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Pediatric GI Potpourri

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Pediatric Gastroenterology

February 11, 2025

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No Disclosures

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Objectives

- Discuss updates on functional GI disorders
- Discuss the evolving landscape of eosinophilic GI disorders
- Describe new and upcoming therapies for pediatric IBD

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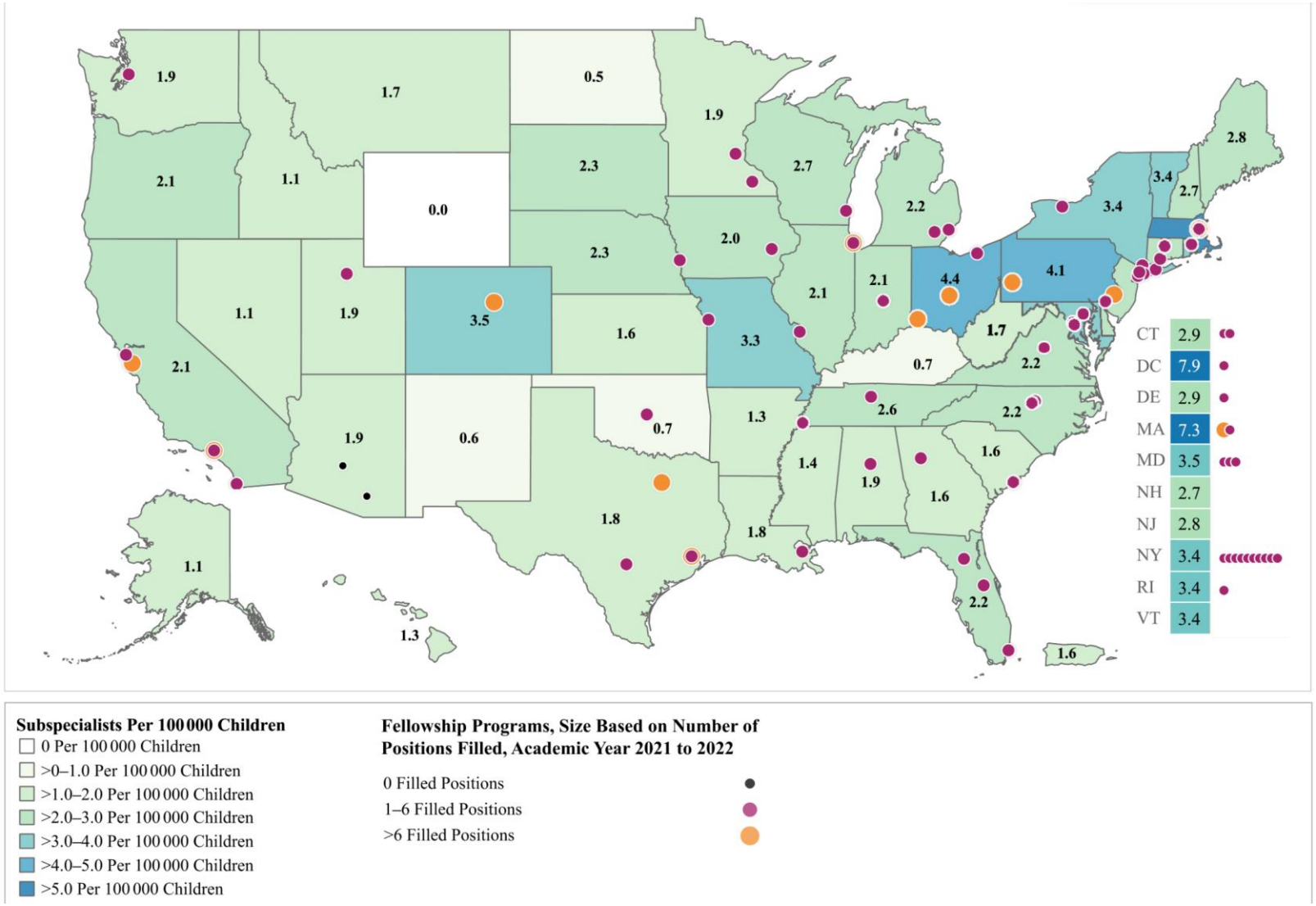
Pediatric GI Disorders on the rise….

- The prevalence of various pediatric GI disorders have been increasing:
  - Inflammatory bowel disease *
    - Very early onset IBD
  - Eosinophilic disorders **
  - Celiac disease ***
  - Obesity and related consequences including metabolic dysfunction associated steatotic liver disease ****
  - Functional GI disorders *****
  - Constipation *****

- (Coward S, et. al. 2019)
** (Navarro P, et al. 2019)
*** (Lebwohl B, Rubio-Tapia A. 2020)
**** (Cunningham Sa et. al. 2022)
***** (Zia JK, et al. 2022)



Cary G. Sauer, John A. Barnard, Robert J. Vinci, Jennifer A. Strople; Child Health Needs and the Pediatric Gastroenterology Workforce: 2020–2040. *Pediatrics* February 2024; 153 (Supplement 2): e2023063678K. 10.1542/peds.2023-063678K

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Functional GI Disorders

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What is in a name?

- Functional gastrointestinal disorders (FGID) = Disorders of the gut-brain interaction (DGBI)

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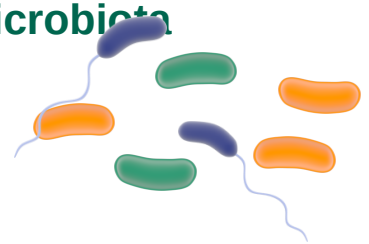
Psychological factors

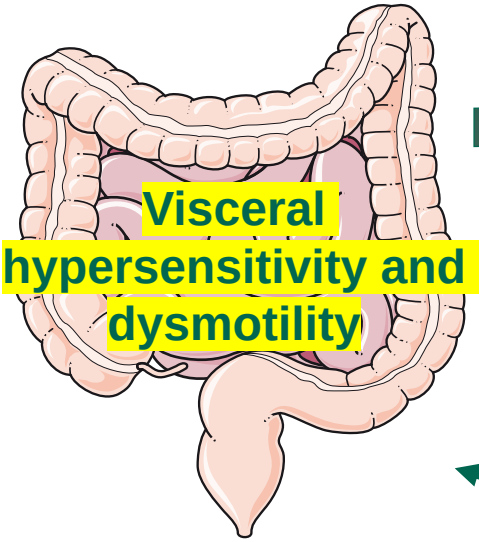
- Hospitalization
- Separation from a best friend
- Failure in an examination
- Loss of parent's job
- Abuse

Gut-Brain Axis

Genetic Predisposition

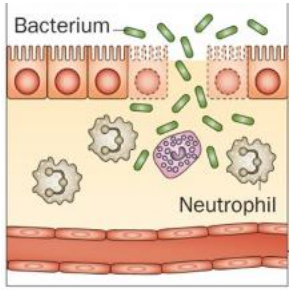
Alterations of gut microbiota

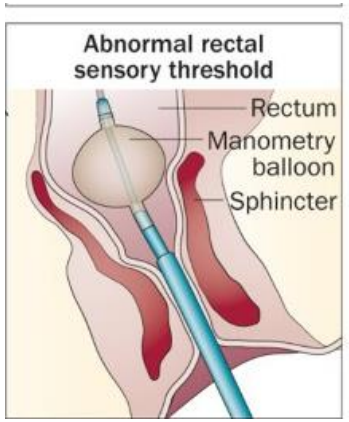




Visceral hypersensitivity and dysmotility

Gastrointestinal Infections





Functional Abdominal Pain

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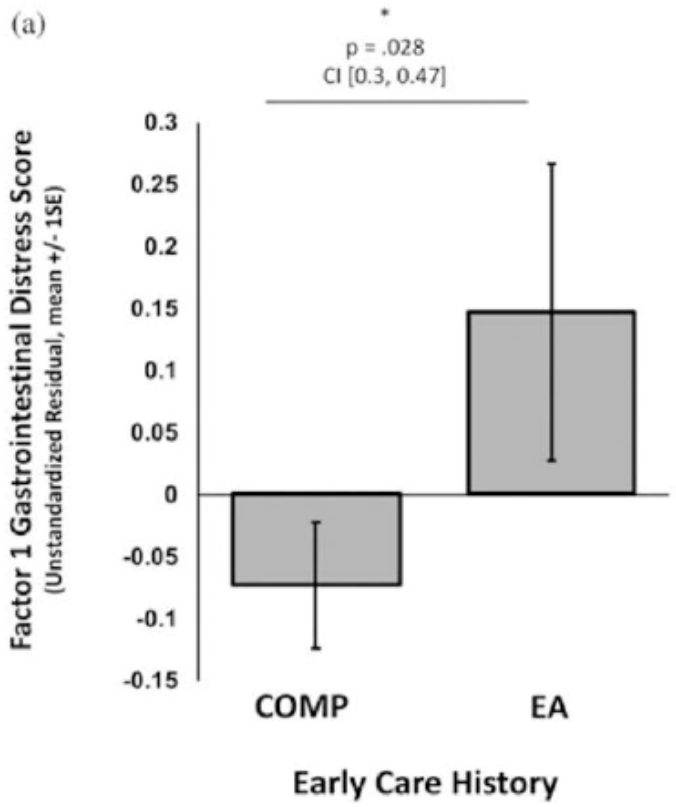
Role of early events



(Callaghan et. al 2020)

