Ulcerative Colitis

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Ulcerative Colitis

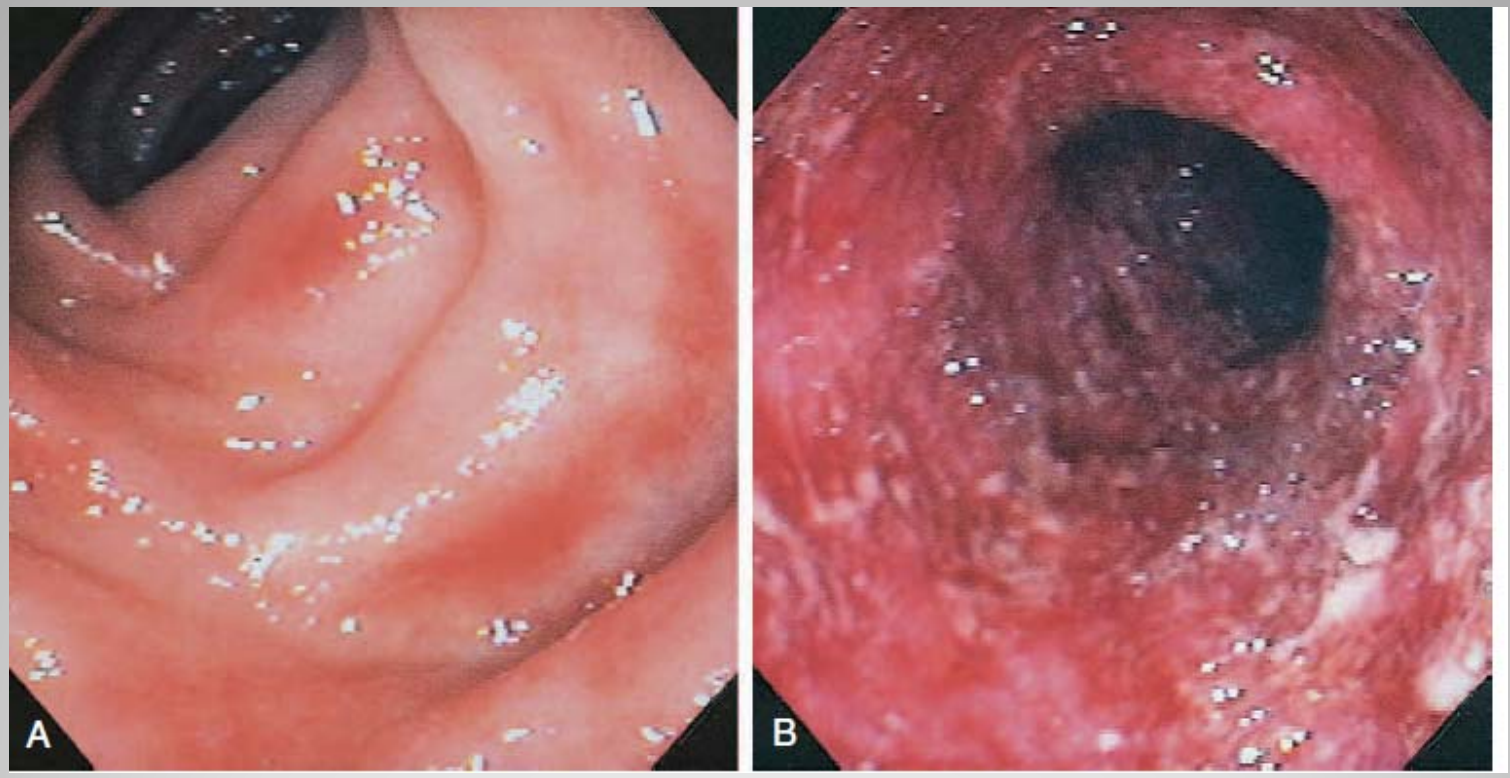
- Initial Symptoms
  - Gradual or sudden
  - Increased bowel movements, diarrhea
  - Hematochezia
  - Fever
  - Abdominal pain, cramping (worse after meals or BM's)
  - constipation and rectal bleeding in 25% of patients with disease limited to the rectum
  - Nocturnal bowel movements
  - Rectal urgency and tenesmus

