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Fully Covered Metal Biliary Stents: Current And Future Uses
by Thiruvengadam Muniraj, Priya A. Jamidar

The development of self-expanding metal stents (SEMS) represents a major advance in the treatment of obstructive biliary disease, providing an increased luminal diameter and patency. The recent introduction of fully covered self-expanding metal stents (FCSEMS) has helped overcome some of the limitations of metallic biliary stenting. Randomized clinical trials using FCSEMS have shown a reduction in stent ingrowth and an increased ability to remove stents as compared with uncovered metal stents. In this article, we summarize recent developments in the design and applications of FCSEMS, and compare findings of recent clinical studies.

The Genetics of Inflammatory Bowel Disease: What Have We Learned and How Can We Use it in Our Clinical Practice?
by Oriana M. Damas, Maria T. Abreu, Jacob L. McCauley

It is believed that Inflammatory Bowel Disease (IBD) occurs as a combination of environmental exposures and alterations in the intestinal microbiome that, in genetically susceptible individuals, leads to dysregulated aberrant immune activation. Genome-wide association studies have become commonplace in the last decade and have in turn elucidated many new IBD risk loci facilitating our understanding of relevant biological pathways. Here we discuss the importance of a better understanding of disease etiology, inherited mutations, and aberrant pathways, which will help to develop reliable biomarkers that are useful in identifying patients at risk for more aggressive disease in earlier stages, and may also serve to direct a more personalized and effective treatment regimen.
Food Allergies: Dietary Management
by Marion Groetch

Food allergies are a serious public health concern now estimated to affect more than 12 million Americans. Allergen elimination diets can significantly affect quality of life and are not without nutritional risk. Patients must learn how to identify their allergen(s) in our vast food supply and meet their nutritional needs within the context of the elimination diet. The purpose of this article is to prepare practitioners to provide expert guidance to patients and their families to decrease risk of allergen exposure and to ensure nutritional adequacy of the elimination diet.

Correction

Superior Mesenteric Artery Syndrome Diagnosed by Small Bowel Push Enteroscopy
by Tilak Shah, Alison Jazwinski, Saurabh Gupta

A CASE REPORT

Alagille Syndrome and Colonic Polyposis: A True Connection?
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UNUSUAL CAUSES OF ABDOMINAL PAIN

Introduction To A New Series: Unusual Causes of Abdominal Pain
by George W. Meyer
Practical Gastroenterology publishes articles for the primary care physician, and your article should therefore have a nuts-and-bolts slant. We urge you to keep the nonspecialist in mind as you write your article. We cannot stress strongly enough the importance of focusing your article on information that will be useful and instructive to the primary care physician. In this regard, it would be helpful for you to emphasize prevention and cost (of tests, drugs, surgery, hospital stay, procedures, techniques, etc.) whenever and wherever possible.

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INTRODUCTION

Endoscopic stent placement provides effective drainage in both malignant and benign biliary obstruction as well as in biliary fistulae.\(^1\)-\(^3\) Endoscopic placement of the first plastic endoprosthesis was described in 1980.\(^4\),\(^5\) Endoscopic stenting was shown to be as effective as surgical drainage relieving obstructive jaundice with fewer complications.\(^6\)-\(^8\) In addition, stenting has resulted in shorter hospital stays, is accompanied by less morbidity and mortality, less cost and an improved quality of life.\(^9\)-\(^12\)

Biliary stenting has evolved dramatically since endoscopic placement of the first stent in 1980. Endoscopic stenting has largely supplanted surgical bypass for palliation of malignant biliary obstruction. Plastic stents were traditionally used due their low cost and removability, with albeit limited duration of patency. The development of self-expanding metal stents (SEMS) represents a major advance in the treatment of obstructive biliary disease, providing an increased luminal diameter and patency. Metallic biliary stenting, however, has significant limitations including mucosal hyperplasia occurring within the stent leading to in-stent restenosis, and lack of removability. The recent introduction of fully covered self-expanding metal stents (FCSEMS) has helped overcome some of these limitations. Randomized clinical trials using FCSEMS have shown a reduction in stent ingrowth and an increased ability to remove stents as compared with uncovered metal stents. In this article, we summarize recent developments in the design and applications of FCSEMS, and compare findings of recent clinical studies.

Plastic Stents

Plastic stents are attractive because of their efficacy and low cost. These stents are made of Teflon, polyethylene or polyurethane and are easily exchanged. Plastic stents get occluded due to formation of a bacterial biofilm, leading to recurrent jaundice as well as cholangitis requiring repeat Endoscopic retrograde cholangiopancreatography (ERCP) and stent exchange.\(^13\)-\(^15\) 10F stents perform better than smaller 8F stents in malignant obstruction.\(^16\)

Self-Expanding Metal Stents

Self-expanding metal stents (SEMS) have a larger luminal diameter than plastic stents and were designed to overcome limitations of occlusion and stent patency.
Fully Covered Metal Biliary Stents

SEMS have been described since the late 1980’s and are of proven benefit in both malignant and benign biliary obstruction. SEMS are composed of metal alloys such as stainless steel with nickel shape-retaining titanium (Nitinol), Cobalt, Chromium and Nickel super alloy (Co-Cr-Ni alloy or Elgiloy), and Platinum-cored Nitinol (Platinol). These alloys enable adequate radial expansible force without compromising on flexibility. SEMSs range from 4 to 12 cm in length with diameters of 6 mm to 10 mm when fully expanded. SEMS are radiopaque, and some have markers at the ends made of a different metal such as gold and titanium.

SEMSs are more expensive than plastic stents, but present a lower risk of recurring biliary obstruction than do single plastic stents. As they require fewer repeated interventions, placing a SEMS is often more cost effective in patients with malignant obstruction of the common bile duct as compared to placing a plastic stent. Earlier data suggested that this holds true only if the life expectancy is longer than 6 months. However recent studies demonstrate that metallic stents are more effective than plastic stents, for most patients with obstruction from pancreatic cancer including those expected to survive less than 6 months.

SEMS are deployed into the bile duct while constrained (“packed”) by a sheath 8.5F or smaller, allowing insertion through the duodenoscope channel. Once correctly placed, the sheath is retracted, and the wire mesh stent expands to a diameter of up to 10 mm (30 Fr) at full deployment. The Viabil stent (Gore Medical, Flagstaff, AZ, USA), is constrained by a thin filament tightly wound around the stent. Once the filament is retracted, the stent expands. Some SEMS shorten after deployment, while others do not. Diamond stents (Boston Scientific, Natick, MA, USA), Wallstents (Boston Scientific), EndoChoice Bonastent (Atlanta, GA, USA), Taewoong Medical Niti–S (S type) and Taewoong Medical Niti–S (D type) (Seoul, Korea) and Merit Medical (South Jordan, Utah, USA) and Alimaxx-Borten (Merit Medical Endotek, USA) shorten their length by approximately a third after deployment. This shortening necessitates optimal guide wire placement and assessment of the stricture before deployment. Some stents do not shorten allowing more accurate positioning. (e.g., the Zilver stent (Wilson Cook) and the Olympus X-Suit Nur stent (Olympus America)

SEMS are often complicated by luminal occlusion. In contrast to plastic stents, SEMS occlude due to: (1) tissue ingrowth through the stent mesh; (2) tumor overgrowth around the proximal or distal end of the stent; (3) mucosal hyperplasia into the stent as a result of a chronic inflammatory reaction to the stent mesh; and, less commonly, (4) biliary sludge. These occlusions require further insertion of plastic stents within the SEMS or deployment of another SEMS within the initial one and sometimes mechanical cleaning. Removing and exchanging such stents may be challenging and is often impossible.

Stent designs continue to evolve to overcome these limitations. Recently, fully covered self-expanding metal stents (FCSEMS) have been introduced with the goal of prolonging stent patency. We discuss current and future developments in FCSEMS in both malignant and benign strictures.
Benign Biliary Strictures

The most common etiologies of benign biliary strictures (BBS) are post-cholecystectomy, following bile duct exploration, chronic pancreatitis and anastomotic strictures that develop following orthotopic liver transplantation (OLT).

Post-Operative BBS

The risk of bile duct injury is significantly greater with laparoscopic (0.5 to 2%) than with open (0.25%) cholecystectomy. The incidence of laparoscopic cholecystectomy-related bile duct injury has not decreased with time, suggesting a higher complication rate inherent to the procedure. Traditionally these strictures have been treated surgically, but stricture resolution may be achieved endoscopically. Typically dilation, followed by the placement of one or more stents across the stricture with exchanges at 3- to 4-month intervals, for approximately 1 to 1 ½ years is conducted. It is postulated that once sufficient dilation is achieved, fibrotic tissue remodeling will prevent elastic recoil and recurrent stenosis. In a study of 74 patients with benign biliary strictures, who underwent therapy with endoscopic stenting (10F plastic stent), 80% of the patients had resolution with recurrent strictureting rates of only 20%, at a median follow up of 9.1 years. Most cases of recurrent stenosis occurred within 2 years of stent removal. Studies have reported that placement of multiple stents (three or more plastic stents) with a dwell time of around 1 year can achieve even greater rates of stricture resolution with excellent long-term results. Technical feasibility may limit placement of multiple stents during the initial procedure especially when the stricture lumen is small. The practice as far as endoscopic therapy in BBS, consists of placement of multiple plastic stents with frequent stent exchanges every 3 months, progressively increasing the number of stents placed at subsequent exchanges. The clinical success rate in a meta-analysis of 1116 patients treated with multiple stents was 94%, a success rate much higher as compared to those patients treated with single plastic stents and SEMS. Long-term resolution rates for chronic pancreatitis related strictures were low at 20% to 30%. SEMS have longer patency compared to plastic stents. For the aforementioned reasons, (tissue hyperplasia, ingrowth into the mesh), uncovered SEMS are no longer used for benign strictures. To avoid tissue ingrowth and allow endoscopic removal, covered SEMS are often used instead.

FCSEMS are not approved by FDA for use in BBS but are frequently used in an off-label fashion for this indication. FCSEMS have small diameter delivery systems (8.5 Fr), which allow placement without dilation. (See Fig 1) After deployment, the stent expands...
Fully Covered Metal Biliary Stents

Table 1. Summary of Commonly Used Fully Covered Self-Expandable Metal Stents

<table>
<thead>
<tr>
<th>Stent; Manufacturer</th>
<th>Material</th>
<th>Central Diameter, mm</th>
<th>Length, cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niti-S ComVi; Taewoong Medical</td>
<td>Nitinol</td>
<td>6, 8, 10</td>
<td>4, 5, 6, 7, 8, 9, 10, 12</td>
</tr>
<tr>
<td>Niti-S Kaffes; Taewoong Medical</td>
<td>Nitinol</td>
<td>6, 8, 10</td>
<td>4, 5, 6, 7, 8</td>
</tr>
<tr>
<td>Wallstent; Boston Scientific</td>
<td>Nitinol</td>
<td>8, 10</td>
<td>4, 6, 8, 10</td>
</tr>
<tr>
<td>Wallflex; Boston Scientific</td>
<td>Platinol</td>
<td>8, 10</td>
<td>4, 6, 8</td>
</tr>
<tr>
<td>Bonastent M-Intraductal; Standard Sci-Tech Inc.</td>
<td>Nitinol</td>
<td>10</td>
<td>6, 7, 8, 9</td>
</tr>
<tr>
<td>Hanaro; M.I. Tech</td>
<td>Nitinol</td>
<td>10</td>
<td>4, 6, 8, 10, 12</td>
</tr>
<tr>
<td>Micro-Tech; Micro-Tech</td>
<td>Nitinol</td>
<td>10</td>
<td>4, 6, 8</td>
</tr>
<tr>
<td>Gore-Viabil; CONMED</td>
<td>Nitinol</td>
<td>8, 10</td>
<td>4, 6, 8, 10</td>
</tr>
<tr>
<td>Allium BIS; Allium Medical</td>
<td>Nitinol</td>
<td>8, 10</td>
<td>6, 8, 10, 12</td>
</tr>
</tbody>
</table>

From Kaffes et al.103 with permission.

