



2021 SCSG GI SYMPOSIUM



Inflammatory Bowel Diseases: A primer

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Learning Objectives

- Describe the clinical features and natural history of IBD
- Highlight commonly reported patient questions about IBD medications
- Summarize the important adverse effects of IBD therapies
- Review preventive care checklists for IBD
- Provide a brief overview of biosimilars

Differential Diagnosis of IBD vs IBS



IBD:
inflammatory
bowel disease

IBS:
irritable
bowel
syndrome

CLINICAL FEATURES	IBD	IBS
Anemia (low hemoglobin)	+	-
Elevated inflammatory markers (C-reactive protein, sedimentation rate)	+	-
Weight loss, fevers	+	-
Perianal disease	+	-
Bloody stools	+	-
Obstructive symptoms	+	-
<u>Elevated calprotectin</u>	+	-

Differential diagnosis of infectious vs inflammatory colitis

	Acute infections	INFLAMMATORY BOWEL DISEASE
Duration of symptoms	< 2 weeks	> 4 weeks
Onset of symptoms	Abrupt	Insidious and chronic
Hematocrit	Normal	Anemia
Biopsy	Neutrophils predominate	Mixed infiltrate, abnormal crypt architecture (“cryptitis”) , increased lymphoid aggregates, basal plasmacytosis , crypt abscesses

Crohn's disease

- Chronic immune-mediated, inflammatory disorder that can involve **any** part of the gastrointestinal tract
- 1-1.5 million people affected in US
- 10,000-47,000 new diagnoses annually
- Up to 75% of patients will require at least 1 surgery
- **Smoking has a NEGATIVE impact on Crohn's disease**
- Increased risks of small bowel, colon cancers

Classic symptoms of Crohn's disease

- **Diarrhea** - chronic, nocturnal, occasionally bloody
- **Crampy abdominal pain**
- Abdominal mass
- **Weight loss/anorexia**
- Fever
- Malnutrition
- Fatigue
- Anemia
- **Growth delay (kids)**

Symptoms of Crohn's disease often reflect the **BEHAVIOR** of the Crohn's disease

Inflammatory phenotype



- **Pain** Abdominal cramping most common
- **Tenderness** Often in the right lower quadrant
- **Diarrhea** “irregular” BMs common
- **Low-grade fever**
- **Weight loss (anorexia)**



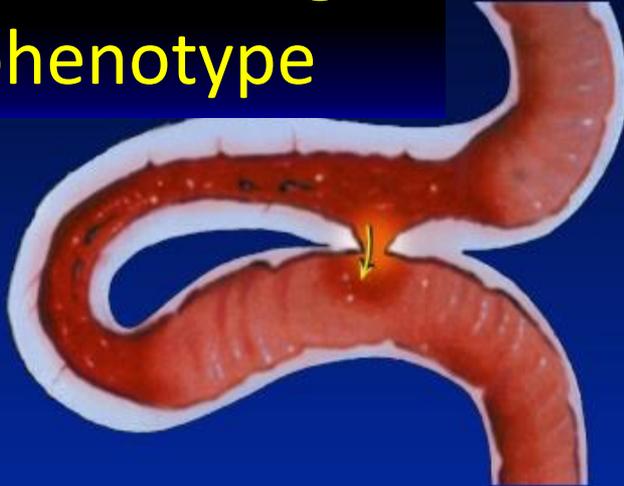
Strictureing phenotype



- Post-prandial cramps
- Distention **Tympanic to percussion**
- Borborygmi **Loud bowel sounds – “gurgling”**
- Vomiting
- Weight loss (food avoidance)



