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### Updates in Diagnosis & Treatment of Inflammatory Bowel Disease: *Practical Aspects for the Primary Care Provider*

Caroline Lois, MPAS, PA-C Ann & Robert H. Lurie Children's Hospital of Chicago May 19, 2024







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### I have no financial disclosures

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### **Objectives**

- At the conclusion of this session, participants should be able to:
  - Recognize the clinical features and complications of inflammatory bowel disease (IBD)
  - Differentiate between the two main subtypes of IBD: Crohn's disease and ulcerative colitis
  - Identify "red flags" in undiagnosed patients in the primary care setting to determine further workup
  - Summarize diagnostic and treatment options in patients with IBD including medications, surgical management, and dietary therapies
  - Describe special considerations for health maintenance in patients with IBD



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## Defining Inflammatory Bowel Disease



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## What is Inflammatory Bowel Disease?

Group of idiopathic disorders characterized by **chronic** inflammation of the GI tract

- No cure
- 2 main subtypes
  - Ulcerative Colitis (UC)
  - Crohn's Disease (CD)

\*Indeterminate colitis (IBD-U) more commonly seen in pediatric IBD





Ann & Robert H. Lurie Children's Hospital of Chicago **Etiology of IBD** • "It's complicated" • Loss of tolerance • Family history Possibly related to response to prior infection Genetic polymorphisms
 >130 IBD loci Immune Dysfunction Genetics Environmental Triggers Microbes Antibiotics  $\bullet \downarrow \text{ diversity}$ • Diet Loss of protective NSAIDS bacteria Smoking • ↑ pathogenic organisms





### Crohn's Disease vs. Ulcerative Colitis Location, Location, Location!







### Characteristics of IBD: Crohn's Disease

- Any part of GI Tract
- Discontinuous (skipped lesions)
- Rectal sparing
- Presence of granulomas
- Transmural inflammation
- Fistulae and abscesses
- Strictures = more common
- Perianal Disease





### **Characteristics of IBD: Ulcerative Colitis**



- Colon/rectum only
- Continuous
- No rectal sparing
- No granulomas
- Mucosal inflammation
- Abscesses very rare
- Strictures = rare



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### Clinical Presentation of Inflammatory Bowel Disease



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### **Clinical Presentation of IBD**

- Classic Presentation (80%)
  - Abdominal Pain
  - Diarrhea
  - GI bleeding
  - Nausea/vomiting
  - Early satiety
  - Weight loss
  - Oral ulcerations
  - Perianal disease

- Atypical Presentations
  - Growth Failure (pediatric)
  - Anorexia
  - Malaise
  - Fever of unknown origin
  - Endocrine
  - Pubertal Delay (pediatric)
  - Hematologic
  - Anemia
    - Micro, macro, or normocytic



1<sup>st</sup> primary care pearl: pay attention to their growth curves! If caught earlier there is a better chance to salvage the growth



### Symptoms in Crohn's Disease



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### Symptoms in Ulcerative Colitis



- Rectal bleeding
- Rectal pain
- Urgency
- Formed stools
- Anorexia
- Weight loss
- Bloody diarrhea
- LLQ pain

- Anorexia
- Weight loss
  - Bloody diarrhea
- Abdominal pain



### **Extraintestinal Manifestations**



- May precede GI symptoms
- 25-35% of patients with IBD
- Parallel disease activity, or have course independent of intestinal disease
- Most common in colonic disease



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### **Extraintestinal Manifestations**



https://www.aao.org/eye-health/diseases/what-is-uveitis



https://carolinefife md.com/wp-content/uploads/2 022/08/Pyrodema-Gangrenosum-4-980x1307.jpg





https://www.dermatologyadvisor .com/home/decision-support-in-medicine/dermatology/erythema -nodosum-leprosum-leprosy/



https://dermnetnz.org/to



https://radiologykey.com/sacroiliitis/



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## Diagnosis of Inflammatory Bowel Disease





### **Mimickers of IBD**

- Disorders of the gut brain interaction
   Polyps (DGBI)
- Celiac disease

- Hemorrhoids
  - Malignancy

- Infectious diarrhea
  - -C. difficile
  - -Stool culture
  - Ova & Parasite

- NSAID use
- Peptic Ulcer disease



### **Red** Flag Signs & Symptoms

- Constitutional symptoms

   Weight loss, fevers
- Poor growth
- Dysphagia/odynophagia
- Nocturnal awakenings
- Pain localized away from the umbilicus