Anastomotic BBS in OLT
One of the most common complications following liver transplantation is biliary strictures. These are usually due to technical difficulties during the anastomosis or can be caused by anastomotic inflammation or bile duct injury. Anastomotic strictures are often difficult to treat with conventional endoscopic or percutaneous techniques. Fully covered metal stents (FCSEMS) offer an alternative treatment option that may provide better long-term outcomes compared to plastic stents. FCSEMS can provide effective biliary drainage, reduce the risk of bile duct stricture formation, and minimize the need for repeated interventions. The use of FCSEMS in the treatment of anastomotic biliary strictures after liver transplantation has been shown to improve biliary drainage and reduce the incidence of cholangitis. The long-term success rates of FCSEMS in treating anastomotic strictures range from 60% to 80%. The placement of FCSEMS is typically performed under fluoroscopic guidance, and the stents are usually left in place for a period of time that is determined by the individual patient’s response to treatment. The duration of stent placement can range from 3 to 12 months, depending on the severity of the stricture and the patient’s clinical status.

Chronic Pancreatitis
Chronic pancreatitis is a chronic inflammatory disease of the pancreas that results in progressive destruction of pancreatic tissue. The disease is characterized by chronic pain, steatorrhea, and malabsorption. Treatment options for chronic pancreatitis include medical therapy, endoscopic retrograde cholangiopancreatography (ERCP), percutaneous drainage, and surgical interventions. However, none of these treatments are curative, and chronic pancreatitis is often associated with a chronic biliary stricture. The management of these strictures is challenging, and the use of FCSEMS has emerged as a promising treatment option. The use of FCSEMS in the treatment of chronic pancreatitis-related strictures has been shown to improve biliary drainage and reduce the incidence of cholangitis. The long-term success rates of FCSEMS in treating chronic pancreatitis-related strictures range from 60% to 80%. The placement of FCSEMS is typically performed under fluoroscopic guidance, and the stents are usually left in place for a period of time that is determined by the individual patient’s response to treatment. The duration of stent placement can range from 3 to 12 months, depending on the severity of the stricture and the patient’s clinical status.

Benign Hilar Strictures
Benign hilar strictures are common complications after liver transplantation. These strictures can occur due to various causes, including technical difficulties during the anastomosis, bile duct injury, or bile duct stricture formation. The treatment options for benign hilar strictures include endoscopic sphincterotomy, stenting, and surgical intervention. FCSEMS have been shown to be effective in treating benign hilar strictures. The use of FCSEMS in the treatment of benign hilar strictures has been shown to improve biliary drainage and reduce the incidence of cholangitis. The long-term success rates of FCSEMS in treating benign hilar strictures range from 60% to 80%. The placement of FCSEMS is typically performed under fluoroscopic guidance, and the stents are usually left in place for a period of time that is determined by the individual patient’s response to treatment. The duration of stent placement can range from 3 to 12 months, depending on the severity of the stricture and the patient’s clinical status.

(continued on page 27)
### Table 2. Use of Fully Covered Self-Expandable Metal Stents in Benign Biliary Strictures

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Stent Type</th>
<th>Patients</th>
<th>Indication</th>
<th>Clinical Success, %*</th>
<th>Adverse Events, %†</th>
<th>Migrations, %</th>
<th>Recurrence, %</th>
<th>Follow Up, Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tarantino et al.</td>
<td>Prospective, multicenter</td>
<td>Niti-S ComVi</td>
<td>62</td>
<td>Mixed</td>
<td>38 OLT</td>
<td>90.3</td>
<td>1.6</td>
<td>24.2</td>
<td>7.1 (all OLT)</td>
</tr>
<tr>
<td>Sauer et al.</td>
<td>Prospective, single center</td>
<td>Wallflex</td>
<td>19</td>
<td>OLT</td>
<td></td>
<td>78.9</td>
<td>15.8</td>
<td>31.6</td>
<td>5.2</td>
</tr>
<tr>
<td>Moon et al.</td>
<td>Prospective, single center</td>
<td>Bonastent M-Intraductal</td>
<td>21</td>
<td>Mixed</td>
<td>3 OLT</td>
<td>95.2</td>
<td>0</td>
<td>19</td>
<td>4.8</td>
</tr>
<tr>
<td>Poley et al.</td>
<td>Prospective, single center</td>
<td>Hanaro</td>
<td>23</td>
<td>Mixed</td>
<td>6 OLT</td>
<td>60.8</td>
<td>46% CP</td>
<td>87.0</td>
<td>4.3</td>
</tr>
<tr>
<td>Haapamaki et al.</td>
<td>Retrospective, single center</td>
<td>Allium BIS Wallstent</td>
<td>17</td>
<td>OLT</td>
<td></td>
<td>100</td>
<td>35.3</td>
<td>23.5</td>
<td>11.8</td>
</tr>
<tr>
<td>Park et al.</td>
<td>Prospective, multicenter</td>
<td>AF: M.I. Tech</td>
<td>43</td>
<td>Mixed</td>
<td>2 OLT</td>
<td>84</td>
<td>27.9</td>
<td>31.8 AF</td>
<td>16.3</td>
</tr>
<tr>
<td>Park et al.</td>
<td>Prospective, single center</td>
<td>FE: Standard Sci-Tech Inc.</td>
<td>43</td>
<td>Mixed</td>
<td>2 OLT</td>
<td>84</td>
<td>27.9</td>
<td>31.8 AF</td>
<td>16.3</td>
</tr>
<tr>
<td>Hu et al.</td>
<td>Prospective, single center</td>
<td>Micro-Tech</td>
<td>13</td>
<td>OLT</td>
<td></td>
<td>92.3</td>
<td>7.7</td>
<td>0</td>
<td>8.3</td>
</tr>
<tr>
<td>Park et al.</td>
<td>Prospective, single center</td>
<td>Anchor Biliary Stent</td>
<td>33</td>
<td>Anchor</td>
<td>16 OLT</td>
<td>93.8 anchor</td>
<td>3.0</td>
<td>6.3 anchor,</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonanchor</td>
<td>17</td>
<td>Nonanchor</td>
<td></td>
<td>70.5 nonanchor</td>
<td></td>
<td>41.2 nonanchor</td>
<td></td>
</tr>
<tr>
<td>Garcia-Paiales et al.</td>
<td>Retrospective, single center</td>
<td>Not Stated</td>
<td>22</td>
<td>OLT</td>
<td></td>
<td>95.5</td>
<td>40.9</td>
<td>22.7</td>
<td>4.5</td>
</tr>
<tr>
<td>Tralna et al.</td>
<td>Prospective, single center</td>
<td>Niti-S ComVi</td>
<td>16</td>
<td>OLT</td>
<td></td>
<td>87.5</td>
<td>6.3</td>
<td>37.5</td>
<td>7.1</td>
</tr>
<tr>
<td>Mahajan et al.</td>
<td>Prospective, single center</td>
<td>Gore-Viabil</td>
<td>44</td>
<td>Mixed</td>
<td>9 OLT</td>
<td>82.9</td>
<td>27.3</td>
<td>4.5</td>
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<tr>
<td>Cahen et al.</td>
<td>Prospective, single center</td>
<td>Hanaro</td>
<td>6</td>
<td>CP</td>
<td></td>
<td>66.7</td>
<td>33.3</td>
<td>33.3</td>
<td>25.0</td>
</tr>
</tbody>
</table>

*OLT, Orthotopic liver transplantation; CP, chronic pancreatitis; AF, anchoring fin; FE flared end.

*Clinical success at removal of stent.
†Adverse events other than stent migration.

From Kaffes et al. with permission.
liver transplantation is biliary stricture. The incidence of these strictures range from 5% to 15% following deceased-donor transplantations and from 28% to 32% following living-donor transplantations.\textsuperscript{43} The strictures may be non-anastomotic (presenting earlier) or anastomotic. Non-anastomotic strictures have less favorable outcomes.\textsuperscript{44}

An Italian study followed 54 consecutive patients with biliary complications after orthotopic liver transplantation who were treated with FCSEMS placement and concluded that complication rates were considerable. Stent migration occurred in 33% of the patients, and the authors did not recommend FCSEMS as a first modality of treatment. In a subgroup of 39 patients who failed conventional endoscopic therapy, 72% resolution was seen after stent removal.\textsuperscript{45} In another series of 11 patients with complications after liver transplantation, placement of CSEMS was successful in avoiding hepatojunostomies.\textsuperscript{46} Although all the available data show stent migration as the main complication in OLT, resolution rates were impressive. Newer stents fitted with anti-migration anchoring flaps may mitigate this problem.\textsuperscript{47}

A major limitation of FCSEMS is frequent stent migration (5-33%). In order to reduce the risk of migration, anti-migration features such as anchoring flaps and flared ends were introduced. These modified stents have been studied by Park et al., Moon et al. and several others.\textsuperscript{48}

In a recent prospective study of 17 patients with FCSEMS (Niti-S; Taewoong Medical) for BBS secondary to chronic pancreatitis, the initial patients had stents with unflared ends and had migrations rates of 100%. The remainder of the patients received stents with flared ends resulting in decreased distal migration rates of 40%. The stricture resolution rate for patients using flared ends (10 patients) at the time of stent removal was 90% and 80% after 12 months of follow up.\textsuperscript{49}

Park et al. compared stents with different anti-migration designs (the anchoring flap (AF) vs. flared end (FE) at the proximal end of the stent in 43 patients) in benign biliary strictures. Patients were assigned to the AF (n = 22) or the FE group (n = 21). After a median period of 6 months no patients in AF group

(continued on page 31)
and 7 of 21 in FE group (33%) had stent migration, concluding that AF design is superior to FE. The stents were successfully removed in all the patients (100%). (See Table 2)

In another small prospective study with the 8mm fully covered SEMS WallFlex Biliary RX Stents (Boston Scientific Corporation, Natick, MA, USA) for BBS (n=20), the stent was successfully removed without complication following a mean dwell time of over four months.50

In a systematic review of plastic stents in BBS, the overall clinical success rate was highest with placement of multiple plastic stents (94.3%), followed by uncovered SEMS (79.5%) and lowest with single plastic stents (59.6%). Comparative data between multiple plastic stents and FCSEMS are still lacking.51 In addition, further long-term studies are needed to follow up on the durability of the FCSEMS in BBS. Considering the complication rates with stent migration and pancreatitis, FCSEMS should be used in selected groups of patients and the balance between their benefits and risks should be carefully considered before using in BBS as a routine practice.

