Endpoints for Stopping Treatment in UC

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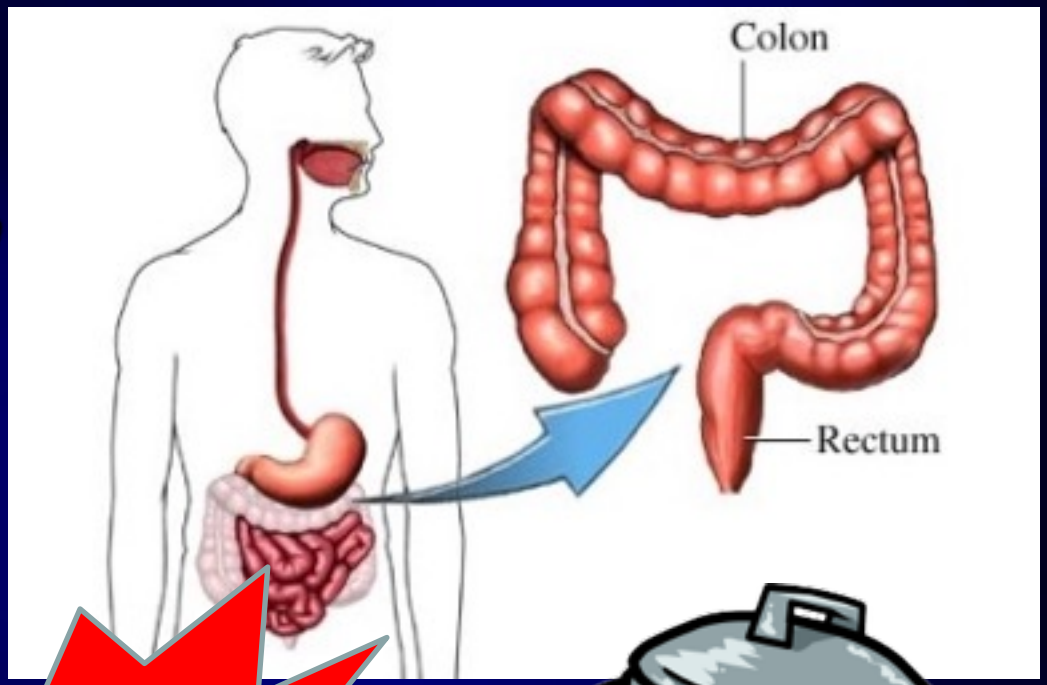
IBD

- CD and UC pts require long term treatment to maintain remission and prevent relapses
  - Side effects which can be rare, yet serious
    - Opportunistic infx, lymphomas, skin ca…
  - High cost
  - Compliance at times is problematic

Correctly identifying pts who can **de-escalate** therapy **and** do well is very important

Who Can we Stop Meds on?

Easy Answer…



CURE

Who to Consider Stopping Meds

- Clinical remission
- Endoscopic remission
- Histologic remission
- Biomarker negative

Deep remission

- No clear guidelines regarding correctly identifying **UC** pts who can stop/de-escalate treatment once they are in remission…..

“Keep Taking Medication Until Something Better Comes Along”

Outline of presentation

- Review current data on stopping treatment in UC pts

- Focus
  - Relapse rates
  - Factors associated with relapse

Four Possible Scenarios

- Stop 5-ASAs
- Stop AZA/6MP
  - Monotherapy → on no meds
  - Continue anti-TNF
- Stop anti-TNF and continue AZA/6MP
- Stop **BOTH** meds (no data at present)

- Most data in Crohn's (less data in UC)

Stopping 5-ASA

- Ulcerative proctitis pts require topical 5-ASA
- First episode of mild ulcerative proctitis
  - Topical 5-ASA x 6-8 wks
  - No need for maintenance
- If ulcerative proctitis pts relapse >1/yr
  - Continue topical 5-ASA nightly

Stopping 5-ASA

- Lt sided, Extensive & Pan UC require oral and topical 5-ASA

- Meta-analysis (2011) of 11 RCTs
  - Risk of relapse in pts with quiescent UC was lower in pts on 5-ASA vs placebo [RR 0.65, 95% CI 0.55-0.76]
  - Recommended dose to maintain remission ~3-3.6 g/d

- ECCO guidelines: The minimum effective dose of oral 5-ASA is 1.2 g/day to maintain remission

What are the data on stopping AZA/ 6MP in UC pts?

