



COLITIS

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Dr. Nawar Alkhamesi

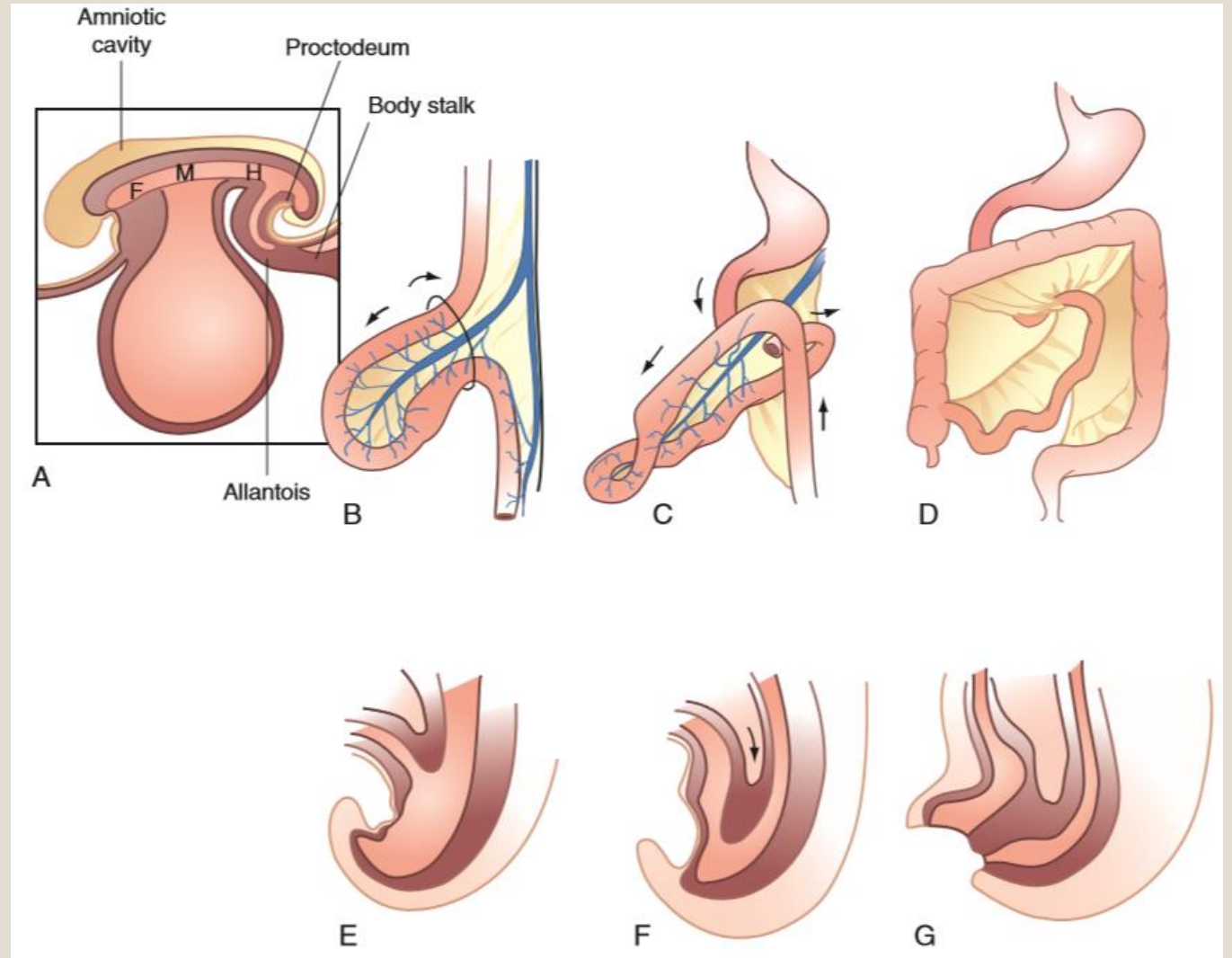
October 14th, 2015.

Objectives

- Anatomy and embryology of colon
- Differential diagnosis and investigation of acute colitis
- Presentation, diagnosis and management of infectious colitis
- Presentation, diagnosis and management of ischemic colitis
- Review of some of the most recent seminal papers on topic
- Epidemiology and etiology of ulcerative colitis
 - Pathology and histology of ulcerative colitis
 - Clinical presentation, investigation and extra-intestinal manifestations of ulcerative colitis
 - Medical management of ulcerative colitis (role of steroids, 5-ASA, immuno-modulators, biologics)
 - Screening and risk of malignancy, management of dysplasia
 - Elective indications for surgery in ulcerative colitis
 - Emergent indications for surgery in ulcerative colitis
 - Surgical options in ulcerative colitis

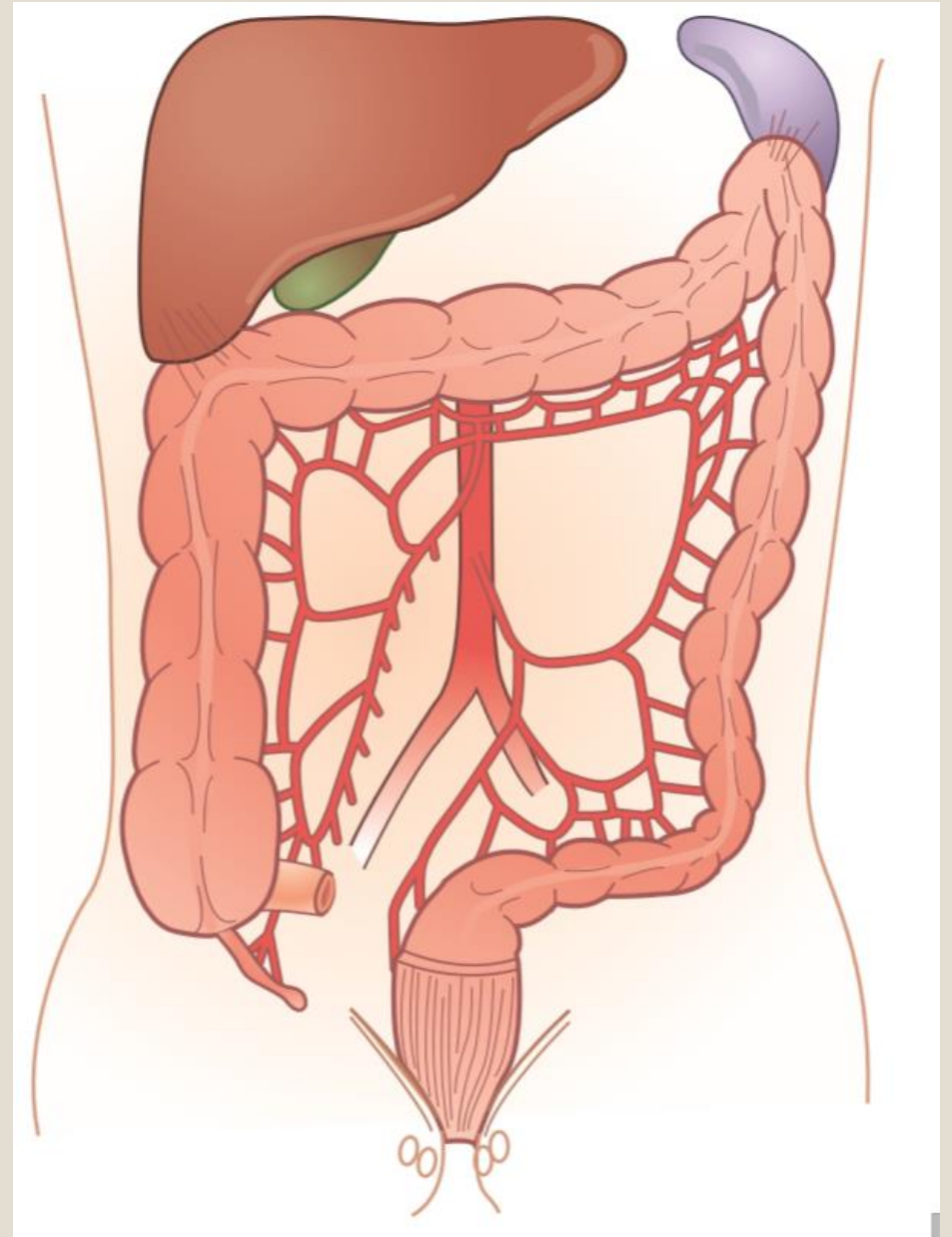
Embryology

- 3 weeks
 - Foregut
 - Midgut
 - Hindgut
- Physiologic herniation
- Return to the abdomen
- Fixation
- Six weeks
 - Urogenital septum migrates caudally
 - Separates GI and GU tracts



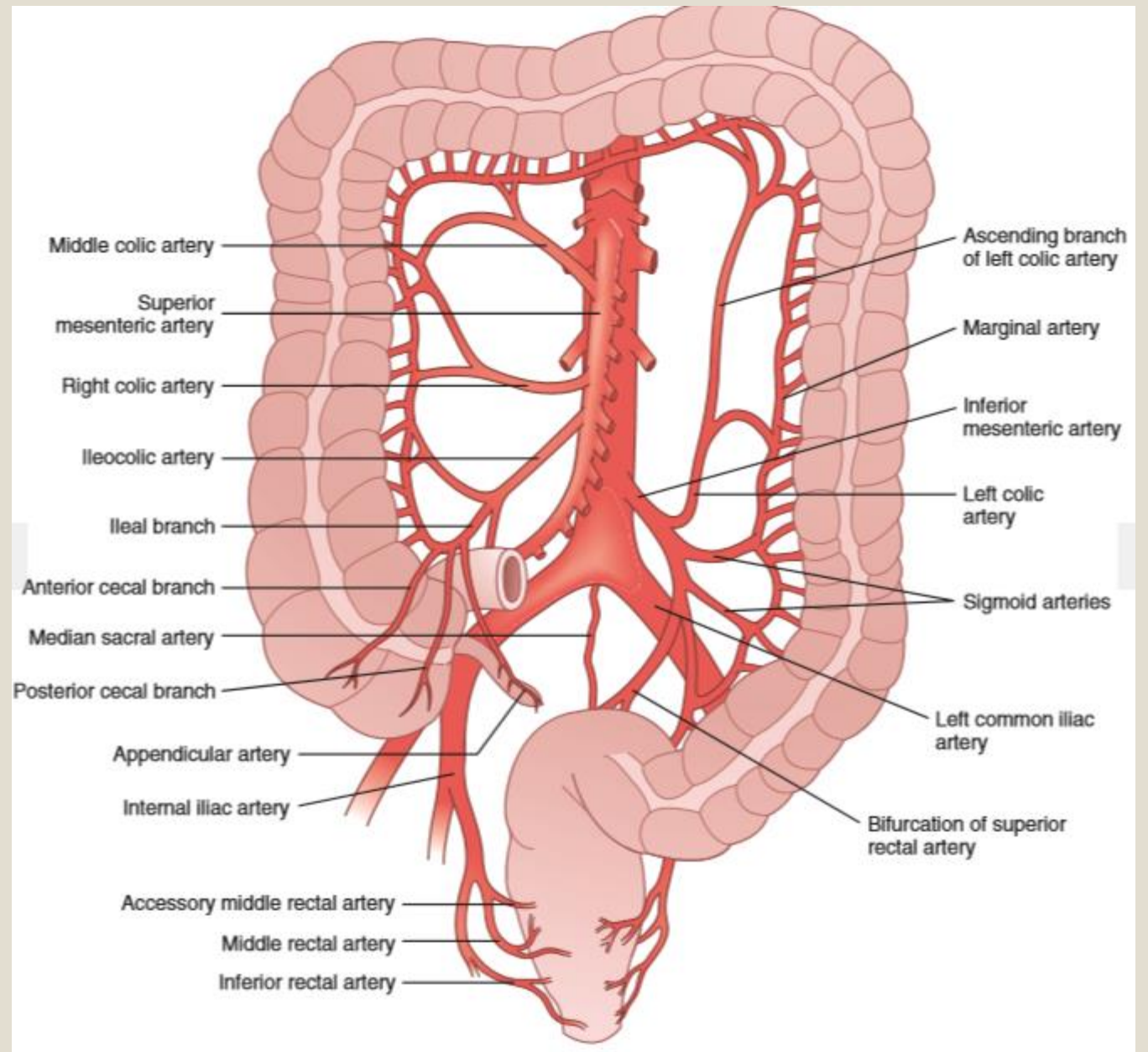
Anatomy

- 150cm
- Terminal ileum → ileocecal valve → cecum
 - Appendix
 - 3 cm below ileocecal valve
 - Retrocecal (65%), pelvic (31%), subcecal (2.3%), preileal (1.0%), retroileal (0.4%)
- Ascending colon
- Hepatic flexure
- Transverse colon
- Splenic flexure
- Descending colon
- Sigmoid colon
- Rectum



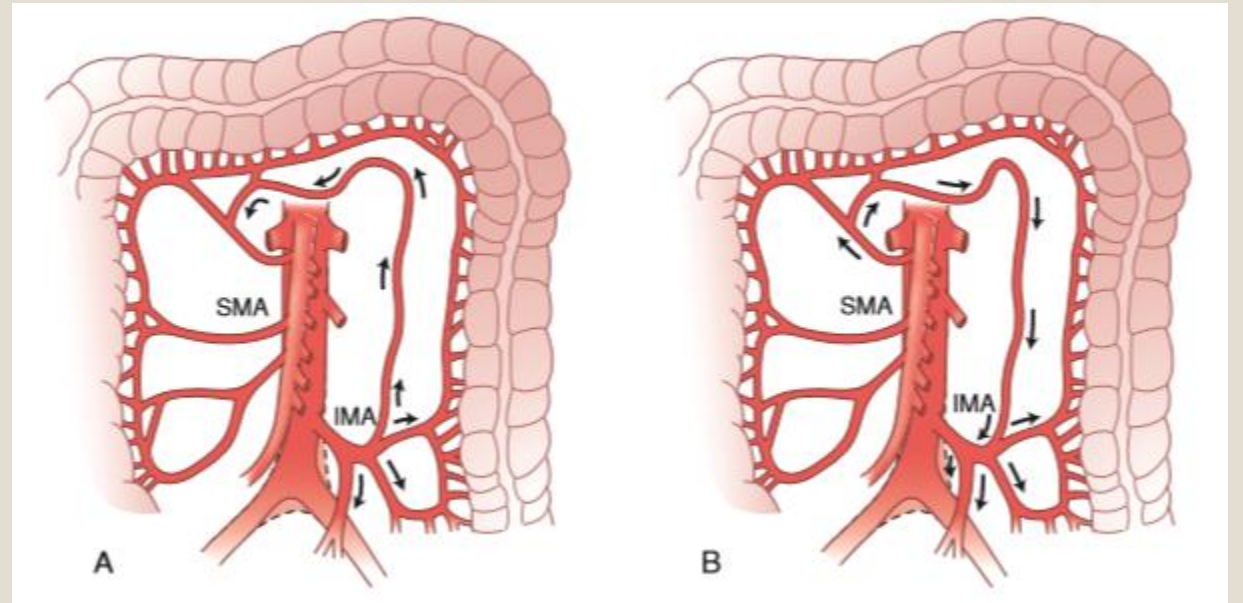
Arteries

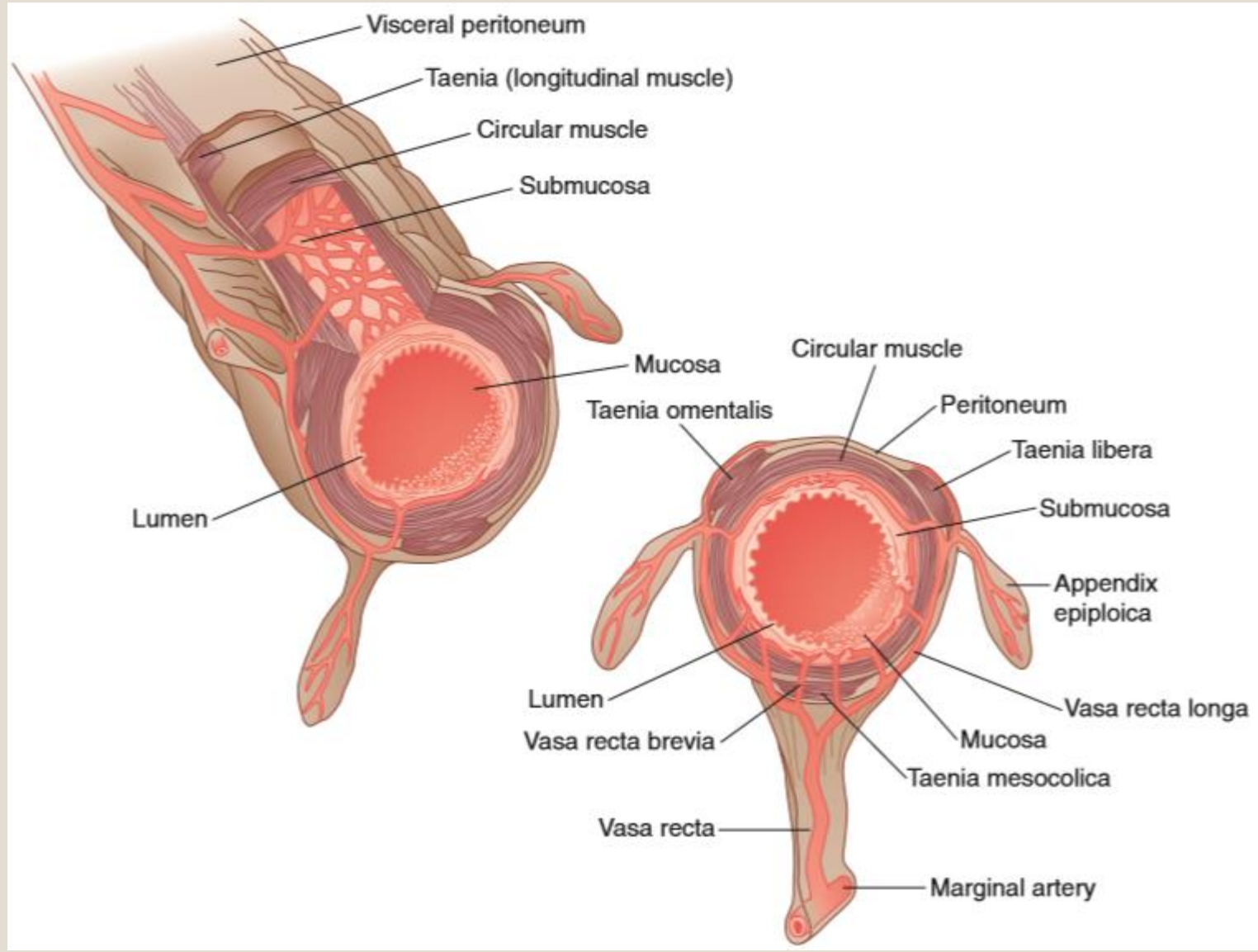
- SMA
 - Ileocolic
 - Right colic
 - Middle colic
- IMA
 - Left colic
 - Sigmoid branches
 - Superior rectal artery
- Redundancy/communication between the SMA and IMA territories
 - Marginal artery
 - Arc of Riolan



Arteries

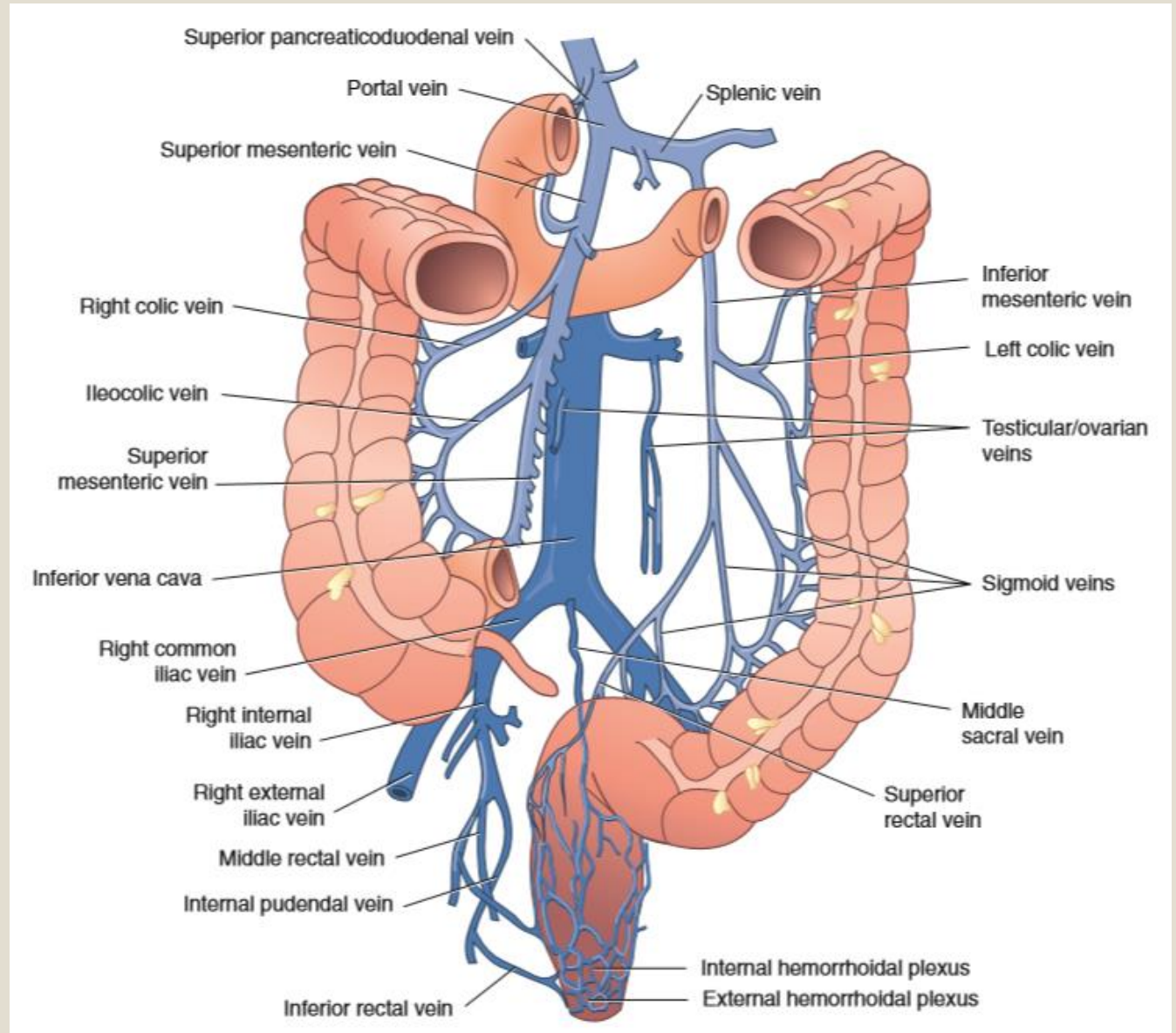
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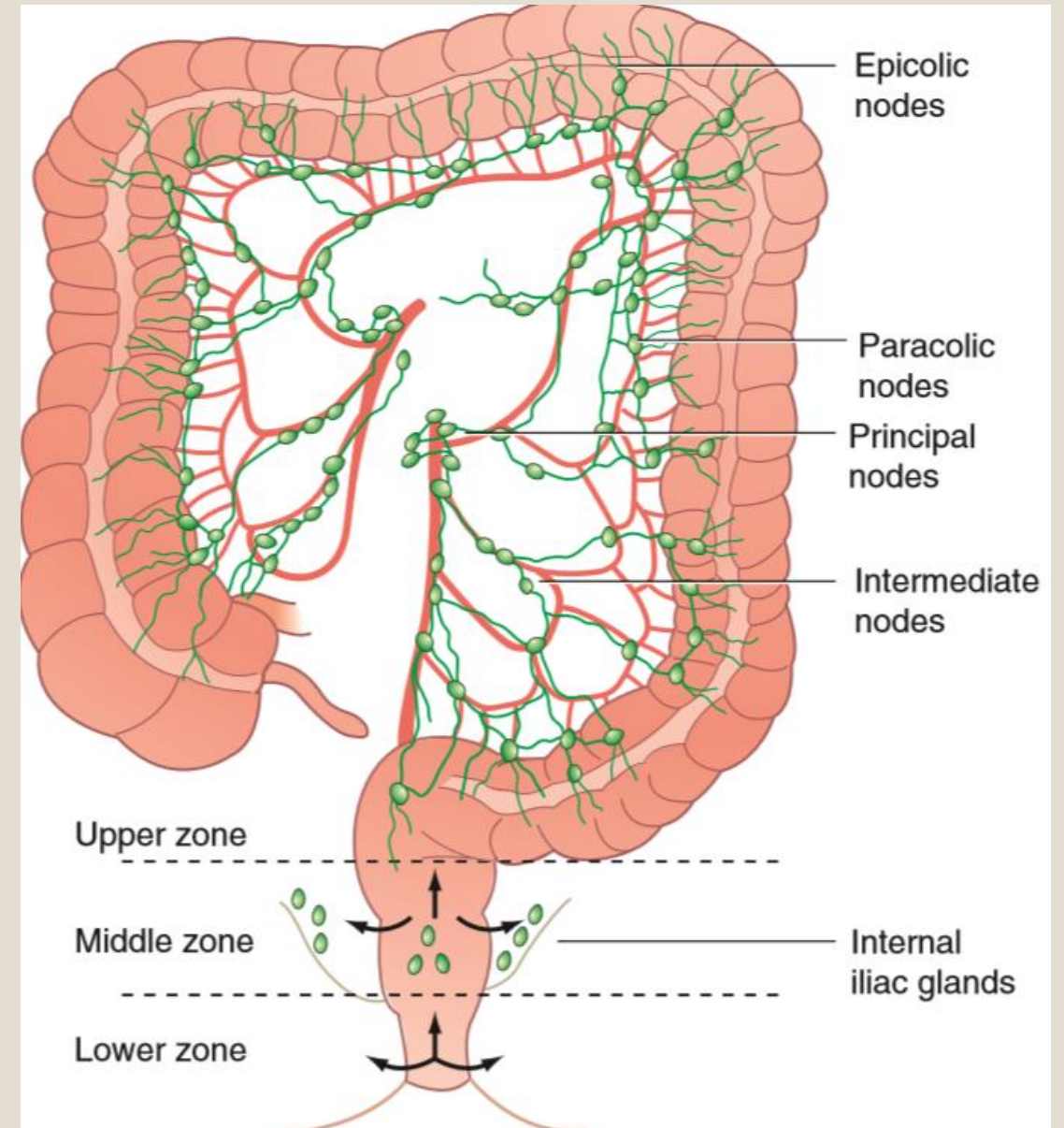
Veins

- SMV
- IMV
- Mirrors arterial blood supply



Lymphatics

- Mirrors arterial blood supply
- Epicolic nodes
- Paracolic nodes
- Intermediate nodes
- Primary nodes
- Para-aortic nodal chain
- Cisterna chyli

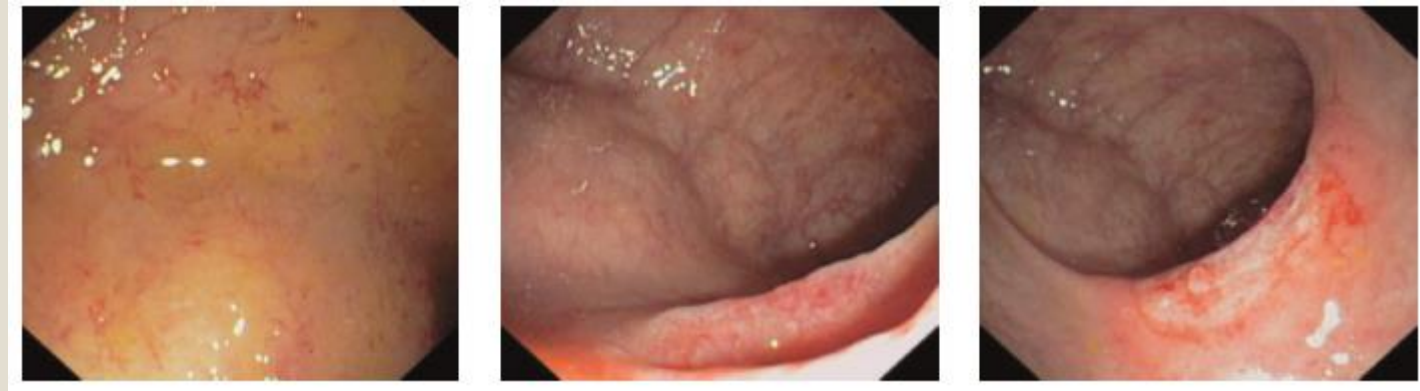


Nerves

- T6-T12 sympathetic nerves → preaortic ganglia → right and transverse colon
- Right vagus nerve → parasympathetic fibers along SMA → right and transverse colon
- L1-L3 sympathetic lumbar splanchnics → preaortic plexus → along branches of IMA → left colon, sigmoid, rectum

