Journey through the GI tract
QUICK HITS!!

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Oral health--Nutritional deficiencies can manifest with oral S & S—B12 deficiency

- Our geriatric patients have an increased risk of developing nutritional/vitamin deficiencies—"tea and toasters"… NO meat in their diet, decreased acid, and the development of B12 deficiency; 39% of adults over 55 have B12 deficiency
- No B12? Anemia (macrocytic), confusion, peripheral neuropathy, and depression…
- PEARL: B12 deficiency can cause a peripheral neuropathy involving the tongue – manifested by a beefy red, "burning" tongue (glossitis)
- 77-year-old w/ 4-week hx of painful, burning tongue; serum vitamin B12 was 77.49 (normal range 147.6–442.8) pmol/L—and one month later after B12 replacement…
- Other high-risk patients for B12 deficiency? Vegans, vegetarians, gastric by-pass, PPI, metformin
- Another PEARL: "menopausal glossitis" due to low estrogen
- (Examination of the Tongue, StanfordMedicine25.Stanford.edu)

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Osteoporosis of the mandible and tooth loss

- Calcium, vitamin D deficiency, estrogen deficiency
- Loss of alveolar/trabecular bone; the mandibular bone is resorbed resulting in tooth loss (mandible > maxilla)
- Postmenopausal women who do NOT take estrogen replacement therapy have fewer natural teeth
- Bisphosphonate therapy (alendronate, risedronate, ibandronate) has it's benefits on hips and vertebrae but…

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It can cause Bisphosphonate-Related Osteonecrosis of the Jaw) (BRONJ)

- Incidence—1.3-7%; (2/3 are mandibular)
- Less than 1 /100,000 patient years in people who take oral bisphosphonates for osteoporosis; most common w/ the IV bisphosphonates given for the hypercalcemia of cancer dosed every 3-4 weeks (pamidronate, zolendronic acid (Zometa) vs. IV zolendronic acid (Reclast) given once a year
- Discuss the risks of dental complications and have them contact their dentist BEFORE starting these drugs
- Hard to treat—stopping therapy does little good because these drugs are metabolized slowly and stay in bone for many years (especially alendronate/Fosamax)
- Conservative therapy (dental hygiene, antibiotics, hyperbaric oxygen, low-intensity laser) vs. surgical debridement

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Iron deficiency anemia and the mouth: Gums and mucous membranes

- First sign of iron deficiency anemia is pallor, manifested in the gums and mucous membranes; pale conjunctivae as well; glossitis and angular cheilitis
- Pica for ice (ask about ice chewing—universal for iron-deficiency anemia)
- Look at their palm creases—if lighter than the skin on their hands their hemoglobin is 8 gm/dl or less
- High risk patients? Kids and vertical growth with lousy diets; Young women and heavy periods or pregnancy; Gastric by-pass surgery and decreased iron absorption; PPIs—no acid, no iron; and, of course—GI bleeding

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The GI tract is a major cause of iron deficiency anemia in adults

- Hematemesis? bloody emesis; Upper GI bleed w/ PUD, esophageal varices
- Coffee grounds emesis—suggests upper GI bleed with slower bleeding than hematemesis--PUD
- Melena—degradation of hemoglobin by bacteria in colon; blood has been in GI tract for a few hours; 90% of time its an upper GI bleed) black, tarry, smelly stools (bismuth, iron, spinach, charcoal, licorice and too many oreo cookies can also cause very dark stools)
- Hematochezia—bright red blood via rectum—lower GI usually left colon or rectum—diverticulosis, AVM, hemorrhoids, cancer or a brisk upper GI bleed
- Occult blood in stool– usually colon cancer
- Scope down and scope up…
- (Edwards M. Guide to the Most Common Internal Medicine Workups and Diseases, 2017)

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Causes of iron deficiency anemia (IDA) in addition to PUD, colon cancer…

- Too much cow's milk (causes loss of blood in GI tract); (maximum is 2 cups/day for kids = 16 oz.)
- Excessive tea or coffee drinking (tannins)– inhibits gastric iron absorption
- Celiac disease in kids and adults (autoimmune response to gluten in diet w/subsequent attack on the villi/microvilli of the duodenum—no iron absorption (#1 cause of Rx resistant IDA)
- Drugs that inhibit gastric acid may eventually lead to iron deficiency anemia—proton pump inhibitors for GERD
- NSAIDs—small bleeds in the stomach, duodenum
- Anti-coagulants—rivaroxaban (Xarelto), dabigatran (Pradaxa), warfarin (Coumadin); apixaban (Eliquis)—in that order of risk; clopidogrel + aspirin
- Just to be thorough: Don't forget DUB (dysfunctional uterine bleeding) in PMF; menorrhagia in premenopausal females or pregnancy

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Oral manifestations in the immunocompromised patient

- 1 in 37 American adults is immunocompromised by either a disease process or drugs used to treat autoimmune disorders and inflammatory disease processes
- Recurrent oral viral infections—HSV
- Candida albicans (yeast infection)—who's at risk? Chemotherapy; Organ transplant therapy, AIDS patients, diabetics with hyperglycemia; Steroids (including steroid inhalers for asthmatics and patients with COPD)
- Patients with autoimmune diseases treated with corticosteroids and the potent TNF-α antagonists (infliximab/Remicade; adalimumab/Humira; golimumab/Simponi; certolizumab/Cimzia; etanercept/Enbrel)

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Human papilloma virus loves the GI tract—warts, benign tumors, oral cancer and anal cancer…

- HPV is easily transmitted via any mucous membrane (over 40 subtypes invade mucous membranes) during sexual activity
- "Pick a hole, any hole…"
- **Oral HPV spreads exclusively through oral sex** NOT "deep" kissing (Gillison M. Jan 26, 2012, *JAMA*)
- Types 6 and 11 cause 90% of warts/papillomas

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HPV-induced oropharyngeal cancer (70% of oral cancers)—

- ~1% of individuals that develop a high-risk type oral HPV infection develop cancer, decades after infection--defined as cancer located in the back of the throat, most commonly at the base of the tongue and tonsils
- The more oral-sex partners you have had, the greater risk of oral HPV cancer; higher risk in males
- 7 high-risk types of HPV-- **16**,18, 31, 35, 45, 52, and 58—
- The Gardasil-9 vaccine includes all 7 oncogenic types plus the 2 that cause papillomas (6 & 11)

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HPV and rectal cancer—Gardasil-9

- Gardasil-9 ALSO protects against anal cancer due to HPV infection
- VACCINATE!! Boys and Girls!

