Why Stool Calprotectin Monitoring is Important

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Disclosure: INOVA [speaking]
Broad Overview

• Clinical Ambiguity
  – IBS vs IBD at diagnosis
  – Health care utilization trends

• Enhancing Value as Clinical Gastroenterologists
  – Utility of fecal calprotectin

• Future of Non-Invasive Monitoring
Healthcare “Value”
Gastrointestinal Presentations

- **IBD**
  - Chronic inflammation of all or part of your digestive tract with symptoms:
    - Diarrhea
    - Abdominal pain and cramping
    - Dysentery
    - Ulcers
    - Reduced appetite and weight loss

- **IBS**
  - Functional bowel disorder in which abdominal pain or discomfort is associated with:
    - Diarrhea
    - Abdominal pain and cramping
    - Flatulence
    - Mucus in stool
    - Disordered defecation

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What is Calprotectin?

- A calcium-bound protein extruded from perturbed inflammatory cells (primarily in neutrophils) within intestinal mucosa
- Makes up 60% of the cytosolic protein of neutrophil and monocytes

Clinical Ambiguity – Two typical scenarios

• **(1) Over-reliance on patient-reported symptoms** leading to over-medicalization (e.g., dosing escalations with biologic agents) or over-utilization of acute care services (e.g., hospitalization and emergency room visits).

• **(2) Under-reliance on patient-reported symptoms** can lead to delayed diagnosis of IBD, disease progression, and collateral damage from indolent or longstanding disease presence.
Inflammatory Bowel Disease (IBD)

- **Prevalence:**
  - Children:
    - CD: 43 per 100,000
    - UC: 28 per 100,000
  - Adults:
    - CD: 201 per 100,000
    - UC: 238 per 100,000

- **Economic burden**
  - $10.9-15.5 billion in the US

- **Cost of care**

<table>
<thead>
<tr>
<th>Mean Annual Cost of Crohn’s Disease</th>
<th>$18,022-18,932/patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceutical</td>
<td>35.3%</td>
</tr>
<tr>
<td>Inpatient</td>
<td>31.4%</td>
</tr>
<tr>
<td>Outpatient</td>
<td>33.3%</td>
</tr>
<tr>
<td>Average cost-per-hospitalization</td>
<td>$37,495</td>
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References:
A Glimpse of Where GI IBD Practice is Heading...

OBJECTIVES: The cost of medical care for Crohn’s disease (CD) and comorbidities in the era of biologics is unclear. We examined insurance claims data from US health plans to understand this relationship.

METHODS: Longitudinal CD patient data and reimbursement information from 11 health plans engaged with Accordant Health Services between 2011 and 2013 were analyzed. The analysis considered data for all CD patients and for the patient subgroup ≤20 years and >20 years of age. Descriptive statistics measured the mean health-plan paid costs per patient, the relative cost contribution of anti-tumor necrosis factor (TNF) agents, and health care costs for 31 specific comorbid conditions among CD patients.

RESULTS: Overall, there were 5,090 CD patients (57% women) of which 587 CD patients were ≤20 years of age. The mean health-plan paid cost per member per year was $18,637 (s.d. $32,023) for all CD patients, $22,796 (s.d. $41,905) for CD patients ≤20 years, and $18,095 (s.d. $30,065) for patients >20 years of age. Twenty-eight percent of CD patients accounted for 80% of total costs. No differences were found in costs based on gender. Increased health-plan paid costs were significantly correlated with the number of comorbid conditions across all ages. Pharmacy utilization costs account for nearly one-half (45.5%) of the total CD-attributable costs, exceeding inpatient care costs. Anti-TNF agents alone comprised nearly one-third (29.5%) of total costs. Aside from anti-TNF costs, other major categories of expense were as follows: inpatient 23.1%, outpatient hospital setting 15.7%, and MD office 8.2%.

CONCLUSIONS: Total health-care costs in CD exceed previous estimates, with the majority of costs being allocated to a relatively small subgroup of patients. Pharmacy utilization costs, owing to anti-TNF use, result in increasing total health-care costs and currently exceed costs for inpatient care. Pragmatic strategies to encourage gastroenterologists in the best clinical practice of optimizing anti-TNF use—in particular for younger age patients and those with multiple comorbidities—are necessary to reduce avoidable pharmacy utilization and inpatient care costs.

