhosis with jaundice may be difficult to differentiate from alcoholic hepatitis, as well as acute alcoholic fatty liver or other acute causes of jaundice in an active alcoholic. These alternative diagnoses may well have confounded the results of published therapeutic trials in which a liver biopsy was not performed.

I also refine the way I use steroids. Currently, steroids, using 40 mg prednisolone/day, are planned for four weeks of therapy. However, there is data to show that if there is no response at seven days in terms of a fall in serum bilirubin, then the prognosis is far, far worse. This has been extended to a Lille score of greater than 0.56 at seven days, a threshold above which the benefit of steroids cannot be shown in the individual meta-analysis.3 Therefore, at seven days, I reassess the patient to decide whether steroid therapy should be stopped and whether supportive therapy should continue. I take into account added history concerning any previous hospital admissions, current clinical status (including that of other organs, particularly kidneys and lungs), and the nature of family support and other support measures accessible outside of the hospital.

This personalized medicine approach tailors the assessment of therapy to the individual patient, based on the individual therapeutic response (given there is nothing else I can offer as specific therapy). It also allows a dialogue with the patient from the outset about the serious prognosis, the therapeutic trial and the assurance that I, as a clinician, will assess the patient’s response to gauge if the initial poor prognosis may not be

CONTINUED ON PAGE 8
those with infection, gastrointestinal bleeding, acute pancreatitis, hepatitis B/C virus infection, renal failure, and poorly controlled diabetes mellitus. This excludes approximately 10 to 30 percent of patients with severe alcoholic hepatitis. Furthermore, patients who do receive corticosteroids are almost certainly more prone towards infection.

From a data-driven perspective, over the last four decades, 17 randomized controlled trials and 12 meta-analyses on the use of corticosteroids have shown discrepant data. The latest meta-analysis from five randomized control trials and a Cochrane review concluded that corticosteroids may be beneficial amongst patients with severe disease defined as Maddrey’s discriminant function or MDF (prothrombin time of patient – control] x 4.6 + serum bilirubin) score greater than 32 and/or hepatic encephalopathy. However, sample size of these analyses is a concern. Meta-analyses are suggested to have a minimum of 100 death outcomes for assessing benefit. The meta-analyses showing survival benefit with corticosteroids as compared to untreated patients had only 52 deaths after pooling individual patient data from the three largest randomized studies. Further, patient-to-patient variation in steroid responsiveness of lymphocytes results in varying clinical response rates with only 50 percent survival benefit and a remaining 15 to 20 percent mortality at one month, even amongst treated patients. While some clinically applicable biomarkers to identify treatment responders are under investigation, at the present time, use of corticosteroids cannot be personalized to those who are likely to respond to corticosteroids.

Fortunately, a series of studies from the Mathurin group from France have provided key guidelines for steroid management in patients who one chooses to treat with corticosteroids. Response to steroids can be clinically assessed at one week with a decrease in bilirubin; steroids can be discontinued amongst patients who do not show a reduction in bilirubin one week after therapy, thereby avoiding unnecessary steroid toxicity. However, with about five patients needing to be treated to save one patient, four patients will remain prone to infectious complications for one week while awaiting response to treatment with corticosteroids.

If not steroids, then what is the alternative? Pentoxifylline is a putative inhibitor of ... steroids may be beneficial in a small group of select patients with alcoholic hepatitis. However, we need to keep up the pursuit for new therapies.

CONTINUED ON PAGE 9
Give your patients with severe alcoholic hepatitis corticosteroids, providing you have a certain diagnosis and have explained to the patient the therapeutic trial involved.

CONTINUED FROM PAGE 6

realized. If new complications have developed during the seven-day period, it also makes it easier to explain that all reasonable therapeutic maneuvers have been tried.

Using the therapeutic response to steroids has another advantage — in the future, it may be a selection criterion for liver transplantation for patients with alcoholic hepatitis. Patients will be severely selected, e.g., on the basis of a first and not a repeated presentation to health-care professionals about their alcoholism, and without psychological contraindications.5 The premise often stated for not administering corticosteroids in alcoholic hepatitis is that, unless a therapy has been shown to be effective (or cost effective in some healthcare systems), it should not be used. However, in clinical settings where there are no proprietary drugs — as is the case in alcoholic hepatitis — the questions cannot be answered by appropriately sized randomized studies. These have not been, and will not be performed; there is no financial investment in this area. An allowance is sometimes made to judge on the merits of the available evidence. Based on this premise, an objective view of the current evidence would attribute at least equal merit to the pro and con evidence of using corticosteroids, but importantly with no evidence of harm.

So what about my patient with severe alcoholic hepatitis? I think he/she would expect me to give his/her situation the benefit of the doubt, thus to prescribe steroids, assess the response at seven days and review. Indeed, I have not encountered any patient who, once the issue of corticosteroid therapy is explained, has refused therapy — this is also informed consent!

Give your patients with severe alcoholic hepatitis corticosteroids, providing you have a certain diagnosis and have explained the therapeutic trial involved. Evaluate the response and be convinced you have been able to offer the current “best deal” to your patient.

Dr. Burroughs delivered a lecture on radio-embolization of hepatocellular carcinoma at the International Liver Cancer Association Sixth Annual Conference. He is also chairman of the European Liver Transplant Association.

REFERENCES
... the appealing safety profile of this drug [pentoxifylline] and its putative ability to prevent hepato-renal syndrome have encouraged many physicians to use this drug over steroids.

In summary, steroids may be beneficial in a small group of select patients with alcoholic hepatitis. However, we need to keep up the pursuit for new therapies. Major new initiatives from the National Institute on Alcohol Abuse and Alcoholism focused on translational research in human alcoholic hepatitis have us on the right track in this regard.

Dr. Singal had no conflicts to disclose.

Dr. Shah is an advisory board consultant for GlycoRegImmune, Inc. and Ferring Pharmaceuticals. He is also a member of AASLD’s grant review committee.

**REFERENCES**


Tumor necrosis factor alpha production, although its more likely mechanism of action is as a phosphodiesterase inhibitor. It is used as both a first-line therapy for alcoholic hepatitis and a second-line therapy in patients with severe disease when steroids cannot be used due to contraindications. In the initial pivotal study, this drug was shown to be beneficial for severe alcoholic hepatitis with about 50 percent survival benefit as seen with steroids. However, further studies have not confirmed its benefit. Nonetheless, the appealing safety profile of this drug and its putative ability to prevent hepato-renal syndrome (a major cause of mortality in alcoholic hepatitis) have encouraged many physicians to use this drug over steroids.

Increasing data are emerging on the use of liver transplantation for select patients with severe alcoholic hepatitis who do not respond to steroids. In a United Network for Organ Sharing database analysis, five-year outcomes of liver transplantation for alcoholic hepatitis were as good as for alcoholic cirrhosis. Further studies are needed to explore the use of liver transplantation as a first-line option for select patients with severe alcoholic hepatitis. However, more experience and refinements in case selection are needed to achieve post-transplantation survival rates of more than 90 percent at one year, as would be the norm for most other transplant indications. Furthermore, a variety of societal and ethical issues accompany the broader application of this treatment option in this patient population.

Dr. Singal had no conflicts to disclose.

Dr. Shah is an advisory board consultant for GlycoRegImmune, Inc. and Ferring Pharmaceuticals. He is also a member of AASLD’s grant review committee.
Liver dysfunction occurs in approximately 3 percent of all pregnancies, and early recognition can improve maternal and fetal outcomes.\textsuperscript{1} However, during pregnancy, women undergo many hormonal and physiological changes with associated alterations of routine liver function tests. These variations represent the “new normal” of pregnancy and it is essential to be aware of them in order to appropriately triage patients for further investigation (see table one). It is also broadly true that liver diseases that are unique to pregnancy generally tend to be trimester specific, and the occurrence of liver abnormalities in relation to gestational age can give a clue about the etiology of liver dysfunction. We keep three broad categories of disorders in mind when evaluating pregnant patients with liver disease, namely:

- Liver diseases that were present before pregnancy.
- Liver diseases that are unique to pregnancy.
- Liver diseases that are coincidental to pregnancy (see table two).