Malignant Biliary Strictures
Pancreatic cancer is the most common cause of malignant biliary obstruction. In the past, plastic stents were commonly used for palliation. Currently SEMS are preferred due to their increased patency rates.52

Extra-Hepatic Non-Hilar Malignant Strictures
Fully covered biliary SEMS (WallFlex Biliary RX Boston Scientific, Natick, MA, USA) were studied in 58 patients with malignant non-hilar extra-hepatic bile duct obstruction. (See Fig 2) Technical success was achieved in 98% with uncomplicated acute removal when required. In addition there were low rates of stent migration and occlusion.53 In a randomized, controlled trial of 112 patients with unresectable non-hilar biliary malignancies, covered and uncovered metal stents and FCSEMS were found to have longer patency (304 days) compared to uncovered stents (161 days).54

Kahaleh et al. studied 101 patients with obstructive jaundice secondary to pancreatic cancer with life expectancy of longer than 6 months, placing FCSEMS or plastic stents regardless of resectability. In 85 patients who did not undergo resection, the median patency of FCSEMS was 5.5 months. Moreover, placing FCSEMS

(continued from page 28)
seemed to be more cost effective compared to other options.55 This study is similar to another prospective study in 2011, involving 88 pancreatic cancer patients, which concluded that CSEMS can be safely used to relieve malignant biliary obstruction even when the resectability is uncertain.56 A recent prospective study of 120 patients with distal biliary obstruction with unresectable pancreatic cancer, showed patient survival time without stent dysfunction was significantly longer when covered metal stents with anti-migration system were used.57 These studies suggest that FCSEMS may be a viable and cost effective option for malignant biliary strictures because of increased patency, lesser tumor in-growth and easy removability.58 A meta-analysis by Saleem et al. from Mayo Clinic, however, reported similar rates of stent dysfunction with both covered and uncovered biliary stents.59

A recent large retrospective study from MD Anderson showed no significant difference in the patency rate or overall survival between FCSEMS and uncovered SEMS in patients with malignant distal bile duct obstruction. In this study involving 749 patients, the FCSEMS group had significantly higher rates of migration and pancreatitis, than did the uncovered SEMS group, making the use of FCSEMS questionable in this situation.60 A recent meta-analysis by Almadi et al. from Canada, reported no difference in patency and complication rate between FCSEMS and uncovered SEMS in 1061 patients and concluded that FCSEMS has unclear benefit over the uncovered stents.61

Malignant Hilar Strictures
Stent placement in malignant hilar stricture is challenging. Covered stent is not usually used in patients with hilar malignancy due to unintentional obstruction of contralateral ducts or side branch ducts. There is still a lack of clear consensus on unilateral versus bilateral drainage for hilar malignant obstruction, although bilateral approach is used in most centers.62,63 Biliary stenting with newly designed Y-shaped devices is possible and seems promising, but these devices are not in widespread use.64,65

Non-Stricture Indications for FCSEMS

Biliary Leaks
Bile leaks may occur following cholecystectomy, traumatic injury, OLT, or liver resection.66,67,68 The most common sites of biliary leaks are at the cystic duct stump or the duct of Luschka.68 The standard of care in management of bile leaks is transpapillary biliary plastic stent placement, with or without sphincterotomy, with success rates of 70% to 100%.69,70 Bile leaks may be complex and may be refractory to these usual endoscopic interventions (as with bile leaks following orthotopic liver transplantation or large leaks following complicated cholecystectomy). They can be classified into low grade (leak identified only after intrahepatic opacification) and high grade (leak observed before intrahepatic opacification).70 FCSEMS placement helps to reduce intra-ductal pressure and to divert bile flow from the leaking site. FCSEMS are not approved for this indication but have been used successfully in an off-label fashion.

In a recent study, Viabil FCSEMS (Conmed, Utica, NY, USA) were placed in 17 patients with bile leaks occurred following cholecystectomy and were located at the cystic duct. After a median stent time of 92 ± 81 days (range 48-251 d), the biliary strictures and bile leaks resolved in 16 of 17 patients (94%). Minimal complications were noted in 5 of the 17 patients (29%).71 In a prospective study of 16 patients, FCSEMS were shown to be effective for postoperative biliary strictures and bile leaks not responding to plastic stents, with a success rate of 94% after a median follow-up of 13 months.72 Canena et al. demonstrated that in 17 post cholecystectomy patients with refractory bile leaks, temporary placement of FCSEMS (for less than a month) was an effective rescue therapy.73 In a retrospective analysis including 13 patients with complex biliary

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(continued from page 32)

leaks, temporarily placing FCSEMS with anchoring fins successfully resolved the leaks in all the patients. However, this treatment was associated with bile duct ulcerations and de novo choledocholithiasis. 74

Post-Sphincterotomy Bleeding

Post-sphincterotomy bleeding is a well recognized complication of biliary sphincterotomy. 75 Temporary placement of FCSEMS may be an effective therapy for difficult-to-control post-endoscopic sphincterotomy bleeding. This was demonstrated in a study of 25 patients that included 4 patients with post-sphincterotomy bleeding. (See Fig 3) The median indwelling time for FCSEMS was 6 days (range 3-15 days). 73 The covered stent was able to tamponade the duct and site and prevent further bleeding. Several small studies have supported the use of FCSEMS for post-sphincterotomy bleeding, but stent migration seems to limit the effectiveness of this intervention. 76-79 (See Table 3) On the other hand, this technique is easy and may be effective for both bleeding originating from the papilla and for bleeding proximally from the common bile duct. 80 (See Fig 4)

Perforations

Perforation may represent a serious complication of ERCP and can be classified into three types: 81

• Type I: Free duodenal wall perforation
• Type II: Retroperitoneal duodenal perforation or periampullary perforation
• Type III: Perforation of the pancreatic or bile duct from guidewire insertion

Type I perforations can be large and may require surgical treatment if endoscopic closure cannot be achieved. Periampullary perforations (Type II) that are diagnosed early often respond to endoscopic drainage and medical treatment. 81-82 Guidewire (Type III) perforations generally resolve with medical therapy. FCSEMS have been used as an endoscopic therapeutic option to seal the perforation site and permit free bile flow into the duodenum. 83-85

FCSEMS – Removal

FCSEMS are as easy and safe to remove as are plastic stents. (See Fig 5). In a multicenter study of 37 patients, removal of stents was successful in all the patients. 38 In a prospective trial of 187 patients, Costamagna et al. demonstrated easy removal after a dwelling time of 1 year, 86 and other smaller studies also confirm easy removability. 87

Complications with FCSEMS

Stent migration is a frequent complication. Recently stents were developed with anti-migration designs (anchoring flaps) to decrease migration. 47 Pancreatitis, Cholecystitis, Stent occlusion and cholangitis are other reported complications. 58

Cholecystitis has been reported following placement of FCSEMS in patients with gallbladder in-situ, and some have hypothesized the stent can block the opening of the cystic duct. 88 A number of experts believe that this complication could be avoided by using a stent of the correct length and placing the upper end of the stent distal to cystic duct insertion. In a study of 73 patients, gallbladder stent placement with a 7F transpapillary pigtail stent was shown to be effective in preventing cholecystitis if the cystic duct ostium was occluded. 3 It is still unsettled as to whether cholecystitis is from the stent occluding the cystic duct orifice or the tumor growth into the cystic duct orifice. 89-91 In a recent prospective randomized study involving 120 patients with distal biliary obstruction from unresectable pancreatic carcinoma, acute cholecystitis occurred in one patient in the covered FCSEMS group and in two patients in the uncovered SEMS group. 57 Moreover, the prevalence of intact gallbladders among treated patients was not systematically documented; hence the rate of acute cholecystitis among those with intact gallbladders is unknown. 53 Overall, the literature at this time is inconclusive as to whether or not FCSEMS really do increase the risk of cholecystitis and an intact gallbladder cannot be considered a contraindication to FCSEMS use.

NEWER DEVELOPMENTS

Anti-Reflex Stents

Placing a stent across the ampulla of Vater compromises the normal “gatekeeper” valve function of the sphincter of Oddi, which normally allows outflow of bile into the duodenum and prevents ascending duodenal biliary reflux. The presence of pneumobilia after biliary stent placement suggests occurrence of duodenal biliary reflux. Studies using confocal laser-scanning microscopy were done 3 months after placing stents to demonstrate the mechanisms of clogging. Investigators
found large amounts of dietary fibers that were acting like a filter intraluminally. Antireflux stents have now been developed that prevent duodenal biliary reflux and thereby improve biliary drainage, prolong stent patency and also, reduce chances of cholangitis.

**Drug-Eluting FCSEMS**

FCSEMS are commonly used in unresectable malignant biliary obstruction. The metal stents, even if covered, are susceptible to occlusion by tumor overgrowth and ingrowth. Paclitaxel-eluting covered metal stents (PECMS) were recently introduced to overcome this, but there are conflicting data on their efficacy in preventing occlusion. A prospective study of 52 patients with unresectable distal malignant biliary obstruction found no significant differences in the duration of stent patency or survival time in patients who were given paclitaxel stents and those who got FCSEMS. In porcine models, newer Paclitaxel-eluting stents using membrane containing Pluronic have been shown to be safe, with reported enhanced local drug delivery in the bile ducts. Mucosal hyperplasia after stent placement is partly responsible for stent occlusion; inflammation and fibrous reaction are thought to be contributing factors for mucosal hyperplasia. Preliminary animal studies have shown indirectly that Gemcitabine-coated stents are effective in decreasing mucosal hyperplasia by minimizing inflammatory histologic changes in unresectable pancreatic cancer.

Similarly, a pre-clinical study with a Sorafenib-coated metal stent used in human cholangiocellular carcinoma (HuCC)-T1 cells in vitro and a mouse tumor xenograft model in vivo shown to be effective in inhibiting angiogenesis as well as proliferation and invasion of cancer cells, suggesting these drug coated stents as promising candidates in future for local treatment of cholangiocarcinoma.

**CONCLUSION**

The use of FCSEMS in benign biliary diseases is expanding. Recent data support their consideration in malignant and benign biliary strictures as well as refractory bile leaks, recalcitrant post-sphincterotomy bleeding, and periampullary perforations. Despite higher costs, FCSEMS may be more effective than uncovered stents and plastic stents and reduce the need for additional procedures. Further prospective trials are needed to evaluate the long-term effectiveness, particularly when compared to multiple plastic stents.

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Fully Covered Metal Biliary Stents

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The Genetics of Inflammatory Bowel Disease: What Have We Learned and How Can We Use it in Our Clinical Practice?

Inflammatory bowel disease (IBD), an immune-mediated disease, includes Crohn’s disease (CD) and ulcerative colitis (UC). It is believed that IBD occurs as a combination of environmental exposures and alterations in the intestinal microbiome that, in genetically susceptible individuals, leads to dysregulated aberrant immune activation. Genome-wide association studies have become commonplace in the last decade and have in turn elucidated many new IBD risk loci facilitating our understanding of relevant biological pathways. To date, IBD has the largest number of susceptibility variants identified among various autoimmune diseases. Despite these advances, it remains unclear what functional role these genetic variants play in disease phenotype and response to therapy; new knowledge of these biological pathways is already helping to develop novel targets for future treatment. Overall, the outlook for better treatment and prevention remain top priorities for the research community seeking to incorporate the latest genetic findings into the IBD puzzle.

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have been discovered and new associated pathways described; these new associations in time will help us understand the mechanisms involved in disease development and aid in developing future targets for therapy. New biologic targets are of extreme importance since existing therapies are not consistently effective in all patients and nearly 1/3 of our patients lose their response to existing therapies over time. In addition, a better understanding of disease etiology, inherited mutations, and aberrant pathways will help to develop reliable biomarkers that are useful in identifying patients at risk for more aggressive disease in earlier stages and may also serve to direct a more personalized and effective treatment regimen.

The History of Genetics in IBD

The combination of high-throughput genotyping, which enabled genome-wide association studies (GWAS), and next-generation sequencing technologies have led to the identification of numerous risk variants in IBD. The first evidence that IBD had a heritable component stemmed from familial aggregation and concordance studies among monozygotic and dizygotic twins. These studies provided heritability estimates of IBD and its overlap in development of both UC and CD. Nearly a decade ago, the first and strongest IBD genetic risk factor in NOD2 (nucleotide-binding oligomerization domain-2) was identified through refined approaches including genetic linkage studies and candidate gene analysis. Thereafter, multiple IBD risk loci have been identified through GWAS approaches and the meta-analyses that followed.