Ulcerative Colitis: Diagnosis

- Stool examination-r/o infectious etiology
  - C-diff, E.coli, ova, HSV, CMV, TB, amebiasis, etc. (in UC, most cases of c-diff appear in the absence of pseudomemebranes)
- Sigmoidoscopy or colonoscopy
- Exacerbating factors:
  - Smoking cessation
  - NSAIDs
- Diagnosis made by clincal, endoscopic and histologic data

Ulcerative Colitis: Diagnosis

- Mucosal Characteristics:
  - Loss of vascularity
  - Granularity
  - Friability
  - Focal ulcerations (Crohn's has "rake ulcers")
  - Involves the rectum in 95% of cases
  - Extends proximally in a circumferential, uninterrupted pattern of inflammation
  - Exceptions:
    - Medical therapy can cause patchy disease
    - Common periappendiceal and cecal inflammation (cecal patch)



Ulcerative Colitis

Ulcerative Colitis: Diagnosis

- Histology
  - Distortion and atrophy of crypts
  - Inflammatory cells in the lamina propria (not transmural as in CD)
  - Paneth cell metaplasia
  - "Crypt abscess" is a nonspecific indicator of inflammation
  - Cryptolytic granulomas may form in response to ruptured crypts; therefore, granulomas are not pathognomonic for CD
  - "Backwash ileitis":
    - Must have cecal inflammation
    - Not to be confused with CD
    - Mild villous atrophy and scattered crypt abscesses

Ulcerative Colitis: Diagnosis

- Serologic Work-up
  - pANCA: 70% in UC, 40% in CD
    - Only 59% sensitive
  - CBir1: 44% pANCA+ CD vs 4% pANCA+ UC
  - ASCA: if pANCA- and ASCA+ then 93%specific for CD but only 55% sensitive.
  - Low sensitivity has limited serologic markers in their ability to diagnose but they may be used in patients whose features are difficult to distinguish between UC or CD

Ulcerative Colitis: Management

- Determine if distal (below descending colon) or proximal.
  - Distal-can use topical therapy
  - Proximal- need to use oral therapy
- Determine if mild, moderate, severe or fulminant disease
  - Truelove-Witts
  - UC Disease Activity Index
  - Mayo Clinic Index
  - Sutherland Index

Table 112-6 Truelove and Witts Classification of the Severity of Ulcerative Colitis

Mild
<4 stools/day, without or with only small amounts of blood
No fever
No tachycardia
Mild anemia
ESR < 30 mm/hr

Moderate
Intermediate between mild and severe

Severe
>6 stools/day, with blood
Fever > 37.5°C
Heart rate > 90 beats/min
Anemia with hemoglobin level < 75% of normal
ESR > 30 mm/hr

Ulcerative Colitis: Management

- UCDAI <2 indicates remission
- UCDAI >10 Indicates severe disease

Table 112-7 Ulcerative Colitis Disease Activity Index*

SCORE	CRITERIA
Stool Frequency	
0	Normal
1	1-2 stools/day > normal
2	3-4 stools/day > normal
3	>4 stools/day > normal
Rectal Bleeding	
0	None
1	Streaks of blood
2	Obvious blood
3	Mostly blood
Mucosal Appearance	
0	Normal
1	Mild friability
2	Moderate friability
3	Exudation, spontaneous bleeding
Physician Global Assessment	
0	Normal
1	Mild
2	Moderate
3	Severe

Ulcerative Colitis: Management

Ulcerative Colitis: Management

- Extra-intestinal manifestations
  - Disease activity dependent:
    - Ocular complications: episcleritis, scleritis,uveitis
    - arthropathies of small and large joints
    - EN
    - pyoderma gangrenosum
  - Disease activity independent:
    - Axial arthropathies
    - Sacroilitis
    - Ankylosing spondylitis
    - PSC
- Vaccinations: UC patients frequently placed on immunosuppressants

- Topical mesalamine, topical steroids or oral aminosalicylates are all effective
- Topical mesalamine is superior to oral 5-ASA or topical steroids
- Combination of a topical and oral 5-ASA is superior than either alone
- Can use oral steroids or infliximab if the above measures fail

Ulcerative Colitis: Mild to Moderate DISTAL Colitis- Active

- Mesalamine associated Nephrotoxicity
  - Rare, 0.26% annually
  - Measure creatinine prior to therapy, then every 6 mos for one year then yearly
- Foam is easier to retain than enemas
  - Hydrocortisone or mesalamine
- Location determines topical therapy
  - Distal 10cm: Suppositories
  - 10-20cm: Foam
  - Splenic flexure: Enemas

