Management Principles of Ulcerative Colitis

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Ulcerative Colitis

- Chronic inflammatory process of the colonic mucosa
- Usually begins with gradual onset of rectal bleeding, urgency, diarrhea and abdominal discomfort
- Inflammation begins in rectum, extends proximally for variable extent
- Must be differentiated from infectious and other causes of mucosal inflammation

UC-Grading Severity

- Severity of disease can be determined by:
  - Truelove and Witt's criteria
    - mild
    - moderate
    - Severe
- Easy to remember:
  - 2 historical points
  - 2 physical exam points
  - 2 laboratory values

Truelove and Witt's Criteria

	Mild Activity	Severe Activity
Daily bowel movements (no.)	< or = to 5	> 5
Hematochezia	Small amounts	Large amounts
Temperature	< 37.5°C	> or = to 37.5°C
Pulse	< 90/min	> or = 90/min
Erythrocyte sedimentation rate	< 30 mm/h	> or = to 30 mm/h
Hemoglobin	> 10 g/dl	< or = to 10 g/dl

- Patients with fewer than all 6 of the above criteria for severe activity have moderately active disease

Ulcerative Colitis Activity Index

1. Stool frequency	*0-3*: normal *1-3*: 1-2 stools daily > normal *2-3*: 3-4 stools *3-3*: 4 stools
2. Rectal bleeding	*0-3*: None *1-3*: Streaks of blood *2-3*: Obvious blood *3-3*: Mostly blood
3.Mucosal appearance	*0-3*: Normal *1-3*: Mild friability *2-3*: Moderate friability *3-3*: Exudation, spontaneous bleeding
4. Physician's rating of disease activity	*1-3*: Normal *2-3*: Mild *3-3*: Moderate *4-3*: Severe
Maximum score 3	*13*

Endoscopic Appearance

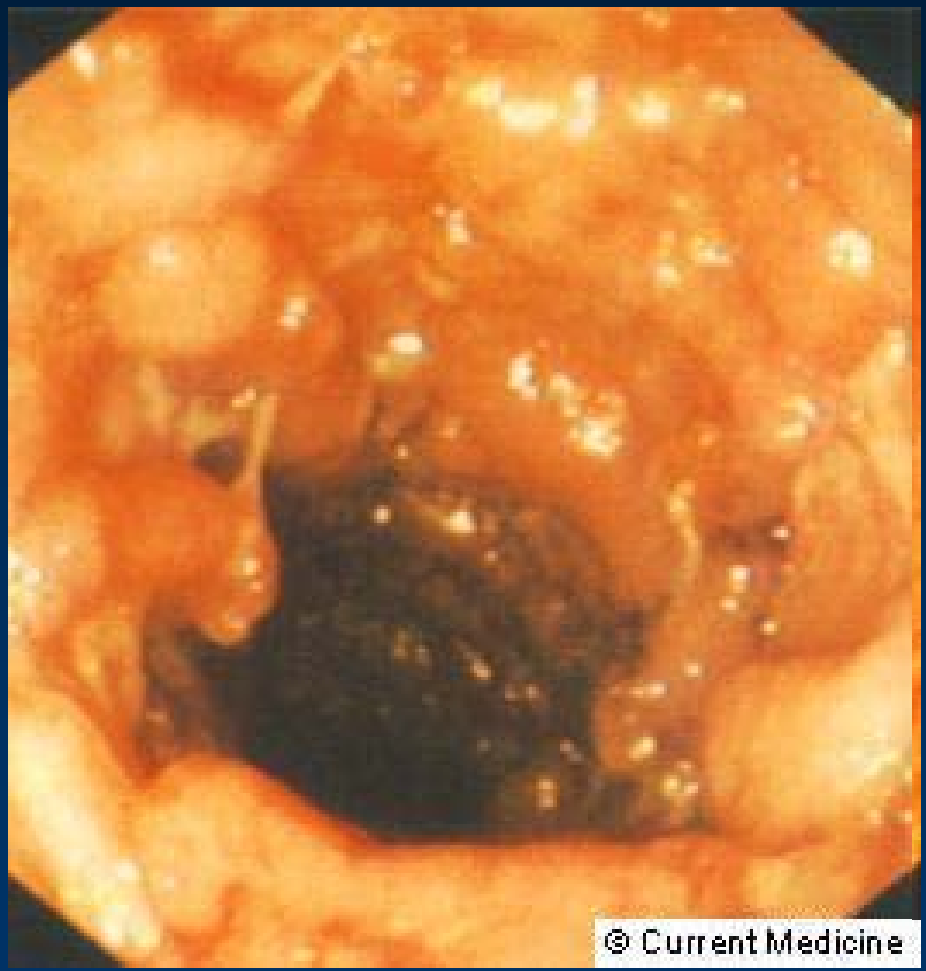
Feature	Ulcerative colitis	Crohn's disease
Disease distribution	Diffuse, continuous	Segmental
Rectal involvement	Always	Occasional
Disease severity distribution	Worse distally	Variable
Ileal involvement	Occasional backwash ileitis	Frequently

