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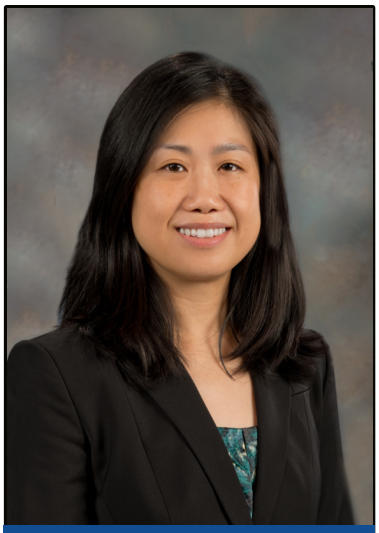


SHE-YAN WONG, MD

IN THIS EDITION

AN OVERVIEW OF DRUG INDUCED LIVER INJURY

Drug induced liver injury (DILI) from prescription medications and over the counter herbal and dietary supplements (HDS) are common occurrences and are often a cause of abnormal liver tests. It is becoming more common as there are now over 100,000 HDS available and many patients are looking for more natural forms of treatment. Diagnosis of DILI can be difficult due to the lack of a diagnostic biomarker. Careful history taking and exclusion of other causes of liver injury is essential.

There are two main mechanisms of DILI. It can be a direct hepatotoxic reaction or it may be idiosyncratic. Direct hepatotoxicity is dose-dependent and predictable. A well-known example is an acetaminophen/Tylenol overdose. Idiosyncratic reactions on the other hand are not dose dependent and are unpredictable. Examples of these causes include antibiotics, most notably Augmentin and Bactrim. Risk factors for idiosyncratic DILI are likely multifactorial including host genetics, co-morbidities, and the drug itself.

The diagnosis of DILI can be difficult. The presentation of abnormal liver tests can vary from mildly asymptomatic elevation of liver tests to fulminant liver failure. The pattern of abnormal liver tests can be hepatocellular, cholestatic or mixed. A detailed history is vital to the diagnosis. This includes a discussion regarding timing of current or prior medications, dose changes, and any OTC or HDS that may not be included on medication lists. Since DILI is a diagnosis of exclusion, other causes of abnormal liver tests should be evaluated. It is necessary to evaluate for viral hepatitis, autoimmune liver disease, metabolic and genetic liver disease, biliary obstruction, masses, or vascular abnormalities. A liver biopsy is indicated for lack of improvement or concern for autoimmune hepatitis. The LiverTox website is a public database of published drug presentations and is a great resource for evaluating DILI.

Herbal and dietary supplements (HDS) are some of the most common causes of DILI. According to the Drug Induced Liver Injury Network registry, HDS make up to 20% of all cases of DILI. Though most are safe, these products often are made of multiple ingredients, some of which are not listed, and overall are not well regulated. Reported HDS that have caused DILI include weight loss supplements such as Hydroxycut, Herbalife and green tea extract.

Statins are often implicated as causes of DILI by both clinicians and patients alike. However, clinically significant hepatic dysfunction from statins is rare. Elevation of aminotransferases are often mild and self-limited. Baseline liver tests are recommended to be checked prior to starting statins, but are not necessary to be monitored while on treatment. Statins may even be beneficial for patients with chronic liver disease. Patients with metabolic associated fatty liver disease are at higher risk from cardiovascular related complications compared to liver related ones, and therefore those patients should be continued on statins. Statin use has also been suggested in some studies to decrease the risk of hepatocellular carcinoma in cirrhosis and improve portal hypertension. Statins should be avoided in patients with decompensated cirrhosis.

The management of DILI is often supportive. Most patients improve on their own with withdrawal of the medication. It may take months for liver tests to improve and normalize. For patients with significant liver injury, N-acetylcysteine (NAC) has been used for both acetaminophen and non-acetaminophen related liver failure. Steroids are used to treat immune-mediated reactions or autoimmune hepatitis. In rare occasions, liver transplant may be indicated.

In conclusion, DILI from prescription medications and HDS are common causes of abnormal liver tests. A detailed history is vital to the diagnosis. The LiverTox website is a great resource. Most patients improve with supportive care and withdrawal of the medication.