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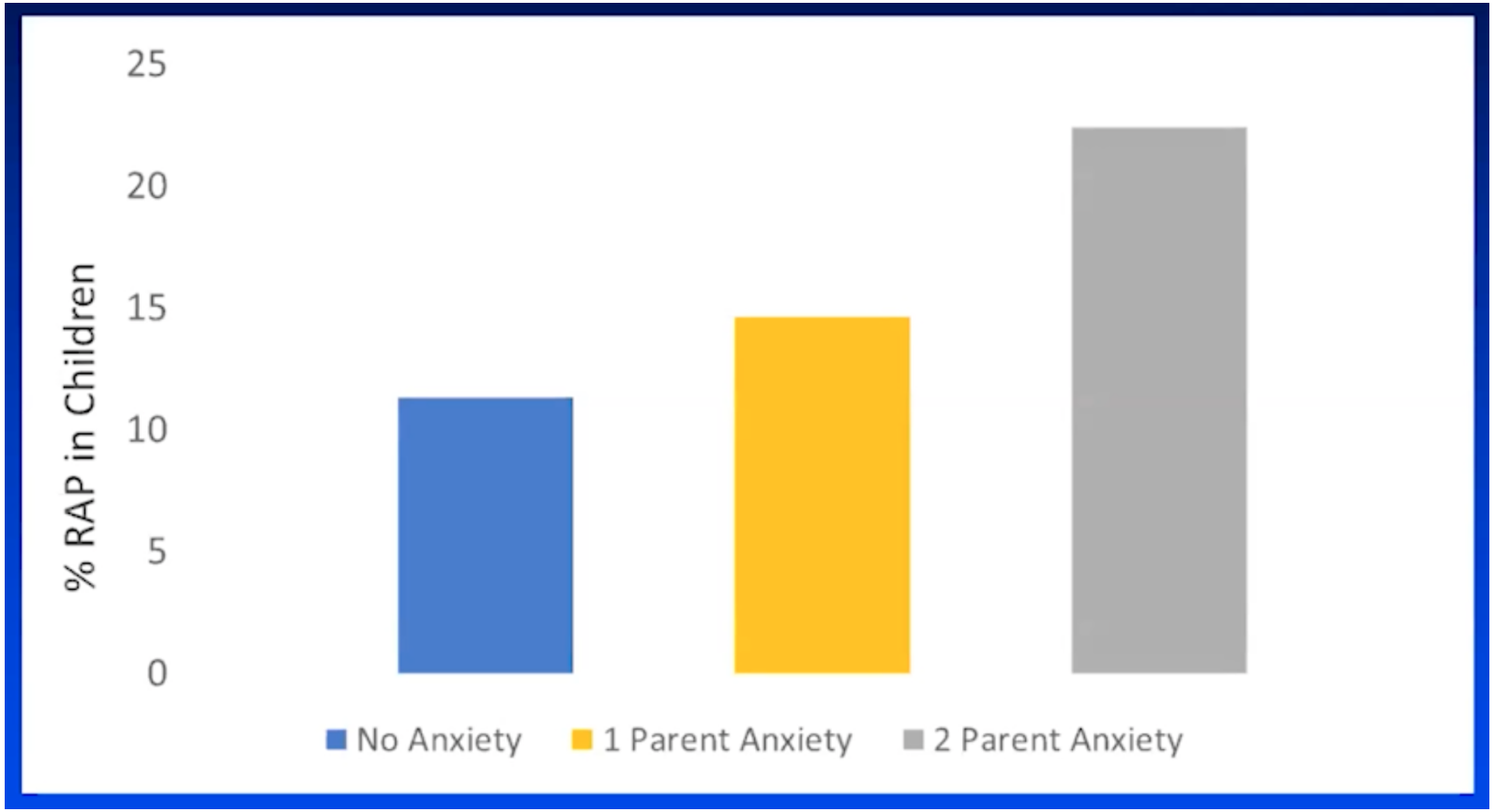
Role of parental anxiety



Ramchandani PG et al J Am

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- A confident and prompt diagnosis is an important first step to make the bowel less irritable!

pISSN: 2234-8646 eISSN: 2234-8840
https://doi.org/10.5223/pghn.2018.21.4.264
Pediatr Gastroenterol Hepatol Nutr 2018 October 21(4):264-270

Original Article

PGHN

Initial Diagnosis of Functional Gastrointestinal Disorders in Children Increases a Chance for Resolution of Symptoms

Ivana Trivić* and Iva Hojsak*,†,‡

*Referral Centre for Pediatric Gastroenterology and Nutrition, Children's Hospital Zagreb, †School of Medicine, University of Zagreb, Zagreb, ‡School of Medicine, University J.J. Strossmayer of Osijek, Osijek, Croatia

Table 3. Prognostic Factors for Symptom Improvement

Variable	Hazard ratio	95% confidence inverval
Sex (male as a reference)	1.628	0.912-2.908
Age at diagnosis	1.018	0.946-1.096
Functional diagnosis from the beginning	2.163	1.029-4.544

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Delivery is key

- Acknowledge patient's pain
- Explain the importance of the gut-brain axis in pathophysiology of functional abdominal pain
- Reassurance, reassurance, reassurance

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How do we diagnose disorders of the gut brain interaction?

- Rome Foundation: “independent not-for-profit organization dedicated to supporting the creation of scientific data and educational information to assist in diagnosing and treating Disorders of Gut-Brain Interaction”
- Bring together scientists and clinicians to appraise the science of DGBIs and make recommendations for diagnosis and treatment

Gastroenterology 2016;150:1456–1468

Childhood Functional Gastrointestinal Disorders: Child/ Adolescent

Jeffrey S. Hyams,[1,*] **Carlo Di Lorenzo,**[2,*] Miguel Saps,[2] Robert J. Shulman,[3] Annamaria Staiano,[4] and Miranda van Tilburg[5]

[1]*Division of Digestive Diseases, Hepatology, and Nutrition, Connecticut Children's Medical Center, Hartford, Connecticut;* [2]*Division of Digestive Diseases, Hepatology, and Nutrition, Nationwide Children's Hospital, Columbus, Ohio;* [3]*Baylor College of Medicine, Children's Nutrition Research Center, Texas Children's Hospital, Houston, Texas;* [4]*Department of Translational Science, Section of Pediatrics, University of Naples, Federico II, Naples, Italy; and* [5]*Department of Gastroenterology and Hepatology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina*

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Rome IV Criteria

- Removed the dictum that there was “no evidence for organic disease” and replaced with “after appropriate medical evaluation the symptoms cannot be attributed to another medical condition.”
  - Supports symptom based diagnosis rather than diagnosis only when organic disease has been excluded
- Functional nausea and functional vomiting are described
- Functional abdominal pain NOS
  - Describes children who do not fit a specific disorder such as IBS, functional dyspepsia, or abdominal migraine

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Treatment of DGBIs

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What about pharmacotherapies?

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FDA approved drugs for treatment of IBS in Adults

- In 2006: None
- In 2025:
  - IBS-D: alosetron, eluxadoline, rifaximin
  - IBS-C: Lubiprostone, linaclotide, prucalopride, tenapanor, tegaserod

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FDA approved drugs for treatment of IBS in Children

- In 2025: Linaclotide

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Available pharmacotherapies

- Anti-spasmodics
  - Dicyclomine
  - Hyoscyamine
- Neuromodulators
  - TCAs
    - Amitriptyline
  - SSRIs
    - Citalopram
- Anti-histamines
  - Cyproheptadine
  - Hydroxyzine
- Prokinetics
  - Erythromycin
  - Metoclopramide

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What about diet and psychotherapy?

- Well defined strategies
- Attractive to parents and families
- Efficacy for all symptoms in 75%
- Self- empowering

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Low FODMAP diet

- **F**ermentable
- **O**ligosaccharides
- **D**isaccharides
- **M**onosaccharides
- **A**nd
- **P**olyols

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Low FODMAP diet

- Developed over 10 years ago at Monash University in Australia
- Aims to reduce the amount of fermentable carbohydrates consumed in the diet
- Part 1: Elimination of high FODMAP foods (6 weeks)
- Part 2: Reintroduction of high FODMAP foods
- Goal: Determine if patient has trigger foods

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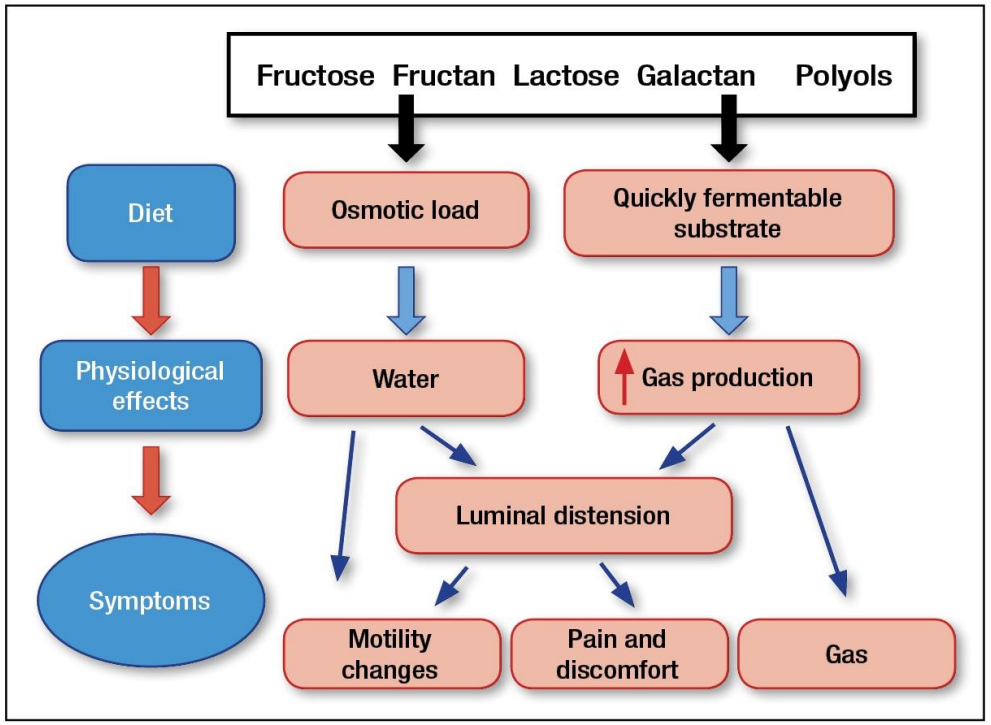
Theory behind the diet



+/- Induction of visceral hypersensitivity

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HIGH-FODMAP FOODS TO AVOID

FRUCTOSE

Fruit:

Apple, mango, pear, tinned fruit in juice, cherries, watermelon, banana (ripe)

Sweeteners:

Fructose, high fructose corn syrup

Hone

Large doses of total fructose:

Fruit juices, large serves of fruit, dried fruit, fruit juice concentrate

LACTOSE

Milk:

Cow, goat, or sheep milks, custard, condensed milk ice cream, yoghurt, buttermilk, kefir, milk from soy beans (milk from soy protein is ok)

Cheeses:

Soft/unripened cheese i.e. cottage, cream, mascarpone, ricotta

FRUCTANS

Vegetables:

Asparagus, beetroot, broccoli, cabbage, brussels sprouts, eggplant, garlic leek, onion, okra, fennel, shallots, spring onion

Cereals:

Large amounts of wheat and rye, such as in bread, cookies, pasta, crackers, couscous

Fruit:

Custard apple, watermelon, persimmon, dates, grapefruit

Miscellaneous:

Inulin, chicory, pistachio

GALACTANS

(AKA: GOS or galacto-oligosaccharides)

Legumes:

Baked beans, chickpeas, lentils, soy beans, kidney beans, hummus, cashews

POLYOLS

Fruit:

Apple, apricot, avocado, blackberry, cherry, lychee, pear, peach, plum, prune, watermelon, nectarine

Vegetables:

Cauliflower, green capsicum, mushroom, sweet corn

Sweeteners:

Sorbitol (420)
Mannitol (421)
Isomalt (952)
Maltitol (965)
Xylitol (967)

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Who may not be a good candidate?

- Picky eaters
- History of disordered eating
- Already on a restrictive diet (vegan, SCD, etc)
- Low health/nutrition literacy
- Disinterest in nutrition/cooking
- Receiving school breakfast and/or lunch (if family is unable to provide food from home)
- High intake of fast food or take out

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Who is a good candidate?

