LEBANESE SOCIETY OF GASTROENTEROLOGY
الجمعية اللبنانية لأمراض الجهاز الهضمي

A User Guide for Inflammatory Bowel Disease

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ULCERATIVE COLITIS

Definitions

Clinical remission:

Resolution of symptoms (stool frequency ≤ 3/day, no bleeding and no urgency)

Endoscopic remission:

Absent or minimal endoscopic lesions

Relapse:

Flare of symptoms (blood in stool, tenesmus, diarrhea) with or without evidence of mucosal inflammation and in the absence of concomitant infection

Steroid-resistant:

Patients who have active disease despite prednisolone of up to 0.75 mg/kg/day over a period of 4 weeks

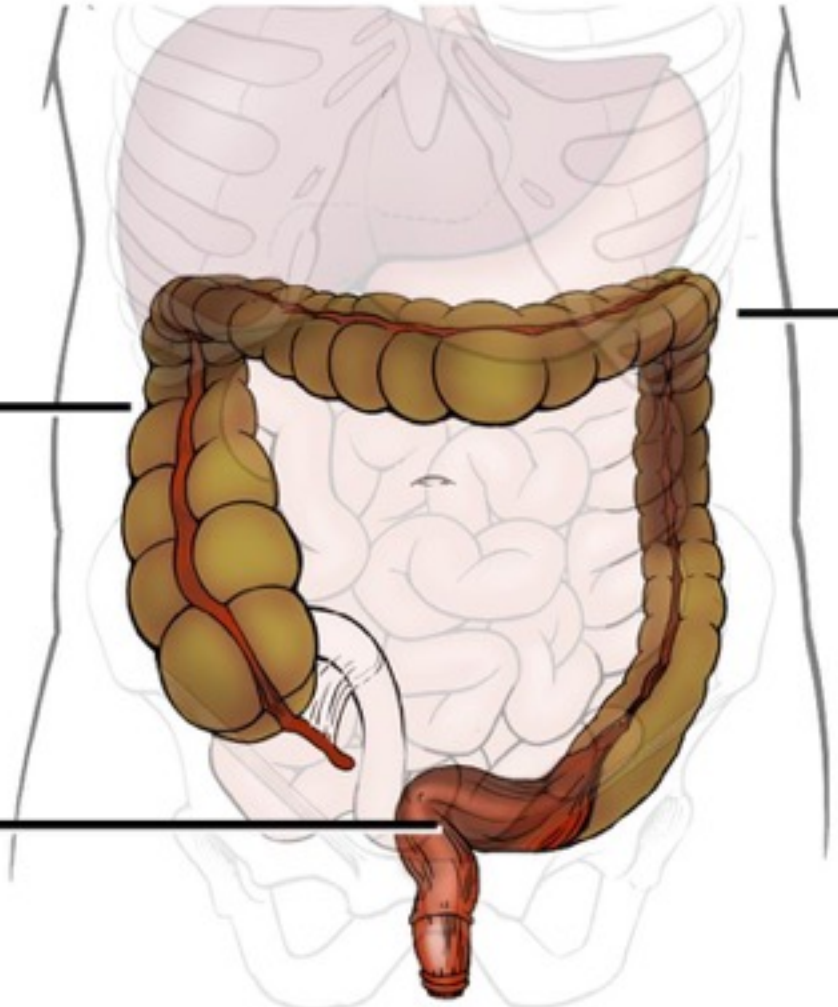
Steroid-dependent:

Patients who are either:

-Unable to reduce steroids below the equivalent of prednisolone 10 mg/day within 3 months of starting steroids, without recurrent active disease, or

-Who have a relapse within 3 months of stopping steroids

Anatomic Extent of Ulcerative Colitis



Pancolitis

Beyond splenic flexure or > 60cm

Left-sided disease

Extends to splenic flexure or <60cm

Proctitis

Rectum only

Severity of active colitis

severity	Stool per day	Blood in stool	Erythrocyte sedimentation rate	Systemic toxicity*
Mild	<4	Present or absent	Normal	Absent
Moderate	4 to 6	Present or absent	Normal or elevated	Absent
Severe	7 to 10	Present	Elevated	Present
fulminant	>10	present	Elevated	Present

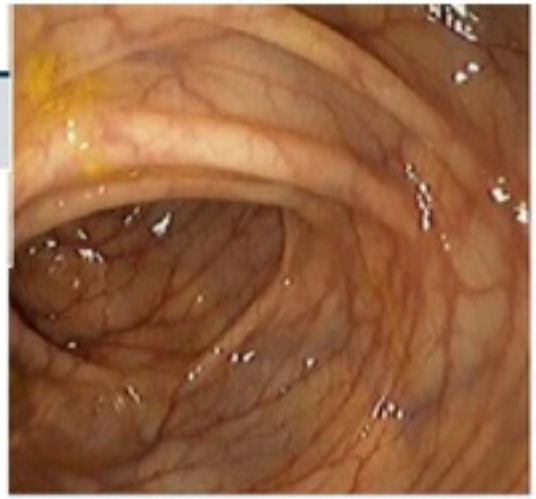
*- Fever, tachycardia, leukocytosis, or anemia
- Fulminant disease may also manifest as abdominal tenderness or distension , continuous bleeding with transfusion requirement or colonic dilatation

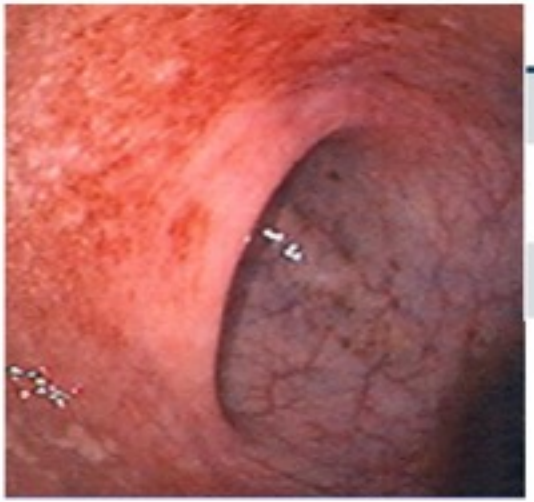
Kombluth A, Am J gastroenterol 2010; 105 (3): 501 - 523

