WHAT'S NEW IN GASTROENTEROLOGY

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****NO DISCLOSURES****
GASTROENTEROLOGY

PULL FINGER FOR SERVICE

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Reynolds
2016 FDA approved a second generation serum assay for detection of circulating methylated Septin 9 for CRC screening.

- 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 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
Updated Guidelines for Barrett's Esophagus (GIE 2012)

- Published in GEIE
- 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 and clarithromycin (~15% assumed in US)
- If there is risk factors for resistance use bismuth quadruple therapy
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 (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.
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."
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).
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 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
For HCV patients who fail oral direct acting antiviral (DAA)

- 2 trial with >600 patient genotype 1-6 who failed NS5A-I or non-NS5A-I DAA regimen
  - 12 weeks sofosbuvir-velpatasvir-voxilaprevir (a novel PI) SVR 96-98% (32)
• Acetaminophen (APAP) poisoning in patients >24 hours after ingestion can be difficult (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
  o 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)
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.
The recommendation for cholecystectomy within 7 days of admission is imprecise. Administrative database study >15,000 cholecystectomies for acute cholecystitis reported the lowest overall morbidity and mortality rates were achieved with surgery on day 1 or 2 of admission (35). Surgery on the day of admission was associated with a lower rate of biliary injury but higher rate of noniliary complications compared with surgery on subsequent days. Thus, patients with acute cholecystitis should undergo surgery within 2 days of admission (only after they have been fully resuscitated).
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.
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 than the AGA guideline.
• 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
Tofacitinib 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 at 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 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
**Browns:** You’re fine. Poop is naturally brown due to the bile produced in your liver.

**Greens:** Food may be moving through your large intestine too quickly. Or you could have eaten lots of green leafy veggies, or green food colouring.

**Yellows:** Greasy, foul-smelling yellow poop indicates excess fat, which could be due to a malabsorption disorder like celiac disease.

**Blacks:** It could mean that you’re bleeding internally due to ulcers or cancer. Some vitamins containing iron or bisulfite搜狐lyl late could cause black poop too. Pay attention if it’s sticky, and see a doc if you’re worried.

**Light-colored, white, or clay-colored:** It’s not what you’re normally eating. It could mean a bile duct obstruction. Some meds could cause this too. See a doc.

**Blood-stained or Red:** Blood in your poop could be a symptom of cancers. Always see a doc right away if you find blood in your stool.

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**Textures of poop**

**Hard lumps, like nuts:** You’re lacking fibre and fluids. Drink more water and chomp on some fruits and veggies.

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

**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.

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

**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 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.
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
- 50% of CRC diagnosed within one year of diagnosis of diverticulitis

This study underscores the importance of endoscopic surveillance in patients with diverticular disease and further supports recommendation of colonoscopy after the complete resolution of an episode of acute diverticulitis is 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.
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
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 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 trial with > 2500 patients with C difficile infection, the addition of bezlotoxumab to standard oral antibiotic therapy lowered the rate of recurrence (16-17% vs 26-28%) (38).
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 170,000 new PPI users and 20,000 new H2 blocker users were followed for over 5 yrs (J Am Soc Nepro)
  o PPI group had increased risk of CKD (HR 1.3) and ESRD (HR 2.0)
  o Increasing duration of use was associated with higher CKD risk
PPI AND CKD (May16)

- 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
THANK YOU

KEEP CALM AND CALL A GASTROENTEROLOGIST


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