MEDICAL BITS FROM YOUR DOCTOR

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"What damages humans? Politicians without principles. Pleasure without compromise. Wealth without effort. Knowledge without character".

1 – **Medical News** Irritable Bowel Syndrome

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New Vaccines

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"Business without ethics. Science without humanity and above all the absence of empathy."

Mahatma Gandhi

Irritable Bowel Syndrome

Welcome to our Medical Bits!

Today, we will delve into Irritable Bowel Disease (IBS) and explore its symptoms, potential causes, review new research and attempt to offer management advice for a better quality of life!

What is IBS?

IBS is one of the most common gastrointestinal disorders. I would venture to say that most of you have a family member who suffers from the condition, since its prevalence is between 10 and 20% of urban settlers. It is a chronic condition where recurrent and intermittent abdominal pain is accompanied by altered bowel habits with abdominal distention and bloating. It can be subtyped into IBS with constipation, IBS with diarrhea, or mixed IBS. It is most common in women and young people and negatively affects quality of life and work productivity.

Fortunately, recent advances in our understanding of IBS and the addition of new pharmacologic and nonpharmacologic treatments have improved the quality of life for those who do not respond to lifestyle and dietary modifications.

In the 1950's, doctors thought that IBS was a "nervous colitis" due to anxiety or depression and people were told "it is all in your head"! But over the past two decades research has demonstrated that food, the bowel flora (microbiome) and genetics all play a role in IBS. We now know that there is bidirectional communication between the brain and the bowel and it is now considered a disorder of gut-brain interaction.

Table 1. Rome IV Criteria for the Irritable Bowel Syndrome.* Patient has recurrent abdominal pain (≥1 day per week, on average, in the previous 3 mo), with an onset ≥6 mo before diagnosis Abdominal pain is associated with at least two of the following three symptoms: Pain related to defecation Change in frequency of stool Change in form (appearance) of stool Patient has none of the following warning signs: Age ≥50 yr, no previous colon cancer screening, and presence of symptoms Recent change in bowel habit Evidence of overt GI bleeding (i.e., melena or hematochezia) Nocturnal pain or passage of stools Unintentional weight loss Family history of colorectal cancer or inflammatory bowel disease Palpable abdominal mass or lymphadenopathy Evidence of iron-deficiency anemia on blood testing Positive test for fecal occult blood

Ford AC et al. N Engl J Med 2022

The diagnosis is relatively straightforward: history, physical exam and "Rome IV criteria" (recurrent abdominal pain > 1d/wk in the past 3 months, defecation change in frequency and stool form).

Limited diagnostic testing is recommended: blood count, Creactive protein, celiac serologies and sometimes fecal calprotectin (stool test that helps elucidate if the bowel is inflamed). Recent <u>guidelines</u> stratify treatments and also suggest when it is reasonable to engage a Gastroenterologist for support:

- Weight loss.
- Iron deficiency anemia.
- Nocturnal symptoms.
- Family history of colorectal cancer, inflammatory or celiac disease.

It is also helpful to categorize patients according to severity and if it is predominantly associated with <u>diarrhea (IBS-D)</u> or <u>constipation (IBS-C)</u>.

• 40% of patients have mild, 35% moderate and 25% severe symptoms.

People with mild symptoms usually respond to education, reassurance, lifestyle changes (routine bowel time, increasing exercise and good sleep hygiene). Also, dietary modifications with low intake of fermentable oligo-, diand monosaccharides and polyols (FODMAPs) may help.

Those with moderate to severe IBS have symptoms that become intrusive and disruptive into work and personal life. For them, the same recommendations apply, but some need treatment, focusing on the most bothersome symptoms. Those with severe disease should also consider psychological support.

Over the past decade, many researchers have started to look at humans as ecosystems containing many collaborating species. There are trillions of bacteria in our mouth, bowel and every orifice subtending from the surface of our bodies. Those trillions of bugs conform our microbiome and interact with our own organs, living in a symbiotic relationship. The microbes obtain raw materials and shelter while protecting and providing some important nutrients to their human hosts. It is postulated that a breakdown in this delicate balance with our microbiome may cause disease.

