  
 Centre universitaire de santé McGill / McGill University Health Centre

**Canadian Society of Internal Medicine**  
**Annual Meeting 2016**

**Treatment and Monitoring**  
**of Inflammatory Bowel Disease**

**Waqas Afif MD, M. Sc, (Epi), FRCPC**  
 Assistant Professor of Medicine  
 McGill University Health Center, Montreal, QC  
 October 28, 2016

W15a/b, McGill (8)  
 08:45am – 10:00am & 10:30am – 11:45am

**Canadian Society of Internal Medicine**  
 Annual Meeting 2016  
*Montreal, QC*

The following presentation represents the views of the speaker  
 at the time of the presentation. This information is meant for  
 educational purposes, and should not replace other sources  
 of information or your medical judgment.

Waqqas Afif: Treatment and Monitoring of Inflammatory Bowel Disease, October 28, 2016

**Canadian Society of Internal Medicine**  
 Annual Meeting 2016  
*Montreal, QC*  
**Conflict Disclosures**

The speaker has received fees/honoraria from the following sources:  
 Janssen, Abbvie, Takeda, Pfizer, Merck, Ferring, Shire, Therdiag

Waqqas Afif: Treatment and Monitoring of Inflammatory Bowel Disease, October 28, 2016

**Treatment and Monitoring of IBD**  
**Objectives**

- Recognize the utility of fecal inflammatory biomarkers for the diagnosis of IBD and the assessment of disease activity
- Recognize the role of biologic medications in the changing treatment paradigm in IBD patients
- Understand the role of therapeutic drug monitoring in monitoring IBD patients on treatment

**IBD Diagnosis and Monitoring**

**Clinical Case**

- 24 F, medical student
- **HPI**
  - Lower abdominal pain x 6 months
  - Frequent loose stools with rare blood PR
  - Decreased appetite & 5 lb weight loss
  - No EIM of IBD
  - Worse with stress and menstrual cycle
- **Physical:**
  - NAD, AVSS
  - Abdomen: soft and non-tender, no HSM

### Further important history ?

- Medication History
- Smoking History
- HPI
  - Travel history
  - Sick contacts
  - Antibiotic history
- Family History of IBD

### Differential Diagnosis

- IBS
- IBD
- Infectious
- Celiac disease
- Gynecologic origin

### IBS vs IBD

- "Alarm" or atypical symptoms which are not compatible with IBS include:
  - Rectal bleeding
  - Nocturnal or progressive abdominal pain
  - Weight loss
  - Anemia, elevated inflammatory markers,
  - Consider investigation in patients with family history or EIM

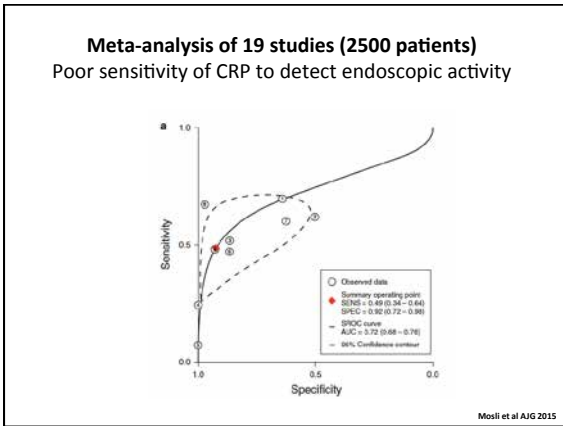
### Further investigations

- Laboratory examination
  - CBC, **CRP**, liver enzymes, IgA, TTG
- Stool studies
  - Stool C+S/O+P/C. difficile
  - **Fecal calprotectin**
- Endoscopic evaluation
  - EGD, colonoscopy, enteroscopy, capsule
- Radiology
  - U/S, cross-sectional imaging

### Non-invasive biomarker to assess intestinal inflammation ?

### What is needed from a biomarker in IBD?

- Non invasive marker of intestinal inflammation
  - Well correlated with intestinal inflammation and lesions
  - Responding to appropriate treatment changes
  - User-friendly
  - Affordable
  - Predicting natural history
    - flares, hospitalizations, surgeries
- **CRP and fecal calprotectin**



## Fecal Calprotectin

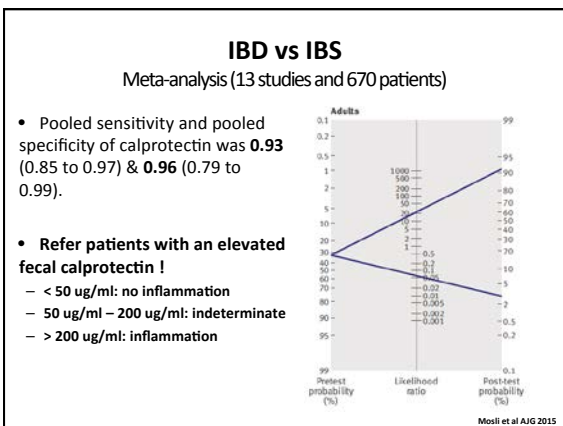
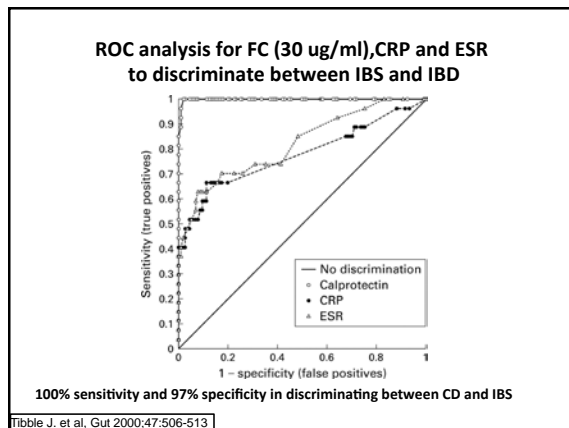
- Calprotectin makes up 60 % of total protein concentration of the cytosol fraction in neutrophil granulocytes and macrophages
  - Hetero-dimeric protein, 2 heavy and one light polypeptide chain, 36.2 kDa.
  - Each strand binds 2 calcium (or zinc)
  - Anti-microbial activity (bacteria and fungi)