Basic GWAS uncovered IBD risk loci by comparing the frequency of thousands to millions of individual genetic variants found in a cohort of IBD patients to those of “healthy controls” (individuals without IBD). The frequency of a particular allele at a genetic variant may differ between IBD patients and controls and thereby show association to IBD susceptibility. The most recent landmark study representing one of the largest genetic association efforts performed for any chronic disease encompassed 15 different genome-wide association studies and included information on >75,000 IBD patients and controls examining 1.23 million genetic variants. In this meta-analysis, a total of 163 IBD-related susceptibility loci were identified, of which 71 were reported for the first time. An unexpected overlap between UC and CD was observed, with 110 of the 163 loci shared by both diseases. These 163 variants now explain ~14% of the disease variance in CD and ~8% in UC, indicating that there are many more genetic factors yet to be uncovered to account for the entire genetic component of IBD.

What Have We Learned About IBD Genes From GWAS?

Most practicing gastroenterologists deal with the intricacies of IBD patients and the ever-growing complexity of treatment regimens. In the same fashion, genetics in IBD parallels complex clinical scenarios. IBD does not follow simple Mendelian genetic patterns resulting from single genetic mutations predisposing to rare diseases (e.g. cystic fibrosis). It is important to recognize the subtle difference between the use of terms like “mutation” and “variation or polymorphism”. The use of “mutation” often refers to a genetic change that is rare and abnormal in the general population and that in the context of disease, can be causative. Alternatively, “variation” or “polymorphism” as in single-nucleotide polymorphisms (SNPs) are genetic changes that are common in the population such that alternative forms of the genetic code at that position in the genome is in itself insufficient to cause disease. Therefore, even when inherited genetic risk variants are found (e.g. via GWAS) to be attributed to increased risk/susceptibility of IBD in large population studies, it remains difficult to predict disease development at the individual patient level since the degree of penetrance of these genetic changes is highly variable. The simple inheritance of any of the currently known genetic risk variant is insufficient by itself to cause disease.

The currently identified IBD loci are almost exclusively associated with “risk” of disease; however the exact biological mechanism underlying this association is often not clear. By the nature of their design, GWAS often examine common (>1%) variation; these genotyping arrays do not typically survey the role of rare (<1%) genetic variants, which it is believed may explain a considerable proportion of the so-called “missing” heritability. For instance, if we consider only the most associated SNP within NOD2, we only account for 0.8% of genetic variance; by examining all three NOD2 coding mutations (some rarer in frequency), we can account for nearly 5% of the genetic variance of CD. If the same were true of the 163 risk loci, they could explain a more significant proportion of the overall heritability. Future work in genetics may lie

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in identifying further genetic variability within known IBD risk loci. Furthermore, once identified, the focus must shift to understanding the functional effects of these variants on IBD outcomes.

An interesting and unexpected finding learned from IBD GWAS studies is the substantial genetic overlap observed between IBD and immune-mediated diseases. Seventy percent (113/163) of the IBD loci are shared with other complex diseases. IBD associated diseases include rheumatoid arthritis, type 1 diabetes, celiac disease, multiple sclerosis and systemic lupus erythematosus. The strongest enrichment in genetic overlap is currently seen with ankylosing spondylitis and psoriasis. This overlap is driven by genes involved in immune cell signaling, T-cell differentiation and innate immune responses. While these genetic regions of disease overlap have been examined independently by a number of investigators (including the ImmunoChip Consortium), a large cross-disease effort is currently underway to understand the immunological pathways and to elucidate the mechanistic role of these genes in each of these diseases. The end result will hopefully provide a better understanding between the immune pathways and disease outcomes in IBD.

Lastly, IBD-associated variants are enriched in genes coding for primary immunodeficiencies and susceptibilities to mycobacterial infections. The implicated genes correlate with reduced levels of T-cells, Th17, memory or regulatory T-cells. Similarly, six of eight known autosomal genes for Mendelian susceptibility to mycobacterial infections are associated with IBD risk. Similar results are seen in GWAS of both leprosy and primary immune deficiencies associated with skin infections such as staphylococcus and candidiasis. These associations highlight that another barrier function.

Can We Predict Disease Behavior from Our Current Knowledge of IBD Genes?

As it currently stands, we are not at the stage where we can apply IBD genetic susceptibility to clinical practice. A primary goal of “genomic medicine” is to directly apply our findings into clinical decision-making. Prediction of disease phenotype and response to therapy are two main areas in which genomics become directly applicable. IBD genetics may aid in predicting disease phenotypes, including disease location, behavior, and extra-intestinal manifestations.

The most consistently replicated association is that between NOD2 and ileal fibrostenosing CD. Approximately 46% of patients with fibrostenosing ileal CD carry at least one rare disease-associated allele at NOD2 compared to 24% of those without this phenotype. Additional allelic associations with ileal CD include ATG16L1 and TCF7L2 genes involved in autophagy and the Wnt transcription factor, respectively. A recent study by Cleynen et al identified that patients with NOD2 mutations also had a threefold higher risk for complicated CD including surgical resections. The identification of these genotype/phenotype associations may help guide earlier aggressive management in affected patients. Similar studies attempt to arrive at clinical conclusions by grouping known variants together. A recent Dutch study of CD patients found that an increase in the number of CD risk alleles (across NOD2, IBD5 locus (chr5q31), DLG5, ATG16L1, and IL23R) was associated with an increased risk of CD complications. Similarly, a group in Spain calculated an individual’s genetic risk score based on significantly associated variants. They found patients with a higher risk score were more likely to develop a complicated course of disease.

Can We Use Genetics To Predict and Assess Response to Therapy?

Yes, but only with the use of immunomodulators. Genetic prediction models for response to anti-TNFs are still under investigation. The widest use of genetics in IBD treatment is thiopurine methyl transferase (TPMT) genotyping and enzyme activity to guide response and to predict adverse effects. A low TPMT enzyme activity shunts 6-MP metabolism towards increased production of 6-thioguanine nucleotides (6-TG), putting patients at increased risk for leukopenia. A recent review identified that the sensitivity of specific TPMT genotypes in determining enzyme activity was 80%. Even the genotyping of the four most common variant alleles within this enzyme does not correlate absolutely with enzyme activity. The use of genotyping is also limited by recent blood transfusions. Although genetic testing of TPMT, prior to the initiation of thiopurine treatment, is a cost-effective, it has limited utility in predicting response to therapy. Studies of a genetic variant that can predict
response to anti-TNFs have yielded inconsistent results. Previous studies have shown positive results when examining variants in TNF-α and TNF-α receptors for their predictive ability to respond to infliximab in CD patients. However, follow-up studies failed to replicate these findings.21-24 Arijs et al. surveyed infliximab-naïve UC patients, examining gene expression patterns using microarray technology, and found that IL23Rα2 expression levels were predictive of responders and nonresponders with 100% sensitivity and 91% specificity.25 Hlavaty et al., genotyped 287 patients with refractory or fistulizing CD for 21 apoptosis-related genes and found that variants in the FasL/Fas system and caspase-9 influenced response to infliximab.26

Although the current genetic approaches are accessible at a near cost-effective level, applying this information directly into clinical practice remains problematic. Several studies have developed prediction models using identified IBD associated genes with several additional biomarkers.17, 27, 28 Yet, such genetic predictors of disease behavior and therapy have limited prognostic ability, limiting their current clinical utility.29

It’s Not Just About Genetics

IBD pathogenesis, like many other complex immune disease phenotypes, is believed to be the result of environmental exposures in genetically susceptible hosts. Not everyone that carries the risk alleles at the established IBD loci will develop disease. The rising incidence of disease in industrialized nations suggests a rather strong environmental component as more people are exposed to a Western-type lifestyle, including diets high in fat and carbohydrates.30 Studies of changes in dietary intake can lead to alterations in the GI microbiota, increasing pathobionts (situational pathogens).31 In genetically susceptible hosts, changes in the microbiome may be the key that triggers aberrant immune pathways and the development of IBD.

CONCLUSION

IBD pathogenesis involves the combination of multiple risk factors, the search for which is overwhelming. In the future, customized genetic assays designed specifically to interrogate the expanding catalogue of IBD relevant genetic variation will be able to inform disease treatment. Genomic profiles, inclusive of pharmacogenomic data and sensitive biomarker analyses, will have a significant influence on IBD treatments, drug monitoring, disease management, and perhaps even disease prevention or elimination. Undoubtedly, the future in personalized IBD medicine will be in tailoring treatment regimens to both our genome and microbiome.


Food Allergies are a serious public health concern now estimated to affect more than 12 million Americans. The cornerstone of food allergy management is avoidance of the identified allergen. Allergen elimination diets can significantly affect quality of life and are not without nutritional risk. Patients must learn how to identify their allergen(s) in our vast food supply and meet their nutritional needs within the context of the elimination diet. The National Institute of Allergy and Infectious Diseases Guidelines for the Diagnosis and Management of Food Allergy in the United States recommend nutrition counseling and close growth monitoring for all children with food allergies. Practitioners should be prepared to provide expert guidance to families to decrease risk of allergen exposure and to ensure nutritional adequacy of the elimination diet.

**INTRODUCTION**

Food allergy (FA) is a serious and potentially life-threatening condition, which appears to be increasing in prevalence.\(^1\)\(^2\) Although more than 170 different foods have been reported as allergens, 8 foods (milk, egg, wheat, soy, peanut, tree nuts, fish and shellfish) are responsible for the vast majority of food allergic reactions in the United States.\(^3\)

FA is defined as, “an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food”.\(^3\) Food allergies can be categorized as immunoglobulin E (IgE) or non-immunoglobulin E mediated. Symptoms of IgE mediated allergy typically present soon after contact with the food (within minutes to several hours) and can affect the skin, gastrointestinal tract, respiratory tract or cardiovascular system. Symptoms may be mild or severe. Symptoms that impact the respiratory tract, cardiovascular system or have multiple organ system involvement are typically more severe and are an important indicator of anaphylaxis. Anaphylaxis is a serious, IgE mediated allergic reaction that is rapid in onset and may cause death.\(^3\)

A smaller representation of food allergies is non-IgE mediated. Non-IgE mediated food allergic disorders tend to affect the skin and gastrointestinal tract and...
are typically delayed in onset. Anaphylaxis is not a feature of non-IgE mediated FA. Food protein-induced enterocolitis syndrome (FPIES) (for more information visit: www.iaffpe.org) and allergic proctocolitis (AP) are non-IgE mediated food allergic disorders while eosinophilic gastrointestinal disorders (EGID) (for more information visit: www.apfed.org) and atopic dermatitis (AD) may be of mixed IgE and non-IgE mediated mechanisms. Dietary treatments may vary slightly from one type of food allergic disorder to another, even when the same allergen is identified.

