Current Treatments for Inflammatory Bowel Disease

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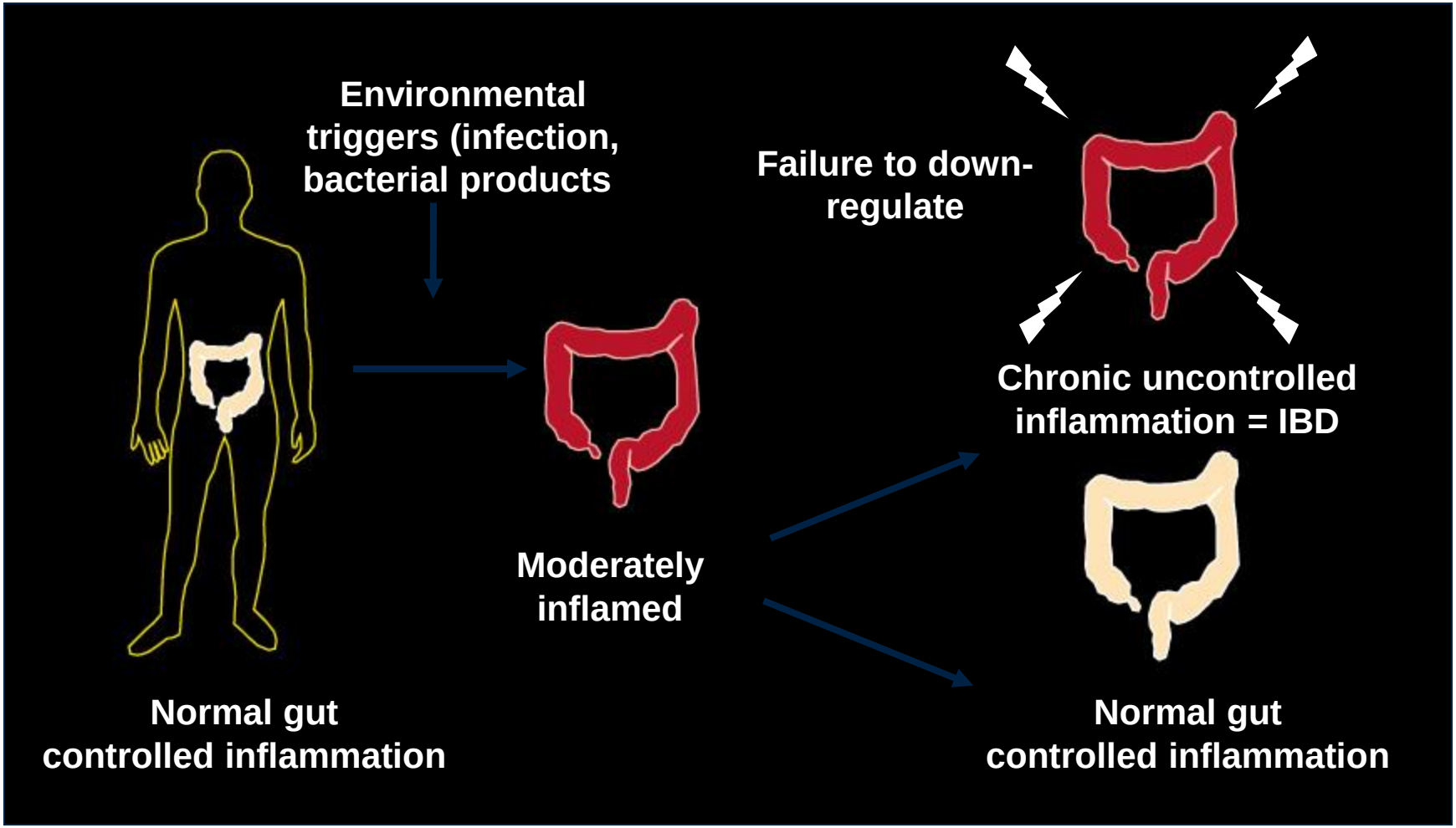
UC Irvine Health