- IBS
- Wide variety of food intake
- Interest in nutrition
- Resources to understand and maintain the diet
  - i.e good health literacy, basic nutrition/cooking knowledge, ability to find/purchase specialty products

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Does it work?

- Adults with IBS
  - Randomized controlled blinded study
  - Randomized to regular (Australian) diet vs. low FODMAP diet → washout period → cross-over alternate diet
  - Results
    - Subjects with IBS had lower GI symptom scores (22.8; 95% confidence interval, 16.7-28.8) while on diet low in FODMAPS as compared to those on standard Australian diet (44.9, 95% confidence interval, 36.6-53.1, P<0.001)
    - No effect on control subjects

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AP&T Alimentary Pharmacology and Therapeutics

Randomised clinical trial: gut microbiome biomarkers are associated with clinical response to a low FODMAP diet in children with the irritable bowel syndrome

B. P. Chumpitazi*, J. L. Cope[‡,§], E. B. Hollister[‡,§], C. M. Tsai*, A. R. McMeans[†], R. A. Luna[‡,§], J. Versalovic[‡,§] & R. J. Shulman*,[†]

- 33 children completed the study
- Less abdominal pain occurred during the low FODMAP diet vs. TACD
- Compared to baseline, children had fewer daily abdominal pain episodes during the low FODMAP diet but more episodes during the TACD

Responders were enriched at baseline in taxa with known greater saccharolytic metabolic capacity (Bacteroides, Ruminococcaceae, Faecalibacterium prausnitzii)

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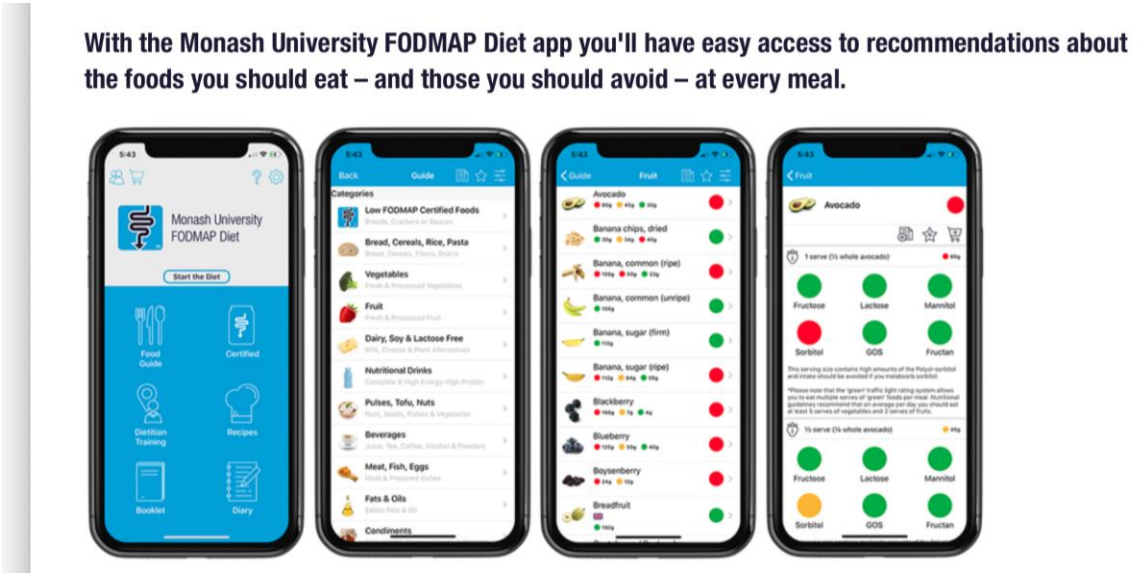
What resources should be given to families?

- Access to dietician/provider knowledgeable about low FODMAP diets
- Low and High FODMAP food lists
- Meal ideas and recipes
- Reliable online/app resources
  – Monash university



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What other options are there?

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Clinical and Cost Effectiveness of Online Cognitive Behavioral Therapy in Children With Functional Abdominal Pain Disorders

Maria Lalouni,[*,‡] Brjánn Ljótsson,[§,‖] Marianne Bonnert,[‡,§,¶] Richard Ssegonja,[#] Marc Benninga,[**] Johan Bjureberg,[‖] Jens Högström,[‡,‖] Hanna Sahlin,[‖] Magnus Simrén,[‡‡,§§] Inna Feldman,[#] Erik Hedman-Lagerlöf,[§,‖‖] Eva Serlachius,[‡,‖] and Ola Olén[*,¶¶]

[*]Department of Medicine, Solna, [‖‖]Osher Center for Integrative Medicine, [§]Division of Psychology, [‖]Center for Psychiatry Research, Department of Clinical Neuroscience, [¶]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; [‡]Stockholm Health Care Services, Stockholm County Council, Stockholm, Sweden; [#]Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden; [**]Department of Paediatric Gastroenterology and Nutrition, Emma Children's Hospital/Academic Medical Center, Amsterdam, The Netherlands; [‡‡]Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg,Gothenburg, Sweden; [§§]Center for Functional Gastrointestinal and Motility Disorders, University of North Carolina, Chapel Hill, North Carolina; [¶¶]Department of Pediatric Gastroenterology and Nutrition, Sachs' Children's Hospital, Stockholm, Sweden

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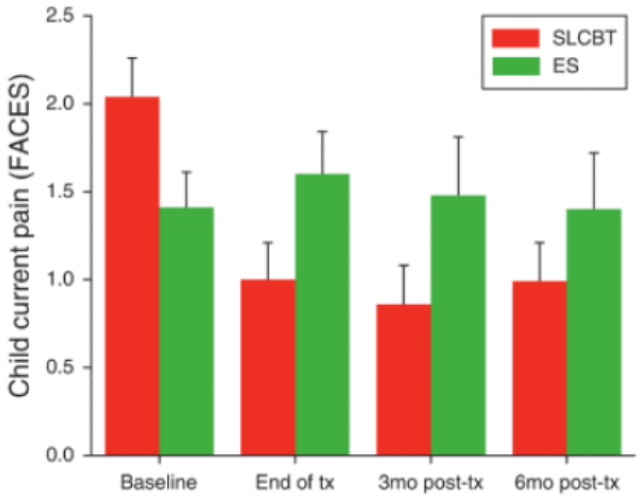
CBT also teaches parents



Study: 200 children between 7-17y, 3 session intervention of cognitive-behavioral treatment targeting parents' response to their children's pain complaints and children's coping responses

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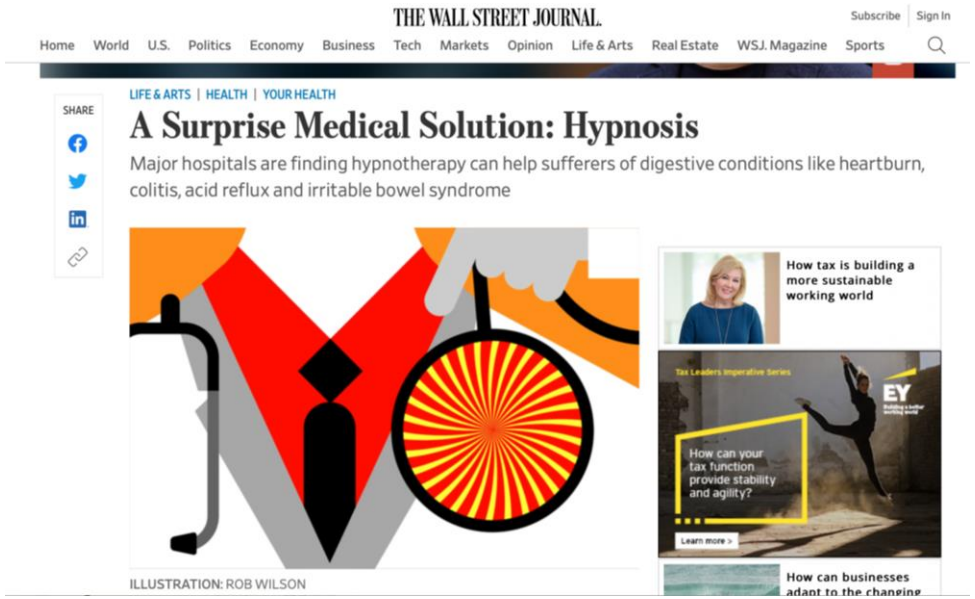
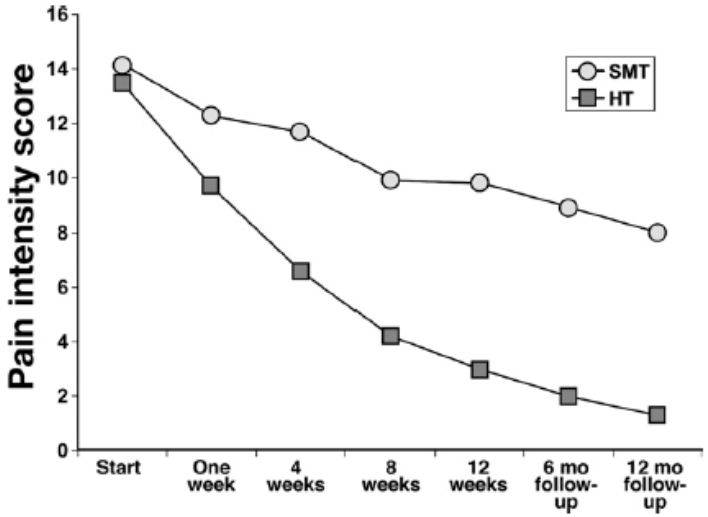
Hypnotherapy

- Uses hypnosis to create a state of focused attention during which guided imagery and positive suggestions can be used to help patients deal with a variety of concerns and issues.





