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Update in Gastroenterology and Hepatology: Evidence Published in 2016

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Abstract

This update summarizes key 2016 publications in gastroenterology and hepatology that the authors believe are of particular relevance to general internists. We reviewed 20 general medicine, gastroenterology, and hepatology journals to identify articles with broad clinical importance or novel findings. This year's liver related topics include a new drug for patients with primary biliary cholangitis who have an inadequate response to ursodiol, the loss of HBsAg with the combination of tenofovir disoproxil fumarate (TDF) and peginterferon alpha-2a (PEG2a) in patients with chronic hepatitis B (HBV), the use of an agonist of the peroxisome proliferator-activated receptor-alpha and –delta in patients with nonalcoholic steatohepatitis (NASH), and lastly the benefit of terlipressin plus albumin in patients with cirrhosis and hepatorenal syndrome type 1. Diseases of the upper gastroenterology tract include a new randomized, controlled trial looking at three different regimens for treatment of *Helicobacter pylori* infection and a large, national study looking at the risk of small bowel enteropathy with the angiotensin receptor blocker olmesartan. We also address the issue of proton pump inhibitor use with recent associations noted with coronary artery, kidney disease and dementia. For colonic disease we will review the recent US Preventive Services Task Force (USPSTF) update on colon cancer screening and discuss stool based screening tests for colon cancer and stool tests for triaging patients who present with bowel symptoms. We will address the use of diet therapy in irritable bowel syndrome with a prospective, randomized diet trial. The last article of interest will review the literature on the increasingly frequent cannabinoid hyperemesis syndrome and stress the importance of diagnosing this entity.

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Introduction

Diseases of the Liver

Background: Primary biliary cholangitis (PBC), previously known as primary biliary cirrhosis, is a chronic cholestatic disease with a progressive course that affects 1/1000 women age >40 years. The rate of progression varies greatly, and most patients are asymptomatic in early disease, but often leads to fatigue, pruritus and Sicca syndrome and rarely liver transplantation. Ursodeoxycholic Acid (UCDA, 13 mg/kg/day to 15 mg/kg/day) was the only FDA-approved therapy for PBC until 2016. UDCA delays progression of disease and improves survival and quality of life; however, up to 40% of patients have a suboptimal response to UCDA. An alkaline phosphatase level <1.67 × ULN and a normal bilirubin after 1 year of UDCA is highly predictive of outcome. Obeticholic Acid (OCA), a farnesoid X receptor agonist, has shown potential benefit in patients with this disease [1].

Findings: In this 12-month, double-blind, placebo-controlled, phase 3 trial (known as POISE), 217 patients who had an inadequate response to UDCA or who found the side effects of UDCA unacceptable were randomly assigned to receive OCA at a dose of 10 mg, or at a dose of 5 mg with adjustment to 10 mg, or placebo. The primary end point was an alkaline phosphatase level <1.67 × ULN, with a reduction of at least 15% from baseline, and a normal total bilirubin level. Of 216 patients who underwent randomization, 93% received UDCA as concomitant therapy. The primary end point occurred in more patients in the 5–10-mg group (46%) and the10-mg group (47%) than in the placebo group (10%; P<0.001 for both comparisons). The average reduction in alkaline phosphatase level was -113 U and -130 U per liter for the OCA groups respectively *vs.* -14 U per liter for placebo (P<0.001). Changes in total bilirubin level were less dramatic (-0.02 and -0.05 mg per deciliter, respectively, *vs.* 0.12 mg per deciliter; P<0.001 for both comparisons).

Pruritus was more common with OCA than with placebo (56% of patients in the 5–10-mg group and 68% of those in the 10-mg group *vs.* 38% in the placebo group).

Cautions: The primary end-point for this trial was a cumulative reduction in alkaline phosphatase and total bilirubin that has been shown previously to be associated with a significant difference in clinical outcome. However, the study was not long enough to actually demonstrate a difference in clinical outcome, nor did it show a difference in noninvasive measures of liver fibrosis between the treatment groups and the placebo group at 12 months. Therefore, the FDA has requested a 5-year long-term study with clinical endpoints as part of the drug approval.