### Conditions associated with elevated fecal calprotectin levels

Infectious	Inflammatory conditions
<ul style="list-style-type: none"> <li>Bacterial dysentery</li> <li><i>Giardia lamblia</i></li> <li><i>H. pylori</i> gastritis</li> <li>Infectious diarrhea</li> <li>Viral gastroenteritis</li> </ul>	<ul style="list-style-type: none"> <li>Inflammatory bowel disease</li> <li>Autoimmune enteropathy</li> <li>Cirrhosis</li> <li>Cystic fibrosis</li> <li>Diverticulitis</li> <li>Eosinophilic colitis/enteritis</li> </ul>
Neoplasms	Other
<ul style="list-style-type: none"> <li>Colonic and gastric polyps</li> <li>Colorectal cancer</li> <li>Gastric carcinoma</li> <li>Intestinal lymphoma</li> </ul>	<ul style="list-style-type: none"> <li>GERD</li> <li>Juvenile polyp</li> <li>Microscopic colitis</li> <li>Peptic ulcer</li> <li>Untreated celiac disease</li> </ul>
Drugs	Other
<ul style="list-style-type: none"> <li>NSAIDs</li> <li>PPIs</li> </ul>	<ul style="list-style-type: none"> <li>Age &lt;5 years</li> <li>Untreated food allergy</li> </ul>

GERD, gastro-esophageal reflux disease; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor

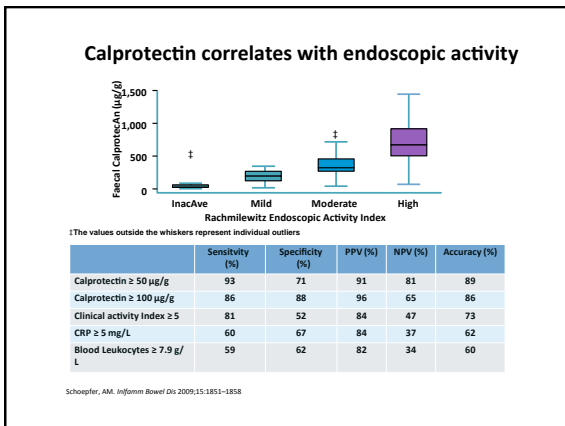
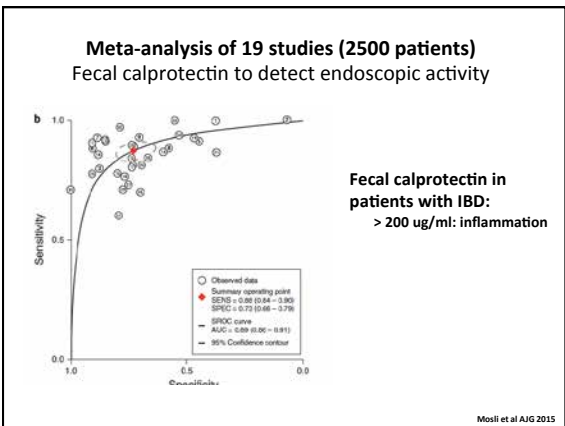
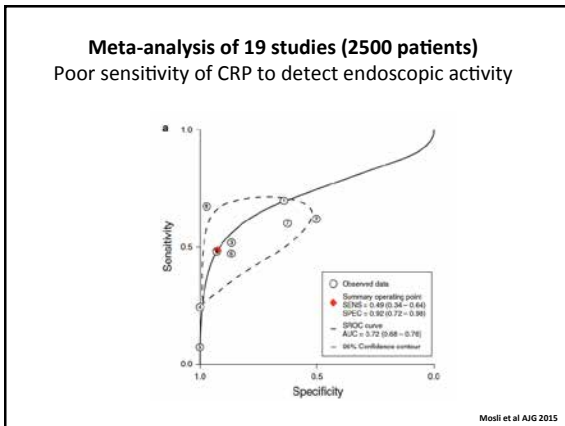
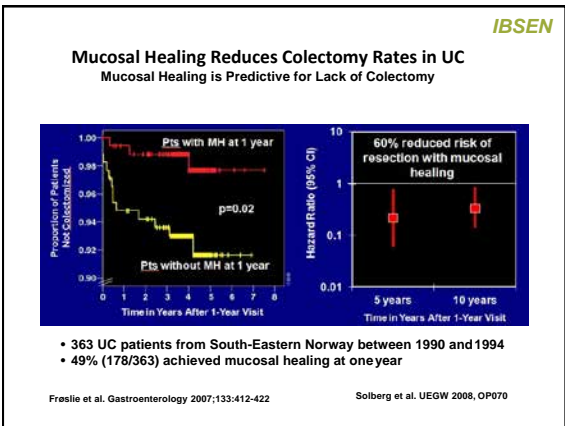
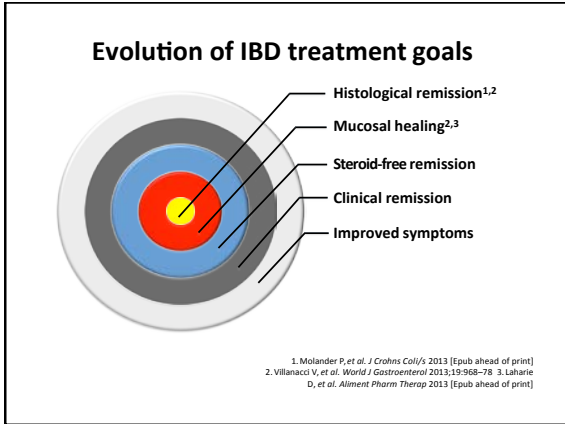
Bressler B et al CJGH 2015

