The Components of Digestion and Their Respective Interventions

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Digestion Is

- Parasympathetic dominant enteric nerve function and hormones
- Chewing
- Stomach acid
- Bile
- Pancreatic enzymes
- Gut lining
- Gut bugs
- MD-land Gastroenterology does not treat digestion, they suppress it or take pictures of it
- Digestion is the mother of the body. It's the primary way in an out. All NDs have to be good at digestion

Enteric Nerves

- The GI tract is innervated by enteric nervous system with 300+ million nerves (as much as a cat...or 2 dogs)
- Extensive neuronal network along the walls w/ local reflex that is able to function with or without input form the CNS. 90% vagus nerves go to the brain, the brain monitors more than controls
- Propulsion, nutrient handling, blood flow regulation, immunologic defense, MMC control, retropulsion of noxious substance
- 3rd division of the autonomic nervous system and the largest part of the peripheral nervous system
- The CNS and ENS share neurochemistry to pathogenic mechanisms that give rise to CNS pathology can effect the ENS
- Enteroendocrine cells produce hormones, neurotransmitters as well as respond to physical, chemical and nutrient stimuli.

Ex: ENS Involvement in GI disease

- GI inflammation: Proinflam cytokines mediated by afferent nerves and enteric glia:
  - Tx: Il-1β, TNF-α, mast cell inhib, 5-HT_3 agonists, Substance P
- Infectious secretory diarrhea: prostanoid (endothelial derived prostaglandin agonist) and 5HT-mediated stim of servomotor neurons released by mast cells and neutrophils
  - Tx: loperamide (Imodium) opioid receptor agonist in the myenteric plexus
- Chronic pseudoobstruction: Hyperactive disordered excitatory motor neurons or damaged inhibitory motor neurons
  - Tx: metoclopramide, erythromycin, neostigmine (Ach inhibitor used to treat myasthenia gravis
- Parkinson's disease: alpha-synuclein in enteric neurons causes GI dysf'n and constipation

Epinephrine and Norepinephrine

- NE & EPI alter blood flow and change absorption rates
  - Epinephrine: α1 & ß2 receptors
  - Norepinephrine: α1& α2 receptors
- Epi ↑glucose absorption through ß2 receptors
- Epi potentiates other hormones like thyroid
- α & ß receptors ↑protein and carb absorption
- NE ↓ host GI immunity by decreasing both cell mediated immunity and IgA production
- EPI ↓GI motility and ↓MMC
- IBS may be associated w/ Catecholamine levels
  - Constipation = ↑NE&EPI, Diarrhea =↓NE
- Tx: Nervines, L-Theanine, Catnip, meditation, being thankful for the food, SAMe, Bacopa, Relora.

Dopamine

- About 50% of total dopamine is produced in the GI tract, which also comprises 50% of urinary excretion
- Multiple types of GI cells contain the enzyme tyrosine hydroxylase, which makes dopamine, including parietal cells, epithelial cells and lamina propria (basement membrane and immune cells
- Stimulate exocrine secretions (glucagon and insulin), ↓motility, modulates Na+ absorption, ↑mucosa blood flow, ↑mucus secretion, ↓acid (protective against duodenal ulcers) and helps with calorie restriction.

Dopamine metabolism

- L-Tyrosine → L-Dopa by tyrosine hydroxylase
- L-Dopa → Dopamine by Dopa decarboxylase with p5p being a co-factor.
- Dopamine is then converted to Norepinephrine by PNMT via methylation using SAMe as a donor or cleared out via metabolism to HVA

- 🧐 Plants have dopamine. Bananas are the highest. Others have less including Potatoes, avocados, broccoli, Brussels sprouts and even less oranges, tomatoes, spinach, beans.
- Dopamine Herbs: Ashwagandha, Rhodiola, Panax ginseng, Mucuna pruriens, Ginkgo biloba
- Nutraceuticals: Curcumin, l-theanine, L-tyrosine, probiotics, caffeine
- Parkinson's, a low dopamine conditions leads to delayed gastric emptying and reduced digestion

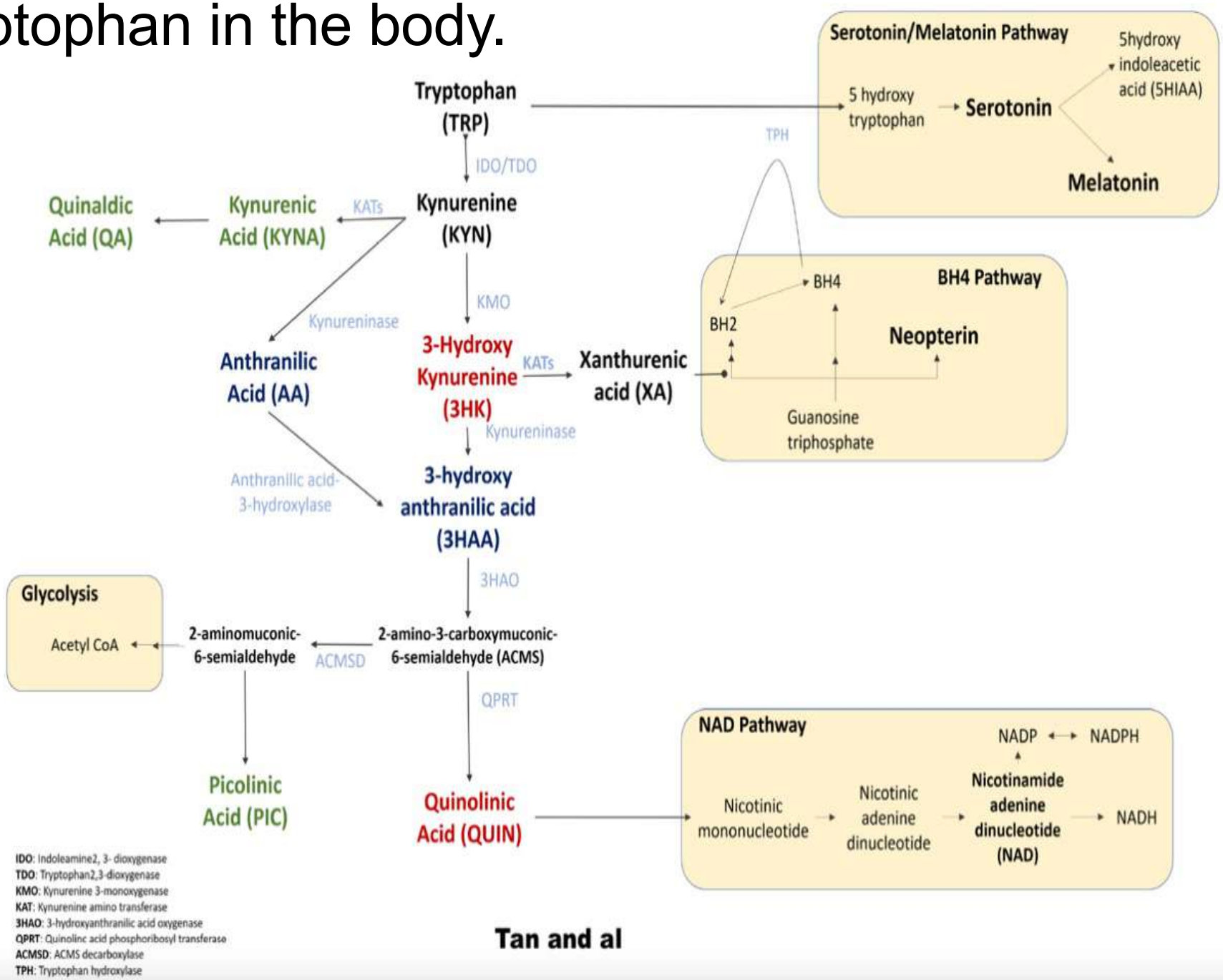
Serotonin (Aka 5-hydroxytryptamine = 5-HT)

- Up to 90% serotonin is made in the GI tract
- Produced by GI flora including candida, E coli, streptococcus and enterococcus as well as Enterochromaffin cells and enteric nerves
- Made from tryptophan → 5 hydroxytryptophan
  - Tryptophan is mainly used in the kynurenine pathway which produces kynurenic acid (neuroprotective) and quinolinic acid (neurotoxic and predominant in inflammation) and picolinic acid (which helps to balance the other 2)
  - Serotonin and the kynurenine pathway compete for available tryptophan which can cause serotonin dysfunction in acute stress and inflammation.
- Serotonin can alter biofilm, quorum sensing and biotoxins of microbiota making infections worse.

Serotonin has many GI actions

- Multiple receptors: 7 classes with at least 14 known receptors of serotonin receptors
- There are many disease states associated with abnormal serotonin function, balance, receptors, transporters (SERT)
- 5-HT is involved in nausea, vomiting, GI motility (including intestinal, stomach and esophagus), pain and sensitivity, gastric emptying, secretion, segmentation, vasodilation
- Serotonin modulation is used in multiple types of treatments

Kynurenine pathway degrades 90% of the total tryptophan in the body.



Modulators of 5HT3 receptors

- Menthol
- Boldine : Peumus boldus
- Citronellol: citronella, oil of rose and pelargonium geranium
- Geraniol
- Citral: E.O. in citrus peel esp orange
- Eucalyptol
- Linalool: multi sources coriander, sweet orange, lavender, basil, mint, birch, cannabis
- Ginger: 6-shogaol, 6 & 10 Gingerol, Zingerone
- Capsaicin
- Thujone
- Cannabidiol
- Quinine
- Ginseng
- Licorice

Molecules 2018, 23, 3186

Gaba

- Gaba (gamma aminobutyric acid) is an inhibitory neurotransmitter in the CNS
  - Low CNS Gaba =↑anxiety and depression
- Gaba is Excitatory in the ENS
  - $Gaba_A$ receptors ↑GI motility and ↑peristaltic reflex in the colon
  - Gabapentin binds to a different receptor but can ↓rectal sensitivity and ↑Rectal compliance in IBS-D (lower resistance to distention) and improve outcomes with omeprazole in resistant functional dyspepsia
- Decreases in gaba may cause dysregulation in GI T-cell response. Low gaba leads to increased downstream inflammatory cytokines.
  - Dysregulation of gaba may effect IBS-D through anti-inflam effect and neurotransmitter effect

Gaba

- GABA can be taken as a supplement
  - Long thought to not cross the blood brain barrier but there is evidence it might crosses the BBB as it was shown to alter brain waves after administration
  - It exerts a parasympathetic augmentation and reduces stress response
  - Gaba containing or boosting foods; Green and black tea, brown rice, soy & adzuki beans, chestnuts, mushrooms, brassicas, spouted grains, sweet potato
  - Lactobacillus and Bifidobacteria produce gaba
    - Levilactobacillus brevis LB01
  - Gaba herbs:valerian, passionflower, lemon balm, lavender, and Californian poppy
  - L theanine, magnesium, taurine

Nervine Herb List

- Sedating (anxiety, panic disorders): *Piper methysticum* , *Valeriana*, *Passiflora*, *Piscidia*, Corydalis, *Scutellaria*, *Tilia*, *Leonurus*
- Stimulating (fatigue, poor concentration): *Bacopa*, *Rosmarinus*, Green tea
- Adaptogenic (adrenal support): *Panax ginseng*, *Withania somnifera*, *Eleutherococcus*, *Glycyrrhiza*, *Avena*
- Dopaminergic (anxiety and depression, low motivation): *Hypericum*, *Actae* (black cohosh), *Verbena*, *Melissa*, *Schisandra*, *Rhodiola*
- Cholinergic: (inc Ach, mental clarity, dementia): *Rosmarinus*, *Salvia off*, *Bacopa*
- GABAnergic: (calming, muscle tension): *Hypericum perforatum*, *Piper methysticum*, *Passiflora incarnata*, *Valeriana*, *Humulus lupulus*, *Schisandra*

SAMe= S-adenosyl-L-methionine

- Produced in the homocysteine cycle: phase 1 detox cycle which methylates B12 & folate acid. B6 and magnesium cofactors. Made from essential amino acid Methionine
  - Not found in food sources. Sources that claim SAMe is found in food are listing methionine foods.
- SAMe is found in almost all body tissues and plays a role in immune function, cell membrane maintenance and neurotransmitter metabolism
  - MTHFR mutations → lower SAMe
- 🩸 homocysteine. High NE/EPI ratio. Methylation testing. B12 and folic acid
-  STUCK IN FIGHT OR FLIGHT= ↑sympathetic = reduced digestion

P5P = Pyridoxal-5-phosphate

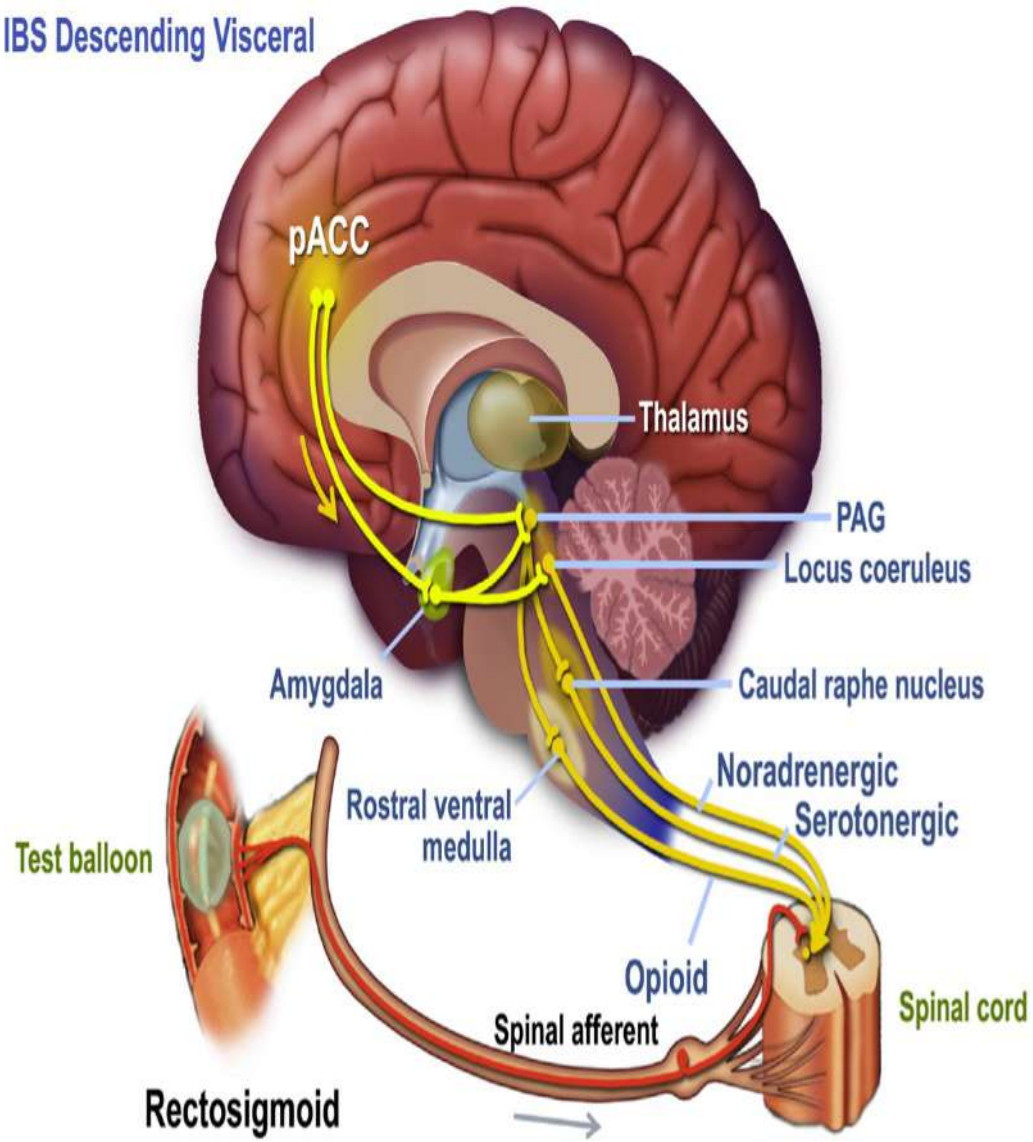
- Produced in the liver from vitamin B6
- P5p is Involved in production of serotonin, dopamine, histamine, glutamate, and gaba
- Cofactor in Methylation creating methyl folate
- Part of the kynurenine pathway and formation of niacin
- Part of collagen formation
- Can be low due to genetic, liver metabolism, alcoholism, absorption (celiac, etc)
- B6 can be toxic and cause nerve damage because it competes with p5p
- Can be helpful in nerve and cardiovascular damage, esp if low level or high homocysteine

Antidepressant Theory #1

- Most accepted: Monoamine Hypothesis
  - Depression is believed to result from deficiency of 1 or more monoamines: Serotonin, Norepinephrine and to lesser extent dopamine
  - Modulation of these neurotransmitters may account for analgesic effect via the brain-gut axis and visceral pain perception
  - Esp useful for people with comorbid mood or anxiety disorders

Antidepressant Theory #2

- Antidepressants may interfere with the complex mechanisms of pain transmission at the level of the dorsal horn of the spinal cord.
- Modulating sensitivity of the dorsal horn neuron signaling and can serve as a central control of pain perception
- Brain regions modulate afferent (incoming) pain transmission at the first synapse of the spinal cord
  - Primarily opioidergic, noradrenergic and serotonergic



Antidepressant Theory #3

- Neuroplasticity
- Nerve cells can die after psychologic trauma, post traumatic stress disorder and chronic pain: including painful IBS and pancreatitis
- Antidepressants (and possibly psychological treatments) increase brain-derived neurotrophic factor levels and likely support nerve regrowth
- This effect is increased with time and leads to better antidepressant treatment and less depression relapses.

