Practical Approaches to the Differential Diagnosis of IBD

Peter D.R. Higgins,
MD, PhD, MSc
The DDx of IBD

• Does this patient with suggestive symptoms actually have IBD?

• Concepts
  – Impractical approaches
  – Pearls from EBM
  – Pattern Recognition
  – Three Lenses
  – Cases
  – Improving your pattern recognition
Impractical Approaches
Impractical Approaches

• Laundry List

• EBM Nirvana
The Laundry List

• Classic example
  – Patient: “I think I have all the symptoms of UC”
  – 3rd year med student in July:
    “We need to rule out ZE, VIPoma, Yersinia......”

• Laundry List PROs:
  ☺ It does provide a complete differential
  ☺ It is safe → defensive medicine

• Laundry List CON:
  ☹ It is inefficient, and does not prioritize diagnoses
Cognitive Problems

• Problems with too many choices
  – Harder to make a choice when options↑
  – Humans tend to make pairwise comparisons
    • Diagnosis A vs. Diagnosis B
  – If 30 possible diagnostic choices
    • \(2^{30} = 1,073,741,824\) diagnostic comparisons

• Human brains generally function better with a short list of likely diagnoses

• How to focus? Three lenses
Another Impractical Approach

- EBM Nirvana
  - Start with pretest probability
  - Engage in multiple calculations of odds and probabilities

Becoming One with the Evidence
How EBM DDx is supposed to work

Pretest Probability → Convert To Odds

Test positive → Odds x LR+ → Post Test Odds

Test negative → Odds x LR- → Post Test Odds

Convert back to Probability

Issues:
- Pretest probability rarely accurately known
- Likelihood Ratios often not published for diagnostic tests
- Way too much conversion
- Only addresses ONE possible diagnosis at a time
Pearls from EBM
Useful Concepts from EBM

• Pretest probability
  – Some diseases ARE more common
  – Varies by practice, referral patterns
  – Can change over time (C. difficile)

• Test results shift the probability
  – Most useful near 50%
  – Less useful at extremes
    • Hard to be 100% certain of anything
What Does Work

Pattern Recognition
What Does Work

• Pattern recognition
  – Most common strategy used in practice
  – Time efficient
  – Remarkably accurate, with sufficient experience

• Integrates all available data
  – History of present illness
  – PMH / FHx / Social Hx / Medication Hx
  – Labs and Imaging
  – Endoscopy and Pathology
Problems with Pattern Recognition

• Premature closure
  – Patient: “I’m calling because I’m having a flare”
  – PCP: “I’ll call in prednisone”
  – Not considering alternatives strongly enough
  – Ignoring warning flags if present

• Lack of knowledge/experience
  – Learners don’t know, or fail to recognize warning flags of alternative diagnoses
How DDx can actually work

• Find middle ground between
  – Premature closure
  – Laundry list

• Two stage workup
  – Start with a short lineup – focused list
  – Reserve the laundry list for diagnostic failures
Three Lenses

Focus your Differential
Pretest Probability
Diagnoses Not to Be Missed

CRC

IBS
Suggestive History

- Clues
First Stage: Lineup of Likely Suspects

- IBD
- IBS
- Acute colitis
- C diff
- CRC
- History-based Dx 1
- History-based Dx 2
Filling the Lineup - Pick 2

• Strategy to prevent Premature Closure
• Warning Flags from History
  – Cancer – radiation? Cancer syndrome?
  – Surgery - post chole? Vagotomy?
  – Pain history – NSAID enteropathy?
  – Older – atherosclerotic Hx? Microscopic colitis?
  – Autoimmune disease – vasculitis?
  – MGUS – intestinal amyloidosis?
  – Antibiotics – C diff?
Gathering Data

• With a lineup in place, characterize symptoms
• Get labs
  – Inflammation (ESR, CRP, fecal marker)
  – SB function (iron, vit D, B12, Alb)
• Consider imaging
  – CTE
    • Find, localize inflammation
      – If small bowel, consider whether DBE needed
Gathering Data

• **Ileocolonoscopy**
  – Define severity
  – Define extent
  – Biopsy for histopathology

• **Additional scoping**
  – EGD, DBE if Sx and imaging suggest proximal dz and no Dx from ileocolonoscopy
Scope Everybody for Dx?