Ulcerative Colitis: Mild to Moderate DISTAL Colitis- Active

- 5-ASA's, topical or oral, are effective
  - Remission rates for mesalamine enemas:
    - Daily: 78%
    - Qod: 72%
    - Every third day: 65%
- Combination of oral and topical is superior than either alone
  - 1.5gm (Apriso) oral mesalamine daily and 4gm mesalamine enema twice weekly
- Topical steroids have not been proven effective
- When the above measures fail, then can consider 6-MP, AZA or infliximab

Ulcerative Colitis: Mild to Moderate DISTAL Colitis- Remission

Ulcerative Colitis: Mild to Moderate Extensive Colitis- Active

- Initially treat with Sulfasalazine (4-6gm/day) or mesalamine 3.0gm/day (Apriso)
- Can use oral steroids if oral and topical 5-ASA's fail or if symptoms demand rapid improvement
- Can use 6-MP or AZA if the above measures fail
- Infliximab-indicated if steroid dependent despite thiopurines
  - 5-10mg/kg at 0,2 and 6weeks then q8weeks

- Sulfasalzine
  - 80% response rate at doses of 4-6gm
  - Achieve maximal affect by 2-4 weeks
  - Greatest advantage over newer aminosalicylates is cost…much cheaper
  - Associated with more side effects, sulfonamide toxicity
    - n/v, anorexia, HA, hepatotoxicity, pancreatitis, BMS, interstitial nephrtitis, hemolytic or magaloblastic anemia and abnormal sperm count and motility
- Nonsulfonamide 5-ASA(mesalamine, balsalazide, olsalazine)
  - Equivalent efficacy to sulfasalazine with less side effects

Ulcerative Colitis: Mild to Moderate Extensive Colitis- Active

- Nicotine:
  - More affective than placebo
  - No advantage over mesalamine
  - Little current utility in treatment of UC

Ulcerative Colitis: Mild to Moderate Extensive Colitis- Active

- Corticosteroids
  - Oral prednisone: 20-60mg/day
    - 60mg/day with the greatest response
    - No randomized trials have studied steroid taper
    - ACG guidelines
      - 40-60mg/day until clinical improvement
      - Then taper 5-10mg weekly until 20mg daily
      - Then taper 2.5mg/week
    - Patients on steroids for >3mos or recurrent users
      - DEXA scan
      - Vitamin D/Calcium (800 U/1,000-1,500mg)
      - Bisphosphonates
    - 44% of IBD patients have osteopenia and 12% have osteoporosis
    - Risk of opportunistic infections is increased 3-fold

Ulcerative Colitis: Mild to Moderate Extensive Colitis- Active

- Infliximab- anti TNF alpha
  - Contraindicated
    - Active infection
    - Latent TB
    - Demyelinating disorder or optic neuritis
    - Moderate to severe CHF
    - Current or recent malignancies
  - Failure to respond by the 2nd dose is indicative of overall therapy failure
  - Reduced response in those who initially responded well
    - Increase from 5mg/kg to 10mg/kg
    - May titrate frequency to every 4 weeks
    - Drug should be stopped if failure to respond to the above adjustments in therapy

Ulcerative Colitis: Mild to Moderate Extensive Colitis- Active

- Infliximab
  - Consider dual therapy with thiopurines to potentially reduce the risk of antibody formation to infliximab
  - Side effects:
    - Infusion reactions-most common
    - Infection
    - Lymphoma
    - Rare
      - Hepatotoxicity
      - MS, optic neuritis
      - Worsening CHF

Ulcerative Colitis: Mild to Moderate Extensive Colitis- Active

- Infliximab
  - Infusion Reactions
    - Flushing, HA,dizziness, CP, cough, fever, pruritis
    - Reduced by regular 8-week dosing intervals
    - Can premedicate with corticosteroid and antihistamines
  - Infections
    - TB-screen prior to therapy
      - If on immunosuppressive therapy or BCG vaccine then Quantiferon is ideal test
    - Opportunistic infections
    - Reactivation of Hepatitis B
      - Screen and vaccinate if high risk