UC Endoscopic Spectrum of Severity

Normal

- No friability or granularity
- Intact vascular pattern



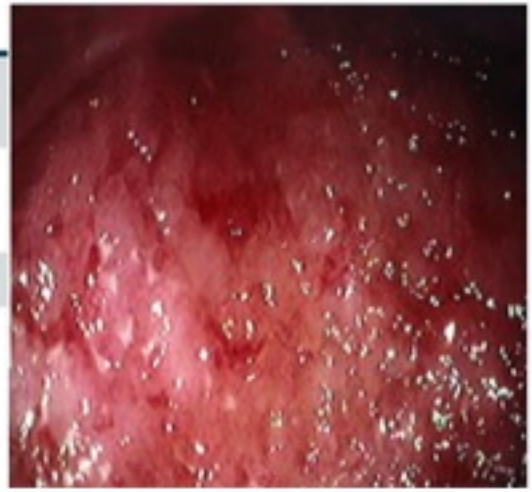


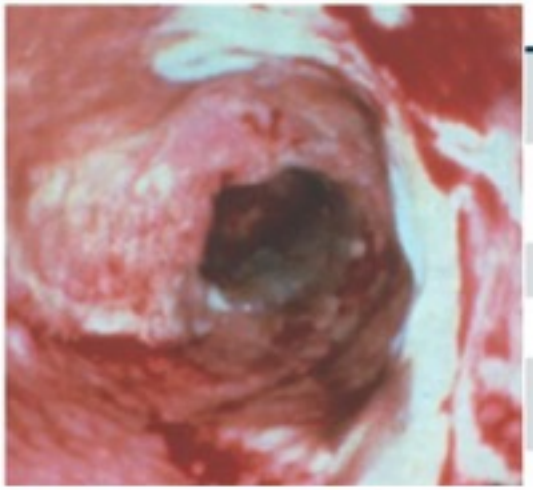
Mild

- Erythema
- Decreased vascular pattern
- Mild friability

Moderate

- Marked erythema
- Absent vascular pattern
- Friability
- Erosions

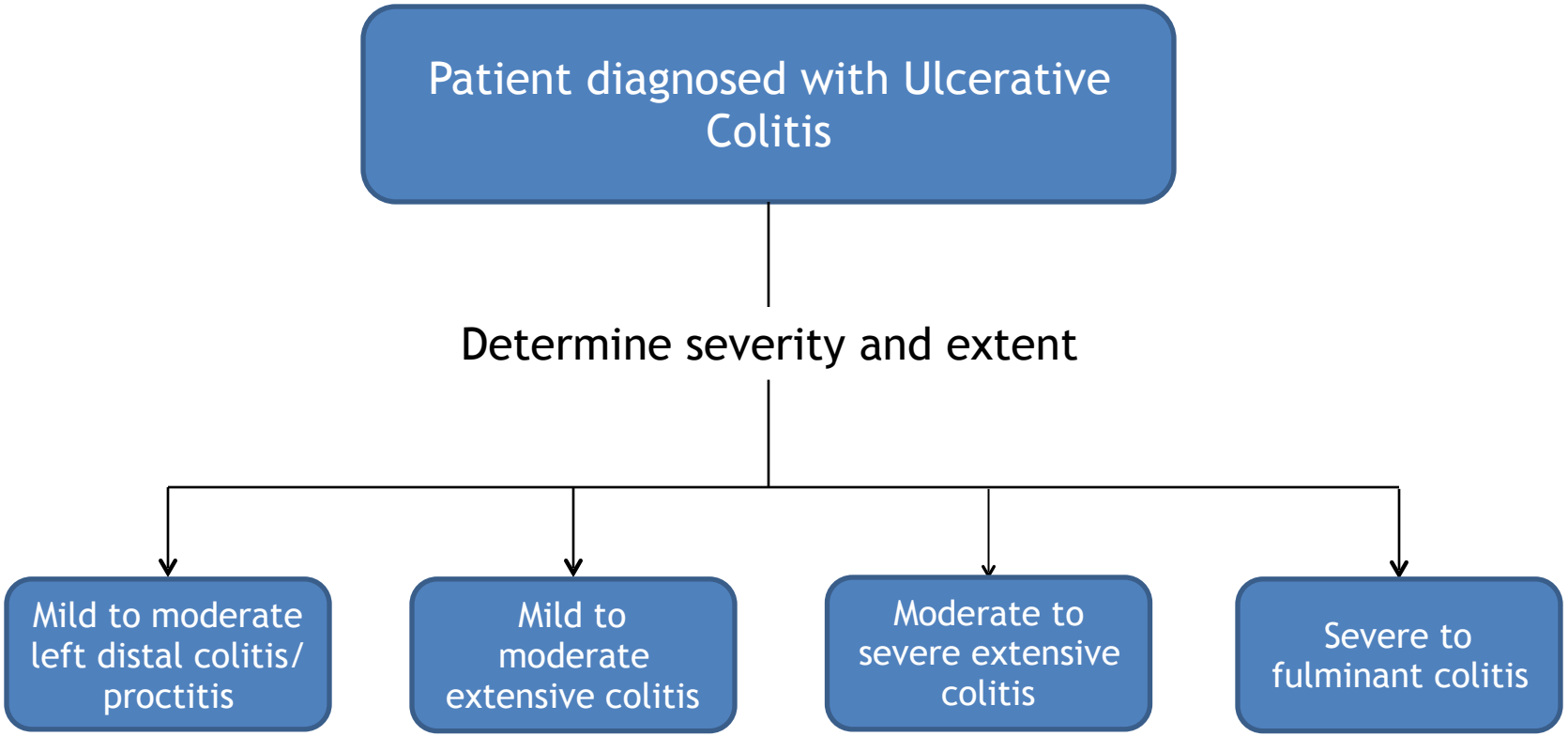




Severe

- Marked erythema
- Absent vascular markings
- Granularity
- Friability
- Spontaneous bleeding
- Ulcerations

Treatment Algorithm for Ulcerative Colitis



Medical therapies for UC

Medication (form)	Dosage for Active disease	Maintenance dosage	Adverse effects
5ASA (oral)	2 to 4.8g/day in 3 divided doses	1.2 to 2.4 g/day	Interstitial nephritis
5ASA (suppository)	1g once per day	0.5g once or twice per day	Anal irritation, discomfort
5ASA (enema)	1 to 4 g per day	1 to 4 g daily to every third day	Difficulty retaining, rectal irritation
Hydrocortisone (10% foam)	90mg once or twice per day	Not recommended	Rectal irritation
Prednisone (oral)	40 to 60 mg per day until clinical improvement then taper by 5 to 10mg per week	Not recommended	Adrenal suppression, bone disease, cataracts, cushingoid features, glaucoma, impaired wound healing, infections, metabolic abnormalities
Methylprednisolone (solumedrol, IV)	40 to 60 mg per day	Not recommended	

Medical therapies for UC

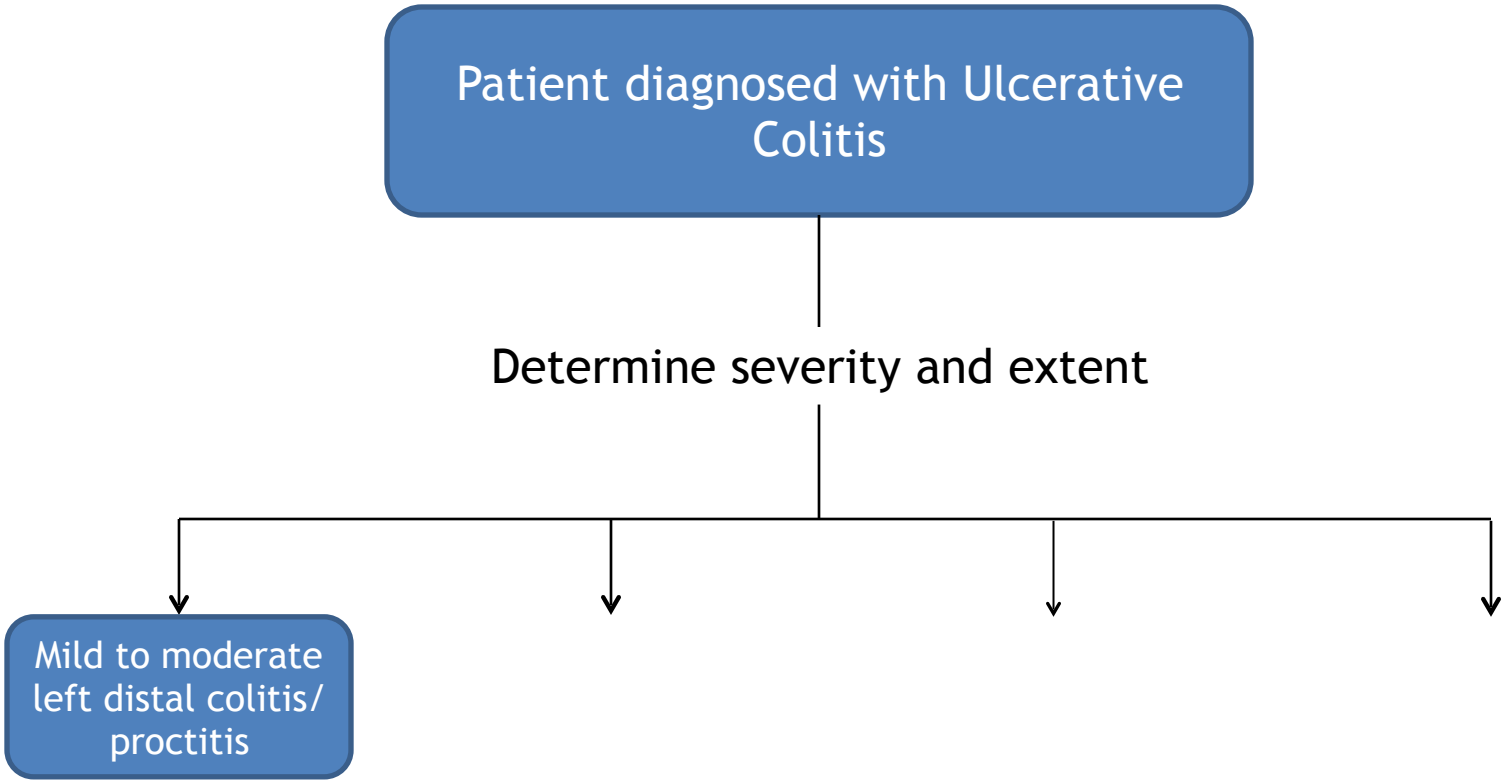
Medication (form)	Dosage for active disease	Maintenance dosage	Adverse effects
Infliximab (IV)	5 mg per Kg on weeks 0, 2, and 6	5mg per Kg every 8 weeks	Increased risk of infection and lymphoma, infusion reaction
Adalimumab (sc)	160mg W0, 80mg W2, than 40mg EOW	40mg EOW	Increased risk of infection and lymphoma
Godilumab	200mg (w0), 100mg (w2)	50–100mg (e4w)	Increased risk of infection and lymphoma
Azathiopyrine (oral)	Not recommended	1.5 to 2.5 mg per Kg per day	Allergic reactions, bone marrow suppression, infection, pancreatitis
Ciclosporine (IV)	2 to 4 mg per Kg per day	Not recommended	Infection, nephrotoxicity, seizures

Kombluth A, Am J gastroenterol 2010; 105(3): 501-523

Zocco MA, Aliment Pharmacol ther. 2006; 23(11): 1567-1574

Kruis W, Gut. 2004; 53(11): 1617-1623

Treatment Algorithm for Ulcerative Colitis



Proctitis/distal colitis

- Colitis limited to the rectum with mild or moderate activity should be initially treated topically.

  Gionchetti P, Aliment Pharmacol Ther 2002; 16 Supp 4:13-19

- 5-ASA suppository
  - is the drug of first choice

    ECCO EL 1b, RG B; DGVS EL A

  - induces remission in 31-80% of patients compared to 7-11% in the placebo-treated group.

    Marshall JK, Gut 1997; 40: 775-781

- There is no dose response to topical therapy above 1 g mesalazine daily.

Proctitis/distal colitis

- Topical corticoids are less effective than topical mesalazine.

  Gionchetti P, Aliment Pharmacol Ther 1997; 11: 1053-1057

- If no therapeutic effect is observed, treatment escalation using a combination of:

  – oral mesalazine (2-6 g/d for induction),
  – with topical mesalazine and/or a topical steroid

  is recommended as second-line therapy

  ECCO EL 1b, RG B; DGVS A

Proctitis/distal colitis

- If symptoms do not resolve within 2-4 weeks, the patient's adherence to medical treatment should be evaluated

- Confirmed persistent proctitis, in spite of combined local and topical therapy, is best treated as if it were more extensive or severe colitis.