Penetrating phenotype



Fevers are common
Palpable mass in the RLQ
if abscess present

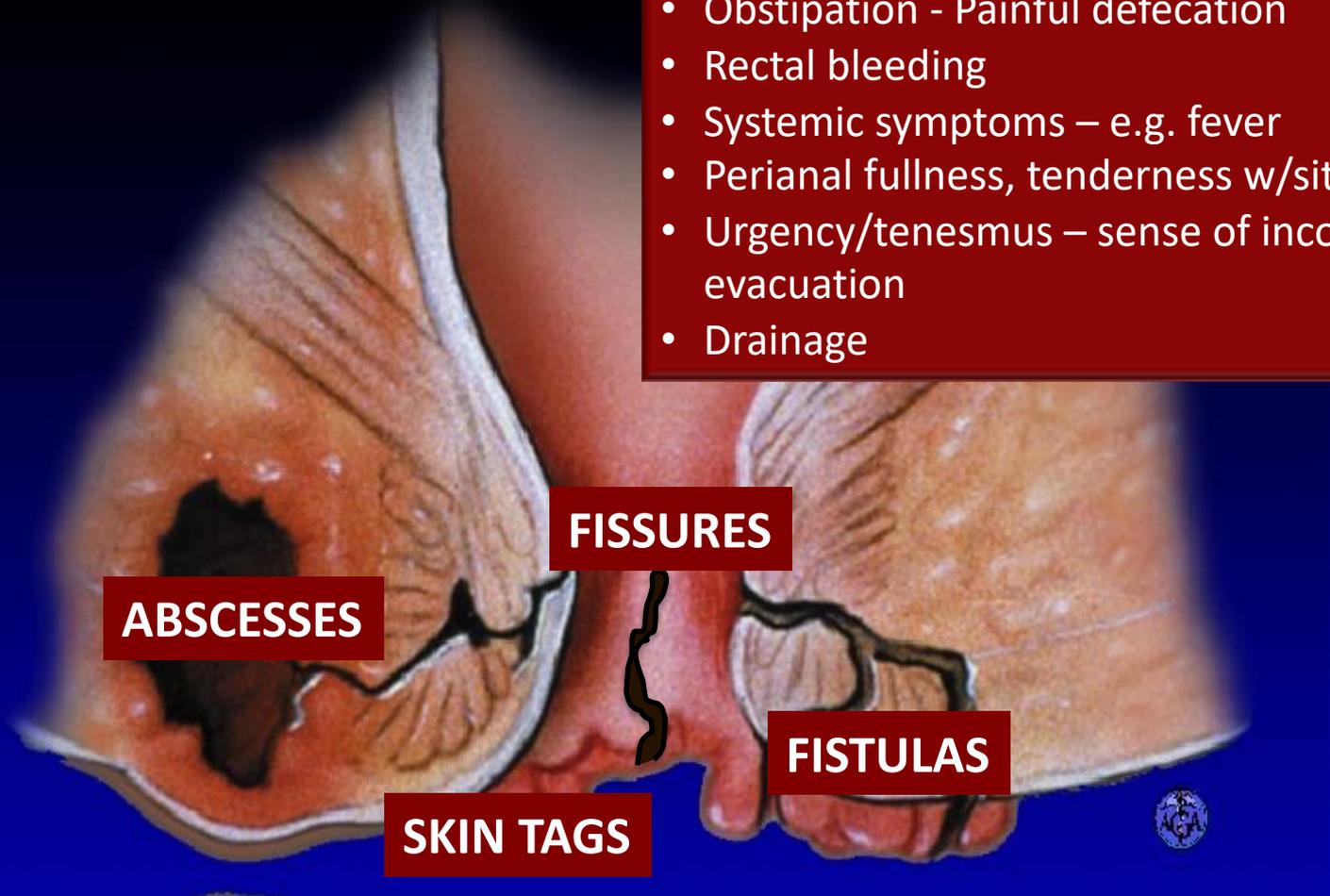


- **Enteroenteric**
May be asymptomatic
- **Enterovesical**
Recurrent UTIs,
pneumaturia
- **Retroperitoneal**
Psoas abscess signs:
back, hip, and thigh pain;
limp
- **Enterocutaneous**
Drainage via scar
- **Perianal**
Pain, drainage
- **Rectovaginal**
Drainage: feces and/or air

Perianal disease

Symptoms:

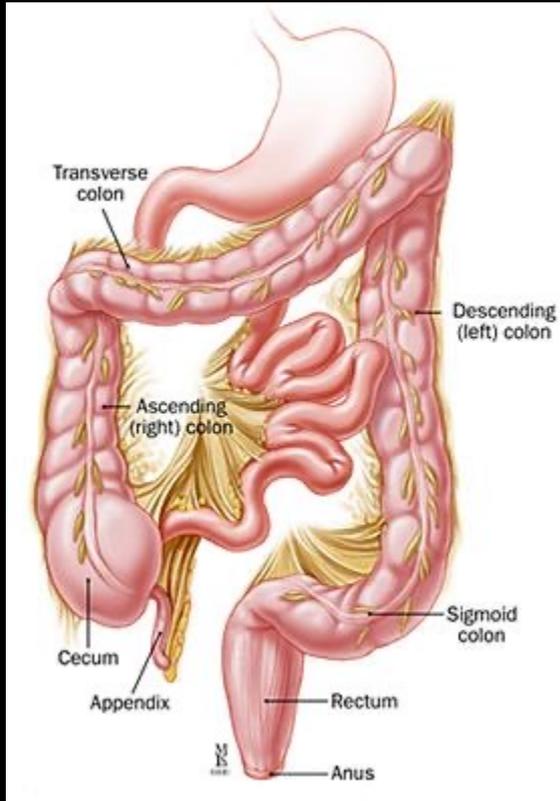
- Obstipation - Painful defecation
- Rectal bleeding
- Systemic symptoms – e.g. fever
- Perianal fullness, tenderness w/sitting
- Urgency/tenesmus – sense of incomplete evacuation
- Drainage



Ulcerative Colitis

- Chronic inflammatory disorder of the colon and rectum
- 1-1.5 million people affected in US
- 30-40% of UC patients eventually require colectomy
- Increased risks of colon cancer
 - Especially with longer disease duration, greater disease extent, primary sclerosing cholangitis

Symptoms of UC



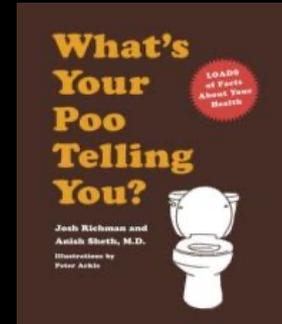
- Bloody diarrhea
- Passage of mucus
- Rectal urgency
- Abdominal cramping
- Weight loss, fever, anemia

Extra-intestinal manifestations (EIM) of IBD

	Corresponds with disease activity	Independent of disease activity
Ophthalmologic	Episcleritis	Iritis/uveitis
Mucocutaneous	Oral aphthae	
Dermatologic	Erythema nodosum	Pyoderma gangrenosum
Hepatobiliary		Primary sclerosing cholangitis (INCREASED COLON CA RISK) Gallstones
Vascular	Thromboembolism	
Musculoskeletal	Large joint arthropathy	Axial arthropathy Small joint arthropathy
Renal		Kidney stones

