

# **The Management of Complicated and Refractory Crohn's Disease**

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# Complex Crohn's Disease : Medical

- **What is it?**
  - “I know it when I see it...”
  - **Patients who are:**
    - Steroid dependent
    - refractory or intolerant to standard therapies
    - Have extensive disease or disease outside of GI tract (lung, skin)
    - Have had multiple surgeries in past (>1) and /or at risk of short bowel
    - At high risk of recurrence after resection (short disease duration, smokers, etc)
    - Significant co-morbid medical conditions such as PSC, HBV, Pregnancy, cancer, HIV, etc
  - **Patients with strictures, fistulas or abscesses**

# Complex / Refractory Crohn's Disease : Medical

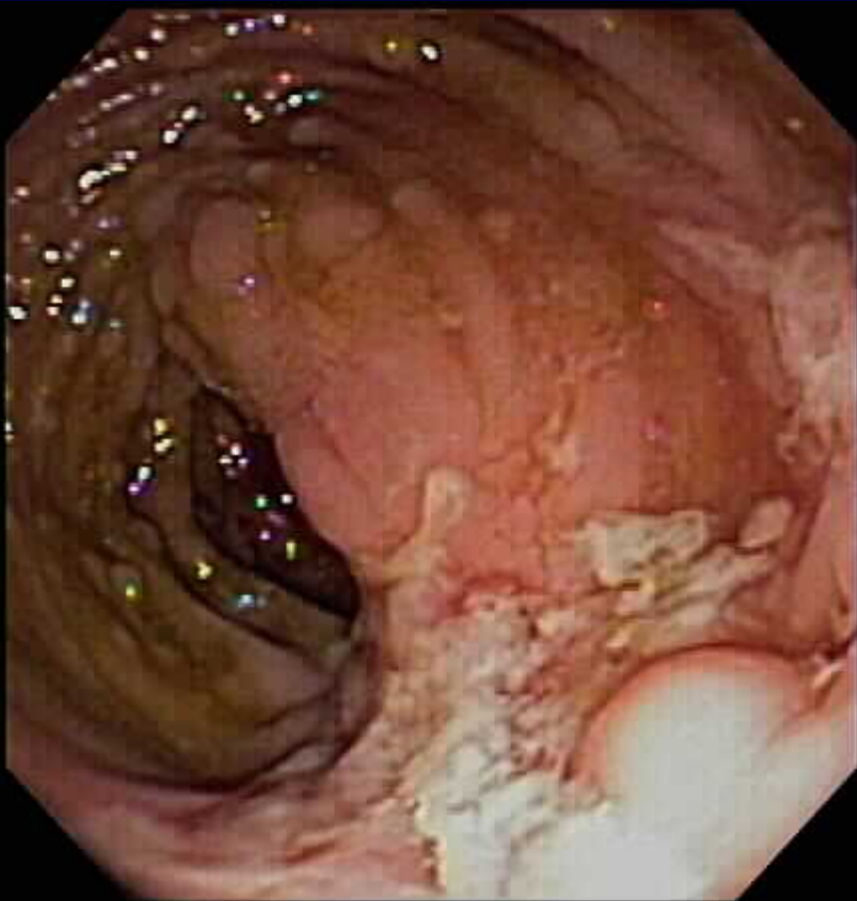
- What is it?
  - “I know it when I see it...”
  - Patients who are:
    - Steroid dependent
    - **Refractory or intolerant to standard therapies**
    - **Have Intra-abdominal abscess**
    - Have had multiple surgeries in past (>1) and /or at risk of short bowel
    - At high risk of recurrence after resection (short disease duration, smokers, etc)
    - Significant co-morbid medical conditions such as PSC, HBV, Pregnancy, cancer, HIV, etc
  - Patients with strictures, fistulas or abscesses

**Patient #1**

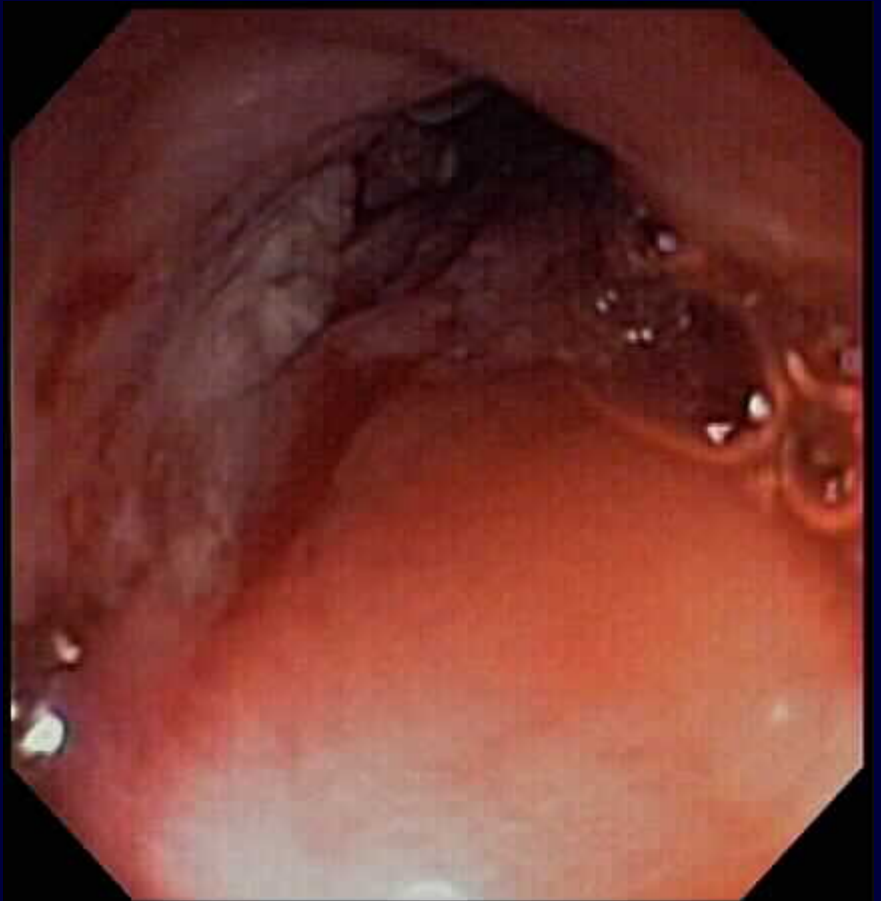
# 45 yo Male with Intra-Abdominal Abscess

- 45 yo male presents with history ileocolic resection 10 years before. No maintenance medication post-op.
- Presents now with 3 month history of abdominal pain after eating. 20# wt loss during this time.
- FH: positive for Crohn's
- PE: Some RLQ tenderness and possible fullness...
- Colonoscopy and Imaging show.....

