Heal the Mucosa or Heal the Patient

(Data vs Dogma)

Heal the Mucosa

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Clinical Director, IBD Program

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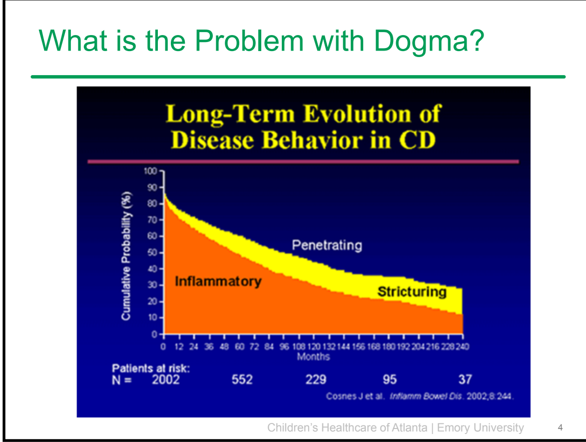
The Facts vs The Force Data vs Dogma

What is "The Force"

- The way I was trained
- What Dr. X said at DDW/NASPGHAN/Advances
- Least Invasive Target (H&P vs Endoscopy)
  - Do no harm mentality
  - "to do good, and not to do harm"
- DOGMA

What is the Problem with Dogma?



What are the FACTS

1. Symptoms alone are not an appropriate construct to MONITOR a disease
2. Mucosal Healing results in improved outcome
3. Mucosal Healing is feasible in clinical practice

Shehzad has DOGMA, I have DATA…….who wins?

Disease Monitoring

Symptoms ≠ Activity

No Symptoms ≠ No Activity

The "History" of Dogma

- Sir William Osler - Father of Modern Medicine (1849 – 1919)
- "Listen to your patient, he is telling you the **diagnosis**"
- What he did NOT say:
  Listen to your patient, he is telling you his disease activity
- Diagnosis ≠ Disease Activity (monitoring)

Clinical Symptoms cannot Predict MH

Table 6 Accuracy of CDAI to predict mucosal healing

CDAI week 26 cut-off	Sensitivity (%)	Specificity (%)	Overall accuracy (%
<50	24.4	76.5	51.6
<100	56.7	54.1	55.3
<150	80.0	34.7	56.4
<220	91.1	19.4	53.7

CDAI, Crohn's disease activity index.

What are the new findings?

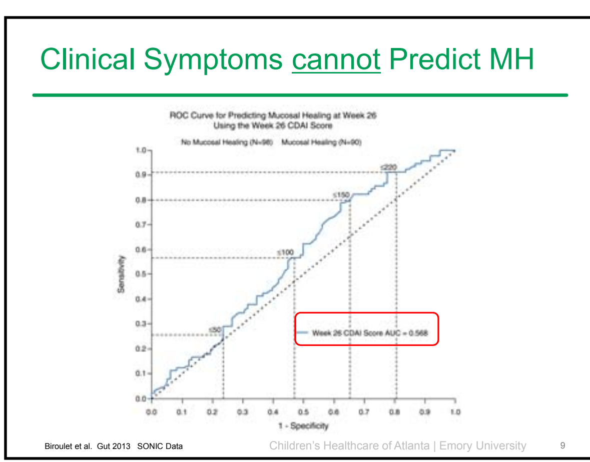
- Half the patients with CD in clinical remission have endoscopic and/or CRP evidence of residual active CD.
- The accuracy of the CDAI to detect endoscopic healing is low in patients with CD.
- Clinical symptoms as scored by CDAI are not a reliable measure of the underlying inflammation in CD.

How might it impact on clinical practice in the foreseeable future?

- Our findings indicate that if achieving mucosal healing is a treatment goal, then decisions regarding medical therapy cannot be guided solely by clinical symptoms.

