INFLAMMATORY BOWEL DISEASE:
A PRACTICAL APPROACH, SERIES #79
CLOSTRIDIUM DIFFICILE INFECTION IN
PATIENTS WITH INFLAMMATORY BOWEL DISEASE
by N.M. Joshi, D.S. Rampton

PRACTICAL APPROACHES TO THE DIAGNOSIS
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Clostridium Difficult Infection in Patients with Inflammatory Bowel Disease
by N.M. Joshi, D.S. Rampton

Patients with inflammatory bowel disease (IBD) are at higher risk of developing Clostridium difficile infection (CDI) than are those without; patients with both IBD and CDI also appear to have poorer outcomes than those with CDI alone. Here we discuss testing and treatment of CDI complicating IBD.

Colonic Polyps: The Harm of Overdiagnosis
by James Allison, Gerrit A. Meijer

The primary care physician and lay people have been led to believe that any polyp is a threat and that advanced polyps (adenomas) are particularly worrisome. Inquisitive clinicians and policy makers are wondering if polyps, even the advanced ones, are “sheep in wolves’ clothing.” Could they be a form of “over diagnosis” thus labeling innocuous tumors as cancer and treating them as though they could be lethal when in fact most are not dangerous? In this article we address these questions.
Dermatitis Herpetiformis: What Practitioners Need to Know
by Freda C. Sansaricq, Vesna Petronic-Rosic

Dermatitis herpetiformis (DH) is an autoimmune blistering disorder with a multifactorial etiology associated with a gluten-sensitive enteropathy. With current medical management and lifestyle adjustments, treatment can be highly successful. This review highlights distinguishing clinical symptoms and serves to aid the reader in the diagnosis and treatment of DH.

Evaluation and Management of Cirrhotic Ascites
by Sohaib Hassan, Mazen Albeldawi, William Carey

The development of ascites is a major event in the natural history of cirrhosis and is associated with a significant deterioration in prognosis. Although cirrhosis accounts for approximately 75% of patients with ascites, other causes should be kept in mind. In this review we discuss key analysis, evaluation and management of ascites.

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Patients with inflammatory bowel disease (IBD) are at higher risk of developing Clostridium difficile infection (CDI) than are those without; patients with both IBD and CDI also appear to have poorer outcomes than those with CDI alone. Stool tests for CDI should be requested in all IBD patients presenting in diarrhoeal relapse. Treatment of CDI complicating IBD should be the same as in patients without IBD, but it is not yet clear whether concurrent corticosteroids and/or immunomodulators should be withheld.

CLOSTRIDIUM DIFFICILE – BACKGROUND

*Clostridium difficile* (*C. difficile*) is a Gram-positive anaerobic spore-forming bacillus which was first described as a human pathogen in 1978.1 *C. difficile* is found in the colonic flora in up to 4% of healthy adults.2 *C. difficile* produces two main toxins (A and B), which are both potent entero- and cytotoxins. Patients can be said to have CDI only when they have diarrhea and have had a confirmatory stool investigation. The latter is now commonly a 2-step process. The first step has a high negative predictive value and should either be a glutamate dehydrogenase detection assay or a polymerase chain reaction for the presence of *C. difficile* organisms: if samples test positive by either of these methods, the second step is a sensitive ELISA to detect toxin.3,4

CDI rates rose sharply in the early 2000s with several well-documented outbreaks in North America5 and in Europe.6 Despite more vigilant infection control practices and greater clinical awareness, rates of CDI in the USA continue to rise.7 CDI remains a hugely important healthcare issue in that hospitalized patients with CDI are nearly 3 times more likely to die during their admission than other inpatients.8

The most common risk factor for CDI is concurrent or recent antibiotic use, with risk persisting for up to 3 months after antibiotic use.9 Other predisposing factors include increasing age, and, for inpatients, prolonged length of hospitalization prior to acquisition, co-morbidities such as renal failure, use of proton pump inhibitors, chemotherapy and enteral feeds.10,11 In the last 20 years, it has become clear that IBD is a major
risk factor for CDI, and the aim of this paper is to review the incidence, presentation, diagnosis, treatment and outcome of CDI in patients with pre-existing ulcerative colitis (UC) or Crohn’s disease.

**INCIDENCE OF CDI IN PATIENTS WITH IBD**

**CDI in Patients with Active IBD**

Over a range of single center studies analyzed for a recent systematic review, the incidence of CDI in adults presenting with relapse of their IBD was about 7-9%, reported rates varying between 2.5 and 15%, with no overt difference between UC and Crohn’s disease. In contrast, in four studies which used diagnostic coding in hospitalized patients in the US, the co-incident rate of CDI and UC was about 3%, and of CDI and Crohn’s 1%, both higher than in the control populations (0.5%). In two studies of children with active IBD, CDI was more common, with an incidence of 16 and 36%, respectively. This may be because feco-oral ingestion of spores is more common in children than in adults, or because children are more likely to have colonic Crohn’s disease and to have extensive UC (see below).

**CDI in patients with inactive IBD**

A prospective study of outpatients with inactive IBD who were not taking any immunosuppressants showed a carriage rate of *C. difficile* of 8% compared to 1% in healthy controls; furthermore, in IBD, the strains of *C. difficile* found in stool were those not normally associated with nosocomial infection. In a six-month follow up period, none of these patients developed CDI.

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**Figure 1.** Suggested management algorithm for CDI in IBD patients. Treatment failure is defined as persistence of diarrhea for 7 days or clinical deterioration.

**Table 1.** Clinical and laboratory features of CDI in IBD patients.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>&gt;3 loose stools/day</td>
</tr>
<tr>
<td>Fever</td>
<td>&gt;38°C</td>
</tr>
<tr>
<td>Abnormal WBC</td>
<td>&gt;12,000/μL</td>
</tr>
<tr>
<td>Abnormal Albumin</td>
<td>&lt;3.5 g/dL</td>
</tr>
<tr>
<td>Urea enzymuria</td>
<td>Urea &gt;20 mg/dL</td>
</tr>
</tbody>
</table>

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**Figure 2.** Comparison of CDI incidence in IBD patients with and without immunosuppression.

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**Figure 3.** Flowchart of CDI diagnosis and treatment in IBD patients.
This may explain the observation that most patients with IBD contract their CDI from multiple community sources rather than nosocomially.\textsuperscript{12}

**Is the Incidence of CDI in IBD Increasing?**

Although single center studies show no temporal trend over the years 1980–2010 in the incidence for CDI in IBD patients,\textsuperscript{12} data from multicenter studies using either diagnostic coding\textsuperscript{13-16} or stool toxin to confirm infection\textsuperscript{20, 21} all suggest a steady increase in incidence of this infection in the last 10 years.

**RISK FACTORS FOR CDI IN PATIENTS WITH IBD**

**Age and Co-morbidity**

In adults with IBD, as in the general population, increasing age and co-morbidity increase the risk of acquisition of CDI.\textsuperscript{15} However, the average age of cohorts of patients with concurrent CDI and IBD is much lower than in the general population, suggesting that patients with IBD have different risk profiles.

**Medication**

Although antibiotic use remains its major single risk factor, only half of IBD patients who contract CDI have had prior antibiotic exposure\textsuperscript{12}. This further highlights the different risk profiles for CDI in IBD patients.

Immunomodulators are increasingly prescribed to treat IBD and one retrospective series found that the use of immunosuppression (including corticosteroids, thiopurines and methotrexate) in IBD doubled the chance of developing CDI.\textsuperscript{20} In contrast, another study found that while steroids increased the risk of CDI 3-fold, infliximab and immunomodulators had no detectable effect.\textsuperscript{22}

**Location of IBD**

Perhaps unsurprisingly, patients with UC and colonic Crohn’s are at higher risk of CDI than patients with isolated small bowel Crohn’s disease.\textsuperscript{16, 20, 23} Furthermore, patients with extensive UC are at greater risk than those with distal disease.\textsuperscript{20} Rare cases of CDI enteritis\textsuperscript{24} and pouchitis\textsuperscript{25} have also been reported in patients who have had colectomies for ulcerative colitis.

**Presentation**

CDI in IBD presents in the same way as in the non-IBD population, with diarrhea, pyrexia and raised inflammatory markers, all features shared with active IBD alone. The diarrhea associated with CDI is not normally bloody but this is not a reliable diagnostic feature. In hospitalized patients being treated for a relapse of their IBD, a sudden worsening of symptoms or fever, or a rise in C-reactive protein or white cell count should raise suspicion of incident CDI.

**Diagnosis of CDI in IBD**

As in the non-IBD population, this is done by requesting microbiological stool investigations (see above) and only diarrheal stool should be tested.

Most patients with CDI complicating IBD do not develop pseudomembranes,\textsuperscript{26} making flexible sigmoidoscopy an unreliable way of diagnosing CDI in this setting, although it can of course be useful in assessing the activity of the associated IBD.

**Management of CDI in IBD (Figure 1.)**

There is no IBD-specific trial data to guide management of CDI in patients with IBD. At present, the principles of antibiotic usage are similar to those for patients without IBD,\textsuperscript{27} the options being oral or intravenous metronidazole and oral vancomycin. A new agent, fidaxomicin, has been licensed by the FDA for use in CDI but the relevant phase III trial excluded patients with IBD.\textsuperscript{28} There is no evidence on which to base decisions about treatment of patients with IBD with apparently refractory CDI or with recurrent CDI.

However, in patients still unwell after several days of treatment of their CDI with an appropriate antibiotic regimen, consideration should be given to flexible sigmoidoscopy and biopsy, in case their non-response is due to a flare of their IBD rather than persisting CDI. Cytomegalovirus (CMV) infection should also be sought and excluded by serology, plasma CMV quantification and biopsy in this situation.

What to do about concurrent immunosuppression is also uncertain at present.\textsuperscript{29} A retrospective series reported a worse outcome when CDI complicating IBD was treated with a combination of antibiotics and immunosuppressants rather than with antibiotics alone,\textsuperscript{30} but prospective data is lacking. Nevertheless, it is probably sensible to withhold immunosuppressants temporarily in patients seriously ill at presentation, and to avoid initiating them or increasing their dose until CDI treatment has been completed. Patients on anti-TNF agents should have their next dose delayed until CDI has been cleared. This advice, however, may, after

(continued on page 23)
Further investigation (see above), need reversing in patients with persisting symptoms, despite apparently appropriate antibiotic therapy, which are considered to be due to active underlying IBD.

Response to Treatment

In patients without IBD, overall failure rates for metronidazole and vancomycin are 26% and 6% respectively, while use of fidaxomycin is associated with fewer recurrences than occur with vancomycin 125mg QID. There is no data for the failure rates of these agents in patients with IBD. A database study reports that, as in the non-IBD population, low serum albumin and a rise in serum creatinine are predictors of a bad prognosis of CDI in IBD.

Outcome of CDI in IBD

Several studies report poor outcome of CDI in IBD, with reported colectomy rates during the acute phase of up to 20%. Furthermore, patients with CDI complicating their UC seem to have a worse prognosis for surgery during the succeeding year, with about 40% needing colectomy compared with 4-25% of patients with UC alone. Length of stay (up to 28 days longer than in controls with IBD alone) and mortality (up to 14% compared with 2.5% in controls) are also increased in patients hospitalized with both CDI and IBD according to large diagnostic coding-based studies. It is worth emphasizing that much of this data relates to hospital admissions in the early 2000s, when the association between CDI and IBD was less well recognized and may have been less well managed than it should be now.

Prevention of CDI in IBD

As in all patients with CDI, isolating infected patients to prevent spread, and washing hands with soap and water are essential. Particular care should be taken in prescribing antibiotics to patients with IBD. Empirical use of broad-spectrum antibiotics should be avoided and, when antibiotics are deemed essential, the clinical purpose should be clearly defined.

CONCLUSION

CDI in IBD patients is an increasing concern in relation to both its incidence and outcome. C. difficile should be sought whenever an IBD patient presents with diarrhea. Flexible sigmoidoscopy in IBD and CDI rarely shows pseudomembranes and should not be relied on to diagnose CDI.

In the absence of IBD-specific clinical trials to date, treatment of CDI in IBD should be as for the non-IBD population. In patients initially presenting seriously ill, withholding of concurrent immunosuppression may be advisable. More prospective studies are required to understand the implications of CDI in IBD and to optimize its management.

