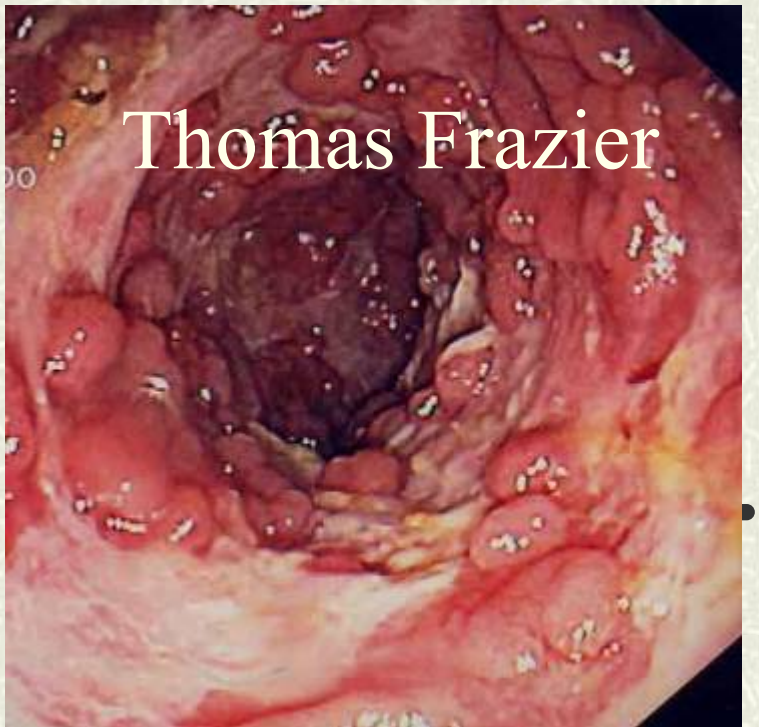
Challenging Issues in Crohn's Disease



Thomas Frazier

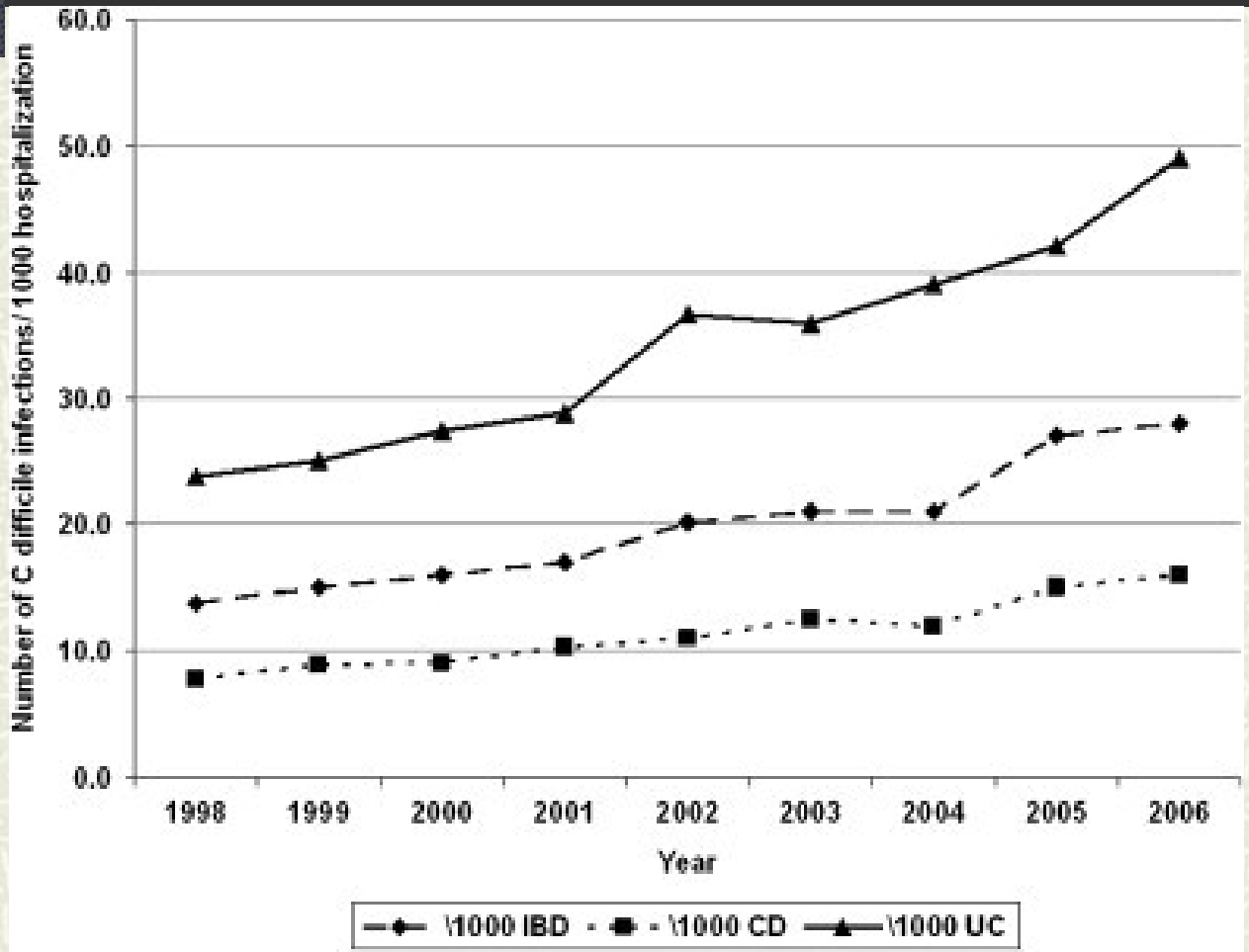
Objectives

- Case presentations of Crohn's Disease
- Emphasize challenges we may encounter
  - boards
  - real life

Case 1

- 25 y/o wm with 5 y/o crohn's colitis presents with diarrhea + leukocytosis. Previously under well control with Imuran. No history of recent antibiotics.
  - What are the patients risk factors for CDI?
  - What are the diagnostic tests of choice?
- Stool toxin A +B is negative in one sample, is it safe to start steroids for IBD flare?
- Flexible sigmoidoscopy reveals diffuse ulcerations and erythema (no pseudomembranes). Is it safe to say they don't have CDI?

C.Diff and IBD



Ananthakrishnan AN, Issa M, Binion DG. Clostridium difficile and inflammatory bowel disease. Gastroenterol Clin North Am. 2009 Dec;38(4):711-28.

IBD patients and *C.difficle*

- Dramatic increasing incidence
- Especially IBD involving colon
- Increased morbidity
- Longer hospital stays
- Increased mortality (4.2%)

C. Diff and IBD

- Abx exposure not required
- Risk Factors
  - Maintenance immunosuppression
  - H/o C.diff (50% risk of reinfection)
  - Ileoanal pouch reconstruction (C.diff can infect J-pouch)