Tricyclic Antidepressants

- Ex: Imipramine, Desipramine, Nortriptyline
- MOA: Antidepressant and Analgesic. Multiple MOA make for more systemic effect and side effects.
  - Presynaptic: serotonin and NE reuptake inhibitor
  - Inhibition of multiple post synaptic (5-HT_2, 5-HT_3, H1, Muscarinic-1, alpha-1) and presynaptic (α-2) receptors
- GI actions: PAIN. Reduce diarrhea, improve sleep
  - Motility: ↓ GI transit (anticholinergic and noradrenergic)
  - Sensitivity: Decrease visceral sensitivity (limited evidence)
- Side effects: **Drowsy**, dry mouth, **Constipation**, sexual dysfunction, arrhythmias, weight gain, orthostatic HTN

SSRI: Selective Serotonin Uptake Inhibitors

- EX: Citalopram, escitalopram, fluoxetine, paroxetine, sertraline
  - 🧐 Fun fact Citalopram and escitalopram are enantiomers and the latter better w/ anxiety.
- MAO: Selective serotonin reuptake inhibitor
- GI actions:
  - Motility: ↑ gastric and small intestine propulsive motility
  - Mainly GI phobia, anxiety and OCD features
- Side effects: agitation, nervousness, diarrhea, insomnia, night sweats, headaches, weight loss, sexual dysfunction, vivid dreams

SNRI: Serotonin and Norepinephrine reuptake Inhibitors

- Ex: duloxetine, milnacipran, venlafaxine
- MAO: Presynaptic SRI and NRI.
  - Duloxetine SRI=NRI. Milnacipran NRI>SRI
    Venlafaxine also dopamine at higher doses

GI actions:

  - ↓ gastric and Colonic tone but less than Tricyclics.
  - Pain esp fibromyalgia, pack pain and GI pain

- Side effects: Nausea, agitation, dizziness, sleep disturbances, fatigue, liver dysfunction (watch enzymes) and cardiac complications

Noradrenergic and Specific Serotonergic (tetracyclic) Antidepressants

- Ex: Mirtazapine, mianserin, trazodone
- MAO: Increases serotonin and NE secretion
  - Increased NE and serotonin activity though α-2 antagonism on NE and 5-HT receptors. Also 5-HT_2, 5-HT_3, H1, muscarinic-1 antagonism...Lots of effects leads to mixed bag of outcomes.
- GI Indications: In gastroparesis improves early satiation, weight loss, and chronic nausea & vomiting (Mirtazapeine) . May improve sleep
- Side effect: Sedation, headaches, dry mouth, weight gain. Orthostatic HTN, Dizzy. Diarrhea or constipation. These tend to show different effects

Azapirones

- Ex: Buspirone, tandospirone
- MAO: Partial pre- and post-synaptic 5-HT_1 agonist
- GI actions: Relaxes stomach for increased accommodation
  - ↑ esophageal contractions and gastric accommodation.
    - Can improve movement in sclerotic or hypomobile esophagus
  - 50% people with functional dyspepsia have impaired gastric accommodation = early redistribution of a meal to the distal stomach and rapid gastric emptying.
- Side effects: Sedation, headaches, vertigo, kidney and liver, tinnitus, paresthesias, cognitive impairment

Delta Ligand Agents

- Ex: Gabapentin, pregabalin
- MAO:
  - mostly presynaptic blockage of α2d subunit voltage sensitive calcium channels
  - Receptor subunit involved heart and nerve function, esp pain processing
  - Lowers excessive excitatory neurotransmitters like Glutamate
- GI effects: Decreased sensitivity to pain. Anxiety and abdominal wall pain. Neuropathic pain
  - Neuropathic pain > Somatic pain due to nerve effect
- Side effects: Sedation, headaches, vertigo, weight pain, sexual dysfunction, and peripheral edema

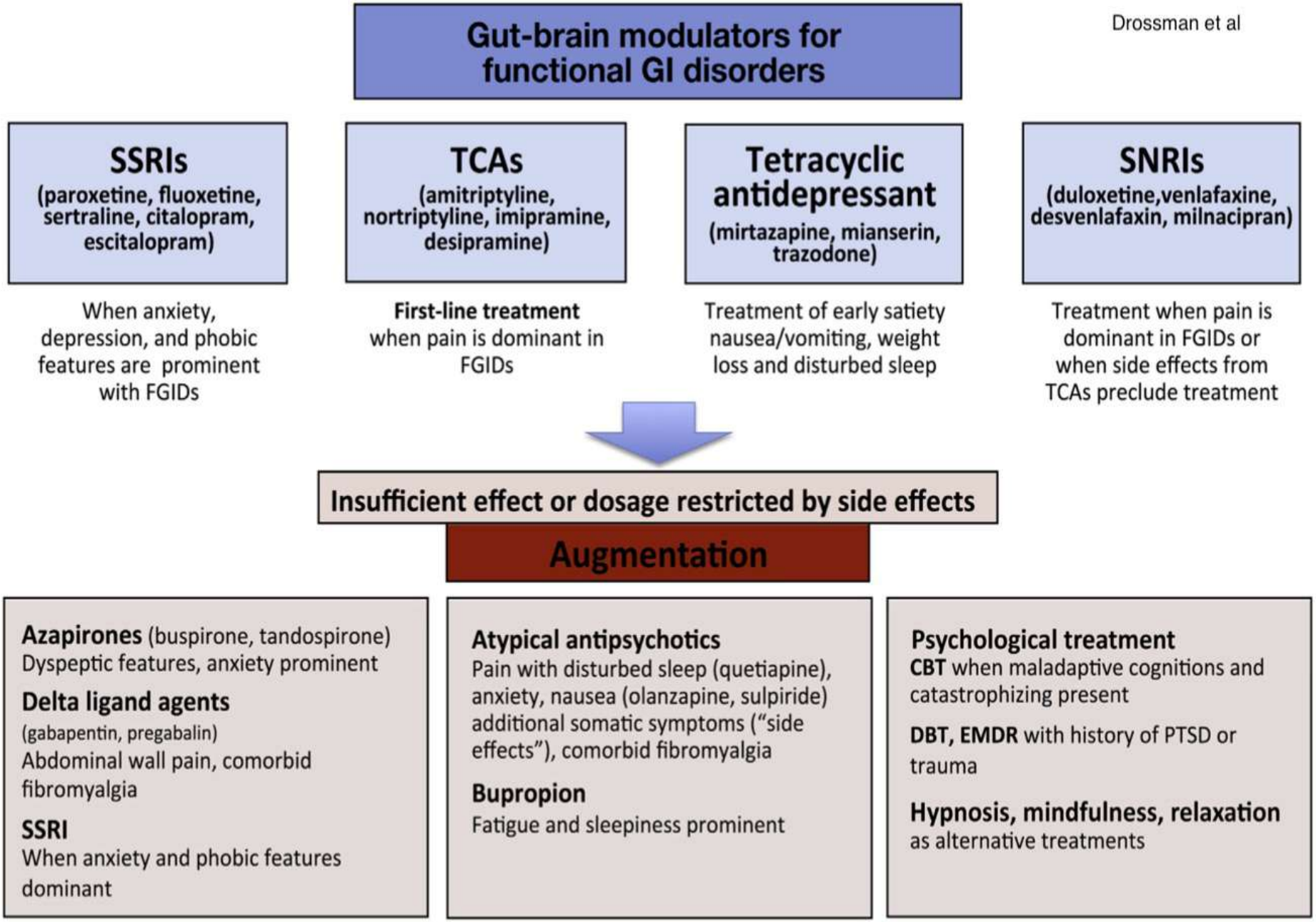


Figure 5. Summary of the clinical characteristics that can be considered when selecting gut–brain neuromodulating pharmacotherapy to treat FGIDs. Those drugs in the *upper part* of the figure can be considered as first-line options. In the *lower part* of the figure, the pharmacologic options most often used to augment treatment effects are depicted, as well as some nonpharmacologic treatment alternatives.

Chewing

- Increases surface area which allows for more efficient digestion and improved nutrient absorption
- Starts digestion by mixing with saliva which contains amylase and lingual lipase to start digestion and helps with lubrication
- Chewing decreases self reported hunger
- Chewing alters gut hormone responses related to satiety
- Swallow after chewing

Functional Dyspepsia STD of Care

“Functional dyspepsia is a chronic disorder with persistence of symptoms occurring in up to 50% of patients. ...Guidelines recommend a stepwise approach to management: first-line therapy being a 4–8 week trial of a PPI and second- line therapy involving the use of a tricyclic antidepressant (usually amitriptyline). Although treatment with PPIs and/or tricyclic antidepressants provides relief for some, a significant number of individuals complain of refractory symptoms. The options for managing refractory functional dyspepsia are limited—consisting of a trial of a prokinetic agent or psychological therapy. Interestingly, a fraction of patients with functional dyspepsia have rapid gastric emptying on Gastric Emptying Study.”

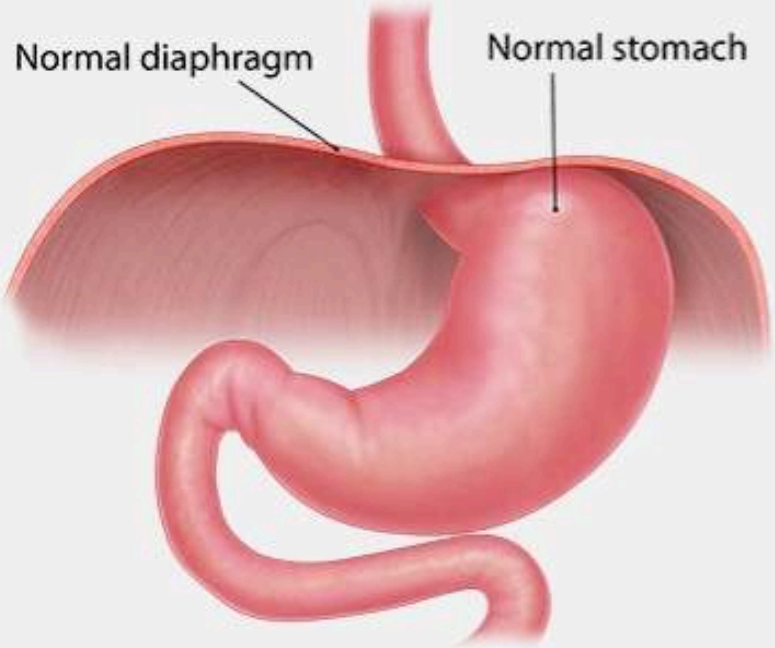
Radetic et al

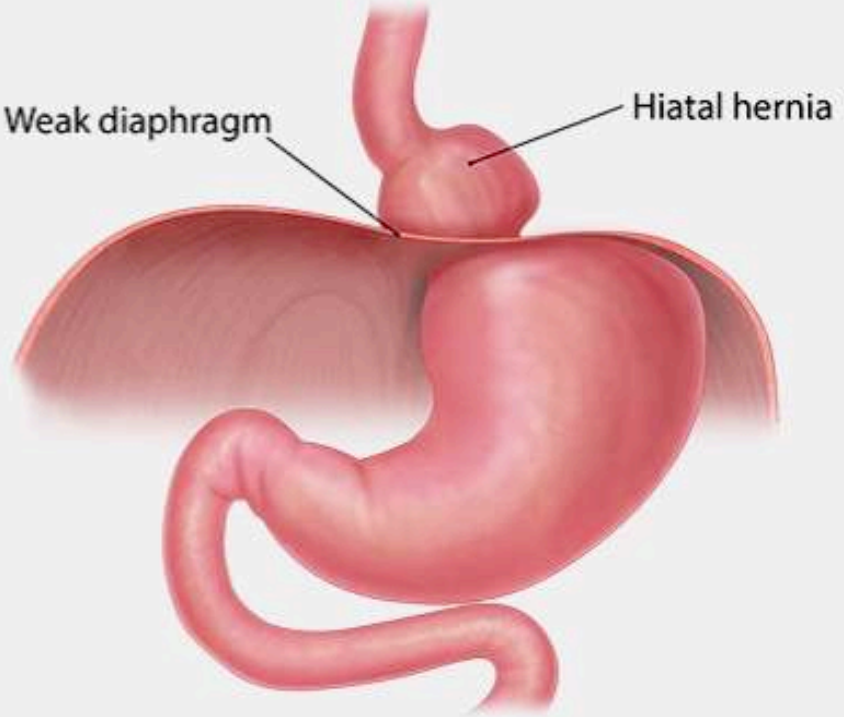
GERD

- Retrograde flow of reflate into esophagus
- Multifactoral: Chemical, mechanical, physiologic & Neurologic
- Patients can continue to have GERD despite long term acid suppression and pH ≥7
- Hiatal hernia (50% general population, 70% >70 y.o)
  - Can increase High acid pockets in the stomach (acid pooling) and increase esophageal exposure
- Bile: Duodenogastroesophageal reflux
  - Presence of bile ↑inflammation, oxidation and damage
- Pepsin: esophagus has no protection against this protease if it's acidic. Pepsin is inactive pH 6.5+
- Hypersensitivity of esophageal nerves (NERD= non erosive reflux disease)

GERD

- Transient LES relaxations (TLESR) not a HH
  - Mixed evidence
    - Drugs tried: metabotropic glutamate receptor 4, CCK receptor agonist, cannabinoid receptor agonists, Nitric oxide synthase inhibitors
  - Most effective: Baclofen, $GABA_B$ receptor agonist. Centrally inhibits vagus nerve relax signals
    - Risk of CNS side effects; fatigue, nausea, emesis, and dizziness
  - Hiatal hernia:
    - Surgeries: Nissen fundoplication, laparoscopic toupet fundoplication and magnetic sphincter augmentation
  - Weight loss
  - Prokinetics, Sequestrants, alginates





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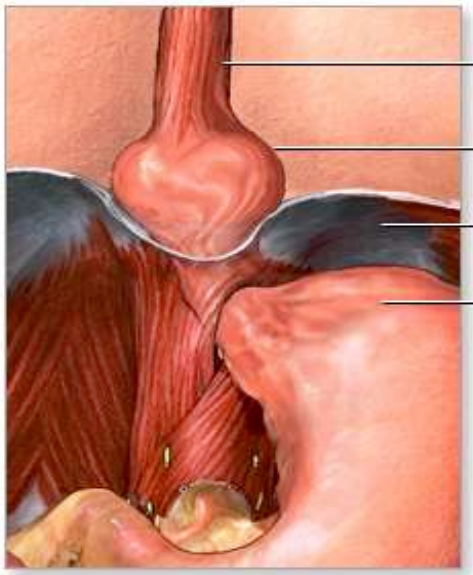
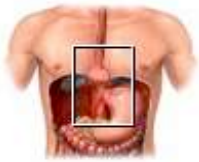




A.D.A.M.

Medlineplus.gov

Carminatives

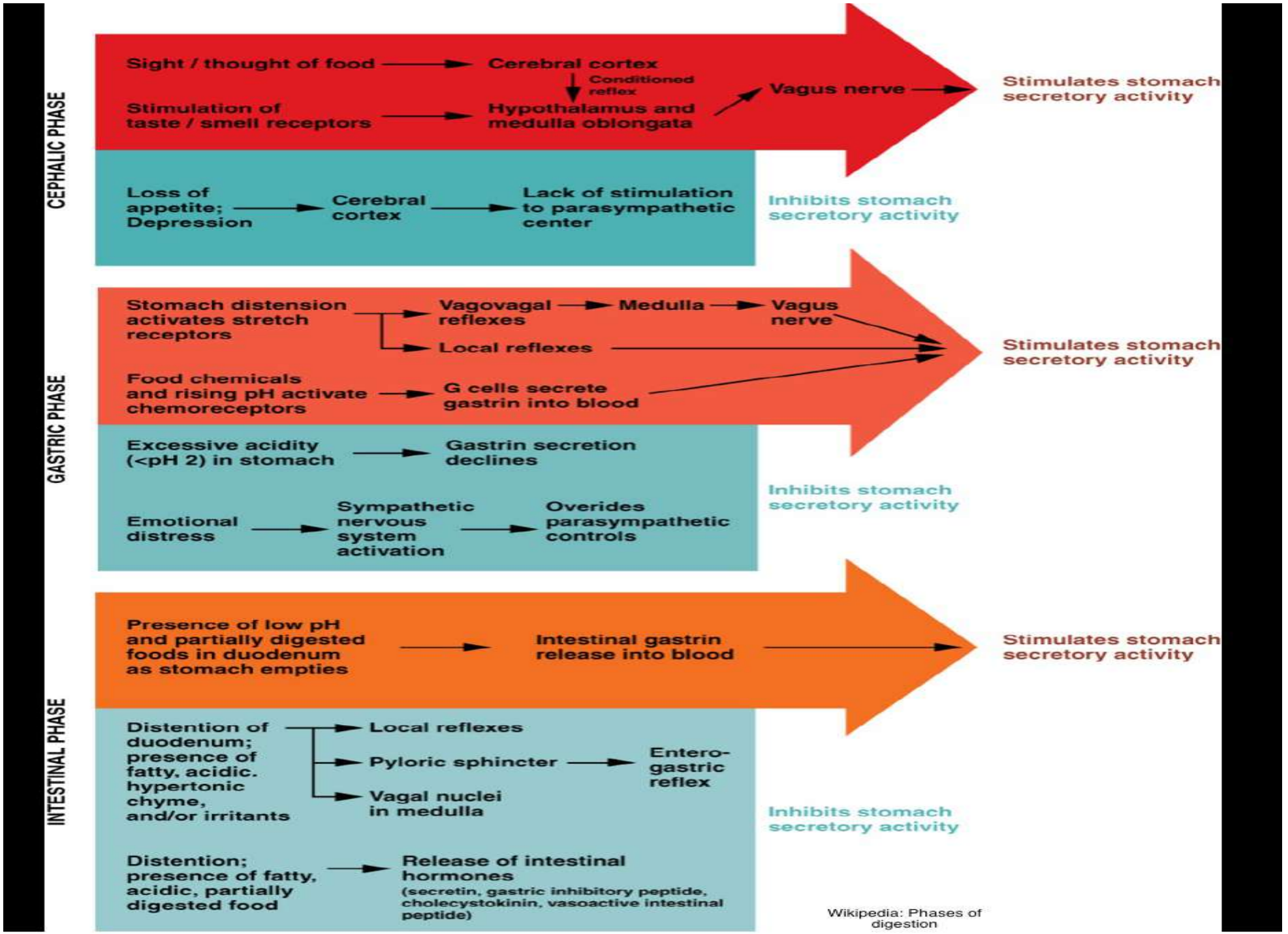
- Herbs used to enhance digestion and relieve nausea, gas, belching and relieve dyspepsia
- Anise, Basil, Bergamot, Calamus, caraway, Cardamom, Catnip, Cayenne, Chamomile, Cilantro, Cinnamon, Cloves, Coriander, Cumin, Dill, Fennel, Galangal, Lavender, Nutmeg, Oregano, Peppermint, Rosemary, Sage, Sassafras, Savory, Spearmint, Spicebush, Thyme
- GI analgesics to support GERD w/ carminative: Wild yam, Kudzu, peach tree leaf, pinellia
- In Chinese Medicine bitters are used to make the digestive energy descent

Stomach Acid Production

- Produced by the parietal cells
- Cephalic: before food. Parasympathetic dominant.
  - Vagus nerve makes acetyl choline before food intake begins in Cephalic phage
  - Ach → G cells → Gastrin → parietal cells ->Hcl
  - ACH->ECL cells → Histamine -> parietal cells (type 2 histamine receptors) ->HC
- Gastric phase: vagus nerve Ach and gastrin
- Parietal cells use a pump called H+-K+-ATPase
  - Pump extrudes cytoplasmic Protons (H+) against a steep concentration gradient while transporting extracellular K+ into parietal cells creating a charge neutral ion exchange