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Aphthous ulcers in the mouth

- Single or recurrent aphthous ulcers—with or without GI symptoms: CONSIDER:
- Idiopathic (clueless)
- PFAPA (Periodic Fever (>102 F), Aphthous Stomatitis, Pharyngitis, Adenitis) --usually starts in kids between 2-5 and usually stops around age 10; (cimetidine or colchicine may help; tonsillectomy may help)
- Celiac disease--aphthous ulcers and dental enamel defects are strongly associated w/ celiac disease (*J Can Dent Association* 2011;77:b39)
- Crohn's disease and ulcerative colitis—autoimmune disorders + aphthous ulcers

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GREAT article for the treatment of acute aphthous ulcers:

- MEDSCAPE: Aphthous Ulcers Treatment & Management
- Updated: May 11, 2020
- Author: Jaisri R Thoppay, DDS, MBA, MS; Chief Editor: Arlen D Meyers, MD, MBA more...

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Oropharyngeal or transfer dysphagia

- Oropharyngeal dysphagia (transfer)—impaired movement of liquids or solids from the oral cavity to the upper esophagus—typically characterized by coughing, gagging, choking, or aspirating food during the initiation of the swallow
- Common complaint in the elderly
- Common causes: painful or diseased teeth, xerostomia (dry mouth—usually due to anticholinergic drug side effects), poorly fitting dentures, hx of uvulpalatopharyngoplasty for sleep apnea

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Esophageal or transit dysphagia

- From the upper esophagus to the lower esophagus--takes 4-8 seconds for a typical food bolus to move from the back of the throat to the LES
- patients c/o foods or pills “sticking”, “catching”, “hanging up” in their esophagus and can usually pinpoint the area with one finger (“SHOW ME”)
- Not taking with enough water with drugs is one BIG reason…
- Vitamin C (ascorbic acid), tetracycline (pH of 3—very caustic), bisphosphonates (alendronate, risedronate, ibandronate)

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Swallowing problems due to neurologic causes are more common with aging.

- Neurologic causes: stroke (usually bulbar/brainstem), Parkinson's disease, MS, ALS, tardive dyskinesia (TD) (side effects of anti-psychotic drugs –
- TD is more common (90%) with the first-generation anti-psychotics (FGA) (haloperidol) vs. the second-generation (SGA) atypical anti-psychotics (30% & dose dependent)—biggest SGA offenders (risperidone (Risperdal), olanzapine (Zyprexa), ziprasidone (Geodon)

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The lower esophageal sphincter (LES) and GERD

- The lower esophageal sphincter is a 2-4 cm segment at the level of the diaphragm; it's is a physiologic sphincter—opens and closes in response to various factors including:
- neurotransmitters-- dopamine and acetylcholine have opposing effects on the sphincter—dopamine opens the sphincter and acetylcholine closes it
- nitric oxide opens the sphincter
- calcium flowing through small channels helps close the sphincter
- progesterone that relaxes the sphincter

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Drugs/pregnancy/intra-abdominal pressure influence the sphincter

- If dopamine opens it, dopamine blockers will tighten up the sphincter and prevent reflux; metoclopramide (Reglan/Maxeran) is a dopamine blocker, closes the sphincter and decreases acid reflux
- Anti-cholinergic drugs block acetylcholine, and relax the sphincter—triggering acid reflux
- Drugs that boost nitric oxide open the sphincter (nitroglycerin, ED drugs—sildenafil, vardenafil, tadalafil, avanafil) "*Barb, I've got the worst heartburn…*"
- Calcium channel blockers open the sphincter
- Bronchodilators relax the sphincter (association with asthma/COPD)
- High levels of progesterone open the sphincter—the third trimester is especially miserable—baby pushing up on diaphragm combined with high levels of progesterone…
- Intraabdominal pressure…2 other causes…

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- Spanx under-garments, in some women, are so tight that they can trigger acid reflux via pressure; bloating, gas and bladder issues are also the result of SPANX as they compress the stomach, intestines and bladder.
- Those at highest risk already have problems with gastrointestinal and bladder issues. (John Kuemmerle, MD, Gastroenterologist, Virginia Commonwealth University Medical Center, Richmond, VA (2014)
- Other cause of increased abdominal pressure? OBESITY

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ACID causes the symptoms

- ACID is the culprit in GERD
- Hence the widespread use of antacids—from TUMS to Tagamet, Maalox to Mylanta, Pepcid (famotidine) to PPIs…everybody is poppin' something for their "heartburn"…
- It's not just about drugs, we need to encourage a few lifestyle changes…some of them DO help…in some patients

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Lifestyle factors and endoscopy- negative (non-erosive) reflux disease

- Lose weight, stop smoking; eliminate dietary factors that trigger "your" acid reflux…in some cases it's caffeinated products, peppermint, fatty foods, chocolate, spicy foods, tomato juice, tomatoes, citrus fruits and juices—and in others? champagne ☺
- Drugs aggravate GERD (some previously listed) or cause burning in the esophagus? drugs with low pH can cause burning if the pill "sticks"; tetracycline (ph3—caustic), quinidine, K+Cl, NSAIDS, Iron salts, bisphosphonates, ED drugs (the "afils"… sildenafil, vardenafil, tadalafil, avanafil"