- Expensive, invasive
- Practical considerations
  - Expectation is to scope
    - Referring doc and patient
  - Get disease extent, distribution *before* Rx
  - Difficult to justify cost, risks of therapy without histopathology
  - If diagnosis missed without scope, made later by others – you will meet lawyers
  - You need a good reason not to scope
Illustrative Fictional Cases
Case 1

• 18 year old female, college freshman
• Bloating, gas, diarrhea 4-10x/d for past 4 weeks
  – No blood or mucus
  – LLQ cramping before BMs
• Midterms start next week
• Cousin has Crohn’s
  – Sure she has Crohn’s
  – Referred from student health
• WBC 8, Hgb 12, Plt 289
• Alb 4.2, iron sat 22%
• ESR 17, CRP 0.2
Lineup

- IBS
- Acute colitis – norovirus?
- C diff
- Crohn’s
- History-based Dx 1 – Caffeine?
- History-based Dx 2 – Lactose intolerance
- CRC
Probabilities

- IBS – new stressor, Sx roughly compatible
- Acute colitis – crowded environment
- C diff – no Abx, maybe
- Crohn’s – atypical
- Caffeine – lots
- Lactose – more than parents
  - possible
Evaluation

- Stop caffeine and lactose
- C diff toxin testing
- Schedule endoscopy for next week
  - Can cancel if resolves after midterms over
  - Or if C diff positive
- If continues, can consider viral testing
Outcome

• IBS – 90% better after midterms
  – Complicated by caffeine overindulgence
  – Complicated by unrecognized lactose intolerance

• Diagnostic Certainty?

Is this good enough?
If not, CTE vs. Capsule?
Case 2

- 25 yo weekend warrior – hockey player
- Recent loose stools 2-4/d x 2m with blood, RLQ abd pain, episodes n/v in past 2 weeks, some fatigue
- No FHx IBD, uncle with CRC
- WBC 6.7, Hgb 10.8, Plt 307
- Alb 3.8, iron sat 15%
- ESR 19, CRP 0.4
Lineup

- Acute colitis – Shigella, EHEC?
- IBS ↓
- IBD?
- CRC?
- History-based Dx – NSAIDs
  - Uses “some”
Data Gathered

- Stool cultures negative
- Scope unrevealing, including TI
  - *Not* striking visceral hypersensitivity
- Admits to remarkable NSAID consumption
  - While on midazolam – *and* driver confirms
  - In bottles of naprosyn/week, not pills
- CTE suggests multiple ileal narrowings
- Maybe capsule endoscopy?
- DBE biopsies – nonspecific injury multiple weblike strictures dilated.
Case 3

• 28 y/o female with 3 m of BLQ pain, 4-7 loose BM/d, 3-5/d with blood, ++ urgency, stiffness in knees, 7 lb wt loss, and worsening fatigue
• Aunt with Crohn’s (2 surgeries)
• Well water, camping this summer
• 4 oral ulcers, RLQ> LLQ tenderness
• WBC 10.2, Hgb 10.5, Plt 512 from PCP
• Alb 3.3, iron sat 7%, 25-OH vitD: 7
• ESR 44, CRP 3.7
Lineup

- Crohn’s ↑
- UC
- Infectious
- NSAIDs for knee pain
- CRC, FAP? ↓
- IBS ↓
Workup

- Stool studies negative
- Scope – active pancolitis
  - Less active in transverse
  - Linear, deeper ulcers in R
  - 2 tiny ulcers in TI
- Denies NSAIDs
- Biopsies: chronic inflammation throughout, basal plasmacytosis, crypt distortion, no granulomas. Distribution c/w UC. TI inflammation nonspecific, could represent backwash ileitis.
Chronic colitis, but...

- Sure it is UC > Crohn’s?