- IMM monotx pts who stop the IMM
- Combotx pts who stop the IMM
  - Now on anti-TNF

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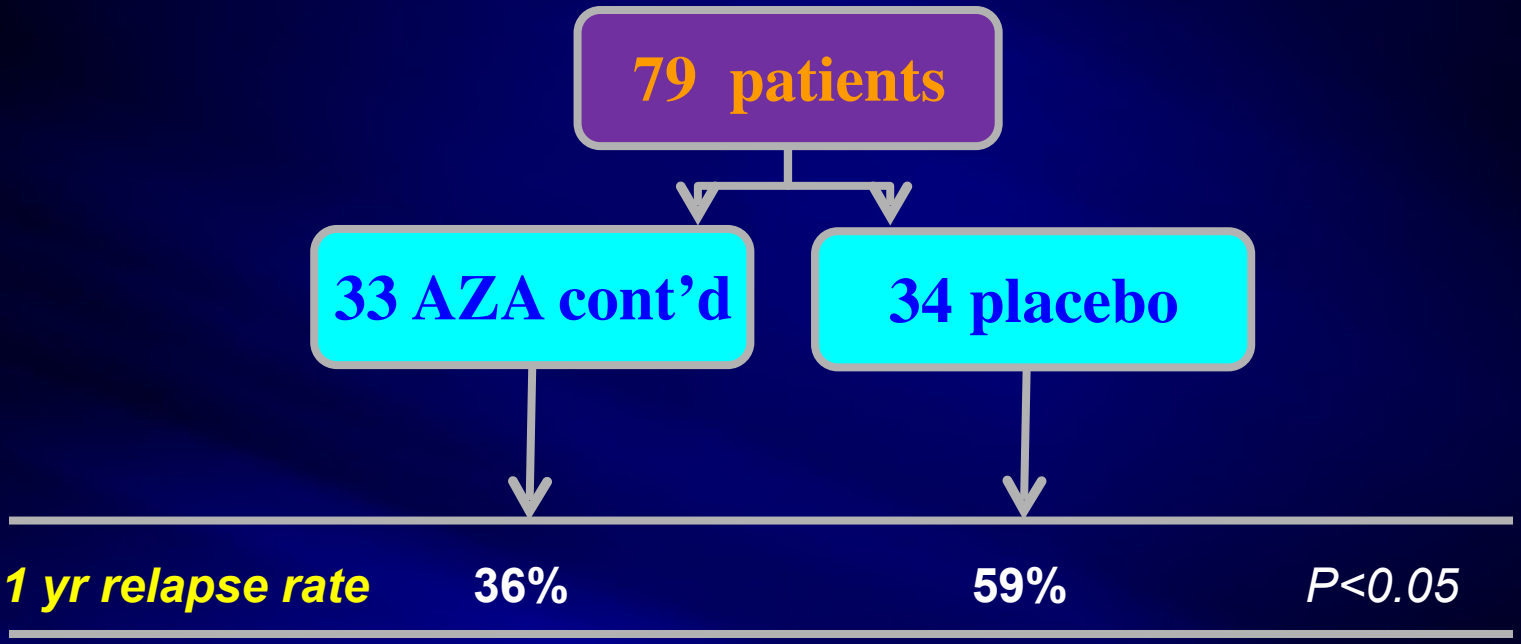
De-escalation of AZA/6MP monotx in UC?

- Hawthorne et al. -- RCT; 1992 BMJ
- Lobel et al. -- Retrospective Review; 2004 AJG
- Fraser et al. -- Retrospective Review; 2002 Gut
- Cassinotti et al. -- Retrospective Review; 2009 AJG

Hawthorne et al.