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Pharmacology of GERD—gold standard

- PPIs (Proton Pump Inhibitors)—the "prazoles" are the **mainstay** of therapy in healing erosive esophagitis and treating symptoms of GERD
- MOA—Inhibition of the proton pump at the luminal/apical surface of the parietal cell…work **best** when taken 30-60 minutes before the first meal of the day or the evening meal if nocturnal symptoms are the problem—or BOTH if GERD is all day and all night…
- Omeprazole (Prilosec/Losec), lansoprazole (Prevacid), deslansoprazole (Dexilant/old name Kapidex), pantoprazole (Protonix, Pantoloc), rabeprazole (Aciphex, Pariet), and "the purple pill"—esomeprazole (Nexium)
- Fastest acting—esomeprazole/Nexium rabeprazole/Pariet, omeprazole/Losec, lansoprazole/Prevacid, pantoprazole/Pantoloc

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H_2 blockers decrease basal acid secretion

- Cimetidine (Tagamet), nizatidine (Axid), famotidine (Pepcid) (use famotidine for long-term use of low-dose ASA in patients with CVD)
- Inhibit the action of histamine at the H2-receptor on the basal surface of the parietal cell, decreasing nocturnal and basal acid secretion all day, and, to a lesser degree, food-stimulated acid secretion
- Work best on acid produced at night
- Faster acting than PPIs (double the OTC suggested dose) in relieving symptoms of dyspepsia or GERD, but not as effective as PPIs in relieving symptoms long-term or in healing erosive esophagitis

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Can you combine a PPI with an H2-blocker?

- Of course—take a PPI before meals and the H2-blocker at bedtime
- Cimetidine (Tagamet) has most drug interactions and side effects; guys, listen up—cimetidine is weakly anti-androgenic and may cause reversible ED and gynecomastia; first dose delirium in elderly; increase INR in patients taking warfarin
- Famotidine (Pepcid) with the least drug interactions and side effects—best choice of the H2 blockers

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PPIs and other long-term side effects—observational studies

- Tubulointerstitial nephritis—acute inflammation of the kidney—AKI
- Community-acquired and hospital-acquired pneumonia (you need acid in the stomach to help prevent the bugs from colonizing the lungs)
- Increased risk of enteric infections especially with pantoprazole (Moayyedi P et al. Randomized Trial Supports Long-Term Safety of Proton-Pump Inhibitors. *Gastroenterology 2019 May 29)*

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PPIs and long-term side effects—low risk

- Iron deficiency anemia (you need acid to absorb iron)—consider PPIs as a cause of iron deficiency anemia when all other of the "usual suspect" causes have been ruled out—like GI bleeding from cancer in people over 40)
- Zinc deficiency
- Magnesium deficiency
- 24% increase in development of T2DM (change in microbiome might be reversible with d/c PPI therapy)(Yuan J et al. Regular use of PPIs and risk of T2DM: Results from three prospective cohort studies. Gut 2020 Sep 28)

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Has your patient been on the "prazoles" or H2 blockers for longer than 2 years?

- B12 deficiency (you need the "pump" to pump intrinsic factor to combine with B12 for absorption in the distal ileum)
- Check B12 levels in your patients…The effect is dose-dependent with B12 deficiency more likely among patients taking PPIs for greater than 2 years, in patients taking greater than 1.5 PPIs per day and in the elderly.

(Lam JR, et al. Proton pump inhibitors and H2 receptor antagonist use and vitamin B12 deficiency. *JAMA* 2013:310(22):2435-2442)

Medical Letter, Drugs for Peptic Ulcer Disease and GERD, April 2014; 12(140)

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Other GI causes of B12 deficiency

- Decreased absorption of B12 over the age of 55
- Vegan or vegetarian (especially vegans) – no intake of meat
- Malabsorption (Crohn's disease, gastrectomy, gastric by-pass)

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"Barb, I can't take a PPI, what else can I do?"

- Coating the stomach with sucralfate (1 gram before meals and 2 grams at bedtime for 2 weeks.
- Another option is OTC deglycyrrhizinated licorice (DGL).
- Nocturnal symptoms primarily? Melatonin, 1-3 mg hs to increase the tone of the LES—reduces reflux
- (David Rakel, M.D. *Primary Care*, March 25, 2016)

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One major complication of untreated long-term acid reflux is Barrett's esophagus (BE)

- Routine screening for BE in women with GERD is not recommended (*NEJM* Feb 2016)
- The clinical value of screening women with GERD for BE has been likened to the value of theoretical routine screening for breast cancer in men.
- The profile of someone with Barrett's esophagus is a 55-year-old big-bellied Caucasian male with a BMI greater than 30 kg/m2

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Eosinophilic esophagitis (EoE)

- A chronic allergic inflammatory condition of the esophagus—swallowing difficulty, food impaction, heartburn (feeding difficulties in young kids)
- IL-4, IL-5, IL-13 are the key cytokine ”drivers” of allergic inflammation with eosinophil migration
- Kids and adults—food allergies may play a significant role in most, but not all
- Associated with asthma and celiac disease
- Endoscopy— demonstrates ”rings” or “feline” esophagus (similarity to rings of a cat esophagus)

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Treatment of eosinophilic esophagitis