Differential diagnosis of colitis

- Infectious
 - Viral
 - Bacterial
 - Protozoan
 - Fungal
- Inflammatory
 - UC
 - Crohn's disease
 - Microscopic
 - Indeterminate
- Ischemic
- Radiation
- Diversion



Ischemic colitis

- “Ischemic colitis” defined in 1963 and described as “reversible component to colonic ischemia”
- Most common form of injury to the gut
- Focal, non-occlusive, transient, usually resolves spontaneously
- Incidence 4.5-44 per 100, 000 person-years
- Most between 6th and 9th decade of life
 - Slightly more common in men
- Precipitating cause found in <20%
- May be associated with aortic surgery, arteriosclerotic disease, conditions causing transient hypotension, oral contraceptives, cocaine, coagulopathies, CMV and E. coli O157:H7.
- Typically involves “watershed” area

Etiology

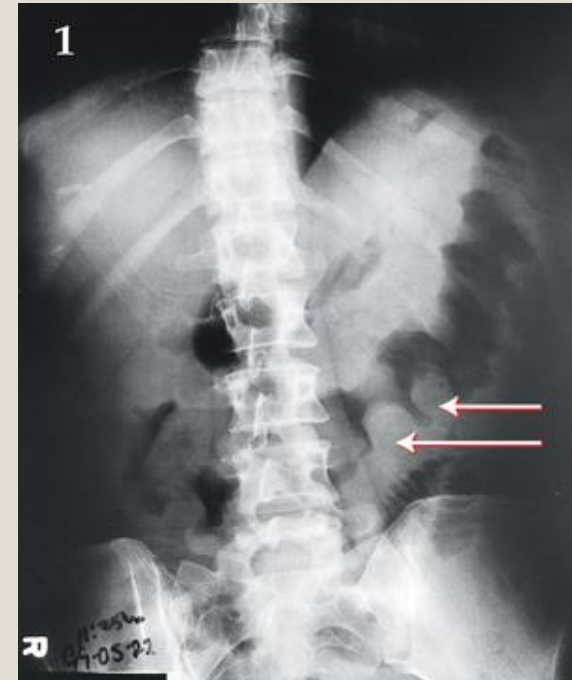
- Not usually associated with major vascular occlusion
- Typically segmental
- Two anatomically vulnerable areas of the colon
 - “Griffith's point” at splenic flexure (SMA and IMA junction)
 - “Sudeck's critical point” (IMA and middle rectal junction)
- Perfusion between these areas may be inadequate during hemodynamic insult
- Severity depends on duration of decreased blood flow, caliber of vessel, metabolic requirements of bowel, and associated conditions like distension, collateral circulation, colonic bacteria.
- Spectrum between transient ischemia, chronic ischemia, and gangrene

Clinical presentation

- Dependent on severity
- Mild crampy abdominal pain associated with tenesmus
- Hematochezia, Diarrhea
- Nausea, vomiting, distension
- In gangrenous ischemia – peritonitis on physical exam
- Investigations:
 - Leukocytosis on laboratory studies
 - Metabolic acidosis
 - Elevated lactate

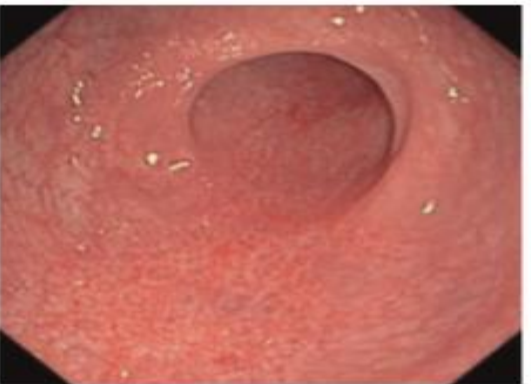
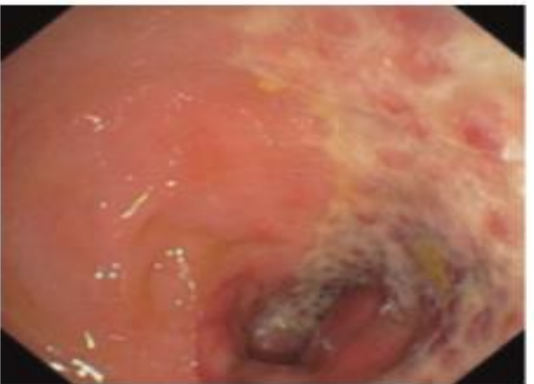
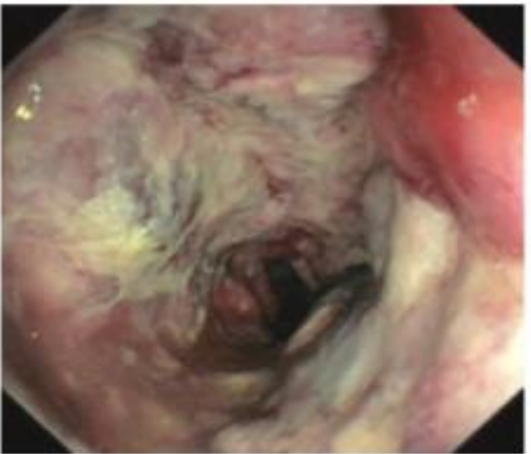
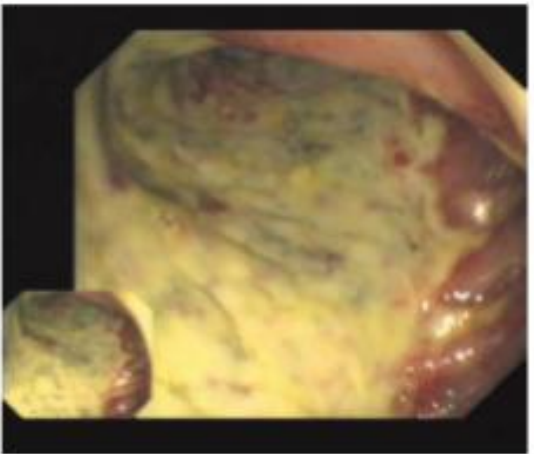
Imaging studies

- Xrays are non-specific
 - May show ileus, distended colon
 - Thumb-printing – intestinal wall edema or submucosal hemorrhage
 - Free air – rare
- Barium enema is obsolete in acute setting
 - Risk of perforation
 - Useful for chronic strictures
- CT scan with IV contrast is useful
 - Visualize entire arterial supply

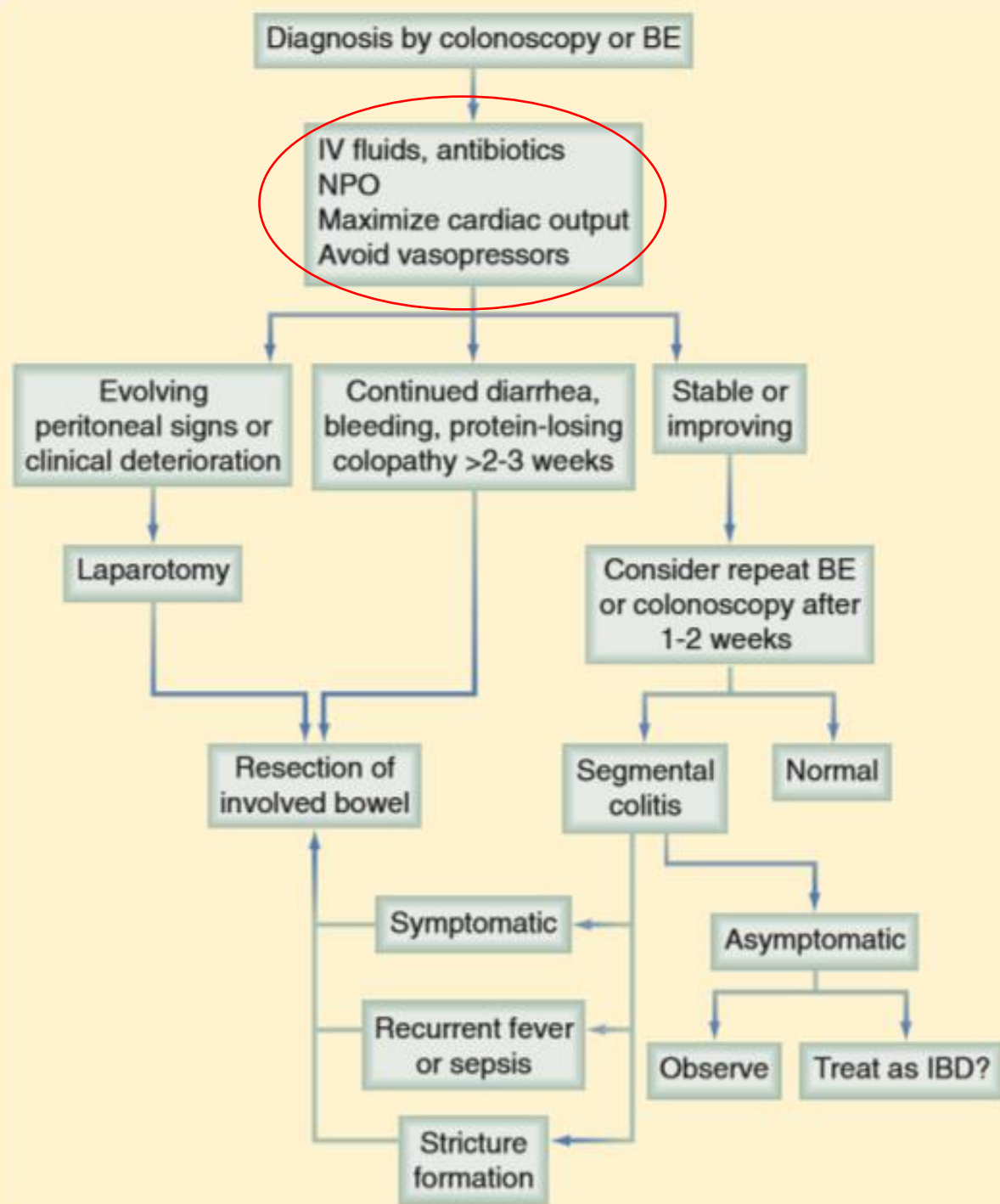


Endoscopy

- Direct visualization of colonic mucosa
- Can take bacterial cultures to rule out infection
- Can take biopsies
 - Mostly non-specific
- Hemorrhagic dusky mucosa
- Unable to distinguish between mucosal and transmural gangrene



Treatment

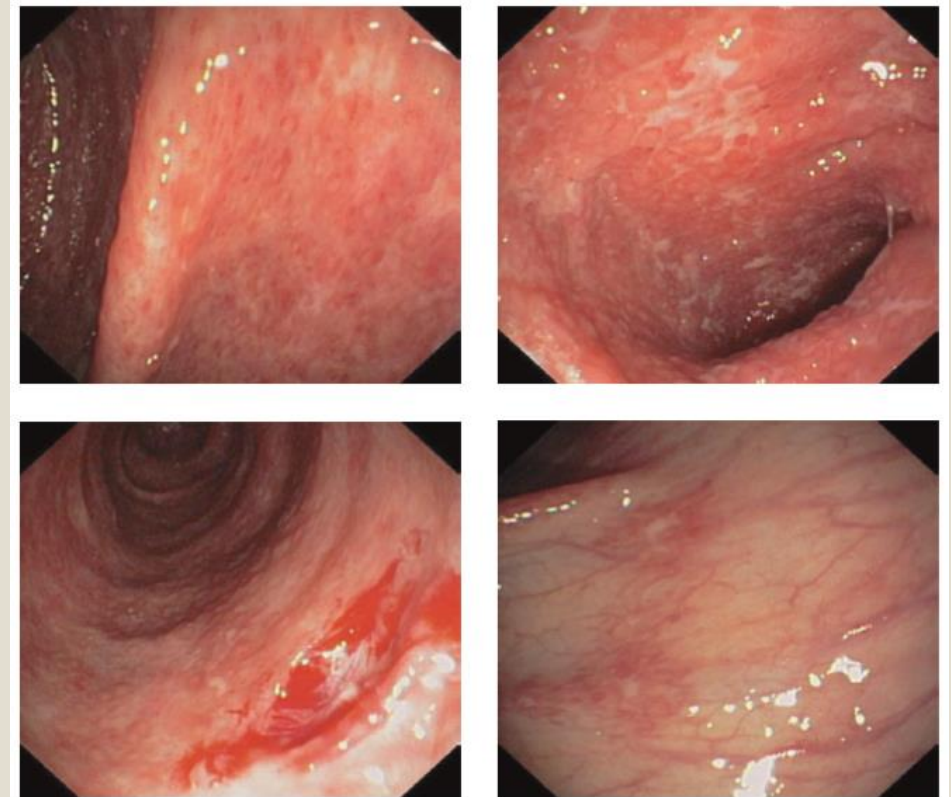


Surgical intervention

- Uncommon
- Subtotal or total colectomy +/- end ileostomy
- Revascularization procedures not indicated
- Acute Indications:
 - Perforation
 - Fulminant colitis or megacolon
 - Massive hemorrhage
 - Persistent symptoms with pain, bleeding, diarrhea, recurrent sepsis, 2-3 weeks with no improvement
- Chronic Indications:
 - Stricture formation – obstruction, diagnostic uncertainty (?cancer)

Infectious colitis

- Colitis defined as >3 unformed stools/day with evidence of colonic inflammation
 - Fecal markers – leukocytes, lactoferrin (more sensitive than WBC) or calprotectin
 - Lactoferrin and calprotectin – constituents of PMN
 - Passage of small volumes with gross blood and mucus
 - Endoscopic evidence of mucosal inflammation
 - Assume infectious if:
 - Microorganism linked with mucosal inflammation or
 - Toxin identified epidemiologically (known outbreak) or
 - Microbiologically diagnosed

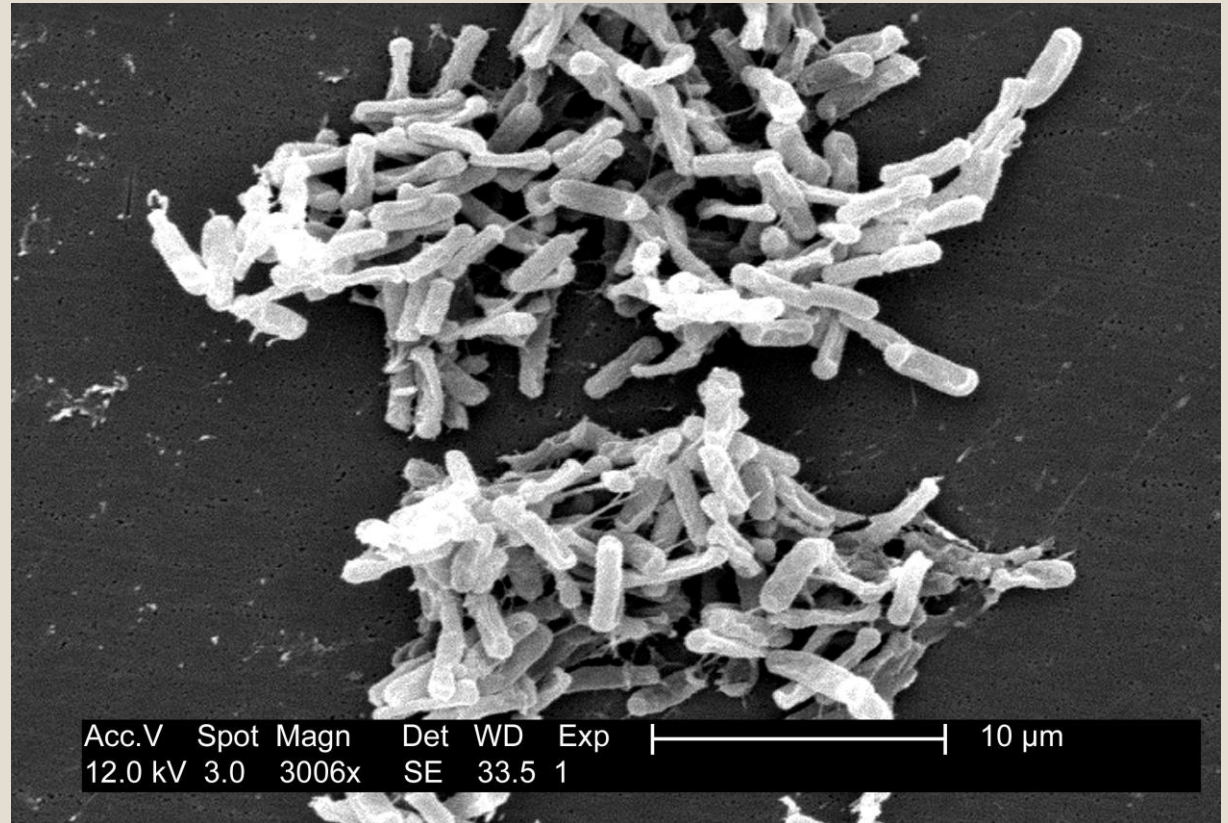


Etiology

- Nosocomial – *C. difficile* colitis
- International traveller
 - *Shigella*
 - *Campylobacter*
 - *Salmonella*
 - Enteroaggregative *Escherichia coli*
 - Enteroinvasive *Escherichia coli*
 - *Aeromonas* (tropical and semitropical)
 - Noncholera *Vibrio* (watery diarrhea/dysentery assoc. with shellfish/seafood)
 - *Yersinia* (watery diarrhea, fever, dysentery – appendicitis-like)
- Foodborne associated dysentery with hemolytic uremic syndrome
- STEC – Shiga toxin-producing *Escherichia coli* (EHEC)

C. Difficile

- Gram-positive, anaerobic, spore forming bacteria
- Produces enterotoxin
 - Toxin A
 - Toxin B
- Mucosal disruption



C. diff associated diarrhea (CDAD)

- Acute watery diarrhea, mild to severe colitis
- Suspect in hospitalized patients with recent antibiotics, immunocompromised, inflammatory bowel disease
- Stool for *C. Diff* Toxin
- CT
- Endoscopy for pseudomembranes (pathognomonic)

Sensitivity

C. difficile common antigen (Glutamate Dehydrogenase): Positive by Enzyme Immunoassay.

97%

C. difficile toxin: Negative by Enzyme Immunoassay.

56%

C. difficile toxin gene: Detected by molecular method.

92%

Molecular testing only detects the C. difficile toxin gene and will not detect active toxin production.

This result must be interpreted in the context of the clinical history, signs and symptoms of the patient.

A repeat test will not be performed within 14 days of a positive result.

Gene testing 98% specific

Sensitivity

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C. difficile toxin gene: Detected by molecular method.

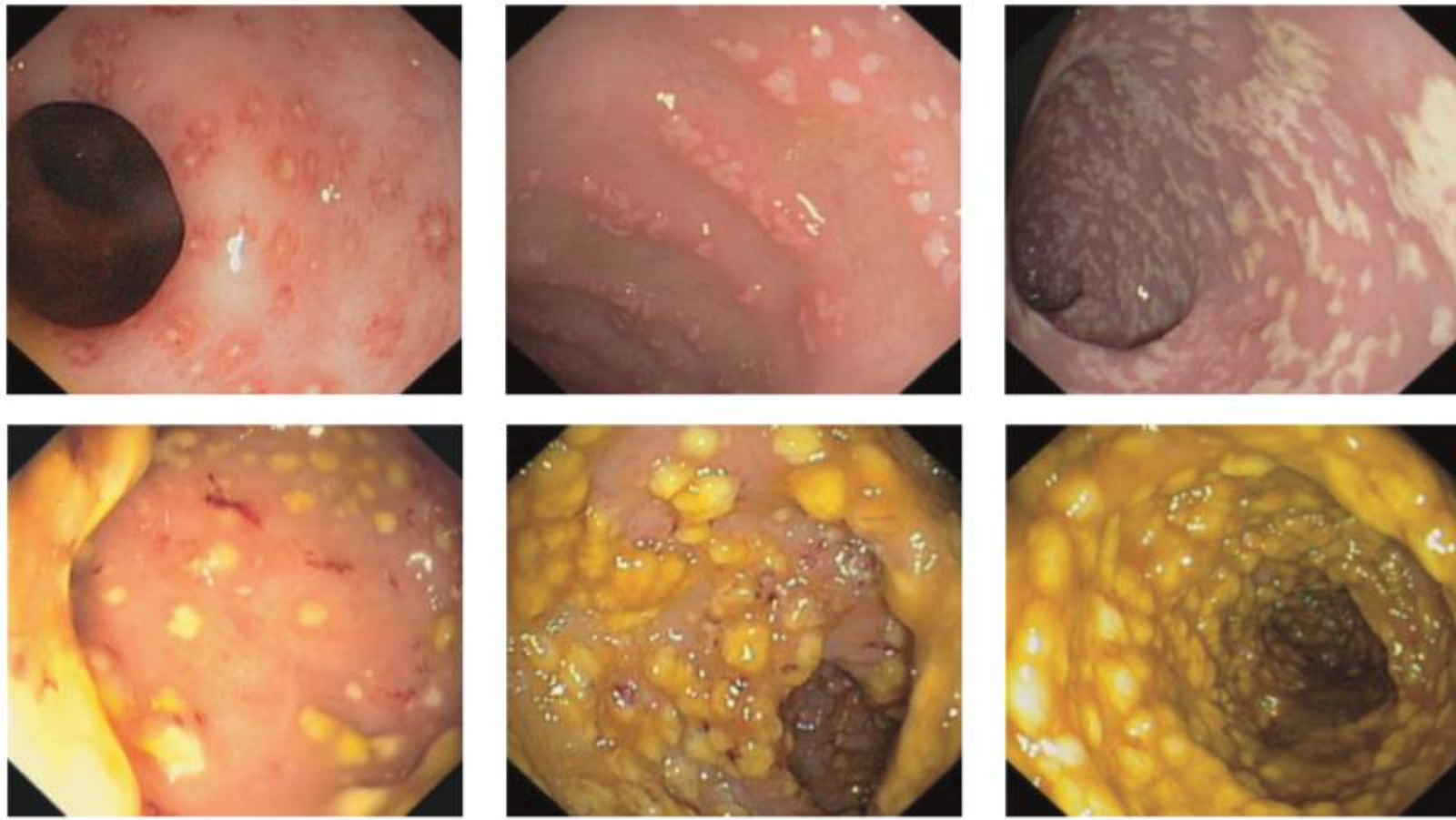
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This result must be interpreted in the context of the clinical history, signs and symptoms of the patient.

A repeat test will not be performed within 14 days of a positive result.

Pseudomembranes



Management

- Discontinue offending antibiotic
- Avoid/Discontinue PPIs

J Crit Care. 2014 Aug;29(4):696.e11-5. doi: 10.1016/j.jcrc.2014.03.002. Epub 2014 Mar 7.

Administration of proton pump inhibitors in critically ill medical patients is associated with increased risk of developing Clostridium difficile-associated diarrhea.

Buendgens L¹, Bruensing J¹, Matthes M¹, Dücker H¹, Luedde T¹, Trautwein C¹, Tacke F², Koch A¹.

Management

First episode

1st line

- Metronidazole 500mg PO TID x 10-14 days
- Metronidazole 250mg PO QID x 14 days
- Metronidazole 500 mg IV q8hr

2nd line

- Vancomycin 125mg PO QID x 14 days

3rd line

- Vancomycin 125mg PO/PR QID x 14 days
- Metronidazole 500mg IV q8hr

No role for f/u stool culture within 6 weeks of treatment completion

Management

First recurrence

1st line

- Vancomycin 125mg PO QID x 14 days

2nd line

- Metronidazole 250/500mg PO TID/QID x 14 days

Management

Subsequent recurrence

1st line

- Tapering vancomycin

2nd line

- Fidaxomicin 200mg po bid
- Rifamixin

3rd line


- Fecal bacteriotherapy
- Probiotics

Mild/Moderate Disease


 Mild to moderate defined as: diarrhea plus leukocytosis with a White Blood Cell Count 15 or lower and a serum Creatinine level less than 1.5 x pre-morbid level

 metroNIDAZOLE 500 mg, tab, ORAL, q8 hours, order duration: 14 day
First dose must be given STAT

Severe Disease

 UNCOMPLICATED: White Blood Cell Count greater than or equal to 15 or Creatinine greater than or equal to 1.5 x baseline


 vancomycin 125 mg, liquid, ORAL, q6 hours, order duration: 14 day
First dose must be given STAT


 COMPLICATED: toxic megacolon, ileus, or shock

 vancomycin 500 mg, liquid, ORAL, q6 hours, order duration: 14 day, ...
First dose must be given STAT

 metroNIDAZOLE 500 mg, injection, IV, q8 hours, order duration: 14 day, P...
First dose must be given STAT

Tapering Dose Optional

 For second recurrence of C-difficile

 For second recurrence of C. difficile follow tapering dose schedule for vancomycin and select all medication orders below.

  vancomycin 125 mg, liquid, ORAL, q6 hours, order duration: 14 day,
Requested Start Date/Time T:N

+8 day   vancomycin 125 mg, liquid, ORAL, q12 hours, order duration: 7 day,
Requested Start Date/Time T+15;N

+15 day   vancomycin 125 mg, liquid, ORAL, daily, order duration: 7 day,
Requested Start Date/Time T+22;N

+22 day   vancomycin 125 mg, liquid, ORAL, q48 hours, order duration: 7 day,
Requested Start Date/Time T+30;N

+29 day   vancomycin 125 mg, liquid, ORAL, q72 hours, order duration: 7 day,
Requested Start Date/Time T+38;N

Severe CDAD

- No consensus on definition

- SHEA/IDSA CPG

- WBC ≥ 15
- Serum Cr $> 1.5x$ baseline
- Hypotension/shock
- Ileus
- Megacolon



Severe, uncomplicated

Severe, complicated

Severe, complicated CDAD

- Requires surgical intervention for source control
- Indications for OR are ill-defined
 - Toxic megacolon
 - Perforation
 - MODS

Impact of Emergency Colectomy on Survival of Patients With Fulminant *Clostridium difficile* Colitis During an Epidemic Caused by a Hypervirulent Strain

François Lamontagne, MD, Annie-Claude Labbé, MD,†‡ Olivier Haeck, MD,† Olivier Lesur, MD,* Mathieu Lalancette, MD,* Carlos Patino, MD,‡ Martine Leblanc, MD,† Michel Laverdière, MD,‡ and Jacques Pépin, MD**

Annals of Surgery • Volume 245, Number 2, February 2007

- Survival benefit with subtotal colectomy for patients with:
 - Age \geq 65
 - WBC \geq 20,000
 - Lactate 2.2-4.9



Meta-analysis

Systematic review and meta-analysis of outcomes following emergency surgery for *Clostridium difficile* colitis

A. Bhangu, D. Nepogodiev, A. Gupta, A. Torrance and P. Singh, on behalf of the West Midlands Research Collaborative*

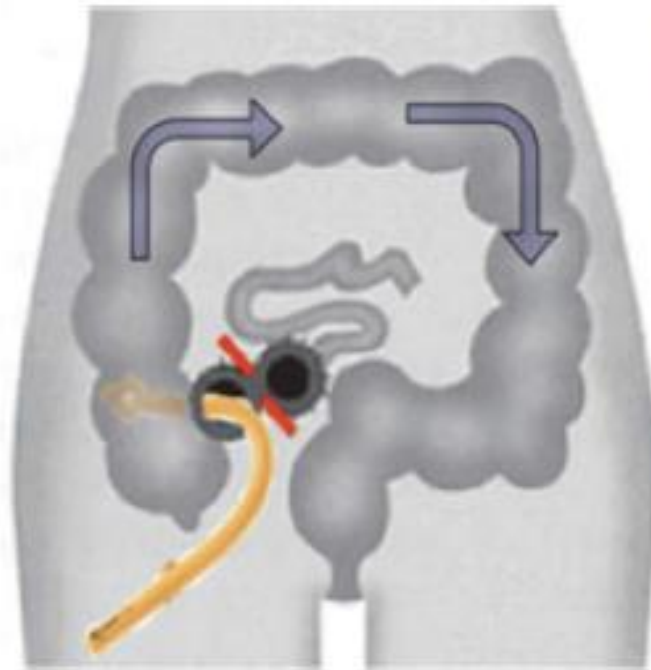
- Total/subtotal colectomy and end ileostomy was primary surgical intervention in 89% of patients
- 30-day post-operative mortality rate was 41.3% (19% to 71%)
- In-hospital mortality rate was 41.6% (25% to 80%)

Diverting Loop Ileostomy and Colonic Lavage

An Alternative to Total Abdominal Colectomy for the Treatment of Severe, Complicated Clostridium difficile Associated Disease

Matthew D. Neal, MD, John C. Alverdy, MD,† Daniel E. Hall, MD,*‡
Richard L. Simmons, MD,* and Brian S. Zuckerbraun, MD*‡*

Annals of Surgery • Volume 254, Number 3, September 2011



1. Creation of diverting loop ileostomy.
2. Intraoperative antegrade colonic lavage with 8 liters of warmed PEG3350/electrolyte solution via ileostomy.
3. Postoperative antegrade colonic enemas with vancomycin (500 mg in 500 mL X 10 days) via ileostomy.