References

Colonic Polyps: The Harm of Overdiagnosis

In the United States, a lot of anxiety has been generated by the media and gastroenterology thought leaders over colonic polyps. Lay people and the primary care physician have been led to believe that any polyp is a threat and that advanced polyps (adenomas) are particularly worrisome. They accept the concern that missing any advanced adenoma by screening tests other than colonoscopy is not worth the risk, but is this concern justified? What are “advanced adenomas” and how likely are they to lead to death from colorectal cancer? Is finding an advanced adenoma important enough to justify population screening with colonoscopy? Some inquisitive clinicians and policy makers are wondering if polyps, even the advanced ones, are “sheep in wolves’ clothing.” Could they be a form of “overdiagnosis” thus labeling innocuous tumors as cancer and treating them as though they could be lethal when in fact most are not dangerous? The article below addresses these and other questions.

INTRODUCTION

In 2000, two articles published in The New England Journal of Medicine demonstrated the usefulness of optical colonoscopy as a screening test for colorectal cancer (CRC). Shortly thereafter, in the United States, several endoscopic societies and gastroenterology thought leaders proclaimed colonoscopy to be the best/preferred screening test and the media was quick to follow. Colonoscopy proponents have claimed that if patients are screened with a test other than colonoscopy, 25-65% of advanced neoplasms could be missed, depending on the other screening modality chosen.

The certainty of the recommendations from experts and the worry that advanced neoplasms would be missed have led to health policy decisions that have had important consequences in the U.S. Until 2001 all CRC screening tests recommended for Medicare coverage by the Centers for Medicaid and Medicare Services (CMS) were extensively evaluated to be sure they were appropriate and effective for Medicare beneficiaries aged 50 years or older. In 2001, CMS evaluation was bypassed and Medicare coverage of colonoscopy was mandated by Congress.

Since 2000, many gastroenterologists and their professional societies have promoted only one screening test as best, colonoscopy. A recent review of colorectal cancer screening by primary care physicians shows how effectively the message has been communicated. (continued on page 31)
Colonoscopy is now the most frequently recommended test and most physicians do not recommend the full menu of test options prescribed in national guidelines. This has led to the following consequences:

1. The number of people undergoing screening colonoscopy has greatly increased and doctors are struggling to keep up with demand.\(^\text{10}\)

2. Some commercial insurance plans are spending more every year on colonoscopies than on cardiac bypass, hip and knee surgeries combined.\(^\text{11}\)

3. Although screening rates for CRC have increased modestly since 2001, they continue to lag well behind those for other cancers.\(^\text{12}\)

4. There has been a significant decline in the use of other effective screening tests particularly in the uninsured, underinsured and underserved population.\(^\text{13}\) Figures 1., 2.

5. Some gastroenterologists are spending up to 50% of their practice time simply performing colonoscopy.

Most advanced neoplasms are advanced adenomas and only a few are cancers. Lay people and primary care physicians accept the concern that missing any advanced neoplasm by screening tests other than colonoscopy is not worth the risk, but is this concern justified? What are advanced adenomas and how likely are they to lead to death from colorectal cancer? Is finding an advanced adenoma important enough to justify population screening with colonoscopy? Do colonoscopies find all advanced neoplasms?

Some clinicians and policy makers are wondering if polyps, even the advanced ones, are “sheep in wolves’ clothing.” Could they be a form of “over diagnosis” thus labeling innocuous tumors as cancer and treating them as though they could be lethal when in fact most are not dangerous?\(^\text{14}\) Barnett Kramer, M.D., Associate Director for disease prevention at the National Institute of Health (NIH), has declared over diagnosis pure unadulterated harm.\(^\text{15}\) Advanced neoplasia may be considered a convenient proxy for colorectal cancer, but its use as an outcome measure may be misleading in screening studies because the natural history of this lesion has not been fully established.\(^\text{16}\)

In the paragraphs and illustrations below, the terms advanced neoplasm, advanced adenoma, polyp, adenoma, villous adenoma, tubulovillous adenoma, adenoma with dysplasia and serrated adenoma will be carefully defined and what is known about their risk for death from colorectal cancer discussed.

Colorectal Cancer Development: The Adenoma-Carcinoma Sequence

The relation between colorectal adenomas/polyps and colorectal cancer is less straightforward than often stated. Colorectal cancer arises in epithelial cells lining the interior of the large intestine. During the process of neoplasia, these cells gradually acquire cancer cell characteristics but, in most cases, this process never passes the precursor adenoma stage.

The concept of the polyp-cancer or adenoma-carcinoma sequence was first described by Morson and coworkers in 1975.\(^\text{17}\) However, hardly any longitudinal data about the actual progression risk of individual lesions exist. Nevertheless, the literature is full of firm statements that the adenoma-carcinoma sequence takes 10-20 years and that the risk of progression is determined by increasing size, villous histology and grade of dysplasia.

It is important to understand that this gap in the formal evidence available will not change because the optimal study for this purpose – i.e. leaving adenomas in situ and sampling them regularly for phenotypic
and molecular features until they become malignant, is unethical. Once adenomas are detected, they are completely removed so that no neoplastic cells are left. As a consequence, only indirect data exist on the average duration of the adenoma-carcinoma sequence, and on the risk of progression of different adenoma phenotypes (e.g. size, histological type, polypoid, flat or serrated appearance).

Adenomas of the colon are quite common, occurring in 30 percent or more of individuals over 60 years of age and, with new high-resolution endoscopes, increasingly more small lesions are detected. It is essential for the clinician to understand that the majority of adenomas ‘never’ progress to cancer, i.e. certainly not within time frames covered by current annual FIT based screening programs. It has been estimated that only five percent of all adenomas actually progress to malignancy.18

Polyps
A colonic polyp is a term describing the gross appearance of a circumscribed lesion (tumor) that protrudes into the lumen of the colon. They are either pedunculated, consisting of a head and a stalk, or sessile, consisting of lesions without a clear stalk but still protruding into the lumen.

The term polyp does not provide any information about the pathological nature of the lesion, be it benign or malignant, epithelial or non-epithelial. Clinically, the most important issue is to identify those polyps most likely to progress to cancer and, in the GI literature, they are the ones designated as advanced adenomas. Advanced adenomas are defined as polyps 1 cm or greater or those with villous features or high-grade dysplasia. Evidence that this category of adenomas is the optimal target for screening is limited.19 The term “advanced adenoma” was introduced to increase statistical power in screening studies, and the risk of dying from colorectal cancer conferred by these lesions is much less than when actual cancer is present. Advanced neoplasms, as used in the clinical gastroenterology literature, are not late stage cancers. They are the term used to describe both advanced adenomas and all stages of cancers.

Adenomas
Adenomas (Figure 3) are benign neoplastic polyps derived from the colorectal epithelium. They show certain phenotypical characteristics, like increased proliferation, nuclear atypia and disturbed glandular architecture. By definition, adenomas do not show...
invasion in surrounding tissue and cannot metastasize. Adenomas can, in a minority of cases, progress to carcinomas hence they are called pre-malignant.

**Histological Type of Adenomas (Figure 4)**

Adenomas are classified by their histological type. Adenomas that have crypts going down from the surface into the stroma of the polyp are called tubular adenomas. Other adenomas on the two-dimensional image under the microscope show leaf- or finger-like processes. These processes are called villi and these adenomas are called villous adenomas. Adenomas with a combination of both histological types are called tubulovillous.

**Adenomas Show Dysplasia (Figure 5)**

Dysplasia is the intermediate stage between normal and cancer and, in the colon, the most common form of dysplasia is an adenoma. Dysplasia is benign because there is not yet invasive growth. The morphologic changes of the neoplastic epithelium in adenomas affect the nuclei, cytoplasm and architecture of the crypts or glands (Figure 5). Nuclei first get elongated, enlarged, slightly hyperchromatic and crowded with some nuclear stratification, and crypts start branching. Further down the spectrum, a combination of features gives rise to an increased nuclear to cytoplasmic ratio. Changes in crypt architecture get more conspicuous and an increased number of mitoses can be found at all levels in the crypt. These changes are classified as low grade or high grade. Histopathologic grading in general is subjective and there are limitations to reproducibility.

**Malignant Polyps (Figure 6)**

Malignant polyp designates an adenomatous polyp with a focus of invasive carcinoma. A polyp consisting entirely of carcinoma, however, is called a polypoid carcinoma.

**Serrated Lesions Including Hyperplastic Polyps (Figure 7)**

In the recent polyp literature much attention has focused on serrated lesions of the large intestine. These are a heterogeneous group of lesions that share a phenotypic characteristic. The epithelial layer of these lesions under the microscope reveals a saw tooth or “serrated” pattern.

Ordinary and innocent hyperplastic polyps (Figure 7) are by far the most common serrated lesions. These

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hyperplastic polyps, especially in the rectum, are usually small (< 0.5 cm) and show a characteristic serrated or saw-tooth appearance of the upper part of the crypts with clear mucin production. The nuclei are smallest in the superficial part of the crypt and show no stratification or hyperchromatism, like nuclei in adenomas. A rare syndrome called hyperplastic polyposis, including a wide variation of phenotypes, with larger hyperplastic polyps and multiple hyperplastic polyps especially proximal to the sigmoid, is associated with an increased risk of colorectal cancer.

Less common variants include serrated adenomas, mixed adenomas and so called sessile serrated lesions. Serrated adenomas do have a serrated epithelium, but nuclear changes resemble those of adenomas (Figure 7), with enlargement, stratification and mitoses. In “ordinary” adenomas, but also adenocarcinomas, individual crypts with a serrated phenotype can occasionally be recognized under the microscope. When this is a very apparent feature, such adenomas are classified as mixed adenomas. In terms of management, serrated and mixed adenomas usually are dealt with like traditional adenomas.

The sessile serrated lesion is a particularly interesting entity. These lesions also have a serrated epithelium, but do not show nuclear atypia and hence no dysplasia and they mostly are flat or slightly elevated, but not polypoid. Typically crypts with a wider basis (“boot like”) can be recognized. These lesions have been associated with BRAF mutations and MSI colorectal cancer and are typically right sided and difficult to recognize. The frequency of these lesions in most series does not exceed 5%.

The pathology discussion above should give clinicians the security to look at most polyps (adenomas) as harmless and to be skeptical of the importance emphasized by some of a 25-65% miss rate in screening with tests other than colonoscopy. In the U.S. in 2011 the “colonoscopy is the best and/or preferred screening test option” remains in place even though there is emerging evidence that protection of the right colon from CRC by screening colonoscopy is significantly less than protection for the left colon.20-24 No randomized controlled trials have been completed showing colonoscopy every 10 years is a better screening test than the others recommended in the USPSTF Guidelines25 though two such trials have just begun. A decision analysis published with the USPSTF guidelines did show that 4 screening strategies provided similar life-years gained: colonoscopy every 10 years, annual Hemoccult SENSA testing or fecal immunochemical testing, and sensitive FOBT every 2 to 3 years with 5-yearly sigmoidoscopy assuming equally high adherence.26 Recently published European Union CRC guidelines27 concluded that it was necessary to wait for the results of a randomized controlled trial before definite conclusions about the effectiveness of colonoscopy can be drawn.
Health policy decisions on which population screening test is best are difficult and should not be made as a result of over diagnosis of one of the main target lesions, the colonic polyp. These decisions will be more informed as more evidence becomes available. Until then, transparency and available evidence behooves gastroenterologists and their societies to encourage use of any and all of the evidence based recommended screening tests in the United States Preventive Services Task Force CRC guidelines. Much more screening will be done if primary care providers and the American public are not made to feel screening tests other than optical colonoscopy are ineffective. Of note, many European countries with national population based screening programs have after thorough evaluation of all evidence, reached the conclusion that fecal immunochemical testing, rather than colonoscopy is their best option for reducing death from colorectal cancer.\(^{27}\)

References

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5. NBC television network. The Today Show. March 2000
11. Health Care Incentives Improvement Institute, Inc.
Dermatitis herpetiformis (DH) is an autoimmune blistering disorder with a multifactorial etiology associated with a gluten-sensitive enteropathy. A chronic disease with a variable course, it is often exceptionally frustrating for patients; however, with current medical management and lifestyle adjustments, treatment can be highly successful. The prevalence in the United States is approximately 11.2 cases per 100,000 and internationally as high as 75.3 cases per 100,000. Health-related practitioners should be able to appreciate and recognize essential features of this disease. This review highlights distinguishing clinical symptoms and serves to aid the reader in the diagnosis and treatment of DH.