- Swallowed liquid corticosteroids—fluticasone, budesonide for 8-weeks)
- Mechanical dilation for strictures
- PPIs may help some patients (PPI-REE)(PPI-responsive eosinophilic esophagitis)
- Clinical trials with dupilumab (Dupixent) in patients with EoE…a monoclonal antibody that decreases IL-4 and IL-13 (Dupilumab was granted FDA breakthrough therapy status for EoE in 2020)
- (Dellon ES et al. ACG clinical guideline: Evidenced based approach to diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). *Am J Gastroenterol* 2013May; 108:679)

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Peptic ulcer disease

- **Imbalance** between the mucosal defense mechanisms (prostaglandin stimulated mucus production and bicarbonate) and the major damaging force—gastric acid
- 80% in stomach, 13% duodenum, 7% multiple ulcers
- 4 causes of peptic ulcers--
- Helicobacter pylori (#’s decreasing)—Why? Dunno.
- NSAIDs – prostaglandin inhibition decreases mucous production, with unopposed acid; anti-coagulants—warfarin, DOACS
- Rare—Zollinger-Ellison syndrome (gastrinoma producing excess acid), smoking, severe illness
- Increasing category: Idiopathic…huh? Multifactorial (prior PUD, male, hospitalization, use of multiple meds)

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Gastric ulcers (peptic ulcer disease)

- *Helicobacter pylori*
- Elaborates urease and produces ammonia which buffers gastric acid in the immediate vicinity (basis for breath test)
- Chronic inflammation (gastritis) and regeneration of the antrum with carcinogenic properties
- HP is the only bacteria known to be "oncogenic"
- (Meng W. et al. Role of H. pylori in Gastric Cancer: Advances and Controversies. Discovery Medicine. November 25, 2015)

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Treating *H. pylori* (HP) to reduce the risk of gastric carcinoma—Medical Letter (April 4, 2022)

- HP-infected individuals have various degrees of chronic gastritis with an increased risk of developing gastric cancer (McColl, 2011).

EMPIRIC THERAPY

- "First Line Therapy" -- Bismuth Quadruple Therapy: PPI, bismuth subsalicylate (262 or 525 mg PO QID), and 2 antibiotics (metronidazole + tetracycline) for 14 days (optimal)
- Alternative "First-line" therapy is Rifabutin Triple Therapy with Rifabutin, Amoxicillin and esomeprazole or rabeprazole x 14 days

SUSCEPTIBILITY BASED TREATMENT

- Clarithromycin Triple Therapy w/ amoxicillin and a PPI
- Levofloxacin Triple Therapy w/ amoxicillin and a PPI (levofloxacin resistance is a concern)
- Metronidazole Triple Therapy w/ amoxicillin and a PPI (metronidazole resistance is a concern)

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NSAIDS as a cause of peptic ulcers (relative risks for comparison purposes):

- Celecoxib (Celebrex) (pure COX-2 inhibitor)– 1.4 RR
- Ibuprofen (Motrin, Advil)—2.1 RR
- Meloxicam (Mobic) – 4.2 RR
- Indomethacin (Indocin)—5.4 RR
- Naproxen (Aleve) and ketoprofen—5.6 RR
- Piroxicam (Feldene) – 9.9 RR
- Ketorolac (Toradol) – 14.5 RR (González)

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Varying Risk for Upper Gastrointestinal Bleeding with Different Anticoagulants

- Incidence of hospitalization for UGI bleeding per 10,000 person-years of use
- Rate of bleeding for patients who did NOT us concomitant PPI therapy was 115 vs. 76 for those who did
- For those NOT taking PPI: 144 for rivaroxaban, 120 for dabigatran, 113 for warfarin, and 73 for apixaban
- For those TAKING a PPI: 108 for rivaroxaban, 59 for dabigatran, 74 for warfarin, 49 for apixaban)
- **Beware of taking an SSRI with an anti-coagulant—40% more likely to develop a severe GI bleed (Yuet WC. PharmD, Univ. North Texas, Ft. Worth. June 2019)
- (Ray WA et al. Association of oral anticoagulants and co-therapy with hospitalization for UGI tract bleeding. *JAMA* 2018 Dec 4;320:2221)

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Fluids and the small intestine

- A typical adult drinks 2 liters of fluid per day, plus 1-1.5 liters of saliva; 2 liters of gastric juice; 1 liter of bile; 2 liters of pancreatic juice, and 1 liter of intestinal secretions = 9 liters
- Of these 9 liters presented to the intestine, less than 200 gm of stool (old cells, carcasses of bacteria and one kernel of corn) is excreted per day; 65 to 85% is water.
- Jejeunal reabsorption is 3 to 5 liters/day; the ileum reabsorption is 2 to 4 liters per day; colon reabsorbs 1 to 2 liters per day but is capable of absorbing almost 6 liters per day.

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Anything over the previously discussed fluid amounts hits the toilet as diarrhea…

- Chronic diarrhea is defined as a predominately loose stool (Bristol Stool Scale Types 5-7) lasting longer than 4 weeks
- Great article: Burgers K, Lindberg B, Cevis ZJ. Chronic Diarrhea in Adults: Evaluation and Differential Diagnosis. American Fam Phys 2020 April 15; 101(8):472-480.