Pathologic Appearance

Feature	Ulcerative colitis	Crohn's disease
Disease location in bowel wall	Superficial, mucosal	Transmural
Lymphoid aggregates	Rare, underneath ulcers	Any location
Fissures	Occasionally superficial in fulminant colitis	Deep, any location
Sinuses and fistulas	Absent	Present
Granulomas	Related to ruptured crypts	Not related to crypts

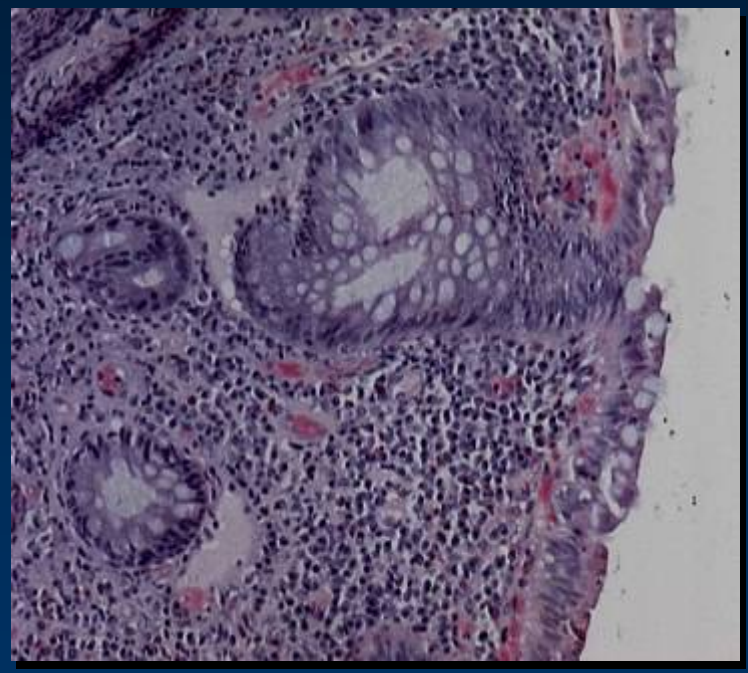
Ulcerative Colitis

Endoscopic severity



Histologic Appearance

- Disrupted mucosal architecture
- Mixed inflammatory infiltrate
- Mucus depletion
- Crypt abscesses



UC Variants Resembling Crohn's Disease

- Discontinuous disease
- Backwash ileitis
- Upper GI tract involvement
- Granulomas
- Apthous ulcers
- Superficial ulcers
- Transmural inflammation

UC Variants Resembling Crohn's Disease

- UC typically involves the colon diffusely and continuously
- Some UC cases may present with:
  - patchy or discontinuous disease
    - Tissue healing of topical medications
    - Quiescent phase of mild UC
  - Absolute or relative rectal sparing
    - Approximately 25% of pediatric UC patients present with rectal sparing

UC Variants Resembling Crohn's Disease

- Other variant presentations of UC include:
  - Segmental sparing
    - UC patients with left sided disease can also have cecal or ascending colon involvement, but sparing of the transverse colon
      - This does not evolve into pancolitis or Crohn's disease
    - Peri-appendiceal involvement as a "skip lesion" is common, occuring in up to 86% of cases[1]

1. Matsumoto Gastrointest Endosc 2002

UC Variants Resembling Crohn's Disease

- Inflammatory changes in the ileum
  - Severe colonic disease may lead to incompetence of the IC valve, which in turn allows retrograde flow of the fecal stream into the terminal ileum
  - A retrospective study of 200 consecutive UC patients demonstrated inflammation in the ileum in 17% of patients[1]

1. Haskell Am J Surg Path 2005

UC Variants Resembling Crohn's Disease

- 88% of cases involved mild inflammatory neutrophilic infiltrates
  - Inflammation occasionally associated with focal cryptitis, crypt abscesses, and superficial ulcerations.
  - A small number of cases involved skip lesions of the cecum or ICV, with patchy involvement of the terminal ileum
    - "Backwash ileitis" can also be explained by infections, drug reactions, bowel prep effects or primary involvement of the terminal ileum

UC Variants Resembling Crohn's Disease

- Inflammation of the ileum could be considered part of UC if the inflammatory changes are:
  - Mild, superficial and limited to the distal 2-3cm of the ileum
  - Occur in a patient who otherwise fulfills the diagnosis of UC

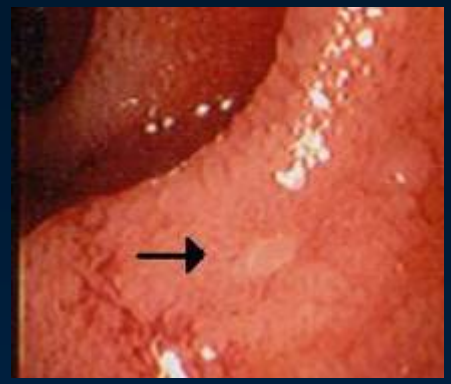
Granulomas in UC

- Approximately 30-40% of CD cases contain non-necrotic granulomas in the mucosa or bowel wall
- Epithelioid granulomas are NOT associated with UC
- However, granulomas associated with ruptured crypts or extravasated mucin occur commonly in UC and other forms of non-IBD colitis