Vlieger et. al. Gastroenterology 2007; 133: 1430-1436

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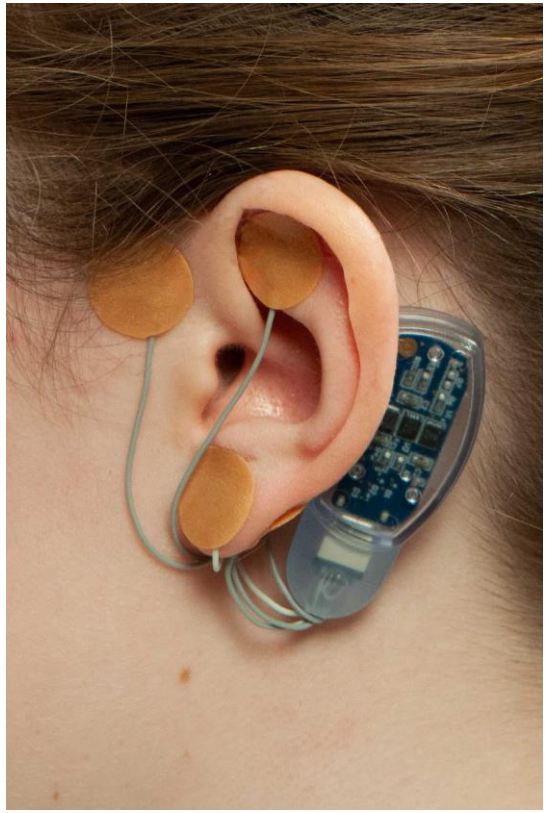
Neurostimulation

- **FDA approved** for use in patients 11-18 years for treatment of IBS
- Works via stimulation of peripheral cranial neurovascular bundles in the external ear

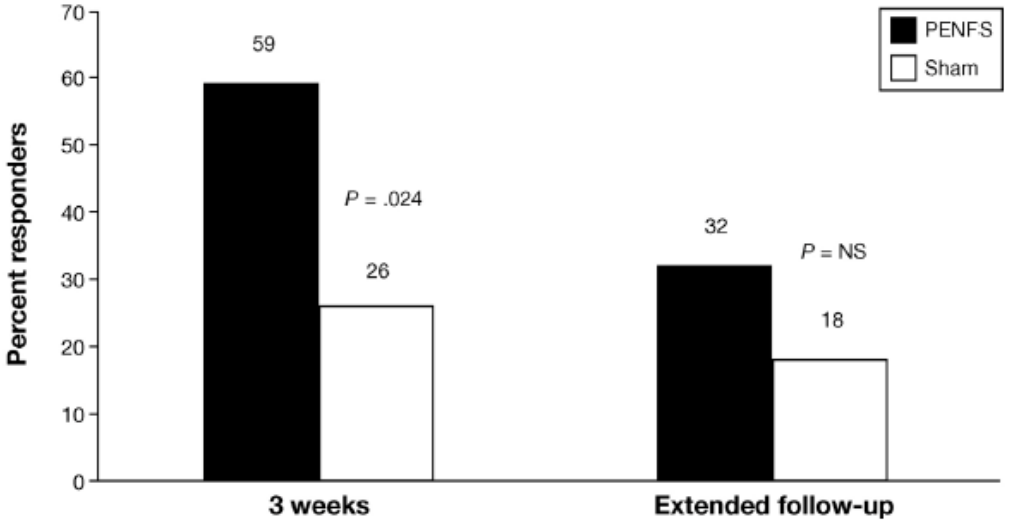


Neurostimulation

Efficacy of Auricular Neurostimulation in Adolescents With Irritable Bowel Syndrome in a Randomized, Double-Blind Trial

Amornluck Krasaelap,* Manu R. Sood,‡ B U. K. Li,* Rachel Unteutsch,* Ke Yan,‡ Melodee Nugent,‡ Pippa Simpson,‡ and Katja Kovacic*

*Division of Pediatric Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Medical College of Wisconsin, Milwaukee, Wisconsin; and ‡Division of Quantitative Health Sciences, Department of Pediatrics, Medical College of Wisconsin, Milwaukee, Wisconsin



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Eosinophilic GI Disorders (EGIDs)

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Eosinophilic Esophagitis (EoE)

- Overview of EoE
  - Chronic, relapsing, immune-mediated esophageal disease characterized by eosinophilic infiltration of the esophagus
  - Prevalence ~ 1:1000 people
  - Up to 23% of EGDs for dysphagia reveal EoE
  - >50% of foods impactions are due to EoE

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1995 Distribution of EoE

2013 Distribution of EoE

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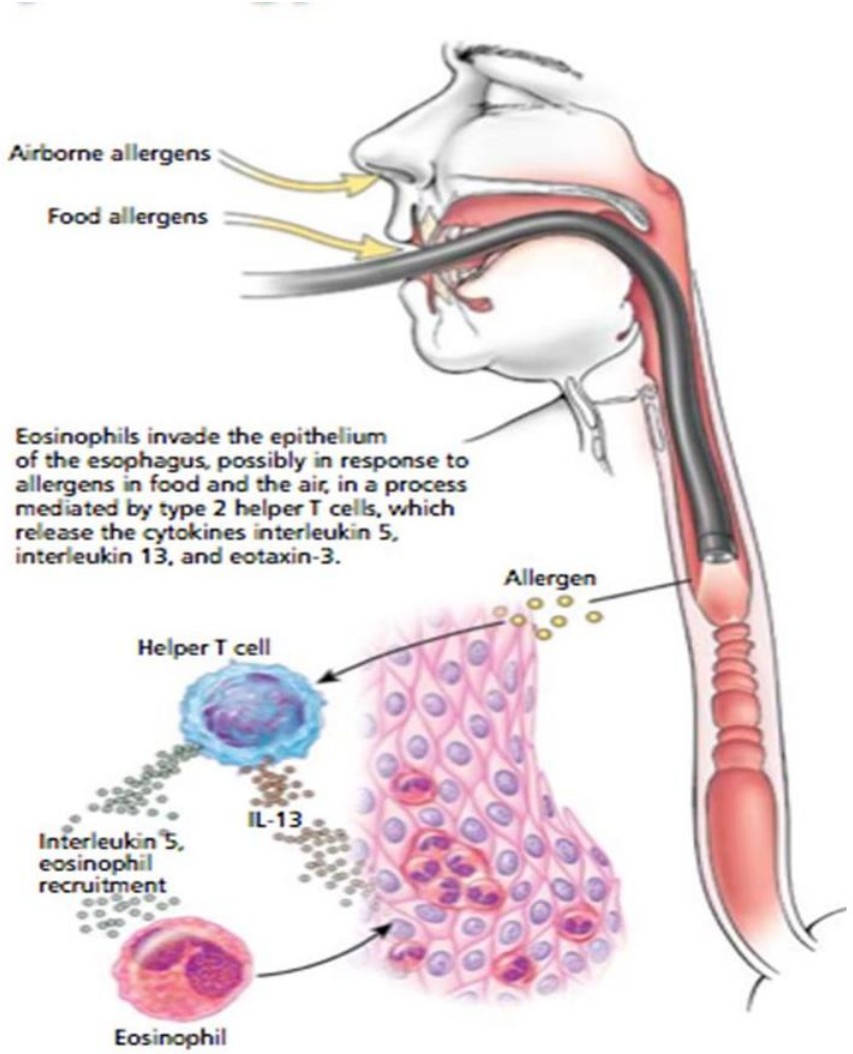
What causes EoE?

- Intraluminal allergen exposure
  - Predominately food antigens
- Mucosal production of eosinophilic chemo-attractants
- Influx of eosinophils
- Release of inflammatory mediators
- Esophageal dysfunction



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EoE and Atopy

- Asthma, allergic rhinitis, atopic dermatitis and IgE mediated food allergies are common and increasing in the general population
- Patients with eosinophilic gastrointestinal disorders have a higher prevalence of all atopic disorders
- Studies report between 50% to 93% of EoE patients have some type of atopic disorder
  - Rise in EoE mirrors rise in atopy
  - Atopy much more common in patients with EoE

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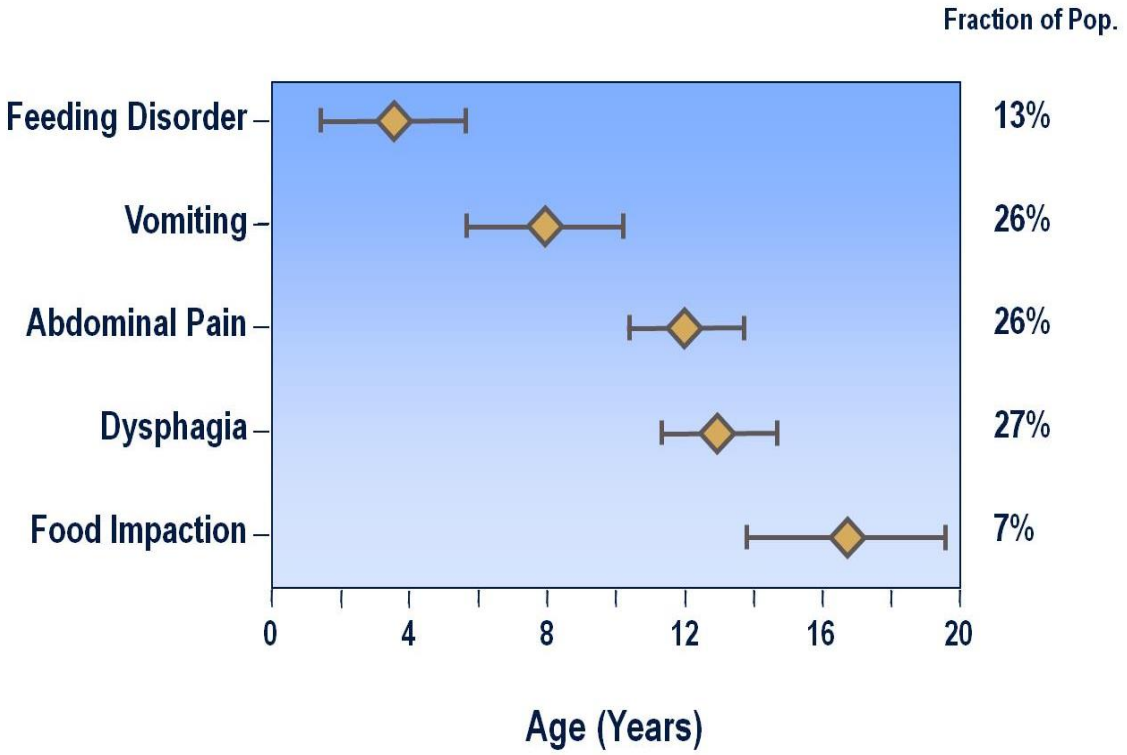
Variable presentation of EoE



