Liver and GI Update 2022

Henry C. Barry, MD, MS
Professor emeritus
Department of Family Medicine
Michigan State University College of Human Medicine

1

At the end of this session, the participant will be able to:

- describe approaches to managing persons with diarrhea
- summarize recent research on screening and managing patients with hepatitis C
- describe a comprehensive approach to managing patients with irritable bowel syndrome

2

Acute gastroenteritis in children

3

Ondansetron in kids with gastroenteritis (1)

- Unblinded pragmatic RCT in primary care practices
  - 175 children (6 months to 6 years)
    - 4 or more episodes of vomiting within 24 hours and
    - at least 1 episode of vomiting within 4 hours of presentation
  - Oral rehydration vs. ondansetron syrup
    - ORT: 10 mL/kg (if child was already dehydrated, they used 15 mL/kg for 4 hours)
    - Ondansetron: 0.1 mg/kg single dose (repeated once if vomited within 15 minutes)
  - Symptom diaries for up to 1 week
- ondansetron vs. ORT
  - Continued vomiting within 4 hours of randomization 19.5% vs. 42.9% (NNT=5)
  - No difference in ER referrals (19.4%) or admissions (14.4%) or adverse events
  - Parents were slightly happier with ondansetron

Bonvanie, Br J Gen Pract 2021

4

Ginger in children with gastroenteritis (2)

- DB RCT
  - 150 children (1 to 10 years of age)
  - symptoms less than 12 hours, and an average of 4 vomiting episodes within the previous 4 hours
  - Randomized to 10 mg ginger or matching placebo (both in liquid form), repeated every 8 hours if vomiting continued
  - All received ORT 30 minutes after first dose
- Ginger vs. placebo
  - Continued vomiting: 64% vs. 86% (NNT=5)
  - None of the children required IV hydration or hospitalization
  - Fewer ginger-treated children did not return to school next day (56% vs. 80%) but was similar in both groups by third day (29% and 30%, respectively)

Nocerino, Aliment Pharmacol Ther 2021

5

Lower GI

6

Fecal calprotectin to identify kids with inflammatory bowel disease in primary care (3)

- Prospective cohort of 195 children (4-18) whose primary car clinician ordered a fecal calprotectin assay
  - Excluded those with established IBD diagnosis, suspected to have cancer and who were using NSAIDs
  - 54% had at least one red flag for IBD (e.g., rectal bleeding, nocturnal symptoms, etc.)
  - ELISA assay where levels 100 mcg/g and above was positive
- Outcome: 7% had IBD diagnosed based on clinical, radiologic, and histopathologic findings during the 12 months after the index assay
- Se/Sp – 100% and 91%
- LR+ 11.1 and LR- 0
- A negative test effectively rules out IBD

Walker, Arch Dis Child 2020

7

AGA guideline for tests in persons with chronic diarrhea (4)

- Panel
  - included primary care but no patient; one had financial ties
  - used SRs as a guide
- Recommendations
  - Definition: watery diarrhea for at least 4 weeks
  - Screen for IBD with fecal calprotectin or fecal lactoferrin, but not ESR or CRP (conditional; low quality evidence)
  - Test for giardia (strong; high-quality evidence)
  - No testing for ova or other parasites without travel to a high-risk area (conditional recommendation, low-quality evidence)
  - Test for celiac disease (tissue transglutaminase or antiendomysium; strong recommendation, moderate-quality evidence)
  - Test for bile acid diarrhea via assay or empiric trial of a bile acid binder (conditional recommendation, low-quality evidence)

Smalley, Gastroenterol 2019

8

ACG guideline on the prevention, diagnosis, and treatment of Clostridioides difficile infections (5)

