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Common Errors in the Management of IBD: What to do when your patient has "failed" everything?

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What do you do when your therapy is failing?

Think!

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Why are they failing?

- Do they have active disease?
  - 20+% of patients entering ACCENT, SONIC trials based on CDAI had **NO endoscopic activity**
- Re-assess objective evidence of inflammation
  - Endoscopy
  - Imaging
  - Biomarkers
    - CRP
    - Calprotectin

No active inflammation

- Stricture?
- SBBO?
- Bile salt wasting?
- Malabsorption?
- IBS?

Active Inflammation

- Non-IBD
  - Infection
    - C. difficile
    - CMV
    - Enteric pathogens
    - TB (India)
  - NSAID or other barrier breakers
  - Ischemia

Active Inflammation

- Failure to induce remission
  - Adequate dose/duration of therapy
    - Mesalamine
    - Corticosteroid
    - Immunosuppressive
    - Biologic

Failure to ***induce*** with mesalamine

- Adequate dose/duration
  - Oral + topical (UC)
- Proctitis/Left sided colitis
  - Combine topical with steroid
- Intolerance?

Failure to ***maintain***

- Dose
  - Induction dose=maintenance dose
- Delivery
  - Continue oral + topical
- intolerance masked by steroids
- Adherence! (applies to all categories)

Failure to ***induce*** with steroids

- Outpatient
  - Don't under-dose!
  - Assess compliance
  - Admit for IV steroids
- Inpatient
  - Assessment in 3-5 days
  - Do not prolong ineffective steroids
  - UC
    - Biologic/Cyclosporine/Surgery
  - Crohn's
    - Re-image to r/o abscess
    - Bowel rest and TPN
    - Biologic/Surgery

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Failure to ***maintain*** with thiopurines

- Optimize dose
  - mg/kg is inappropriate use of EBM
  - Dose according to
    - WBC
      - Leucopenia simply requires dose-reduction
    - Metabolites
- Elevated LFTs?
  - High functional TPMT (6-MMP>6-TG)
    - Consider adding allopurinol
      - Reduce dose first!
- Allergy (Pancreatitis, Fever, Arthritis)
  - Consider thioguanine
  - Switch to MTX

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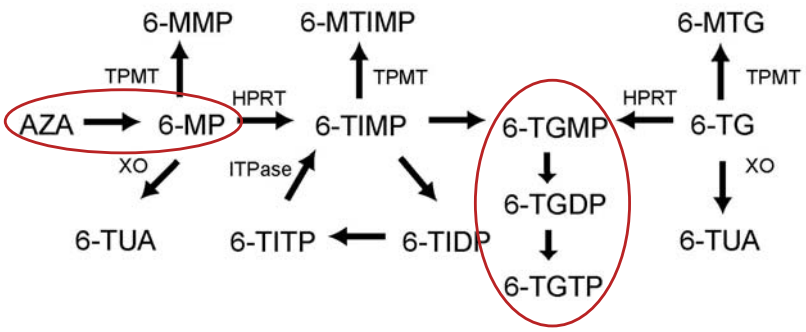
Background: thiopurine metabolism



Maintenance of Remission
Myelotoxicity

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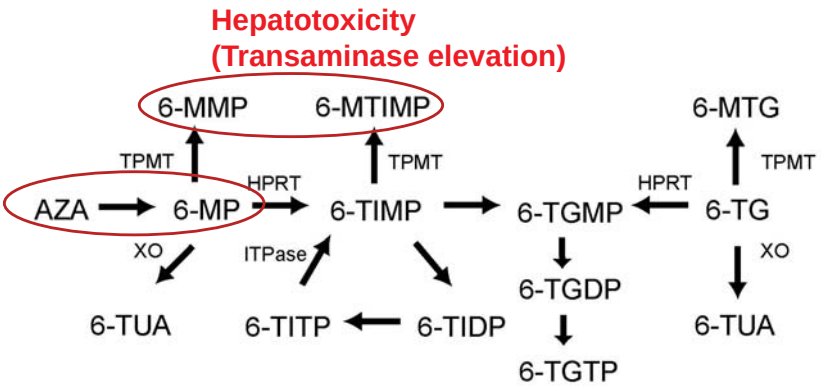
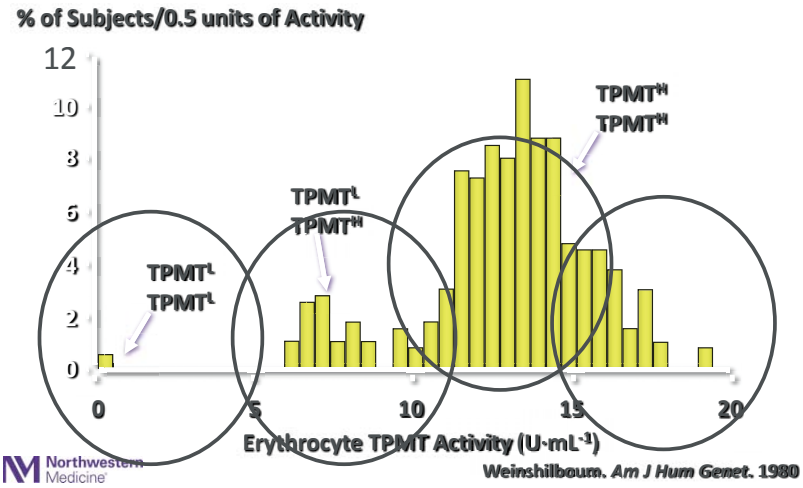
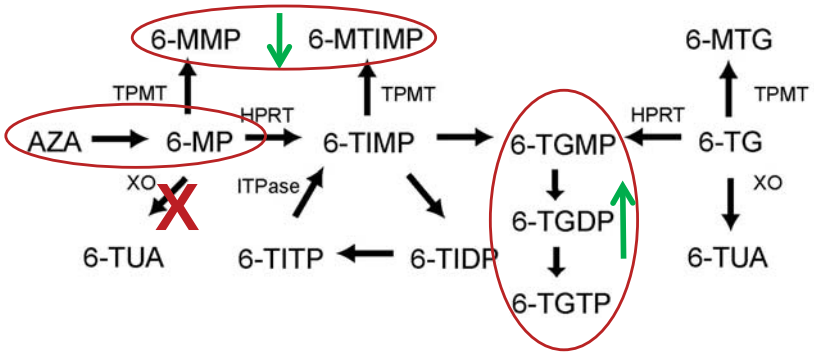