Noel et al. N Engl J Med. 2004; 351: 940-941

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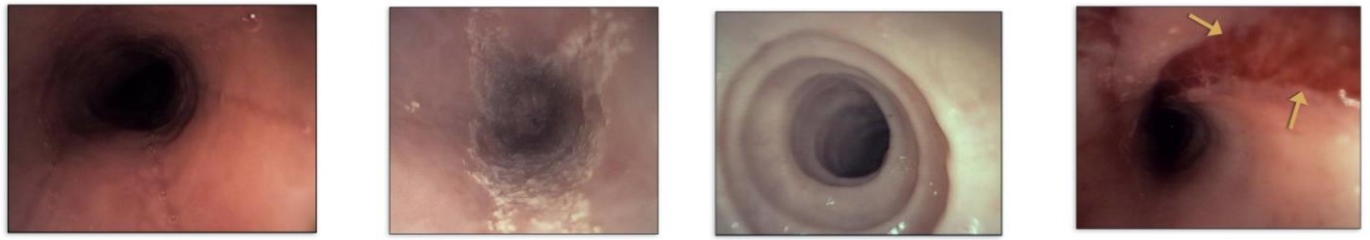
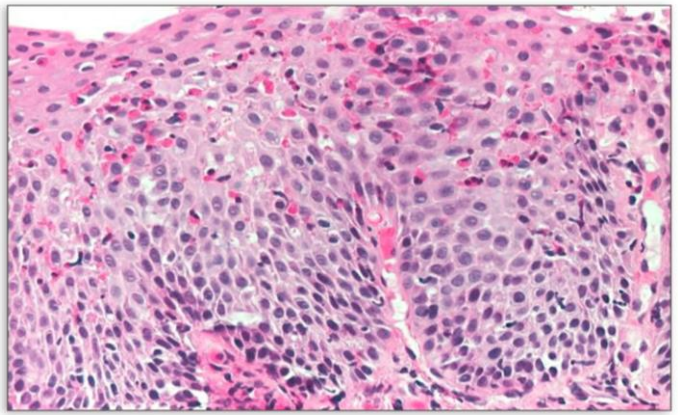
Diagnosis

- Endoscopy



- Histology
  - >15 eosinophils per HPF



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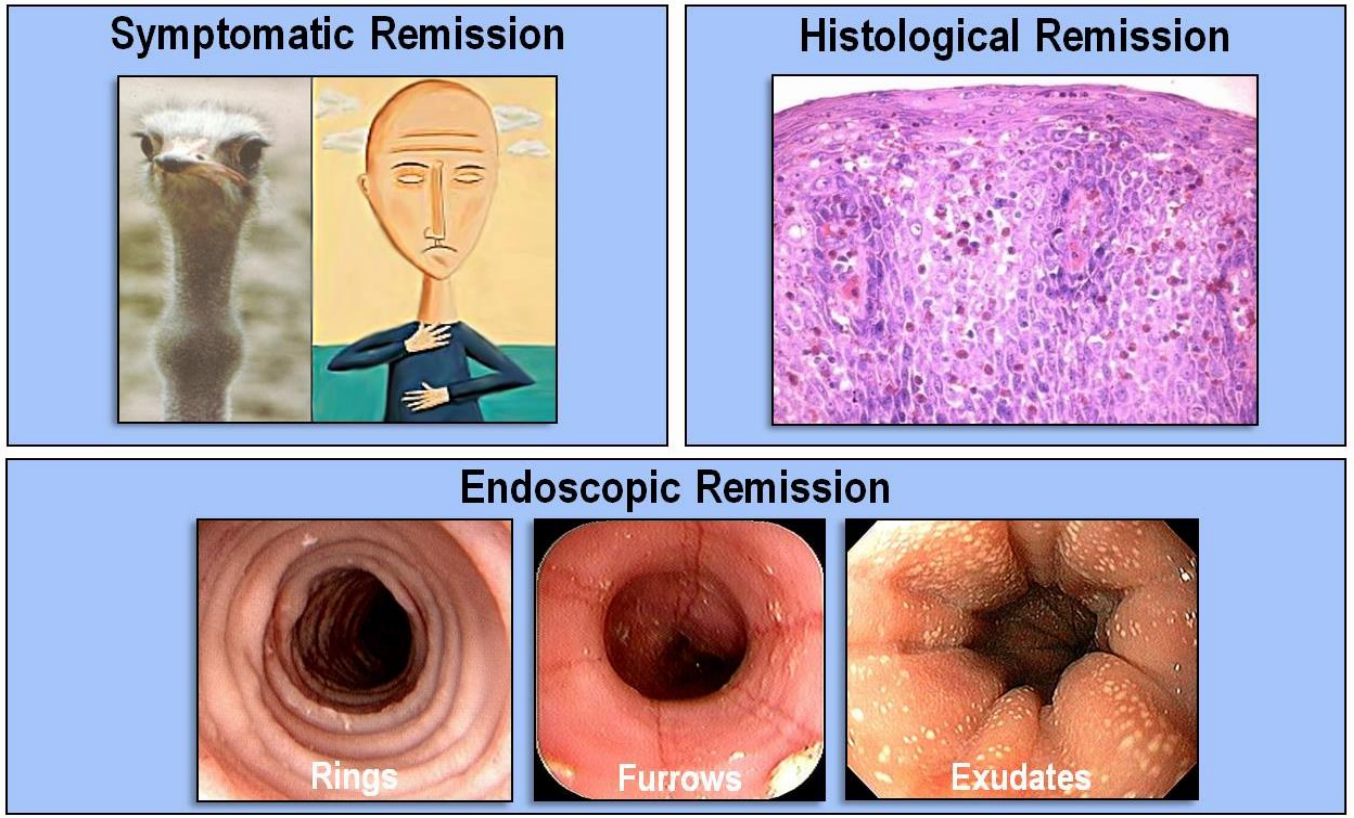
Treatment Goals for EoE



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EoE Treatments

- Traditional treatment options
  - PPI
  - Diet
  - Swallowed steroids

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Proton Pump Inhibitors

- Standard dose = High dose (ex. Omeprazole 40mg BID)
- Can consider dose reduction for maintenance
- Efficacy 40-50%
- Most patients are started on PPIs as initial treatment choice

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Swallowed steroids

- Budesonide
  - Respule mixed with Splenda or other vehicle to make oral slurry
  - FDA approved an oral suspension specifically for EoE (2024)
- Fluticasone
- Rince mouth after use (to avoid thrush)
- Avoid food/water for 30 minutes after each dose
- Few studies on long term effects

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Dietary Therapies

- Traditional:
  - 6 food elimination:
    - Dairy, wheat, soy, egg, tree nuts, seafood
    - Histologic remission in about 61%
  - Elemental formula
- Newer Dietary therapies
  - 4 food eliminations
    - Dairy, wheat, soy, egg
    - Histologic remission in up to 50% of patients
  - Dairy elimination
    - Histologic remission in up to 51%

Mayerhofer C, Kavallar AM, Aldrian D, Lindner AK, Müller T, Vogel GF. Efficacy of Elimination Diets in Eosinophilic Esophagitis: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2023 Aug;21(9):2197-2210.e3. doi: 10.1016/j.cgh.2023.01.019. Epub 2023 Jan 31. PMID: 36731591.

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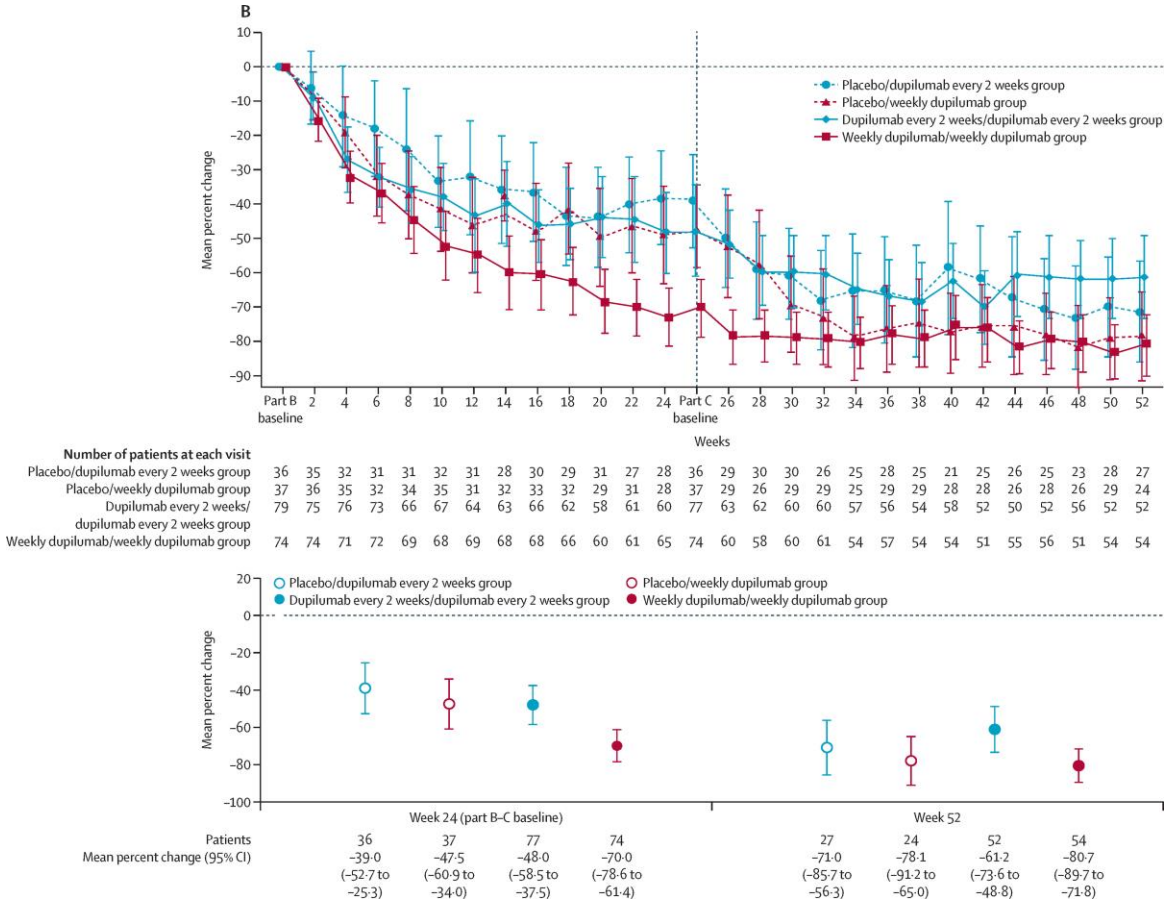
Eosinophilic Esophagitis

- Dupilumab (Dupixent)
  - Mechanism
    - IL4 receptor antagonist
    - Also blocks IL-13 activity
  - Dosing
    - SubQ weekly injection
    - Pen vs. syringe
  - Approved down to age 1
  - Good safety profile, no routine lab monitoring required



(Rothenberg ME, et. al 2023)