Granulomas in UC

- Multiple tissue levels may demonstrate the relationship between the gramuloma and crypt epithelium
- Rupture induced granulomas may contain a mixture of neutrophils and lymphocytes, which are not characteristic of CD granulomas

Apthous Ulcers in UC



- Apthous ulcers-mucosal erosion or superficial ulcer overlying a lymphoid aggregate
- These lesions are commonly seen in CD, in the terminal ileum and proximal colon
- However, a recent study demonstrated that 17% of colectomy specimens from UC patients contained apthous ulcerations (Yantis Am J Surg Pathol 2004

UC-Treatment Principles

Determine extent/severity of disease

Determine most appropriate therapy

Achieve and maintain remission

Improve quality of life

UC-Treatment Principles

Selection of Treatment

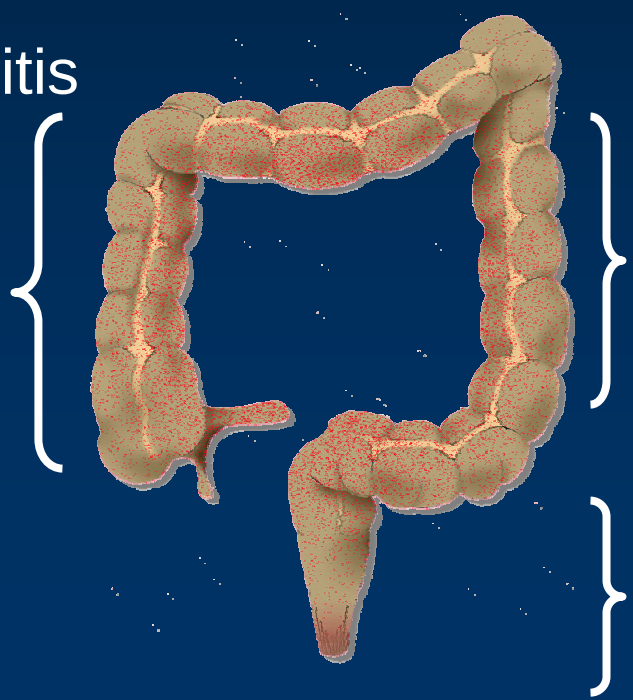
- Nature of disease allow heavy reliance on surface active medications
- Treatment plan designed is based on
  - Severity
  - Extensive vs. distal
  - Presence of complications/extra-intestinal manifestations
  - Prior response to specific drugs
- Therapeutic decisions rarely based on histologic/endoscopic severity of inflammation

Site of Delivery
Based on 5-ASA Formulation

- Topical therapy's ability to reduce inflammation directly linked to ability to reach site of inflammation

20% pancolitis

Oral



30-40% beyond sigmoid

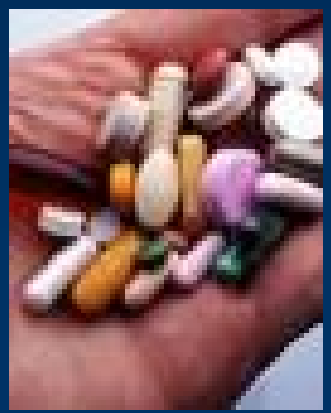
Enema

40-50% rectosigmoid

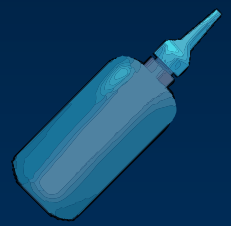
Suppository

5-ASA Therapy

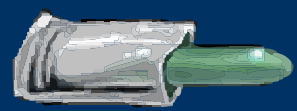
- Sulfasalazine
- Asacol (mesalamine)
- Pentasa (mesalamine)
- Dipentum (olsalazine)
- Colazal (balsalazide)