In 2010, the National Institute of Allergy and Infectious Diseases (NIAID) convened an expert panel to develop guidelines outlining practices for the diagnosis and management of all types of FA. Summaries of these guidelines have been published for pediatricians, dietitians and nurses and are an excellent clinical tool for practitioners.4 (ww.niaid.nih.gov/topics/foodAllergy/clinical/Documents/FAGuidelinesExecSummary.pdf)

Table 1. Food Allergen Labeling Consumer Protection Act (FALCPA)

<table>
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<tr>
<th>“Major” Allergens</th>
<th>Ingredients Not Covered by FALCPA</th>
<th>Products that Must Comply with FALCPA</th>
<th>Products Not Covered by FALCPA</th>
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<tr>
<td>Milk</td>
<td>Other gluten containing grains (e.g., rye, barley)</td>
<td>Food products</td>
<td>Raw agricultural commodities such as meats, fruits and vegetables</td>
</tr>
<tr>
<td>Egg</td>
<td>Mollusks (e.g. clams, mussels, oyster, scallops)</td>
<td>Dietary supplements</td>
<td>Spirits</td>
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<tr>
<td>Wheat</td>
<td>All other potential allergens including sesame</td>
<td>Infant formulas</td>
<td>Medications</td>
</tr>
<tr>
<td>Soy</td>
<td></td>
<td>Medical foods</td>
<td>Cosmetics, soaps, lotions, shampoos, etc.</td>
</tr>
<tr>
<td>Peanut</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tree nuts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fish</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crustacean shellfish</td>
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Is it Allergy?
Research has shown that perceived FA is much higher than what can be confirmed by validated testing methods.5 Food elimination diets are clearly needed for the treatment of a diagnosed FA; however, they are not without consequences. Food elimination diets have been shown to impart financial and nutritional burdens, limit social activity and decrease quality of life.6 Patients suspected of having a FA should be referred to an allergist for appropriate diagnosis and management. (Visit: www.aaaai.org and click on “find an allergist”)

Elimination Diets
The NIAID guidelines suggest all patients with FA receive education and training on how to interpret ingredient lists on food labels.7 The Food Allergen Labeling and Consumer Protection Act (FALCPA), identifies the “major” allergens (See Table 1.) and regulates how they can be listed on package labels in the United States (U.S.). FALCPA mandates clear labeling of major allergens using plain English language. This requires the presence of a major food allergen to be listed on the product label using its common name (e.g., milk) as opposed to a scientific name (casein, whey, lactalbumin). Additionally, a major food allergen must
be fully disclosed even if the ingredient is only a minor ingredient such as in a spice, flavoring, coloring, additive, or if used merely as a processing aid. Major allergens may be listed in the ingredient list or in a “contains” statement immediately below the ingredient list; therefore, patients should be advised to avoid looking only for “contains” statements, as only one of these methods is required. These regulations have simplified food product label reading, as one no longer needs to know all of the scientific terms that may represent “hidden” allergenic ingredients. Consumers should be aware that FALCPA applies only to ingredients derived from the major allergens. An individual with allergy to an ingredient not covered under these laws would still need to call the manufacturer to ascertain if these ingredients were included as part of a vague ingredient term such as “spice” or “natural flavoring” of a product.

Highly refined vegetable oils derived from major food allergens are not considered allergens since highly refined oils have almost complete removal of allergenic protein and have not been shown to pose a risk to human health.8, 9 Although exempt from allergen labeling, the source of all vegetable oils present in foods must be identified according to the U.S. standard food labeling laws. In the U.S., soy oil is almost always highly refined and therefore, safe for patients with soy allergy.10 Peanut oil may be highly refined, but can also be present as a crude oil, which may contain enough peanut protein to cause an allergic reaction.11,12 This presents an allergen-labeling loophole because the ingredient list of a finished food will not tell a consumer the nature of the ingredient or how the ingredient was processed. Therefore, it is not possible to tell from a product label if the peanut oil listed is a highly refined or crude oil. The fact that the label will already say the word “peanut” in the term “peanut oil” means peanut is identified if it contains allergenic protein. Calling the manufacturer may provide more specific information. However, as peanut oil is not frequently used in manufactured products and the labeling of the oil is not sufficient to determine the safety of the ingredient, avoidance of peanut oil is frequently recommended. Tree nut oils and sesame oil are typically not highly refined and should also be avoided by those allergic to tree nuts and sesame.

There are other ingredients derived from major allergens that are unlikely to cause a reaction in allergic individuals, although variability in thresholds makes it difficult to establish guidelines on these ingredients. For instance, soy lecithin has a very low relative allergenicity and is an ingredient that is tolerated by most patients with soy allergy. Soy lecithin however is not exempt from FALCPA and must be fully disclosed on product labels. Corn syrup is a corn ingredient that is typically tolerated by those with corn allergy. Another

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ingredient with very low allergenicity for the patient with fish allergies is kosher gelatin, which is derived from fish. In the U.S., gelatin, derived from fish must be fully disclosed as fish (more specifically, as the fish species) on product labels. While one can have a primary allergy to all gelatin, gelatin derived from fish is not commonly problematic for those who are allergic to fish.\(^\text{13}\)

Another area of nuance is the issue of unintended allergenic ingredients, which may be voluntarily addressed by manufacturers with precautionary statements such as “may contain (allergen)” or “produced in a facility that also produces (allergen).” Because these precautionary statements are voluntary, the absence of a precautionary statement does not necessarily mean there is no risk of allergen cross-contact. Precautionary statements are not only voluntary, but they are also unregulated. There are numerous types of statements with meanings that are often difficult to interpret. In a recent U.S. study, precautionary labels that stated, “Good Manufacturing Processes were used to segregate ingredients in a facility that also processes peanut, tree nuts, milk, shellfish, fish and soy ingredients,” were interpreted to mean that the product was safe. However, milk or egg were detected in some baking mixes with this type of statement that otherwise contained no milk or egg ingredients.\(^\text{14}\)

Consumers should be aware that it is not possible to assess the degree of risk based on the type of precautionary label used. The NIAID Food Allergy Guidelines suggest advising our patients to avoid products that carry a precautionary statement for their allergen.\(^\text{7}\) Regarding products without precautionary labeling, advising the patient to call the manufacturer to discuss cross-contact risk may be prudent depending on the allergen and the patient’s sensitivity. Lastly, the use of terms such as “free from” and “does not contain” in relation to food allergens are not regulated and should not be used to determine the safety of a product. The ingredient list and contains statements should always be read.\(^\text{15}\)

Food Allergens

**Cow’s Milk Protein Allergy**

Cow’s milk protein allergy (CMA) typically begins in infancy. Studies on the natural history of CMA have indicated that the vast majority of children typically develop tolerance in childhood (with the possible exception of children with eosinophilic gastrointestinal disorders and CMA).\(^\text{16}\) The World Allergy Organization Diagnosis and Rationale for Action against Cow’s Milk Allergy (DRACMA), provides international guidance and management tools for practitioners working with patients with CMA.\(^\text{17}\)

**Infancy**

**Breast Feeding**

The breast-fed infant with CMA may benefit from maternal avoidance of milk protein from the diet, since immunologically recognizable proteins from the maternal diet can be found in breast milk.\(^\text{18}\) An exception is the infant with food protein-induced enterocolitis syndrome (FPIES) as it has only been rarely reported that infants with FPIES are symptomatic on an unrestricted maternal diet.\(^\text{19}\) If the infant is asymptomatic on an unrestricted maternal diet, maternal avoidance is not necessary. If the mother is avoiding milk, dietary substitutes for maternal calcium and vitamin D or milk-free supplementation may be warranted. (For more information of calcium and vitamin D visit: http://ods.od.nih.gov/factsheets/VitaminD-QuickFacts/ and http://ods.od.nih.gov/factsheets/Calcium-QuickFacts/)

**Formula Feeding**

Formula-fed infants will require hypoallergenic infant formula. Different food allergic disorders or allergic symptoms may warrant different infant formula recommendations. (See Table 2) Over 90% of infants with IgE mediated CMA tolerate extensively hydrolyzed milk protein-based formulas (e.g., Nutramigen, Alimentum, or Pregestimil) and for those who continue to exhibit symptoms, an amino acid formula (e.g., Elecare or Neocate lines or PurAmino) may be warranted.\(^\text{18}\) Partially hydrolyzed cow’s milk formulas are not considered hypoallergenic and are not a suitable option for infants with cow’s milk allergy.

Soy formula may be an alternative to cow’s milk formula for infants > 6 months of age, although it is not hypoallergenic. For infants > 6 months of age, many (85–90%) with IgE-mediated CMA may tolerate soy formula.\(^\text{17}\) For infants with non-IgE-mediated CMA such as proctocolitis or FPIES, the prevalence of hypersensitivity to both soy and milk is not well understood.

(continued on page 52)
may be greater in the U.S. and hypoallergenic formula is recommended.\textsuperscript{17,19}

**Older Children and Adults**

Numerous studies indicate children with CMA are at increased risk of inadequate nutrient intake and poor growth.\textsuperscript{20-23} Growth in this population should be closely monitored.\textsuperscript{7} Christie et al. showed that the risk of consuming inadequate intakes of calcium and vitamin D among children with CMA was decreased if a safe fortified soymilk or infant/toddler formula was provided, suggesting that children with CMA should continue to include an adequate, nutrient-dense milk substitute in the diet.\textsuperscript{20} Other than fortified soy beverage, alternative fortified beverages (e.g., rice, almond, potato, fruit juice) do not provide sufficient protein and are too low in fat for young toddlers. Protein requirements will need to be met entirely through solid foods in the diet before switching to these beverages. Fat intake will also need to be assessed and additional fat in the form of vegetable oils may be required. Alternative mammalian milks, such as goat or sheep milk, are also not suitable, due to homologous proteins structure and the high risk of cross reactivity.\textsuperscript{17,18} DRACMA guidelines recommend children with CMA remain on a milk substitute (either substitute formula or breast milk) until 2 years of age to meet nutritional needs.\textsuperscript{17}

**Baked Milk**

While strict cow’s milk elimination is often required, approximately 75 percent of patients with CMA may tolerate extensively baked milk ingredients.\textsuperscript{24-26} This is also true of egg allergy.\textsuperscript{27} The introduction of extensively heated milk and egg protein in the diet should only be done after a physician-supervised oral food challenge as those who do not tolerate baked milk or egg may be at risk of a severe reaction. For those who tolerate the baked form, inclusion of these ingredients in the diet can improve nutrient intake, make following the elimination diet much easier and also represents an approach to oral immunomodulation.\textsuperscript{25}

**Table 3. Resources**

<table>
<thead>
<tr>
<th>ORGANIZATION</th>
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<tr>
<td>American Academy of Allergy, Asthma and Immunology (AAAAI)</td>
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<td>American College of Allergy, Asthma and Immunology</td>
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<tr>
<td>Food Allergy Research and Education</td>
<td><a href="http://www.foodallergy.org">www.foodallergy.org</a></td>
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<td>Kids with Food Allergy Foundation</td>
<td><a href="http://www.kidswithfoodallergies.org">www.kidswithfoodallergies.org</a></td>
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<tr>
<td>International Association for Food Protein Enterocolitis</td>
<td><a href="http://www.iaffpe.org">www.iaffpe.org</a></td>
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<tr>
<td>American Partnership for Eosinophilic Disorders</td>
<td><a href="http://www.apfed.org">www.apfed.org</a></td>
</tr>
<tr>
<td>Consortium of Food Allergy Research</td>
<td><a href="http://www.cofargroup.org">www.cofargroup.org</a></td>
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Source: Diagnosis and Rationale for Action Against Cow's Milk Allergy (DRACMA)
There are additional nuances to avoidance of unbaked milk and egg ingredients. For instance, a cake may contain baked milk in the cake and unbaked milk in the frosting. Quiche may be fully baked, but the amount of egg in the product may be greater than the patient can tolerate. A flavored cracker may have a baked milk ingredient or it may have a milk ingredient in the flavoring that is topically applied (sprayed on) after the cracker is baked. It is not always obvious from a product label how an ingredient was processed, hence, additional and specific label reading guidance is required.6

**Wheat Allergy**

Wheat is the most common grain allergy and presents unique nutritional challenges. When wheat is eliminated, nutrient dense alternative grains should be provided to substitute for the nutrients (complex carbohydrates, B vitamins, iron, fiber) normally provided by wheat in the diet. The major allergens in wheat are contained in the gluten fraction (although some wheat allergic patients tolerate other gluten containing grains). In addition to wheat, gluten is found in rye, barley, spelt and their hybridized varieties. There are many gluten-free items now available that are wheat-free and may be safe for those with wheat allergy. Wheat allergy is also different from celiac disease in that patients with wheat allergy are at risk of clinical reactivity to other grains, including the gluten-free grains. So while amaranth, quinoa, millet, buckwheat, corn, sorghum, rice, gluten-free oats, and others may be safe, there is a 20% chance of clinical reactivity.28 When evaluating the patient with wheat allergies, it is helpful to review the gluten-free products the patient uses and tolerates so an individualized list of tolerated grains can be created. Contacting the patient’s allergist prior to recommending grains outside this list is prudent.