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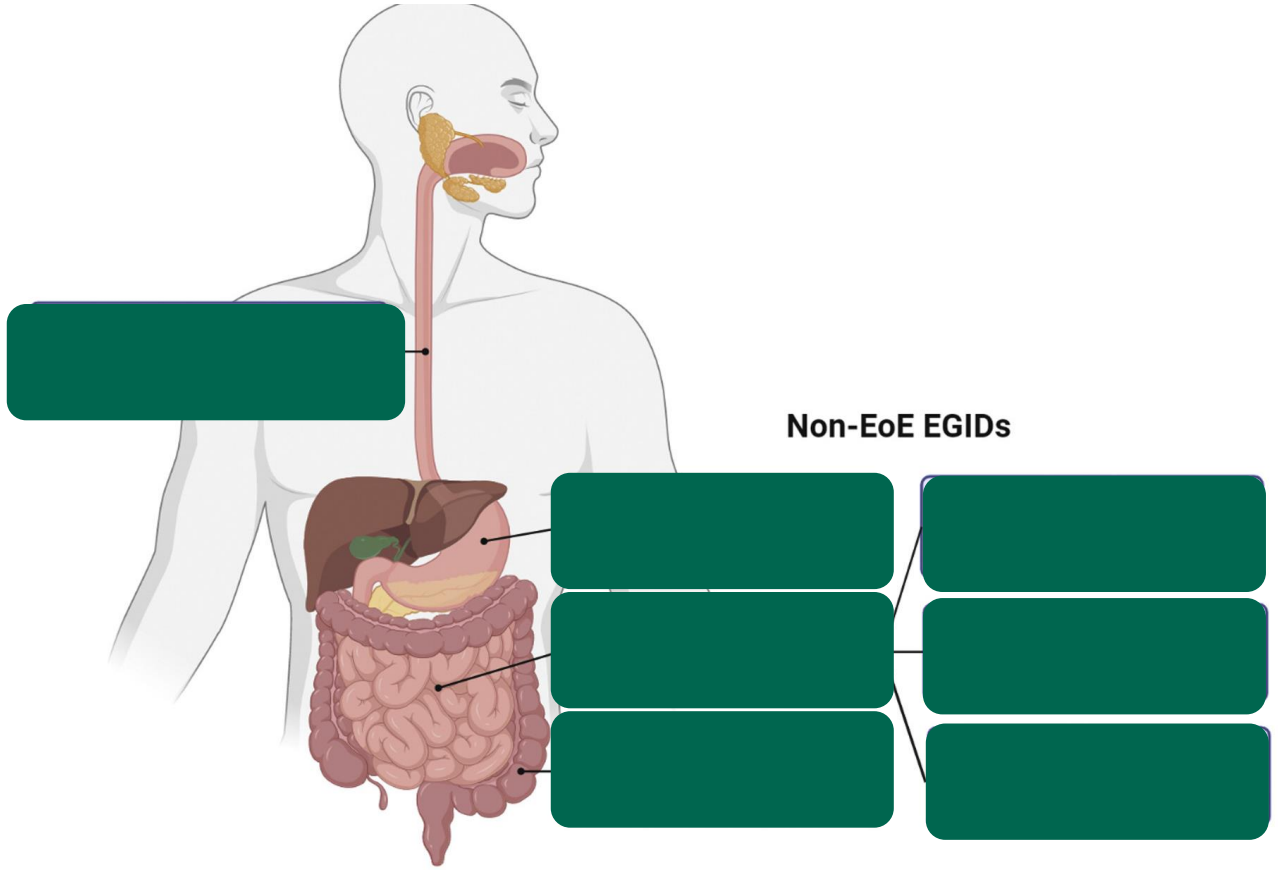
There’s more than EoE?



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Diagnostic challenges

- Eosinophils are naturally found in various quantities along the intestinal tract
- Presentation can be variable depending on segment of GI tract affected
  - vomiting, abdominal pain, diarrhea
- Tissue eosinophilia can be seen in other conditions- parasitic infections, IBD, drug exposure (immunosuppressants)
- Believed to be chronic but no long term studies available, unknown long term consequences
- Traditional reliable biomarkers for intestinal inflammation (ex. Calprotectin) are not reliable

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Non-EoE EGIDs

- Chronic immune-mediated disorders of the GI tract characterized by eosinophilic inflammation of the mucosa that can lead to organ dysfunction
- Clinicopathologic diagnosis
- Treatment studies are limited

Eosinophilic Gastrointestinal Disorders beyond EoE (Non-EoE EGIDs) diagnosis requires **all three** of the following:

a. **Symptoms and/or signs** of GI dysfunction
b. **Dense eosinophilic infiltrates** found in GI tract

Mucosal site	Consensus threshold peak eos/0.27 mm^2 HPF	Consensus threshold peak eos/mm^2
Stomach	≥30	≥110
Duodenum	≥50	≥185
Terminal Ileum	≥60	≥220
Cecum and Ascending Colon	≥100	≥370
Transverse and Descending Colon	≥80	≥300
Rectum and Sigmoid Colon	≥60	≥220

c. **Absence of other diseases** associated with GI mucosal eosinophilic inflammation.

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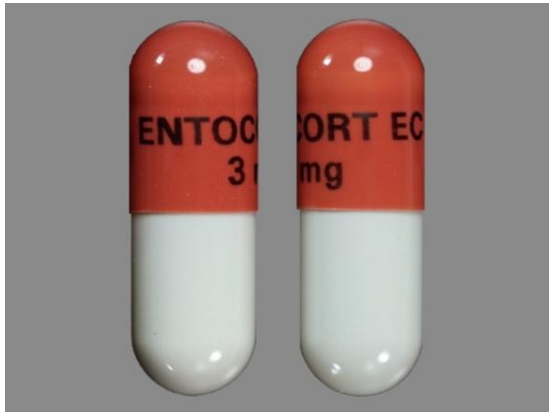
Treatment of non-EoE EGIDs

- PPIs
  - May play a role in EoG and EoD but insufficient studies currently
- Systemic steroids
  - May be used to induce remission
- Topical steroids
  - Enteric coated budesonide capsules
- Dietary interventions
  - Empiric elimination diet (6 food vs. 4 food vs. dairy)
  - Elemental diet
- Biologics
  - Dupixent



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Non EoE EGIDs

- Much remains unknown regarding natural history of non EoE EGIDs
- Current goals of treatment:
  - maximizing growth and development
  - improving quality of life
  - balancing the risks and benefits of treatment with potential side effects
  - improving gross and histological evidence of inflammation
- In the coming years, different approaches to EoG, EoN, and EoC are likely to emerge

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Pediatric Inflammatory Bowel Disease

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Inflammatory Bowel Disease

- Family of diseases (Crohn's disease and Ulcerative colitis) that results in chronic inflammation of the gastrointestinal tract
- Affects approximately 1.2 million people in North America
- 25% of all diagnoses are made before the second decade of life
- Increasing incidence in the pediatric population

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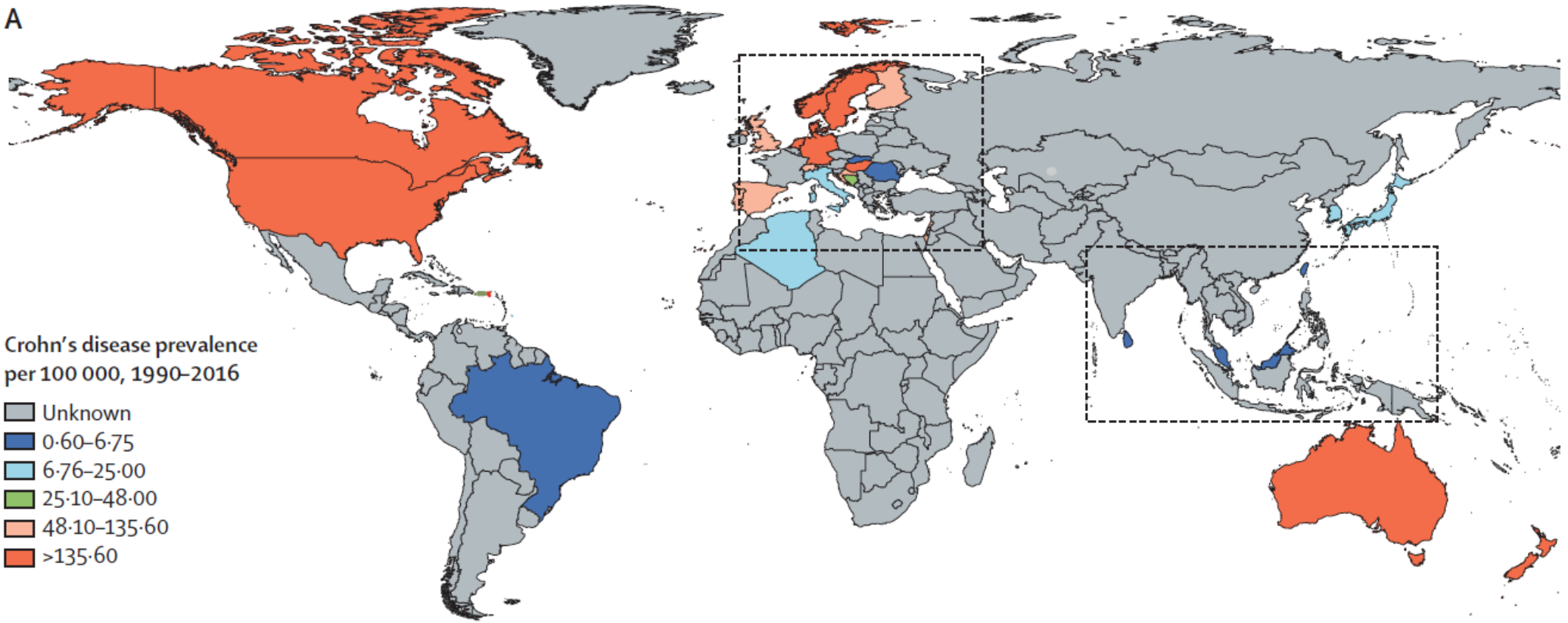
Global Prevalence of IBD



(Kaplan et al 2017)