**INTRODUCTION**

Dermatitis herpetiformis (DH) was first described in 1884 by Dr. Louis Duhring at the University of Pennsylvania.¹ It is an autoimmune blistering disorder associated with a gluten-sensitive enteropathy. The etiology is multifactorial with strong genetic and autoimmune influences.² Patients with DH can demonstrate varying degrees of enteropathy. Earlier research has shown that patients with mild celiac disease can have notably increased intraepithelial lymphocyte counts and yet display normal gross intestinal mucosa.³ The intraepithelial lymphocyte infiltration lessens after one to three years on a gluten-free diet (GFD).³ DH clinically presents with erythematous papules, vesicles and excoriations. It is remarkably pruritic, so the vesicles are often excoriated to erosions by the time of presentation to medical practitioners. A gluten-free diet remains the cornerstone of therapy, while dapsone provides the most rapid relief of skin signs and symptoms.

**Epidemiology**

In the United States the prevalence of DH is 11.2 cases per 100,000 population.⁴ Internationally, the prevalence of DH has been reported as high as 75.3 cases per 100,000 population.⁵ Although, women seem to be more frequently affected by celiac disease,⁶,⁷ prevalence studies of DH in the United States have shown a male-to-female ratio of 1.44:1⁴ while internationally, the male-to-female ratio is up to 2:1. In one study of patients with gluten-sensitive enteropathy, 16% of the men and 9% of the women had DH.³,⁸ DH commonly presents in individuals of Northern European ancestry. It is rare in Asians and persons of African descent due to the shared
Table 1: Clinical Presentation of Dermatitis Herpetiformis

<table>
<thead>
<tr>
<th>Physical Examination</th>
<th>Lesion Distribution</th>
<th>Typical Symptoms</th>
<th>Diagnosis</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clusters of small clear vesicles atop flesh-colored–to–erythematous papules or plaques, often excoriated</td>
<td>Symmetrical distribution over extensor surfaces: elbows, knees, buttocks, and shoulders Less commonly: oral mucosa, scalp and face</td>
<td>Itching, stinging, burning; rarely asymptomatic</td>
<td>Lesional skin biopsy; direct immunofluorescence of unaffected perilesional skin; serologic testing</td>
<td>Life-long disease requiring long-term management</td>
</tr>
</tbody>
</table>

HLA associations of DH and celiac disease, including DQA1*0501 and B1*02, which encode HLA-DQ2 heterodimers. Classically, it appears in the second to fourth decade and is a rare occurrence in prepubertal children.

Clinical Presentation (Table 1.)

DH typically presents with clusters of tiny, clear vesicles atop flesh colored or erythematous papules or plaques symmetrically distributed on extensor surfaces of the body such as the elbows, arms, shoulders, knees and buttocks (Fig 1). Progression to a generalized distribution is uncommon. Due to DH’s intensely pruritic nature, intact vesicles are rarely seen as patients mechanically disrupt them by scratching. Less commonly, lesions occur on the oral mucosa, scalp and face. DH can also present as digital purpura that resembles a vasculitis. Palms and soles are routinely spared. Symptoms include painful burning, stinging, and variations in the intensity of itching. It is uncommon for it to be asymptomatic. Patients who present with DH may not report any gastrointestinal discomfort or symptoms. Additionally, intestinal biopsy may appear normal due to a number of reasons including as a result of treatment, the biopsy sample being taken from a skip lesion (or an unaffected site), or simply because the intestine may not be affected by the disease.

Diagnosis

The diagnosis of DH is definitively established with a lesional skin biopsy for microscopic evaluation and a perilesional skin biopsy for direct immunofluorescence in patients with clinical manifestation suspicious for the disease. Diagnosis can also be confirmed by a simple blood test for serum markers such as IgA endomysial antibodies, tissue transglutaminase antibody - tTG (IgA), deamidated gliadin peptide antibody - dGP (IgA and IgG) and gliadin assay (IgA and IgG). However, serum markers such as IgA endomysial antibodies are negative in as many as 10-37% of patients with DH. Additionally, many physicians would recommend obtaining tTG for diagnosis; however, because of...
Impurities and cross-reactivity, tTG enzyme-linked immunosorbent assay positivity can occur in many autoimmune diseases. All serology positive tests should be confirmed by small bowel biopsy before the patient starts a gluten free diet (GFD) or they might generate negative results.

Characteristically, direct immunofluorescence (DIF) testing demonstrates the presence of granular deposits of IgA in the papillary dermis. DIF testing is highly sensitive and found to be positive in 92.4% of patients. IgA deposits in the skin may be seen with other dermatological conditions including bullous pemphigoid and cicatricial pemphigoid; however, their distribution differs from that of DH. The most likely differential diagnosis is depicted in Table 2.

Serologic testing for circulating antiendomysial antibodies in the sera of DH patients is a less sensitive test compared to DIF and was positive in 40 of the 63 patients tested (63.5%) in one study. Histopathologic examination of lesional skin with hematoxylin and eosin staining shows clusters of neutrophils in the dermal papillae, with fibrin deposition, some eosinophils and papillary dermal edema. Vesiculation due to release of neutrophil lysosomal enzymes can occur in the lamina lucida.

### Management

Definitive treatment of DH includes a strict GFD with which the patient can expect some skin improvement in several months, although it may take years for GFD to suffice as the sole treatment. Gluten is found in wheat, rye and barley, as well as their derivatives, and can be a source of contamination even in gluten-free products, thus making complete avoidance challenging. Additionally, a strict GFD may require vitamin and mineral supplementation to avoid nutritional deficiencies. See February 2012 Practical Gastroenterology for a GFD update.

Pharmacotherapy for DH includes dapsone (diaminodiphenyl sulfone) and sulfa pyridine. Medical management with dapsone quickly improves skin manifestations and provides rapid symptomatic relief although it has no effects on gastrointestinal pathology. Possible adverse effects of dapsone include hemolytic anemia, methemoglobinemia, agranulocytosis, neuropathy, as well as others. Sulfa pyridine may be used in place of dapsone for those who develop severe adverse effects. If a patient fails therapy with dapsone or sulfa pyridine, other possible treatments include colchicine, cyclosporine, systemic corticosteroids, and less commonly heparin, tetracycline and nicotinamide. Nonsteroidal anti-inflammatory drugs (NSAIDs) may aggravate symptoms as demonstrated by a small controlled, double-blind cross-over study where nine of the thirteen DH patients that were given indomethacin in addition to dapsone or sulphamethoxypyridazine developed an exacerbation of their rash and pruritis. Therefore, caution should be used in prescribing NSAIDs, however, one study investigating the use of NSAIDs in DH patients demonstrated that ibuprofen may not have an effect on serum dapsone levels and disease activity in DH. A GFD remains the cornerstone of therapy, while dapsone provides the most rapid relief of skin signs and symptoms. An algorithm of the therapeutic approach is presented in Table 3.

### Prognosis/ Recommendations

DH is a life-long disease that requires long-term management. Patients can have worsening symptoms of DH with dietary intake of gluten; spontaneous remissions have been reported with its reduction in the diet. In one small study, six of the eight patients demonstrated spontaneous remission with an estimated mean daily intake of gluten below 12 grams. Patients with DH should work with both a gastroenterologist and a dietician for evaluation of a gluten-sensitive enteropathy and formulation of a gluten-free diet to help alleviate future symptomatology.
**SUMMARY**

Although DH is a chronic disease, patients can have exceptional control over clinical symptoms after they have made the necessary lifestyle modifications; specifically, strict adherence to a gluten-free diet and if possible. In addition, medical management may be necessary as dictated by the patient’s symptoms. Although medications prescribed strictly for the treatment of DH; namely, dapsone and/or sulfapyridine, have no effect on the underlying gastrointestinal disease, they offer the advantage of rapid symptomatic relief and improvement in skin manifestations. DH patients can be reassured that although this is a chronic and sometimes unpredictable disease, lifestyle adjustments and medical treatment can be highly successful.

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**References**


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**Table 3: Treatment of Dermatitis Herpetiformis**

<table>
<thead>
<tr>
<th>Treatment of DH</th>
<th>Medical management</th>
<th>Additional instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle modification</td>
<td>Mainstay: strict gluten-free diet</td>
<td>Avoid NSAIDS*; iodides</td>
</tr>
<tr>
<td></td>
<td>Possible alternative: Atkin’s diet</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dapsone and sulfapyridine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Others: colchicine, cyclosporine, azathioprine, systemic corticosteroids</td>
</tr>
</tbody>
</table>

*Ibuprofen may be acceptable for use 30*


Ascites is the pathologic accumulation of fluid in the peritoneal cavity. The development of ascites is a major event in the natural history of cirrhosis and is associated with a significant deterioration in prognosis. It occurs in approximately 60% of patients with cirrhosis within 10 years. Although cirrhosis accounts for approximately 75% of patients with ascites, other causes should be kept in mind especially malignancy (10%), cardiac failure (3%), tuberculosis (2%), pancreatitis (1%) and other rare causes.

PATHOPHYSIOLOGY
The most important mechanism contributing to development of ascites in cirrhosis is renal sodium retention, which is a consequence of arterial splanchnic vasodilation. The main mechanism for arterial splanchnic vasodilation is via the actions of nitric oxide, a vasodilator released due to the development of portal hypertension. Eventually, activation of the sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) may occur, accentuating retention of sodium and further expansion of extracellular fluid volume with subsequent formation of ascites. Decreased colloid osmotic pressure and increased permeability of peritoneal capillaries also contribute to the development of ascites that may result from nephrotic syndrome, malnutrition, protein-losing enteropathy and diminished protein synthesis due to liver disease.

EVALUATION OF ASCITES
Single or multi-factorial insults to the liver ultimately lead to cirrhosis, the most common being alcohol abuse, chronic hepatitis C and obesity with concomitant nonalcoholic fatty liver (Table 1). The main goals in

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the assessment of a patient with suspected ascites are to confirm its presence, establish a likely etiology and to determine whether it is infected or malignant. An appropriate medical history, physical examination and subsequent evaluation with imaging studies are integral in this process. A focused history should be directed towards establishing the presence of ascites (i.e. recent weight gain, change in abdominal girth and other signs of fluid retention such as peripheral edema) and inquiring about known history or risk factors for hepatic or non-hepatic diseases that may cause ascites (Table 2.).

Some common symptoms of ascites include increased abdominal girth, early satiety and shortness of breath, depending on the amount of fluid accumulation in the abdomen. The physical examination should focus on stigmata of cirrhosis and clinical signs suggesting the presence of ascites. Physical examination findings such as shifting dullness usually require the accumulation of at least 1500ml of fluid, however no single physical sign for ascites has been found to be both sensitive and specific. The most useful findings for helping diagnose ascites is a positive fluid wave or shifting dullness while the most useful findings for ruling out ascites is the absence of bulging flanks, flank dullness or shifting dullness. When the diagnosis is in doubt, abdominal ultrasonography is the imaging modality of choice. Additionally, ultrasonography provides information regarding hepatic echogenicity and vasculature.

