

## IBD TREATMENT: TARGETS FOR THE MODERN AGE



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## OBJECTIVES

- Review the concepts of 'mucosal healing' and 'deep remission' in pediatric IBD
- Determine which targets best predict prognosis
- Assess current methods of measuring remission in children with IBD



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## TREAT TO TARGET: WHAT DO WE MEAN?

- Regular assessment of disease activity using objective clinical and biologic outcome measures
- Adjust treatment if not accomplishing the goal
- Enables better outcomes in RA, hypertension, diabetes, hypercholesterolemia

Bouguen, Clin Gastroenterol Hepatol ePub 2013 Sep 10. PMID 24036054



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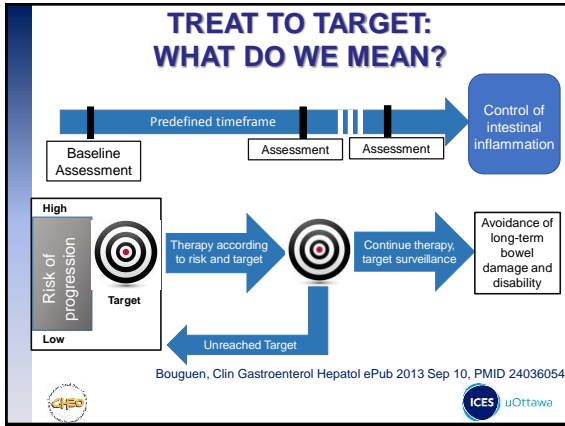
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- ### GOALS OF TREATMENT
- “Clinical Remission”
  - “Feeling better”
  - Short Term:
    - ▶ Crohn’s: No pain, no diarrhea
    - ▶ UC: No urgency, no bleeding
    - ▶ Normal growth and development
    - ▶ Nutrition
    - ▶ Improved laboratory markers
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### PEDIATRIC TRIALS

- **6MP/Prednisone Trial:**
  - ▶ Primary: Harvey-Bradshaw Index
  - ▶ Secondary: Corticosteroid use, growth, AEs, surgery

Markowitz, Gastroenterol 2000;119:895-902
- **Budesonide in Crohn's:**
  - ▶ Primary: CDAI
  - ▶ Secondary: PCDAI, AEs, cortisol

Escher, Eur J Gastroenterol Hepatol 2004;16:47-54
- **REACH:**
  - ▶ Primary: PCDAI
  - ▶ Secondary: QoL (IMPACT), steroid use, growth, ADAs, AEs

Hyams, Gastroenterol 2007;132:863-73



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### WHY NOT USE DISEASE SCORES?

- **Active disease ≠ abnormal laboratory markers**

Mack, Pediatrics 2007;119:1113-9.
- **Active symptoms ≠ active disease**

Vivinus-Nébot, Gut 2014;63(5): 744-52.



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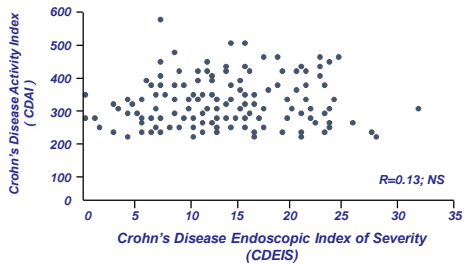
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### Relationship Between Clinical Symptoms and Endoscopic Indices at Presentation of Acute CD



Modigliani, Gastroenterology 1990;98:811  
Slide courtesy of Dr. David Rubin



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## WHY NOT USE DISEASE SCORES?

- **Active disease ≠ abnormal laboratory markers**  
Mack, Pediatrics 2007;119:1113-9.
- **Active symptoms ≠ active disease**  
Vivinus-Nébot, Gut 2014;63(5): 744-52.
- **No clear evidence of correlation between DAIs, symptoms, labs, and mucosal disease**
  - ▶ **(Except PUCAI)** Turner, Gastroenterol 2007;133:423-32.

**Table 3.** Validation Results of the PUCAI and PUCAI With Laboratory Tests, Compared With Lichigger and Sesi Indices

	PGA	Colitis score	Mayo score
PUCAI	0.91*	0.76*	0.93*
PUCAI with laboratory tests	0.90*	0.77*	0.92*
Lichigger index	0.83*	0.72*	0.89*
Sesi index	0.77*	0.69*	0.84*

NOTE: Numbers represent Pearson rho correlation coefficient.  
PGA, Physician Global Assessment on a 100-mm visual analogue scale.  
\*P < .001.




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## WHICH TARGETS SHOULD WE USE?

