Conventional therapies in the management of IBD

Dr Abdullahi Hadi Omar

Department of Gastroenterology

Steve Biko Academic Hospital

University of Pretoria

Facilitator: Prof Gill Watermeyer

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Conventional therapies

5-aminosalicylates (5-ASAs)

Thiopurines

Corticosteroids

Methotrexate

Conventional therapies in UC

Selection of therapies should be based on:

I. Disease extent

II. Severity

III. Prognosis

The Montreal classification of UC

Extent	Anatomy	Definition
E1	Proctitis	Distal to the rectosigmoid junction
E2	Left sided	Distal to the splenic flexture
E3	Extensive	Proximal to the splenic flexture

Gut. 2006 Jun;55(6):749-53. doi: 10.1136/gut.2005.082909.

The Montreal classification of UC

Severity		Definition
S1	Mild	<4 stools per day, no systemic toxicity, normal inflammatory markers
S2	Moderate	4-6 stools per day, minimal systemic toxicity
S3	Severe	>6 stools per day, PR>90, T>37.5 C, Hb<10.5g/100ml, ESR>30mm/h

Paris Classification of UC

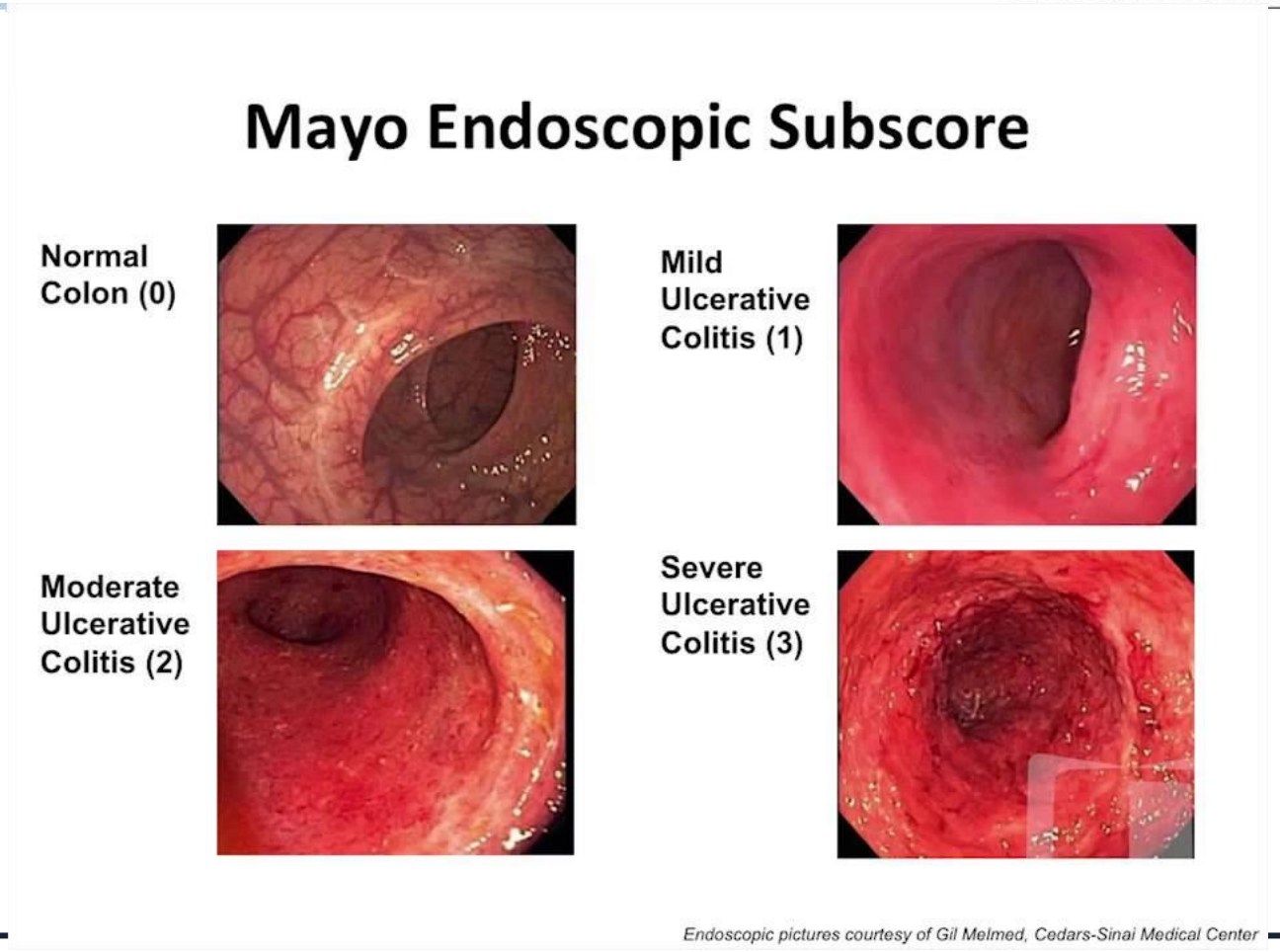
Extent	Definition
E1	Ulcerative Proctitis
E2	Left sided UC (Distal to splenic flexture)
E3	Extensive (hepatic flexture distally)
E4	Pancolitis (Proximal to hepatic flexture)