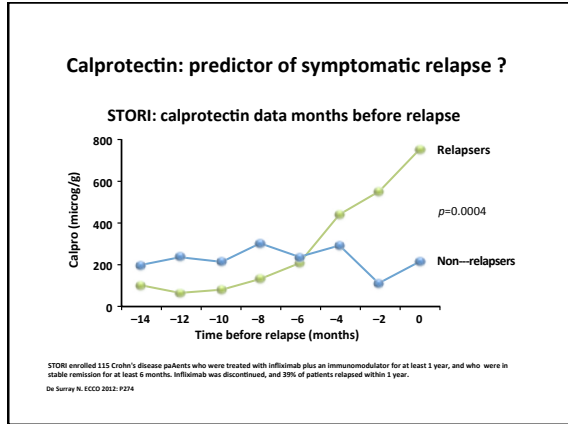
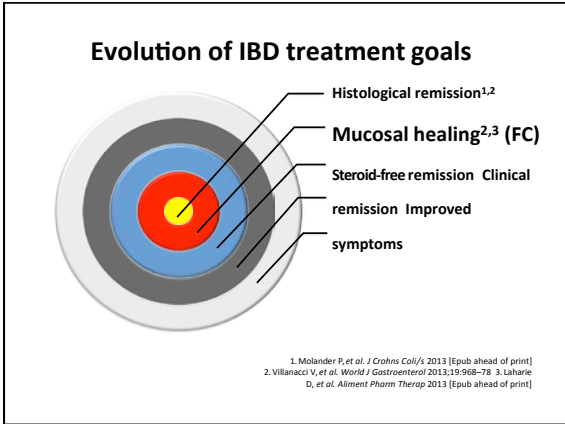


## Monitoring in IBD

## Choosing Wisely in IBD

**“Avoid using only clinical symptoms to make treatment decisions”**





### How to Take a Stool Sample: 11 Steps (with Pictures)

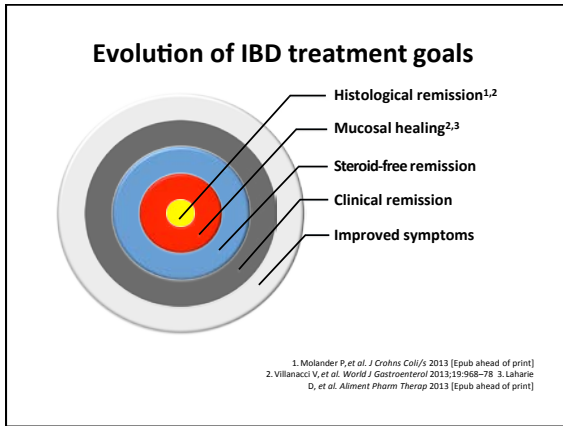
<http://www.wikihow.com/Take-a-Stool-Sample>

### It's all about the stool in 2016 ...

- Fecal microbiota transplantation !
- Two recent RCT's (2015) in patients with UC
- One positive (n=70) for clinical remission using fecal enemas and one negative (n=37) using UGI tract
  - Positive study demonstrated fecal donor affected outcomes
- FMT for IBD should remain in clinical trials and not in clinical practice (FDA, Health Canada and CAG)

So you have confirmed disease activity ... now what ?

### Changing Treatment Paradigms in IBD

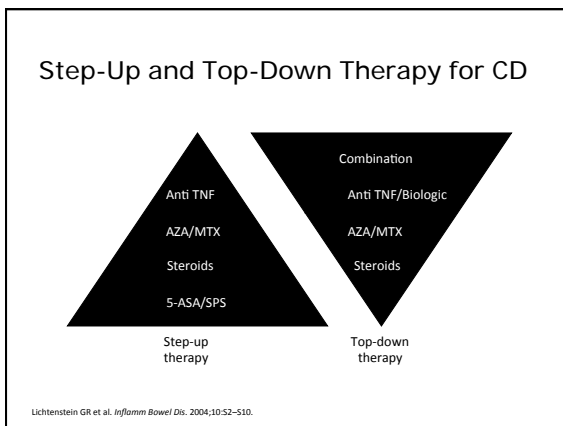
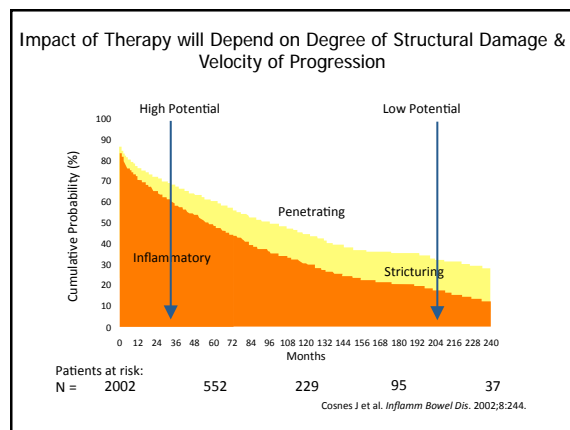
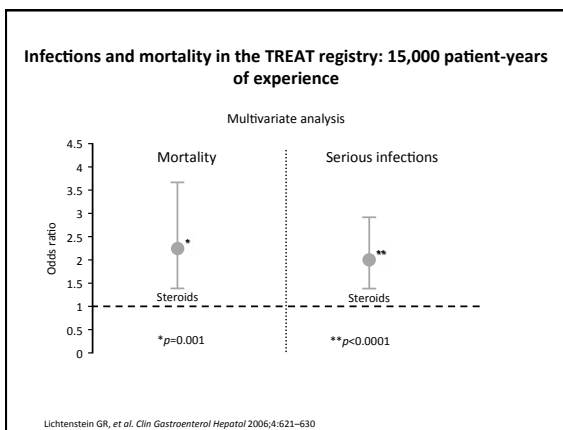


Canadian Association of Gastroenterology / Association Canadienne de Gastroentérologie

**Choosing Wisely Canada**

**Don't routinely use long term steroid therapy in inflammatory bowel disease.**

The risks of long term steroid therapy (therapy for more than 4 months and/or more than two courses in a year) outweigh any benefits in inflammatory bowel disease and should not be given to patients. Instead, they should be offered more effective maintenance therapy such as immunosuppression or biologic therapy that are safer and have more evidence for efficacy.



