Management of Inflammatory Bowel Disease in 2022

“The Story of Laura”

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Learning Objectives

- To understand the diagnostic and therapeutic algorithm for IBD

- To discuss the efficacy and safety of treatments for the management of IBD
Laura

19 year old female college student

3 months history of **bloody diarrhea, 5-8 times per day, 2 times at night.**

**Intermittent crampy abdominal pain associated with a BM**

Non-smoker

No family history of IBD

Abdominal exam reveals **mild Lt LQ tenderness.**

Physical exam is unremarkable

Laboratory findings include **mild anemia (Hb 11, MCV 79).** Albumin is **3.4 g/dL**
“Laura”

- You recommend a colonoscopy but Laura is reluctant to have an invasive procedure.

- “Are there other tests that can help establish a diagnosis?”
Non-invasive tests for IBD

- **Fecal calprotectin and Lactoferrin**
  - Non-specific markers of gastrointestinal inflammation
  - Does not differentiate from other inflammatory GI diseases
  - Can also be used to monitor inflammation in those with established IBD

![Table of Fecal Calprotectin Cut-off, Sensitivity, and Specificity](image)
"Laura"

- You suspect underlying inflammatory bowel disease and recommend a colonoscopy.

- Colonoscopy:
  - Confluent inflammation from anus to splenic flexure with erythema and granularity
  - Normal terminal ileum

- You decide to image her small bowel to rule out more proximal involvement given her abdominal pain
Imaging in IBD
CT enterography

- CT scan with IV contrast and **large volumes of neutral oral** contrast to achieve luminal distention
- Allows for better mucosal resolution (active inflammation), obstructive lesions (by distending lumen)
- Less useful for extra-luminal complications

![Diagram showing lumen, mucosal enhancement, and submucosal edema]
Imaging in IBD
CT enterography

- Active inflammation
  - Mural hyperenhancement
  - Mural stratification
    • Acute (water), chronic (fat)
  - Engorged vasa recta
  - Fat stranding

- Fistulas
Imaging in IBD

MR enterography

- No radiation exposure
- Similar (or slightly superior) performance as CTE for assessment of active inflammation
Management of IBD

Therapeutic Goals in IBD

- Normal bowel function and improved quality of life (QOL)
- Induce remission rapidly
- Maintain steroid-free remission over time (deep remission)
- Modify long-term outcomes of the disease
  - Avoid hospitalization and surgery
  - Eliminate disability
  - Minimize exposure to steroids
Management of IBD

Probiotics and Antibiotics

Probiotics
- No evidence of efficacy in Crohn’s disease
- VSL#3 is effective in inducing and maintaining remission in mild-to-moderate ulcerative colitis

Antibiotics
- Effective for treating abscesses and preventing post-operative recurrence in Crohn’s disease (metronidazole)
- Single RCT demonstrated benefit for rifaximin in ileal Crohn’s disease
Management of IBD

Fecal transplantation

• Four randomized controlled trials in ulcerative colitis
  • Three demonstrated benefit
    • Daily enema therapy x 6 weeks
    • Colonoscopic FMT once a week for 6 weeks
  • No benefit in a third trial with FMT via NG tube administration

• There likely is a donor effect

• No evidence of efficacy in Crohn’s disease (except for case series)
Management of IBD

5-Aminosalicylates

**Mechanism:** Local anti-inflammatory effect on the small intestine and colon

**Pros**
- Asacol HD® (mesalamine), Lialda ®, Apriso®, sulfasalazine, balsalazide (colazal ®)
  - Available in oral and topical formulations (enemas, suppositories) for local therapy
  - No systemic immunosuppression
  - Effective in mild-to-moderate ulcerative colitis
  - Limited (No) efficacy in Crohn’s disease
Management of IBD

Steroids, Immunomodulators

**Steroids**
- Very effective for induction of remission
- Also available as controlled-release formulations - budesonide (Entocort®)
- No role in maintenance of remission
- Associated with significant long-term consequences

**Immunomodulators**
- Azathioprine, 6-MP, methotrexate
- Effective for moderate severity disease
- Not effective for induction of remission (lag of 6-8 weeks of onset of action)
Management of IBD
Biologics and Small Molecules