Ulcerative Colitis: Mild to Moderate Extensive Colitis- Active

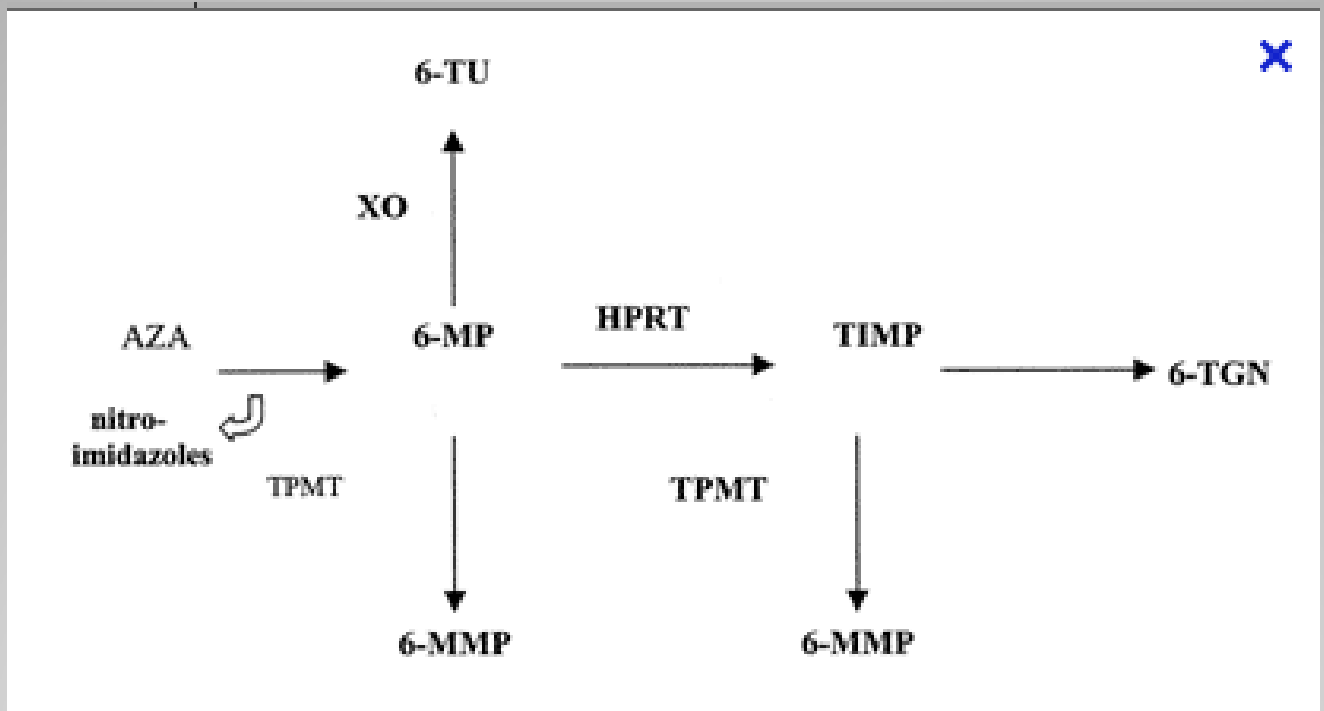
- Infliximab
  - Malignancy
    - No overall increase risk in malignancy
    - Increased risk in lymphoma (7x more likely)
      - Hepatosplenic T-cell Lymphoma
        - Rare
        - Concomitant thiopurine use
        - Almost universally fatal

Ulcerative Colitis: Mild to Moderate Extensive Colitis- Active

- Thiopurines: 6-MP or AZA
  - 3-6 mos to achieve optimal effect
  - Steroid sparing agent
  - Toxicities
    - BMS (especially leukopenia)
      - CBC measured first weeks to months
    - Hepatoxicity (2-17%)
      - Soon after initiation of therapy
      - Dose dependent
      - Usually reversible
    - Pancreatitis- 2%
    - No increased risk of solid tumors
  - TPMT phenotype (preferred over genotype because provides quantitative level of enzyme acitivity)

Ulcerative Colitis: Mild to Moderate Extensive Colitis- Active

- Thiopurine Metabolism



Ulcerative Colitis: Mild to Moderate Extensive Colitis- Active

- Thiopurine Metabolism
  - 1 in 300 have low or absent TPMT
  - Absent TPMT results in exceedingly high 6-TG and these patients will not tolerate thiopurine therapy
  - Higher levels of 6-TG are indicative of remission but cause worse leukopenia/BMS
  - Heterozygotes for TPMT require lower doses of AZA/6-MP
  - No response in 3-4 mos
    - Shunting: high TPMT level (high 6-MMP and low 6-TG)
      - A 6-MMP:6-TG ratio greater than 10:1 will not likely lead to clinical benefit
      - Allopurinol- inhibits XO and can increase 6-TG levels
  - Monitor CBC and CMP