Left-sided UC

- Left-sided active UC of mild-to-moderate severity should be initially treated with topical aminosalicylates combined with > 2 g/d oral mesalazine

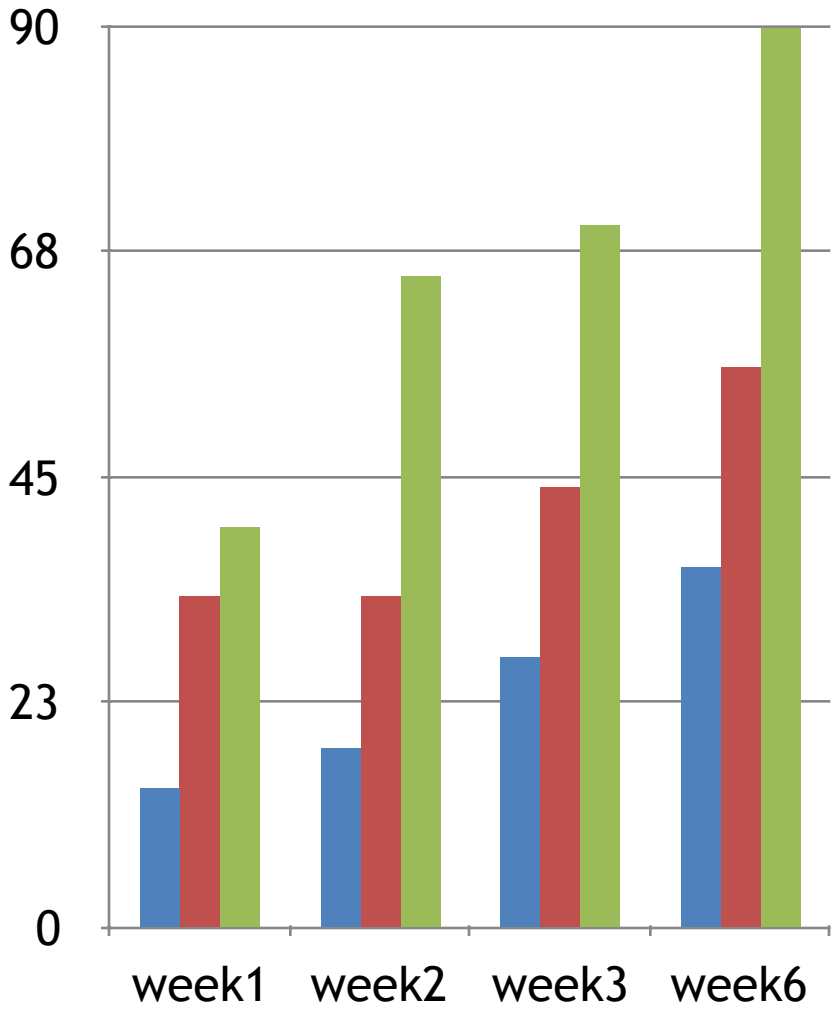
  (ECCO EL1b, RG B; ACG EL A)

- Comparative trials
  - revealed a dose-response of oral mesalazine (< 2.4 g vs 4.8 g/d) with more rapid clinical improvement and cessation of rectal bleeding in patients taking a higher dose (16 d vs 9 d, $P < 0.05$)
  - failed to show significant differences in remission rates 20.2% vs 17.7% (not significant)

    - Hanauer SB, Am J Gastroenterol 2005; 100: 2478-2485 13
    - Sutherland L, . Cochrane Database Syst Rev 2006; CD000543

Active left-sided UC: combination therapy superior to solo therapy with oral mesalamine 2.4g or mesalamine enemas 4.0g

percent of patient reporting no blood seen in stool



Combination versus

	oral 5ASA 2.4g	enema 5ASA 4g
Week2	0.001	0.052
Week 3	0.010	0.126
Week 6	0.004	0.053

(p-values)

Safidi et al, Am J Gastroenterol. 1997, 92(10) 1867-1871

Induction of response: 2.4g to 4.8g/day

Left-sided UC

- If rectal bleeding persists after 10-14 d despite combined treatment, systemic steroids should be introduced

  ECCO EL 1b, RG C; DGVS EL B; ACG EL C

- Steroid starting dose is 40-60 mg orally once daily. Marked differences between 40 and 60 mg starting doses have not been found

  DGVS EL A
  Baron JH, Br Med J 1962; 2: 441-443

Left-sided UC

- Severe left-sided colitis is usually an indication for hospital admission and systemic therapy (ECCO EL 1b, RG B)

Maintenance of remission proctitis/ left side colitis

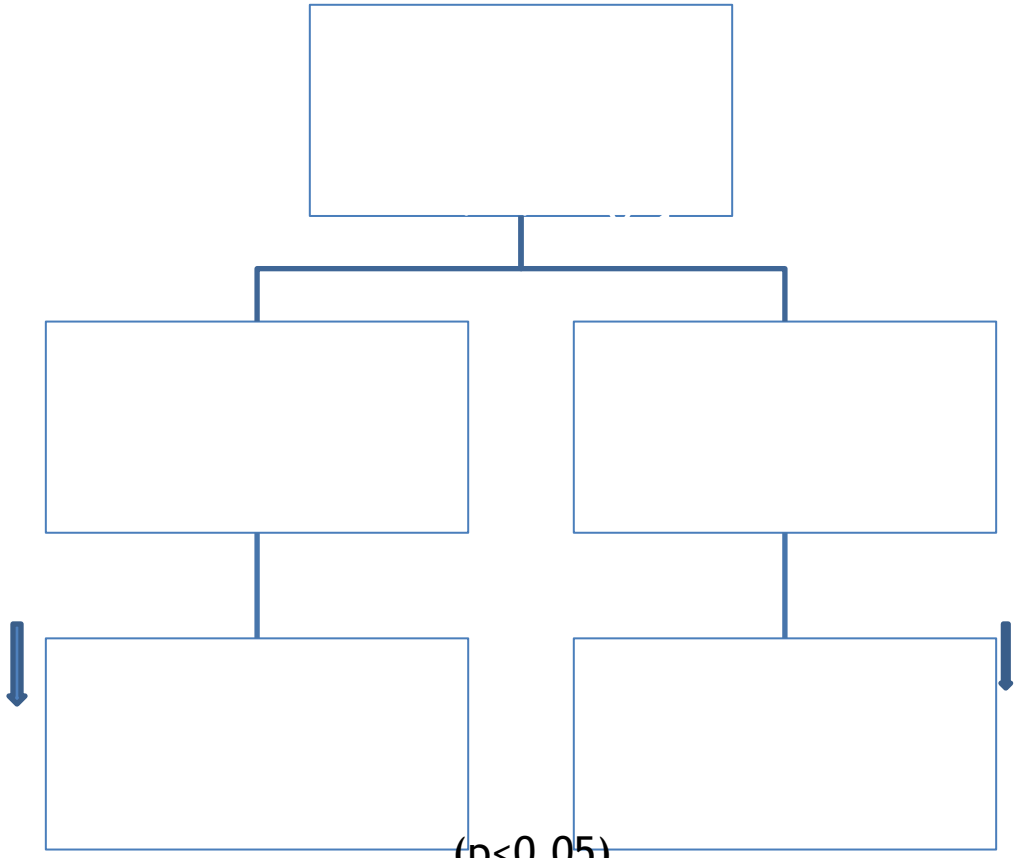
- First-line medical therapy for proctitis and left sided colitis consists of topical 5-ASA with a minimum dose of 1 g 3 times a week

  ECCO EL 1b, RG B; ACG EL A

- Oral mesalazine can be added as second-line therapy and has been shown to be superior compared with monotherapy, or it can be given alone if long-term rectal treatment is not accepted by the patient.

