How to treat IBD like an expert

Bruce E. Sands, MD, MS
Chief of the Dr. Henry D. Janowitz Division of Gastroenterology
Dr. Burrill B. Crohn Professor of Medicine
Icahn School of Medicine
at Mount Sinai
New York, NY
Disclosures

- AbbVie
- American Academy of CME
- American Gastroenterological Association
- AGA Institute
- Catrille & Associates Ltd.
- Celgene
- Focus Medical Communications, LLC
- Forest Research Institute
- Indiana University
- Janssen Biotech
- Jefferson University
- Luitpold Pharmaceuticals
- MedImmune
- Millennium Pharmaceuticals/Takeda
- Pfizer
- Prometheus Laboratories
- Salix Pharmaceuticals
- Shire
- Strategic Consultants International
Learning Objectives

• Summarize evidence-based guidelines for treating IBD
• Recommend interventions associated with improved outcomes in IBD management
What is an expert?

“Make three correct guesses consecutively and you will establish a reputation as an expert.”

Laurence J. Peter

“My definition of an expert in any field is a person who knows enough about what's really going on to be scared.”

P.J. Plauger

“An expert is one who knows more and more about less and less.”

Nicholas Butler
IBD: What’s the big deal?
The burden of inflammatory bowel diseases

• Prevalence of IBD is 1% in North America and some European countries

• Incidence of Crohn’s disease is still increasing in these countries

• Rapid increases in the incidence of IBD are now being observed in Japan, South Korea, Australia, New Zealand and some regions of India and China

• IBD will emerge as a worldwide epidemic in the coming years

Incidence of IBD in Rhode Island, 2008-10

What do patients think? The IMPACT survey

- Online patient survey by EFCCA in 10 European languages
- 24 European countries participated
- 4,990 IBD surveys analysed
- 63% of respondents had CD and 33% had UC
- Most (68%) respondents were aged 19–44 years

Data from IMPACT. http://efcca.org/media/files/press-Join-Fight/3.PRESS_KIT_IBD_IMPACT_REPORT_BCN.pdf
Work disability in IBD

Norwegian population-based study of IBD patients (n=518) receiving disability pension (DP)

Crohn’s disease

RR for DP: 2.0 (95% CI 1.4–2.7)

Ulcerative colitis

RR for DP: 1.8 (95% CI 1.4–2.3)

Estimates of mortality in IBD

Risk of dying according to age at, and time since, IBD diagnosis (Denmark 1982–2010) 36,080 UC and 15,361 CD vs 2,858,096 matched controls

- Mortality increased in the first year after diagnosis
- Intermediate and long-term mortality increased by 10% in UC and 50% in CD
- Mortality from UC decreased from 1982 to 2010, because of reduced mortalities from gastrointestinal disorders and colorectal cancer
- Mortality from CD did not change

So, you want to be an IBD expert!

• Avoid pitfalls in diagnosis

• Treatment
  - Judgment: Know best indications, timing, expected efficacy, sequence/combination, risk/benefit, when to move on
  - Sometimes defy convention
  - Always have a back-up plan

• Know “something extra” about the disease
Diagnosing IBD like an expert
NIDDK IBD Genetics Consortium Diagnostic Criteria for IBD

• **Symptoms:** one or more of
  - Diarrhea
  - Rectal bleeding
  - Abdominal pain
  - Fever
  - Complicated perianal disease
  - Extraintestinal manifestations
  - Weight loss
  - Failure to thrive

  AND
NIDDK IBD Genetics Consortium Diagnostic Criteria for IBD

• Symptoms on 2 or more occasions
• Separated by at least 8 weeks OR ongoing for at least 6 weeks*

*If single episode of colitis (<6 wk) with colectomy, pathology should be consistent with idiopathic IBD and microbiology studies should be negative

AND

• Objective evidence on 1 or more of endoscopy, radiology, or histology
NIDDK IBD Genetics Consortium Diagnostic Criteria for IBD

• Endoscopic
  – Mucosal edema*
  – Erythema*
  – Loss of normal submucosal vasculature*
  – Friability*
  – Ulceration
  – Stricture formation
  – Pseudopolyps

*Considered minor changes, and require mucosal biopsies to confirm IBD

OR
NIDDK IBD Genetics Consortium Diagnostic Criteria for IBD

• Radiology
  – Mucosal thickening and/or nodularity*
  – Ulceration
  – Stricture
  – Pseudopolyps
  – Fistula formation
  – Pseudosacculation