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- 19% (8 of 42) mortality versus 50% (21 of 42) mortality of a historical control
- 19% of surviving patients had ileostomy reversed
- Termed “Pittsburgh Protocol”

The London Protocol

1. Insertion of NJ tube
2. Confirmation with AXR
3. Insertion of Flexiseal
4. Colonic lavage with PEG 8L NJ over 2 days
5. Vancomycin 500 mg NJ/PO q6h x 14 days
6. Metronidazole 500 mg IV q8h x 14 days

Ulcerative colitis



Epidemiology

- Developed countries
 - Northern latitudes
- Seasonal variation
- Stable incidence
 - 4-6/100,000
- Prevalence 40-100/100,000
- Age<30
 - Small secondary peak 6th decade
- Equal among genders
- White, Jewish, northern European

Prevalence of Ulcerative colitis in the United States.

	Prevalence (95% CI)
Northeast	255 (248–263)
South	209 (202–216)
Midwest	234 (227–241)
West	263 (253–273)

The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. Kappelman et al. Clin Gastroenterol Hepatol. 2007 Dec;5(12):1424-9.

Etiology

- Cause is unknown
 - Environmental
 - Dietary
 - Infectious
 - Drugs
 - Genetic
 - Altered immunologic response
- Smoking may confer a protective effect
- Appendectomy may confer a protective effect

A Prospective Study of Cigarette Smoking and the Risk of Inflammatory Bowel Disease in Women

Leslie M. Higuchi, MD, MPH¹, Hamed Khalili, MD², Andrew T. Chan, MD, MPH^{2,3}, James M. Richter, MD², Athos Bousvaros, MD, MPH¹ and Charles S. Fuchs, MD, MPH^{3,4}

OBJECTIVES: Long-term data on the influence of cigarette smoking, especially cessation, on the risk of Crohn's disease (CD) and ulcerative colitis (UC) are limited.

METHODS: We conducted a prospective study of 229,111 women in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHS II). Biennially, we collected updated data on cigarette smoking, other risk factors, and diagnoses of CD or UC confirmed by medical record review.

RESULTS: Over 32 years in NHS and 18 years in NHS II, we documented 336 incident cases of CD and 400 incident cases of UC. Compared with never smokers, the multivariate hazard ratio (HR) of CD was 1.90 (95% confidence interval (CI), 1.42–2.53) among current smokers and 1.35 (95% CI, 1.05–1.73) among former smokers. Increasing pack-years was associated with increasing risk of CD (Ptrend < 0.0001), whereas smoking cessation was associated with an attenuation of risk. By contrast, the multivariate HR of UC was 0.86 (95% CI, 0.61–1.20) among current smokers and 1.56 (95% CI, 1.26–1.93) among former smokers. The risk of UC was significantly increased within 2–5 years of smoking cessation (HR, 3.06; 95% CI, 2.00–4.67) and remained persistently elevated over 20 years.

CONCLUSIONS: Current smoking is associated with an increased risk of CD, but not UC. By contrast, former smoking is associated with an increased risk of UC, with risk persisting over two decades after cessation.

Pathology

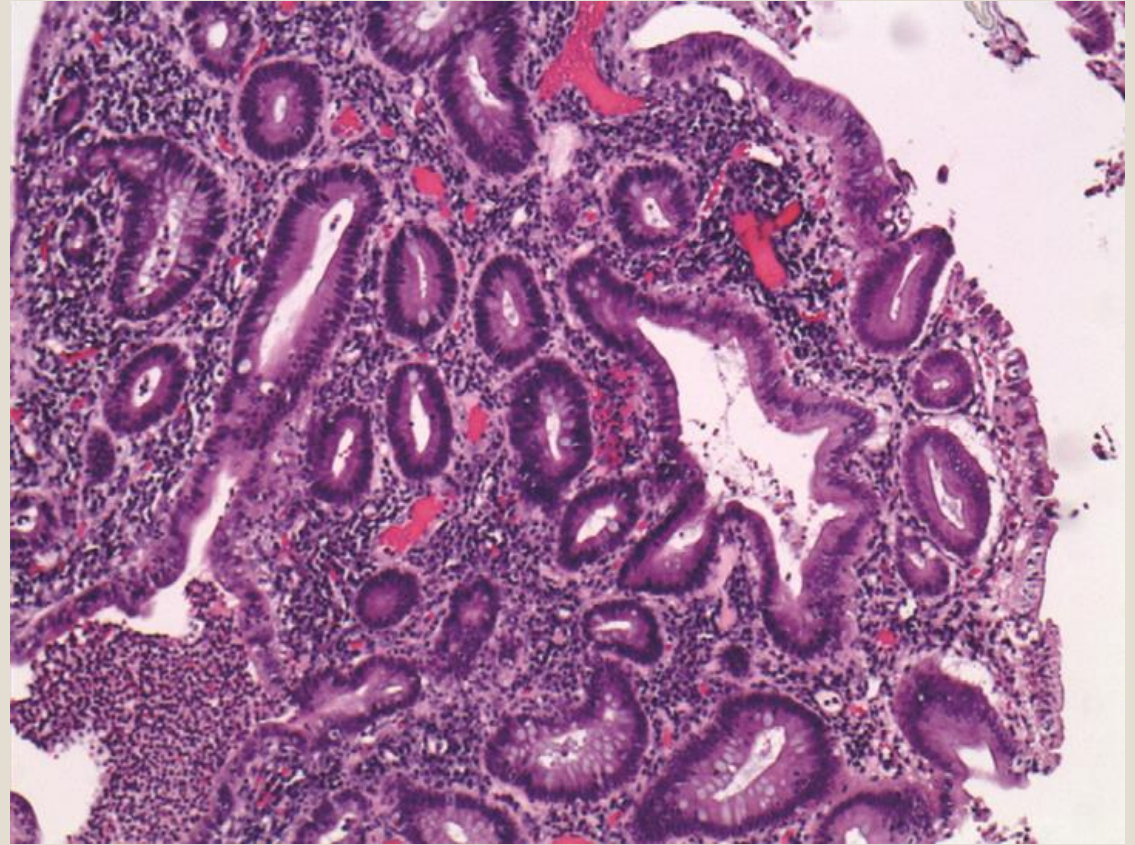
- Mucosa and submucosa
- Rectal involvement (proctitis)
 - Extends proximally
 - May involve entire colon
 - No TI
- Continuous inflammation
- Pseudopolyps
- Strictures (5-12%)



	ULCERATIVE COLITIS	CROHN'S COLITIS
Colonoscopic Features		
Distribution	Continuous	Discontinuous
Rectal disease	4+	1+
Friability	4+	1+
Aphthous ulcers	0	4+
Deep longitudinal ulcers	0	4+
Cobblestoning	0	4+
Pseudopolyps	2+	2+

Histology

- Inflammation of mucosa and submucosa
 - Crypt abscesses
 - Vascular congestion
 - Crypt branching
- Sparing of muscularis
 - Except in megacolon
- pANCA in 86% patients with UC



Clinical presentation

- Gradual onset over weeks
- Diarrhea and mucus
- Urgency, tenesmus, incontinence
- Rectal bleeding
- Abdominal discomfort
- Fever, fatigue, weight loss
- Often similar presentation to Crohn's disease
 - Less urgency in Crohn's
 - Less bleeding in Crohn's
 - More pain in Crohn's
 - More perianal disease in Crohn's

	ULCERATIVE COLITIS	CROHN'S COLITIS
Clinical Features		
Bleeding per rectum	3+	1+
Diarrhea	3+	3+
Obstructive symptoms	1+	3+
Anal or perianal disease	Rare	4+
Risk for cancer	2+	3+
Small bowel disease	0	4+

Extra-intestinal manifestations

- Arthritis in 20%
- Ankylosing spondylitis in 3-5%
- Erythema nodosum in 10-15%
- Pyoderma gangrenosum
- Uveitis, episcleritis
- Primary sclerosing cholangitis in 5-8%
- Venous/arterial thromboembolism
- Colectomy typically improves arthritis, ankspan, erythema nodosum, and pyoderma gangrenosum
- Colectomy does not improve PSC
 - Usually progressive and requiring liver tx

Hypercoagulability in inflammatory bowel disease

Clinical characteristics
Unusual sites
Associated with active disease and better when disease controlled
Associated with use of steroids (possibly indicating active disease)
Recurrent
Serious
Younger age
Abnormalities described
Abnormal fibrinolysis
Abnormal platelet aggregation
Activated protein C increased
Circulating immune complexes
Decreased antithrombin III
Factor V Leiden mutation
Increased cytokines (interleukin-6, thrombopoietin)
Increased factors V and VIII
Increased plasminogen activator inhibitor
Increased sedimentation rate, fibrinogen
Lupus anticoagulant
Thrombocytosis and leukocytosis (uniformly present in most studies)

Severity

Montreal classification

Table 3 Montreal classification of severity of ulcerative colitis (UC)

Severity	Definition
S0	Clinical remission
S1	Mild UC
S2	Moderate UC
S3	Severe UC

ESR, erythrocyte sedimentation rate.

Severity

- At presentation:
 - Most are mild
 - 27% moderate
 - 1% severe
- Acute complications:
 - Severe bleeding
 - Fulminant colitis
 - Toxic megacolon
 - Perforation

Mayo score (0-12)

Stool pattern

- Patient reports a normal number of daily stools (0 points)
- One to two more stools than normal (1 point)
- Three to four more stools than normal (2 points)
- Five or more stools than usual (3 points)

Most severe rectal bleeding of the day

- None (0 points)
- Blood streaks seen in the stool less than half the time (1 point)
- Blood in most stools (2 points)
- Pure blood passed (3 points)

Endoscopic findings

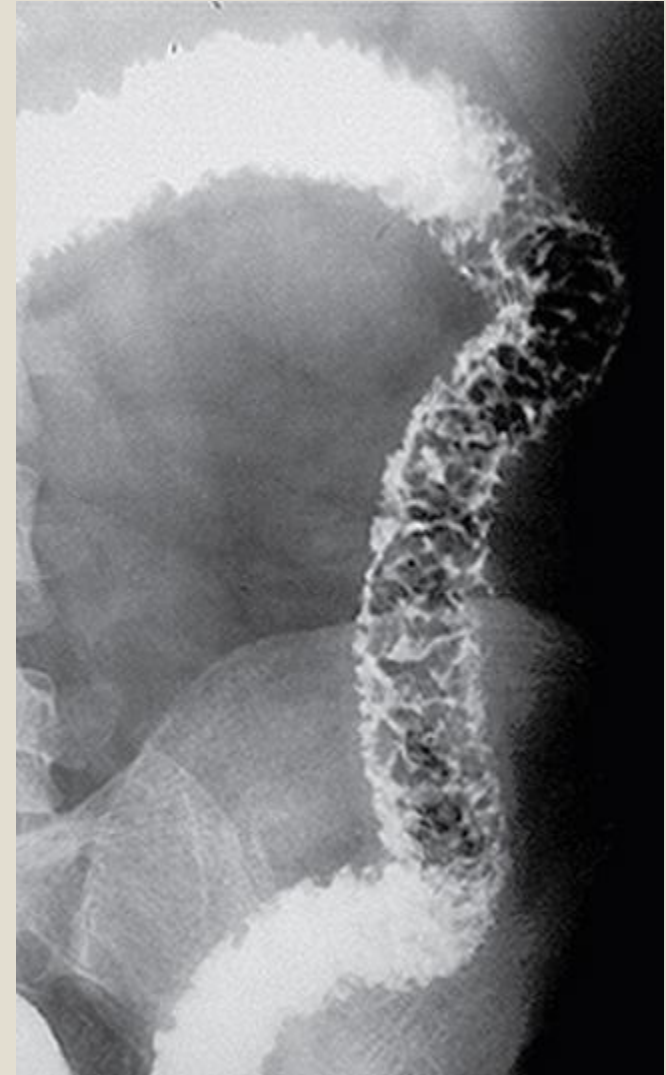
- Normal or inactive colitis seen (0 points)
- Mild colitis: mild friability, erythema, decrease in vascularity (1 point)
- Moderate colitis: friability, marked erythema, vascular pattern absent, erosions seen (2 points)
- Severe colitis: ulcerations and spontaneous bleeding (3 points)

Global assessment by physician

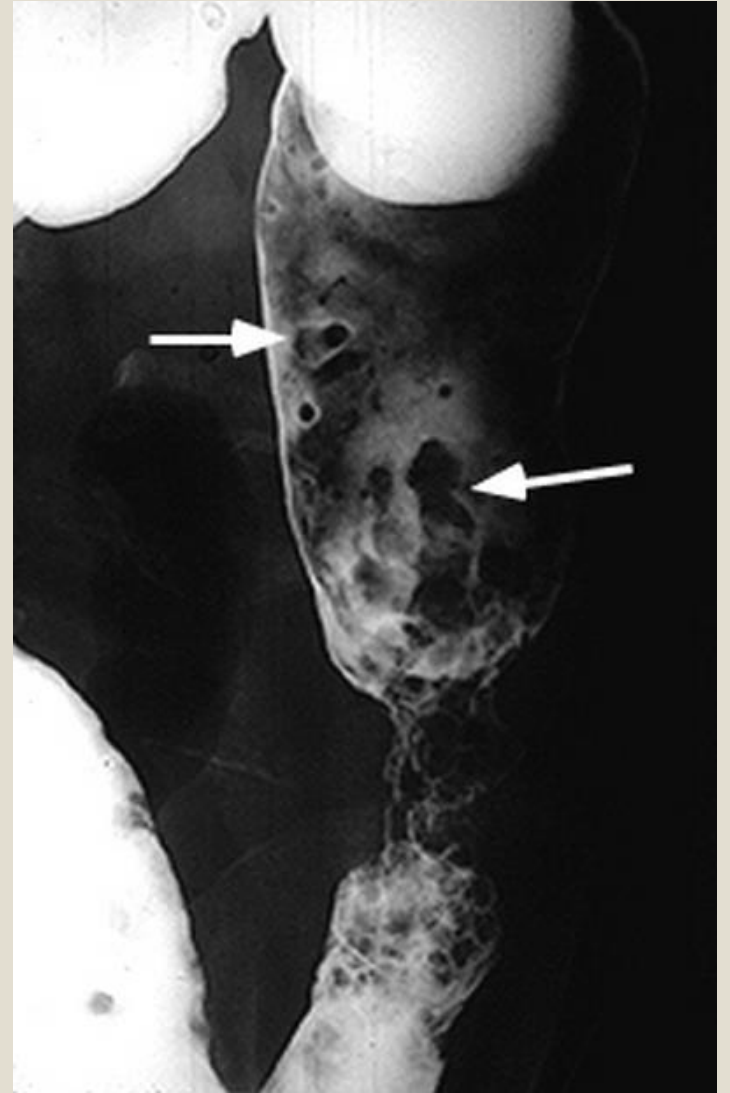
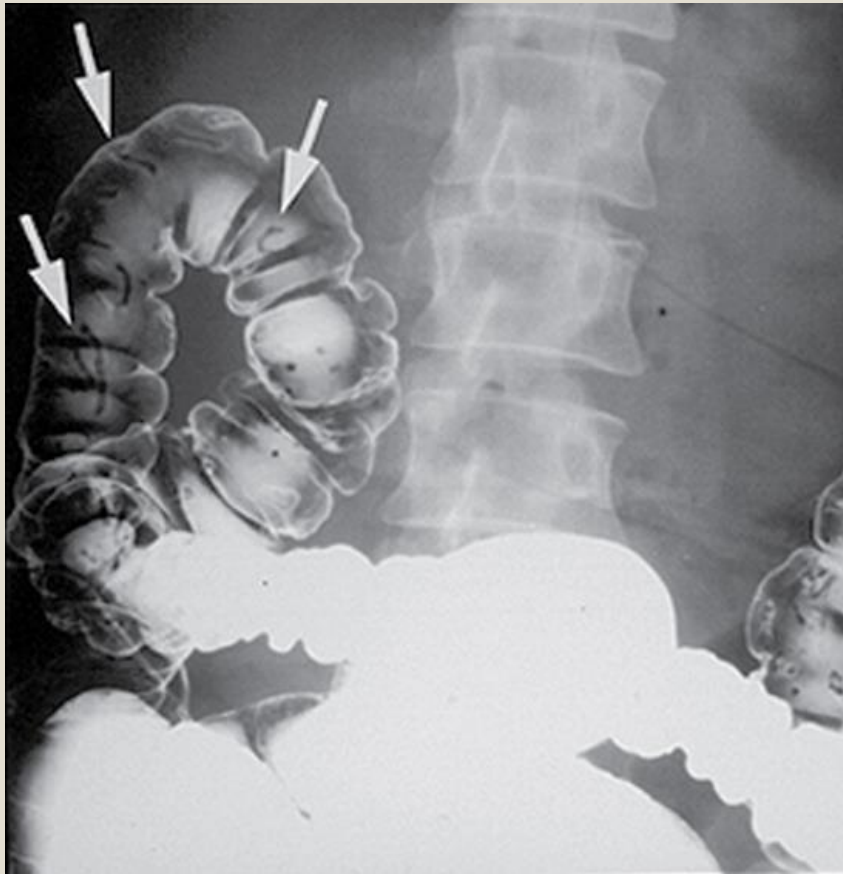
- Normal (0 points)
- Mild colitis (1 point)
- Moderate colitis (2 points)
- Severe colitis (3 points)

Investigations

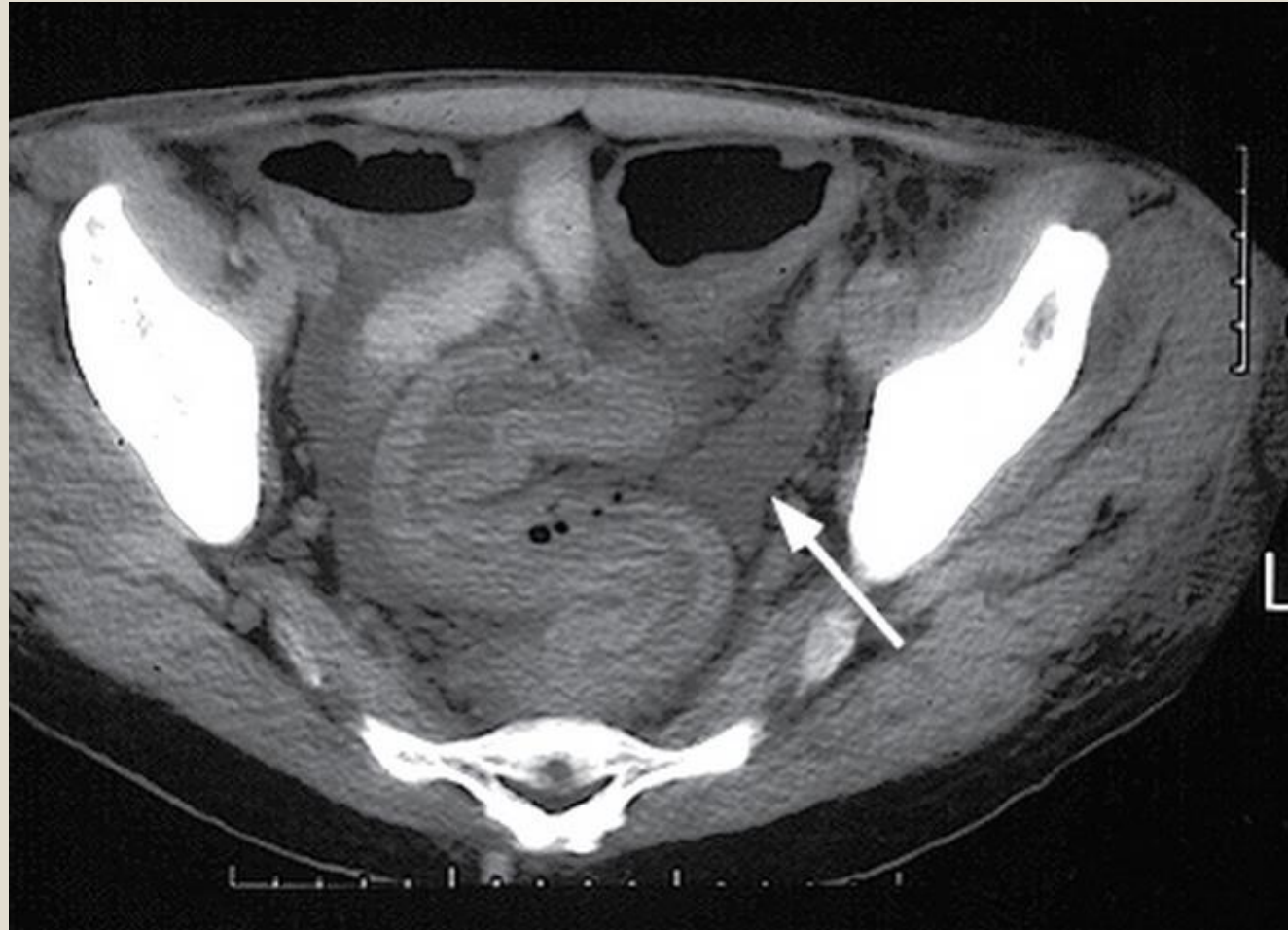
- Laboratory
 - Anemia, low albumin
 - ESR, CrP, Electrolyte abnormalities
 - pANCA?
 - Stool cultures to rule out infection
- Imaging
 - Radiographs
 - Barium enema
 - CT/MRI
 - Ultrasound
- Endoscopy



Barium enema

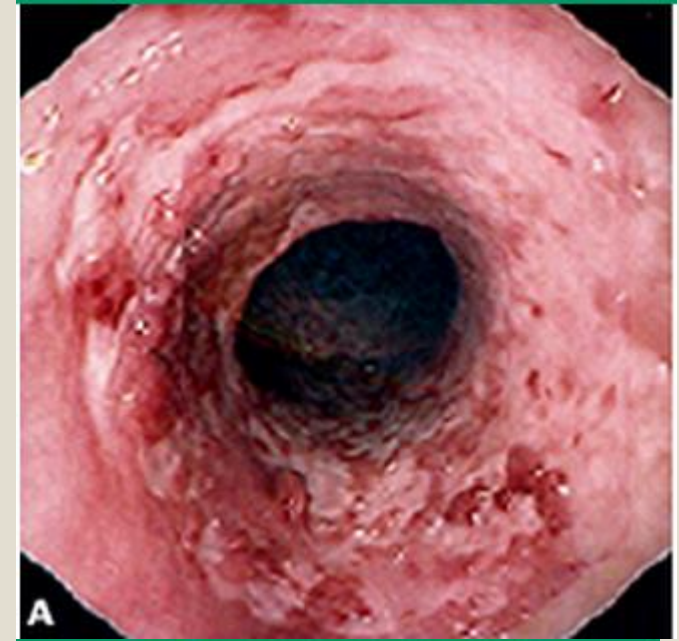


CT



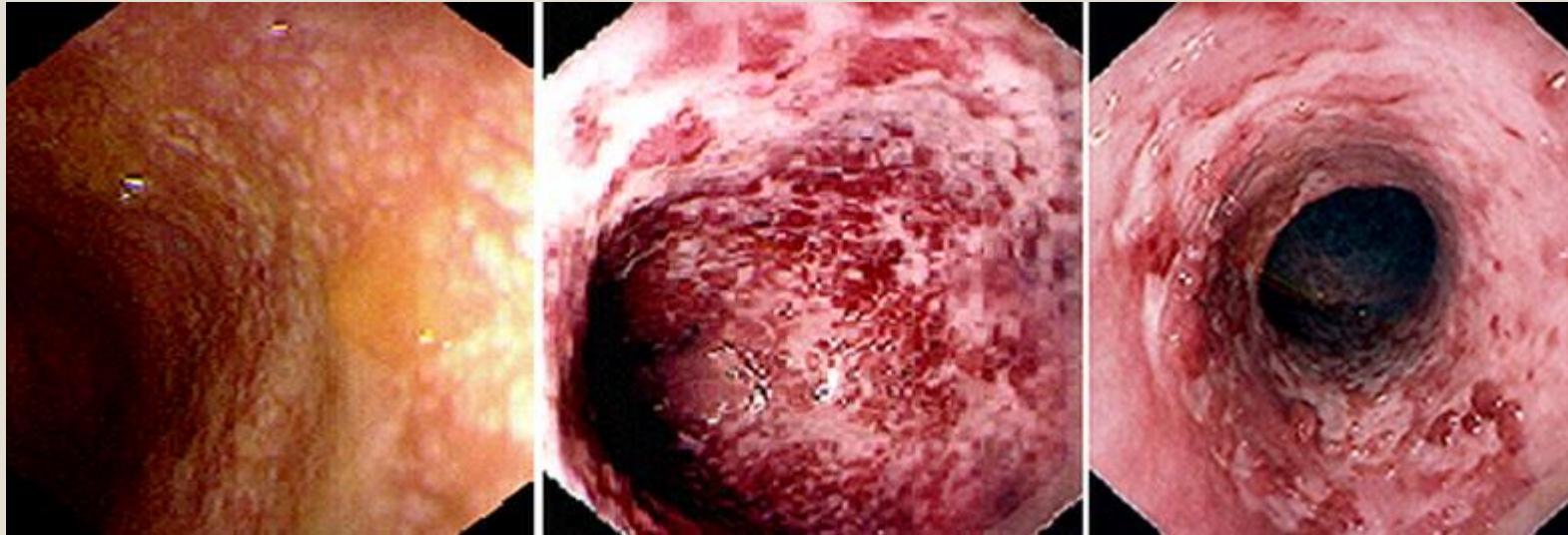
Endoscopy

- Ileocolonoscopy allows evaluation of TI inflammation (which would suggest Crohn's disease) and extent and severity of colonic disease
- Should be avoided in severe colitis
- Flexible sigmoidoscopy should be performed instead
- Loss of vascular markings, engorgement of mucosa, erythema
- Granularity, petechiae, exudates, edema, erosions, friability, spontaneous bleeding
- Macroulcerations, profuse bleeding, copious exudates
- Pseudopolyps