Diagnosing IBD: Physical exam

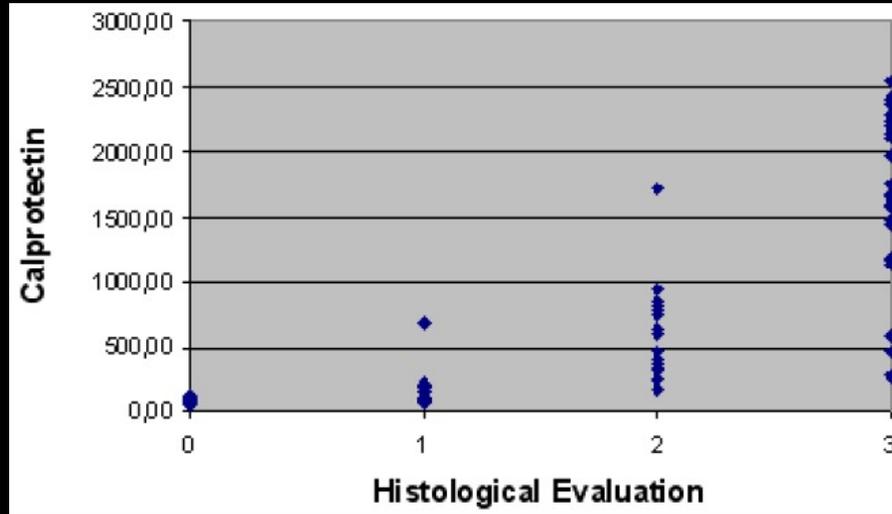
- Vital signs – tachycardia? **Fever?** **Weight loss?**
- Conjunctival pallor, pale nail beds
- Abdominal tenderness – **palpable mass** present?
- **Bowel sounds – hyperactive?**
- **Abdominal distention** – tympanic to percussion?
- **Extraintestinal manifestations?**
 - Joint pain, perianal disease



Diagnosing IBD: Laboratory data

- **Complete blood count (CBC)**
 - Anemia, inflammation, infection
- **Complete metabolic panel**
 - Dehydration, electrolyte depletion, liver abnormalities
 - **LOW ALBUMIN** → **increased** disease severity
- **C-reactive protein**
 - Higher values correlate with more severe disease
- **Stool studies**
 - Infection: *Clostridium difficile*
 - **Inflammation: *fecal calprotectin***

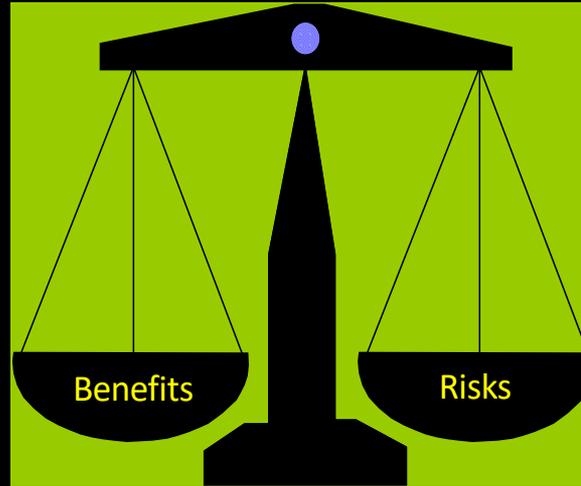
Elevated fecal calprotectin is associated with increased colonic inflammation



- Sensitive and specific marker of intestinal inflammation
- **Levels are directly proportional to degree of colonic inflammation**

Current Therapeutic Goals for IBD: maximize benefit, minimize risk

- Induce and maintain remission with mucosal healing
- Improve quality of life
- Avoid surgery and hospitalizations
- Reduce cancer risk
- Minimize steroid exposure
- Reduce disease progression



- Minimize infection related adverse effects
- Monitor for complications of therapy including cancer
- Loss of response over time
- Costs of care

The Traditional IBD “Medicine Cabinet”



Over-the-Counter

Antibiotics

Aminosalicylates

Corticosteroids

Immunomodulators

Biologics

Small Molecules (e.g. Jak inhibitors)

5-ASAs: commonly reported adverse effects

- Headache
- Muscle or joint pain
- Nausea/vomiting
- Heartburn
- Burping/gas/bloating
- Constipation
- Slight hair loss
- Diarrhea

Consider:

Electrolyte deficiencies:

- Potassium, Magnesium
- Can be associated with muscle cramps, bloating/cramping,

Foods rich in magnesium and potassium

- Leafy greens (Mg, K)
- Nuts and seeds (Mg)
- Fish (Mg, K)
- Beans/lentils (Mg, K)
- Whole grains/Brown rice (Mg)
- Avocados (Mg, K)
- Dark Chocolate (Mg)
- Bananas (Mg, K)
- Low fat dairy – e.g yogurt (Mg, K)
- Dried fruit – e.g figs (Mg, K)
- Squash (K)

Not always compatible with a low fiber diet

I'm trying so hard not to like you because I know I can't have YOU.

Magnesium supplements may have a laxative effect



5-ASAs: common adverse effects

- Headache
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- Nausea/vomiting
- Heartburn
- Burping/gas/bloating
- Constipation
- Slight hair loss
- Diarrhea.

Consider:

Vitamin/Minerals deficiencies- Check iron, B12, folate, Zinc levels

- **Iron deficiency**: headaches, numbness, restless legs, fatigue, weakness, hair loss
- **Folic acid deficiency**: loss of appetite, diarrhea, irritability
- **B12 deficiency**: diarrhea, fatigue, swollen tongue
- **Zinc deficiency**: hair loss, eczema-like rash

5-ASA hypersensitivity

- Sulfasalazine – up to 30% of patients are sensitive to the sulfa component
 - Symptoms include nausea/vomiting, diarrhea, rashes
- Mesalamines/5-ASAs can also be associated with worsened symptoms of colitis.
 - If continued/worsened symptoms while on these agents, consider discontinuation

Help! There are tablets in my stool!

