New Goals for IBD Management – Do They Translate to Better Outcomes?

Sir Francis Avery Jones Lecture

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Sir Francis Avery Jones

“No matter the hour, he would take his own careful and detailed history, make a full and painstaking clinical examination and then discuss the whole problem with both patient and house physician after writing a note in his characteristic spidery handwriting.”

– Sir Christopher Booth
The big complaint that patients have is not that we don’t know enough, but that we don’t care enough. (2003)

Joseph B. Kirsner, MD, PhD

The treatment of the “untreatable” patient-revisited

Joseph B. Kirsner

Joseph B. Kirsner. The Louis Block Distinguished Service Professor of Medicine. Section of Gastroenterology, Department of Medicine, personal improvement and ultimate recovery, was provided for the patient. The patient’s parents were informed daily as to
Disclosures

Consultant and Grant Support

- Abbvie
- Amgen
- Cellgene
- Janssen
- Pfizer
- Prometheus
- Takeda
- UCB

Board Membership/Other

- ACG Board of Trustees
- VP, Cornerstones Health, Inc (non-profit medical education organization)
Learning Objectives

• Define the emerging and modified goals of IBD management.

• Review the available evidence supporting improved outcomes with objective goals of management.

• Develop a systematic approach to achieving the modified goals of IBD.

• Explore what the future may incorporate for IBD monitoring and prevention strategies.
We Have Made Great Progress in IBD.... But More Work to be Done

- Regional enteritis
- Ulcerative colitis

- Empiric
- Evidence-based
- Targeted
- Cures

- Societies
- Quality Measures
- Access to Care
- Certification

- Location
- Behavior
- Age of onset
- Prognostic indicators

- Observations among affected families
- Co-disease associations
- Linkage analysis
- GWAS
- Functional genomics, etc.

- Serotypes
- Immunotypes

- Top-down care?
- Longer-term studies
- Objective endpoints
- Chronic care model
- Quality of life

- Diet
- Epiphenomenon
- Microbiome

- Research funding
- Disease awareness

- Recognition of heterogeneity of care
- Defined quality measures
- Identified process improvements
- Improved outcomes

- Assessment of resource allocation
- Access to experts
- Affordable care for all

- Recognition of continuous improvement
- Systematic method to raise water level of care
What are the Preferred Outcomes in IBD?

**Preferred Outcomes**
- Cure
- Stable Remission
- No surgery/repeat surgery
- No cancer
- Improved quality of life
- No hospitalization
- No infections
- Affordable care

**Surrogates of Outcomes**
- Symptom improvement
  (poor marker)
- Avoidance of steroids
- Healed mucosa
Movement to Objective Measures of Control and Chronic Care Model of IBD: Improved Outcomes

Goal
- Response
- Remission
- Deep remission

Clinical parameters
- Improved symptoms
  - No symptoms
  - Normal labs
- Normal endoscopy
  - Mucosal healing

Outcomes
- Improved QoL
- Decreased hospitalization
- Avoidance of surgery
  - Minimal/no disability

SUSTAINED DISEASE CONTROL
Current Goals in IBD

• **Make the diagnosis** quickly and accurately
  – include elements of prognosis

• **Achieve normal bowel function**
  – improve quality of life

• **Induce remission** rapidly

• **Maintain steroid-free remission** over time
  – Emphasis on mucosal healing, other biological markers (“deep remission”)

• **Modify long-term outcomes** of the disease
  – Avoid hospitalization and surgery
  – Eliminate disability
  – Minimize exposure to steroids
  – Reduce costs of care
Have IBD Outcomes Improved? (YES)
Corticosteroids introduced in 1952

Steroids subsequently associated with worst outcomes in IBD, are used short-term only!
## Surgical Rates Decreasing in IBD

<table>
<thead>
<tr>
<th></th>
<th>Crohn’s Disease&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Ulcerative Colitis&lt;sup&gt;2&lt;/sup&gt;</th>
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<tbody>
<tr>
<td></td>
<td>1-Year Surgery Incidence</td>
<td>1-Year Surgery Incidence</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Midpoint Year of Study Before</td>
<td>37.76 (30.86-46.20)</td>
<td>9.39% (8.37-10.53%)</td>
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<tr>
<td>1990</td>
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<tr>
<td>Midpoint Year of Study Between</td>
<td>15.13 (11.62-19.69)</td>
<td>5.80% (3.79-8.86%)</td>
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<tr>
<td>1990-2000</td>
<td></td>
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</tr>
<tr>
<td>Midpoint Year of Study After</td>
<td>11.63 (8.84-15.29)</td>
<td>1.79% (0.46-6.87%)</td>
</tr>
<tr>
<td>2000</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Meta-regression p-value</td>
<td>&lt;0.0001</td>
<td>0.07</td>
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### Meta-regression p-value

- **<0.0001**: **0.0001**: **0.0189**: 
- **0.07**: **0.32**: **0.02**

### In Crohn’s disease, the overall 1-year incidence of surgery is 16.07%, 5-year is 32.27%, and 10-year is 48.28%. *P*-value of time trend <0.0001 – a significant reduction in 1-year surgery incidence with time.