- Significant change in bowel patterns
- Persistent diarrhea
- GI bleeding
- Perianal Disease (LOOK!!!)
- Family history of significant GI disease autoimmunity

Abdominal pain: Persistent, No apparent correlating factors, Lingers after bowel movements OR relief with vomiting





### What Does Normal Bowel Look Like?





## Endoscopic Findings of Inflammatory Bowel Disease



#### Crohn's Disease



#### **Ulcerative Colitis**



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### Indications for Small Bowel Imaging

- Determine degree of small bowel involvement
- Evaluate response to medical therapy
- Assess for strictures, abscesses, or fistulae



Abdominal wall abscess



Rectovaginal fistula



ibrostenotic stricture

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# Treatment of Inflammatory Bowel Disease





### **Goals of IBD Management**

Induction of Remission	<ul> <li>Turning "off" the inflammation</li> <li>Feeling well</li> <li>Normalization of labs, growth, development and nutrition</li> </ul>
$\sim$ /	
	<ul> <li>Stable disease control and optimization of therapy</li> <li>NO STEROIDS</li> </ul>
Maintenance	• Prevention of return of inflammation over time (sustained and durable)
of Remission	Changing the natural course of the disease
	Monitoring for early return of inflammation
	Monitoring therapies
Disease	Prevention of infections
Monitoring	• Access
and Prevention	• Cost-effectiveness
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### **Treatment Targets in IBD**



### **Modern Treatments for IBD**



#### Immune modification/suppression

- 5-ASA (?)\*
- Steroids
- Thiopurines/methotrexate
- Anti-TNF $\alpha$  therapies\*
- Anti-integrin therapies
- Anti-IL12/23
- JAK inhibitors
- S1P receptor modulators

## Dietary therapies (exclusion diets) Antibiotics

**Microbiota manipulation** 

- Prebiotics
- Probiotics
- Intestinal microbiota transfer

#### Surgery

- Resection of fibrostenosis
- Resection in medically resistant disease



### **Patient Risk Stratification**

Inflammatory bowel disease (IBD) encompasses a heterogeneous group of conditions

Appropriateness of "top down" vs. "step up" approach needs to be individualized based upon patient risk stratification





### Medications in IBD: 5-Aminosalicylates

- Oral or rectal preparations
- Medications
  - Sulfasalazine
  - Balsalazide
  - Mesalamine
    - Oral: Asacol, Asacol HD, Delzicol, Pentasa, Apriso, Lialda, Colazal
    - Rectal: Rowasa, Canasa
- Induction and maintenance of remission for mild-moderate ulcerative colitis
  - NOT Crohn's disease!
- Adverse effects
  - Worsening diarrhea, bloody diarrhea, nausea, headache



http://www.ibdclinic.ca/treatment/medications/5-asa/



### Medications in IBD: Corticosteroids

- Medications
  - Methylprednisolone
  - Prednisone
  - Budesonide
    - Uceris
  - Entocort
- Suppress immune system
- Induce remission
- Adverse effects
  - Many...

### Take pred they said, You'll be fine they said...





### Adverse Effects of Corticosteroids

Event	Estimated Frequency
Any side-effect leading to stopping prednisone	55%
Ankle swelling	11%
Facial swelling	35%
Easy bruising	7%
Acne	50%
Psychosis - confusion/agitation	1%
Infections	13%
Cataracts	9%
Increased intraocular pressure	22%
High blood pressure	13%
Osteoporosis	33%
Diabetes	Chance increases 10x

Rutgeerts PJ. N Engl J Med. 1994;331(13):842-845 34



### Medications in IBD: Immunomodulators

- Medications
  - Azathioprine (AZA)
  - 6-mercaptopurine (6-MP)
  - Methotrexate (MTX)
- Oral or SQ injection
- Interfere with DNA and RNA synthesis ightarrow immune suppression
- Maintenance of remission for moderate-severe disease
- Slow onset of action (2-3 months)
- Side effects: leukopenia, elevated LFTs, nausea, pancreatitis, increased risk of lymphoma with 6-MP
  - Initial EBV exposure