Multiple grading systems for ascites are available. Recently, a revised grading system for ascites has been proposed by the International Ascites Club.3,4

- Grade 1: Mild ascites detectable only by ultrasound
- Grade 2: Moderate ascites with moderate symmetrical distention of abdomen
- Grade 3: Large or gross ascites with marked abdominal distention

### Table 1. Etiologies of Hepatic Cirrhosis

<table>
<thead>
<tr>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholic liver disease</td>
</tr>
<tr>
<td>Chronic hepatitis B</td>
</tr>
<tr>
<td>Chronic hepatitis C</td>
</tr>
<tr>
<td>Non-alcoholic fatty liver disease</td>
</tr>
<tr>
<td>Hemochromatosis</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
</tr>
<tr>
<td>Primary sclerosing cholangitis</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
</tr>
<tr>
<td>Biliary obstruction</td>
</tr>
<tr>
<td>- Biliary atresia/neonatal hepatitis</td>
</tr>
<tr>
<td>- Congenital biliary cysts</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Genetic metabolic disease</td>
</tr>
<tr>
<td>- Wilson's disease</td>
</tr>
<tr>
<td>- Alpha-1 antitrypsin deficiency</td>
</tr>
<tr>
<td>Vascular abnormalities</td>
</tr>
<tr>
<td>- Chronic, passive hepatic congestion caused by right-sided heart failure</td>
</tr>
</tbody>
</table>

### Table 2. Etiology of Ascites

<table>
<thead>
<tr>
<th>Disease</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>81%</td>
</tr>
<tr>
<td>Cancer</td>
<td>10%</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>3%</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>2%</td>
</tr>
<tr>
<td>Pancreatic disease</td>
<td>1%</td>
</tr>
<tr>
<td>Dialysis</td>
<td>1%</td>
</tr>
<tr>
<td>Other</td>
<td>2%</td>
</tr>
</tbody>
</table>

Cirrhotic Ascites

PARACENTESIS
Abdominal paracentesis with appropriate ascitic fluid analysis is the most efficient way to determine etiology and establish the presence or absence of infection.\(^5\) Paracentesis is a safe procedure with a low incidence of complications (<1%) despite comorbid coagulopathy often present in patients with cirrhosis. Serious complications such as hemoperitoneum and bowel perforation occur in less than 0.1% of patients.\(^6,8\) Coagulopathy should only preclude paracentesis when there is clinical evidence of disseminated intravascular coagulopathy (DIC).

In order to select the appropriate site for paracentesis, ultrasound guidance is frequently used. Indications for abdominal paracentesis in patients with cirrhosis include fever, abdominal pain, hepatic encephalopathy, gastrointestinal bleeding and worsening liver or renal function. Additionally, patients with cirrhosis admitted with ascites should undergo paracentesis to exclude spontaneous bacterial peritonitis (SBP).

APPEARANCE
The gross appearance of ascitic fluid is of limited value in evaluation of ascites, but may help in the differential diagnosis and provide valuable clinical information regarding the etiology of ascites. For example, turbid or cloudy fluid suggests infectious etiology, bloody fluid suggest traumatic ascites or malignancy where as milky fluid suggests chylous ascites with increased triglycerides contents.

ASCITIC FLUID ANALYSIS
Measurement of the serum-ascites albumin gradient (SAAG) is useful when the diagnosis of cirrhosis is not established. To calculate SAAG, ascitic fluid albumin concentration is subtracted from the serum albumin concentration. A SAAG > 1.1 g/dL indicates portal hypertension though it does not determine the specific cause.\(^9\) A SAAG < 1.1g/dL indicates that the patient does not have portal hypertension-related ascites and suggests pancreatitis, serositis, peritoneal carcinomatosis, peritoneal tuberculosis or nephritic syndrome as the cause.\(^10,11\) (Table 3.). To evaluate for spontaneous bacterial peritonitis, ascitic fluid should

\(\text{(continued on page 50)}\)

<table>
<thead>
<tr>
<th>Table 3. Classification of Ascites</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIGH ALBUMIN GRADIENT (SAAG &gt; 1.1g/dL)</strong></td>
</tr>
<tr>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Alcoholic hepatitis</td>
</tr>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Budd-Chiari syndrome</td>
</tr>
<tr>
<td><strong>LOW ALBUMIN GRADIENT (SAAG &lt; 1.1g/dL)</strong></td>
</tr>
<tr>
<td>Peritoneal carcinomatosis</td>
</tr>
<tr>
<td>Peritoneal tuberculosis</td>
</tr>
<tr>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Serositis</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4. Ascitic Fluid Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ROUTINE</strong></td>
</tr>
<tr>
<td>Cell count and differential</td>
</tr>
<tr>
<td>Bacterial culture with bedside inoculation into blood culture bottle</td>
</tr>
<tr>
<td>Albumin</td>
</tr>
<tr>
<td>Total Protein</td>
</tr>
<tr>
<td><strong>SOMETIMES USEFUL</strong></td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
</tr>
<tr>
<td>Glucose</td>
</tr>
<tr>
<td>Amylase</td>
</tr>
<tr>
<td>Gram stain</td>
</tr>
<tr>
<td>Triglyceride (ascites appear milky)</td>
</tr>
<tr>
<td><strong>RARELY HELPFUL</strong></td>
</tr>
<tr>
<td>pH</td>
</tr>
<tr>
<td>Lactate</td>
</tr>
<tr>
<td>AFB smear and culture (might be helpful in certain circumstances)</td>
</tr>
<tr>
<td>Cytology</td>
</tr>
<tr>
<td>Bilirubin</td>
</tr>
</tbody>
</table>
(continued from page 48)

be sent for a differential cell count and fluid should be inoculated into blood culture bottles at bedside and sent for culture (Table 5).

SBP can be diagnosed if the ascitic fluid has an absolute polymorphonuclear (PMN) count ≥ 250 cells/mm³ and patients should receive antibiotics soon after cultures have been drawn. A total ascitic protein level of < 1.5g/dL confers an increased risk of SBP, and these patients may benefit from antibiotic prophylaxis.

MANAGEMENT OF ASCITES

The initial management of ascites should begin with dietary sodium restriction to < 2 grams/day (88 mmol/day), which requires a “no added salt” diet and avoidance of pre-prepared foods. Dietary sodium restriction is only successful in 10-20% of patients. Minimizing the use of nephrotoxic medications including non-steroidal anti-inflammatory drugs (NSAID), angiotensin converting enzyme-inhibitors, angiotensin II antagonists, alpha-adrenergic blockers and aminoglycoside antibiotics may reduce risk of developing acute renal failure, hyponatremia and diuretic resistance.

Patients who do not respond to conservative measures may benefit from oral diuretics. First line therapy is a combination of spironolactone and furosemide. Typical starting doses are 100 mg/d of spironolactone and 40 mg/d of furosemide. Maximum accepted doses are 400mg/d of spironolactone and 160mg/d of furosemide. Furosemide in particular should be administered on a once daily schedule. Response should be monitored on the basis of changes in daily body weight, clinical examination and laboratory tests such as electrolytes level. The recommended maximum weight loss to prevent renal failure and/or hyponatremia is 0.5 kg/d in patients without peripheral edema and 1 kg/day in those with peripheral edema. Diuretics should be discontinued if there is progressive renal failure, severe hyponatremia (sodium < 120 mmol/L), worsening hepatic encephalopathy or incapacitating muscle cramps.

For patients with large volume ascites, therapeutic or large volume paracentesis (LVP) is well tolerated. LVP does not often produce adverse hemodynamic changes, although it may result in further activation of RAAS. This has been termed paracentesis-induced circulatory dysfunction (PICD) and administration of albumin after LVP may blunt development of PICD. Current practice guidelines from the American Association for the Study of Liver Diseases (AASLD) state that it is reasonable (but not mandatory) to give 5 to 10g of albumin (25%) per liter of ascites removed in patients (Table 8.) with greater than 5L of fluid removed to prevent circulatory dysfunction.

Table 5. Definition and Diagnosis of Bacterial Peritonitis in Cirrhotics

<table>
<thead>
<tr>
<th>TYPE</th>
<th>ASCITIC CELL COUNT</th>
<th>ASCITES CULTURE</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterile</td>
<td>&lt; 250 PMNs</td>
<td>Negative</td>
<td>None</td>
</tr>
<tr>
<td>Spontaneous bacterial peritonitis</td>
<td>≥ 250 PMNs</td>
<td>Monobacterial infection</td>
<td>3rd generation Cefalosporin</td>
</tr>
<tr>
<td>Culture negative neutrocytic ascites</td>
<td>≥ 250 PMNs</td>
<td>Negative</td>
<td>3rd generation Cefalosporin</td>
</tr>
<tr>
<td>Non neutrocytic bacterascites</td>
<td>&lt; 250 PMNs</td>
<td>Monobacterial infection</td>
<td>Only if symptomatic or persistently positive culture</td>
</tr>
<tr>
<td>Secondary</td>
<td>≥ 250 PMNs</td>
<td>Polymicrobial infection</td>
<td>(1) Base on culture and sensitivities (2) Identify the source of infection</td>
</tr>
</tbody>
</table>

Refractory ascites (RA) signifies a poor prognosis. The definition of refractory ascites is the (1) lack of response to maximum dose diuretics while remaining compliant with low-sodium diet, (2) frequent re-accumulation of ascites shortly after therapeutic paracentesis and (3) inability to tolerate diuretics due to recurrent side effects (i.e. hyponatremia, hypokalemia, hyperkalemia, renal insufficiency, or encephalopathy). Measurement of urinary sodium may be beneficial in identifying patients who are non-compliant with their sodium restriction diet. Either a 24-hour urine collection or spot urine sodium concentration can be performed. In clinical settings, if the random urine sodium concentration is greater
than urine potassium, this suggests non-compliance to a sodium-restricted diet. Treatment options for RA include therapeutic paracentesis with albumin infusion, transjugular intrahepatic portosystemic shunt (TIPS) and liver transplantation. Repeated LVP with albumin infusion is the most widely used therapy for refractory ascites and is generally performed every 2 to 4 weeks in an outpatient setting. TIPS reduces the portal pressure, the cardinal pathophysiologic event that causes inappropriately increased renal sodium reabsorption.26 TIPS is costly and portends an increased risk of encephalopathy related morbidity but it does reduce the need for diuretics and LVP.27, 28 The ideal candidate for TIPS has relatively preserved liver function (i.e. bilirubin < 5mg/dl, INR < 2 or Child-Pugh score < 11), preserved renal function, no concomitant active infection and is free of encephalopathy.28, 29 A meta-analysis of individual patient data from four randomized trials of TIPS compared to LVP showed a survival advantage of TIPS. Moreover, survival superiority of TIPS is apparent at higher as well as lower MELD scores.30 Given the fact that patients with refractory ascites have a particularly poor prognosis, referral to a liver transplantation center should be considered.

SPONTANEOUS BACTERIAL PERITONITIS
Spontaneous bacterial peritonitis (SBP) has been found in approximately 15% of hospitalized patients with cirrhosis and ascites; as such diagnostic paracentesis should be performed routinely at time of admission.14 Suspicion for SBP is raised if there is a change in the clinical status of the patient that may include one or more of the following: fever, abdominal pain, altered mental status, gastrointestinal bleed and/or worsening liver or renal function. Occasionally, a patient with cirrhosis and ascites may develop peritonitis from an independent event, such as diverticulitis, abscess or complications from surgery. Such cases of secondary bacterial peritonitis are often characterized by polymicrobial bacteria or fungal species in ascites.

Diagnosis of SBP is established with an ascitic fluid neutrophil count > 250 cells/mm$^3$.31 Culture negative SBP can be seen in as many as 60% of patients with infection and increased ascitic fluid neutrophil count; management and treatment is similar to culture positive SBP.32 When the ascites culture is positive, the most common pathogens include gram-negative bacteria (i.e. Escherichia coli) and gram-positive cocci (i.e. streptococci and enterococci).33, 34 Therefore, ascitic fluid culture is not necessary for the diagnosis of SBP, but it is important in guiding antibiotic therapy. Positive ascitic fluid culture and an ascitic neutrophil count less than 250 cells/mm$^3$ is termed bacterascites (Table 4.). Only those patients who exhibit signs of infection or in whom a second paracentesis reveals a neutrophil count > 250 cells/mm$^3$ should be treated with antibiotics, otherwise they should be followed clinically for worsening symptoms.14

(continued on page 54)
Management of Spontaneous Bacterial Peritonitis

Empiric antibiotic therapy, third generation cephalosporins, should be started immediately after diagnostic paracentesis. Alternative options include amoxicillin/clavulanic acid and quinolones such as ciprofloxacin. For uncomplicated SBP, a 5-day course of antibiotics has been shown to be as effective as 10 days. Treatment may be switched to oral quinolone therapy after 2 days of intravenous antibiotics. SBP resolves in approximately 90% of patients with antibiotic therapy. A routine second paracentesis within 48 hours after treatment may help gauge the effectiveness of therapy though it is not supported by evidence. However, if symptoms such as fever or abdominal pain persist, repeat paracentesis can be performed to assess the response of the PMN count to antibiotics. At 48 hours, the ascitic PMN count will be below the pretreatment value and frequently a 25% decrease in pretreatment PMN is observed if treatment has been appropriate. The use of albumin as an adjunct to antibiotics in cases of SBP is discussed later.