*Considered minor changes, and not sufficient to make diagnosis

OR
NIDDK IBD Genetics Consortium Diagnostic Criteria for IBD

- **Histology**
  - Mucosal erosion or ulceration
  - Architectural changes of crypts
  - Paneth cell metaplasia (in colon)
  - Transmural inflammatory infiltrate*
  - Fibrosis of muscularis propria*
  - Noncaseating granuloma*

*Changes consistent with Crohn’s disease
Unusual pathologic manifestations of other forms of colitis

- Acute self-limited colitis
- NSAID-induced colitis mimicking IBD
- Ischemia
- Radiation
- Microscopic colitis with features of IBD
- Diverticular disease associated colitis
- Diversion colitis
- Other
Endoscopic Appearance in UC: Modified Baron Score

0 = NORMAL

1 = MILD

2 = MODERATE

3 = SEVERE

“Rake ulcers” in Crohn’s disease
Lymphoid Hyperplasia or Cobblestoning?
Agreement between Junior and Senior Phenotypers using the NIDDK IBD Genetics Consortium Diagnostic Criteria

<table>
<thead>
<tr>
<th>Variable</th>
<th>Kappa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>0.83 (0.74-0.90)</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td></td>
</tr>
<tr>
<td>Behavior</td>
<td>0.70 (0.59-0.80)</td>
</tr>
<tr>
<td>Location</td>
<td></td>
</tr>
<tr>
<td>Esophagogastroduodenal</td>
<td>0.45 (0.25-0.62)</td>
</tr>
<tr>
<td>Jejunal</td>
<td>0.73 (0.59-0.85)</td>
</tr>
<tr>
<td>Ileal</td>
<td>0.67 (0.52-0.80)</td>
</tr>
<tr>
<td>Colonic</td>
<td>0.60 (0.44-0.75)</td>
</tr>
<tr>
<td>Perianal</td>
<td>0.53 (0.41-0.64)</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td></td>
</tr>
<tr>
<td>Disease extent</td>
<td>0.73 (0.57-0.86)</td>
</tr>
</tbody>
</table>

Crohn’s Disease - Distinguishing Features

- Granuloma
- Focal lesions
- Fistulization
- Asymmetric involvement
- Strictures
- Perineal disease
- Rectal sparing
- Skip lesions
- Small bowel involvement
- Endoscopic features

20-30% without gross bleeding
Beware of granuloma worship!

Yantis RK, Odze RD. Am J Gastroenterol 2007;102:890–904
Defining the genetic architecture of CD vs. UC

IBD vs. control odds ratio

CD vs. UC odds ratio

110 IBD loci

23 UC specific loci

MHC

30 CD specific loci

IL23R

NOD2

PTPN22

Courtesy of Dr. Judy Cho
Differentiating CD and UC: Twelve exceptions to the rules

1. UC following oral or enema medical therapy
2. Pretreatment presentation of UC in children
3. Cecal inflammation and left-sided colitis (with sparing of the ascending and/or transverse colon)
4. Appendiceal inflammation in patients with subtotal or left-sided colitis
5. “Fulminant” UC
6. Crohn’ s-like aphthous ulcers in UC

Yantis RK, Odze RD. Am J Gastroenterol 2007;102:890–904
Differentiating CD and UC: Twelve exceptions to the rules

7. Ileitis in UC
8. Upper GI Tract Involvement in UC
9. CD involving the mucosa in a UC-like pattern with minimal or no submucosal inflammation
10. CD with continuous disease involving the entire colon (pancolitis)
11. Rectovaginal fistula in UC
12. Anal fissure in UC
Key Reasons to Use Cross-Sectional Imaging in IBD

• To identify presence and activity of small bowel disease
• To identify complications of disease (stricture, fistula, abscess) in Crohn’s disease
• To monitor for progression of Crohn’s disease
• To monitor response to therapy in Crohn’s disease
CTE or MRE?