Decrease Stomach Acid

- Duodenal stretch of intestinal wall, hyperosmolarity, protein degradation products and fat all trigger ↓ acid.
- Cholecystokinin, GIP *(renamed glucose-dependent insulinotropic polypeptide), Secretin and somatostatin all decrease acid production
  - These hormones inhibits acid secretion
- These hormone also stimulate nutrient storage ie
  - Stimulates insulin (incretin effect)
  - Increases lipogenesis, and is higher in obese people
  - Acts like ACTH and can cause hypersecretion of cortisol causing a sugar surge and food induced Cushing's syndrome
  - Broken down by the enzyme DPP4 and DPP4 inhibitors cause incretins to accumulate and cause insulin release, hence diabetes meds the Gliptins



Wikipedia: Phases of digestion

Hyperchlorhydria Herbs

- *Nepeta cataria*, *Matricaria*, *Melissa officinalis*: esp w/ stress and nervous stomach=nervines
- Glycyrrhiza glabra: also anti-inflam, demulcent and antimicrobial
- Filipendula ulmaria: High in salicylates, GI anti-inflam, esp combined w/ mucilaginous herbs.
- *Azadirachta indica* (neem), bitter yet reduces hypersecretions.
- Prunus persica (peach tree leaf): irritation of the stomach lining w/ nausea and vomiting

Hypochlorhydria

- Bloating, burping
- Diarrhea, gas
- Hair loss, weak nails
- HEARTBURN
- Intestinal infection
- Nausea w/ supps
- Nutr def: Fe, B12
- Muscle cramps
- BM changes
- FOOD JUST SITS!
- Worse w/ meat
- Associated diseases
- Allergies
- Anemia
- Asthma
- AI disorders
- Skin: acne, psoriasis
- SIBO
- Dysbiosis
- Food allergies
- Low anion gap

Causes of Hypochlorhydria

- Medications that reduce acid: PPIs, H2 blockers, Calcium Carbonate. Buffers
- Being older than 65
- High stress on an ongoing bases (cortisol. Digestions is parasympathetic dominant)
- Low or poor zinc absorption
  - Zinc is a cofactor for carbonic anhydrase which is an essential enzyme to make stomach acid but zinc treatments have also been shown to reduce stomach acid.
- H pylori infection can cause lower acid
  - It has urease which can convert urea to CO2 and ammonia which can neutralize acid
- Stomach surgery

Treatments to Increase HCl

- Low anion gap can be an indicator of low stomach acid. The pumps don't work well at a low gradient.
- Betaine/Pepsin/HCl, increasing/decreasing protocol or continuous use
- Apple cider vinegar. 1/2 TBSp mixed into water. Rinse mouth after. 15-30 minutes before eating
- Zingiber Off, *Juniperus commununis*, Orange peel (Citrus spp.), *Zanthoxylum clava-herculis*
- Other bitters
- Reduce stress response
- Treat mineral balance esp potassium

Antacids

- Neutralize stomach acidity to relieve heart burn, indigestion or upset stomach, and also may be indicated for constipation or diarrhea
- Different types of salts are used as antacids including calcium carbonate, magnesium carbonate, sodium citrate, and aluminum hydroxide
  - Reported: Effervescent sodium salts may increase risk of stroke & CV events (but this is compared to non-sodium containing products, it's not about the effervescent per se, but rather increased sodium)
  - Magnesium containing products tend to lead to loose stools
  - Aluminum and calcium salts may cause constipation
  - Calcium carbonate needs acid for absorption. Calcium citrate is better absorbed in achlorhydria.

Acid Blockers: :PPI

- PPI: proton pump inhibitors
  - Prilosec was the first used clinically in 1989
  - Binds to the H+-K+-ATPase via **irreversible** covalent binding and lasts longer than H-2 blockers
  - Block acid regardless of which type of stimulation (gastrin or histamine)
  - Take several doses for full strength, wears off before 24 hours as **pumps are replaced** (inactivating drug). Taken before meals to reach effect.
    - 20 mg pantoprazole = 4.5 mg omeprazole
    - Lansoprazole 15mg = 13.5 mg omeprazole
    - Esomeprazole 20 mg = 32 mg omeprazole
    - Rabeprazole 20 mg= 36mg omeprazole

PPI side effects (long term):

- **Research is mixed**. My takeaway: Depends on dose, duration and pre-existing factors.
- Increased risk of cancer from hypergastrinemia, ECL hyperplasia and changes in GI flora (including *H. pylori*)
- Nutrient Deficiency incl B12, calcium, magnesium, iron
- SIBO, *C. diff*, *H. pylori*, other GI flora changes
- ↑Fractures esp hip: May be nutrient malabsorption, hypergastrinemia and increased histamine
- Dementia: B12 deficiency? Inc β-amyloid plaque (in mice). There is Na+/K+-ATPase pumps in the CNS.
  - PPIs might decrease CNS inflam and improve NSAID outcomes
- Pneumonia: ie strep pneumonia
- Rhabdomyolysis, thrombocytopenia, kidney disease

PPI Best Practices: MD 2017 Gastro Recommendations

- GERD and erosive esophagitis should take PPI short term for healing and then long term
- Uncomplicated Gerd should try to stop, but then take them for long term sx control
- Barrett's and symptomatic gerd = long term ppi
- Asymptomatic Barrett's = long term ppi
- If long term NSAIDS then long term PPI
- If long term PPI Try to reduce the dose and reevaluate
- Should NOT use probiotics w/ long term PPI
  - A 2023 study suggested using them w “more studies necessary” kiecka et al
- Long term PPI: Should NOT use Calcium, B12 or magnesium beyond RDA
- Long term PPI should NOT screen DEXA, creatinine, magnesium or B12

Potassium competitive acid blockers (P-CABs)

- Vonoprazan: first in class. Available in Japan (2015) and Russia (2021). Not in the US yet
- Binds to H+-K+-ATPase and blocks K+ binding inhibiting the pump
- Reversible. Based on blood level. Effective after the first dose.
- Same efficacy as PPIs.
- Longer acting, quicker acting. More consistent in pH management and stability, less variability with CYP2C19 polymorphisms

Histamine & Mast Cells

- Histamine stimulates stomach acid production from the parietal cells. It stimulates smooth muscle cell contraction, vasodilation and cytokine production
  - Both Gastrin and Histamine stimulate acid production
  - Histamine in the stomach is stored in ECL cells AND Mast Cells
  - Histamine is also a neurotransmitter
    - Wake promoting and rapid eye movement (REM) sleep-suppressing neurotransmitter with effects on feeding and endocrine function
- Mast Cells # may be higher in irritable bowel syndrome, mastocytic enterocolitis, and systemic mastocytosis.
- Eosinophils can also increase in the GI lining in gastrointestinal eosinophilia which is inflammatory, They tend to release other cytokines and eosinophil activation protein, not histamine

Mast Cells

- Mast cells are effected by acute and chronic stress. This is one reason that stress effects leaky gut, motility and visceral sensitivity.
- Mast cells release serotonin, proteases, inflammatory cytokines and histamine
- Mast cells are stimulated by IgE antibody and can be stimulated or inhibited by IgG antibody!
  - IgG antibody can bind a mast cell FcgRIIIa receptor and trigger anaphylaxis with platelet aggravating factor from macrophages
  - Desensitization can cause production of blocking IgG antibody.
  - IgE antibody bind to the FcεRI and cause allergic reaction associated with histamine
    - Drug: **Palforzia** Peanut allergen powder

H2 blockers: Famotidine, Cimetidine, Nizatidine

- Histamine receptor 2 blockers block histamine from stimulating parietal cell from producing acid
  - H2 receptors are in parietal cells but also found in the brain, endocrine and exocrine glands, GI muscle, genitourinary system immune cells and skin
- H2 blocker block histamine and reduce the effect of acetylcholine and gastrin. Duration 6-10 hours.
- H2 blockers are less potent than PPIs
- They may reduce bladder spasms, cystitis
- (2022 meta analysis) Side effects can include: Hypotension, headache, fatigue, rash, Pneumonia, C diff, liver and gastric cancer and osteoporosis

H2 blockers (receptor antagonists)

- More effective at controlling nocturnal, as opposed to meal related acid secretion, because postprandial acid is stimulated via histamine and acetylcholine
- People can develop tolerance to H2 receptor antagonists in weeks to months
- Cimetidine has been reported to delay gastric emptying whereas ranitidine and nizatidine accelerate it
- Ranitidine was recalled by the FDA in 2020 because it tends to accumulate NDMA, a cancer causing chemical, over time and esp if stored in high heat
  - Ranitidine is off the market and other PPIs or H2RA are suggested
    - Zantac is now Famotidine
- Nizatidine was recalled for the same reason. OTC discontinued, still available by Rx

Natural histamine blockers

- EGCGs from green tea reduce histamine from ECL cells and mast cells reducing GI inflammation and gastric pathology
- Herbs: Sophora flavescens, Mosla dianthera, Urtica dioica (Nettles):
  - alters cytokines and reduces mast cell degranulation
- Quercetin: alters IgE production, alters cytokines
- Garcinia mangostana: blocks histamine receptors
- Neem (Azadirachta indica). Nimbidin extract H2 blocker similar to acid blocker
- Tinospora cordifolia (guduchi): Anti-inflam, anti-microbial and histamine

Mast Cell Activation Syndrome

- Over-activation of Mast cells which causes a release of their stored allergy mediators, not related to IgE or normal secondary activation (ie meds, infections, venoms)
- Involves skin, GI, CV, respiratory and Nerves
  - Urticaria, angioedema, nausea, vomiting, diarrhea, abd cramping, hypotensive syncope, wheezing, itching, improved w/ Histamine blockers, anti-leukotrienes and mast cell stabilizers
- Mast cell activation syndrome tests
  - Serum histamine & Tryptase (within 2 hours of episode start)
  - 24 hour urine histamine metabolites:N-methylhistamine, prostaglandin F2α & Leukotriene E_4
  - IL-4(from mast cells) & IL-9 (stim mast cell growth), prostaglandin D2 (from mast cells)
  - IgE total level and food IgE reactions (scratch, plasma)

Histaminosis or Mast Cell Activation Syndrome

- Functional, nonspecific, non-allergic gastrointestinal complaint due to an accumulation of histamine
  - Can be transient and reversible
    - Maybe a lack of DAO, an enzyme that degrades most of the exogenous histamine from food
      - DAO, HNMT and alcohol dehydrogenase all break down histamine.
- Used to be called scombroid fish poison because histamine is high in tuna, herring, mackerel, other seafood, Also cheese, alcohol, spoiled food (amines)
  - Maybe aggravated w/ spoiled food or EtOH
- Generally short acting and it can be systemic including urticaria, hypotension, heart palps, headache, esp Migraines, rashes, eczema, GI upset

DAO: Testing and Modulation

- Dx: Possible elevated histamine, Reduced plasma DAO, Histamine 50 skin prick test. Food elim/reintro
- Genetic testing: polymorphisms
  - L-histidine decarboxylase, DAO, HNMT and histamine receptors
- DAO deficiency: Mucosal damage: Chemotherapy, GI disorders incl Carb malabsorption and non-celiac gluten sensitivity.
- DAO activity reducing drugs:
  - **Acetylcysteine**, chloroquine, clavulanic acid, cefuroxime, verapamil, clonidine, dihydralazine, diclofenac, amitriptyline, metoclopramide, cimetidine, **ascorbic acid**, **thiamine**
- Rule out allergies, IgE sensitivity & mastocytosis.

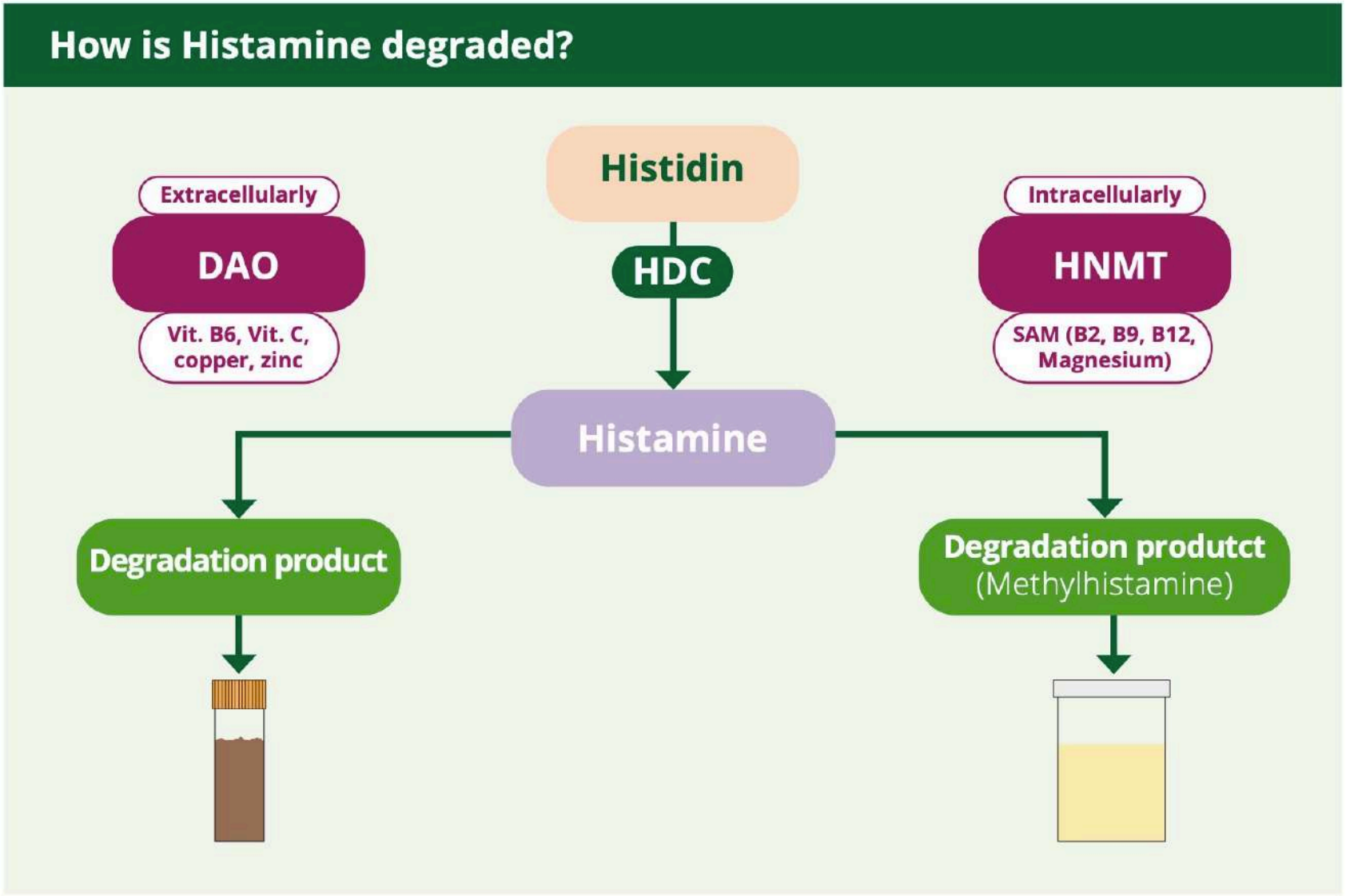


Figure 1
Enzymatic degradation of histamine (Mod. after 4, 7)
HDC - Histidin-Decarboxylase

BioVIs histamine intolerance
www.biovis.de
expert info 6/2020

Meds That Influence DAO or Histamine

Table 2. Medications which may influence diamine oxidase and/or histamine.

Medications	Generic Name
Analgesics	Acetylsalicylic acid, Metamizole, Morphines, Nonsteroidal anti-inflammatory drugs, Pethidine
Antiarrhythmics	Propafenon
Antibiotics	Cefuroxime, Cefotiam, Isoniazid, Pentamidine, Clavulanic acid, Chloroquine
Antidepressants	Amitriptylline
Antifungal	Pentamidine
Antihypertensives	Verapamil, Alprenolol, Dihydralazine
Antihypotensives	Dobutamine
Antimalarial	Chloroquine
Broncholytics	Aminophylline
Cytostatics	Cyclophosphamide
Diuretics	Amiloride
H2 receptor antagonists	Cimetidine
Local anesthetics	Prilocaine
Motility agents	Metoclopramide
Mucolytics	Acetylcysteine, Ambroxol
Muscle relaxants	Pancuronium, Alcuronium, D-Tubocurarin
Narcotics	Thiopental
Radiological contrast media	
Vitamines	Ascorbic acid, Thiamine

Wolfegang et al

Allergy, Histamine, Mast Cell Treatments

- Antihistamines
  - First generation histamine type 1 receptor blockers
    - Diphenhydramine, hydroxyzine ->SLEEPINESS
      - Esp for itching, abdominal discomfort and flushing
  - Second generation antihistamines
    - Loratadine, cetirizine, fexofenadine → less side effects
- Histamine 2 receptor blockers:
  - Famotidine or Ranitidine (oops recalled cancer)
    - Esp in abdominal pain and nausea
- Aspirin blocks Prostaglandin D2 associated w/ flushing
- Leukotriene blockers:
  - Montelukast and zafirlukast block LTC_4 effects and Zileuton blockers LTC_4 production
    - Esp wheezing and abdominal cramping

