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By Sharon Carey

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March 2013
Vol. XXXVII No. 3

PRACTICAL GASTROENTEROLOGY

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Development and Treatment of Fibrosis in Crohn’s Disease
by Anas A. Alsaleh, John F. Kuemmerle

Several factors are associated with higher rates of progression to intestinal fibrosis in Crohn’s disease patients. In this article we discuss these factors, available imaging studies to distinguish between inflammatory and fibrotic strictures (key to effective management), treatment options and future directions in therapy.
How Would You React to Intermediate Values of Lipase?
by Gabriel M. Aisenberg

The aim of this study is to determine physicians’ interpretation of intermediate values of serum lipase (IVSL, a lipase level above the upper normal limit but below 3 times that value), and in which cases pancreatitis is diagnosed. Since IVSL is not sufficient to diagnose acute pancreatitis, this retrospective study aims to determine what additional parameters are utilized by physicians to establish the diagnosis of pancreatitis.

Bone Health After Major Upper Gastrointestinal Surgery
by Sharon Carey

Bone Mineral Disease can be painful, debilitating and result in increased fracture risk. It is highly prevalent in those having had major upper gastrointestinal surgery with multiple contributing factors. Awareness of the risk factors and early screening can help prevent or slow the onset of disease. Here we discuss the need for health professionals to be vigilant in screening for and managing BMD.

Simultaneous Detection of IgM Anti-Hepatitis E Virus and Anti-Epstein-Barr Virus in Acute Hepatitis
by Damian Casadesus, Syed Hassan, Tania Calzada, Isabella Zathureczki, Joseph DeAntonio, Daniel Goldsmith
Crossword Puzzle 68
by Myles Mellor

Medical Bulletin Board 61
News items of interest to the nation’s gastroenterologists.

Meetings Calendar 67
Meetings, events, courses, symposia, and their contacts.

Reader Request Fax Form 66
Readers may obtain additional information about products and services that appear in Practical Gastroenterology.
Welcome to “Frontiers in Endoscopy,” a new Practical Gastroenterology series. Endoscopy continues to progress and develop at a rapid pace, with advancement coming along multiple different lines. Along one line, entirely new techniques are being developed, most notably natural orifice transluminal endoscopic surgery (NOTES) and interventional endoscopic ultrasound (EUS) approaches to new and old problems. Along other lines, old techniques such as biliary cannulation in endoscopic retrograde cholangiopancreatography (ERCP) continue to undergo development and refinement, with small changes in technique manifesting with significant differences in outcomes, success, and complication rates. Furthermore, device technology itself is progressing, allowing endoscopists to perform procedures that in the past were considered “impractical” or “unsafe” in a routine manner. The introduction of covered metal stents, for example, has driven the tremendous expansion of indications for the use of biliary and esophageal stents. Not so long ago, biliary and esophageal metal stents had only one indication each: the palliation of malignant biliary obstruction and malignant dysphagia, respectively. Any use of these devices beyond these indications was considered out of bounds by most physicians. Covered metal stents create the potential for removability, and has opened up the use of these devices in a wide range of settings including the treatment of benign strictures and leaks, the management of postsurgical complications, and even cross-modality uses such as combining interventional ultrasound with covered metal stent technology to drain an abscess or a pseudocyst in a trans-mural manner.

This series will bring to the reader a selection of some of the most interesting and exciting aspects of endoscopy, including new takes on some old favorites and updates on new, cutting-edge technologies. ERCP, EUS, and luminal endoscopy will all be covered in detail. We hope you find these papers to be both useful and enjoyable.
Biliary Cannulation: An Update on Tools and Techniques

INTRODUCTION

Endoscopic Retrograde Cholangiopancreatography (ERCP) is a commonly performed endoscopic procedure to assess and manage biliary and pancreatic conditions. Achieving cannulation of the desired duct is a prerequisite for any successful ERCP procedure. The overwhelming majority of ERCP procedures involve deep biliary cannulation (DBC). Failed ERCP can lead to complications and the need for subsequent procedures, which may be more invasive. Many different cannulation techniques have been developed and refined over time, and this manuscript will review the current state-of-the-art of biliary cannulation.

Initial Positioning

Once the duodenoscope has been advanced to the second duodenum, the endoscopist usually attempts to achieve a “short position” of the scope by deflecting fully the lateral wheel (or ratchet) towards the right with upward deflection of the large wheel and then simultaneously torquing the scope’s shaft clockwise while withdrawing the endoscope. This transitions the endoscope to a point where the shaft is lying along the lesser curvature of the stomach. This maneuver will almost always result in the tip of the endoscope being distal to the ampulla, with the ampulla appearing to be “above” the endoscope’s tip. “Long position” (where the shaft of the endoscope lies along the greater curvature of the stomach) is often helpful in obtaining an adequate position for cannulation if a short position provides a suboptimal vantage point.

Biliary Cannulation

Biliary cannulation is the most challenging step in ERCP to master during training. It is pivotal for any successful ERCP. A retrospective study of the training of a single operator showed that biliary cannulation of a native papilla is a skill that improves during training and continues to improve after training. In this study, which only evaluated cannulation attempts in patients with native papillary anatomy and excluded those who had previously undergone a biliary sphincterotomy and counted any hands-on assistance from the attending physician as a cannulation failure, the operator achieved successful biliary cannulation of 43% at the beginning of the training and was well over >80% at the end of training. He reached >96% successful biliary
Cannulation as independent operator at the end of his first year of practice which included many referrals for failed cannulation. The study emphasized that trainees and practicing physicians should track their cannulation success rates and only count patients with native papillary anatomy, as the success rate in cannulation of patients with prior sphincterotomy is virtually 100%.

In current practice, common biliary cannulation methods include:

1. Straight biliary catheter with a guidewire and/or dye
2. Sphinctertomes with a guidewire and/or dye
3. Initial pancreatic cannulation with wire placement followed by biliary cannulation (Double wire technique)
4. Initial pancreatic cannulation with pancreatic stent placement followed by biliary cannulation (Double wire technique)
5. Precut (Needle Knife) Sphincterotomy
6. Rendezvous techniques

**Cannulation Using Contrast vs. Wire**

Guidewire cannulation refers to a set of cannulation techniques in which selective biliary or pancreatic cannulation is achieved using catheters and/or sphincterotomes and hydrophilic guidewires. The term “guidewire cannulation” implies that contrast injection is not performed during cannulation but only after deep biliary or pancreatic ductal access has been obtained as confirmed fluoroscopically. Thus, if contrast is used during cannulation the operator cannot be said to have been performing “guidewire cannulation.”

Guidewire cannulation can be performed via several different techniques. The most common approach involves gentle insertion of the tip of a catheter or sphincterotome into the ampulla, followed by gradual guidewire advancement through the working channel of the device in an attempt to access the desired duct. This technique involves direct contact between the tip of the cannulation device and the ampulla before the wire is advanced.

Another common technique involves the tip of the cannulation device being advanced near to, but not into, the ampulla, with the guidewire being advanced across a short distance into the ampulla. With this technique, the tip of the device does not contact the ampulla directly; the guidewire itself is what makes contact with the ampulla in an attempt to access the desired duct.

Guidewire cannulation has been a source of great interest in recent years and has been widely adopted. Several studies have shown a lower rate of post-ERCP pancreatitis when guidewire cannulation is used when compared to contrast-assisted cannulation techniques. The largest single study on guidewire cannulation to date is a single operator, retrospective study of 822 consecutive ERCP’s described a high success rate of deep biliary cannulation (96.7%) using dye-free, guidewire techniques. Only 11 patients (1.3%) developed post ERCP pancreatitis (all of which were mild). Eleven cases (1.3%) were complicated with a guidewire perforation; all were managed conservatively and no patients who developed guidewire perforations required any intervention beyond fluids and antibiotics.

A recent meta-analysis reviewing 7 randomized, controlled trials (including 5 non-crossover trials and 2 crossover trials) demonstrated positive findings regarding increased cannulation success rates and fewer complications when using guidewire cannulation as compared to conventional contrast guided bile duct cannulation. In the 5 non-crossover trials, there was...
a significant reduction in the frequency of episodes of post-ERCP pancreatitis when guidewire cannulation was used (3.2%) as compared to contrast guided cannulation (8.7%) (Relative risk 0.38). Cannulation success rates were also higher when using guidewire cannulation (89%) versus contrast guided cannulation (78%) (Relative risk 1.19). Overall, the pooled rates of post-ERCP pancreatitis in the two crossover studies were statistically insignificant. (RR 0.97).8, 9

Although much guidewire cannulation data is encouraging, some studies have been far less enthusiastic. A multi-center, prospective study of 400 patients randomized patients to 4 groups (sphincterotome versus conventional catheter and guidewire versus non-guidewire based approaches).10 This study demonstrated that wire guided cannulation trended towards shortened cannulation and fluoroscopy times. There were no significant differences in the rates of post-ERCP pancreatitis or cannulation success.

A more recent systematic Cochrane review of 12 randomized controlled trials with 3450 participants comparing guidewire cannulation to contrast-assisted cannulation found a significantly lower incidence of post ERCP pancreatitis in guidewire cannulation groups compared to contrast assisted cannulation groups (RR 0.51, 95% CI 0.32 to 0.82). Furthermore, the guidewire cannulation group achieved a greater primary cannulation success (RR 1.07, 95% CI 1.00 to 1.15) and reduced need for precut sphincterotomy (RR 0.75, 95% CI 0.60 to 0.95) with no increase in other ERCP complications. The authors concluded that guidewire cannulation appeared to be the most appropriate first line to achieve cannulation in ERCP.11

The major concerns associated with guidewire techniques include creating a false tract (sinus) or perforation by the wire. Both of these complications can be minimized by using soft-tip guidewires. If the guidewire is advanced forcefully into a side branch pancreatic duct, post ERCP pancreatitis can ensue, although in practice this is mild in severity and rare in occurrence.5

There are different diameters of the wires that can be used. The most commonly used wires are 0.025 and 0.035” wires. It should be noted that a recent randomized prospective study (n=100) showed no difference between the two wires in regard to achieving cannulation or resulting in complications, although individual preferences among operators are often strong.12

Occasionally, during attempts to cannulate the bile duct the guidewire is advanced inadvertently into the pancreatic duct. If this occurs repeatedly, it is become increasingly common in these situations for the endoscopist to use this wire in the pancreas to their advantage via the so-called “double wire” or “two wire” technique.