Am J Gastroenterol advance online publication, 21 July 2015; doi:10.1038/ajg.2015.207
Acute Care is costly, but it’s really PHARMACY COSTS outpacing others.

Figure 1 – Percent health plan paid costs by cost-driver category.
Figure 1a – The whole study population
- Emergency room, 2.6%
- Home, 1.4%
- MD Office, 8.2%
- Outpatient hospital procedures, 15.7%
- Other, 3.2%
- Pharmacy (includes injectible drugs and drugs billed by hospitals using revenue codes), 45.5%
- Inpatient, 23.1%

Figure 3b – 0 to 20 years old.
- Emergency room, 5.2%
- Home, 0.8%
- MD Office, 7.5%
- Outpatient hospital procedures, 15.4%
- Other, 2.2%
- Pharmacy (includes injectible drugs and drugs billed by hospitals using revenue codes), 48.6%
- Inpatient, 20.8%

Figure 3c – Older than 20 years.
- Emergency room, 5.2%
- Home, 1.5%
- MD Office, 8.4%
- Outpatient hospital procedures, 15.8%
- Other, 3.3%
- Pharmacy (includes injectible drugs and drugs billed by hospitals using revenue codes), 45.3%
- Inpatient, 23.4%
A clinical case from 2012

16 year old adolescent female reports 2 months of abdominal pain and occasional diarrhea, but no weight loss. She’s a lead cheerleader, academically high-achieving, and is overall health-conscious and without medical problems (except for seasonal allergies). No sick contacts, no travel, no precipitating events, and dietary habits have remained constant. PMDs workup with CBC, CMP, celiac panel, and stool cultures are negative. GI workup for stool occult blood is positive, and...

...so is the C diff toxin PCR.
Patient finishes a course of oral metronidazole and reports improvement at 1 month follow up. 3 months later, she comes back to clinic reporting abdominal pain, early satiety, occasional diarrhea, and fatigue. Repeat C diff testing is negative. CBC is normal, CMP is WNL except for a slightly low albumin of 3.2 (but patient reports decreased appetite).

EGD / Colonoscopy 2 weeks later shows normal histopathology (except for mild gastritis).

Reassurance is provided in clinic, and education is given on IBS management. Request for a symptom/trigger diary...
Patient changes providers / health system, and returns to GI clinic as a “new patient” (second opinion) for the same symptoms.

Repeat labs are unremarkable. MR-enterogram is performed and is normal without any evidence of mucosal enhancement.

Hesitant to repeat the EGD/colo, a stool calprotectin is sent and comes back 2 weeks later at 98mcg/g.

Literature is reviewed...
What does the literature say?

• The decision to proceed with endoscopy is not always clear, particularly when classic signs are absent such as frank anemia, markedly elevated inflammatory markers, and gross hematochezia.

• Patients often present with nonspecific symptoms, including mild abdominal pain, intermittent diarrhea, and generalized malaise.

• **More than half of all patients** who undergo endoscopy for nonbleeding symptoms are diagnosed with functional conditions, particularly irritable bowel syndrome in adults and functional abdominal pain in children.

• The pooled sensitivity and specificity of fecal calprotectin were 0.93 and 0.96 in adults and 0.92 and 0.76 in children.
Calprotectin levels in CD and IBS

- Calprotectin is effective in differentiating IBD from IBS
- Calprotectin is specific for intestinal inflammation which can be elevated by other factors including:
  - Infections
  - Parasites
  - Cancer

Clinical case – Duodenal Crohn’s

Although initially hesitant, repeat EGD / colo was performed and in the fourth portion of the duodenum, ulcers were found with histopathology confirming duodenal Crohn’s

She’s on infliximab monotherapy and is doing well.

BTW, C diff was a surrogate marker for worse disease / dysbiosis.
Utility in Diagnosis

Patient with suspected IBD

Screen with fecal calprotectin

+ 

Suspect IBD (Urgent Endoscopy)

- 

Suspect IBS (Plan other investigations)

+ 

Start treatment for UC or CD

- 

Plan other investigations

Adapted from Van Rheenan, BMJ 2010

Effectiveness and Cost-effectiveness of Measuring Fecal Calprotectin in Diagnosis of Inflammatory Bowel Disease in Adults and Children

Zhuo Yang,* Nick Clark,* and K. T. Park‡,§

Figure 1. Overview of model structure. (A) Model 1 and (B) Model 2. *Endoscopy = upper endoscopy and colonoscopy with histopathology.
What we found...