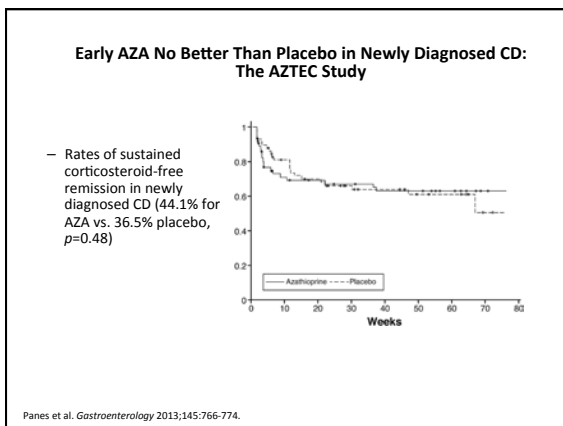
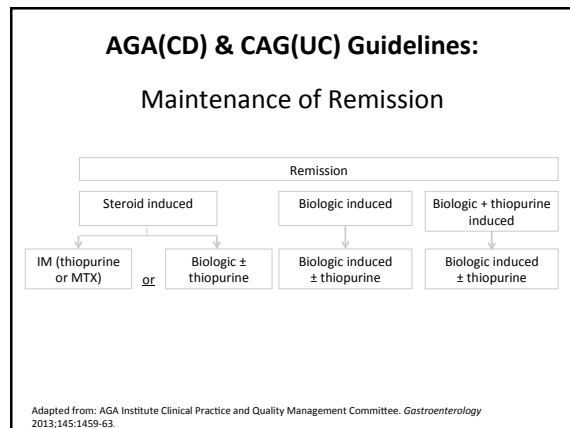
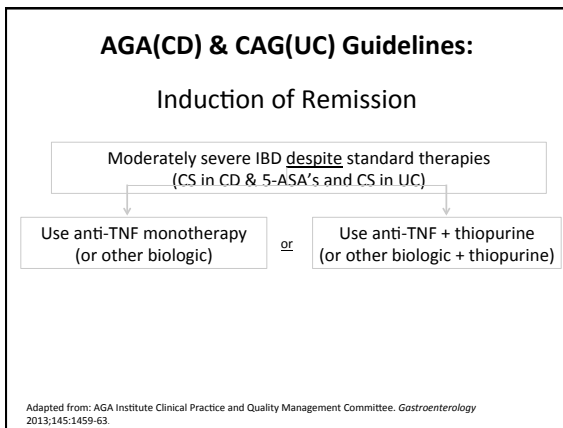
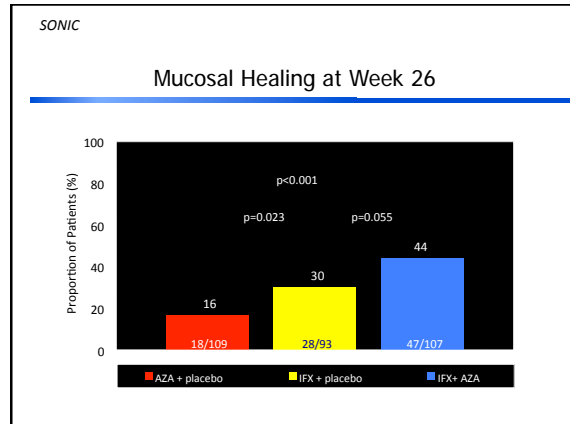
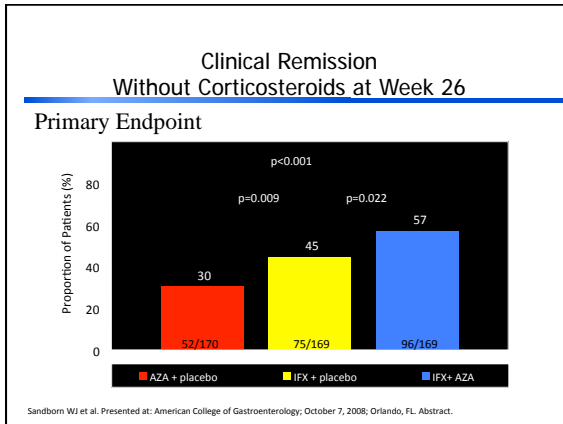
THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

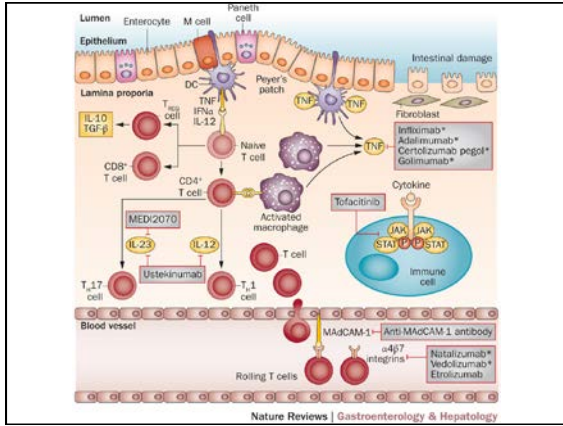
### Infliximab, Azathioprine, or Combination Therapy for Crohn's Disease