1998: Infliximab
2007: Adalimumab
2008: Certolizumab
2014: Vedolizumab
2016: Ustekinumab
2005: Infliximab
2012: Adalimumab
2013: Golimumab
2014: Vedolizumab
2018: Tofacitinib
2021: Ozanimod
2019: Ustekinumab
2018: Tofacitinib
2022: Upadacitinib
Management of IBD

Anti-TNF biologics

Week 2/4 Response
Week 26/30 remission
Week 26/30 Overall remission

Patient (%)

- Infliximab
- Adalimumab
- Certolizumab pegol

Chart showing percentages of patients responding to different treatments over different time frames.
Management of IBD
Other Biologics

Vedolizumab:
- Monoclonal antibody against α4β7 integrin.
- Approved for use in both Crohn’s disease and ulcerative colitis.
- Gut-selective in its target → no increase in risk of infections or malignancy.

Ustekinumab
- Anti-cytokine targeting IL12/IL23.
- Relatively targeted in its action.
- No increase in risk of infection or malignancy compared to placebo (in RCTs).
Management of IBD
Small molecules

**JAK inhibitors:**
- Small molecule that inhibits Janus-kinase enzymes (Tofacitinib: JAK 1-3, TYK2; Filgotinib, upadacitinib: JAK1 selective inhibitors)
- Relative quick onset of action
- Increases risk of shingles, VTE and malignancy (when compared to anti-TNF)

**Ozanimod:**
- S1P modulator; results in sequestration of lymphocytes in the lymph nodes
- Slight increase in risk of cardiac arrhythmias
- Interactions with SSRI and MAOI.
Management of IBD
New Therapeutic Paradigms

Sx
- Anti-integrin
- Anti IL-12/23
- Anti-S1P
- JAKi

Anti-TNF

Immunomodulators

5-Aminosalicylates

Early effective treatment

Traditional “Step-up” approach
Management of ulcerative colitis

Management of UC depends on (1) extent and (2) severity of disease
Management of ulcerative colitis

**Initial treatment**

- **Proctitis**: Topical 5-ASA or CS
- **Extensive colitis**
- **Mild/Moderate**
  - Oral 5-ASA +/− CS
- **Severe**
  - Steroids

**Subsequent Rx**

- **Topical 5-ASA**
- **Oral 5-ASA**
- **AZA / 6-MP**
- **Biologics**
- **Small molecules**
- **Surgery**
Management of IBD

Complications of therapy

- **Unpredictable side-effects**
  - Drug hypersensitivity
  - Pancreatitis (Azathioprine / 6-MP)
  - Paradoxical flare (5-ASA)

- **“More” predictable side-effects**
  - Infections
  - Cancer
    - Lymphoma: Approximately 5 in 10,000
    - Skin cancers (melanoma – anti-TNF; NMSC – thiopurines), Cervical cancer
Pregnancy and IBD

- Crohn’s disease and ulcerative colitis are not associated with reduced fertility (except with J-pouch).

- Disease activity at conception is an important determinant of patient outcome during pregnancy.

- Most medications are safe during pregnancy (except methotrexate; steroids may cause cleft lip / palate).

- Slight increase in LBW and SGA but otherwise comparable fetal outcomes.
Health maintenance in IBD

Colon cancer surveillance

- Ulcerative colitis (not proctitis) and colonic Crohn’s disease are at increased risk for colon cancer.
  - Estimated risk at 20 years: 10%

- Recommended surveillance:
  - Begin at 8 years after diagnosis
  - Every 1 – 3 years with a colonoscopy
  - Newer techniques include chromoendoscopy
  - Fecal DNA is under study
  - No clear guidance on when to stop → depending on age and comorbidity
Summary

- Advances in diagnosis
  - Non-invasive markers of inflammation
  - Markers of prognosis
  - newer imaging modalities

- Changing therapeutic paradigms
  - Recognition of new goals of treatment
  - New paradigms of treatment ("Early" / "Top-down")
  - Treat to target approach

- "Comprehensive” IBD care