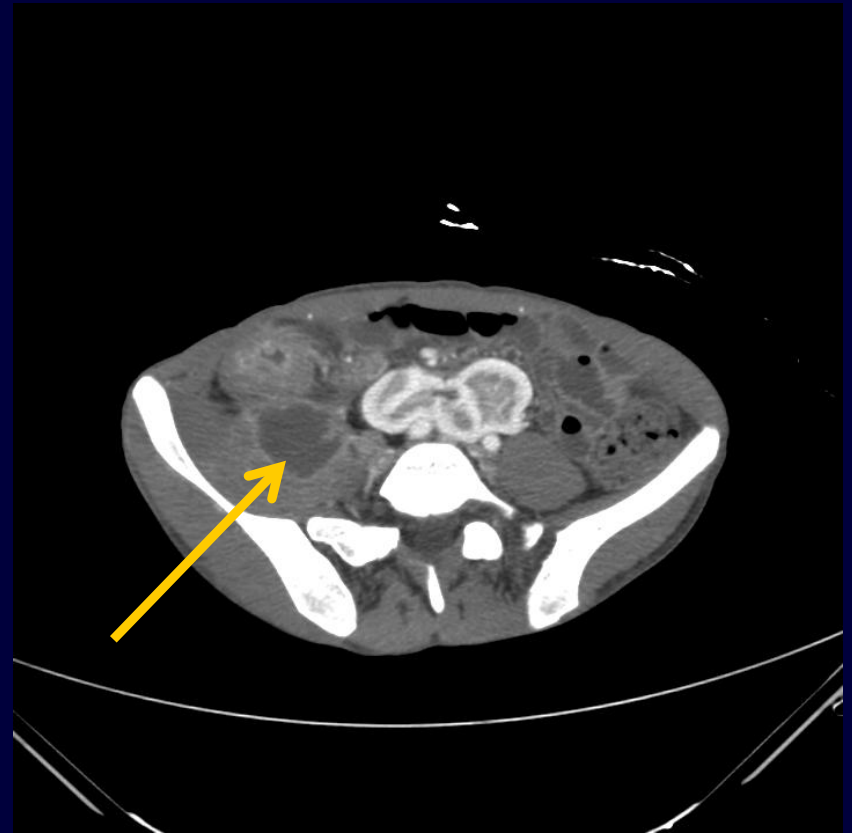
**Severe right-sided colitis**



**Stricture at anastomosis**



# CTE



# Initial Management

- Patient admitted for IV antibiotics
  - Use ones that have Gram negative and anaerobic coverage
- Abscess needs to be drained especially if > 3 cm. (poor penetration of antibiotics)
  - Perc drainage successful in 77% of the time in largest study. <sup>1</sup>





# Drainage is achieved.... Now what?

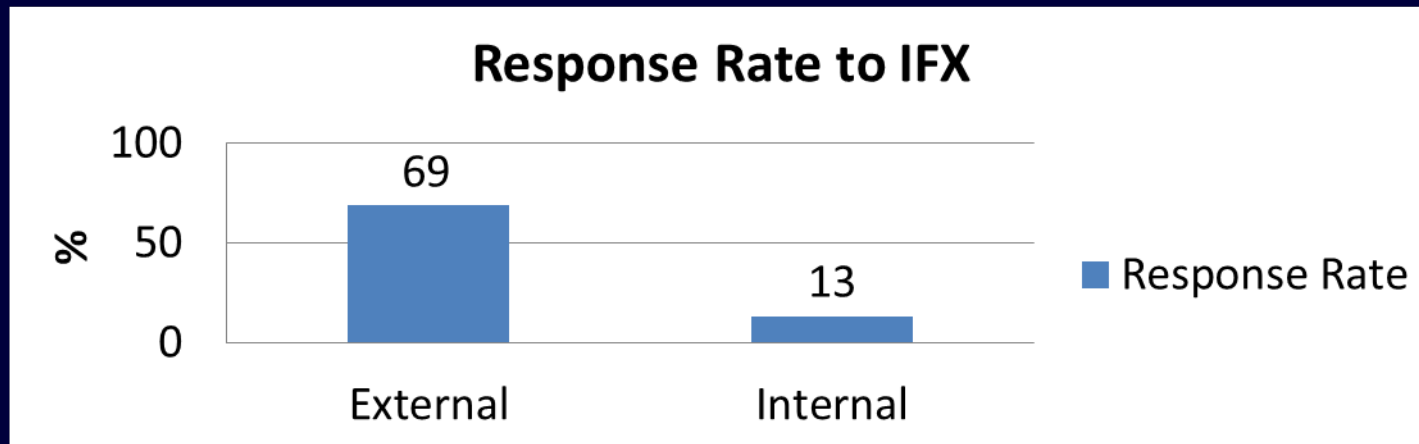
- **Continue antibiotics. Wait for patient to be afebrile for 48-72 hrs and reimaging.**
  - If wbc remains elevated and /or fever persists re-interrogate the drain
  - Consider scope (if one has not been done recently to help guide treatment)
- **Decisions to make at this point?**
  - TPN vs. resuming diet
  - Early Surgery (with diverting stoma) vs. trial of medical treatment

# TPN vs. Diet

- Retrospective report of the use of short-term TPN in pts with penetrating disease
  - 78 pts given pre-op nutritional treatment (median 23 days) and weaned off steroids, immunosuppressives<sup>1</sup>
- Need for stoma was only 8%
  - major complications 5%

# Early Surgery vs. Attempt at Medical Treatment

- 1<sup>st</sup> determine if abscess related to stricture /fistula and if stricture is fibrotic vs. inflammatory
- If stricture is present (especially if fibrotic) treatment is largely Surgical
- No prospective trial to look specifically at internal fistulas.
  - In general, internal fistulas less likely to respond to Anti-TNF treatment.



# Early Surgery vs. Attempt at Medical Treatment

- In general, if fistula present chance of non-surgical success is low
  - Sahai et al. found in retrospective study of 27 pts with intra-abd abscess that associated fistulas was associated with need for surgery within 30 days despite drainage<sup>1</sup>
  - Golfieri et al, found in a study of 70 patients that all failures of perc drainage were associated with a fistula to the bowel<sup>2</sup>

**1 Sahai et al. Am J Gastro 1997**

**2-Golfieri et al. Tech Coloproct 2006**

# Early Surgery vs. Attempt at Medical Treatment

If no stricture present or stricture is inflammatory can consider medical treatment.