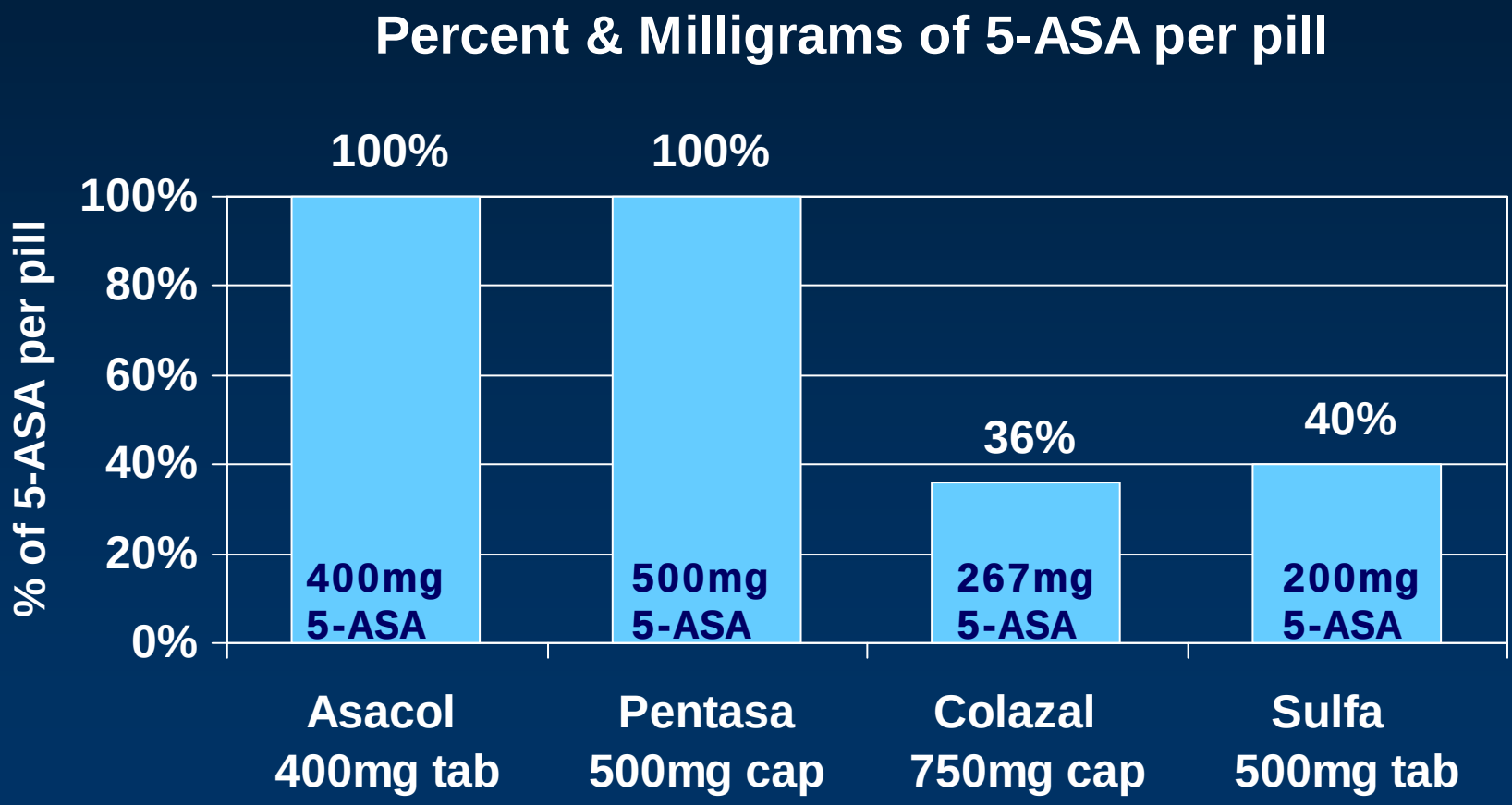
- Rowasa (mesalamine)



- Canasa (mesalamine)



5-ASA amounts per pill



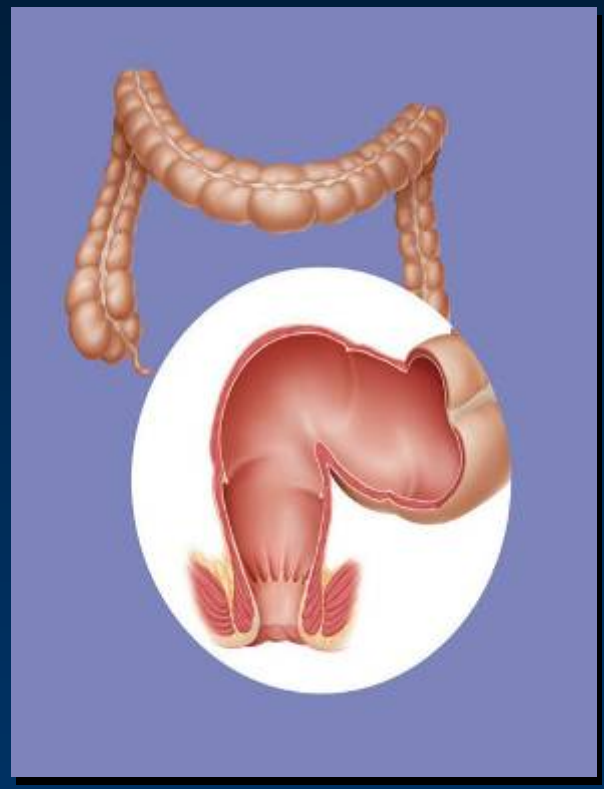
Higher Dose Mesalamine More Effective in Moderately Active UC

- ASCEND I and II trials
  - Randomized, controlled phase III trials comparing 2.4gm/day with 4.8gm/day
  - Total of 687 patients randomized
  - Adverse events similar in both arms
  - Clinical remission
    - 4.8gm/day 72%
    - 2.4gm/day 58%
  - Therapeutic dose response only seen in moderate disease activity, not in mild disease activity

Sandborn et al. AJG 2005;100(11):2478-85.

