Pharmacology Review 2023

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Main Topics

- IBD (Inflammatory Bowel Disease)
- GER (Gastro-Esophageal Reflux)

IBD vs. IBS

- IBD - Inflammatory Bowel Disease
- IBS - Irritable Bowel Syndrome

IBD

- IBD
  - Crohn's
  - UC
  - Indeterminate

Crohn's

- Peaks
  - Young Adulthood/50-60's
- Males: more in childhood
- Females: Overall more by 20-30%

Crohn's

- Affected Parents - more likely in kids
- 44-58% concordance in mono-twins
- CARD 15/NOD2
  - explains 20% of predisposition to CD
- TNF Alpha Gene

CARD 15

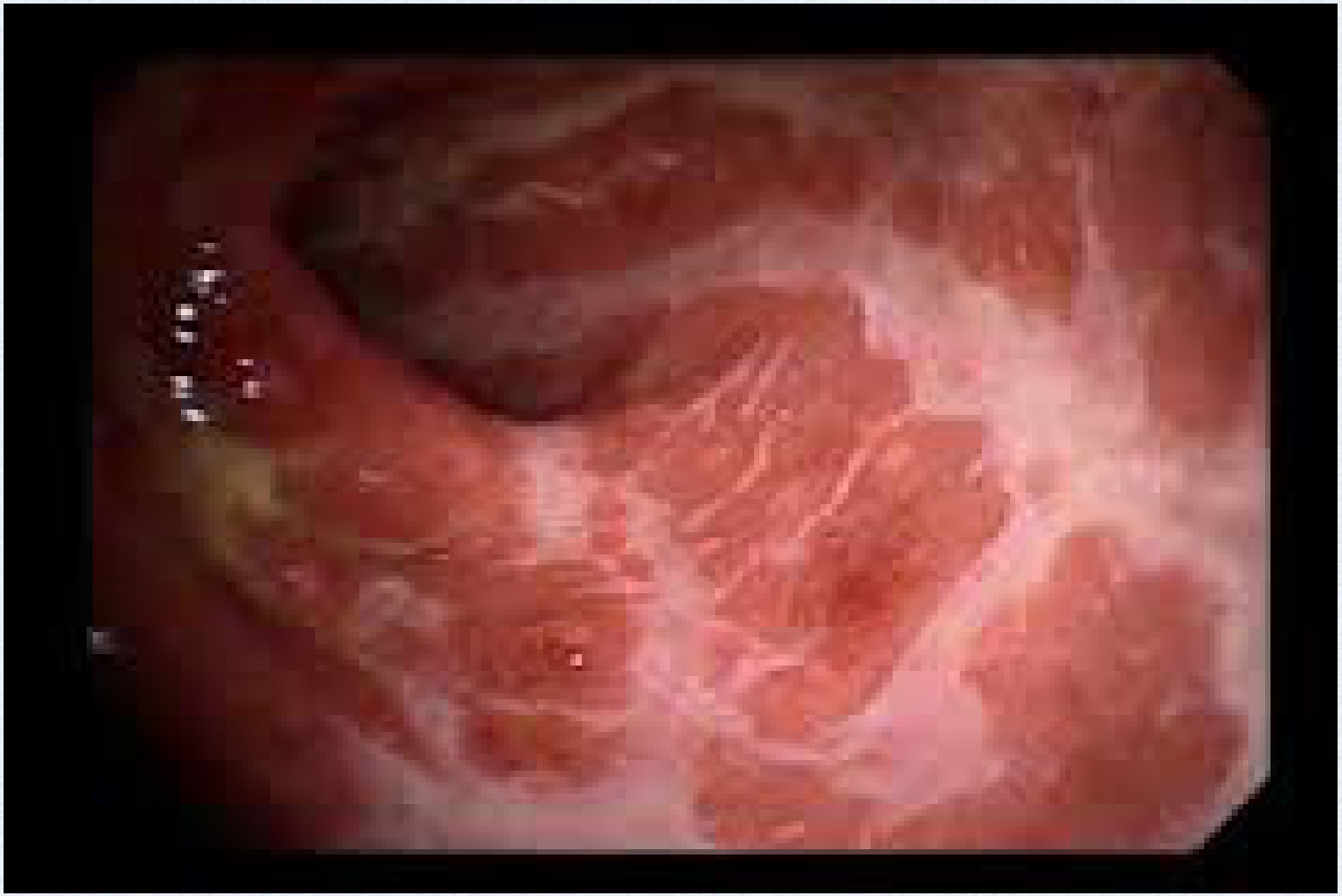
- Activation of kB (NF-kB) signaling cascade
- Mutations result in T-cell dysfunction
- Results in unrestrained Th1 activation