The initial clue that liver dysfunction may be present is patient-reported nausea, vomiting, pruritus and upper abdominal pain. This should result in basic laboratory testing. Any increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and serum bilirubin levels should be considered pathologic, and further evaluation needs to be carried out. We advocate a comprehensive diagnostic approach for all patients who are referred to us (see table three on Page 12). After going through this general schema for initial evaluation, specific patterns in liver function tests can be allied to clinical course and gestational age to try and arrive at a diagnosis.

### Pre-existing liver disease

In patients with known liver disease, it is paramount to have a candid pre-pregnancy discussion about the risks of complications in the mother, especially in individuals with established portal hypertension. In the pregnant patient, each pre-existing liver disease is managed differently. However, all pregnant patients are screened for hepatitis B and all babies born to hepatitis B surface antigen positive mothers receive the hepatitis B immunoglobulin and first dose of the hepatitis B vaccine within 12 hours of birth. Patients with hepatitis C are generally monitored closely, but there is no role for treatment during pregnancy. Patients with autoimmune hepatitis who are on azathioprine prior to pregnancy are generally kept on it. In carefully selected patients, therapy may be discontinued. However,

### Table 1: Normal Biochemical Changes During Pregnancy

<table>
<thead>
<tr>
<th>TEST</th>
<th>PREGNANCY-RELATED CHANGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin</td>
<td>No change or slight decrease</td>
</tr>
<tr>
<td>AST</td>
<td>No change</td>
</tr>
<tr>
<td>ALT</td>
<td>No change</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>Increased by 200–400% (placenta and bone)</td>
</tr>
<tr>
<td>Gamma-glutamyl transferase</td>
<td>No change or slight decrease</td>
</tr>
<tr>
<td>Albumin</td>
<td>Decreased (hemodilution)</td>
</tr>
<tr>
<td>Prothrombin time/international normalized ratio</td>
<td>No change</td>
</tr>
<tr>
<td>Platelets</td>
<td>No change</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Decreased (from second trimester)</td>
</tr>
<tr>
<td>White cell count</td>
<td>Increased</td>
</tr>
<tr>
<td>Total cholesterol and triglycerides</td>
<td>Increased</td>
</tr>
</tbody>
</table>
Table 2: Classification of Liver Diseases in Pregnancy

<table>
<thead>
<tr>
<th>PRE-EXISTING UNDERLYING LIVER DISEASE</th>
<th>TYPICAL TIME OF PRESENTATION (TRIMESTER)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic hepatitis B and C</td>
<td>Present throughout pregnancy and can have a variable course from patient to patient</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td></td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td></td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Primary sclerosing cholangitis</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis from any cause</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LIVER DISEASES RELATED TO PREGNANCY</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperemesis gravidarum</td>
<td>First, but can persist during second/third</td>
</tr>
<tr>
<td>Intrahepatic cholestasis of pregnancy</td>
<td>Second/third</td>
</tr>
<tr>
<td>Acute fatty liver of pregnancy</td>
<td>Third</td>
</tr>
<tr>
<td>Pre-eclampsia and eclampsia</td>
<td>Second/third or shortly after delivery</td>
</tr>
<tr>
<td>HELLP syndrome</td>
<td>Third, during or shortly after delivery</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LIVER DISEASES COINCIDENTAL TO PREGNANCY</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute viral hepatitis</td>
<td>First/second/third</td>
</tr>
<tr>
<td>Gallstones</td>
<td>Second/third, but can occur in first trimester</td>
</tr>
<tr>
<td>Budd-Chiari syndrome</td>
<td>First/second/third or during post-partum period</td>
</tr>
<tr>
<td>Drug-induced hepatotoxicity</td>
<td>First/second/third</td>
</tr>
<tr>
<td>Sepsis</td>
<td>First/second/third</td>
</tr>
</tbody>
</table>

As pregnancy represents a relatively immunosuppressed state, patients with either hepatitis B or autoimmune hepatitis may have a flare in the postpartum phase. Therefore, patients with hepatitis B are monitored closely for three to six months after delivery, and if discontinued, therapy for autoimmune hepatitis should be reinstated prior to delivery. Additionally, anyone with suspected portal hypertension should have an upper endoscopy in the second trimester to look for esophageal varices.

**Pregnancy-related liver disease**

Liver diseases unique to pregnancy are always part of the differential diagnosis in patients with abnormal liver function tests; history, clinical course and biochemical testing help to differentiate between them (see table two). With the exception of hyperemesis gravidarum, they usually present in the second and third trimester. Obtaining the correct
diagnosis is important because delivery is the primary treatment. High AST and ALT levels may be seen in all of these disorders and they can recur during subsequent pregnancies.²

Hyperemesis gravidarum is defined by persistent vomiting, dehydration and weight loss in the first trimester. It usually resolves by week 20, but can be present throughout pregnancy. Intrahepatic cholestasis of pregnancy is associated with severe pruritus and high bile acid levels. Pre-eclampsia is characterized by hypertension and proteinuria, whilst hemolytic anemia with low platelets are markers of HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelet counts). Acute fatty liver of pregnancy can present in many different ways, including with coagulopathy, renal failure and jaundice. The differential diagnoses include HELLP syndrome and acute viral hepatitis.

Diseases coincident to pregnancy

Acute viral hepatitis can occur throughout pregnancy and accounts for up to 40 percent of jaundice seen in pregnant patients. It usually tends to have the same disease course as in the non-pregnant population. The exceptions are hepatitis E and herpes simplex infections, which have significant mortality and morbidity. We have a low threshold to test for them, as early diagnosis is associated with improved outcomes.³ Gallstones are more common in pregnancy, especially during the second and third trimesters and should always be considered, especially in the presence of any abdominal pain. Drug-induced hepatotoxicity may occur at any time during the pregnancy and a detailed history of all prescription and nonprescription medications should always be obtained.

All management decisions must account for the health of both the mother and fetus. This is especially true when treating chronic diseases such as autoimmune hepatitis or hepatitis B dysfunction, we employ a comprehensive approach to evaluation and look for clinical and biochemical patterns that will allow us to make an accurate and rapid diagnosis.

In summation, when we are confronted with a pregnant patient with liver dysfunction, we employ a comprehensive approach to evaluation and look for clinical and biochemical patterns that will allow us to make an accurate and rapid diagnosis.

Table 3: Diagnostic Approach to Liver Disease in Pregnancy

COMPREHENSIVE HISTORY

Pertinent questions that should be asked include gestational age and history of:

- Existing liver disease such as hepatitis B, C or autoimmune hepatitis.
- Previous pregnancy with complications, including pre-eclampsia/eclampsia, ICP or HELLP syndrome.
- Pruritus during current or previous pregnancies.
- Gallstones.
- New onset abdominal pain, nausea or vomiting.
- Polyuria and polydipsia.
- All medications (prescription and herbal).
- Illicit drug use or blood transfusions.

EXAMINATION

Detailed physical examination, including full set of vital and urine dipstick. Particular attention should be paid to the presence of:

- Fever.
- Hypertension.
- (Tender) hepatomegaly.
- Ascites.
- Peripheral edema.
- Ecchymoses or petechiae.
- Proteinuria.

FURTHER INVESTIGATIONS

Blood and urine tests:

- Complete blood count with platelets.
- Basic metabolic panel, including creatinine.
- Liver function tests.
- PT/INR.
- Routine hepatitis serologies, including hepatitis A, B and C.
- CMV and EBV PCR.
- Hepatitis E serologies, especially if from or have history of travel to Asia (especially India), Africa, Middle East or South America.
- HSV PCR if immunocompromised.
- Uric acid.
- Urinalysis, including urine microscopy.

