NYU Langone Health

Use of Medications for the Treatment of Mild to Moderate IBD

Mild to Moderate IBD: Features

Crohn's Disease

- Ambulatory
- Tolerates PO
- No systemic symptoms
- Age > 30 years
- Limited ileal disease
- Superficial ulcers
- No perianal disease
- No penetrating disease
- No prior surgeries

Ulcerative Colitis

- Ambulatory
- Tolerates PO
- No systemic symptoms
- Age > 40 years
- < 4-5 bowel movements / day
- Limited left-sided disease
- Mild endoscopic findings
- No hospitalizations
- No prior *C diff* or CMV infection

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Sandborn WJ. *Gastroenterology* 2014;147(3):702-705.
Dassopoulos T et al. *Gastroenterology* 2015;149(1):238-245.

5-Aminosalicylates

5-Aminosalicylates (5-ASAs)

- Modulate inflammatory cytokine production, decrease transcriptional activity of nuclear factor-kappa ß (NF-κ ß), inhibit production of prostaglandin and leukotrienes
  - **Work without affecting systemic immune system
- Topical contact with inflamed mucosa required; oral and rectal formulations available
- First line for induction and maintenance of mild to moderate ulcerative colitis
- Debated use in Crohn's disease
  - Cochrane analysis noted sulfasalazine is superior to placebo for inducing remission in Crohn's colitis (45% vs 29%; RR 1.38, 95% CI 1.00 to 1.89) at 17-18 weeks

Egan LJ et al. *J Biol Chem* 1999;274(37):26448-26453.
Wang YJ et al. *Cochrane Review DB* 2016.
Hanauer S et al. *Cochrane Review* 2016.

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Rectally Introduced 5-ASAs

- Ideal for treating disease within 50cm from the anus or distal to the splenic flexure
- Superior to topical steroids
- 2010 Cochrane review confirmed that topical 5-ASA therapy achieves induction of remission in 67% of patients with mild to moderate disease
- Doses of at least 1g/day are warranted
- Compliance and acceptance of this strategy are integral to its success

Marshall JK et al. *Gut* 1997; 40(6): 775-781.
Marshall KJ et al. *Cochrane Database Syst Rev* 2010;11.
Marshal JK et al. *Cochrane Database Syst Rev* 2012;11.
Rubin DT et al. *Am J Gastro* 2019;114(3):384-413.

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Rectally applied 5-ASA Formulations

- First-line agents for proctitis and left-sided colitis (ulcerative colitis)
- Ideal for management of tenesmus, urgency, rectal pain, incontinence, bleeding, and paradoxical constipation

10-15cm	40-50cm	40-50cm
Suppository (mesalamine)	Foam (mesalamine*)	Enema (mesalamine)

**Foam formulation is not available in the USA*.

Oral ASAs

- Systematic review and meta-analysis show efficacy for inducing remission and preventing relapse
- Doses of ≥ 2.0g/day have greater efficacy than lower doses
- Moderate disease had improvements in clinical symptoms and rates of remission with 4.8g vs 2.4g
- All formulations show similar systemic absorption, pharmacokinetics, excretion
- Once daily dosing is comparable to divided dosing
- Decision-making based on clinical response, toxicity, compliance, and cost

Feagan BG et al. *Inflamm Bowel Dis* 2013;19(9):2031-2040.
Ford AC et al. *Am J Gastroenterol* 2011;106(4):601-616.
Hanauer SB et al. *Am J Gastroenterol* 2005;100(11):2478-2485.
Ford AC et al. *Am J Gastroenterol* 2011;106(12):2070-2077.