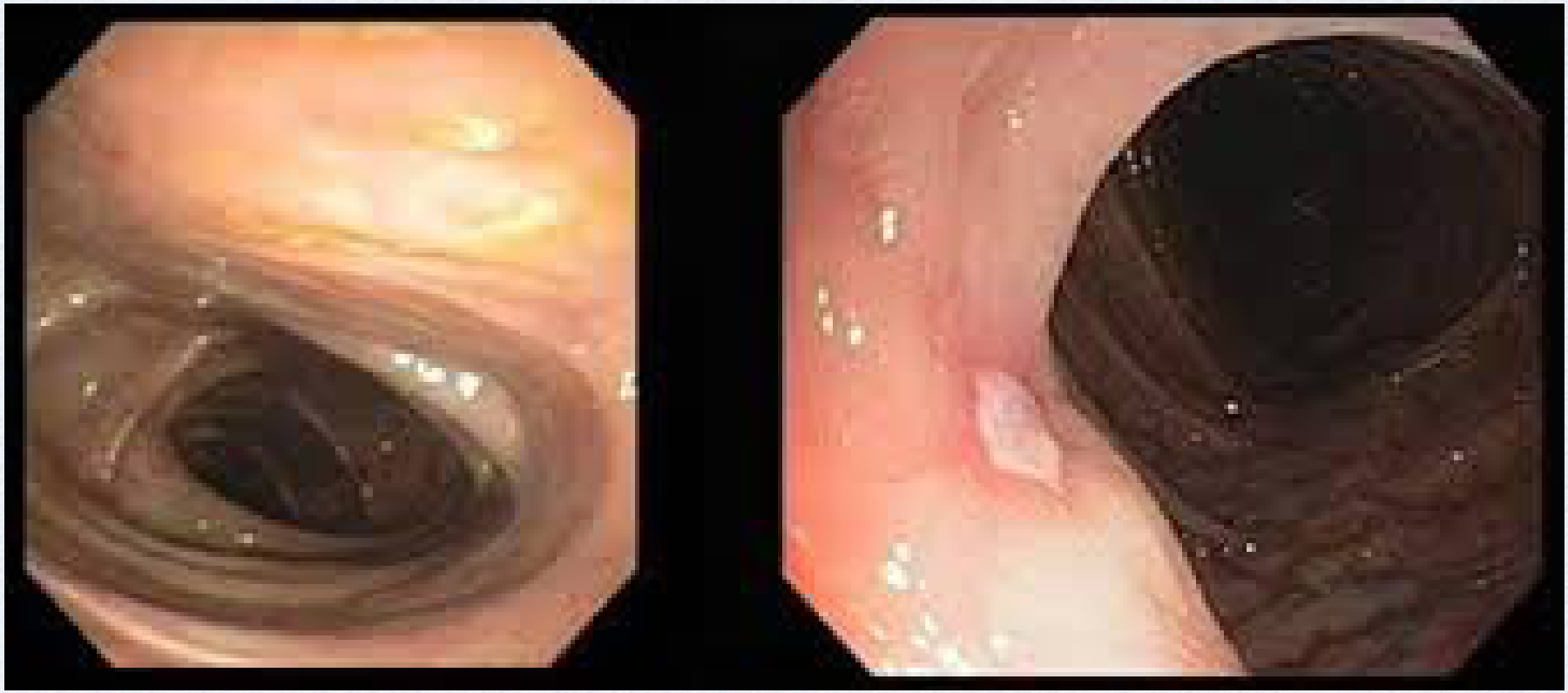
Crohn's

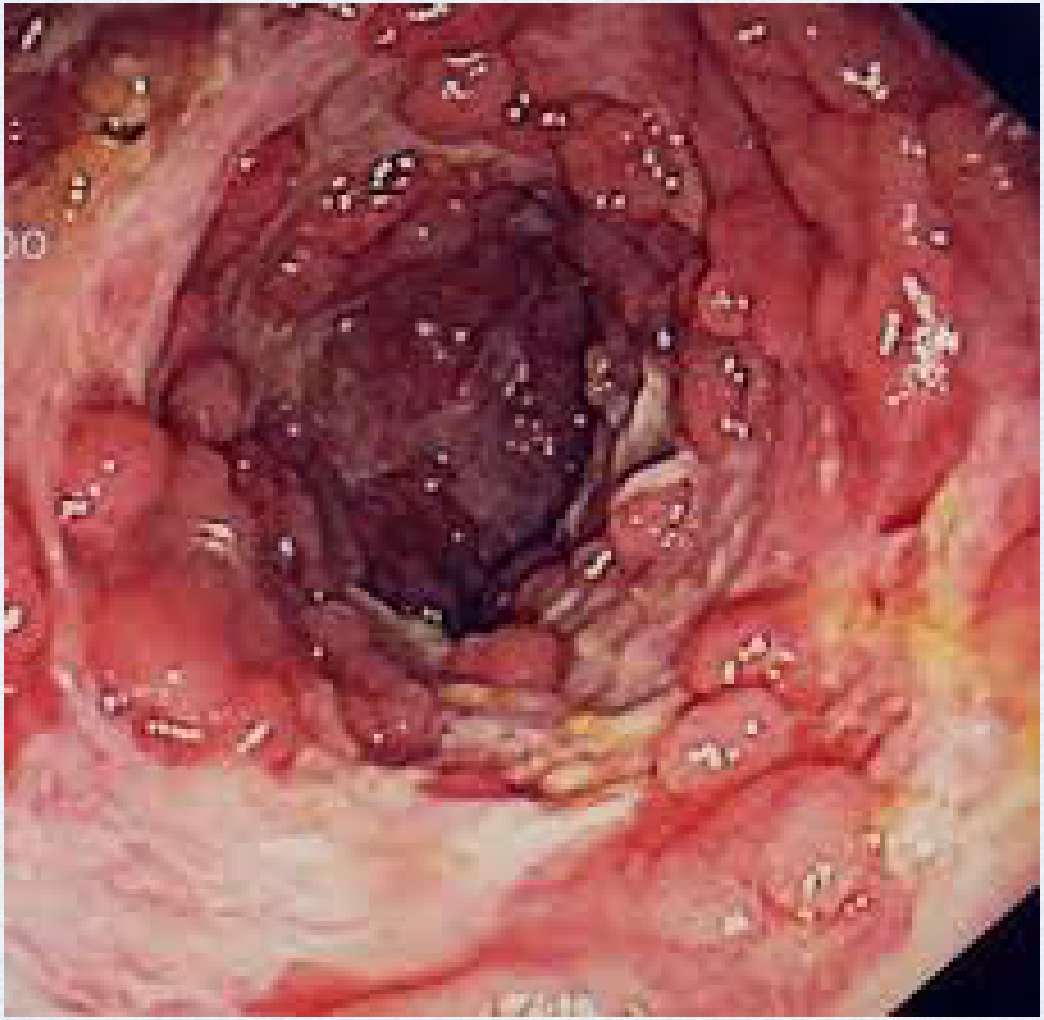
- Environmental
  - Maternal/Neonatal infections
  - Breastfeeding (? may reduce)
  - Smoking
  - OCP

Crohn's

- Panenteric
- Ileocolic>Colon>SB only>UGI
- Transmural
- Non-caseating Granuloma (like TB)
  - submucosa>mucosa (20-40% of Bx)
- Histology does not always correlate with clinical response