## ● Pros:

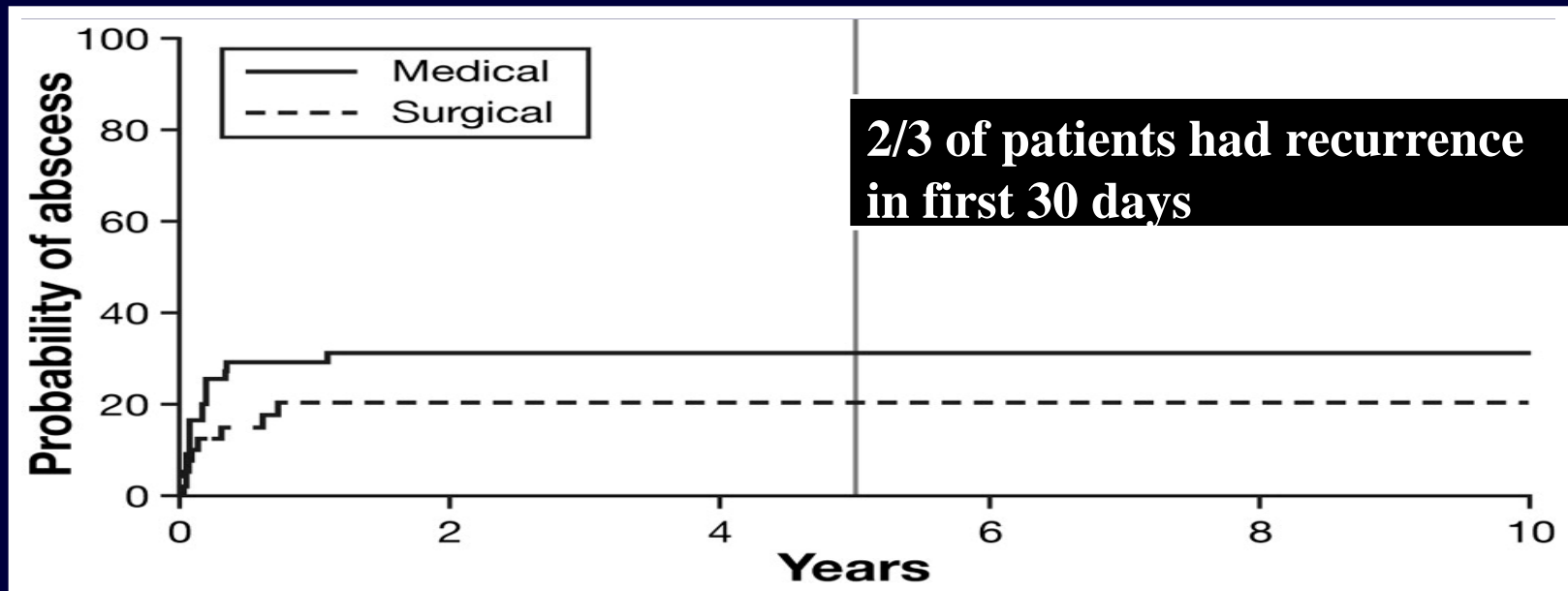
- Largest study from Mayo Clinic shows equivalent outcomes
- May delay or prevent surgery
- Decrease length of stay

## ● Cons:

- Use of anti-TNF may be associated with increased post-op complications
- May delay inevitable
- May “handicap” anti-TNF agents as disease is at an irreversible stage
- Patients failing aggressive therapy unlikely to respond

# Early Surgery vs. Attempt at Medical Treatment

- How about the rest of the patients? Can we treat medically?
  - Retrospective review of 95 patients from Mayo Clinic (1999-2006) (55 had perc drainage)<sup>1</sup>
  - 5 year recurrence was 31% (med) vs. 20% (surg)  $p=0.25$
  - Median LOS was less for med treated pts 15.5 days vs. 5 ( $p<0.001$ )



1- Nguyen, D. L. et al. (2012). Clin Gastroenterol Hepatol.

# Anti-TNF Associated with an Increased Risk of Post-Operative Infection

- 325 surgeries at UMB in 211 CD patients
- 150 had anti-TNF  $\leq$  8 weeks before surgery
- Anti-TNF group had higher rates of surgical site (32% v. 22%) and infectious complications (36% v. 25%) compared to controls
- After adjustment for confounding,
  - OR 2.84 (1.1-3.1) for surgical site
  - OR 2.02 (1.2-3.4) for infectious complications

# Summary

- **Initial treatment should focus on draining abscess and treating infection**
- **Risk stratify based on size of abscess, presence of fistulas, strictures and nature of the process (inflammatory vs. fibrotic)**
- **Use bowel rest and TPN to help bridge to definitive treatment**
- **Medical treatment reserved for those with a primary inflammatory process (ie those with higher chance of success)**



**Patient # 2**

# 28 yo with Refractory Disease

- 28 yo male comes to office for 2<sup>nd</sup> opinion with 6 year history of Crohn's ileocolitis.
- He has abdominal pain and diarrhea (10-12x / day) with urgency and 10# wt loss. Despite being on infliximab for last 3 years. Now on 10 mg/kg q5 weeks
  - Had initial response to IFX but requiring more over time
- He is also on 2.5 mg /kg/day of azathioprine
- He is a non-smoker
- No previous h/o surgery

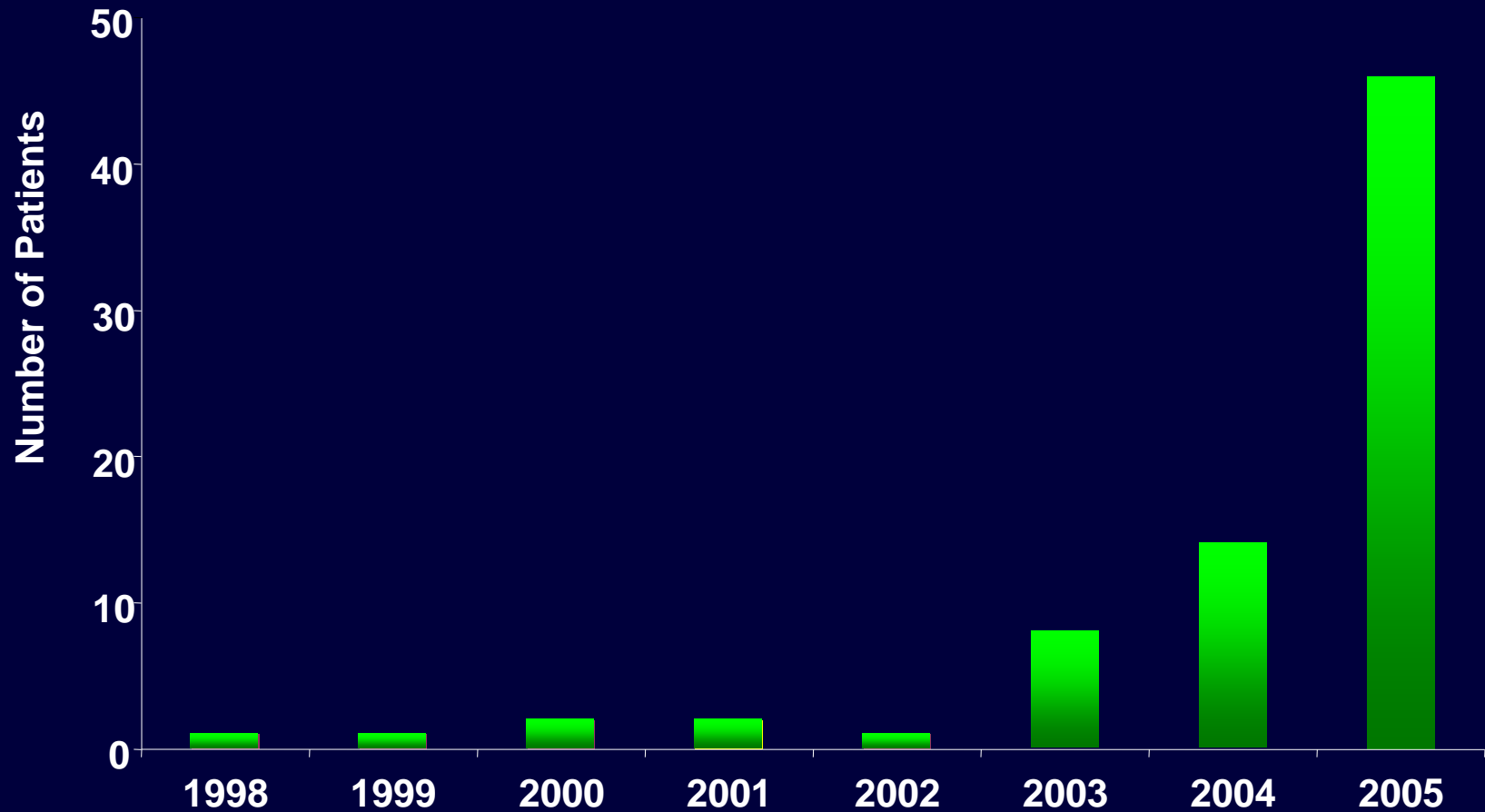
# 28 yo with Refractory Disease (Part B)