<table>
<thead>
<tr>
<th>UC</th>
<th>Crohn’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous</td>
<td>? Transverse skip</td>
</tr>
<tr>
<td>Blood in stools</td>
<td>SB function ↓</td>
</tr>
<tr>
<td>Urgency</td>
<td>Family History CD</td>
</tr>
<tr>
<td></td>
<td>Ulcers with depth</td>
</tr>
</tbody>
</table>
What next?

• Is there real SB disease?
  – CTE, capsule, DBE, serologies
  – Need tissue
• Imaging-guided endoscopy
  – CTE first
    • DBE if clear target
    • Capsule if not
• When serologies for Dx?
  – When all endoscopes are broken.
Findings

• CTE – distal ileum, not in TI
  – Mucosal enhancement
  – Increased vascularity
• DBE Biopsies
  – Confirm CD in small bowel
When it is IBD
When it is IBD

- Don’t stop at diagnosis
- Gather data for future use
- Document extent of disease before therapy
A Public Service Announcement

• Vaccinate!
  – *Before immunosuppressed if possible*

Mahedevan and Kane handout from Friday breakout
Sands and Siegel handout from Saturday breakout
More Problems with Pattern Recognition in IBD

• ‘Pattern’ of IBD varies – no one pattern!
  – Type: Crohn’s vs. UC
  – Location: ileal vs. colonic vs. rectal
  – Variation in patients
    • Some never get voluminous diarrhea
    • Some rarely see blood
    • Some rarely have ↑ CRP
Improve Your Pattern Recognition

• Characterize this patient’s pattern of flare
  – Detailed symptoms
  – Inflammatory markers
  – Imaging, endoscopy
Improve Your Pattern Recognition

- Measure the baseline when the patient is well
  - ESR, CRP, fecal markers, baseline bowel pattern
- Compare new flares to this pattern
  - Does everything – symptoms, history, noninvasive markers, fit?
  - If not, strongly consider alternative diagnoses, further diagnostic testing
Case 4

- 25 y/o male with pan-UC x 7 years
- Doing well x 5y on Aza 150 mg daily
- New flare
  - 12 bm/d, blood in about 25% of BMs
  - Large volume stools, aching abdominal pain
  - *Start a biologic?*
- Lineup
  - UC flare, infectious colitis, CMV
  - C diff, CRC, NSAID-induced
### Does the Pattern Match?

<table>
<thead>
<tr>
<th>Marker</th>
<th>Index UC flare</th>
<th>Baseline</th>
<th>New Flare</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMs</td>
<td>18/d, most AM</td>
<td>2-3/d</td>
<td>12/d</td>
</tr>
<tr>
<td>Blood</td>
<td>Most BMs, large amounts</td>
<td>Rare traces ~ monthly</td>
<td>1-2/d, small amount</td>
</tr>
<tr>
<td>Stool Volume</td>
<td>Small frequent</td>
<td>normal</td>
<td>Large frequent</td>
</tr>
<tr>
<td>Abd Pain</td>
<td>Cramp before BM</td>
<td>None</td>
<td>Aching constantly</td>
</tr>
<tr>
<td>WBC</td>
<td>12</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td>CRP</td>
<td>4</td>
<td>0.3</td>
<td>6</td>
</tr>
<tr>
<td>FLA</td>
<td>400</td>
<td>18</td>
<td>1300</td>
</tr>
</tbody>
</table>
Outcome

- Stool Cx, C diff toxin negative
- Flex sig – erythema, loss of vascularity, few shiny ulcers
- Biopsies + for C diff
- Responds to flagyl + prednisone
- No test is perfect....
A Few Bad Zebras to Keep in Mind

- Nonhealing firm fistula → adenoCa?
- Food right through me – bypass fistula?
  - Terminal ileum to sigmoid
- Obstruction – SB adenoCa or lymphoma?
- Bad headache in IBD – cerebral sinus thrombosis?
- Intractable steady bleeding out of proportion to diarrhea – CRC?
Summary

• Efficient diagnosis uses pattern recognition
• Focus your differential with 3 lenses
  – Likely
  – Ones you would not want to miss
  – Pick 2 – force yourself to avoid premature closure
• Measure and document individual disease patterns in *your patients* to improve your pattern recognition
Thank you
When Serologies?