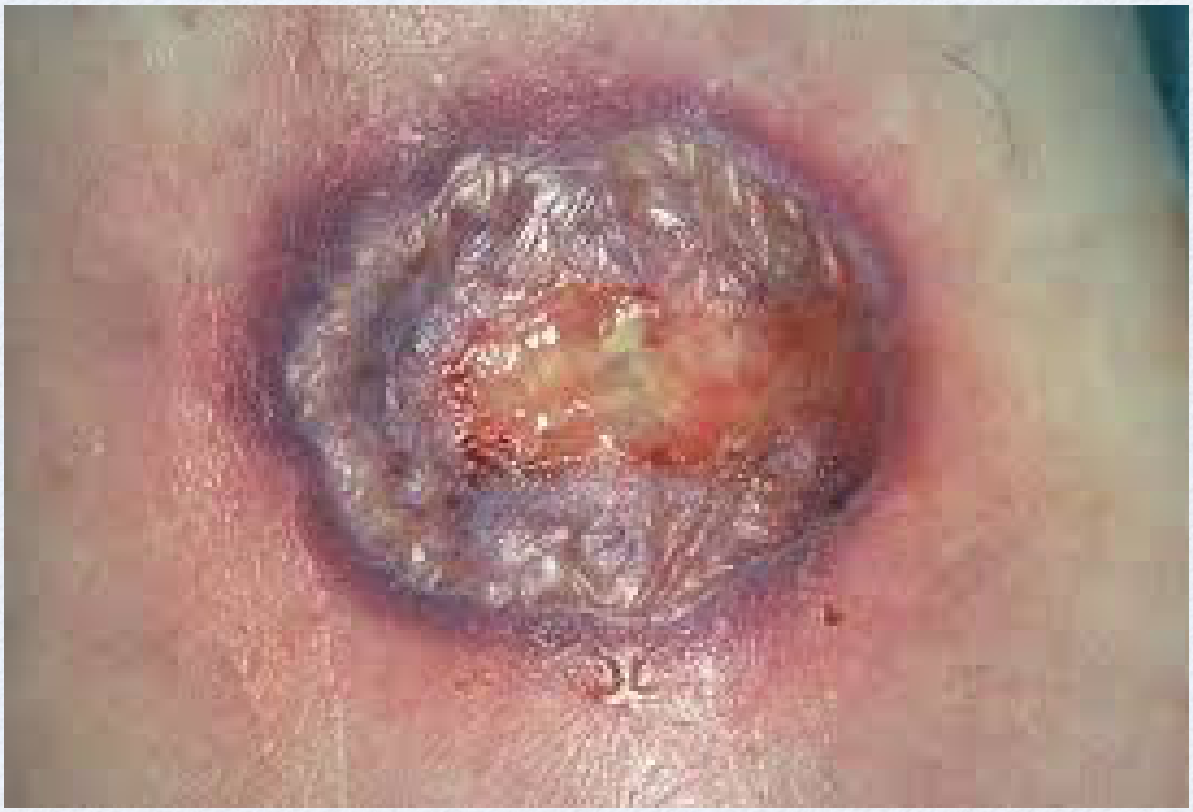


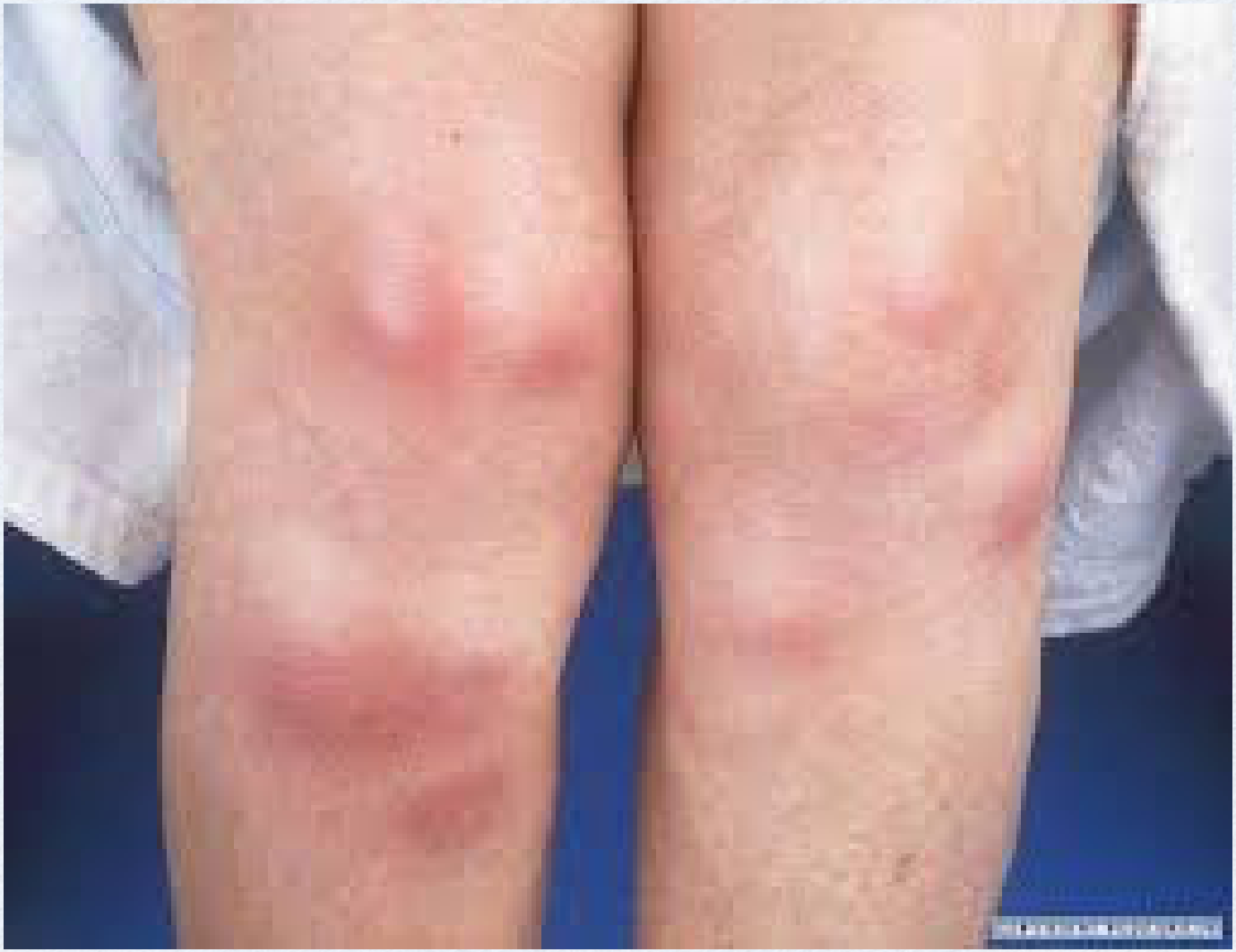


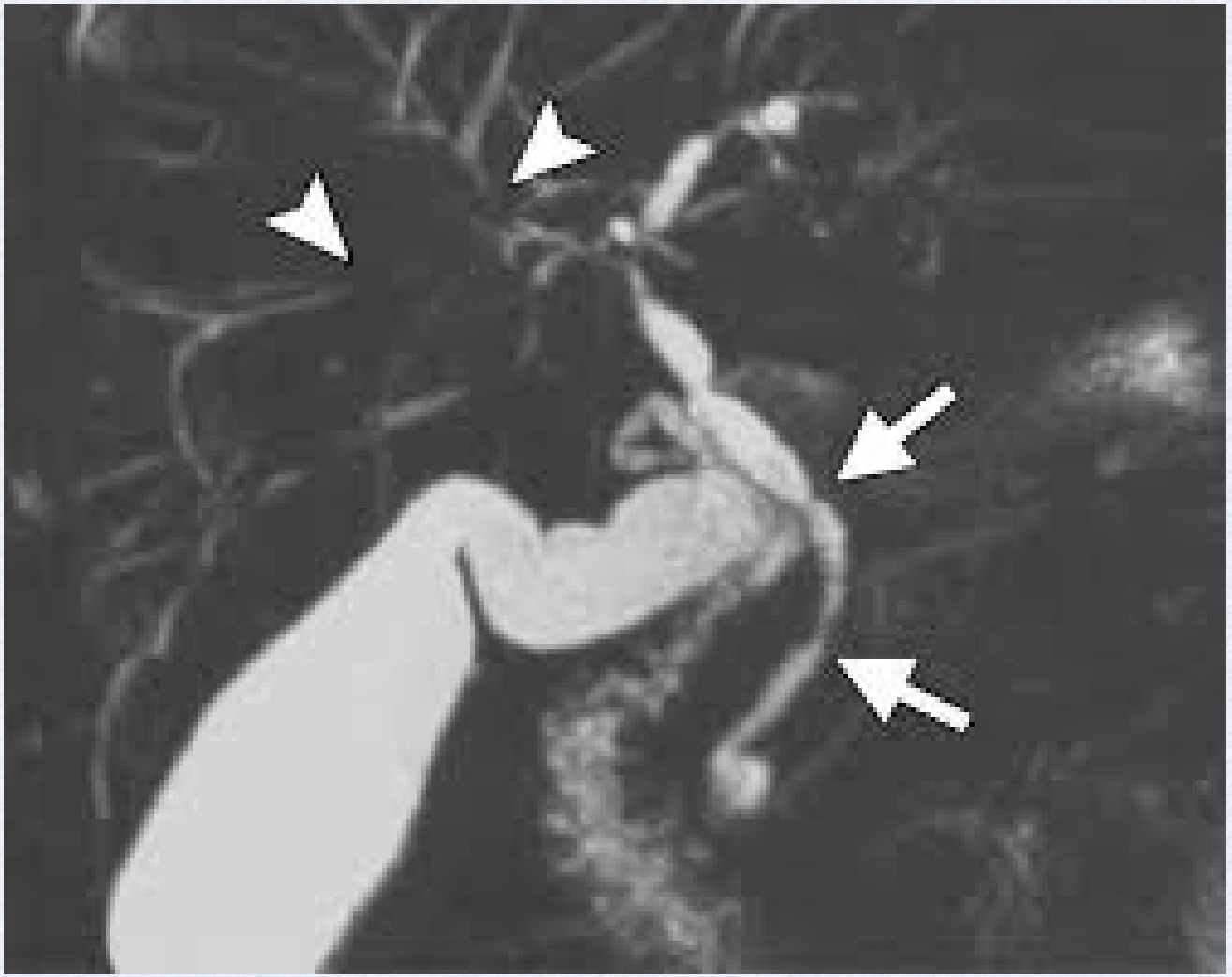


Crohn's

- Extraintestinal
  - Arthralgia/Arthritis
  - Erythma Nodosum/Pyoderma Gang.
  - PSC
  - Nephrolithiasis
  - Hypercoag (inc. 5&7&fibrin, dec. AT-III)
  - Decreased bone density

