

WHATS NEW IN GASTROENTEROLOGY



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******NO DISCLOSURES******

COLORECTAL CANCER (April 16)



- 2016 FDA approved a second generation serum assay for detection of circulating methylated Septin 9 for CRC screening (1)
 - Detects Septin 9 DNA which is hypermethylated in CRC but not in normal tissue
 - Intended for average risk patients
 - Positive serum test should be followed up with a colonoscopy
 - Until further evidence is available, serum tests for CRC screening are not recommended

COLORECTAL CANCER



- Cologuard is a stool DNA test uses a gene amplification technique (allow detection of low frequency mutations with increased sensitivity for advanced adenomas)
- Detects patterns of DNA methylation while also testing for hemoglobin
- Cologuard vs. fecal immunochemical test (FIT) demonstrated sensitivity of 92.3% vs 73.8% in one test (2) (*NEJM*)
- Sensitivity of the DNA test was not affected by cancer stage or location of the lesion
- Based on above data, Cologuard approved by FDA 2014 as a screening test for CRC (if positive followed by colonoscopy) (3)

COLORECTAL CANCER



- The implications of "false positives" are uncertain
- In a study of screening with three modalities (stool DNA, colonoscopy, and fecal immunochemical tests) in average-risk patients, nearly 10 percent of those with an entirely negative colonoscopy had a positive stool DNA test (4) (*NEJM*)
- The appropriate interval between screening fecal DNA tests is unknown
- Centers for Medicare and Medicaid Services (CMS) include coverage for this test once every three years for asymptomatic Medicare beneficiaries age 50 to 84 years at average risk for CRC as of 10/14 (5)

FECAL IMMUNOCHEMICAL TESTING



- FIT has improved sensitivity for CRC and advanced adenomas
- Better patient adherence (one stool sample and no dietary restrictions) compared to guaiac reagent (gFOBT)

UPDATED GUIDELINES FOR ENDOSCOPIC SURVEILLANCE AFTER CRC TX (March 16)



- US Multi –Society Task Force on CRC
- Flexible sigmoidoscopy or EUS every 3-6 months for the first 2-3 years after surgery for rectal cancer for those at risk for local recurrence: (6)
(Gastroenterology)
 - Localized rectal cancer who have undergone surgery without total mesorectal excision (TME)
 - Those who have undergone transanal local excision or endoscopic submucosal dissection alone
 - Those with locally advanced rectal cancer who didn't receive neoadjuvant chemoradiotherapy followed by TME

HELICOBACTER PYLORI (June 16)



- The Toronto consensus has published new guidelines for the treatment of *Helicobacter pylori* in adults (7) (*Gastroenterology*)
 - Guidelines recommend a longer duration of treatment for all eradication regimens (14 versus 10 days)
 - Triple therapy in areas with low clarithromycin resistance or high eradication rates
 - Quadruple therapy as a first line in all other areas
 - ✦ Quadruple therapy = PPI + bismuth subsalicylate (524 mg four times daily) + two antibiotics (eg, metronidazole 250 mg four times daily and tetracycline 500 mg four times daily) for 14 days
 - ✦ If tetracycline is not available, doxycycline (100 mg twice daily) may be substituted

H. PYLORI ERADICATION AND RISK OF GASTRIC CANCER (May 16)



- It has been unclear if eradication of *Helicobacter pylori* infection reduces the risk of gastric cancer among asymptomatic individuals in populations that are not at high risk for gastric cancer
- A meta-analysis of 27 studies included approximately 48,000 individuals, among whom 4800 were infected with *H. pylori* and approximately 700 had incident gastric cancers (8)
(Gastroenterology)
 - Individuals with eradication of *H. pylori* had a lower incidence of gastric cancer compared with those who did not receive eradication therapy

VONOPRAZAN-BASED TRIPLE THERAPY FOR H. PYLORI ERADICATION (March 16)



- Vonoprazan is a novel oral potassium-competitive acid blocker (PCAB)
- In a randomized trial, 650 H. pylori-positive patients with a history of a gastric or duodenal ulcer were assigned to first-line triple therapy with amoxicillin, clarithromycin, and either lansoprazole or vonoprazan (9) (*Gut*)
 - Open label
 - Vonoprazan-based first-line therapy was superior to lansoprazole-based therapy with H. pylori eradication rates of 93 and 76 percent, respectively
 - There were no significant differences in adverse effects (higher serum gastrin noted in vonoprazan)
 - The eradication rate with vonoprazan-based second-line triple therapy was 98 percent
 - Vonoprazan appears effective in eradication of HP and LA C/D, however further studies are needed