Diagnostic Dilemma

- One stool sample for toxin A + B = 50% detection rate
- Four stool samples = detection rate of 90%
- Endoscopically NOT CHARACTERISTIC in ~ 50%

CDI + IBD: Treatment

- 10% of patients at the initial diagnosis of IBD have concomitant C.diff
- C.diff will precipitate IBD flare
  - Both must be treated
  - You must be persistent with testing
- Outpatients: (~40%) rx with flagyl
- Hospitalized patients: oral vancomycin

CDI + IBD: Treatment

- Treatment of concomitant IBD is important but..
  - Maximal doses of IV steroids SHOULD NOT BE USED
  - TNF-alpha blockers can be used in an attempt to avoid colectomy (may be important to c.diff mediated toxicity)
  - Enteral nutrition
  - IV flagyl
  - *Saccharomyces boulardii*
- Relapse/Recurrence = 50%
  - 50% of these patients required colectomy

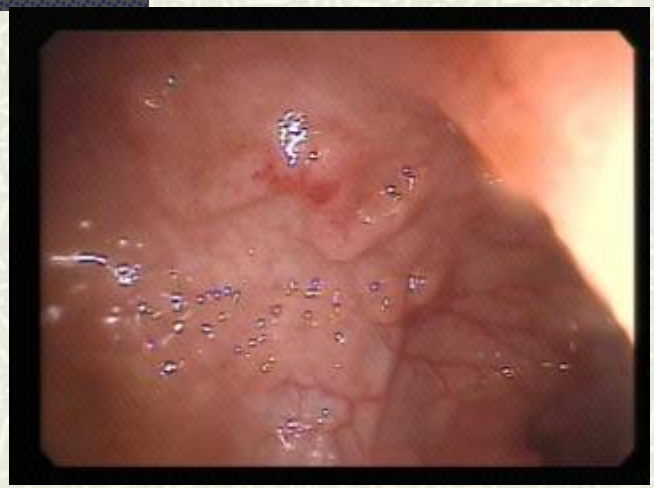
CASE 2. AIM Clinic Patient

- 35 y/o wm presents to multiple E.D.'s with 2 weeks of severe left sided abd pain, N/V, diarrhea. +10lb unintensional wt loss
- PMHx: chronic abd/back pain, gunshot wound to abdomen
- Meds: Lortab + Xanax
- Exam: not an acute abdomen, ill appearing, mildly obese (BMI~30)
- Labs
  - WBC: 17K (87% GRAN)
  - ESR: 7, CRP: 0.43. TOX: + THC/Benzo's