Prophylaxis of Spontaneous Bacterial Peritonitis

Given the cost and risk of developing resistant organisms, the use of prophylactic antibiotics should be restricted to patient at high risk of SBP. The high-risk population includes patients with (1) acute gastrointestinal bleed, (2) low total ascitic protein (< 1.5g/dl) and (3) previous history of SBP (secondary prophylaxis).

Primary prophylaxis (no prior history of SBP) with oral quinolones for SBP should be considered in cirrhotics with ascitic fluid total protein less than 1.5 g/dL who fulfill at least one of the following criteria: serum creatinine ≥ 1.2 mg/dL, blood urea nitrogen ≥ 25 mg/dL, serum sodium ≤ 130 mEq/L or Childs Pugh > 9 points and bilirubin ≥ 3 mg/dL. In patients who had one or more episodes of SBP, secondary prophylaxis with norfloxacin (400 mg/day) or trimethoprim-sulfamethoxazole therapy is recommended (Table 6.). In settings where norfloxacin is unavailable, ciprofloxacin (500 mg PO once daily) is an acceptable alternative. Due to theoretical risk of developing bacterial resistance, it is generally not recommended to use intermittent dosing of antibiotics for prophylaxis.

HEPATORENAL SYNDROME

Hepatorenal syndrome (HRS) can be defined as renal failure in a patient with advanced liver disease in the absence of an identifiable alternative cause (Table 7.). HRS occurs in approximately 30% of patients with SBP and is associated with a high mortality. All patients with HRS should have an expedited referral for liver transplantation and receive prompt treatment prior to liver transplantation, as treatment may improve post-transplant outcomes. HRS can be classified into two types, each having different clinical and prognostic characteristics. Type 1 HRS is characterized by doubling of serum creatinine above 2.5 mg/dL in less than 2 weeks and Type 2 HRS is a slowly progressive or stable renal dysfunction not meeting criteria for Type 1 HRS. Type 1 HRS may be precipitated by SBP, gastrointestinal bleeding or any systemic infection leading to multi-organ dysfunction; whereas Type 2 HRS is characterized by a stable progressive course in patients with refractory ascites. The risk of developing HRS can be markedly reduced by administrating intravenous albumin 1.5 g/kg at diagnosis of SBP and 1.0 g/kg on day 3.
the evidence is not conclusive, vasoactive drugs, such as octreotide and midodrine in combination with albumin infusion may be considered for the treatment of Type 1 HRS. Other treatment options, including TIPS may improve renal function in selected patients however there is insufficient data to support the routine use of TIPS in patients with HRS. Renal replacement therapy, including intermittent hemodialysis, continuous renal replacement therapy and hybrid therapies such as sustained low efficiency dialysis, may be useful in patients who do not respond to pharmacological therapy and fulfill the criteria for renal support and are deemed eligible for liver transplantation.

CONCLUSION

Patients with cirrhosis and ascites have a poor long-term survival without liver transplantation. Most respond well to general lifestyle modifications and diuretic treatment. For patients with refractory ascites, large volume paracentesis plus albumin administration is the most widely accepted therapy. TIPS placement is an alternative treatment option for patients without severe liver failure or encephalopathy and for those who are unwilling to undergo repeated paracentesis. Patients with ascites are at risk of developing several complications, including spontaneous bacterial peritonitis and hepatorenal syndrome that can lead to severe morbidity and mortality. It is important to examine ascitic fluid and rule out infection. Those patients at risk of developing SBP should receive prophylactic antibiotic treatment. The most severe complication of SBP is HRS. Type 1 HRS develops rapidly and has a very poor prognosis. Type 2 HRS develops gradually in patients with refractory ascites. Combination treatment with albumin and vasoactive drugs in HRS type 1 yields the best survival data. For those patients whose liver disease is not responsive to medical therapy liver transplantation is the only treatment option.

References

Cirrhotic Ascites

A SPECIAL ARTICLE


Osseous Metaplasia in a Colon Polyp
Michael Hjelkrem, Kevaghn Fair, Ajay Pabby

Osseous metaplasia occurring in colorectal neoplasia is extremely rare. The incidence, severity, morbidity and mortality are poorly documented in the literature. A 44-year-old male presented for colonoscopy due to a report of bright red blood per rectum. During the colonoscopy, a 5mm sigmoid polyp was removed with snare electrocoagulation. Histology showed osseous metaplasia embedded within a hyperplastic colon polyp. Eleven cases have now been described in the literature of osseous metaplasia in benign colorectal neoplasia. Osseous metaplasia is predominately found in left colon lesions as 64% of cases occurred in the rectum and sigmoid. Isolated cases have been found in the ileum, jejunum, stomach and esophagus. This is the first case of osseous metaplasia in a hyperplastic polyp of the sigmoid colon. Osseous metaplasia is a rare finding in colorectal polyps with undetermined clinical significance.

CASE REPORT

A 44-year-old male presented to his primary care provider reporting bright red blood per rectum. He had no prior history of a colonoscopy and no family history of colon cancer. Review of systems and physical examination were unremarkable. Laboratory examination showed normal complete blood count and normal metabolic panel including calcium and phosphate. The patient was referred for a colonoscopy. Internal hemorrhoids were found and this was likely the cause of bleeding. A 5mm sigmoid polyp was found upon colonoscopy and removed by snare electrocoagulation. Macroscopic examination of the resected specimen showed a fungating, normal appearing polyp without any unusual features. The polyp was fixed in 10% formalin and processed routinely for paraffin embedded, hematoxylin and eosin-stained sections. Microscopic examination revealed lobules of metaplastic bone and cartilage within hyperplastic intestinal-type epithelium. Dysplasia or other atypical changes were not seen. (Figure 1.)

Discussion

The ectopic formation of bone occurs in many pathological conditions. It has been described in both benign and malignant tumors of the breasts, prostate, uterus, salivary glands, skin appendages, pulmonary system and gastrointestinal organs.1 It has also been found in the metastases of gastrointestinal tumors to include pulmonary metastases of gastric adenocarcinoma,2 skeletal muscle metastasis of gastric cancers,3 retroperitoneal metastasis of colon cancers4 and metastatic axillary lymph node from transverse colon adenocarcinoma.5 Other gastrointestinal lesions with ectopic bone formation have included gastric carcinoid,6 hepatocellular carcinoma7 and lesions of the appendix and gallbladder.8 The most frequent tumor in the digestive system containing bone formation...
Osseous Metaplasia in a Colon Polyp

A CASE REPORT

Figure 1.

appears to be adenocarcinoma of the rectum. Yet osseous metaplasia in an adenocarcinoma of the rectum is still extremely rare. Dukes estimated the incidence to be 0.4%, however, less than 30 cases of osseous metaplasia in any GI lesions have been reported, thus, the actual incidence is probably a lot less.

In 1981, Sperling first described bone formation within a benign lesion, a rectal polyp. Since then, upon literature review, it has been described 11 more times (Table 1.). The majority of the occurrences have been rectal or left sided lesions (7 cases including the present case). Other case reports comment on lesions located in the ileum, stomach and Barrett’s esophagus. In one case report of a patient with Peutz-Jeghers Syndrome, osseous metaplasia was found in 3 of 15 polyps in the jejunum. Also of note is the young age of many patients as 6 of the 11 cases were younger than 50. None of the cases discussed repeat colonoscopies or follow up care.

The exact mechanism of bone formation within gastrointestinal neoplasia is unknown but is likely due to mesenchymal precursor cells transforming into osteoblasts capable of osteoid production. The stimuli responsible for this abnormal differentiation into osseous tissue have yet to be identified. Dukes first described the process in 1939 and suggested osseous formation followed dystrophic calcification of necrotic tissue. Van Patter and Sanerkin thought mucinous stromal infiltration was associated with osseous metaplasia and, similar to dystrophic calcification, frequently occurred close to tumor necrosis or squamous metaplasia. Groisman first described bone formation within a benign tubulovillous adenoma without signs of necrosis or mucinous accumulation. Randall observed that the heterotopic ossification was not in regions of necrotic tissue but in areas adjacent to the metastatic adenocarcinoma. Heterotopic bone formation can occur in both benign and malignant tumors without the
Osseous Metaplasia in a Colon Polyp

A CASE REPORT

Table 1. Heterotopic Bone Formation in Benign Gastrointestinal Neoplasia

<table>
<thead>
<tr>
<th>Author</th>
<th>Age/Sex</th>
<th>Location</th>
<th>Size (Cm)</th>
<th>Neoplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sperling,10 1981</td>
<td>25 M</td>
<td>Rectum 10 cm form anus</td>
<td>1.0</td>
<td>Benign</td>
</tr>
<tr>
<td>Ohtsuki,16 1987</td>
<td>71 M</td>
<td>Gastric</td>
<td>NA</td>
<td>Hyperplastic polyp</td>
</tr>
<tr>
<td>Byard,12 1988</td>
<td>28 M</td>
<td>Rectum</td>
<td>NA</td>
<td>Juvenile polyp</td>
</tr>
<tr>
<td>Byard,12 1988</td>
<td>59 M</td>
<td>Ileum</td>
<td>NA</td>
<td>Fibrosarcoma</td>
</tr>
<tr>
<td>Groisman,13 1994</td>
<td>67 M</td>
<td>Rectum 10 cm from anal margin</td>
<td>1.8</td>
<td>Tubulovillous adenoma</td>
</tr>
<tr>
<td>Groisman,13 1994</td>
<td>3 F</td>
<td>Rectum 2 cm from anal margin</td>
<td>2.0</td>
<td>Juvenile polyp</td>
</tr>
<tr>
<td>Narita,18 1995</td>
<td>40 M</td>
<td>Jejunum (3 of 15 polyps) (Peutz-Jeghers Syndrome)</td>
<td>NA</td>
<td>Hamartomatous polyp</td>
</tr>
<tr>
<td>Haque,17 1996</td>
<td>76 M</td>
<td>Barrett’s Esophagus</td>
<td>NA</td>
<td>Barrett’s Esophagus</td>
</tr>
<tr>
<td>Nakajima,14 1997</td>
<td>29 F</td>
<td>Rectum 3 cm from dentate line</td>
<td>1.6</td>
<td>Hyperplastic polyp</td>
</tr>
<tr>
<td>Al-Daraji,15 2004</td>
<td>85 F</td>
<td>Left colon, 30 cm from anus</td>
<td>1.5</td>
<td>Tubular adenoma</td>
</tr>
<tr>
<td>Present Case</td>
<td>44 M</td>
<td>Sigmoid</td>
<td>0.5</td>
<td>Hyperplastic polyp</td>
</tr>
</tbody>
</table>

Cm (centimeter), F (female), M (male), NA (not available)

Table 1 (continued on page 62)

preoccurrence of necrosis, inflammation, calcification or extracellular mucin.

Ossification within tumors, both benign and malignant, is most likely caused by local factors released from cells undergoing differentiation and/or by the tumor epithelial cells. These local factors have yet to be defined. Randall5 found alkaline phosphatase in osteoblast like cells and in surrounding epithelial cells; although probably involved in mineralization, its role in inducing osseous formation is unknown. Other factors of osteogenesis may include growth factors such as TGFβ1 and β2 or other paracrine factors;19 however, this warrants further investigation. Nakajima13 discussed that predisposing factors for osseous metaplasia may be repeated local trauma or special properties of rectal mucosa itself. There is evidence that local trauma may be involved as heterotopic bone formation has occurred in abdominal scars after surgical procedures20 and after radiotherapy in soft tissues.11

CONCLUSION
This is the first reported case of osseous metaplasia in a hyperplastic polyp of the sigmoid colon. Heterotopic bone formation can occur in both benign and malignant tumors without the preoccurrence of necrosis, inflammation, calcification or extracellular mucin.
Osseous Metaplasia in a Colon Polyp

A CASE REPORT

(continued from page 60)

inflammation, extracellular mucin, calcification and/or increased stromal vascularity. It is likely due to local osteogenic factors released from cells undergoing differentiation or metaplasia and may be induced by repeated local trauma. The significance and clinical prognosis of heterotopic bone formation is undefined.