### Medications in IBD: Advanced Therapies

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- Classes
  - Anti-TNF
  - Anti-integrins
  - S1P Receptor Modulators
  - Anti-IL-12/23
  - JAK Inhibitors
- MOA: Target specific pathways of the immune system in patients with IBD


# Medications in IBD: Advanced Therapies

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Class	Medications	Administration	Onset of action
Anti-TNF (tumor necrosis factor)	<ul> <li>Infliximab*</li> <li>Adalimumab*</li> <li>Golimumab Certolizumab pegol</li> </ul>	• IV • SQ	2-4 weeks
Anti-integrins	<ul><li>Vedolizumab</li><li>Natalizumab</li></ul>	• IV	Up to 14 weeks
S1P receptor modulators	<ul><li>Ozanimod</li><li>Etrasimod</li></ul>	• Oral	Up to 10 weeks
IL-12/23 inhibitors	<ul><li>Ustekinumab</li><li>Risankizumab</li><li>Mirikizumab</li></ul>	Combination (IV then SQ)	Up to 12 weeks
JAK inhibitors	<ul><li>Tofacitinib</li><li>Upadacitinib</li></ul>	• Oral	Up to 8 weeks



# Potential Adverse Effects of Advanced Therapies

	Anti-TNF	Anti- Integrin	S1P	IL12/23 Inhibitors	JAK Inhibitors
Serious infection	+	-	+	-	+
Herpes zoster	-	-	+	-	+
Non-Hodgkins lymphoma	+	-	-	-	?
Demyelination	+	-	-	-	-
DVT/PE	-	-	-	-	+
Hyperlipidemia	-	-	-	-	+
Arrhythmias	-	-	+	-	-

Generally, anything that affects the immune system can put patients at risk of certain infections

Cancer screening is important as well for this class of medications

### **Modern Treatments for IBD**



#### Immune modification/suppression

- 5-ASA (?)\*
- Steroids
- Thiopurines/methotrexate
- Anti-TNF $\alpha$  therapies\*
- Anti-integrin therapies
- Anti-IL12/23
- JAK inhibitors
- S1P receptor modulators

#### **Microbiota manipulation**

- Dietary therapies (exclusion diets)
- Antibiotics
- Prebiotics
- Probiotics
- Intestinal microbiota transfer

#### Surgery

- Resection of fibrostenosis
- Resection in medically resistant disease

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## **Dietary Therapy in IBD**

- Exclusive Enteral Nutrition
  - Aka "EEN"
  - Formula diet only
  - 4-12 weeks
  - PO vs NG
  - Can be used as maintenance therapy or bridge to therapy in place of steroids
  - Limitations: COMPLIANCE!





### **Dietary Therapy in IBD**

- Crohn's Disease Exclusion Diet (CDED)
  - 3 phases  $\rightarrow$  start with 50% formula and 50% approved foods, then reduce amount of formula in each phase
  - Limitations: somewhat restrictive, only approved in CD currently





## Other Dietary Therapies in IBD

- Not a comprehensive list:
  - Anti-inflammatory Diet
  - Autoimmune Protocol Diet
  - Crohn's Disease Exclusion Diet
  - CD-TREAT Diet
  - EEN
  - Low FODMAP Diet
  - Mediterranean Diet
  - Specific Carbohydrate Diet
  - Semi-vegetarian Diet
  - Ulcerative Colitis Exclusion Diet +/- Fecal Microbiota Transplant

- General concept = whole foods, less processed
- Mediterranean diet recommended by IOIBD
- Can help with symptom control





### What are the risks of untreated IBD?



Peyrin-Biroulet et al. Am J Gastroenterol 2010 Colombel et al. Gastroenterology 2017 Solberg et al. Clin Gastroenterol Hepatol 2007 Jess et al. Clin Gastroenterol Hepatol 2012

- Surgery
  - Strictures and/or fistula occur in >50% of patients with Crohn's disease after 10 years of disease
- Colon cancer
  - Significantly increased risk compared to the general population
- Blood clots
  - Greater risk for deep vein thrombosis
- Hospitalizations/surgeries
- Poor quality of life