Jean Frédéric Colombel, M.D., William J. Sandborn, M.D., Walter Reinisch, M.D., Gerassimos J. Mantzaris, M.D., Ph.D., Asher Kornbluth, M.D., Daniel Rachmilewitz, M.D., Simon Lichtiger, M.D., Geert D'Haens, M.D., Ph.D., Robert H. Diamond, M.D., Delma L. Broussard, M.D., Kezhen L. Tang, Ph.D., C. Janneke van der Woude, M.D., Ph.D., and Paul Rutgeerts, M.D., Ph.D., for the SONIC Study Group\*

N ENGL J MED 362:15 NEJM.ORG APRIL 15, 2010

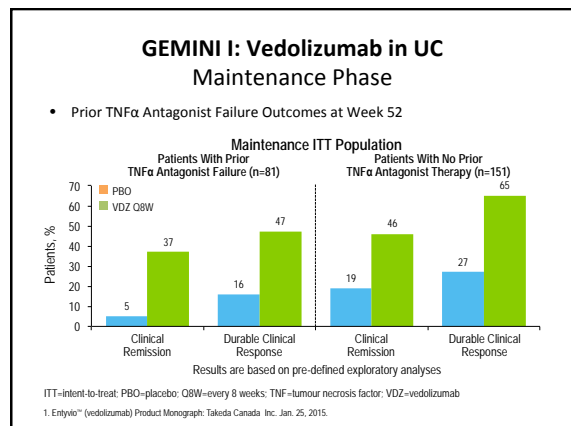
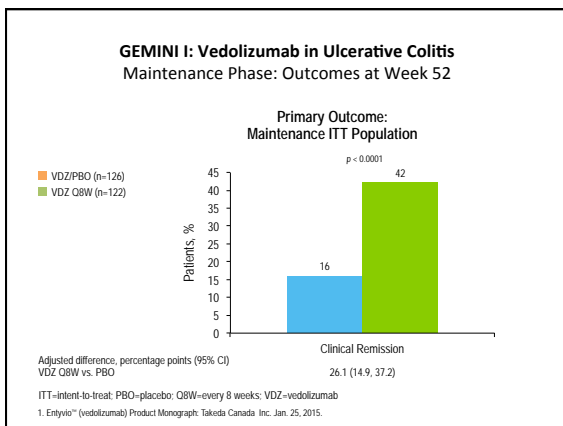
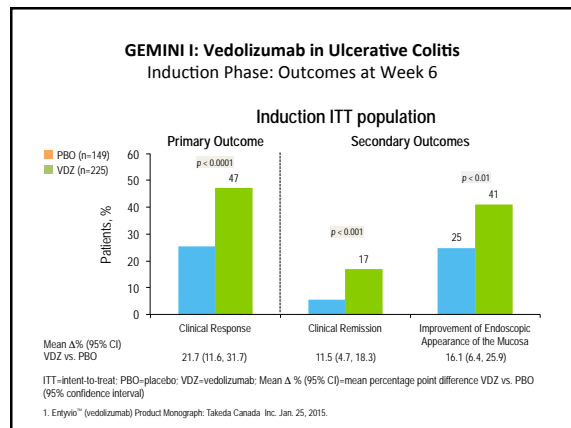


## New Treatments for IBD

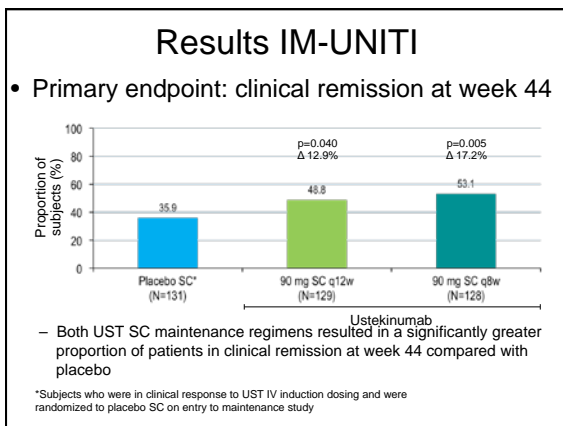
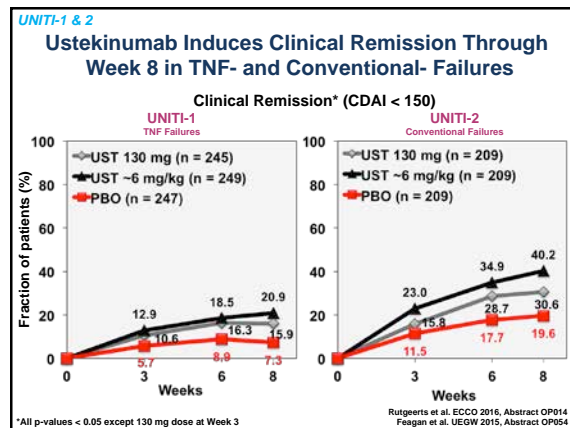
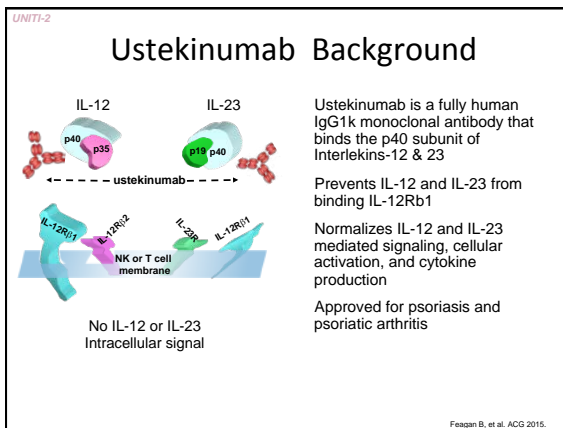
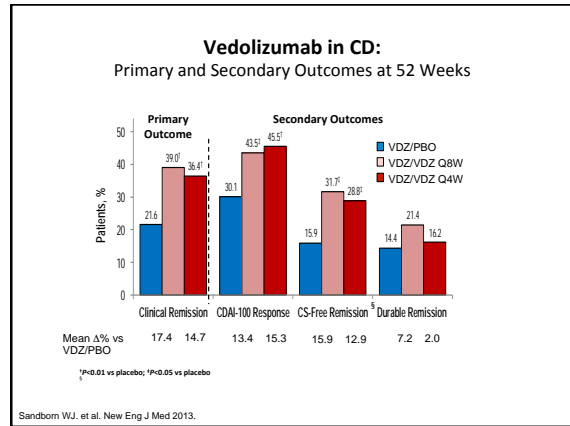
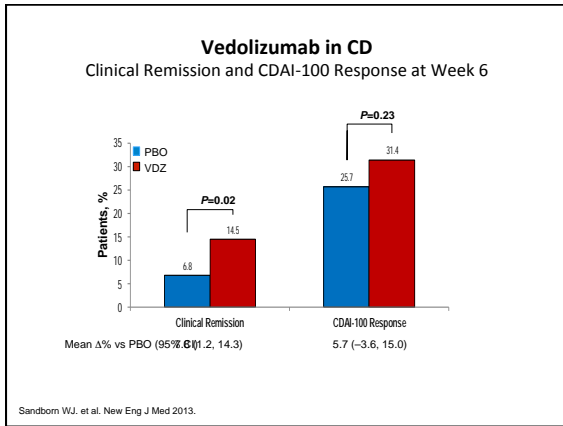