References

**Practical Gastroenterology** Case Report Guidelines for Authors

- The aim of Case Reports is to provide challenging yet clinically relevant and informative cases to primary care physicians.

- The Case should center around one (1) to three (3) high quality images that are completely described in the report. Images should be endoscopic, pathologic, and/or radiographic (without any patient identifiers) with clear labeling as appropriate.

- The Case must be a concise report submitted as a Word document consisting of no more than 1250 words.

- The images must be submitted as .jpg files separate from the Word document.

- There should be a brief introduction/abstract, relevant presentation of the case, relevant case discussion and conclusion.

- The conclusion should include one or two clinical pearls that the reader may apply to their practice or add to their knowledge set.

- References should be limited to 8. References should follow AMA style and journal names should be abbreviated according to Index Medicus practice. Inclusive page ranges should be indicated.

- Authors should be limited to 3 on each submission. No author photographs are necessary. All authors must provide their names, addresses, phone numbers, complete titles and affiliations.

- Case Reports must not have been published previously. Each Case Report is subject to review by members of our Editorial Board. Case Reports are subject to final editing. Upon publication, Case Reports will be copyrighted by Practical Gastroenterology Publishing, Inc.

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H. Pylori-Associated Gastric Mucosal Lymphoma and Risk For Secondary Cancers

Cure of Helicobacter pylori infection induces remission in most patients with gastric mucosa-associated lymphoid tissue lymphoma (GML). To determine the long-term outcomes of these patients in a prospective, multi-center trial and investigate development of second cancers or potential histologic residual disease, 120 patients were followed with Stage E-11 GML for a median of 122 months after H. pylori eradication. Remission was determined by histology analysis and development of second cancers was documented.

Of the patients, 80% achieved complete remission from GML, and 80% of those remained disease-free. Estimated mean survival time in the Kaplan-Meier Analysis was 147 months (138 to 156 months). Of the patients that achieved complete remission, 17% (16 of 96) had histologic residual disease after a median of 32 months. Disease did not progress in any of these patients and all but one achieved a second complete remission.

Standardized morbidity rates revealed a significantly higher incidence of gastric cancer (8.567), or non-Hodgkin’s lymphoma (18.621), in the 96 patients that achieved a complete remission compared with the general German population.

It was concluded that cure of H. pylori infection leads to continuous complete remission in most patients with H. pylori-associated GML. Patients are at risk for development of secondary cancers (i.e., gastric cancer and non-Hodgkin’s lymphoma).

**Ed. Note:** Appropriate surveillance is indicated.

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**Gastric and Esophageal Malignancies are Increased in People with AIDS**

To evaluate the risks of different histologic and anatomic subtypes of carcinomas and non-Hodgkin’s lymphomas (NHLs) of the stomach and esophagus in people with AIDS, data was analyzed from the HIV-AIDS Cancer Match Study, which linked data collected from 1980 to 2007 for 16 US population-based HIV and AIDS and cancer registries.

Risks of stomach and esophageal malignancies in people with AIDS (596,955), with those of the general population using standardized incidence ratios (SIRs) were evaluated. Calendar trends were assessed using Poisson regression.

People with AIDS had increased risk of carcinoma of the esophagus (SIR 1.69) and stomach (SIR 1.44). Risk was increased for esophageal carcinoma (SIR 1.91), and squamous cell carcinoma (SIR 1.47). People with AIDS had greater risk of carcinoma of the gastric cardia (SIR 1.36) and noncardia (SIR 1.53). Compared with the general population, most stomach and esophageal NHLs developed in people with AIDS were diffuse large B-cell lymphomas, but these individuals also had an increased risk of gastric mucosa-associated lymphoid tissue lymphoma (SIR 5.99).

The incidence of carcinomas remained fairly constant over time, but rates of NHL decreased from 1980 to 2007.

It was concluded that people with AIDS are at increased risk for developing esophageal and stomach carcinomas and NHLs, although the incidence of NHL decreased from 1980 to 2007 as treatments for HIV infection improved. HIV-infected individuals face continued risks of esophageal and stomach carcinomas.

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**EUS-FNA in Diagnosis of Autoimmune Pancreatitis**

To determine whether EUS-guided FNA by using 22-gauge needles is useful for the diagnosis or evaluation of autoimmune pancreatitis (AIP), a retrospective study was carried out in which a total of 273 patients, including 25 with AIP, underwent EUS-FNA and histologic examination. This procedure using 22-G needles provided adequate tissue samples for histopathologic evaluation because more than 10 high-power fields were available for evaluation in 20 of 25 patients (80%).

The mean immunoglobulin-G4 positive cell count was 13.7/high-power field. Obliterative phlebitis was observed in 10 of 25 patients (40%), in the context of the ICD criteria for AIP, with 14 and 6 of 25 patients judged to have Level 1 (positive for three or four (continued on page 66)
items), and Level 2 (positive for two items), histologic findings, respectively, meaning that 20 of 25 patients were suggested to have lymphoplasmacytic sclerosing pancreatitis based on the ICD criteria. The diagnosis in one patient was Type 2 AIP because a granulocytic epithelial lesion was identified in this patient.

In this retrospective study with a small number of patients, the results suggest that EUS-FNA by using 22-gauge needles provides tissue samples adequate for histopathologic evaluation and greatly contributes to the histologic diagnosis of AIP.


Effect of Inadequate Bowel Preparation on Screening Colonoscopy

To determine the prevalence of missed adenomas on average-risk patients presenting for screening colonoscopy who are found to have inadequate bowel preparation, a retrospective chart review was carried out with endoscopic and pathology reports examined to determine the characteristics of polyps. Data from repeat colonoscopies were collected through 2010 at an outpatient endoscopic center as part of an academic medical center.

The study involved patients who underwent outpatient average-risk screening colonoscopy between 2004 and 2009 that were documented to have the inadequate bowel preparation and with colonoscopy to the cecum.

Initial adenoma detection rate and adenoma detection rate on followup examination was measured. Inadequate bowel preparation was reported on 373 patients with an initial adenoma detection rate of 25.7% of 133 patients who underwent repeat colonoscopy. A total of 33.8% had at least one adenoma detected and 18% had high-risk states detected, including greater than 3 adenomas, an adenoma greater than 1 cm, or adenoma with villous features or high-grade dysplasia.

Per adenoma miss rate was 47.9% among patients with at least one adenoma on repeat colonoscopy, 31.1% had no polyps on initial colonoscopy. The mean time between colonoscopies was 340 days.

Among patients with high-risk states, 25% had no polyps on initial colonoscopy and the mean time between colonoscopies was 271 days. The study was limited by its retrospective design.

It was concluded that adenomas and high-risk lesions were frequently detected on repeat colonoscopy in patients with inadequate bowel preparation on initial screening colonoscopy, suggesting that these lesions were likely missed on initial colonoscopy.


Cocaine-Related Ischemic Colitis

A retrospective review of medical records at two affiliated teaching hospitals located in a downtown area of Milwaukee was carried out over a 9-year period. A total of 208 patients were identified by ICD-9 codes with a confirmed diagnosis of bowel ischemia, with imaging and endoscopic findings and self-report of recent cocaine use or positive urine toxicology screen within 6 months of a hospital admission for ischemia. Controls were individuals who met the same criteria without cocaine use and a negative urine test for cocaine.

Patients with cocaine-related ischemia were significantly younger and had a significantly higher mortality rate than patients with ischemic colitis unrelated to cocaine. The cause of death in all cases was septic shock caused by extensive bowel ischemia. Multivariate logistic regression analysis showed that cocaine-related ischemic colitis was a significant risk factor for mortality, with an odds ratio of 5.77, and with need for surgical intervention.

It was concluded that cocaine-related ischemic colitis has a high mortality. In young patients presenting with acute abdominal pain and/or rectal bleeding with evidence of bowel wall thickening or pneumatosis on imaging studies or colonoscopy, cocaine-related ischemia should be considered and particularly to identify patients at high risk of sepsis and death.

Varying Appearance of Proximal Colorectal Neoplasms
To investigate the differences in endoscopic appearance (i.e., diminutive size and nonpolypoid shape), of proximal compared with distal colorectal neoplasms, endoscopists in the Netherlands who were previously trained in the detection and classification of nonpolypoid colorectal lesions, carried out examination on consecutive patients undergoing elective colonoscopy and including 3,720 patients.

The endoscopic appearance (i.e., diminutive size – less than 6 mm, or nonpolypoid shape – height less than one-half the diameter), of colorectal adenomas and serrated polyps (SPs), with a focus on adenomas with advanced histology included high-grade dysplasia or early CRC and SPs with dysplasia or large size.

In the 3,720 consecutive patients, there were 2,106 adenomas and 941 SPs. We found that in both men and women, proximal adenomas with high-grade dysplasia/early CRC (N = 181), were more likely to be diminutive or nonpolypoid than distal ones (76.3% vs. 26.2%). Of the proximal adenomas, 84.4% were diminutive or nonpolypoid, compared with 68% of the distal ones. Likewise, large and dysplastic SPs in the proximal colon were more often nonpolypoid than distal ones (66.2% vs. 27.8%).

It was concluded that proximal colorectal neoplasms with advanced histology frequently are small, or have a nonpolypoid appearance. These findings were considered to support careful inspection of the proximal colon, if quality of cancer prevention with the use of colonoscopy is to be optimized.


Serrated Polyposis and Risk in Relatives For Carcinoma
In order to explore cancer risk for relatives of patients who have identified serrated polyps, including hyperplastic polyposis with serrated architecture in the colon and rectum, while the patients themselves are at increased risk of colorectal carcinoma, the aim of this study was to estimate the risks of CRC and extracolonic cancers for relatives of these patients.

A cohort of 1639 first and second-degree relatives of 100 indexed patients with serrated polyposis were included, regardless of the family history of polyps or cancer from genetic clinics in Australia, New Zealand, Canada, and the USA. These were retrospectively analyzed to estimate the country, age, and sex-specific standardized incidence ratios (SIRs) for relatives, compared with the general population.

A total of 102 CRCs were observed in first and second-relatives (SIR 2.25), with 54 in first-degree relatives (SIR 5.16), and 48 in second-degree relatives (SIR 1.38). Six pancreatic cancers were observed in first degree relatives (SIR 3.64). There was no statistical evidence of increased risk for cancer of the stomach, brain, breast, or prostate.
It was concluded that relatives of serrated polyposis patients are at significant increased risk of colorectal and pancreatic cancer and supporting the interpretation of a hereditary component.


Risk of HCC in Hepatitis B Patients with a Low HBV Load

To evaluate whether higher levels of HBsAg increase risk for hepatocellular carcinoma (HCC), a total of 2688 Taiwanese HBsAg-positive patients without evidence of cirrhosis were followed for a mean time period of 14.7 years. In addition to the known risk factors of HCC, the association between levels of HBsAg and the development of HCC were investigated.

Of the patients followed, 191 developed HCC with an average annual incidence rate of 0.5%. Baseline levels of HBsAg and HBV were associated with development of HCC and risk increase with increase in levels.

Compared to the HBsAg level, HBV DNA better predicted the development of HCC during 10 year and 15 year periods. However, evaluating hepatitis Be antigen-negative patients with levels of HBV DNA less than 2000 IU/mL, factors that determined HCC risk included sex, age, ALT and HBsAg 1000 international units or less, but did not follow the level of HBV DNA.

Multivariate analysis showed that the adjusted hazard ratio for HCC in patients with levels of HBsAg equal or greater than 1000 IU/mL versus less than 1000 IU/mL was 13.7.

It was concluded among patients infected with HBV genotype B or C that determinants of HCC risk include their sex, age, hepatitis Be antigen status, HBV genotype, and levels of alanine aminotransferase (ALT) and HBV DNA, but not the level of HBsAg. Among hepatitis Be antigen-negative patients with low viral loads, HCC risk is determined by levels of HBsAg and ALT and age, but not HBV DNA.