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Oral 5-ASA Formulations

Type	Mechanism of Action	Benefits
Diffusion–dependent (**mesalamine**, controlled release)	Time-released, coated in ethylcellulose, and releases starting in upper small bowel	Less impacted by rapid transit than other formulations; can be used when stricture is present; pouchitis
pH-dependent (**mesalamine**,delayed release formulations, multi-matrix system [MMX] mesalamine)	Coated with acrylate resin and released at pH 6.0-7.0 (distal ileum or proximal colon)	Dosage can be maximized with less toxicity than sulfasalazine
Colonic flora-dependent; azo-bonded (**sulfasalazine, balsalazide, olsalazine**)	3 different types of azo-bonded 5-ASAs, which are cleaved by colonic bacteria when the drug reaches the colon	Lower pill burden; best for pancolitis or distal colitis, generic so cheaper

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5-ASAs: Combined Oral & Topical Approach

- Meta-analysis by Ford et al evaluated oral vs topical vs combined 5-ASA therapy
  - Combined 5-ASA therapy was superior to oral 5-ASA alone for induction of remission of mildly to moderately active extensive ulcerative colitis
  - Trend toward superiority of topical over oral approach in distal ulcerative colitis
- No data on optimal dosing with this approach
- Patients who continue on the same dose from time of initiation maintain remission more frequently than those that dose de-escalate

Ford AC et al. *Am J Gastroenterol* 2012;107(2):167-176.
Sandborn WJ et al. *Am J Gastroenterol* 2005;100:S312.

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5-ASAs: Side Effects

- Common: headache, hair loss
- Hypersensitivities
- Sulfa moiety in sulfasalazine is responsible for:
  - Hemolytic anemia
  - Reversible hypospermia, decreased sperm motility
  - Allergic phenomena
  - Nausea
- Monitoring
  - Periodic BUN and creatinine, given rare idiosyncratic cases of interstitial nephritis

Corticosteroids

Corticosteroids

- Prevent migration of inflammatory mediators to the GI tract
- Interfere with production of nuclear factor-kappa ß (NF-κ ß), interleukins 1 & 6 and TNF
- Used to induce remission in both ulcerative colitis and Crohn's disease
- Parenteral, oral, and rectal formulations
- Budesonide exhibits 90% first-pass metabolism, formulated to treat local activity
- No role for long term maintenance therapy, given side effect profile

Goulding NJ et al. *Curr Opin Pharmacol* 2004;4(6):629-636.
Ford AC et al. *Am J Gastroenterol* 2011;106(4):590-599.
Vavricka SR et al. *Drugs* 2014;74(3):319-324.

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Corticosteroids: Oral Use

- Optimum dose unclear; common use prednisone 40mg (0.5-0.75mg/kg/day) for acute symptoms
- Doses of 60mg have moderately more efficacy but at the expense of side effects
- Budesonide MMX induced clinical and endoscopic remission in 17.7% of mild to moderate ulcerative colitis patients vs 6.2% receiving placebo by 8 weeks
- Budesonide (enteric coated) 9mg daily is superior to placebo in induction of symptomatic remission in mild to moderate Crohn's disease
- Standard steroids are more efficacious than budesonide preparations

Summers RW et al. *Gastroenterology* 1979;77 (4, pt 2):847-869.
Baron JH et al. *Br Med J* 1962;2(5302):441-443.
Ford AC et al. *Am J Gastroenterol* 2011;106(4):590-599.
Sandborn WJ et al. *Aliment Pharmacol Ther* 2015;41(5):409-418.

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Corticosteroids: De-escalation

- Have an Exit Strategy! Tapering needs to be considered as soon as steroids are initiated to avoid adverse outcomes
- Appropriate maintenance therapy should be in place
- Once clinical response achieved, doses are tapered by 5–10mg/week until 20mg
- Once at 20mg daily, the taper should be slowed to reduction of 2.5–5mg/week

Vavricka SR et al. *Drugs* 2014;74(3):319-324.

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Corticosteroids: Rectal Use

- Topical steroids are first line for those intolerant to 5-ASA topical preparations
- Best to treat symptoms of tenesmus, urgency, rectal pain, incontinence, and bleeding
- Maybe adjunctive to topical 5-ASA therapy
- Foam and liquid enema preparations
- Meta-analysis of budesonide foam noted that is was superior to placebo for induction of clinical remission in mild to moderate ulcerative colitis

Seibold F et al. *J Crohns Colitis* 2014;8(1):56-63.
Mulder CJ et al. *Eur J Gastroenterol Hepatol* 1996;8(6):549-553.
Zeng J et al. *J Gastroenterol Hepatol* 2017;32(3):558-566.