Type of Recommendation	Intervention
Strongly in favor	Oral vancomycin, fidaxomicin, or metronidazole for treating persons with nonsevere infections
	Oral vancomycin or fidaxomicin for treating those with severe infections
	Fluid resuscitation plus oral vancomycin +/- parenteral metronidazole for patients with fulminant infections
	Fecal microbiota transplant in persons with severe and fulminant C. difficile infection refractory to antibiotic therapy and to prevent recurrence in those experiencing their second (or more) C. difficile infection
Conditionally in favor	Testing algorithms should use highly sensitive and highly specific tests to distinguish colonization from active infection
	Vancomycin enemas in persons with ileus
	Repeat fecal microbiota transplant for persons experiencing a recurrence within 8 weeks of an initial transplant
Conditionally against	Use of probiotics to prevent C. difficile in persons taking antibiotics
Strongly against	Use of probiotics to prevent recurrence

Much more in the guideline, including useful resources

Kelly, Am J Gastroenterol 2021

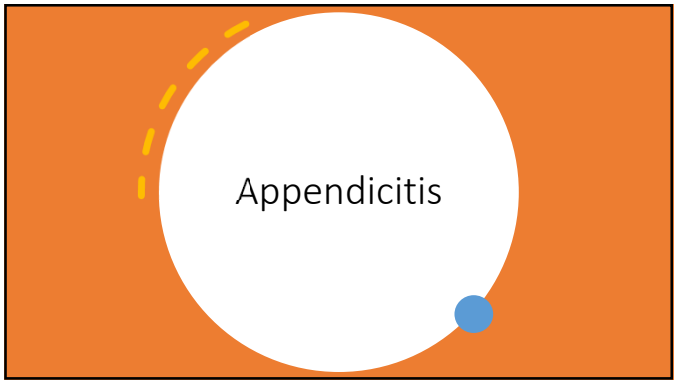
9

Cancer found in fewer than 1% of patients after uncomplicated diverticulitis (6)

- MA of 17 observational studies with 3296 patients
  - Dx was confirmed by CT
  - 959 had uncomplicated diverticulitis
  - Moderate methodologic quality
- Colorectal carcinoma
  - Overall 2.1%
  - Uncomplicated disease 0.5%
  - Complicated disease 8.3%

Rottier, Br J Surg 2019

10



11

Pediatric Appendicitis Laboratory Score (7)

- Cohort of 361 children (2-14 years of age) in ER with suspected appendicitis
  - Developed prediction rule on 278 and validated it on 83
  - Also used US during the work up (messy)
  - Based on pathology and 15-day clinical follow-up, 36% in the development cohort and 49% in the validation cohort had appendicitis
- PALabS has 6 parts
  - Nausea = 3 points
  - Maximum pain in RLQ = 4 points
  - ANC > 7500/uL = 7 points
  - WBC > 10,000/uL = 4 points
  - CRP > 10 mg/L = 2 points
  - Fecal calprotectin > 50 ng/mL =3 points

Benito, Am J Emerg Med 2020

12

Pediatric Appendicitis Laboratory Score (7)

- Compared PALabS with 2 other scores
  - Pediatric Appendicitis Score and the Kharbanda Score were less accurate
- PALabS of 6 or less
  - 99.2% sensitive
  - LR- 0.03
- An example of a SnNOut

Benito, Am J Emerg Med 2020

13

Point-of-care ultrasound for diagnosis of appendicitis (8)

- Meta-analysis
  - 17 studies with 2385 patients
  - 3 studies used appendix diameter > 7 mm and the other 14 studies used 6 mm as the criterion for appendicitis
  - Low to moderate risk of bias ☺
  - Prevalence ranged from 24 to 75%
- POCUS was accurate
  - Se 84%; Sp 91%; LR+9.3; LR-0.18
  - Even better in children: Se 95%; Sp 95%; LR+ 19.4; LR- 0.05

Lee, Am J Emerg Med 2019

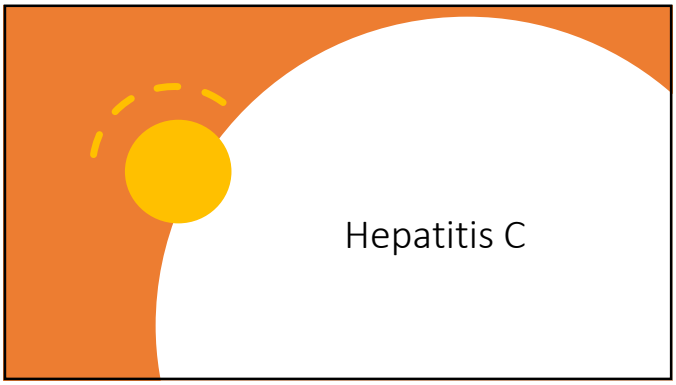
14

Trade offs in using antibiotics to treat appendicitis (9)