(continued on page 21)
technique. In this situation, the endoscopist will remove the sphincterotome or the cannula while leaving the guidewire in the pancreatic duct. Then the sphincterotome or the cannula can be loaded with a second wire and is advanced through the working channel to the level of the ampulla, at which point further attempts to cannulate the bile duct are commenced. The wire in the pancreatic duct can help in obtaining biliary access via several means: the angle of the PD is seen endoscopically and fluoroscopically (and can be thus avoided), the wire in the PD can help to straighten the ampulla, can allow the physician to extrapolate the presumed location of the bile duct, and can allow placement of a PD stent if it is felt to be clinically indicated at any point during the procedure.5

Several studies have demonstrated the efficacy of double wire techniques in achieving deep biliary cannulation in adult and pediatric populations with high success and low complication rates.6, 13, 14 On the downside, a multicenter randomized study that enrolled 166 patients raised concern about a higher risk of post ERCP pancreatitis in cases with difficult biliary cannulation where the two wire technique was used compared to patients undergoing standard biliary cannulation (17% in the double wire technique vs. 8% in the standard biliary cannulation (OR 2.13; 95% CI, 0.89-5.05)(9).15 A subsequent prospective randomized controlled Japanese study (n=70 patients) recommended placement of a pancreatic stent in those who undergo cannulation via the two-wire technique.16 Overall, the two-wire technique is felt to be highly valuable and can lead to success in cases of difficult biliary cannulation, but the need for a pancreatic duct stent in these patients is unclear.

Use of Pancreatic Stent to Facilitate Biliary Cannulation

The placement of a pancreatic stent can itself serve as an aid to biliary cannulation beyond its benefits in reducing post-ERCP pancreatitis. The stent provides many of the same potential benefits of pancreatic wire in case of double wire cannulation, namely straightening the ampulla, providing information about the angle and location of the pancreatic duct, and allowing extrapolation of the angle of the bile duct. (Figure 2)

In this situation, considering placement of a pancreatic stent is very appealing since placement of a pancreatic stent itself minimizes the risk of post ERCP pancreatitis with absolute risk reduction ranges from 1 to 13%.17,18 With regards to the use of a pancreatic duct stent to aid biliary cannulation, one retrospective study that included 2345 ERCP cases with native papillae, 76 (4.9%) cases required a pancreatic stent placement to facilitate biliary cannulation. Among those, 71/76 (93%) patients had a successful biliary cannulation, with 60 (78.9%) patients avoiding a needle-knife sphincterotomy. Mild pancreatitis was recorded in only 4 patients (5.3%).19

Needle-Knife Sphincterotomy

Needle-knife sphincterotomy refers to performing an access sphincterotomy with a needle-knife catheter to establish biliary access. In general, needle-knife sphincterotomy is generally selected when other, less invasive means of obtaining biliary or pancreatic access have failed or if standard techniques are not felt to be feasible (i.e. impacted stone at the ampullary orifice that does not allow sphincterolysis or guidewire passage. It must be stressed that needle-knife sphincterotomy is considered a high-risk procedure. Complications from needle-knife sphincterotomy include, but are not limited to, bleeding, perforation and pancreatitis - all of which can be severe.

The terms “needle-knife sphincterotomy” and “precut sphincterotomy” are sometimes used interchangeably in an erroneous manner. The term “precut sphincterotomy” may often refer to the use of a standard sphincterotome to perform a biliary sphincterotomy before deep biliary access has been obtained with a catheter and/or wire.

Contrary to what one might anticipate, limited data suggest that complications rates from needle-knife sphincterotomy may not fall as operator experiences increase. A key 2002 study reported the success and complication rates from a single endoscopist performing needle-knife sphincterotomy in 253 consecutive patients undergoing ERCP over a 7½-year interval.20 Success rates remained high throughout the entire time period but the overall complication rates and the severity of those complications remained similar throughout the study. This suggested that even in the hands of an expert, needle-knife sphincterotomy should be considered a high-risk procedure.

Modern data have, overall, been more encouraging, with a trend towards lower complication rates. The exact reason for this is unclear, but may represent the use of modern electrosurgical generators and more
understanding of how and when to perform needle-knife sphincterotomy. A 2010 study of cannulation noted that needle-knife sphincterotomy was not an independent predictor of post-ERCP pancreatitis.21

A different prospective study evaluated patients undergoing ERCP where the endoscopist was unsuccessful at achieving biliary cannulation with standard techniques after 10 minutes.22 In this study, patients were randomized to an immediate needle-knife sphincterotomy versus a second group in which cannulation was then attempted for an additional 10 minutes. The incidence of complications between the two groups was quite similar. Interestingly, the rate of pancreatitis was higher in the second group (14.9% versus 2.6%, p=0.008). This study can thus be seen to argue in defense of early needle-knife sphincterotomy in the setting of a difficult biliary cannulation when performed by an experienced operator.

Several techniques were described to perform needle-knife sphincterotomy including free-hand needle-knife (where the cut starts from the ampullary orifice and extends cephalad for variable distance-this is the most common approach), fistulotomy (where the endoscopist cuts into the ampulla above the level of the ampullary orifice), intramural incision (which involves unroofing a “false tract” created by a guidewire through a prominent papilla using a sphincterotome) and a transpancreatic sphincterotomy or also known as endoscopic transpancreatic papillary septotomy (wherein the endoscopist places the tip of the needle knife or sphincterotome in the pancreatic duct orifice and then cuts across the ampullary septum in the direction of the biliary duct).23, 24

Utilization of Precut sphincterotomy is variable among endoscopists and has been reported to range from 0-38%.16 There is controversy about whether or not the reported high risk of complications is related to the technique itself or the fact that it is usually considered after prolonged attempts at cannulation, which themselves increase the risk of complications. As such, it is recommended by many authorities to have a low threshold to place a pancreatic stent prophylactically to minimize the risk of post ERCP pancreatitis if a needle-sphincterotomy is to be performed. This recommendation was validated in a randomized controlled trial which showed significantly lower incidence of post ERCP pancreatitis when a pancreatic stent was used in conjunction with needle-knife sphincterotomy (2% vs. 14%, P< 0.05).25

There are mixed results reported regarding the use of endoscopic transpancreatic papillary septotomy to facilitate biliary cannulation. One randomized trial that evaluated both the biliary cannulation rate and complications among patients who underwent either endoscopic transpancreatic papillary septotomy or traditional needle-knife sphincterotomy concluded that
endoscopic transpancreatic papillary septotomy resulted in a higher rate of successful biliary cannulation (100% vs. 77%, p< 0.01) and lower complications rate (3.5% vs. 17.7%). This technique is relatively new with few published studies to date, although most have reported encouraging results.27, 28

Failed Biliary Cannulation
Despite the variety of currently available biliary access techniques, attempts at biliary cannulation may prove unsuccessful. In these situations, physicians have multiple additional options to consider including but not limited to:

1. Repeat ERCP on a different day by the same provider.
2. Transferring the patient to another medical center for repeat ERCP by a preferably more experienced provider.
3. Endoscopic Ultrasound guided biliary drainage.
4. Percutaneous Transhepatic biliary drainage, with or without subsequent endoscopic internalization of biliary drainage.
5. Surgery (rarely).

One study that reported the results of 500 consecutive ERCPs noted a 91.8% success rate in achieving biliary cannulation. Around half of the unsuccessful ERCPs were repeated by the same endoscopist on a different day. This resulted in an 87% successful cannulation rate, endorsing the notion that simply repeating the procedure on a different day may be the best first option in the setting of a failed cannulation.29

Two studies that looked at the success rates of patients with failed biliary cannulation who were referred to another center showed the second ERCP had a success rate that was close to 96%.30, 31

Recently, EUS assisted biliary access techniques has emerged as a new technique for obtaining biliary access in patients with failed ERCP or on whom ERCP is not possible due to anatomic constraints. During this procedure, a linear echoendoscope is used to visualize the intra- or extrahepatic bile duct from either the stomach or the small bowel. Biliary access can be obtained in a transgastric or transduodenal manner with a 19-gauge needle. A guidewire is passed through the needle in an antegrade manner. In some cases transgastric or transduodenal stenting is performed over the wire and in other cases the wire is advanced across the papilla and into the duodenum where it can be used as an aid to retrograde cannulation using standard techniques. These techniques are new, not widely performed, and are still in development. A recent representative retrospective study that included 58 patients who underwent EUS assisted biliary access. The success rate was close to 98% with a 3.4% complication rate.32

Rendezvous procedures and percutaneous biliary access are occasionally required. Percutaneous biliary access is usually established by an interventional radiologist by placing a catheter or wire into the bile ducts to the ampulla to the level of the 2nd duodenum. In some cases an endoscopist can access the bile duct endoscopically following placement of a transampullary catheter or wire and place a stent (internal drainage) to allow the percutaneous catheter to be removed.

Post-Surgical Anatomy
A full discussion of ERCP in patients with post-surgical anatomy is beyond the scope of this manuscript, but a few key points are worth making. ERCP in the setting of surgically altered anatomy is becoming increasingly common. ERCP in such settings can be challenging and, in some cases, impossible. ERCP is sometimes
required in patients who have undergone antrectomy with either Billroth I or Billroth II reconstructions, bariatric procedures such as a Roux-en-Y gastric bypass, or a pancreaticoduodenectomy (Whipple procedure), to name the most common post-surgical situations encountered.

Chahal et al. described their experience performing ERCP in 51 patients who had undergone a prior pancreaticoduodenectomy. Technical success was achieved in 84% of the procedures for biliary indications, 8% for pancreatic indications, and 72% for both indications. In most of the cases a duodenoscope was used.

Single and double balloon enteroscopes allow access to the distal small bowel and may be useful in some situations where a duodenoscope is unable to reach the ampulla. One study evaluating the success of double balloon enteroscopy in patients with a history of a Billroth II gastrectomy included 32 patients. In these patients, a standard duodenoscope was able to reach the papilla in 22/32 patients (69%) and successful cannulation was achieved in 20/32 patients (63%). A double balloon enteroscope (DBE) was selected for use in 6 patients where cannulation had failed, and this approach allowed access to the papilla in all 6 patients; cannulation ultimately was successful in 5/6 patients (83%).