### Overall, approximately 1 in 5 patients with ulcerative colitis will require surgery within 10 years of diagnosis.

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Colorectal Cancer in UC is Decreasing in Incidence

Colorectal Cancer in Inflammatory Bowel Disease is Declining

Meta-analysis that included 9 population-based studies

323,536 person-years

Standardized Incidence Ratio equal for CD, UC and IBD combined

1.7 (95% CI, 1.3-2.1)

Cumulative Risk in IBD Patients

St. Mark’s 40 Year Surveillance Data (UK)

Incidence Rate of CRC over 40 Years

Per-decade incidence rate of overall CRC (per 1,000 patient-years)

- 1973–1982: 9.0
- 1983–1992: 5.0
- 1993–2002: 4.0
- 2003–2012: 4.0

Decade

Shift to Earlier Stage Cancers

Per-decade incidence rate of CRC by Dukes' stage (per 1,000 patient-years)

- Dukes' A or B
- Dukes' C or D

Decade

1973–1982:
- Dukes' A or B: 6.0
- Dukes' C or D: 1.0

1983–1992:
- Dukes' A or B: 4.0
- Dukes' C or D: 2.0

1993–2002:
- Dukes' A or B: 2.0
- Dukes' C or D: 1.0

2003–2012:
- Dukes' A or B: 2.0
- Dukes' C or D: 1.0

Why Might Outcomes be Improving in IBD?

- **Improvements in therapies**
  - Achieve more **stable** disease control, modify natural history
  - Achieve deeper levels of remission, i.e. mucosal healing

- **Improvements in goals of management**
  - More emphasis on steroid-free care
  - Movement to proactive management rather than reactive management (from “crisis care” to “chronic care”)
  - Inclusion of long-term improved outcomes in goals

- **Better evidence**
  - Are we just performing better research? Asking better questions?

- **Other interventions have improved**
  - i.e. surgery, surveillance colonoscopy

- **The diseases have changed.**
  - People with IBD now are less ill than those of the past.
Treatments and Improved Outcomes
What we’ve learned about therapy and achieving preferred outcomes in IBD

• Ask the right questions....
• As therapies evolve, so does our ability to achieve preferred outcomes
• A personalized approach to management can optimize therapy
• Timing matters
• Individual pharmacokinetics matter
• Adherence to therapy matters
Infliximab Associated with Decreased Rates of Hospitalization and Surgery


*Endoscopic assessment at weeks 0, 10, and 54; mucosal healing was defined as the absence of mucosal ulceration

Early Combination Immunosuppressive Therapy vs. Conventional Management:

No difference in primary outcome!

Patients in remission (%)

Remission was defined as a CDAI score <150, absence of corticosteroid treatment, and no intestinal resection.

CIS, combined immunosuppression (IFX + AZA); CM, conventional management (corticosteroids)

*p<0.01; †p<0.05

Steroid Avoidance Had More Endoscopic Healing at 2 Years

Secondary End Point of the Top-Down/Step-Up Trial

...and these patients did better in the next 2 yrs!

Patients In Remission (%)

- Remission Off Steroids: 70.8%
- Off Steroids, No Anti-TNF: 62.5%

Patients In Remission (%)

- Simple endoscopic score 0: 73%
- Simple endoscopic score 1–9: 30%

Complete endoscopic healing at 2 years

- Step-up: 30%
- Top-down: 73%

$P=0.0028$

Mucosal Healing with Infliximab Associated with Less Colectomy in Ulcerative Colitis

Earlier Use of Anti-TNF Biologic Therapy in Crohn’s Disease Has Better Outcomes

- Claims data assessment
- >3700 patients all who received anti-TNF at some point

Continuous corticosteroid use during anti-TNF therapy.

CD-related Surgery during anti-TNF therapy

*P < 0.05 IS-to-TNF group versus other groups.

Thiopurine\(^1\): \(6\text{-TGn} \geq 125\) pmol/8 x \(10^8\) RBCs

Methotrexate\(^2\): \(\geq 15\) mg/w

Correlation Between 6-TGN and IFX Concentrations

Maintenance of Remission by MTX Dose

Improvements in Quality of Life in IBD Associated with Effective Therapy

- ECCO-Epicom Study (2014) compared quality of life of 1560 unselected IBD patients from Eastern and Western Europe.

- Quality of life during the first year of diagnosis improved if disease activity reduced.

Why don’t we achieve preferred outcomes in everyone?