MATTHEW SULLIVAN, DO

MICROBIAL MISCHIEF: SMALL INTESTINAL BACTERIAL OVERGROWTH

The role of the microbiome in gastrointestinal disease is a rapidly growing focus of research. It is well known that the colon has a significantly higher microbial colonization compared to the small bowel. Alterations in this balance can lead to gastrointestinal distress. Small intestinal bacterial overgrowth (SIBO) is the name given to this alteration where elevated numbers of bacteria, chiefly gram-negative coliforms, colonize the small bowel and produce gastrointestinal symptoms[1]. In this article, we will focus on the clinical manifestations, diagnosis, and treatment of SIBO, as well as a possibly separate condition known as intestinal methanogen overgrowth (IMO).

The most commonly reported symptoms of SIBO include abdominal pain, bloating, gas, flatulence, abdominal distention and diarrhea. Over two-thirds of patients with SIBO report some combination of those symptoms. Extra-intestinal symptoms, such as fatigue and poor concentration, have also been reported. In more severe cases, deficiencies of vitamin B12, vitamin D and iron can be seen.

Symptoms of SIBO often present similarly to other conditions such as irritable bowel syndrome, or can overlap with concomitant diagnoses such as exocrine pancreatic insufficiency and Crohn disease. Therefore, it is important to keep a high index of suspicion, especially in patients with risk factors for SIBO. In fact, the American College of Gastroenterology (ACG) suggests testing for SIBO in patients with IBS[1].

Various conditions predispose people to developing SIBO, typically through promotion of stasis in the small intestine. This includes systemic conditions such as systemic sclerosis, celiac disease, and diabetes, as well as immunodeficiency syndromes like common variable immunodeficiency and HIV. Structural abnormalities such as small bowel diverticulosis, mechanical obstructions such as small bowel tumors, and Roux-en-Y gastric bypass or an ileocolonic anastomosis can also increase the incidence of SIBO[1].

Aspiration and culture of small bowel fluid is the gold standard for SIBO diagnosis. However, the most common diagnostic test for SIBO, and the one recommended by the American College of Gastroenterology, is the hydrogen (+/- methane) breath test. As hydrogen and methane are not capable of being produced naturally in the gastrointestinal tract, any detection of these gases in breath samples is indicative of another source. One such source is the fermentation of carbohydrates by the microbial flora in the gut leading to hydrogen production. Hydrogen is then absorbed into the blood stream and exhaled through the lungs[1].

To perform breath testing, the North American Consensus recommends a standardized carbohydrate ingestion of 75 grams of glucose or 10 grams of lactulose with 1 cup of water. Breath samples are obtained prior to ingestion and every 15-20 minutes after ingestion for up to 3 hours. An increase in hydrogen concentration of ≥20 ppm from baseline within 90 minutes is diagnostic for SIBO. In order to improve accuracy of breath testing, it is recommended that patients avoid antibiotics for 4 weeks and avoid laxatives and promotility agents for one week prior to testing. Avoiding complex carbohydrates for 24 hours and fasting for 8-12 hours before the test is also recommended[1].

Many breath tests also measure exhaled methane. The symptoms of excess methane can differ as methane can slow gastrointestinal transit time and lead to constipation. Therefore, the term intestinal methanogen overgrowth (IMO) has been introduced and is more accurate[1] for these patients.

Table 1. Alternative Antibiotics for SIBO

Trimethoprim-sulfamethoxazole	160/800 mg twice daily
Ciprofloxacin	500 mg twice daily
Amoxicillin-clavulanate	875 mg twice daily
Metronidazole	250 mg three times daily
Doxycycline	100 mg once or twice daily
Tetracycline	250 mg four times daily

The mainstay of SIBO treatment is antibiotics to reduce small intestinal bacterial colonization. Multiple antibiotics have been studied and demonstrate varying levels of efficacy. UpToDate recommends rifaximin, a non-absorbable derivative of rifamycin, as the first-line agent. Rifaximin is prescribed for SIBO treatment at 550 mg three times daily for 14 days and is typically well tolerated. Alternative antibiotic regimens are listed in Table 1 and are all given for a 10 day course.

Unfortunately, ~40% of patients with SIBO will have persistent symptoms after treatment[2]. This has led to studies looking at alternate strategies for antibiotic administration such rotating antibiotics. A European study from 2020 showed that rotating nitroimidazole and quinolone antibiotics for 10 consecutive days per month for 3 months was more effective than using a single course of either antibiotic[3].