A study comparing the success rates of performing single balloon assisted ERCP versus spiral assisted ERCP in patients with Roux-en-Y anatomy was recently published. The authors found similar results (100% success or single balloon as compared to 87.5% for spiral enteroscopy). A “short” (152 cm) double balloon enteroscope (DBE) was recently made available. There are few publications that describe the use of this device to perform ERCP in patients with post-surgical anatomy. In a representative study that reported on results of ERCPs performed on 20 post-surgical patients in 29 sessions, technical success occurred in 25/29 procedures (85%).

Similarly, a different study evaluating 68 patients with post-surgical anatomy including Roux-en-Y total gastrectomy (n = 36), Billroth II gastrectomy (n = 17), and pancreaticoduodenectomy (n = 15), 103 ERCP’s were performed with the “short” DBE device. In this study, deep insertion of the device into the small bowel was successful in 100/103 procedures (97%). A cholangiogram was successfully obtained in 98/100 procedures (98%). Treatment was accomplished in all 98 procedures in which a cholangiogram could be obtained (100%). Therapeutic interventions including stone extraction (n = 47), nasobiliary drainage (n = 38), stent placement (n = 36), sphincterotomy (n = 31), choledochojejunostomy dilation (n = 29), tumor biopsy (n = 10), and naso-pancreatic duct drainage (n = 1) were performed successfully with only a 4% complication rate.

CONCLUSION

Biliary cannulation is the cornerstone for any successful ERCP. It is the one of the most challenging skill to acquire during ERCP techniques. Failure to achieve biliary cannulation can result in significant morbidities and/or more invasive studies/procedures. Currently, endoscopists have at their disposal an ever-widening array of tools and techniques to allow successful biliary cannulation in almost all settings. Further developments in this realm are almost certain to be forthcoming as dedicated tools for special situations, most notably post-surgical anatomy, continue to be developed.

References


(continued on page 31)


Intestinal fibrosis is a common complication of Crohn’s disease resulting in significant morbidity in 30% of patients. Several factors are associated with higher rates of progression to intestinal fibrosis in Crohn’s disease patients. These factors include genetics, location (ileal, jejunal or perianal disease), early age at diagnosis, the presence of more severe disease, smoking and the number of serologic markers present. Distinguishing intestinal fibrosis from inflammation is important because it affects treatment decisions. Of the available imaging studies, MRE is the most sensitive and specific. Once fibrosis is diagnosed, treatment options include endoscopic dilation, which is appropriate for shorter and less complicated strictures, or surgery, including resection or stricturoplasty. Following surgery, smoking cessation, 5-aminosalicylates, azathioprine/6-MP, antibiotics (metronidazole/ornidazole) and anti-TNF agents can all reduce the risk of disease recurrence, albeit modestly. However, no therapy has been identified that specifically targets the development of fibrosis in the susceptible patient.

INTRODUCTION

Crohn’s disease is a focal, asymmetric, transmural and occasionally granulomatous inflammation primarily affecting the gastrointestinal tract. In North America, the incidence of Crohn’s disease ranges between 3.1 to 14.6 cases per 100,000 person-years, and prevalence ranges between 26 to 199 cases per 100,000 persons. Disease location and behavior tend to vary not only between different patients but also in the same patient at different times. In one retrospective cohort of 297 patients with Crohn’s disease, while only 10.8% of patients had intestinal strictures (Vienna class B2) at the time of diagnosis, this percentage increased in the subsequent years to 32.2 and 31.3 in 10 and 25 years respectively.

Classification of Crohn’s disease has evolved over time. In 1998 the World Congress of Gastroenterology Working Party suggested a classification system based on age at diagnosis (A1<40 or A2>=40), location (L1: Ileal, L2: Colonic, L3: Ileo-colonic, L4: Upper gastrointestinal) and behavior (B1: Non-stricturing, non-penetrating, B2: Stricture, B3: Penetrating). This was referred to as the Vienna classification. Based on this classification, any Crohn’s disease patient can be assigned to one out of 24 categories. A Montreal modification was suggested in 2005, preserving the main structure while adding another age category for
Fibrosis in Crohn’s Disease

Table 1. Predictors of Fibrostenotic Crohn’s Disease

<table>
<thead>
<tr>
<th>Genetic:</th>
<th>NOD2 mutation, metalloproteinases</th>
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<tr>
<td>Early age at</td>
<td>diagnosis</td>
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<td>Long duration</td>
<td>of disease</td>
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<tr>
<td>Isolated ileal</td>
<td>disease</td>
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<td>Jejunal disease</td>
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<td>Perianal disease</td>
<td>at diagnosis</td>
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<td>Serologic Markers:</td>
<td>ASCA, anti-I2, OmpC, ACCA, AMCA</td>
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<tr>
<td>Smoking</td>
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<tr>
<td>Frequency of relapses</td>
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<td>Steroid use</td>
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<td>Prior appendectomy</td>
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below 16 and changing perianal disease into a modifier that can be added to other classes. It also made it possible to combine L4 to L1-3 as a modifier. The main challenge with these classification systems is that while the location for Crohn’s disease is relatively stable, the disease commonly changes behavior with time, with the majority of patients progressing from non-stricturing, non-penetrating (B1) to stricturing (B2) or penetrating (B3) disease in subsequent years.

Stricturing and penetrating phenotypes are associated with a more complicated disease course, resulting in higher morbidity and surgery rates. Several factors have been linked to the development of stricturing disease in Crohn’s patients. Knowing these factors will help in predicting the disease course early on and maybe affecting the approach to management, thus patient outcomes.

The body responds to tissue injury by a series of tightly regulated events triggered by secretion of various mediators inducing cell proliferation, migration, and extracellular matrix (ECM) production. The normal wound healing process concludes with the resolution of inflammation and tissue remodeling. Structuring Crohn’s disease occurs when the process of wound healing becomes dysregulated. Mesenchymal cells (MSC) in the intestine including smooth muscle cells, myofibroblasts and fibroblasts, are key players in dysregulated wound healing and stricture formation. They undergo excess proliferation and hypertrophy and produce excess ECM proteins, particularly collagen I, that lead to obliteration of the submucosa and expansion of the muscularis propria leading to focal stricture formation. What is unique about Crohn’s disease is the focal nature of fibrosis with adjacent normal intestine, in contrast to other organs that undergo fibrosis, like the skin in systemic sclerosis, the liver in cirrhosis and the lungs in pulmonary fibrosis.

This review will discuss what is known about the predictors of fibrostenotic disease in a susceptible patient, the diagnosis of stenosis in symptomatic patients and the management of intestinal fibrosis and highlight the gaps in our knowledge regarding effective non-surgical treatments.

Predictors of Fibrostenotic Disease

Genetic Predisposition

Over 160 genes identified by linkage analysis and genome wide association scan (GWAS) have been associated with IBD. These can be susceptibility genes predisposing the patient to developing the disease or disease modifying genes affecting the disease behavior. Several genetic variants that may relate to a predisposition or the development of fibrosis include NOD2, ATG16L, TNFSF15, STAT3 and Smad3. The most studied gene is NOD2, which has been linked to fibrostenotic Crohn’s disease; however, this association was not universal in all studies. A recent meta-analysis suggested that the presence of two NOD2 mutations is highly predictive of complicated disease course while the predictive power of a single mutation is weak. Genetic variants of several metalloproteinases and their inhibitors have also shown some association with a fibrostenotic course of Crohn’s disease.

Disease Location

Isolated ileal disease has been linked to the development of stricturing disease, in part explained by the small diameter of the small intestine which would lead to higher incidence of clinical signs and symptoms requiring intervention when a stricture forms. The presence of perianal disease at diagnosis is associated with progression to more severe disease forms, including fibrostenotic disease. A recent study reported that
Fibrosis in Crohn’s Disease

Inflammatory bowel disease: a practical approach, series #81

Patients with jejunal disease have a significantly higher risk of developing stricturing behavior. 

Disease Severity

Frequency of relapses and steroid use have been associated with changing behavior of Crohn’s disease from inflammatory to fistulizing or stricturing disease. Severity of the disease and long duration of disease are associated with the development of strictures or obstruction in Crohn’s disease patients.

Serologic Markers

The presence of multiple serologic markers (antibodies against microbial peptides) is associated with fibrostenotic Crohn’s disease and higher need for surgery. These include anti-Saccharomyces cerevisiae antibodies (ASCA), anti-Pseudomonas-associated sequence I2 antibodies (anti-I2), anti-outer membrane porin C (OmpC) of Escherichia coli antibodies, anti-chitobioside carbohydrate antibodies (ACCA), anti-laminarin antibody (Anti-L) and anti-mannobioside carbohydrate antibodies (AMCA).

Patient Related Factors

Early age at diagnosis is linked to progression to stricturing disease. Conversely, patients diagnosed at older ages are more likely to have strictures at the time of diagnosis. Prior appendectomy is also linked to the development of a stricturing disease.

Crohn’s disease patients that smoke are at higher risk of progressing into a more severe disease behavior, including fibrostenotic disease, and tend to have higher risk of needing surgery for Crohn’s when compared to non-smokers.

Diagnosis of Fibrostenotic Disease

Small intestinal strictures are a major cause of intestinal obstruction and surgery in Crohn’s disease patients. The main challenge when a Crohn’s disease patient presents with intestinal obstruction is determining whether the stricture is predominantly inflammatory, which makes it amenable to medical treatment, or predominantly fibrotic, which would likely need invasive intervention. Clinical signs and symptoms of active disease, inflammatory markers, specifically CRP, and stool studies, including presence of blood and leukocytes, can help differentiate between the two. However, these markers are not phenotype specific, and given the multifocal nature of the disease, determining

(continued on page 36)
whether the positive markers are reflective of a different inflamed area of the gut is not always possible. Imaging studies can be helpful in distinguishing between these two entities, thus guiding the management.

CT/CTE
CT scan is widely used for the diagnosis of Crohn’s disease and its complications. CT enterography (CTE) is a modification of conventional CT that uses multi-detector CT (MDCT) scanners for high spatial and temporal resolution imaging of the small bowel and multi-planar reconstruction following the ingestion of enteric contrast, typically PEG solution or ultra low dose barium with sorbitol. CTE has good sensitivity and specificity in detecting active Crohn’s disease, with sensitivity ranging between 60%-90% and specificity around 90%. However, small bowel stricture without CTE findings of inflammation does not correlate with tissue fibrosis.

MRI/MRE
Magnetic Resonance Imaging (MRI) has been utilized in the diagnosis of Crohn’s disease, with reported sensitivities and specificities ranging between 88-98 and 78-100% respectively for the detection of the disease. Addition of enteric contrast, Magnetic resonance enterogram (MRE) is useful for detecting intestinal and other intra-abdominal complications of Crohn’s disease. MRE has greater efficacy than CTE or MRI alone at distinguishing the relative proportion of inflammation and fibrosis in intestinal strictures. These findings correlate best with surgical histopathology.