Siddiki HA. AJR 2009;193:113–121
Single CT Scan: Lifetime Attributable Risk of Cancer Death By Age*

*Assumes linear-no threshold model of cancer risk

Enterography is complementary to ileocolonoscopy in evaluating Crohn’s disease

- TI normal on ileoscopy: 43.8% (n=67)
- Active SB Crohn’s disease based on reference standard: 53.7% (n=36)
- Skipping of distal TI on CTE: 30.6% (n=11)
- Intramural TI disease on CTE: 63.9% (n=23)
- Upper GI Crohn’s: 5.6% (n=2)

Treating IBD like an expert
Adherence to guidelines on prevention of venous thromboembolism

Venous thromboembolism during active disease and remission in inflammatory bowel disease: a cohort study

US survey about prevention of DVT in hospitalized IBD patients (n=591 physicians)

- **29%** were unaware of any recommendations addressing pharmacological prophylaxis included in ACG IBD guidelines

- **35%** would give pharmacological VTE prophylaxis to a hospitalized patient with severe ulcerative colitis


Case-fatality rates and occurrence of \textit{C}.\textit{difficile} in small or large bowel Crohn’s disease

Data from the Nationwide Inpatient Sample

\cite{Ricciardi2009}
Goals of Therapy

• Induce symptomatic remission
• Maintain **steroid-free** remission
• Enhance quality of life
• Prevent/treat complications of disease
• Avoid short and long term toxicity of therapy
How to achieve goals of therapy?

- Risk stratification
- Optimize each medication
- Monitor for and act upon objective evidence of inflammation
## Medications for IBD

### Crohn’s Disease
- Infliximab
- Adalimumab
- Certolizumab pegol
- Vedolizumab
- Methotrexate
- Mercaptopurine/Azathioprine

- **Penetrating disease**
- **Post-operative prophylaxis**

### Severe acute UC
- **Corticosteroids**
  - Budesonide MMX
  - Budesonide foam
  - 5-Aminosalicylates
- **Cyclosporine**

### Biologics
- Infliximab
- Adalimumab
- Golimumab
- Vedolizumab
- Anti-TNF Abs
- Anti-α4β7 integrin Ab

### Antibiotics
- Crohn’s Disease

### Immune Modulators
- Methotrexate
- Mercaptopurine/Azathioprine

### Penetrating disease

- Post-operative prophylaxis
5-Aminosalicylates

- Small clinical benefit in CD\(^1\)
- Effective for induction of remission in UC\(^2\); generally in 2 to 8 weeks
- No difference in rates of induction of remission among various preparations\(^2\)
- High dose not more effective than moderate dose in mild disease; possibly more effective in moderate disease and those exposed to prior therapy\(^3\)
- Once daily as effective as split dosing and better adherence\(^4\)
- Combination of oral and rectal 5ASA more effective in distal and extensive disease\(^5,6\)
- All doses effective for maintenance of remission\(^2\)

---

\(^1\)Clin Gastroenterol Hepatol 2004;2:379-388
\(^2\)Cochrane Database of Systematic Reviews, 17 OCT 2012 DOI: 10.1002/14651858.CD000543.pub3
Patient meets criteria for IS therapy

Update vaccination status

Steroids
- Calcium/vitamin D
- DEXA
  “Exit strategy”

Immunomodulators
- TPMT for thiopurines
  CBC, liver enzyme monitoring

Biologics
- HBV testing
  TB testing
  monitor for infection

IS, immunosuppressant; TPTM, thiopurine methyltransferase; DEXA, dual-energy x-ray absorptiometry; CBC, complete blood count; TB, tuberculosis; HBV, hepatitis B virus
Corticosteroids: Topical and Budesonide

- Steroid enemas, foam, suppositories effective for induction of remission in mild to moderate UC
  - Hydrocortisone enema less effective than mesalamine enema

- Budesonide effective for induction of remission in mild to moderate ileocolonic CD (CIR), UC (MMX), proctitis/proctosigmoiditis (foam)
  - Limited role in maintenance of remission
Corticosteroids: Oral

- Effective for induction of remission, no role in maintenance
  - Indicated for those failing 5ASAs, budesonide, moderately severe disease
  - Poor side effect profile
  - May be used in combination with an anti-TNF to induce remission in moderate to severe CD
  - Doses >60 mg/d not more effective
  - Effective in 1 to 3 weeks
  - Anticipate steroid dependence in ~25% of patients
IV Steroids

• Indicated for severe flare, not responding to oral steroids, other therapies
• No need to give more than 60 mg methylprednisolone or 300 mg hydrocortisone
• Can give once daily
• Response generally occurs within 5-7 days!
• ~60% of patients completely respond to IV steroids

Truelove SC, Jewell, DP. Lancet 1974
Truelove SC et al. Lancet 1978
Thiopurines: Mercaptopurine and Azathioprine