Biroulet et al. Gut 2013 SONIC Data

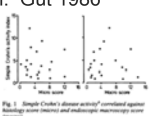
Clinical Symptoms cannot Predict MH



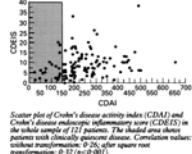
Biroulet et al. Gut 2013 SONIC Data

Symptoms do not correlate with endoscopy

- Gomes P et al. Gut 1986



- GETAID - Cellier C et al, Gut 1994

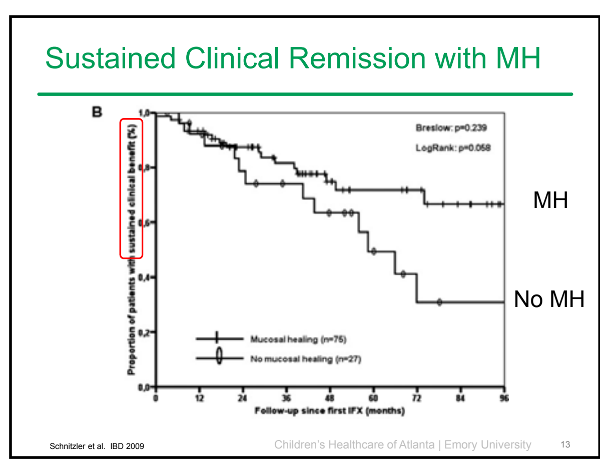


- ACCENT 1 (Lancet 2002)
  (data not shown)

Mucosal Healing results in Improved Outcome (our ultimate goal)

Improved Outcome

- Long-term (deep?) Clinical Remission
- Decreased hospitalizations
- Decreased Surgery (Decreased colectomy in UC)
- Decreased Flares
- Improved Quality of Life
- Decreased risk of colon cancer



Sustained Clinical Remission with MH
B
Breslow: p=0.239
LogRank: p=0.058
MH
No MH
Proportion of patients with sustained clinical benefit (%)
Mucosal healing (n=75)
No mucosal healing (n=27)
Follow-up since first IFX (months)
Schnitzler et al. IBD 2009
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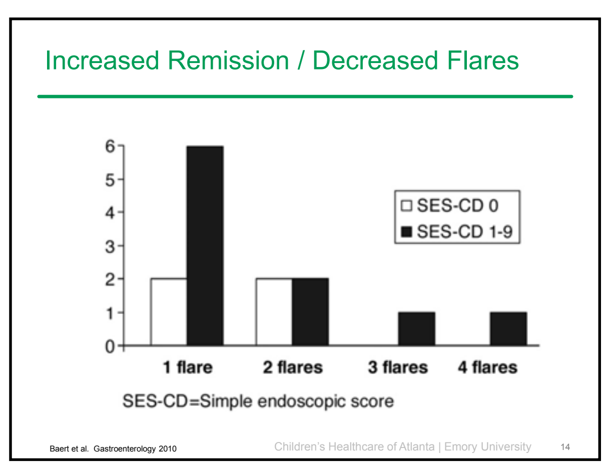

Increased Remission / Decreased Flares
SES-CD 0
SES-CD 1-9
1 flare
2 flares
3 flares
4 flares
SES-CD=Simple endoscopic score
Baert et al. Gastroenterology 2010
Children's Healthcare of Atlanta | Emory University
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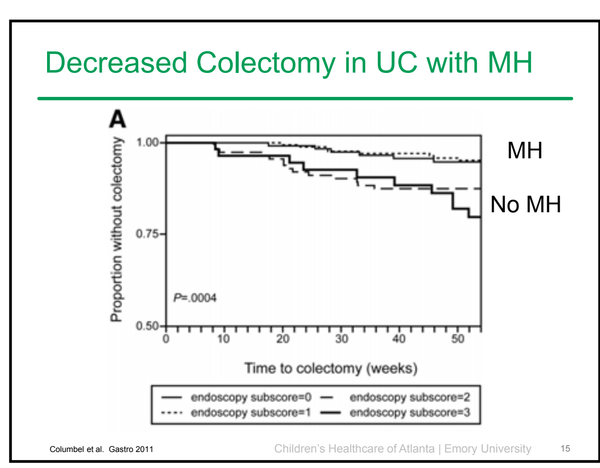