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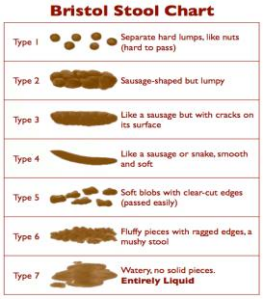

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Acute Diarrhea…

- Bloody diarrhea? (enterohemorrhagic)—*E. Coli O157:H7*, *salmonella, shigella, Campylobacter,* hemorrhoids, ulcerative colitis, ischemic colitis
- Non-bloody diarrhea? *C. diff*, norovirus, SARS-CoV-2, medications
- Length of time? In adults? No greater than 3 days before looking for the cause… Dehydration, K+ depletion with subsequent cardiac arrhythmias
- Longer than 4 weeks? Cancer?
- Kids—much sooner due to dehydration issues

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Treatment for diarrhea

- Do NOT try to stop the diarrhea until you figure out what's causing it!!! Anti-motility agents should not be used in most diarrheal food borne illnesses -- -- can lead to prolonged illness
- Antibiotics for certain bacterial causes of gastroenteritis—*Salmonella, Shigella, Campylobacter* but ONLY SUPPORTIVE care for *E. coli* O157:H7—NO ANTIBIOTICS
- Drug-induced? Metformin for example…SSRIs…
- Lomotil for diarrhea (atropine sulfate + diphenoxylate HCl)--"Lomotil is so good, it will…"
- Loperamide (Imodium)
- Known as Undiarrhea in Taiwan and Stopit in Israel

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"C. diff"—antibiotic-associated diarrhea

- *1935 in Quebec (named Bacillus difficilis)* (difficult to culture, hence, *difficilis)*
- 1960s and early 70s—pseudomembranous colitis
- 1970s renamed: *Clostridium difficile or C. diff*
- *Newest NAME CHANGE: 2018--Clostridioides difficile* new name, still *C. diff*
- (Clinical Laboratory and Standards Institute Update February 2018)

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Antibiotic-Associated Risk of *Clostridioides difficile* infection—Odds ratios (95% CI)

- Clindamycin – 16.80 (7.48 – 37.76)
- Cephalosporins, monobactams, carbapenams -- 5.68 (2.12 -- 15.23)
- Fluoroquinoloines -- 5.50 (4.26 – 7.11)
- Penicillin – 2.71 (1.75 -- 4.21)
- Macrolides – 2.65 (1.92 – 3.64)
- Sulfonamides and trimethoprim – 1.81 (1.34 to 2.43)
- Tetracyclines – 0.92 (0.61 – 1.4)

(Mounsey A, Smith KL, Reddy VC. *Clostridioides difficile Infection: Update on Management.* American Family Physician 2020 Jan 1;101(3):168-175)

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Risk factors in addition to antibiotics

- Ask about previous history of *C. diff*—higher risk for recurrent disease (20%); 60% after 2 recurrences
- Increased exposure to CD patients--"fecal cloud"
- ISOLATE patients with CD to protect other patients
- High incidence among patients admitted to a room with previous CD patient—housekeeping and special cleaning of room
- Greater than 2 hospitalizations in past 60 days
- Older age—10 x higher among patients older than 65 vs. younger patients
- IBD, chemo, CKD, organ transplant patients

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RX: antibiotics (huh? or fecal transplants for patients

- Oral vancomycin---first line therapy (forget the metronidazole)
- Fidaxomicin (Dificid) –narrow spectrum AB for non-responders to the above regimen
- 5% mortality related to infection; 15-20% all cause mortality
- PREVENTION: Minimizing antibiotic use; prohibiting routine use of ceftriaxone and ciprofloxacin accompanied by an educational campaign reduced *C. diff* by 77% in a hospital in Scotland (Dancer)
- Changing the microbiome with a healthy donor fecal transplant appears to be the most efficacious with a range of 70-93% cure with first transplant
- Infusing new, healthy stool from a willing donor changes the environment
- Oral capsules are just as effective as colonoscope insertion of fecal material -- 96% cure rate (40/1 hour)

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The duodenum (12 fingerbreadths)—the organ of nausea

- 5-HT_3 (5-hydroxytryptamine)(serotonin) receptors are located in the duodenum and brainstem vomiting center—CTZ (chemoreceptor trigger zone)
- Serotonin release causes nausea--Makes ya' sick to your duodenum and vomiting from your CTZ
- 5-HT_3 blockers--The "setrons"—ondansetron (Zofran), granisetron (Kytril), dolasetron (Anzemet), palonosetron (Aloxi)
- Nausea and vomiting from chemotherapy; post-anesthesia nausea and vomiting; migraine nausea and vomiting—don't use these with diabetic gastroparesis—can exacerbate gastroparesis

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Chronic Cannabis use and hyperemesis/cyclical vomiting syndrome

- Definition: A condition of cyclic nausea, vomiting, and abdominal pain in chronic cannabis users without other identifiable etiologies.
- CHS is also associated with compulsive showering in hot water, age younger than 50 years, morning predominance of symptoms, excessive use of cannabis (one or more times per week over at least one year), and cessation of symptoms with cannabis abstinence

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Chronic Cannabis use and hyperemesis/cyclical vomiting syndrome

- What causes it? It's a paradoxical effect of cannabis—we use cannabis to stop N, V, D; Animal studies indicate that cannabinoid has a biphasic effect in rodents, with low doses attenuating vomiting, but high doses potentiating emesis
- Topical Capsaicin cream— Transient receptor potential vanilloid 1 (TRPV1) receptor inhibition—impairs substance P (pain) signaling in the area postrema and nucleus solitarius via overstimulation of TRPV1 (antiemetic effect)
- Haloperidol works, too
- *Case Rep Psychiatry.* 2016; 2016: 3614053

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Celiac disease and the duodenum

- Ingested gluten stimulates an autoimmune response causing atrophy of the villi and microvilli resulting in malabsorption
- Classic GI symptoms -- chronic diarrhea, foul-smelling stools, abdominal pain, bloating, vomiting, weight loss, flatulence, and long-term nutritional deficiencies including vitamin D deficiency with osteopenia and osteoporosis, iron deficiency anemia (resistant to iron replacement until the underlying problem is treated)
- PEARL: Atypical presentations -- gait ataxia, seizures, peripheral neuropathy, aphthous stomatitis, arthritis, migraine headaches (~20% may have celiac disease)—try a gluten free diet for 3 months and see if the headaches diminish in # and intensity