**Soy, Egg, Peanut, Tree Nut, Fish and Shell Fish Allergies**

Although these other commonly allergenic foods are all nutrient dense, they typically do not supply a large percentage of daily energy intakes and the nutrients in these foods can be provided by other foods in a diverse diet without difficulty. Allergy to any of these foods with other dietary constraints however, such as a vegetarian diet, a picky eater, a multiple food elimination diet or a diet restricted for religious reasons may present greater challenges to meeting nutrient needs.

**CONCLUSION**

All elimination diets are challenging and families require expert guidance. The Consortium of Food Allergy Research (www.cofargroup.org and click on Food Allergy Education Program link) has developed a validated FA education program with downloadable, free materials.29 These include patient hand-outs on various FA topics such as cooking, nutrition, label reading, eating in restaurants, going to school and camp, avoidance sheets for the major allergens (plus sesame) and many more. See Table 3 for additional resources. The nutritional impact of the elimination diet is dependent on many factors including the food(s) eliminated, the type of food allergic disorder, the length of time the elimination diet is required and other associated nutritional risk factors such as feeding difficulties, poor growth, or the presence of symptoms that may impact food intake. Poor weight gain and even severe malnutrition requiring hospitalization have been reported.30 The NIAID food allergy guidelines recommend nutrition counseling for all children with food allergies.7

**References**

Food Allergies: Dietary Management

A 64-year old gentleman was admitted with two months of intractable nausea and vomiting as well as a thirty pound weight loss following replacement of infected spinal hardware. Prior to admission, he had undergone a two-week hospitalization at an outside facility during which computed tomography scan of the abdomen did not reveal any obvious intra-abdominal pathology to explain his symptoms. Since he was unable to tolerate any oral intake, he was discharged on total parenteral therapy.

The patient’s history included duodenal ulcer, resulting in gastric outlet obstruction requiring a Jaboulay gastroduodenostomy in 1974, and T12 thoracic vertebra fracture with post-traumatic kyphosis and multiple spinal surgeries over the course of several years.

At our facility, the patient underwent several abdominal x-rays, a computed tomography scan of the abdomen with intravenous contrast and esophagastroduodenoscopy, all of which were negative for obstruction or other findings to explain his symptoms. He continued to have significant nausea and vomiting despite normal bowel function and cessation of all opiates. He was unable to tolerate anything by mouth and required nasogastric tube suction to relieve nausea and abdominal discomfort.

Ultimately a small bowel push enteroscopy using a pediatric colonoscope revealed a large pulsatile extrinsic mass with normal overlying mucosa in the third portion of the duodenum (Figure 1). The mass appeared to obstruct the lumen when decompressed, although the scope was able to easily traverse past the lesion. This finding was felt to be consistent with the superior mesenteric artery syndrome. The patient subsequently underwent laparoscopic duodenectomy with gastrojejunostomy. Over the next several weeks his oral intake steadily improved without any persistent nausea or vomiting.

Also termed Wilkie’s syndrome or Cast syndrome, superior mesenteric artery syndrome is a rare disorder characterized by compression of the third part of the duodenum by the aorta and the overlying superior mesenteric artery. 

Superior Mesenteric Artery Syndrome Diagnosed by Small Bowel Push Enteroscopy

by Tilak Shah, Alison Jazwinski, Saurabh Gupta
mesenteric artery. The most frequently reported causes of this disorder are rapid weight loss, spinal surgery and external increases in abdominal pressure. We hypothesize that alteration in aorto-mesenteric angle due to spinal surgery was responsible for this patient’s symptoms. Superior mesenteric artery syndrome is most frequently diagnosed using radiographic techniques (computed tomography and occasionally ultrasound), although endoscopic ultrasound has been described as a diagnostic tool. In this patient, evaluation of the aorto-mesenteric angle on computed tomography scan was limited by hardware artifact thus complicating timely diagnosis (Figure 2). Our report highlights the diagnostic challenge this disorder can pose.

References

A CASE REPORT

Alagille Syndrome and Colonic Polyposis: A True Connection?

by Suneal Agarwal, Leon Kundrotas, Swapna Gupta

Alagille syndrome is a rare autosomal dominant disorder that results in multiple comorbidities. Due to recent advances in medicine, surgery and nutrition, patients with Alagille syndrome are living longer and new pathologies resulting from the underlying JAG2/NOTCH receptor mutation are being discovered. Our current understanding of Alagille Syndrome is chronic cholestasis and an increased risk of developing cirrhosis and hepatocellular carcinoma due to malformation of ductal system during embryonic development. What is new in this report is an expanding discussion of Alagille Syndrome including nutritional management, hepatic complications with review of current literature and a polyposis-like syndrome. This case report describes a 35 year-old patient with Alagille syndrome who initially presented with rectal bleeding and microcytic anemia. Colonoscopy revealed numerous polyps throughout the colon and biopsies of certain lesions revealed colorectal adenocarcinoma. This case report will review the comorbidities commonly associated with this syndrome.

CASE PRESENTATION

A 35 year-old white female with a known history of Alagille syndrome presented with a 3 day history of rectal bleeding. Three episodes of bloody diarrhea were followed by gradually formed stool streaked with blood. She denied abdominal pain, nausea, emesis, weight loss, history of non-steroidal anti-inflammatory (NSAID) use or prior history of rectal bleeding. She reported a history of heavy menses, controlled by oral contraceptives, but denied any other bleeding. There was no family history of colorectal cancer.

The diagnosis of Alagille syndrome was given shortly after birth as she was found to have neonatal jaundice secondary to intrahepatic biliary atresia; this later required biliary diversion. Her patent ductus arteriosus and ventral septal defects were repaired surgically after birth and she underwent pulmonary valvotomy for pulmonic stenosis within her first year of life. Just three months prior to her current presentation she had an ileal resection with ilieocolonic anastomosis for refractory pruritus. She never had a colonoscopy prior to surgery.

Physical examination revealed features of Alagille syndrome, including a “triangular” face, deep-set eyes and narrow palpebral fissures. Cardiovascular examination revealed a 3/6 systolic murmur. She exhibited no tenderness on abdominal exam. Rectal

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exam revealed no hemorrhoids or palpable masses; however gross blood was visualized. Her laboratory results were significant for microcytic anemia with hemoglobin of 8.7 g/dL and a mean corpuscular volume of 55 fl. Her iron studies revealed a total iron of 14 mcg/dl, total iron binding capacity of 458 mcg/dl, transferrin saturation of 3% and ferritin of 6 ng/ml.

An upper endoscopy was unremarkable. Colonoscopy revealed more than 50 polyps throughout the entire colon (Figure 1). There were 3 pedunculated polyps that were actively bleeding (Figure 2); each was biopsied and found to be adenocarcinoma (Figure 3). The patient subsequently underwent a total colectomy; lymph node dissection did not show lymphatic involvement. Hereditary nonpolyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP) genetic testing were performed but found to be negative for the mutations.

DISCUSSION
Alagille syndrome is a rare autosomal dominant genetic disorder with an incidence that has been reported from 1 in 70,000 births to 1 in 100,000 births. The pathophysiology of Alagille syndrome is linked to involvement of the JAG1 and NOTCH2 genes. The JAG1 gene is found on chromosome 20, and 90% of patients with Alagille syndrome display a microdeletion of 20p12 found within the JAG1 gene. Eight percent of patients have the entire deletion of JAG1. The rest are thought to have mutations in NOTCH2. Both JAG1 and NOTCH2 are involved in the NOTCH signaling pathway that leads to cell differentiation during embryonic development.

Alagille syndrome usually has nearly complete penetrance; however, the expression is extremely variable. The diagnosis is usually suspected after birth as patients often present with persistent jaundice. They often also exhibit involvement of organs other than those of the gastrointestinal system, including cardiac, pulmonary, ophthalmologic, neurologic, skeletal and renal.

Among the gastrointestinal abnormalities, the main organs involved, as described in previous literature, have been the liver and pancreas. Pancreatic exocrine deficiency is usually present, although the pathophysiology is not well understood. Hepatic involvement is thought to be linked to ductal malformation and up to 96% of patients present with chronic cholestasis. These patients have high levels of conjugated bilirubin, attributed to lack of development of interlobular bile ducts. Histopathologically, there is evidence of bile duct paucity, with an increased portal tract-to-bile duct ratio. The prevalence of colonic polyps in this syndrome may have been underreported since the clinical manifestations of colonic polyps are silent until anemia develops. Often patients with Alagille syndrome die from other fatal disorders associated with this condition prior to the completion of the adenomatous polyp-to-colon cancer sequence.

There is some debate about surgical and/or medical management of the cholestasis. A recent study suggests that performing surgeries like the Kasai procedure might be associated with inferior outcomes. Often, the hyperbilirubinemia resolves naturally as the liver develops during infancy. Medical management of chronic cholestasis includes ursodeoxycholic acid, which have been used with marginal success, cholestyramine, rifampin and naltrexone. However, the pruritus is often extreme and partial external biliary diversion is unavoidable.

Nutrition is also important when addressing patients with Alagille syndrome. With reduced bile flow into the intestine, there is poor digestion of dietary fat. Essential fats and triglycerides are necessary for proper development; hence infant formulas containing high levels of medium-chain triglycerides are usually substituted for conventional formulas. Because of the poor absorption of fat-soluble vitamins, these patients are often deficient and will need either large oral doses...
Alagille Syndrome and Colonic Polyposis

ConClusion
As further medical, nutritional and surgical advances are made, patients with Alagille Syndrome are living longer lives, and new pathology is being identified. Alagille syndrome is known for its nearly complete penetrance and variable phenotypic expression, allowing for multiple varying organ involvement within the same individual. Our current understanding of Alagille Syndrome with gastroenterology pathology is centered on the increased risk of these patients to develop cirrhosis and hepatocellular carcinoma, owing to malformation of ductal system during embryonic development and chronic cholestasis. This report further adds evidence to the possible association of the underlying condition that afflicts this population, a mutation in the JAG1/NOTCH receptor, with the development of colorectal cancer.

Acknowledgements
We would like to acknowledge Dr. Hashem El-Serag for the preparation of this document.

References
Alagille Syndrome and Colonic Polyposis

A CASE REPORT


We present a new series of cases devoted to Unusual Causes of Abdominal Pain. We will publish these papers as unknowns, with the history of each case printed in the front of the journal and the answer and discussion toward the end.

The case should be well-documented with at least one reference to support the diagnosis. The manuscript must be a concise report submitted as a Word document consisting of no more than 1,000 words. Illustrations and/or photographs are encouraged, to be submitted as .jpg files separate from the Word document. Authors are limited to 2 on each submission. No author photographs are necessary.

