NYU Langone Health

# Management of Loss of Response to IBD Therapies

IBD 101

# Why Is This Topic Important?

- Since IBD is a chronic, inflammatory disease, it's important to monitor patients to ensure continued response to therapeutic strategy over time
- If symptoms recur, must confirm symptoms reported are truly related to underlying persistent inflammation
- Other etiologies that can have similar symptoms to IBD won't respond to IBD treatments!

Papamichael K et al. *Inflamm Bowel Dis* 2015;21(1):182-197.



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# Non-IBD Causes of Diarrhea (in the IBD Patient)

- Non-compliance
- *C. difficile*
  - Previous antibiotic use is not required to develop this infection
  - Usually no pseudomembranes
  - Higher morbidity and mortality rates
  - Increased colectomy rate as high as 20%
- Neoplasm

# Non-IBD Causes of Diarrhea (in the IBD Patient)

- Medications  (NSAIDs, antibiotics)
- Small intestinal bacterial overgrowth
  - Can be seen in 25% of patients with Crohn's disease
  - Risk factors: longer duration of disease, fibrostenotic disease, colonic involvement, previous/multiple surgical procedures
- Bile-salt diarrhea
  - Most commonly seen with ileal resection
- Overlapping Irritable Bowel Syndrome

# How to Assess the Patient with Loss of Response

- Detailed history on behaviors:
  - smoking cessation in UC
  - New meds
  - Dietary indiscretion
- Stool studies to rule out infection
- Bloodwork including CRP level
- Fecal calprotectin level
- Colonoscopy and or cross-sectional imaging

# Loss of Response When Nothing Else Is to Blame…

*Maybe the medication regimen is the problem?!*

- Drug monitoring has been used for years; initially with the immunomodulator medications
- Drug monitoring with biologics is utilized more frequently today; the most data are available for infliximab (our oldest biologic medication)

# Why Is This TDM Important?

- Biologics are very effective for moderate to severe IBD.
- Nevertheless:
  - 10%-30% of patients have primary non-response (total lack of clinical response to induction doses)
  - Up to 50% of patients who initially respond have a secondary loss of response or serious adverse event
  - Most data on this topic exist for anti-TNF medications



Papamichael K et al. *Inflamm Bowel Dis* 2015;21(1):182-197.

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# Pharmacokinetics of Anti-TNF Agents

| | |
|---|---|
| **Low albumin** | **Increased clearance** |
| **CRP level** | **Higher CRP = increased clearance** |
| **Body mass index (BMI)** | **Higher BMI = increased clearance** |
| **Male sex** | **Increased clearance** |



Ordas I et al. *Clin Pharmacol Ther* 2012;91(4):635-646.

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# Therapeutic Drug Monitoring

- Measures serum drug concentration and anti-drug antibodies
- Can be used to optimize biologic therapy and improve therapeutic decision making
  - Optimal serum drug concentrations are associated with favorable outcomes in **retrospective** analyses
  - Low or undetectable drug concentrations are linked to anti-drug antibody formation and subsequent treatment failure
  - Drug concentrations can be directly compared between the different assays (eg, Enzyme-linked immunosorbent assay [ELISA], radio-immunoassay, homogenous mobility shift assay [HMSA]), and electrochemiluminescence immunoassay [ECLIA] for infliximab). Antibody levels cannot be compared directly.
  - Assay choice based on cost, local availability, insurance & provider preference



Papamichael K and Cheifetz A. *Frontline Gastroenterol* 2016;7(4): 289-300.

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# Optimal Trough Concentrations

- Infliximab
  - Level of > 5mcg/mL is the **suggested** trough level
  - Many will dose-optimize patients to a level of > 10mcg/mL before discontinuing therapy and trying an alternate agent
  - In perianal Crohn's disease, higher trough levels ( ~20mcg/mL) were associated with increased fistula healing
  - Antibodies to infliximab (ATI) > 9.1U/mL during loss of remission associated with a LR of 3.6 for an unsuccessful intervention to overcome them
- Adalimumab
  - Level of >7.5mcg/mL is the **suggested** trough level when conducting TDM

Feuerstein JD et al. *Gastroenterology* 2017;153:827-834.
Casteele NV et al. *Am J Gastroenterol* 2013;108:962-971.
Yarur A et al. *Aliment Pharmacol Ther* 2017;45(7):933-940.