Probiotics are an area of interest for the management of SIBO, but the literature has been mixed. A meta-analysis published in 2017 found that probiotics reduced hydrogen production and showed improvement in abdominal pain, however most of the included studies were small and of poor quality. Also, a study from 2018 showed a possible link between probiotics, SIBO, and D-lactic acidosis causing gas and bloating. In this study, stopping probiotics and treating with antibiotics led to symptom improvement[1].

Dietary modification may also be beneficial for SIBO. Eating a low fermentation diet, such as the low FODMAP (Fermentable Oligo-, Di-, Mono-saccharides And Polyols) diet has been shown in some studies to reduce exhaled hydrogen on breath testing. However, a meta-analysis published in 2018 found “very low quality evidence” to support following a low FODMAP diet to treat SIBO symptoms in patients with IBS[1]. Regarding treatment for IMO, UpToDate recommends a combination of neomycin and rifaximin[1] as the treatment for IMO[2]. There is also interesting literature showing that statins can inhibit methanogenesis, but this is still experimental[4].

When evaluating patients with complaints of altered bowel habits and bloating, it is important to keep SIBO in the differential diagnosis. Breath testing is readily available through our office and can guide treatment. It is also imperative to consider the conditions that increase the risk for SIBO development as treatment of these underlying conditions is part of adequate treatment.