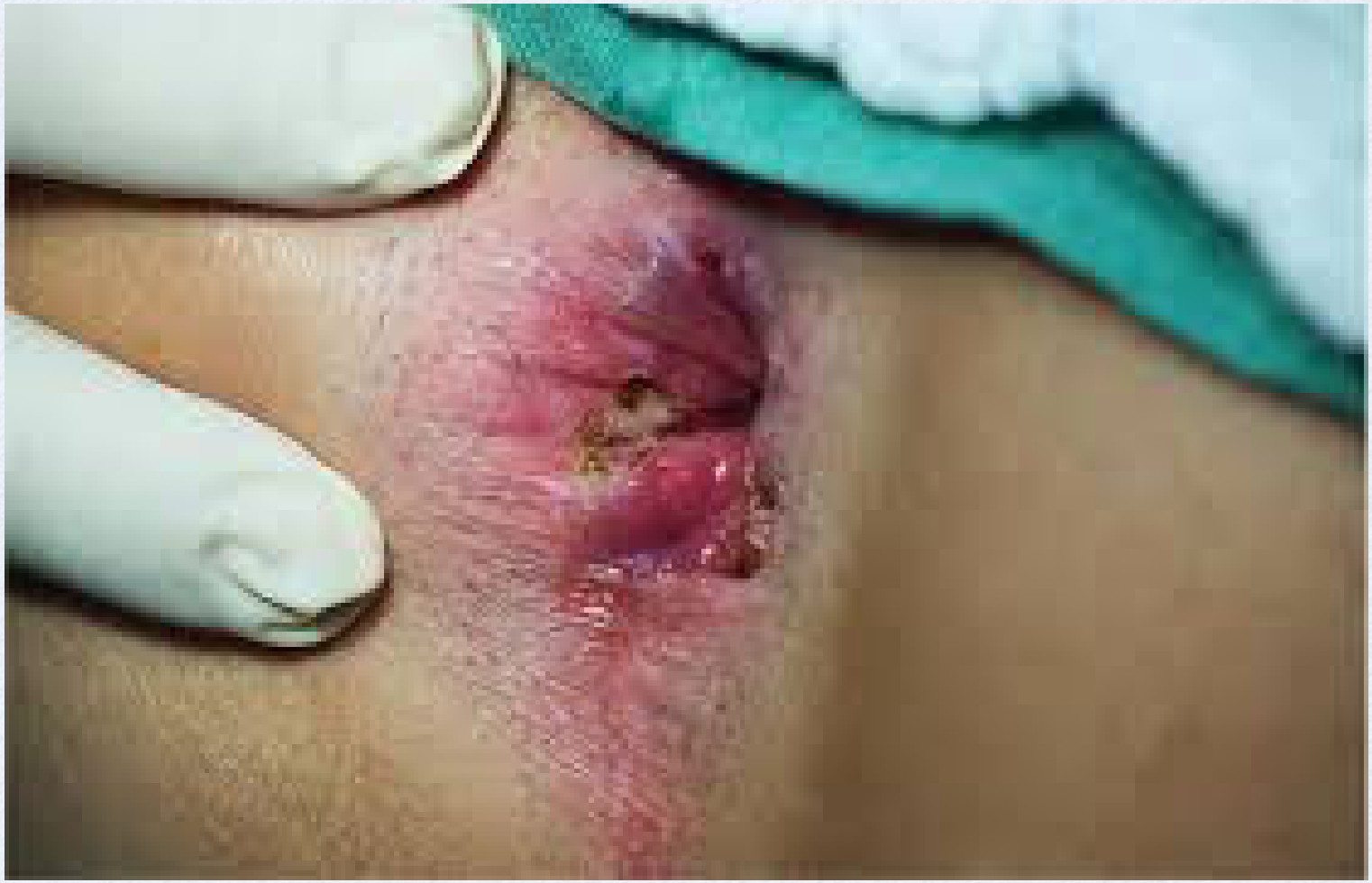


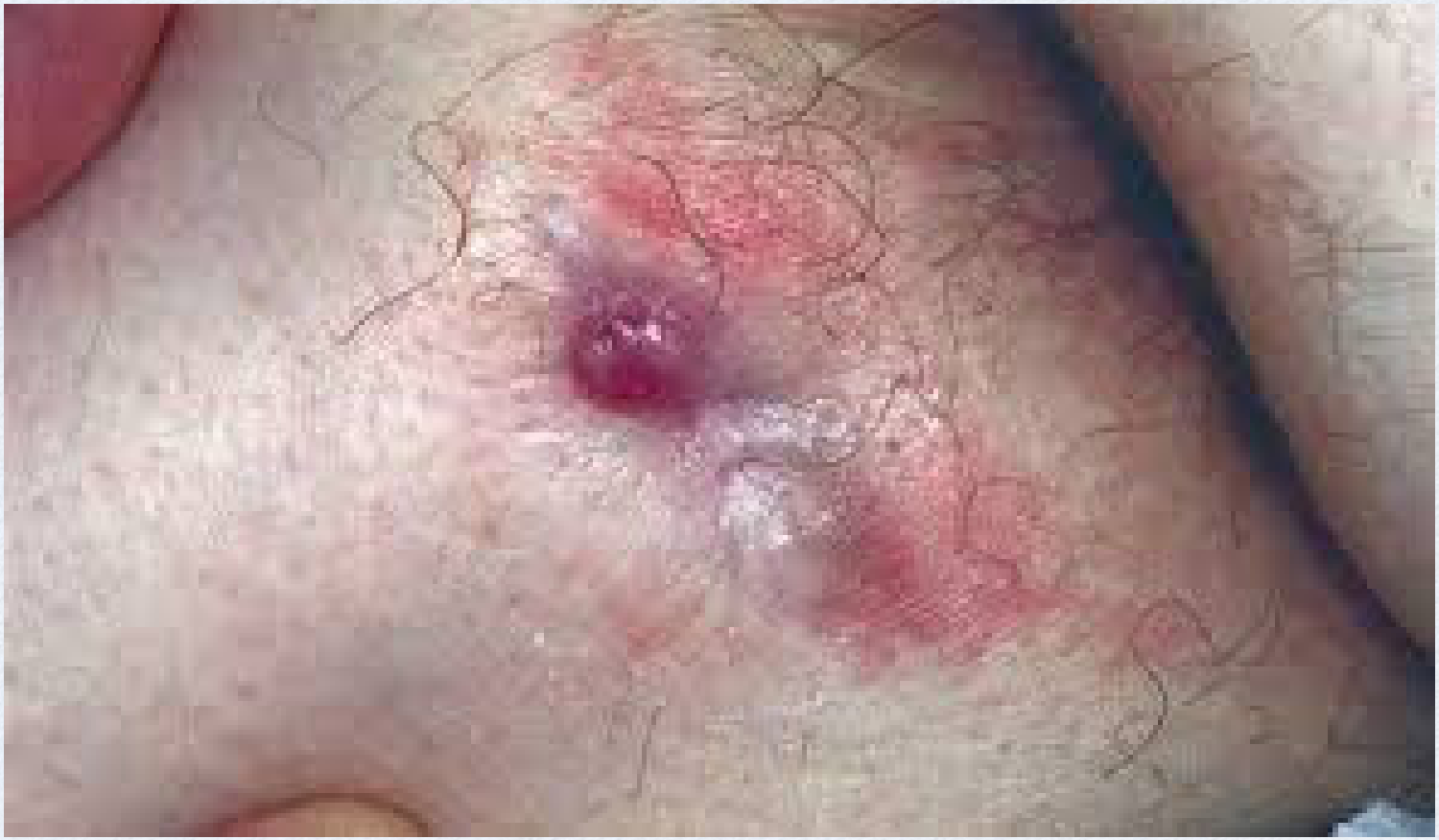


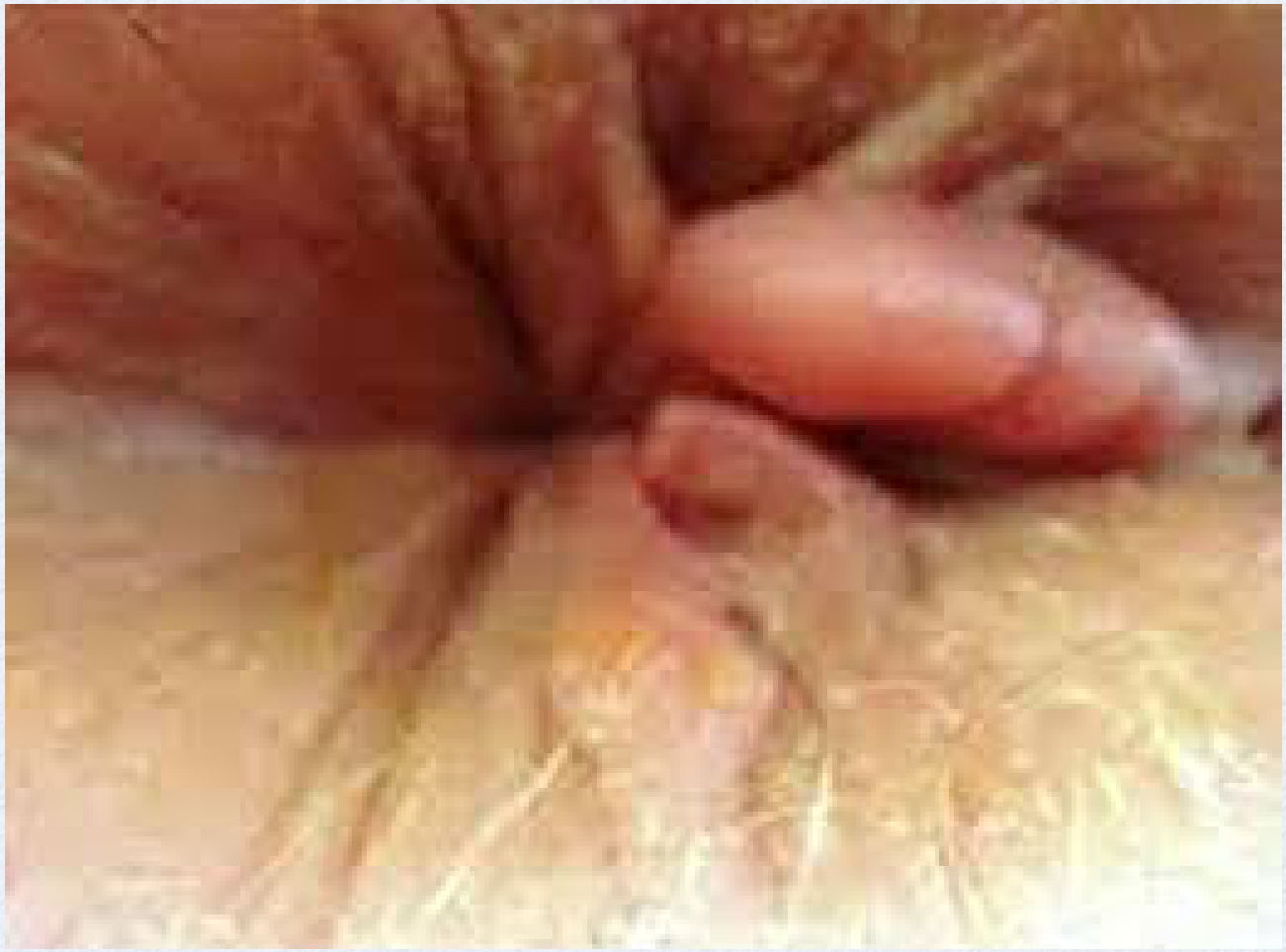


Crohn's

- FTT
  - Poor calorie intake
  - Low IGF-1 (high IL-6, malnut., steroids)
- Perianal Disease - 1/3 of patients
  - IBD 5 gene haplotype, 5q31







Crohn's

- Diagnosis
  - Biopsy
  - Exclude Infection
  - Serology
    - ASCA +, pANCA -

IBD Serology

- ☐ Pattern Consistent with IBD: Crohn's Disease
- ☐ Pattern Consistent with IBD: Ulcerative Colitis
- ☒ **Pattern Not Consistent with IBD**

Note: Pattern test results are based on the Smart Diagnostic Algorithm which interprets patterns among the assay values.

Prometheus diagnostic services provide important information to aid in the diagnosis and management of certain diseases. Test results should be used with other clinical and diagnostic findings to make a diagnosis and prognosis.

Assay	Assay Value	Reference Value
ASCA IgA ELISA	< 12.0 EU/ml	< 20.5 EU/ml
ASCA IgG ELISA	< 12.0 EU/ml	< 22.2 EU/ml