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# Loss of Response Mechanisms

Primary and secondary loss of response can be divided into:

- **Mechanistic pharmacodynamic failure**: optimal drug trough with failure to respond
- **Non-immune-mediated pharmacokinetic failure**: low drug trough with absence of antibodies
- **Immune-mediated pharmacokinetic failure**: low drug trough with either low or high antibodies

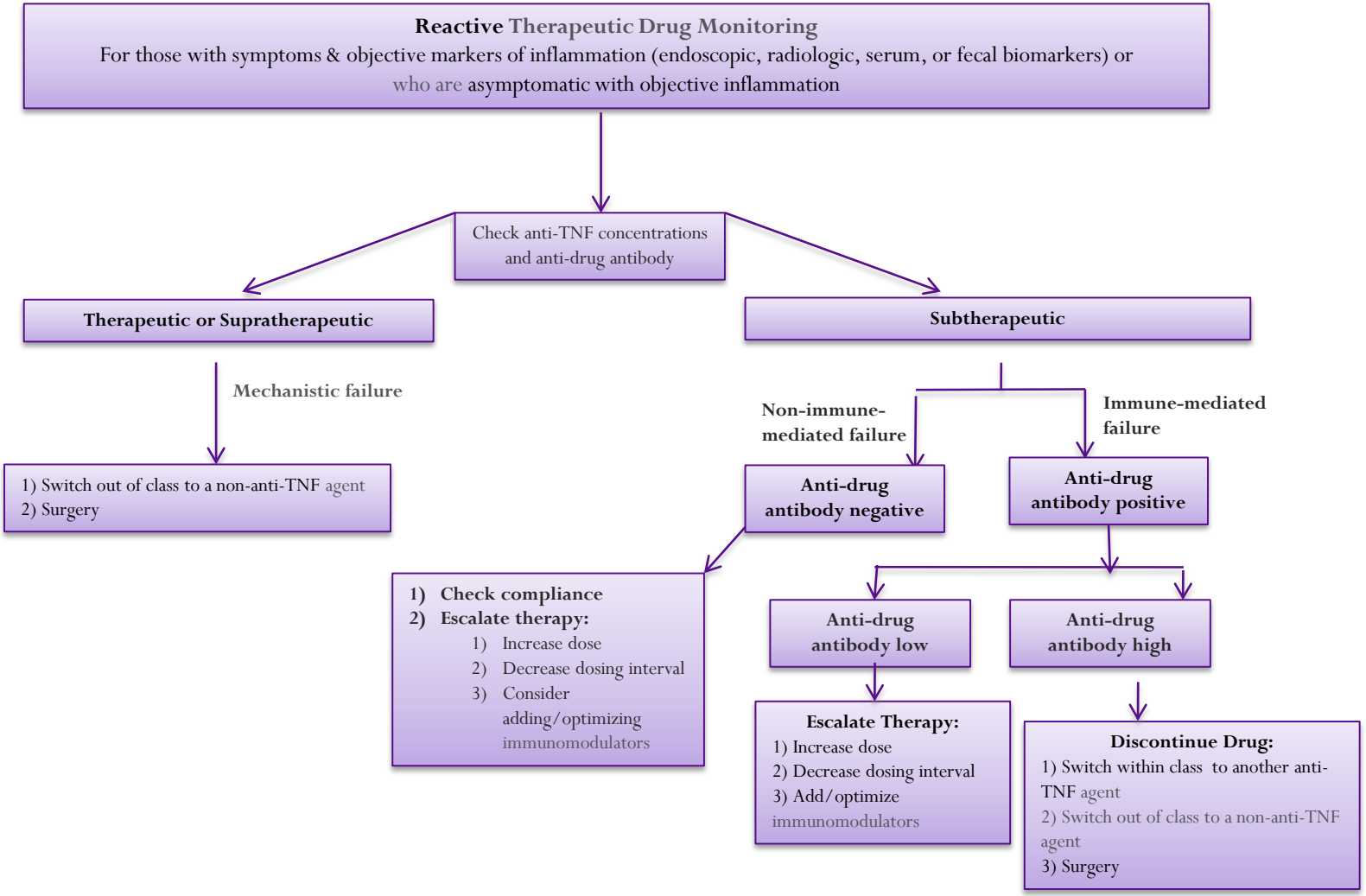


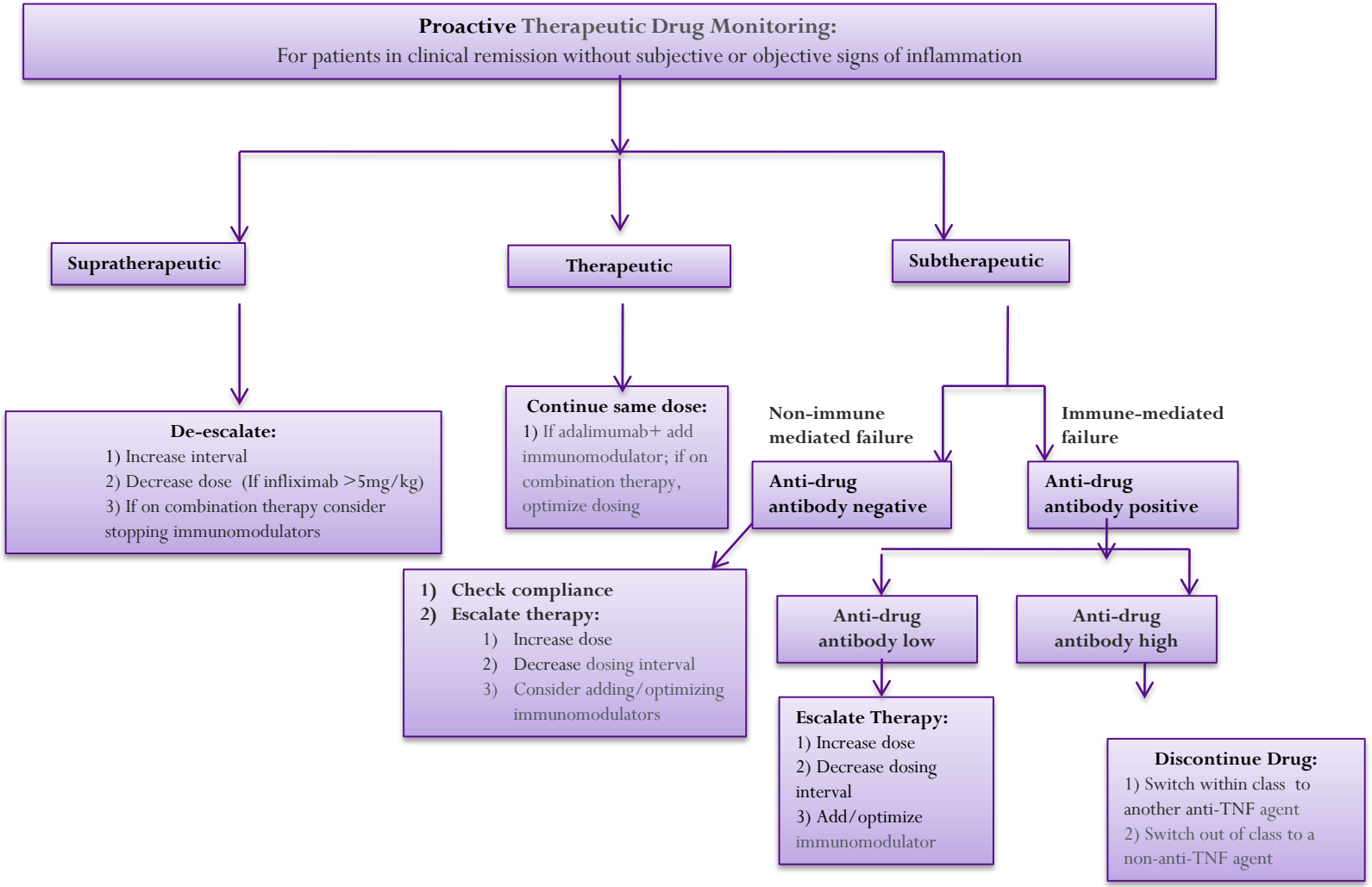
Vande Casteele N et al. *Gastroenterology* 2017;153:835-857 e6.

# Types of Therapeutic Drug Monitoring

- Reactive TDM
  - When symptoms worsen
  - Improves clinical care
  - Cost-effective

- Proactive TDM
  - During induction or maintenance
  - Withdrawing therapy
  - Data (mainly retrospective) show improved outcomes


Reactive Therapeutic Drug Monitoring
For those with symptoms & objective markers of inflammation (endoscopic, radiologic, serum, or fecal biomarkers) or who are asymptomatic with objective inflammation
Check anti-TNF concentrations and anti-drug antibody
Therapeutic or Supratherapeutic
Subtherapeutic
Mechanistic failure
1) Switch out of class to a non-anti-TNF agent
2) Surgery
Non-immune-mediated failure
Immune-mediated failure
Anti-drug antibody negative
Anti-drug antibody positive