- **High correlation with outcomes**
  - ▶ Flares
  - ▶ Surgery
  - ▶ Hospitalization
  - ▶ Complications
- **Measurement is achievable, feasible**
- **Cost effective**
- **Relevant to patients**
  - ▶ PROs




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## WHAT ARE THE NEW TARGETS?



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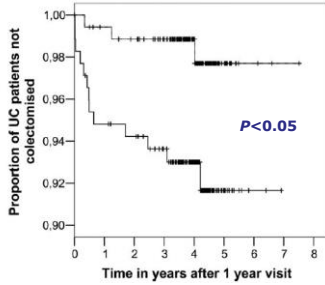
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### Mucosal Healing at Year 1 Associated with Risk of Subsequent Colectomy in Ulcerative Colitis



Freslie, Gastroenterology 2007;133:412-422.



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### CONCLUSION:

There is ample retrospective evidence that MH is associated with improved long-term outcomes but...

IS THIS ACHIEVABLE?



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### IS MUCOSAL HEALING ACHIEVABLE?

- Likelihood of mucosal healing:

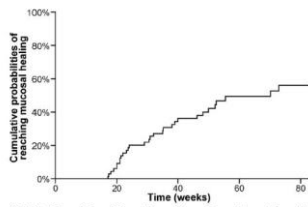


Figure 1. Cumulative probability of achieving MH.

Bouguen, Clin Gastroenterol Hepatol 2014;12:978-85.



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## SURROGATE MARKERS

- **Prospective: Fecal Calprotectin associated with MH in UC (AUROC 0.754)**

Guardiola, Clin Gastroenterol Hepatol ePub 2014 Jun 30, PMID 24993368

- **BUT calprotectin not as accurate in children**
  - ▶ Sensitivity 97.8%, specificity 68.2%

Henderson, Am J Gastroenterol 2014;109:637-45.




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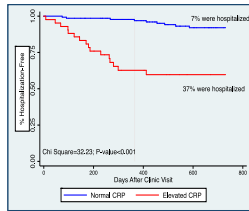
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## SURROGATE MARKERS - CRP

- “Silent” Crohn’s patients have no symptoms
- But majority have an elevated CRP
- Higher risk of hospitalization
  - ▶ Obstruction
  - ▶ Surgery



Vargas, Gastroenterology 2013;144(5):S102 (DDW Abstract 557).




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## SURROGATE MARKERS - CRP

- **BUT...**

Table II. Frequency of normal laboratory values

Disease/severity	CRP < 8 mg/L, %	ESR ≤ 20 mm, %	Normal Hb, platelets, albumin; ESR ≤ 20 mm, %	Normal Hb, platelets, albumin; ESR > 20 mm; CRP < 8 mg/L, %
CD				
Mild (n = 82)	15.7	27.2	12.0	6.0
Moderate/severe (n = 64)	1.6	20.3	3.1	0.0
UC				
Mild (n = 27)	59.3	48.1	40.7	33.3
Moderate/severe (n = 75)	40.0	18.7	2.7	1.3
Controls (n = 137)	97.5	79.0	NA	NA

Tsampalieros, J Pediatr 2011;159:340-2.

- **In UC, ESR+CRP may be valuable**

Turner, J Crohns Colitis 2011;5:423-9.




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### SUMMARY

• What is the optimal target?



- Mucosal healing by endoscopy
  - Prospective validation
  - Optimal intervals
  - Pediatric studies
- Imaging (MRE, capsule)
  - Association with outcomes
  - Pediatric studies
- Surrogate markers (ESR/CRP, fecal biomarkers)
  - More accurate markers
  - Validation vs. endoscopy
- Optimized disease activity scores
  - Validation vs. endoscopy
  - Association with outcomes

**NEEDS**

**WHAT ABOUT THERAPY DE-ESCALATION?**




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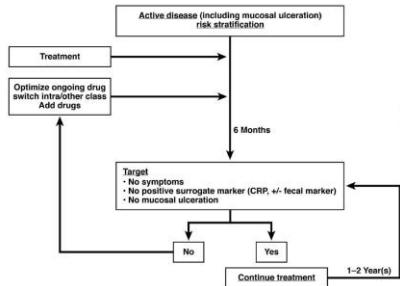
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### SUGGESTED ALGORITHM



Bouguen, Clin Gastroenterol Hepatol ePub 2013 Sep 10, PMID 24036054




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### CONCLUSIONS

- Ample evidence mucosal healing improves long-term outcomes
  - Retrospective, observational, post-hoc analyses
- Requires aggressive endoscopy, changes in treatment
- Unanswered questions
  - RCTs
  - Surrogate markers
  - Pediatric data
  - Patient preference
  - Histologic inflammation
  - De-escalation
  - Risk, Cost-benefit




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