Implications: For 20 years, UDCA has been the only drug for patients with PBC, many of who had an inadequate biochemical response to therapy. The POISE trial demonstrated that close to half of these patients may achieve a combined biochemical response with the addition of OCA to UCDA or as monotherapy. The drug requires careful dosing, starting at 5 mg and increasing to 10 mg after 3-6 months in order to reduce the most common side effect of pruritis.

Background: Nonalcoholic steatohepatitis (NASH) is the progressive form of nonalcoholic fatty liver disease (NAFLD) and has become a tremendous clinical and economic burden that is growing globally. Elafibranor is an agonist of the peroxisome proliferator-activated receptor-α (PPAR-α) and peroxisome proliferator-activated receptor-δ (PPARδ), a class of drug that favorably affects metabolism in patients with diabetes. Elafibranor improves insulin sensitivity, glucose homeostasis, and lipid metabolism and reduces inflammation [2].

Findings: This study assessed the safety and efficacy of elafibranor in an international, randomized, double-blind placebo-controlled trial of patients with NASH without cirrhosis who were randomly assigned to groups given elafibranor 80 mg (n=93), elafibranor 120 mg (n=91), or placebo (n=92) daily for 52 weeks at sites in Europe and the US. In intention-to-treat analysis, there was no significant difference between the elafibranor and placebo groups in the protocol-defined primary outcome. However, NASH resolved without fibrosis worsening in a higher proportion of patients in the 120-mg elafibranor group *vs.* the placebo group (19% *vs.* 12%; odds ratio=2.3; 95% confidence interval: 1.02-5.24; P=0.045), based on a post-hoc analysis for the modified definition. Patients with NASH resolution after receiving elafibranor 120 mg had reduced liver fibrosis stages compared with those without NASH resolution (mean reduction of 0.65 ± 0.61 in responders for the primary outcome *vs.* an increase of 0.10 ± 0.98 in non-responders; P<0.001) and liver enzymes, lipids, glucose profiles, and markers of systemic inflammation were significantly reduced in the elafibranor 120-mg group *vs.* the placebo group.

Cautions: Elafibranor was well tolerated and did not cause weight gain or cardiac events, but did produce a mild, reversible increase in serum creatinine (effect size *vs.* placebo: increase of 4.31 μmol/L ± 1.19 μmol/L; P<0.001). Because this trial missed its protocol-defined primary outcome, a larger phase 3 study must be done using the newer definition of NASH resolution without fibrosis worsening, and this trial is currently underway.

Implications: A post-hoc analysis of data from trial of patients with NASH showed that elafibranor (120 mg/d for 1 year) resolved NASH without fibrosis worsening, based on a modified definition and in patients with moderate or severe NASH. However, the predefined end point was not met in the intention to treat population. Elafibranor was well tolerated and improved patients' cardiometabolic risk profile.

Background: Clearance of HBsAg from the serum is associated with a functional remission of HBV and improved long-term outcomes and is therefore recognized as the optimal therapeutic goal. Unfortunately, HBsAg loss is uncommon with current therapies. In the trials of pegylated interferon (PEG IFN) alpha-2a given for 48 weeks, only 4% of HBeAg-negative and HBeAg-positive had HBsAg loss 6 months after the end of therapy. In the phase 3 trials of tenofovir (TDF), the rate of HBsAg loss was only 3% in HBeAg-positive and 0% in HBeAg-negative patients after 48 weeks of therapy. This trial compared the efficacy and safety of TDF and PEG IFN combination therapy with TDF and PEG IFN alone in patients with chronic HBV [3].

Findings: At week seventy-two, 9.1% of subjects in the combination therapy group had HBsAg loss compared with 2.8% of subjects receiving PEG IFN alone, and none of the subjects receiving TDF alone (P<0.003 and P<0.001 respectively). HBsAg loss in the combination group occurred in hepatitis B e antigen-positive and hepatitis B e antigen-negative patients with all major viral geno types.

Cautions: The incidence of common adverse events (including headache, alopecia, and pyrexia) and treatment discontinuation due to adverse events was similar among groups. Although there was no increase in adverse events compared with PEG IFN alone, these are substantial and prevents most patients from accepting PEG IFN therapy for 48 weeks.