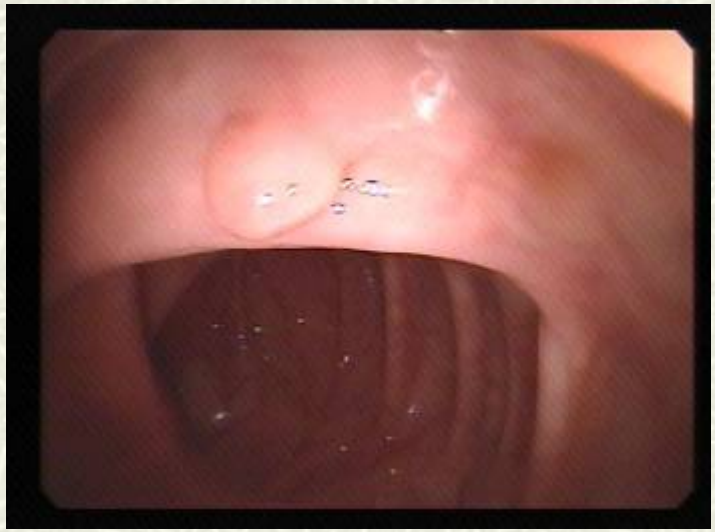
CASE 2

- Stool Negative for Salmonella, Shigella, E coli O157:H7, and Campylobacter
- Stool WBC, Cdiff, and occult blood negative
- CT abd/pelvis
  - 1. Marked bowel wall thickening of the ascending colon, measuring up to 9 mm in width, with mild wall thickening of the sigmoid colon, measuring up to 5 mm in width. The density of the wall appears more fatty than edematous. This likely represents a chronic colitis. An acute component is not excluded however.
  - 2. Lingular atelectasis in both lung bases.

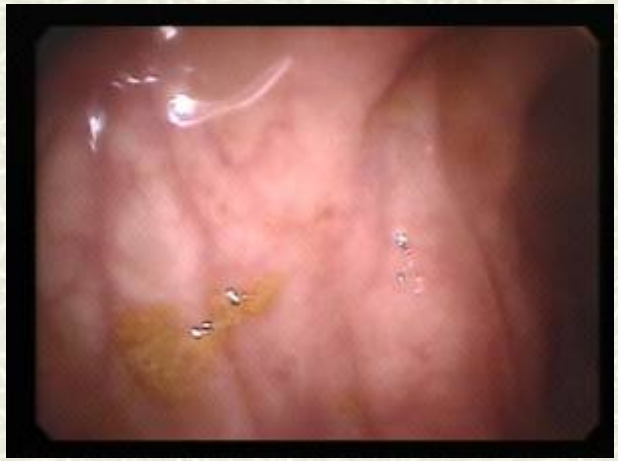
Case Endoscopic Views



petechia and erythema in the Terminal ileum



ascending colon polyp



erythema in descending colon

Biopsies

- Terminal Ileum, Biopsy: - Chronic active inflammation. - Villous blunting and crypt loss. - Regenerative changes.
- COMMENT: diffuse lymphoid infiltrate, immunohistochemical stains and in situ hybridization were performed to characterize the nature of the lymphoid infiltrate. Morphology, immunohistochemistry, and in situ hybridization favor a reactive lymphoid infiltrate.

Biopsies

- Ascending Colon Polyp, Biopsy: - Chronic active inflammation. - One crypt abscess. - No crypt architectural abnormalities or crypt loss. - Focal fibrosis of lamina propria. - No epitheloid granulomas identified.
- COMMENT: These histomorphologic features can be seen in an inflammatory pseudopolyp.

Biopsies

- Random Right Colon, Biopsies: - Poorly formed granulomas. - No active inflammation. - Focal lymphoid infiltrates.
- COMMENT: Immunohistochemical stains and in situ hybridization were performed to characterize the nature of the lymphoid infiltrate (M10-10482). Morphology, immunohistochemistry, and in situ hybridization favor a reactive lymphoid infiltrate.

Biopsies

- Descending and Sigmoid Colon, Biopsies: - Nonspecific inflammation. - Poorly formed granulomas.
- COMMENT: The histopathologic changes could be seen in Crohn's disease. Clinical and endoscopic correlation are required.

Case 2

- Given 2 weeks of flagyl + levaquin
- Continued wt loss + pain.
- What should we do?
  - 5-ASA
  - Refill percocet
  - Trial of steroids
  - Watch
  - Capsule
  - Sbft
  - Repeat course of abx

CASE 3

- 19-yr-old female patient with a 1.5-yr h/o Crohn's illeitis.
- Well controlled with Imuran 50mg.
- 1 month h/o N/V and unintentional wt loss. + early satiety.
- Abd U/S and CT enteroclysis normal.
- Recently had egd/colonoscopy with normal findings.
- Labs normal

CASE 3

- Any thoughts?
- GET delayed throughout 4hr window
- Antroduodenal manometry studies have also shown that upper gastrointestinal motor disorders occur in up to 74% of patients with CD.
- BE AWARE: Delayed gastric emptying occurs in inactive Crohn's disease
  - Thought to be secondary to feedback from abnormal small bowel motility.