- Can occur with *delayed-release tablets*
- May be a factor of rapid gut transit
- Pills may not be readily dissolved to absorb in the colon
- If this happens frequently, may need to consider a different formulation of medication

Is this weird? My toilet bowl is stained purple...

- Can occur with mesalamine enemas, occasionally tablets/suppositories

Potential adverse effects to **STEROIDS**

Osteoporosis

- Bone density tests recommended
Avascular Necrosis
Myopathy

Fatty liver

GI upset
Nausea

Glaucoma
Cataracts

Sleep disturbances, psychiatric effects
Hyperactivity, increased appetite

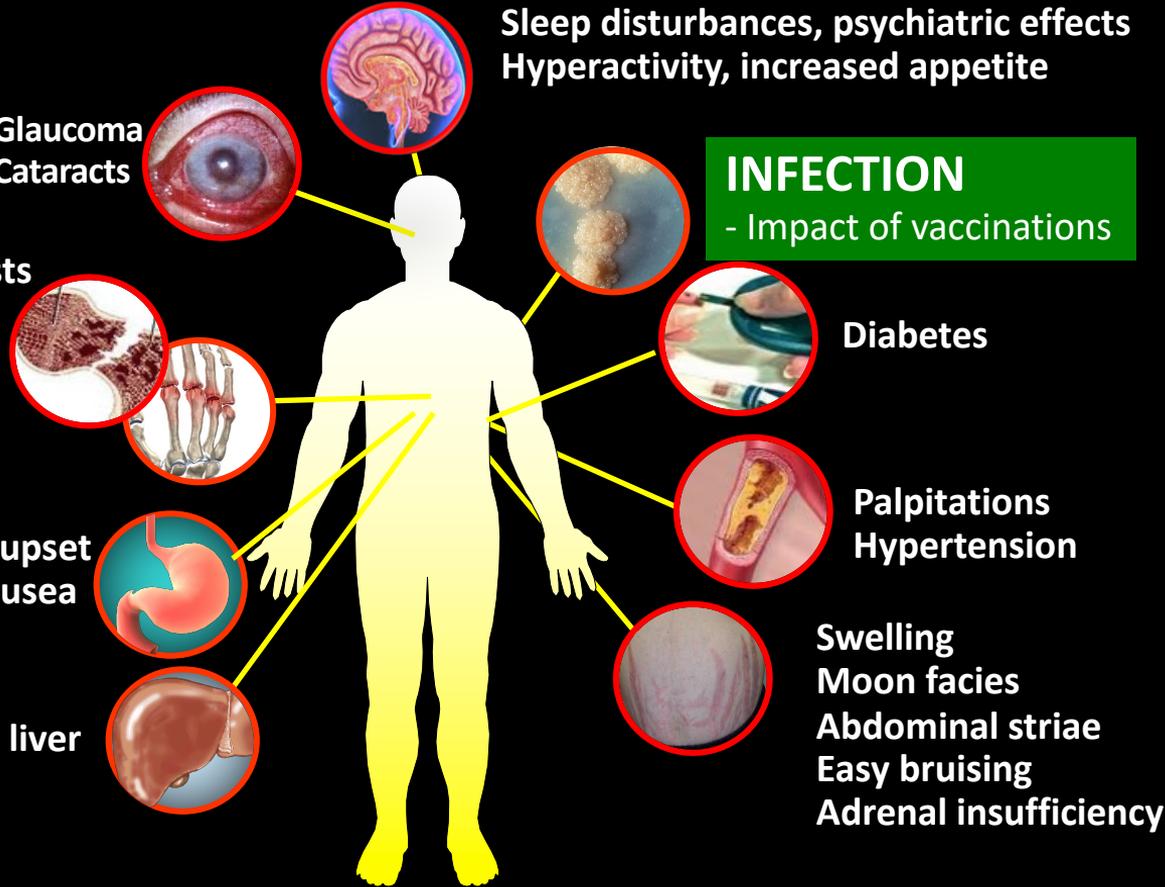
INFECTION

- Impact of vaccinations

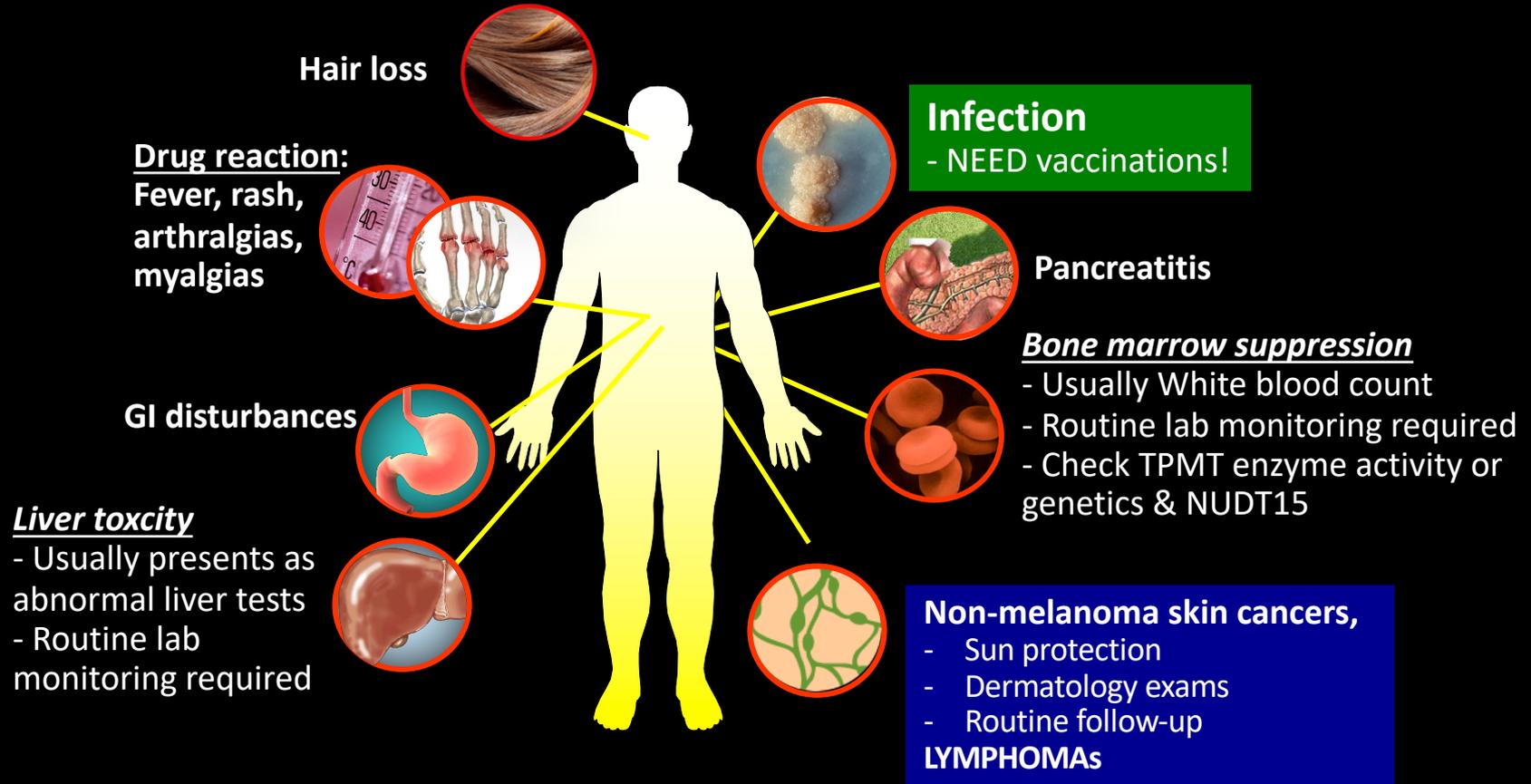
Diabetes

Palpitations
Hypertension

Swelling
Moon facies
Abdominal striae
Easy bruising
Adrenal insufficiency



Potential adverse effects to THIOPURINES



Potential adverse effects of Jak-inhibitors

Cardiovascular events

- lipid elevation



Infections

- NEED vaccinations!
(esp zoster)



Monitor liver enzymes



Monitor blood counts while on medication

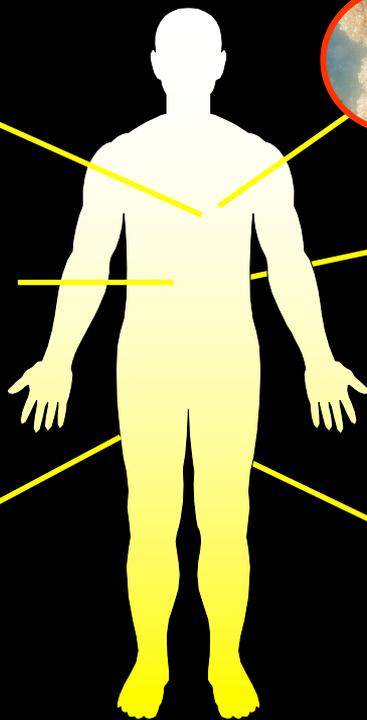
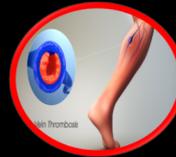