• **In adults, calprotectin testing saves $417/patient** but delayed diagnosis for 2.2/32 patients with IBD among 100 screened patients.

• **In children, FC screening saved $300/patient** but delayed diagnosis for 4.8/61 patients with IBD among 100 screened patients.

• Going directly to biopsy without calprotectin testing would cost an additional **$18,955 in adults and $6250 in children** to avoid 1 false-negative result from FC screening.

• Compared with the FC cutoff level of 100 mg/g, the cutoff level of 50 mg/g cost an additional $55 and $43 for adults and children, respectively, but it yielded 2.4 and 6.1 additional accurate diagnoses of IBD per 100 screened adults and children, respectively.

• If pre-test probability is more than ~75% that the patient has IBD, then direct endoscopy without calprotectin wins.
Changed the way I practice...

- Arguably one of the most important test when the chief complaint is “Abdominal Pain” or “diarrhea”

- Cut-offs I use: <50mcg/g, <100mcg/g
  - IBD monitoring: <150mcg/g

- Limitations:
  - point-of-care information delay (2 weeks at Stanford to come back)
  - higher variability at higher numbers
  - shouldn’t use at time of clean out
  - first morning stool is best
Editorial

Fecal calprotectin: towards a standardized use for inflammatory bowel disease management in routine practice.

Complete Mucosal Healing (aka “Deep Remission”)

- Definition – Complete absence of any visible lesions on a full endoscopic evaluation (technically different from “Histologic Remission”)

- Rationale for “Tight Control” – Europeans are ahead of the U.S. – as OUTCOME MEASURE OF CHOICE
  - Patients with sub-clinical inflammation were at high risk for clinical relapse during 12 month F/U Ghosh Dig Dis Sci 2001

  - *Future disease-modifying potential (particularly important in pediatric IBD)

- Most of the IBD community ascribes to complete mucosal healing as an optimal endpoint.

CRP for Mucosal Healing?

- 104 pts with CD underwent ileocolonoscopy (and SBFT or CTE)

  Intro: We sought to examine the relationship between C-reactive protein (CRP) and clinical, endoscopic, histologic, and radiographic activity in inflammatory bowel disease (IBD).

  - Clinically active CD; 55 % had CRP < 8 mg/L
  - Endoscopic active CD; 46% had CRP < 8 mg/L
  - No correlation between histology and CRP
  - No correlation between CRP and ileal disease activity


- Large variation in CRP response due to single nucleotide polymorphism

  Clin Gastroentrol and Hepatol. 2008;6:1218
Calprotectin Predicts Endoscopic Activity

- Prospective UC study- 123 UC patients with previous diagnosis– 146 Mayo Endoscopic subscore
  - Calprotectin prediction of endoscopic remission (Mayo≤1) AUC was 0.906 and 0.924 for QB LF and ELISA.
Calprotectin predicts IBD Relapse

- 43 CD & 37 UC patients in clinical remission: 58% & 51% relapsed within 12 months.
- Calprotectin at 50 mcg/g predicted relapse with 90% sensitivity and 83% specificity.
- Patients in clinical remission with low calprotectin as compared to those with high fCAL had better prognosis: 13% vs. 85% risk of relapse in 1 yr.
- ESR & CRP did not significantly differ between relapse and non-relapse group.
Calprotectin predicts drug responsiveness

- Clinical Monitoring
  - Fecal calprotectin as a therapeutic endpoint
  - Predicting remission with fecal calprotectin
    - Alter treatment protocols to improve response / outcomes

![Graph showing the evolution of calprotectin levels under infliximab therapy.](image)

**Figure 1** Evolution of calprotectin levels under infliximab therapy in function of the induction of endoscopic remission at week 10. Legend: Boxplots describe medians and interquartile ranges of the completers. Lines show the result of the mixed models analysis (ITT analysis).

Non-responders to therapy

Remission at week 10
Thank You

Questions?

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