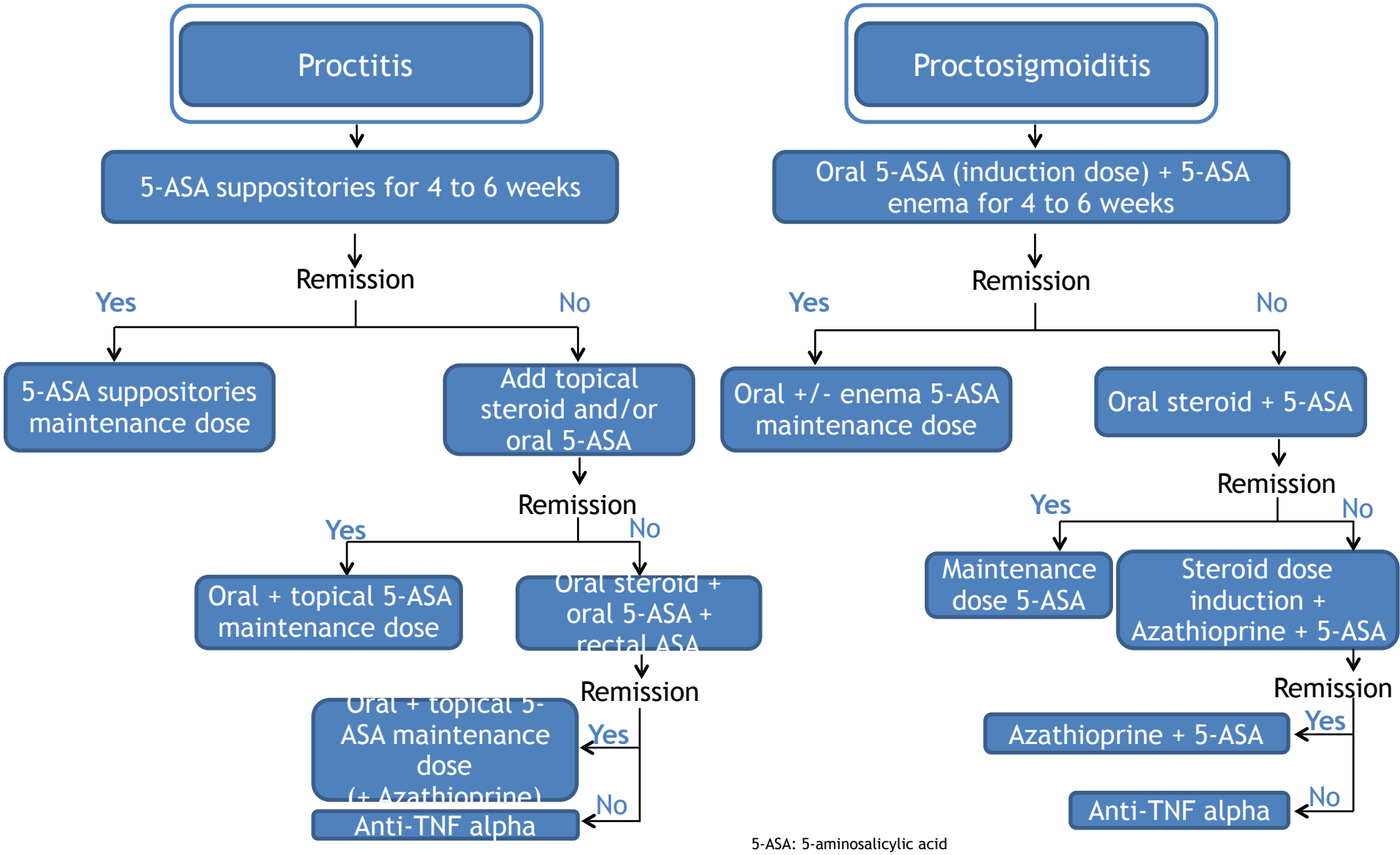
  ECCO EL 1b, RG B

Remission maintenance UC: combination therapy superior to solo therapy with oral mesalamine 1.6g



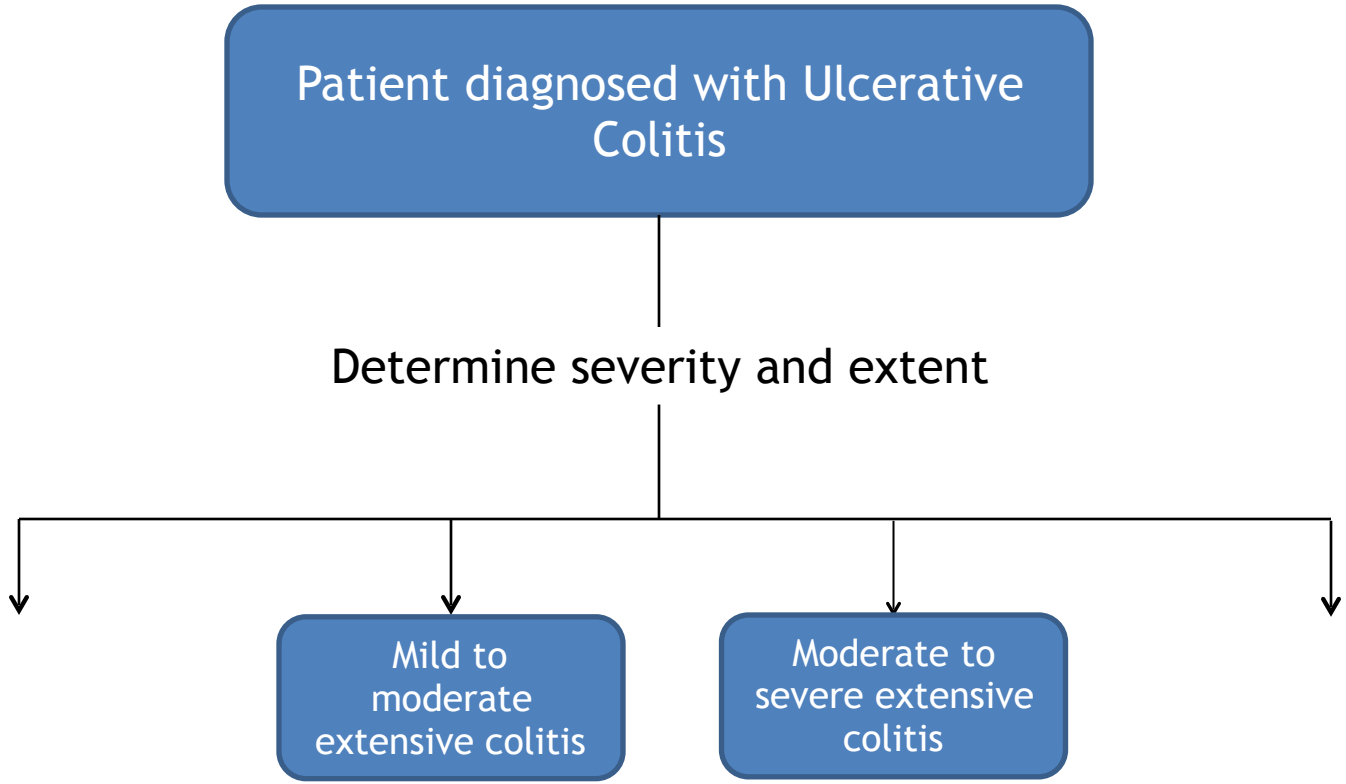
($p<0.05$)

Mild to Moderate Distal Colitis



5-ASA: 5-aminosalicylic acid

Treatment Algorithm for Ulcerative Colitis



Extensive UC of mild-to-moderate severity

- Systematic review and meta analysis that investigated the effect of high or standard dose 5ASA (≥ 2 g) vs low dose 5ASA (< 2 g) on induction of remission demonstrated
  - that **doses of ≥ 2 g/d were more effective than doses of < 2 g/d for inducing remission** with a RR of failure to achieve remission of 0.91 (95%CI: 0.850.98).
    - Ford AC, Am J Gastroenterol 2011; 106: 601-616]
  - This finding was based on data showing that
    - 380 (58.7%) of 647 patients receiving high or standard dose 5ASA failed to achieve remission
    - compared with 257 (69.8%) of 368 patients assigned to low dose 5ASA

Hanauer S, Am J Gastroenterol 1993; 88: 1188-1197
Levine DS,. Am J Gastroenterol 2002; 97: 1398-1407
D'Haens G,. Aliment Pharmacol Ther 2006; 24: 1087-1097

Extensive UC of mild-to-moderate severity

- Initially treated with oral sulfasalazine at a dose titrated up to 4-6 g/d (ACG EL A)

  or

- A combination of oral and topical mesalazine (ECCO EL 1a, RG A; DGVS EL A).

- **Oral 5-ASA formulas induce remission in only approximately 20%** of patients.

  Bebb JR, Aliment Pharmacol Ther 2004; 20: 143-149

- Patients who do not respond to this treatment within 10-14 d or who are already taking appropriate maintenance therapy should be treated additionally with a course of oral steroids (ECCO EL 1b, RG C; ACG EL B).

Extensive UC of mild-to-moderate severity

- Standard corticosteroids were superior to placebo for UC remission with a
  - RR of failure to achieve remission of 0.65 (95%CI: 0.450.93).

- This finding was based on analysis of data showing that
  - 122 (54.0%) of 226 patients assigned to standard oral glucocorticoids failed to achieve remission

  compared with
  - 173 (79.0%) of 219 patients allocated to placebo.

Ford AC, Am J Gastroenterol 2011; 106: 590-599
Truelove SC, Gut 1992; 33: 711-714
Rizzello F, Aliment Pharmacol Ther 2002; 16: 1109-1116
Bossa F, Am J Gastroenterol 2008; 103: 2509-2516

Maintenance of remission
Extensive UC of mild-to-moderate severity

- Systematic review and meta analysis of the efficacy of 5ASA vs placebo in preventing relapse in quiescent UC demonstrated that
  - **5ASA is highly effective for preventing relapse** in UC with a RR of relapse of 0.65 (95%CI: 0.550.76).
  - finding was based on data showing that
    - 342 (40.3%) of 849 patients randomized to 5ASA relapsed
    - compared with 409 (62.6%) of 653 patients allocated to placebo.

Misiewicz JJ, Lancet 1965; 285: 185-188
Lichtenstein GR, Aliment Pharmacol Ther 2010; 32: 990-999

- Doses of **≥ 2 g/d may be more effective than doses of < 2 g/d** for preventing relapse with a RR of relapse of 0.79 (95%CI: 0.640.97). finding based on data showing that:
  - 225 (34.7%) of 649 patients receiving high or standard dose 5ASA relapsed, compared with 379 (42.8%) of 885 patients assigned to low dose 5ASA.