CASE 4

- 55 y/o wm with crohn's illeocolitis is going to start therapy with Remicade. What questions regarding vaccination and what vaccinations are appropriate? Should you delay treatment to address any immunization concerns?

Immunization and IBD

- Standard recommended immunization schedules for children and adults should be generally adhered to.
- At diagnosis, review of immunization history for completeness. catch-up vaccination recommended prior to rx.
- no clear history of chickenpox = serologic testing for varicella. Nonimmune individuals should receive varicella vaccine.

Titers to check at first office visit

- MMR—if vaccination history unknown
- Varicella—if vaccination history or history of chicken pox/zoster unknown
- Hepatitis A—except those with evidence of protective titer within 5 years of vaccine administration
- Hepatitis B—except those with evidence of protective titer within 5 years of vaccine administration

Vaccinations to administer in specific patient groups regardless of immunosuppressive drug use

- Tdap
- HPV
- Influenza
- Pneumococcal
- Hepatitis A
- Hepatitis B
- Meningococcal

Vaccinations to consider if no plans to start immunosuppressive therapy in 4–12 weeks

- MMR
- Varicella
- Zoster

Live vaccines

- Avoid in the following
  - Treatment with glucocorticoids for 2 weeks or more, and within 3 months of stopping
  - Treatment with 6-MP/AZA
  - Treatment with MTX
  - Treatment with infliximab (biologics)
  - Significant protein-calorie malnutrition

Confirming Immune Response

- If possible check it and give boosters if necessary.

CASE #5

- 32 y/o wf with crohn's illeocolitis, well controlled on Humira presents with questions regarding pregnancy and such.
- Should I stop Humira if I am trying to get knocked up?
- Am I at increase risk of infertility?
- Can my IBD or meds hurt the baby?

J Gastroenterol. 2010;45(1):9-16.

Fertility and IBD

- Fertility is probably normal, except
  - impotence following proctocolectomy
  - oligospermia, reduced sperm motility, and abnormal sperm morphology in more than 80 percent of patients on sulfasalazine
  - Surgery may reduce fertility

Pregnancy and CD

- Quiescent CD is likely to stay quiescent and active is likely to stay active
- Some OB/Gyn's prefer Cesareans over vaginal deliveries for fear of fistula formations, but this is more opinion than data.
- Fetal mortality risk (spontaneous abortion, stillbirth or neonatal death) is not higher for IBD patients
- Women with Crohn's disease are at increased risk for low birth weight infants and premature delivery

Pregnancy and IBD

- the majority of women with IBD will have a normal outcome of pregnancy
- Breastfeeding is not associated with an increased risk of disease flare and may even provide a protective effect against disease flare in the postpartum year.
- If conception occurs with active IBD, inducing remission with medical therapy carries less risk than continuing pregnancy without treatment.

Pregnancy and IBD

- The effect of Crohn's disease on birth weight = children of mothers who smoke moderately
- the risk of an abnormal pregnancy outcome in women with Crohn's disease is greatest in those who have active disease at the time of conception, in whom remission may be difficult to achieve during pregnancy

Tests

- Avoid xrays and colonoscopy unless absolutely necessary
- Flex sigmoidoscopy is safe

Meds

- 5-ASA: safe for pregnancy and lactation
  - Extra folic acid supplementation is recommended for sulfasalazine
  - Higher doses of greater than 3 g/d carry a potential risk of fetal nephrotoxicity, specifically interstitial nephritis
- Flagyl: short courses only
  - carcinogenic/mutagenic in animal model
  - infants of women exposed to metronidazole in the second to third months of pregnancy have shown higher rates of cleft lip with or without cleft palate
- Cipro: don't use it or other Fluoroquinolones
- 6MP/Imuran: okay if nothing else will control. No breast feeding
  - retrospective studies have also shown that these medications are safe in pregnant patients with IBD
  - Prospective studies show safety in transplant patients

Meds

- Corticosteroids
  - Animal studies show increased frequency of cleft lip and cleft palate
  - steroid use in IBD patients is not associated with pregnancy complications
  - defer breastfeeding until 4 h after taking oral dosing of steroids to reduce neonatal exposure
  - no data on the safety of oral budesonide in pregnancy
- **Methotrexate (FDA Class X)**
  - Methotrexate is contraindicated in pregnancy and breastfeeding
- Cyclosporine
  - CsA should not be used during pregnancy, except to prevent urgent colectomy in patients with fulminant UC
  - No breast feeding
- Anti-TNFα
  - Likely safe for pregnancy and breastfeeding but long term data is lacking

CASE #6 CRC surveillance

- When should the following patients be screened for colon cancer and how often should it be done?
- 30 y/o with Crohn's colitis since age 20.
  - Now (10 yrs)
- 50 y/o with Crohn’s illeitis since age 30.
  - Now (avg risk screening)
- 40 y/o with Crohn’s colitis since age 35 with colonic stricture
  - Now (stricture = cancer until proven otherwise)

CRC surveillance for CD

- For colonic involvement
  - Begins: 8–10 years from onset of symptoms
  - Repeat c-scope Q 2 years
- small intestinal CD:
  - avg risk parameters
- Strictures in CD always biopsy and repeat within 1 year if an endoscopic passage is possible.
  - barium enema or ct for impassable strictures
  - 20 years of disease duration (12% rate of concomitant CRC), surgery should be considered.