Anti-OmpC IgA ELISA	< 3.1 EU/ml	< 28.6 EU/ml
Anti-CBir1 ELISA	6.2 EU/ml	< 34.9 EU/ml
IBD Specific pANCA		
AutoAntibody ELISA	< 12.1 EU/ml	< 18.7 EU/ml
IFA Perinuclear Pattern	Not Detected	Not Detected
DNAse Sensitivity	Not Detected	Not Detected

Crohn's

- 1/3
  - No steroids
  - Remit and relapse
  - Chronically active disease
- Colorectal CA - 8% after 20 years
- 36% undergo intestinal resection by 5 years

UC

- Peaks at 2-3rd decade/5-6th Decades
- Highest incidence in 10-18yrs
- Equal in M:F
- Decreased risk in Smokers
- Jews>non-jews

UC

- +Fam Hx - 15-25%
- MonoZyg Twins > DiZyg Twins
- HLA class II genes
- Increased with Turners
- NSAIDS

UC

- Appendectomy - at early age, may decrease risk
- Early illnesses may increase risk

UC

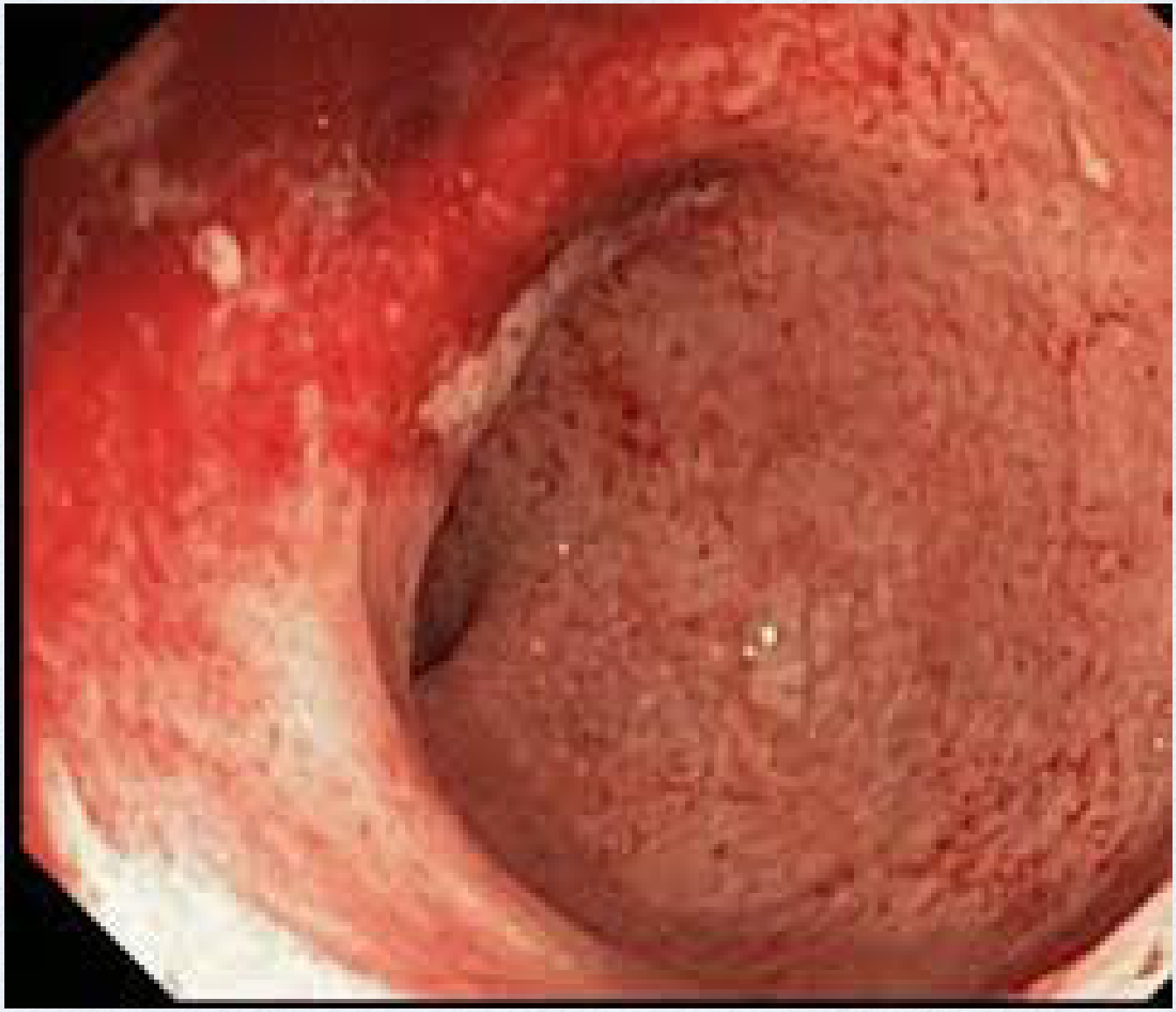
- Confined to the Colon
- Pancolitis>(?Rt Colon)>Left>Isolated Rectal
- Overall however, Rt colon most affected and rectum is almost always involved
  - But can have rectal sparing