Ford AC, Am J Gastroenterol 2011; 106: 601-616

Maintenance of remission
Extensive UC of mild-to-moderate severity

- **Oral mesalazine is the therapy of first choice**. It is effective and well tolerated

  Sutherland L,. Cochrane Database Syst Rev 2006; CD000543

- In the case of:
  - steroid-dependency

    ECCO EL 1a, RG A

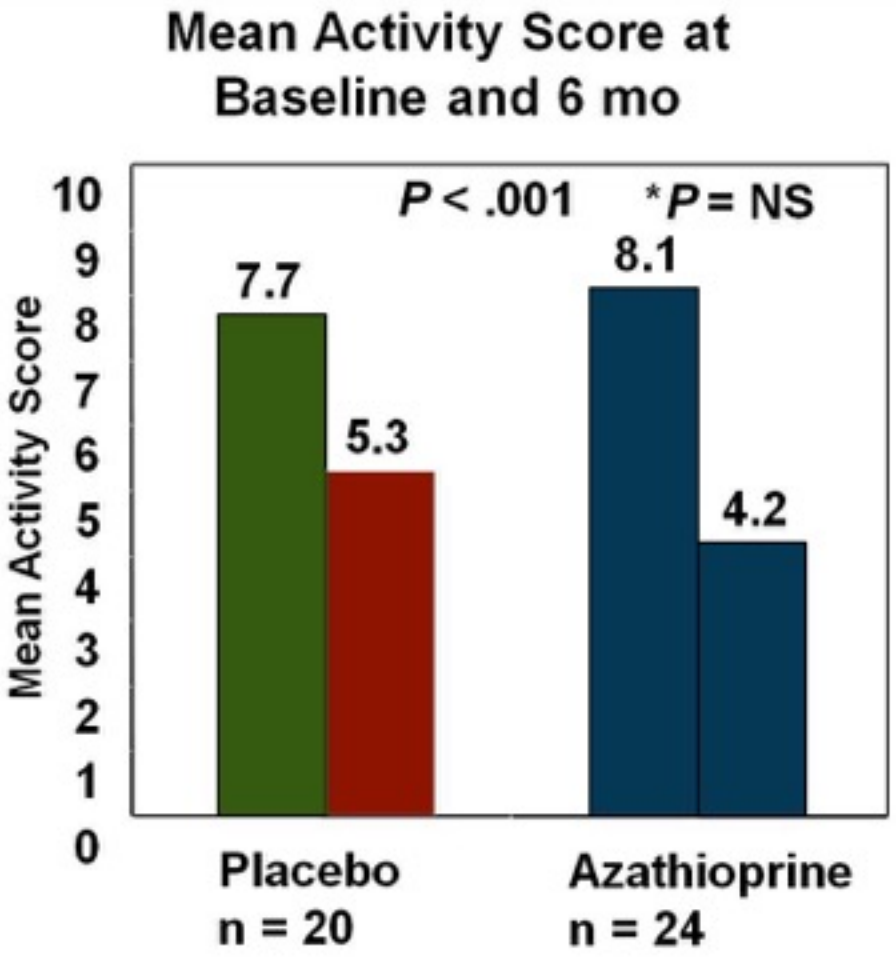
  or

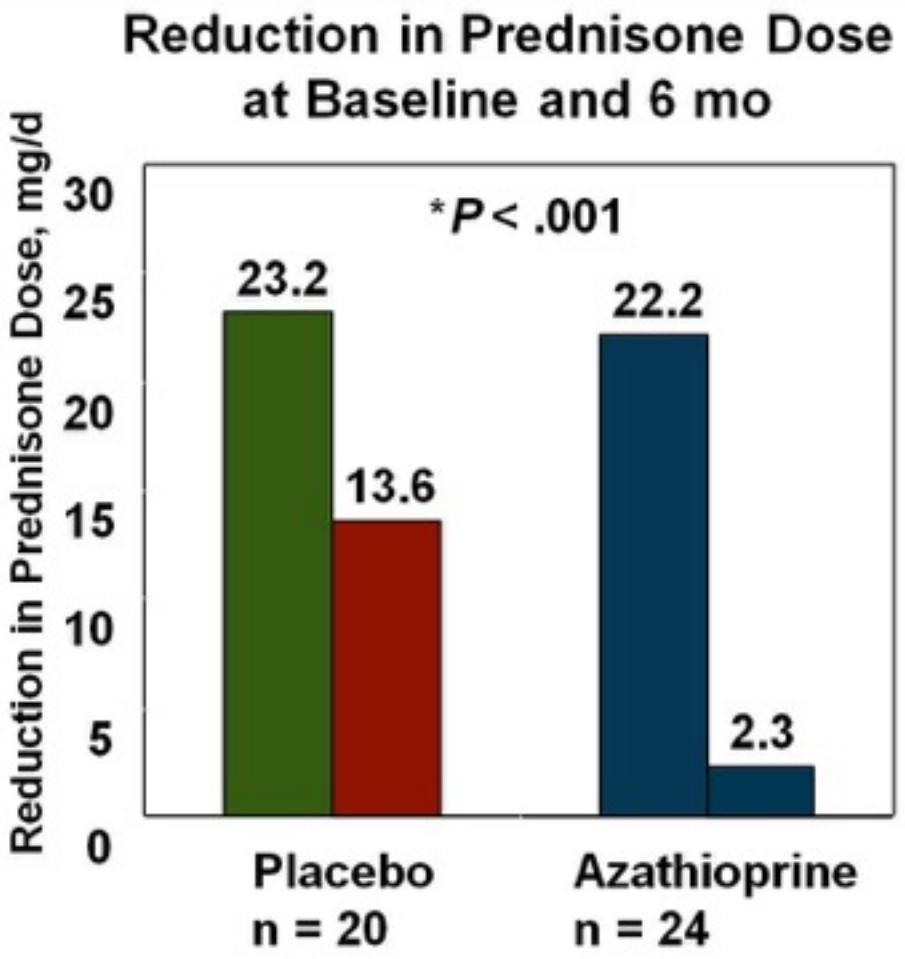
  - Steroid refractory course

    ECCO EL 1a, RG B, ACG A

- **Azathioprine (2.5 mg/kg per day)** or 6-mercaptopurine (1.5 mg/kg per day) should be introduced for induction of remission and remission maintenance.

Azathioprine in the Management of Chronic UC

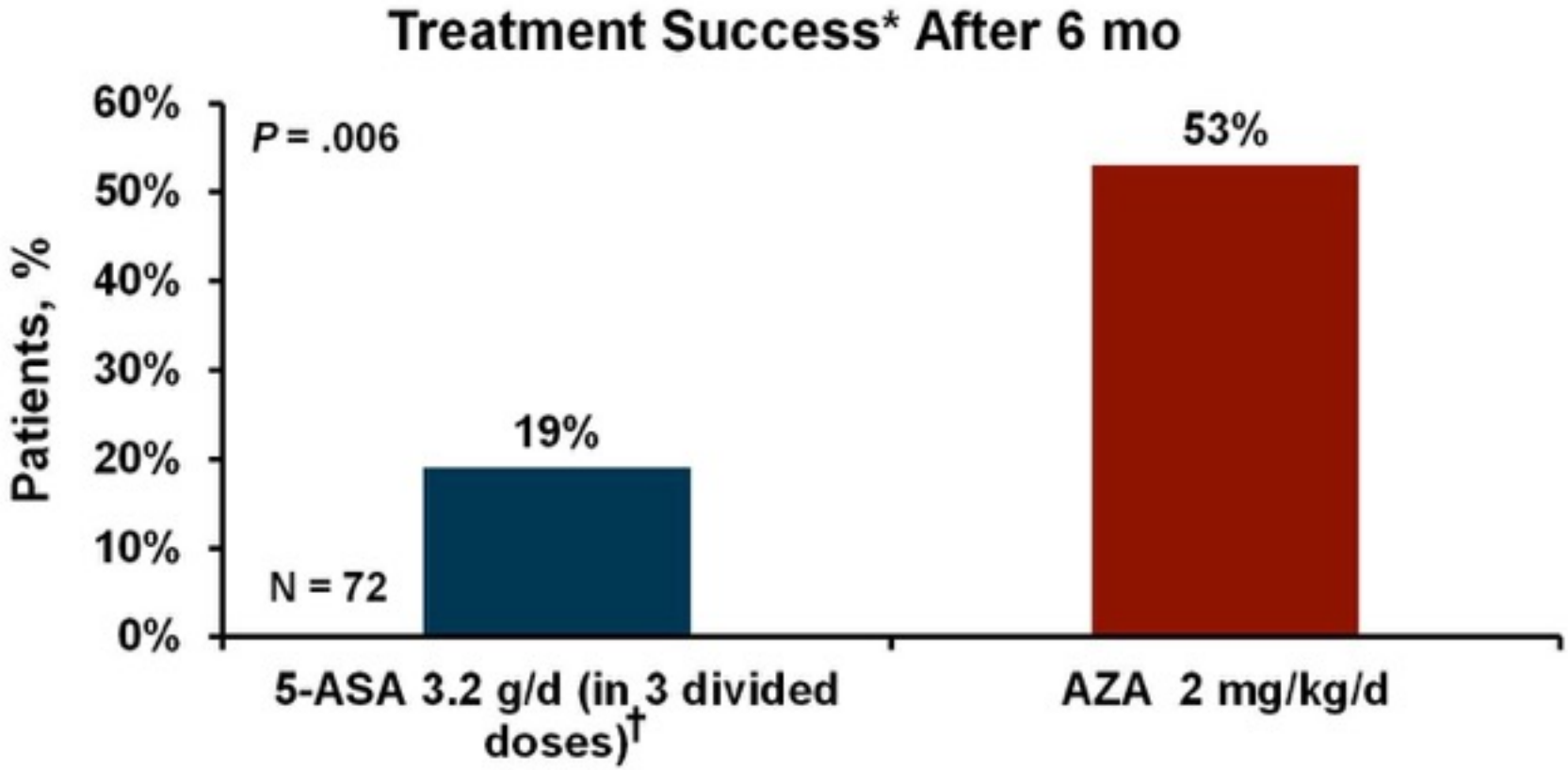




*Comparison between azathioprine and placebo at 6 mo.