IMAGING

- Ultrasound of the liver and biliary system and doppler imaging of hepatic vessels if indicated (e.g., suspicion of Budd-Chiari).
- MRI without contrast if additional imaging required.
- ICP: intrahepatic cholestasis of pregnancy; CMV: cytomegalovirus; EBV: Epstein-Barr virus; PCR: polymerase chain reaction; HSV: herpes simplex virus

where therapy can impact both the mother and fetus. Ultrasonography is safe and is first line for imaging. MRI without contrast can also be employed as it does not use ionizing radiation. A liver biopsy is rarely necessary for diagnosis during pregnancy and we only obtain one if the etiology of liver dysfunction is unclear and the biopsy result has the potential to alter clinical management.

In summation, when we are confronted with a pregnant patient with liver dysfunction, we employ a comprehensive approach to evaluation and look for clinical and biochemical patterns that will allow us to make an accurate and rapid diagnosis.

REFERENCES

Avoiding and Managing the Risks of Endoscopy

Digestive endoscopy has come to dominate the lives of most practicing gastroenterologists. Not all procedures go well. Reasons for disappointment include technical and clinical failure, adverse events and process issues.

Technical and clinical failure

Sometimes it is just not possible to get where you need to go (to the cecum or the bile duct), or to do what you had planned to do (dilate a stricture or place a stent). In some cases, the “fault” may lie with the patient. There may be anatomical issues (prior pelvic surgery or a biliary bypass) or awkward pathology (tortuous stricture or large polyp).

Many of these factors cannot be overcome — even by experts — but many are known beforehand, leading to the development of scales of predictable difficulty or complexity. These can be used to advise patients about the likelihood of success in their particular case. Technical failure is more often due to lack of training and expertise by the endoscopist. Variations in the ability to reach the cecum or to access the bile duct are well documented, as are variations in detecting lesions. Clearly, these problems can be addressed and overcome (at least partially) only by better training and by ensuring that procedures are done only by those with proven competence. This should involve stringent credentialing processes, with accountability, using report cards and benchmarking. I favor a certification process for more complex and risky procedures, such as endoscopic retrograde cholangiopancreatography (ERCP), which is often done in the U.S. by endoscopists with inadequate volumes.

Some procedures may fail because of poor patient toleration, which is one reason for the trend towards using anesthesia for more complex procedures. Others are completed according to plan, but fail to help the patient. This may involve missing a diagnosis (perhaps a technical error), but more often because a treatment provides little or no benefit (stenting for chronic pancreatitis or sphincterotomy for sphincter of Oddi dysfunction). Reducing the likelihood of a poor clinical outcome, despite technical success, depends on our knowledge of the literature and of our own results. This is essential if we are to advise patients effectively, including the possibility of referral to someone with more expertise in that context.

Adverse events

Patients are most unhappy when something goes wrong and they suffer an adverse event. This can happen before the endoscope is introduced (reaction to prophylactic antibiotics or bowel preparation), during the procedure (hypoxia), immediately afterwards (pain due to perforation), a few hours later (pancreatitis after ERCP), or can be delayed for several days or weeks (delayed bleeding). Some events (viral transmission) may be so far delayed that the connection is difficult to make or is missed completely. Documentation of these events requires a precise lexicon.

Factors increasing the risk of an adverse event include the patient’s chronic health status (especially cardiac, pulmonary and other co-morbidities, coagulopathy and immunosuppression), any effect of the presenting illness (sepsis, anemia) and the setting (urgency and environment). The nature of the planned procedure affects the risk (bleeding after treating varices, or pancreatitis after ERCP), as does the expertise of the endoscopist.

Managing adverse events

When things go wrong, the specific issues have to be addressed promptly and efficiently, and explained carefully to the patient and family — who hopefully will remember that they were informed about the possibilities beforehand. No matter how bad you feel, it is a mistake to grovel in distress. However, it is important to show that you care and that you share possibilities beforehand. No matter how bad you feel, it is a mistake to grovel in distress. However, it is important to show that you care and that you share.

Process issues

Delays, discourtesies and lack of rapport may leave patients and families unhappy even when the technical and clinical outcomes are good, and when there have been no adverse events.

It is self-evident that all of these risks are less likely to occur when the endoscopist, team, patient and family are all well prepared for the specific procedure. Professionals strive to do better every day.

REFERENCES

Conclusions of comparative efficacy cannot be drawn from this information.

**DEXILANT WORKS A SECOND SHIFT TO HELP SHUT DOWN ACID PUMPS**

**96% OF 24-HOUR PERIODS REMAINED HEARTBURN FREE IN A 6-MONTH STUDY**

**Overall treatment** Median percentage of 24-hour heartburn-free periods of the maintenance of healed EE study vs 29% with placebo. Secondary efficacy endpoint, p<0.0025.\(^1\)

DEXILANT 30 mg (n=132), Placebo (n=141)

DEXILANT 30 mg provides effective maintenance of EE healing

- 66% 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.\(^1\)

Results of a 6-month, multicenter, double-blind, placebo-controlled, randomized study of patients who had successfully completed an EE study and showed endoscopically confirmed healed EE. Based on crude-rate estimates, patients who did not have endoscopically documented relapse or prematurely discontinued were considered to have relapsed.

**Indications for DEXILANT (dexlansoprazole)**

- 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
- 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.
- PPI therapy may be associated with increased risk of Clostridium difficile associated diarrhea.
- Long-term and multiple daily dose 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 esters, digoxin, 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. DEXILANT may increase serum levels of methotrexate. Please see adjacent brief summary of prescribing information for DEXILANT.

**References:**


**DEXILANT WORKS WITH A DUAL DELAYED RELEASE FORMULATION**

**Granule 1 begins releasing drug within an hour of dosing**

**Granule 2 provides a second release of drug with another peak concentration several hours after dosing**

**Artistic rendition of granules.**

**References:**


**©2012 Takeda Pharmaceuticals U.S.A., Inc.**

**Join the DEXILANT Select Program**

**Visit DexilantHCP.com today!**

**DEXILANT and DEXILANT (with design) are trademarks of Takeda Pharmaceuticals U.S.A., Inc. registered in the U.S. Patent and Trademark Office and used under license by Takeda Pharmaceuticals America, Inc. Dual Delayed Release is a trademark of Takeda Pharmaceuticals U.S.A., Inc. and used under license by Takeda Pharmaceuticals America, Inc.**

**Join the DEXILANT Select Program**

**Visit DexilantHCP.com today!**

**DEXILANT and DEXILANT (with design) are trademarks of Takeda Pharmaceuticals U.S.A., Inc. registered in the U.S. Patent and Trademark Office and used under license by Takeda Pharmaceuticals America, Inc. Dual Delayed Release is a trademark of Takeda Pharmaceuticals U.S.A., Inc. and used under license by Takeda Pharmaceuticals America, Inc.**

**Join the DEXILANT Select Program**

**Visit DexilantHCP.com today!**
BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION
DEXILANT (dexlansoprazole) delayed-release capsules for oral use

INDICATIONS AND USAGE
DEXILANT is indicated for:
- Healing of all grades of erosive esophagitis (EE) for up to 8 weeks
- Maintaining healing of EE and relief of heartburn for up to 6 months
- The 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
Gastric Malignancy
Symptomatic response with DEXILANT does not preclude the presence of gastric malignancy.

Clostridium Difficile Associated Diarrhea
Published observational studies suggest that PPI therapy like DEXILANT may be associated with an increased risk of Clostridium difficile associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve [see Adverse Reactions].

Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Bone Fracture
Several published observational studies suggest that 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 conditions 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 PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required 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].

Concomitant use of DEXILANT with Methotrexate
LITERATURE SUGGESTS THAT CONCOMITANT USE OF PPIs WITH METHOTREXATE (PRIMARILY AT HIGH DOSE; SEE METHOTREXATE PRESCRIBING INFORMATION) MAY ELEVATE AND PROLONG SERUM LEVELS OF METHOTREXATE AND/OR ITS METABOLITE, POSSIBLY LEADING TO METHOTREXATE TOXICITIES. IN HIGH-DOSE METHOTREXATE ADMINISTRATION, A TEMPORARY WITHDRAWAL OF THE PPI MAY BE CONSIDERED IN SOME PATIENTS [SEE DRUG INTERACTIONS].