Ulcerative Colitis: Mild to Moderate Extensive Colitis- Active

- 5-ASA's are effective in reducing relapses
- 6-MP or AZA are effective in steroid-dependent patients
- Infliximab can also be used if the patient responded to induction therapy

Ulcerative Colitis: Mild to Moderate Extensive Colitis-Remission

- If urgent hospitalization is not necessary then can attempt trial of infliximab
- Toxicity
  - Rule out c-diff
    - Vancomycin preferred if (increased failure rate to Flagyl)
      - recent cephalosporin use
      - C-diff+ on admission
      - Transferred from an OSH
  - No benefit to antibiotics (in absence of infection) has been proven however they are often included (cipro, flagyl, vanc)
  - Consider CMV as majority of patients are immunosuppressed
    - Flex-sig with biopsies and viral culture
  - IV steroids (16-20mg q8 Solumedrol or 100mg hydrocortisone q8)

Ulcertive Colitis: Severe Colitis

Ulcertive Colitis: Severe Colitis

- If no response to steroids in 3-5 days
  - Surgical consult (steroids have a 20-40% failure rate)
  - Consider infliximab or cyclosporine
  - Cyclosporine: 2mg/kg/day IV then transition to 8mg/kg/day PO after response to IV is noted.
    - 82% of steroid refractory patients with severe colitis responded to CSA
      - 88% still required colectomy within 7 years
    - Higher long term success if the patient was on a thiopurine prior to CSA
    - No increase in postopertive infections as opposed to steroids.
      - Still conflicting evidence regarding infliximab but most studies showed no increased post operative complications
  - Start 6-MP or AZA at discharge while continuing CSA and start slow steroid taper.
    - PCP prophylaxis in patients on CSA, steroids and thiopurine

Ulcertive Colitis: Severe Colitis

- Megacolon: >6cm
  - Correct hypokalemia or hypomagnesemia
  - Avoid anticholinergics and narcotics
- DVT
  - 2x more frequent in hospitalized UC patients
  - Heparin prophylaxis is recommended
  - Colectomy may be life saving in a patient with multiple DVT's in a course of severe colitis
- TPN not beneficial and deprivation of SCFA may prolong disease as they are needed for enterocyte repair
- Oral 5-ASA not beneficial but are often still included

Ulcerative Colitis: Surgery

- Absolute indications for surgery:
  - Exsanguinating hemorrhage
  - Perforation
  - Carcinoma
- Surgery recommended:
  - Severe colitis unresponsive to maximal medical therapy
- Surgical Options:
  - Ileal pouch-anal anastomosis (IPAA): Most common
  - Total proctocolectomy with ileostomy
  - Subtotal colectomy with ileorectal anastomosis: rarely advisable because of risk of disease recurrence and CA risk
  - Continent ileostomy (Koch pouch)- rarely performed due to complications

- IPAA
  - Pouchitis: 50% of patients with occurence in long term follow up
  - Anastomotic leak or stricture
  - Pelvic abscess (12%)
  - Fistula (4%)
  - Sepsis (8%)
  - Bowel obstruction

Ulcerative Colitis: Surgery

Ulcerative Colitis: Surgery

- IPAA
  - 2x increase in mortality in low volume centers
  - 3x increase in infertility in women
  - 20% of women will have dyspareunia or fecal incontinence during intercourse
  - Most men reported improvement in sexual quality likely related to overall improvement in general health

Ulcerative Colitis: Pouchitis

- Pouchitis
  - Increased stool frequency, rectal bleeding, tenesmus, incontinence, fevers
  - Confirmed by endoscopy and histology but symptoms do not always correlate with findings
  - Occurs in up to 60% of patients within 40 months
  - More common in patients with PSC, EIM, and those who never smoked
  - Rule out c-diff and NSAID use
- Treatment
  - Flagyl 400mg TID or 20mg/kg daily or Ciprofloxacin 500mg BID
  - VSL-3 (lactobacilli, bifidobacteria, streptococcus salivarius)