- On exam he looks thin, afebrile. Tender to palpation in RLQ. HR is 100
  - Labs: WBC= 10k, Hgb 11, Plt 600, CRP 20
  - Stool studies negative

# 28 yo with Refractory Disease (Part C)

- **What is your approach to this patient?**
  - **Rule out other causes for symptoms**
    - Infection
    - Bile salt diarrhea
    - Stricture / EC fistula
    - IBS
  - **Make sure there is active luminal disease**
  - **Make sure current therapy is maximized**
    - If current meds optimized then consider alternative treatment options (another TNF, meds with alternative mechanism of action)

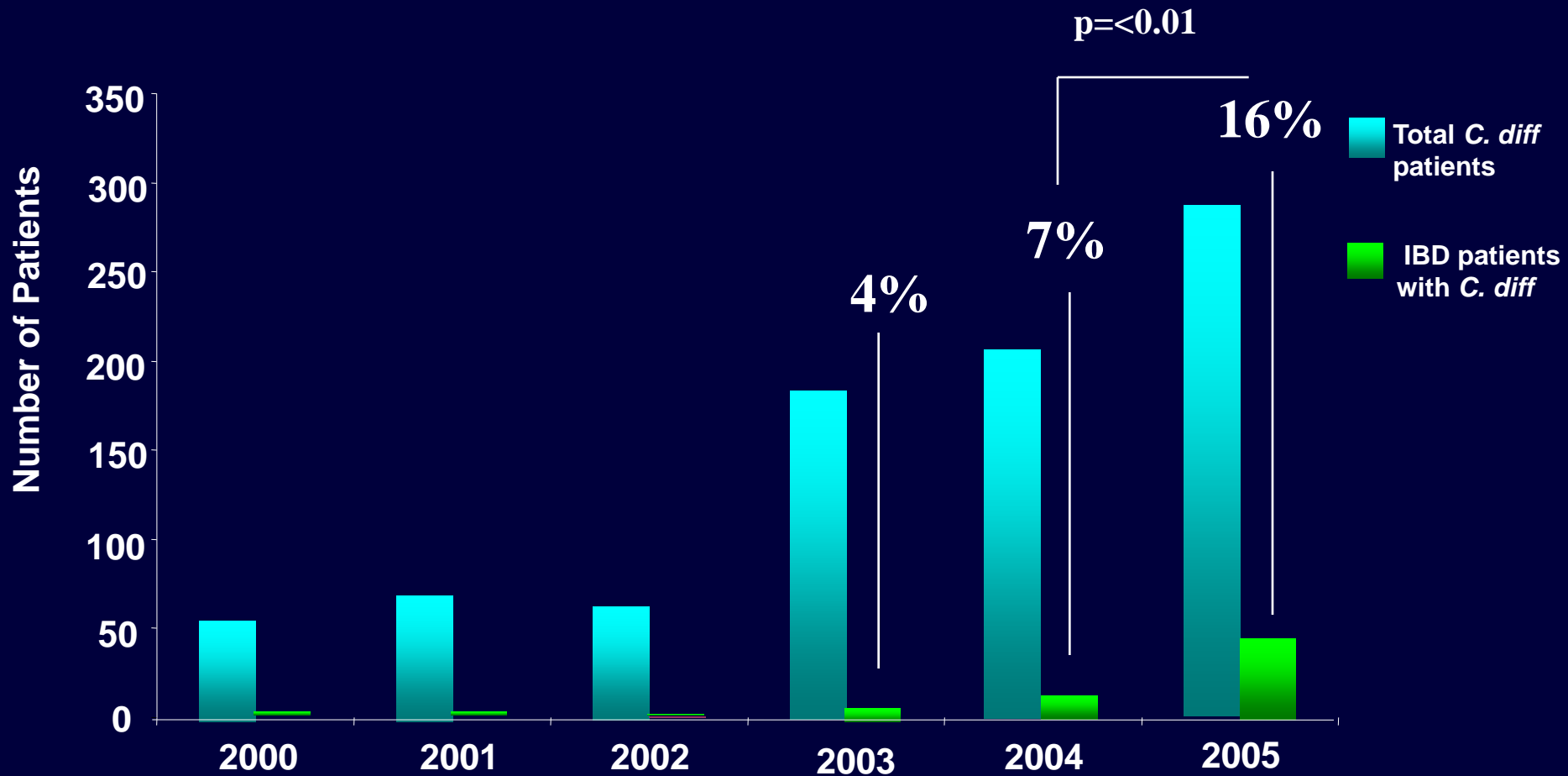
# Increasing Impact of *Clostridium difficile* on IBD



$P \leq 0.01$

Issa M et al. Clin Gastroenterol Hepatol. 2007;5: 345-51.