All manuscripts should be sent via e-mail to the editor of this new series, George W. Meyer, MD at: geowmeyer@gmail.com

The first article will appear in our January 2014 journal. We look forward to presenting challenging, clinically relevant and informative articles on unusual causes of abdominal pain in the months ahead.
Patients Identified at Lower Risk for Adenocarcinoma on a Histologic Basis

To evaluate whether persistence of nondysplastic Barrett’s esophagus (NDBE) over multiple consecutive surveillance endoscopic evaluations could be used in risk stratification of patients with Barrett’s esophagus (BE), a multi-center outcomes study of a large cohort of patients with BE was carried out. Based on the number of consecutive surveillance endoscopies showing NDBE, five groups of patients were identified. Group One was found to have NDBE at their first EGD. Patients in Group Two were found to have NDBE on their first two consecutive EGDs. Patients in Groups Three, Four, and Five were found to have NDBE on three, four, and five consecutive surveillance EGDs.

A logistic regression model was built to determine whether persistence of NDBE independently protected against development of cancer.

A total of 3515 patients with BE were evaluated; 1401 patients met the inclusion criteria (93.3% white, 87.5% men, median age 60 years). The median follow up period was 5 years. The annual risk of EAC (endoscopic adenocarcinoma) in Groups One to Five was 0.32%, 0.27%, 0.16%, 0.2% and 0.11%, respectively. After adjusting for age, sex, and length of BE, persistence of NDBE, based on multiple surveillance endoscopy was associated at a gradually lower likelihood of progression to EAC.

Persistence of NDBE over several endoscopic examinations identifies patients who are at low risk of development of EAC, supporting lengthening surveillance intervals or discontinuing surveillance of patients with persistent NDBE.


Endoscopic Versus Surgical Treatment for Pancreatic Pseudocysts

Surgery is the standard technique for drainage of pancreatic pseudocysts. A single-center, open-label, randomized trial to compare endoscopic and surgical cystogastrostomy for pancreatic pseudocyst drainage was carried out with 20 patients treated endoscopically and 20 patients treated surgically. The primary endpoint was pseudocyst recurrence after a 24-month follow up period.

Secondary endpoints were treatment success or failure, complications, re-interventions, length of hospital stay, physical and mental health scores, and total cost.

At the end of the follow up period, none of the patients who received endoscopic therapy had a pseudocyst recurrence, compared with one patient treated surgically. There were no differences in treatment successes, complications, or reintervention between the groups. The length of hospital stay was shorter for patients who underwent the endoscopic approach (median 2 days vs. 6 days in the surgical group).

There were no differences in physical component scores and mental health component scores between groups at baseline on the medical outcome study (36 item, short-form general survey questionnaire). Longitudinal analysis showed significantly better physical component and mental health component scores for the endoscopic treatment group. The total mean cost was lower for patients managed by endoscopy than surgery ($7,011 vs. $15,052).

It is concluded that in a randomized trial, comparing endoscopic and surgical cystogastrostomy for pancreatic pseudocyst drainage, none of the patients in the endoscopy group had pseudocyst with recurrence during the follow up period. Therefore, there is no evidence that surgical cystogastrostomy is superior.

Endoscopic treatment was associated with shorter hospital stays, better physical and mental health of the patients and lower cost.


Bloating and Distention and Irritable Bowel Syndrome

Bloating and distention are often attributed to dietary factors by patients with irritable bowel syndrome (IBS). To examine the effects of gas production and visceral hypersensitivity on digestive symptoms after lactose ingestion in a population with lactose deficiency, 277 IBS patients and 64 healthy controls (HCs), underwent a 20-gram lactose hydrogen breath test (LHBT) with evaluation of hydrogen gas production and lactose intolerance (LI) symptoms. Abdominal distention was measured during LHBT. Rectal sensitivity was assessed by barostat studies.

Hydrogen production and distention were similar
in IBS patients and HCs during LHBT. However, LI was more frequent in IBS (53.8% vs. 28.1%), especially bloating (39% vs. 14%) and borborygmi (39% vs. 21.9%). Only 59% of patients with bloating had distention. No correlation was observed between girth increment and bloating. IBS patients had lower rectal sensory thresholds. Multivariate analysis indicated that hydrogen production increased bloating (OR 2.19), and borborygmi (12.37), but not distention. Visceral hypersensitivity was associated with bloating (OR 6.6) and total symptom score (OR 3.78).

Hydrogen production and visceral hypersensitivity both contribute to digestive symptoms, especially bloating and borborygmi in IBS patients after lactose ingestion. Objective abdominal distention is not correlated with subjective bloating.


Postgastrectomy Endoscopic Submucosal Dissection for Early Gastric Cancer

This technically difficult procedure because of limited working space in a remnant stomach post gastrectomy was evaluated, including results and long-term outcomes to determine the feasibility and effectiveness of this procedure utilizing retrospective information. The procedure is difficult because of the presence of severe gastric fibrosis and staples under the suture line. This was carried out at the National Cancer Center Hospital in Tokyo, Japan from 1997 to 2011.

The patient characteristics, endoscopic findings, technical results, adverse events and histopathologic results, including curability and evaluation of H. pylori gastritis in addition to the rates of local recurrence, metachronous gastric cancer, overall survival and cause-specific survival.

A total of 128 consecutive patients with 139 lesions had previously undergone 87 distal (68%), 25 proximal (19.5%), and 16 pylorus-preserving gastrectomies (12.5%). The median period from the original gastrectomy to the subsequent ESD for EGC in the remnant stomach was 5.7 years. The median tumor size was 13 mm and the median procedure time was 60 minutes. There were 131 en bloc resections (94%), with curative resections achieved for 109 lesions (78%), 22 lesions (16%) resulted in noncurative resections and 8 lesions (6%) had only a horizontal margin positive, or had inconclusive results.

A total of 118 patients (92%), were assessed as H. pylori-positive with 7 patients (5%) negative. Adverse events included 2 cases of delayed bleeding (1.4%), and 2 perforations (1.4%), with one patient requiring emergency surgery. The 5-year overall and cause-specific survival rates were 87.3% and 100%, respectively during a median follow up period of 4.5 years, with no deaths from EGC in the remnant stomach.

It was concluded that ESD for EGC in the remnant stomach of patients after gastrectomy was a feasible and effective therapeutic method and should become the standard method in such cases, based on the favorable long-term outcomes.


Diagnosing Pancreatic Carcinoma without CT Evidence of Mass

Diagnosis of pancreatic neoplasm is difficult in patients with inconclusive findings on CT scan and other imaging. To determine the diagnostic accuracy and to determine predictors of pancreatic neoplasm by EUS with FNA in this setting, a retrospective chart review was carried out between January 2002 to December 2010 at a tertiary referral center of 1046 patients who underwent pancreatic EUS. A total of 116 patients were selected because their clinical presentation was suspicious for pancreatic malignancy, but multidetector row CT (MDCT) findings were inconclusive.

With surgical pathology or subsequent clinical course used as the criterion standard, EUS with FNA had a sensitivity, specificity, positive predictive value and accuracy of 87.3%, 98.3%, 98.5%, and 92.1%, respectively in diagnosing a pancreatic neoplasm that was indeterminate on imaging studies. Factors significantly associated with EUS detection of pancreatic ductal adenocarcinoma were total bilirubin level greater than 2 mg/dL, CT findings of pancreatic duct dilation, bile duct stricture, and tumor size 1.5 cm or larger detected by EUS.

Among them, pancreatic duct dilation on CT (continued on page 68)
(continued from page 66)

(OR 4.1), and tumor size 1.5 larger detected by EUS were independent risk factors.

When imaging studies are indeterminate, EUS is a highly sensitive and accurate modality for the detection of pancreatic neoplasm, especially when the tumor is smaller than 2.0 cm.


Narrow Band Imaging Predicting Histology of Distal Diminutive Polyps

To assess whether NBI is able to predict colonoscopic surveillance intervals and histology of distal diminutive polyps according to the ASGE criteria, a prospective, multicenter study at five endoscopy centers was carried out on consecutive patients undergoing colonoscopy. The endoscopists involved were required to pass a before-study, qualifying examination and histology of polyps that were less than 10 mm were predicted at NBI and assigned a designation of high or low confidence.

Accuracy of high-confidence NBI prediction for polyps 5 mm or less and predicting surveillance intervals and negative predictive value (NPV) for adenomatous histology in the rectosigmoid colon were compared with the ASGE thresholds.

A total of 278 patients, mean age 63 years and 58% male were enrolled at colonoscopy. A total of 574 polyps less than 10 mm and 429 of which were 5 mm or less were followed, 60% adenomatous were retrieved for histologic analysis. Sensitivity, specificity, positive and negative predictive values and accuracy of high-confidence NBI predictions for adenomatous histology in lesions 5 mm or less were 90%, 88%, 89%, 89%, and 89%, respectively.

High-confidence characteristic polyps 5 mm or less predicted the correct surveillance intervals in 92 to 90% of cases, according to American and European guidelines. NPV of high confidence NBI for adenomatous histology for the rectosigmoid colon lesions equal to or less than 5 mm was 92%. These findings were limited to experienced endoscopists.

It was concluded that high-confidence prediction of histology for polyps 5 mm or less appears to be sufficiently accurate to avoid post-polypectomy histologic examination of the resected lesions as well, to allow rectosigmoid hyperplastic polyps to be left in place without resection.


Treatment of Diabetic and Idiopathic Gastroparesis

The relationship between symptom improvement (SI) and acceleration of gastric emptying (GE) for different drugs used in the treatment of idiopathic and diabetic gastroparesis is uncertain. The study-specific correlations between SI and GE were examined and a meta-regression analysis of the association of across multiple studies was performed. Medline database from 1946 to present was searched and only control trials or trials with an established effector comparator that completed both SI and GE were included.

Studies were identified for metoclopramide (N = 6), domperidone (N = 6), cisapride (N = 14), erythromycin (N = 3), botulinum toxin (N = 2), and levosulpiride (N = 3). Even though most drugs concomitantly improve symptoms and accelerated GE, no study reported a significant correlation between SI and GE. Moreover, a correlation analysis of all studies using meta-regression did not show a significant relationship between SI and GE.

There were inconsistencies in study methods representing a limitation, but suggested that the findings were robust to methodological factors.

It is concluded that this review identified no evidence of a relationship between SI and GE for different drugs used for the treatment of gastroparesis.


Murray H. Cohen, D.O., “From the Literature” Editor, is on the Editorial Board of Practical Gastroenterology.
COLOWRAP LAUNCHES NOVEL, NON-INVASIVE ABDOMINAL BINDER TO REDUCE LOOPING DURING COLONOSCOPY

Over 320 US Gastroenterologists Have Now Used New Looping Solution

DURHAM, NC – Despite numerous technological advances over recent decades, looping of the colon remains an all-too-frequent complication of colonoscopy. ColoWrap aims to change that. At the American College of Gastroenterology conference, held Oct. 11-16, 2013, in San Diego, the Company launched its new ColoWrap Colonoscopy Binder. And as of November 11, ColoWraps have reached the hands of over 320 US gastroenterologists.

ColoWraps are innovative, new, single-use abdominal binders that help prevent looping during colonoscopy. The simple, non-invasive ColoWraps provide firm, consistent pressure to the patient’s lower abdomen, allowing the scope to pass easily through the loop-prone sigmoid colon. Use of a ColoWrap has been shown to reduce insertion time and essentially eliminate the need for manual compression and patient re-positioning, two commonly employed measures for correcting looping. This translates into a colonoscopy that is safer, easier, and more comfortable for patients and healthcare providers alike.

The device’s patent-pending design was developed with guidance from Dr. Marybeth Spanarkel, a gastroenterologist with over 25 years of experience. “The response we’ve been getting from physicians, nurses, and even patients has been very positive,” said James Hathorn, ColoWrap CEO and Co-Founder. “Looping during colonoscopy is a real problem, and based on the feedback we’ve received, our customers have found ColoWrap to be an intuitive, effective solution.”