Transabdominal Ultrasound and Contrast-Enhanced Ultrasound
Abdominal ultrasound can be used to diagnose Crohn’s disease, with sensitivity between 84-93% and specificity of 98% in some studies. Newer ultrasound modalities including doppler ultrasound, contrast enhanced ultrasound and ultrasound elasticity imaging have shown promising results in distinguishing between inflammatory and fibrotic strictures, therefore predicting patients that will require surgery.

18F-FDG PET
18F-FDG PET and PET/CT have been gaining increased interest lately with studies showing potential use in diagnosing Crohn’s disease and providing a noninvasive, quantitative measure of inflammation. By itself, PET scanning does not provide good measure of intestinal fibrosis.

Capsule Endoscopy
Although capsule endoscopy has good diagnostic yield in the detection of mucosal lesions of Crohn’s disease, the presence of strictures, either symptomatic or silent, puts the patient at risk for capsule retention. If necessary, a patency (dummy) capsule should be tried first to insure that no blockage is present.

Which Imaging Study Should be Chosen?
Ultrasound is a safe, widely available and radiation free test, but is operator dependent. The availability of newer US based modalities is limited which limits its use as a primary diagnostic tool in IBD.

MRE and CTE have comparable diagnostic yield in the detection of the extent of the disease and its complications, with MRE being slightly more sensitive. Current data suggest that MRE is superior to CTE in detecting strictures, with sensitivity and specificity of 92% and 90% respectively for MRE versus 85% and 100% respectively for CTE. They also can help guide operative approach. In terms of distinguishing between strictures caused by fibrosis and those caused by active inflammation, when compared to histology, detection rates were 57% for MRE, 53% for 18-FDG-PET/CT, and 40% for ultrasound. Notably the combination of FDG-PET/CT and US or MRE and US resulted in 100% detection rate and was better than either alone in the detection of strictures requiring surgery or endoscopic dilation. CTE findings of active inflammation in a stricture correlated well with histology; however, CTE findings of a stricture without inflammation did not predict the presence or absence of tissue fibrosis. In one study the accuracy of MRE for detecting mural fibrosis was 64.9%; this increased to 83.3% when inflammation was absent. Contrast enhanced US offers additional benefit in distinguishing inflammation from tissue fibrosis.

CT/CTE is widely available which makes it an appealing test for many clinicians; however, radiation exposure with repeated imaging, especially in the predominantly young-aged Crohn’s disease population, raises concerns for both patients and clinicians. MRI has no radiation exposure. The limitations against the widespread utilization of MRE are mainly the lack of standardized MRE protocols, high cost, lack of experienced MR radiologists and long scanning
times. More data is needed, including efficacy and cost-effectiveness, before 18F-FDG PET and PET/CT can be recommended for Crohn’s disease.

Can We Change the Natural History of Fibrostenotic Crohn’s Disease?

Based on the available data, there is evidence to suggest that early intervention can affect the course of disease; however, more data is needed in order to understand how this affects the development of fibrostenotic disease. Early azathioprine (AZA) or AZA/biologic therapy decreases the probability of progression from inflammatory into a more complicated disease behavior, decreases the risk of surgery and prolongs time to first surgery. One study in the pediatric population showed that early use of AZA/6-MP was associated with fewer hospitalizations but did not affect the rates of surgery for these patients in the first two years after diagnosis; however, surgery is a rare event in the first two years of pediatric Crohn’s disease. Maintenance therapy with infliximab induced mucosal healing, with a trend toward lower rates of hospitalization that was not statistically significant. Early combined immunosuppression (infliximab and azathioprine) provided significantly better mucosal healing with a trend towards fewer intestinal resections compared to conventional therapy with corticosteroids followed by step up therapy if needed. Subset analysis of the CHARM study showed that Adalimumab therapy compared to placebo was associated with lower hospitalization rates in children with Crohn’s disease. Several factors have been found to affect recurrence.

Management of Intestinal Fibrosis

Once significant fibrosis is established in the intestine, medical therapy alone has little to offer. Although initial trials of infliximab were stopped due to concern that infliximab can induce stricture formation, subsequent data did not reproduce these findings. The effect of infliximab correlates well with the degree of inflammation in the stricture, with better response in strictures with higher inflammatory component, but there is no evidence that infliximab can induce stricture formation or worsen an existing stricture. In one small study, oral Tranilast (N-3’,4’ dimethoxycinnamoyl) showed positive results in prevention of stricture progression in patients with Crohn’s disease.

Endoscopy

Endoscopic dilatation is an appropriate option in Crohn’s disease strictures, especially strictures less than 4-7 cm in length. It is still not clear whether injection of steroids into the strictures after dilatation reduces the risk of recurrence or not. Intraluminal injection of infliximab was effective in relieving colonic stricture in one small series.

Surgery

Two surgical options are available: Stricturoplasty and resection. Stricturoplasty is usually preferred for short strictures and when trying to preserve the length of the small intestine, while resection is usually needed for long strictures and for cases complicated by abscess, peritonitis, infection or suspicion of cancer. It is still not clear whether surgery is superior to endoscopic dilation in management of strictures. A recent meta-analysis did not demonstrate superiority of one method over the other, primarily due to the limited availability of comparable data.

Disease Recurrence

After endoscopic dilatation, two meta-analyses have reported a surgery-free outcome rate of 79% and 58% of the patients in a median follow up of 21 and 33 months, respectively, outcomes were better in short strictures (less than 4-5 cm). Following surgery, recurrence rates steadily increase with time, reaching up to 50% in 20 years. Several studies have evaluated factors increasing the risk of clinical, endoscopic or surgical recurrence after initial surgery secondary to any cause (i.e. stricture, fistula, obstruction from active inflammation), but limited data specifically examined the actual incidence of tissue fibrosis before and after surgery. Several factors have been found to affect recurrence.

Smoking

Smokers with Crohn’s disease have a higher risk of disease recurrence after surgery. Meta-analysis showed that these patients have 2.5 fold increased risk of surgical recurrence and 2 fold increased risk of clinical recurrence compared to non-smokers. Ex-smokers have lower recurrence rates when compared to smokers, suggesting that smoking cessation can improve outcomes post-surgery.
5-aminosalicylates
Evidence suggests that mesalamine has a minimal effect in reducing the clinical but not endoscopic recurrence post-surgery in Crohn’s disease.56, 62, 63, 64

Antibiotics
Use of metronidazole or ornidazole after surgery is superior to placebo in preventing both clinical and endoscopic recurrence; however, this effect did not persist beyond the first year after surgery.60, 63, 64

Azathioprine/6-MP
Use of AZA/6-MP may have modest effect in preventing post-operative recurrence; however, positive results have not been seen in all studies.60, 62, 63, 64, 65

Anti-TNF Therapy
The available data show that infliximab is effective in preventing post-operative clinical and endoscopic recurrence.60, 62, 63 Adalimumab too can prevent endoscopic recurrence up to one year post-surgery.63, 66 These studies have not specifically examined patients resected for fibrotic strictures, however.

Probiotics, corticosteroids including budesonide have not been shown to have a significant effect on postoperative recurrence, and in the case of corticosteroids, have the potential disadvantage of increasing collagen production.60, 62, 63, 64

Future Directions
It is increasingly clear that once initiated, fibrosis and stricture formation can progress in the absence of active inflammation. A number of experimental therapies directed more specifically at stricture formation have been the subject of recent investigations. These include such agents as angiotensin-converting enzyme (ACE) inhibitors, HMG-CoA-reductase inhibitors, resveratrol, anti-integrin directed therapy, and IGF-I antagonists.67, 68

Macrophages exhibit different functional phenotypes during the phases of wound healing. Thus, they have been a point of interest for therapeutic target in reducing fibrosis and improving chronic wound healing.69 The supplementation of exogenous macrophages has been shown by Dannon and colleagues to accelerate wound healing.70 Therefore, altering a macrophage’s phenotype, ex vivo, could drive it towards a reparative phenotype promoting tissue regeneration once re-introduced.

TGF-β is a key mediator of both the intestine’s immune response and disordered wound healing and fibrosis that follows inflammation. TGF-β or its Smad signaling intermediates could be considered as therapeutic targets to inhibit or prevent fibrosis. The lessons learned from transgenic animals, however, have shown us that absence of TGF-β or TGF-β signaling, with the exception of Smad3, is associated with significant perinatal mortality. This occurs as a result of a loss of a potent immune regulator and thus, multifocal inflammation and massive infiltration of inflammatory cells into major organs. Other potential targets could be matrix metalloproteinases (MMP), proteinases that regulate dissolution of extracellular matrix (ECM), or tissue inhibitors of metalloproteinases (TIMP). Since the effects of increased MMP expression, e.g. collagenases, could decrease net ECM levels, it would be expected, however, to increase mucosal ulcerations and worsen the inflammatory complications of Crohn’s disease.

Altering the gut microflora can affect the expression of profibrotic genes. Several ongoing lines of investigation will inform us on how to therapeutically intervene in patients with specific phenotypes.

1. Studies to analyze the diversity, composition, and structure of the intestinal microbiome.

2. Studies to define the metabolic environment (metabolom) at the mucosal interface between intestinal microbiota and the host (patient) susceptible to CD.

The ultimate goal is to elucidate the mechanisms by which genetic variants in a patient susceptible to CD lead to the development of clinical CD and its specific phenotypes, such as fibrostenosis; thereby, in addition to identifying potential therapeutic targets, providing the ability to predict its development and likely disease course.

SUMMARY
About one third to one half of patients with Crohn’s disease experience strictures at some point in their lives. Both genetic and environmental factors play a role in the development of fibrosis. While early medical therapy can potentially prevent stricture formation, more studies are needed to better define those patients that will likely benefit from aggressive medical therapy early

(continued on page 40)
in the disease course. Key to effective management is distinguishing between inflammatory and fibrosis as their management is different. Clinical signs and symptoms, laboratory values and imaging studies such as CTE and MRE can be helpful in distinguishing between the two. CTE is more widely available while MRE is more sensitive and avoids exposure to ionizing radiation. Accurate pre-operative evaluation of the stricture guides therapy, endoscopic dilatation is an effective strategy for short (less than 4-7 cm) strictures, while surgery is needed for longer and more complicated strictures. After surgery, smoking cessation, metronidazole, ornidazole, azathioprine, 6-MP and anti-TNF agents offer some help in preventing post-operative recurrence; however, no medical therapy specifically targets the development of intestinal fibrosis. Whether future strategies will be effective in identifying the susceptible patient and whether fibrosis can be prevented is unknown.