CRC and IBD

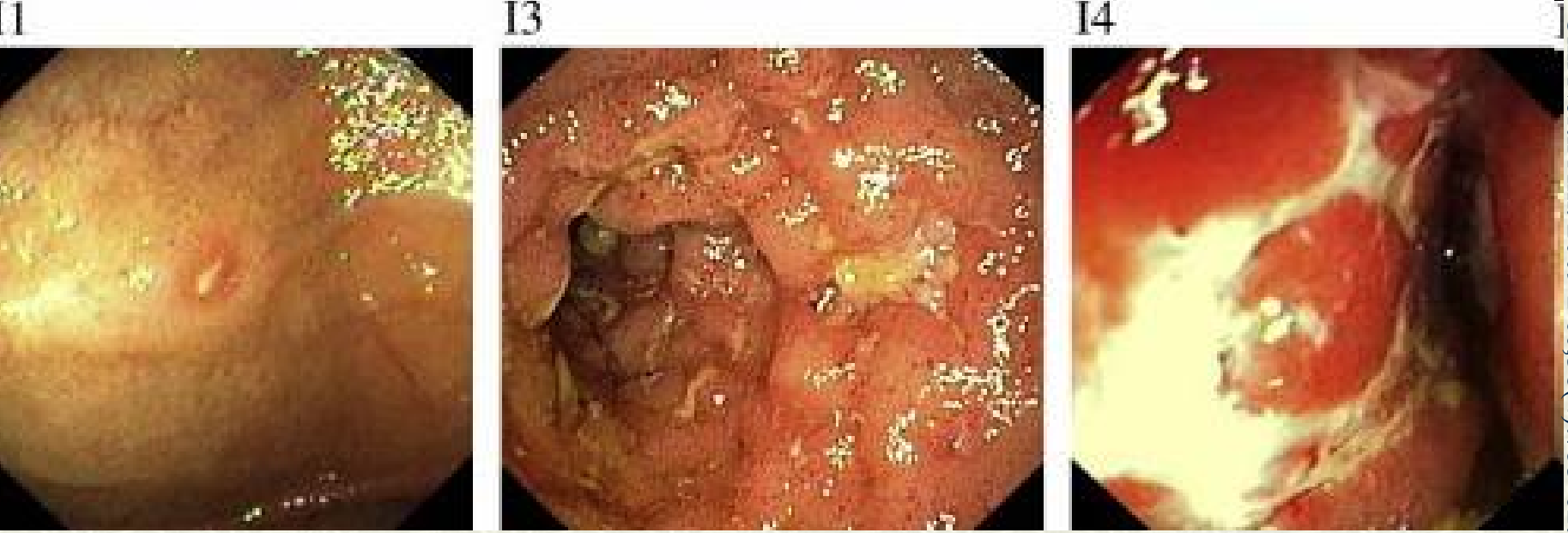
- Risk factors for CRC in IBD
  - Younger age at diagnosis
  - Greater extent and duration of disease
  - Increased severity of inflammation
  - Family history of colorectal cancer
  - Coexisting primary sclerosing cholangitis

Case #7

- 40 y/o wf with history of Crohn's illeitis x 15 yrs presents 1 week after small bowel resection for short stricture (~10cm removed).
- Nonsmoker
- Anastamosis was side-to-side.
- What is her risk of clinical/endoscopic recurrence?
- What, if any, medicines should be started?
- How do you survey her recurrence?

Post op Management of CD

- 75% of CD patients will require surgery
- 30% of CD patients that undergo suregy will require additional surgery within 5yrs
- Endoscopic recurrence @ 1yr = 90%
- Symptomatic recurrence @ 3 yrs = 30%
- Risk Factors for clinical recurrence
  - Smoking
  - Perforating
  - Small Bowel Involvement
  - End-to-end anastamosis (vs side-to-side)
  - Endoscopic recurrence