Severity	
S0	Never severe *
S1	Ever severe *

*Severe defined by pediatric UC activity index (PUCAI) >65.

Endoscopic assesment of severity

	Mayo
Mild	1
Moderate	2-3
Severe	3



5-aminosalicylates

5 ASA Drug	Molecular structure and location of action	Dose
Mesalamine suppositories	Treats the distal 5-8 cm of the rectum	1 gm daily
Mesalamine enemas	Reaches the splenic flexture	60 ml(4gm) at bed time, or BID
Oral medications		
Mesalamine (Asacol)	pH dependent release at pH>7 in the distal ileum and colon	2.4 – 4.8 gm/day TDS
Mesalamine (Pentasa)	Diffusion dependent release starting from the deudenum and the rest of small bowel and colon	1 gm QID
Sulfasalazine	Bacterial dependent release, 5- ASA ring attached to sulfapyridine with an azo bond	2-4 gm daily divided QID
Olsalazine	Two 5-ASA rings attached together with an azo bond	500mg BID

5-ASA

Anti- inflammatory agents

How 5-ASAs are used depends on disease extent and severity

Topical effect on gut mucosa

Ulcerative proctitis

1- To induce remission

- Rectal 5-ASA at a dose of 1 gm daily
- suppositories preferable to enemas which bypass rectum

2- To maintain remission

- Rectal 5-ASA suppositories at a dose of 1 gm/day
- Can decrease dose to 3 times a week overtime

Left sided or Extensive disease

1. To induce remission

- Rectal 5-ASAs
- Combined with oral 5- ASAs

2 gm per day for mild disease

4 gm for more severe UC

Ideally as a single dose or twice daily

-5-ASA enemas or foams are options

-Foams reach to 15-20 cm

-Enamas reach the splenic flexture

- expensive and not widely available

Left sided or Extensive disease

1. To maintain remission

-Continue oral 5-ASA therapy at the dose that proved effective

-2 to 4 gm daily

-patients on<2gm daily are more likely to relapse

-The type of 5-ASA does not influence efficacy

-Usually continued indefinitely

-discontinuation can be considered in patients who are in deep remission > 2 years

Monitoring patients on 5-ASA

Generally are safe and well tolerated.

8 % get paradoxical diarrhea

Salfasalazine:

-Sulpha side effects

-reversible oligospermia

-blood dyscrasias

-folate deficiency

-FBC and LFTs at regular intervlas

-All 5-ASAs carry the risk of renal dysfuction. UECs at 3 months then annually

Corticosteroids

-corticosteroids are given to induce remission

-patients admitted with acute severe ulcerative colitis

-they are not given to maintain remission

Corticosteroids

-Budesonide foam is FDA approved for induction of remission in mild to moderate UC up to 40 cm from the anal verge. It is effective in inducing remission and is easier to administer and retain in the rectum compared to liquid enemas.

-Dose: 2 mg (one metered dose) twice daily for 2 weeks, followed by 2 mg once daily for 4 weeks.

-Corticosteroids are given to induce remission in patients who do not respond to topical and oral 5-ASAs, and in patients admitted with acute severe ulcerative colitis. They are not given to maintain remission. Budesonide is a synthetic corticosteroid that can be given orally to induce remission in patients with mild to moderate ulcerative colitis. It has minimal systemic bioavailability and enhanced topical potency. It is available in several formulation to control the location of its release in the GI tract.

-The multimatrix (MMX) formulation consists of coated tablets to control the release of budesonide at pH ≥7 homogenously throughout the colon.

Dose: 9 mg daily x 8 weeks

In patients with more severe colitis, treatment with conventional steroids (prednisone) is indicated.

Corticosteroids

1. Oral prednisone is given to patients with mild to moderate disease not requiring hospitalization.
-Dose is 40-60 mg PO for 2-4 weeks. Start dose taper once the patient is in stable remission.

Total treatment duration is usually 6-8 weeks.
-Continue 5-ASAs for maintenance therapy.
-Consider thiopurines and/or anti-TNF.