- Indications
  - Steroid-dependence/refractoriness
  - As part of combination therapy with biologics
  - Post-operative prophylaxis (CD)
  - Fistulas (CD)
- TPMT testing advised before starting
- Dosing
  - Mercaptopurine: 1 – 1.5 mg/kg
  - Azathioprine: 2 – 3 mg/kg
- Onset of effect: 8 – 16 weeks
- Metabolite testing helpful in inadequate response
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th># Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhodes</td>
<td>1971</td>
<td>12</td>
</tr>
<tr>
<td>Klein</td>
<td>1974</td>
<td>26</td>
</tr>
<tr>
<td>Candy Part 1</td>
<td>1994</td>
<td>63</td>
</tr>
<tr>
<td>NCCDS Group 1</td>
<td>1979</td>
<td>136</td>
</tr>
<tr>
<td>Phase 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ewe</td>
<td>1993</td>
<td>42</td>
</tr>
<tr>
<td>Present</td>
<td>1980</td>
<td>72</td>
</tr>
<tr>
<td>Willoughby Group 1</td>
<td>1971</td>
<td>12</td>
</tr>
<tr>
<td>Common odds ratio</td>
<td>367</td>
<td></td>
</tr>
</tbody>
</table>

**Odds Ratio of Response**

- Favors Placebo
- Favors Therapy

6-Mercaptopurine & Azathioprine: Adverse Effects

- GI intolerance
- Bone marrow suppression
- Infection
- Liver function abnormality / frank hepatitis
- Pancreatitis
- Hypersensitivity syndrome (serum sickness)
- Lymphoma
- Squamous cell skin cancer, cervical cancer
TPMT genotype associated with early but not late severe myelosuppression

6- MP dose does not correlate with clinical response

$p = 0.6$

Interpreting Thiopurine Metabolites

Interpreting Thiopurine Metabolites

Interpreting Thiopurine Metabolites

Thiopurine Resistance (if not responding)

Interpreting Thiopurine Metabolites

Thiopurine resistance
6MMP:6TGN > 12

Interpreting Thiopurine Metabolites

Exposure to Thiopurines and Lymphomas in IBD

Overall rate on therapy:
0·90 per 1000 (95% CI 0·50–1·49) patient-years

Cases of Lymphoproliferative Disorders

- Thiopurine therapy
  - Continuing
  - Discontinued
  - Never received

Patient-years

- 5 years: 13,595
- 0 years: 7,924
- 0 years: 15,732
- 6 years: 2,325
- 1 year: 1,524
- 2 years: 4,965
- >65 years: 739
- 1 year: 533
- 4 years: 2,375

Methotrexate

• **Indications**
  - Steroid-dependence
  - Steroid-refractory
  - As part of combination therapy with biologics

• **Dosing**
  - SC or IM: 25 → 15 mg weekly
  - PO: 7.5 - 15 mg weekly

  ▪ **Onset of effect:** 8 – 16 weeks
  ▪ Anticipate nausea (folate, ondansetron)
  ▪ Effective contraception needed
  ▪ Monitor AST, ALT, bilirubin, albumin

Moderate–Severe CD: Efficacy of MTX

The most influential paper of the last 20 years in IBD

Mucosal healing in Crohn’s disease with anti-TNF antibody (infliximab)

Van Dullemen HM et al. Gastroenterology 1995
Anti-TNF Antibodies

- CD: infliximab, adalimumab, certolizumab pegol
- UC: infliximab, adalimumab, golimumab

Indications
  - Moderate to severe disease
  - Steroid-dependent/refractory disease
  - Refractory to immune modulators
  - Severe, IV steroid-refractory UC
  - Fistulizing CD
  - Selected patients with early CD
  - Post-operative prophylaxis of CD

- Onset of effect: 2-6 weeks
Evidence for Combination Therapy in Immunosuppressant-Naive Patients

SONIC

Corticosteroid-free clinical remission at Week 26

AZA, azathioprine; IFX, infliximab

Pragmatic Approach to Combination Therapy

- Combination therapy is most effective, least risky induction therapy
- Limited data on benefits and risks of combination therapy with biologic therapies other than infliximab
- Infection risk driven more by steroids
- Neoplasia risk driven more by thiopurines
- Consider reducing to monotherapy for
  - Young males
  - Individuals in deep, sustained remissions
    - Can be re-treated with combination therapy
Symptoms (Crohn’s Disease Activity Index) vs Endoscopic Findings (Crohn’s Disease Endoscopic Index of Severity)

Correlation of CDAI vs CDEIS at D₀ (n=142)

CDAI, Crohn’s Disease Activity Index; CDEIS, Crohn’s Disease Endoscopic Index of Severity

Poor Correlation Between Clinical Remission and Mucosal Healing

Treatment of UC with infliximab (ACT 1)