• We are too late
• Therapies don’t work
• Therapies are not optimized
• We are treating the wrong problem
• We aren’t trying - symptom improvement is “enough”

Errors of commission vs Errors of omission
How can we systematically achieve better outcomes and modify the disease course in IBD?
The Concept of Treat to Target: PROACTIVE Rx

• Shared decision-making between rheumatoid arthritis patient and doctor

• Primary goal: maximize health-related quality of life
  – Control symptoms
  – Prevent progressive structural damage
  – Normalize function and social participation

• Abrogation of inflammation is the most important mean to achieve goals

• *Treatment to target by measuring disease activity and adjusting therapy accordingly optimizes outcomes in RA*

A Proposed Algorithm for Achieving and Maintaining Targets of Control in IBD

Baseline assessment of disease activity by endoscopy paired with surrogate marker (Fecal Calprotectin, CRP)

Choice of initial therapy based on severity and prognosis of patient

3-6 months

Re-assessment of disease activity directly or with surrogate marker

Target Achieved

Yes

“No”

Discussion with patient treatment options

Clinical follow-up that includes assessment of disease stability

6-12 months

“Disease Monitoring”

No

Is patient willing to proceed with your recommendations?

Yes

Clinical follow-up

If no other treatment options left

Adjust therapy

3-6 months

“Treat to Target”
So what should the targets be?

Selecting Therapeutic TaRgets in Inflammatory Bowel Disease Endpoints

- **Methods:** 28 IBD specialists developed recommendations based on a systematic literature review and expert opinion.

- **Results:** 12 recommendations for UC and CD.

- **UC TARGET:**
  - PRO: resolution of rectal bleeding and diarrhea/altered bowel habit *and*
  - *endoscopic remission:* Mayo endoscopic subscore of 0-1. Histological remission is an *adjunctive goal.*

- **CD TARGET:**
  - PRO: resolution of abdominal pain and diarrhea/altered bowel habit; *and*
  - *endoscopic remission:*
    - resolution of ulceration at ileocolonoscopy, *or*
    - resolution of findings of inflammation on cross-sectional imaging in patients who cannot be adequately assessed with ileocolonoscopy.

- **Biomarker remission (normal CRP and calprotectin) was considered an adjunctive target.**
Can it Actually Be Done?
More often than you think.


Studying this approach: complicated!
REACT: Randomized Evaluation of an Algorithm for Crohn’s Treatment

Without fistula

Active Luminal CD (HBS >4)

Evaluate in 12 wks

MRI, US, EUA to rule out abscess

Antibiotics / fistulotomy

No

Drainage / seton + antibiotics

Complex fistula

Yes

Abscess present?

No

Follow algorithm for active luminal CD without fistula

Yes

Re-evaluate in 4 wks – remission? (HBS ≤4)

Taper GCS

Add adalimumab + AZA or MTX

Taper GCS, re-evaluate in 12 wks – remission?

Yes

Adalimumab + AZA or MTX (GCS as needed)

No maintenance therapy

Re-evaluate in 12 wks – remission?

Yes

Continue combination maintenance therapy

No

Increase adalimumab to weekly dose

Re-evaluate in 12 wks – remission?

Yes

Continue combination maintenance therapy

No

Switch antimetabolite

Re-evaluate in 12 wks – remission?

Yes

Continue combination maintenance therapy

No

Switch TNF blocker

Re-evaluate in 12 wks – remission?

Yes

Continue combination maintenance therapy

No

Consider resection

* For patients in Belgium, evaluate in 12 wks

Khanna R, et al. ECCO. 2014, Copenhagen; OP004
REACT: Symptomatic Remission
Harvey Bradshaw Index ≤4 and no corticosteroids

- Conventional management
- Early combined immunosuppression

- **Baseline**: P = 0.790
- **Month 6**: P = 0.498
- **Month 12**: P = 0.389
- **Month 18**: P = 0.250

Khanna R, et al. ECCO 2014, Copenhagen; OP004
REACT: Algorithm-Based Treatment with Early Combined Immunosuppression Reduced Complications in CD Secondary Endpoints

HR (95% CI) = 0.73 (0.62, 0.86), p<0.001

Khanna R, et al. ECCO 2014, Copenhagen; OP004
POCER study: Post Operative Crohn’s Endoscopic Recurrence

Methods: Multicentre RCT

SURGERY: curative resection

RISK Stratification: Low or High
(High risk: smoker, ≥ second operation, perforating disease)

Randomization

One third of patients

No Endoscopy (“Standard”)
Risk driven best drug therapy

All patients: Metronidazole: 0-3
Low risk: No further treatment
High risk: thiopurine or adalimumab if thiopurine intolerant

Endoscopic Intervention (“Active”)