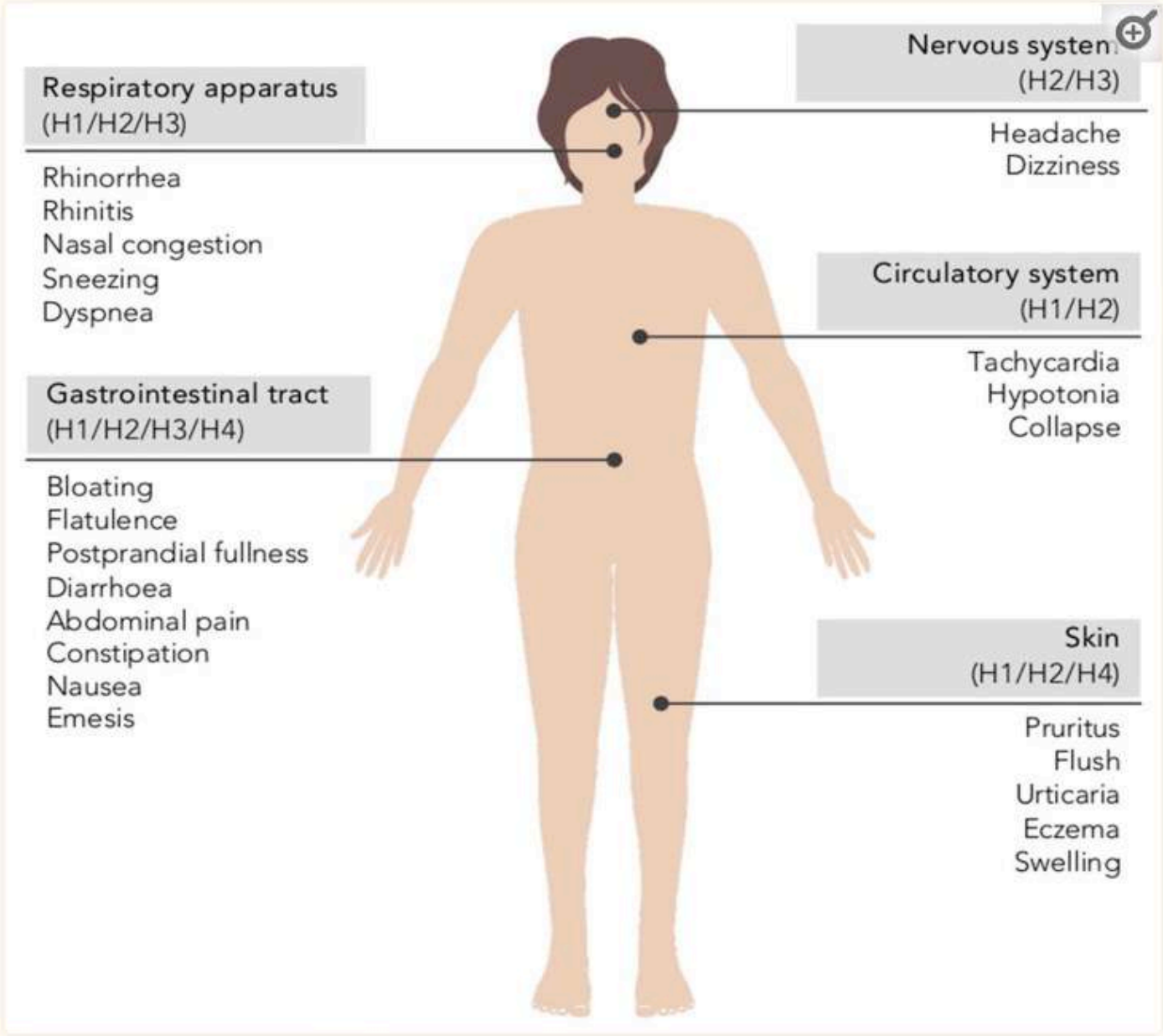


Figure 6

Comas-Baste et al

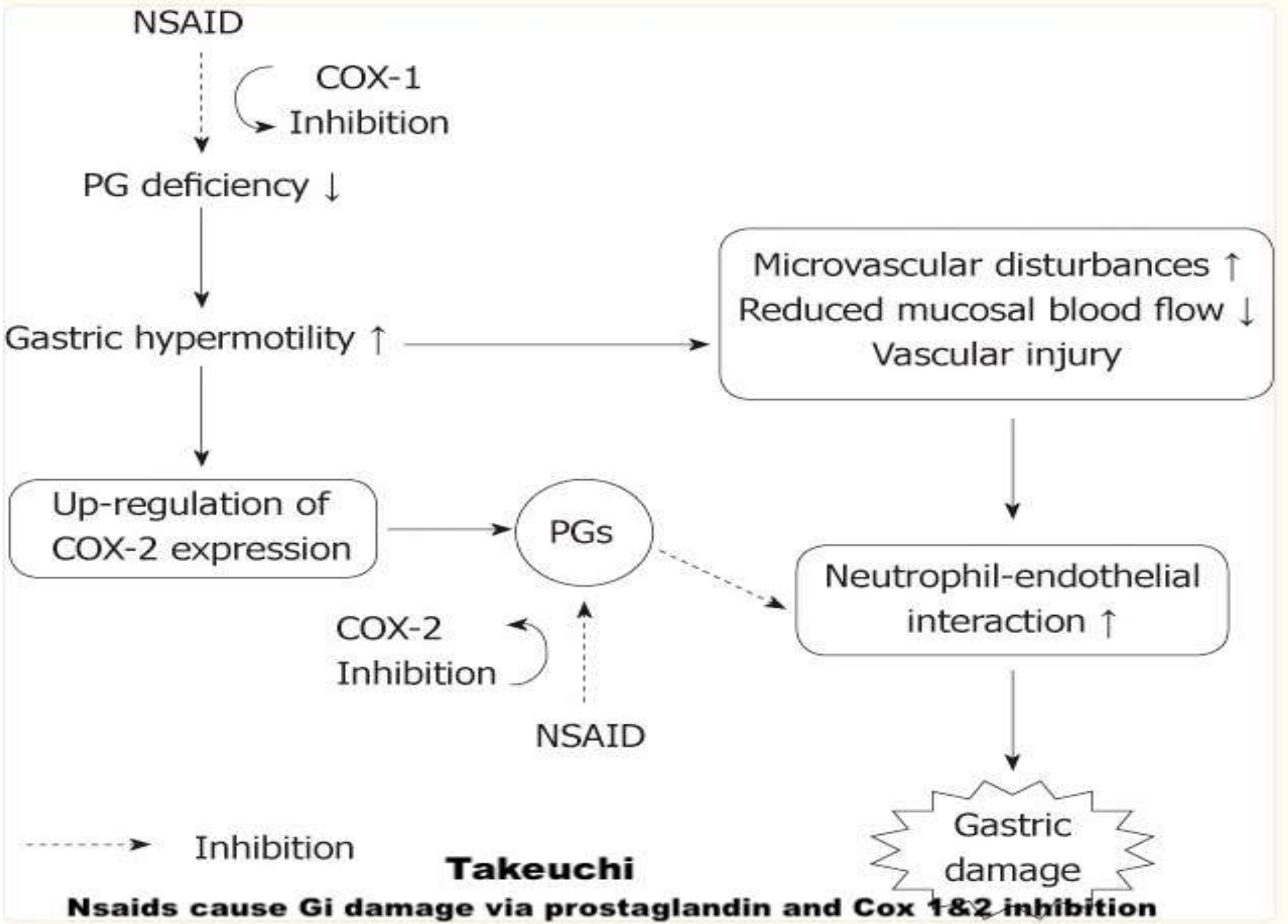
Main symptoms of histamine intolerance and possibly corresponding histamine receptors [10,64].

Omalizumab

- Recombinant humanized IgG antibody that binds the Fc portion of the IgE antibody
- Much more effective at binding to free IgE than bound IgE = blocks IgE binding
- Downregulates allergies by binding IgE antibody and down regulating FcεRI receptors (IgE r on Mast cell)
- FDA approved to treat asthma, nasal polyps and recurrent urticaria
- “significantly increased the tolerated dose of multiple foods; increased the threshold of tolerated dose for milk, egg, wheat, and baked milk; improved QoL; and reduced food-induced allergic reactions”.
    - Meta-analysis in 2023 J Allergy Clin Immunol Pract . 2023 Apr;11(4):1134-1146.

Mucus Creation

- MUC2 Mucin protein is the main component
- Reduces damage from acid by forming a layer
- Mucus is dependent and impenetrable to bacteria and is a nutritional source for the bacteria, ie for *Akkermansia*
- Aids in peristaltic movement
- Inflammatory components SUPPORT mucus production: Production is increased via PGE2 (prostaglandin) . COX-1 is critical for maintaining the GI mucosa.
  - PGE2 production is inhibited by NSAIDS
  - Pyridine derivatives reduce inhibition of NSAIDS back to basal level: Nicotinic acid, pyridinol carbamate (drug), pyridoxine hydrochloride (B6) and pyridostigmine bromide (Myasthenia gravis drug acetylcholinesterase inhibitor used in trials for acute colonic pseudo obstructions)
    - Cystine and b6 increase mucus production (at least in rats) and reduce NSAID damage



Nsaids cause Gi damage via prostaglandin and Cox 1&2 inhibition

Mucogenic & Mucilaginous

- Gamma-oryzanol (rice bran oil): ↑Mucin
  - Also anti-inflam, antineoplastic, hypoallergenic, antidiabetic, antiulcerogenic, hypoglycemic
    - MOA may be antioxidant and ↓NF-KappaB, ↓COX-1&2
- Butyric acid
- Zinc L-carnosine: anti-inflam, anti-oxidant, increased growth factors, increase mucus + goblet secretion
- Epidermic ("Acosta" in Asia and Russia): Esp in aphthous and gastric ulcers
  - Enhances mucus production, antioxidant, ↑ COX-2, ↑nitric oxide, ↓TNF and inflammation. Likely not approved due to edema
- Cetraxate (Japan) increases mucosal blood flow, mucus production, and improves H pylori treatments & pancreatitis

Mucogenic & Mucilaginous

- *Syzygium guineense* (water berry/pear): edible leaves and berries. South African. Increase 65-84% increase mucus production
- Mucilaginous: Zinc
- Herbs: *Althea off*, *Verbascum thapsus*, *Cumulus fulvus*, *Plantago lanceolata* (plantain), *Plantago ovate* (psyllium), *Trigonella foenum-graecum*, *Symphytum off* (PA warning!), Glycyrrhiza glabra (HTN warning!), *Foeniculum vulgare*, M*atricaria chamomill*a, *Phyllanthus emblica* (amla), *Hibiscus rosa-sinensis*, *Salvia hispanica* (chia), *Linum usitatissimum* (flax), Aloe, cactus, *Chondrus crispus* (Irish moss), drosera, kelp and seaweed, Okra, *Smilax*, *Centella asiatica*, calendula
- Propolis: gastroprotective as well as anti-microbial
- Polysaccharides: alginates (seaweed), pectin, hyaluronic acid, bean and guar gum, Tamarindus indica

Bile

- Aqueous solution produced by the liver made of bile salts, phospholipids, cholesterol, conjugated bilirubin, electrolytes and water. Main function lipid absorption and elimination of waste products
  - Made in the liver. Stored in the gall bladder and concentrated.
    - People without gall bladders still produce the same amount of bile, but it gets secreted and pools in the small intestines. (rifaximin still work, it needs bile?)
- Cholecystokinin (CCK) stimulates the gall bladder to contract and push bile into the duodenal lumen
  - Secretin also helps by stimulating biliary and pancreatic cells to secrete bicarbonate and water in response to bile acids in the duodenum
- 5% of bile is excreted into the stool. The rest are efficiently reabsorbed from the ileum and returned to the liver. Bile is resecreted several times during the same meal.

Bile

- Unsaturated fats have greater aqueous solubility than saturated so their absorption is less effected w/ low bile
- Bile is conjugated with glycine & taurine.
  - Unconjugated bile is more easily absorbed into cells and is cytotoxic
  - Conjugated bile is more soluble in ↓pH and more resistant to ppt in presence of high calcium
  - Bacterial enzymes unconjugate bile acids
- Bile is too large to get through tight junctions which allows for high concentrations of bile
- Conjugated bile is absorbed in the terminal ileum and bacterially unconjugated bile is absorbed passively

Bile

- Biliary obstruction (stones, inflam, scarring) can cause bile to get stuck, sulfonated and then end up in urine.
- Increased deconjugation from bacteria (sibo, dysbiosis) can cause an increase in reabsorption irritating the cells and impairing fat absorption
- Nicotinic acid and d-thyroxine can increase biliary cholesterol concentration
- Phase II conjugated liver detox metabolites are cleared from the body through bile.
  - Some of those metabolites can be reabsorbed after GI flora unconjugate the metabolites from the bile and are then reabsorbed in enterohepatic circulation.
    - GI flora can alter potency of meds and hormones via bile deconjugation in the intestines and that varies based on diet and flora

Bile Symptoms

- BAM: Bile acid malabsorption. BAD: Bile acid diarrhea
- Greasy or hard to wipe stools!!!!! Green or pale stools. Dark urine
- Nausea, dizziness, fatigue.
- Esp worse with high fat food.
  - (“I can't eat fried food”. Which: Fat, gluten, eggs? Are your stools greasy?)
- High GGT, alk phos, cholesterol. Fecal bile acids serum C4 test (Liver making bile acids. Elevated C4=Make sure dt absorbing less
- SeHCAT (“see-cat”). Radioactive bile used to observe concentration, secretion and reabsorption
- Fat malabsorption and associated vit A, D, E, K deficiencies.
- Gall bladder pin point pain, often worse with fatty meals

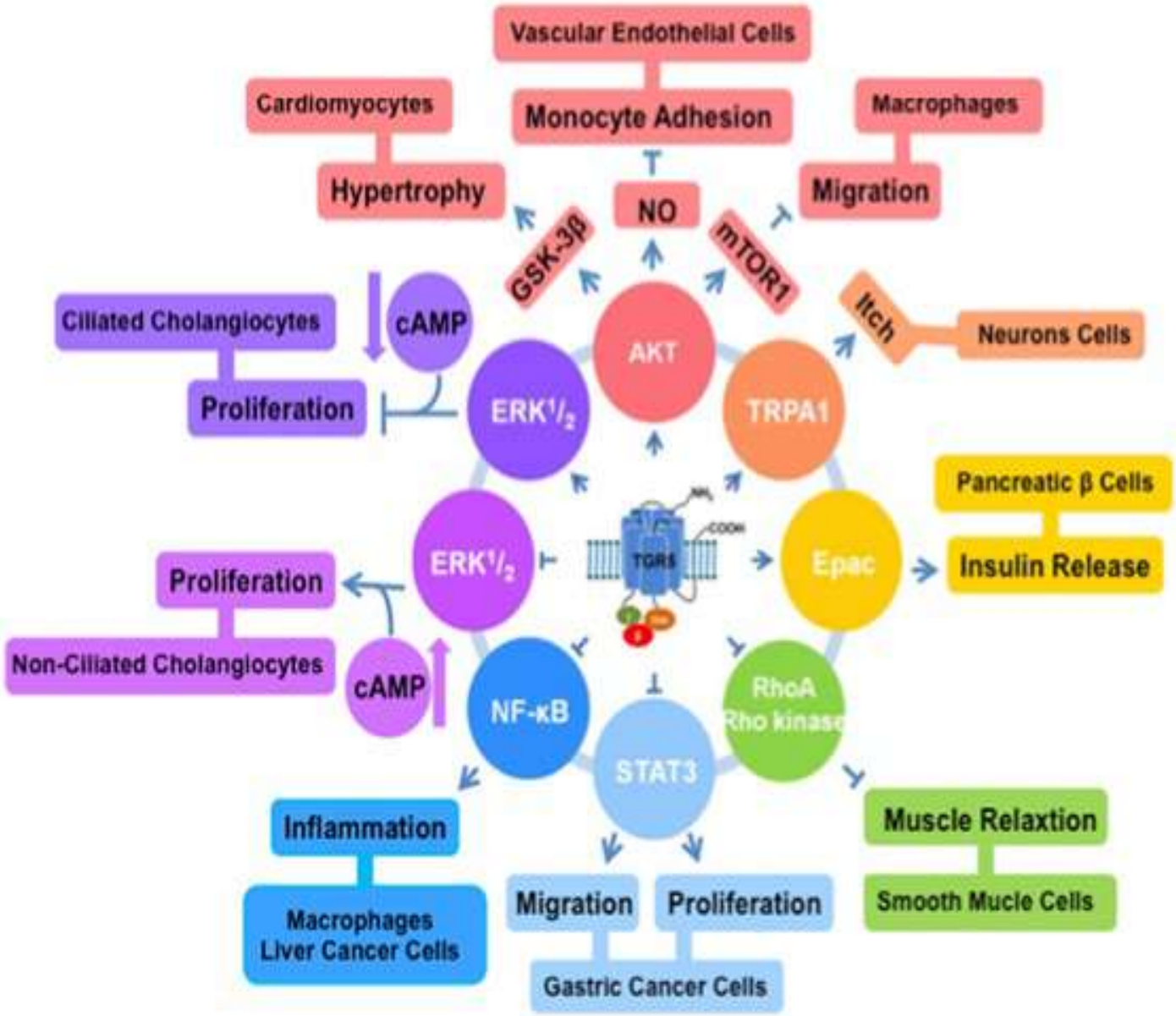


FIGURE 1 | TGR5 regulates different cell signaling pathways. TGR5 activates AKT (Kida et al., 2013; Perino et al., 2014), TRPA1 (Lieu et al., 2014), and Epac (Kumar et al., 2012) pathways. And it inhibits NF-κB (Pols et al., 2011; Wang et al., 2011; Yoneno et al., 2013), STAT3 (Guo et al., 2015b), and RhoA/Rho kinase (Rajagopal et al., 2013) pathways. TGR5 has opposite functions in ERK1/2 pathway. In ciliated cholangiocytes, ERK1/2 is activated by TGR5 (Masyuk et al., 2013). But in non-ciliated cholangiocytes, TGR5 activation inhibits ERK1/2 (Masyuk et al., 2013).