Implications: This study is the first to provide definitive evidence that patients receiving TDF in combination with PEG IFN can achieve higher rates of HBsAg loss than those receiving monotherapy.

The study serves as a model for future non-interferon therapies that in development with TDF designed to achieve HbsAg loss.

Background: Hepatorenal syndrome type 1 (HRS-1) in patients with cirrhosis and ascites is a functional, potentially reversible, form of acute kidney injury characterized by rapid deterioration of renal function in less than 2 weeks time. Terlipressin is a synthetic vasopressin analogue that acts, via vascular vasopressin V1 receptors, as a systemic vasoconstrictor. This was a phase 3 study to evaluate the efficacy and safety of intravenous terlipressin plus albumin *vs.* placebo plus albumin in patients with HRS-1 [4].

Findings: Adults patients with cirrhosis, ascites, and HRS-1 were assigned randomly to IV terlipressin (1 mg, n=97) or placebo (n=99) with intravenous albumin at 6-hour intervals. The primary endpoint was achieved at or until day 14 was confirmed HRS reversal on treatment without renal replacement therapy or liver transplantation, or serum creatinine (SCr) at or higher than baseline on day 4. Secondary end points included the incidence of HRS reversal, transplant free survival, and overall survival. The primary endpoint was observed in 19 of 97 patients (19.6%) receiving terlipressin *vs.* 13 of 99 patients (13.1%) receiving placebo (P<0.22). HRS reversal was achieved in 23 of 97(23.7%) patients *vs.* 15 of 99 (15.2%) receiving placebo (P<0.13). SCr decreased by 1.1 mg/dL in patients receiving terlipressin and by only 0.6 mg/dL in patients receiving placebo (P<0.001). Transplant-free and overall survivals were similar between groups. A significantly greater proportion of patients who achieved the primary endpoint on terlipressin survived until day 90 than patients who did not meet the primary endpoint after receiving terlipressin (P<0.001).

Cautions: Ischemic events led to discontinuations in 7 of 19 patients receiving terlipressin and 1 of 6 patients receiving placebo. No ischemic events were fatal; however patients had similar rates of HRS reversal with terlipressin as they did with albumin. Therefore

caution should be used when considering treatment of patients with cardiovascular disease who are at high risk for ischemic events.

Implications: Terlipressin plus albumin was associated with greater improvement in renal function *vs.* albumin alone in patients with cirrhosis and HRS-1.Terlipressin is the standard of care for treatment of HRS-1 in most countries in the world but not yet approved in the US. It is unclear if this trial will allow approval by the FDA, as the primary endpoint was missed.

Diseases of the stomach and small intestine

Bismuth therapy may need to be first line therapy for *Helicobacter pylori* infection due to increasing resistance patterns.

Background: *Helicobacter* infection remains a significant problem encountered by primary care physicians. The organism has increasing resistance to metronidazole (25% to 30%) and clarithromycin (15%). Recent studies have supported using concomitant therapy as second line therapy for those who have failed standard therapy. This study prospectively investigated three different regimens for first line treatment. Subjects were randomized to one of three regimens, 10 day concomitant therapy (lansoprazole 30 mg BID, amoxicillin 1 g BID, clarithromycin 500 mg BID, and metronidazole 500 mg BID), 10 day bismuth quadruple therapy (bismuth 300 mg QID, tetracycline 500 mg QID, metronidazole 500 mg TID, and lansoprazole 30 mg BID), or 14 day triple therapy (lansoprazole 30 mg BID, amoxicillin 1 g BID, clarithromycin 500 mg BID). Eradication was documented by urea breath testing. Safety and efficacy were assessed. All treatment failures had repeat therapy with a bismuth containing regimen [5].