Distribution of Thiopurine Methyltransferase Enzyme Activity in the Population



Background: Allopurinol

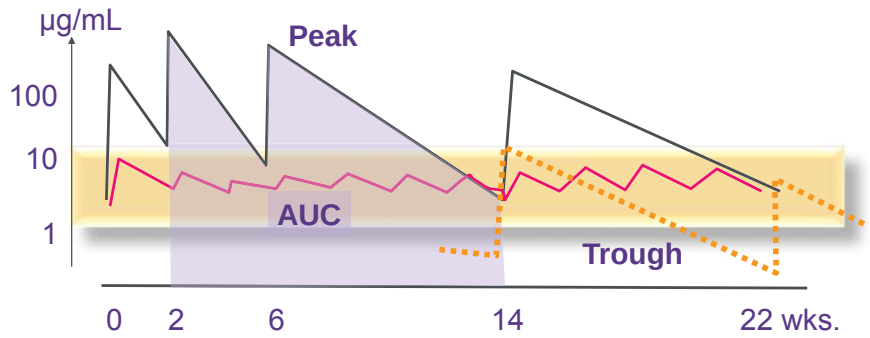


Failure to ***induce*** with Biologics

Factors that Influence the PK of TNF Antagonists

Ordas I et. al. *Clin Gastroenterol Hepatol*. 2012; 10:1079-1087. 16

Therapeutic Windows with Biologics



Sub-treshold trough levels associated with:

- Loss of response
- Immunogenicity

Factors that Influence the PK of TNF Antagonists

	Impact on TNF antagonist PK
Presence of ADAs	Decreases drug concentration Increases clearance Worse clinical outcomes

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Concomitant use of immunosuppressives	Reduces ADA formation Increases drug concentration Decreases drug clearance Better clinical outcomes

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High baseline CRP concentration	Increase drug clearance

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High baseline TNF concentration	May decrease drug concentration by increasing clearance

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High body size	May increase drug clearance
Sex	Males have higher clearance

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Failure to ***induce*** with biologic

- Dosing
  - Factors associated with rapid clearance
  - Inflammatory burden
  - High CRP
  - Body weight
  - Fixed dose vs mg/kg
  - Low albumin
    - Protein losing colopathy
- High dose or repeat dose for transient response

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Implications of Low Trough Levels

- Disease Recurs
  - No longer maintenance but re-treatment
- Development of anti-drug antibodies
  - Eventual loss of response

- Do Not Administer Intermittently!

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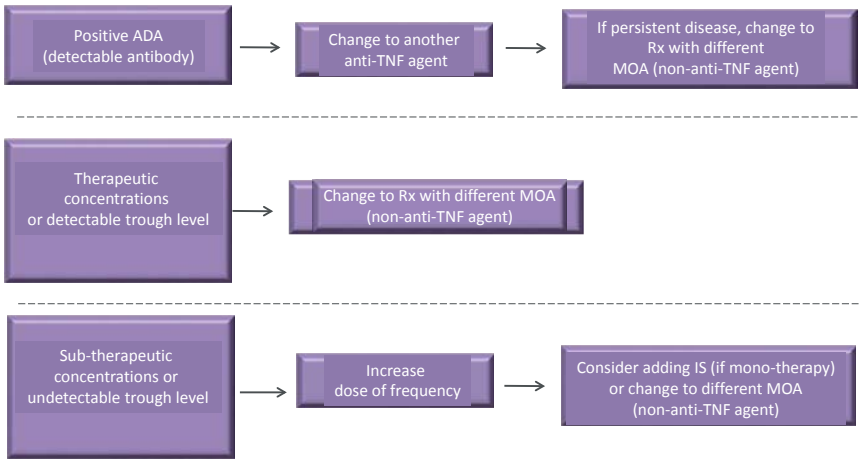
Failure to ***maintain*** with anti-TNF

- Consider dosing/clearance
  - Check trough level (and ADA if available)

"Reactive" Testing

Confirmed active inflammation



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Afif W, et al. Am J Gastroenterol. 2010; 105:1133-1139.

Don't be a "macho gastro"

- Surgery restores QOL in both UC and CD
  - Failure to induce remission
  - Failure to maintain remission
  - Side effects of medications
    - Steroid dependency
    - Opportunistic infections
    - Neoplasia?

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Consider Referral

- If you don't…your patient will!
  - Second opinions
  - Clinical trials