Ulcerative Colitis: Pouchitis

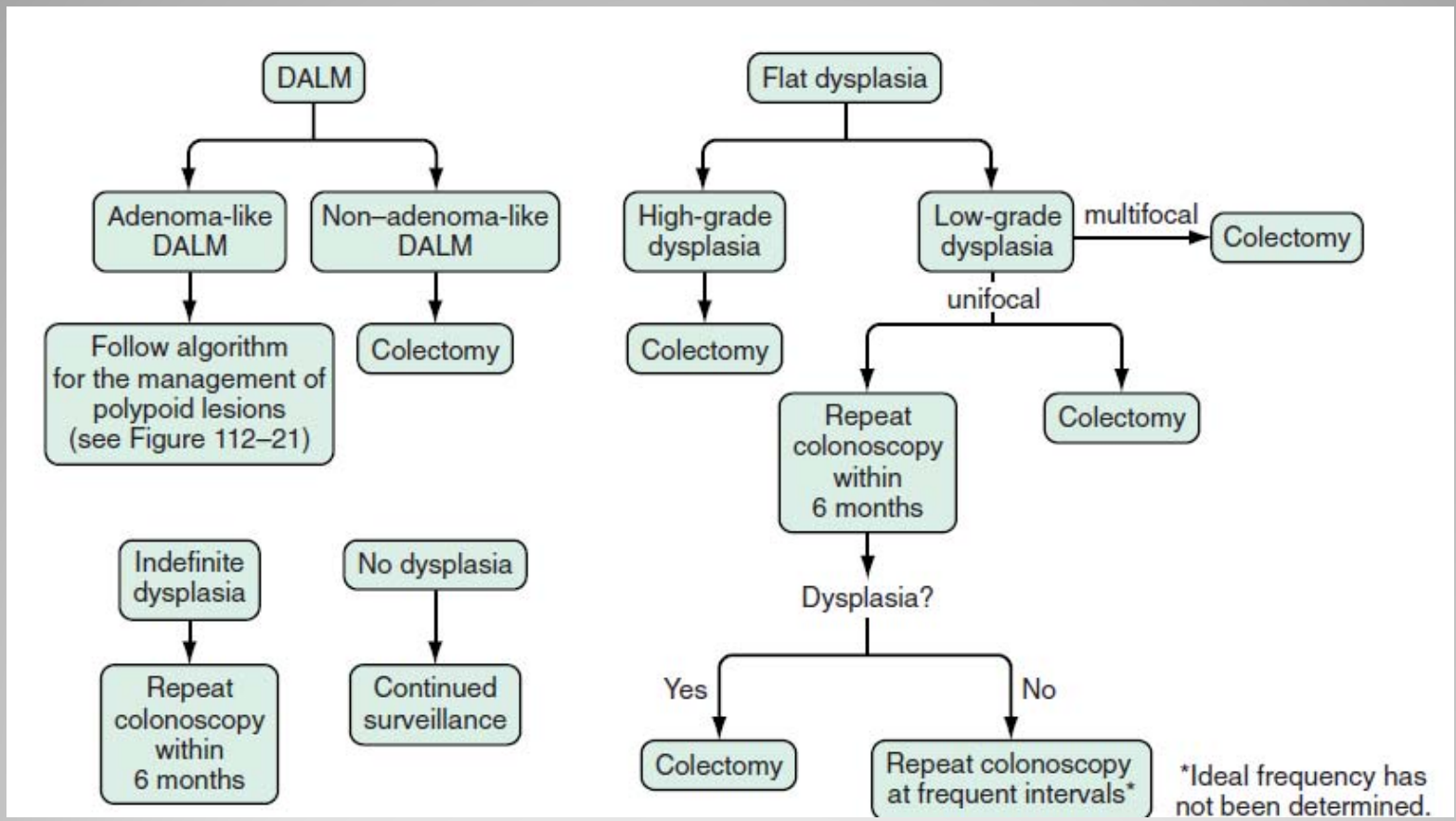
- Mimickers of pouchitis
  - Irritable pouch syndrome
    - Normal endoscopy but increased stool frequency and cramping
      - SSRI's, anticholenergics and anti-diarrheal agents
  - CD of the pouch
    - Fistula formation, usually 6-12 mos post op, in the absence of postoperative anastomotic leak, abscess or sepsis
  - Leak or stricture
- Dysplasia or adenocarcinoma surveillance is not recommended however they are at a higher risk