Bile as treatment

- Bile acids increase energy expenditure, glucose metabolism, regulates inflammation and support liver regeneration Through TGR5 receptor , found throughout the body
- UDCA: Ursodeoxycholic acid: Gall stones, gall sludge, liver tonic, primary biliary cholangitis and bile reflux
  - Alterations of bile pool, cytoprotectant, immunomodulating, choleretic and inhibits cholesterol absorption in the intestines
  - Reduces the oxidative cellular damage from bile acid induced damage by displacing concentration of toxic unconjugated bile acids and increasing absorption of conjugated
- Bile acids induce energy expenditure by promoting thyroid hormone activation
- TUDCA (tauroursodeoxycholic acid): is neuroprotective and may help in neurodegenerative diseases
- Ox bile supplement with food support fat absorption and reduce steatorrhea

Bile Treatments

- Bile acid sequestrants to prevent reabsorption:Cholestyramine
- Ezetimibe (Zetia) inhibits bile reabsorption in the small intestines by blocking receptor NPC1L1 at the brush boarder
- Taurine and glycine : key compounds for the synthesis of bile salts. Lecithin enhances bile secretion and prevents bile acid-induced cholestasis
- Malic acid or apple cider vinegar may help soften bile stones (traditional use).
  - Gall bladder flush? Rule out stones first (ultrasound, only 10% of gall stones are calcified and not on Xray)
- Artichokes leaf (*Cynara scolymus*), *Cnicus benedictus*, *Chelidonium majus*, *Chicorium intybus* (chicory), *Veronicastrum virginicum*, Tarax off root, *Chionanthus virginicus*, *artemisia vulgaris*, *Curcuma longa*). Baicalin from *Scutellaria baicalensis* improve flow and lowers inflammation and interacts TGR5
- Reducing estrogen: high estrogen or estrogen replacement tends to cause bile sludge or stones

Bitters

- Bitter taste increase plasma ghrelin within 40 minutes and activates bitters taste receptors (TAS2R) which increases proton secretion
  - Defense against pathogens? Toxic things tend to be bitter.
- Hops, caffeine, polyphenols in red wine (red>white)
- Green tea: over steeped green tea turns bitter due to polyphenols and catechins which are antioxidant and increase stomach acid
- Also GI anti-inflammatory: Devils claw (*Harpagophytum procumbens*) & Licorice (*Glycyrrhiza glabra*), Ginger (*Zingiber off*), Turmeric (*Curcumin longa*)

Bitters

- Also cholagogues and liver support: Artichoke (*Cynara cardunculus var scolymus*), burdock (*Articum lappa*), Dandelion root (*Taraxicum off*), Gentian (*Gentiana lutea*), Bhumyamalaki (*Phyllanthus niruri* “stone breaker”, Guduchi *Tinospora cordifolia*),
- Also antimicrobial: Artemisia (*Artemisia vulgaris*), *Angelica archangelica*, *Andrographis paniculata* Berberine containing plants (ie *Hydrastis*, *Mahonia*, *Berberis*, *Coptis)*,
- Bitter foods: Arugula, coffee, dill, dandelion green, Jerusalem artichokes, saffron, kale, sesame seeds, ginger, citrus, peppermint, cocoa, eggplant

Compound	Plant species	Reference
Menthol, menthone, isomenthone	*Mentha piperita*	[8]
Eugenol, acetyleugenol	*Syzygium aromaticum*	[9]
Borneol	*Dryobalanops aromatica*	[9]
Zygophillin, quinovic acid	*Zygophyllum coccineum*	[9]
Crocin, crocetin	*Gardenia florida*	[9]
Loganin	*Patrinia villosa*	[9]
Syringopicroside	*Syringa oblate*	[9]
Ferulic acid, caffeic acid	different species	[9]
Caffeine	*Coffea arabica*	[9]
Theophylline	*Camellia sinensis*	[9]
Glycyrrhizinic acid and derivatives	*Glycyrrhiza glabra*	[12]
Liquiritigenin	*Glycyrrhizae uralensis*	[20]
Xanthone glycosides and aglycones	*Gentianopsis barbata*	[21]
Chamiloflan	*Chamomilla recutita*	[22]
Cynarin, cynaropicrin	*Cynara scolumis*, *Saussurea amara*	[23]
Gingerol	*Zingiber officinale*	[24]
Dicaffeoylquinic acids	*Achillea millefolium*	[25]
N-demethyl ricinine	*Ricinus communis*	[26]
Silymarin, silibinin	*Silybum marianun*	[27]
Andrographolide	*Andrographis paniculata*	[28]
Protopine	*Fumaria officinalis*	[29]
Picroliv	*Picrorrhzia kurroa*	[30]
Platycodin D	*Platycodon grandiflorum*	[34]
Geniposide, genipin	*Gardenia fructus*, *G. jasminoids*	[37]
4-Hydroxyacetophenone	*Aster* and *Artemisia* species	[39]
Phloracetophenone	*Curcuma comosa*	[40]

Table 1: Plant secondary metabolic compounds with cholagogue and choleretic activity.

Pancreatic enzymes

- Pancreas secretes more than 2 L of high protein juice a day able to digest lipids, proteins, carbohydrates.
- Pancreas makes concentrated bicarbonate that buffers incoming stomach acid
- Greatest rate of protein synthesis of any organ
- Enzymes: trypsinogens, chymotrypsinogens, procarboxypeptidase, procarboxypeptidase, prophospholipase, proelastase, mesotrypsin, α-amylase, lipase, DNase, RNase & enzyme inhibitors to prevent autolysis
- Pancreatic enzymes are ineffective at gastric pH
- Pancreas makes “interdigestive phase” enzymes and buffers during the MMC as part of house cleaning
- Hormones, sensors (I cells in the epithelium “taste” nutrients=intestinal luminal sensors) and the enzymes themselves help regulate secretions

Pancreatic enzymes

- Enteropeptidase is an enzyme produced by cells in the duodenum that converts trypsinogen to trypsin and results in activation of pancreatic digestive enzymes
- The pancreas stores enzymes in a far greater amount than needed to digest a meal
- Lipase breaks down faster than proteases so fat digestion is often lost first in insufficiency. Causing confusion w bile
- Pancreatic exocrine insufficiency: a reduction in pancreatic enzymes to less than 10% causes: pancreatitis, AGING, pancreatic cancer, Cystic Fibrosis, hemochromatosis, diabetes 1&2, gastrointestinal disease, celiac disease, IBD, alcohol and drugs
  - More common azathioprine (immunosuppressant), thiazides (diuretics), sulfonamides (sulfa drugs), furosemide (loop diuretic), estrogens, tetracycline, alcohol, heroin and cocaine

Pancreatic Exocrine Insufficiency Sx

- Excessive flatulence: bloating, distension, cramps, belching (gut bugs overfed?)
- Stools; Steatorrhea. Loose, greasy, bad smelling, Pale, gray, bulky, frothy
- Malnutrition: weight loss, anorexia, fatigue
- Vit D (bones), vitamin K (bone, bleeding and bruising), Vitamin A (night blindness and immune incompetence), vitamin E Ataxia and peripheral neuropathy
- Hypocalcemia (muscle spasms, bones)
- Hypoalbuminemia (nail leukonychia= white spots or color)
- Pain in center of stomach w rads to the back
- Systemic: bone pain, muscle pain

Pancreas

- Stool tests elastase, undigested food, fecal fat
- Blood: amylase, lipase, trypsinogen
- Endoscopic ultrasound. Biopsy
- Treatment: Pancreatic enzymes
- Rx Pancrelipase: Creon, pig enzymes, recombinant
- Supplements: animal based (porcine), Plant (papain from papaya) microorganism based (*Aspergillus*, *Saccharomyces*, *Candida*, *Bacillus*)
  - May contain betaine/pepsin/HCl or Ox bile
  - Generally measured in units
- Bitters, increasing stomach acid and increasing parasympathetic tone to stimulate pancreatic output

Endothelial cells=Enterocytes

- Structure and function changes through the GI tract. Single layer. Renewed every 4-5 days.
- Involved in absorption: Protein, fats, sugars, water, electrolytes, vitamins and unconjugated bile salts
- Secretions: Enteroendocrine endothelial cells ie Goblet and Paneth: Leptin, gastric inhib peptide, VIP
- Transport: sIgA & sIgM Antibody, nutrients
- Brush boarder enzymes for terminal digestion of carbohydrates and protein
- **They eat glutamine, ketone bodies and short chain fats mainly from enteral nutrition**
- Active in shaping intestinal immune environment to food and microbial agents by keep balance between suppression and stimulation of inflammatory responses.
  - They cooperate with cells of the intestinal mucosa-associated lymph tissue

Enterocytes

- Create a barrier to prevent intact antigens from contacting lymphoid tissue esp via tight junctions
  - Tight junctions vary in their permeability along the intestines and are more permeable in the large intestine than the jejunum
- Digestive process can not lyse all food proteins and a small amount of intact proteins are endocytosed by enterocytes and broken down in the lysosomal compartment
- Endothelial cells create antimicrobial peptides like β-defensins, secreted into mucus, to manage flora and fight infections
- Have Toll like receptors to help with microbial recognition and sense LPS to trigger inflammation
- Secrete regulatory cytokines to suppress inflammatory response and stimulate B cells to make sIgA
- They can express MHC1&II, esp in response to stress and infection to present antigen to T cells. (Some complexes, called tolerosomes and can mediate oral tolerance)

Brush Border Enzymes

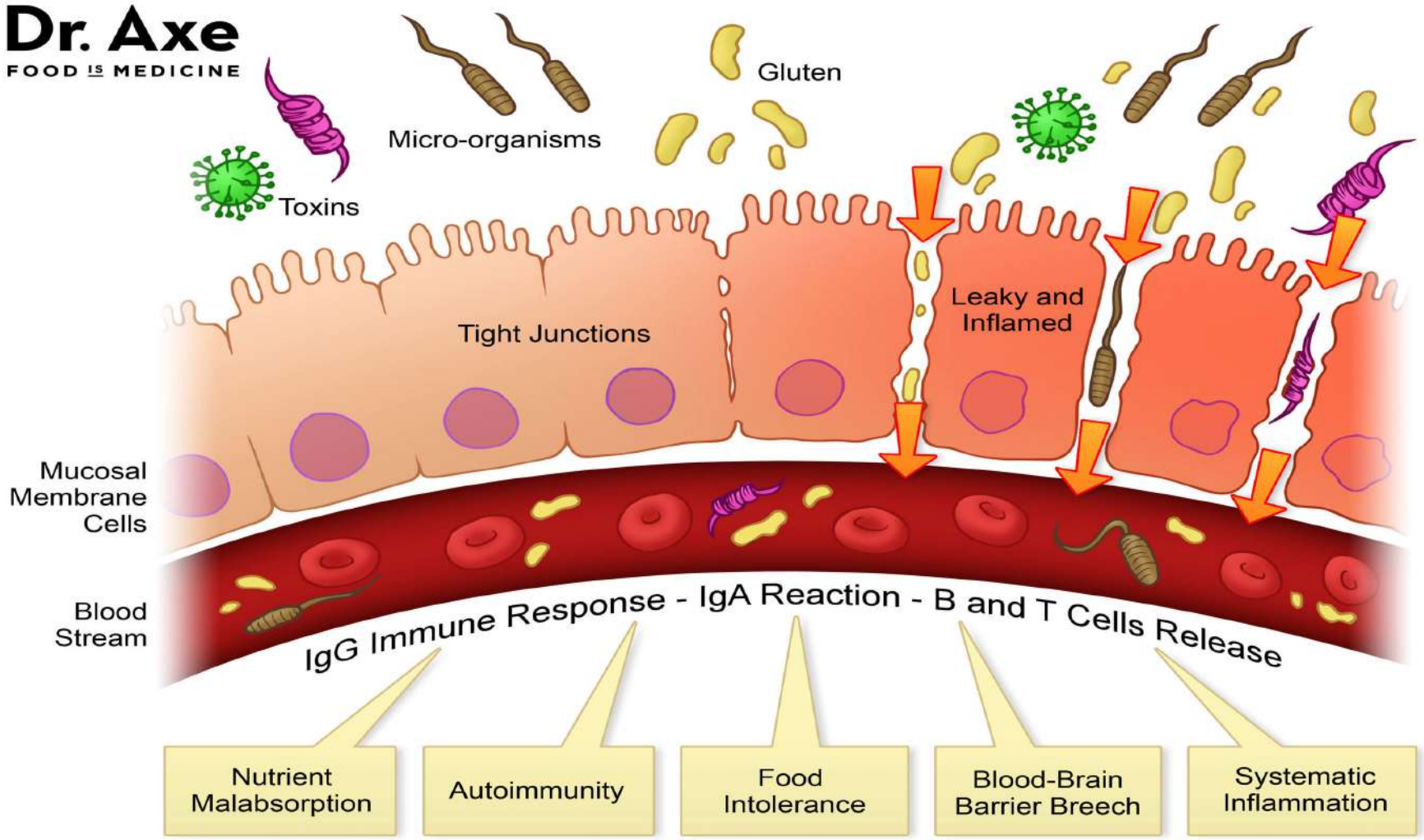
- Terminal digestion of protein and starches(FODMAPS)
  - Maltase-glucoamylase & sucrase-isomaltase to digest starches partially digested by amylase
  - Lactase (approx 65% lose lactase after infancy, variable by biogeographical ancestry)
  - Peptidases (many): both to further digest protein and activate pancreatic enzymes.
  - Lipases: multiple incl phospholipase B1, neutral ceramidase and sphingomyelinase
- The location and quantity of these enzymes varies by genetic and age. Ex: lactase.
- There is primary and secondary brush boarder damage.
  - Ex: Celiac: celiac causes abnormally short microvilli with brush boarder enzymes reduce to about 10% and recover with removal of gluten with exception of β-glucosidase and lactase where are slower and have a less complete recovery.

Tight junctions

- Between enterocytes to maintain intestinal integrity which prevents pathogens and toxins absorption
- ACTIVE and interact with stimulate to to control entry of ions, nutrients and water
  - Remodel transmembrane proteins in response to physiologic stimuli and signal pathways.
  - Regulated by protein kinase C, occludin, zonula occludens (ZO1&2) and claudin 1
- Zonulin: protein hormone that increases tight junction permeability.
  - Zonulin alters intestinal permeability together with luminal antigen (Ag) sampling by enterocyte to allow molecular trafficking of microorganisms, nutrients, pollutants, and other materials.
  - Gliadin increases zonulin irrespective of celiac

Leaky Gut

Bacterial translocation plus their metabolites plus non-fully digested food via blood stream or mesenteric lymphatic vessels



Diseases Zonulin Has Been Linked To As A Biomarker Of Permeability

- Autism
- Aging
- Ankylosis Spondylitis
- Celiac Disease
- Chronic Fatigue
- Colitis IBD
- Gestational Diabetes
- Glioma
- Insulin Resistance
- IBS
- Hyperlipidemia
- HIV
- Depression
- MS (in mice)
- Necrotizing enterocolitis
- Non EtOH fatty liver dz
- Non celiac gluten sensitivity
- Obesity
  Schizophrenia
- Sepsis
- Type 1&2 diabetes
- Fasano Et al

Modulating Zonulin

- Lowering zonulin
- Probiotics
- Larazotide acetate: synthetic peptide in study
- Polyphenols incl resveratrol, curcumin and quercetin
- Butyrate and butyrate producing bacteria
- Bovine colostrum
- Apple derived pectin
- Vitamin A & D

- Raising Zonulin
- Gluten
  - chemokine receptor CXCR3 as the target intestinal receptor for gliadin. CXCR3 regulate leukocyte trafficking and inc Th1 response
- Obesity
- Insulin resistance
- LPS from dysbiosis = enteric bacterial exposure
- Inflammation esp w/high CRP or IL-6

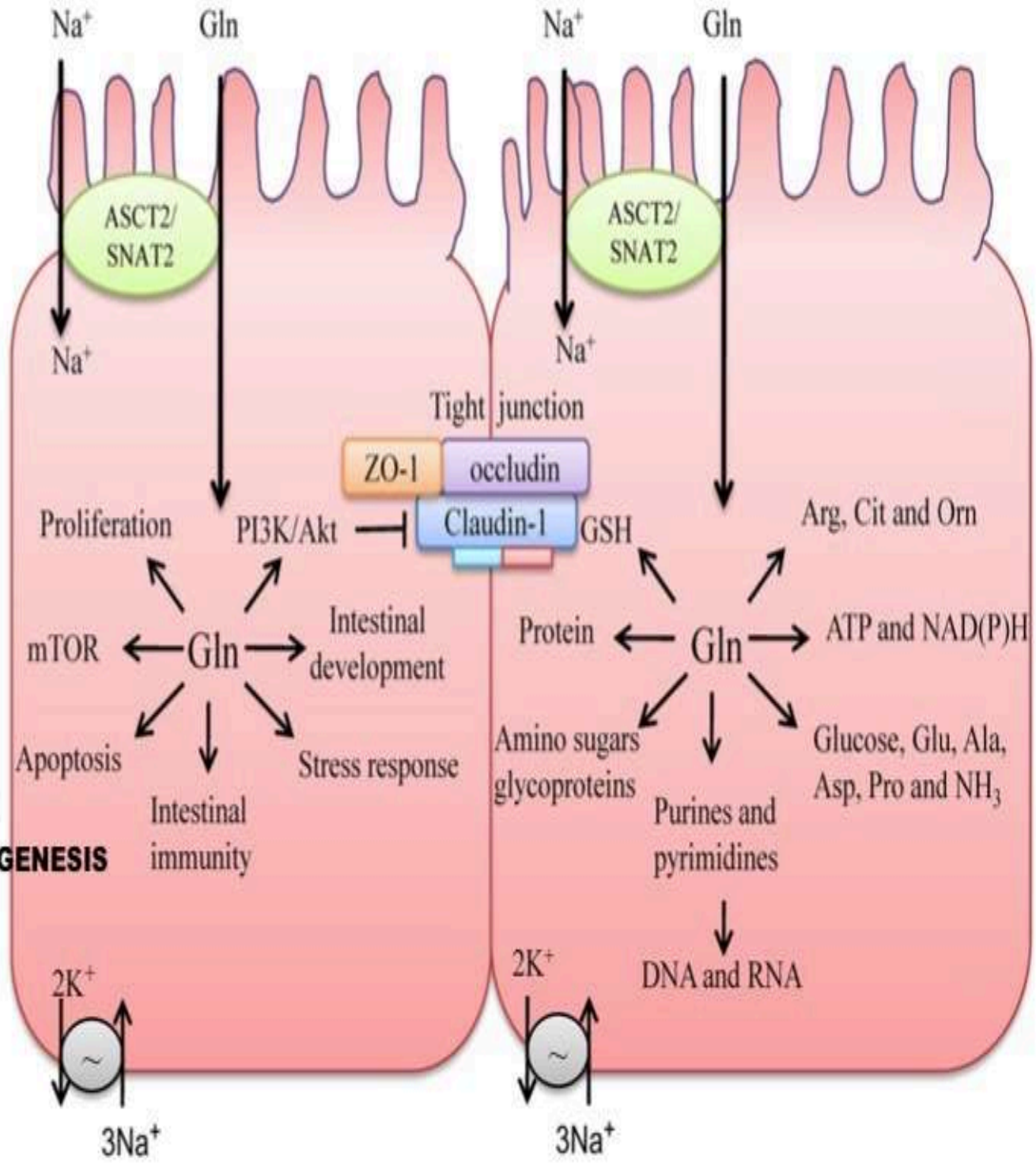
Brush Border Damage

- In Crohn's disease not involving the jejunum, brush boarder disaccharidase activity were reduced but diseased ileal mucosa show essentially normal distribution of marker enzymes
  - Aka: It matters where the damage is to effect the enzymes
- SIBO: lectins of microorganisms bind to oligosaccharides of microvillus membranes and the enzymes have reduced action due to bacterial proteases.
- *Giardiasis*: significant reduction of lactase, sucrase and aminopeptidase which is reversible w/ treatment
- *E. coli* and *Yersinia* bind to microvillar glycoproteins and provoke secretion
- Clostridial enterotoxin A binds to microvillar glycoprotein and induce diarrhea via paracellular permeability

Glutamine

- Glutamine is the most abundant free amino acid
  - a non essential amino acid that can be essential in catabolic conditions
- Main source of energy for small intestines
- Promotes enterocyte proliferation, regulates tight junction proteins, suppresses proinflammatory pathways, protects cells against apoptosis and cell stress
- Depleted in metabolic stress, trauma, sepsis, and inflammatory bowel disease.
  - Animal provided a low glutamine diet had increased gut permeability and decrease mucosal functioning
- 75% enteral glutamine and 25% plasma glutamine is used by enterocytes.