Kirk AP, et al. *Br Med J (Clin Res Ed)*. 1982;284:1291-1292.[2]

Azathioprine vs 5-ASA for Corticosteroid-Dependent, Active UC



*Defined as clinical remission (Powell-Tuck Index score of 0) and endoscopic remission (Baron Index score ≤ 1) plus corticosteroid discontinuation. Patients treated with a concurrent tapering dose of corticosteroids. AZA = azathioprine

†Doses were taken as 0.8 g at breakfast and lunch and 1.6 g at dinner.

Ardizzone S, et al. *Gut*. 2006;55:47-53.[6]

Extensive UC of mild-to-moderate severity

- **Azathioprine** have been proven to be **effective in steroid-dependent or steroid-refractory UC** patients.
- **Other indications** of thiopurines for UC patients include:
  - Patients with severe relapses
  - Patients who need ≥2 courses of steroid within a 12 months period
  - Patients with relapses when the dose of steroid is < 15 mg
  - Patients with relapses <3 months of discontinuing steroids

Carter M, Gut 2004;53 (suppl 5):V1-V16.
Lawson MM, Cochrane Database Syst Rev 2006;(3):CD005112.

Extensive UC of mild-to-moderate severity

- Systematic review and meta analysis of the effect of AZA on active UC demonstrated
  - A trend to benefit of AZA over placebo in a total of 130 UC patients allocated to AZA or placebo with no statistical significance (RR = 0.85; 95%CI: 0.711.01; P = 0.07).
  - AZA is of **benefit in preventing** relapse in quiescent UC (RR = 0.60; 95%CI: 0.370.95; P = 0.03). This finding was based on data
    - that 26 (39.3%) of 66 patients receiving AZA experienced a relapse of UC,
    - compared with 40 (65.6%) of 61 patients allocated to placebo, with a statistically significant benefit of AZA
- AZA/6-MP appears to be of little benefit for inducing remission in active UC, but may prevent relapse in quiescent UC.

Khan KJ, Am J Gastroenterol 2011; 106: 630-642
Sood A, Indian J Gastroenterol 2000; 19: 14-16
Sood A, Indian J Gastroenterol 2002; 37: 270-274

Extensive UC of mild-to-moderate severity

- Comparing AZA with placebo or 5-ASA for the:
  - induction of remission in UC patients did not show statistically significant benefit of AZA over placebo
    - OR= 1.59, 95% CI, 0.59-4.29
  - maintenance of remission in UC, demonstrated a benefit of AZA with statistically significant results
    - OR=2.56; 95% CI, 1.51-4.34

Gisbert JP, Aliment Pharmacol Ther 2009;30(2):126-37

- Generally, thiopurines should not be used for induction of remission in active UC patients.

Extensive UC of mild-to-moderate severity

- Systematic review and network meta analysis of the efficacy of biological agents on UC in a total of 2282 mild to moderate UC patients randomized to
  - biological agents (n = 1167) or placebo (n = 1115) demonstrated that
    - all biological agents (ADA, golimumab, IFX, and vedolizumab) were superior to placebo for
      - induction of clinical response,
      - clinical remission,
      - mucosal healing.
    - IFX was shown to be more likely to induce a favorable clinical outcome than ADA for induction of
      - clinical response (OR = 2.36, 95%CI: 1.22-4.63),
      - clinical remission (OR = 2.79, 95%CI: 0.95-8.83),
      - mucosal healing (OR = 2.02, 95%CI: 1.13-3.59).
    - All biological agents also suggested superiority over placebo for maintenance.

Danese S, Ann Intern Med 2014; 160: 704-711

Moderate to Severe Extensive UC

- Systematic review and meta analysis of the efficacy of all anti-TNF-α antibodies on moderately to severely active UC demonstrated that
  - **Anti-TNF-α antibodies are superior to placebo in inducing remission** (RR of failure to achieve remission, 0.72; 95%CI: 0.57- 0.91).
  - This is based on data showing that remission of UC was not achieved
    - in 231 (42.9%) of 539 patients that were randomized to receive IFX for 6 to 12 wk, compared with
    - 201 (69.8%) of 288 patients allocated to placebo.

Probert CS, Gut 2003; 52: 998-1002
Gastroenterology 2005; 128: 1805-1811
Ford AC, Am J Gastroenterol 2011; 106: 644-659
Rutgeerts P, N Engl J Med 2005; 353: 2462-2476

- Anti-TNF-α antibodies are **effective in maintaining improvement and remission** and is therefore recommended for those patients who initially respond to the Anti-TNF-α antibodies induction regime

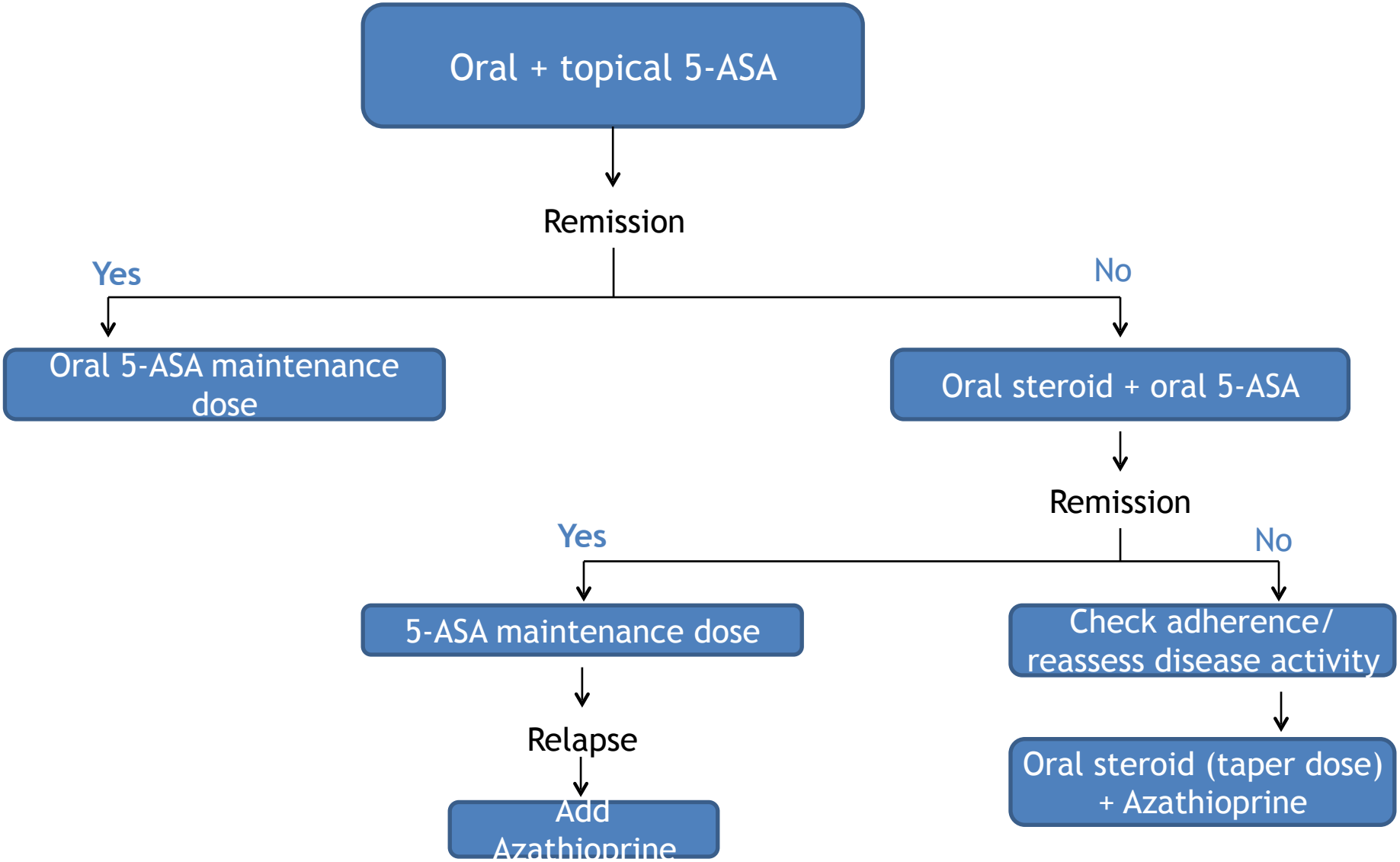
ECCO EL 1b, RG A
Rutgeerts P, N Engl J Med 2005; 353: 2462-2476

Moderate to Severe Extensive UC

- Anti-TNF-α antibodies and cyclosporine are effective for the treatment of patients with moderate or severe corticosteroid dependent/ refractory UC.