2. IV methylprednisolone is given to patients admitted with acute severe UC.

-Dose is 40-60 mg IV once daily or divided every 12 hours.

Side effects of corticosteroids: acne, hirsutism, hyperglycemia, hypertension, ecchymosis, skin striae, infections, osteoporosis, osteonecrosis, cataracts, glaucoma, myopathy.

Thiopurines in UC

Azathioprine and 6-mercaptopurine

Disrupt DNA replication of rapidly dividing cells

Such as activated T cell lymphocytes

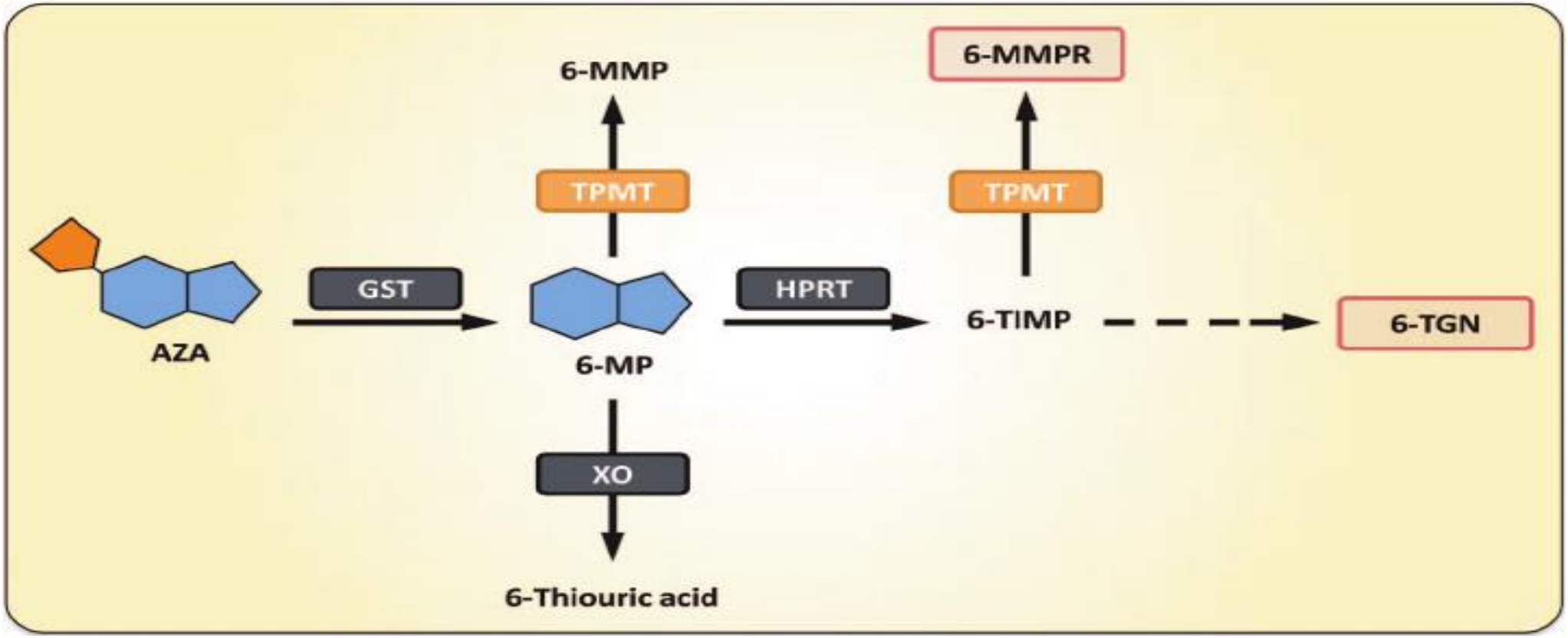
Aslo induce apoptosis

Take 8-12 weeks to work

Not effective in inducing remission

Maintaining remission

Thiopurine metabolism



Complications of thiopurines

Commonest: Nausea and vomiting, and flu-like symptoms

May resolve with switching from azathioprine to 6-MP

Pancreatitis:

Usually within 1 month of initiation

Usually mild and dose dependent

Stop therapy and do not re-challenge

Abdominal pain in newly initiated patient: Check lipase

Thiopurine Induced Hepatotoxicity

Most commonly increased transaminase levels

Resolve with dose reduction or drug discontinuation

Correlates with high 6-MMP levels

Usually within 8 weeks (85% of patients)

Idiosyncreatic chlestasis- less commonly

Nodular regenerative hyperplasia leading to PH

Alopecia (dose-related adverse event)