Findings: A total of 1620 subjects were enrolled over three years. By intent to treat analysis bismuth quadruple therapy had 90.4% eradication, concomitant therapy has 85.9% eradication, and 14 day triple therapy had 83.7% eradication. The bismuth regimen was significantly superior to the 14 day triple regimen. Per protocol analysis demonstrated the bismuth quadruple therapy (94%) was superior to 14 day triple therapy (88%, $P<0.0001$). The bismuth regimen was superior to either regimen if clarithromycin resistance was present. Adverse events were quite common (47% to 67%) and 10% of patients discontinued bismuth quadruple therapy.

Cautions: This Taiwanese population may not mirror patients in the US but resistance patterns are similar in the US as were found in this study. The best regimen also had the highest adverse events and discontinuation of therapy. Rescue therapy with bismuth therapy was highly successful. The doses of some of the medications were higher than previous studies which may partially explain the higher adverse events.

Implications: The first regimen to treat *H. pylori* needs to be highly effective. Standard triple therapy even at 14 days should be avoided especially if clarithromycin resistance is suspected. Regimens with bismuth appear to most effective although concomitant therapy is still a good choice particularly in the US. Whatever regimen is chosen, both the clinician and the patient must be committed to therapy due to numerous side effects and adverse events.

The angiotensin receptor blocker, olmesartan, is increasingly recognized as a cause of a severe small bowel enteropathy.

Background: In 2013, the FDA issued a warning about case reports of an enteropathy associated with olmesartan therapy. Since then many more case reports and series have been reported. However, it has been difficult to assess the actual risk of this event. Severe malabsorption requiring prolonged hospitalization has been reported. In this observational study, the French national database was used to determine the frequency and risk of this adverse event. From 2007 to 2012, all patients prescribed angiotensin receptor blockers (ARBs) or (define) (ACEIs) were assessed for admission to the hospital for malabsorption or enteropathy. Patients with known celiac disease were excluded [6].

Findings: Over a 5-year period, 218 admissions were reported in 4.5 million patients. The ARR *vs.* all other ACEIs or ARBs was 2.49 for intestinal malabsorption and 4.39 for celiac disease ($P<0.0001$ for both events). The risk increased with duration of therapy with an ARR of 10.65 for therapy over 10 years. No other ACIs or ARBs appeared to have similar adverse events.

Cautions: Although the risk for enteropathy is small, it can be quite severe. This study likely underestimates the true incidence since only patients requiring admission were assessed. Although this demonstrates an association, direct causation is unclear. The mechanism as how this specific ARB causes enteropathy is not known at this time.

Implications: Clinicians need to be aware of this rare but serious association. The enteropathy can develop anytime during therapy. Discontinuing the medication leads to resolution of the enteropathy.

Proton pump Inhibitors should be used for clear indications at the lowest dose for the shortest duration as needed.

Background: Proton pump inhibitors (PPIs) are some of the most commonly prescribed medications in the world and are available over the counter (OTC). Recent studies have suggested associations with coronary artery disease, chronic disease, and dementia. Previous studies have also show associations with hip fracture, hypomagnesemia, and recurrent *Clostridium difficile* infection. Direct causation has not been shown and there are no clear mechanisms reported. However, practicing clinicians need to be aware of these associations and counsel patients on the risks and benefits of these medications [7].

Findings: In this article, the authors review the difference between associative and causal studies and provide guidance for clinicians prescribing these medications. They provide a review of the FDA approved uses of these medications and discuss dosing and duration of therapy. Proton pump inhibitors remain the mainstay of therapy for healing peptic and esophageal ulceration. There are no superior medications for the treatment of active gastrointestinal bleeding. Problems arise when patients remain on PPIs past the indicated duration or have been prescribed long term PPIs for less clear indications such as dyspepsia or non-erosive esophagitis. Previous studies have shown that patients have been placed on these medications for unclear reasons and despite this remain on the PPI for years. Therefore, it is imperative that clinicians use these medications for clear indications at the lowest dose and shortest duration as needed.

Cautions: The legal system has become active with respect to PPI prescribing and documentation of patient counseling for risks and benefits is recommended. Eosinophilic esophagitis is a common condition for which we use PPIs for long duration but is not an FDA approved indication.

Implications: PPIs have revolutionized our treatment of acid peptic diseases but the use of these medications needs to be for clear

indications and with documentation of patient counseling for long term use.