PROTON PUMP INHIBITORS AND RISK OF DEMENTIA IN OLDER ADULTS (Feb 16)



- A new study has identified a possible link between proton pump inhibitors (PPIs) and risk of dementia in older adults
- In a prospective cohort study of >73,000 adults aged 75 years and older who were free of dementia at baseline, regular use of a PPI was associated with a 1.4-fold increase in the risk of incident dementia, independent of age, gender, depression, stroke, heart disease, and polypharmacy (10) (*JAMA*)
 - Possible factors that could contribute to this finding include PPI-induced vitamin B12 deficiency or an interaction between PPIs and amyloid beta deposition, although these factors were not examined in this study
 - More studies are needed to confirm or refute this association

DEFIBROTIDE FOR HEPATIC SINUSOIDAL OBSTRUCTION SYNDROME (April 16)



- Hepatic sinusoidal obstruction syndrome (SOS) is an uncommon but serious complication of allogeneic hematopoietic cell transplantation (HCT)
- It accounts for a significant fraction of transplant-related mortality
- Small single-arm prospective trials have demonstrated modest improvement in patients with severe SOS treated with defibrotide (enhances plasmin enzymatic activity to hydrolyze fibrin clot)
- In the largest international study, 102 adults and children with SOS and multiorgan failure were treated with defibrotide (11) (*Blood*)
 - Defibrotide was associated with higher response rates and improved survival (38 versus 25 percent at day +100)
 - Approved by USDA for the treatment of severe SOS (12)

LIVER CANCER DEATH RATES INCREASING IN THE US (March 16)



- Over the past 30 years, death rates in the United States have declined for all common cancers except liver cancer
- In the Annual Report to the Nation on the Status of Cancer, 1975-2012, the overall cancer death rates for men and women (all racial and ethnic populations) decreased by 1.5 percent per year between 2003 and 2012 (13) (*Cancer*)
 - Liver cancer death rates increased by 2.8 percent per year in men and 3.4 percent per year in women
 - Liver cancer incidence rates increased by 3.5 percent per year in men and 3 percent per year in women

CT-COLONOGRAPHY VS COLONOSCOPY FOR SSA POLYPS (April 16)



- Sessile serrated adenomatous polyps (SSPs) are suggested to be the precursors of 15–30% of all colorectal cancers (CRCs)
- Randomized controlled trial compared CTC with colonoscopy for population screening were used for the analysis (*Am J Gastro*)
- The current CTC strategy showed a marked lower detection for especially flat high-risk SSPs (17 vs. 0), high-risk SSP located in the proximal colon (32 vs. 1), and SSPs with dysplasia (30 vs. 1)
- The detection rate of high-risk SSPs was significantly higher with colonoscopy than CTC (14)

ZIKA VIRUS AND TISSUE DONATION (March 16)



- Zika virus has been detected in tissues and body fluids
- FDA issued donor deferral recommendations for hematopoietic stem cells, tissues, sperm or eggs (does not apply to solid organs) (15)
- Living donors with Zika infection or exposure (residence or travel to area where Zika virus infection has been reported, or unprotected sexual contact with a person who meets criteria) considered ineligible for donation for six months
- Deceased donors with Zika virus infection within 6 mo considered ineligible
- Deferral period recommended by the FDA for blood donors with risk factors for Zika virus infection remains at four weeks

HCV TREATMENT IN RENAL FAILURE PATIENTS (Feb 16)



- Safety concerns have limited options for patients with severe renal impairment, who have been excluded from trials of most available regimens
- In January 2016, the USDA approved the new combination regimen elbasvir-grazoprevir (Zepatier) for treatment of genotypes 1 and 4 HCV, including patients with any degree of renal impairment (including dialysis)
- Randomized, placebo-controlled trial of genotype 1-infected patients with eGFR <30 mL/min per 1.73 m², the sustained virologic response (SVR) rate was 94 percent among the 122 patients who received elbasvir-grazoprevir for 12 weeks
 - Adverse event rates were similar between treatment and placebo groups (16) (*Lancet*)
 - These results were comparable to those among patients with normal renal function