Decreased Colectomy in UC with MH
A
MH
No MH
Proportion without colectomy
P=.0004
Time to colectomy (weeks)
endoscopy subscore=0
endoscopy subscore=1
endoscopy subscore=2
endoscopy subscore=3
Columbel et al. Gastro 2011
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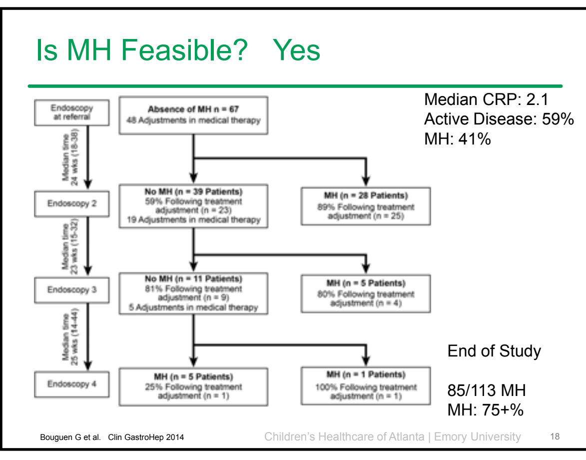
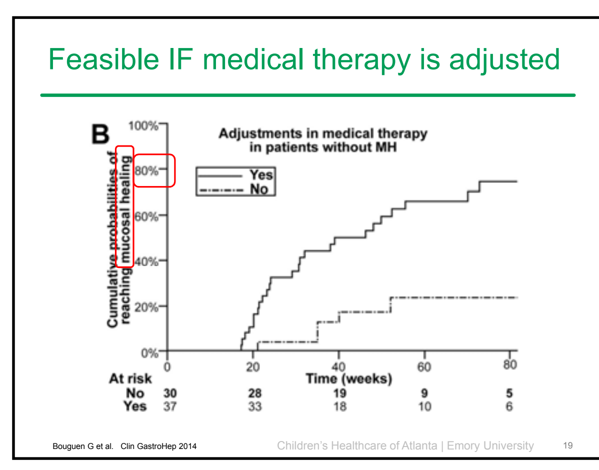
Additional Studies – Improved Outcome

- Colectomy – 62% vs 8% at 8 years in Colonic CD
- ACCENT 1
  - Hospitalization 28% vs 19%
- MH at 1 year follow-up
  - Surgery 23% vs 12%
  - Fistulae 13% vs 2%
  - Corticosteroids 32% vs 13%
- Abdominal Surgery 38% vs 14%
- Hospitalization 59% vs 42%

Allez M et al Am J Gastro 2002
Rutgeerts P et al. Gastroint Endo 2006
Froslie KF et al. Gastro 2007
Schnitzler F et al. IBD 2009

Mucosal Healing is Feasible in Clinical Practice




Feasible IF medical therapy is adjusted
B
Adjustments in medical therapy in patients without MH
Yes
No
Cumulative probabilities of reaching mucosal healing
100%
80%
60%
40%
20%
0%
0
20
40
60
80
Time (weeks)
At risk
No 30 28 19 9 5
Yes 37 33 18 10 6
Bouguen G et al. Clin GastroHep 2014
Children's Healthcare of Atlanta | Emory University
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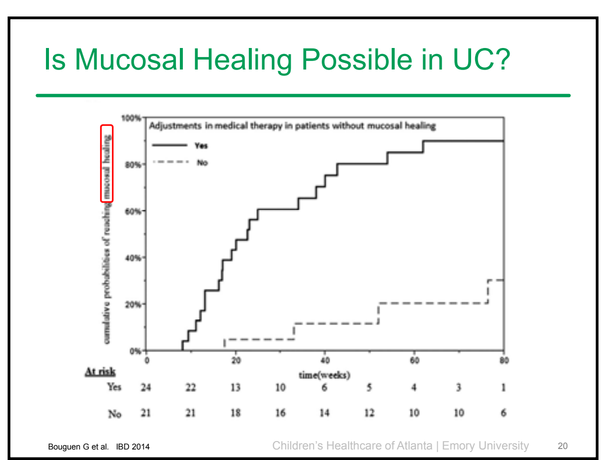
Is Mucosal Healing Possible in UC?
Adjustments in medical therapy in patients without mucosal healing
Yes
No
cumulative probabilities of reaching mucosal healing
100%
80%
60%
40%
20%
0%
0
20
40
60
80
time(weeks)
At risk
Yes 24 22 13 10 6 5 4 3 1
No 21 21 18 16 14 12 10 10 6
Bouguen G et al. IBD 2014
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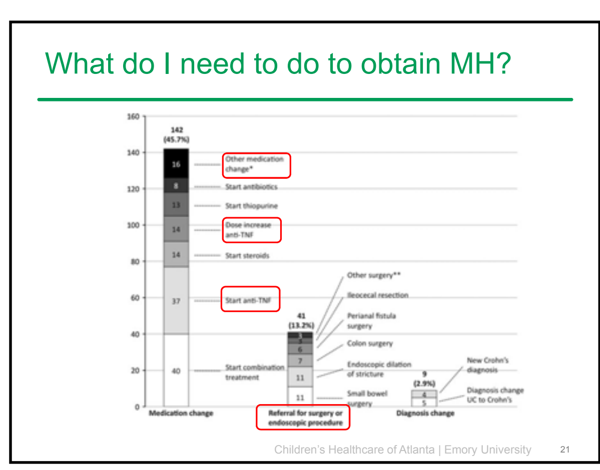
What do I need to do to obtain MH?
160
140
120
100
80
60
40
20
0
142
(45.7%)
16
8
13
14
14
37
40
Other medication change*
Start antibiotics
Start thiopurine
Dose increase anti-TNF
Start steroids
Start anti-TNF
Start combination treatment
41
(13.2%)
7
11
11
Other surgery**
Ileocecal resection
Perianal fistula surgery
Colon surgery
Endoscopic dilation of stricture
Small bowel surgery
9
(2.9%)
4
5
New Crohn's diagnosis
Diagnosis change UC to Crohn's
Medication change
Referral for surgery or endoscopic procedure
Diagnosis change
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Final Thoughts