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 safety of DEXILANT was evaluated in 4548 patients in controlled and uncontrolled clinical studies, including 863 patients treated for at least 6 months and 203 patients treated for one year. Patients ranged in age from 18 to 90 years (median age 48 years), with 54% female, 82% Caucasian, 6% Black, 4% Asian, and 3% other races. Six randomized controlled clinical trials were conducted for the treatment of EE, maintenance of healed EE, and symptomatic GERD, which included 896 patients on placebo, 455 patients on DEXILANT 30 mg, 2218 patients on DEXILANT 60 mg, and 1363 patients on lansoprazole 30 mg once daily.

Most Commonly Reported Adverse Reactions
The most common adverse reactions (≥2%) that occurred at a higher incidence for DEXILANT than placebo in the controlled studies are presented in Table 2.

Table 2: Incidence of Adverse Reactions in Controlled Studies

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (N=926)</th>
<th>DEXILANT 30 mg (N=465)</th>
<th>DEXILANT 60 mg (N=2218)</th>
<th>DEXILANT Total (N=2621)</th>
<th>Lansoprazole 30 mg (N=1363)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>2.9%</td>
<td>5.1%</td>
<td>4.7%</td>
<td>4.8%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>3.5%</td>
<td>3.5%</td>
<td>4.0%</td>
<td>4.0%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.6%</td>
<td>3.3%</td>
<td>2.8%</td>
<td>2.9%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>0.8%</td>
<td>2.9%</td>
<td>1.7%</td>
<td>1.9%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.8%</td>
<td>2.2%</td>
<td>1.4%</td>
<td>1.6%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Flatulence</td>
<td>0.6%</td>
<td>2.6%</td>
<td>1.4%</td>
<td>1.6%</td>
<td>1.2%</td>
</tr>
</tbody>
</table>

Table: Incidence of Adverse Reactions in Controlled Studies

Adverse Reactions Resulting in Discontinuation
In controlled clinical studies, the most common adverse reaction leading to discontinuation from DEXILANT therapy was diarrhea (0.7%).

Other Adverse Reactions
Other adverse reactions that were reported in controlled studies at an incidence of less than 2% are listed below by body system.

Gastrointestinal System: abdominal discomfort, abdominal tenderness, abnormal feces, anal discomfort, Barrett’s esophagus, bezoar, bowel sounds abnormal, breath odor, colitis, eosinophilic colitis, folate deficiency, fungal infection, gastritis, gastroenteritis, gastroesophageal reflux disease, gastritis, hemorrhoids, impaired gastric emptying, irritable bowel syndrome, mucus stools, oral mucosal blistering, painful defecation, proctitis, rash, retching, rectal bleeding

Hypersensitivity: skin reaction, urticaria

Hepatobiliary System: biliary colic, cholelithiasis, hepatic failure

Immune System Disorders: hypersensitivity

Infections and Infestations: candida infection, influenza, nasopharyngitis, oropharyngeal herpes, rhinitis, urinary tract infection, vulvar-vaginal infection

Injury, Poisoning and Procedural Complications: falls, fractures, joint sprains, nerve palsy, procedural pain, subumbilical hernia

Laboratory Investigations: ALP increased, ALT increased, AST increased, bilirubin decreased/increased, blood creatinine increased, blood gastrin increased, blood glucose increased, blood potassium increased, liver function test abnormal, platelet count decreased, total protein increased, weight increase

Hypertensive Disorders: hypertension

Metabolism and Nutrition Disorders: appetite changes, hypercalcemia, hypokalemia, hyperlipidemia

Musculoskeletal and Connective Tissue Disorders: arthralgia, arthritis, muscle cramps, musculoskeletal pain, myalgia

Nervous System Disorders: altered taste, convulsion, dizziness, headaches, migraine, memory impairment, paresthesia, psychomotor hyperactivity, tremor, trigeminal neuralgia

Psychiatric Disorders: abnormal dreams, anxiety, depression, insomnia, libido changes

Renal and Urinary Disorders: dysuria, micruria, urgency

Reproductive System and Breast Disorders: dysmenorrhea, dyspareunia, menorrhea, menstrual disorder

Respiratory, Thoracic and Mediastinal Disorders: aspiration, asthma, bronchitis, cough, dyspnea, hiccupps, hyperventilation, respiratory tract congestion, sore throat

Skin and Subcutaneous Tissue Disorders: acne, dermatitis, erythema, pruritus, rash, skin lesion, urticaria

Vascular Disorders: deep vein thrombosis, hot flush, hypertension

Additional adverse reactions that were reported in a long-term uncontrolled study and were considered related to DEXILANT by the treating physician included: anaphylaxis, auditory hallucination, B-cell lymphoma, burn, central obesity, cholecystitis, dehydration, diabetes mellitus, dysphagia, epistaxis, folliculitis, gout, herpes zoster, hyperlipidemia, hypothyroidism, increased neutrophils, MI/HOC decrease, neutropenia, rectal tenesmus, restless legs syndrome, somnolence, tinnitus

Other adverse reactions not observed with DEXILANT, but occurring with the racemate lansoprazole can be found in the lansoprazole prescribing information, ADVERSE REACTIONS section.

Postmarketing Experience
The following adverse reactions have been identified during post-approval of DEXILANT. As 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.

Blood and Lymphatic System Disorders: autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura

Ear and Labyrinth Disorders: deafness

Eye Disorders: blurred vision

Gastrointestinal Disorders: oral edema, pancreatitis

General Disorders and Administration Site Conditions: facial edema

Hepatobiliary Disorders: drug-induced hepatitis

Immunologic System Disorders: anaphylactic shock (requiring emergency intervention), exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal)

Infections and Infestations: Clostridium difficile associated diarrhea

Metabolism and Nutrition Disorders: hypoglycemia, hypotremia

Musculoskeletal System Disorders: bone fracture

Nervous System Disorders: cerebrovascular accident, transient ischemic attack

Renal and Urinary Disorders: acute renal failure

Respiratory, Thoracic and Mediastinal Disorders: pharyngeal edema, throat tightness

Skin and Subcutaneous Tissue Disorders: generalized rash, leukocytoclastic vasculitis

**DRUG INTERACTIONS**

**Drugs with pH-Dependent Absorption Pharmacokinetics**

DEXILANT causes inhibition of gastric acid secretion. DEXILANT is likely to substantially decrease the systemic concentrations of the HIV protease inhibitor atazanavir, which is dependent on the presence of gastric acid for absorption, and may result in a loss of therapeutic effect of atazanavir and the development of HIV resistance. Therefore, DEXILANT should not be co-administered with atazanavir.

DEXILANT may interfere with the absorption of other drugs where gastric pH is an important determinant of oral bioavailability (e.g., ampicillin esters, digoxin, iron salts, ketoconazole).

**Warfarin**

Co-administration of DEXILANT 90 mg and warfarin 25 mg did not affect the pharmacokinetics of warfarin or INR. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concurrently. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with DEXILANT and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

**Tacrolimus**

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.

**Clodipogrel**

Concomitant administration of dexlansoprazole and clopidogrel in healthy subjects had no clinically important effect on exposure to the active metabolite of clopidogrel or clopidogrel-induced platelet inhibition. No dose adjustment of clopidogrel is necessary when administered with an approved dose of DEXILANT.

**Methotrexate**

Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of high-dose methotrexate with PPIs have been conducted (see Warnings and Precautions).

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Teratogenic Effects**

Pregnancy Category B. There are no adequate and well-controlled studies with dexlansoprazole in pregnant women. There were no adverse fetal effects in animal reproduction studies of dexlansoprazole in rabbits. Because animal reproduction studies are not always predictive of human response, DEXILANT should be used during pregnancy only if clearly needed.

A reproduction study conducted in rabbits at oral dexlansoprazole doses up to approximately 9 times the maximum recommended human dexlansoprazole dose (60 mg per day) revealed no evidence of impaired fertility or harm to the fetus due to dexlansoprazole. In addition, reproduction studies performed in pregnant rats with oral lansoprazole at doses up to 40 times the recommended human lansoprazole dose and in pregnant rabbits at oral lansoprazole doses up to 16 times the recommended human lansoprazole dose revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole.