Ulcerative Colitis: Cancer Surveillance

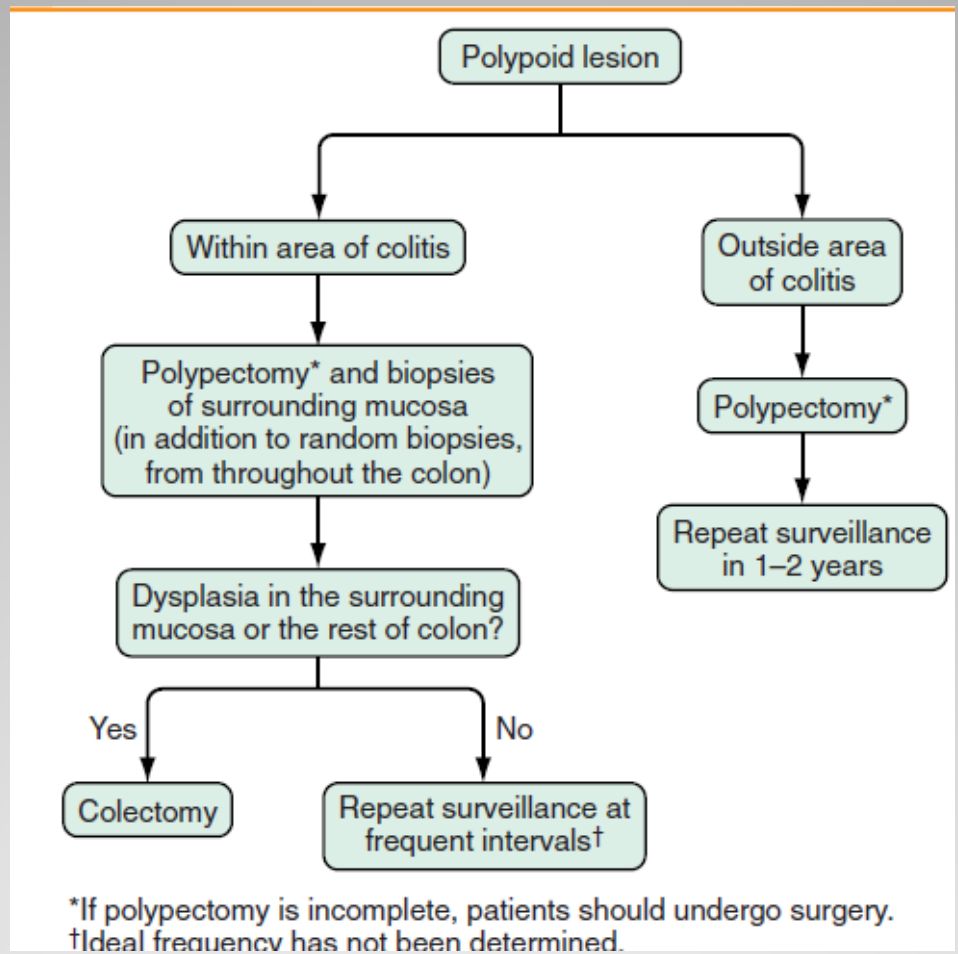
- After 8-10 years of colitis, surveillance colonoscopies should be performed every 1-2 years in patients with extensive and left sided colitis
  - Patients with left sided colitis reach a cumulative CA risk equal to those with extensive colitis after 3-4 decades
- Proctitis or proctosigmoiditis do not have an increased CA risk
- Surveillance colonoscopies begin at diagnosis in patients with PSC and UC due to increased risk of CRC
- Random biopsies every 10cm in all 4 quadrants
  - 90% probability in diagnosing dysplasia or CA if 33 biopsies obtained
  - 95% probability if 64 biopsies obtained

Ulcerative Colitis: Cancer Surveillance

- HGD in flat mucosa is indication for colectomy
- LGD in flat mucosa may also be indication for colectomy to prevent progression
  - 5 year predictive value of HGD or CA is 54%
  - Surveillance series in patients with LGD who underwent colectomy within 6 months
    - 26% with concurrent cancer
    - 12% with HGD
  - 9 fold increase in cancer and 12 fold increase in developing CA or HGD within 5.2 years
- Adenomatous lesions
  - If resected entirely and no dysplasia in surrounding mucosa or entire colon then no increased risk of CA



Ulcerative Colitis: Cancer Surveillance



Ulcerative Colitis: Cancer Surveillance

- Surveillance colonoscopies should only be performed during periods of remission because epithelial cells undergoing regenerative changes during healing appear eccentric and can be confused as dysplastic.

Ulcerative Colitis: Cancer Surveillance