Diseases of the colon

Colon cancer screening guidelines revisited and updated.

Background: This year the USPSTF issued an update of colon cancer screening guidelines from 2008.

Overall colorectal cancer remains the second most common cause of cancer death in both men and women. Colon cancer is an ideal disease for a national screening strategy and the colon cancer death rate is now declining due to focus on screening. There are multiple modalities for screening and these guidelines review the literature and provide recommendations for screening [8].

Findings: The USPSTF does not provide preference for any one screening modality to prevent or detect colon cancer. Instead, the review the available literature and provides a clinical summary for each modality then creates charts that outline the benefits and harms. The Task Force suggests that clinicians and health systems should individualize screening based on age, demographics, and availability.

Patients should be made aware of the published risks and benefits. The Task Force strongly recommends screening for all persons 50-75 years old and individualized screening for those between 75 and 85 years old. Additionally, the USPSTF now recommends the use of aspirin in adults over 50 years to decrease colon cancer death old if they have more than a 10% risk for coronary artery disease.

Cautions: Around one third of eligible Americans do not get any colorectal screening. The USPSTF and the GI societies have efforts to increasing screening. The National Colorectal Cancer Roundtable and the American Cancer Society are striving to have 80% of eligible Americans screened for colorectal cancer by 2018.

Implications: The current theme is to have eligible persons screened for colorectal cancer. The exact modality for screening should be based on availability of resources and patient and provider preference.

The fecal immunochemical test (FIT) of stool is more cost effective than multitarget DNA stool testing.

Background: The new USPSTF colorectal guidelines do not give recommendations for which modality is preferred. The clinician and patient must determine which screening strategy is best for that person. With staggering health care costs, cost effectiveness studies are needed to guide clinicians and health care systems when designing prevention studies. Two stool studies have similar performance characteristics. The fecal immunochemical test (FIT) detects human globin in stool and requires only one stool specimen and no dietary changes with testing and costs between 15 to 30 USD. The multitarget stool test includes a FIT test and additionally detects abnormal DNA from neoplastic tissue released in the stool and costs about 600 USD. Multitarget DNA testing has superior neoplasia detection but higher false positivity compared to FIT. Current guidelines support annual FIT and every 3 year multitarget DNA testing [9].

Findings: In this study, a Markov model was used to compare FIT, multitarget DNA stool testing, and colonoscopy. The performance characteristics and costs of the studies were varied to determine the most effective and cost effective modality. Compliance data from previous studies was also used in the determination. FIT was preferred in 99.3% of the iterations over multitarget DNA stool testing for effectiveness and cost effectiveness. Using their model, the authors also concluded that colonoscopy was preferred over multitarget DNA testing. To more cost effective, the multitarget DNA would need to be 60% less costly and have higher participation rate.

Cautions: All cost effectiveness models are only as good as the data that was used to determine the test characteristics. These authors have done a thorough review but this model may need to be adapted as further studies as published. All of these models use the premise that a positive stool test leads to a complete colonoscopy.

Implications: FIT is a cost effective modality for screening for colorectal cancer and will be a key tool as we strive for screening 80% of eligible Americans by 2018.

Non-invasive stools tests may help us triage patients with gastrointestinal symptoms.

Background: Determining which patient with intestinal symptoms should be referred for an endoscopic procedure can be difficult when the patient does not have any of the classic warning features. Non-invasive tests that could better triage this large cohort of patients would be welcome. FIT has been well described in colorectal cancer screening and is reviewed above. Fecal calprotectin (FC) is a protein released from inflamed bowel and has been used is assessing disease activity in inflammatory bowel disease. Neither test is routinely performed on typical, symptomatic GI patient [10].

Findings: All patients referred by their primary care physicians for endoscopic procedures were studied. The subjects had FIT and FC performed before endoscopy or colonoscopy was performed. The investigators and subjects were blinded to the results. Of referred subjects, 1,043 received fecal tests and 755 had endoscopic procedures. Only those who had endoscopic procedures are reported. Positive tests for FIT and FC were seen in 57.6% and 60% respectively. The negative predictive value (NPV) of FIT was 100% for colorectal cancer, 97.8% for advanced adenomas, and 98.4% for inflammatory bowel disease (IBD). FC detected two additional cases of IBD but additional cancer case. The authors conclude that FIT has an excellent NPV for bowel disease and may eliminate unnecessary testing is some symptomatic patients.