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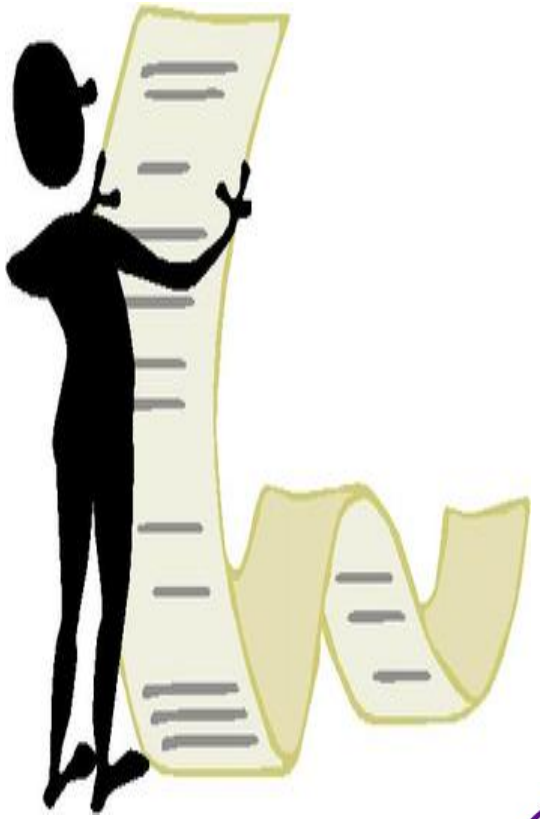
Corticosteroids: Side Effects

- Hypertension
- Glucose intolerance
- Dermatologic consequences (striae, acne)
- Infections
- Adrenal suppression
- Weight gain
- Glaucoma
- Bone loss
- Avascular necrosis
- Psychiatric symptoms



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Antibiotics

Antibiotics

- Use investigated due to theory that immune response to flora drives inflammation in Crohn's disease
- Strategies evaluated include:
  - **Ciprofloxacin**
    - Similar efficacy to mesalamine
    - No more effective than placebo for induction of remission
  - **Metronidazole**
    - No more effective than placebo
  - **Antimycobacterial agents**
    - No more effective than placebo

Lichtenstein GR et al. *Am J Gastro* 2018;113(4):481-517.

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Immunomodulators

Immunomodulators

- The “original” drugs for steroid-dependent or steroid-refractory patients
- These include:
  - **Thiopurines**: azathioprine (AZA) and 6-mercaptopurine (6-MP)
    - Purine antagonists
    - Cause DNA damage, cell-cycle arrest, cytotoxicity, and apoptosis
  - **Methotrexate**
    - Converted to methotrexate-polyglutamate, which blocks de novo purine synthesis and dihydrofolate reductase, resulting in reduced inflammation and increased apoptosis

Neurath MF et al. *Clin Gastroenterol Hepatol* 2005;3(10):1007-1014.
Goldman ID et al. *Pharmacol Ther* 1985;28(1):77-102.
Grim J et al. *Clin Pharmacokinet* 2003;42(2):139-151.

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Immunomodulators

- Lack of robust data
- Have been used for nearly 40 years for IBD
- Used for maintenance of remission; no role for induction, given delayed onset of activity (~8-12 weeks)
- Thiopurines are used in Crohn’s disease and ulcerative colitis
- AZA use more common as 6-MP does not have IBD-approved indication worldwide
- Small studies support the use of methotrexate in Crohn’s disease
- Based on existing data, currently no recommendation for methotrexate in ulcerative colitis

Nielsen OH et al. *Expert Rev Gastroenterol Hepatol* 2015;9(2):177-189.