- Determine whether AZA prevents relapse in UC
- 1 yr placebo controlled double blind trial
- 79 UC outpts on AZA for ≥6 mths
- Pts in full remission for ≥ 2 mths (clinical & endoscopic)



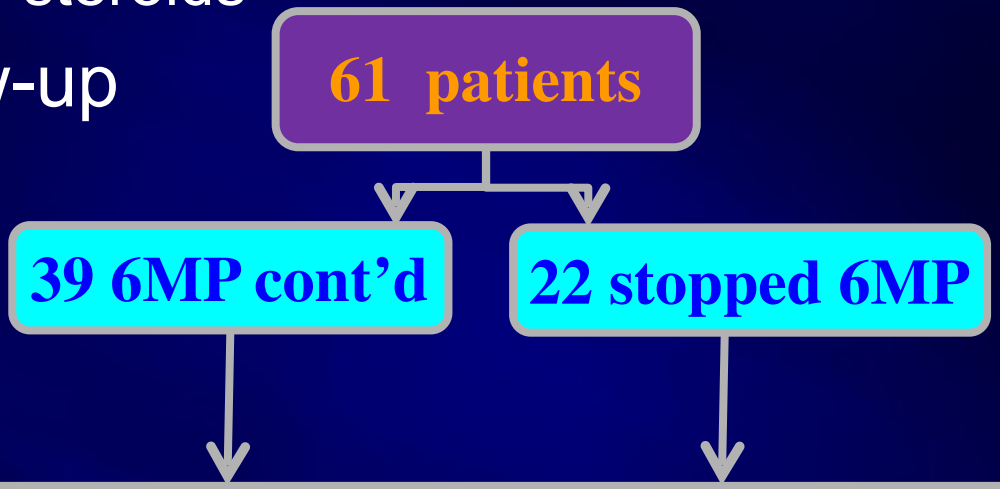
Hawthorne et al. BMJ. 1992; 305(6844): 20-22.

Retrospective Reviews

- Cohort studies with very heterogeneous designs and f/u times
  - Relapse rates from:
    - 11% to 77% at 12 months
    - 21% to 100% at 24 months

Lobel et al.

- Retrospective study
- 61 UC pts on 6MP ≥6 mths
- Remission for >3 mths while on 6MP
  - No need for steroids
- 1-year follow-up



1 yr relapse rate	43%	77%	*P<0.05*
Median time to relapse	58 wks	24 wks	*P<0.05*
2 yr relapse rate	69%	100%	*P<0.05*

Lobel et al. Am J Gastroenterol 2004; 99:462-465.

Fraser et al.

- Retrospective review over a 30-year period
  - factors predicting response to AZA
  - optimal duration of treatment
- Subgrp of 222 IBD (143 UC; 79 CD) outpt stopped AZA
- Pts had to be in remission
  - No oral steroids for ≥3 mths AND
  - Harvey–Bradshaw index of <4
- Relapse rates defined as
  - active disease requiring steroids or
  - need for a surgical procedure

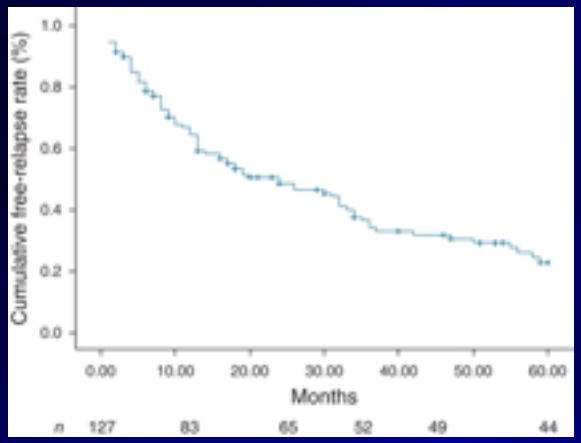
Relapse Rate	Off AZA
1 year	37%
3 years	66%
5 years	75%

Fraser et al. Gut 2002; 50:485-489.

Cassinotti et al.

- Retrospective observational study
- Clinical outcomes and predictive factors after withdrawal of AZA in UC

- 127 UC pts in steroid-free remission >3 mths
- f/u x 55 months or until relapse



Relapse Rate	Off AZA
1 year	1/3
3 years	1/2
5 years	2/3

Cassinotti et al. Am J Gastroenterol 2009; 104:2760-2767.