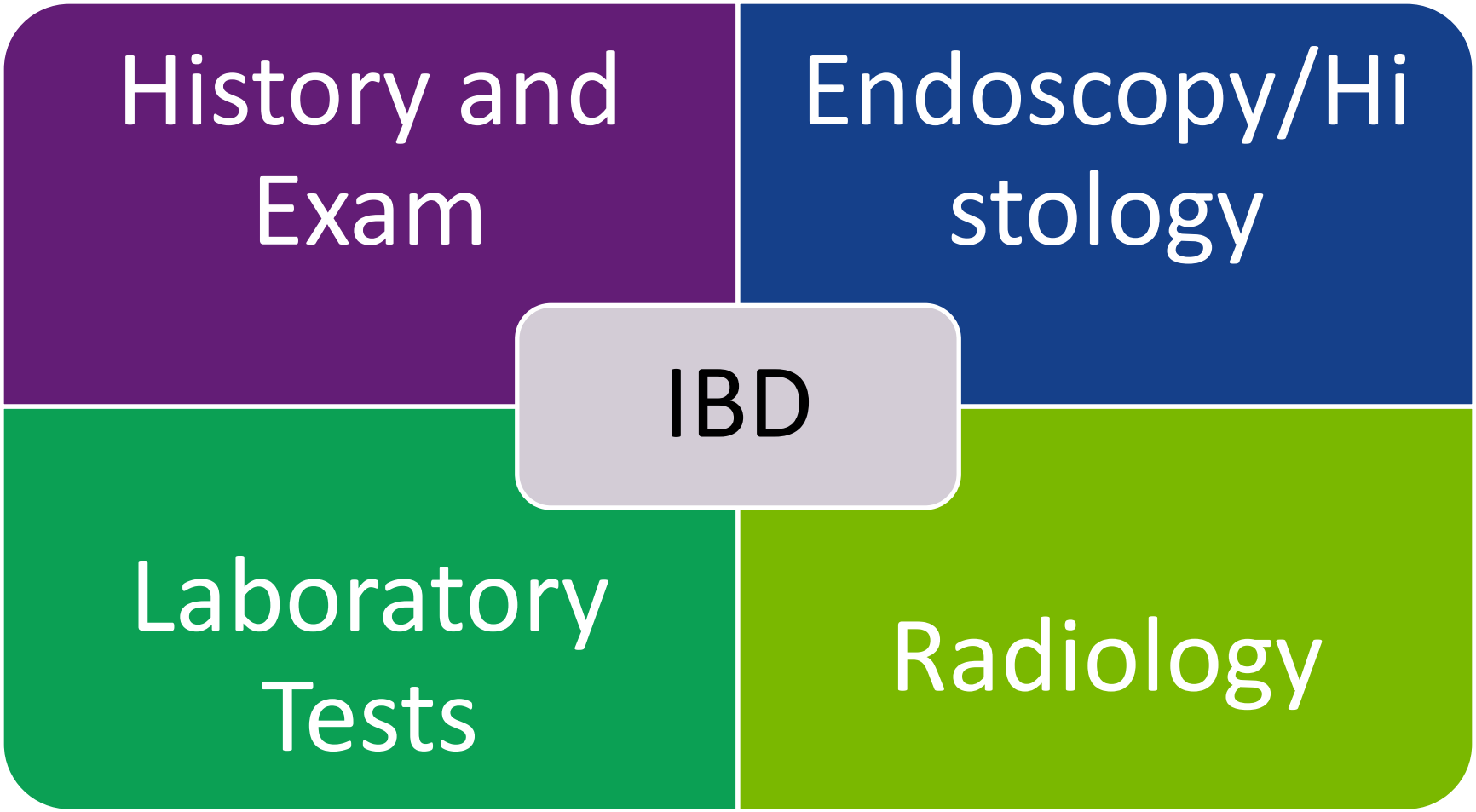
Disclosures

None

Pathogenesis of Inflammatory Bowel Disease



Pre-treatment Evaluation



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