WHATS NEW IN GASTROENTEROLOGY

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****NO DISCLOSURES****
GASTROENTEROLOGY

PULL FINGER FOR SERVICE

Search ID: dre0404
• 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 (100%) in CRC (circulating DNA fragments) but not in normal tissue
  • Epi proColon 2.0 ~ 92% sensitivity
  • Intended for average risk patients
  • Positive serum test should be followed up with a colonoscopy
  • Studies now for indication in surveillance after CRC diagnosed
  • Serum testing for CRC is not yet recommended in guidelines as primary test
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 guideline approved 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 (JAN 17)

- FIT has improved sensitivity for CRC and advanced adenomas (L>R)
- Colon only
- Medications and food do not interfere (gFOBT)
- Uses antibodies directed against human hemoglobin
- Better patient adherence (one stool sample and no dietary restrictions) compared to guaiac reagent (gFOBT)
- US Multi-Society Task Force has published consensus guidelines recommending FIT > gFOBT (30)
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
FOUR FOOD ELIMINATION DIET FOR EOSINOHILIC ESOPHAGITIS (JULY 2017)

• Traditional sis-food elimination diet (cow’s milk, hen’s egg, soy, wheat, peanut/tree nuts, and fish/shellfish) for EoE results in ¾ of patients
  • Difficult to adhere

• Prospective study of four-food elimination (milk, soy, egg, wheat) in 78 children with EoE, histologic remission was achieved in 64% and decreased symptoms of 91%
UPDATED GUIDELINES FOR BARRETT'S ESOPHAGUS (GIE 2017)

- **NDBE**
  - Consider no surveillance, however if surveillance elected EGD Q3-5 years with 4 quadrant biopsies and RFA in select cases

- **LGD**
  - Confirm with expert GI path and repeat EGD 6 months to confirm LGD
  - Consider RFA or EMR
  - Surveillance EGD Q1 year with 4 quadrant biopsy every 1 cm

- **HGD**
  - Confirm with expert GI path
  - EGD Q3 month with 4 quadrant biopsy every 1 cm
  - Consider RFA or EMR
  - Consider EUS for local staging and lymphadenopathy
  - Consider surgical consultation
TRACHEA! What's up DOG?

hello esophagus.

Dude. Here comes some water, you're up, man.

No thanks, I don't drink.

Don't be such a square, guy! Loosen up!

I don't think you understand what I'm saying.

DRINK! DRINK! DRINK!

ACK AH GRGLL
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
• American College of Gastroenterology published guidelines on treatment (31)

• Initial antibiotic guided by risk factors for macrolide resistance and penicillin allergy
  • Risk factors are prior exposure to macrolides (erythromycin or clarithromycin (~15% assumed in US))
  • If there is risk factors for resistance use bismuth quadruple therapy
    • Pepto-Bismol/PPI/metronidazole and tetracycline
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

• 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
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.
PPI USE AND MORTALITY (JULY 2017)

• It is unclear if PPI use is associated with increase risk of death

• Observational cohort study incident death rate among 275,977 PPI users 4.5% vs 73,335 H2 blockers 3.3%
  • Adjusting for confounders risk was associated with length of use

• PPI’s should be prescribed at lowest dose for shortest duration
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.
"I have the results of your liver scan. You don't have all your ducts in a row."
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 vs. colonoscopy for population screening (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)
In January 2016, the USDA approved the new combination regimen elbasvir-grazoprevir (Zepatier, Merck) for treatment of genotypes 1 and 4 HCV, including patients with any degree of renal impairment (including dialysis) (who have been traditionally excluded from trials).

Randomized, placebo-controlled trial of genotype 1-infected patients with eGFR <30 mL/min, the sustained virologic response (SVR) rate was 94% among the 122 patients who received Zepatier for 12 weeks.

Adverse event rates were similar between treatment and placebo groups (16) (*Lancet*)
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% (17) (Annals IM).
- Antiviral therapy administered during chemotherapy was associated with an approximately 90% 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
FUTURE OPTIONS FOR HCV DIRECT ACTING ANTIVIRAL FAILURE (JUNE 17)

• For HCV patients who fail oral direct acting antiviral (DAA)

• 2 trials with >600 patients genotype 1-6 who failed NS5A-I or non-NS5A-I Antiviral regimen
  • 12 weeks Epclusa (sofosbuvir-velpatasvir)-voxilaprevir (a novel PI) SVR 96-98% (32)
• Acetaminophen (APAP) poisoning in patients >24 hours after ingestion can be difficulty (APAP may no longer be detectable)
• Recent observation cohort study found rapid immunoassay that measures serum APAP-protein adducts in patients with APAP-induced liver injury well beyond 24 hours (Clinical Gastro and Hep)
  • Point of care immunoassay (AcetaSTAT) had 100% sensitivity and 100% negative predictive value (33)
• ACG published new guidelines on the evaluation of liver chemistries

• These define aminotransferase (ALT) ranges as 29 to 33 international units/L for males and 19 to 25 international units for females
  
  • Lower than reference ranges of many clinical labs (34)

  • Ex. Quest Diagnostic high end normal ALT men 46 and female 29
68-GA DOTATATE FOR IMAGING OF NEUROENDOCRINE TUMORS (JUNE 16)

- Most well-differentiated PNET, carcinoid and sarcoid 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 imaging (OctreoScan) for detection of small lesions (18) (J Clin Onc)
- A kit for preparation of 68-Ga DOTATATE injection as an agent for PET imaging (Netspot) was approved by the FDA in June 2016 (19)
- Due to greater sensitivity, 68-Ga DOTATATE PET may be preferred over conventional 111-In pentetretotide scanning where available
The recommendation for cholecystectomy within 7 days of admission is imprecise.