Skin cancers

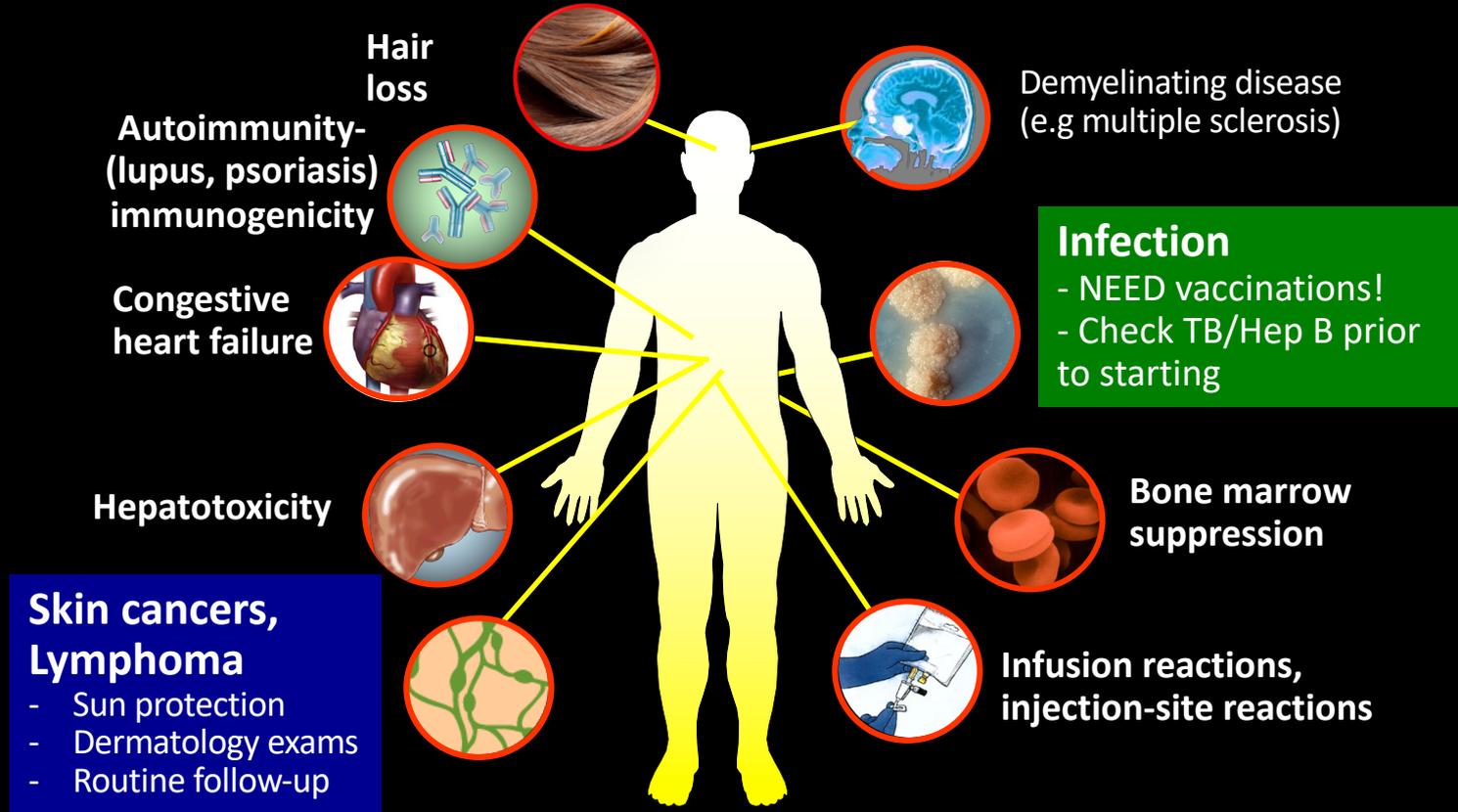
- Sun protection
- Dermatology exams
- Routine follow-up



Thromboembolic events
- Esp if older, CV risk factors present



Potential adverse effects of **BIOLOGICS**



Dermatologic side effects of biologic therapy

- **Psoriasis**
- Female predominance
- Estimated incidence of 1:1000 patient-years
- 50% of patients are able to continue TNF therapy with the use of treatment for psoriasis



Hair loss with IBD

- Vitamin/mineral deficiencies: Iron, B6, B12, Zinc
- Medication effect
 - 5-ASAs, thiopurines, anti-TNF therapies, steroids
 - Psoriasis associated alopecia
 - Drug-induced lupus



Hair loss with IBD

- Telogen effluvium – due to change in the number of hair follicles of growing hair
 - Decreased # of hair follicles producing hair results in an increased # of dormant/resting hair follicles
 - Results in shedding
 - Seen in chronic disease states, usually transient
- Autoimmune conditions associated with IBD
 - Alopecia areata



Recommended health care maintenance for IBD patients

- Physical exam & labs
- Bone densitometry – if steroid exposure history
- Eye & Dental exams
- Colonoscopy
- Skin exam
- Smoking cessation
- Pap smears
- Mammograms
- Prostate exams
- Anxiety/depression screens
- Vaccinations
 - Influenza *
 - Pneumovax/Prevnar *
 - Hepatitis A & B
 - HPV
 - Meningococcal
 - Tetanus
 - **Shingles**, chickenpox #
 - **MMR (live vaccine)** #

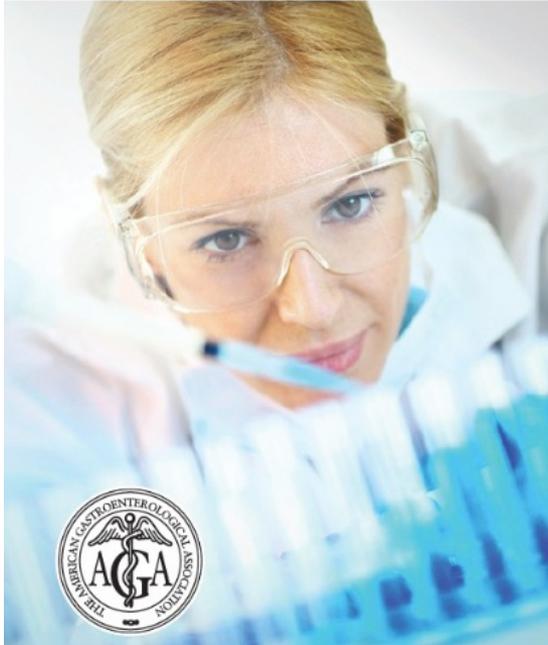
* Particularly if immunosuppressed

No Live vaccines if immunosuppressed

Biosimilars ≠ Generics

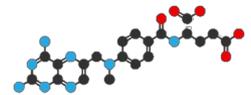
PHYSICIANS' POCKET GUIDE TO

Understanding Biologics and Biosimilars

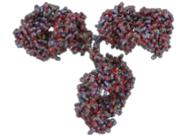


	Generics	Biosimilars
Size	Small	Large
Structure	Simple, well-defined	Complex (made up of many ingredients that are not well-defined)
Manufacturing	Predictable chemical process; exact copy can be made	Each manufactured in a unique living cell; similar, but not exact, copy can be made
Stability	Relatively stable	Highly sensitive to changes in environment (manufacturing and handling conditions)
Development cycle	Takes about 3 years to develop	Takes about 7 to 8 years to develop
Quality Assurance	About 50 QA tests done before possible approval	About 250 QA tests done before possible approval