**Nursing Mothers**

It is not known whether dexlansoprazole is excreted in human milk. However, lansoprazole and its metabolites are present in rat milk following the administration of lansoprazole. As many drugs are excreted in human milk, and because of the potential for tumorigenicity shown for lansoprazole in rat carcinogenicity studies (see Nonclinical Toxicology), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**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, and other reported clinical experience has not identified significant differences in responses between geriatric 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 hypotension 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, contusion, 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 653 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/QTc interval in healthy adult subjects. DEXILANT doses of 90 mg or 300 mg did not delay cardiac repolarization compared to placebo. The positive control (moxifloxacin) produced statistically significantly greater mean maximum and time-averaged QT/QTc 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 on a body surface (mg/m²) basis. In rats, 150 kg person of average height (1.46 m² body surface area [BSA]) given the recommended human dose of lansoprazole 30 mg per day.

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 of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15 to 150 mg per kg per day.
(4 to 40 times the recommended human lansoprazole dose 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 lansoprazole dose based on BSA. Lansoprazole produced a dose-related increased 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) exceeded the ranges of background incidences in historical controls for this strain of mice. Lansoprazole treatment produced adenoma of rete 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 the in vitro human lymphocyte chromosomal aberration assay. Lansoprazole was not genotoxic in the ex vivo rat hepatocyte unscheduled DNA synthesis (UDS) test, the in vivo mouse micronucleus test or the rat bone marrow cell chromosomal aberration test.

Dexilansoprazole was positive in the Ames test and in the in vitro chromosome aberration test using Chinese hamster lung cells. Dexilansoprazole was negative in the in vivo mouse micronucleus test.

The potential effects of dexilansoprazole 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**

See FDA-Approved Medication Guide To ensure the safe and effective use of DEXILANT, this information and instructions provided in the FDA-approved Medication Guide 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 patients to immediately report and seek care for diarrhea that does not improve. This may be a sign of *Clostridium difficile* associated diarrhea [see Warnings and Precautions].

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

Advise the patient to tell their health care provider if they take atazanavir, tacrolimus, warfarin and drugs that are affected by gastric pH changes [see Drug Interactions].

Advise the patient to follow the dosing instructions in the Medication Guide 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 administered 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.

Distributed by
Takeda Pharmaceuticals America, Inc.
Deerfield, IL 60015
Revised: September 2012

DEXILANT is a trademark of Takeda Pharmaceuticals U.S.A., Inc. and used under license by Takeda Pharmaceuticals America, Inc. Trademark registered with the U.S. Patent and Trademark office. All other trademark names are the property of their respective owners. ©2009-2012 Takeda Pharmaceuticals America, Inc.

DEX006 R19 _BS L-LPD-0912-3

---

** Classifieds**

**Place GI Position Listings and Activity Announcements**

For as little as $82.50, you can place a classified ad of up to 100 words in AGAs weekly email newsletter, AGA eDigest, or AGAs bi-monthly magazine, AGA Perspectives. If you place ads in both AGA Perspectives and AGA eDigest, you will receive a 10 percent discount. Advertising in either includes a free online classified listing. Learn more by contacting Alissa Cruz at 301-272-1603 or email communications@gastro.org.

The deadline for the February/March 2013 issue is Dec. 17, 2012.

**CALIFORNIA**

Opportunity to assume retiring gastroenterologist’s practice in the San Francisco Bay Area town of San Mateo. Office in prime building location with endoscopy center two floors above. Local hospital newly built with state-of-the-art endoscopy suite. Hospital call schedule every eighth weekend. Potential partnership in profitable endoscopy ASC.

Contact Michael Mainardi, MD, at 650-773-2105 or 650-685-6105. Email: m.mainardi@comcast.net.

**KENTUCKY**

University of Louisville — The Division of Gastroenterology, Hepatology and Nutrition at the University of Louisville School of Medicine is seeking faculty with a career interest in IBD, general GI, hepatology and endoscopic ultrasound. There is considerable support for both clinical/bench research and excellent collaboration. J-1 visa conversion will be considered. The University of Louisville is an equal opportunity affirmative action employer. Interested candidates are invited to submit a *curriculum vitae*.

Contact Kristine Krueger, MD, professor and chief, clinical and academic affairs, Division of Gastroenterology, Hepatology and Nutrition, University of Louisville School of Medicine, Louisville, KY 40292.

Email: gimed@louisville.edu.

**NEW JERSEY**

Part-time Gastroenterology Associate — Northern New Jersey

Well-established GI practice in northern New Jersey looking for a part-time gastroenterology associate. Long-term position. Two to three days per week. No night or weekend call. Malpractice, health and pension.

Contact Cathy Shanahan at 973-633-1484. Fax: 973-633-7980. Email: cshanahan999@hotmail.com.
It is increasingly apparent that sporadic recurrent acute pancreatitis and chronic pancreatitis, as well as familial clustering of pancreatitis cases, typically have a genetic basis. Current research will further expand our knowledge of disease, including new genes that are linked to alcoholic pancreatitis risk.

The first problem is that most patients with recurrent acute or chronic pancreatic disease do not have classic Mendelian genetic disorders, but rather exhibit complex trait genetics. Complex means that multiple risk factors which, by themselves, are neither sufficient nor necessary to cause disease, come together in various combinations to markedly lower the threshold for triggering pancreatitis that then occurs when the gland is challenged by common stressors or minor injuries. Thus, the combination of multiple genes and environmental factors must be considered, with therapy targeted to the appropriate situation.

The second problem is that the framework for considering multiple combinations of factors and predicting optimal treatment is not clinically available. True personalized medicine approaches are needed that are based on disease modeling and simulation. The most exciting development in the past decade has been the use of standardized research protocols to achieve this goal.

The third problem is patient management. A historically poor understanding of the underlying etiology of pancreatic disease has funneled patient treatment into the only mechanisms that we know, including endoscopic treatment for possible functional obstruction or microscopic biliary particles, and radical surgical treatment for poorly defined chronic pain. I am especially alarmed at the growing popularity of total pancreatectomy with autologous islet autotransplantation (TPAIT) for recurrent pancreatitis or for fear of pancreatic cancer, especially in patients with genetic variants. What is needed is a better understanding of recurrent acute pancreatitis and chronic pancreatitis from the standpoint of the natural history of the disease.

Important questions for patient management include whether the physician can predict the clinical course of individual patients. If this can be answered, then the physician needs to know where the patient is now in the process, how fast the condition is changing from past states, and what is likely to happen in the future — with or without intervention. Continued alcohol consumption and smoking accelerate rates of progression and therefore severity of disease at proximal time points, as does serine protease inhibitor Kazal-type 1 mutations. Understanding the natural history of disease and the predicted history of individual patients with and without interventions is the foundation of personalized medicine.

I am convinced that a revolution in the evaluation and management of pancreatic disorders is at hand. The transformative technologies that will move us from the 20th century to the 21st are next-generation sequencing (which provides details on nearly all genes simultaneously at minimum cost), biomarkers based on “omic” technologies, and powerful computers that can organize and store valuable health data information. Data from these technologies will soon be useful for future disease modeling and simulation calculators. Amazingly, all of the pieces are here, but we continue practicing last century’s medicine because no one has connected them. We need the future now.

Patient Flow Through a Personalized Clinic

Legend: If simple etiologies or approaches fail and patients develop recurrent acute pancreatitis (RAP) or signs of early chronic pancreatitis (CP) (top box), they undergo a comprehensive evaluation, including genetic testing. Analysis of all data (including biomarkers such as CT scan, functional studies, IgG4, etc.) are used to develop a disease model with predictions of outcomes, optimal interventions and (surrogate) endpoints for monitoring. Personalized approaches are generally directed into one of four etiological processes, allowing for treatments to be targeted to the etiology rather than only the symptoms.