The current understanding is that IBS patients have a brain-gut axis problem.



susceptible In those (genetic predisposition or exposure to environmental factors) an abnormal stress response along with psychological distress (e.g., anxiety, depression, or somatization), and possibly an infectious or inflammatory response may alter intestinal permeability and initiate a cascade of events (e.g., infiltration of inflammatory cells, localized edema, and release of cytokines or chemokines) that results in the development of IBS symptoms. It appears that in up to $\frac{1}{2}$ of

patients. GI symptoms develop first and may lead to mood alterations which can mediate changes in gut permeability. our immune system and also our microbiome. These in turn, may prompt the release of inflammatory mediators affecting the central nervous system and our mood: negative "vicious" cycle with further IBS exacerbations.



In healthy persons, tight junctions between cells inside the bowel, prevent that bowel content (e.g., chemicals, bacteria, medications, and food antigens) from entering the subepithelial space (below the superficial cell layer), and a healthy intestinal flora may play a critical role in maintaining the proper acidity and nourishing environment for those superficial epithelial cells and help with completion of digestion, which results in the production of intestinal gas (e.g., hydrogen, carbon dioxide, and methane).

In susceptible persons, however, it is postulated that infection or consumption of certain foods (e.g., foods containing fructans or gluten) increases intestinal permeability by altering those tight unions between superficial cells. Localized inflammation then develops, with a subsequent influx of inflammatory cells leading to release of inflammatory mediators and the alteration of neuromuscular function in the gastrointestinal tract and the familiar symptoms of abdominal pain and accelerated or delayed transit through the gastrointestinal tract with consequent diarrhea or constipation, respectively.

Symptoms of bloating and distention may develop, in part because of changes in the normal gut flora and excess gas production, with abnormal intestine-somatic reflex responses. Disaccharidase deficiency (e.g., congenital sucrose–isomaltase deficiency) and alterations in normal ion-channel function may lead to IBS symptoms in some patients.

Treatment:

- A good patient-physician relationship and adequate communication are important in the management of all patients with IBS.
- Daily exercise, with emphasis on aerobic activity such as walking, running or biking are particularly beneficial, since they decrease stress levels and promote bowel function.

Dietary modification

- Limiting gas-producing foods ((beans, onions, celery, prunes, apricots, wheat germ brussel sprouts).
- Low content of fermentable oligo-, di-, and monosaccharides and polyols

Foods suitable on a low-fodmap diet (FODMAPs).



Eliminate foods containing fodmaps



• One randomized trial compared low FODMAP diet with traditional IBS diet (regular meal pattern, avoiding large meals, low fat, low insoluble fibers, caffeine and gasproducing foods) with equivalent positive results after 4 weeks

 In some cases, lactose avoidance, as patients with IBS may have an exaggerated symptom response to lactose ingestion.

• **Gluten** may alter bowelbarrier functions in some patients with IBS-D.

• Exceptionally, **food allergy testing** may be warranted, but skin and immunoglobulin testing is not well standardized and results are equivocal, requiring dietary avoidance and close observation.

 Soluble fiber (ispaghula husk / psyllium) but not insoluble (Bran) has significant benefit and

improvement in IBS symptoms, confirmed by more than 15 RCTs. Psyllium has been shown to improve both, IBS-D and with constipation.

Pharmacologic treatments

Patients with moderate to severe symptoms and impaired quality of life, require symptom directed treatment:

IBS – Diarrhea (Here – extensive AGA guidelines)

1. Add soluble fiber – psyllium daily.

- 2. Add antidiarrheals such as loperamide (Imodium A-D) 2 mg 45 min before meals and up to 16 mg/day as needed. Avoid in those with alternating symptoms of diarrhea and constipation.
- 3. Add bile acid sequestrants such as cholestyramine, colestipol or colesevelam as up to 50% of pts with IBS-D have bile acid malabsorption which stimulates colonic secretion and motility.
- 4. Add serotonin 3 receptor antagonists: Alosetron or Cilansetron. More than 14 RCTs demonstrate global improvement in IBS symptoms but reported side effects of ischemic colitis and severe constipation led to initial withdrawal of Alosetron and re-introduction at a lower dose. Ondansetron is also beneficial but not in terms of abdominal pain.
- 5. Eluxadoline (mu-opioid agonist / delta-opioid antagonist) should only be used in severe IBS-D refractory to all other agents, as a trial and stop if no response after 12 wks.
- Antispasmodic agents should be used as needed: Dicyclomine 20 mg up to 4x daily as needed or Hyoscyamine at 0.125 – 0.25 mg orally or sublingual 3-4 x daiy as needed.
- 7. Antidepressants can be attempted in low doses, particularly old tricyclic antidepressants at bedtime such s 20 mg of Amitriptyline, nortriptyline, desipramine or imipramine with RCTs supporting use and good long-term results.
- 8. Antibiotics are not routinely recommended but in those with refractory symptoms, a two-week trial of rifaximin at 550 mg thrice daily should be considered.
- 9. Probiotics are not routinely recommended, but have been associated with improvement in symptoms. Most effective species and strains are uncertain.
- 10. Refractory disease: Consider psychotherapy, CBT, acupuncture, fecal microbiota transplantation, anxiolytics and mast-cell stabilizers such as Aldafermin or Ketotifen.