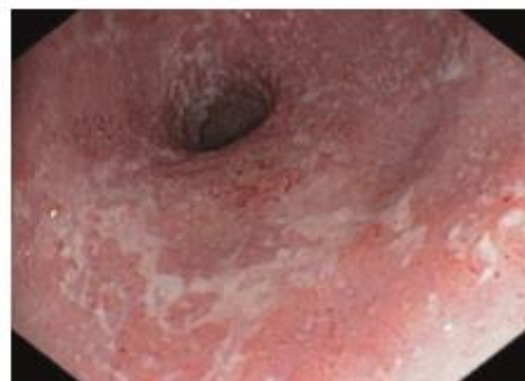
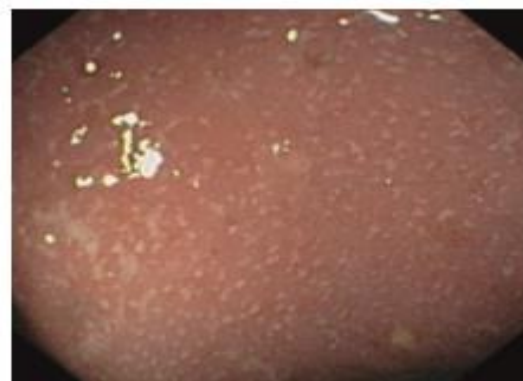
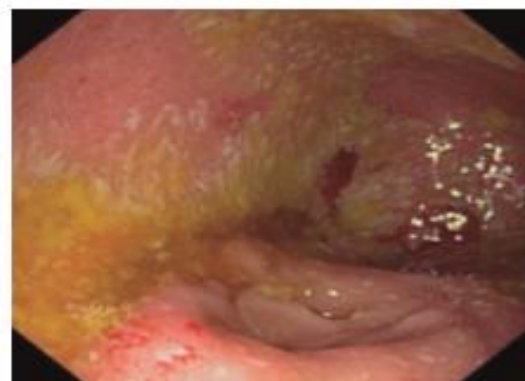
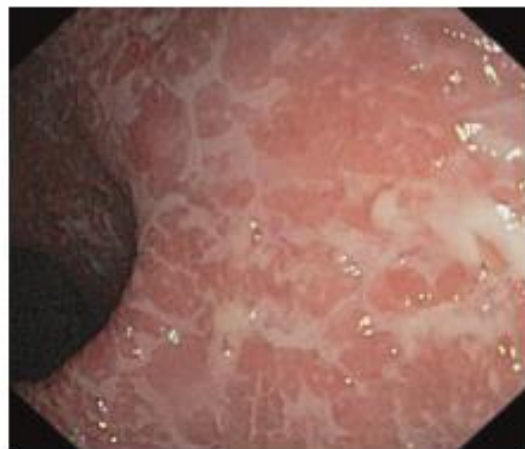
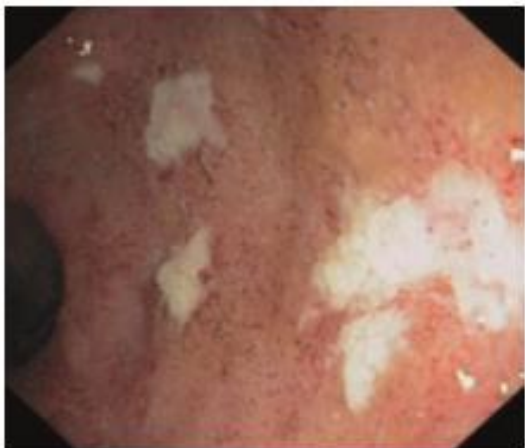
Endoscopy

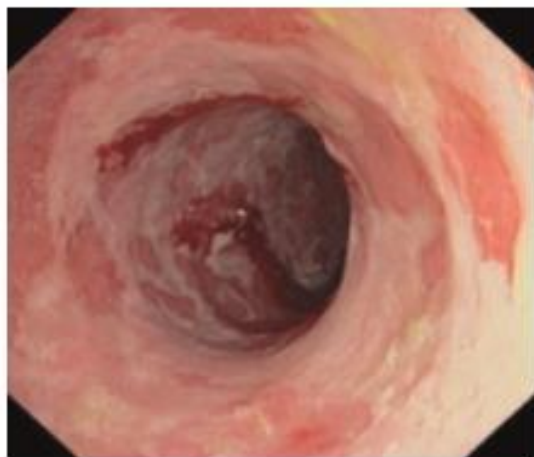
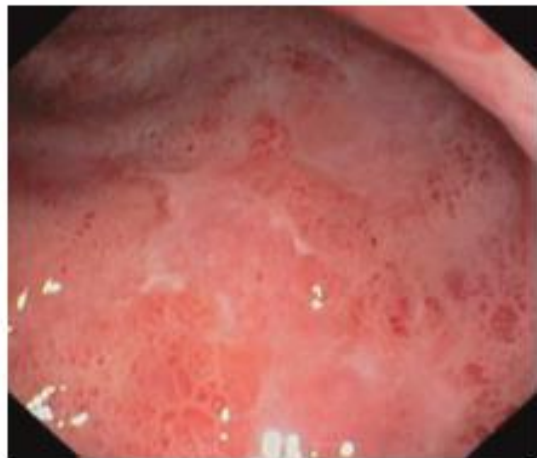
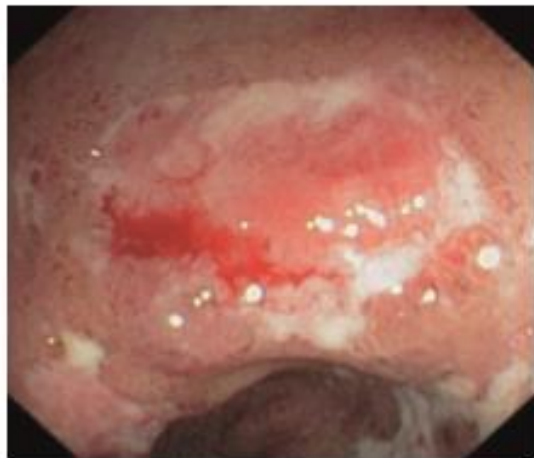
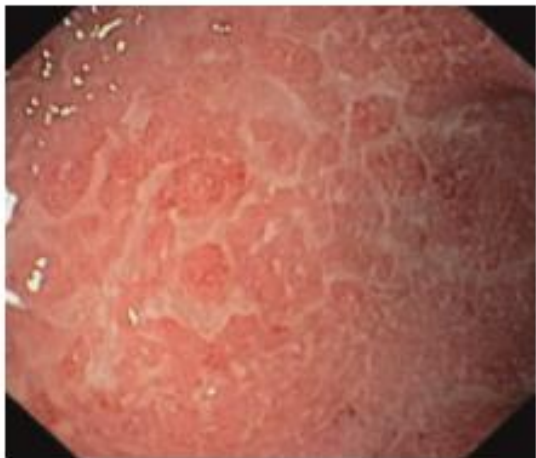
- Rectum – continuous
- 30-50% limited to rectum/sigmoid, 20-30% left sided colitis
- 20% pancolitis
 - Occasional backwash ileitis



Endoscopic Criteria for Mayo Score

	0	1 Points	2 Points	3 Points
E N D O S C O P I C A L	N O R M A L	Mild Erythema ↓ vascularity Mild friability	Moderate Marked erythema Lack vascular pattern Friability	Severe Spontaneous bleeding ulceration
				





Biopsy

- Crypt abscesses
- Crypt branching, shortening, disarray, atrophy
- Mucin depletion in epithelial cells, paneth cell metaplasia
- Increased lamina propria cellularity, basal plasmacytosis, basal lymphoid aggregates, lamina propria eosinophils
- None are specific for UC, but two or more is suggestive
- Biopsies also done to rule out CMV – enlarged cytomegalic cells, eosinophilic intranuclear inclusions, immunoperoxidase staining
- Severe urgency and tenesmus – should do Neisseria/HSV cultures also.

Natural history

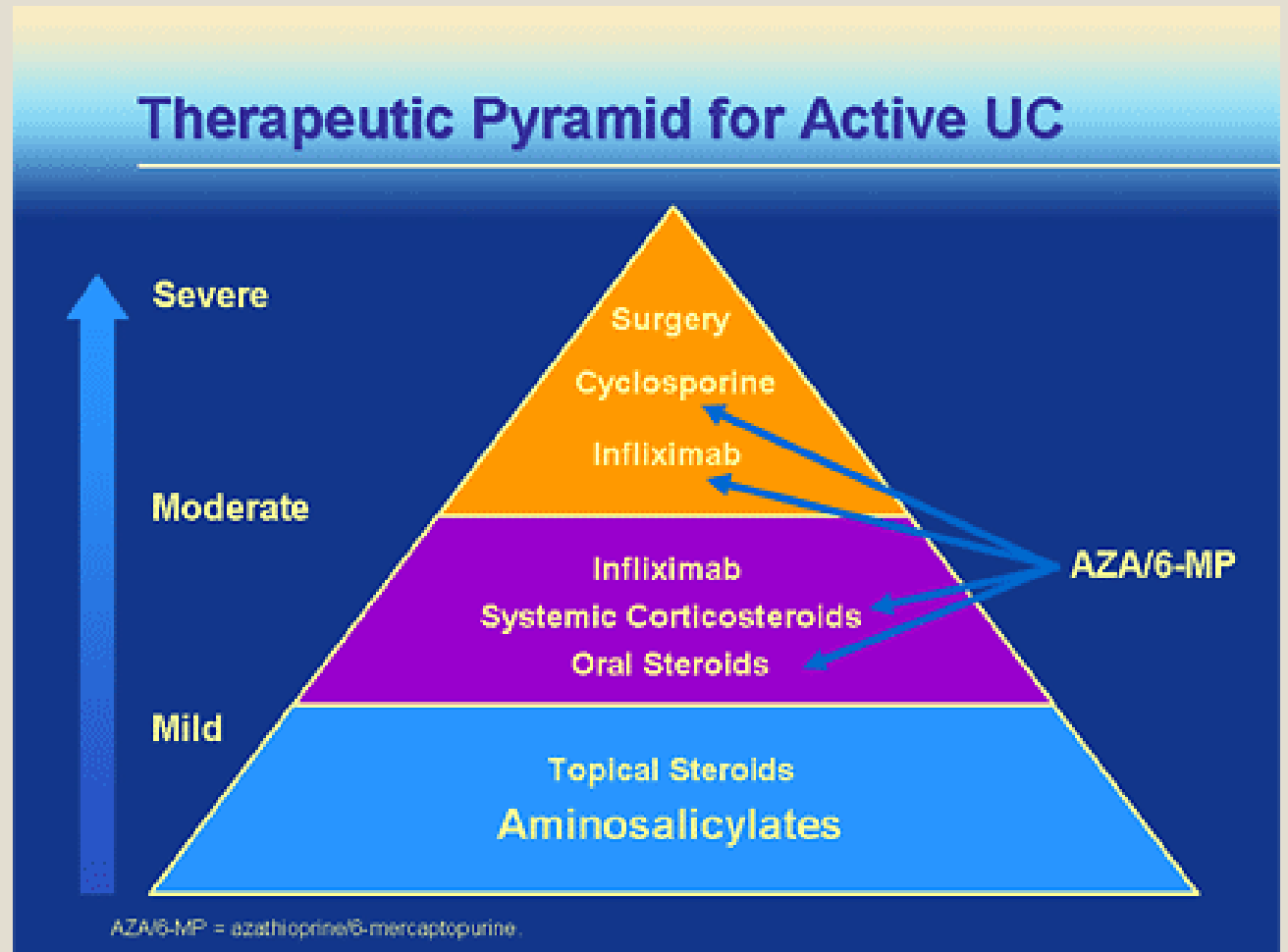
- Starts with weeks to months attacks of bloody diarrhea
- With treatment, intermittent exacerbations and long periods of asymptomatic remission
- Small percentage ongoing symptoms
- Patients presenting with proctitis are more likely to have a benign course and to respond to topical therapy
- Those with extensive disease are more likely to need systemic therapy or colectomy

Medical management

- Medical therapy is targeted at controlling underlying inflammation to induce remission
- A careful assessment of disease severity should guide management
 - Mild to severe severity
 - Proctitis to pancolitis extent
- Surgical management should be reserved for complications or cases unresponsive to medical therapy

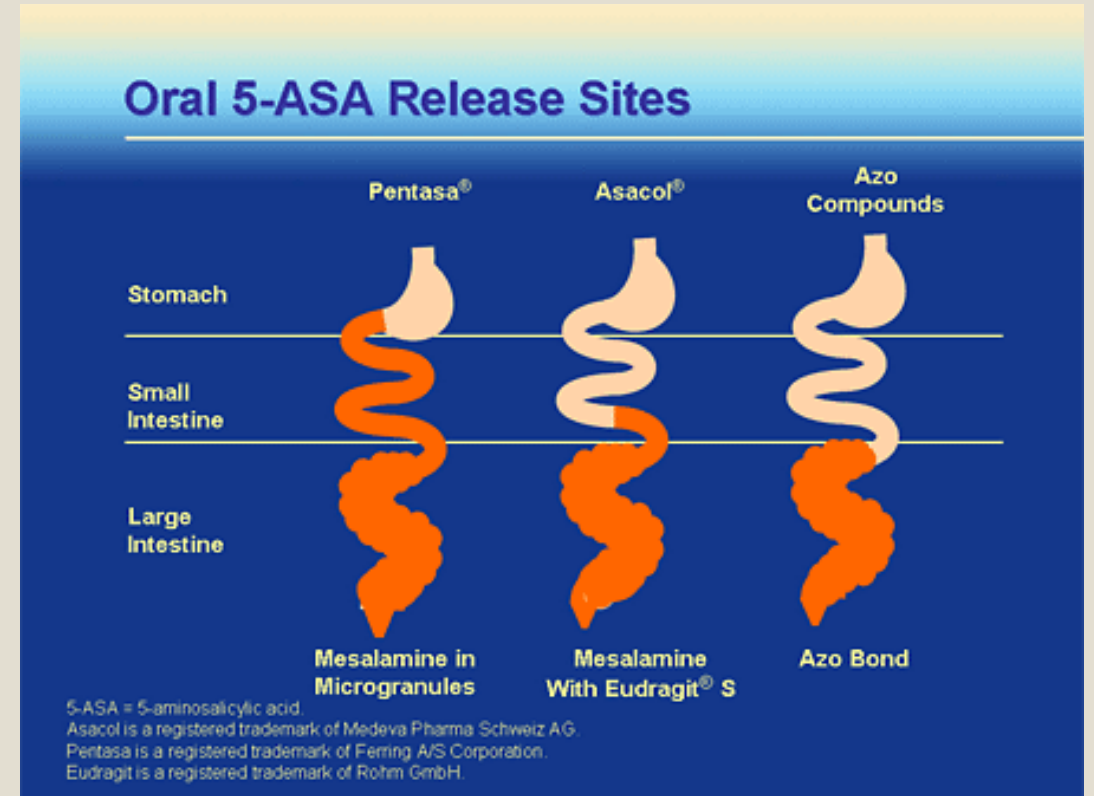
Medical management

- Three broad categories
 - 5-aminosalicylic acid (5-ASA)
 - Pentasa, Asacol
 - Corticosteroids
 - Oral vs. IV
 - Immunomodulators
 - Azathioprine
 - Methotrexate
 - Biologics
 - Cyclosporine
 - Tacrolimus



Mild to Moderate Colitis

- 5-aminosalicylic acid (5-ASA) often used
- Topical 5-ASA or topical steroid for initial treatment of distal colitis
 - 5-ASA may be superior
 - Foams may be better than enemas
- Oral plus topical 5-ASA if extends to splenic flexure
 - Minimum duration: 4 weeks
- For more severe left-sided colitis, can combine oral steroids and 5-ASA
- Pancolitis: initially oral 5-ASA
 - If refractory, oral steroids should be commenced



Severe colitis

- Mainstay of therapy is IV steroids
 - 400mg hydrocortisone daily
 - 40-60mg methylprednisolone daily
- 40% complete response
- 30% will require colectomy during admission
- In those with partial response:
 - 50% will require colectomy within 1 year
 - 70% will require colectomy within 5 years



Rescue therapy

- If no response to high dose steroids in 3-5 days **and** no indication for surgery:
 - Single infusion of infliximab (5mg/kg)
 - Daily cyclosporine infusion (4mg/kg)
 - Ongoing RCT to compare the two
- Prolonged response can be achieved to avoid colectomy
- May only be a delay tactic
 - Perhaps patients are then in a better condition for surgery?
- Only case series so far on Tacrolimus

CLINICAL-ALIMENTARY TRACT

Infliximab as Rescue Therapy in Severe to Moderately Severe Ulcerative Colitis: A Randomized, Placebo-Controlled Study

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See editorial on page 2161.

Background & Aims: Despite treatment with corticosteroids, severe to moderately severe attacks of ulcerative colitis have a high colectomy rate. We intended to find a rescue therapy other than cyclosporin A, which imposes a high risk of side effects and cyclosporine-related mortality. **Methods:** This was a randomized double-blind trial of infliximab or placebo in severe to moderately severe ulcerative colitis not responding to conventional treatment. Patients were randomized to infliximab/placebo either on day 4 after the initiation of corticosteroid treatment if they fulfilled the index criteria for fulminant ulcerative colitis on day 3 or on day 6-8 if they fulfilled index criteria on day 5-7 for a severe or moderately severe acute attack of ulcerative colitis. Results were analyzed according to the intention-to-treat principle. The primary end point was colectomy or death 3 months after randomization. Secondary end points were clinical and endoscopic remission at that time in patients who did not undergo operation. **Results:** Forty-five patients were included (24 infliximab and 21 placebo). No patient died. Seven patients in the infliximab group and 14 in the placebo group had a colectomy ($P = .017$; odds ratio, 4.9; 95% confidence interval, 1.4-17) within 3 months after randomization. No serious side effects occurred. Three patients in the placebo group required operation for septic complications. **Conclusions:** Infliximab 4-5 mg/kg is an effective and safe rescue therapy in patients ex-

tack of ulcerative colitis not responding to conventional treatment.

Traditionally, acute attacks of ulcerative colitis (UC) have been treated intensively with high doses of corticosteroids intravenously (IIVT). Despite IIVT, severe attacks had a high colectomy rate varying from 38% to 47% in 2 frequently quoted series.^{1,2} Of patients with UC affecting the entire colon, 60% had surgery within 3 months.² Also, a moderately severe attack was associated with a risk for operation in approximately 20% of the patients.²

Cyclosporin A (CyA) was shown to be an effective rescue therapy in acute attacks of UC not responding to steroids.³ However, this increases the risk of side effects⁴ and of CyA-related mortality.^{3,6} For this reason, CyA has not been adopted as rescue therapy for patients with failed steroid treatment in Sweden and most Danish centers, because the risks were considered greater than those for surgical therapy.

Infliximab (Remicade; Centocor Inc, Malvern, PA) has become an established treatment in Crohn's disease (CD). It is a chimeric monoclonal antibody to human tumor necrosis factor (TNF)- α that is constructed by linking the variable regions of a mouse antihuman TNF mono-

Abbreviations used in this paper: CI, confidence interval; CRP, C-reactive protein; CyA, cyclosporin A; OR, odds ratio; TNF, tumor necrosis factor.

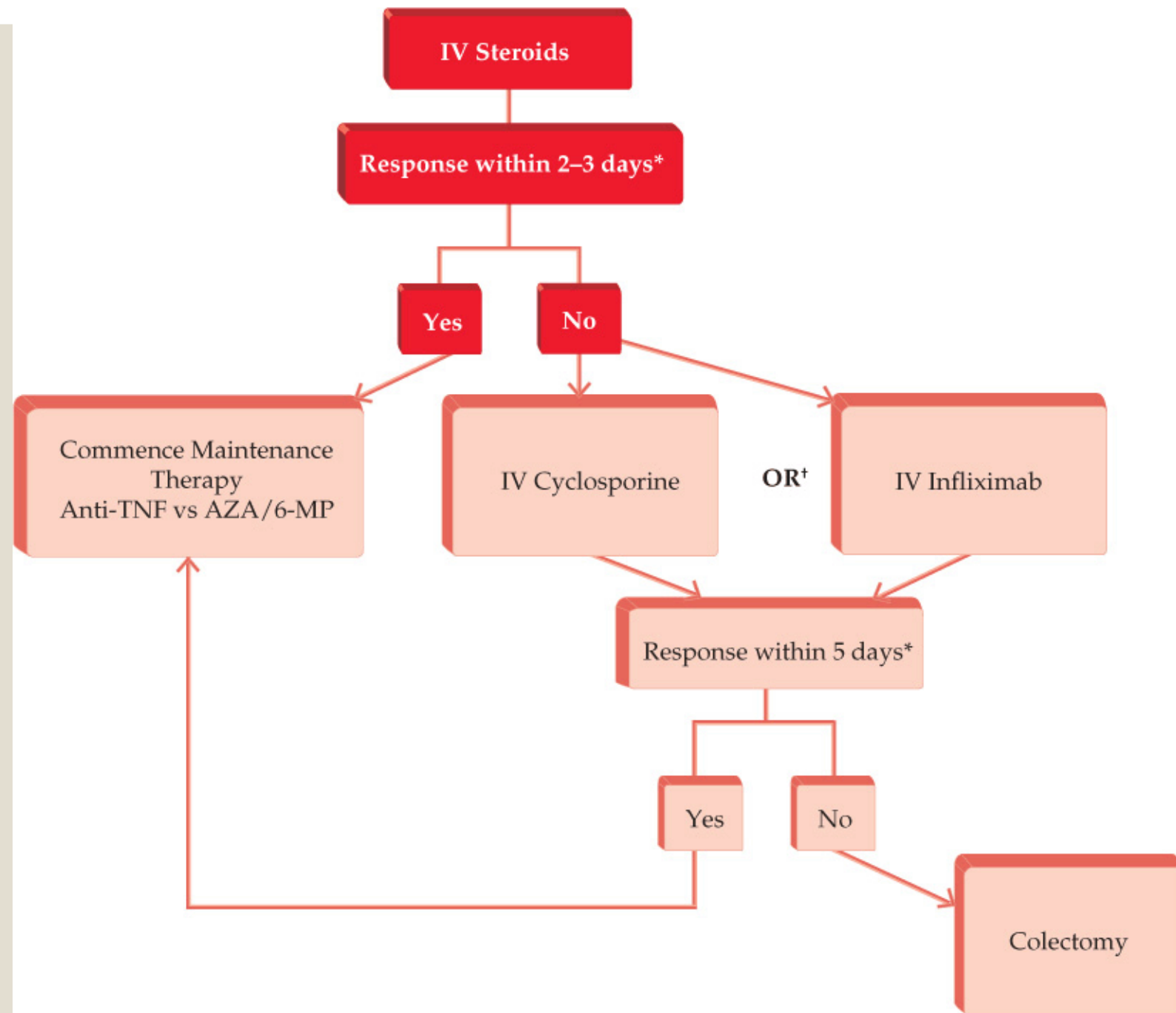
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0016-5085/05/\$30.00

Infliximab

- Chimeric monoclonal antibody against tumour necrosis factor alpha (TNF α), a cytokine that:
 - Induces proinflammatory cytokines like IL1, IL6
 - Leukocyte movement into tissues by permeability of endothelial layer of blood vessels
 - Increases release of adhesion molecules
- Used for the treatment of Crohn's and Ulcerative Colitis, as well as rheumatoid arthritis, psoriasis, ankylosing spondylitis, etc.
- IV infusion typically in 6-8 week intervals
- Binds with high affinity to soluble and transmembrane (TNF α) and neutralizes biologic activity

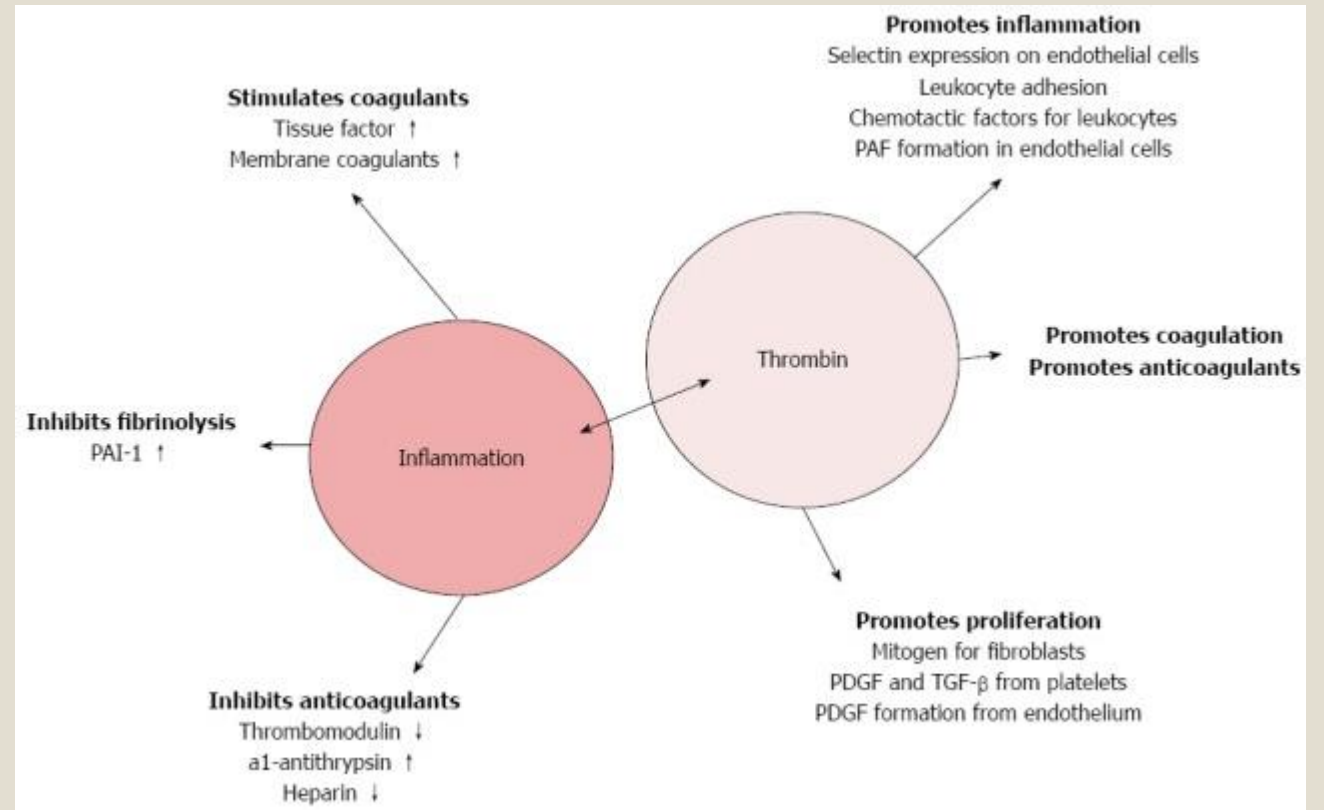


Suggested algorithm



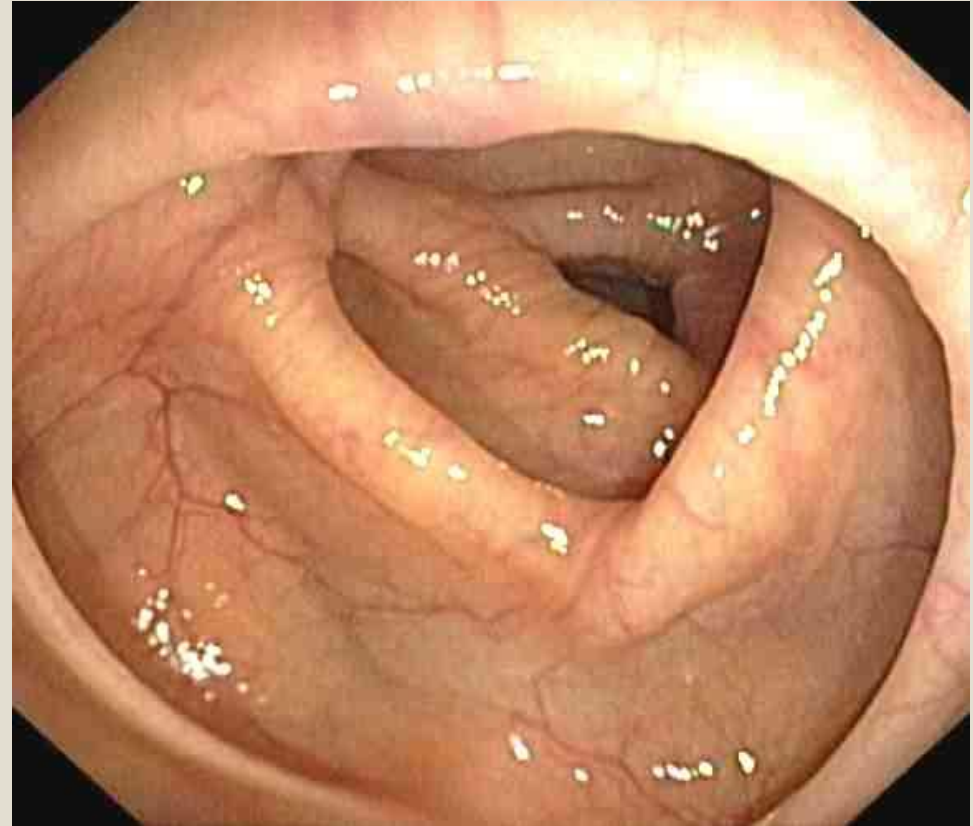
Optimization

- IV rehydration and electrolytes
- Anemia
- Malnutrition
 - Enteral: less complications
 - NPO + TPN: no benefit
- Thromboembolism prophylaxis
- Identifying and treating superimposed infections
 - C. diff and CMV
- Avoiding precipitants of toxic megacolon
 - Anticholinergics, antidiarrheals, NSAIDs, opiates



Remission

- No diarrhea (<3 BM/day)
- No blood
- No urgency
- Best confirmed by endoscopic mucosal healing



Maintenance

- Oral and topical 5-ASA
 - Response vs. toxicity
- Probiotics
- Azathioprine or 6-mercaptopurine
- Infliximab
- Methotrexate?
- Steroid avoidance

Infliximab for Induction and Maintenance Therapy for Ulcerative Colitis

Paul Rutgeerts, M.D., Ph.D., William J. Sandborn, M.D., Brian G. Feagan, M.D., Walter Reinisch, M.D., Allan Olson, M.D., Jewel Johanns, Ph.D., Suzanne Travers, M.D., Daniel Rachmilewitz, M.D., Stephen B. Hanauer, M.D., Gary R. Lichtenstein, M.D., Willem J.S. de Villiers, M.D., Ph.D., Daniel Present, M.D., Bruce E. Sands, M.D., and Jean Frédéric Colombel, M.D.