*\(P \leq 0.001\) vs placebo based on a two-sided Cochran-Mantel-Haenszel chi-square test
Mucosal healing = Mayo score 0 or 1

Causes of Symptoms Other Than Active Inflammation in Patients With Crohn’s Disease

• Disease complications
  – Strictures
  – Fistulas
  – Abscesses

• Complications of surgical resection
  – Bile salt diarrhea
  – Steatorrhea
  – Small intestine bacterial overgrowth

• Infection
  – Clostridium difficile
  – Cytomegalovirus

• Irritable bowel syndrome (with/without mood disorder)
“Trust, but verify.”
Mucosal Healing in the Management of IBD

- Severe endoscopic disease is associated with a worse clinical course
- Mucosal healing is associated with improved outcomes
- Endoscopy can be helpful in confirming active disease and guiding clinical decisions
- Need to define mucosal healing
- Validated endoscopic indices exist—but not easy to use!
- Mucosal healing cannot consistently be obtained with currently used therapies

**Currently, insufficient evidence to support an increase in therapy for all patients in clinical remission that continue to have endoscopic evidence of ongoing inflammation.**
Pharmacokinetics 101: Drug levels matter!

Steroid-free Clinical Remission at Week 26 by Median Trough Infliximab Concentration at Week 30 (SONIC)

<table>
<thead>
<tr>
<th>Trough Concentration</th>
<th>Proportion of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>19/32 59</td>
</tr>
<tr>
<td>&gt;0-1</td>
<td>13/23 57</td>
</tr>
<tr>
<td>&gt;1-3</td>
<td>43/59 73</td>
</tr>
<tr>
<td>&gt;3-6</td>
<td>36/49 74</td>
</tr>
<tr>
<td>&gt;6</td>
<td>31/43 72</td>
</tr>
</tbody>
</table>

IFX + placebo or IFX/AZA-treated patients who had serum samples collected prior to infusion at Week 30 (N=206)

Infliximab Concentration and Clinical Outcome in Adult Patients with Moderate to Severe UC (ACT 1 & ACT 2)

Increasing Dose of Infliximab in the Presence of ATI Formation is Inferior to Changing Anti-TNF

Clinical outcomes in patients with detectable HACA (n=35)*

- Complete / partial response (%)

<table>
<thead>
<tr>
<th>Anti-TNF changed (11/12) Infliximab increased (1/6)</th>
<th>92</th>
<th>17</th>
</tr>
</thead>
</table>

P<0.004

Clinical outcomes in patients with sub-therapeutic concentrations (n=69)*

- Complete / partial response (%)

| Anti-TNF changed (11/12) Infliximab increased (1/6) | 86 |

P<0.016

* 6 discontinued IFX, 3 continued same dose 3, 3 proceeded to surgery, 5 patients could not be assessed

* 10 continued same dose, 9 discontinued IFX, 8 proceeded to surgery and 7 patients could not be assessed

Management of loss of response to anti-TNF antibodies

Symptoms suggestive of relapse

Trough levels detectable
- Endoscopy shows inflammation
  - Switch to drug with different mode of action
- Endoscopy shows no inflammation
  - R/O stenosis, consider treating IBS

Trough levels undetectable
- Antibodies high
  - Switch within class
- No or low antibodies
  - Optimize within same anti-TNF (dose intensify, add IMMOD)

Adapted from Vermeire S, Gils A. Frontline Gastroenterology 2013;4:41–43
Therapeutic Drug Monitoring (TDM) of Anti-TNF Antibodies

- Minimum effective concentration roughly defined
  - IFX trough \( \sim 3 \, \mu g/mL \)\(^1\)
  - ADA trough \( \sim 5 \, \mu g/mL \)\(^2\)
- Role of TDM best established in assessing loss of response
- Growing interest in early TDM to dose optimize in severe disease (especially UC)\(^3,4\)
- TDM appears to be cost effective when dose-reduction incorporated into treatment algorithm, but will be highly dependent upon cost and frequency of assay\(^5\)

Vedolizumab

- **Indications**
  - Active UC or CD despite corticosteroids, immune modulators, or anti-TNF\(^1,2\)
  - Effective in steroid sparing\(^1,2\)

- **Dose**: 300 mg IV weeks 0, 2, 6 and every 8 wk

- **Onset of effect**
  - as early as 2 weeks
  - 6 to 8 weeks more typical
  - at least 10 weeks needed in CD with prior anti-TNF\(^3\)