IBS-Constipation (Here extensive new AGA Guidelines).

- 1. Add soluble fiber psyllium daily.
- 2. Add polyethylene glycol (PEG Miralax) at 17 g dissolved in 8 oz once or twice daily but it may cause bloating and abdominal discomfort.
- 3. Linaclotide (Linzess) or plecanatide are guanylate cyclase agonists that stimulate intestinal fluid secretion and transit, and have proven efficacy in almost 40% (compared to 20% for placebo) with improvement in abdominal pain/ discomfort, bloating, straining, stool consistency and number of BM's weekly. This agent has high quality evidence and is recommended by the AGA.
- 4. Consider Lubiprostone locally acting chloride channel activator that increases intestinal fluid secretion at 8 mcg twice daily and should be stopped after 12 wks if no improvement.
- 5. Tenapanor (Na / H exchanger 3 inhibitor) reduces absortion of sodium and phosphate and increases the intestinal fluid volume and transit. At 50 mg twice daily, it improves spontaneous BM's and abdominal pain compared to placebo.
- 6. Tegaserod (Serotonin 4 receptor agonist) reduced abdominal symptoms and constipation but is not available in the US at present.
- 7. A <u>recent study</u> concluded that the consumption of 2 green kiwifruits daily improved measures of GI comfort and bowel movements by 2/wk.

In conclusion:

- IBS is a condition that affects quality of life but fortunately major morbidity is rare and longevity is not impacted.
- Symptoms fluctuate with periods of relatively good health.
- There is no conventional Western medicine or unconventional Oriental remedies that are universally effective.
- Review of the AGA clinical practice guidelines is sobering: the best treatments increase the rate of response by only 15% over placebo! And some drugs are costly.
- There were remarkable differences in quality of life (QoL) changes among the different drugs:
- In IBS-D, rifaximin improved QoL in 240 more patients per1000 patients vs. placebo. Eluxadoline improved QoL in 64 additional patients per 1000.
- In IBD-C, linaclotide led to an improvement of QoL in 135 per1000 patients vs. placebo. Tenapanor or tegaserod did not improve QoL.