UC

- Regenerating granulation tissue and residual mucosa may form pseudopolyps
- Paneth cell metaplasia of left colon
- Cryptitis, crypt abscess, surface erosions

UC

- Superficial inflammation
- Confluent (no-skip lesions)
- 1/3 - 1/2 of all cases of isolated left sided disease will extend to involve more proximal colon over time



UC

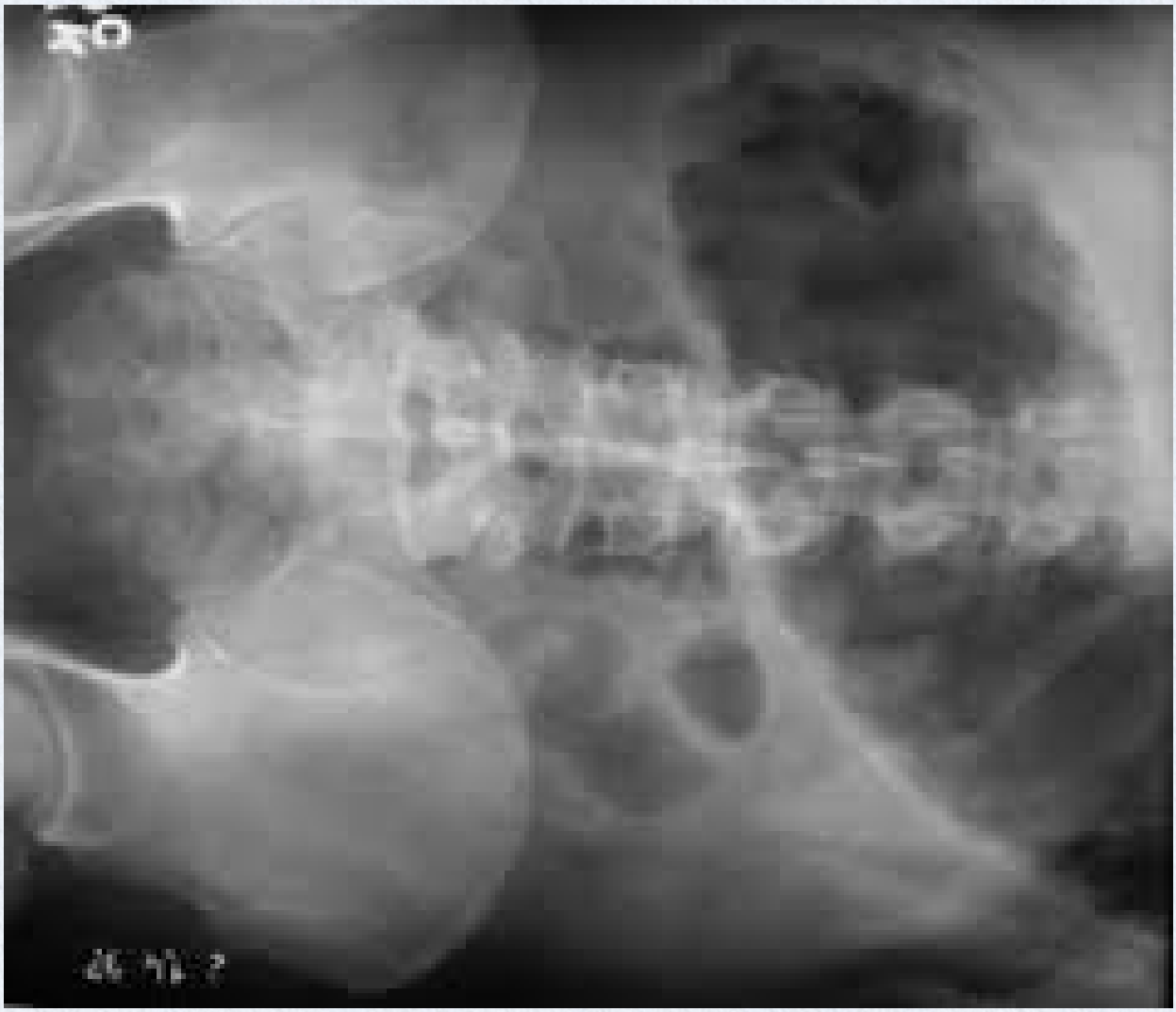
- Extraintestinal - 25-35% of patients
  - Arthropathy (20-25%)
  - Pyoderma Gang. (UC>CD)
  - Erythema Nod. (CD>UC)
  - Optho - Episcleritis/Uveitis
  - PSC

UC

- Hypercoagulopathy
- Osteopenia (steroids)
- Chronic recurrent Osteomylitis

UC

- Toxic Megacolon
  - >6cm dilation
  - Impaired motility agents
  - Rapid taper steroids, removal of 5-ASA



UC

- Colonic Strictures
  - Fibrotic
  - Associated with CA in adults
  - Usually occur in Rectum and Sigmoid
    - Smooth muscle hypertrophy

UC

- Colon CA Risk
  - Minimal at 8-10yrs of disease, but then increases 1% every year after
  - Risk correlates with extent of disease
  - Screening every 1-3 years after the initial 6-8years of disease

Peds IBD Treatment

- In-patient Vs. Out-Patient
  - Severity
    - Symptoms
    - Labs
    - Disease Distribution

Peds IBD Treatment

- Steroids
- 5-ASA
- Immunomodulators
- Biologics
- Other
- New

Steroids

- Induction of remission in mild-severe Disease
- Mechanism – Immune suppression via gene transcription
- Suppresses Pro-Inflammatory Mediators
  - Prostoglandins
- Anti-Inflammatory Mediators Increased
  - Interluekins (IL-10)
- Often leaves Mucosal Healing incomplete

Steroids

- Side Effects
  - Growth Delay, Bone Loss, Hyperglycemia, Hypertension, Mood Changes, Moon Facies, Buffalo Hump, Cataracts, Acne, Hirsutism, Insomnia
- ? Monitoring before starting therapy
  - PPD
  - CXR
  - Varicella
- ? Monitoring while on therapy
  - Growth
  - Eye Exam
  - Blood Sugar

Steroids

- PO
  - Prednisone
  - Budesonide
- IV
  - Solumedrol
- PR
  - Proctofoam
  - Steroid suppositories

Steroids

- Prednisone/Solumedrol
  - 1mg/kg/day, Max 40mg, Div. q12-q6
- Budesonide
  - Entocort
    - 9mg po q24 x8 weeks, then 6mg po q24 x2 weeks (then ? 3mg po q24 x2 weeks)
  - Uceris
    - 9mg po q24, x up to 8 weeks (I've done up to 12 wk)
- GI – Prophylaxis
  - H2 Blockers
  - PPI

5-ASA

- Sulfasalazine
- Mesalamine
- Use
  - Induction and remission of mild-mod UC
- Mechanism
  - Location
    - Depends on formulation of the drug
  - Anti-inflammatory action
    - Inhibits prostaglandin synthesis
    - Inhibits Leukotriene synthesis