ABSTRACT

BACKGROUND

Infliximab, a chimeric monoclonal antibody directed against tumor necrosis factor α , is an established treatment for Crohn's disease but not ulcerative colitis.

METHODS

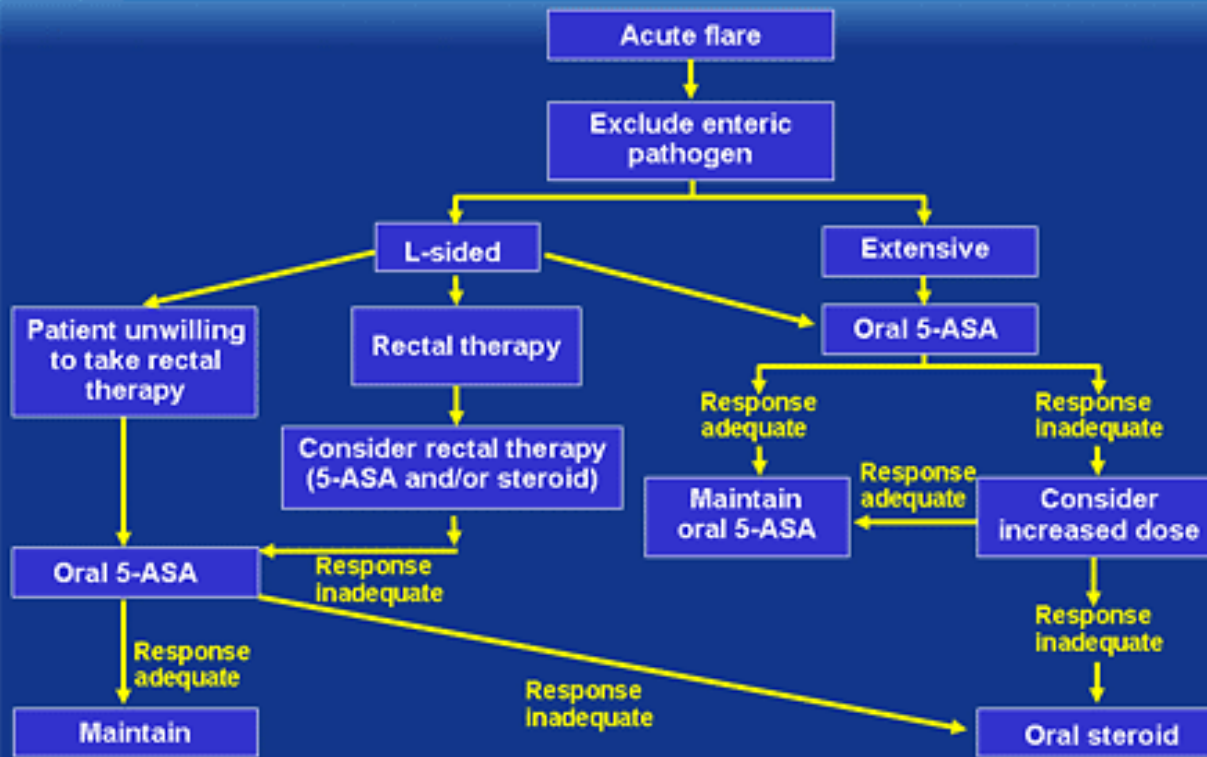
Two randomized, double-blind, placebo-controlled studies — the Active Ulcerative Colitis Trials 1 and 2 (ACT 1 and ACT 2, respectively) — evaluated the efficacy of infliximab for induction and maintenance therapy in adults with ulcerative colitis. In each study, 364 patients with moderate-to-severe active ulcerative colitis despite treatment with concurrent medications received placebo or infliximab (5 mg or 10 mg per kilogram of body weight) intravenously at weeks 0, 2, and 6 and then every eight weeks through week 46 (in ACT 1) or week 22 (in ACT 2). Patients were followed for 54 weeks in ACT 1 and 30 weeks in ACT 2.

RESULTS

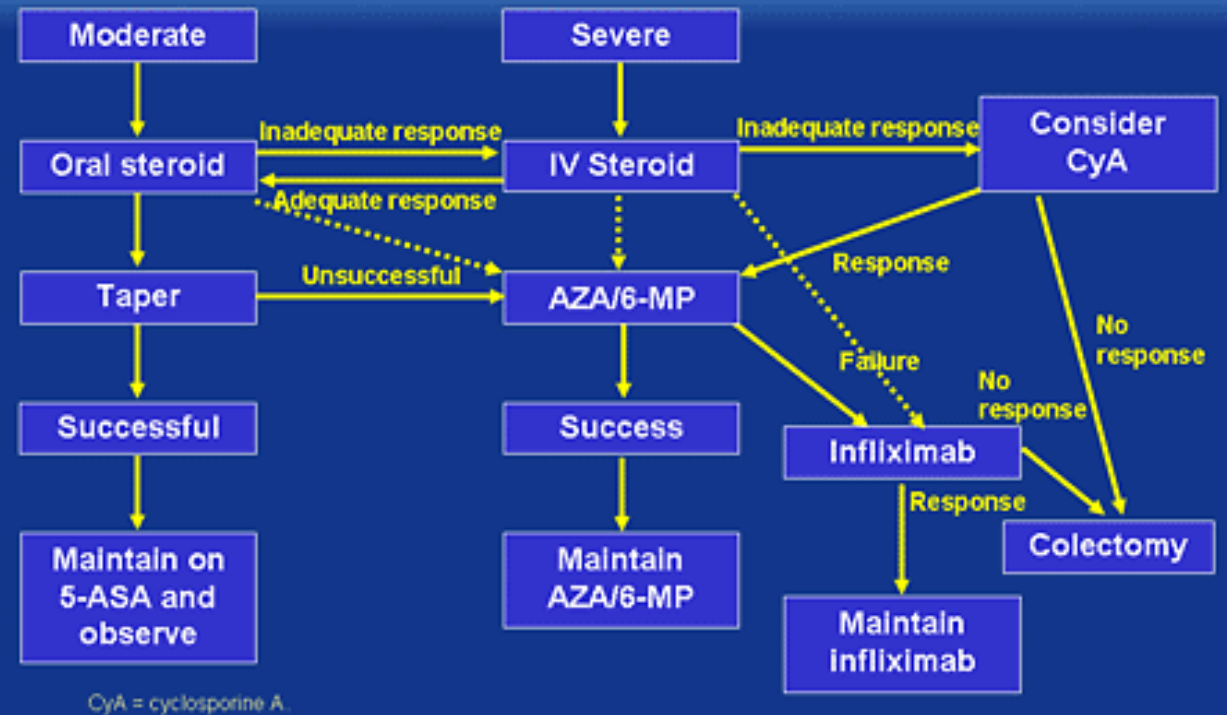
In ACT 1, 69 percent of patients who received 5 mg of infliximab and 61 percent of those who received 10 mg had a clinical response at week 8, as compared with 37 percent of those who received placebo ($P < 0.001$ for both comparisons with placebo). A response was defined as a decrease in the Mayo score of at least 3 points and at least 30 percent, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or an absolute rectal-bleeding subscore of 0 or 1. In ACT 2, 64 percent of patients who received 5 mg of infliximab and 69 percent of those who received 10 mg had a clinical response at week 8, as compared with 29 percent of those who received placebo ($P < 0.001$ for both comparisons with placebo). In both studies, patients who received infliximab were more likely to have a clinical response at week 30 ($P \leq 0.002$ for all comparisons).

Summary of medical management

Ulcerative Colitis: Mild to Moderate



Ulcerative Colitis: Moderate to Severe



Surgical management

- Surgery for complications of UC
 - Emergent surgery for acute complications
 - Acute severe colitis
 - Toxic megacolon
 - Massive hemorrhage
 - Perforation and peritonitis
 - Elective surgery for chronic complications
 - Dysplasia and cancer
 - Stricture
 - Systemic complications
- Elective surgery for failure of medical management
- Preoperative evaluation and management
- Surgical options (emergent and elective)

Emergent surgery

- Catastrophic complications have been reduced by advances in medical therapy
 - Hemorrhage, perforation, fulminant colitis, obstruction
- 15-50% of patients in emergent setting still require operation during admission

Acute abdomen

- Absolute indication for immediate surgery in patients with acute fulminant colitis
- Results from:
 - Toxic megacolon
 - Perforation
 - Hemorrhage
- Impending perforation – dilatation with thumbprinting
- Free perforation – rare
- Walled off perforation more common

Toxic megacolon

Severe potentially fatal complication of colonic inflammation characterized by:

- Radiographic evidence of colonic distension of $> 6\text{cm}$ in the transverse colon

AND

- Systemic toxicity
- Inflammatory or infectious etiology of underlying disease



Epidemiology



Larger studies on toxic megacolon are outdated and focussed only on IBD

- Incidence 6% in patients admitted to hospital with IBD (10% UC, 2.3% Crohn's) in a study from 1980's
- Incidence 7.9% in patients admitted with UC in more recent study from 2002
- Toxic megacolon in pseudomembranous colitis 0.4-3%, but this is increasing
 - Annual increase of 23% in rate of *C. diff* hospitalizations
 - Increase in *C. diff* mortality from 1.2% in 2000 to 2.2% in 2004
 - Frequent use of broad spectrum antibiotics, emergence of hypervirulent *C. difficile* strain (BI/NAP1/027), increase in community acquired *C. difficile* infections

Etiological Factors for Toxic Megacolon

Inflammatory (48%)

Ulcerative colitis (46%)

Crohn's disease (2%)

Behcet's disease

Infectious (34%)

***Clostridium difficile* pseudomembranous colitis (31%)**

Salmonella, Shigella, Yersinia, Campylobacter, E. coli

Entameba (3%)

CMV, Rotavirus

Aspergillosis

Cryptosporidium

Ischemic (11%)

Ischemic colitis (11%)

Other (7%)

Collagenous colitis

Colonic lymphoma

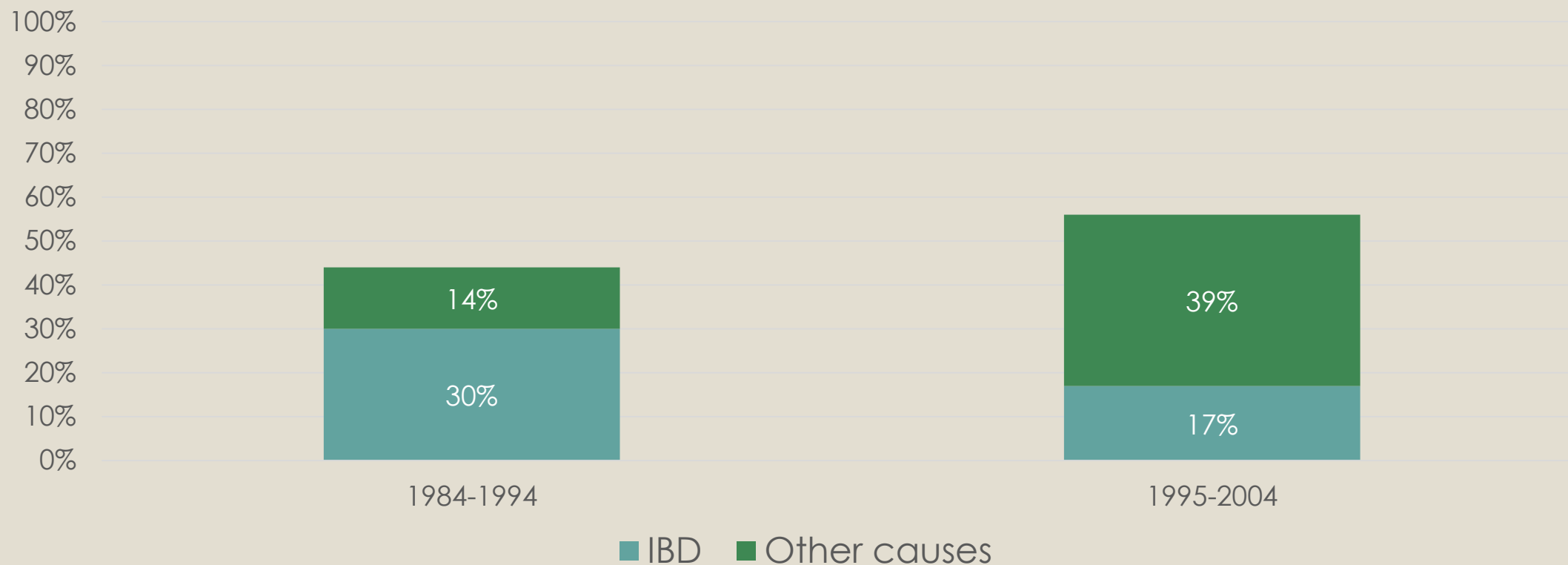
Kaposi's sarcoma

Cytotoxic chemotherapy (3%)

Beta mimetics (4%)

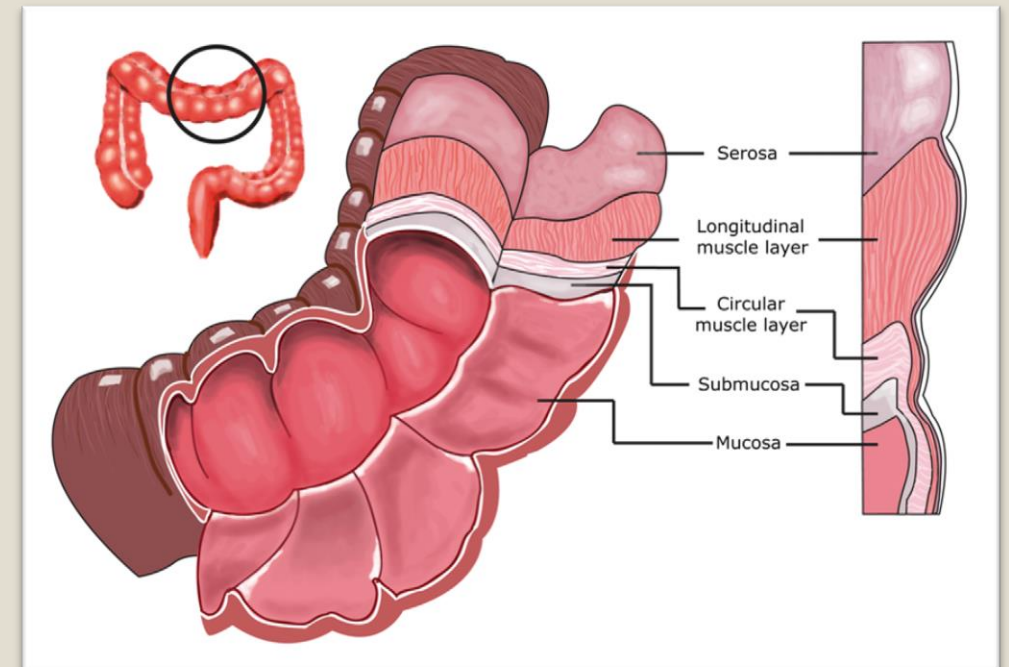
Changing Etiology

Distribution of toxic megacolon etiology during observation period



Pathogenesis

- Not fully understood
- Link between inflammation and decreased smooth muscle contractility
- Mucosal inflammation of UC penetrates into muscularis propria
 - Depth correlates with severity of dilation
 - Neutrophils from mucosa also invade muscle layer, release proteolytic enzymes, cytokines, leukotrienes
- Inflammatory mediators have inhibitory effect on colonic motility
 - Nitric oxide (NO), Inducible nitric oxide synthase (iNOS)
 - Hydrogen peroxide (H₂O₂), IL-1 β
 - Changes in neuromuscular signaling but **NOT** decreased neurons in myenteric ganglia (like in Hirschsprung's)



Diagnosis

Clinical Criteria for Diagnosis of Toxic Megacolon	
Main criteria: (3 of 4)	Fever ($>38.6^{\circ}\text{C}$)
	Tachycardia ($>120\text{bpm}$)
	Leukocytosis ($>10.5 \times 10^9/\text{l}$)
	Anemia
AND at least one of the following:	Dehydration
	Altered level of consciousness
	Electrolyte imbalances ($\downarrow\text{K}^+$, $\downarrow\text{Albumin}$)
	Hypotension

Jalan et al. *An Experience of Ulcerative colitis. Toxic dilation in 55 cases.* Gastroenterology. 1969; 57:68-82.

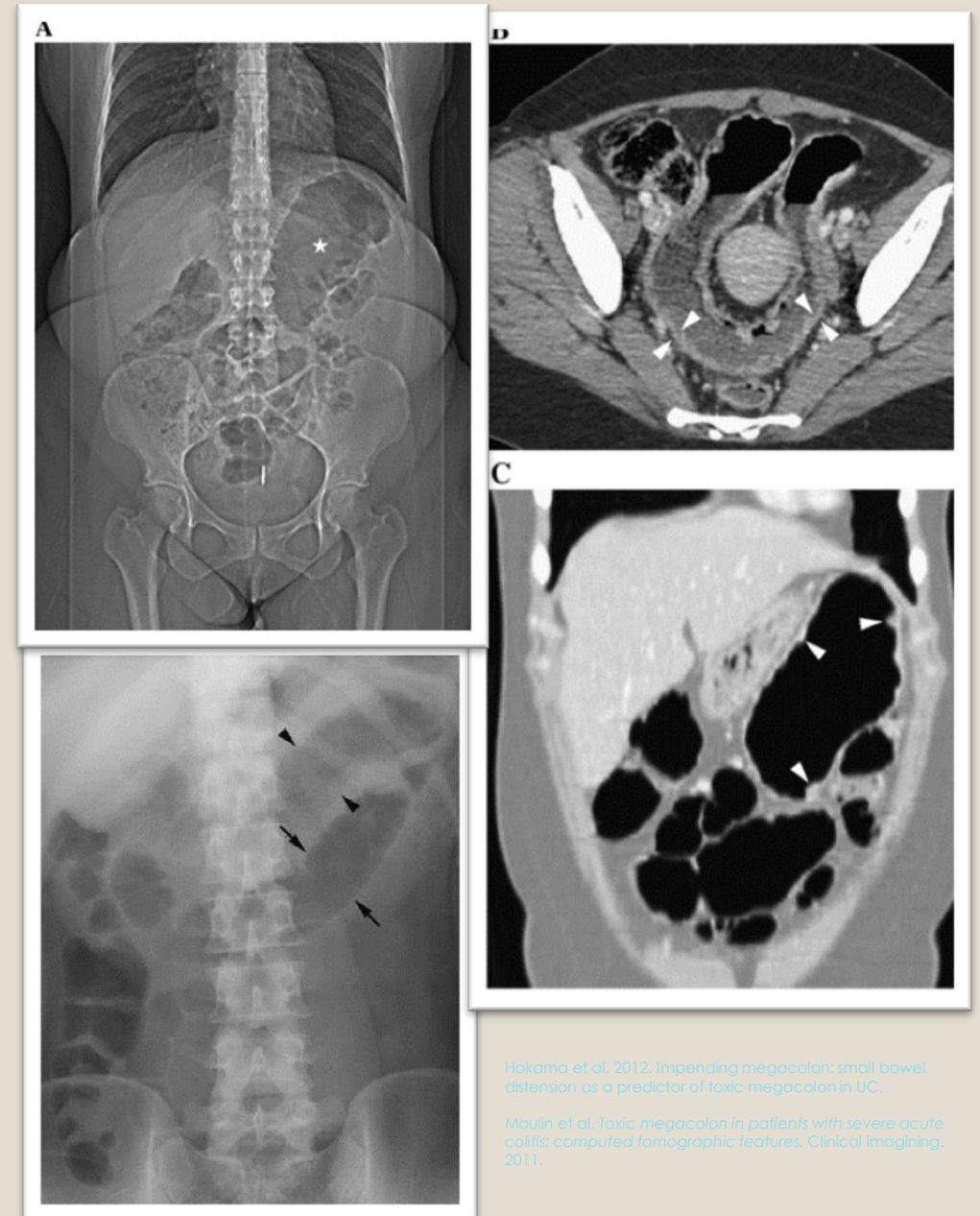
Imaging

Plain abdominal radiographs:

- Colonic dilation $>6\text{cm}$
 - Mean 9.2cm (Fazio et al), ascending and transverse more dilated, disturbance of haustration, air-fluid levels
- Small bowel dilation
 - Persistent small bowel distension on plain films may indicate “impending” megacolon.

CT:

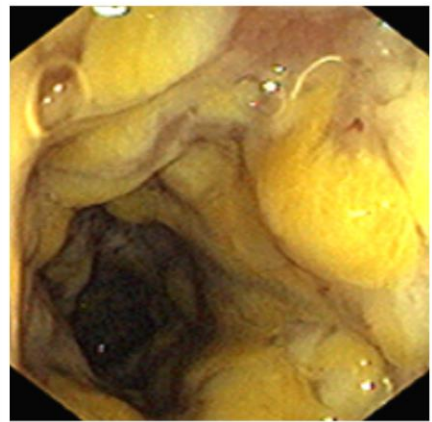
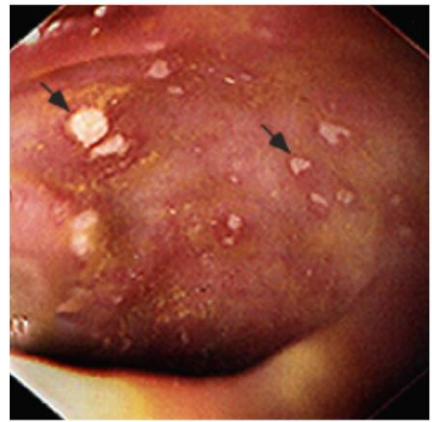
- 4/12 patients were able to pick up missed complications, but did not predict clinical outcome (Balthazar et al)
- Air-filled distension $>6\text{cm}$, abnormal haustral pattern, segmental colonic parietal thinning pathognomonic for TM. (Moulin et al)



Hokama et al. 2012. Impending megacolon: small bowel distension as a predictor of toxic megacolon in UC.

Moulin et al. Toxic megacolon in patients with severe acute colitis: computed tomographic features. Clinical Imaging. 2011.

Endoscopy



- Total colonoscopy has high risk of perforation in acute setting and is generally contraindicated
- Limited sigmoidoscopy valuable to differentiate etiology (eg. pseudomembranes in *C. diff*)
 - Contradictory findings in studies regarding usefulness and safety (Johal et al, Hall et al)
 - If necessary, should use minimal air insufflation

Management

- Early medical and surgical involvement
 - Treatment of underlying cause and toxemia
 - Close monitoring, supportive care with IV fluids
 - Stopping opiates, anticholinergics, anti-diarrheals
 - NPO, bowel rest
 - TPN has no proven benefit
 - Some suggest repositioning patients (rolling, prone knee-elbow position) to redistribution of colonic gas to distal colon and rectum



Medical Therapy



- High dose IV steroids started immediately and re-evaluated frequently
 - Not to be delayed by pending microbiology
 - 400mg hydrocortisone daily (100mg q6hrs) **OR** 60mg methylprednisolone daily for 5 days
 - No data to support higher steroid doses causing perforation **BUT** can mask signs of it
 - Should be stopped if infectious cause established
- Empiric treatment with antibiotics
 - Metronidazole 500mg TID
 - Many advocate antibiotics even without infectious cause (eg. Ceftriaxone, metronidazole)
 - If PMC cause for megacolon, antibiotics maintaining *C. diff* should be stopped

Role for biologics or calcineurin inhibitors?

- No studies in toxic megacolon specifically
- Two case reports for Infliximab in toxic megacolon
 - One due to UC, one due to Crohn's
 - Rapid clinical response and remission
 - Avoided surgery

Surgery

Indications for Surgery

Progressive colonic dilatation

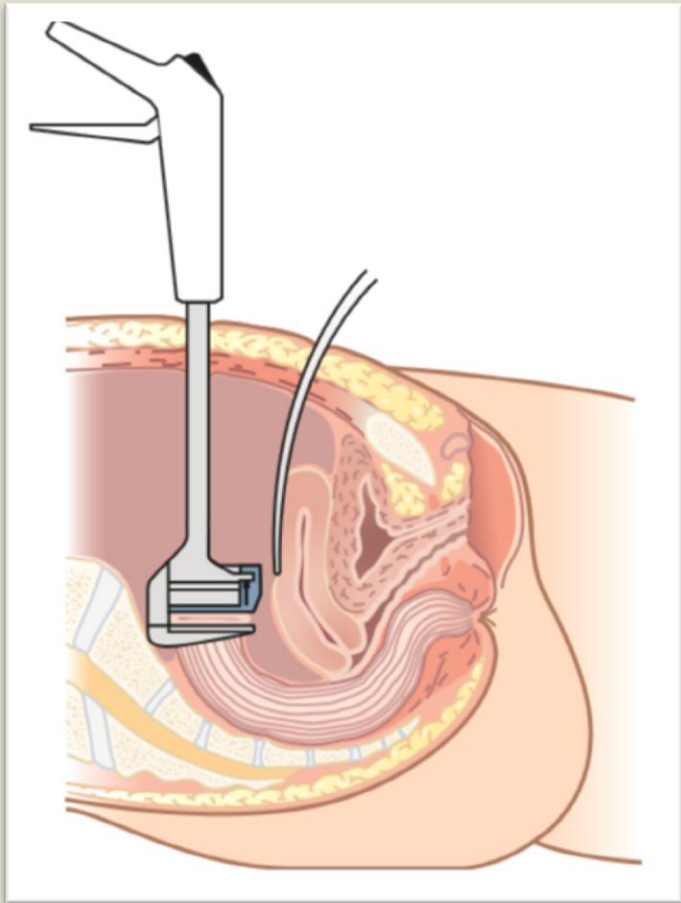
Peritonitis +/- free air

Clinical deterioration



- Timing of surgery in toxic megacolon is still controversial:
 - Goal of medical treatment is to avoid surgery
 - Delay in surgery has risk of complications like perforation, compartment syndrome

Surgery



- First-line surgery for acute toxic megacolon:
 - Subtotal colectomy
 - Ileostomy
 - Hartmann's pouch **OR** sigmoidostomy **OR** rectostomy
- For patients with UC as underlying cause:
 - Elective resection of remaining rectum and ileal pouch once acute phase has resolved
- Studies suggest subtotal colectomy with end ileostomy and Hartmann closure of rectum has lower mortality than total proctocolectomy

Acute fulminant colitis with **no** acute abdomen

- Joint involvement of gastroenterologists and surgeons at early stage
 - Even if rescue therapy is being trialed
 - Frequent reassessment
 - May help mentally prepare patients
- Treatment choice for steroid-refractory colitis is controversial (infliximab trial of rescue therapy vs colectomy)

Elective surgery

- 20 to 30% of patients with UC will eventually require a colectomy
- Retrospective cohort study – surgery associated with improved survival
- Continence-preserving procedures has made surgery more attractive

ORIGINAL RESEARCH

Annals of Internal Medicine

Mortality Associated With Medical Therapy Versus Elective Colectomy in Ulcerative Colitis

A Cohort Study

Meenakshi Bewtra, MD, MPH, PhD; Craig W. Newcomb, MS; Qufei Wu, MS; Lang Chen, PhD; Fenglong Xie, MS; Jason A. Roy, PhD; Cary B. Aarons, MD; Mark T. Osterman, MD, MSCE; Kimberly A. Forde, MD, MHS; Jeffrey R. Curtis, MD, MS, MPH; and James D. Lewis, MD, MSCE

Background: Ulcerative colitis (UC) can be treated with surgery or medications. Patients often must choose between long-term immunosuppressant therapy or total colectomy. Whether one of these treatment approaches has a mortality benefit is uncertain.

