WHATS NEW IN GASTROENTEROLOGY

CHARLENE LEPANE DO MSPH FACG FACOI
GASTROENTEROLOGIST

ORLANDO VAMC
****NO DISCLOSURES****
• 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 that uses a gene amplification technique (allowing 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).
• 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).
FIT has improved sensitivity for CRC and advanced adenomas

Better patient adherence (one stool sample and no dietary restrictions) compared to guaiac reagent (gFOBT)
• 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
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
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 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 (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
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)
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
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
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.
Patients with HBV infection (HBsAg+ anti-HBc+) are at risk for HBV reactivation if they 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 (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
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 pentetreotide 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 pentetreotide scanning where available.
Patients with advanced pancreatic cancer often have pancreatic exocrine insufficiency leading to malabsorption, 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.
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).
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.
The Rome Foundation has released revised criteria (Rome IV) for the diagnosis of functional gastrointestinal disorders (25) *Gastroenterology*

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 (e.g., opioid-induced constipation)
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 (e.g., digital evacuation, support of the pelvic floor)
- Fewer than three spontaneous bowel movements per week
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.
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.
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.
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)
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 associated with increased risk of CKD compared to no PPI use (hazard ratio 1.5) and compared to H2 blockers (HR 1.4)

Second study 170,000 new PPI users and 20,000 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
The mechanism underlying the association 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 compared to nonusers

Clearly, additional studies needed to define causal relationship between PPI use and the development and worsening of CKD
REFERENCES


REFERENCES

14. CT-Colonography vs. Colonoscopy for Detection of High-Risk Sessile Serrated Polyps J.E.G. IJspeert, MD; C.J. Tutein Nolthenius, MD; E.J. Kuipers, MD, PhD; M.E. van Leerdam, MD, PhD; C.Y. Nio, MD, PhD; M.G.J. Thomeer, MD, PhD; K. Biermann, MD, PhD; M.J. van de Vijver, MD, PhD; E. Dekker, MD, PhD; J. Stoker, MD, PhD Am J Gastroenterol. 2016;111(4):516-522


THANK YOU