Before I turn it over to Shehzad

Mucosal Healing is SIMPLE (not confusing)

- Clinical Symptoms do not predict Mucosal Healing
- MH results in better outcome (our goal)
- MH is feasible (if YOU decide it is YOUR target)
- MH can be obtained through:
  - Endoscopy (timing to be determined)
  - Optimizing Current Therapy / Change Therapy

Heal The Mucosa or Heal The Patient?

NASPGHAN Annual Meeting
October 10th, 2015
Debate

Shehzad A Saeed, MD
Professor
Clinical Director
Schubert-Martin IBD Center
Cincinnati Children's Hospital Medical Center

"Dogma"

- Principle or set of principles
  - laid down by an authority as incontrovertibly true.

Overview

- Definition of Mucosal healing(MH) and its assessment and effect on outcomes
- Who and when to assess depends upon clinical scenarios and shared decision making due to cost and safety considerations
- Alternative assessment tools are equally effective in assessing MH and may dictate appropriate selection of patients who would benefit from an endoscopic evaluation

Why is Mucosal Healing (MH) Important?

- Data form studies show that achieving MH relates to better outcomes
  - Less complications, less hospitalizations, less surgeries
- But does it really translates into better care?

- Definition of Mucosal healing(MH) and its assessment and effect on outcomes

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MH

- What is MH?
  - There is no internationally accepted definition of MH, and
- Several different endoscopic score systems of mucosal inflammation are used in clinical practice.
- CD
  - Crohn's Disease Endoscopic Index of Severity (CDEIS)[1]
  - Simple Endoscopic Score for Crohn's Disease (SES-CD)[2]
  - Rutgeerts endoscopic grading scale[4]
- UC
  - Mayo Endoscopic Score(MES)[3]
  - Ulcerative colitis endoscopic index of severity(UCEIS)[5]
  - Ulcerative colitis colonoscopic index of severity (UCCIS)[6]

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1. Gut 1989;30:983–989
2. Gastrointest Endosc 2004;60:505–512
3. Gastro 1990;99:956–963.
4. NEJM . 2005 Dec; 353(23):2462– 2476
5. Gut 2012;61:535–42
6. Clin Gastro Hepatol 2013;11:49–54.

MH vs Histologic Healing(HH)

- Does MH equate HH?
- Is HH achievable?
- Does HH translate into better outcomes?

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MH vs HH?

- Metanalysis- 2951 articles reviewed
- No valid definition of histologic remission
- 22 different histologic scoring systems for IBD, none are fully validated
- Microscopic inflammation noted in 16-100% of endoscopically quiescent disease
- Some evidence of histologic remission predicting risk of complications in UC but scarce data for CD

Journal of Crohn's and Colitis (2014) 8, 1582–1597

When to assess for MH?

- What is the optimal timing for assessing MH?
- Will intensifying treatment in those who have not achieved MH result in improved outcomes?