Fig. 1 Glutamine plays important roles in intestinal epithelial cells (see text for detail). *AKT* protein kinase B, *ASCT2* neutral amino acid transporter type 2, *ATP* adenosine triphosphate, *mTOR* mammalian target of rapamycin, *NADH* reduced nicotinamide adenine dinucleotide, *NADPH* reduced form of nicotinamide adenine dinucleotide phosphate, *PI3K* phosphoinositide 3 kinase, *SNAT2* sodium coupled neutral amino acid transporter 2, *ZO-1* zonula occludens protein 1



mTOR=REGULATES PROLIFERATION

P13K= REGULATES GROWTH, ANGIOGENESIS MOTILITY & METABOLISM

Wang et al

Glutamine

- Steve's treatment suggestion
- 3 grams power mixed into water sipped
  - Caps don't feed esophagus as it's not available to those cells
- 1X/day when your gut is happy, up to 3X/day or more when your gut is upset.
- Indications? ANY gut problem or prevention from damage unless intolerant
  - Ie reduce the risk of NSAIDS, antibiotics, GI irritating meds
- Note: glutamine can be converted to glutamate, which can act as a excitatory neurotransmitter
  - Watch for over stim symptoms: headaches, anxiety, irritation, jitters, palps, cognitive dysfunction

Zinc

- Modulates resistance to infectious agents and reduces the duration, severity and risk of diarrheal disease via...
- Improved regeneration of intestinal epithelium
  - Zinc deficiency ↓ membrane barrier integrity & associated with inflammatory cell infiltration
- Improved absorption of water and electrolytes
- Increased brush boarder enzymes
- Helps to maintain membrane barriers despite continuous noxious and infectious exposures esp with zinc finger proteins such as ion transport and DNA & RNA interactions and signal transduction
  - 🧐 Zinc Fingers: one of the most abundant groups of proteins including in many molecular functions esp important to epithelium due to fast reproduction

Sucralfate (Carafate)

- Medication to treat stomach ulcers, GERD, Proctitis, stomach inflam and stress ulcers
- Duodenal ulcers not related to NSAIDS and Gastric ulcers off label
- Non systemic . Can cause constipation
- Acts locally in an acidic environment to crosslink and cause a viscous paste that acts as a barrier and buffer.
- Attaches to proteins at the surface of ulcers like albumin and fibrinogen
- Protects against acid, blocks and binds pepsin and bile
- Stimulates prostaglandin $E_{2,}$ epidermal growth factors and gastric mucus production

GI Immunity

- GALT: Gut associated lymphoid tissue, plus lymph follicles and nodes
  - GALT makes cytokines, immunoglobulins, growth molecules, lysozyme, defensin and support renewal of enterocytes
- 75% lymphatic cells, 50% lymphocytes and the production of 80% of all immunoglobulins are associated with the GALT
- Predominantly the antibody are locally made sIgA antibody but also includes sIgM antibody. They are secreted by epithelial cells for to create a surface barrier
  - Secretory antibodies can also be effective INSIDE epithelial cells
- Suppressive mechanisms(Treg cells) prevent hypersensitivity to innocuous antigens esp food and commensal microbiota

GI Immunity

- GI immunity is a balance between pro-inflammatory and anti-inflammatory cytokines
- Anti-inflammatory. IL-10 dominant, inhibit proinflam cytokines and are reduce inflammation
  - IL-10 is Th2 dominant and suppresses cell mediated immunity (NK cells and macrophages) and lowers inflammatory cytokines
    - Too much IL-10 response would turn down a proper infection fighting response
- Pro-inflammatory: IL-12 predominant. Th1 cells develop, activate NK cells.
  - Infections, cancers and allergies are reduced

Inflammatory Bowel Disease (IBD)

- Chronic inflammation with pain and swelling in the intestines. Most common Crohn's disease and Ulcerative Colitis
  - Crohn's any part of the GI tract, non continuous, can include abscesses, fistulas and structures.
  - Ulcerative colitis: Colon mucosal inflammation
- Symptoms:
  - GI incl pain, blood or pus in stool
  - Extraintestinal: fever, sweats, fatigue, arthralgia, delayed growth, liver disease, uveitis, arthritis, perianal disease
  - Dx: inflammation, Calprotectin, perinuclear antineutrophil cytoplasmic antibody (ANCA UC>CD low sensitivity), anti-saccharomyces cerevisiae antibody (ASCA CD>UC low sensitivity), stool cultures. CT, MRI, US, colonoscopy, etc

IBD Theory

- Cause unknown. Complex interaction between genetic, environmental or microbial factors and immune response.
- Multiple genes involved
- Dysfunctional autophagy leads to dysfunctional epithelial lining (=process of reusing old and damaged cell parts
  - >Causes Dysf'n in intracellular bacteria killing, alters antimicrobial secretions by Paneth cells, goblet cell function, pro-inflam cytokines by macrophages, antigen presentation and endoplasmic reticulum dysf'n
- Environmental exposures
  - ie smoking, drugs, diet, stress, antibiotics (modulating flora) or low Vit D(decrease Th17 response)

IBD Theory

- Flora: alterations in flora: Decrease diversity, less firmicutes and Bacteroidetes, over representation of enterobacteria
- Immunologic factors: dysfunction in innate and adaptive immunity
  - Multiple cytokine modulations ie IL-23 ↑Th17 cells
    - Th17 cells regulate inflammation and fight infection at mucosal lining & regulate immune response, esp in neutrophils
    - Th17 cells discovered in 2005 as a third way to fight infections compared to Th1 (cell mediated) and Th2 (antibody mediated). Highly inflammatory and implicated in autoimmune and inflammatory disorders
- Toll like receptors (TLR) may pay a central role in the pathogenesis of IBD
  - TLR help modulate flora and balance immunity
  - Low Dose Naltrexone modulates TLR

IBD Treatments

- 5-aminosalicylic acid derivative:sulfasalazine, mesalamine, balsalazide, olsalazine
- Antibiotics: metronidazole, cipro, rifaximin
- Corticosteroids: prednisone, methylprednisolone, prednisolone, budesonide, dexamethasone
- Immunosuppressants: azathioprine, 6-mercaptopurine, methotrexate, cyclosporine, tofacitinib=JAK1&3↓inflam mediators
- Biologics: TNF inhib (infliximab, adalimumab, certolizumab) Anti-integrin antibody (natalizumab=prevent WBC passing thru), inhibitors of IL-12&23 (ustekinumab= ↓T cell activation)
- H2 receptor blockers: cimetidine, ranitidine, Famotidine, etc
- Proton pump inhibitors:omeprazole, lansoprazole, etc
- Antidiarrheal agents: diphenoxylate and atropine, loperamide
- Anticholinergic antispasmodics: dicyclomine, hyoscyamine

Types of food reactions

- IgE mediated food allergy. Immediate reaction. IgE activation of mast cells in specific tissues incl skin, respiratory tract, GI, mucosal and CV systems
  - MD-Iand Scratch tests are considered valid due to skin reactions. Steve prefers blood testing and elim.
- IgG, IgM and IgA medicated food reactions. Delayed type hypersensitivity. Take take 72 hours to react.
  - Upregulation of IgG_4 may be protective
- Celiac disease: an autoimmune disease triggered by gluten associated with anti-transglutaminase antibody and anti-endomysial antibody
- Lack of brush boarder enzymes: ie lactose intolerance, sucrase-isomaltase deficiency, etc
- Cell medicated immunity: eosinophils GI disorder and allergen specific T cells (food protein-induced enterocolitis syndrome)

Celiac Disease

- A permanent systemic disorder triggered by ingested gluten and related proteins with variable degrees of Gi symptoms from inflammatory enteropathy and systemic symptoms. Often triggered by stress or infections.
- Antigen presenting cells associated with HLA II haplotypes DQ2 and DQ8 cause Gluten specific CD4 T cells
- Villous atrophy is often seen on a colonoscopy
- Celiac disease causes damage through both cell mediated and antibody mediated autoimmunity
- Extraintestinal symptoms can include mitochondrial myopathy,Dermatitis herpetiformis (tTg3), neurologic problems, liver disorders, arthritis and obstetric problems, peripheral neuropathy and cerebellar ataxia (tTg6)
- Celiac is often associated with other issues including osteoporosis and autoimmune disorders including, , type-1 diabetes, autoimmune thyroid, cytoskeletal actin antibody, Multiple transglutaminases, gangliosides and collagen

Alpha-gal Syndrome

- IgE allergy to mammalian meat and meat derived produced associated with tick bites to the oligosaccharide galactose-α-1,3-galactose
  - Alpha gal IgE blood test or food challenge, r/o food allergies with other IgE testing
- Non-Classical IgE symptoms
  - Symptoms range from pruritus, hives, angioedema to anaphylaxis and maybe strictly gastrointestinal
  - Reactions may be delayed 3-8 hours after exposure
  - Symptoms can start intermittently and often are at night
- IgE levels might decrease over time if avoiding further tick bites

Alpha-gal symptoms

- Treatment: Avoid pork, beef, venison and lamb and products made from these (gelatin, glandular thyroid, pancreatic enzymes, glandular supplements)
  - Increased fat and alcohol increase reaction
  - 80-90% do NOT react to dairy products
  - Reaction pattern is variable and often at night
- 2nd generation antihistamines
  - fexofenadine or levocetirizine
- Oral Cromolyn Sodium. Mast cell stabilizer
- Oral corticosteroids esp severe reactions
- Omalizumab
- Metformin: Limited data, may be helpful

GI Flora

- Complex endocrine organ capable of producing hundreds of products...it's far larger and biochemically heterogeneous than any other endocrine organ. The biochemical complexity exceeds that of the brain
- Far exceeds number of host cells. 90% of cells found in the human are prokaryotic. Different reported number likely 100 trillion! 40,000 species, 1800 genera. Average weight 1-2kg in an adult.
- The complexity is difficult to measure. Most of the flora can't be cultured and the variety is actively being discovered thanks to genomic techniques.
- Large scale colonization of infant gut commences at birth when exposed to complex microbiota from maternal sources
  - Babies born C section develop different microbiota w/ aberrant short term immune responses and greater long term risk of developing AI disease and potential changes in subsequent endocrine capability of the microbiota.

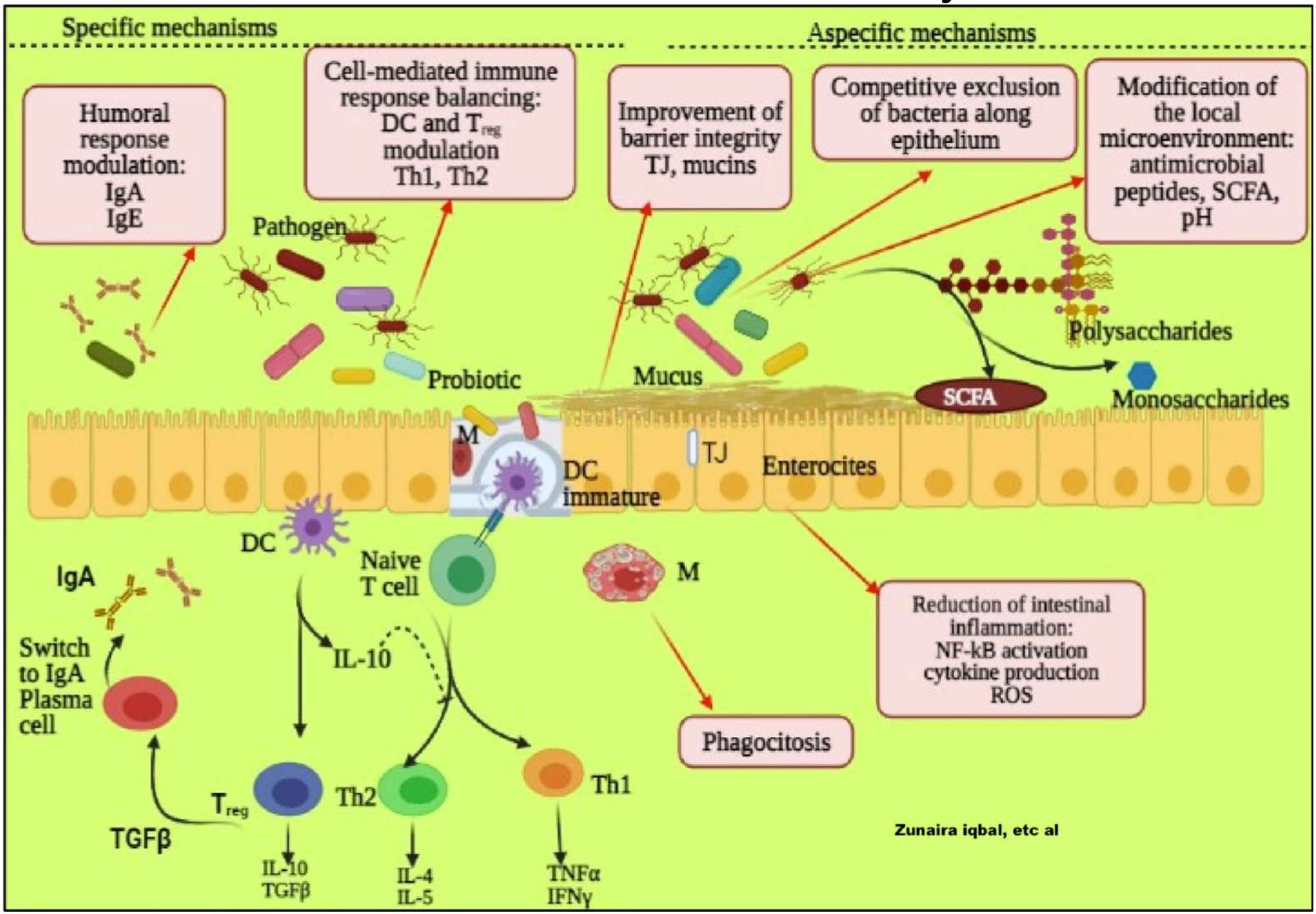
GI Flora

- Complex adult like microbiome is evident at 1-3 years of age. Homeostatic mechanisms within the microbiota become less effective in the elderly and the microbiota diverges between healthy and health deteriorating individuals
- The flora is functionally specialized for energy harvest from particular diets
- Transform primary bile acids to secondary bile acids which are antimicrobial and involved in glucose and lipid metabolism
- Flora stimulates immune activity in the mucosal membranes
- Probiotics may be harmful w/ immunocompromised individuals
- Flora may transfer antibiotic resistance between bacteria

GI Flora

- Microbiota influence human energy metabolism
- Microbiota composition influences response to chemotherapy and immunotherapy
- Microbe composition defines glucose response
- Microbiota is different between vegan and meat eating people
- Low fiber diet reduces production of small chain fatty acids and shift GI microbiota to less favorable nutrients, reduces colonic mucus barrier and can cause leaky gut and inflammation
- Detrimental effects of high fat diets on the mucus layer can be lessened with prebiotics (inulin)

Flora Effects on Immunity



Probiotics

- Reduce size of adipose deposits
- *L. plantarum* KY1021 reduced adipogenesis
- *L. paracasei* NCC2461 inc sympathetic nerve activity in white and brown adipose
- *Lactobacillus reuteri* ATCC reduced body weight
- *Bifidobacterium infantis* increases circulating tryptophan
- *Bacteroides fragilis* has a tryptophanase enzyme to produce indole which has been linked to GI abnormalities and autism spectrum disorders

Autism Spectrum and GI flora

- Autism spectrum is multifactorial including genetic, biological and environmental risk factors.
- Children on the spectrum with developmental disorders tend to have altered fecal microbiota and metabolome with altered neurotransmitter molecules
  - Made worse by altered diet due to taste and texture sensitives
  - Including alterations in levels of VOCs, alcohols, aldehydes, esters, sulfur compounds, hydrocarbons, ketones, terpenes, indoles and furanones
  - Clostridia species are present at the highest levels in children w/ Autism. They tend to make potentially toxic metabolites and are recalcitrant due to spore forming.
  - Faecalibacterium which produce SCFA and are anti-inflam tend to be low

Gas and Flatulence

- Gas in digestion is predominantly from fermentation of GI flora
- Different flora can ferment difference nutrients
  - Raffinose: A complex sugar found in beans, brassicas, asparagus
  - Lactose: milk sugar, esp if missing in brush boarder enzymes. Then lactose is a laxative. Gassy diarrhea w/ dairy better w/ lactase
  - Sugar alcohols. Natural occurring ie fruits or as a food/supplement source. Some are absorbed better than other. Ie xylitol is absorbed
  - Fibers: Bacteria can ferment fiber. We can't digest it
  - Starches, esp when broken down in the Lg intestine. Rice is the only starch that doesn't cause gas.

Gas and Flatulence

- Gas is normal. Everyone has some wind
- The quantity or odor of gas may indicate the underlying etiology
- Sulfur smell may indicate sulfur SIBO or toxic fermentation. Hydrogen sulfide is toxic and can lead to IBD or cancers. Diet alone is not sufficient to resolve. H_2S is a result of dysbiosis and diet
- VERY gassy people tend to have organisms that ferment a lot or SIBO
  - steve says pseudomonas or clostridia overgrowth
- Insufficient digestion can lead to too many nutrients reaching flora and causing more fermentation.
  - Therefore: Excessive gas can be due to flora or incomplete digestion!

Prebiotics

- Mucin can feed GI flora but human diet is the chief source of energy for flora growth
- Most reach the lg intestine unchanged and undergo bacterial fermentation to stimulate flora growth
- Ie inulin or inulin-type prebiotics stimulate *Bifidobacteria* and influence production of GI hormones, SCFA and glucagon-like peptide 1 & ghrelin which may influence appetite regulation
- Ex: Fructooligosaccharides (FOS), galacto-oligosaccharides (GOS), and trans-galacto-oligosaccharides (TOS), inulin, resistant starch (ie polydextrose), pectin
- Non-carbohydrate prebiotics ie cocoa derived flavonoids
- No brainer: A diet high in complex carbs, fruit and veggies have more prebiotics than the SAD

Postbiotics

- Metabolites created by the microbiome: “a preparation of inanimate microorganisms and their components that confer a health benefit on the host”
- Immunobiotics and Post-Immunobiotics
  - Probiotics and postbiotics have immunomodulatory activity. May be strain specific.
- Mammalian probiotics and organisms from vegan sources (fermented foods, plants) all have the capability to make postbiotics and are immunomodulatory
  - Even if they do not colonize and naturalize
- Sterilized extract from flora have specific physiologic effects because components of the flora and their metabolic products contain bioactive components
  - Assuming the postbiotics aren't damaged in the sterilization. Ie membrane structures, vessicles...