Principles of Topical Therapy

- Directly delivers high concentrations of 5-ASA to rectal mucosa
- Best initial choice for active ulcerative proctitis/sigmoiditis



Topical Therapy Caveats

- Topical mesalamine agents are superior to topical steroids or oral 5-ASA alone for left sided disease
- The combination of oral and topical aminosalicylates are more effective than either alone
- In patients refractory to oral aminosalicylates or topical steroids, mesalamine enemas or suppositories may still be effective (not dose dependent)

Safdi AJG 1997 1867-71
Green Gastro 1998 15-22
Yang AJG 2001 S311-312

Summary of Topical Advantages

- Quicker response time
- Less frequent dosing
- Fewer side effects than oral

Safdi AJG 1997 1867-71
Green Gastro 1998 15-22
Yang AJG 2001 S311-312

Ulcerative Colitis

Moderate to Severe

- Moderate severity often responds to oral prednisone (40-60mg/day)
- More severe cases will need admission and IV steroids
- Careful monitoring for response if treating as an outpatient

Ulcerative Colitis

Moderate to Severe

- Begin steroid taper only after patient clinically "well" (2-4 weeks)
  - Decrease prednisone by 5mg/wk until reaching 20mg
  - Below 20mg, taper by 2.5mg to 5mg per week
- Flare during taper should prompt increase to lowest level prior to flare
- Inability to complete taper should prompt consideration of adding immuno-modulators

Moderate to Severe UC
Immunomodulators

- May require use of concomitant immuno-suppression
- 6-mp/AZA have been shown to be helpful
- No role for methotrexate

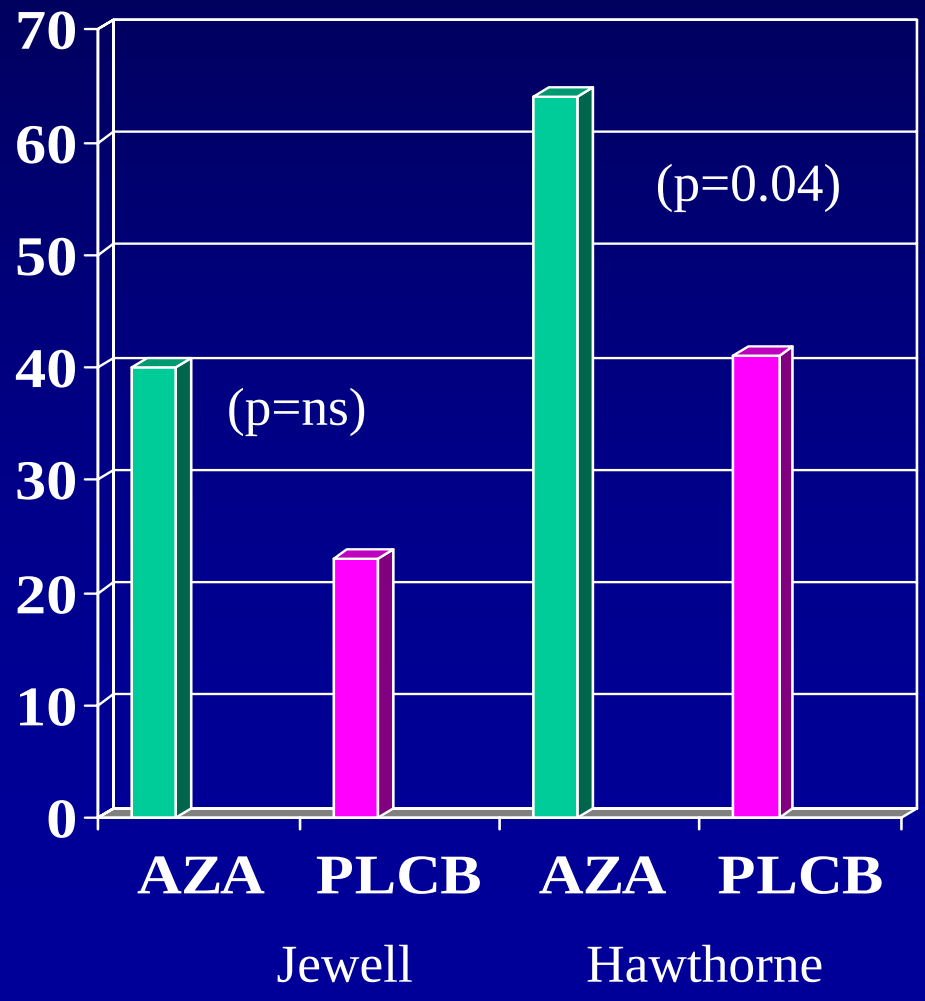
UC Maintenance with Azathioprine Controlled data: 1yr Remissions