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Immunomodulators

	Azathioprine	6-Mercaptopurine	Methotrexate
Dosage	2.0-2.5mg/kg/day	1.0-1.5mg/kg/day	15-25mg/week + folic acid (5-10mg/week)
Route of Administration	Peroral	Peroral	Intramuscular / subcutaneous injection
Dosing Intervals	Daily or bid	Daily or bid	Once weekly

Nielsen OH et al. *Expert Rev Gastroenterol Hepatol* 2015;9(2):177-189.

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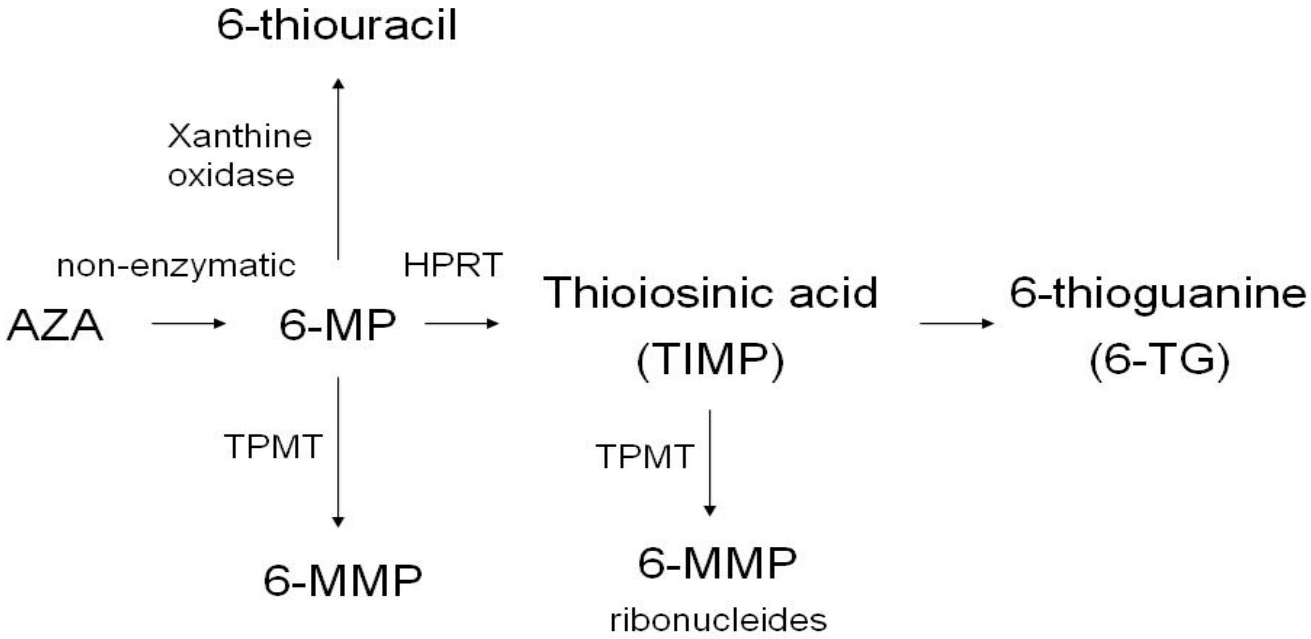
AZA and 6-MP: Metabolism



AZA and 6-MP: Thiopurine S-Methyltransferase Testing (TPMT)

- Some societies recommend checking TMPT prior to starting an immunomodulator
- Risk of myelosuppression with AZA and 6-MP due to elevated levels of 6-TGN
- Genotype and phenotype testing available
  - 89% wild type → normal or high TPMT activity
  - 10% heterozygous for mutations → low TPMT activity
  - 0.3% homozygous for mutations → negligible TPMT activity
- TPMT activity level can vary based on other medication exposure
- Recently discovered *NUDT15 R139C* variation can induced leukopenia in Asians
- Not all mutations are detectable, so CBC and liver enzymes must be followed periodically regardless of TMPT results

Nielsen OH et al. *Expert Rev Gastroenterol Hepatol* 2015;9(2):177-189.
Lennard L et al. *Clin Pharmacol Ther* 1989;46(2):149-154.
Gillisen LP et al. *Aliment Pharmacol Ther* 2005;22(7):605-611.
Zhu X et al. *J Crohn's Colitis* 2016;10:S475..