Colombel JF et al. Gastroenterology 2017; 152:351-361 45

### **Prognostic Predictors of Severe Disease Course**



### Crohn's Disease

#### (CD)

- Young age at diagnosis <30 yrs
- Stricturing or penetrating disease
- Perianal disease
- Ileal, ileocolonic disease
- Cigarette smoking
- Disease duration > 10 yrs
- Severe/deep mucosal ulceration
- Extensive disease
- Steroid dependence/resistance
- Hospitalization
- Previous surgery

#### **Ulcerative Colitis**

(UC)

- Young age at diagnosis (<40 yrs)
- Male gender
- Disease duration > 10 yrs
- Severe mucosal disease
- Extensive colitis
- Steroid dependence/resistance
- Hospitalization



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### Health Maintenance in Inflammatory Bowel Disease





### Teamwork Makes the Dream Work!

- GI provider often treated as PCP by many patients
- Partnership with GI and PCP is key!
- GI often will make recommendations though importance of following up with PCP





### **Psychosocial Health**

- Anxiety and depression are common in IBD
  - 25-40% of patients with pediatric disease (both active and inactive disease)
    - Decreased quality of life
    - Poor adherence to therapy/appointments
    - Loss of control
    - Substance abuse (need to ask!)
- 15% of children have thoughts of death on screening tools
  - Pain is a frequent trigger for suicidal thoughts
- Regular screening recommended
  - Variety of tools: Patient Health Questionnaire-9 (PHQ-9) and Beck Depressive Inventory (BDI) most commonly used, high sensitivity and specificity
- Treatment: Nonpharmacologic and Pharmacologic

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## **Ocular Health**

- Annual screening with *ophthalmologist* recommended
  - IBD-associated manifestations
    - Uveitis
    - Episcleritis
    - Orbital myositis
  - Corticosteroid-associated manifestations
    - Glaucoma
    - Early cataracts



https://www.aao.org/eye-health/diseases/what-is-uveitis



### **Skeletal Health**



https://monib-health.com/files/blogpost/03afdbd66e7929b125f8597834fa83a4\_63\_thumb.jpg.webp?=1640515274

- Osteopenia and osteoporosis are common in patients with IBD
  - Decreased BMD at diagnosis in 43% of CD and 39%, compared to 29% of controls (n=58)
  - Elevated inflammatory cytokines inversely correlated with BMD
- Risk factors
- Hypovitaminosis D is prevalent in IBD
  - 25-OH vitamin D levels suboptimal in 58.3%, insufficient in 14.3%, deficient in 5.8% (n=448)
  - Levels inversely associated with ESR



### **Skeletal Health Recommendations**

- Regular monitoring of linear growth, growth velocity and pubertal development
- DXA at baseline and every 1-2 years if low BMD noted or risks factors
- Monitor vitamin D levels at least annually
  - -Treat hypovitaminosis D with high doses
  - -Once optimal status achieved, continue 800-1000 IU daily
- RDA of elemental calcium daily
- Encourage weight bearing activities and resistance training



### **Immunizations in IBD**

- Vaccinate as scheduled in patients who are <u>not</u> on immunosuppressive therapy
  - 5-ASA, dietary therapy, antibiotics
  - ACIP guidelines:

- Special considerations for immunosuppressed patients
  - Ideal world—immunize before start of immunosuppression
    - Live vaccines ≥ 4 weeks before, inactivated vaccines ≥ 2 weeks
  - Real world—treatment should not be delayed
    - Role for dietary therapy as a bridge to allow immunization?
  - Immunosuppressed patients respond to inactivated vaccines!

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# Immunogenicity of Vaccines





### Immunogenicity of Vaccines



### Pneumococcal Vaccine Recommendations in Immunocompromised Children (Abbreviated)



- Age 2-5\*:
  - Unvaccinated or Incomplete PCV series with <3 doses before 2 y/o
    - Give 2 doses of PCV15 or **PCV20** (give the second dose at least 8 weeks after the first)
  - Children who received 3 PCV doses before 12 months, but have not received 4<sup>th</sup> booster
    - Give 1 dose of PCV15 or PCV20