References


Fibrosis in Crohn’s Disease

(continued from page 38)


How Would You React to Intermediate Values of Lipase?

According to the American College of Gastroenterology, the diagnosis of acute pancreatitis requires at least 2 of the following 3 elements: characteristic abdominal pain, specific tomographic findings and a lipase level three times above the upper limit of normal. The aim of this study is to determine physicians’ interpretation of intermediate values of serum lipase (IVSL, a lipase level above the upper normal limit but below 3 times that value), and in which cases pancreatitis is diagnosed. The diagnosis of pancreatitis was more likely to be made when episodes of abdominal pain with IVSL were accompanied by either nausea and vomiting, serum lipase values at least 2 times above normal, concomitant elevations of serum amylase, or combinations thereof. These results suggest that diagnosing pancreatitis depends on the mindset of the treating physician, regardless of clinical, laboratory and imaging data.
excluded as this finding confirms acute pancreatitis. Only patients who had at least 2 determinations of intermediate values of serum lipase (IVSL) per episode were included.

In February 2011, a new lipase test with a new set of reference values (73-393 U/L) was implemented at LBJH. To assess eligibility and to analyze laboratory data among patients with the new values, data were tabulated after using a factor to convert them into the old reference range.

A standardized questionnaire was implemented to retrieve information from the electronic medical records regarding demographic, clinical, laboratory, and imaging data. Included were: exposure to alcohol or medications, history of gallstones, diabetes mellitus, obesity, hypertriglyceridemia, and concomitant amylase levels (normal= 25-115 U/L).

The use of complementary studies in each event, such as abdominal X ray, abdominal ultrasound, abdominal computerized tomography (CT) or magnetic resonance (MRI), magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP) and/or intraoperative cholangiogram was evaluated. The need for surgery was also noted.

The medical decision-making portion of the chart was examined to assess whether an explanation for the elevated lipase was offered, and if so, if pancreatitis was included in the differential diagnosis, regardless of the lipase values.

An episode of IVSL was defined as any event with at least 2 lipase determinations in a month period or shorter. When the determinations were more than 1 month apart, they were considered as belonging to separate episodes.

Statistics

Categorical variables were analyzed using the Fisher exact test, and discrete variables were analyzed using the Student t test for unpaired samples. A two-sided P < 0.05 was considered indicative of statistical significance.

RESULTS

Ninety episodes of persistent intermediate values of serum lipase in 88 patients were documented.

In 34 events among 33 patients the final diagnosis was acute pancreatitis (group P). In 56 events in 55 patients the final diagnosis was not acute pancreatitis (group NP). The age (44±14 for P and 43±14 for NP, P=1.00), gender (21 men for P and 28 for NP, P=0.64) and racial distribution were comparable.

When comparing groups P and NP, there were no significant differences in the presence of obesity, type 1 or type 2 diabetes, hypertriglyceridemia, previous diagnosis of gallstones, ingestion of more than 20 g/day of ethanol, recent abdominal surgery or use of drugs known to be associated with acute pancreatitis.

With respect to clinical presentation, patients in group P were more likely to complain of nausea and vomiting than those in group NP (76% vs. 50%, P=0.01; and 71% vs. 43%, P=0.01), whereas abdominal distention or pain, jaundice, evidence of gastrointestinal bleeding, hypotension, fever (greater than 38ºC), tachycardia, ascites and dehydration were about the same in both groups. The APACHE II score for both groups was also comparable (3.47±4.11 vs. 4.45±4.55, P=0.53).

The patients in group P were more likely to have had previous episodes of IVSL (62% vs. 21%, P=0.0002). Most of the patients in both groups were admitted to the hospital (88% in the group P vs. 80% in the group NP, P=0.36) with virtually no difference in their length of stay.

Patients in groups P and NP underwent similar percentages of radiologic or endoscopic evaluations: abdominal X rays (9% vs. 16%, P=0.53), abdominal CT scans (41% vs. 48%, P=0.66), MRI (6% vs. 2%, P=0.55), abdominal ultrasound (47% vs. 41%, P=0.66) and ERCP (15% vs. 12%, P=0.76). The percentage of cholecystectomy and operative cholangiogram was also similar (24% vs. 14%, P=0.27; and 24% vs. 11%, P=0.13).

Because abdominal CT contributes to the diagnosis of pancreatitis, positive tomographic findings in both groups were analyzed. Four of 14 patients in group P had tomographic findings that confirmed the diagnosis of acute pancreatitis (29%) whereas the positive findings in group NP were 2 of 27 (8%, P=0.16).

There were no significant differences in the number of patients from both groups presenting with serum bilirubin higher than 2 mg%, glucose above 200 mg%, calcium higher than 11 mg%, creatinine above 2 mg%, lactic acidosis, hypertriglyceridemia and total leukocyte counts above 15,000/ml.

The patients in group P had significantly higher initial and peak lipase levels when compared with the NP patients (484±146 vs. 403±123, P=0.0061, and
Intermediate Values of Lipase

529±163 vs. 442±136, P=0.0078). More patients in group P than in NP had values between 2 and 3 times above the upper normal level (35% vs. 14%, P=0.03). In addition, more patients in group P had serum amylase values above normal (29% vs. 5%, P=0.003), although never 3 times above normal. The change in the range of normal lipase made no difference in the selection of patients as belonging to group P or NP.

DISCUSSION

In this retrospective study, physicians were likely to diagnose acute pancreatitis when episodes of abdominal pain were accompanied by serum lipase at least twice normal. Moreover, nausea and vomiting, or concomitant elevations of serum amylase, or both also prompted a final diagnosis of acute pancreatitis. Small elevations of pancreatic enzymes (less than three times above the upper normal level) have been considered diagnostic of pancreatitis previously as long as concomitant elevations of amylase are present.

Classical risk factors for acute pancreatitis had no effect on physicians’ diagnoses but having had previous similar events did. Patients in group P had previous episodes of IVSL more frequently than those in group NP. Although the workup for both groups was similar, 92% of patients in the NP group who underwent abdominal CT had no tomographic findings of pancreatitis. This absence of CT specific abnormalities likely accounts for the patients being allocated to group NP.

The American College of Gastroenterology (ACG) guidelines recommend using abdominal CT when lipase values are less than three times above the upper normal limit either to support the diagnosis of pancreatitis or to broaden the diagnostic considerations. Other authors assign less value to abdominal CT believing that it is associated with increased length of stay and is of no diagnostic or management benefit to patients with pancreatitis.

The main limitation of this study is its retrospective nature, which prevents confirming the presence of subjective symptoms (pain, nausea, vomiting) or clearly ascertaining the thought process of the attending physician. It can be suggested, however, that since lipase levels were ordered, pancreatitis was at least being considered in the differential.

CONCLUSION

In conclusion, the diagnosis of acute pancreatitis depends primarily on the mindset of the treating physician, regardless of clinical, laboratory and imaging data. How would you react to an intermediate level of serum lipase?

ACKNOWLEDGEMENT

I am thankful to Dr. Herbert L. Fred for his mentoring and guidance on the development of the present manuscript.

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Bone Health After Major Upper Gastrointestinal Surgery

Bone Mineral Disease can be painful, debilitating and result in increased fracture risk. It is highly prevalent in those having had major upper gastrointestinal surgery with multiple contributing factors. Increasing awareness of the risk factors and early screening can help prevent or slow the onset of disease. Once identified, disease progression can be managed with thorough medical and dietetic assessment and intervention. Lifestyle changes, vitamin supplementation, drug therapies and regular bone scans can all play a role in preventing deteriorating bone health.

INTRODUCTION

Bone Mineral Disease (BMD) predominantly affects the aged population and postmenopausal women. It is currently estimated that 44 million US citizens have developed, or are at risk of developing BMD, with 1.5 million people presenting with a fracture each year. Chronic pain and high fracture risk lead to high morbidity and mortality rates and greatly reduce quality of life for people with BMD. The yearly health economic burden is estimated to be 17 to 19 billion US dollars for fracture treatment alone. The incidence of BMD continues to increase as our population ages. Chronic disease and cancer survivors are also at high risk of BMD, and as survivorship improves, the incidence of BMD in these patient populations is also expected to increase.

Bone Mineral Disease Revisited

Bone metabolism is a complex and detailed process. It relies on the availability of calcium, which is stored within the bone, providing density and strength to bone cells. Calcium homeostasis in turn relies on the presence of parathyroid hormone (PTH), vitamin D and calcitonin. An imbalance in this system can lead to BMD, altered bone remodelling, and some degree of osteoporosis or osteomalacia.

Osteoporosis vs. Osteomalacia

Osteoporosis is defined as a disorder of reduced bone strength resulting in quantitative loss of bone, bone fragility, and an increased risk of fractures. It results from an imbalance in bone turnover and is most commonly found in postmenopausal females and the elderly. Osteomalacia (or rickets in children) is less common than osteoporosis and is a disease in which the newly formed bone is not mineralized properly, and is often referred to as a softening of the bone.

(continued on page 48)
Bone Health After Major Upper Gastrointestinal Surgery

NUTRITION ISSUES IN GASTROENTEROLOGY, SERIES #115

(continued from page 46)

Primary and Secondary Bone Mineral Disease

The most common reasons for primary BMD include post-menopause in females, aging and genetics (for example race and family history). Primary BMD accounts for the majority of people who suffer BMD and it is usually associated with osteoporosis. Guidelines for treating primary osteoporosis are well documented.

Secondary BMD does not have the same clear guidelines. Secondary BMD affects both males and females, usually resulting from a predisposing medical condition, disease or as a side effect of other treatments or medications such as excessive use of glucocorticoids. Secondary BMD usually manifests as osteomalacia. It commonly results from inadequate calcium intake and/or vitamin D deficiency. Low serum vitamin D levels alone lead to poor calcium absorption as well as calcium resorption from the bone. Treatment of secondary BMD must not only address bone health, but also where possible, address the underlying cause. Secondary BMD has been well documented in patients on long term parenteral nutrition also.