HBV REACTIVATION IN PATIENTS UNDERGOING CHEMOTHERAPY FOR SOLID TUMORS (Jan 16)



- Patients with HBV infection (HBsAg+ anti-HBc+) are at risk for HBV reactivation if receive immunosuppressive therapy
- In a systematic review, the risk of reactivation among HBsAg+ ranged from 4 to 68 percent, with most studies reporting a reactivation risk greater than 10 percent (17) (*Annals IM*)
- Antiviral therapy administered during chemotherapy was associated with an approximately 90 percent reduction in HBV reactivation risk as well as reductions in HBV-related hepatitis and the need for chemotherapy interruption

EPCLUSA (June 16)



- Epclusa (Gilead) (Sofosbuvir + velpatasvir) NS5A Inhibitor + NS5B Polymerase Inhibitor (400/100 mg)
- Approved June 2016
- Treatment for 12 weeks
- Treatment of genotype 1,2,3,4,5,6 chronic hepatitis C for non-cirrhosis and compensated cirrhosis
- Combo ribavirin for decompensated cirrhosis
- Cost \$890 per pill, therapy \$74,760

68-Ga DOTATATE FOR IMAGING OF NEUROENDOCRINE TUMORS (June 16)



- Most well-differentiated NET can be imaged using radiolabeled somatostatin analogs
- Newer positron-emitting somatostatin analogs such as 68-Ga DOTATATE, when combined with high-resolution PET scanning are more sensitive than conventional 111-In pentetretotide imaging (OctreoScan) for detection of small lesions (18) (*J Clin Onc*)
- A kit for preparation of 68-Ga DOTATATE injection as a radioactive diagnostic agent for PET imaging (Netspot) was approved by the FDA in June 2016 (19)
- Due to its greater sensitivity, 68-Ga DOTATATE PET may be preferred over conventional 111-In pentetretotide scanning where available

UNDERUTILIZATION OF ENZYMES IN PANCREATIC CANCER (April 16)



- Patients with advanced pancreatic cancer often have pancreatic exocrine insufficiency leading to maldigestion, fat malabsorption, steatorrhea, and weight loss
- These patients should be treated empirically with oral pancreatic enzyme replacement therapy (PERT), evidence suggests that PERT is underutilized (21) *BMJ Support Palliat Care*
- In a review of 129 patients with metastatic pancreatic cancer, over 70 percent had symptoms that could be attributed to malabsorption, yet only 21 percent were prescribed PERT

AGA GUIDELINES AND EVALUATION OF PANCREATIC CYSTS (Feb 16)



- The optimal approach to evaluating pancreatic cysts is unclear
- AGA published guidelines on the evaluation and management of pancreatic cysts 2015(22) *Gastroenterology*
- Data suggests if the AGA guidelines are applied, many cysts with advanced neoplasia will be missed (23) *Gastrointestinal Endoscopy*
- In a series of patients who underwent EUS with FNA of pancreatic cysts, the AGA guideline was 62 percent sensitive and 79 percent specific for detecting advanced neoplasia
 - missed 45 percent of IPMN with adenocarcinoma or high-grade dysplasia
- UpToDate authors advise a lower threshold for evaluating cysts (algorithm 5) than in the AGA guideline (see handout)

ORAL VACCINE TO PREVENT CHOLERA IN HIGH-RISK TRAVELERS (June 16)



- *Vibrio cholera* infection is characterized by severe watery diarrhea, which can rapidly lead to dehydration
- In June 2016, a live attenuated oral cholera vaccine (Vaxchora) was approved by the US FDA for prevention of cholera caused by serogroup O1 in adults 18 through 64 years
- Those who warrant vaccination include aid, refugee, and health care workers planning to work among or near displaced populations in endemic or epidemic settings, and long-stay travelers in very high-risk countries
- A single dose of vaccine given prior to an oral challenge with a *V. cholerae* O1 strain was 90% effective (@10 Days) and 80% (@3 mo) in preventing moderate to severe cholera (24) *Clin Infect Dis*

ROME IV CRITERIA FOR FUNCTIONAL GI DISORDERS (June 16)