Crohn’s Ileocolitis and Mucosal Healing with Adalimumab

To investigate the efficacy of adalimumab for inducing and maintaining mucosal healing in patients with Crohn’s disease (CD), a randomized, double-blind, placebo-controlled trial (EXTEND) evaluated that drug for induction and maintenance of mucosal healing in 135 adults with moderate to severe ileocolonic CD. The baseline degree of mucosal ulceration was documented by ileocolonoscopy. All patients received induction therapy (subcutaneous adalimumab 160/80 mg at weeks 0/2, and at week 4 were randomly assigned to groups given 40 mg of medication or placebo every other week through week 52).

Open label adalimumab was given to patients with flares or no response starting at week 8. Mucosal healing was reassessed by ileocolonoscopy at weeks 12 and 52.

A total of 27% of patients receiving the drug had mucosal healing at week 12 versus 13% given placebo. At week 52, rates of mucosal healing were 24% and 0%, respectively. Remission rates based on Crohn’s disease endoscopic index of severity were 52% for adalimumab and 28% for placebo at week 12, and 28% and 3%, respectively, at week 52.

Rates of clinical remission based on Crohn’s disease activity index were greater among patients given continuous adalimumab therapy versus placebo at week 12 (47% versus 28%), and week 52 (33% versus 9%). Five serious infections occurred during induction and four during open-label therapy. Three opportunistic infections, one in each group during double-blind therapy occurred, with one during open-label therapy reported.

It was concluded that following induction therapy with adalimumab, patients with moderately to severe active CD who continued to receive the drug are more likely to achieve mucosal healing than those given placebo.


Murray H. Cohen, D.O., “From the Literature” Editor, is on the Editorial Board of Practical Gastroenterology.
SYNERGY PHARMACEUTICALS HIGHLIGHTS MECHANISTIC FEATURES OF PLECANATIDE, A NOVEL INVESTIGATIONAL DRUG FOR CHRONIC IDIOPATHIC CONSTIPATION

Scientific Poster Presentations at ACG 2012 and UEG Week

NEW YORK--Synergy Pharmaceuticals Inc. (Nasdaq: SGYP), a developer of new drugs to treat gastrointestinal disorders and diseases, announced the preclinical findings being presented by Synergy scientists at two key gastroenterology congresses.

The scientific poster presentations describe the site of action and other mechanistic features of plecanatide, Synergy’s investigational drug for the treatment of chronic idiopathic constipation (CIC) and constipation-predominant irritable bowel syndrome (IBS-C). Plecanatide is an agonist of the guanylate cyclase-C receptor and an analog of the natriuretic peptide, uroguanylin, the physiologic ligand of GC-C. As a uroguanylin analog, plecanatide is a member of a new class of non-systemic oral drugs, known as guanylate cyclase-C (GC-C) agonists, that act locally to promote intestinal fluid secretion.

“These preclinical studies helped to define plecanatide as the superior candidate for clinical testing in patients with chronic constipation,” said Dr. Kunwar Shailubhai, Chief Scientific Officer of Synergy Pharmaceuticals, presented the data at the America College of Gastroenterology annual meeting in Las Vegas, NV. “In phase I and early phase II clinical testing, plecanatide exhibited an excellent safety profile, and patients in the phase IIa trial experienced relief from constipation without any remarkable diarrhea,” said Stephen Comiskey, Synergy’s Vice President for Product Development, who presented the preclinical data at the 20th United European Gastroenterology Week in Amsterdam, The Netherlands. “This summer Synergy achieved target enrollment in an ongoing phase IIb/III clinical trial of plecanatide in patients with chronic constipation, and we look forward to the results later this year.”

Key preclinical findings being presented that informed the clinical testing of plecanatide as an optimal drug candidate include:

• Orally administered plecanatide acts primarily in the proximal intestine to stimulate water secretion essential for normalizing bowel movement.

• In vitro binding studies demonstrate that plecanatide binds to the same receptors in the proximal intestine as human uroguanylin.

• Plecanatide is highly stable and potent, with even greater affinity for the human GC-C receptors than the natural uroguanylin hormone.

“There is a compelling need to find safe and effective treatments for patients with CIC,” said Douglas Drossman, Adjunct Professor of Medicine and Psychiatry and Co-Director Emeritus, UNC Center for Functional GI and Motility Disorders, UNC School of Medicine. “I am encouraged by the preclinical and early phase clinical data that demonstrate proof of concept for plecanatide as a treatment approach for chronic constipation, and look forward to seeing data from the ongoing trials.”

Earlier this fall, in a poster session at the Joint International Neurogastroenterology and Motility Meeting, September 6-8, in Bologna, Italy, Synergy scientists also shared data describing the identification and selection of plecanatide (formerly SP-304) as the superior analog of uroguanylin based on physiochemical properties.
About Plecanatide

Plecanatide is a member of a new class of essentially non-systemic drugs, referred to as guanylate cyclase C (GC-C) agonists, that are currently in development to treat CIC and IBS-C. Plecanatide is a synthetic analog of uroguanylin, a natriuretic hormone that regulates ion and fluid transport in the GI tract. Orally-administered plecanatide binds to and activates GC-C receptors expressed on epithelial cells lining the GI mucosa, resulting in activation of the cystic fibrosis transmembrane conductance regulator (CFTR), and leading to augmented flow of chloride and water into the lumen of the gut. Activation of the GC-C receptor pathway is believed to facilitate bowel movement as well as producing other beneficial physiological responses including improvement in abdominal pain and inflammation. In animal models, oral administration of plecanatide promotes intestinal secretion and also ameliorates GI inflammation.

Forward-Looking Statements

Certain statements in this press release are forward-looking within the meaning of the Private Securities Litigation Reform Act of 1995. These statements may be identified by the use of forward-looking words such as “anticipate,” “planned,” “believe,” “forecast,” “estimated,” “expected,” and “intend,” among others. These forward-looking statements are based on Synergy’s current expectations and actual results could differ materially. There are a number of factors that could cause actual events to differ materially from those indicated by such forward-looking statements. These factors include, but are not limited to, substantial competition; our ability to continue as a going concern; our need for additional financing; uncertainties of patent protection and litigation; uncertainties of government or third party payer reimbursement; limited sales and marketing efforts and dependence upon third parties; and risks related to failure to obtain FDA clearances or approvals and noncompliance with FDA regulations. As with any pharmaceutical under development, there are significant risks in the development, regulatory approval and commercialization of new products. There are no guarantees that future clinical trials discussed in this press release will be completed or successful or that any product will receive regulatory approval for any indication or prove to be commercially successful. Investors should read the risk factors set forth in Synergy’s Form 10-K for the year ended December 31,
2011 and other periodic reports filed with the Securities and Exchange Commission. While the list of factors presented here is considered representative, no such list should be considered to be a complete statement of all potential risks and uncertainties. Unlisted factors may present significant additional obstacles to the realization of forward-looking statements. Forward-looking statements included herein are made as of the date hereof, and Synergy does not undertake any obligation to update publicly such statements to reflect subsequent events or circumstances.

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**GIVEN IMAGING REPORTS DATA SHOWING GREATER ROLE FOR CAPSULE ENDOSCOPY IN DETECTING AND MONITORING CROHN’S DISEASE**

**Capsule Endoscopy Found to Be Superior to Magnetic Resonance Enterography for Detecting Crohn’s Disease Lesions**

**AMSTERDAM, THE NETHERLANDS** – Given Imaging Ltd. (NASDAQ: GIVN), a world leader in GI medical devices and pioneer of capsule endoscopy, announced results of two studies suggesting an increased role for capsule endoscopy in detecting Crohn’s lesions in the small bowel. The studies were presented at the United European Gastroenterology Week (UEGW), Europe’s largest gastroenterology conference in Amsterdam, October 20-24, 2012.

“Capsule endoscopy for the detection of Crohn’s disease in the small bowel has been clinically validated by a substantial and growing body of peer-reviewed research,” said presenter Roberta Pica, M.D., Department of Clinical Sciences, Gastroenterology Unit at the Sapienza University of Rome. “As physicians, it’s important to gather as much information as possible about the structural changes in the lining of the patient’s small and large intestines to determine an accurate diagnosis and proper course of treatment. In this new study, early evidence shows that capsule endoscopy, widely considered the gold standard in small bowel visualization, is superior to magnetic resonance enterography (MRE) as a reliable tool to evaluate the type and extent of mucosal lesions associated with small bowel Crohn’s disease. This information can lead to a more precise course of treatment with the goal to improve patient outcomes.”

Dr. Pica and colleagues presented the results of a prospective study (P1414) comparing use of wireless capsule endoscopy (WCE) to magnetic resonance enterography (MRE) in the small bowel of 16 consecutive patients with confirmed or suspected Crohn’s disease. In nine of 10 patients (90%), WCE detected significant lesions as indicated by the presence of erythema, aphthous, ulcers, fissures or mucosal hemorrhages, with four patients showing lesions in both the jejunum and ileum and five only of the terminal ileum. MRE was less accurate than WCE, detecting inflammatory lesions in 11 of 15 patients (73%), with two patients showing lesions in both the jejunum and ileum and nine in only the terminal ileum. In a group of nine patients who were evaluated with both examinations, WCE detected lesions in eight patients (90%), while MRE detected lesions in eight patients (90%), while MRE detected lesions in six (67%). In addition, 2 patients had a false negative on MRE and showed significant lesions in the terminal ileum with capsule endoscopy, and capsule endoscopy was able to exclude a false positive diagnosis of lymphoma suggested by MRE. The authors concluded that both tools are complementary methods for diagnosing small bowel Crohn’s disease, noting that WCE represents a reliable tool in the evaluation of mucosal lesions for the direct visualization of the mucosal surface, while MRE enables physicians to diagnose specific alterations of the bowel wall.

Separately, Efstathios Saprikis, M.D., 2nd Department of Gastroenterology, Evangelismos Hospital, Athens, Greece, presented a poster (P0203) showing that small bowel capsule endoscopy in patients with established Crohn’s disease is safe and associated with a low percentage of capsule retention. When capsule retention did occur, the majority of the cases were adequately managed with conservative treatment. Dr. Saprikis and colleagues identified 301 patients who underwent ileocolonoscopy prior to small bowel capsule endoscopy. Among the 301 eligible patients with established Crohn’s disease, capsule endoscopy identified signs of Crohn’s disease in the small bowel in 196 (65.1%). Capsule retention only occurred in five patients (1.66%). These reported capsule retention rates are in line with previously reported data as well as society guidelines for CE use in patients with suspected Crohn’s or established Crohn’s disease.

**About PillCam® SB**

The PillCam®SB video capsule is a minimally invasive procedure to visualize and monitor lesions (continued on page 74)
associated with inflammatory bowel disease (IBD), Crohn’s disease and obscure GI bleeding (OGIB). The PillCam measures 11 mm x 26 mm and weighs less than four grams. Now in its second generation, PillCam SB 2 contains an imaging device and light source and transmits images at a rate of two images per second generating more than 50,000 pictures during the course of the procedure. Initially cleared by the U.S. Food and Drug Administration in 2001, PillCam SB is clinically validated by more than 1,500 peer-reviewed studies. It is an accurate, patient-friendly tool used in patients two years and older by physicians to visualize the small bowel. PillCam SB is the gold standard in small bowel evaluation.

The risks of PillCam® capsule endoscopy include capsule retention, aspiration, or skin irritation. The risks of the PillCam patency capsule include capsule retention and aspiration. Endoscopic placement may present additional risks. Medical, endoscopic, or surgical intervention may be necessary to address any of these complications, should they occur.

**GIVEN IMAGING REPORTS NEW STUDIES CONFIRMING CLINICAL UTILITY OF ITS FUNCTIONAL GASTROINTESTINAL DIAGNOSTICS PRODUCTS**

**Studies Show Value of Incorporating High Resolution Manometry in the Diagnostic Examination of Achalasia and Anorectal Disorders.**

**Expanding the Duration of pH Measurement Allows Doctors to Confidently Separate Healthy Patients From Those With Reflux**

**AMSTERDAM, THE NETHERLANDS -** Given Imaging Ltd (NASDAQ: GIVN), a world leader in GI medical devices and pioneer of capsule endoscopy, announced new studies confirming the clinical utility of its functional GI products including ManoScan™ and the Bravo® pH monitoring system. The data were presented at the United European Gastroenterology Week (UEGW), Europe’s largest gastroenterology conference in Amsterdam, October 20-24, 2012. Among the abstracts presented were those discussing an optimal technique for high resolution manometry (HRM), as well as data on Bravo® pH monitoring showing that prolonged pH measurement helps predict treatment outcomes with confidence.