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AZA and 6-MP: Monitoring

- Baseline CBC and liver enzymes: every other week for 6 to 8 weeks after initiation or following any dose adjustments; at least once every 3 months thereafter
- 6-thioguanine (6-TGN) and 6-methylmercaptopurine (6-MMP) levels can be measured: 2013 meta-analysis showed the pooled odds ratio for clinical remission was 3.2 when 6-TGN levels were between 230 and 260 (95% CI 2.4-4.1)
- 6-TGN levels >400 picomoles per 8 X 10^8 erythrocytes predict refractoriness and an increased risk of myelotoxicity
- 6-MMP levels >5000 picomoles per 8 X 10^8 erythrocytes correlates with hepatotoxicity

Lichtenstein GR et al. *Gastroenterology* 2006;130(3):935-939.
Moreau AC et al. *Inflamm Bowel Dis* 2014;20(3):464-471.
Dubinsky MC et al. *Gastroenterology* 2000;118(4):705-713.
Roblin X et al. *Am J Gastroenterol* 2008;103(12):3115-3122.

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AZA and 6-MP: Monitoring

Patient Classification	6-TGN	6-MMP	Consequence	Approach
Non-compliance	Negligible or undetectable	Negligible or undetectable	Inefficacy	Patient education
Underdosing	Low	Low	Inefficacy or poor response	Increase thiopurine dosage
Thiopurine “resistant”	Low	High	Poor response or hepatotoxicity	Add allopurinol and decrease thiopurine dosage
Overdosing	High	Low	Overdosing with risk of myelotoxicity	Decrease thiopurine dosage and close monitoring
Thiopurine “refractory”	High	High	Thiopurine refractory or overdose	Switch to another drug

Nielsen OH et al. *Expert Rev Gastroenterol Hepatol* 2015;9(2):177-189.

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AZA and 6-MP: The “Resistant” Patient

- Characterized by low 6-TGN levels, high 6-MMP levels and often transaminitis
- Allopurinol 100mg daily directs reaction away from 6-MMP towards 6-TGN
- Requires dose reduction of AZA or 6-MP by 25%-50% to avoid myelotoxicity
- Bi-weekly CBCs needed during this adjustment phase
- Metabolite levels reassessed within 2-6 weeks

Sparrow MP et al. *Aliment Pharmacol Ther* 2005;22(5):441-446.

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AZA and 6-MP: Side Effects

Seen early (2-3 weeks)

- Myelosuppression
- Pancreatitis
- Hepatitis
- Polyarthralgias
- Fevers
- Nausea/vomiting

Seen later

- Myelosuppression
- Infection
- Malignancy
  - Non melanoma skin cancers
  - Cervical cancer
  - Lymphoma

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Methotrexate: Side Effects

- GI distress: nausea/vomiting*
- Mouth sores*
- Headache*
- Fatigue*
- Myelosuppression
- Hepatitis
- Pulmonary fibrosis
- Infection