P DeCruz et al. Inflamm Bowel Dis 2013;19:429–444)

Effect of follow-up endoscopy on the outcomes of patients with inflammatory bowel disease.

- 188 patients with IBD-follow-up endoscopies in 130 patients
- Treatment changes were categorized as ''changed aggressively,'' ''changed lightly,'' ''unchanged,'' and ''changed to medication for other diseases.''
- Treatment was unchanged in **68.8 %** of CD patients and in **65.9 %** of UC patients.
- Treatment plans were changed after follow-up endoscopic examination more frequently in the group with an endoscopic indication, which included ''unexplained abdominal pain,'' ''diarrhea,'' ''hematochezia,'' ''fever,'' ''weight loss,'' and ''checking short-term treatment response.''
- In UC but not in CD, such indications for colonoscopy were also predictive of hospitalization.
- The authors concluded that follow-up endoscopy might not have a significant impact on the overall clinical course and outcomes in patients with IBD

Dig Dis Sci. 2014 Oct;59(10):2514-22.

A systematic review of measurement of endoscopic disease activity and mucosal healing in Crohn's disease: recommendations for clinical trial design.

- Both the endoscopic evaluative instrument selected and the definition chosen for mucosal healing affect the validity of assessing endoscopic disease activity during a clinical trial for CD.
- Currently, the CDEIS and SES-CD have the most data regarding operating properties; however, further validation is required

Inflamm Bowel Dis. 2014 Oct;20(10):1850-61

CONSENSUS/GUIDELINES

European evidence based consensus for endoscopy in inflammatory bowel disease

Vito Annese[a,*,1,2], Marco Daperno[b,2], Matthew D. Rutter[c,d,2], Aurelien Amiot[e], Peter Bossuyt[f], James East[g], Marc Ferrante[h], Martin Götz[i], Konstantinos H. Katsanos[j], Ralf Kießlich[k], Ingrid Ordás[l], Alessandro Repici[m], Bruno Rosa[n], Shaji Sebastian[o], Torsten Kucharzik[p], Rami Eliakim[q,**,1,2] on behalf of ECCO

> ECCO Statement 2E
>
> Routine endoscopy for patients in clinical remission is unnecessary, unless it is likely to change management [EL5] [Voting results: 100% agreement].

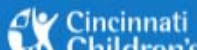
Journal of Crohn's and Colitis (2013)
7, 982–1018

Management of Pediatric Ulcerative Colitis: Joint ECCO and ESPGHAN Evidence-based Consensus Guidelines

[*]Dan Turner, [†]Arie Levine, [‡]Johanna C. Escher, [§]Anne M. Griffiths, [||]Richard K. Russell, [¶]Axel Dignass, [#]Jorge Amil Dias, [**]Jiri Bronsky, [††]Christian P. Braegger, [‡‡]Salvatore Cucchiara, [‡]Lissy de Ridder, [§§]Ulrika L. Fagerberg, [||||]Séamus Hussey, [¶¶]Jean-Pierre Hugot, [##]Sanja Kolacek, [***]Kaija Leena Kolho, [†††]Paolo Lionetti, [‡‡‡]Anders Pærregaard, [§§§]Alexander Potapov, [***]Risto Rintala, [||||||]Daniela E. Serban, [¶¶¶]Annamaria Staiano, [||||]Brian Sweeny, [###]Gigi Veerman, [****]Gabor Veres, [††††]David C. Wilson, and [‡‡‡‡]Frank M. Ruemmele

Assessing and Predicting Disease Activity

Endoscopic evaluation is recommended at diagnosis, before major treatment changes and when the clinical assessment is in question; endoscopic evaluation in children is not routinely recommended during flares, which are not severe or during clinical remission aside from cancer surveillance

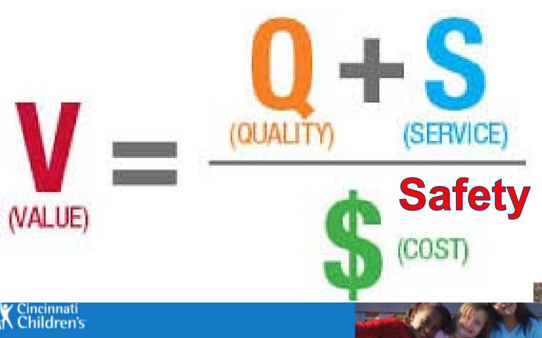


JPGN 2012;55: 340–361

Value Equation

- Under the unfolding healthcare environment, and under the ACO model, volume based reimbursement is to be replaced by value based reimbursement