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Normal intestinal epithelium vs. Celiac disease

- DX: Blood tests for gluten antibodies (tissue transglutaminase autoantibodies)
- small bowel biopsy (taken from the jejunum) for diagnosis

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Gastroenteritis…the "stomach flu"

- There is NO SUCH thing as the "stomach flu"… period.
- Causes of gastroenteritis—appendicitis, food poisoning, viral infections (noroviruses, SARS-CoV-2), bacterial infections (*Salmonella, Shigella,* and every other little fella, *C. jejuni* spp., *Yersinia entercolitica* (mimics acute appendicitis)

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Noroviruses—the 'vacation of a lifetime'

- Responsible for 58% of food-borne epidemic gastroenteritis in older children and adults
- The inoculum—only 18 viruses can wreak havoc—incredibly contagious
- Salad bars (cold foods, raw shellfish), person-to-person, water on cruise ships, church picnics, casinos, and in nursing homes
- start shedding virus before symptoms occur and shed virus for 4 days after symptoms subside (hence, the rapid spread of infection); can shed virus up to 4 to 8 weeks after illness

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Noroviruses—clinical signs and symptoms

- When infected, patients have bodily fluids flying out of every GI orifice—vomiting and diarrhea at the same time—affectionately known as "shuking".
- median duration of S & S = 23 hours
- In theory, one batch of vomit contains enough viral particles to infect 3 million people. When vomit splashes on hard surfaces billions of viruses fly into the surrounding air and can be inhaled or swallowed.
- Stay home for 3-4 days after the norovirus symptoms subside, especially if you handle food or work in healthcare. You are still shedding billions of virus particles in those three to four days and you can infect co-workers and contaminate food. (Jones D. The Mark of Noro. *New Scientist* 2013 March;42-45)
- Treatment? Supportive
- (*Journal of Medical Virology*, vol. 80, p. 1468)

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Food-borne gastroenteritis: Salmonella

- #1 bacterial cause of food-borne illness—GI symptoms and sepsis!
- #1 cause of hospitalization and #1 cause of death from food-borne illness…
- High risk in immunocompromised patients and patients on acid suppressing drugs!
- CAUTION with raw egg-containing delights—mousses, Hollandaise sauce, eggnog, French toast (dragging the toast through a raw egg)…use pasteurized eggs
- Peanut butter…chicken…other foods

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Campylobacter jejuni

- #2 cause of bacterial food-borne illness
- Undercooked chicken, turkey
- Major manifestation: diarrhea
- Guillain-Barre syndrome—the risk from campylobacteriosis is 300x higher than that of the general population
- GBS ~ 4 weeks after exposure

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Another cause of *Campylobacter jejuni?*

- Cuddly puppies from puppy breeders? 😢
- The whole family with diarrhea
- ARCHIE!!
- Don't kiss your puppies on the lips…
- Why?

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GI Manifestations of COVID-19

- Pooled prevalence of GI manifestations ~18% of COVID-19 patients (17% with severe manifestations of COVID-19)—similar among adults, kids, and pregnant women
- Anorexia (27%)
- Diarrhea (12%)(viral shedding occurs throughout the disease—fecal-oral spread of COVID-19)
- N & V (10%)
- Abdominal pain (9%)
- (Cheung KS et al. GI manifestations of SARS-CoV-2 infection…Gastroenterology 2020 Apr 3;{epub}.

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Acute appendicitis

- *"There are only 2 things you need to know in medicine…the common and the dangerous. For everything else there is time."*
- Entities that are **common and dangerous**, like appendicitis, should enter our thoughts immediately with acute abdominal pain
- Pain migration has been described as the "most discriminating feature of the patient's history…" with a sensitivity and specificity of 80%
- Psoas sign is fairly specific 95% but not sensitive 16%
- Possible peritoneal signs—rebound tenderness; Markle sign—drops from standing on toes to heels with a jarring landing; guarding

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Acute appendicitis—major cause of the acute abdomen

- Consider from ages 2 to 92
- Presents initially with peri-umbilical pain and subsequently migrates to the RLQ; vomiting in infants and preschool kids; anorexia, and nausea, then pain to RLQ followed by vomiting > 13 yo.
- Median time from onset of symptoms to presentation is 24 hours or less with appendicitis
- CT scan (sensitivity and specificity of 91% and 90%) vs. Ultrasound (78% and 83%); using CT scans has reduced the negative-finding appendectomy rate from 24% to 3% (Cartwright S, Knudson MP. Diagnostic Imaging of Acute Abdominal Pain in Adults. Am Fam Phys 2015;91(7):452-459
- In adults, if nausea and vomiting precede abdominal pain, consideration should be given to a diagnosis of gastroenteritis rather than appendicitis

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In kids? Ask about the "Hamburger sign."

- *"If the child wants to eat, consider ANY diagnosis other than appendicitis…"*

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Irritable bowel syndrome (IBS)

- Pain or discomfort that occurs in association with altered bowel habits over 3+ months
- Brain-bowel connection—serotonin sensitivity? Too little serotonin? Constipation-predominant--IBS-C. Too much serotonin? Diarrhea-predominant—IBS-D
- Global IBS—both C and D -- ???
- Cannabis use disorder is correlated with an 80% increased risk for IBS in the general population with men, Caucasians and Hispanics at highest risk. (Presentation at the World Congress of Gastroenterology at ACG 2017)

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Treatment of IBS based on symptoms—Constipation? Consider:

- Psyllium (fiber) or polyethylene glycol (Glycolax, Miralax) for IBS-C
- Plecanatide (Trulance) or tenapanor (Ibsrela) in patients who haven't responded to fiber and polyethylene glycol
- Linaclotide (Linzess) for IBS-C and chronic idiopathic constipation
- Lubiprostone (Amitiza) for IBS-C for women only
- SSRIs for IBS-C

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Treatment of IBS based on symptoms—Diarrhea?