REFERENCES


Dr. Whitcomb is a consultant for Abbott, Lilly, Novartis and Millennium. He also owns license rights to testing for trypsin mutations through Ambry Genetics.
are taking this approach in our pancreas clinic (see chart).

The benefits of embracing and utilizing new technologies should be profound. Moving genetic testing to the initial evaluation often allows the underlying mechanistic defect to be determined immediately. Knowledge of the underlying mechanism then allows therapies to target the cause rather than the symptoms. More importantly, it allows a mechanistic diagnosis to be made years before chronic pancreatitis can be diagnosed. Chronic pancreatitis is a pathologic description of irreversible damage to the pancreas caused by inflammation. Therefore, the goal should be to use knowledge of the underlying molecular defect to prevent the development of irreversible damage and thus eliminate development of pathology in susceptible patients. Furthermore, the genetic and molecular basis of pain syndromes is also being discovered,\(^2\) and the same next-generation DNA sequencing test for pancreatitis provides information on possible pain mechanisms. This means we may achieve targeted treatment.

In summary, we are seeing a rapid advancement into personalized treatment of pancreatic disorders based, in part, on DNA sequencing of a bunch of new genes. This approach should yield marked improvement in the outcomes of patients, a hypothesis we are testing. Hopefully, this approach will avoid radical and irreversible treatments such as TPAIT in nearly all cases. Advances should be distributed and available everywhere so that physicians and health-care providers can prevent the development of life-altering pancreatic conditions, such as chronic pancreatitis, for which there is no cure.

---

**Clinic Entry**
Patient with confirmed RAP or early CP (after failed initial treatment)

**Comprehensive Evaluation**
- Environmental risk
- Family history
- Biomarkers
  - Genetics

**Disease Model**
- Etiology/syndrome
- Risk factors (fixed, variable)
- Biomarkers (activity, progression)
- Prediction/intervention/endpoints

**Personalized Approach**

**Duct Obstruction**

**Duct Flushing**

**Acinar Trypsin Activation**

**Autoimmune/Immune**

---

**Demonstrate Quality and Earn Rewards for Treating IBD**

Introducing AGA’s Bridges to Excellence (BTE) IBD Care Recognition, a part of the AGA Digestive Health Recognition Program™ (DHRP)

**Easily Report Quality Performance for IBD Care**

BTE, a program of the Health Care Incentives Improvement Institute, enables health-care providers to easily report quality performance to multiple health plans through a single program, and gain rewards such as recognition and incentive payments. Participants can also use the AGA DHRP to submit data for the CMS Physician Quality Reporting System to ensure Medicare incentive payments and avoid penalties.

Learn more by visiting [www.agarecognition.org](http://www.agarecognition.org) or contacting recognition@gastro.org.
Recertification — Here We Go Again

Gastroenterologists practicing in the U.S. who have completed fellowship training after 1990 are — or will become — very familiar with the American Board of Internal Medicine (ABIM) Maintenance of Certification (MOC) Program. In order to remain a certified diplomate, the applicant must register for the program, complete eight self-assessment modules and one practice improvement module, and pass the day-long closed-book cognitive skills examination. This exercise must be repeated every 10 years. Physicians that completed fellowship training before 1990 are encouraged to complete this program, but it is not required. Not surprisingly, of the 69,000 diplomates of the ABIM with this grandfather status, less than 1 percent have elected to recertify in the MOC program.1

The goals of recertification are laudable if patient care is improved, standards are improved/maintained, lifelong learning is established, and physicians’ knowledge and skills remain current. While these goals and outcomes are difficult to argue, the recertification process does require time and financial commitments that are quite measurable.

The monetary commitment includes the direct costs of preparation, registration and supporting study materials. Registration for MOC is $1,875 and the eight self-assessment modules cost another $320. Many opt to attend board preparation courses ($1,600), which require lodging ($1,000), food ($375) and travel ($250), and some purchase the course study questions/books ($1,200). The missed opportunity costs are likewise high considering the five to six billable days out of the office/hospital that are needed to prepare for and take the exam. Taken collectively, it costs thousands of dollars to complete the MOC program.

Current certification does not guarantee passage of the recertification examination. The GI recertification pass rates for first-time takers have ranged from as high as 90 percent in 2007 to as low as 84 percent in 2010.1 The pass rate for recertification takers has been consistently lower than that of first-time takers (see table). Possible explanations include the fact that the exam is not reflective of one’s practice and/or insufficient preparation time of the busy gastroenterologist.

Most recertifying practitioners are facing very high stakes for passage. These include the stigma of non-passage and subsequent loss of certification as well as possible loss of income, partnership and affiliation with hospitals and insurance companies that require MOC. Even after one successfully completes the recertification process, the black cloud remains since the entire process must be repeated every decade.

There currently exist two standards for certified diplomates. If the recertification process improves patient care and continues physician learning, why would this process be optional to a substantial number of practicing gastroenterologists? While this population of grandfathered practitioners is a shrinking pool, older physicians might benefit more from MOC than younger colleagues. A systematic review of 62 studies revealed declines in physician performance with greater years in practice, decreasing medical knowledge, less likelihood of adherence to current standards, and worse health-care outcomes.3 However, we are unaware of any studies demonstrating improved patient outcomes in our specialty of gastroenterology.

Recently, CMS has proposed an MOC payment incentive of 0.5 percent. To qualify, one must successfully complete the MOC process. We are unaware of any third party payors that differentiate payment based on board certification, but we will not be surprised if they do not follow the federal government’s initiative in the near future.

While the recertification process is here to stay, practitioners are encouraged to start the process early and become active participants. Ideally, we would like to see improvement in the MOC process to have it more pertinent to the practicing physician, less costly and more time-efficient.

References

1. ABIM data.
2. ABIM data.

Exam Trends

ABIM MOC GI Exam: First-Time Takers with Valid Time-Limited Certificates Pass Rates1*

<table>
<thead>
<tr>
<th>Year</th>
<th>#</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>168</td>
<td>87%</td>
</tr>
<tr>
<td>2007</td>
<td>432</td>
<td>90%</td>
</tr>
<tr>
<td>2008</td>
<td>207</td>
<td>85%</td>
</tr>
<tr>
<td>2009</td>
<td>288</td>
<td>89%</td>
</tr>
<tr>
<td>2010</td>
<td>346</td>
<td>84%</td>
</tr>
</tbody>
</table>

Subspecialty Certification GI Exam: First-Time Taker Pass Rates1*

<table>
<thead>
<tr>
<th>Year</th>
<th>#</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>421</td>
<td>95%</td>
</tr>
<tr>
<td>2007</td>
<td>440</td>
<td>95%</td>
</tr>
<tr>
<td>2008</td>
<td>446</td>
<td>94%</td>
</tr>
<tr>
<td>2009</td>
<td>437</td>
<td>97%</td>
</tr>
<tr>
<td>2010</td>
<td>457</td>
<td>89%</td>
</tr>
</tbody>
</table>

KEY: #: number of first-time takers; %: percent passing

*Because the performance of small numbers of examinees can have a significant effect on results, pass rates for examinations with less than 100 takers should be interpreted cautiously.
CREDENTIALING

Credentialing Issues: New Technologies and Techniques

In 2001, a few years after I had completed my gastroenterology fellowship, wireless capsule endoscopy was introduced into general gastroenterology practice. I was already managing small-bowel disorders and performing enteroscopy; therefore, it was an easy transition to understanding the indications and contraindications for wireless capsule endoscopy, as well as interpreting the images. I further developed competency in this new technology by attending meetings and short courses. In particular, the hands-on courses and lectures at DDW provided substantial benefit in advancing my ability to add new skills to my endoscopic toolbox. Although a guideline for granting privileges in capsule endoscopy has been published, my experience is that most credentialing committees do not require the same criteria.1

Credentialing

As new techniques evolve and are developed in gastroenterology, hospitals and ambulatory surgery centers (ASCs) may be faced with credentialing issues as gastroenterologists update their technical skills to deliver high-quality medical care. Credentialing is a vital part of the privileging process where hospitals or ASCs verify that the gastroenterologist has documentation of appropriate licensure, education, training and experience. After completing fellowship training, the initial verification of credentials is provided by the gastroenterology fellowship director because there is not a board examination specific to endoscopic procedures. Gastroenterology board certification is an assessment of cognitive skills. Privileges should be requested and granted separately for each procedure. Recredentialing serves as an interval assessment of competence to perform procedures typically two to three years after the initial granting of privileges.2

Minor versus major skills

With regards to obtaining privileges for a new technique for the practicing gastroenterologist, the new skills required to perform the new technique or technology can be separated into two groups. A minor skill has been defined as a new development that is a minor extension of an accepted and widely practiced technique or procedure. A major skill describes a new technique or procedure that involves a high level of complexity, interpretative ability and/or new type of technology.3 An example of a minor skill would be the use of endoscopic clip placement by gastroenterologists who already demonstrate competency in the use of other endoscopic modalities for the control of bleeding (e.g., injection and cautery techniques). Endoscopic ultrasound would be an example of a major skill because of the high degree of complexity of the procedure and the skills required to interpret the sonographic images.