Postbiotics

- GI flora produce neurotransmitters including serotonin, dopamine, Gaba and Nor/Epinephrine as well as tryptophan and kynurenine
- Balance of kynurenine and quinolinic acid influence CNS and ENS neurotransmitters and inflammation Lipoteichoic acid: anti-inflam and promotes host production of anti-infectious peptides (defensin, cathelicidin)
- Short chain fats: feed cells, signal distal cells, anti-inflammatory. Interact w/ brain, lung, etc...
- Exopolysaccharides: GI protective biofilms, anti-inflam, Stimulate endogenous anti-ox production incl glutathione and SOD, antimicrobial
- Antioxidant enzymes
- Some bacterial LPS can help modulate immune function ie in COPD

Postbiotics

- Antimicrobial peptides: bacteriocins esp from lactic acid bacteria. Some are heat stable. Broad spectrum antimicrobials
- Exopolysaccharides from lactic bacteria are a potent antioxidant
  - Promotes intestinal barrier function via upregulating zonula occludens-1 and occludin
  - Promotes immune response to maintain lining
  - Pro-inflam IL-18 produced by antigen presenting cells increases mucosal barrier and tight junctions as a response to the competitive actions of flora
- Production of micronutrients including:
  - Thiamine, folate, biotin, riboflavin, pantothenic acid, vitamin K, multiple amino acids. B12

Short Chain Fatty Acids

- Short chain fats (SCFAs) are a major product of bacterial fermentation of carbs, fibers and proteins in the gut
  - modulate both enteroendocrine hormones and important neuropeptides in the gut-brain axis
  - SCFA feed enterocytes, 70% lg intestine enterocytes food.
  - Fiber ↑SCFA production such as butyrate and propionate and those can travel far, including specific receptors to help them cross the BBB
  - SCFA effect epithelial cell transport, epithelial growth and differentiation
  - SCFA support hepatic control of lipid and carbohydrate metabolism
  - SCFA profoundly effect inflammatory responses

Enteric Infections

- 1.5 billion cases of enteric infections, mostly diarrhea, in children. Food contamination constitutes 70% of all diarrheal infections world wide
- Can be bacterial, viral or parasitic. 22 pathogens are strictly monitored ie salmonella, several E coli, Hepatitis A, etc
- Enteric infections can lead to dysbiosis, a consequence of disruption of microbiome homeostasis
- Steve says: Enteric infections can become chronic and are harder to test for, ie parasites when they come out less. O&P testing becomes less accurate. “Send out” lab testing tends to find more organisms. Consider PCR & culture for multiple organisms at once
- Steve Says: Do a test, the start the treatment while waiting for results. Start with glutamine, antimicrobials, probiotics, colostrum, butyric acid, anti-inflam

Table 3 Mechanism of action of probiotics against pathogens (Corr et al. 2009; O'Hara and Shanahan 2007)

Mechanism of action of probiotic	Pathogen	Probiotic bacterial Strain	Function	References
Competitive exclusion	*Enteropathogenic E. coli* *L. monocytogenes,* *Yersinia pseudotuberculosis* *S.enterica serovar Typh-imurium*	*L. johnsonii* *L. acidophilus*	*Inhibited adhesion of Caco-2 cells to pathogenic organisms*	Otte et al. (2004)
	Klebsiella pneumonia *Enterotoxigenic E. coli* *EPEC*	*L. casei*	Inhibited adhesion of Caco-2 cells to pathogenic organisms	Corr et al. (2009)
	E. coli O157:H7	*L. acidophilus* *L. rhamnosus*	Pathogen adhesion inhibited to T-84 epithelial cell	Corr et al. (2009)
Production of inhibitory substances	H. pylori	L. acidophilus	Production of lacticins A164 and BH5	O'Hara and Shanahan (2007)
	E. coli *Clostridium difficile*	*B. longum*	*Bacteriocin Production*	O'Hara and Shanahan (2007)
	L. monocytogenes	*L. salivarius*	*bacteriocin Abp118 production*	Corr et al. (2009)
	C. difficile	*L. lactis*	*lacticin 3147 production*	Corr et al. (2009)
Modulation of Immune System	*Salmonella spp.*	*L. reuteri*	*Enhance the production IgM (anti-Salmonella)*	Corr et al. (2009)
	E. coli O157:H7	*L. rhamnosus*	*Increase anti-E. coli IgA (Intestinal) response* *Leukocyte phagocytic activity*	O'Hara and Shanahan (2007)
Enhanced barrier function	*E. coli*	*L. acidophilus*	*Regulated against rearrangement to F-actin*	Qin et al. (2005)
	Enteroinvasive E. coli	*L. acidophilus* *S. thermophilus*	*Enhanced trans-epithelial resistance, development and maintenance of cytoskeletal as well as tight junctional phosphorylation of its protein*	Qin et al. (2005) Resta-Lenert and Barrett (2003)

Dysbiosis

- Imbalance, dysfunction or disturbance of gut microbiota. The wrong organisms in the right place or too many of the right organisms in the right place.
- “Complexity with huge interindividual variation” and multiple measurement indexes
- Multiple disease states both GI and systemic can be related to dysbiosis including inflammatory associated diseases or CNS related (mental/emotional)
  - Leads to proinflammatory cytokines and leaky gut
- Multiple causes: Drugs, hormones, laxatives, antibiotics, diet, immune function, stress, food poisoning, environment exposures, maternal transmission, incomplete digestion, disease states (ie Sjogren's), food additives, sugar alternatives and high intensity sweeteners (sucralose aspartame and saccharin)

Dysbiosis and Inflammation

- Dysbiosis alters inflammatory factors and tight junctions
- Ie Increase in pro- inflammatory cytokines (ex, IL-1β, TNF-α and IL-18) and NLPR3 (inflammasome on macrophages)
- Decrease in tight junction barrier function through decreasing occludin and zonula occludens-1 levels
- Testing: stool testing for GI flora and digestive function. Including cultures, DNA probes (esp parasites to improve sensitivity and non-culturable bacteria) and microscopy (fungal elements, parasites). Cytokine testing. GI inflammation testing. Blood in stools.

LPS: lipopolysaccharide

- Outer membrane component of gram negative bacteria and is part of bacterial cell wall integrity and interaction with other bacteria. Gram negative bacteria make biofilm which can incorporate and protect LPS
- Generate a robust pro-inflammatory stimulus for immune response.
- Thermostable, not destroyed cooking. Still present after the infection is Lysed. Serologically reactive bioactive toxin
- *E. coli*, *Pseudomonas*, *Klebsiella pneumonia*, *Haemophilus influenza*, *P. gingivalis*, *Bacteroides*, *H. pylori*, *Salmonella*, etc
- Healthy gut lining reduces absorption. Leaky gut or high fat diet can increase absorption.
- Can aggravate autoimmune problems or allergies and inc pro-inflam cytokines, nitric oxide and eicosanoids and lead to chronic inflam dz like CV, type 2 diabetes, liver dz, Alzheimers, Autoimmune arthritis, coagulopathy and maybe Autism

Parasites

- CDC says fecal stool exam and O&P is the main test for parasites esp related to diarrhea, loose or watery stools, cramping, flatulence or other abdominal sx. Sensitivity has improved as technology as improved. AI supported microscope analysis
- DNA based stool test for parasites have a greater sensitivity compared to O&P but requires specific primers
- Some parasite infections persist and the sensitivity of the testing decreases as less organisms are shed in the stool
- Some parasites ie *blastocystis* and *entamoeba* are opportunistic and and be found in people with or without symptoms
- Parasites can cause extraintestinal infections & post infection gastrointestinal complications ie reactive arthritis, chronic fatigue, impaired cognitive function

Dysbiosis Treatments

- Treat infections. Herbal antimicrobials, antibiotics, antimicrobial nutraceuticals
- Diet: Low sugar, high prebiotics. Digestible foods. Many diet options...dealers choice
- Heal lining: Glutamine, colostrum, butyric acid
- Make sure regular BM, no constipation during treatment. Mag citrate. Other laxatives
- Probiotics: Mixed flora, high potency flora or flora that is suitable based on testing
- Organisms that fight infections: *Saccharomyces boulardii*, phages

GI Anti-Inflammatory

- *Aloe vera* Gel
- *Andrographis paniculata*
- *Boswellia serrata*
- *Uncaria tomentosa*
- *Scutellaria baicalensis*
- *Glycyrrhiza glabra*
- *Commiphora molmol*
- Butyrate
- MSM
- *Smilax ornata*
- *Panax notoginseng* (esp w/ bleeding)
- *Curcuma longa*
- *Achillea millefolium* (esp w/ bleeding)
- *Zanthoxylum*
- *Zingiber*

Anti-inflammatory

- Steve's first line: *Smilax ornata*, *Glycyrrhiza glabra*, *M. chamomile*, *Zanthoxylum*, *Curcumin*, *Calendula*, *Zingiber*
- Clove, *Portulaca*, *Tribulus*, *Eryngium*, cinnamon, fennel, chamomile, mint, burdock, eucalyptus, lemon balm, mallows, *Boswellia*, cat's claw, fenugreek
- MSM, Butyric acid
- Drugs: Low Dose Naltrexone
- Aminosalicylates: mesalamine, balsalazide, olsalazine, sulfasalazine
- Corticosteroids
- Immunosuppressant: azathioprine, mercaptopurine, methotrexate
- Biologics: tofacitinib, upadacitinib, oxanimod, Infliximab (Remicade), adalimumab (Humira), golimumab (Simponi), certolizumab (Cimzia)

IL-10 increasing treatments

- Immune modulating. Increase Th2 and antibody mediated immunity
- Many options. Some GI associated treatments include:
- CBD
- “anti-inflam” Licorice, Curcumin, Calendula
- *Bacteroides fragilis*, *L. plantarum*, *L. casei*, *Bacillus subtilis*
- *S. boulardii* inhibits LPS induced activation
- Serotonin
- Colostrum
- Antimicrobial: Olive leaf, *Calendula*, *Artemesia*, High-dose Garlic, elderberry/flower
- Styptic: *Achillea*, cinnamon

Antimicrobials

Antimicrobial herbs if indicated : SO SO MANY! *Artemesia*, mastic gum, *tripterygium*, *C. myrrh*, Berberine containing herbs, *A. Uva ursi*, Grapefruit seed extract, Oil of Oregano, *Acorus calamus*, *Thymus vulgaris*, *Hypericum*, *Allium*, *Melissa*, plant tannins, *Barosma*, *Uncaria tomentosa*, *Stephania tetrandra*, *Picrorhiza* (esp *Yersinia enterocolitica*), Kaempferol (anti-inflam too and found in multiple plants) , monolaurin and derivatives, gentian, Bilberry, noni, *Echinacea*, black walnut, tea tree oil, lavender oil, colloidal silver, *Glycyrrhiza glabra*, *Trifolium pratense*,Cranberry

Ginger, eucalyptus, mint, *Tribulus*, *Portulaca*, fennel, cinnamon, *Eryngium*, burdock, mallows, turmeric, chamomile, calendula, holy basil

Fecal Transplant

- First recorded used 1700 years ago. Chinese researcher, Ge Hong, in the fourth century made “yellow soup” to cure severe diarrhea
  - Poop soup didn't catch on
- Veterinarians started using it in the 17th century
- Camel stool was used by German soldiers to treat bacteria dysentery during WWII
- 1958 Eiseman et al published use w/ good success in recovery from diarrhea
- 1978 study 95% recovery rate in *C. diff* and is in use for that in multiple medical institutions. Fresh and frozen
  - Approved in 2013 by the FDA for *C. diff*
- This “organ transplant” is now being studied in both chronic intestinal and extra-intestinal conditions.

Migrating Motor complex

- Migrating Motor Complex: 4 phases.
    - 1: near quiescence
    - 2: small amplitude contraction
    - 3: Burst of high amplitude propulsive contractions which move down intestines help clear food and bacteria from the Sm intestines
    - 4: Decline back to baseline
- Predominant in fasting state and interrupted by eating
- It's absence is associated with gastroparesis, pseudo-obstruction and SIBO
- Mediated between the interaction of Motilin and serotonin
- Suppressed by stress
- Mechanical and chemical cleansing of the stomach and digestive tract in prep for the next meal. Important to prevent postprandial dyspeptic symptoms

SIBO: Small Intestinal Bacterial Overgrowth

- Excessive bacteria in the small intestines. Not universally accepted by gastroenterologists
- More commonly diagnosed due to access to breath testing (hydrogen, methane and H_2S)
- Severe gas and bloating, esp quickly after eating is an indication. Symptoms tend to include bloating, diarrhea or constipation and abdominal pain
- Methane sibo tends to cause constipation
- Sibo is not inflammatory and is not indicated by inflammatory markers
- Steve says; Sibo is not about the organisms. It's a movement disorder. Treat MMC! Antibiotics can suppress down the organisms in the small intestines but they move back up if movement or digestion is not corrected. Right bacteria in the wrong place.

Table 1. Diseases and Disorders Associated With Small Intestinal Bacterial Overgrowth—A Pathophysiological Approach

Abnormal small intestinal motility	Anatomic abnormalities	Hypochlorhydria	Immune deficiency	Multifactorial	Relationship to SIBO unclear
Diabetic autonomic neuropathy	Small intestinal diverticulosis	Post-surgical	Inherited immune deficiencies (eg, common variable immunodeficiency	Chronic pancreatitis	Rosacea
Systemic sclerosis/ scleroderma	Surgically-induced alterations in anatomy (Billroth II gastrectomy, bariatric surgery, end-to-side anastomosis)	Long-term acid suppression	Acquired immune deficiency (eg, AIDS, severe malnutrition)	Celiac disease	Interstitial cystitis
Amyloidosis				Diabetes mellitus	Restless legs syndrome
Hypothyroidism				Tropical sprue	Parkinson's disease
Idiopathic intestinal pseudo-obstruction				Crohn's disease	Erosive esophagitis
Acromegaly				Cystic fibrosis	Severe obesity
Gastroparesis	Strictures (Crohn's disease, radiation, surgery)			Intestinal failure	Irritable bowel syndrome
Myotonic muscular dystrophy				Radiation enteropathy	
Chronic opiate use	Blind loops			Liver disease	
Long-standing use of motility-suppressing drugs	Gastrocolic or jejunocolic fistula			End-stage renal disease	
	Ileocecal valve resection			The elderly	

SIBO

- Sibo is multifactorial: Dysfunctional MMC, Hypochlorhydria, brush boarder damage, h pylori, bypass surgery, hypothyroid, obstruction (or similar), gastroparesis, abdominal adhesions, antibiotic, narcotics and diseases that affects motility: pancreatitis, celiac, lupus, scleroderma, IBD/S, diabetes, alcoholism, hormone/enteric communication issues, pancreatic insufficiency, low bile
- SIBO treatments tend to be successful and then SIBO has a very high relapse rate after treatment because it's not about where the bacteria are, it's about how they got there!
- SIBO is to many bacteria BEFORE brush boarder enzymes
- Lactulose breath testing tends to indicate sibo more than lactose breath testing. Debate if it should be 2 hours or 3 hours.
- Breath testing requires a strict prep and a normal baseline. Methane has 4 hydrogen/molecule so hydrogen raise is quantitatively higher than a methane rise

SIBO treatment

- Sibo treatments might include an antibiotics such as rifaximin, rifampin, metronidazole, neomycin, erythromycin (also a prokinetic), TMP/SMZ, etc
- Or herbal antimicrobials common suggestions oil of oregano, grapefruit seed extract, berberine, artemesia, thyme essential oil
- FODMAP diet is suggested because it removes a majority of the nutrients that require brush boarder enzymes to digest them. More opportunity to absorb food prior to the bacteria fermenting it
- Prokinetics are helpful to stimulate the MMC.
  - Consider ginger, 5HTP, bitters
- Correct underlying pathology. Emphasize movement disorder!
- SIBO is almost opposite as dysbiosis. Fermentable items and probiotics can make it worse!

SIBO treatment and Flora

- Flora treatments may make SIBO worse. Monitor to determine if they are making gas and bloating worse
- Consider using low FODMAP probiotics, ie no prebiotics
- Some probiotics have been shown to have prokinetic effect (in animals)
  - *Lactobacillus rhamnosus* and *Bifidobacterium lactis* enhances the speed and strength of phase III and the migrating motor complex
  - *Lactobacillus acidophilus* and *Bifidobacterium bifidum* increase small intestinal motility with a reduction in duration of MMC cycles and increased the number and velocity of phase III contractions
  - *Lactobacillus reuteri* in infants and *lactobacillus casei* and *Bifidobacterium breve* in children and *Lactobacillus plantarum* in adults reduce constipation

Prokinetics

- Acetylcholine is the principle mediator of the physiological pattern and rhythm of movement but isn't targeted because it lacks selectivity
- Dopamine has inhibitory effect on motility via D2 receptors. Dopamine receptor antagonists are effective prokinetic agents.
  - They also effect chemoreceptor trigger zone and relive nausea and vomiting
- Motilin secreted by the duodenum and increases gastric emptying and MMC.
  - It is not made in response to food, but rather in the duodenum and enhances acetylcholine action
- Ghrelin is similar to Motilin, but tends to act outside the GI tract and likely stimulates hunger

Prokinetics

- Metoclopramide (Reglan); Dopamine receptor antagonist as well as 5-HT3 antagonist and 5-HT4 agonist. First line therapy
  - Helps to enhance acetylcholine action and improved coordinated contraction and ↑ LES tone
  - Extrapyramidal symptoms & pseudoparkinsonism
    - Irreversible side effect, can start in weeks!
- Itopride: inhibit dopamine and acetylcholine esterase
  - Not FDA approved, similar to Metoclopramide
- Cisapride: 5-HT4 agonist stimulates antral and duodenal motility and accelerates gastric emptying
  - Increased risk of cardia arrhythmias and only filled with investigational limited-access program

Prokinetics

- Domperidone: Mexico and Canada. Not FDA approved. D2 receptor antagonist
  - Doesn't cross BBB less CNS effects
- Macrolide antibiotics mimic motilin
  - Erythromycin, azithromycin, clarithromycin
  - Rapid development of tolerance and long term antibiotic use risk esp prolonged QT interval
- Bethanechol; Cholinergic agonist increasing acetylcholine release. Parasympathomimetic
  - Side effects cholinergic effects incl syncope, dizziness, diarrhea and urinary urgency
  - FDA approved for post operative urinary retention, overflow incontinence

Prokinetics

- Prucalopride (Resolor and Motegrity):
  - High affinity 5-HT4 receptor ↑motility in chronic constipation.
- Tegaserod and cisapride (discontinued
  - Also high affinity 5-HT4 receptors but had high risk severe cardiovascular side effects
- Alpha$_2$-Adrenergic Receptor antagonists: Mirtazapine
  - Tricyclic antidepressant. Interacts with multiple neurotransmitters incl histamine, norepi and serotonin.