#### • Age 6-18\*:

- Never received PCV13, PCV15, or PCV20
  - Give 1 dose of PCV15 or PCV20 regardless of whether child has received PPSV23 or PCV7
    - When PCV15 is used, it should be followed by PPSV23 if not previously given
    - When PCV20 is used, no PPSV23 needed
  - Received PCV13 or PCV15 before age 6, never received PCV 20
    - Received PPSV23?
      - Yes: Give PCV20 or second dose of PPSV23 5 years later
      - No: Give PCV20 or PPSV23, if PPSV23 is used, will need another PCV vaccine 5 years later

https://www.cdc.gov/vaccines/vpd/pneumo/hcp/who-when-to-vaccinate.html 56

### Pneumococcal Vaccine Recommendations in Immunocompromised Adults 19-64 (Abbreviated)



- Never received any pneumococcal vaccine (or only PCV7)
  - Give 1 dose of PCV15 or **PCV20.** 
    - When PCV15 is used, it should be followed by a dose of PPSV23 at least 1 year later. When PCV20 is used, it does not need to be followed by a dose of PPSV23. Their vaccines are then complete
- Only received PPSV23
  - Give 1 dose of PCV15 or **PCV20** at least 1 year after the most recent PPSV23 vaccination.
- Only received PCV13
  - Give 1 dose of **PCV20** or PPSV23.
    - The PCV20 dose should be given at least 1 year after PCV13. When PCV20 is used, their vaccines are then complete. The PPSV23 dose should be given at least 8 weeks after PCV13. When PPSV23 is used, they need another pneumococcal vaccine at least 5 years later
- Received PCV13 and 1 dose of PPSV23
  - Give 1 dose of **PCV20** or a second PPSV23 dose.
    - The PCV20 dose should be given at least 5 years after the last pneumococcal vaccine. The second dose of PPSV23 should be given at least 8 weeks after PCV13 and 5 years after PPSV23.

https://www.cdc.gov/vaccines/vpd/pneumo/hcp/who-when-to-vaccinate.html 57

#### Pneumococcal Vaccine Recommendations in Immunocompromised Adults >65 (Abbreviated)



- Never received any pneumococcal vaccine (or only PCV7)
  - Give 1 dose of PCV15 or **PCV20.** 
    - When PCV15 is used, it should be followed by a dose of PPSV23 at least 8 weeks later. When PCV20 is used, it does not need to be followed by a dose of PPSV23. Their vaccines are then complete
- Only received PPSV23
  - Give 1 dose of PCV15 or **PCV20** at least 1 year after the most recent PPSV23 vaccination.
- Only received PCV13
  - Give 1 dose of **PCV20** or PPSV23.
    - The PCV20 dose should be given at least 1 year after PCV13. When PCV20 is used, their vaccines are then complete. The PPSV23 dose should be given at least 8 weeks after PCV13.
- Received PCV13 and 1 dose of PPSV23
  - PPSV23 given BEFORE age 65  $\rightarrow$  Give 1 dose of **PCV20** or PPSV23
  - PPSV23 given AFTER age 65  $\rightarrow$  Use shared clinical decision-making to decide whether to administer PCV20

https://www.cdc.gov/vaccines/vpd/pneumo/hcp/who-when-to-vaccinate.html 58

### Varicella and Zoster Recommendations



- IBD patients have higher risk of VZV infection (IRR 1.21-1.68)
   Patients with IBD have higher rate of hospital admission for zoster (OR 2.4)
- Obtain varicella titers if vaccine history is not clear
- Recognize that partially vaccinated patients may have atypical presentations
- Administer Shingrix to eligible patients!
  - Adults 19 years and older who are or will be immunocompromised
  - 2 dose series given within 2-6 months



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### **COVID Vaccination**

- "In patients with IBD taking immunosuppressive drugs, including biologics and small-molecule inhibitors, the key concerns are related to the theoretical risk of suboptimal vaccine response rather than side-effects"<sup>1</sup>
  - Corticosteroids may decrease vaccine efficacy
- Administer at the earliest opportunity
- Patient's can receive any of the currently approved vaccinations
  - Can be co-administered with other vaccines

- Recommendations vary by age and immune status
- <u>https://www.cdc.gov/vaccines/covid-</u> <u>19/clinical-considerations/interim-</u> <u>considerations-us.html</u>

<sup>1</sup>Alexander JL, Moran GW et al. Lancet Gastroenterol Hepatol 2021;6:218-224