Objective: To determine whether patients with advanced UC treated with elective colectomy have improved survival compared with those treated with medical therapy.

Design: Retrospective matched cohort study.

Setting: Data from all 50 states for Medicaid beneficiaries (2000 to 2005), Medicare beneficiaries (2006 to 2011), and dual-eligible persons (2000 to 2011).

Patients: 830 patients with UC pursuing elective colectomy and 7541 matched patients with UC pursuing medical therapy.

Measurements: The primary outcome was time to death. Cox proportional hazards models were used to compare the survival of patients with advanced UC treated with elective colectomy or medical therapy. The models controlled for significant comorbid conditions through matched and adjusted analysis.

Results: The mortality rates associated with elective surgery and medical therapy were 34 and 54 deaths per 1000 person-years,

respectively. Elective colectomy was associated with improved survival compared with long-term medical therapy (adjusted hazard ratio [HR], 0.67 [95% CI, 0.52 to 0.87]), although this result did not remain statistically significant in all sensitivity analyses. Post hoc analysis by age group showed improved survival with surgery in patients aged 50 years or older with advanced UC (HR, 0.60 [CI, 0.45 to 0.79]; $P = 0.032$ for age-by-treatment interaction).

Limitations: Retrospective nonrandomized analysis is subject to residual confounding. The source cohort was derived from different databases throughout the study. Sensitivity and secondary analyses had reduced statistical power.

Conclusion: Elective colectomy seemed to be associated with improved survival relative to medical therapy among patients aged 50 years or older with advanced UC.

Primary Funding Source: National Institutes of Health and Agency for Healthcare Research and Quality.

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For author affiliations, see end of text.
This article was published online first at www.annals.org on 14 July 2015.

Colorectal cancer in UC

- Risk of colorectal cancer increases by 0.5 to 1% per year after first 10 years of disease
- Cumulative risk 5-10% after 20 years, 12-20% after 30 years
- Longstanding and extensive colitis (>10 years and involving >50% of the colon) increased risk of CRC compared to general population
 - Extent to or beyond hepatic flexure increases risk
- Patients with PSC may have increased risk of cancer compared to those without PSC
- Risk of colorectal cancer may be reduced by use of ASA, NSAIDs, 5-ASA and by surveillance colonoscopy
- Most common in rectum and sigmoid and always in areas of chronic inflammation

Dysplasia

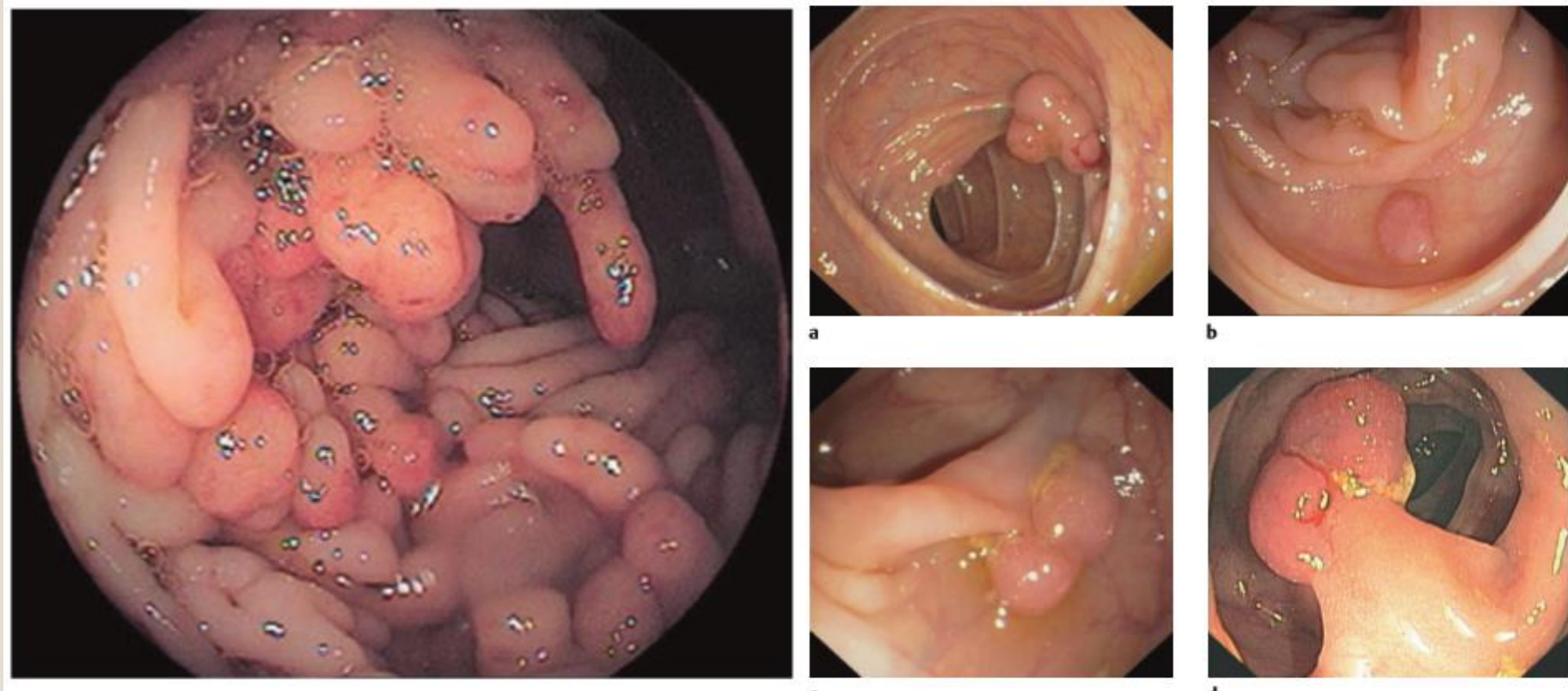
- CRC in UC is always preceded by dysplasia
- Dysplasia is a marker for coexisting malignancy → surveillance
- Classification:
 - Negative, indefinite, positive (low vs. high grade)
- Flat, slightly elevated, plaque-like, polyps, masses [**DALM**]

DALM

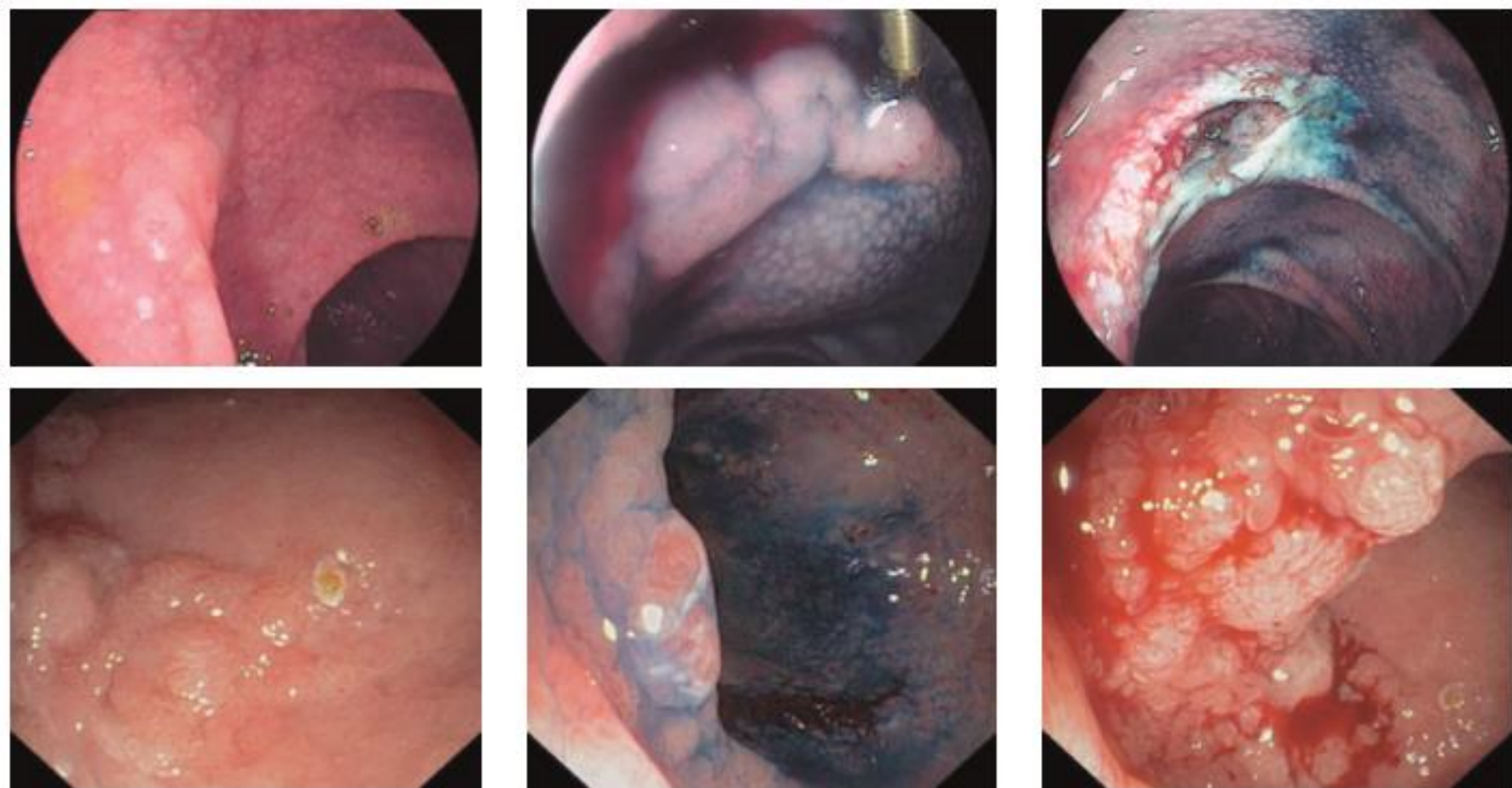
- Patients with DALMs may have underlying invasive carcinomas not detectable on biopsy
- Sporadic adenomas occur at the same rate as in the general population and can be removed endoscopically
- Both are distinct from inflammatory pseudopolyps

Feature	CUC-associated sporadic adenoma	CUC-associated polypoid dysplastic lesion
Clinical		
Patient age	Older, >50 years	Younger, <50 years
Disease activity	Active or inactive	Usually active
Disease duration	Shorter, <10 years	Longer, >10 years
Pathological		
↑ LP mononuclear cells	Uncommon, <20 percent	Common, >50 percent
↑ LP neutrophils	Uncommon, <40 percent	Common, >50 percent
Tubulovillous/villous	Uncommon, <10 percent	Occasional, >10 percent
Admixture	Uncommon, <20 percent	Common, >50 percent
Immunohistochemical		
p53	Negative or weak	Strong, diffuse
Beta-catenin	Strong, diffuse	Negative, weak
Molecular		
LOH for vHL (3p25)	Uncommon	Common
LOH for P16 (9p)	Rare	Common
LOH for P53 (17q)	Rare	Common

Inflammatory pseudopolyps and adenomas



DALM



DALM

- High grade dysplasia → colectomy
 - High rate of synchronous CRC (42%)
- Low grade dysplasia → rates of CRC highly variable among studies
- Diagnosis difficult; experienced pathologist necessary
- Optimal surveillance controversial
- Unclear if surveillance improves survival
- Patients with Crohn's likely have similar risk of CRC as those with UC

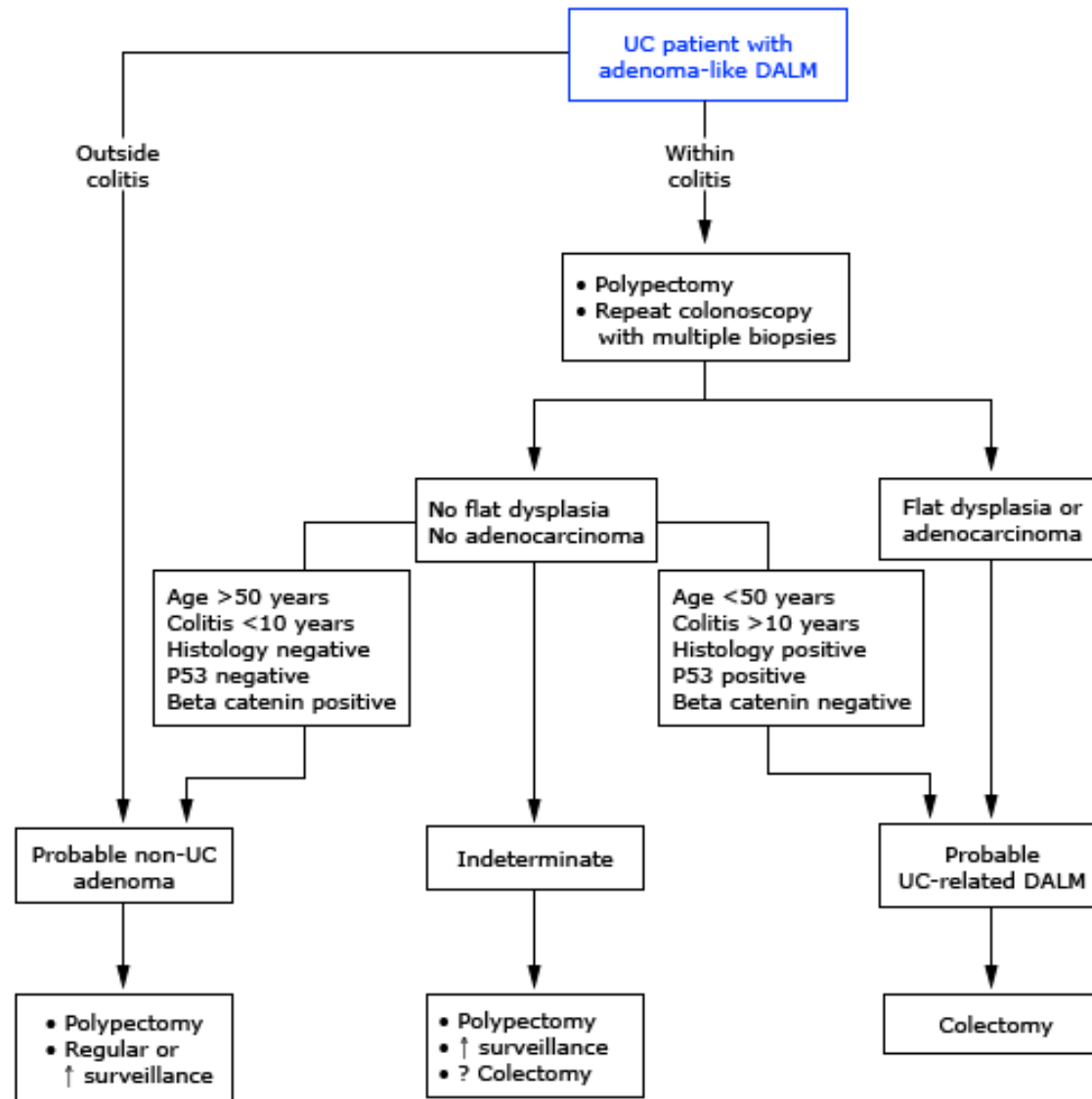
Screening

- UC extending proximal to splenic flexure or Crohn's (2B)
 - 8 years of disease
 - Yearly
- Left sided UC (2C)
 - 12 years of disease
 - Yearly
- UC post subtotal colectomy with rectum in situ (2B)
 - Yearly
- UC limited to rectum (2B)
 - No surveillance
- Pouch patients
 - Flex sig 3-5 years (yearly if severe inflammation)

Screening

- 4 biopsies every 10 cm plus irregular areas
- High grade dysplasia → proctocolectomy (1B)
- Low grade dysplasia → proctocolectomy (controversial) (2B)
 - If not acceptable to patients, biopsies to be repeated 4-6 months
- If endoscopically/pathologically an adenoma → extensive biopsies in area and remaining colon

Treatment of patients with an adenoma-like DALM



Surgery for intractable disease

- Intractable is difficult to define
- “disease is intractable when it or its treatment is associated with severe or persistent impairment in the quality of life”
 - Persistent despite high dose steroids
 - Dependence upon steroids to maintain remission
 - Progression of disease with worsening of symptoms or new onset of complications while on max. medical therapy
 - Severe side effects or treatment related complications

Pre-operative considerations

- Patients are young but seriously ill, malnourished, immunosuppressed
- Medical optimization
 - Anemia
 - Fluid depletion
 - Electrolyte abnormalities
 - Nutritional deficiencies
 - ?TPN
- Immunosuppressive therapy
 - Steroids to be tapered
 - Other immunomodulators can be stopped
 - May be an association between infliximab and increased complications, but evidence is weak

A Prospective, Randomized, Noninferiority Trial of Steroid Dosing After Major Colorectal Surgery

Karen Zaghiyan, MD,* Gil Y. Melmed, MD,† Dror Berel, MS,‡ Gayane Ovsepyan, BS,* Zuri Murrell, MD,* and Phillip Fleshner, MD*

Objective: To evaluate the safety of perioperative low-dose steroids (LDS) versus high-dose steroids (HDS) in steroid-treated patients with inflammatory bowel disease (IBD) undergoing major colorectal surgery.

Background: Corticosteroid-treated patients undergoing major colorectal surgery are commonly prescribed HDS to prevent perioperative adrenal insufficiency and cardiovascular collapse. There is little evidence to support this practice.

Methods: We performed a single-blinded noninferiority trial to compare perioperative hemodynamic instability in 92 steroid-treated IBD patients undergoing major colorectal surgery. Patients were randomly assigned to receive perioperative high-dose corticosteroids (HDS; hydrocortisone, 100 mg, intravenously 3 times daily, followed by taper) or low-dose corticosteroids (LDS; intravenous hydrocortisone equivalent to presurgical oral dosing, followed by taper). The primary outcome was the absence of postural hypotension on postoperative day 1, defined as a decrease in systolic blood pressure by 20 mm Hg after sitting from a supine position.

Results: The primary outcome, absence of postural hypotension on postoperative day 1, occurred in 95% of those randomized to receive high doses of corticosteroids compared with 96% of those who received low doses (noninferiority 95% confidence interval = -0.08 to 0.09 ; $P = 0.007$).

Conclusions: In IBD patients undergoing abdominal surgery, the incidence of postural hypotension or adrenal insufficiency is similar among those receiving high doses or low doses of corticosteroids in the perioperative period. To reduce complications associated with unnecessarily high doses of steroids, steroid-treated IBD patients undergoing major colorectal surgery should be treated with low doses of steroids in the perioperative period. (Clinicaltrials.gov ID# NCT01559675)

patients not taking steroids at the time of surgery who have previously been treated with steroids within 12 months before surgery.⁶ However, sufficient evidence to support these recommendations is lacking. Furthermore, high-dose steroids (HDS) are not without consequence and have been associated with impaired wound healing, hyperglycemia, hypertension, fluid and electrolyte imbalance, immunosuppression, and psychological effects.⁷

Retrospective data suggest that perioperative low-dose steroids (LDS) may be as safe as HDS in steroid-treated patients undergoing major colorectal surgery.⁸⁻¹⁰ We therefore sought to prospectively compare the safety of perioperative LDS against HDS in steroid-treated patients with inflammatory bowel disease (IBD) undergoing major colorectal surgery.

METHODS

Study Design

This was a single-center, patient-blinded, randomized, noninferiority study to assess the safety of LDS compared with HDS in steroid-treated IBD patients undergoing major colorectal surgery. The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki¹¹ and local regulations. All research-related activities were approved by the Cedars Sinai Medical Center Institutional Review Board (#22170) and all subjects provided written informed consent. A data safety and monitoring committee reviewed safety data after 50% of subjects were enrolled.

Study Population

Pre-operative considerations

- Patient education
 - Should understand indications, remaining medical options, surgical alternatives, expected outcome and potential complications
- Ostomy site selection
- Mechanical bowel preparation
- Antibiotic prophylaxis
 - Oral and IV antibiotics may decrease SSI
- VTE prophylaxis
 - Increased risk of VTE in UC patients
 - Heparin/low molecular weight heparin and intermittent pneumatic compression devices
 - Extended VTE prophylaxis after discharge?

Preoperative Oral Antibiotics and Intravenous Antimicrobial Prophylaxis Reduce the Incidence of Surgical Site Infections in Patients With Ulcerative Colitis Undergoing IPAA

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Hiroki Matsuoka, M.D., Ph.D.¹ • Kazuhiko Nakajima, M.D., Ph.D.²
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BACKGROUND: The usefulness of preoperative oral antibiotics for the prevention of surgical site infection in elective colorectal surgery remains controversial.

OBJECTIVE: This study aimed to investigate the effects of oral antimicrobial prophylaxis in addition to intravenous antimicrobial prophylaxis on patients with ulcerative colitis undergoing restorative proctocolectomy.

DESIGN: This study was a randomized, nonblinded, single-center clinical trial.

SETTING: This study was conducted between July 1, 2006, and April 30, 2009, at Hyogo College of Medicine.

PATIENTS: Two hundred patients with ulcerative colitis scheduled to undergo restorative proctocolectomy with IPAA with an open approach were randomly assigned to either group A or B (n = 100). Combined use of preoperative oral antibiotics and intravenous antimicrobial prophylaxis were given to group A, and

underwent preoperative mechanical bowel preparation, and intravenous antimicrobial prophylaxis with second-generation cephalosporin was given for 24 hours.

MAIN OUTCOME MEASURES: The primary end point of this study was the incidence of overall surgical site infection according to intention-to-treat analysis.

RESULTS: The incidence of overall surgical site infection was significantly lower in group A (6/97 patients, 6.1%) than in group B (22/98 patients, 22.4%) ($p = 0.0024$). In multivariate analysis, the administration of oral antibiotics (OR, 0.178; 95% CI, 0.057–0.552; $p = 0.003$) and ASA score ≥ 3 (OR, 5.343; 95% CI, 1.595–17.891; $p = 0.007$) were independent risk factors for surgical site infection.

LIMITATIONS: This study is limited because of its open-label nature.

CONCLUSIONS: Combined oral and intravenous

Ulcerative Colitis Is Associated With an Increased Risk of Venous Thromboembolism in the Postoperative Period

The Results of a Matched Cohort Analysis

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Objectives: To determine the rates of venous thromboembolism (VTE) during admission and within 30 days of hospital discharge in inflammatory bowel (IBD) patients undergoing colonic resection using the ACS National Surgical Quality Improvement Project (NSQIP) database and to compare these rates to VTE rates in cohorts of patients undergoing colonic resection for several other colonic pathologies.

Background: High rates of VTE have been demonstrated in hospitalized IBD patients. However, rates of postdischarge VTE in IBD patients are understudied.

Methods: Demographic, operative, and outcomes data for 96,999 patients undergoing colonic resection for diverticulitis, colorectal cancer (CRC), benign neoplasms, ulcerative colitis (UC), and Crohn's disease (CD) between 2005 and 2011 was obtained. Student *t* and χ^2 tests were used for univariate analysis. A logistic multivariate analysis was performed with all significant variables. Propensity score matching was utilized to compare the VTE incidences between the groups.

Results: Highest VTE risk was seen in obese patients [odds ratio (OR) = 1.41], those older than 73 years (OR = 1.58) and with bleeding disorders (OR = 1.44), American Society of Anesthesiology class III/IV (OR = 1.52/1.86), preoperative systemic inflammatory response syndrome (OR = 1.55), sepsis (OR = 1.48) or steroid use (OR = 1.63), and primary diagnosis of UC (OR = 2.10). The UC group had the highest incidence of VTE (2.74%), followed by CRC patients (1.74%). A 1.2% incidence was seen in the CD population, and 41.5% of the UC-VTEs were diagnosed after discharge.

Conclusions: This study affirms that inpatient UC patients undergoing colonic resection are at high risk for VTE and suggests that this risk persists into the postdischarge period. Thus, these patients should be given appropriate prophylaxis.

In addition, postoperative VTEs are associated with hospital lengths of stay (LOS) up to 3 times longer⁴ and costing twice as much when compared with non-VTE admissions.⁵ The increased mortality in inflammatory bowel disease (IBD) patients with VTEs has been demonstrated to be up to 4 times greater that of IBD patients without VTE.^{4,6}

VTE rates in colorectal surgery patients, particularly after undergoing resections for colorectal cancer (CRC), are greater than VTE rates in surgical patients from other surgical specialties^{7,8} with reported incidences as high as 40% in those not given VTE prophylaxis.⁹ Recommendations for postdischarge thromboprophylactic treatment in patients undergoing CRC resections are clearly defined because of the known high risk in this cohort. IBD is a chronic immune mediated inflammatory condition and, as such, constitutes a hypercoagulable state with relatively high rates of VTE demonstrated in medically and surgically managed patients. Studies comparing the 2 main forms of IBD have suggested higher VTE rates in ulcerative colitis (UC) versus Crohn disease (CD) for reasons not yet known.^{4,10-12} Despite these high rates of VTE, particularly in UC patients, little data exists on VTE rates postdischarge after colonic resections. Although clear guidelines regarding postoperative anticoagulation to prevent VTE in the CRC population are found,¹³ guidelines that specifically address the pharmacoprevention of postoperative VTE in IBD patients have yet to be defined.¹⁴ In addition, no large scale investigation into postdischarge VTE rates in IBD has yet been undertaken.

The American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) records postoperative outcomes including incidence of postoperative VTE from more than 450 institutions across the United States and Canada. The aims of this

The Importance of Extended Postoperative Venous Thromboembolism Prophylaxis in IBD: A National Surgical Quality Improvement Program Analysis

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BACKGROUND: The National Comprehensive Cancer Network recommends that patients who have colorectal cancer receive up to 4 weeks of postoperative out-of-hospital venous thromboembolism prophylaxis. Patients with IBD are at high risk for venous thromboembolism, but there are no recommendations for routine postdischarge prophylaxis.

OBJECTIVE: The purpose of this study was to compare the postoperative venous thromboembolism rate in IBD patients versus patients who have colorectal cancer to determine if IBD patients warrant postdischarge thromboembolism prophylaxis.

DESIGN: This study is a retrospective review of IBD patients and patients who had colorectal cancer who underwent major abdominal and pelvic surgery.

PATIENTS: Data were collected from the American College of Surgeons National Surgical Quality Improvement Program (2005–2010).

MAIN OUTCOME MEASURES: The primary outcome was 30-day postoperative venous thromboembolism in IBD patients and patients who had colorectal cancer. Risk factors for venous thromboembolism were analyzed.

RESULTS: A total of 45,964 patients were identified with IBD (8888) and colorectal cancer (37,076). The 30-day postoperative rate of venous thromboembolism in IBD patients was significantly higher than in patients who had colorectal cancer (2.7% vs 2.1%, $p < 0.001$). In a model with 15 significant covariates, the OR for venous thromboembolism was 1.26 (95% CI, 1.021–1.56; $p = 0.03$) for the IBD patients in comparison with the patients who have colorectal cancer.

LIMITATIONS: This study was limited by the retrospective design and the limitations of the data included in the database.

CONCLUSIONS: Patients with IBD had a significantly increased risk for postoperative venous thromboembolism in comparison with patients who had colorectal cancer. Therefore, postdischarge venous thromboembolism prophylaxis recommendations for IBD patients should mirror that for patients who have colorectal cancer. This would suggest a change in clinical practice to extend out-of-hospital prophylaxis for 4 weeks in postoperative IBD patients.