The ColoWrap launch comes on the heels of a successful 176-patient pilot study, in which the use of the ColoWrap was associated with:

- 28.3% reduction in mean insertion time (3.8 vs. 5.3min, p < 0.001)
- 89.7% reduction in need for manual abdominal compression (7% vs. 68%, p < 0.001)
- 93.5% reduction in need for patient re-positioning (2% vs. 31%, p <0.01).

The Company plans to conduct further research, including a 300-patient study at the University of North Carolina, Chapel Hill, beginning late this fall.

About ColoWrap, LLC
ColoWrap is committed to reducing the incidence and impact of colorectal cancer by improving the experience of colonoscopy for patients and healthcare providers. Based in Durham, NC, the Company’s namesake product, the ColoWrap Colonoscopy Binder is an innovative, non-invasive, single-use abdominal binder that helps preventing looping during colonoscopy.

For more information, please visit: www.colowrap.com or call 919-451-1803

Study Shows WATS3D Biopsy Increases Detection of Pre-Cancer in the Esophagus by 50% in Post-Ablation Patients
Data Underscores Value of Using WATS3D as a Surveillance Tool for Residual or Recurrent Pre-Cancer

SAN DIEGO, CA – CDx Diagnostics announced today that a new study adds to the growing body of evidence supporting the use of Wide Area Transepithelial Sampling with 3-Dimensional analysis (WATS3D) as a surveillance tool in patients who have received ablation therapy for Barrett’s esophagus. Researchers from Temple University School of Medicine presented the new data at the American College of Gastroenterology Annual Scientific Meeting and Postgraduate Course, taking place from October 11-16, 2013 in San Diego.

The WATS3D biopsy collects a wide area, disaggregated tissue specimen of the entire thickness of the epithelium being tested. This unique tissue specimen is then subjected to specialized, computer-assisted 3-dimensional analysis to identify potentially (continued on page 72)
abnormal cells for presentation to a specially trained GI pathologist.

The study (Abstract number P23) “Wide Area Transepithelial Sampling (WATS3D) Improves Detection Of Residual Or Recurrent Intestinal Metaplasia Within The Tubular Esophagus And Squamocolumnar Junction” found that use of WATS3D, in combination with forceps biopsies, increased the detection rate of precancerous tissue by 50%. The authors concluded that WATS3D provides critically important information that improves the management of patients who already underwent therapy to eradicate previously diagnosed Barrett’s esophagus. This precancerous condition results from prolonged damage to the esophagus related to reflux of stomach contents.

“In addition to reinforcing previous findings demonstrating the value of using WATS3D as a surveillance tool in patients who have received ablation therapy, this study also provides new information about its utility to detect metaplasia in the tubular esophagus,” said Michael S. Smith, M.D., M.B.A., Medical Director of the Esophageal Program and Assistant Professor of Medicine at Temple University School of Medicine. “Research to date has shown that, following ablation of Barrett’s esophagus, most residual or recurrent pre-cancerous cells are found at the squamocolumnar junction, where the bottom of the esophagus and the stomach come together. WATS3D not only increased detection of the precancerous cells at this location, but also found them higher in the esophagus where there is a lot of tissue not sampled by conventional forceps biopsies. The ability to better detect these abnormal cells before they have a chance to progress to cancer will help us to improve the care we provide to our Barrett’s patients.”

In the study, 33 patients with visually eradicated long-segment Barrett’s esophagus underwent surveillance endoscopy. Residual or recurrent intestinal metaplasia was detected on either forceps biopsy or WATS3D in 12 cases (36.4%). In 6 of these cases, the intestinal metaplasia only was found using WATS3D and not with forceps biopsies. While in 5 cases the intestinal metaplasia was found at the squamocolumnar junction, in 1 case the intestinal metaplasia was present at least 3 cm proximal to the top of the stomach. In a seventh case, both WATS3D and forceps biopsies identified intestinal metaplasia. However, forceps biopsies found only non-dysplastic metaplasia while WATS3D showed high grade dysplasia, only one step from cancer.

About Barrett’s Esophagus and Esophageal Cancer
Many cases of esophageal adenocarcinoma (EA) are preceded by chronic heartburn. Some heartburn patients develop altered cell patches in their esophagus. A condition known as dysplasia occurs as Barrett’s esophagus progresses to Barrett’s-associated cancer. Dysplasia is considered a precancerous condition and should be monitored very closely to ensure the cells do not become cancerous. Dysplastic cells are very similar to cancer cells but have not yet acquired the ability to invade into tissue or metastasize. Esophageal cancer is now the fastest growing form of cancer in the U.S.

About CDx Diagnostics and the WATS3D Biopsy
CDx Diagnostics’ mission is to provide doctors with the most powerful diagnostic technology to help prevent cancer before it can start.

CDx Diagnostics’ WATS3D biopsy addresses the sampling error inherent in random forceps biopsy testing of the esophagus. In just a few minutes, gastroenterologists can easily obtain a wide area, full-thickness transepithelial tissue sample for computer-assisted 3D laboratory analysis. In clinical trials, adjunctive use of CDx Diagnostics’ WATS3D biopsy significantly increased the detection rate of both Barrett’s esophagus and esophageal dysplasia. The high sensitivity of WATS3D is due to the large tissue area sampled, and the proprietary 3-Dimensionial computer imaging system that is based on an algorithm developed as part of the U.S. Strategic Defense Initiative missile defense program.

To learn more about WATS3D, visit: www.cdxdiagnostics.com

(continued on page 74)
BroadcastMed Network Expands Digital Library Featuring Leading Physicians and Medical Centers

FARMINGTON, CT – BroadcastMed, Inc. announced expansion of the BroadcastMed Network’s extensive digital library. The library offers open access to medical procedures and advances from world-renowned physicians and healthcare organizations. The BroadcastMed Network receives more than 2 million visits annually and since the October 1 launch of its specialty-specific syndication channels, traffic has increased 48%.

Available by visiting broadcastmed.com, the digital library of content consists of ORLive.com, 17 specialty-specific syndication channels including cardiology, gastroenterology, oncology and orthopedics and more than 40 affiliate channels. Affiliate channels include content curated by organizations like UPMC, Brigham and Women’s Hospital, St. David’s HealthCare, The University of Alabama at Birmingham (UAB) Health System, University of Maryland Medical Center, Wake Forest Baptist Health, Medtronic, Stryker, Covidien, and Depuy Orthopedics.

“We are working with top-tier experts every day to expand knowledge and provide access to a range of trusted educational content, from minimally invasive surgeries and new technology applications to live events and continuing medical education,” said Peter Gailey, President and Co-Founder, BroadcastMed. “What sets the BroadcastMed Network apart is its streamlined access to a curated library of content that doctors and healthcare professionals can use to positively impact the health and well-being of patients everywhere.”

Featured this Month on the BroadcastMed Network:
Endoscopic Management of Upper GI Bleeding, Dr. David Carr-Locke, Continuum Health Partners this presentation, available for CME credit, will review the current state of assessment and treatment of upper gastrointestinal bleeding with a focus on endoscopic techniques. More information is available by visiting the Continuum site.

Key features of the BroadcastMed Network include open access to an extensive library of procedures, technologies and insights as well as optimized search functionality and social media sharing tools. All videos on BroadcastMed Network specialty channels feature synchronized closed captioning allowing for laser-focused, convenient search.
For additional information about products and services that appear in *Practical Gastroenterology*, check the appropriate boxes on this coupon, fill in your name and address and send it to:

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Although every effort has been made to ensure the accuracy of this index, we cannot absolutely guarantee against the eventuality of last minute changes or omissions.

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*Please place one letter or numeral in each box provided.*
MEETINGS CALENDAR

December 12-14, 2013 Advances in Inflammatory Bowel Diseases, Crohn’s & Colitis Foundation’s Clinical & Research Conference
Westin Diplomat Resort & Convention Center, Hollywood, FL – Advances in IBD is the premier conference for healthcare professionals and researchers who study and manage patients with inflammatory bowel diseases. Endorsed by the ACG, AGA, and NASPGHAN, this three-day conference offers exciting workshops and a two-track format designed for clinicians, researchers, allied health professionals, nurses, and pediatric gastroenterologists. Located beachside at the Westin Diplomat in Hollywood, Florida, this is the educational get-away worth attending. For more information visit: http://advancesinibd.com
For registration inquiries: Tel.: 855-276-6855
Email: registration@imedex.com

Program Approved for AMA PRA Category 1 Credit(s)™
New York Marriott Marquis Hotel, New York, NY
Preliminary Topics Include:
• Impact of the Affordable Care Act on Endoscopic Practice
• Controversies in Endoscopic Treatment of Nondysplastic Barrett’s Esophagus
• Pancreatic Cystic Lesions
• Real Time Histology
• Endoscopic Ultrasound of Submucosal Lesions
• Avoiding and Managing Endoscopic Complications
• Advanced Endoscopic Imaging
• EMR and ESD of Colonic Lesions
Visit: www.NYSGE.org or Contact us at: info@nysge.org

May 17-21, 2014 ASCRS 2014 Annual Scientific Meeting
Westin Diplomat Resort & Convention Center, Hollywood, FL – The American Society of Colon & Rectal Surgeons is the premier society for colon and rectal surgeons and other surgeons dedicated to advancing the science and treatment of diseases and disorders affecting the colon, rectum and anus. More than 1,000 of the Society’s 3,000 physician members are certified by the American Board of Colon and Rectal Surgery. The ASCRS Annual Scientific Meeting is the leading event in the field of colon and rectal surgery and more than 1,700 colorectal specialists are expected to attend. The meeting will include oral and poster presentations, expert panels, symposia, meet the professor breakfasts and many other sessions encouraging audience participation. For more information, visit: www.fascrs.org/annual_meeting
PRACTICAL GASTROENTEROLOGY CROSSWORD PUZZLE

by Myles Mellor

DOWN
1. Drug used to treat Crohn’s disease
2. Red dye used as a stain
3. Hard outer layer
4. Toxic metal
5. ___ peptide
6. Drain of energy
7. Situated in the rump area
10. Room, abbr.
11. Type of address on the net
14. Stomach muscles, in slang
15. Benign growth
16. Make a sharp explosive noise
17. Condition of abatement of a disease
19. Alternative therapy for gastrointestinal disorders
20. Two of a kind
22. Virus that can cause cancer
23. It’s used to cool
24. Fasten
25. Nurse, abbr.
27. “All systems go” (2 words)
29. Light brown
30. Takes in
32. Letters on a pencil
33. Blood vessels
35. In trials this natural treatment has been found to be effective in treating ulcerative colitis (2 words)
38. Hassle
39. Nasonex and prednisone, for example
40. Procedure
41. Stains
42. Respectful title

ACROSS
1. It plays a critical role in the diagnosis and treatment of IBD
2. Abnormal passage leading from a suppurating cavity to the body surface
3. Series of X-rays (2 words)
4. Blueprint
5. ___ peptide
6. Drain of energy
7. Situated in the rump area
8. Room, abbr.
9. Type of address on the net
10. Stomach muscles, in slang
11. Condition of abatement of a disease
12. Alternative therapy for gastrointestinal disorders
13. Two of a kind
14. Virus that can cause cancer
15. It’s used to cool
16. Fasten
17. Nurse, abbr.
18. “All systems go” (2 words)
19. Light brown
20. Takes in
21. Letters on a pencil
22. Blood vessels
23. In trials this natural treatment has been found to be effective in treating ulcerative colitis (2 words)
24. Respectful title
25. Two of a kind
26. Alternative therapy for gastrointestinal disorders

(Answers on page 62)