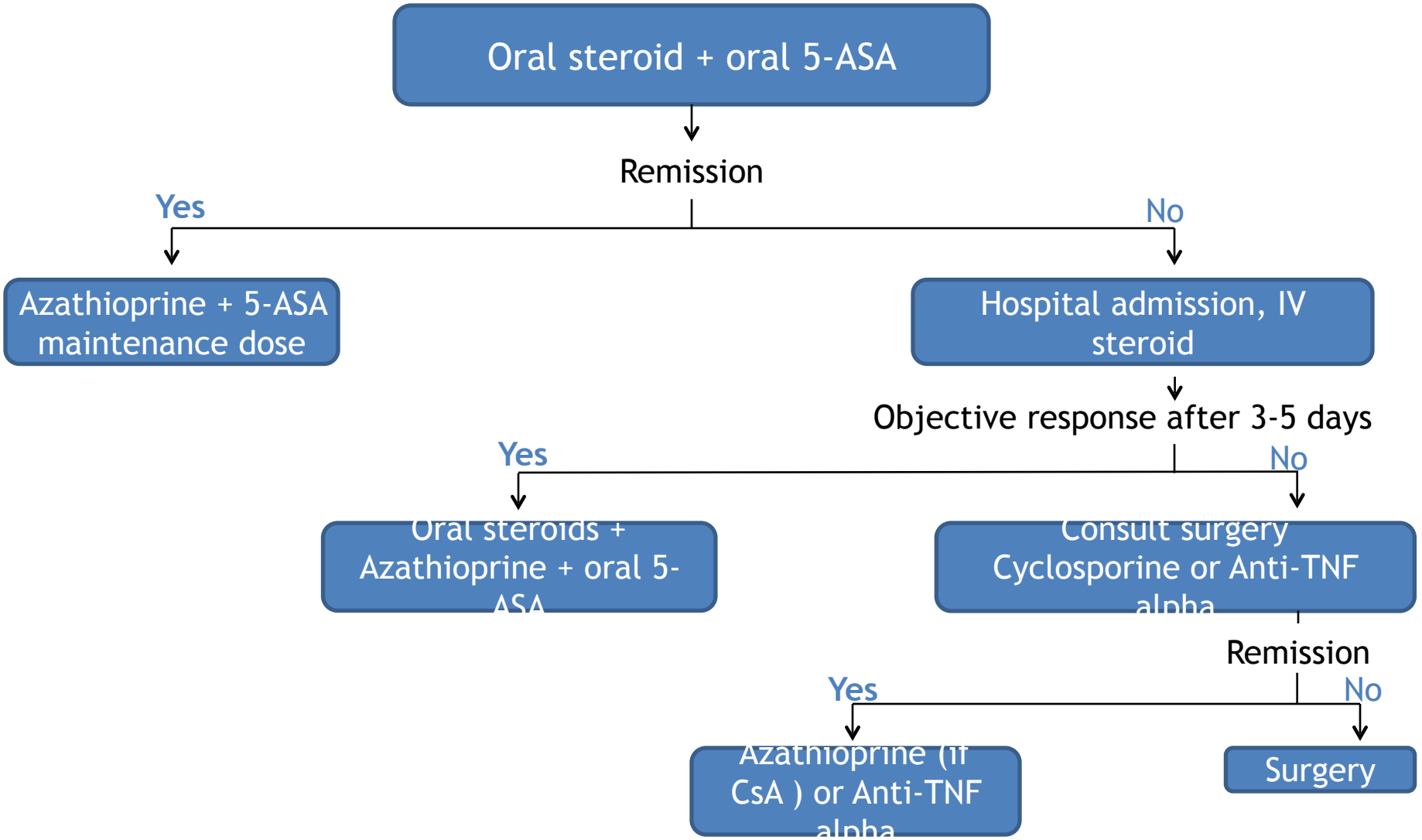
- Whether cyclosporine therapy should precede Anti-TNF-α antibodies as a second line therapy currently remains controversial.

Mild to Moderate Extensive Colitis



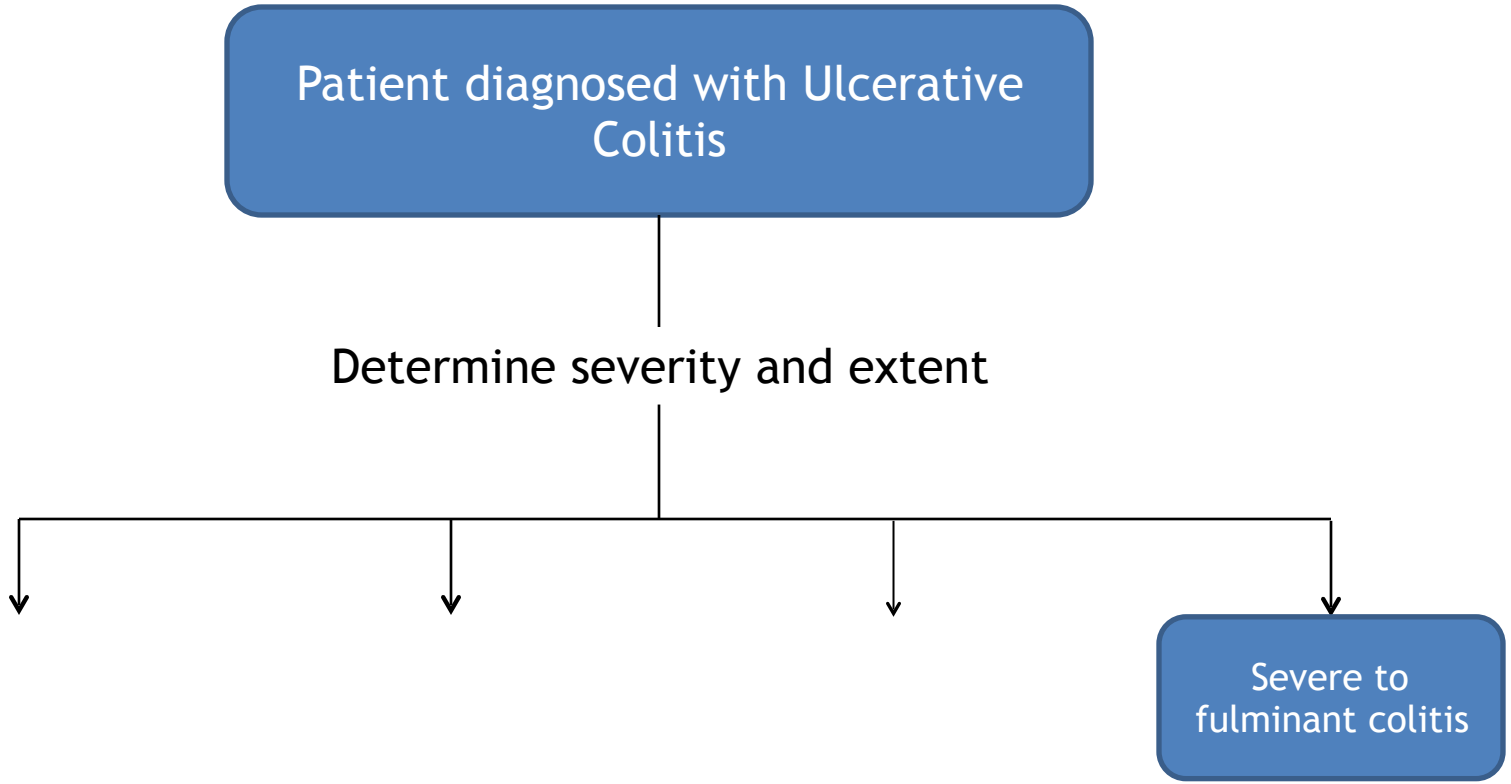
5-ASA: 5-aminosalicylic acid

Moderate to Severe Extensive Colitis



5-ASA: 5-aminosalicylic acid
CsA: Cyclosporine

Treatment Algorithm for Ulcerative Colitis



Severe to Fulminant Ulcerative Colitis

- Patients should be **hospitalized for intensive treatment and surveillance** as the development of a toxic mega colon and perforation is a potentially life-threatening condition.

  ECCO EL 5, RG D

- **Intravenous steroids** (e.g. methylprednisolone 60 mg/d or hydrocortisone 400 mg/d) remain the mainstay of conventional therapy to induce remission

  ECCO EL 1b, RG D; DGVS C

Severe to Fulminant Ulcerative Colitis

- Colectomy rates are as high as 29% in patients with severe UC and who need intravenous corticosteroids.
- They should therefore be presented to the colorectal surgeon on the day of admission
- In the case of a worsening condition or a lack of amelioration after 3 d of steroid therapy, colectomy should be discussed.
- Extending steroid therapy beyond 7 d without clinical effect carries no benefit, but causes otherwise preventable postoperative wound healing disorders.

Turner D, Walsh CM, Clin Gastroenterol Hepatol 2007; 5: 103-110
Aberra FN, Gastroenterology 2003; 125: 320-327

Severe to Fulminant Ulcerative Colitis

- The response to intravenous steroids is best assessed by:
  - stool frequency
  - CRP
  - abdominal radiography on day 3

  ECCO EL 2b, RG B.

- If drug therapy fails, either
  - proctocolectomy

    DGVS EL C, ACG EL B

  or

  - rescue therapy with TNF-α blocker or CsA is recommended.

    ACG EL A

Severe to Fulminant Ulcerative Colitis

- ECCO and ACG guidelines:
  - IFX may be effective in the prevention of colectomy.
- Patients who required IFX to induce remission should receive regular maintenance therapy with IFX for at least 6 months.