Thiopurine Induced myelotoxicity

The most serious thiopurine induced side effect

IR 3% per patient year of treatment

East asian populations, it can be as high as 15%

Can occur anytime during treatment

Can lead to life threatening bone marrow suppression

Leucopenia is the commonest abnormality

Thrombocytopenia, and panctopenia can rarely occur

Much more common with certain genetic mutations

TPMT deficiency

1 in 300 are homozygotes, 1 in 10 are heterozygotes

Loss of function TPMT mutations

Low TPMT increases 6-TG levels

High risk of neutropenia—check TPMT(genotype or activity) before treatment

Homozygotes or very low activity: avoid

Heterozygotes or intermediate activity: half doses

NUDT15 mutation

NUDT15 encodes nudix hydrolase 15

Converts cytotoxic TG to non-toxic TG metabolites

Cause low NUDT15 activity and high levels of TG

Genotyping recommended

Homozygotes: Avoid, Heterozygotes: half dose

TPMT and NUDT15 variants in combination

Even higher risk of early myelosuppression

Thiopurine metabolism

To avoid or overcome complications or inefficacy

Metabolite testing is best prctice

Measurement of TGs and MeMP in RBCs

Useful after steady state is reached

4-6 weeks

Aim to achieve therapeutic range of 235-450 TGN

Hypermethylators

High levels of TPMT activity

MP preferentially metabolised to MeMP

Shunt away from 6-TG pathway (lower levels of 6-TG)

Reduced efficacy

Increased side effects

Low dose allopurinol blocks xanthine oxidase

Increased shunting into 6-TG pathway

Weight based dosing

We use weight based dosing

Azathioprine 2-2.5 mg/kg

6-mercaptppurine 1-1.5 mg/kg

Not ideal because metabolism of thiopurines is not uniform

Clues:

Lymphopenia (not less than 0.5)

Raised MCV (a rise of 7 above baseline)

Monitoring of thiopurines

White cell count at baseline

Then at 2 4 8 and 12 weeks

Then 3 monthly

LFTs

Initially monthly then 3 monthly when stable

Continue monitoring for the entire duration of therapy

Thiopurines and malignancies

Greatest risk

An increase in incident cancer rates

Especially in older IBD patients

Mostly urinary tract cancers, lymphomas and NMSC

Lymphoma and thiopurines

Typically post transplant EBV B cell lymphoma

The risk becomes significant after 1 year of exposure
Men younger than 30 have the highest RR

Absolute risk is highest in patients >50 years (1:300)

Also at increased risk of hepatosplenic T-cell lymphoma

A rare cancer linked to thiopurine use

Either in monotherapy or in combination with anti TNFs

Typically in young males

Nearly universally fatal

Methotrexate in UC

Doesnot work

Recommenended against use

For remession or maintannce

ACG guidelines. Am J Gastroenterol 2019;114:384--413

Conventional therapies in CD

Choice of therapy depends on location, severity and prognosis

Age at Dx (A)

A1 <16 yrs

A2 17-40 yrs

A3 > 40 yrs

Behaviour (B)

B1 non stricturing/penetrating

B2 stricturing

B3 penetrating

Location (L)

L1 TI

L2 Colon

L3 Ileocolon

L4 Upper GI

***P**

Perianal dz

Montreal classification. *Gut. 2006 Jun;55(6):749-53.*

5-ASA

Oral 5-ASAs

Generally ineffective in small bowel CD

No longer used

Modest efficacy in colonic CD

Especially salazopyrin

Proctitis: Rectal 5-ASAs may be used

Corticosteroids in CD

Use is similar in UC

Short courses to control symptoms

Should never be used as maintenance therapy

In contrast to UC

Ileal release budesonide is effective in right sided CD

1st line steroid of choice for mild disease ileocecal CD

More severe disease requires conventional steroids

Thiopurines in CD

Predictors of poor outcome:

Young age
Need for steroids

Extensive disease

Previous surgery

Perianal disease

Strictures or fistulas

Smoking

Identify high risk patients

Who will likely develop severe disease overtime

Good candidates for thiopurines or

Methotrexate at diagnosis

The approach to thiopurine is same in UC

Methotrexate

MTX is effective in CD

For inducation of remission

25mg IM or SC weekly with folic acid

For maintainance of remission

15mg weekly IM or SC with folic acid

Watch for ILD and liver dysfunction

Regular monitoring of LFTs

Conclusion

Conventional therapies remain the mainstay of treatment

Need to be explored fully before persuing biologics

5-ASA are excellent in UC

Poor efficacy in CD

Corticosteroids should only be used as a short courses

Thiopurines are effective in both conditions

Methotrexate is only used in CD