“They new studies indicate that the medical community continues to find additional insights to be gained through high resolution manometry and pH monitoring that will help us improve patient care,” said Sabine Roman, MD, PhD., Lyon. “Different disease states, including achalasia and diabetes, cause different problems with motility. HRM allows physicians to diagnose the cause underlying the problem, which informs treatment. In addition, a new study on Bravo pH monitoring demonstrates the value of prolonged pH measurement in predicting outcomes with confidence.

**Among the Studies Presented about HRM at UEG Week:**

**Esophageal High Resolution Manometry (HRM) in Achalasia: Evaluation of the Classification in a French Multicentric Cohort (P1562) by Sabine Roman, MD, PhD., of the Hospices Civils de Lyon, Edouard Herriot Hospital, Digestive Physiology, (Chief of department : Pr Mion), Lyon, France, and colleagues.** In this study, the researchers used HRM and the Chicago Classification to evaluate and classify patients diagnosed with achalasia. They successfully classified the patients by subtype, which assisted them in drawing conclusions about the pathophysiology of the various types of achalasia.

**What Diagnosis Obtained in High Resolution Manometry Depending on the Body Position Correlates Better with Gastroesophageal Reflux Assessed by pH-Metry? (P1556) by Constanza Ciriza de Los Rios, MD, of the Hospital 12 de Octubre-Gastroenterology in Madrid, Spain, and colleagues.** This study focused on optimal body position for esophageal motility assessment by HRM, and aimed to determine which results obtained in HRM depending on body position predict better gastroesophageal reflux. The study authors performed HRM upright and in supine on 111 patients, all of which had double channel 24 hour-pH metry. The researchers concluded that hypotensive lower esophageal sphincter and hiatus hernia were more frequently diagnosed upright in patients with abnormal pH-metry, and thus the sitting position is better at identifying predisposing pathophysiological mechanisms of gastroesophageal reflux.

**In addition, the following study was presented on Bravo® pH monitoring system:**

**Reflux Associated Symptoms Per Day and Symptom Index with Confidence Intervals: New Indices of Reflux-Symptom Association For Diagnosis Of Reflux Disease That Improve Prediction of Treatment Outcome From Prolonged pH-Monitoring (P0446)**
by Mark Fox, MD MA MRCP, Department of Gastroenterology, Nottingham Digestive Diseases Centre, NIHR Biomedical Research Unit, Nottingham University Hospital, Queen’s Medical Centre, Nottingham, United Kingdom, and colleagues. This study aimed to obtain metrics from prolonged wireless pH-studies using Bravo technology to discriminate healthy patients from those with reflux, and then predict proton-pump inhibitor (PPI) response. To accomplish this, the researchers recruited healthy volunteers and patients with reflux symptoms and assessed their symptoms with and without PPI medication. They were able to differentiate healthy volunteers from patients using Bravo pH monitoring to evaluate reflux symptoms, and concluded that prolonged pH-measurement is required to predict treatment outcomes with confidence.

About United European Gastroenterology

UEG, or United European Gastroenterology, is a professional non-profit organization combining all the leading European societies concerned with digestive disease. Together, their member societies represent over 22,000 specialists, working across medicine, surgery, pediatrics, GI oncology and endoscopy. This makes UEG the most comprehensive organisation of its kind in the world, and a unique platform for collaboration and the exchange of knowledge.

UEG’s mission is continually to improve standards of care in gastroenterology, and promote ever greater understanding of digestive and liver disease -- among the public and medical experts alike. As part of that work, it runs a number of education and training courses facilitated by highly respected experts. UEG also organizes UEG Week -- the largest and most prestigious meeting of its kind in Europe. UEG Week has been running since 1992, in a variety of major cities, and now attracts more than 14,000 people from across the world. For more information, please visit www.ueg.eu

About Digestive Motility

Motility disorders occur when the natural muscle movements of the digestive tract that help to propel food content are impaired. These disorders can impact a portion or all of the digestive tract. Examples of digestive motility diseases and disorders include chronic intestinal pseudo-obstruction (CIP), gastroparesis, dysphagia, and diffuse esophageal spasm (DES). Achalasia is a motility disorder that occurs when there is a complete lack of muscle movement within the esophagus, preventing food from entering the stomach. Symptoms are difficulty swallowing liquids and solids and can also include regurgitation, vomiting, weight loss, and atypical chest discomfort.

About ManoScan™ ESO

ManoScan ESO is a test used to assess esophageal motor function by providing complete physiological mapping, from the pharynx to the stomach, with a single placement of a catheter. This advanced diagnostic technology allows physicians to evaluate causes of gastric reflux, difficulty swallowing, functional chest pain and pre-operative evaluations. As the first solid-state commercially available high resolution manometry technology, ManoScan™ remains the global market leader in technologically advanced solutions for assessing gastrointestinal motility. It is the only platform validated for the Chicago Classification System, the industry’s standardized categorization scheme for identification of motility disorders. All ManoScan ESO systems incorporate the new ManoView ESO v 3.0.

About the Bravo® pH Monitoring System

The Bravo® pH monitoring system is the only catheter-free pH test. The procedure uses a pH capsule that is temporarily attached to the wall of the esophagus to wirelessly transmit pH data continuously for up to 96 hours. Like catheter-based pH tests, the Bravo pH Monitoring System is an ambulatory method of pH monitoring, considered the gold standard for pH measurement and monitoring of gastric reflux. The Bravo pH monitoring system collects data that are more reflective of the patient’s normal daily routine to assess if the patient has GERD.

The risks of Bravo pH monitoring include: premature detachment, discomfort, failure to detach, failure to attach, capsule aspiration, capsule retention, tears in the mucosa, bleeding, and perforation. Endoscopic placement may present additional risks. Medical, endoscopic, or surgical intervention may be necessary to address any of these complications, should they occur. Because the capsule contains a small magnet, patients should not have an MRI study within 30 days of undergoing the Bravo pH test.

Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the “safe harbor” provisions of the
U.S. Private Securities Litigation Reform Act of 1995. These forward-looking statements include, but are not limited to, projections about our business and our future revenues, expenses and profitability. Forward-looking statements may be, but are not necessarily, identified by the use of forward-looking terminology such as “may,” “anticipates,” “estimates,” “expects,” “intends,” “plans,” “believes,” and words and terms of similar substance. Forward-looking statements involve known and unknown risks, uncertainties and other factors which may cause the actual events, results, performance, circumstances or achievements of the Company to be materially different from any future events, results, performance, circumstances or achievements expressed or implied by such forward-looking statements. Such forward-looking statements include statements relating to the Company exploring strategic alternatives and considering possible strategic transactions involving the Company. Factors that could cause actual events, results, performance, circumstances or achievements to differ from such forward-looking statements include, but are not limited to, the ability of the Company to reach agreement on any strategic alternative and/or to complete any such alternative, as well as the following: (1) our ability to develop and bring to market new products, (2) our ability to successfully complete any necessary or required clinical studies with our products, (3) our ability to receive regulatory clearance or approval to market our products or changes in regulatory environment, (4) our success in implementing our sales, marketing and manufacturing plans, (5) the level of adoption of our products by medical practitioners, (6) the emergence of other products that may make our products obsolete, (7) lack of an appropriate bowel preparation materials to be used with our PillCam COLON capsule, (8) protection and validity of patents and other intellectual property rights, (9) the impact of currency exchange rates, (10) the effect of competition by other companies, (11) the outcome of significant litigation, (12) our ability to obtain reimbursement for our product from government and commercial payors, (13) quarterly variations in operating results, (14) the possibility of armed conflict or civil or military unrest in Israel, (15) the impact of global economic conditions, (16) our ability to successfully integrate acquired businesses, (17) changes and reforms in applicable healthcare laws and regulations, (18) quality issues and adverse events related to our products, such as capsule retention, aspiration and failure to attach or detach, bleeding or perforation that could require us to recall products and impact our sales and net income, and (19) other risks and factors disclosed in our filings with the U.S. Securities and Exchange Commission, including, but not limited to, risks and factors identified under such headings as “Risk Factors,” “Cautionary Language Regarding Forward-Looking Statements” and “Operating Results and Financial Review and Prospects” in the Company’s Annual Report on Form 20-F for the year ended December 31, 2011. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date of this press release. Except to the extent expressly required under applicable law, the Company undertakes no obligation to release publicly any revisions to any forward-looking statements, to report events or to report the occurrence of unanticipated events.


About Given Imaging Ltd.

Since pioneering the field of capsule endoscopy in 2001, Given Imaging has become a world leader in GI medical devices, offering health care providers a range of innovative options for visualizing, diagnosing and monitoring the digestive system. The company offers a broad product portfolio including PillCam® capsule endoscope for the small bowel, esophagus and colon. The company also offers industry-leading GI functional diagnostic solutions including ManoScan™ high-resolution manometry, Bravo® capsule-based pH monitoring, Digitrapper® pH-Z impedance, and the SmartPill® GI monitoring systems. Given Imaging is committed to delivering breakthrough innovations to the GI community and supporting its ongoing clinical needs. Given Imaging’s headquarters are located in Yoqneam, Israel, with operating subsidiaries in the United States, Germany, France, Japan, Australia, Vietnam, Hong Kong and Brazil.

For more information, please visit: www.givenimaging.com

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MEETINGS CALENDAR

December 13-15, 2012
2012 Advances in Inflammatory Bowel Diseases, Crohn’s & Colitis Foundation’s Clinical & Research Conference
The Westin Diplomat, 3555 South Ocean Drive, Hollywood, FL. The premier IBD meeting of the year. Two workshops, The Future of IBD and The Basics of IBD, will be held at the conference. This “can’t miss” event will inform healthcare professionals and researchers of advances and breakthroughs in the field in an effort to stimulate better care and research for patients. The outstanding faculty is comprised of expert specialists who will lead the sessions and interact with the conference attendees. For more information visit: www.advancesinibd.com/2012/index.asp

May 17–22, 2013
SGNA 40th Annual Course
Austin, Texas—Celebrating 40 years of Annual Course education, The Society of Gastroenterology Nurses and Associates brings together the best and brightest GI/endoscopy professionals to drive the future of our field. SGNA is the leading organization of nurses and associates dedicated to the safe and effective practice of gastroenterology and endoscopy nursing. SGNA advances the science and practice of gastroenterology and endoscopy nursing through education, research, advocacy and collaboration, and by promoting the professional development of its members in an atmosphere of mutual support. Our membership spans across the United States and 16 other countries with a full range of members from Registered Nurses, Licensed Practical/Vocational Nurses, Associates (assistants and technicians) and Advance Practice Nurses. For more information visit: www.sgna.org

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

by Myles Mellor

DOWN
1 Important prognostic factor in patients with cirrhosis, abbr.
2 Proportion in relation to the whole
3 Poisonous
4 Patient’s record
6 The R in RFA
7 Like some vaccines
8 Patient measurement
11 Ilia location
13 Long fish
15 Female reproductive cells
17 Type of test
18 Temporary loss of consciousness caused by a fall in blood pressure
20 Expert
21 A vertebra
22 Calcium symbol
23 Rigid
24 Spirally twisted elongate rodlike bacteria
26 Key point
28 Depression
31 Sarcoma, for example
33 Breathing devices
34 Head cover
35 Bones, anatomically
38 Low-density lipoprotein
39 Diagnostic procedure, for short
41 Silver symbol

(Answers on page 70)

ACROSS
1 The H in HVPG
5 Mathematical model used in medical studies
9 Unwanted vein
10 Enzyme that catalyzes the removal of water from a material
12 Disease also known as Silk Road, ______’s disease
14 The P in BPA
16 Kilogram, for short
19 Abnormal change of body tissue
22 Abnormal body growth
24 Sound
25 _____graphy, medical imaging technique
27 Brightened, in a way (2 words)
29 Type of scan, for short
30 Feel bad about
32 Non-invasive medical imaging technique that detects tumors
36 Erode, with away
37 Abnormal enlargement of the spleen
40 Input/output, for short
41 Administrative branch
42 Referring to the inability of the body to create new cells
43 The value of this accurately predicts a portal hypertensive cause, abbr.