Severe to Fulminant Ulcerative Colitis

- Continuous intravenous CsA monotherapy with 4 mg/kg per day is effective

- Effect of cyclosporine on severely active UC, in which a response was defined as symptomatic improvement demonstrated that
  - **cyclosporine was of benefit over placebo in improving symptoms** (RR no improvement with cyclosporine, 0.22; 95%CI: 0.07- 0.67).
  - This finding was based on data showing that
    - 2 (18%) of 11 patients receiving cyclosporine had no response

    as compared with
    - 9 of 9 patients allocated to placebo.

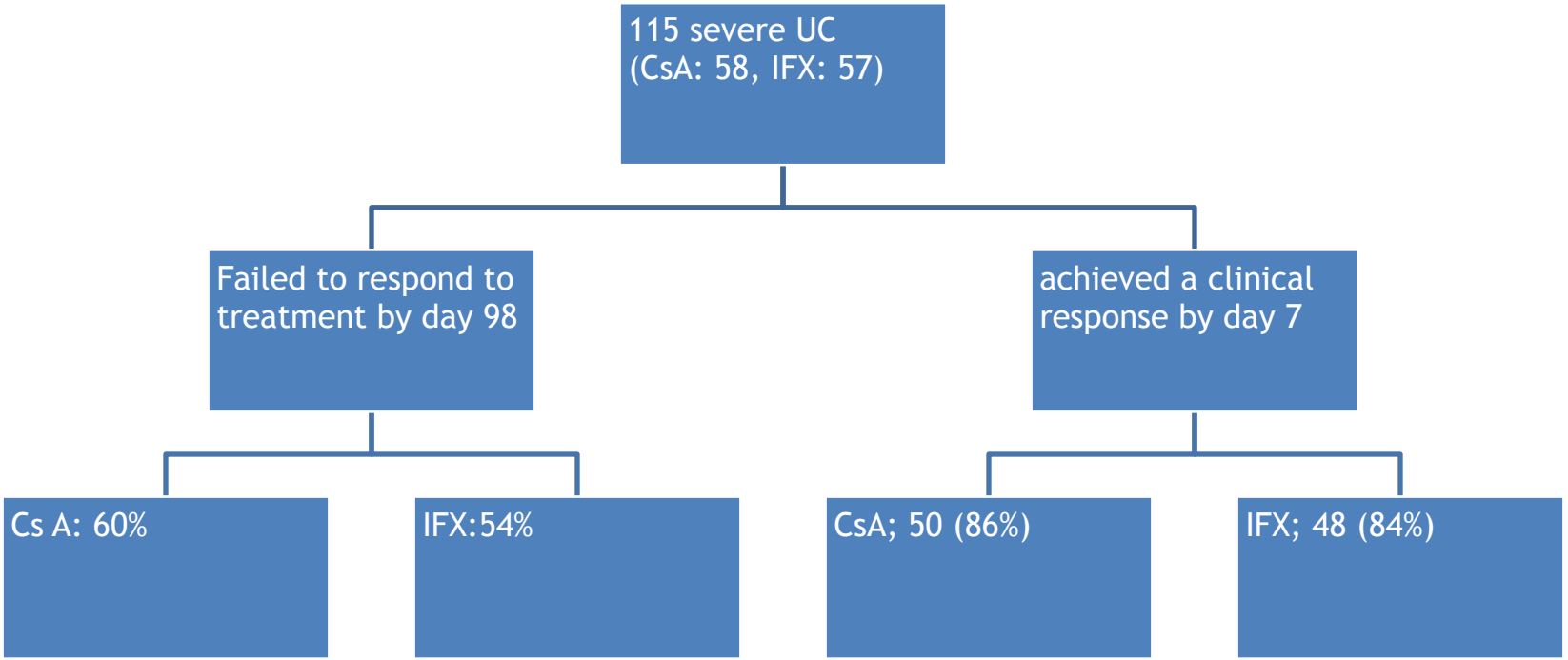
Khan KJ, Am J Gastroenterol 2011; 106: 630-642
Lichtiger S, N Engl J Med 1994; 330: 1841-1845

- After successful induction of remission, azathioprine (2.5 mg/kg per d) should soon be added, CsA switched to oral therapy with tacrolimus and tapered over a period of 3-6 months

DGVS C.

Severe to Fulminant Ulcerative Colitis

Open label randomized controlled trial compared the efficacy of cyclosporin and IFX on acute severe UC that was refractory to intravenous corticosteroid



OR = 1.3; 95%CI: 0.62.7; P = 0.52

OR = 1.2; 95%CI: 0.43.3; P = 0.76

Laharie D, Lancet 2012; 380: 1909-1915

Severe to Fulminant Ulcerative Colitis

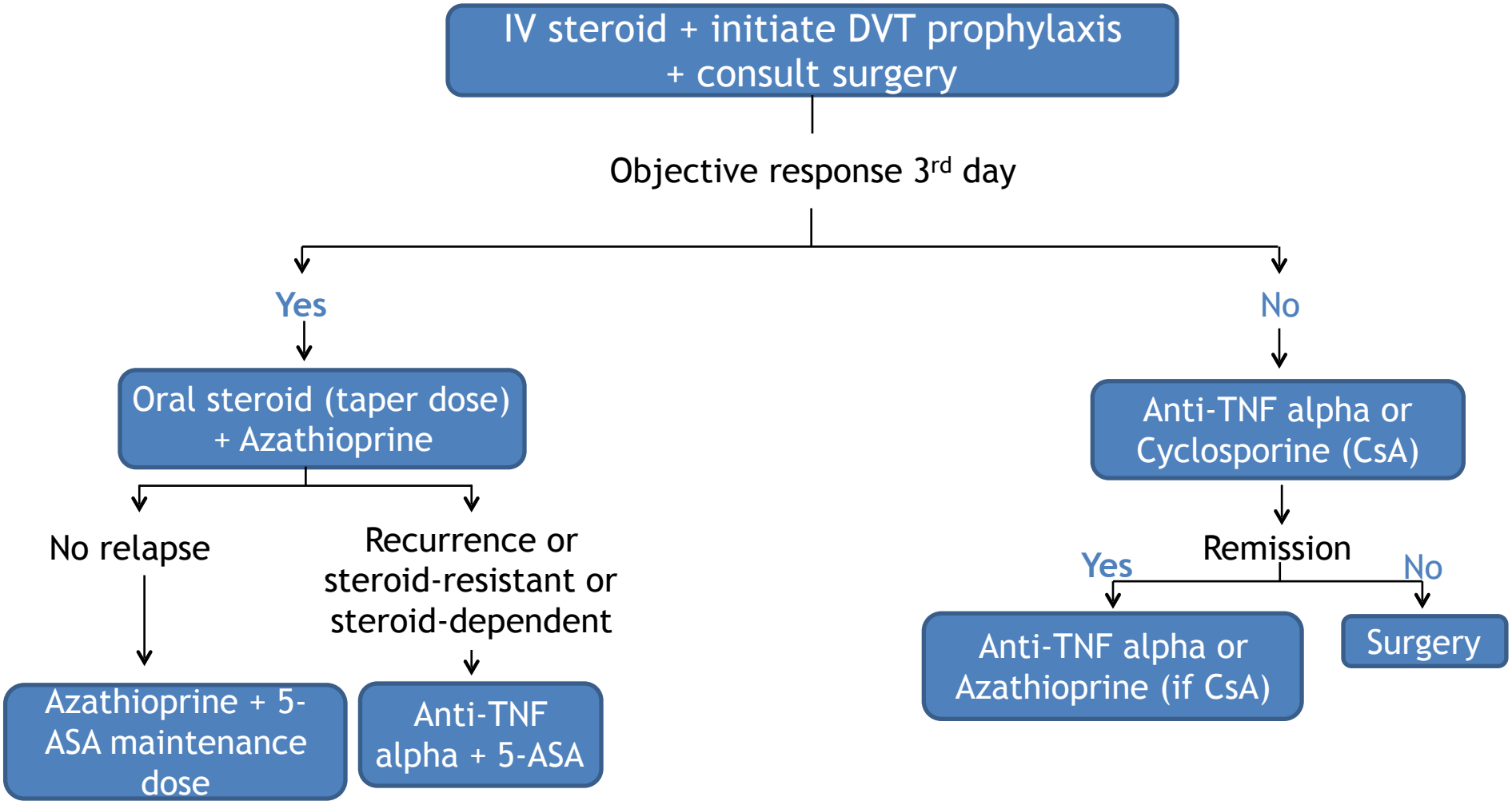
- 13 patients receiving IFX for severe or moderate UC who showed refractoriness or loss of response to cyclosporine, or no tolerance
  - the mean partial Mayo score of UC activity was significantly decreased ($P < 0.05$) to
    - 5.69 at baseline
    - 3.07, at 8 wk
    - 2.77, at 30 wk
  - Clinical remission:
    - 46.2% at 8 wk
    - 30.8% at 30 wk
  - rates of clinical remission at 8 and 30 wk of IFX therapy were
    - 60.0% and 40.0%, respectively in cyclosporine responders
    - 37.5% and 25.0%, respectively, were also obtained in cyclosporine no responders

Tsukamoto H, Eur J Gastroenterol Hepatol 2013; 25: 714-718

Severe to Fulminant Ulcerative Colitis

- IFX salvage therapy following cyclosporine tended to be more efficacious in cyclosporine responders (loss of response or no tolerance) than in nonresponders (refractoriness), and that sequential therapy may prove useful and well tolerated

Severe to Fulminant Ulcerative Colitis



5-ASA: 5-aminosalicylic acid
CsA: Cyclosporine
DVT: Deep Venous Thrombosis