The education and training to obtain proficiency in new techniques or technologies will vary by the complexity of the skills needed. For example, a minor skill can be mastered with reading the literature, attending lectures or viewing expert video presentations. With a combination of didactics, attending short courses and hands-on education, gastroenterologists can expand their major skills and repertoire of endoscopic interventions. In bariatric surgery, some experts have proposed a mini-fellowship to develop adequate skills to perform a new surgical technique.4 A similar approach with hands-on mentoring and proctoring in more complex techniques and procedures could help gastroenterologists attain competency and privileges of a new major skill. In the future, endoscopic simulators may offer another pathway to learn and enhance new skills. Also, registries such as the AGA Digestive Health Outcomes Registry may be utilized to track findings and outcomes for new technologies and techniques that could support recredentialing.

Conclusions

Hospitals and ASCs will continue to face the challenge of assessing the credentials of gastroenterologists requesting privileges for new techniques and/or technology. Unfortunately, there is a paucity of data in the medical literature to provide meaningful guidelines to assist those in granting privileges. One criterion for granting privileges in a new technique or technology could be monitoring of patient selection, indications and outcomes for continuous quality and practice improvement. Ultimately, each local credentialing committee must set a formal process with criteria to credential gastroenterologists in new technologies and techniques.

REFERENCES

SOCIAL MEDIA “KUDOS”
How to Be Ethical in the Digital Wild West
We are living in a period of great transition. Social media such as blogs, wikis, discussion forums, ratings sites and online social networks are completely changing the ways in which patients and physicians create, share and understand health information. We can now find, recommend and discuss symptoms, diagnoses and treatments with pretty much anyone, anywhere in the world, almost instantly. Cast your mind back to just ten years ago before Facebook, before Twitter, and the seismic nature of this transition becomes apparent.

Historically, periods of profound transition are difficult because the moral norms which upheld the old ways don’t always seem to apply to the exciting new world. Rather like the ancient Romans dealing with the shift from republic to empire, or sheriffs bringing the rule of law to the wild west, it is difficult for us to deal with a new digital world in which the old ethical standards of professionalism and respect for medical authority sometimes seem to have gone out of the window. Yet, physicians and other health-care professionals are a key part of the new digital world. Doctors, nurses and their colleagues are important creators, collators and curators of accurate and reliable health-care information in social media spaces. Professionals who wish to create and share social media content can use the KUDOS acronym to help them navigate the uncertain ethics of the digital wild west. KUDOS stands for Knowledge (which is) Useful, Desirable, Open and Shareable, and it serves as a guide to the ethical nature and quality of the content professionals should create and share online.

Knowledge

Any content that you create or share online as a health-care professional should be recognizable as a piece of accurate, reliable knowledge. It seems obvious, but in the midst of all the sound and fury which constitutes much of online discussion, physicians and their colleagues should be mindful only to proffer that social media content based on their medical expertise. You should also recognize that in social media spaces, there are many different types of knowledge and expertise. Where you are an expert in your scientific field, patients are experts in the everyday experience of living with their diseases and conditions. Respect their knowledge and offer your own expertise, not in competition but in collaboration.

Useful

The knowledge you offer as a medical professional should also be useful. To be useful, expert medical knowledge should be both aimed at solving a specific problem or issue, and packaged in such a way that lay persons can make sense of it. Don’t just go spouting off a stream of decontextualized scientific data. Stop and think about who could use your knowledge and how you can help them do so. Identify the right social media spaces and the right format for your knowledge. Offering knowledge which no one can use is a waste of time and opportunities.

Desirable

It is not enough, in social media, for expert knowledge simply to be useful. It should be desirable, meaning that the social media users you aim the knowledge at should actually want it. Before you enter into a social media space in order to offer advice — say a disease discussion forum — ask yourself whether or not your input will be valued. Does it seem like you are barging into a private conversation? Is medical expertise sought here? Social media spaces are often very much like communities, and you need to work with their desires and needs in order not to cause offense or insult anyone when sharing your medical expertise. Physicians can do more harm than good when they ignore the desires of social media users.

Open

You should also be open about who you are (your professional affiliations, where you work, any relevant funding) and where your expertise and knowledge comes from. Be honest and upfront about why you are sharing and what you hope to gain by doing so.

Shareable

Finally, you should only share or create content which you are happy to share across the Internet. What you say online stays online. Privacy might not be what it once was, but patient anonymity remains vital, as does maintaining a professional attitude. If you wouldn’t say it offline, don’t share it online.

The ethics of social media are still emerging, but physicians who follow KUDOS will find themselves able to be good in the digital wild west whilst those moral standards sort themselves out.
The AGA International Committee organized a symposium at DDW® 2012 entitled “Obesity and the Impact on GI Disease.” Speakers included Luigi Ricciardiello, MD; Arun Sanyal, MD; and me; the aim of the symposium was to emphasize the importance of obesity and its complications, and how these are not restricted to North America and Western Europe, but are a major worldwide problem.

So why study complications of obesity? Principally, because we do not envisage an effective non-surgical approach to the treatment of obesity in the near future. Thus, it is appropriate to accept the fact that obesity will continue to be a widespread problem in the foreseeable future so that an approach to defining the mechanisms and potential therapy for these complications is an appropriate goal. The major complications of obesity that commonly result in death: type II diabetes, cardiovascular disease, liver disease and cancer can all now be seen as a result of low-grade tissue inflammation. Such inflammation appears to derive in many obese individuals as a result of T-cell and macrophage infiltration in visceral and subcutaneous adipose tissue stores. The association between obesity and cancer of the breast, colon and endometrium, as well as adenocarcinoma of the esophagus, may all be directly related to an inflammatory response in these organs in obese individuals before cancer develops. Such chronic inflammation is a well-accepted epidemiologic, clinical and molecular harbinger of cancer and that such a mechanism has a major factor in cancer causation is very plausible. Recent studies have directly described inflammation of the breast and colon in obese individuals as previously shown in blood vessels as well as in the liver — as non alcoholic steatohepatitis (NASH) — and the pancreas.

The international epidemiologic data on the link between obesity and colorectal cancer (CRC) is particularly strong. Obesity trends in developed and developing nations mimic each other even though those in the latter are somewhat less. BMI is related to CRC incidence and mortality in Europe, North America and Northern Asia, and the relationship to visceral fat stores as measured by MRI or waist circumference is even stronger. In men, for each 10 cm increase in waist circumference, the risk increases by one-third. Obesity progressively increases the risk of death from CRC by 80 percent in men and 45 percent in women overall. Similar data has been published in the Asia-Pacific CRC cohort studies and studies from Israel. The data for the relationship of obesity to the presence of adenomatous polyps is somewhat less convincing since the incidence of obesity worldwide is increasing exponentially, better understanding of the mechanisms and the treatment of obesity-related GI complications is mandatory.
but sufficient to recommend closer screening as well as surveillance after adenomatous polyps have been found and removed. The relationship between the presence of the metabolic syndrome and CRC is stronger for adenomatous polyps, suggesting that such individuals require even greater attention.