# Increasing Proportion of *Clostridium difficile* Patients with IBD

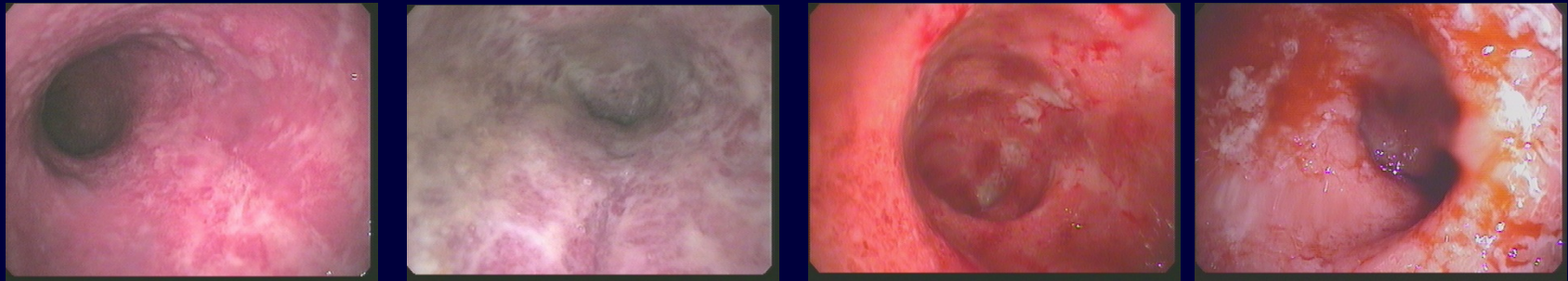


# Endoscopic Appearance of *Clostridium difficile*

Endoscopic appearance of *C. diff* in control patients



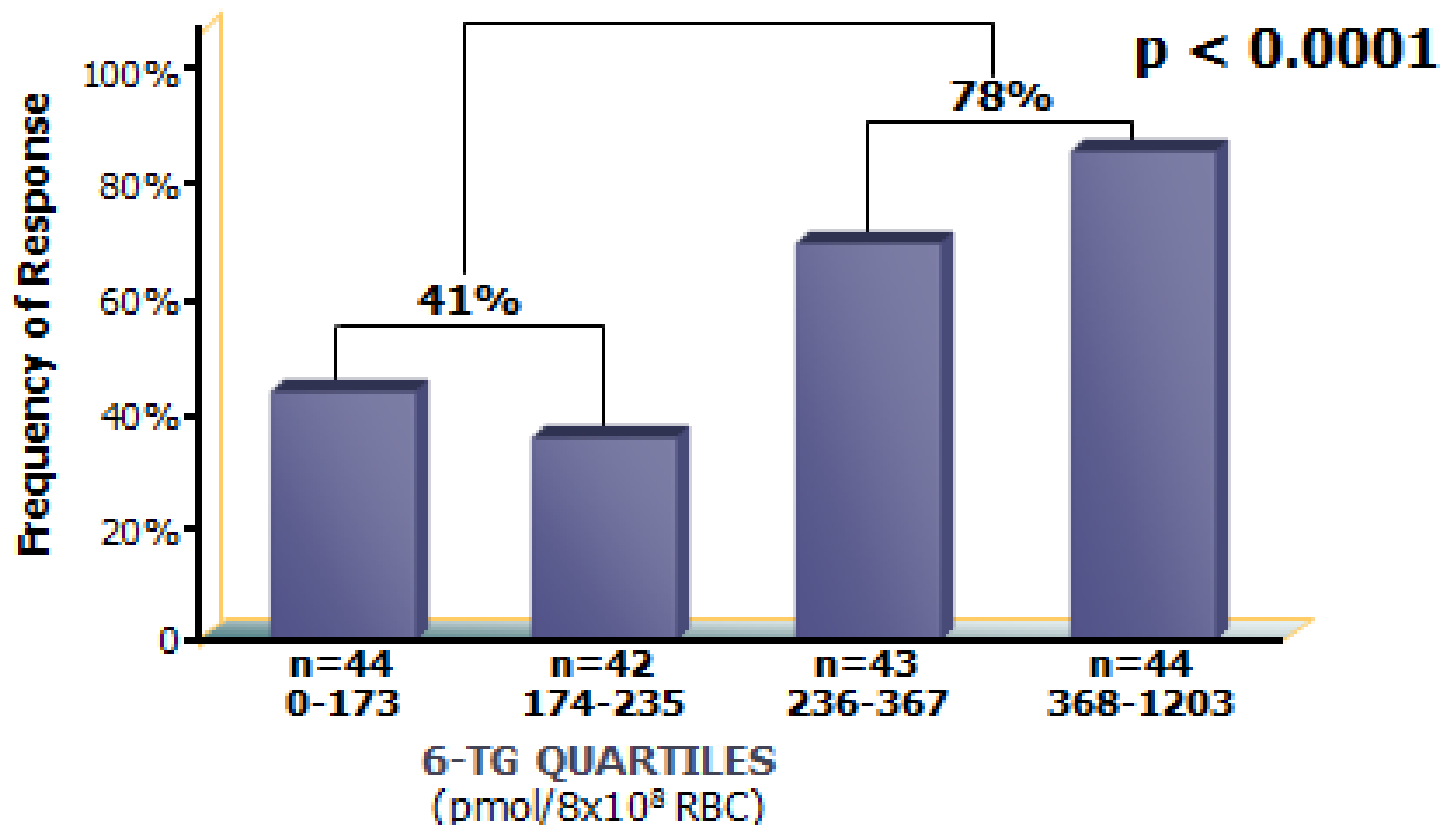
Endoscopic appearance of *C. diff* in patients with IBD



Ulcerative Colitis

Crohn's Disease

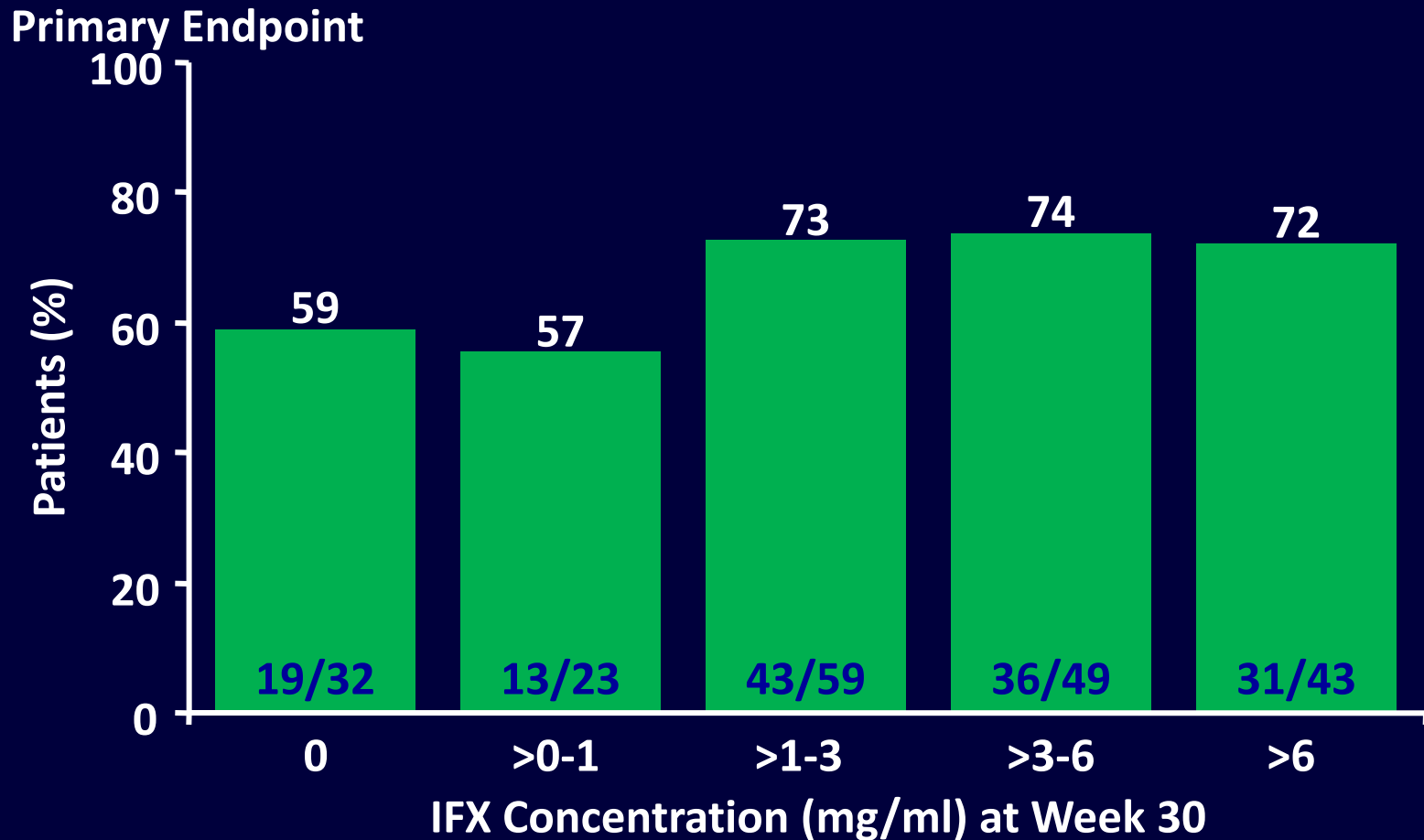
# Optimizing Meds: 6-TG Levels and Clinical Response