Evidence of Bone Mineral Disease after Major Upper Gastrointestinal Surgery

Bone health is often forgotten in people having had major upper gastrointestinal (GI) surgery as health professionals attempt to manage the many other aspects of post-operative care. Yet bone mineral disease is highly prevalent in this population with multiple contributing factors. Upper GI surgeries such as esophagectomy, partial and total gastrectomy and Whipples procedures have all been shown to increase the risk of BMD.

The reasons for this increase in risk are still largely unknown, yet suspected reasons include:

1. Reduced oral intake. People often struggle after gastric surgery to consume adequate amounts of food to maintain their nutritional status, and this reduced intake results in a reduced intake of calcium and vitamin D.
2. Inadequate oral intake also results in weight loss and subsequent malnutrition. There is also a strong correlation between low body weight and BMD.
3. Higher losses of calcium and vitamin D in the presence of malabsorption. Steatorrhea leads to the formation of insoluble calcium soaps. Poor mixing of the body’s pancreatic enzymes also increases fat (and fat soluble vitamin) malabsorption.
4. Rapid transit and dumping means less time for calcium and vitamin D absorption. Surgical reconstruction that bypasses the absorptive region of the duodenum and proximal jejunum.
5. Absence of the stomach, which appears to play an important role in calcium absorption. Firstly, the stomach turns insoluble dietary calcium into soluble calcium salts that are easily absorbed. Secondly, the stomach lowers the pH of the proximal duodenum, again favorable for calcium absorption. Finally, there is also some evidence to suggest that the acid producing mucosa of the stomach produces a hormone called gastrocalcin, which stimulates bone uptake of calcium.
6. The possible role of bacterial overgrowth, which leads to inactivation of lipase resulting in fat and fat soluble vitamin malabsorption, alterations in bile salts, hence micelle formation.
7. Possible lactose intolerance where anatomy bypasses key absorptive sites. Many people with symptoms of malabsorption may also naturally avoid foods containing lactose.
8. Reduced exposure to sunlight. If patients have significant ongoing weight loss after surgery and are not feeling well, they may be less likely to leave the house. Therefore, outdoor activity may be limited.
9. The patient groups that undergo major upper GI surgeries may already have primary risk factors for BMD, including post-menopausal females, smokers and higher than recommended alcohol intakes.
10. Increased osteoclastic activity in the setting of ongoing inflammatory processes such as malignancy, untreated celiac disease, Crohn’s etc.

In partial or total gastrectomy, physiologic changes occur in an attempt to compensate. Urinary calcium losses are much reduced, and raised PTH and 1,25-dihydroxy vitamin D levels increase calcium
as to whether the BMD is predominantly osteoporosis or osteomalacia. However this compensation does not appear to be sufficient to prevent BMD.

Incidence of Bone Mineral Disease after Major Upper Gastrointestinal Surgery

Much of the research on BMD in upper GI surgeries is dated, and the actual incidence of BMD in this population is still under debate. This is due to the inconsistent use of tools to measure bone density, as new tools have steadily emerged since the 1960’s. Early studies used x-ray and bone biopsy, while recent studies have used dual-energy X-ray absorptiometry (DXA) and computed tomography (CT).

Partial and Total Gastrectomy

Of the major upper GI surgeries, the incidence of BMD has been most widely investigated in post-gastrectomy patients. Approximately 20-50% of people having had partial or total gastrectomy surgery will develop BMD. Changes in bone health have been well reported, and at greatest risk are those with significant weight loss, rheumatic pains, raised PTH levels, reduced serum 25-hydroxy vitamin D, anemia, people having had chemotherapy, poor nutritional status prior to surgery, and increased length of time since surgery.

Type of reconstructive surgery does not appear to influence the severity of disease, and debate continues as to whether the BMD is predominantly osteoporosis or osteomalacia.

Esophagectomy & Pancreoduodenectomy (Whipple) Procedure

Esophagectomy and Whipples procedures are primarily undertaken as a result of cancer and prognosis remains poor. Hence, very little data exists regarding BMD for these groups. It would not be surprising to find that the prevalence of BMD in these groups would be similar to that of the post-gastrectomy patient population. This is supported by studies that have found hypocalcaemia and vitamin D deficiency in a cohort of esophagectomy patients.

Monitoring BMD After Major Upper Gastrointestinal Surgery

There are currently no specific guidelines on monitoring bone health in this patient group, however, DXA at time of surgery, would allow initiation of treatment of any pre-existing bone disease, and provide a basis to assess changes in bone health over time. Recommendations in managing secondary BMD include DXA every 2 years; more frequent screening is not recommended.

Nutritional Assessment after Major Upper Gastrointestinal Surgery

Ideally, patients having had major upper GI surgery

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<th>Table 1. Key Areas of Nutrition Assessment to Determine Risk of BMD</th>
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<tr>
<td>1. People of a low BMI or with significant weight loss</td>
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<td>2. Biochemical review indicating possible BMD (Table 2)</td>
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<tr>
<td>3. Signs of malabsorption - steatorrhoea or dumping syndrome</td>
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<td>4. Medications - high intake of PPI (common in upper GI surgical patients who may suffer ongoing reflux) antacids, glucocorticoids, and bile acid sequestrants</td>
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<td>5. Poor intake, especially limited intake of foods high in calcium and vitamin D</td>
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<td>6. A medical history that indicates existing risk factors or recent history of fracture</td>
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<tr>
<td>7. A social history that indicates poor exposure to sunlight, for example people who are housebound, or who cover their skin for cultural or religious reasons, or use sunscreen</td>
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should receive nutrition intervention during their acute hospital admission. Outpatient follow-up may only encompass the initial months following discharge and screening for long term complications following surgery are often overlooked. Nutritional review of people following surgery should include assessment of BMD risk (Table 1 and 2).

Management of Bone Mineral Disease

Diagnosis

Diagnosis of BMD is based on bone density and clinical assessment. The World Health Organization definitions of bone health, ranging from normal to severe osteoporosis are based on hip or spine DXA readings (Table 3). Plain x-ray can be helpful in flagging bone health as a concern, where it may otherwise have gone undiagnosed and untreated; and in differentiating between osteoporosis and osteomalacia. Specialist interpretation of DXA and x-rays are needed to determine the degree and type of bone disease. Risk equations also exist to help refine future fracture risk utilising BMD and other clinical risk factors (FRAX). CT and magnetic resonance imaging (MRI) are also highly sensitive tools that can be used in diagnosing BMD, but both are expensive in comparison to DXA, and so are not usually used specifically for this purpose, nor are they validated in predicting future risk of fractures. Clinical assessment should involve assessing presence of risk factors and biochemistry. Biochemical testing should include serum calcium, phosphate, creatinine, liver function, blood count, testosterone in males, 25-hydroxy vitamin D, and thyroid-stimulating hormone (TSH), as recommended by the American Association of Clinical Endocrinologists. Additional tests may also include, but are not confined to, serum PTH, 24-hour urinary calcium and celiac serology.

Treatment

There is no evidence to suggest that supplementation of calcium and vitamin D should be uniformly recommended in all people who have had major upper GI surgery. Nutrient supplementation and medications are still only recommended for those with diagnosed BMD. However, lifestyle recommendations should be encouraged not only for people with diagnosed BMD, but for all people who have had major upper GI surgery, with the aim to prevent or slow the onset of disease. Treatment recommendations are summarized in Table 4.

Dietary Recommendations

Dietary intervention should include counselling to ensure adequate calcium and vitamin D intakes, and supplementing where needed. The current US RDA for calcium and Vitamin D are 1500mg and 600-800IU respectively for the older population. Choosing foods naturally high or fortified in calcium and vitamin D should be recommended. People should also be encouraged to enhance calcium uptake at the brush

(continued on page 52)
border by avoiding iron-rich foods, oxalates and caffeine when consuming calcium rich foods or supplements.

As BMD is strongly linked to low body weight and weight loss, counselling also needs to be tailored to prevent or correct weight loss through a high energy and protein diet, and oral nutrition supplements if required. Meeting a persons’ protein requirements appear particularly important in improving lower extremity muscle mass and strength, and reducing the risk of fracture.25

Identifying symptoms of malabsorption as an impediment to weight gain should be a priority. Pancreatic enzyme replacement therapy should be considered in people who have had pancreatic resection, but also in those with other upper GI surgeries where there is a mismatch of foodstuffs and pancreato-biliary secretions, resulting in symptoms of malabsorption.29

Lifestyle Recommendations

Smoking and heavy alcohol consumption are both independent risk factors for the development of BMD.8 All people should be encouraged to cease smoking and limit their intake of alcohol to within recommended guidelines. People must be encouraged to spend small amounts of time exposed to sunlight, which is needed for the activation of vitamin D₃. For this patient group, sun exposure may be limited due to weakness secondary to weight and muscle loss, or debilitating symptoms such as steatorrhoea. Time of day and year, cloud cover, degree of pollution, skin type, and sunscreen all effect vitamin D synthesis rates. Although people living in high latitudes will not get enough sun exposure in the winter months to meet their vitamin D requirements, geographical latitude does not appear to be a strong contributor to vitamin D deficiency.28 As the liver and fat cells store vitamin D, there is opportunity for people to have adequate sunlight exposure in the spring, summer and fall months to allow vitamin D synthesis for the full year.28 In direct sunlight, it may only take approximately 8-10 minutes of sunlight per day on the face, arms and hands to produce a third of a persons’ daily vitamin D requirements. Exercise is well known to promote bone growth and strength, especially high impact weight bearing activity. Most people having had major surgery usually do not return to such intense exercise regimens, so less intense weight bearing exercise such as walking and resistance training should be encouraged. Exercise that is not weight bearing such as swimming and cycling do not promote bone health. When people have already presented with a fracture, gentle strengthening exercise under the supervision of a physical therapist is advised.

Calcium Supplementation

Calcium supplementation of 1500mg/day is recommended for the elderly and those with existing BMD.30 The most easily accessible and cheapest form of calcium supplementation is calcium carbonate. This specific supplement requires an acidic environment to optimise absorption, and so does not work well in people who are taking Proton Pump Inhibitor’s (PPI) or H₂-antagonists, which work to reduce gastric acid secretions, or in those with low acid states as a result of gastric resection or truncal vagotomy. Many people who have had major upper GI surgery require these medications to aid in reducing side effects of reflux.4 Other forms of calcium supplementation, such as calcium citrate do not require gastric acidity for absorption, and may be better absorbed and tolerated in this patient group. Calcium citrate should be taken on an empty stomach.