5-ASA

- Side Effect
  - Headache
  - Nausea
  - Diarrhea
  - Nephritis (interstitial)
  - Leukopenia
  - Hepatitis
- Monitoring
  - CBC, LFT, BUN, Crt, UA (at least once per year)

5-ASA

- Dosing
  - Sulfasalazine
  - Mesalamine
    - Pentasa, Lialda, Apriso, Delzicol/Asacol
    - 50mg/kg/day div q8-24hr
      - Q8 – Pentasa
      - q12 – Delzicol/Asacol
      - Q24 – Apriso and Lialda
  - Balsalazide (Colazal)
    - 50mg/kg/day – div q12 (750mg tab)

Immunomodulators

- MTX
- Imuran (Azathioprine)
  - 6MP

AZA/6-MP

- Maint and Remission of IBD
- Mechanism
  - Anti-metabolite actions leading to immunosuppression and Toxicity
- Side Effects
  - Pancreatitis
  - Hepatitis
  - Sun Sensitivity
  - Bone Marrow Suppression
  - HSTCL
  - NMSC

AZA/6-MP

- Monitoring
  - Pre-Labs
    - Varicella
    - Acute Hep (A, B, C)
    - TPMT
      - 6-TG
      - 6-MMP
  - Labs While using
    - CBC
    - LFT

AZA/6-MP

- Dosing
  - 1.5-3mg/kg/day po q24hrs
    - Takes 2-3 months to build to therapeutic levels

MTX

- Induction and Remission of Mod-Severe Disease (not really used as mono-therapy)
- Help Fight Formation of Antibodies to other meds
- Mechanism
  - Effect Cytokine production (IL-2)
  - Blocks DNA Synthesis

MTX

- Side Effects
  - Nausea/Vomiting
  - Stomatitis
  - Anorexia
  - Diarrhea
  - Bone Marrow Suppression
  - Teratogenicity
  - Folate Deficiency

MTX

- Monitoring
  - Varicella
  - Acute Hep
  - CBC
  - LFT
  - ? Folate
  - ? Pregnancy Test

MTX

- Dosing
  - 1-1.5 (Up to 2.5) mg/meter-squared; up to 25mg per week
    - ½ dose if only using for suppression of antibody formation

Biologics

- Infliximab – Remicade, Renflexis, Inflectra, Avsola
- Adalimumab – Humira, Amjevita (2023), and 6 others not quite out yet
- Certiluzimab - Cimzia

Biologics

- Induction and Remission of Mod-Severe Disease
- Mechanism
  - MonoClonal IgG1 antibody to TNF-Alpha
    - Infliximab – Chimeric
    - Adalimumab – Fully Human
  - Neutralizes TNF
  - Blocks LT Migration
  - Induces apoptosis of T-Cells and Lymphocytes
  - Stops Compliment Fixation

Biologics

- Dosing
  - Infliximab
    - 5-10mg/kg/dose (q4-8 weeks)
  - Adaliumamb
    - <40 KG – 80, then 40, then 20mg qow
    - >40 KG – 160, then 80, then 20mg qow
  - Certiluzimab
    - 400mg qow

Vedoluzimab

- Entyvio
- Mechanism
  - Binds Alpha4Beta7 Integrin and blocks interaction with mucosal addressin cell adhesion molecule-1
  - Leads to an inhibition of memory T-cell migration into inflamed tissue
  - Monoclonal Antibody
- Dosing
  - 300mg Infusion; 0, 2, 6, 14 weeks

Ustenkinumab

- Stelara
- Mechanism
  - Binds to IL-12 and 23 cytokines
  - Reduces inflammation and altering immune response
  - Monoclonal Antibody
- Dosing
  - <55kg – 260mg
  - 55-85kg – 390mg
  - >85 kg – 520mg
  - Then 90mg q8 weeks

New(er) IBD Meds

- Xeljanz (Toficitinib)
- Ozanimod (Zeposia)
- Skyrizi (Risankizumab)

Xeljanz

- Tofacitinib
- Mechanism
  - Inhibits JAK 1, 2 and 3
  - Disrupts cytokine and growth factor signaling pathways
  - Clotting Seems to be an issue
- Dose
  - Tablet – PO
  - 5mg, po q12
    - Start at 10mg po q12 for 8 weeks, then decrease to 5mg po q12
      - May need to do 10mg q12 for up to 16 weeks

Zeposia

- Ozanimod
- Mechanism
  - ? Not exactly Sure
  - Selectively Binds Sphingosine 1 Phosphate Receptors
  - Reduces lymphocyte release from lymph nodes and migration into the CNS and Intestines
- Dose
  - Capsules
  - 0.23mg po q24 x 4 days
  - Then, 0.46 mg po q24 x 3 days
  - Then, 0.92mg po q24

Skyrizi

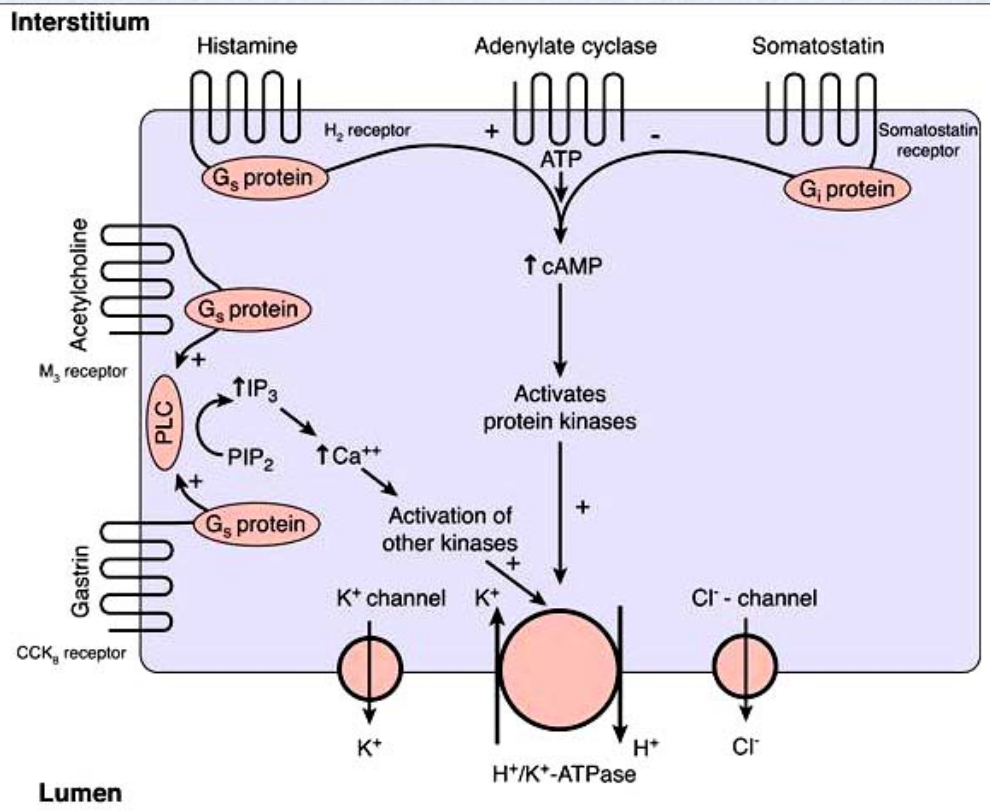
- Risankizumab
- Mechanism
  - Selectively Binds p19 Subunit of IL-23
  - Inhibits IL-23 Cytokine induced responses
  - Monoclonoal Antibody
- Dose
  - 600mg IV – 0, 4, 8
    - 360mg q8 weeks every 8 weeks

Considerations of GER

- What are we trying to accomplish?
  - Pain
  - Weight
  - Apnea/Cyanosis
  - Blood/Bile

Antacid Medications

- H2 Blockers
- PPI (Proton Pump Inhibitors)
- Other



Control of acid secretion in the parietal cell. ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; CCK = cholecystokinin; H_2 = histamine 2; IP_3 = inositol trisphosphate; PIP_2 = phosphatidylinositol 4,5-bisphosphate; PLC = phospholipase C.