Jewell (Gut 1974)

AZA 2.5 mg/kg (n=40)
PLCBO (n=40)

Hawthorne (BMJ, 1992)

AZA (x 100mg) (n=33)
PLCBO (n=34)
[withdrawal trial]



UC Maintenance Aza/6-MP Uncontrolled Remission data

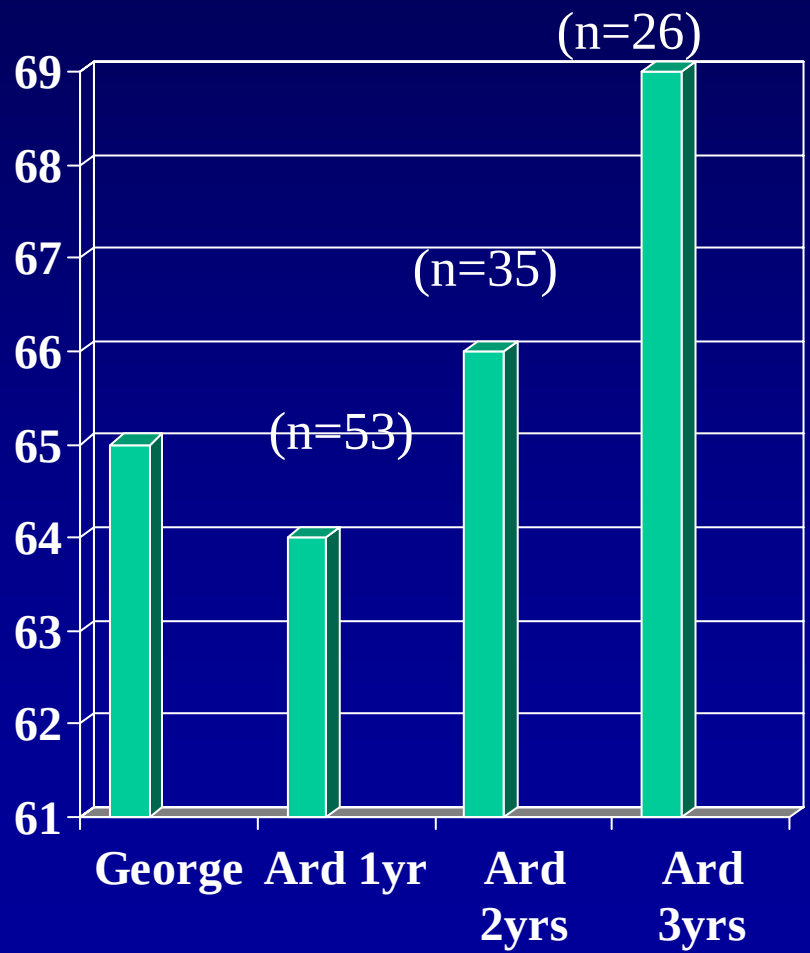
George (AmJGastro,96)

105 retrospective pts treated with 6-MP

Ardizzone (J.Clin.Gastro'97)

56 retrospective pts treated AZA 2mg/kg

Remission off steroids

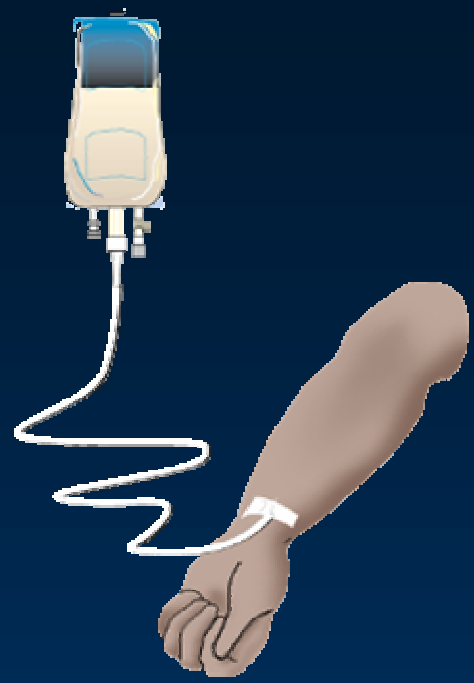


Moderate to Severe UC
Anti-TNF Therapy

- If concomitant immuno-suppression ineffective, maximize therapy
- Consider Remicade for persistently active disease
  - 5mg/kg IV infusion 0, 2, 6 weeks, then q8 weeks
  - Same principles apply

Severe Ulcerative Colitis

General Treatment Guidelines



- Admit to hospital
  - 15% require at some point
- IV fluids/steroids
- GI consultation
- Surgical consultation
- Daily KUB

Severe Ulcerative Colitis

Steroid Therapy

- Steroids may be administered in continuous or split dose
  - ACTH 120 units/24 hours as continuous infusion
    - If no steroids within previous 30 days
  - Hydrocortisone 100mg q 8 hours
  - Methylprednisolone 16-20mg q 8 hours*
  - Prednisolone 30mg q 12 hours*
- Continue for 7-10 days, as long as improvement continues
  - If no improvement in 5-7 days, consider other therapy