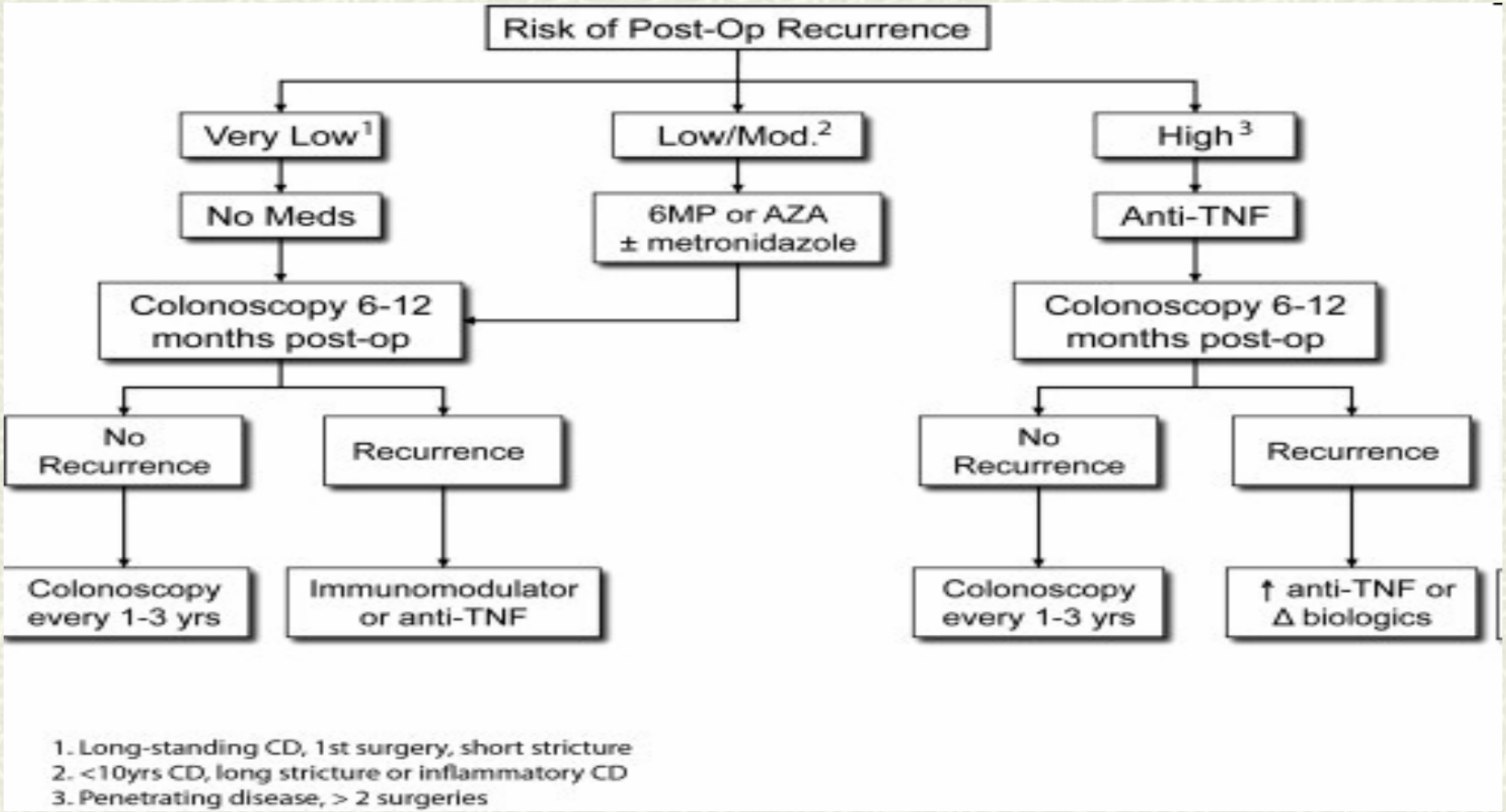
Cho SM, Cho SW, Regueiro M. Postoperative management of crohn disease. Gastroenterol Clin North Am. 2009 Dec;38(4):753-62.

- I0: No lesions
- I1: ≤5 aphthous lesions
- I2: >5 aphthous lesions with normal mucosa between the lesions, or skip areas of larger lesions, or lesions confined to the ileocolic anastomosis
- I3: Diffuse aphthous ileitis with diffusely inflamed mucosa
- I4:Diffuse inflammation with already larger ulcers, nodules, and/or narrowing
- Remission: endoscopic score of i0 or i1; Recurrence: endoscopic score of i2–i4.

Post op Management of CD

- Meds accepted to reduce postop endoscopic recurrence
  - 5-ASA: reduce by only 13%
  - Flagyl: reduce by ~20%, but high side effects
  - Imuran: reduce by 25%
  - Biologics: 80%
- Meds not accepted
  - Cortiocosteroids including budesonide

Post op Management of CD



Cho SM, Cho SW, Regueiro M. Postoperative management of crohn disease. Gastroenterol Clin North Am. 2009 Dec;38(4):753-62.