Therapy†	Study Outcomes	Reported Efficacy	Quality of Evidence	Limitations of Data	Side Effects	Monthly Co without Insurance (U.S. \$)
Soluble fiber (e.g., psyllium, one sachet three times daily)	Global symptoms	Effective; start at a low dose and increase slowly	Moderate	Only one trial of high quality, and no FDA- approved end points	Diarrhea, constipa- tion, bloating, and flatulence	\$15-\$30
Low-FODMAP diet	Global symptoms, abdominal pain, bloating	May be effective; nutrition- ist's guidance helpful	Very low	Few RCTs, many of crossover design with a small number of participants, and no FDA-approved end points	Potential effect on the colonic micro- biome, with un- known long-term consequences	NA
Gluten-free diet	Global symptoms, abdominal pain, bloating	May be effective	Very low	Only one placebo-controlled trial, with a small number of participants and no FDA-approved end points; no additive effect over that of a low-FODMAP diet in another small RCT	Potential effect on the colonic micro- biome, with un- known long-term consequences	NA
Antispasmodic drugs (e.g., dicyclomine, 20–40 mg four times daily)	Global symptoms, abdominal pain, diarrhea	May be effective but class- dependent	Low	No high-quality trials, only a small number of RCTs assessing each drug, and few trials with FDA-approved end points; none of the drugs identified as effective are available in the U.S.	Abdominal pain, constipation, dry mouth, and dry eyes	\$50
Peppermint oil (e.g., Colpermin [McNeil Products], two cap- sules three times daily)	Global symptoms	Effective	Moderate	Few RCTs and no FDA-approved end points.	Heartburn, dyspep- sia, headache, and dry mouth	\$9-\$19
Lubiprostone, 8 µg twice daily	Global symptoms, abdominal pain	Effective	Moderate	Only a modest benefit over placebo, partic- ularly for abdominal pain	Nausea, diarrhea, and abdominal distention	\$348-\$358
Linaclotide, 290 μ g once daily	Global symptoms, abdominal pain, bloating	Effective	High	Few RCTs	Diarrhea, abdominal pain, and head- ache	\$350
5-HT ₃ receptor antagonists (e.g., alosetron, 0.5–1 mg once daily)	Global symptoms, abdominal pain	Effective	High	Only one crossover RCT of ondansetron, which may have no benefit over placebo for abdominal pain; potentially serious side effects with alosetron	Constipation, ab- dominal pain, nausea, and is- chemic colitis	\$360-\$1,10
Eluxadoline, 75–100 mg twice daily	Global symptoms	Effective	High	Only a modest benefit over placebo for global symptoms, and no benefit over placebo for abdominal pain; potentially serious side effects	Constipation, nausea, abdominal pain, sphincter of Oddi spasm, and pan- creatitis	\$1,076
Rifaximin, 550 mg three times daily	Global symptoms, abdominal pain, bloating	Effective	Moderate	Few RCTs and only a modest benefit over placebo	Headache, abdomi- nal pain, nausea, and diarrhea	\$1,400- \$1,900
Probiotics (e.g., <i>Bifidobacterium</i> <i>infantis</i> 35624, one capsule daily)	Global symptoms, abdominal pain	May be effective	Low	Few high-quality trials and no FDA- approved end points; bacterial species or strains that are of benefit is unclear	Poorly reported‡	\$21
Tricyclic antidepressants (e.g., amitriptyline, 25 mg once daily; if tolerated, can in- crease dose to 50–75 mg once daily)	Global symptoms, abdominal pain	Effective	Moderate et al. N Engl	Few high-quality trials and no FDA- approved end points J Med 2022	Sedation, dry mouth, dry eyes, ortho- static hypoten- sion, arrhythmias, and sexual dys- function	\$4–\$9
Psychological therapies	Global symptoms, abdominal pain	Effective	Low	Few high-quality trials and no FDA- approved end points	Poorly reported‡	NA

Recommended first-line pharmacologic treatments are antispasmodics and either, an osmotic laxative for IBS-C or loperamide or bile acid sequestrants for IBS-D.

We should be cautions prescribing drugs with a risk for life-threatening adverse events (e.g., tegaserod, eluxadoline, or alosetron) for benign disorder such as IBS.

Again, it is important to establish a relationship of trust with our patients, to provide reassurance on the benign, fluctuating, and chronic nature of the condition and preserve function and quality of life!

Immunization Schedule and New vaccines

We frequently discuss the immunization schedule and updated recommendations over the course of our annual reviews. Here is the current CDC recommendations.





Table 2 Recommended Adult Immunization Schedule by Medical Condition or Other Indication, United States, 2024



Respiratory Syncytial Virus (RSV) vaccine (repeated)

RSV is an important cause of lower respiratory tract disease in older adults and



as anticipated earlier this year, two recombinant RSV vaccines have now been approved for individuals > 60 yo. Both are subunit vaccines based on the prefusion RSV F glycoprotein with efficacy over 80% compared to placebo and were approved by the FDA in May 2023 and recommended Adult by the Committee on Immunization Practices.

Vaccine efficacy with respect to a first episode of RSV-associated lower respiratory tract illness for the evaluable efficacy population (16,306 participants in the RSV preF vaccine group and 16,308 participants in the placebo

group).

Other recent <u>studies</u> have also demonstrated adequate safety and efficacy. Another phase 3 clinical trial evaluated efficacy and safety in almost 8000 pregnant women at 24 through 36 weeks' gestation, randomized to a single IM injection of 120 ucg of bivalent RSV prefusion F protein-based vaccine or placebo demonstrated safety and efficacy.