**Can be reduced or alleviated with folate supplementation*

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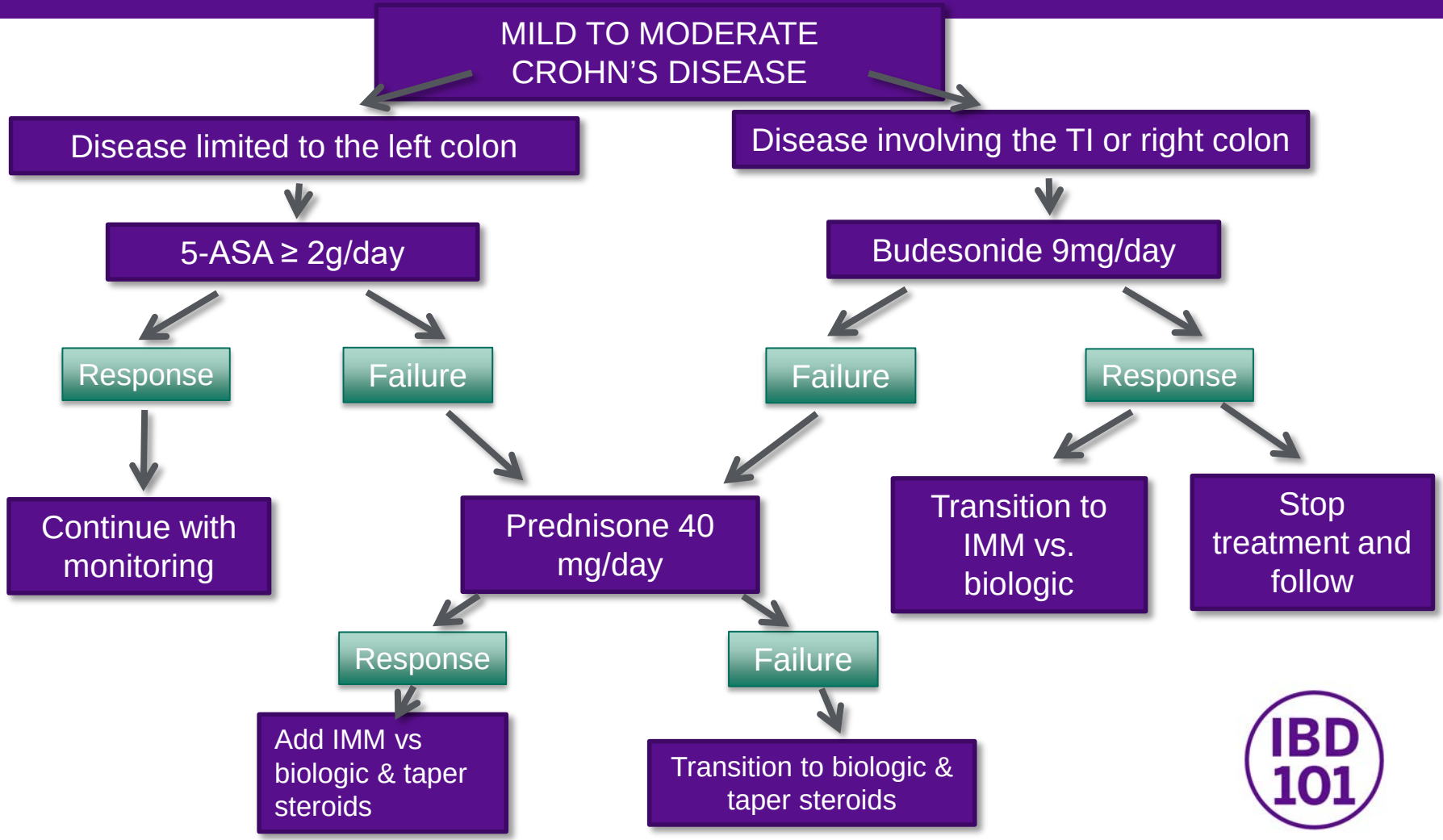
MILD TO MODERATE CROHN'S DISEASE
Disease limited to the left colon
Disease involving the TI or right colon
5-ASA ≥ 2g/day
Budesonide 9mg/day
Response
Failure
Failure
Response
Continue with monitoring
Prednisone 40 mg/day
Transition to IMM vs. biologic
Stop treatment and follow
Response
Failure
Add IMM vs biologic & taper steroids
Transition to biologic & taper steroids