Surgical options - emergent

- Total abdominal colectomy and end ileostomy is the best operation for acute fulminant UC +/- toxic megacolon
 - Rectum is not removed
 - Mucous fistula or Hartmann procedure (plus rectal tube)
 - Rectum is divided at sacral promontory
 - Superior rectal artery preserved

Surgical options - emergent

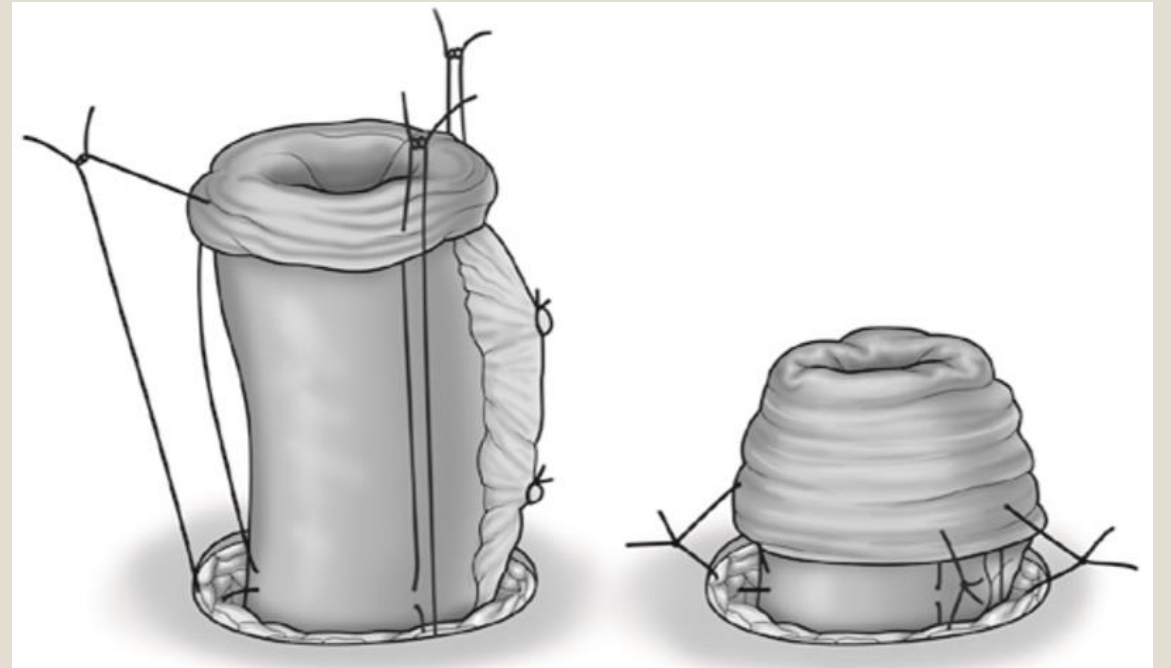
- Subsequent elective completion proctectomy or ileal pouch-anal anastomosis
 - +/- third operation for reversal of loop ileostomy
- Historical: blowhole colostomy and ileostomy

Surgical options - elective

Operation	Advantages	Disadvantages
Rectal mucosectomy with ileal pouch-anal canal anastomosis	Complete excision of large intestinal disease. Transanal defecation and fecal continence preserved. No ileostomy.	Two operations required. At risk for pouchitis. Nocturnal fecal spotting present.
Stapled, ileal pouch-distal rectal anastomosis	Transanal defecation and fecal continence preserved. No ileostomy. Easier technically.	At risk for pouchitis and cancer from residual rectal mucosa.
Continent ileostomy	Complete excision of large intestinal disease. Fecal continence preserved. No external appliance.	Stoma present. Intubation of pouch required. At risk for pouchitis and need for valve revision.
Brooke ileostomy	Complete excision of large intestinal disease. One operation.	Stoma present, risk of parastomal hernia. Incontinent for faeces. Need of external appliance.
Ileorectal anastomosis	Transanal defecation and fecal continence preserved. No ileostomy.	Diseased rectum remains to produce symptoms, require treatment and predispose to cancer.

Total proctocolectomy and Brooke ileostomy

- Removal of all rectal mucosa in one operation – curative for UC
- Indications:
 - Elderly patients
 - Poor sphincter function
 - Rectal carcinoma
 - Patient choice
 - Morbidity is associated with perianal wound healing, parastomal hernias, complications of pelvic dissection
- Can be performed laparoscopically



Systematic review and meta-analysis of laparoscopic *versus* open colectomy with end ileostomy for non-toxic colitis

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Background: This review compared short-term outcomes after laparoscopic *versus* open subtotal colectomy for acute, colitis medically refractory.

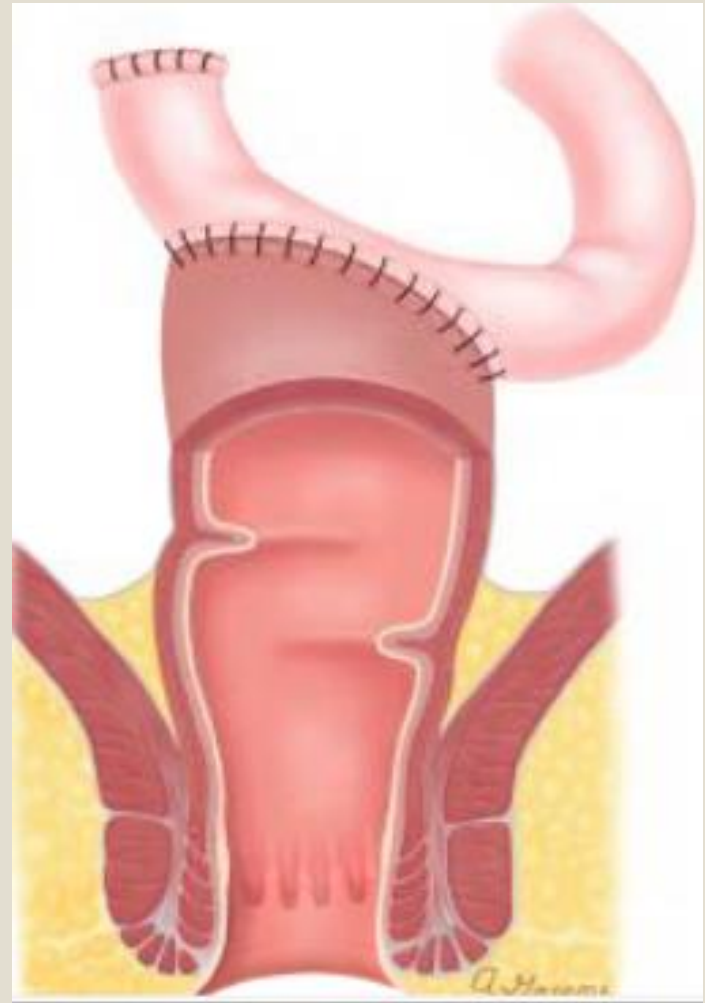
Methods: A systematic review of the literature was carried out using MEDLINE, Embase and the Cochrane databases. Overall study quality was assessed by the modified Methodological Index for Non-Randomized Studies (MINORS). Meta-analysis was performed for conversion, reoperation, wound infection, ileus, gastrointestinal bleeding, intra-abdominal abscess, postoperative length of stay and mortality.

Results: The search identified nine non-randomized studies: six cohort studies and three case-matched series, comprising 966 patients in total. The pooled conversion rate was 5.5 (95 per cent confidence interval (c.i.) 3.6 to 8.4) per cent in the laparoscopic group. The pooled risk ratio of wound infection was 0.60 (95 per cent c.i. 0.38 to 0.95; $P = 0.03$) and that of intra-abdominal abscess was 0.27 (0.08 to 0.91; $P = 0.04$), both in favour of laparoscopic surgery. Pooled risk ratios for other complications showed no significant differences. Length of stay was significantly shorter after laparoscopic subtotal colectomy, with a pooled mean difference of 3.17 (95 per cent c.i. 2.37 to 3.98) days ($P < 0.001$).

Conclusion: Where the procedure can be completed laparoscopically, there may be short-term benefits over open colectomy for colitis. These results cannot be generalized to critically ill patients in need of an emergency subtotal colectomy.

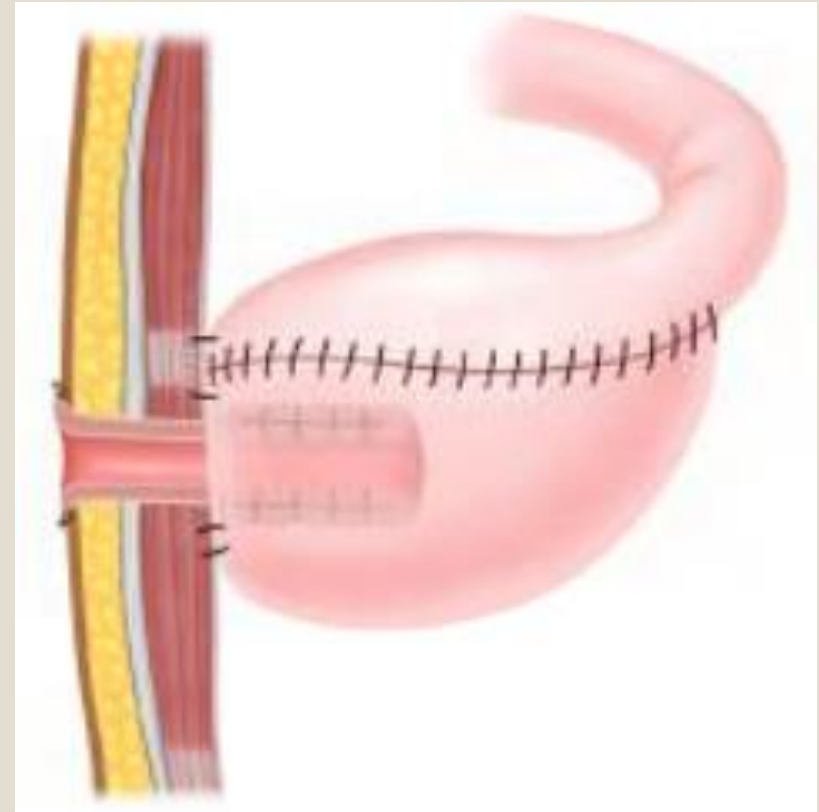
Total colectomy and ileo-rectal anastomosis

- Patients who are not suitable for IPAA but refuse ileostomy or have relative contraindications to ileostomy (eg. Ascites)
- ?women of childbearing age
- Crohns disease
- Residual rectum not excised
 - Persistent symptoms
 - Future malignancy
 - 6% at 20 years, 15% at 30 years
 - Strict rectal surveillance necessary



Total proctocolectomy and continent (Kock) ileostomy

- Continent pouch of 30 cm ileum constructed and 20cm is intussuscepted to create a valve
- Intubated by patient via wide bore catheter and drained 3-4 times per day
- Many complications:
 - Strictures
 - Volvulus
 - Herniation
 - Fistulisation
 - Valve slippage (30%)
- Up to 50% underwent revision



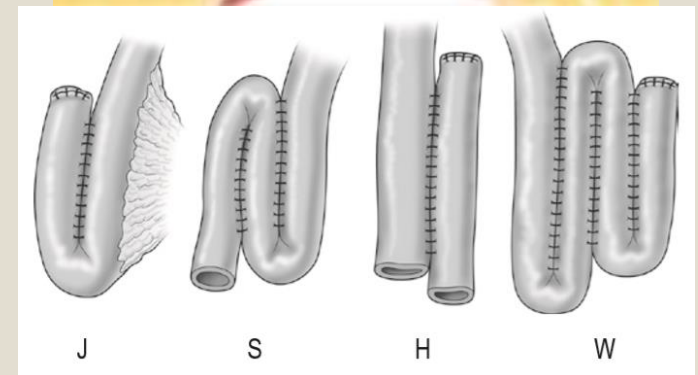
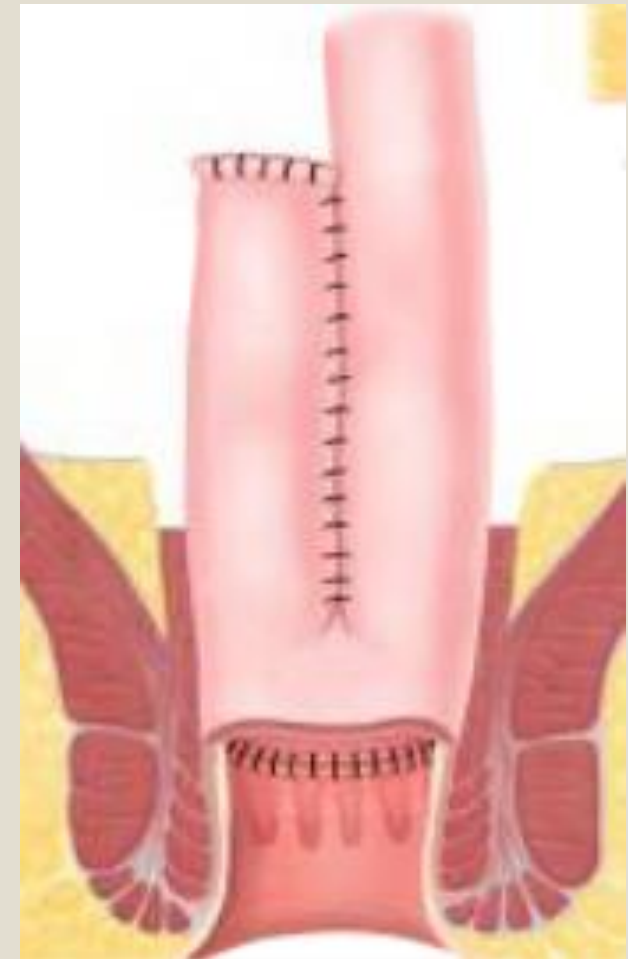
Total colectomy and stapled ileal pouch-distal rectal anastomosis (IPDRA)

- IPAA sometimes abandoned intraoperatively due to technical reasons, Crohn's evidence, or cancer (4.1%)
- IPDRA technically easier
- But leaves diseased rectal mucosa behind
- May be considered in older patients or where a tension free anastomosis cannot be achieved



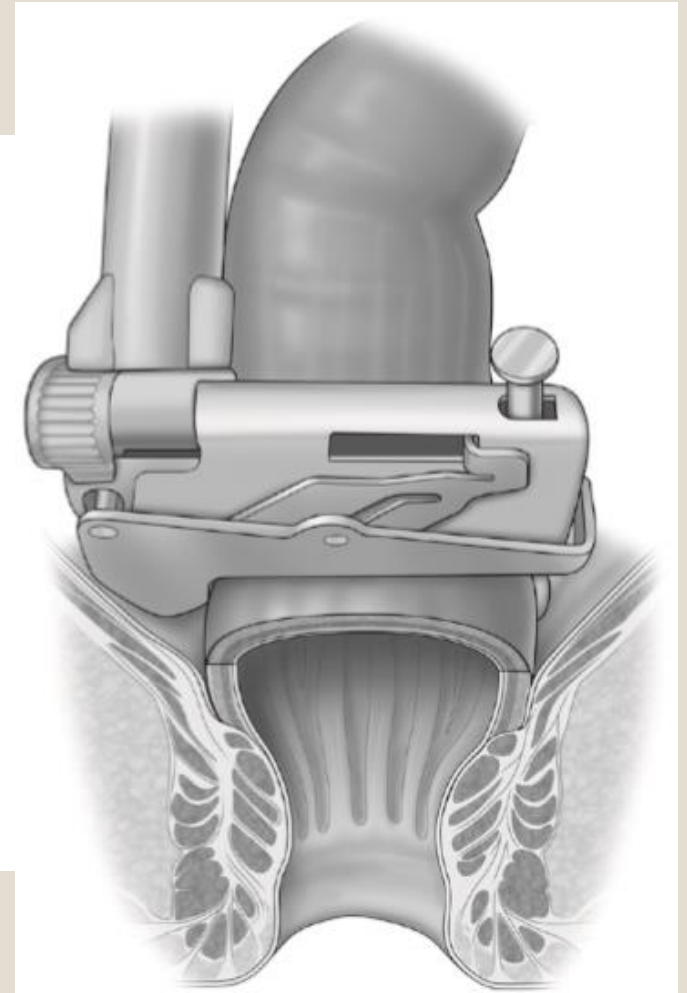
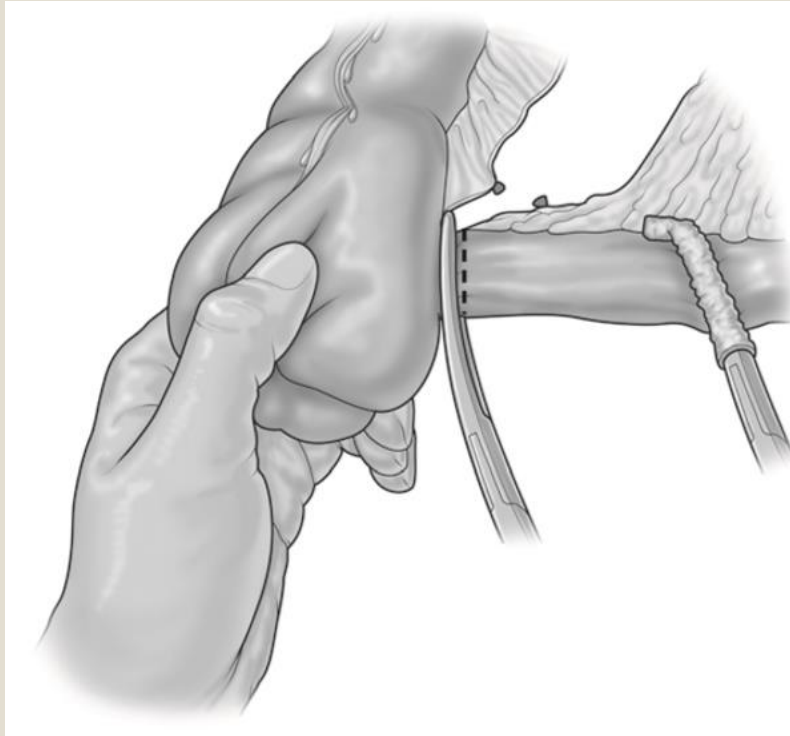
Total proctocolectomy and ileal pouch-anal anastomosis

- A neo-rectum fashioned from ileum and anastomosed to the anus
- Contraindications:
 - Crohn's
 - Incontinence
 - Rectal cancer
 - Emergent surgery
- J-pouch most common
 - Also S, H, W
- Can also be done laparoscopically



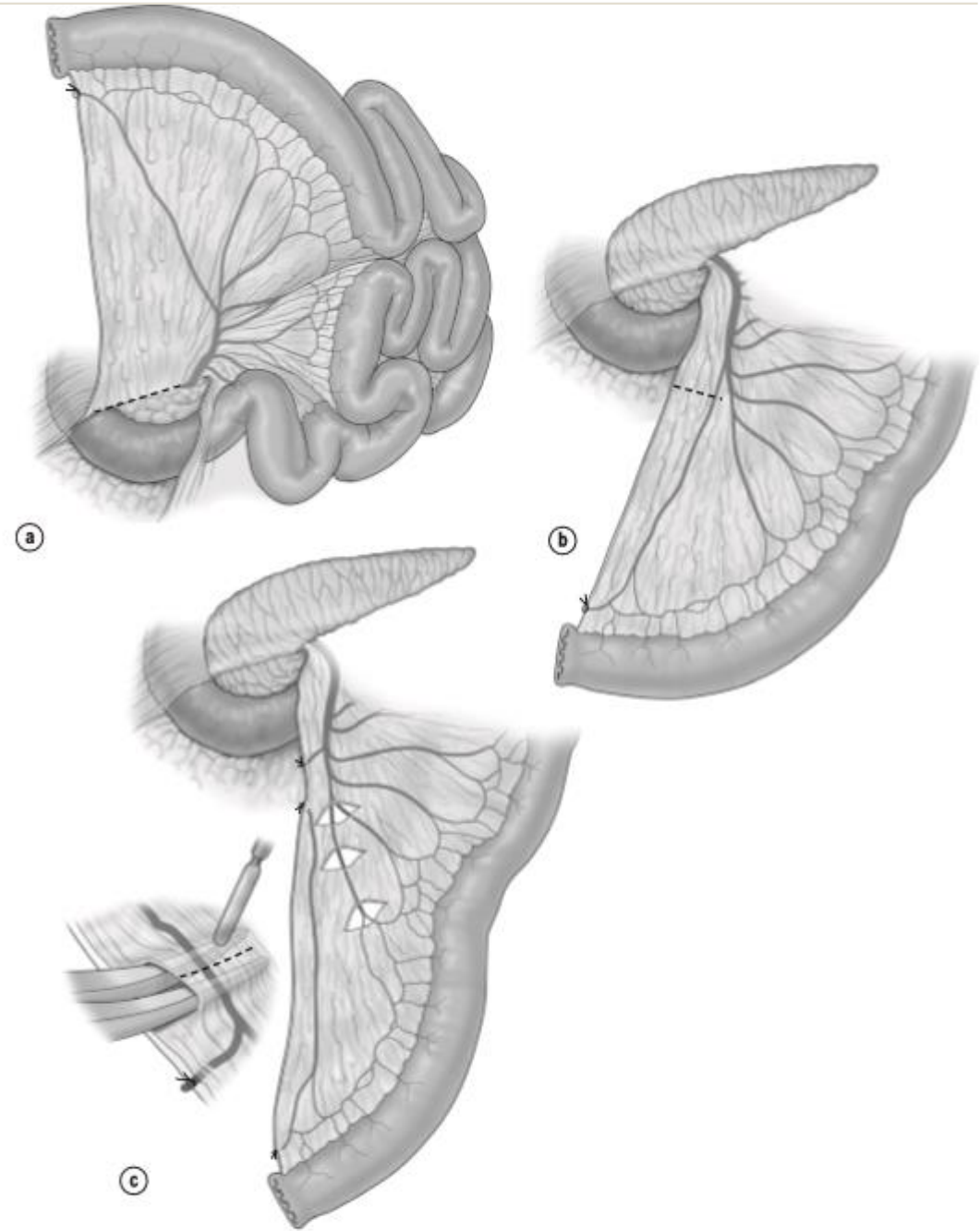
Steps:

1. Modified lithotomy
2. Laparotomy
3. Total colectomy with division of ileum flush with the caecum
4. Dissection of rectum (TME excision to levators)
5. Rectum divided 1-2 cm above dentate line



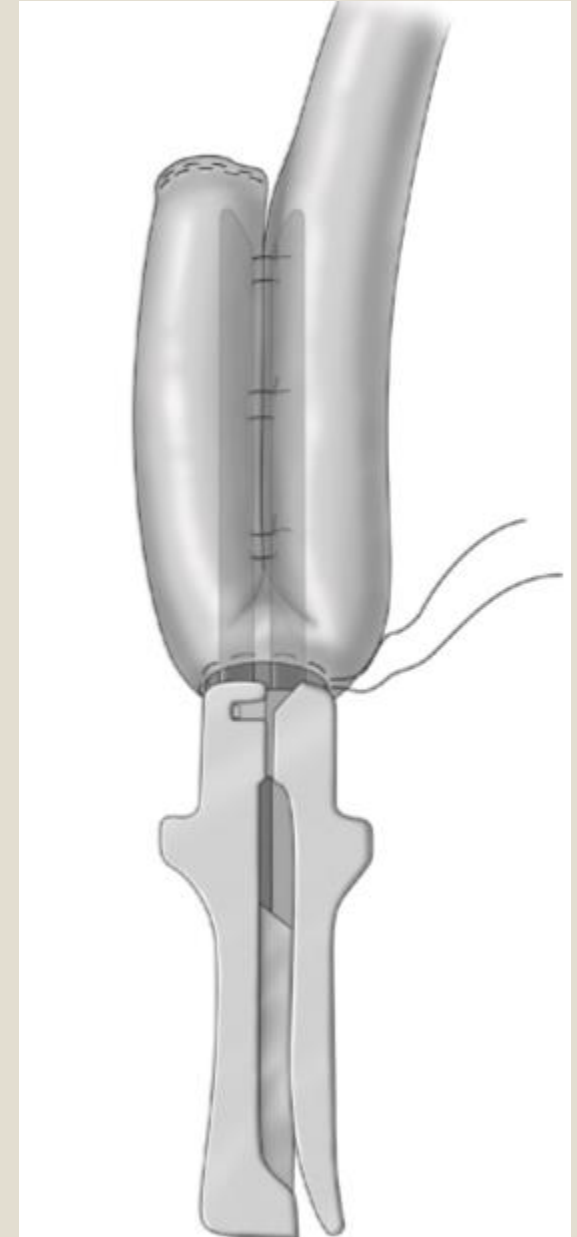
Steps:

6. Mobilization of small bowel mesentery



Steps:

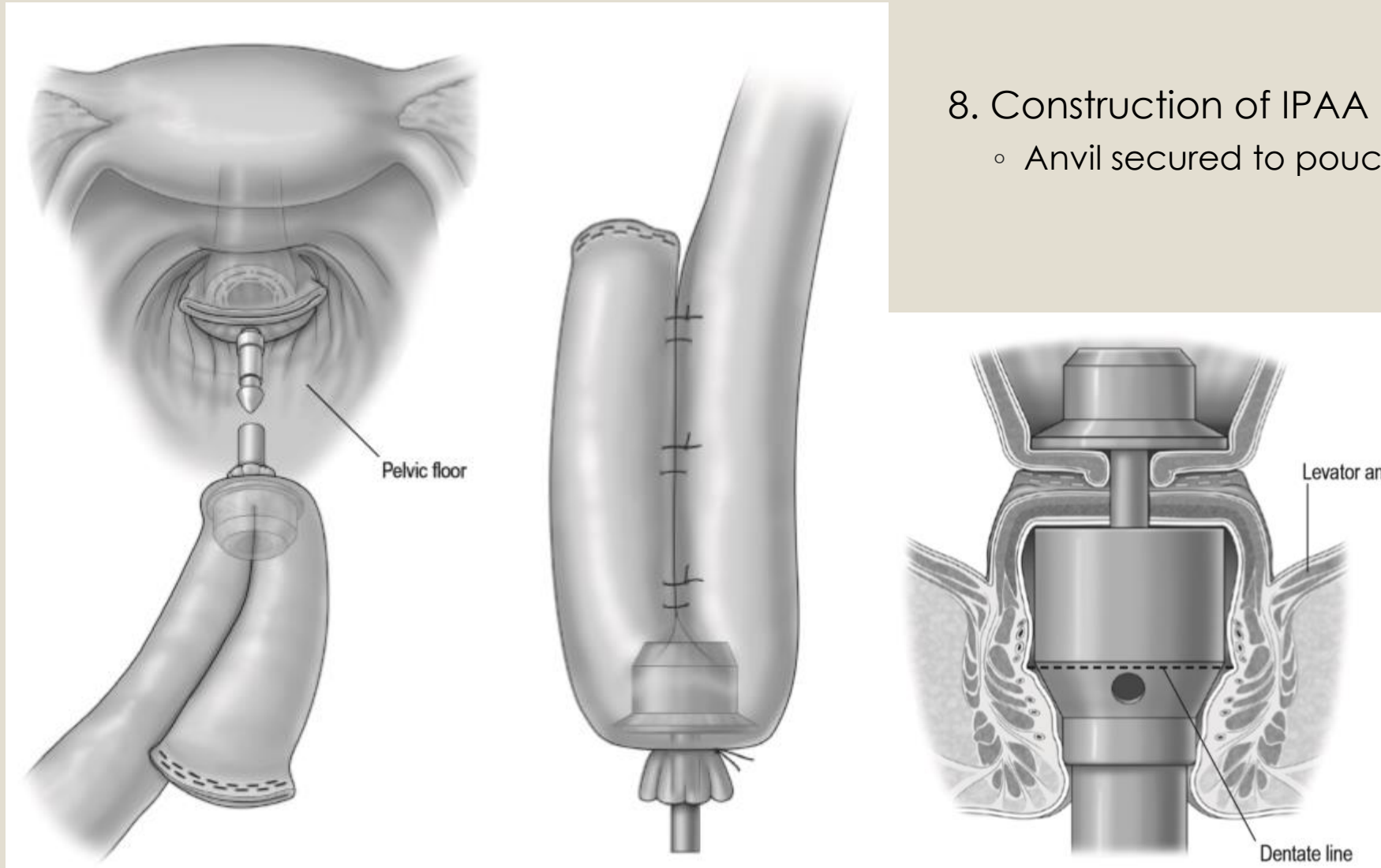
- 7. Creation of J-pouch
 - 30 cm of ileum and enterotomy at the apex
 - Anti-mesenteric side-to-side anastomosis



Steps:

8. Construction of IPAA

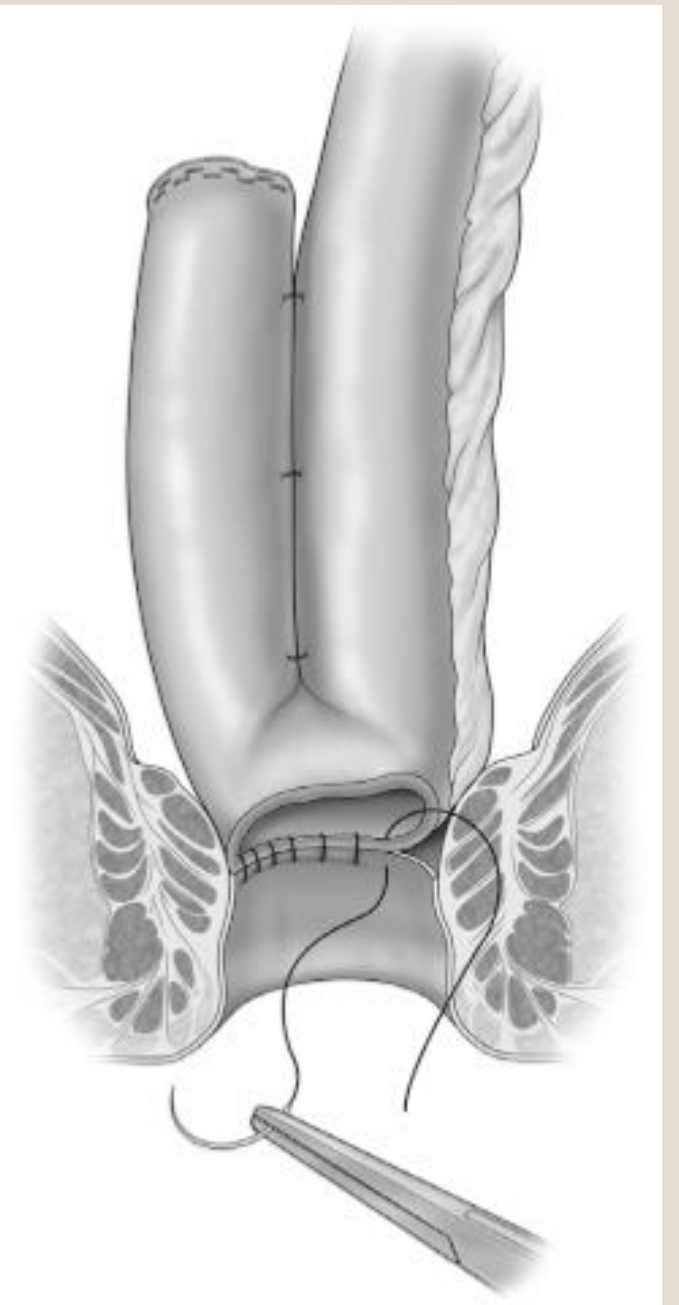
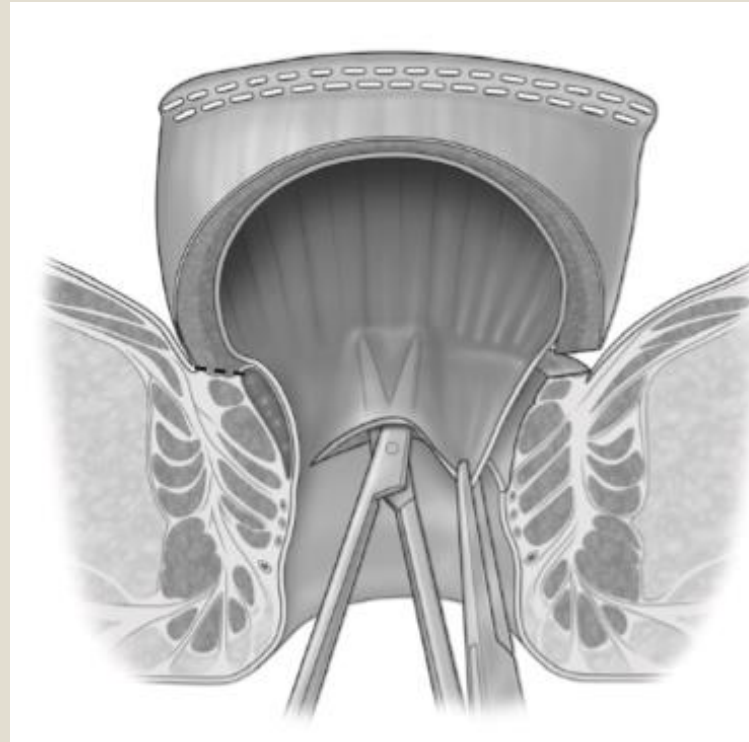
- Anvil secured to pouch and stapled



Steps:

vs.

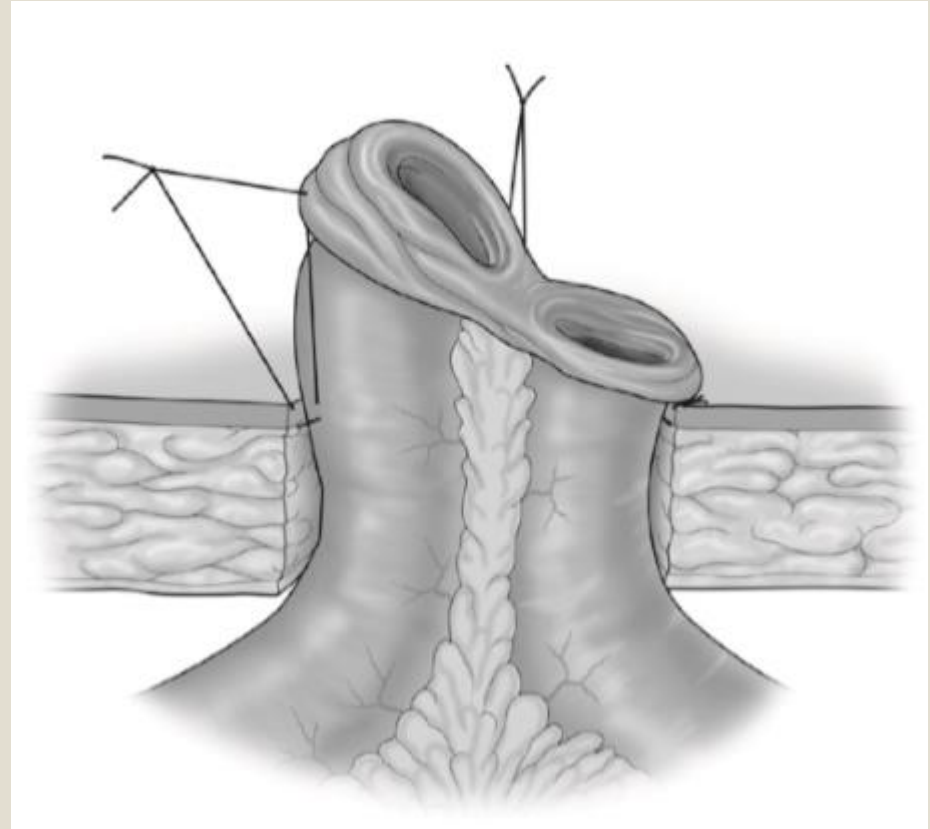
8. Mucosectomy and hand-sewn pouch-anal anastomosis



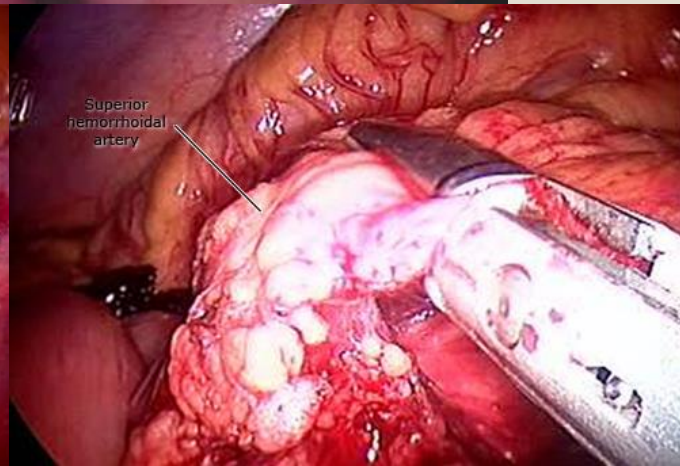
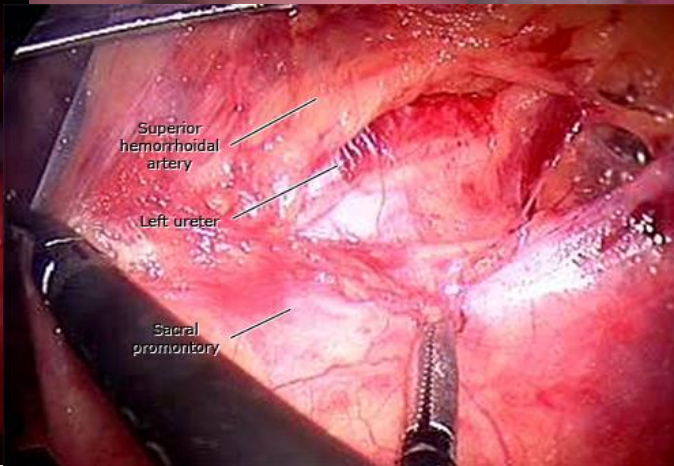
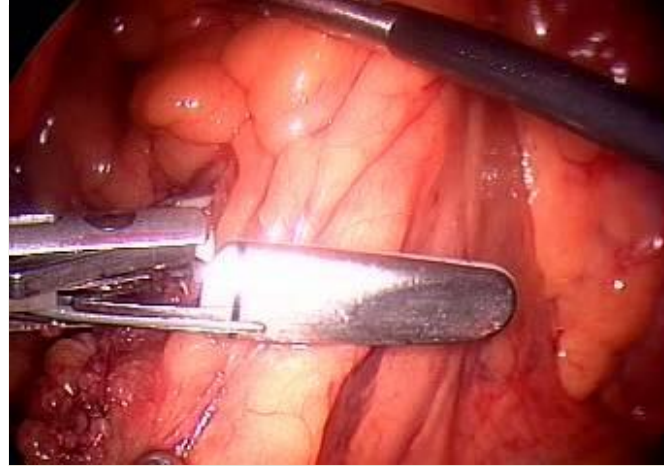
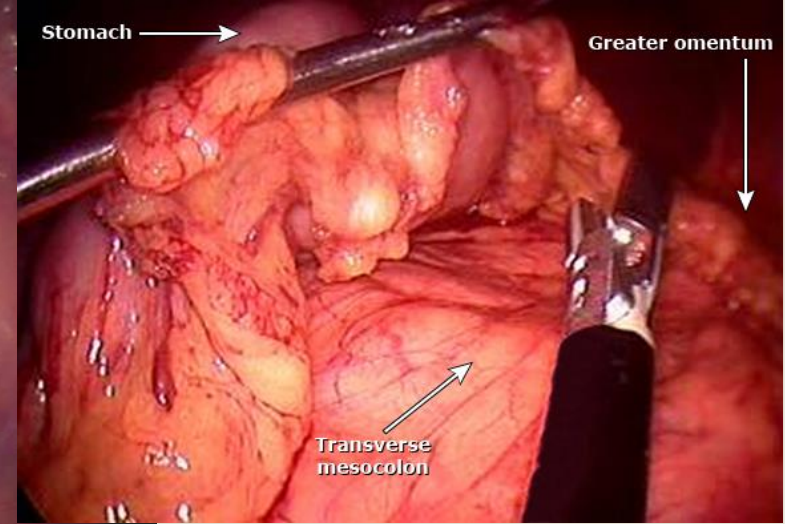
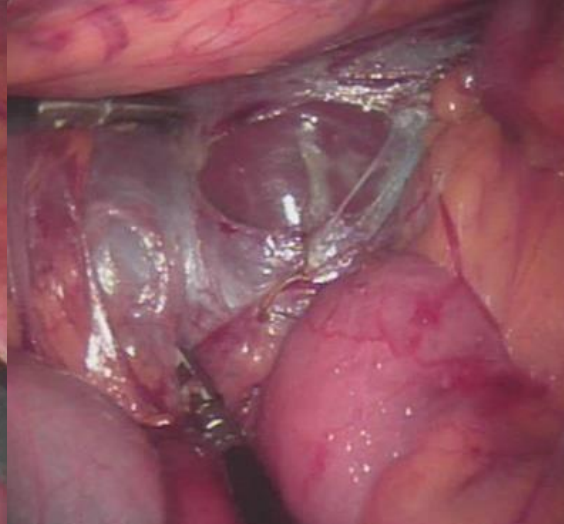
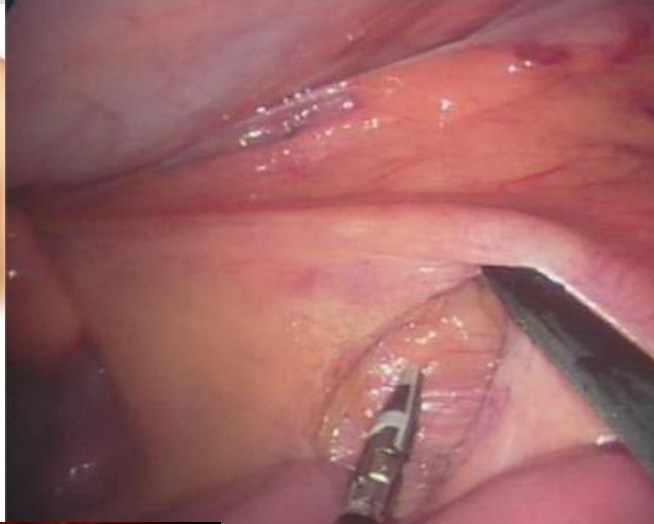
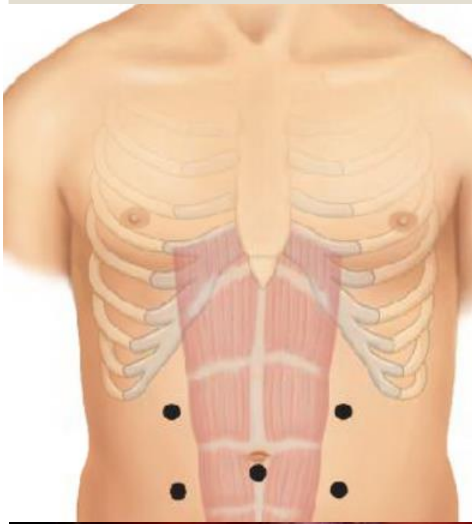
Steps:

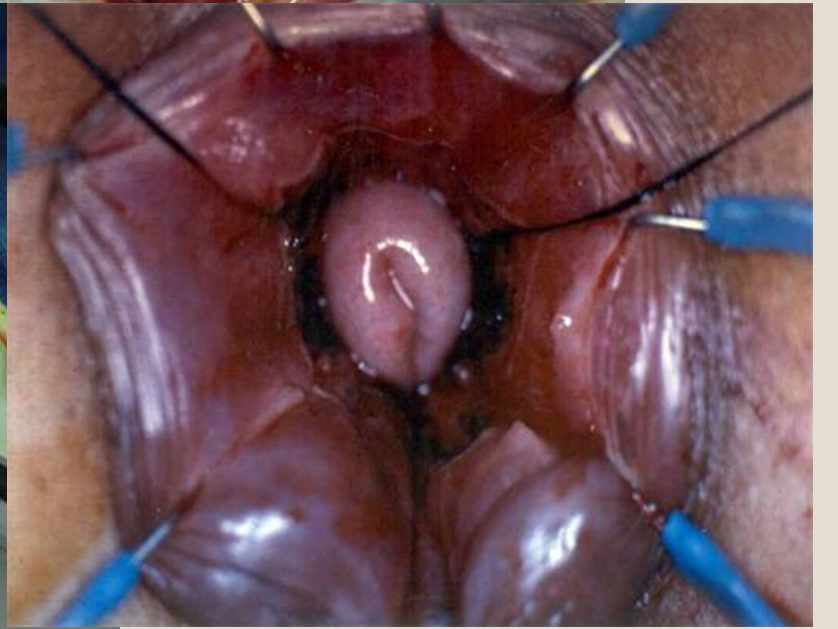
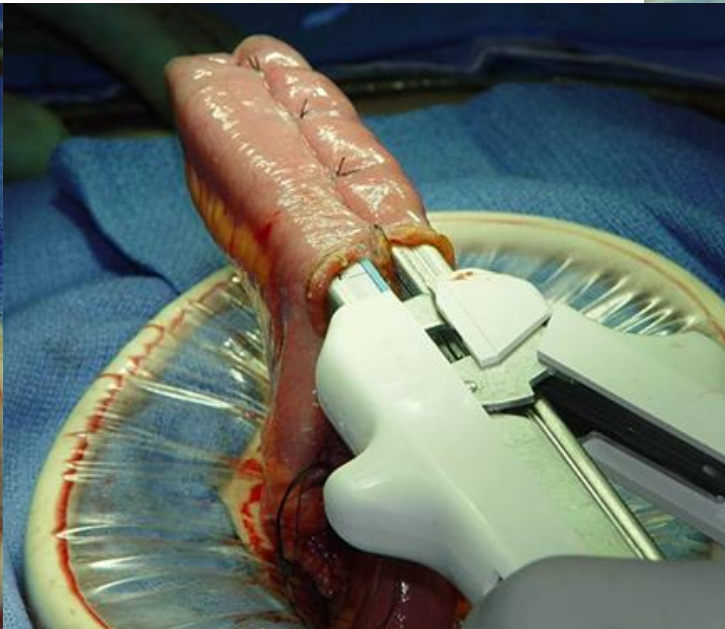
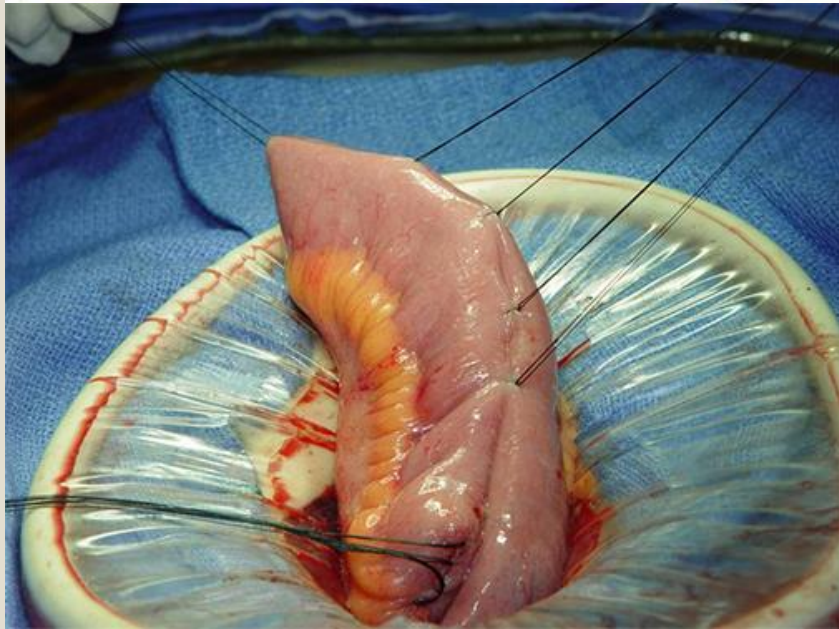
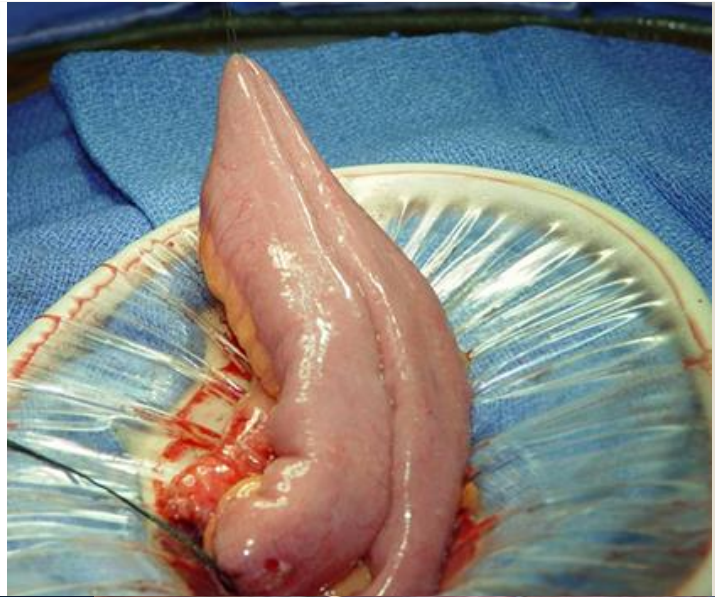
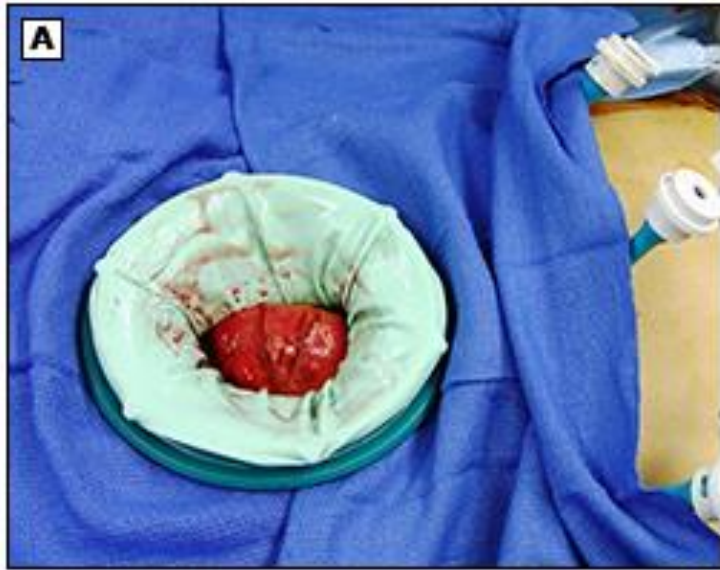
8. Anastomosis is tested

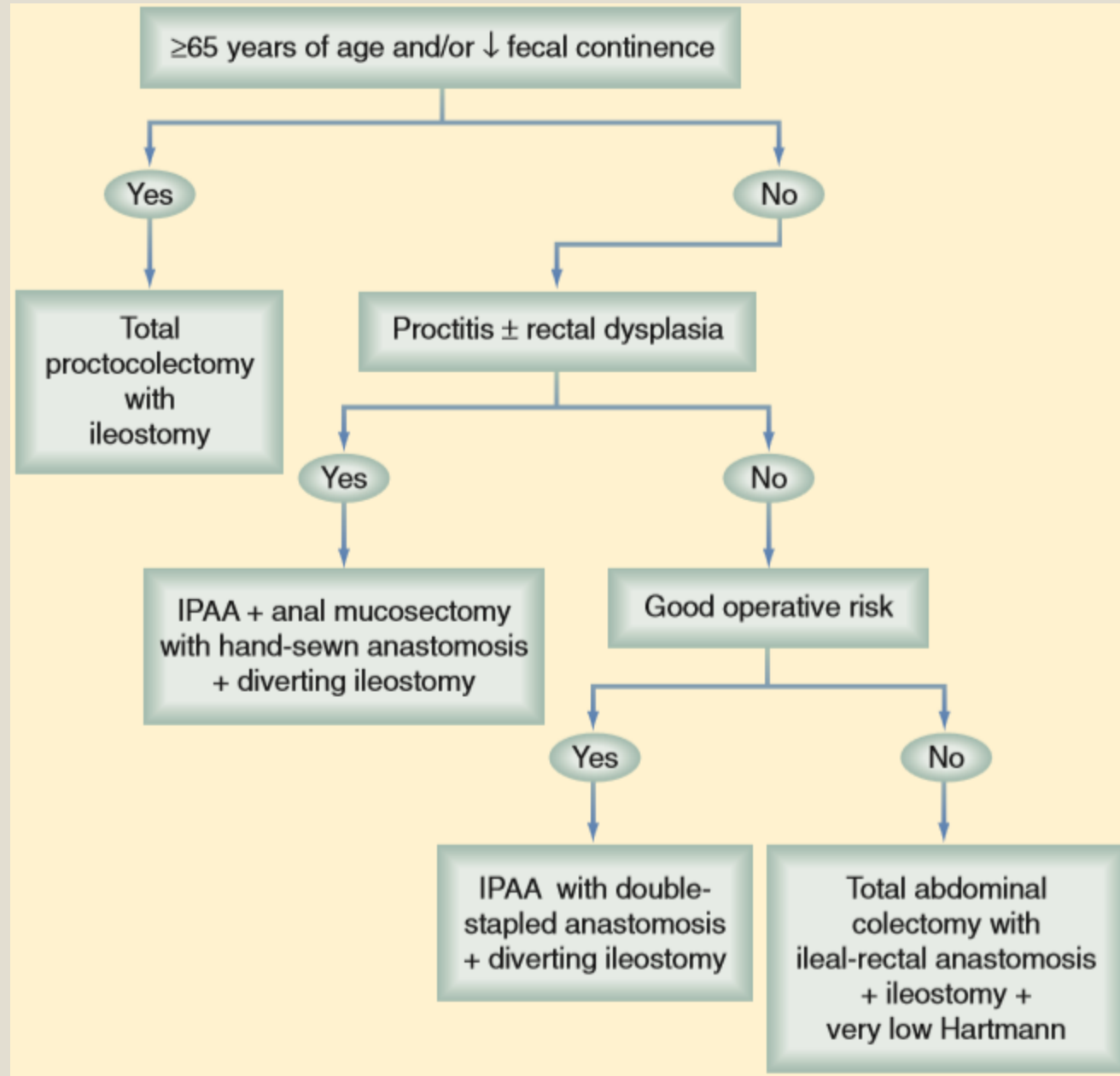
9. Loop ileostomy is created



Laparoscopic approach







Perioperative complications

- Small bowel obstruction (11-26%)
- Pelvic abscess or leak (2-15%)
 - Most commonly at pouch-anal anastomosis
 - ?steroid use
- Pouch fistula formation (2.8-12%)
- Cuffitis (5%-14%)
- Sexual dysfunction (5-20%)
- Pouch failure (5-10%)
- Cancer (rare)

Long-term functional outcomes

- Mean number of stools:
 - 5.7/day at 1 year
 - 6.4/day at 20 years
- Incontinence:
 - 5 to 11% during day
 - 12 to 21% at night
- Pouch success:
 - 5 years – 96%
 - 10 years – 93%
 - 15 years – 92%
 - 20 years – 92%
- Quality of life same
- 92% in same employment

Results at up to 20 years after ileal pouch–anal anastomosis for chronic ulcerative colitis

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Long-term functional outcomes

- 11% anal canal strictures
 - Nonfibrotic – responded to dilatation
 - Fibrotic – required surgery
- Pouch failure – 6.8%
- Pelvic sepsis – 9.5%
- Severe incontinence 3.7%
- Mild incontinence 17%
- Current techniques are still not perfect and require further development
- IPAA can have effects on female reproductive health
 - Dyspareunia
 - Significant decrease in fertility (adhesions?)
 - Pregnancy/delivery is safe

Follow-up

- All patients with IPAA should be followed for complications including dysplasia
- Inflammation in retained rectal cuff associated with dysplasia long term
- Systematic review – 1.13% of dysplasia
- Therefore risk of neoplasia not completely eliminated
 - Surveillance recommended
 - Optimal frequency not well documented

Surgery for indeterminate colitis

- Acute fulminant colitis during first presentation requiring colectomy before definitive diagnosis is available
- Uncertain diagnosis (Crohn's vs. UC) despite investigations
- Indications for surgery are the same **BUT:**
 - **Surgery should be total abdominal colectomy and ileostomy and Hartmann procedure or mucous fistula**
 - Subsequent proctectomy and IPAA is an option for those with confirmed UC

Surgery for extraintestinal manifestations of UC

- Role of colectomy for these indications not well defined
- Improvement in extraintestinal manifestations is variable
 - VTE, erythema nodosum, massive hemolytic anemia, arthralgia of joints improve
 - Pyoderma gangrenosum, PSC, and ankylosing spondylitis do not improve

Thank you!

Management of Fulminant Ulcerative Colitis