Payment Reform and Transformation



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Safety of endoscopy and anesthesia

- Emerging data about the effect of general anesthesia on developing brain
- Animal studies suggest that neurodegeneration, with possible cognitive sequelae, is a potential long-term risk of anesthetics in neonatal and young pediatric patients
- Repeated exposure to anesthesia below age 2 yrs associated with significant learning disabilities

Anesth Analg 2007;104:509–20
Pediatrics 2011;128:e1053-1061

Cost of Endoscopy

- Nationally EGD- ranges from $1600-$12,000-avg-$3,000
  - http://www.newchoicehealth.com/procedures/upper-gi-endoscopy
- Colonoscopy- $1800-$12500-avg $2625
  - http://www.newchoicehealth.com/procedures/colonoscopy

When told that you need a scope despite the fact that you are feeling good and labs are normal

When told that you need a scope despite the fact that you are feeling good and labs are normal

When told that you need a scope despite the fact that you are feeling good and labs are normal

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When told that you need a scope despite the fact that you are feeling good and labs are normal

KEEP CALM AND SCHEDULE A COLONOSCOPY

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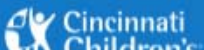
If not using scope, then alternatives?

- Fecal markers-**FC, FL**
  - Fecal biomarkers correlate well with clinical and endoscopic response- *IBD* 2008;14:40–46; *Am J Gastrol* 2010;105:162–169.
  - Have been show to be effective for monitoring response to therapy and post-operative recurrence- *Scand J Gastro* 2010;45:325–331
  - FC correlates well with relapse after anti-TNFα withdrawal in pts with deep remission *Jr Crohns Colitis 2015;9:33-40*
- Serum markers-CRP,ESR, CD64, others
- Imaging-CTE, **MRE**, CE
- QOL scores



Level of FC Correlates With Endoscopic and Histologic Inflammation and Identifies Patients with MH in both CD and UC

- FC and LF correlate closely with the CDEIS and SES-CD. *IBD* 2008;14:40–46; *Am J Gastrol* 2010;105:162–169.
- Normal FC level was shown to correlate well with mucosal healing. *Scand J Gastro* 2004;**39**:1017–1020.; *IBD* 2008;14:1392–1398; *Clin Gastro* 2015
- FC and LF normalized among endoscopic responders but remained elevated among nonresponders irrespective of the type of drug therapy used *Scand J Gastro* 2010;45:325–331
- FC correlates well with relapse after anti-TNFα withdrawal in pts with deep remission *Jr Crohns Colitis 2015;9:33-40*
- A recent meta-analysis of prospective studies showed a pooled sensitivity of 78% and a specificity of 73% for FC in predicting IBD relapse, especially in ileocolonic and colonic CD and UC, demonstrating the usefulness of a simple and noninvasive FC test in predicting relapse in quiescent IBD patients. *IBD* 2012;18:1894–1899.

Imaging-MRE

- An MRI activity index (MRAI) for CD activity that correlates well with the CDEIS has been devised by Rimola et al, and validated recently
- Sauer et al, recently showed that MRE remission correlated well with clinical remission and outcomes
- In the postoperative setting MRE has a sensitivity of 100% and specificity of 89% in detecting postoperative recurrence.

Gut 2009;58:1113–1120
JPGN 2015:
Euro Radiol 2008;18:2512-21

Preliminary Results of survey of Pedi GI practices

- Design: Web based survey distributed to members of the Pedi GI Listserv
- Objective: Assess physician practice trends for using endoscopy to evaluate for mucosal healing as therapy target in IBD
- 161 responders from all over the world - majority in the US: 36% NE/East Coast; 14% South; 19% Midwest; 13% West; 5% each Asia and Europe; 2 % each Australia and South America; 1% North America other than US
- 90% practicing GI docs - seeing 11->20 patients per month (on the average); 61% from academic centers.

