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

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
**TREAT TO TARGET: WHAT DO WE MEAN?**

- Predefined timeframe
- Baseline assessment
- Assessment
- Control of intestinal inflammation
- Low risk of progression
- Target
- Therapy according to risk and target
- Continue therapy, target surveillance
- Avoidance of long-term bowel damage and disability
- Unreached target

**WHAT WERE THE OLD TARGETS?**

**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
PEDIATRIC TRIALS

- **6MP/Prednisone Trial:**
  - Primary: Harvey-Bradshaw Index
  - Secondary: Corticosteroid use, growth, AEs, surgery
    - Markowitz, Gastroenterol 2000;119:995-902

- **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

WHY NOT USE DISEASE SCORES?

- Active disease ≠ abnormal laboratory markers

- Active symptoms ≠ active disease

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

- Crohn's Disease Activity Index (CDAI)
- Crohn's Disease Endoscopic Index of Severity (CDEIS)
- $R=0.13$; NS

Slide courtesy of Dr. David Rubin
WHY NOT USE DISEASE SCORES?

• Active disease ≠ abnormal laboratory markers

• Active symptoms ≠ active disease

• No clear evidence of correlation between DAIs, symptoms, labs, and mucosal disease
  (Except PUCAI)

| Table 5: Correlation Results of the PUCAI with PUCAI with Outcomes
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<tr>
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<td>Outcomes</td>
<td>Mean corr.</td>
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<tr>
<td>PUCAI</td>
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<td>PUCAI with labs</td>
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<td>Symptom score</td>
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<td>Bowel score</td>
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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

WHAT ARE THE NEW TARGETS?
MUCOSAL HEALING – CROHN’S

- Post-hoc/secondary analyses of RCTs
  - Accent-I (Rutgeerts, Gastroenterol 2004;126:402-13)
  - EXTEND (Rutgeerts, Gastroenterol 2012;142:1102-11)
  - Step-Up/Top-Down (Baert, Gastroenterol 2010;138:463-68)
- Retrospective Cohort Studies
  - IBSEN (Frøslie, Gastroenterol 2007;133:412-22)
  - Leuven Infliximab Cohort (Schnitzler, Inflamm Bowel Dis 2009;15:1295-1301)

MUCOSAL HEALING – UC

Mucosal healing at 3 months after first course of steroids is associated with favorable prognosis

Group A: Clinical and endoscopic remission (Powell-Tuck, 0–1; Baron Score, 0)

Group B: Clinical but no endoscopic remission (Powell-Tuck, 0–1; Baron, 1–3)
Mucosal Healing at Year 1 Associated with Risk of Subsequent Colectomy in Ulcerative Colitis

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

IS THIS ACHIEVABLE?

IS MUCOSAL HEALING ACHIEVABLE?

• Likelihood of mucosal healing:

IS MUCOSAL HEALING ACHIEVABLE?

- Predictors of mucosal healing:
  
  ![Graph showing HR 2.35 (95%CI 1.15-4.97) and HR 4.28 (95%CI 1.9-11.5) with intervals]


CONCLUSION:
MH is achievable, with aggressive monitoring and management but...

SURROGATE MARKERS?

IMAGING

- Prospective study, segmental analysis
  - Kappa 0.73-0.76
    - Moreno, J Crohn Colitis 2014;8:1079-87.
- MR Enterography, CDEIS vs. MaRIA scores
  - Ulcer healing: 90% accuracy
  - Endoscopic remission: 83% accuracy

![Graph showing ulcer healing and endoscopic remission with accuracy percentages]
**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%
  

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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


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**SURROGATE MARKERS - CRP**

- BUT…

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- In UC, ESR+CRP may be valuable

**SURROGATE MARKERS - PUCAI**

- At 3 months:
  - Area Under the ROC: 0.75 (95% CI 0.60-0.89)
  - PUCAI>10: Sens 90%, NPV 91% for SSFR
  - For colectomy: Sens 82%, Spec 64%

- Schechter, Gut ePub 2014 May 21, PMID 24848266

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**SURROGATE MARKERS**

- ACT-I and ACT-II: Serum infliximab trough levels associated with MH

- Adedokun, Gastroenterology ePub 2014 Aug 27, PMID 25173754

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**SURROGATE MARKERS**

- ACT-I and ACT-II: Serum infliximab trough levels associated with MH

- Adedokun, Gastroenterology ePub 2014 Aug 27, PMID 25173754

- Adalimumab level <4.9 predictive of absence of MH
  - Sens 66%, Spec 85%, PPV 88%, NPV 51%, LR 4.3

- Roblin, Clin Gastroenterol Hepatol 2014;12:80-84
SUMMARY

- What is the optimal target?
  - Mucosal healing by endoscopy
  - Imaging (MRE, capsule)
  - Surrogate markers (ESR/CRP, fecal biomarkers)
  - Optimized disease activity scores

NEEDS
- Prospective validation
- Optimal intervals
- Pediatric studies
- Association with outcomes
- More accurate markers
- Validation vs. endoscopy
- Pediatric studies

WHAT ABOUT THERAPY DE-ESCALATION?

SUGGESTED ALGORITHM

- Active disease (including maximal treatment) risk stratification
  - Optimal ongoing drug therapy per initial risk
  - Clinical response
  - Target fulfillment
  - No symptoms
  - No active surrogate marker (ESR <10, fecal biomarkers)
  - No mucosal abnormalities

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