# Optimizing Meds: Infliximab Levels

By Trough IFX Concentration at Week 26



# Optimizing Meds: Measurement of IFX Levels and ATIs

Test results impacted treatment in 73 % of patients

N=155

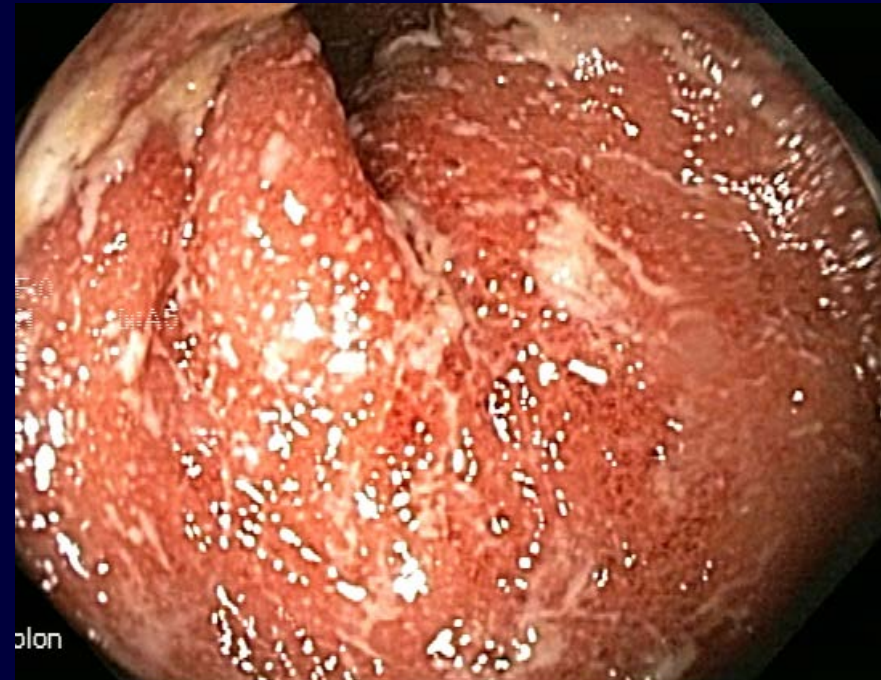
Subtherapeutic IFX	Dose escalation	Complete or partial response - 86%
Subtherapeutic IFX	Switch anti-TNF	Response - 33%
Therapeutic IFX		No evidence of active inflammation in 62% of the patients
ATIs + patients	Switch anti-TNF	Response - 92%
ATIs + patients	Dose escalation	Response - 17%

“Increasing the infliximab dose in patients who have HACAs is ineffective, whereas in patients with subtherapeutic infliximab concentrations, this strategy may be a good alternative to changing to another anti-TNF agent.”

Afif W, et al. *Am J Gastroenterol* 2010;105(5):1133-9.

# 28 yo with Refractory Disease (Update)

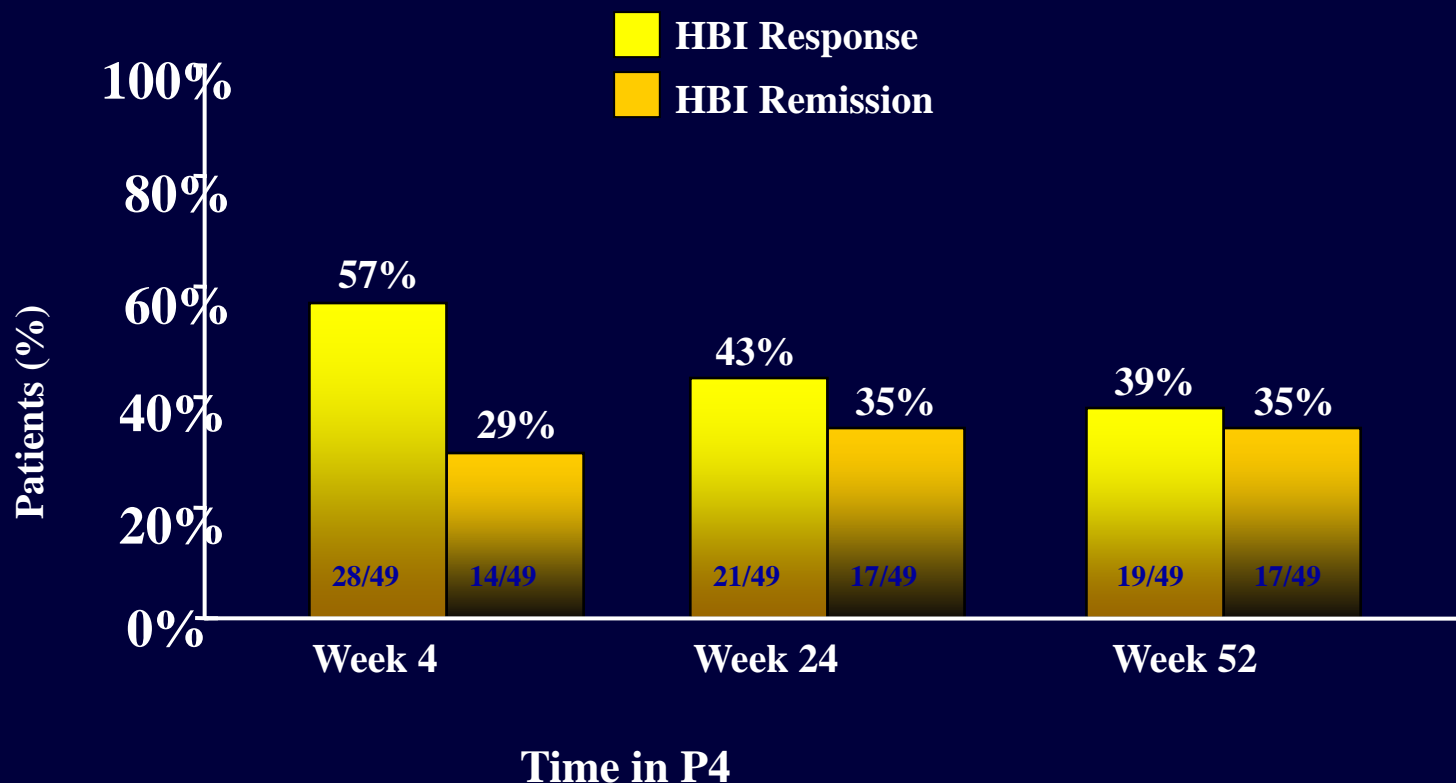
- Colonoscopy shows ulcerations, friability, and muco - purulence involving the whole colon. There is also active ileitis.
- CTE: Active ileitis in distal 8 cm without stricture
- Lab testing
  - CRP 20
  - 6-TG 300, 6-mmp 5800
  - IFX trough < 1mcg / ml
  - ATI 29 U/ml