### α4β7 Integrin–MAdCAM-1 is One of the Interactions That Contributes to Chronic Inflammation in UC

### Specific Binding Action Designed for a Gut-homing Inflammatory Pathway





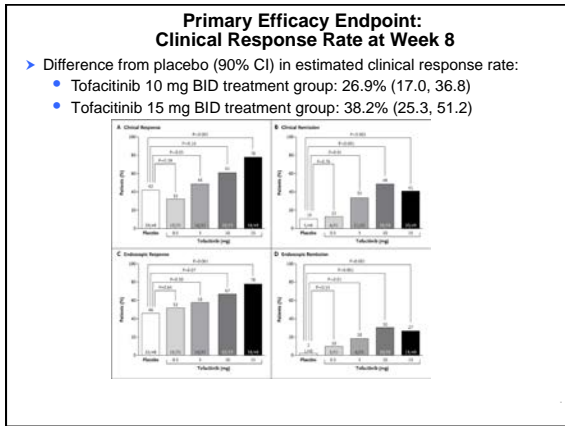


### Cytokine Signaling of Janus Kinase (JAK)

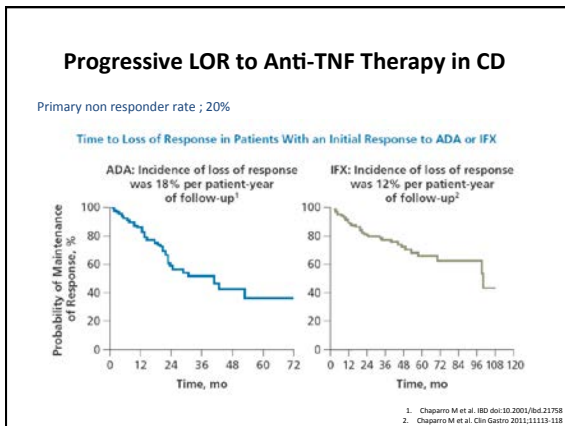
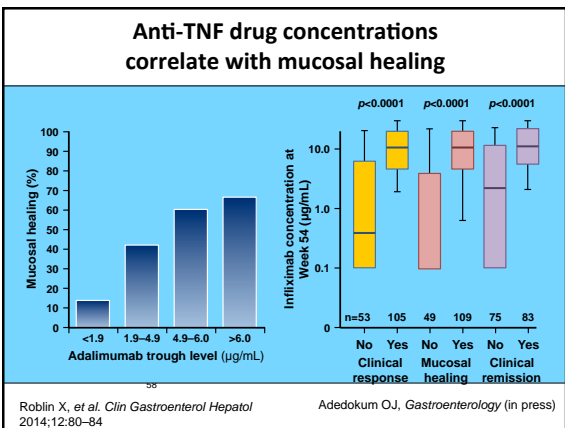
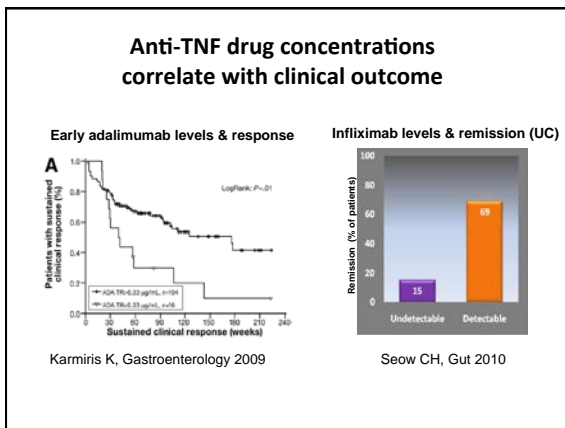
Cytokine	Effects on the immune system
IL-2	Stimulate the proliferation and differentiation of Th, Tc, B, and natural killer (NK) cells
IL-4	Induce the differentiation of Th0 to Th2. Induce immunoglobulin switching
IL-7	Promote the development, proliferation and survival of T, B, and NK cells
IL-9	Stimulate intrathymic T cell development
IL-15	Promote the proliferation, cytotoxicity and cytokine production of NK cells
IL-21	Enhance T and B cell function