Calcium absorption is inhibited in the presence of caffeine and iron-rich foods or supplements; and absorption peaks at 500mg, therefore doses >500mg are not beneficial.4 Total supplementation therefore should be split into morning, midday and evening doses. As oral absorption can be inefficient, careful monitoring of a range of biochemical markers is needed, including 24-hour urinary calcium levels, to ensure therapeutic levels are reached resulting in normocalcemia.31

Calcium supplementation in high doses can result in gas, bloating or constipation. Doses meeting RDA do not appear to contribute to the formation of kidney stones in those adequately hydrated.32, 33

Vitamin D Supplementation

Supplementation of vitamin D (usually referred to as Calciferol) should be guided by serum 25-hydroxy vitamin D levels. For people with chronic disease and reduced serum 25-hydroxy vitamin D levels, oral vitamin D₃ supplementation of 800-1000 IU/day is recommended.27

For those individuals with severe vitamin D deficiency (25-hydroxy vitamin D levels below 20nmol/ml or 8ng/ml), higher vitamin D supplementation doses may be needed to treat and then sustain serum levels.

(continued on page 54)
Medications and Bone Health
Absorption of calcium or vitamin D can be altered or inhibited by many medications and have been discussed in detail elsewhere. Medications of particular relevance for people who have had major upper GI surgery include antacids and PPI’s. Medications that affect vitamin D and/or calcium metabolism include anti-seizure medications (phenobarbital, phenytoin, primidone and valproic acid), glucocorticoids, bile acid sequestrants (cholestyramine otherwise known as questran™ or prevalite™) and anti-tuberculosis medications (rifampin). If it is suspected that medications are impacting on BMD, then consultation with a pharmacist is needed to consider alternate options. In these cases higher doses of calcium or vitamin D may also be required.

Drug Therapy
There is a lack of research assessing the use of drug therapies in managing post-surgical BMD; however, bisphosphonates are often used in clinical practice. Prior to commencing drug therapy vitamin D levels need to be replenished to prevent hypocalcaemia. Bisphosphonate medications should be taken first thing in the morning with water, and the person should remain upright for 30 minutes afterwards. As they interact with calcium they should be taken separately to any calcium supplementation. Hormone replacement therapy and calcitonin are well researched, but largely outdated treatment options in postmenopausal BMD, and have not been trialled in people who have undergone major upper GI surgery. The enormity of the burden of BMD on health costs means that new drug therapies will continue to emerge in upcoming years.

CONCLUSION
It is evident that people who have had major upper GI surgeries have an increased incidence of BMD. The exact reasons for this appear to be multifaceted. In addition, many people who have had major upper GI surgery already have underlying risk factors for BMD, such as cigarette smoking, high alcohol intakes and increased age. Health professionals need to be vigilant in screening for and managing BMD. BMD can be managed through calcium and vitamin D supplementation, lifestyle changes and, where necessary, medications. While there is still a lack of research and consensus in this area, all patients should have baseline screening and ongoing monitoring for BMD.

Table 4. Key Recommendations for Managing BMD Following Major Upper GI Surgery

1. Addressing significant weight loss with dietary modification and nutrition support.
2. Assess and treat malabsorption with dietary counselling where needed, and pancreatic enzyme replacement therapy if required.
3. Educate on meeting recommended oral intakes for calcium and vitamin D. Do not mix foods high in iron, oxalates and caffeine with calcium-rich foods.
4. Encourage lifestyle changes:
   a. Cease smoking
   b. Limit alcohol to within recommended guidelines
   c. Weight bearing exercise
   d. Sunlight exposure
5. Calcium and vitamin D supplementation in consultation with medical advice.
6. Drug therapies where medically recommended.
7. Ongoing regular monitoring, including DXA every 2 years.
References

2. Cole RE. Clinical strategies to address patients’ concerns in osteoporosis management with bisphosphonates. Postgraduate Medicine, 2011;123:131-144.
Simultaneous Detection of IgM Anti-Hepatitis E Virus and Anti-Epstein-Barr Virus in Acute Hepatitis

by Damian Casadesus, Syed Hassan, Tania Calzada, Isabella Zathureczki, Joseph DeAntonio, Daniel Goldsmith

Worldwide, hepatitis E virus (HEV), the diagnosis established by antibody and HEV RNA detection, is a major cause of acute viral hepatitis. This case describes a 39-year-old Indian male with recent onset of anorexia, weight loss and jaundice after traveling to India. Laboratory data showed a positive serology for hepatitis E immunoglobulin M (IgM) and Epstein-Barr virus (EBV) viral capsid antigen (VCA) Antibody (Ab) IgM thus establishing the diagnosis of acute hepatitis E (likely infected via fecal-oral transmission during a trip to India). During his admission he received supportive treatment and was asymptomatic at the time of discharge two weeks later. These results demonstrate the need for caution and careful evaluation of the serological results utilized in the diagnosis of EBV and HEV, as lack of awareness of the cross reactivity of the tests may result in misdiagnosis.

BACKGROUND

Worldwide, viral infection is the most common cause of hepatitis. In areas with tropical or subtropical climate and poor sanitary conditions, hepatitis E virus (HEV) is the major cause of enterically transmitted non-A, non-B hepatitis and is responsible for both water-borne outbreaks and sporadic cases of acute hepatitis. In the Indian subcontinent, HEV accounts for 30-60% of sporadic hepatitis; however, it is no longer confined to Asia and developing countries, and it appears to be an emerging disease in industrialized countries.1 Although relatively uncommon, primary Epstein-Barr virus (EBV) infection may also result in hepatitis. If primary infection occurs in adolescence or in adulthood, the most common manifestation is acute infectious mononucleosis. The confirmation of acute infectious mononucleosis is made by viral and serologic tests, and the most important evidence of acute primary EBV infection includes IgM class antibodies detected using EBV virus-capsid-antigen (EBV VCA). It has been documented that false-positive EBV detection can occur due to cross-reactivity with IgM against other viruses such as cytomegalovirus, adenovirus, rubella virus and human immunodeficiency virus (HIV).2 A false positive may also be the result of the reappearance of EBV specific IgM due to polyclonal activation induced by pathogens that produce an infectious mononucleosis-like syndrome.3

(continued on page 58)
IgM Anti-Hepatitis E Virus and Anti-Epstein-Barr Virus in Acute Hepatitis

A CASE REPORT

(continued from page 56)

CASE REPORT

A previously healthy, 39 year-old Indian male presented to the emergency department (ED) with one week of jaundice and pruritus. He reported anorexia, malaise and asthenia for about 15 days associated with five pounds of weight loss. Three months prior to his arrival in the ED, he had traveled to India. The patient’s partner, who had traveled with him and shared the same food, had not developed any symptoms. He had no previous vaccination for Hepatitis A or B. On examination, the patient had scleral icterus and jaundice. There was no fever, diarrhea, abdominal pain, sore throat, nausea or vomiting. Cardiopulmonary examination was normal and there was no lymphadenopathy or abdominal organomegaly.

His initial laboratory evaluation revealed: aspartate aminotransferase (AST) 1734 U/L, alanine aminotransferase (ALT) 2125 U/L, alkaline phosphatase 215 U/L, total bilirubin 14.9 mg/dl, prothrombin time 13.7 seconds and ferritin 2768 ug/L. Acute hepatitis panel (hepatitis A Ab IgM, hepatitis B core Ab IgM, hepatitis B surface Ab, hepatitis C Ab and RNA qualitative PCR) was negative. A right upper-quadrant ultrasound exhibited a normally sized liver that was heterogeneous in appearance. Given the markedly elevated liver enzymes without a clear etiology, a core needle biopsy was performed. Pathology reported moderate to severe hepatitis of uncertain chronicity and uncertain etiology with mixed hepatocellular and reticuloendothelial siderosis.

With the additional information of the abnormal biopsy pathology, other possible viral causes of acute hepatitis such as EBV, hepatitis E and cytomegalovirus were considered. The new set of laboratory data showed EBV VCA Ab IgM, EBV VCA immunoglobulin G (IgG) and Epstein-Barr nuclear antigen (EBNA) IgG positive and hepatitis E Ab IgM positive. The serologic studies for cytomegalovirus were negative. Overall, a diagnosis of acute hepatitis E was made.

DISCUSSION

We describe herein a case with a positive serology for two viral agents, EBV and HEV, which may be implicated in the etiology of acute hepatitis. Review of three other such documented cases suggests that simultaneous detection of EBV and HEV may be indicative of dual infection. However, the serological tests should be interpreted with caution as there is the possibility for false-positive detection. One possibility includes the presence of an acute infection by HEV with false positivity for EBV detection. Ghinoiu et al. describe a patient with similar serological findings to ours. They concluded that their patient had HEV confirmed by PCR, and the positive serology for EBV and negative EBV PCR was likely related to immune reactivation after hepatic cytolysis caused by the HEV infection.4 An additional possibility involves an acute infection by EBV resulting in false reactivity for anti-HEV IgM. Fogeda et al. describe a patient with markers of acute primary infection by EBV who also demonstrated positive reactivity to anti-HEV and suggested that it might reflect either a dual infection by HEV and EBV or a false reactivity to anti-HEV by polyclonal B-cell stimulation.5 Through differential evaluation of the EBNA and VCA IgM and IgG, the authors concluded that the serological findings were more consistent with a diagnosis of EBV infection, however HEV infection could not be excluded. In a recent case, Tappea et al. described a patient with initial negative EBV VCA IgM and HEV positive IgG and IgM. Serology tests performed one week and 4 months later showed positive EBV VCA IgM and loss of HEV IgM reactivity, respectively. They concluded that the patient had an acute EBV infection with an old unrecognized infection by autochthonous HEV.6

(continued on page 60)
In the diagnosis of primary EBV infection, an important piece of evidence is IgM class antibody detection using EBV VCA which appears early in the primary infection and lasts for 1 to 2 months. In our patient, the detection of EBV IgG suggests an older infection, and his recent travel to an endemic area of hepatitis E and the presence of HEV IgM make the diagnosis of hepatitis E with false positive reactivity for EBV most probable. Others have also reported the detection of anti-EBV IgM in patients with other types of hepatitis supporting the theory of a possible false positive anti-EBV during other viral hepatitis syndromes. 7, 8, 9, 10

CONCLUSION
Immigration from and touristic travel to endemic areas of hepatitis E is a source of introduction of the disease into the United States. This case illustrates the need for primary care physicians to be aware of the presence of HEV in the United States, and should cautiously evaluate serological evidence of EBV infection with an awareness of the possibility of false positive results. Travel advisories and travel health precautions such as safe food and water consumption practices should be emphasized to visitors of endemic regions. ■
Surgical treatment of reflux disease had been limited to a procedure called a Nissen fundoplication, which involves recreating the esophageal sphincter. While fundoplication is recommended for those with severe reflux, it is a complicated procedure that prevents the ability to belch or vomit and often leads to bloating or gas problems.