Summary…

- Relapse rates were significantly higher in UC pts who stopped 6MP/AZA compared to those who continued treatment

- After stopping 6MP/AZA
  - average 1-yr relapse rate was 53% (range 35%–77%)
  - by 5 years, relapse rate was 70% (range 65%–75%)

What are the data on stopping AZA/6MP in UC pts?

- IMM monotx pts who dropped the IMM
  - Now on no medications
- **Combotx pts who dropped the IMM**
  - **Now on anti-TNF**

Stopping IMM

- The only study on stopping IMM after combo tx supported continued IMM use

Filippi J et al.

- Retrospective study
  - IMM withdrawal from combotx
- Pts in remission ≥6 mths on combo tx (IFX/AZA)
- 82 pts with f/u for ~22.3 mths

- Higher relapse rate in discontinuation cohort
  - 12% vs. 3%; p=0.049
- Mean time to relapse
  - 16.6 mths combo vs. 7 mths IFX; $p<0.05$

What are the data on stopping anti-TNF in UC pts?

What are the data on stopping anti-TNF in UC pts?

- 14 studies described outcomes after anti-TNF withdrawal in UC
  - 5 were retrospective
- Significant heterogeneity in study design, pt population (proportion of pts on combo ~20-100%), definition of relapse, clinical remission
- Duration of remission was vague
  - only stated in 2 studies (>6 mths)

What are the data on stopping anti-TNF in UC pts?

- In adults:
  - 12 month relapse rates: 14% - 41.8%
    - Lower value in pts who had to have **mucosal healing** prior to de-escalation (17%-25% relapse rate)
  - 24 month relapse rates: 25% - 47.1%
    - Lower value in pts who had to have **mucosal healing** prior to de-escalation (25%-35% relapse rate)

Putting the data all together….

To Date…

- Discontinuation of tx in UC pts needs to be personalized based on preference, disease markers, consequence of relapse, safety & cost

- IMM and anti-TNF tx should NOT be stopped as long as remission is maintained, cost is not an issue, there are no significant side effects, and the patient is tolerating treatment

To Date…

- Further studies are required to accurately identify subgroups of pts who are good candidates for discontinuing tx

Question…

- 37 year old male with panUC
  - Diagnosed 10 yrs ago
  - Maintained on AZA and IFX for at least 5 yrs
  - Has been feeling great for the past few years

- Colonoscopy the last 3 yrs has been normal
- Random biopsies unremarkable
- Blood work looks good; CRP normal

- **He is very worried about HSTCL and would like to d/c meds**

What would you do…

- Continue meds?
- Continue AZA/stop IFX?
- Continue IFX/stop AZA?
- Stop all meds?

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DEEP REMISSION

Question…

- His twin brother: 37 year old male with panUC
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- Colonoscopy the last 3 yrs has showed mild erythema
- Random biopsies with mild colitis
- Blood work looks good but CRP mildly elevated

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The WRONG pt to stop meds on

Associated with future relapses:

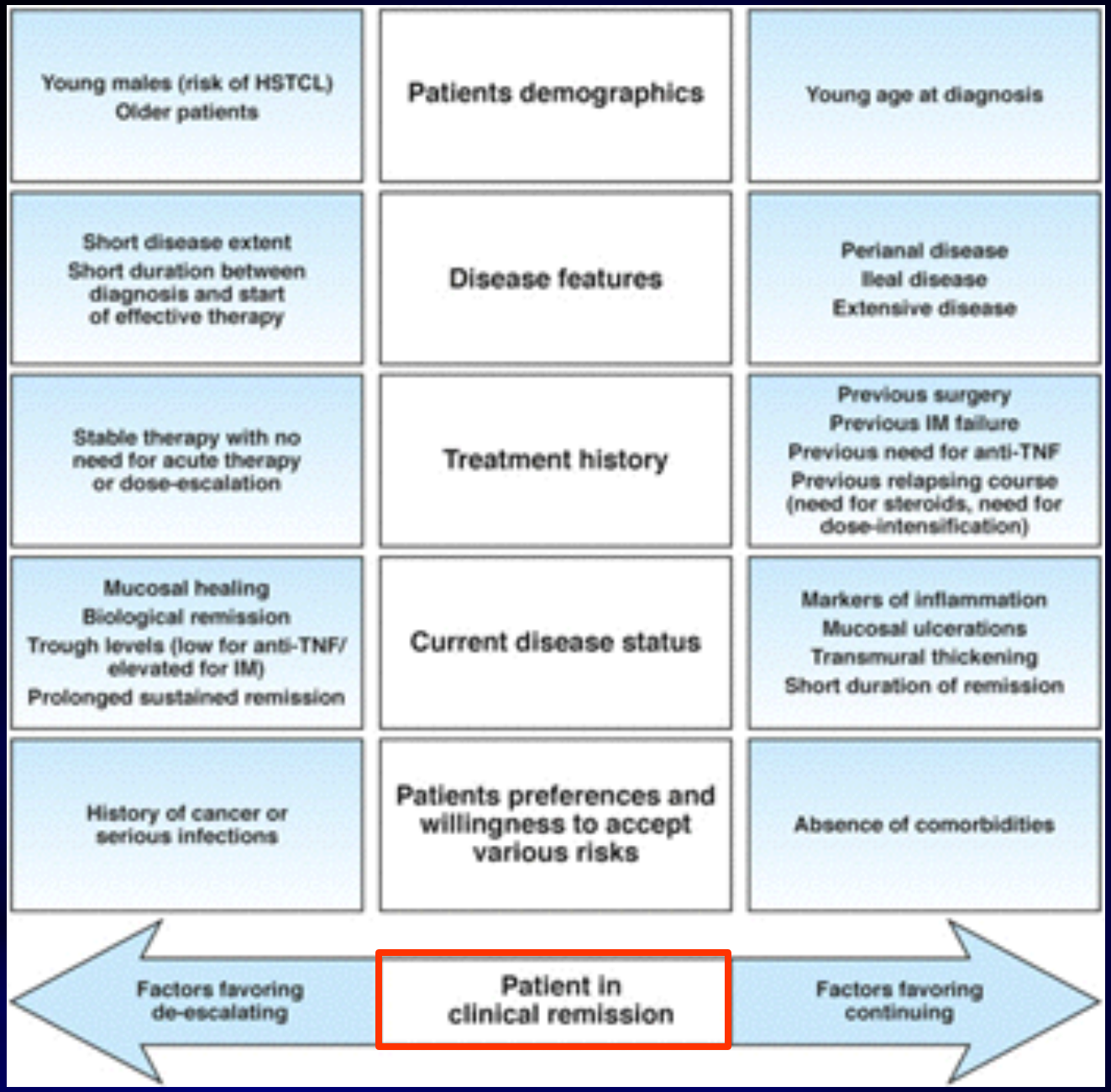
- Markers of disease activity
  - ongoing inflammation on endoscopy
  - elevated CRP, WBC, etc..
- More extensive disease
- Complicated/relapsing disease course
- Short duration in remission before d/c tx
- Male Gender
- Lack of a second concomitant medication; IMM after stopping anti-TNF

The RIGHT pt to stop meds on

…..the patient in a deep remission without recent steroid use….. But for how long???

Associated with reduced relapse rates:

- Older age
- Longer duration of IMM tx
- Biologic remission



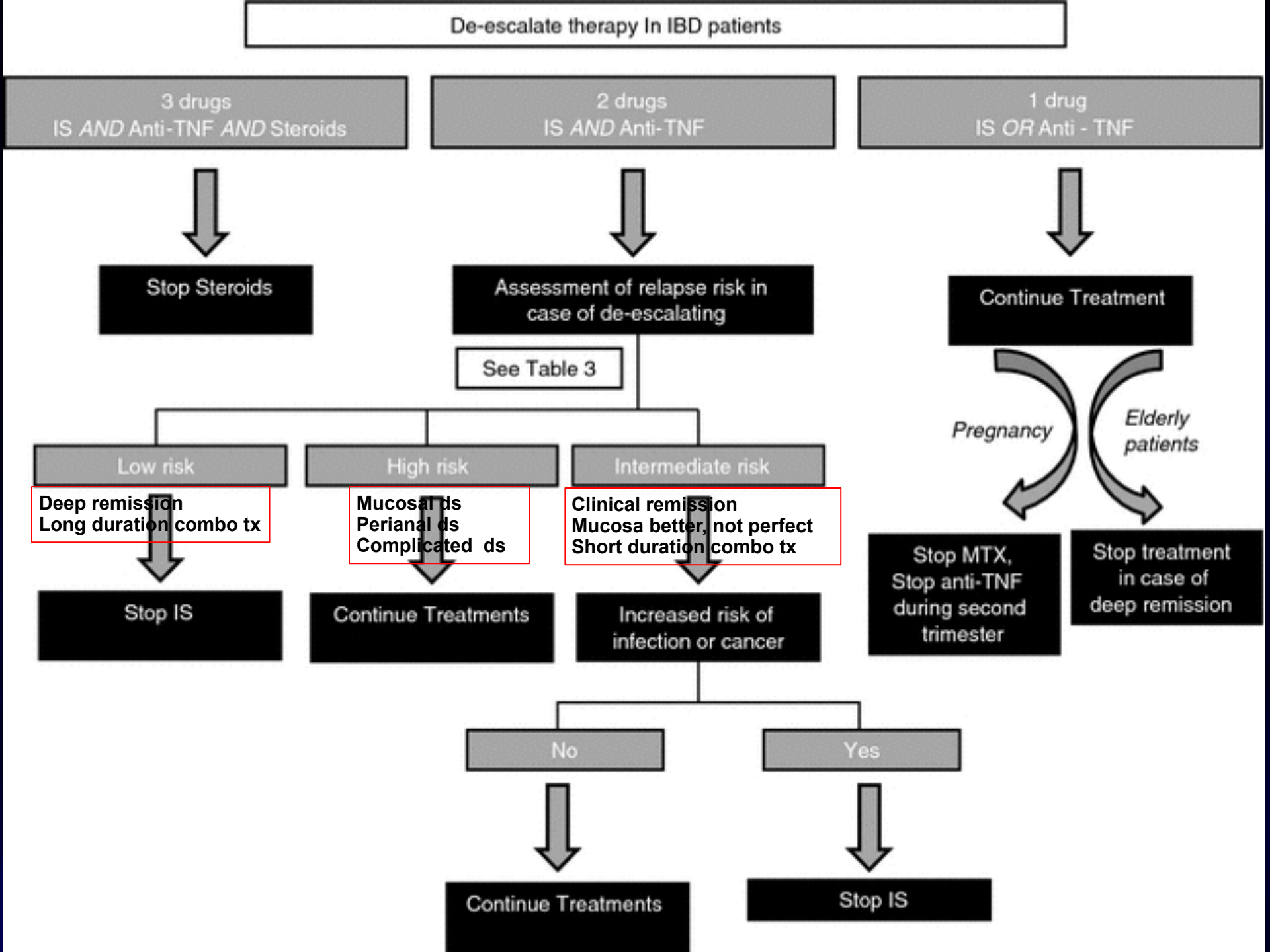
Torres J et al. Gastroenterology, 2015, Available online 14 September 2015

Synthesis and Consensus: Algorithm from

Review article: why, when and how to de-escalate therapy in inflammatory bowel diseases

Alimentary Pharmacology & Therapeutics

Pariente B and Laharie D, 10:338-353, JUN 2014


De-escalate therapy In IBD patients
3 drugs
IS AND Anti-TNF AND Steroids
2 drugs
IS AND Anti-TNF
1 drug
IS OR Anti - TNF
Stop Steroids
Assessment of relapse risk in case of de-escalating
See Table 3
Continue Treatment
Pregnancy
Elderly patients
Low risk
High risk
Intermediate risk
Deep remission
Long duration combo tx
Mucosal ds
Perianal ds
Complicated ds
Clinical remission
Mucosa better, not perfect
Short duration combo tx
Stop IS
Continue Treatments
Increased risk of infection or cancer
Stop MTX, Stop anti-TNF during second trimester
Stop treatment in case of deep remission
No
Yes
Continue Treatments
Stop IS


UPMC
Thank you


DEANXIT


UPMC
Thank you