Herbal prokinetics

- Herbal Prokinetics:
  - Ginger, *Cynara cardunculus* (cardoon), *Magnolia henryi* (magnolia), *Rheum palmatum* (turkey rhubarb), *Gentiana macrophylla* (std to gentiopicroside)
- Ferulic acid (natural phenolic in many plants)
- Meranzin hydrate in Traditional Chinese Medicine Chaihu-Shugan-San (CSS)
- XBP inc Motilin and movement (TCM as well)
  - 6 g of amomum villosum lour, 10 g of lindera aggregate (Sims) kosterm, 10 g of prunus persica, 9 g of panax ginseng, and 10 g of aeca catechu
- Ninjinto (Japanese Kampo med): increases motilin, gastrin and somatostatin
  - *Ginseng Radix* (3.0g), *Glycyrrhizae Radix* (3.0g), *Atractylodis* rhizoma (3.0g), and *Zingiberis Siccatum* Rhizoma (3.0g)

Prokinetic herb combos

- STW5: *Iberis amara, Metha piperita, Matricaria chamomilla, Glycyrrhiza glabra, Angelica archangelica, Corum carvi, Silybum morianum, melissa officinalis, Chelidonium majus*
- Da Cheng qi tang: *Rheum palmatum, Citrus Aurantii Fructus Immaturus* (immature bitter orange), *Magnolia henryi* , sodium sulfate
- Rikkunshito (Japanese formula, increases Motilin): *Glycyrrhizae radix, Zingiberis rhizoma, Atractylodis lanceae rhizoma* (18.6%), *Zizyphi fructus*, *Aurantii nobilis pericarpium* (satsuma), *Ginseng radix*, *Poria cocos* (Hoelen), *Pinelliae tuber* (contains ephedrine)

Anticholinergic medication

- Multiple classes of meds have anti-Ach effects
  - Used to treat cholinergic toxicity, urinary incontinence, Parkinson's disease, respiratory disorders, cardiovascular disease and more
  - Side effects include reduced gut motility, constipation, vomiting, reduced saliva and acid
- Antipsychotics, tricyclic antidepressants, diphenhydramine (Sleep?)
  - Scopolamine: antiemetic
  - Surgery meds: Vecuronium, Succinylcholine
  - Oxybutynin: urge incontinence and hyperhidrosis
  - Bupropion (Welbutrin), Paroxetine (Paxil)
  - Dextromethorphan: Cough suppressant
  - Hyoscyamine...

Hyoscyamine: Toxic botanical

- Naturally occurring alkaloid and biochemical precursor to scopolamine
  - Antagonist Muscarinic acetylcholine receptors
  - Related to atropine and hyoscine
  - Similar to other anti-Ach drugs like cyclobenzaprine (Flexeril Muscle relax), trihexyphenidyl (Parkinson's) and orphenadrine (muscle relax and antihistamine)
- Symptomatic relief spasms in various disorders including peptic ulcers, IBS, diverticulitis, pancreatitis, colic, IC, hyper· mucus secretion in lung disease and Parkinson's.
- Reduces secretions (acid, saliva, tears, mucus)
- Parasymp for heart and GI
- Lots of side effects! Mult nerves use it

Bowel Movement Consistency

- YOU HAVE TO FIGURE IT OUT!!!!! BM give you an indication of the entire process. Don't treat diarrhea or constipation without trying to figure out why first. That's what this lecture was about!
- Evaluate diet and water intake, including fiber
- Evaluate lifestyle, stress, dysbiosis, digestion
- Consider symptom complexes and stool testing
  - Gas: dysbiosis, SIBO, GI infections
  - Food just sits: acid
  - Greasy/Hard to Wipe stools: Bile
  - Anxiety: Sympathetic dominant
  - Pancreatic enzymes: incomplete digestion
  - Mental/emotional health
  - Underlying disease states

Bristol Stool Scale

Type 1	Separate hard lumps	**SEVERE CONSTIPATION**
Type 2	Lumpy and sausage like	**MILD CONSTIPATION**
Type 3	A sausage shape with cracks in the surface	**NORMAL**
Type 4	Like a smooth, soft sausage or snake	**NORMAL**
Type 5	Soft blobs with clear-cut edges	**LACKING FIBRE**
Type 6	Mushy consistency with ragged edges	**MILD DIARRHEA**
Type 7	Liquid consistency with no solid pieces	**SEVERE DIARRHEA**

Diarrhea

- Acute Diarrhea might be self limited
- Risks of dehydration or electrolyte replacement should be considered
- MD-land standard of care tends to treat symptomatically and assumes antibiotic therapy is not required in most patients.
- Diarrhea can be inflammatory or non-inflammatory
- Non inflammatory: absent of blood, pus, severe abdominal pain or fever.
- Inflammatory diarrhea: may include blood, mucus, pus, fever, leukocyte in stool, +lysozyme, + Calprotectin
  - Also includes non infectious etiology such as IBD & food reactions

Causes of Acute Infectious Diarrhea[legend]

Rotavirus	Shigella	Giardia lamblia
Norwalk virus	Salmonella	Entamoeba histolytica
Norwalk-like agents	Campylobacter	Cryptosporidium
Enteric adenovirus	Enterotoxigenic *Escherichia coli*	Cyclospora
Calcivirus	Enterohemorrhagic *E. coli*	
Astrovirus	Enteroinvasive *E. coli*	
Small round viruses	Enteropathogenic *E. coli*	
Coronavirus	Yersinia	
Herpes simplex virus	Clostridium difficile	
Cytomegalovirus	Clostridium perfringens	
	Staphylococcus aureus	
	Bacillus cereus	
	Vibrio	
	Chlamydia	
	Treponema pallidum	
	Neisseria gonorrhoeae	
	Aeromonas	
	Pleslomonas shigelloides	

Aranda-Michel J

Diarrhea Treatments

- Bismuth subsalicylate: stimulates intestinal sodium and water absorption, binds enterotoxins, antibacterial effects and anti-inflammatory
- Opiate and opiate derivatives : Loperamide (Imodium), diphenoxylate (often combined with atropine
- Binding agents: kaolin, clay (various types, ie green, bentonite or Kaopectate), charcoal
- Colostrum: Heal lining, complex biologic components. Infections, inflammation and injury. Helps to heal the lining
- Probiotics esp antibiotic associated diarrhea

Laxatives

- Types of laxatives:
- **Bulk forming laxatives**: Retain fluid and increase weight and consistency
- Fermentable fibers have prebiotic properties that helps some and aggravates others. Increases SCFA. Watch for gas/bloating!
  - Psyllium: Steve says tends to “dry” and help wet stools, although others say it's a constipation treatment and may be less fermentable
    - Tends to lower cholesterol better than others
  - Chia and flax: Mucilaginous, tends to lubricate constipation
  - Guar gum & Pectin: soluble, fermentable.
  - Non Fermentable : SIBO friendly doesn't inc gas. No prebiotic effect to feed flora
    - methylcellulose & Sterculia:

Laxatives

- **Osmotic laxative**: Poorly absorbable and draws water into the bowel. Bloating, N/V, diarrhea. Metabolic disturbances ie kidney and heart dysfunction
  - Magnesium citrate: Steve's fav!
  - Milk of magnesia, lactulose, sorbitol, polyethylene glycol (PEG, petroleum derivative made from ethylene glycol).
- **Prokinetic agents**: Cisapride (d/c), Tegaserod (D/c), Prucalopride, metoclopramide (extrapyramidal sx), cisapride, pyridostigmine. Headaches, nausea
  - Side effects! Neurotransmitter modulators get removed from market frequently due to side effect ie movement disorders and heart effects.
- **Lubricant**: Mineral oil by lubricating, historically common for kids with low side effect but PEG is now recommended. (aspiration and lipid pneumonia)

Laxatives

- **Stimulant:** stimulate the myenteric plexus (Auerbach plexus) to increase secretions and motility. Decrease water absorption. Cramps
  - Bisacodyl, *Senna*, *Rhamnus purshiana* (cascara*)*, sodium picosulfate
    - Senna and cascara are herbal
    - Can be addictive, Can build tolerance. Neuronal or muscular injury inn chronic use
- **Surface active agents:** Docusate lowers surface tension leading to water and fat penetrating the stools
- Confusing (and brand name warning):
  - Ducolax laxative is bisacodyl and Ducolax stool softener is Ducosate. The later being safer and non addictive
  - Blue box says stimulant free on it!

Laxatives

- **Guanylate cyclase agonist:** linaclotide (Linzess) & plecanatide (less diarrhea); Increases enzyme activity of glutamate and Ach which leads to water and electrolyte secretion into the lumen
- **Chloride Channel Activator:** Lubiprostone. Leads to water and chloride secretion
- Laxative abuse ie in anorexia and bulimia. Can lead to mineral imbalance hyponatremia, hypokalemia, hyperuricemia, hyperaldosteronism (aldosterone saves Na+ and loses K+), dehydration, renal insufficiency
- Constipation is common in the elderly esp in Hospital stays.

Diverticular disease

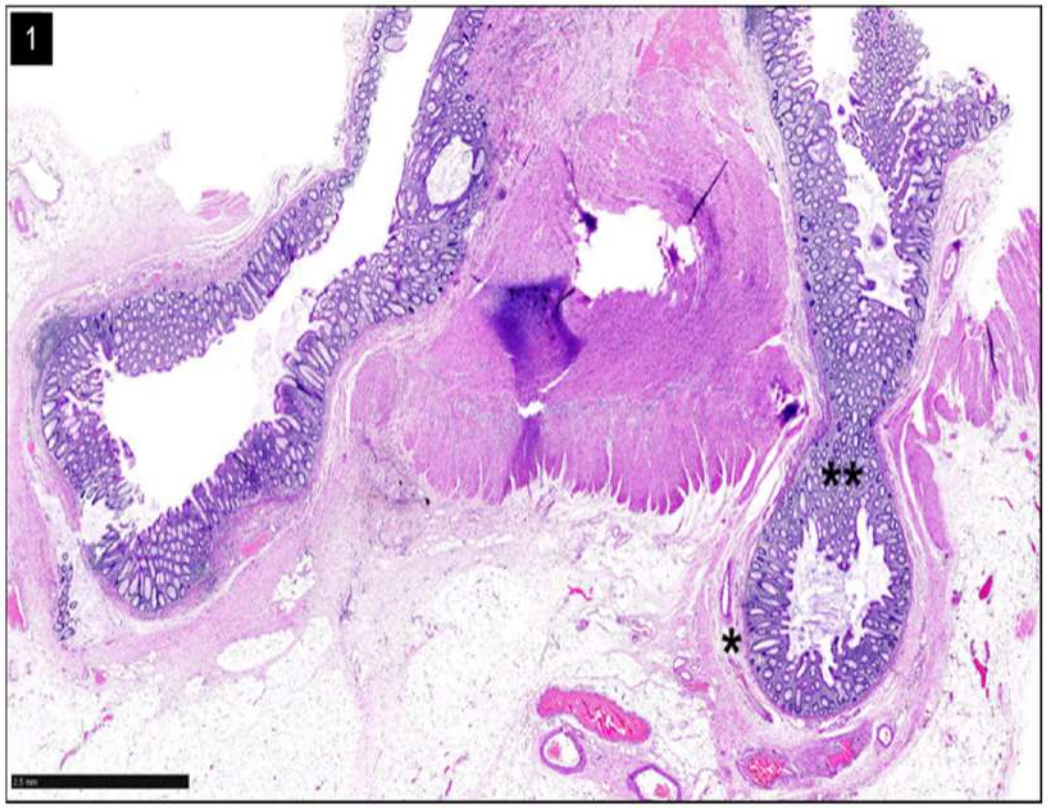
- One of the most common GI conditions. 1:7 diagnosis in the US is diverticular disease
- 50% of Americans over 60yo have diverticulosis, almost all at 80yo.
- Diverticula are sac like protrusions of the colonic wall. Left sided more common in the west and right sided more common in Asian countries.
- Risk factors: diet, lifestyle, medication, age, colonic motility, colonic microbiota, genetic factors, change in colonic structures
- “Ischemic theory”: (not fecal entrapment) Colonic motility. Recurrent contract impulse of the colon results in persistent compression leading to ischemia and microperforation
  - Associated with decreased SCFA and *Akkermansia*
    - *Akkermansia;* A mucin degrading bacteria that suppresses inflammation

Diverticulitis

- Diverticular disease is a continuum of diverticular pockets and associated symptoms
- Diverticular disease (not -itis) can include bleeding, inflammation, cramps, hematochezia, diarrhea
- Diverticulitis is increased acute inflammation of the diverticulum
  - Localized, generally pinpoint pain.
- The lifetime risk of diverticulitis in a person w/ diverticular disease is 5% with an increasing incidence (getting more common)
- Diverticulitis increased risk factors: NSAIDS, steroids, opiates, obesity and smoking increase risk, low fiber, lack of exercise
- Lack of fiber, sedentary lifestyle, high meat, low fruits and veggies...Standard American Diet

Diverticulitis

Figure 1. Diverticulosis: Hematoxylin and eosin (H&E) stain shows the colonic mucosa (**) and submucosa (*) protruding through the muscularis propria in the sigmoid colon (H&E, ×15).



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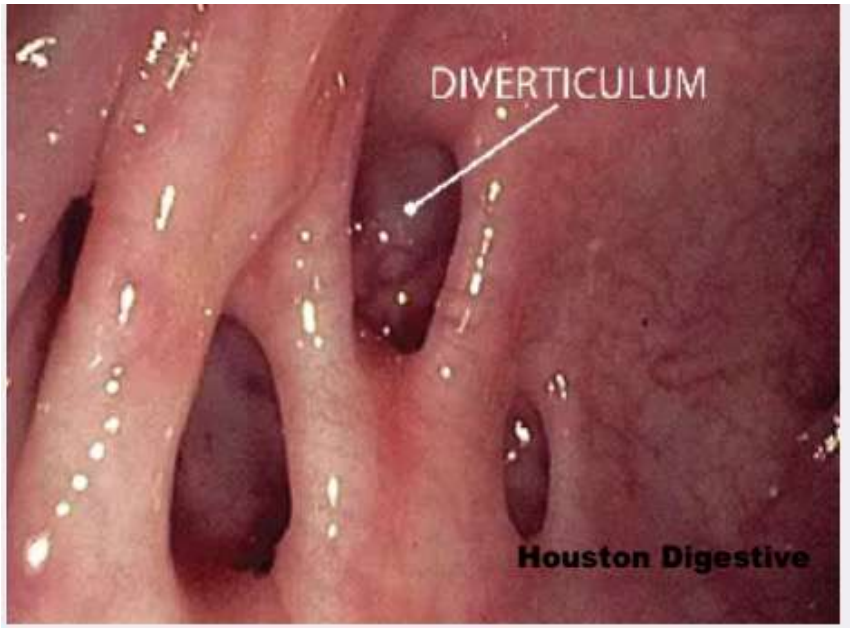

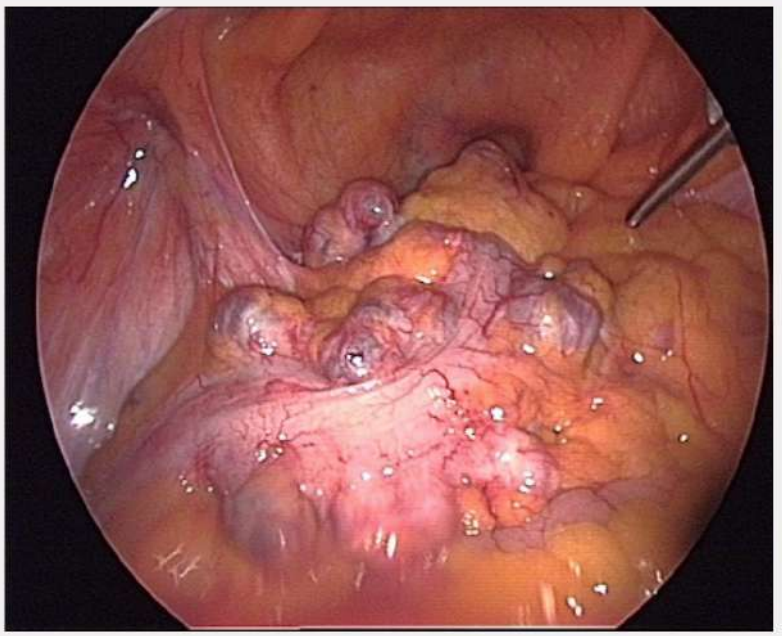

Diverticulitis [1]

Operative review

Diverticulitis Treatments

- Uncomplicated diverticulitis: 90% cases. Localized inflammation limited to the colonic wall. Fever, abd pain, leukocytosis
  - Evolving treatment toward not using antibiotics
  - Std of care: Clear liquid or normal diet, oral broad-spectrum antibiotic ie clav-amox, cipro or metronidazole 7-14 days. 10% progress to hospitalization
- Complicated: includes perforation, local or distal abscess, fistula, structure or obstruction
  - Hospitalization w/ bowel rest, IV antibiotics, IV fluid. Abscesses drained
  - 25% have a recurrent episode. Abscess >3-5cm=↑relapse
  - Surgical removal is also being debated
- Steroids are sometimes used

Steve's Diverticulitis Treatment

- Brings the lecture together!
- Antimicrobial herbs: C. myrrh, *Hydrastis*, *Berberis*, *Artemesia*, *Juglans nigra* (tend to be high alcohol extract that form waxy ppt when aqueous solution)
- Anti-inflam: *Curcuma*, *Boswellia*, *Zanthoxylum*, *Glycyrrhiza*, *Smilax ornata*, *M. chamomilla*
- Glutamine: 3 grams mixed into water sipped, 1X/day when gut is well and up to 3X/day or more if GI upset
- Anti-inflam smoothies. Premade products or home made. Cooked smooth foods. Bone broth.
- Probiotics: Usually high potency, broad spectrum. Minimal prebiotics. No extra herbs in the probiotics
- Optional: colostrum, Butyric acid, Cramp/muscle spasm herbs (*Kava*, *Viburnum opulus*, *Valeriana*, *Corydalis*, *Piscidia*)
- Make sure they have a “diverticulitis tincture” to have at home which is a mix of the antimicrobials & anti-inflam. Start early!

Few Clinical Pearls

- *C. Diff* toxin can show up on a stool test without severe diarrhea. MD-Land will only test C diff toxin w/ severe diarrhea, but it shows up on send out tests.
- Visceral adhesions can cause chronic pain. These require physical medicine modalities
- You need optimized gut to have optimized mental/emotional health. You can't separate them
- Digestion is always improved with empowerment and education. There is fear if you don't know why it isn't working.
- Therapeutic treatment trials are necessary to help diagnose the problem
- Prepare people to “manage digestion” with tools. It's complicated. Optimize to “recovery time”. ie. It used to take 2 weeks to recover and now it's 1 day...

In Closing

- 61% American report having a GI symptoms in the past week!
- “Anxiety is a prediction of the future, based by our past, colored by our affect.” -Dr. Lisa Feldman Barrett PhD
  - People who feel badly perceive the future with increase anxiety. Institutions capitalize on that anxiety to control people
- *Docere*: to teach. We should be teaching the “human manual” to people so they can engage in their own health improvement
  - “Greatest American Hero” health care
- “I feel” the current solution to the “Human Crisis” of anger, anxiety, fear and divisive politics is to improve digestion, absorption and assimilation of life, so we can all be happy, productive and have improved sense of safety.
- The American Dream should include “Wellness Freedom” and to do that we ALL have to understand and engage in how health and wellness works...as well as the science behind proper disease management and preventive tools