Courtsey: Carolina S. Cerezo, MD, FAAP

Preliminary Results of survey of Pedi GI practices

- For the question " Do you routinely perform follow-up endoscopy to assess mucosa healing on newly diagnosed IBD patients who are in clinical remission (no symptoms, normal labs and growth)?" 72% NO; 28% YES
- These 72% will consider repeating endoscopy for any of the top 5 symptoms: weight loss, blood in the stool, poor weight gain, chronic diarrhea and delayed puberty
- 52% will repeat endoscopy if fecal calprotectin is elevated
- 35% do not do endoscopy at all whether with symptoms or abnormal labs - they just adjust therapy and monitor clinical symptoms.

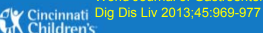
Courtsey: Carolina S. Cerezo, MD, FAAP

Summary

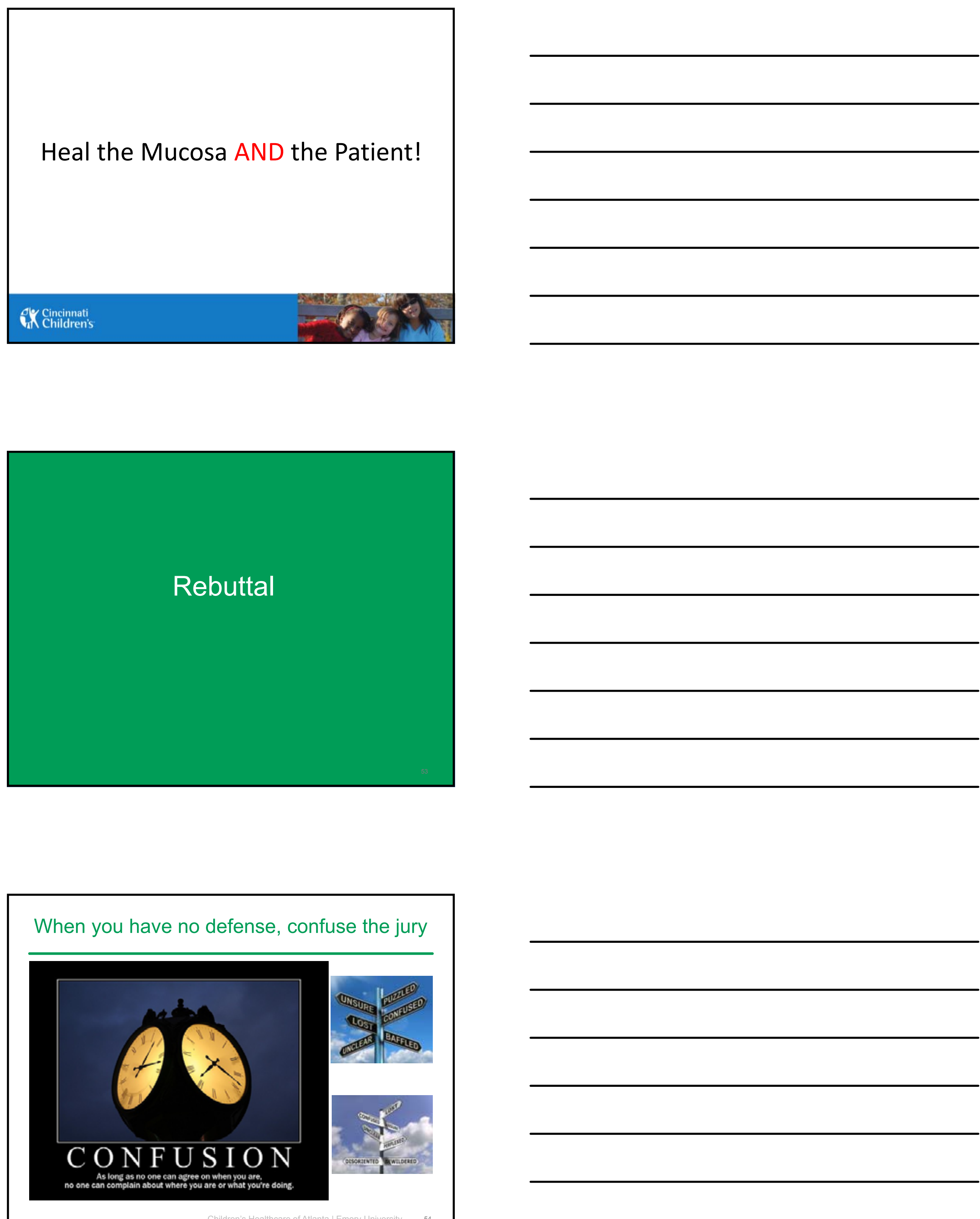
- Not all patients need endoscopy post treatment to document mucosal healing
- Appropriate selection of patients based on phenotype, non-invasive markers of inflammation and shared decision making is the most cost effective way of documenting and managing IBD