### **Immunization Pearls**

- Ensure pediatric patients receive recommended immunizations as per ACIP schedule
- Avoid live virus vaccines in immunocompromised patients
   Administer 4 weeks before starting, or 3 months after stopping (1 month for steroids)
- Immunize IBD patients annually against influenza
- Give pneumococcal vaccination to immunocompromised patients
- Recommend COVID vaccination in all patients
- Immunize household contacts





### **Cancer Screening Recommendations**

- Colorectal cancer
  - Applies to patients with colonic disease (UC or colonic involvement in CD)
    - Surveillance colonoscopy 8-10 years after diagnosis and then every 1-3 years
    - More frequent colonoscopies in patients with PSC
- Skin cancer
  - Screen for melanoma INDEPENDENT of biologic use (ACG)
  - Screening for NMSC in patients on immunosuppression
    - Annual dermatology exams

- Cervical cancer
  - Women on immunosuppression including biologics, small molecules and immunomodulators
    - Annual pap smear starting at age 21 (all patients)
    - AGA: yearly screening for sexually active females
    - HPV vaccination per ACIP guidelines (also applies to men)



### **Reproductive Health**

- Use of OCP in patient with IBD not associated with increased risk of a flare
- Estrogen based contraception may increase risk of venous thromboembolism (2 fold increase)
  - -Further compounded by active disease
- Choice of contraceptive—shared decision making
  - -Patient, prescribing clinician, gastroenterology clinician should provide input
  - -Efficacy, tolerability and risk of VTE should be considered



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### Considerations for Specific Populations in Inflammatory Bowel Disease

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### **Pregnancy in Inflammatory Bowel Disease**

- Biggest risk to fetus = active disease!
- PIANO Study
  - NO increased risk of adverse events (congenital malformations, spontaneous abortions, preterm birth, low birth weight) in patients on biologics and/or thiopurines
  - Increased risk of infections if preterm birth
  - https://gastroenterology.ucsf.edu/research/piano
- Medication guidance
  - Contraindicated: methotrexate
  - Avoid: corticosteroids, ozanimod, JAK inhibitors (tofacitinib, upadacitinib)
  - Continue: mesalamine/sulfasalazine, azathioprine/6-MP, anti-TNF, IL 12/23 inhibitors, vedolizumab, low dose aspirin



## Pregnancy in Inflammatory Bowel Disease

- Breastfeeding is safe for patients on biologics 🙂
  - No adverse effects on growth, milestones, or infection rate
  - Not enough data for small molecules
- Infant vaccinations
  - Give all inactivated vaccines as scheduled
  - Avoid live vaccines within the first 6 months if immunosuppressed; 12 months if breastfeeding (Rotavirus)



## Aging in Inflammatory Bowel Disease

- Older adults are living longer
  - Projected increase of 200% for older adults with IBD
  - 2015: 26% of IBD patients were over age 65
- No change in disease phenotype
- Considerations in aging population
  - Comorbidities
  - Infections
  - Malignancies
  - SCREEN FOR OSTEOPOROSIS!



# Aging in Inflammatory Bowel Disease

- Medication guidance
  - Avoid: thiopurines, corticosteroids
  - Consider: vedolizumab, IL 12/23 inhibitors
  - Discuss based on clinical picture:
    - Anti-TNF: if minimal melanoma and leukemia/lymphoma risks
    - Methotrexate: if minimal melanoma risks
    - JAK inhibitors: if minimal cancer risks
    - S1P receptor modulators: if minimal leukemia/lymphoma risks



### A Few Pearls...

- PCP involvement = key
- Contraception
- Antibiotic treatment
- Medications to avoid
  - NSAID's
  - Clindamycin
  - Loperamide
  - Opioids
- Flare vs infection management





### In Summary...

- Presentation of IBD is heterogeneous and includes both GI and extraintestinal manifestations
- Risks of disease and treatment change across the lifespan
- Treatment targets have evolved—goal is to modify disease course and change outcomes
  - Increasing use of advanced therapies (biologics, small molecules)
    - Helpful to know key side effects that you may see in the primary setting
- Partnering between primary care providers and IBD clinicians is necessary to ensure adequate preventative care, including all appropriate vaccinations



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## **Questions?**

Thank you! Caroline.c.lois@gmail.com




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