- Unblinded RCT
  - Adults in ER with uncomplicated appendicitis confirmed by US
  - Randomized to Abx (IV for 24 hours then oral; n=776) or surgery (mostly, laparoscopic; n=776)
- 30-day outcomes between those treated with Abx vs. surgery
  - QOL: similar between groups
  - Missed work: 5.3 vs. 8.7 days
- 90-day outcomes between those treated with Abx vs. surgery
  - ER visits: 9% vs. 4%
  - Hospitalizations: 24% vs. 5%
  - Surgery in 29% treated with antibiotics
- Patients with appendicoliths were more likely to require appendectomy and have complications following antibiotic treatment

CODA Collab, NEJM 2020

15



16

USPSTF Recommends Hep C Screening (10)

- Guided by SR
- No direct evidence that screening improves patient-oriented outcomes, but:
  - Diagnostic tests are accurate
  - Current treatment protocols are safe and effective at achieving SVR of 95%
  - Consistent association between SVR and improved patient outcomes: all-cause mortality; cirrhosis; hepatocellular carcinoma
- B recommendation to screen adults 18-79 at least once

USPSTF, JAMA 2020

17

Direct acting antivirals for chronic hepatitis C infection (11)

- Cochrane SR
  - 138 RCTs with 25232 participants
  - 51 different DAAs
  - 11 RCTs of drugs still on the market or in development
  - All were at high risk of bias
- Hepatitis C mortality (OR 3.72; 95% CI 0.54-26.18)
- SVR (RR 0.44, 95% CI 0.37-0.52)
- "The clinical relevance of the effects of DAAs on "sustained virological response" is questionable, as it is a non-validated surrogate outcome"

Jacobsen, Cochrane 2017

18

Medications for acute hepatitis C infection (12)

- Cochrane SR
  - 10 RCTs with 488 participants
  - All were at high risk of bias
  - Interferon alpha, interferon beta, pegylated interferon-alpha, pegylated interferon-alpha + ribavirin
  - All compared against no intervention – no placebos
  - FU ranged from 6 to 36 months
- Limited data on mortality, cirrhosis, HRQOL, adverse events
- Lower SVR with interferon-alpha (OR 0.27, 3 trials, 99 participants)

Jacobsen, Cochrane 2017

19

Irritable Bowel Syndrome

20

Fecal transplant (13)

- MA of 4 RCTs with 254 participants
  - 2 only available in abstract form
  - 1 administered via colonoscopy, 1 via NJ tube, 2 via capsule
  - Only 1 was at low risk of bias
  - Did not pool the data
- Global improvement
  - 2 reported greater improvement in the placebo-treated participants
    - Used oral capsules
    - (NNTH=3)
  - 2 reported greater improvement in the transplanted participants
- QOL improved during the first 12 weeks but not afterwards

Xu, Am J Gastroenterol 2019

21

Altering the biome (14)

- SR of 58 RCTs and 7350 participants
  - 53 trials (n=5545) of multiple probiotics and probiotic combinations
  - 5 trials (n=1805 adults with IBS with diarrhea) of rifaximin
- Probiotic studies
  - Variable quality, only half were at low risk of bias
  - Mixed results that varied among various agents/combinations
- Rifaximin
  - 4 were at low risk of bias
  - Improvement in "persistence of symptoms" – NNT = 11
  - Adverse effects generally were not reported

Ford, Aliment Pharmacol 2018

22

Minesapride in patients with IBS-C (15)

- DBRCT of 411 adults with IBS-C (86% women)
  - 2-week placebo run-in to establish baseline scores
  - Randomized to placebo or minesapride 10 mg, 20 mg, or 40 mg daily for 3 months
- Outcome: an increase in one or more complete spontaneous bowel movements plus an improvement of 30% or more from baseline
- After 6 and 12 weeks, no significant difference in any of the minesapride doses and placebo