DEBUNKING MYTHS: Q & A

1. Patients with history of PCN allergy should be evaluated by an allergist prior to challenge with penicillin or derivatives. Incorrect! This recent study demonstrates, oral challenge is safe and event rates very low.

Outcome	Event rates				
	Direct oral challenge Usual care				
Positive oral penicillin challenge	0.53%	0.52%	2% (-90 to 934)		
No difference for immune-mediate	ed or adverse even	nts at 2 or 5 days.			
No serious adverse events were rer	ported.				

We should consider that despite the availability of other antibiotics, penicillin is a very valuable antibiotic due to its effectiveness, narrow spectrum, low cost, tolerability, and proven track record. Most patients who report a history of penicillin allergy are in fact, able to tolerate penicillins. Additionally, reactions to cephalosporins in patients with a penicillin allergy label is exceedingly low, and below 3% with minimal risk for potential cross-reactivity with cephalosporins.

2. All elderly adults should take aspirin for primary prevention of strokes and cardiovascular complications. Incorrect!

Outcomes	Even	At a median 4.7 y	
	Aspirin	Placebo	HR (95% CI)
Ischemic stroke	3.4%	3.9%	0.89 (0.71 to 1.11)
Intracranial bleeding‡	2.5%	1.8%	1.38 (1.03 to 1.84)
Nonstroke intracranial bleeding	1.4%	1.0%	1.45 (0.98 to 2.16)

Results: Aspirin vs. placebo in healthy, community-dwelling, older adults (intention-to-treat analysis)

The American Heart Association primary prevention (no prior episodes) guidelines recommend aspirin for cardiovascular prophylaxis in adults aged 40-70 years with high risk for atherosclerotic CV disease but not in those aged > 70 years or Hispanics and African Americans > 65 yo as demonstrated by this international prospective trial which included almost 20,000 patients.

Conclusion: in healthy older adults, low-dose aspirin is no better than placebo and increases risk for intracranial bleeding and also the <u>risk of iron deficiency</u> <u>anemia by almost 20%</u>.





HAPPY HOLIDAYS !!!

If you have 10 minutes, enjoy this <u>time-lapse of the Entire</u> <u>Universe</u>.

If you have another 10 minutes, read Dr. Fauci's reflections.

If you have 6 more minutes, the <u>massive expanse of our</u> <u>Universe</u> and the magnificent insignificance of humanity will delight you.

You will not be able to watch these two <u>videos</u> without <u>smiling</u>.

If you have <u>7 minutes daily</u>, you can start to improve your <u>fitness</u> right now with the Scientific 7- Minute Workout. <u>Get</u> <u>the app</u> on your phone! <u>11 more minutes</u> will get you in shape! For core strength, try this <u>9-minute routine!</u> Can you pass this 10-second BALANCE TEST?

AND START EXPLORING AND PRACTICING <u>MINDFULNESS</u>! It will also help you lower your blood pressure and levels of stress. It will raise pain threshold and your overall sense of well-being.

THERE ARE MULTIPLE <u>RESOURCES</u> ON THE WEB.

Let's all remember that the only certainty in life, is death and the only fountains of youth proven by science and experience are love, exercise, laughter, humor and a positive attitude!

OFFICE UPDATES

- I will be away with my family from January 10th through January 16th hopefully catching a few safe turns on the slopes. My partners will cover as usual but never too far from email.
- Olivia Dragovits (<u>oliviad@chevychasepulmonary.com</u>) is my assistant, always ready to help with her wonderful demeanor and multi-tasking abilities, as she works towards her Medical School acceptance.
- Emily Swearingen, Moghaddaseh Hosseini and Lauren Roling joined us this past summer and along with Nicole Loy and Jonathan Sir are always ready to help with your office needs as they continue to work towards their Medical School acceptances.
- Some of our former assistants whom you know, continue to make progress towards their Medical degrees. Patty Zhao is now a 4th year student at UVa. Emily Ferguson is a 3rd year student at Jefferson University in PA. Simran Singh is now a second-year Med School

student at University of Buffalo. Samantha Morales is a 1st year-student at University of South Carolina School of Medicine. Andrew Fookes is a freshman at Georgetown University School of Medicine

Wishing you Happy and Peaceful Holidays!

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