- Tofacitinib (CP-690,550) is a novel, small-molecule, oral JAK inhibitor that is being investigated as a targeted immunomodulator for several inflammatory diseases including ulcerative colitis (UC) and Crohn's disease<sup>1,2</sup>
- Tofacitinib inhibits JAK1, JAK2, and JAK3 in vitro with functional cellular specificity for JAK1 and JAK3 over JAK2.<sup>3</sup>

Sandborn, DDW 2011

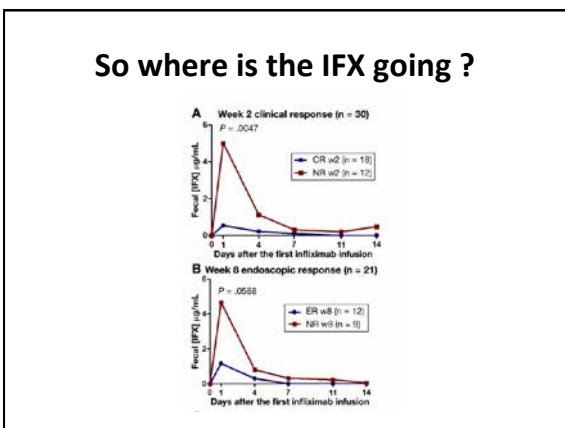
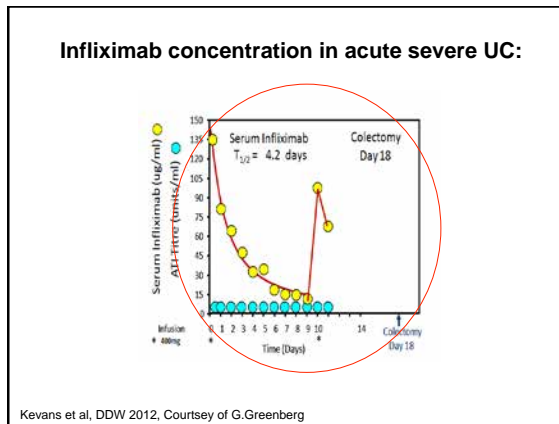
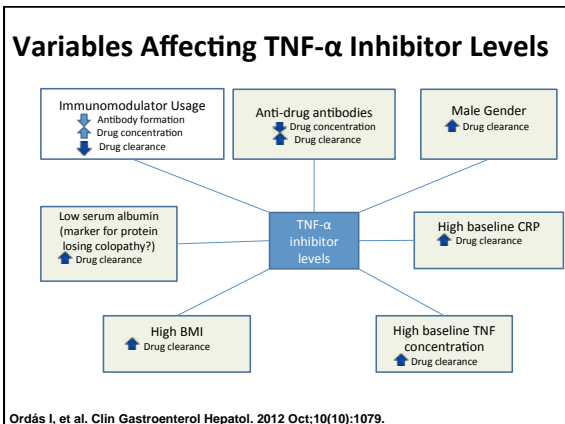


**Optimizing Biologic Treatment: Therapeutic Drug Monitoring**



**Why Do Some Patients Lose Response?**

- Symptoms are not IBD (IBS, infections, SBBO)
- Inadequate drug to fight disease burden
  - PK effect (absorption, distribution, metabolism, elimination)
  - PD effect (drug is present; change in therapeutic effect, adverse events, etc.)



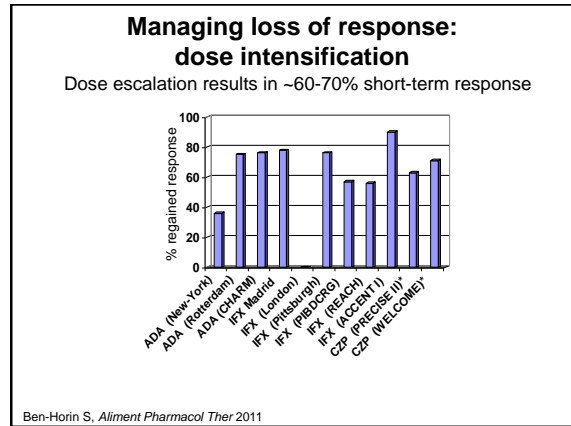
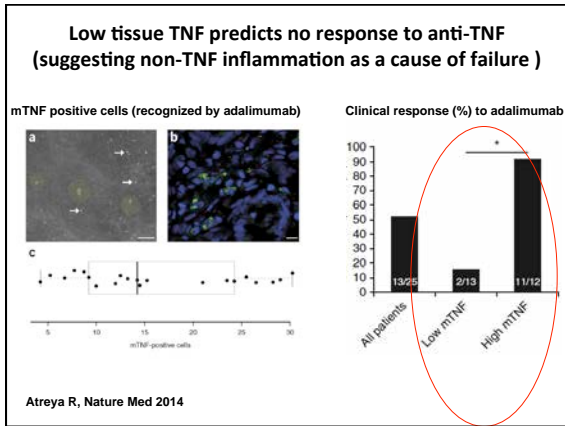
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  3. Symptoms are IBD, but non-inflammatory (i.e. strictures, fistulae)

### Mechanisms for loss of response

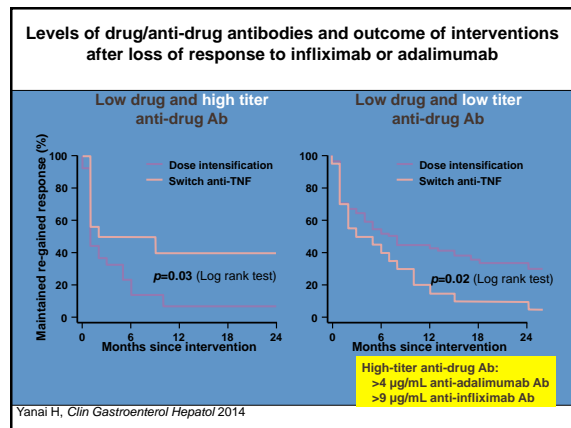
CD patient with increasing pain, bloating, minimally elevated CRP and adequate anti-TNF concentration