Summary

- Endoscopy remains the gold standard for diagnosis and to support therapeutic decision making.
- Endoscopic re-evaluation should be used to identify
  - non-responder patients,
  - in whom an increased dosage, anticipated administration, or use of other drugs should be attempted.
- To improve the follow-up of IBD patients, it should be established whether histology should be included in the definition of MH.
- The timing of the endoscopic evaluation and a proper definition of MH need to be defined in prospective studies. To date, MH in IBD is still an underestimated issue



World Journal of Gastroenterology 2013;19:968–78
Dig Dis Liv 2013;45:969-977


Heal the Mucosa AND the Patient!
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Rebuttal
When you have no defense, confuse the jury
UNSURE
PUZZLED
LOST
CONFUSED
UNCLEAR
BAFFLED
CONFUSION
As long as no one can agree on when you are,
no one can complain about where you are or what you're doing.
DISORIENTED
BEWILDERED
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Who Needs Endoscopy?

- Dr. Saeed: “Not all patients need endoscopy post treatment to document mucosal healing”
- I ask “How do you know which patients do and which patients do not need endoscopy?”

Who needs Endoscopy?

- Calprotectin

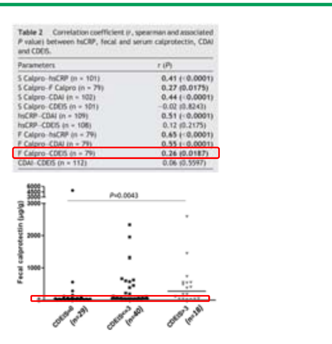

Table 2 Correlation coefficient (r, spearman and associated P value) between hsCRP, fecal and serum calprotectin, CDAI and CDEIS.

Parameters	r (P)
S Calpro–hsCRP (n = 101)	0.41 (<0.0001)
S Calpro–F Calpro (n = 79)	0.27 (0.0175)
S Calpro–CDAI (n = 102)	0.44 (<0.0001)
S Calpro–CDEIS (n = 101)	−0.02 (0.8243)
hsCRP–CDAI (n = 109)	0.51 (<0.0001)
hsCRP–CDEIS (n = 108)	0.12 (0.2175)
F Calpro–hsCRP (n = 79)	0.65 (<0.0001)
F Calpro–CDAI (n = 79)	0.55 (<0.0001)
F Calpro–CDEIS (n = 79)	0.26 (0.0187)
CDAI–CDEIS (n = 112)	0.06 (0.5597)

Meuwis et al. GETAID Journal Crohns Colitis 2013

Who needs Endoscopy?

- Clinical + CRP ?
- SONIC Data
  - 90 patients with CDAI<150 <u>and</u> Normal CRP
  - 38/90 demonstrated mucosal healing

  = 42% of patients with minimal symptoms and normal CRP obtained mucosal healing

  = 58% of patients with minimal symptoms and normal CRP demonstrated ACTIVE disease

What type of EBM do you practice?

Experience-Based Medicine	Evidence-Based Medicine
• Heal the Patient	• Heal the Mucosa
• The asymptomatic patient is OK (screening?)	• The mucosal healed patient is OK
• Problem: The natural history of treated IBD is poor	• Problem: This requires a change in physician mindset (Dogma)

Shehzad ------ Shazam

- Most popular superhero of the 1940s (outsold superman)
- **S**olomon, **H**ercules, **A**tlas, **Z**eus, **A**chilles, **M**ercury
  - Wisdom, Strength, Stamina, Power, Courage, Speed
- Superheroes have adapted
- IBD Monitoring should adapt

Disease Monitoring with Symptoms - ?Wrong

- Charles Sidney Burwell – Harvard Dean (1893-1967)
- "Half of what we are going to teach you (dogma) is wrong, and half of it is right. Our problem is that we don't know which half is which."
- Objective disease monitoring is the future
- Objective = Mucosal Healing

Thank You and Questions

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