Two thirds of patients

6 month colonoscopy Step up Rx if ≥ i2 on Rutgeerts scale

18 Month Colonoscopy

One third of patients

Post Operative Crohn’s Endoscopic Recurrence Prevention Based on Risk and Endoscopy (POCER)

<table>
<thead>
<tr>
<th></th>
<th>Rutgeerts ≤ i2 at 18 months</th>
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<tbody>
<tr>
<td>Active Care (n=122)</td>
<td>62/122 (51%)</td>
<td>P = 0.028</td>
</tr>
<tr>
<td>Standard Care (n=52)</td>
<td>17/52 (33%)</td>
<td></td>
</tr>
<tr>
<td>ADA immediately postop (n=28)</td>
<td>16/28 (57%)</td>
<td>P = 0.2</td>
</tr>
<tr>
<td>ADA initiated if i ≥ 2 at 6 months</td>
<td>13/32 (41%)</td>
<td></td>
</tr>
</tbody>
</table>

- Treatment according to risk of recurrence at 6 month colonoscopy, is superior to drug therapy alone.

- Step up with anti-TNF therapy, based on colonoscopy findings at 6 months, is a viable strategy in high risk patients

What’s next?
Ongoing Movement to Disease Modification and Improved Outcomes in IBD

• Development of better monitoring tools (valid surrogates)

• Evidence to support stable disease monitoring and pre-emptive adjustment of therapies to change outcomes

• Appreciation for deeper levels of remission

• Cures!
‘Silent’ Crohn’s Patients Have 6-Fold Higher Risk of Hospitalizations

178 CD patients with clinical remission defined by SIBDQ scores in a prospective registry

Chi Square = 32.23; $P$-value <0.001

SIBDQ, short inflammatory bowel disease questionnaire

Fecal Calprotectin Correlates with Endoscopic Activity in UC

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>ROC area</th>
</tr>
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<tbody>
<tr>
<td>Calprotectin ≥ 57 µg/g</td>
<td>91</td>
<td>90</td>
<td>0.939</td>
</tr>
<tr>
<td>Lichtiger index ≥ 4</td>
<td>82</td>
<td>74</td>
<td>0.841</td>
</tr>
<tr>
<td>CRP ≥ 6 mg/L</td>
<td>68</td>
<td>72</td>
<td>0.778</td>
</tr>
</tbody>
</table>

CRP: c-reactive protein
FC: fecal calprotectin
Monitoring of CRP and Fecal Calprotectin Predicts Clinical Relapse in CD Patients after Infliximab Withdrawal: A Sub-Analysis of the STORI Study

- FC and CRP Lead clinical relapse by 4 mo
- CRP of 6.1mg/L and calprotectin of 305mcg/g best for prediction of relapse
Future of Patient Disease Monitoring: Home Fecal Calprotectin

Comparison* of Home FC (CalproSmart, n=638) with FC Analyzed in Lab (ELISA, n=894) in IBD Patients (N=221)

CalproSmart:
- >600 μg/g
- 200-600 μg/g
- <200 μg/g

Total test time: 25 minutes

Diagnostic Performance of CalproSmart

- AUC=0.856
- 4.4% inter-assay variability
- 10.9% intra-assay variability
- 150 ug/g FC cut-off
- rho=0.685, P<0.0001

*Measured monthly for 6 months.
Dose optimization Increases Probability of Remaining on Infliximab Up to 5 years

• Retrospective cohort of patients in clinical remission, single physician practice
  – Infliximab dose optimisation to trough concentrations 5–10 µg/mL (n=48)
  – No infliximab dose optimisation (n=78)

Optimized Infliximab Levels (3-7 mcg/mL) Associated with Stable Maintenance (TAXIT)

Clinically based (CB) and trough level based (LB) groups

Clinical remission

CB Group: 62.3% (N=122)  
LB Group: 64.3% (N=126)  
p = 0.79

Maintenance phase (weeks)

Relapse-free survival

LogRank p = 0.0038  
Breslow p = 0.0058

TAXIT: Prospective controlled Trough level Adapted infliXImab Treatment

Histological Normalization in UC Patients Is Associated with Lower Clinical Relapse Rates Compared to Those With Histologic Activity

Clinical Relapse Free Survival vs Histological Healing

- Complete histological normalization
- Histological quiescence
- Histological activity

Analysis Time (years)
Summary: Practical Recommendations for Improvement of IBD Outcomes

• Outcomes of IBD patients have improved for multiple reasons, one of which has been the evolution of treatment goals emphasizing objective disease control.

• Adopting objective markers of disease control as treatment endpoints makes sense, but doing so when patients are already feeling well requires shared decision making.

• Treating to achieve a target of disease control should also include a plan for monitoring subsequently, to anticipate “drift”.

• Future modifications will include proactive therapeutic drug monitoring and more specific targets of inflammation control.
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