CASE #8

- NSAIDS
- A 54-year-old man is seen for follow-up of ileal Crohn's disease (CD) that was first diagnosed 20 years ago.
- He has been doing well for the past 8 years on azathioprine alone, and he has no bowel complaints today.
- He does complain of chronic joint pains, especially in his hands, that his rheumatologist thinks are caused by osteoarthritis.
- He has taken acetaminophen with no relief.
- His rheumatologist would like to prescribe a non-steroidal anti-inflammatory drug (NSAID) for the arthritis, but he is concerned that this medication might cause the Crohn's disease to flare.
- How should this patient be counseled?

NSAIDs + IBD

- Do NSAIDs exacerbate IBD?
  - Inconclusive data
  - Short term COX-2= no harm in UC (?CD)
  - Non-selective NSAID + IBD = ? (conflicting results)
  - Advice
    - Avoid in poorly controlled
    - Trial is Ok for well controlled

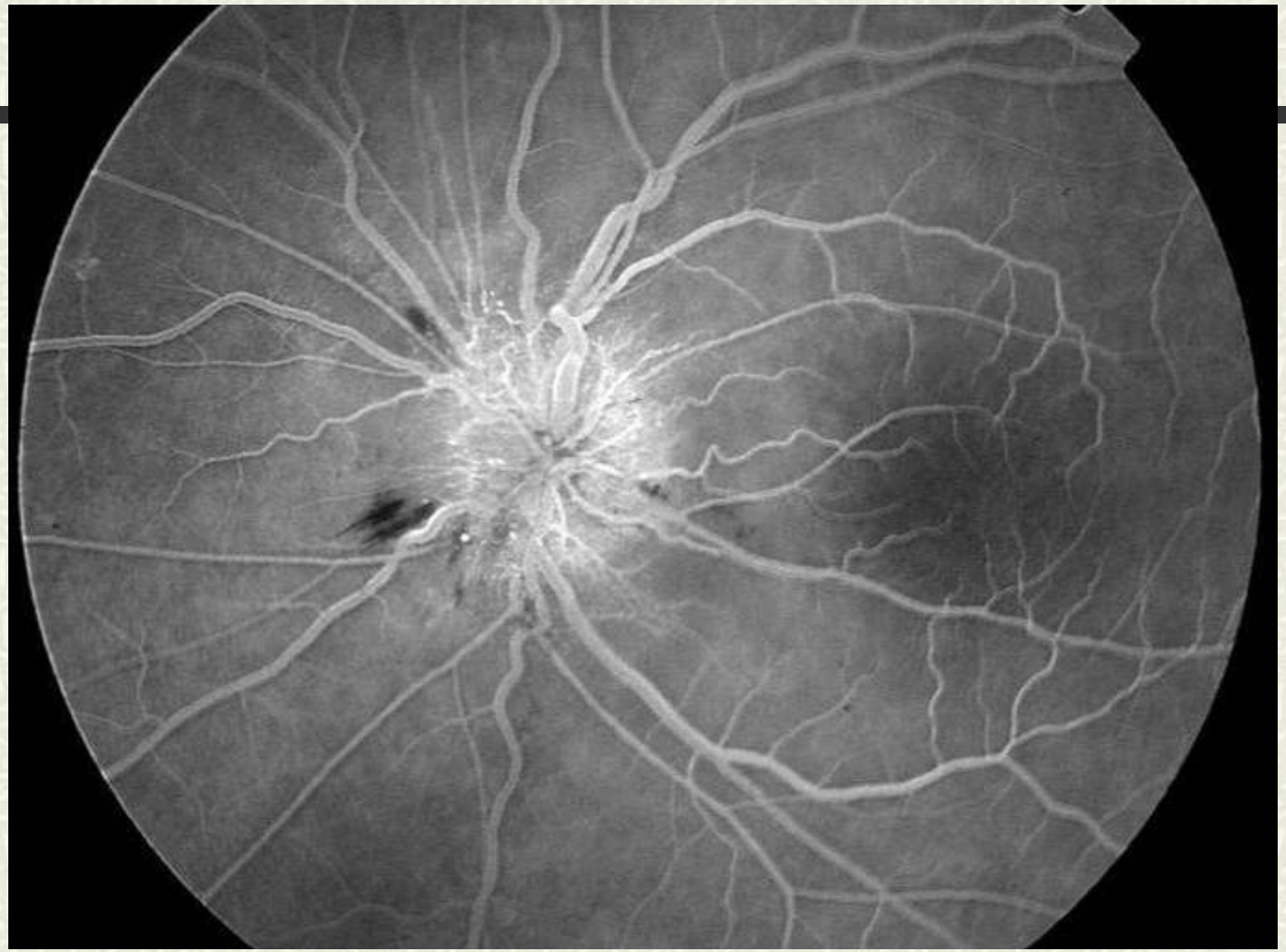
Dig Dis Sci. 2010 Feb;55(2):226-32.

Case 9

- A 45-year-old woman presents with pain and blurred vision in the L eye occuring one week after infliximab infusion.
- PMHx: Bell's palsy, nongranulomatous uveitis, DM and Crohn's Illeitis h/o enterovaginal fistula
- Meds: Infliximab 5mg/kg
- ROS: No symptoms of colitis.
- Visual acuity was 20/70.