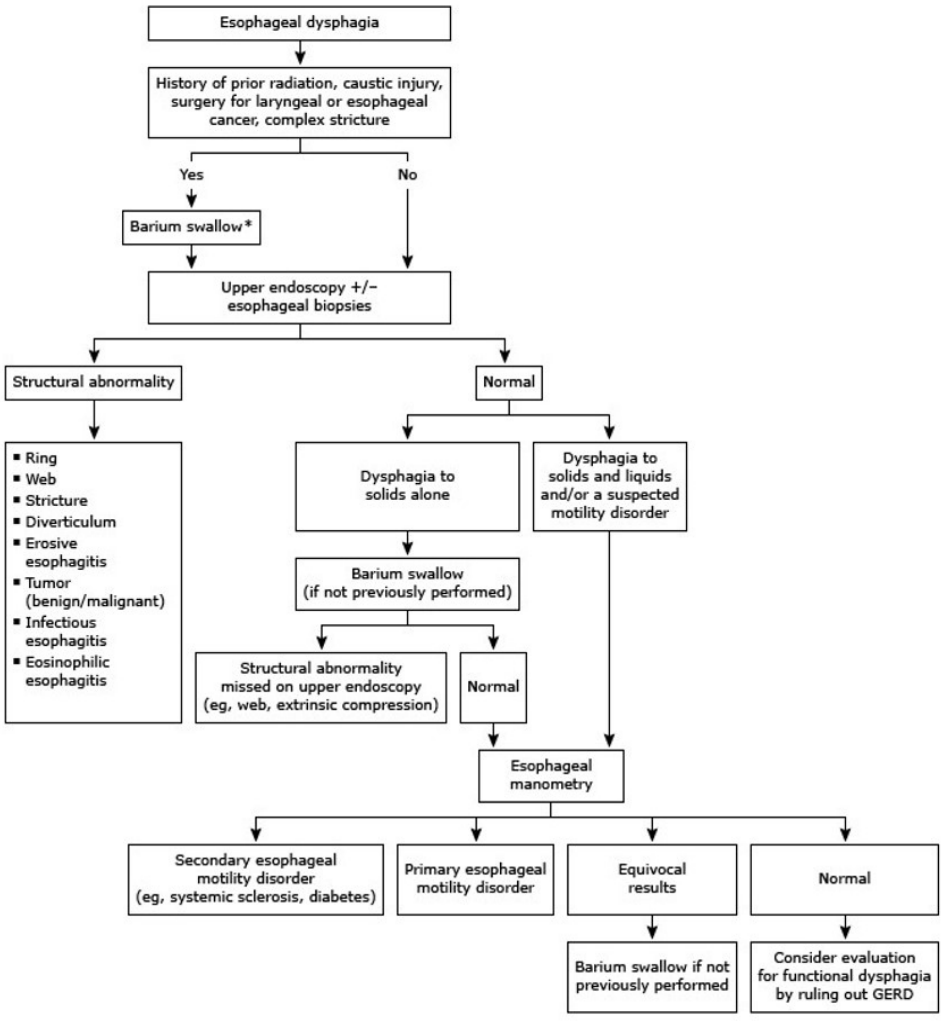
HIRAL SHAH, MD

APPROACH TO CHRONIC ESOPHAGEAL DYSPHAGIA IN ADULTS

Dysphagia is an alarm symptom that warrants prompt evaluation to define the exact cause and initiate appropriate therapy. Causes can be structural or due to a motility abnormality with the passage of solids or liquids through the esophagus. This synopsis focuses on esophageal dysphagia. Patients with esophageal dysphagia may complain of difficulty swallowing upon initiating a swallow or a sensation that foods and/or liquids are being obstructed in their passage from the upper esophagus to the stomach. While retrosternal dysphagia usually corresponds with the location of the lesion, suprasternal dysphagia is commonly referred from below.

A large number of conditions are associated with esophageal dysphagia. Dysphagia to both solids and liquids from the onset of symptoms is often due to a motility disorder of the esophagus. Dysphagia to solids only is usually present when the esophageal lumen is narrowed to 13 mm or less (e.g. by a stricture). Progressive dysphagia, (transition from solids to liquids as well) is generally caused by a peptic stricture or an obstructing lesion. Symptoms of peptic stricture are slowly and gradually progressive, whereas those due to a malignancy progress more rapidly. Intermittent dysphagia may be related to a lower esophageal ring or web. Patients with motility disorders may also exhibit progressive dysphagia (e.g. achalasia) or may exhibit intermittent or nonprogressive dysphagia (e.g. distal esophageal spasm).

Approach to the patient with esophageal dysphagia



GERD: gastroesophageal reflux disease.

* Performing a barium swallow prior to an upper endoscopy is controversial.

Psychologic factors may influence the expression and severity of dysphagia symptoms. While psychologic factors have been identified as predictors of disease severity for patients with other gastrointestinal disorders (e.g. gastroesophageal reflux disease, irritable bowel syndrome, etc.), studies have suggested that anxiety and hypervigilance may also contribute to dysphagia severity.

A **barium contrast esophagram (barium swallow)** as the **initial test** (prior to upper endoscopy) should be considered in patients with the following:

●History/clinical features of proximal esophageal lesion (e.g., surgery for laryngeal or esophageal cancer, Zenker's diverticulum, or radiation therapy).

●Known complex (tortuous) stricture (e.g., post-caustic injury or radiation therapy)

Although intubation of the proximal esophagus in these patients during upper endoscopy may be associated with the risk of perforation due to upper esophageal pathology, it is important to note that performing a barium esophagram prior to an upper endoscopy in such patients has not been demonstrated to decrease the rate of endoscopic complication or improve outcomes.

Consideration should be given to barium esophagram after a negative upper endoscopy in patients in whom a mechanical obstruction is still suspected, as lower esophageal rings or extrinsic esophageal compression can be missed by an upper endoscopy.

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1501 N. Cedar Crest Blvd
Suite 110
Allentown PA, 18104

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Patients with esophageal dysphagia should be referred for an **upper endoscopy (EGD)** to determine the underlying cause, exclude malignancy, and perform therapy if needed (e.g., dilation of an esophageal ring). In a study of over 1600 patients with dysphagia who underwent upper endoscopy, the diagnostic yield was 54 percent and risk factors for having major pathology included male sex, heartburn, and odynophagia.

Esophageal manometry should be performed in patients with dysphagia in whom upper endoscopy is unrevealing and/or an esophageal motility disorder is suspected. Although certain motility disorders (e.g., achalasia) can be strongly suspected based upon their characteristic radiographic appearance when in advanced stages, confirmation with an esophageal manometry study is required to establish the diagnosis. Aging alone causes mild esophageal motility abnormalities, which are rarely symptomatic. Delayed esophageal clearance of barium in patients over 90 years old was originally referred to as "presbyesophagus"; however, we now avoid this term because it might imply that changes in esophageal motility are a normal consequence of aging and do not require further evaluation.

At EPGI we routinely see patients with complex issues related to dysphagia. Along with these diagnostic options, we provide comprehensive care in our foregut program which includes treatment options such as endoscopic myotomy for achalasia and other approaches to difficult/altered anatomy.

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