*Less Na retention, K wasting

Severe Ulcerative Colitis
5-ASA Considerations

- No role for NPO (low residue diet)
- If already on 5-ASA products-STOP!!
- However, if not intolerant, concomitant administration of 5-ASA may improve short and long term response rates
  - 90% response rate when started early
  - 71% response without 5-ASA

Loftus AJG 2001 S299

Severe Ulcerative Colitis

Pitfalls of Treatment

- Prematurely withdraw acute therapy
- Wait too long to discard ineffective therapy
- Mistake steroid dependency for maintenance effect
- Withdraw patients from maintenance therapy
- Fail to educate patients on consequences of non-compliance

Severe Ulcerative Colitis

Predicting Need for Second-Line Therapy

- Much of the morbidity/mortality associated with severe UC comes from delayed surgery
- Need to select patients who will benefit from additional therapy early in course of disease
- Two models predicted medical failure, need for early surgery:
  - Stool frequency >8/day, or 3-8/day with CRP>45mg/dL after 3 days steroid therapy: 85% require colectomy[1]
  - #BM + 0.14 x CRP (mg/L)>8.0 as optimal cut-off to predict medical failure[2]

1. Travis et al. Gut 1996;38:905-10
2. Lindgren et al. Eur J Gastroenterol Hepatol 1998;10:831-5

Severe Ulcerative Colitis

Risk Score for Early Detection

- 167 patients with severe UC
  - Multiple logistic regression to analyze parameters within first 3 days of medical therapy
    - 67 (40%) failed to respond to medical tx
- Three factors identified by multiple logistic regression:
  - Mean stool frequency (<4=0, 4≤6=1, 6≤9=2, >9=4)
  - Colonic dilation within first three days (4)
  - Hypoalbuminemia <30g/L (1)
- Risk score formulated
  - ≥4 predicts non-response

Ho, et al. Aliment Pharmacol Ther 2004 May;19:1079-87

Diagnostic Dilemma Scenarios Fulminant Colitis

- Severe form of colitis with systemic toxicity
- Resected specimens often show extensive ulceration-right and transverse colon more severely affected than distal colon
- Ulcerations fissuring or knife-like defects extending into superficial muscularis propria
- Often associated with transmural lymphoid inflammation
  - Can confuse picture with Crohn's disease

Diagnostic Dilemma Scenarios Fulminant Colitis

- Yantiss found 27% had superficial fissuring ulcers in their colectomy[1]
- No patients developed Crohn's disease
- Swan found that 87% of fulminant colitis specimens could be accurately classified based on histological evaluation[2]
  - The presence of granulomas and transmural inflammation in regions of intact mucosa predicted development of Crohn's disease

1. Yantis et al. Am J Surg Pathol 2005
2. Swan et al. Dis Colon Rectum 1998

Diagnostic Dilemma Scenarios Comorbid Diseases-CMV

- Presence of a superimposed “secondary disease” may alter interpretation of the underlying IBD
- Cytomegalovirus
  - May be associated with a flare of inflammation that is segmentally distributed in the right colon or ileum, and is more severe that the inflammation in the remainder of the colon

Diagnostic Dilemma Scenarios Comorbid Diseases-C. diff

- Pseudomembranous colitis
  - C. difficile can spontaneously complicate IBD
  - Presence of characteristic pseudomembranes and necrotic crypts affecting areas uninvolved with IBD help establish diagnosis
- Chemical injury (NSAIDs)

Options for Severe Refractory UC

- Cyclosporine
- Infliximab
- Clinical trial
- Colectomy

Severe Ulcerative Colitis
Cyclosporine

- Severe UC failing to respond to IV steroids
  - Must weigh risks of infection, renal dz, HTN against colectomy
  - Short term response rates 70-80%
- Prior to initiating drug, check
  - Cholesterol (>120mg/dL)
  - Magnesium (>1.5mg/dL)
- 2mg/kg infused over 24 hours[1]
  - target cya levels of 150-250 ng/mL whole blood
- Response in 3-5d on average, most within 7d