Case 9

- The patient had a constricted visual field, afferent pupillary defect, and normal left eye on slip-lamp examination.
- There was pain on palpation of the orbit, and extraocular movements were full but induced pain with upward gaze.
- MRI: normal
- CBC, ESR: normal



ten Tusscher, M. P M et al. BMJ 2003;326:579

BMJ

Case 9

- What is the diagnosis?
  - Optic Neuritis 2/2 Anti-TNFα therapy
- What is the treatment?
  - intravenous methylprednisolone, followed by slowly tapering steroid
- What is the prognosis?
  - Good but based on case reports

Anti-TNFα therapy + Optic Neuritis

- Well known complication of anti TNFα therapy
- Has been described as manifestation of IBD
- We MUST know complications of Anti-TNFα therapy!

CASE #9 Optic Neuritis

- Contraindications for anti-TNFalpha therapy
  - Sepsis
  - TB
  - Optic neuritis
  - Cancer

CASE #10

- 23 y/o WF with mild crohn's illeitis under good control says she has been seeing Torr the "spiritual healer" who has prescribed a mixture of probiotics and advised her to discontinue her 5-ASA. Is this a good idea?
- Have probiotics been shown to be of benefit in CD?

CASE #10

- Probiotics have not been proven to be beneficial in preventing post-op recurrence
- Not proven to be effective in induction of remission or in maintenance of remission in patients with Crohn's disease.
- S. boulardii improves intestinal permeability
- Jury is still out: need more RCT’s

The Finale: Case 11

- 20 y/o aam with newly diagnosed fistulizing crohn's illeocolitis with a CDAI score of 449 needs medicine. Colonoscopy shows Mucosal ulceration involving TI and cecum. CRP=10 (<1). What would you like to start and what is the evidence behind your decision? Do you need any tests prior to starting therapy?
  - Top down therapy with an anti-TNF alpha drug +/- immunomodulator (imuran) is indicated
  - CXRAY + PPD or quantiferon should be ordered
  - Hepatitis B studies should be ordered if + risk factors
  - TPMT should be ordered
  - Immunization history should be taken

Top down vs Step Up Therapy

- Increased efficacy and similar safety
- Head to head trial steroid-free remission @ week 26 and week 52 (60% vs 36% and 61 vs 42%)
- More adverse events in Top down approach but not statistically significant
- SONIC trial: combo>infliximab>imuran for both endoscopic and clinical remission
  - Elevated crp and mucosal ulceration most likely to benefit
- Corticosteroids = increased mortality
- Imuran should be used if episodic infliximab is the plan to reduce immunogenicity
- MTX is not a useful adjunct (COMMIT trial)

Picking the Right Patient

- Short duration of disease (<5 years)
  - REACH, ACCENT and CHARM agree
- Elevated CRP
- Young age at diagnosis
- Mucosal ulceration
- Post op in a patient with aggressive disease

The Finale

- Same patient responds well to Imuran + Remicade. At 6months the patient has recurrent symptoms and increased inflammatory markers without evidence of infection. What is the likelihood of secondary loss of response and what do you want to do?

Secondary Loss of Response

- ~30% rate of 2ndary loss of response over 1 year
- Etiology
  - Immunogenicity
  - Mechanistic escape
- Work up
- Rule out abscess (closing a fistula too fast results in an abscess)
- Abdominal scarring or intrabdominal complication due to rapid healing
- MUST DETERMINE IF THE PATIENT IS ACTIVELY INFLAMMED

Immunogenicity

- Assess therapeutic levels of drug if possible (measure infliximab ≥ 3weeks after infusion)
  - If high levels: switch to MTX or natalizumab. Little evidence supports changing to different anti tnf drug.
  - If low levels: check antibodies, dosing and compliance
  - If immunogenicity is confirmed with serum antibodies (≥ 8µg/mL for anti-infliximab antibodies) use alternative anti-TNFalpha drug
- Risk is different with each drug
  - @10months remicade antibodies were present in 61% of patients
  - Others are lower
  - Data is still being worked out

Summary

- CD + NSAIDS
- CD + post op recurrence
- CD + TNF alpha
  - Top down vs step up
  - Immunization
  - Choice of patient
  - Complications/SE
- CD + Pregnancy
- CD + delayed gastric emptying
- CD + CDI
- CD + probiotics

CME

- Which of the following results in increased immunogenicity with anti-TNFα therapy?
  - a) adding immunomodulator
  - b) episodic dosing
  - c) switching anti-TNFalpha therapies

- ANSWER: b

CME

- Which of the following is not effective in prevention of postoperative recurrence of Crohn's disease with ileocolonic resection?
  a. Corticosteroids
  b. Immunomodulators
  c. Oral mesalamine
  d. Biologics

Answer: a