1) Check compliance
2) Escalate therapy:
1) Increase dose
2) Decrease dosing interval
3) Consider adding/optimizing immunomodulators
Anti-drug antibody low
Anti-drug antibody high
Escalate Therapy:
1) Increase dose
2) Decrease dosing interval
3) Add/optimize immunomodulators
Discontinue Drug:
1) Switch within class to another anti-TNF agent
2) Switch out of class to a non-anti-TNF agent
3) Surgery


Proactive Therapeutic Drug Monitoring:
For patients in clinical remission without subjective or objective signs of inflammation
Supratherapeutic
Therapeutic
Subtherapeutic
De-escalate:
1) Increase interval
2) Decrease dose (If infliximab >5mg/kg)
3) If on combination therapy consider stopping immunomodulators
Continue same dose:
1) If adalimumab+ add immunomodulator; if on combination therapy, optimize dosing
Non-immune mediated failure
Immune-mediated failure
Anti-drug antibody negative
Anti-drug antibody positive
1) Check compliance
2) Escalate therapy:
1) Increase dose
2) Decrease dosing interval
3) Consider adding/optimizing immunomodulators
Anti-drug antibody low
Anti-drug antibody high
Escalate Therapy:
1) Increase dose
2) Decrease dosing interval
3) Add/optimize immunomodulator
Discontinue Drug:
1) Switch within class to another anti-TNF agent
2) Switch out of class to a non-anti-TNF agent