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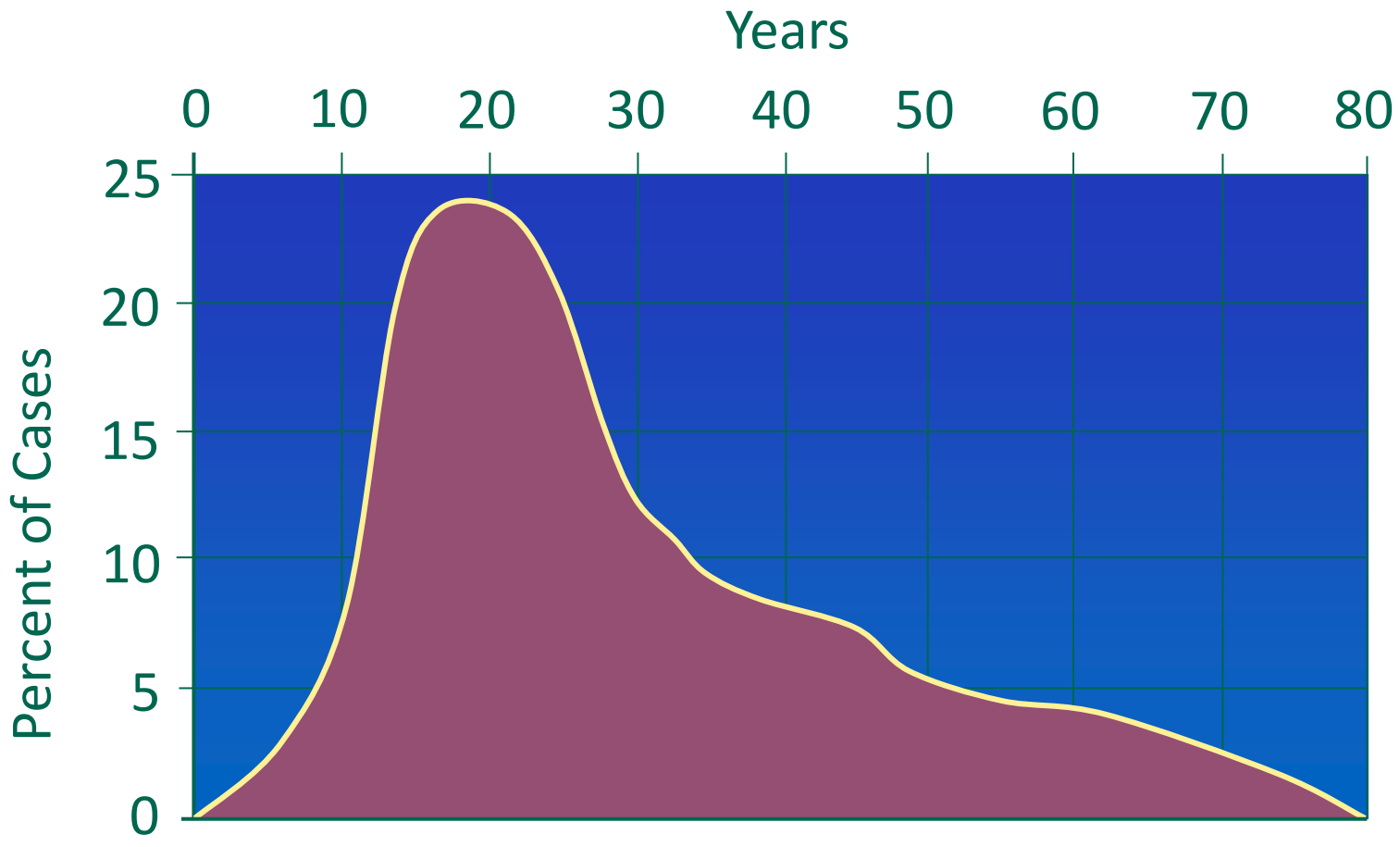

20-25% of IBD cases diagnosed by 20 years

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Pediatric IBD

- Pediatric onset: age of diagnosis < 18 years
- Very early onset: < 6yo
- While IBD is generally a polygenic disease with numerous gene associations identified, early onset IBD has a much higher rate of monogenic disease
- Early onset IBD more refractory to conventional therapies

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How common is pediatric IBD in the US?

- Incidence increasing among children
- Pediatric Incidence in USA:
  - CD: 4.5-9/100,000
  - UC: 2/100,000
- Pediatric Prevalence:
  - 100,000 cases diagnosed annually in North America

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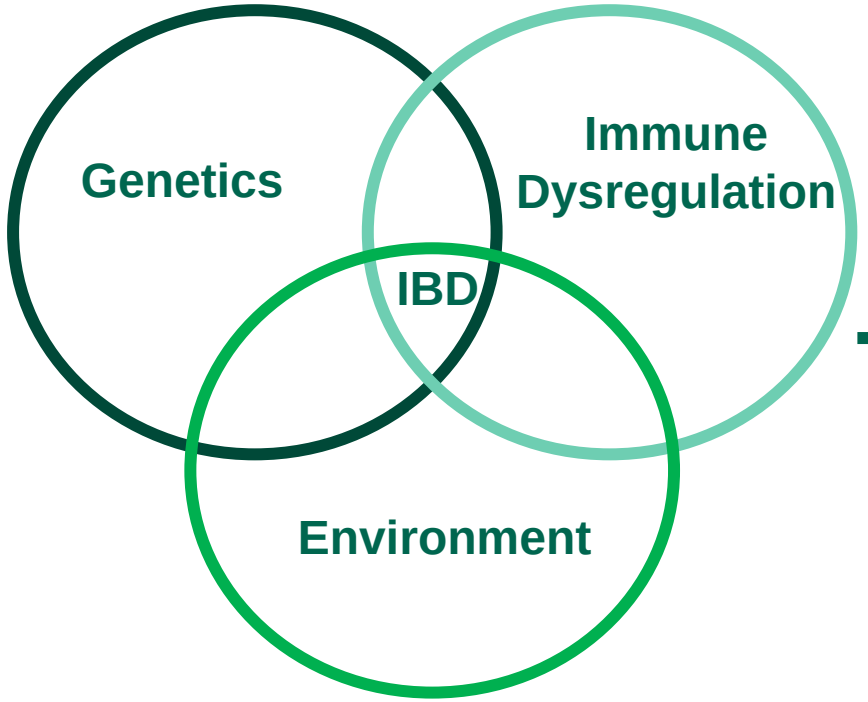
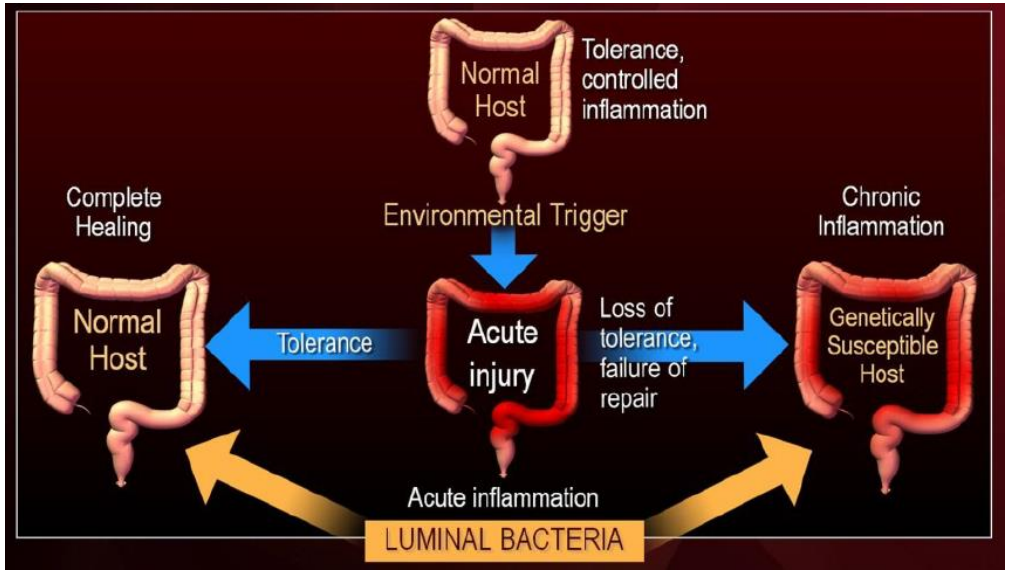
Pathophysiology





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Clinic Presentation

- Weight loss
- Diarrhea
- Abdominal pain
- Hematochezia
- Joint pains
- Perianal disease
- Fevers
- Mouth ulcers

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Diagnosis

- Laboratory work-up:
  - Complete blood count and differential
    - Anemia, thrombocytosis
  - ESR, CRP
    - Typically though not always elevated
  - Comprehensive metabolic panel
    - Screen for liver abnormalities
    - Hypoalbuminemia
  - Rule out enteric infection, celiac disease
  - Fecal calprotectin

Endoscopic evaluation

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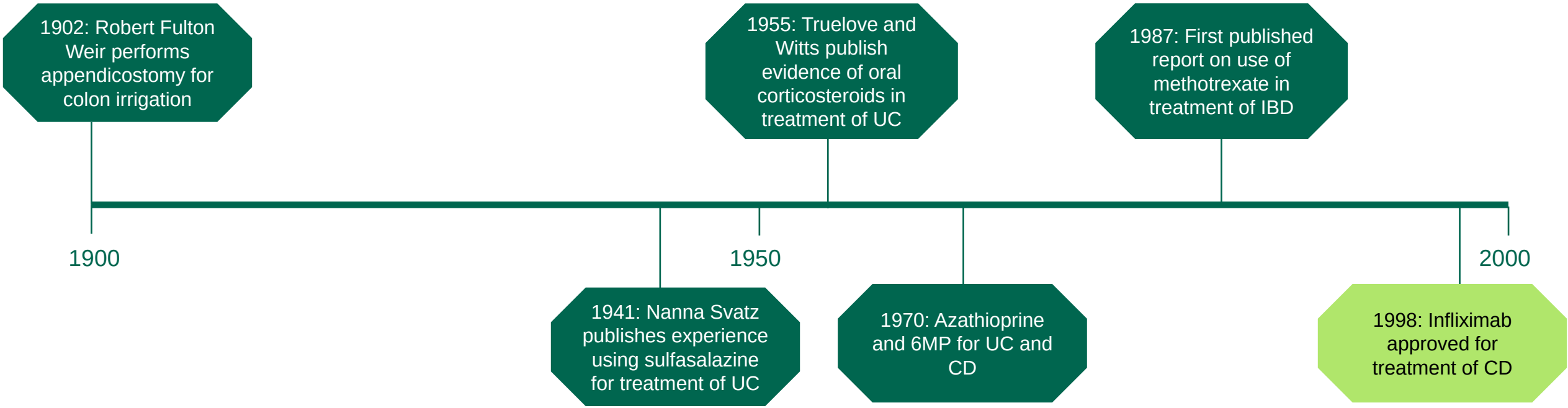
Evolution of IBD treatments



Actis GC, Pellicano R, Fagoonee S, Ribaldone DG. History of Inflammatory Bowel Diseases. J Clin Med. 2019 Nov 14;8(11):1970. doi: 10.3390/jcm8111970. PMID: 31739460; PMCID: PMC6912289.