1. Van Assche et al. Gastro 2003;125:1025-31

Severe Ulcerative Colitis
Cyclosporine

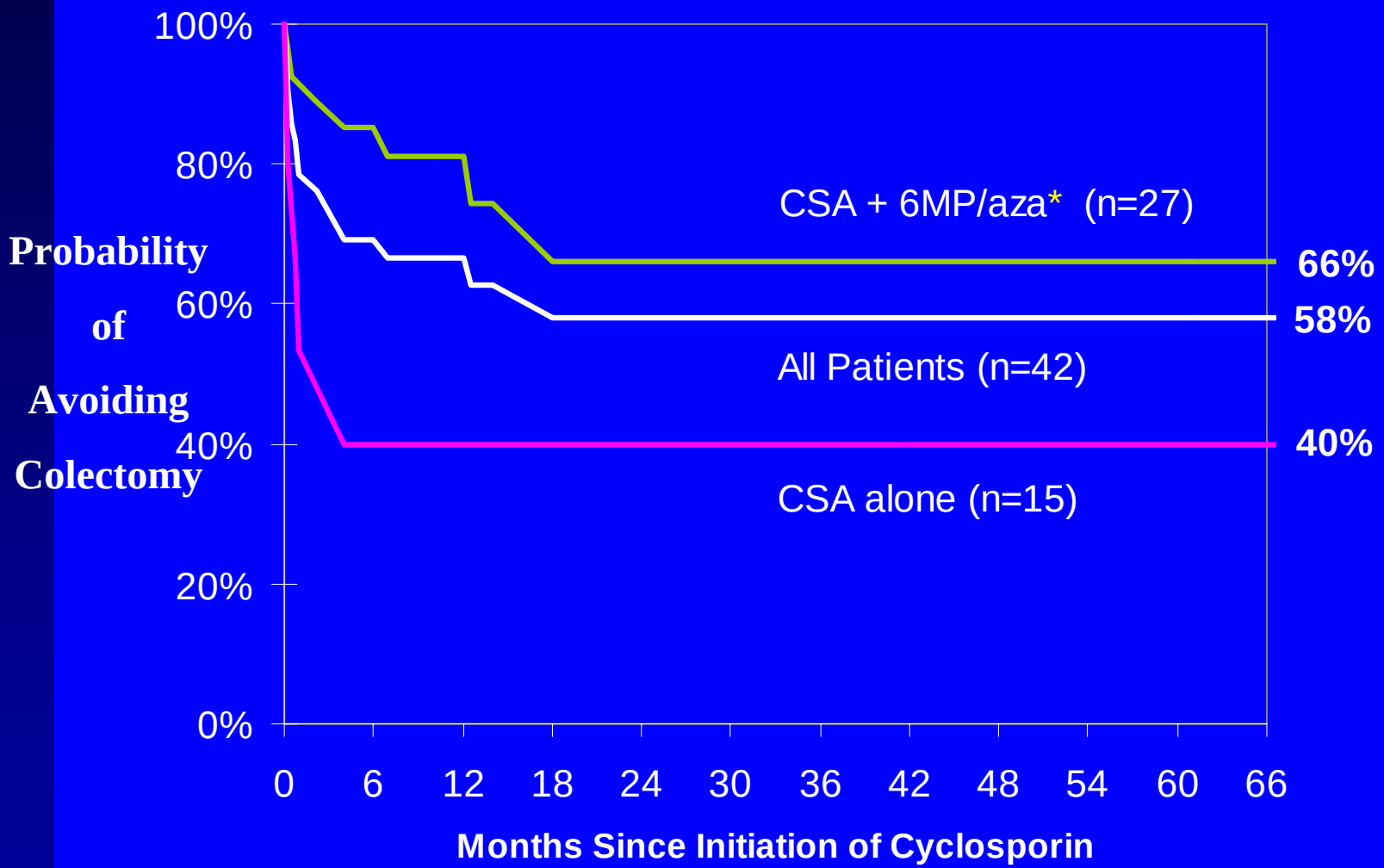
- Responders transition to 5-6mg/kg/day Neoral
  - Target trough level at 100-200ng/mL
- Prophylax against *Pneumocystis carinii* while on triple immunotherapy
  - Bactrim tiw
- During first month after discharge, taper prednisone from 40-60mg/day to 20mg/day.
- After three to four months, cyclosporine can be discontinued.
- One week after cyclosporine discontinued, can begin to taper prednisone from 20mg/day to 0mg/day.

Severe Ulcerative Colitis
Cyclosporine

- Those who achieved remission on cyclosporine and were maintained on AZA, two thirds remain in remission at 5 years

- If the patient relapses during the drug taper, surgical resection warranted

Avoidance of Colectomy After CysA Induction



Cohen, Stein, Hanauer. Am J Gastroenterol 1999;94(6):1587-1592

Cyclosporine
Monitoring Toxicity

- Check following at 0, 1, 2 weeks, then monthly
  - Blood pressure
  - CBC
  - Renal function
  - CsA concentration (100-200ng/mL)

Biologics in Severe UC

Fulminant Colitis

Patients Ineligible for Medical Therapy

- Medical emergency manifested by
  - high fever
  - abdominal tenderness
  - abdominal distension
  - hemorrhage
- May or may not have colonic distension
- Morbidity increased by delaying surgical therapy

UC-Indications for Surgery

- Immediate
  - Exsanguinating hemorrhage
  - Toxicity and/or perforation
- Urgent
  - Unresponsive severe colitis
  - Severe/acute complications of disease or therapy
    - Opportunistic infections
    - Steroid psychosis
    - Hemolytic anemia
- Elective
  - Suspected cancer
  - Dysplasia
  - Growth retardation
  - Osteonecrosis/compression fracture
  - Intractability

Ulcerative Colitis
Surgical Options