- The Rome Foundation has released revised criteria (Rome IV) for the diagnosis of functional gastrointestinal disorders (25) *Gasroenterology*
- Revisions include:
 - Changes to the criteria for IBS and its subtypes (used with Bristol Stool Form Scale)
 - New criteria for reflux hypersensitivity
 - Inclusion of diagnoses with known etiologies that alter gut-brain interaction (eg, opioid-induced constipation)

DIAGNOSTIC CRITERIA FOR OPIOID INDUCED CONSTIPATION (May 16)



- Diagnostic criteria for OIC per ROME-IV criteria include new or worsening symptoms of constipation when initiating, changing, or increasing opioid therapy that must include two or more of the following:
 - Straining during more than one-fourth of defecations
 - Lumpy or hard stools more than one-fourth of defecations
 - Sensation of incomplete evacuation more than one-fourth of defecations
 - Sensation of anorectal obstruction/blockage more than one-fourth of defecations
 - Manual maneuvers to facilitate more than one-fourth of defecations (eg, digital evacuation, support of the pelvic floor)
 - Fewer than three spontaneous bowel movements per week

OZANIMOD FOR UC (May 16)



- Ozanimod is an oral agonist of the sphingosine-1-phosphate receptor subtypes 1 and 5, that decreases circulating activated lymphocytes
- In a randomized trial, 197 patients with moderate to severe ulcerative colitis were assigned to Ozanimod (1 mg or 0.5 mg daily) vs placebo for 32 weeks (26) *NEJM*
- At eight weeks, patients treated with the higher dose of Ozanimod had a slightly higher rate of clinical remission vs placebo (16 versus 6 percent)
- No significant differences in adverse effects
- Larger trials with extended treatment are needed to establish the clinical efficacy and safety of ozanimod

SKIN DISORDERS ASSOCIATED WITH TNF INHIBITOR USE (Feb 16)



- A variety of skin disorders have been reported in association with the use of TNF's
- Cohort of 917 patients with IBD on TNF inhibitors for a median of 3.5 years, where 29 percent developed skin lesions (12.4 per 100 patient-years) (27) *Ann Intern Med*
- Cutaneous lesions included (most to least common) eczema, xerosis cutis, palmoplantar pustulosis, and psoriasis
- The majority of patients were managed without discontinuation of TNF inhibitor therapy

OUTBREAK OF BURKHOLDERIA CEPACIA INFECTION ASSOCIATED WITH CONTAMINATED ORAL LIQUID DOCUSATE

- In June 2016, a multistate outbreak of Burkholderia cepacia infection was reported by the CDC
- B. cepacia typically causes lung colonization and infection in patients with cystic fibrosis (CF)
- Most cases in this outbreak involved mechanically ventilated ICU patients without CF
- Because cases in one state have been associated with contaminated oral liquid docusate, the CDC recommends that facilities not use liquid docusate products for any patient
- PharmaTech LLC, the manufacturer of the contaminated product, Diocto Liquid, has voluntarily recalled all non-expired lots

FROZEN FECAL MICROBIOTA TRANSPLANT FOR CDT (JAN 16)



- Randomized trial of 219 patients with recurrent C difficile infection or refractory CDI assigned to frozen and thawed, or fresh FMT via rectal enema (*JAMA*)
- Rates of clinical resolution higher in frozen FMT group
- No differences in AR
- Frozen FMT has potential advantage of immediate delivery
- Under further investigation (28)

PPI AND CKD (May)



- 2 observational studies suggest PPI's may increase the risk of CKD
- One study over 10,000 participants in the Atherosclerosis Risk in Communities (ARIC) study were evaluated (*JAMA*) (29)
- Analysis adjusted for multiple variable, PPI use was assoc with increased risk of CKD compared to no PPI use (hazard ratio 1.5) and compared to H2 blockers (HR 1.4)
- Second study 170,00 new PPI users and 20,00 new H2 blocker users were followed for over 5 yrs (*J Am Soc Nepro*)
 - PPI group had increased risk of CKD (HR 1.3) and ESRD (HR 2.0)
 - Increasing duration of use was associated with higher CKD risk

PPI AND CKD (May)



- The mechanism underlying the assoc between PPIs and risk of CKD unknown
- Not clear whether decreasing PPI use decreases the risk of CKD
- Only the second study evaluated NSAID use and found it higher among PPI users compare to nonusers
- Clearly, additional studies needed to define causal relationship between PPI use and the development and worsening of CKD

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THANK YOU