- Non absorbable antibiotic rifaximin for global IBS symptoms especially for IBS-D and the symptom of bloating
- Tricyclics, loperamide (Imodium), ondansetron (Zofran), eluxadoline (Viberzi) for IBS-D
- Peppermint oil (small intestinal-release form) for abdominal pain works better when compared to placebo
- Probiotics--??optimal strains, species and doses remain to be established
- Dietary changes—are dietary FODMAPs a cause of IBS? (Halmos EP et al. A diet low in FODMAPs reduces symptoms of IBS. Gastroenterology, 2014 Jan;146:67)

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Crohn disease (CD)—autoimmune inflammatory bowel disease

- Primarily small intestine, but can include anywhere from the esophagus to the rectum; Full thickness lesions; skip lesions; fistulas; fibrosing strictures; loss of albumin, malabsorption (B12, bile salts leading to steatorrhea)
- Cause? Multifactorial--A change in our healthy microbiome? Previous norovirus infection?? Abnormal immune response
- Autoimmune response with significant inflammation secondary to tumor necrosis factor-alpha (more on treatment in a few minutes)

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Signs and symptoms

- Acute disease: ages 15-30 for first peak (20-30% under age 20); Usually begins with intermittent attacks of relatively mild diarrhea, fever, and abdominal pain; occasionally begins with an abrupt onset, with acute RLQ pain, fever, and diarrhea
- Diff dx –may mimic acute appendicitis, acute bowel perforation, ovarian torsion (girls: 9-14)

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Ulcerative colitis—inflammatory bowel disease

- Limited to the colon and affects only the mucosa and submucosa; extends in a contiguous fashion proximally from the rectum
- Inflammation due to excess TNF-alpha
- Peak onset between 20 and 25 years of age—diarrhea with blood and pus, abdominal cramping, rectal pain and bleeding, urgency to defecate (tenesmus), weight loss, fatigue, IDA
- Risk for colon cancer—risk is highest in patients with pancolitis of 10 or more years duration; 30% @ 35 years after diagnosis

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Treatment of Inflammatory Bowel Disease

- Depends on severity of disease symptoms
- Goals for UC—resolution of rectal bleeding and diarrhea and endoscopic remission
- Goals for CD—resolution of abdominal pain and diarrhea and resolution of ulceration at ileocolonoscopy
- Aggressive early intervention (within 18 months of diagnosis) is associated with better outcomes (especially Crohn's disease)
- Do NOT use probiotics for IBD outside of a clinical trial

(Su GL et al. AGA clinical practice guidelines on the role of probiotics in the management of GI disorders. Gastroenterology 2020 Jun 9)

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Treatment of inflammatory bowel disease

- Oral corticosteroids (Prednisone)(Budesonide) for both Crohn's and UC for the acute inflammation/flares
- Then taper and discontinue
- Rectal corticosteroids for distal ulcerative colitis
- Budesonide (Entocort EC) enemas can reach the splenic flexure, while foam coats only the last 15-20 cm of the colon

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Medical treatment of mild UC/Crohn's

- Aminosalicylates—the active moiety of all the aminosalicylates used to treat IBD is 5-aminosalicylate (5-ASA), aka mesalamine—Pentasa, Delzicol, Canasa, Asacol HD, Pentasa, Rowasa, Lialda, and Apriso
- MOA: Antiinflammatory--Anti-leukotrienes, reduction in IL-1, and decreases TNF-alpha signaling
- Not used as much anymore except for mild disease
- Azathioprine (Azasan, Imuran), mercaptopurine (Purinethol, Purixan), and methotrexate may also be added to Rx regimen

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Monoclonal antibodies are the "go-to" drugs toda-—moderate to severe CD and UC

- Monoclonal antibodies that block TNF-alpha include
- infliximab (Remicade) – most experience
- adalimumab (Humira) – for patients who are intolerant to infliximab or lack of response to infliximab;
- certolizumab pegol (Cimzia) (pegol)long acting form
- golimumab (Simponi)

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Monoclonal antibodies

- Verdolizumab (Entyvio)(SQ)—binds to integrin alpha4 beta7…decrease neutrophil migration into the colon, decreasing severe inflammation—head-to-head trial of verdolizumab vs adalimumab—verdolizumab w/ 31.3% remission vs. 22.5% for adalimumab—the clear winner was verdolizumab
- Ustekinumab (Stelara) for Crohn's disease/UC—MAB to IL-12 and IL-23—decreases inflammation (first approved to treat psoriasis and psoriatic arthritis)—(Sands BE, et al. Ustekinumab as indection and maintenance therapy for UC. N Engl J Med 2019 Sep 26;381:1201)

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Constipation in older adults

- *"If you need time to think, ask older patients to describe their bowel habits".*

  Clifton Meador, M.D
- 33% of adults over 60 experience occasional constipation; bump that number up to 50% in LTCF
- Defined as incomplete elimination of stool, difficulty passing stool, or both.
- Primary or secondary (medication use, for example; cancer)

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Constipation—causes?

- Drugs—drugs with anticholinergic properties, opioids (codeine, oxycodone, morphine), laxative abuse ("prune abuse" for example)
- dementia—the "neglect of the call to stool"

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Behavioral interventions

- Take advantage of the gastrocolic reflex—schedule toileting after a meal
- CLINICAL PEARL: Place feet on a small step stool instead of on the floor to straighten the anorectal junction
- Take adequate time
- Avoid bedpans if at all possible
- EXERCISE programs DO NOT improve symptoms of constipation in nursing home residents and older adults
- What helps? increasing fluid (1.5 to 2 L) and fiber intake (20-35 g/day)

75

Great article on the pharmacologic treatment of constipation

- Mounsey A, Raleigh M, Wilson A. Management of Constipation in Older Adults. Am Fam Phys 2015; 92(6):500-504.