It is clear that the incidence and death rate from CRC is changing. For example, there has been a dramatic four-fold increase in CRC risk in Eastern Europe over the past 40 years, so that now the incidence in some Eastern European countries is even greater than in the U.S. Furthermore, in certain precincts in Japan, the CRC incidence also exceeds U.S. CRC incidence rates. In China, the incidence in middle-aged men is rising at a remarkable rate. In addition, there has been a noticeable increase in right-sided colon cancers in women above the age of 70 in Japan. Overall, there has also been an emphasis on the frequency of depressed or flat neoplasms in Asia. However, the suggestion that this is a particular phenomenon in Asian countries is probably incorrect, since incidence with enhanced colonoscopic techniques in North America and Europe also shows similar rates of such neoplasms.

It is well accepted that liver disease occurs commonly amongst obese individuals — usually as NAFLD, but not uncommonly as NASH. Epidemiologic studies suggest that NAFLD increases overall mortality by 40 percent and liver-related mortality nine fold. In the liver, inflammation is not marked by accumulation of macrophages, but rather by stellate cell activation. It is well recognized that circulating gut-derived microbiota can exacerbate the fat associated with liver disease related GI complications is mandatory.

The optimal therapeutic measure to alleviate these serious obesity-associated complications is through weight loss, although hypothetically, safe anti-inflammatory agents should work. Recent studies suggest that NASH may improve following treatment with vitamin E or with pioglitazone. Overall, since the incidence of obesity worldwide is increasing exponentially, better understanding of the mechanisms and the treatment of obesity-related GI complications is mandatory.

Journal Editors’ Picks

**CGH FOR DECEMBER**

- **Quality Improvement in Gastroenterology Clinical Practice**
  By Rakhi Kheraj, et al.

- **Low-Dose Hydroxychloroquine Is as Effective as Phlebotomy in Treatment of Patients With Porphyria Cutanea Tarda**
  By Ashwani K. Singal, et al.

- **Nonalcoholic Fatty Liver Disease and Hepatocellular Cancer: A Systematic Review**
  By Donna L. White, et al.

- **Risk of Esophagitis Among Individuals Born Preterm or Small for Gestational Age**
  By Lina Forssell, et al.

- **Factors Associated With Diagnosis of Obstructive Gastrointestinal Bleeding by Video Capsule Enteroscopy**
  By Lucie Lepileur, et al.

**GASTRO FOR DECEMBER**

- **Teduglutide Reduces Need for Parenteral Support Among Patients With Short Bowel Syndrome With Intestinal Failure**
  By Palle B. Jørgensen, et al.

- **Efficacy of Ursodeoxycholic Acid in Treating Intrahepatic Cholestasis of Pregnancy: A Meta-Analysis**
  By Yannick Bacq, et al.

- **Segregation of a Missense Variant in Enteric Smooth Muscle Actin γ-2 With Autosomal Dominant Familial Visceral Myopathy**
  By Heli J. Lehtonen, et al.

- **Similar Efficacies of Biliary, With or Without Pancreateic, sphincterotomy in Treatment of Idiopathic Recurrent Acute Pancreatitis**
  By Gregory A. Coté, et al.

- **Redundant Sources of Wnt Regulate Intestinal Stem Cells and Promote Formation of Paneth Cells**
  By Henner F. Farin, et al.

**CGH FOR JANUARY**

- **Classification, Diagnosis, and Management of Cholangiocarcinoma**
  By Nataliya Razumilava, et al.

- **Management of Belching, Hiccups, and Aerophagia**
  By Albert J. Bredenoord

- **Covered vs. Uncovered Self-Expandable Metal Stents in Patients With Malignant Distal Biliary Obstruction: A Meta-Analysis**
  By Majid A. Almadi, et al.

- **Validation of the Ulcerative Colitis Colonoscopic Index of Severity and its Correlation With Disease Activity Measures**
  By Sunil Samuel, et al.

- **Boceprevir With Peginterferon Alfa-2a–Ribavirin Is Effective for Previously Treated Chronic Hepatitis C Genotype 1 Infection**
  By Steven L. Flamm, et al.

**GASTRO FOR JANUARY**

- **Measurement of Spleen Stiffness by Acoustic Radiation Force Impulse Imaging Identifies Cirrhotic Patients With Esophageal Varices**
  By Yoshitaka Takuma, et al.

- **Elastography, Spleen Size, and Platelet Count Identify Portal Hypertension in Patients With Compensated Cirrhosis**
  By Annalisa Berzigotti, et al.

- **Replication of Hepatitis C Virus Genotype 3a in Cultured Cells**
  By Mohsan Saeed, et al.

- **Development of Robust Hepatitis C Virus Genotype 4 Subgenomic Replicons**
  By Betty Peng, et al.

- **Incomplete Polyp Resection During Colonoscopy — Results of the Complete Adenoma Resection (CARE) Study**
  By Heiko Pohl, et al.
Now more than ever, the AGA Research Foundation needs your support. At a time when funds from NIH and other traditional sources of support are in decline, the foundation plays an important role in medical research by providing grants to young scientists at a critical time in their research careers. Your contribution will help us fulfill our vision of fostering the future of young researchers in gastroenterology and hepatology. By joining others in donating to the AGA Research Foundation, you will ensure that researchers have opportunities to continue their life-saving work.

Mark Donowitz, MD, AGAF  
*Johns Hopkins University*  
Past AGA president and AGA Legacy Society member

“The future of our field depends on advances made in research: bench, clinical and translational. I see firsthand that it’s increasingly difficult for investigators to secure funding, particularly those in the early stages of their career. We can’t afford to have our pipeline of researchers dry up. The AGA Research Foundation provides the funds that are necessary for these young investigators to continue their work and contribute to the field. That’s why I support the foundation.”

Join your colleagues in supporting the foundation’s work. Demonstrate that you also see the value of research to the future of gastroenterology and as the basis of the work you do every day.

Patrick Quinn, MD, AGAF  
*Northern New Mexico Gastroenterology*  
AGA Legacy Society member

“I reached a point in my career where I realized how much of my ability to care for patients is a result of both clinical and basic research, and recognized that I have been fortunate enough to have the opportunity to give back and make a substantial gift to help continue research to benefit future generations.”

Donate today at [www.gastro.org/contribute](http://www.gastro.org/contribute).
Your gift will make an immediate difference in the careers of young physician-scientists like these — and in the lives of countless patients who will benefit from their work.

Adam J. Bass, MD
Dana Farber Cancer Institute
2012 R. Robert and Sally Funderburg Research Award in Gastric Cancer recipient

“As a medical oncologist I have witnessed firsthand the horrible burden of [gastric cancer] and our urgent need to make progress in our ability to prevent, detect and treat this disease. With this support from the AGA, my laboratory at the Dana-Farber Cancer Institute will be able to follow up on new results with immediate potential translational relevance to the care of patients with gastric cancer.”

Ashwin Ananthakrishnan, MD, MPH
Massachusetts General Hospital
2011 AGA Research Scholar Award recipient

“Thanks to an AGA Research Scholar Award I’m able to continue research that will help us better understand the environmental risk factors for the development of Crohn’s and ulcerative colitis. This award came at a critical next step in my development into a leader in clinical and translational IBD research.”

Join your colleagues in making a gift to the future of GI. Your tax-deductible contribution supports the foundation’s portfolio of research awards, which ensures that studies are funded, discoveries are made and patients are treated.
AGA-ASGE Clinical Congress of Gastroenterology and Hepatology

BEST CLINICAL PRACTICES: 2013

Jan. 17–19, 2013
HOTEL DEL CORONADO
SAN DIEGO, CA

NEW HANDS-ON COURSES:
STATE-OF-THE-ART EXPERT
TECHNIQUES 2013

- Upper GI Endoscopy:
  Esophagus and Gastric Therapies

- Lower GI Endoscopy:
  Colonic and Intestinal Therapies

Register early to take advantage of discounted rates and save.

www.gastro.org/clinicalcongress