H2 Blockers

- MOA
  - Reversibly inhibits parietal cell H2 receptors
  - Decreases gastric acid secretion
  - Decreases pepsin activity due to higher gastric pH
  - Decreases gastrin-stimulated gastric acid secretion
  - ***Does not affect gastric emptying or intestinal motility***

H2 Blockers

- Continued
  - May prevent heartburn if taken prior to meals
  - Onset of action within 20-60 minutes
  - Effects last up to 12 hours
  - Examples:
    - Zantac® (ranitidine)
    - Axid® (nizatidine)
    - Pepcid® (famotidine)
    - Tagamet® (cimetidine)

H2 Blockers

- Indications
  - Symptomatic relief of GERD and dyspepsia/pyrosis
  - Ulcers (but not as well as PPI)
  - Used as an adjunct in treating systemic allergic reactions because of histamine antagonism
  - Less effective than proton pump inhibitors overall
  - Main action is reduced secretion of the parietal cell

H2 Blockers

- Side Effects
  - 1%–6% of patients experience fatigue, dizziness, headaches, dyspepsia, nausea, abdominal pain, flatulence, constipation or diarrhea
  - Ranitidine use is associated with increased risk of pneumonia in ICU patients.
    - Mechanism may be related to reduction in antibacterial effect of gastric acid and alterations in intestinal flora
      - ? increased issue with PPI as well
  - Cimetidine blocks activity of cytochrome P-450 (more so than other H2 blockers), leading to higher risk of drug interactions

H2 Blockers

- Can alter heart rate
- Patients may experience nocturnal breakthrough of symptoms
- Limited long-term use: rapid development of tachyphylaxis
- Cimetidine can cause reversible gynecomastia via binding to androgen receptors
- Renal excretion of drug requires reduced dosing for renal insufficiency

H2 Blockers

- Dosages
  - Famotidine - 1-2mg/kg/day div q12
  - Ranitidine - 4-10mg/kg/day div q6-12

PPI

MOA

- Irreversible binding to the final common pathway of gastric acid secretion, parietal cell H+/K+ ATPase
- Produces >90% decrease in total daily gastric acid secretion
- Most effective when given 15–30 minutes prior to meal
- Delayed onset of action (2–5 days) and longer duration (24 hours–3 days) than H2 receptor antagonists
  - Children may benefit from twice-daily dosing because of a higher metabolic rate
    - But then compliance becomes an issue...

PPI

- MOA
  - Degrading capsules reduces efficacy secondary to reduced absorption with exposure to gastric acid
    - Capsules can be opened and mixed with an acidic substance (yogurt, juice, applesauce or pudding)
  - Metabolized by cytochrome P450 to inactive metabolites which are excreted in the urine
  - Examples: Nexium® (esomeprazole), Prevacid® (lansoprazole), Prilosec® (omeprazole), Protonix® (pantoprazole), Aciphex® (rabeprazole), Dexilant® (dexlansoprazole)

PPI

Indications

- More effective acid suppression than that obtained with H2 antagonists
- Indicated and effective for treatment of moderate-severe GERD symptoms, acute or chronic esophagitis, erosive esophagitis or complicated GERD (stricture, ulcers, Barrett esophagus)
- Upper GI bleeding
- Peptic ulcer disease
- Zollinger-Ellison syndrome
- Helicobacter pylori infection

PPI

Side Effects

- (?) No dose-dependent side effect profiles (I have to wonder about this)
- Metabolized in the liver (use with caution in patients with severe liver disease) and excreted via urine
- Headaches, neurologic/psychiatric (fatigue, dizziness, confusion, rash/urticaria, gynecomastia, GI (4% – constipation, abdominal pain, diarrhea, flatulence, or 2% nausea and dyspepsia), vomiting, abdominal pain, transaminitis, urinary sodium loss
- Prolonged hypochloridia increases gastric bacterial overgrowth
  - ? related issues of increased GI infections (? C diff)

PPI

Side Effects, Cont'

- N-nitrosamine metabolites are generated secondary to gastric bacterial overgrowth (can be carcinogenic)
- B12 deficiency (alters activity of Intrinsic factor)
- Fundic polyps/nodules
- Rebound hypersecretion warrants gradual dose reduction/weaning - MAYBE
- Drug interactions: decreased absorption (ketoconazole, itraconazole, iron salts, vitamin B12, griseofulvin), increased absorption (digoxin, nifedipine)
- Can increase levels (CYP 450) of some antiepileptics, warfarin and methotrexate

PPI

- Dosing
  - Pediatrics - 0.5-2mg (1mg)/kg/day (oral)
  - IV – Continuous (Pantoprazole) – 80mg x1, then 8mg/hr, x 72hrs
    - Protonix (pantoprazole) and Nexium (Esomeprazole) – Nexium (Esomeprazole)
      - <55kg – 10mg IV q24 x10 days
      - >55kg – 20mg IV q24 x 10 days

Sucralfate

- Mucosal barrier agent
- Sulfated disaccharide linked to AL(OH)3
- Mechanism of Action
  - In an acid environment (pH <4), sucralfate undergoes cross-linking, producing a adhesive polymer attracted to positively charged protein molecules of the mucosa
  - Increases local production and release of prostaglandins

Sucralfate

- Sucralfate should be taken on an empty stomach 1-2 hour prior to meals
- Sucralfate functions better in an acid environment
  - Should not be taken within 20-30 minutes of antacids
- Doses of 40–80 mg/kg/day divided every 6 hours have been used (I shoot for 60mg)
  - Use the liquid, not the pills

Sucralfate

- Constipation is the most frequent adverse effect
- Other side effects: diarrhea, nausea, vomiting, gastric discomfort, flatulence, indigestion, dry mouth, pruritis, back pain, headache, dizziness, insomnia, sleepiness and vertigo
- Aluminum salt is minimally absorbed but can accumulate in renal failure; use with caution in premature patients, and in those with renal failure or on dialysis
- Sucralfate can inhibit absorption of other drugs

Calcium Carbonate

- $CaCO_{3(s)} + 2\ HCl_{(aq)} \rightarrow CaCl_{2(aq)} + CO_{2(g)} + H_2O_{(l)}$
- Directly binds with acid, to produce Bicarb and water
- Causes increased eructation, and can cause constipation
- Also can be Magnesium Carb or Sodium Bicarb
  - Be careful, as Mag and Na have to be excreted by renal pathway
  - Take care in use for renal impairment

- 1) S. Guandalini, et al. Essential Pediatric Gastroenterology, Hepatology & NutritionMcGraw-Hill, NY, 2005. Chapters #5 (constipation), #13 (GERD), #21 (Crohns disease and colitis), #30 (Commonly Employed Drugs: Dosage Recommendations and Side Effects
- 2) Kleinman, et al. Walker's Pediatric Gastrointestinal Disease 5 People's Medical Publishing House - USA, Chelton, CT, 2008. Chapter 9.2 (Acid-Peptic Disese), 11.2 (Motility Disorders), 20.5 (a & b - Chronic IBD), 24.2A (Functional Constipation
- 3) Wyllie, et al. Pediatric Gastrointestingal and Liver Disease 4th EditionElsevier-Saunders, Philadelphia, PA, 2011. Chapter 12 (Constipation and Fecal Incontinence), 22 (Gastroesophageal Reflux), 29 (Gastric Motility Disorders), 44 (Crohn's Disease), 45 (Ulcerative Colitis in Children and Adolecesnts
- 4) Judith Sondheimer, et al.The NASPGHAN Fellows Concise Review of Pediatric Gastroenterology, Hepatology and Nutrition - 1st EditionCastle Connolly Graduate Medical Publishing, Ltd, 2011, NY, NY Section 1 (Mouth and Esophagus), 2 (Stomach), 4 (Colon), 10 (Therapy

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