The most common adverse events experienced with the LINX included difficulty swallowing, pain when swallowing food, chest pain, vomiting, and nausea. It is important to note that patients with LINX will no longer be able to undergo magnetic resonance imaging (MRI) procedures. The magnetic beads interfere with the machine and can cause the device to be damaged and the patient to be injured.

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Funding for the clinical trial came from Torax Medical, ClinicalTrials.gov No. NCT00776997.

Article cited: Ganz, R.A., Peters, J.H., Horgan, S., Bemelman, W.A., Dunst, C.M., Edmundowicz, S.A., Lipham, J.C., Luketich, J.D., Melvin, W.S., Oelschlager,
Swallow Solutions LLC, a company dedicated to improving the health and quality of life of individuals suffering with swallowing disorders -- known as dysphagia -- has launched a therapeutic device specifically designed to treat this disorder.

Swallow Solutions LLC is registered and the MOST® (Madison Oral Strengthening Therapeutic) device is listed with the FDA. The MOST device is allowed for sale a Class 1 device in the United States. Multisite clinical trials are underway to provide the data necessary to garner Medicare and private health care reimbursement.

To head up the product launch and outreach efforts, the Madison, WI-based company has hired Brent Benson, a 13-year veteran of medical device and pharmaceutical sales to the health care sector, to the newly-created position of Director of Sales and Marketing.

Already, the first generation MOST device, introduced in August, is being shipped to hospitals, extended care facilities and speech pathologists around the country; the next generation MOST 2.0 will be launched in the coming year.

Benson points out that swallowing disorders negatively impact the health and quality of life of a sizeable portion of the US population. Affecting more than 15 million adults and many millions of infants and children, dysphagia becomes increasingly common as the population ages. As we get older, our muscles weaken – including the muscles of the head and neck. Aspiration of foods “down the wrong pipe” leading to pneumonia, malnutrition, and dehydration, which are just a few of the swallowing-related complications older people can face.

“The products offered by Swallow Solutions have been developed to address these swallowing problems in patients of all ages and medical conditions,” Benson explains. By strengthening head and neck muscles integral to swallowing, the device has been shown to improve dysphagia after an eight-week regimen.

The possibility of providing an alternative to tube feeding and the complications that may result from that method of nutritional intake, as well as the positive impact improved swallowing can have on a person’s quality of life and overall health, were important motivators in the founding of Swallow Solutions.

Benson enthuses, “A lot of these patients who are dysphagic and can’t swallow can go back to normal lives and eat regular food after just the initial eight-week study, removing any connection to a feeding tube for sustenance. It can be truly life changing.”

The MOST device consists of a relatively high tech instrument that works with a laptop. It has a customized, adjustable mouthpiece that provides pressure readings from embedded sensors that indicate performance levels and calculate therapeutic strengthening targets. Dysphagic stroke patients who completed an eight-week regimen using target values for strengthening goals in a federally funded study improved swallowing function; as well, healthy older adults demonstrated “younger” swallow pressures after performing the same protocol.

Swallow Solutions CEO Dr. Robert Carlson, MD is delighted with the enthusiasm that has greeted the MOST device to date. He is convinced that Benson’s appointment as Director of Sales and Marketing will position the company to build the sales infrastructure, customer service and support that will help put the devices in the hands of those who can benefit from them. “We are very fortunate to have someone of Brent’s caliber and experience join us,” he says. “With Brent, we are confident our product reach will expand

(continued on page 64)
as the company grows.”

“It’s a steep learning curve,” says Benson, “but there are exciting challenges ahead to look forward to.”

To place an order for the most device, please call 608-238-6678 (most) or email brentbenson@swallowsolutions.com

The MOST device is manufactured in Madison WI, and is based on pioneering research at the University of Wisconsin School of Medicine and the Madison VA Hospital by a team of leading clinicians and researchers in the field of swallowing and dysphagia, headed by Dr. JoAnne Robbins, PhD, CCC-SLP, BRS-S, Professor at the University of Wisconsin School of Medicine and Public Health and Associate Director of the Geriatric Research Education and Clinical Center (GRECC) of the Veterans Hospital in Madison. The research is protected by patents owned by the Wisconsin Alumni Research Foundation (WARF), which are licensed to Swallow Solutions.

For additional information on Swallow Solutions LLC or the MOST device, visit their website at www.swallowsolutions.com To schedule an interview with a representative of Swallow Solutions, kindly contact Falk Associates at 773.883.2580.

REIMBURSEMENT ANNOUNCEMENT FOR CELLVIZIO OPTICAL BIOPSIES

Mauna Kea Technologies, leader in the optical biopsy market and developer of Cellvizio®, the fastest way to see cancer, announced recently that Cellvizio procedures in the upper GI tract have been added to the Ambulatory Surgical Center (ASC) approved procedure list.

Ambulatory Surgical Centers are health care facilities focused on providing same-day surgical care, including diagnostic and preventative services, often times found to be more convenient than hospital-based outpatient procedures. The U.S. Centers for Medicare and Medicaid Services (CMS) has approved the payment rate of $520 per previously-awarded Category 1 Current Procedural Terminology (CPT®) codes for the use of Cellvizio® during endoscopy procedures in the upper gastrointestinal tract.

GI related procedures make up 24% of all specialties served at ambulatory surgical centers. There are approximately 5,000 ambulatory surgical centers across the United States, each one performing more than 3,700 GI endoscopy procedures each year, representing a total of about 18 million GI procedures.

Cellvizio is used at hospitals throughout the United States and the rest of the world to provide physicians live-cellular level views of the GI tract to help identify and rule out cancer and guide treatment decisions in real-time.

“We’re pleased with the addition of Cellvizio optical biopsies to the list of approved procedures performed in ambulatory surgical centers across the country and believe this opens a much larger market segment for Cellvizio in the United States, our largest clinical market,” said Sacha Loiseau, PhD, Founder and CEO of Mauna Kea Technologies. “This is a major milestone in our efforts to make optical biopsies available to a majority of patients with suspected GI diseases, in order to grant them access to a streamlined diagnostic work-up and to a faster treatment decision.”

The Category I CPT codes issued by the American Medical Association (AMA) include 43206 for the Cellvizio esophageal optical endomicroscopy and 43252 for esogastroduodenoscopy with optical endomicroscopy. The CPT codes went into effect on January 1, 2013.
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<table>
<thead>
<tr>
<th>Company Name</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>AbbVie, Inc. Humira</td>
<td>Cover 2, 1-4</td>
</tr>
<tr>
<td>Balneol</td>
<td>57</td>
</tr>
<tr>
<td>Beutlich LP, Pharmaceuticals HurriCaine ONE</td>
<td>51</td>
</tr>
<tr>
<td>Bracco</td>
<td>53</td>
</tr>
<tr>
<td>Braintree Laboratories, Inc. SuPrep</td>
<td>13, 14</td>
</tr>
<tr>
<td>CCA Alliance</td>
<td>65</td>
</tr>
<tr>
<td>CCFA</td>
<td>63</td>
</tr>
<tr>
<td>Ferndale Healthcare, Inc. Prepopik</td>
<td>18-20</td>
</tr>
<tr>
<td>Forest Laboratories, Inc. Linzess</td>
<td>25-30</td>
</tr>
<tr>
<td>Given Imaging</td>
<td>39</td>
</tr>
<tr>
<td>HMB Endoscopy Products</td>
<td>67</td>
</tr>
<tr>
<td>Konsyl Pharmaceuticals, Inc. Sitzmarks</td>
<td>43</td>
</tr>
<tr>
<td>Montefiore</td>
<td>35</td>
</tr>
<tr>
<td>Otsuka BreathTec</td>
<td>9, 10</td>
</tr>
<tr>
<td>Prometheus Anser ADA</td>
<td>7</td>
</tr>
<tr>
<td>Quintron Instruments Breath Testing</td>
<td>47</td>
</tr>
<tr>
<td>Takeda Pharmaceuticals North America, Inc. Dexilant</td>
<td>Covers 3, 4; 69, 70</td>
</tr>
</tbody>
</table>

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MEETINGS CALENDAR

April 19, 2013 Maryland Viral Hepatitis Summit
Four Points by Sheraton BWI, Baltimore, MD – This event is a “must attend” for anyone and everyone working with those who are infected with or affected by viral hepatitis. 5.5 Continuing education credits for physician assistants, nurses, certified public health and addiction professionals. Register by April 12, 2013 for only $75! Attendees may register online at: http://www.hepatitisfoundation.org/NEWS/Summits.html

May 17–22, 2013 SGNA 40th Annual Course
Austin, TX – Celebrating 40 years of Annual Course education, The Society of Gastroenterology Nurses and Associates brings together the best and brightest GI/endoscopy professionals to drive the future of our field. For more information visit: www.sgna.org

May 18–21, 2013 Digestive Disease Week
Orange County Convention Center, Orlando, FL – Digestive Disease Week® (DDW) is the largest and most prestigious meeting in the world for the GI professional. Every year DDW attracts approximately 15,000 physicians, researchers and academics from around the world. Choose from over 400 sessions, including clinical and research symposia, state-of-the-art lectures and research and topic fora, covering a wide array of topics and presented by a world-renowned faculty unsurpassed in their field. For more information visit: www.ddw.org

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Shanghai Expo Center, Shanghai, China – A World Congress in Asia! Submit your abstract and register today and take advantage of Early Bird Registration fees. The Early Bird Registration deadline is April 15, 2013. The Regular Registration deadline is August 15, 2013. For further information regarding the upcoming Congress, visit the Gastro 2013 APDW/WCOG Shanghai website at: www.gastro2013.org

October 24–26, 2013 Annual Probiotic Symposium
Probiotics: Current Perspectives and Controversies
San Antonio, TX – Attend the 7th Annual Probiotic Symposium for a unique opportunity to learn about the current perspectives and controversies in probiotics research and use in clinical practice. CME Credit for Physicians and other Healthcare Professionals will be available. Save $100 – Register before October 6, 2013. For more information visit: www.ProbioticSymposium.com