# Response and Remission Rates for PRECiSE 4:

## PRECiSE 4:

Origin: PRECiSE 2 CZP arm

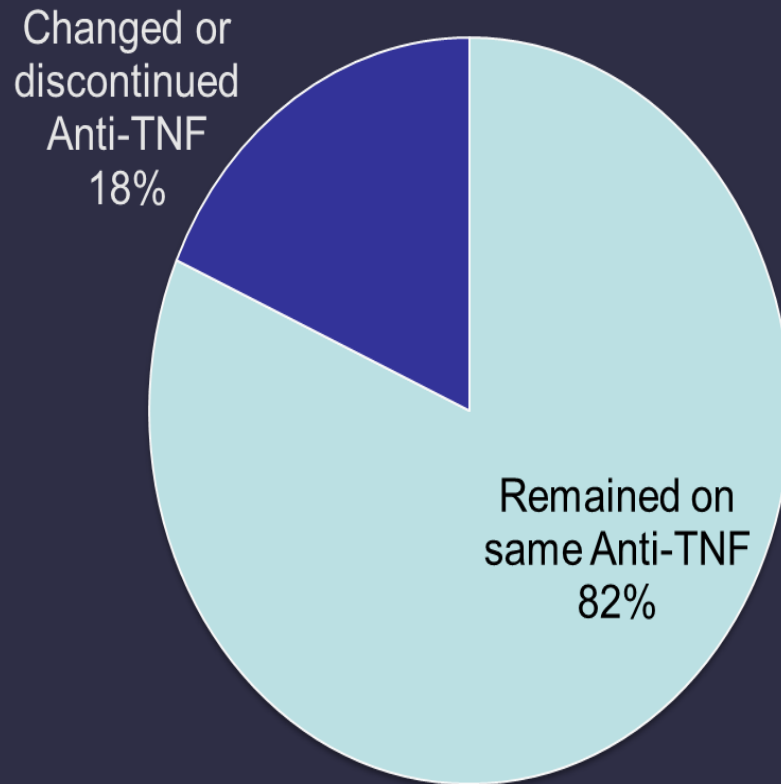


Sandborn WJ et al. *Gastroenterology*. 2007;132(suppl 1):A505.

Serious and sometimes fatal side effects have been reported with CIMZIA, including tuberculosis and other serious infections.

Please see important safety information on slide 41 and accompanying prescribing information