- Trying to prognosticate risk of CD prior to colectomy
  - FHx CD and ASCA IgA best predictors (Melmed)
- Truly high risk scope
  - Trying to find reasons not to pursue scope
- Diagnostics
  - If no endoscopy available
- Prognostic
  - Maybe, but is it better than clinical history?

Characterizing Flares

- Stool – number, form, blood content, mucus content
- Rectal Sx – urgency – time to BM, number urgent episodes, # awaken from sleep, unproductive urges
- Pain – where, when, in assoc with BM or not, intensity
- Systemic Sx – fatigue, napping, fevers
- Extraintestinal Sx – joints, eyes, mouth, skin
Using Fecal Markers

• Noninvasive approach
• Imperfect Sens/Spec – better in colonic dz
• Tracks well with endoscopic activity
• Pick one – available, cheapest for you
  – See if it is helpful in tracking individual patients
Vaccinations

- **Killed**
  - Injected *influenza*
  - Human Papilloma Virus
- **Component**
  - *Pneumococcus* (PPV23)
  - *HBV*, *HAV*
  - *H flu* (Hib)
- **Toxoid**
  - *Tetanus* (Td, DTaP)
- **Live** (*avoid* within 3m of immunosuppression!)
  - *Varicella* – chickenpox and shingles
  - Typhoid
  - Vaccinia – smallpox
  - Nasal spray: Flumist
  - Yellow fever, MMR
Appendix

The Laundry List
A Laundry List

• Osmotic Diarrheas
  – Magnesium, phosphate, sulfate
  – Intolerance of lactose, fructose
A Laundry List

- Fatty diarrheas
  - Pancreatic insufficiency
  - Small intestinal bacterial overgrowth
A Laundry List

- Other inflammatory diarrheas
  - Ulcerative jejunoileitis
  - Diverticulitis
  - Ischemic colitis
  - Radiation colitis
A Laundry List

• Abnormal motility
  – Post-vagotomy
  – Diabetes
  – Hyperthyroid
  – Post-sympathectomy syndrome
A Laundry List

• Infections
  – Clostridium difficile, CMV, Campylobacter, Salmonella, Shigella, E coli 0157:H7, Aeromonas, Plesiomonas
  – Entamoeba, tuberculosis, Yersinia, Chlamydia, Giardia, HSV, HIV
A Laundry List

• Neuroendocrine tumors
  – Gastrinoma
  – VIPoma
  – Somatostatinoma
  – Mastocytosis
  – Carcinoid syndrome
  – Medullary carcinoma of thyroid
A Laundry List

- Neoplasia
  - Colon carcinoma
  - Lymphoma
  - Small bowel adenocarcinoma
  - Villous adenoma
Impractical Approaches

• Premature Closure
  – Patient: “I have UC and I’m having a flare”
  – PCP: “I’ll call in the prednisone”

• Zebra Hunting
  – Patient: “I think I have all the symptoms of UC”
  – 3rd year med student:
    “We need to work you up for ZE and VIPoma”
A Laundry List

- Ileal bile acid diarrhea, post-cholecystectomy
- Pancreatic insufficiency
- SIBO
- Microscopic, lymphocytic, collagenous colitis
- Post-vagotomy, diabetes, hyperthyroid
A Laundry List

- Appendicitis, Lymphoma, SB adenocarcinoma, vasculitis, eosinophilic gastroenteritis, sarcoidosis
- ischemic colitis, radiation colitis or enteritis, diverticular colitis
- NSAID enteropathy
- CRC
- Endometriosis
- Carcinoid
- Medication induced colitis – nsaid, retinoids, gold, penicillins, mesalamine allergy
A Methodology of Pattern Recognition

• Know your practice
  – What is the pretest probability in your setting?

• Know your individual patients
  – What does a typical flare look like?
  – Stools, blood, mucus
  – Urgency, tenesmus
  – Abdominal pain, fatigue
  – ESR, CRP, fecal markers, flex sig, imaging?
  – Measure, record, and document what that patients bad flare looks like