**Consider colonoscopy !**

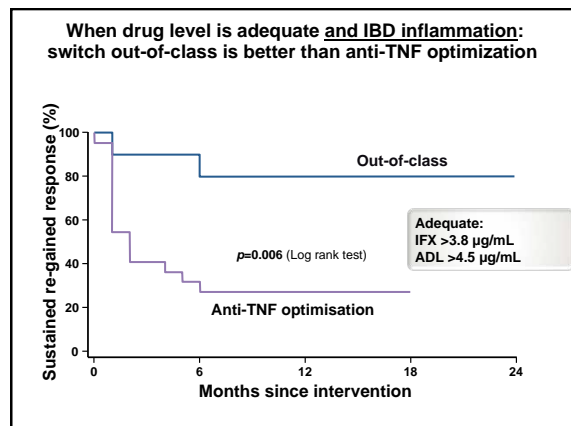
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1. Symptoms are not IBD (IBS, infections, etc.)
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    - b. PD effect (drug is present; change in therapeutic effect, adverse events, etc.)
  3. Symptoms are IBD, but non-inflammatory (i.e. strictures, fistulae)
  4. Disease has 'shifted mechanism' (non-TNF driven; may be PD related)



**Can drug (and anti-drug antibodies) levels guide which intervention is best for loss of response?**



**Anti-TNF concentrations**

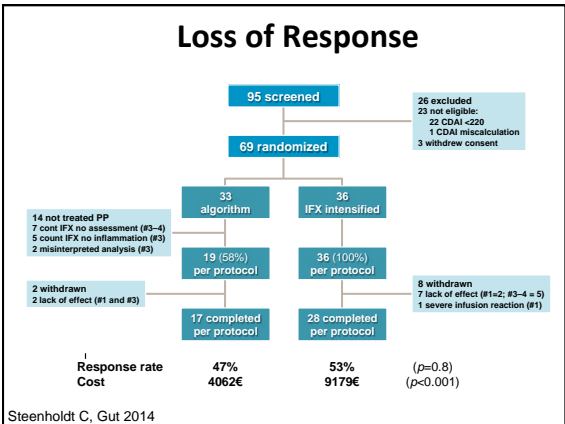
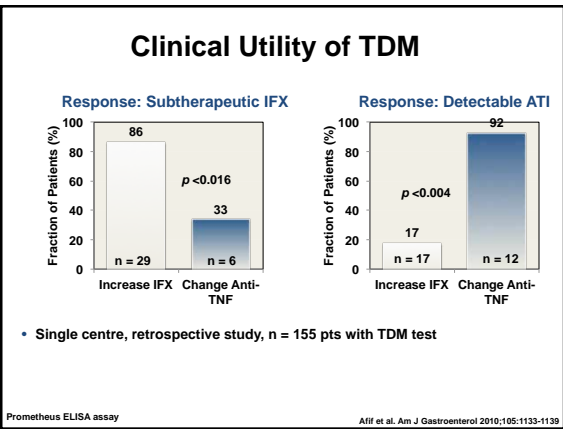
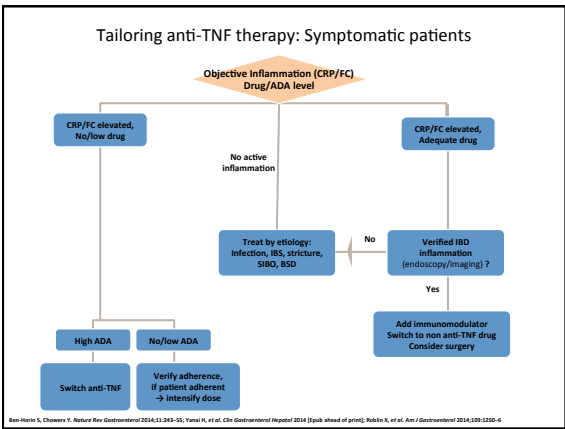


# TDM RESULTS & ALGORITHM

## Verify that the patient is taking the drug!

Up to 15%–29% of adalimumab/infliximab-treated patients are not adherent to their injections  
(Missed at least one injection/infusion during the last 3 months)

Billioud V, et al. *Inflamm Bowel Dis* 2011;17:152–9  
Lopez A, et al. *Inflamm Bowel Dis* 2013;19:1528–33



### Clinical cut-points at trough:

**Anti-TNF Concentrations (ug/ml)**

**Dose Escalate:**  
<3 for IFX & < 5 for ADAL

**Consider Dose Escalation**  
3-10 for IFX & 5-20 for ADAL

**Switch out of class**  
> 10 for IFX and > 20 for ADAL

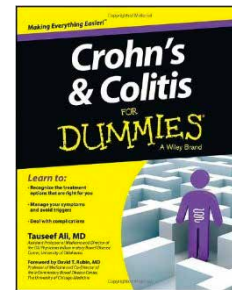
**High Titer Antibodies**  
>8 ug/ml (>130 AU/ml) for IFX/?ADAL

## Conclusions

- Clinical symptoms are not an accurate measure of active inflammation (need objective markers)
- Monitor for disease activity objectively (fecal calprotectin > 200 ug/ml) and adjust treatment according to TDM
  - (use FC > 50 ug/ml to distinguish between IBD and IBS)
- Aim for mucosal healing (avoid long-term corticosteroids) → increased use of biologic medication in moderate to severe IBD
  - New biologic medications available
- Use therapeutic drug monitoring to help optimize patients losing response

## References

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McGill University Health Centre



Thank you, any questions ?