# Micro-Reinduction with Adalimumab for loss of response

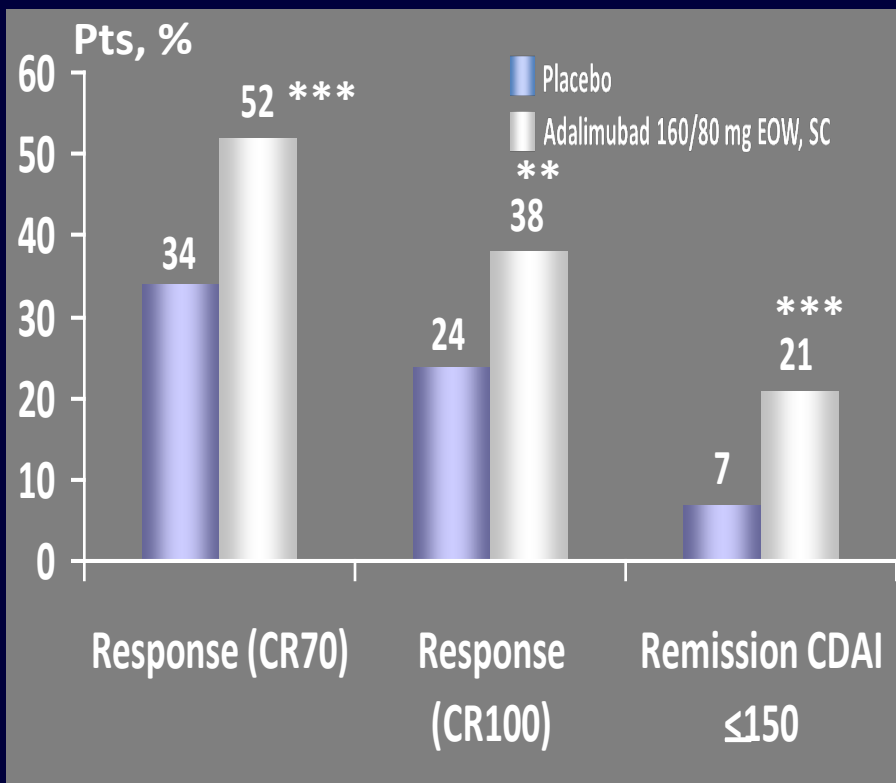


**N=87**

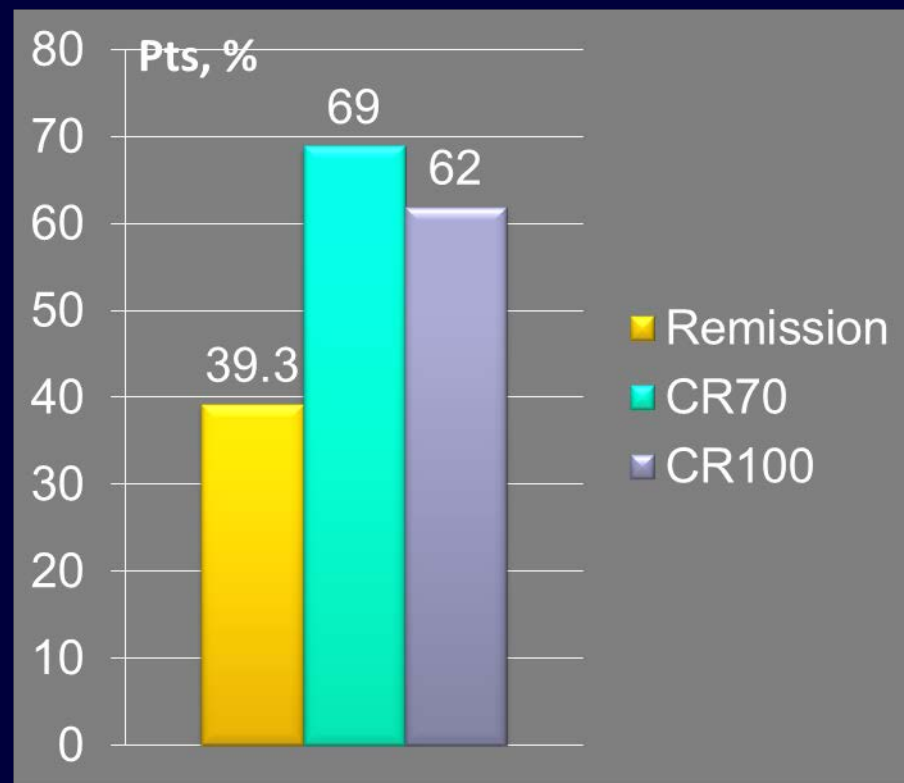
**Pts given 80  
mg x 2 doses**

# Switching to Another TNF

## Adalimumab for IFX Failures at Wk 4



## Certolizumab pegol for IFX Failures at Wk 6 (open label)



1- Sandborn, Ann Int Med 2007

2- Sandborn, Clin Gastro Hep 2010

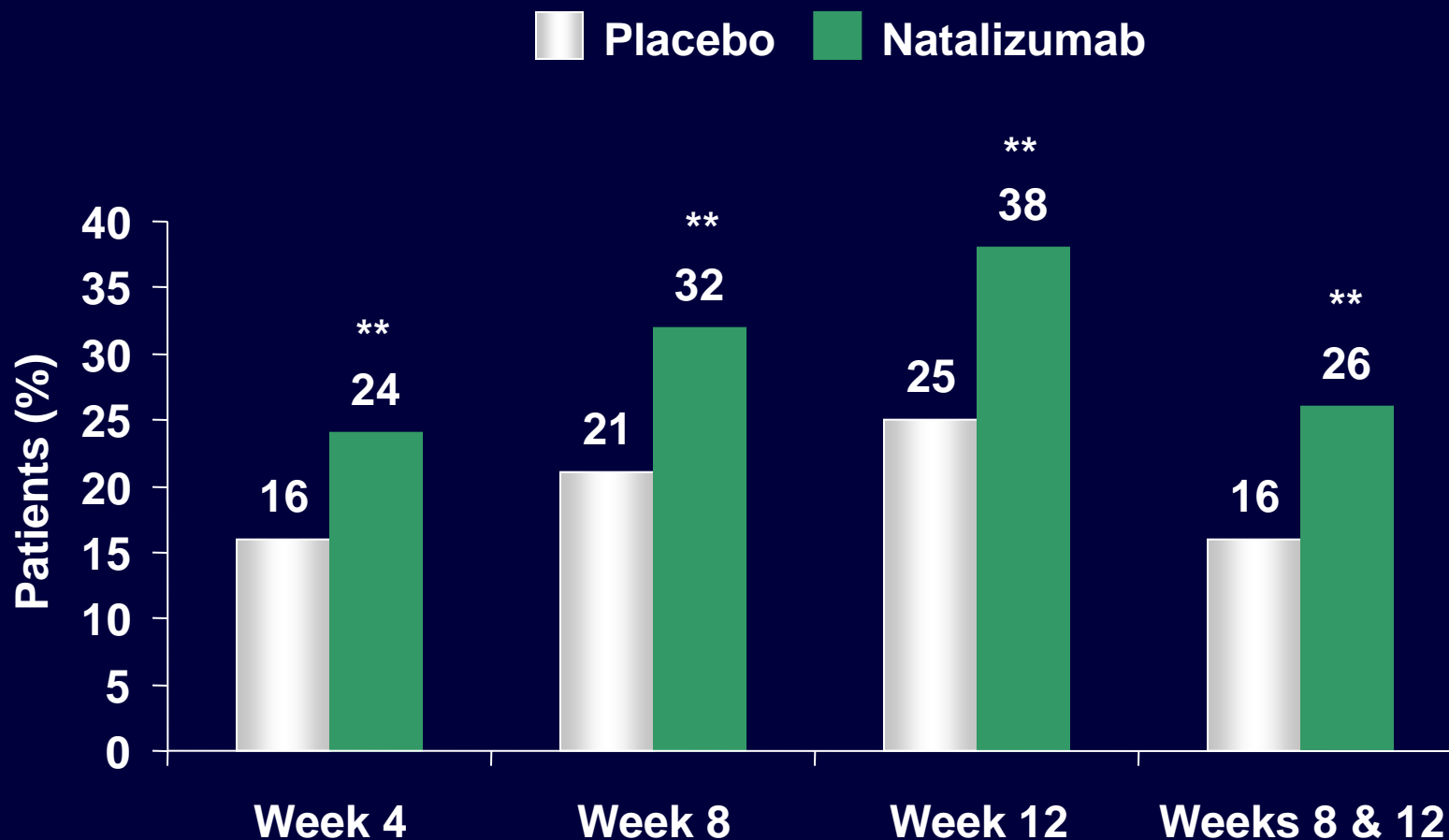
# Alternate Scenarios: Primary Non-responders

- **Primary Non-Responders:**
  - **Switch to 2<sup>nd</sup> Anti-TNF: Subsets of 2 studies show remission rates of 18-36% at ~ week 20 with adalimumab<sup>1-2</sup>**
  - **Add azathioprine or methotrexate if not already on**
  - **Switch to Natalizumab**
  - **Surgery**

1-Lofberg , J Crohn's Colitis 2012

2- Pannaccione , Can J Gastro 2011

# Induction of Remission with Natalizumab: ENCORE\* Trial



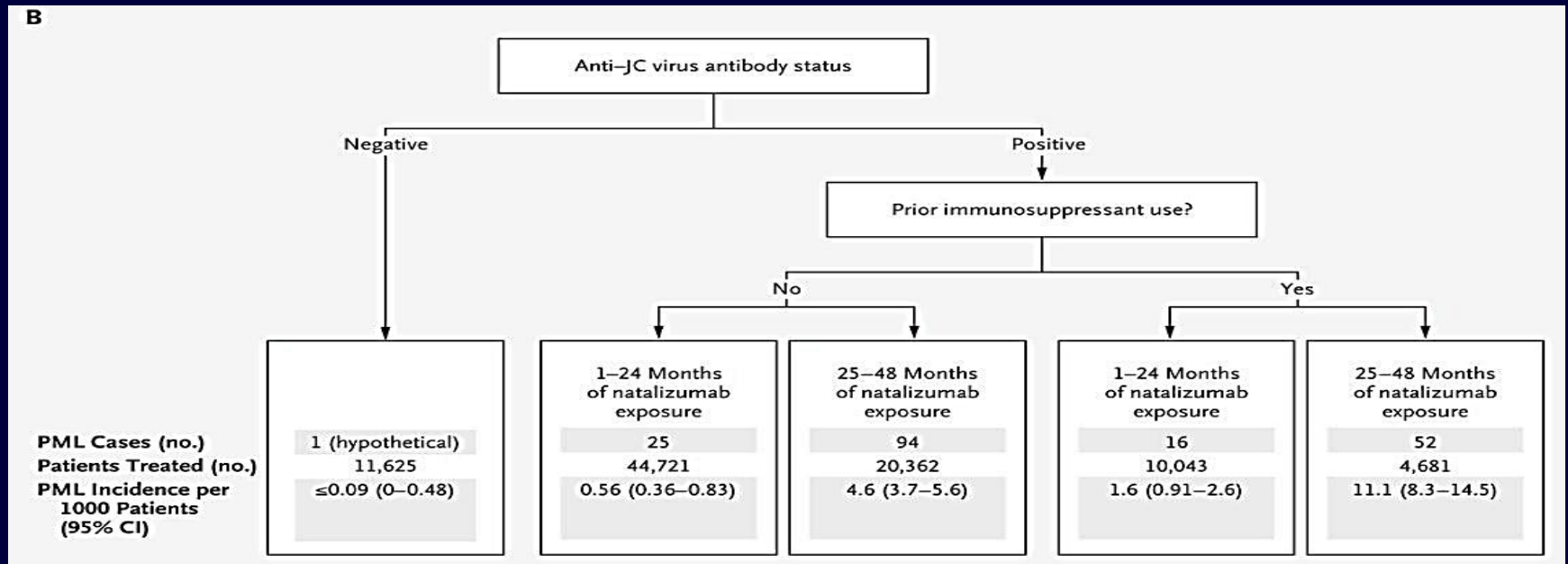
\* All randomized patients (secondary end point).

\*\*  $P \leq 0.001$  vs placebo.

Targan et al. *Gastroenterology*. 2007;132:1672-1683.



# Natalizumab and Risk of PML



- ~ 99,600 pts have received natalizumab
- 264 cases of progressive multifocal leukoencephalopathy (PML)
  - Only 2 case with CD (1 in clinical trial, 1 post-trial after 35 doses)
- All PML cases > 8 months of natalizumab therapy
- Rate approximately 2.36 per 1000 treated patients

Bloomgren G. *N Engl J Med.* 2012;366(20):1870-80.

# Summary

- Rule out other causes of for symptoms (infections, etc)
- Document active disease
- For secondary non-responders check levels if available and optimize meds
- For patients who are primary non-responders consider adding anti-metabolite, trying a 2<sup>nd</sup> anti-TNF , or switching to natalizumab



**Thank you for your time!**