Methotrexate
Simple² and well defined³



Monoclonal antibody
MW≈150,000 Da



Complex, with many options for post-translational modification⁵

Biosimilars: FDA definitions and requirements

- A biological product that is **HIGHLY similar** to the reference product notwithstanding **minor** differences in **clinically inactive** components
- No **clinically meaningful difference** between the biological product and the reference product in terms of:
 - Safety
 - Purity
 - Potency



Large and generally complex molecules



Produced from living organisms



Carefully monitored to ensure consistent quality



Purity



Molecular structure

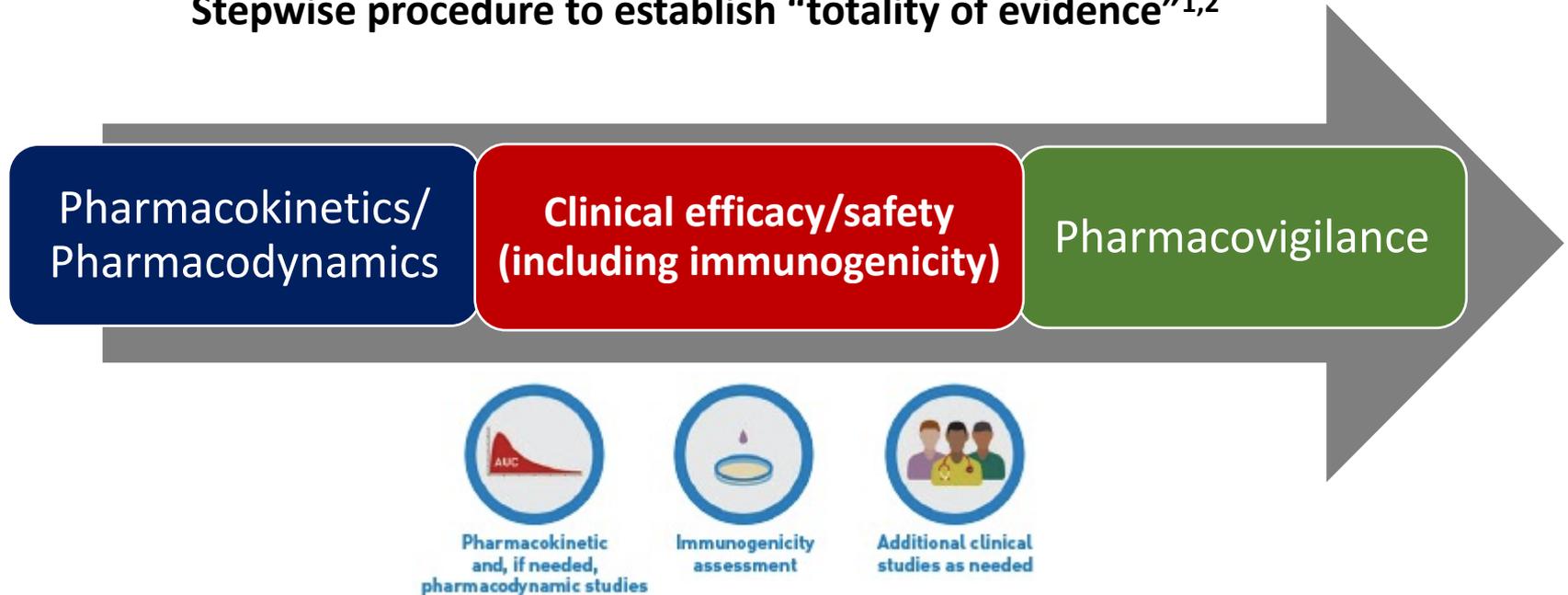


Bioactivity

The data from these comparisons must show that the biosimilar is highly similar to the reference product.

General Principles to demonstrate biosimilarity: “Totality of Evidence” Is Evaluated

Stepwise procedure to establish “totality of evidence”^{1,2}



1. FDA Guidance for Industry. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. HHS FDA/CDER/CBER, Apr 2015; 2. EMA CHMP Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-clinical and Clinical Issues, Jan 2015; 3. EMA CHMP Guideline on Similar Biological Medicinal Products, Oct 2014; 4. WHO Guidelines on Evaluation of Similar Biotherapeutic Products. Geneva, 19–23 Oct, 2009

IBD Biosimilars in the United States

Adalimumab Biosimilars

Abrilada (adalimumab-afzb)
Amjevita (ABP 501) (adalimumab-atto)
Cyltezo (BI 695501) (adalimumab-adbm)
Hadlima (SB5) (adalimumab-bwwd)
Hulio (adalimumab-fkjp)
Hyrimoz (adalimumab-adaz)

Infliximab Biosimilars

Avsola (infliximab-axxq)
Ixifi (infliximab-qbtx)
Renflexis (infliximab-abda)
Inflectra (CT-P13) (infliximab-dyyb)

...and many more to come

Positioning Biosimilars within IBD treatment paradigms:

- Same positioning as originator products for Infliximab or adalimumab naive patients
- If clinically significant antibodies present to Humira™, Remicade™ do not use the biosimilar
- If primary non-response to Humira™, Remicade™, then would not use the biosimilar
- If drug holiday (+ history of response), could use biosimilar in re-challenge
- Combination therapy with thiopurine or MTX still recommended in the right clinical context
- Biosimilar interchangeability is not permitted at the pharmacy level, but is appropriate at the provider level discussion

How to approach biosimilars with patients

- Inform early about biosimilar use
 - **ESPECIALLY IF SWITCHING**
- Define biosimilars and experience with the agents
- Emphasize biosimilars are not a new mechanism of action
- Same indications and dosing as originator agents (Remicade™, Humira™)

<https://www.fda.gov/media/130918/download>

Biosimilar Basics

Biosimilars are safe and effective biologic medications for treating many illnesses such as chronic skin and bowel diseases, arthritis, kidney conditions and cancer.



Biologic medications are generally made from **natural sources** and developed using advanced science.

Biosimilars are **FDA-approved** medications that are compared to another medication — the original biologic.



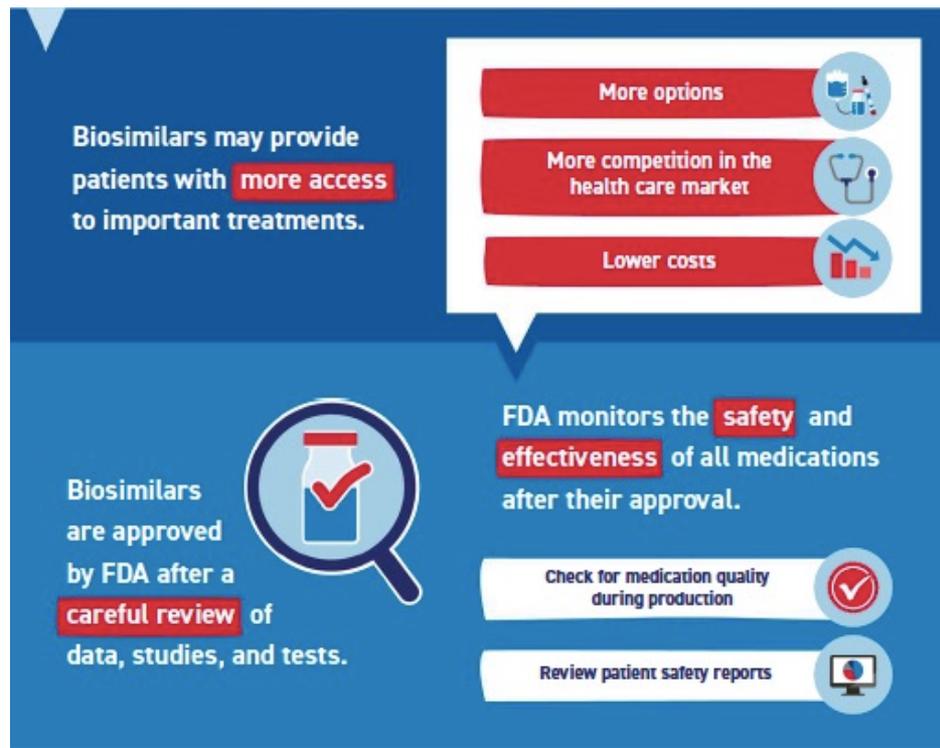
Biosimilar & Original Biologic

- Same benefits
- Same potential side effects
- Same strength and dosage
- Given the same way

Biosimilars are made with the same types of natural sources as the original biologic they were compared to — and **provide the same treatment benefits.**

How to approach biosimilars with patients

- Not compromising quality of care for costs of care
- Same monitoring strategy applies → “treat to target”
- Same therapeutic drug monitoring
- Same monitoring for adverse reactions



The infographic is set against a blue background. It features several text boxes and icons. A white speech bubble in the top right contains three red boxes with white text and icons: 'More options' with a pill and syringe icon, 'More competition in the health care market' with a stethoscope icon, and 'Lower costs' with a bar chart icon. A white box in the bottom right contains two white boxes with black text and icons: 'Check for medication quality during production' with a red checkmark icon, and 'Review patient safety reports' with a computer monitor icon. A magnifying glass icon is positioned over a pill bottle icon in the bottom left section.

Biosimilars may provide patients with **more access** to important treatments.

Biosimilars are approved by FDA after a **careful review** of data, studies, and tests.

FDA monitors the **safety** and **effectiveness** of all medications after their approval.

More options

More competition in the health care market

Lower costs

Check for medication quality during production

Review patient safety reports

Managing patients using biosimilars: Clinical considerations

- Help patients understand the difference between biologics to biosimilars
- Help patients feel comfortable using or switching to biosimilars.
- Understand that living with chronic illness is expensive, so cost-savings may matter to many patients.
- Show confidence about treatment choices.
- Remember the nocebo effect (patient doing fine on biologic, so any change is going to be attributed to biosimilar)

Resources for reference:

- For providers:

- <https://www.gastro.org/practice-guidance/practice-updates/biosimilars>
- <https://www.crohnscolitisfoundation.org/science-and-professionals/education-resources/whitepapers/biosimilars>
- <https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/biosimilars>
- <https://www.fda.gov/drugs/biosimilars/health-care-provider-materials>

- For patients:

- <http://www.aga-resources.com/biologics/guide/pubData/mobile/index.htm>
- <https://www.fda.gov/drugs/biosimilars/patient-materials>
- <https://www.crohnscolitisfoundation.org/what-is-ibd/medication/biosimilars>