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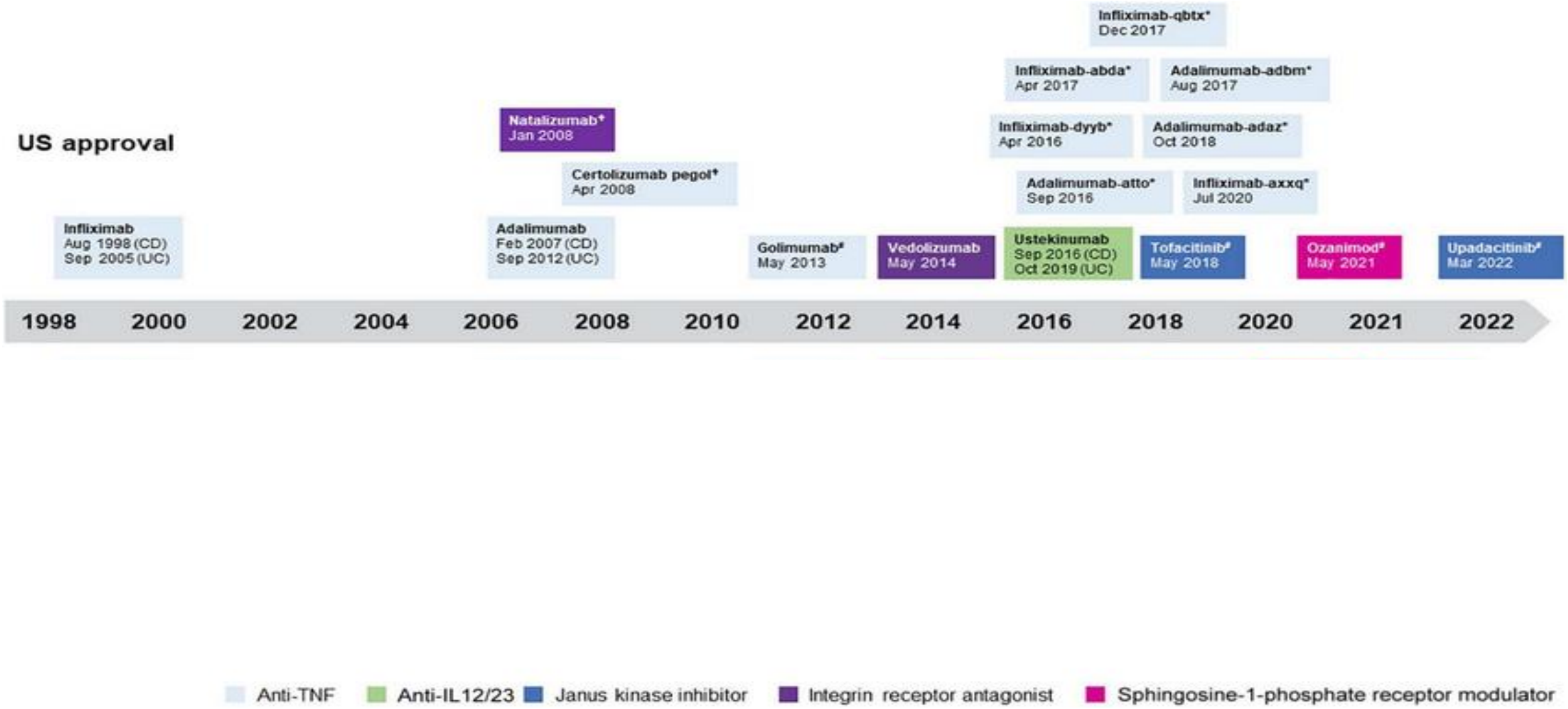

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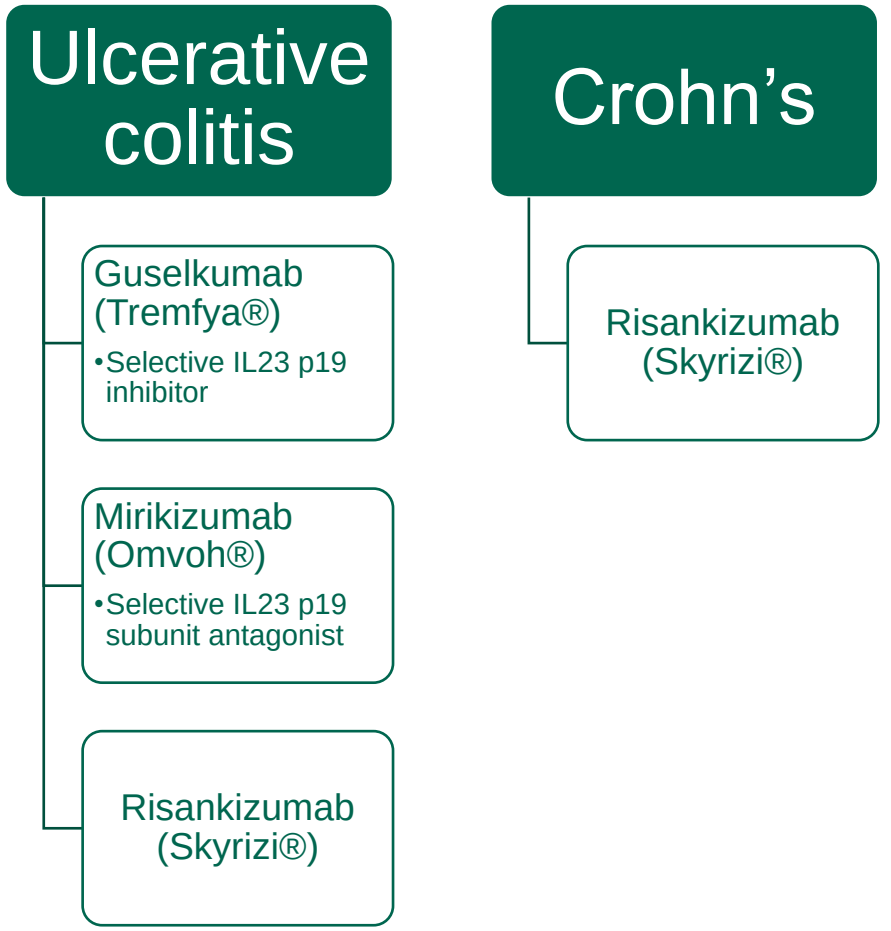
FDA Approval 2022-2023



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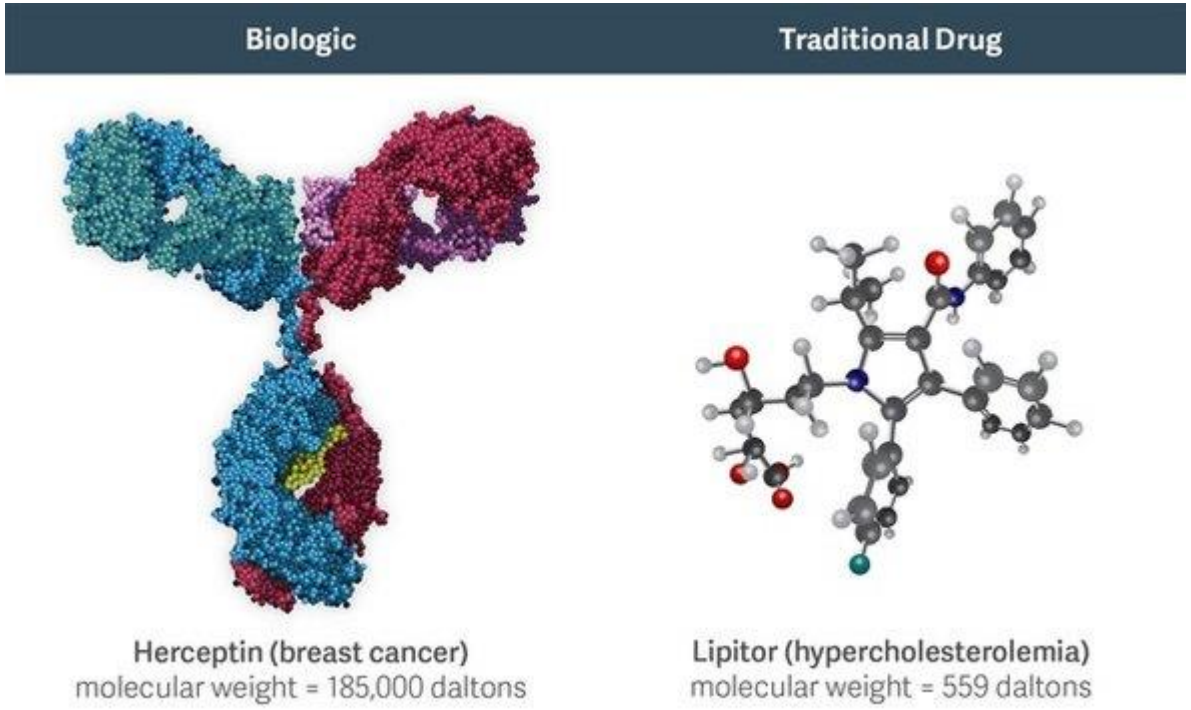
Biosimilars in IBD



- In principle, biosimilars are the biologics equivalent of chemical generics
- Biologics, however, are much more complex molecules than traditional small chemicals and are derived from living cells and organisms
- Sometimes the exact structure of a biologic may not be defined or known

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Biosimilars in IBD

- Due to inherent variability of the biologic system, any resulting biologic will display a certain degree of variability
- A biosimilar and the respective originator product will never be entirely identical, usually only minor differences in clinically inactive components
- There can be no clinically meaningful differences between the biosimilar and the reference product in terms of safety, purity, and potency
- Biologics Price Competition and Innovation Act of 2009

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Biosimilars

- Infliximab (originator)
  - Inflectra
  - Renflexis
  - Ixifi
  - Avsola
- Adalimumab (originator)
  - Amgevita
  - Amsparity
  - Hulio
  - Hukyndra
  - Hyrimoz
  - Idacio
  - Imraldi
  - Yuflyma

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Precision medicine?

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Health Maintenance in IBD

- Vaccinations:
  - Non-immunocompromised patient
    - Follow standard vaccine schedule
    - No contra-indications for live viruses
  - Immunocompromised patient
    - Live virus vaccines contra-indicated
      - MMR, Varicella, Intra-nasal flu
      - If planning on giving vaccine before starting immunosuppressive therapy, recommend waiting at least 6 weeks post vaccination

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Health Maintenance in IBD

- Vaccinations cont.
  - Immunocompromised patient
    - Inactivated vaccines
      - Given according to recommended schedule
      - Pneumococcal vaccine
        - If no previous vaccination: PCV13→PPSV23 or Pneumovax. 2nd dose 5 years later
        - If previously vaccinated: PPSV23 at least 8 weeks after last PCV13. 2nd dose 5 years late
      - Rates of cervical dysplasia and cancer higher in immunosuppressed girls.
        - HPV vaccine highly recommended

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Health Maintenance in IBD

Ophthalmologic Health	Annual ophthalmologic examination: • visual acuity • slit lamp examination • intraocular pressure measurements
Dermatologic Health	Annual dermatology evaluation for skin cancer screening and monitoring for other dermatologic manifestations of IBD • erythema nodosum • pyoderma gangrenosum • psoriasis
Joint Involvement	Regular physical examination of joints for symmetry and complete range. Consider rheumatologist evaluation for patients with persistent joint complaints despite control of intestinal symptoms.
Mental Health	Monitoring for symptoms of depression/anxiety

(DeFilippis et al. 2016)

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Health Maintenance in IBD

Vitamin/Mineral	
Vitamin D	• Monitor serum 25-OH Vitamin D yearly • Maintain levels above 30ng/mL
Folate	• Concern in patients on an antifolate medication (methotrexate) or have significant terminal ileal disease or ileal resection • Monitor serum folate
Latent TB	• Screen with QuantiFERON GOLD prior to starting anti-TNF therapy • No recommendations for on-going monitoring while on therapy

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