Administrative database study >15,000 cholecystectomies for acute cholecystitis reviewed:
- Lowest overall morbidity and mortality rates were achieved with surgery on day 1 or 2 of admission (35) (J of GI Surgery)
- Surgery on the day of admission was associated with a lower rate of biliary injury but higher rate of nonbiliary complications compared with surgery on subsequent days

Concluded patients with acute cholecystitis should undergo surgery within 2 days of admission (only after they have been fully resuscitated)
EARLY REFEEDING IN ACUTE PANCREATITIS (AUGUST 2017)

• 11 randomized trial included 948 patients with acute pancreatitis
  • Early feeding ($\leq$ 48 hours after hospitalization) did not increase adverse effects or exacerbate symptoms compare to delayed feeding
  • In 4/7 trials it reduced LOS
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% had symptoms that could be attributed to malabsorption, yet only 21% 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% sensitive and 79% specific for detecting advanced neoplasia
  • missed 45% of IPMN with adenocarcinoma or high-grade dysplasia
• UpToDate authors advise a lower threshold for evaluating cysts than the AGA guideline
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
IT'S OKAY... I'VE GOT DIARRHEA!
TOFACITINIB FOR ULCERATIVE COLITIS (MAY17)

- Tofacitinib (Xeljanz, Pfizer) is an oral inhibitor of Janus kinase 1-3 used for rheumatoid arthritis and appears promising for UC
- 2 randomized trials each > 500 patients with mod-severe UC (36)
  - Induction therapy with tofacitinib resulted in higher rate of remission vs placebo (17-19% vs 4-6%)
  - Second trial > 600 patients who had clinical response to induction therapy, maintenance therapy with 2 different doses resulted in higher remission rates to 52 weeks vs placebo (35-41% vs 11%)
- Increased infections including herpes zoster seen
- Future trials needed to determine exact role for UC
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 (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
**Textures of poop**

- **Separate hard lumps, like nuts**
  You're lacking fibre and fruit. Drink more water and chew on some fruits and veggies.

- **Sausage-shaped, smooth and soft**
  Optimal poop! You're doing fine!

- **Sausage-shaped but lumpy**
  Not as serious as separate hard lumps, but you need to load up on fibre and fibre.

- **Soft blobs with clear-cut edges**
  Not too bad. Pretty normal if you're pooping multiple times a day.

- **Sausage-shaped but with cracks on surface**
  This is normal, but the cracks mean you could still up your intake of water.

- **Fluffy pieces with ragged edges, a mushy stool**
  You're on the edge of normal. This type of poop is on its way to becoming diarrhoea.

- **Watery, no solid pieces, all liquid**
  You're having diarrhoea! This is probably caused by some sort of infection and diarrhoea is your body's way of cleaning it out. Make sure you drink lots of liquids to replace the liquids lost otherwise you might find yourself dehydrated.

- **Soft and sticks to the side of the toilet bowl**
  Presence of too much oil, which could mean that your body isn't absorbing the fats properly. Diseases like chronic pancreatitis prevent your body from properly absorbing fat.
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% s. 6%)

- No significant differences in adverse effects

- Larger trials with extended treatment are needed to establish the clinical efficacy and safety of Ozanimod
Utility of colonoscopy after diverticulitis is debated

Analysis of data from Danish registry showed that patients who were hospitalized for diverticulitis were 2x more likely to develop CRC over the 18-year study period, as those without diverticulitis (Annals of Surgery)
  - 50% of CRC diagnosed within one year of diagnosis of diverticulitis

This study underscores the importance of endoscopic surveillance in patients with diverticular disease

Further supports colonoscopy after the complete resolution of an episode of acute diverticulitis (3 mo) in patients who have not had a colonoscopy within a year (37)
...IF SOMETHING WERE TO HAPPEN AND YOU NEEDED A VENTILATOR OR MACHINE TO HELP YOU BREATHE, IS THAT OH WAIT NEVER MIND.
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% developed skin lesions (12.4 per 100 patient-years) (27) Ann Intern Med

• Cutaneous lesions included (most to least common) eczema, xerosis cutis, and psoriasis

• The majority of patients were managed without discontinuation of TNF inhibitor therapy
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)
Bezlotoxumab (Zinplava, Merck) is a monoclonal antibody against C difficile toxin B (essential for the virulence of the organism).

Received US FDA approval in 2016 for secondary prevention of C difficile in patients at high risk for recurrence.

2 randomized trials with > 2,500 patients with C difficile infection.

Addition of bezlotoxumab to standard oral antibiotic therapy lowered the rate of recurrence (16-17% vs 26-28%) (38) (NEJM)
PPI AND CKD (MAY16)

• 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 variables, 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 (MAY16)

• 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
KEEP CALM AND CALL A GASTROENTEROLOGIST
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