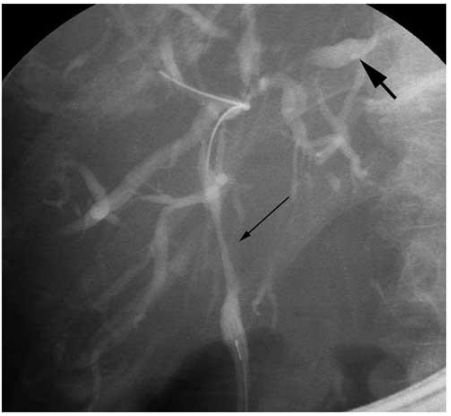
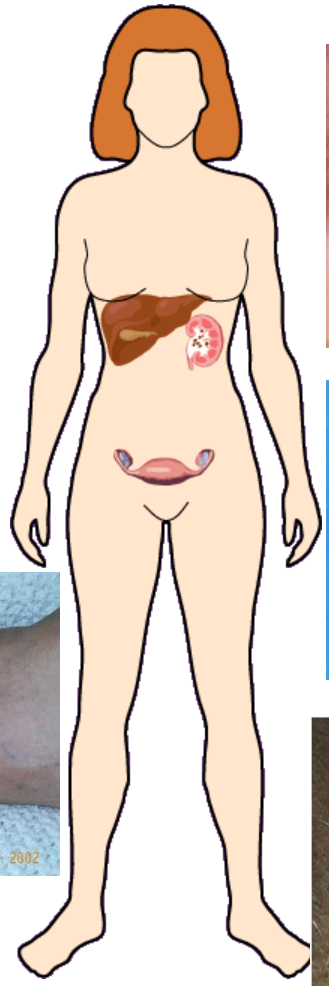
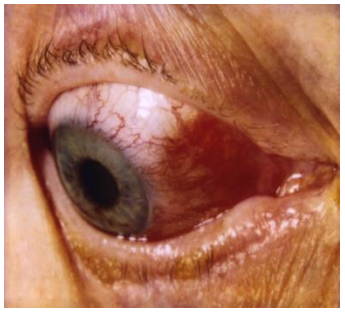
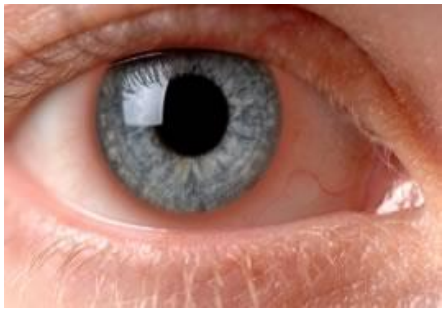
IBD: Systemic Manifestations