- **Consider using in combination with immune modulator**

---

\(^3\)Sands BE, et al. Gastroenterology 2014;147:618–627
Putting it together in specific clinical situations

- Acute severe UC
- New diagnosis CD: top-down?
Prognostic factors in ulcerative colitis

• Greater extent of disease
• Failure of 5ASA/need for corticosteroids (especially for first flare)
• Deep ulceration
• High CRP, ESR
• Low albumin
Severe acute ulcerative colitis

- Switch from oral to IV steroids may be effective
- Stop 5ASAs
- Decision for next steps in 3 days (not more than 5)
- Cyclosporine and infliximab roughly same efficacy\(^1\)
- Infliximab: consider induction doses higher than standard 5 mg/kg at weeks 0, 2 and 6

Impact of Therapy Depends on Degree of Structural Damage and Velocity of Progression

Cumulative Probability (%)

High Potential

Low Potential

Inflammatory Stricturing

Patients at risk:
N = 2002 552 229 95 37

Progression of digestive disease damage and inflammatory activity

Digestive Damage

Disease onset
Diagnosis
Early disease

Inflammatory Activity (CDAI, CDEIS, CRP)

Pre-clinical
Clinical

Surgery
Stricture

Fistula/abscess

CDAI: Crohn's Disease Activity Index; CDEIS: Crohn’s Disease Endoscopic Index of Severity; CRP: C-Reactive Protein

Pariente B et al. Inflamm Bowel Dis 2011;17(6):1415-22
Response and remission to certolizumab pegol in Crohn’s disease vs disease duration

Data from the PRECiSE 2 study

Remission by disease duration with adalimumab at week 26

Placebo  All adalimumab

<2 years  |  n=23, n=39
Remission (%)  |  P=0.008

<2-5 years  |  n=36, n=57
Remission (%)  |  P=0.56

≥5 years  |  n=111, n=233
Remission (%)  |  P<0.001

Evolving treatment strategies for Crohn’s disease

- Severe
  - Conventional step-care
  - TNF antagonist ± IMS
  - Corticosteroids

- Moderate
  - Accelerated step-care
  - TNF antagonist ± IMS
  - Corticosteroids + IMS

- Early top-down
  - IMS + TNF antagonist

Early disease: Who should get top-down?

Early Crohn’s Disease
(Moderate To Severe)

High risk for rapid progression to bowel damage and disability

Potential predictors from literature
- Early onset (<40 yrs)
- Small bowel involvement
- Perianal disease at diagnosis
- Endoscopic severe lesions

Potential predictors in clinical practice
- Diagnosis age <40 yrs
- Extensive anatomic involvement
- Perianal or severe rectal disease
- Deep ulcers
- Prior surgical resection
- Stricturing and/or penetrating behavior

YES

Early top-down IMM + TNF antagonist

NO

Accelerated step-care IMM + TNF antagonist

Fail to respond

TNF antagonist ± IMM

Management of Crohn’s disease: from the start

Mild Crohn’s disease

- Budesonide (terminal ileum) or systemic steroids (colon)

Moderate Crohn’s disease without poor prognostic factors AND without disease complication

- Steroids + azathioprine or methotrexate

Severe disease, complicated disease (presence of bowel damage) and/or poor prognostic factors

- Anti-TNF therapy

Monitoring objective signs of inflammation at 6-9 months: endoscopy, cross-sectional imaging and/or fecal calprotectin

New approach to treatment of IBD: Treat to target

1. Active Symptoms
   - Yes: Objective evidence of inflammation
     - Yes: New treatment begun
       - Yes: Reassess for symptoms and objective inflammation
         - Yes: CONTINUE Treatment
         - No: Optimize dosing
       - No: Symptomatic Treatment
     - No: Symptomatic Treatment
   - No: Active Symptoms

STOP Treatment:
- Symptoms resolved? Inflammation improved?
  - Yes: CONTINUE Treatment
  - No: Optimize dosing

Optimize dosing:
- BNo

Symptomatic Treatment:
- Yes: New treatment begun
  - Yes: Reassess for symptoms and objective inflammation
  - No: STOP Treatment
- No: Active Symptoms

Periodic reassessment of symptoms and inflammation:
- t₀
- Appropriate treatment duration
- √t₁

Continuous Treatment:
- Yes: CONTINUE Treatment
Summary

- Finer points of diagnosis
- Knowing how and when to combine medications is key
- Objective monitoring of disease activity/response to therapy, and judicious use of drug level monitoring very helpful in achieving best long-term results