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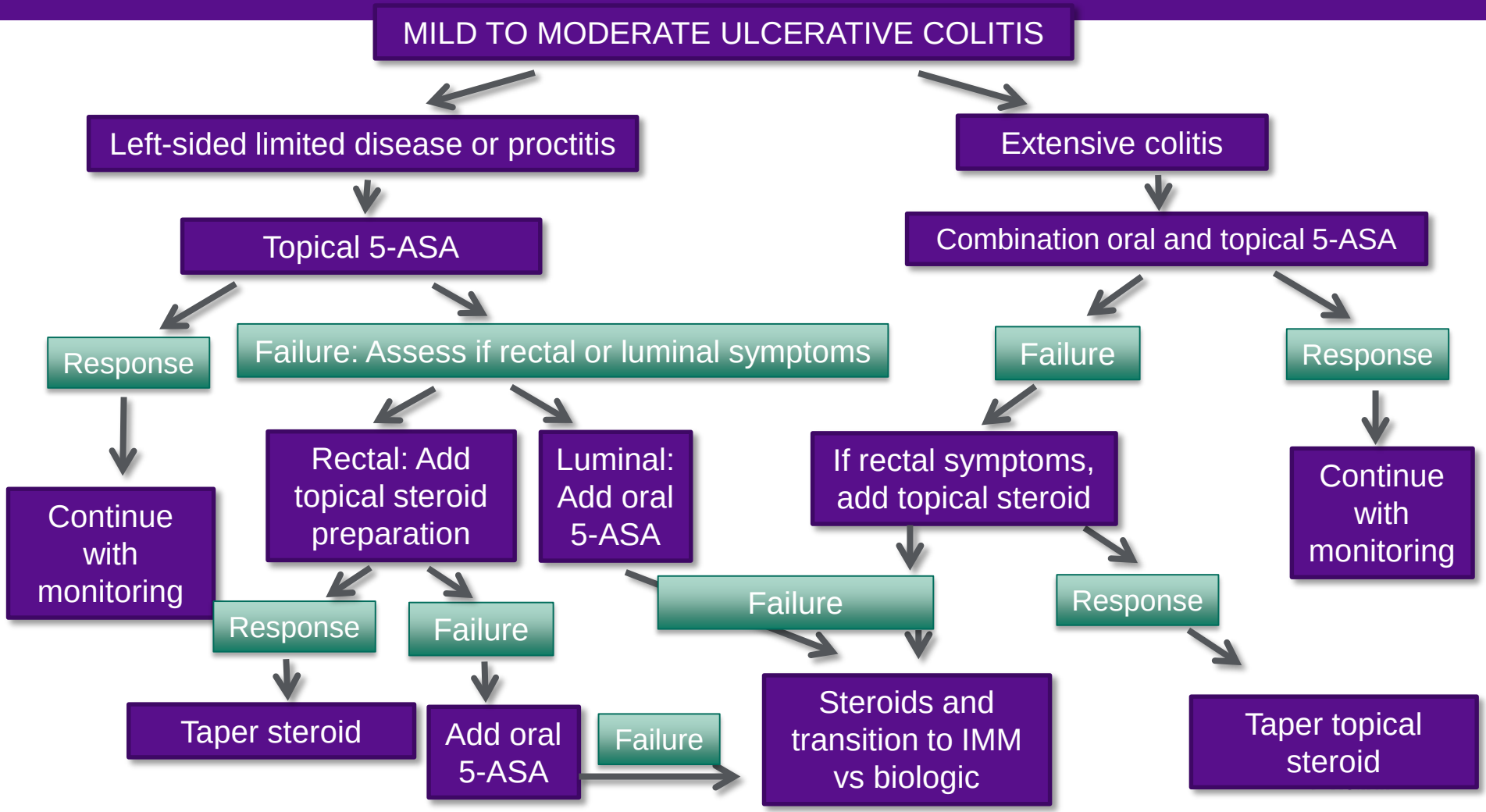
MILD TO MODERATE ULCERATIVE COLITIS
Left-sided limited disease or proctitis
Extensive colitis
Topical 5-ASA
Combination oral and topical 5-ASA
Response
Failure: Assess if rectal or luminal symptoms
Failure
Response
Continue with monitoring
Rectal: Add topical steroid preparation
Luminal: Add oral 5-ASA
If rectal symptoms, add topical steroid
Continue with monitoring
Response
Failure
Failure
Response
Taper steroid
Add oral 5-ASA
Failure
Steroids and transition to IMM vs biologic
Taper topical steroid