Cautions: This study does not apply to patients with warning symptoms such as weight loss, bleeding, or anemia. The study does not define the 288 subjects who had fecal tests but no endoscopic procedures. This patient population might not compare to the average US practice.

Implications: FIT is a useful and inexpensive test to triage symptomatic patients without warning symptoms for endoscopy. It has an excellent NPV for bowel disease.

Other GI articles of interest

Diet therapy is safe and effective for diarrhea predominant irritable bowel syndrome.

Background: Irritable bowel syndrome (IBS) is a common diagnosis and a cause of significant symptoms and lost productivity. No definitive therapy exists and symptom control has been the major goal of therapy. There have been conflicting diet-studies in IBS and many of the studies have been under powered or have poorly defined outcomes. Most clinicians recommend a diet similar to the modified NICE (define) (mNICE) guidelines for IBS. Recent focus has been on the fermentable oligo-, di-, and monosaccharides and polyols

(FODMAPs) diet. Recent studies have assessed the diet in bloating, IBS, and IBD. This study is a prospective, randomized, controlled study comparing the FODMAP diet to the modified NICE diet [11].

Findings: Ninety-two subjects were randomized to either diet for 4 weeks. There was a two run in period prior to randomization. Investigators were not blinded and subjects given diet 1 or 2. Only patients with IBS-D were included. Daily diary and symptom scores were obtained. Primary outcome was a 50% reduction in IBS-D symptoms in last 2 weeks of study. Secondary outcomes were composite scores, stool scores, and pain scores. Subjects on the FODMAP diet had a 52% reduction in IBS-D symptoms compared to 43% in the mNICE but this did not reach statistical significance. The FODMAP diet did have significant decrease in pain score compared to the mNICE diet (51% *vs.* 23%, P<0.0083) and a difference in bloating (P<0.0001). The authors conclude that both diets had a 40% to 50% decrease in IBD-D scores and can be used for treatment of IBS-D. The low FODMAP diet had superior improvement in pain and bloating.

Cautions: Only IBS-D patients were studied and the results may not applicable to all IBS patients.

There was no placebo are but the mNICE diet is what most clinicians use currently. However, this study illustrates the high effect any directed intervention has on patients with IBS as opposed to medication studies, though, diet intervention is safe and relatively in expensive. Dietary counseling is an effective resource but not offered by many insurance plans.

Implications: Diet therapy is a safe and effective intervention in IBS-D patients and the low FODMAP diet is superior to the mNICE diet for relieve of bloating and pain.

The great paradox of cannabis and vomiting.

Background: Marijuana use is increasing with the expanded medical use and increasing legalization in many states. Advocates support its use for many conditions including pain and nausea. Over 10 years ago, a condition now termed cannabinoid hyperemesis syndrome (CHS) was reported. Gastroenterologists have been aware of this entity for many years but awareness in the primary care community is low. Widespread education is needed [12].

Findings: An extensive literature review was undertaken and 1,254 articles, case reports, and cases were found. The review noted that daily or at least weekly cannabis use was needed. Symptoms that were noted in all cases included severe nausea (100%), cyclic vomiting (100%), relief of symptoms with cessation of cannabis (96.8%), temporary relief of symptoms with hot showers or baths (92.3%) and abdominal pain (85%). All patients used cannabis, 73% were male and 100% were less than 50 years old. Various treatments have been reported but none is as safe and reliable as cessation of the drug. No definite mechanism for this syndrome has been identified.

Cautions: Most clinicians have encountered patient with CHS and it can unrecognized for months to years and lead to needless testing. Our experience in California is that the syndrome is increasing and some patients are reluctant to accept that the cannabis is the source of their symptoms.

Implications: All young patients, especially males, with nausea and epigastric pain should be questioned about cannabis use. The demographics and clinical presentation are sufficient for diagnosis.

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