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Diverticulosis and diverticulitis

- MYTH: It was a long-held assumption that patients with diverticulosis should refrain from eating nuts and foods containing seeds
- It's just a myth—yeth, you can eat NUTHS…they're good for you!!
- (McNally PR. GI/Liver Secrets Plus, 2010 4th edition)

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Colorectal cancer—2/3 colon, 1/3 rectal cancers; men > women (25%)

CRC is the 2nd most commonly diagnosed cancer in women worldwide, and 3rd most common cancer diagnosed in men

ASK ABOUT FAMILY HISTORY!! 20-30% of all colorectal cancer patients have a positive family history of CRC and 3-5% of patients have an inherited genetic syndrome (Lynch syndrome, Familial Adenomatous Polyposis, Peutz-Jager)

… increased risk with 1 first degree relative (parents, siblings, children) and with 2 second-degree relatives (grandparents, aunts, uncles, nephews, nieces, half-siblings)

WHEN TO START SCREENING? Age 45 in patients with no risk factors, but let's say you have a Dad with colon cancer diagnosed at age 40? Start screening at age 30; Patients with a family history of two second-degree relatives w/ colorectal cancer should also start screening at age 40

- (MD Anderson, SEER program, 2014; NEJM Resident Briefing, April 21, 2022)

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Stats on colon cancer in younger adults…

- ~12% of all new **colon cancer** cases are diagnosed in patients **younger** than 50. 58% of early colon cancer patients have metastatic disease (stages III and IV) when diagnosed; rectal cancer is more common in younger adults
- DO A RECTAL EXAM on your younger patients at high risk for colorectal cancer
- CHADWICK BOSEMAN (T'Challa in Black Panther; Levee in Ma Rainey's Black Bottom) -dx @ 39; died at 43…

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Hereditary colon cancers

- Screening should start as young as 20 in FAP patients
- Sulindac (Clinoril)—a NSAID for chemoprevention of FAP
- (Yang J et al. Am Soc for GI Endoscopy guidelines on the role of endoscopy in FAP, 2020 March 10; N Engl J Med 1993; 328:1313-1316)

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Aspirin, Omega-3 Fatty Acid (EPA) or Both to Prevent Colorectal Cancer (CRC)

- 700 patients at high risk for CRC (multiple adenomas on colonoscopy) were randomized to either aspirin 300 mg daily or EPA (fish oil) (1000 mg twice daily) or both or neither
- Total # of adenomas was reduced in patients taking either aspirin (right-sided) or EPA (left sided) vs patients taking placebo
- (Hull MA et a. Eicosapentaenoic acid (EPA) and aspirin, alone and in combination, for the prevention of colorectal adenomas (seFOod Polyp Prevention trial): A multicentre, randomized, double-blind, placebo-controlled, 2 x 2 factorial trial. Lancet 2018 Dec 15;392:2519)

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What else can you tell your "average risk" patients about prevention of colorectal cancer?

- ASA – (-14% to -29%)
- NSAIDS – (-27% to -43%)
- Magnesium – (-11% - 22%)
- Folate – (-12% to - 15%)
- Fiber – (-22% to -43%)
- Diary products – (-13% to – 19%)
- Fruits and vegetables -- (- 8 to -52%)
- Soy – (-8% to -15%)

(Chapelle N et al. Recent advances in clinical practice: Colorectal cancer chemoprevention in the average risk population. Gut 2020 Sep 28)

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TWO WORDS TO REMEMBER: EARLY DETECTION

- One in three people who develop CRC die from their disease—**early detection is the KEY to decreasing this number.**
- 20% of colon cancer is diagnosed after it has metastasized**—early detection is the KEY to decreasing this number.**
- Most colorectal cancers arise from polyps/adenomas**—**and it takes 10-15 years for a polyp to progress to CANCER, so…guess what? **EARLY DETECTION IS THE KEY—colonoscopies every 5-10 years and removing polyps to prevent the transformation of a polyp into a colorectal cancer**

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And test those stool samples…

- FIT – (fecal immunochemical test for human hemoglobin)—has a higher sensitivity (80%) for colorectal cancer (CRC) and advanced (20-30%) adenomas-
- perform colonoscopy after a + FIT
- Cologuard: FECAL DNA Testing-- for molecular mutations for known cancer genes, including KRAS mutations, NDRG4, BMP3 methylation, and Beta actin + FIT for fecal blood
- Single sample is sufficient
- Sensitivity 73-79% Specificity 94%

(Lee JK et al. *Ann Intern Med* 2014 Feb 4; 160:171)

- (RobertsonR K, et al. *Gastro Endosc* 2016 Oct 18)

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Colonoscopy…

- Colonoscopy is still the gold standard for detecting CRC
- Reduce colon cancer by 54% over a 20 years period
- Yucky test…worth it.
- Colonoscopies should be performed every 10 years, but more frequently if the patient has ulcerative colitis, a a history of polyps, previous colon cancer, or one of the colon cancer syndromes

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Colonoscopy timing

- Earlier in the day…morning is best; plus the longer you wait, the hungrier you get…ask for first or second appointment in the day.
- (Chan MY, et al. Fewer polyps detected by colonoscopy as the day progresses at a Veteran's Administration teaching hospital. Clin Gastroenterol Hepatol.2009 Nov;7(11):1217-23)

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Last Parting Pearl:

- As a general rule, kids insert things into holes ABOVE the belt…
- Adults insert things into holes below the belt—rectums and vaginas are popular
- Vibrator—tongs trying to remove it
- *"Do you want me to remove it or just turn it off?"*

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Thanks.

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