Hamatani , Aliment Pharmacol 2020

23

Antidepressants and psychological therapies in adults with IBS (16)

- MA of 53 trials (range 15 to 172 patients)
  - 17 studies compared antidepressants with placebo
  - 35 compared psychological therapies with control therapy or usual care
  - 1 compared both psychological therapy and antidepressants with placebo
  - Only 4 were at low risk of bias
- Outcome: improvement in global IBS symptoms
  - Antidepressants (mainly TCAs): 57% vs. 34% on placebo (NNT=5)
  - CBT: NNT = 4*
  - Relaxation: NNT=6*
  - Multicomponent therapy: NNT=4*
  - Hypnotherapy: NNT=5*
  - Dynamic psychotherapy: NNT=4*
- Outcome: improvement in pain
  - Antidepressants (mainly TCAs): 52% vs. 27% (NNT=4)
- Outcome: adverse events
  - Antidepressants: 36% vs. 21% (NNTH = 9)

* heterogeneity; publication bias

Ford , Am J Gastroenterol 2019

24

ACG guideline for IBS (17)

- Expert panel and a methodologist (no primary care, no patient, no definition of "expert")
- **100% of the authors reported COIs**
- Strong recommendations
  - serologic testing for celiac disease
  - C-reactive protein or fecal calprotectin in pts with IBD alarm symptoms
  - Use of soluble fiber, TCAs, lubiprostone, linaclotide or plecanatide, rifamaxin
- Conditional recommendations
  - against routine colonoscopy in younger pts and those without alarm symptoms
  - Initial trial of FODMAP diet
  - Against antispasmotics, probiotics, PEG, bile acid sequestrants, fecal transplant
- Consensus recommendations (i.e., no evidence)
  - Categorize patients based on Bristol Stool Scale
  - Against routine testing for food allergies or other food intolerances (other than gluten)
  - Anorectal physiology in pts with signs/symptoms of pelvic floor disorder or refractory constipation

Lacy, Am J Gastroenterol 2021

25

BSG guideline for IBS (18)

- Multidisciplinary panel
  - Included patients
  - Guided by systematic reviews (299 references!)
  - Unclear role of COI
- Pragmatic definition: at least 6 months of abdominal pain or discomfort accompanied by altered bowel habits but no red flags
- Testing
  - Everybody gets CBC, CRP or SR, serology for celiac disease
  - Under 45 with diarrhea – fecal calprotectin
  - Screen for CRC using established guidelines
  - Colonoscopy only in presence of alarm symptoms or if at increased risk for microscopic colitis (e.g., female; over 50; known autoimmune disorders; weight loss; diarrhea <12 months; severe, nocturnal or watery diarrhea
  - Bile acid diarrhea in presence of nocturnal diarrhea or prior cholecystectomy
  - Do not test for pancreatic insufficiency, small intestinal bacterial overgrowth, or carbohydrate intolerance in presence of typical IBS symptoms
- Treatment
  - First line: exercise, soluble fiber, FODMAP. Loperamide for diarrhea. Consider PEG for constipation, probiotics, antispasmodics, peppermint oil (weak recommendation)
  - Second line: tricyclic antidepressants and selective serotonin reuptake inhibitors

Vasant, Gut 2021

26

Bottom Lines

- Fecal calprotectin is accurate in identifying kids with inflammatory bowel disease
- POCUS is accurate in diagnosing appendicitis
- Surgery vs. Abx for appendicitis: trade offs provide an opportunity for shared decision-making
- Screen adolescents and adults for hepatitis C
- In adults with suspected IBS, testing should be limited to serologic testing for celiac disease and to C-reactive protein or fecal calprotectin in pts with IBD alarm symptoms
- Treat persons with IBS withsoluble fiber followed by FODMAP, loperamide for diarrhea, PEG for constipation and secondary treatment with TCAs, lubiprostone, linaclotide or plecanatide, rifamaxin

27