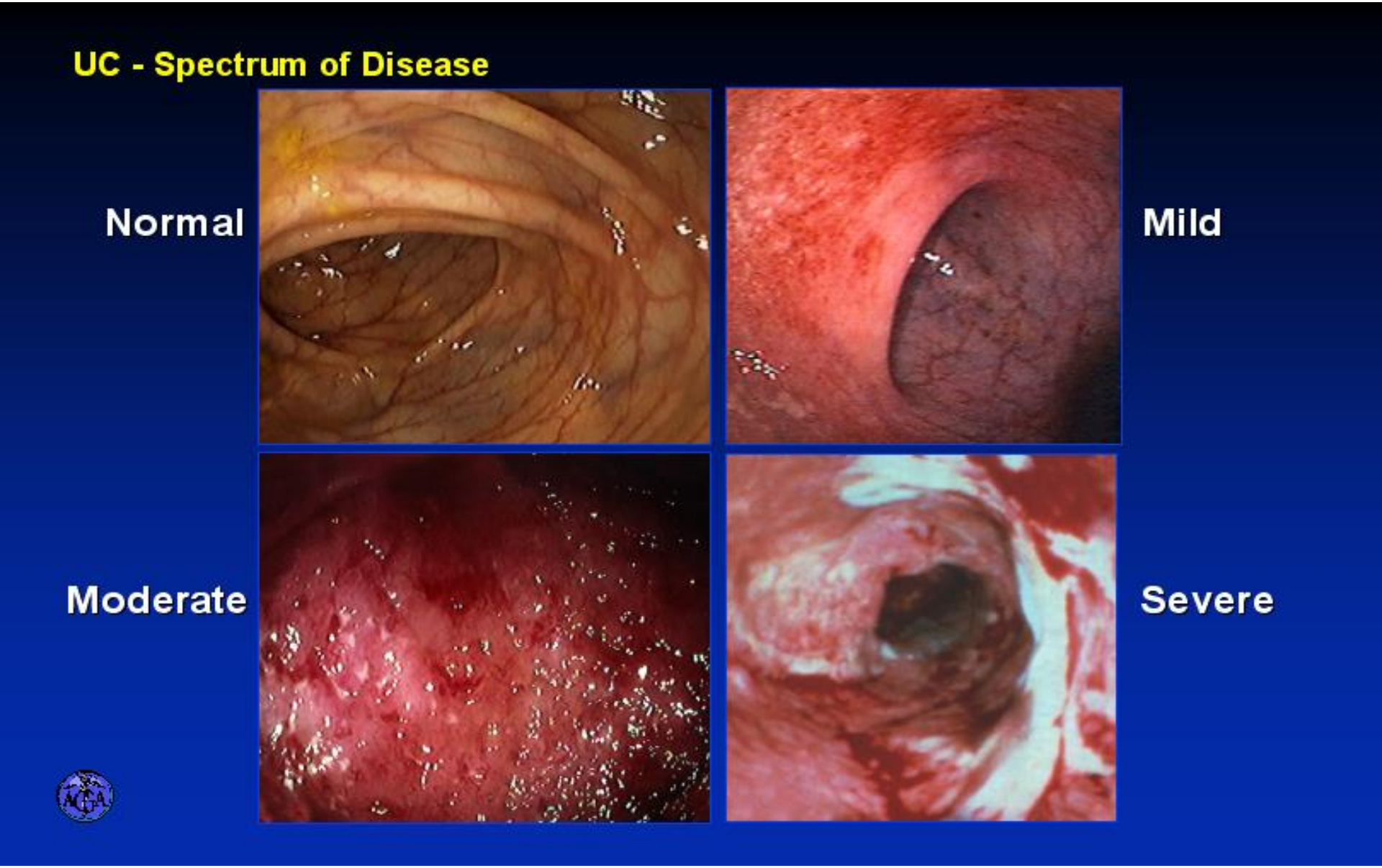




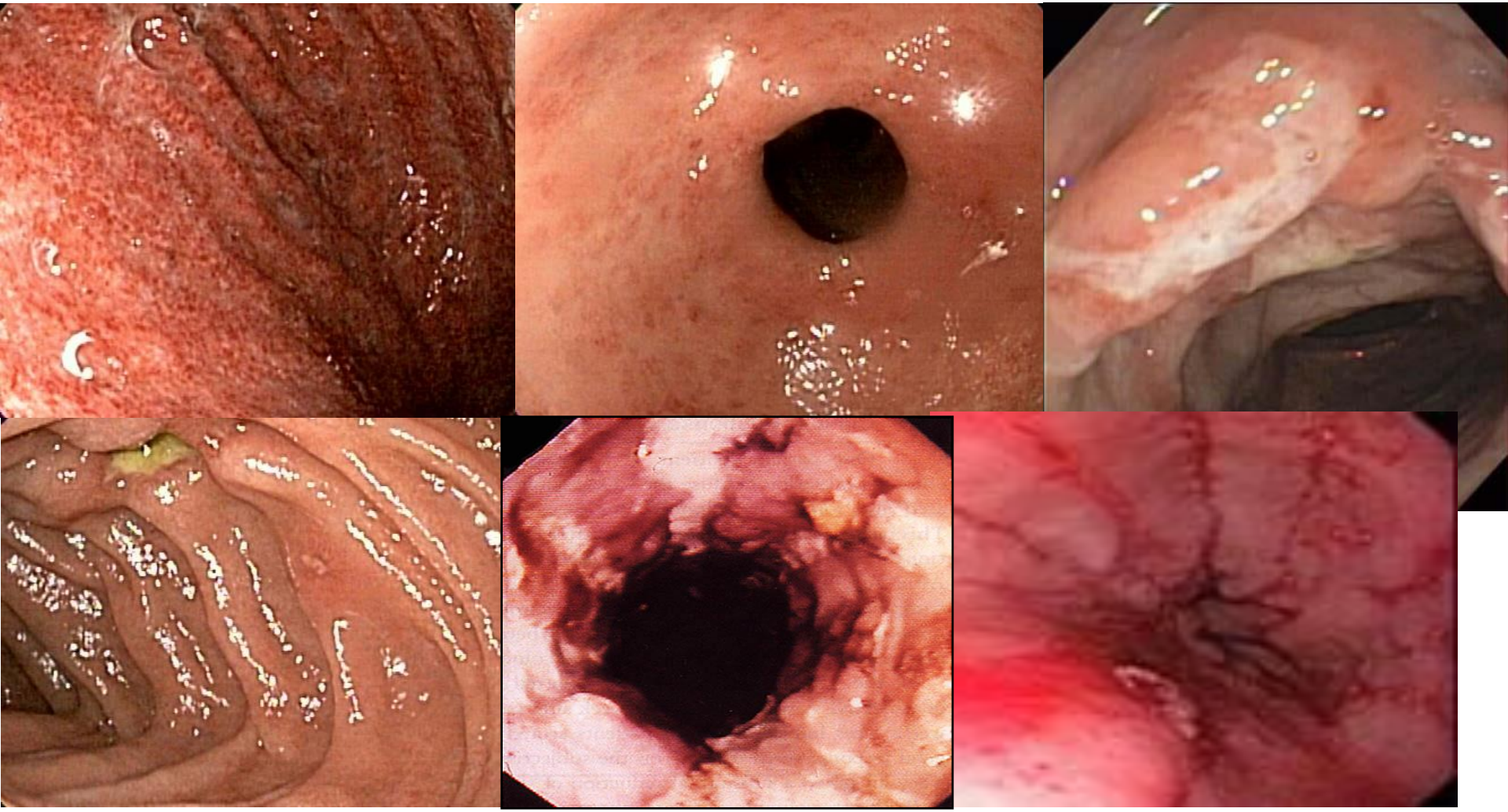




Endoscopic Spectrum of Severity



Crohn's Disease



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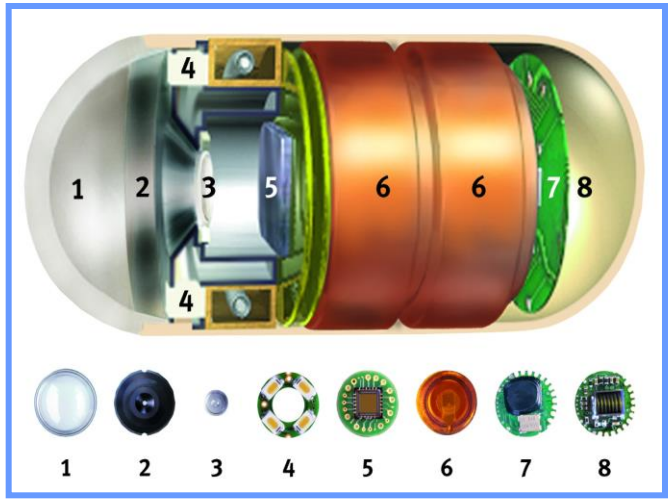
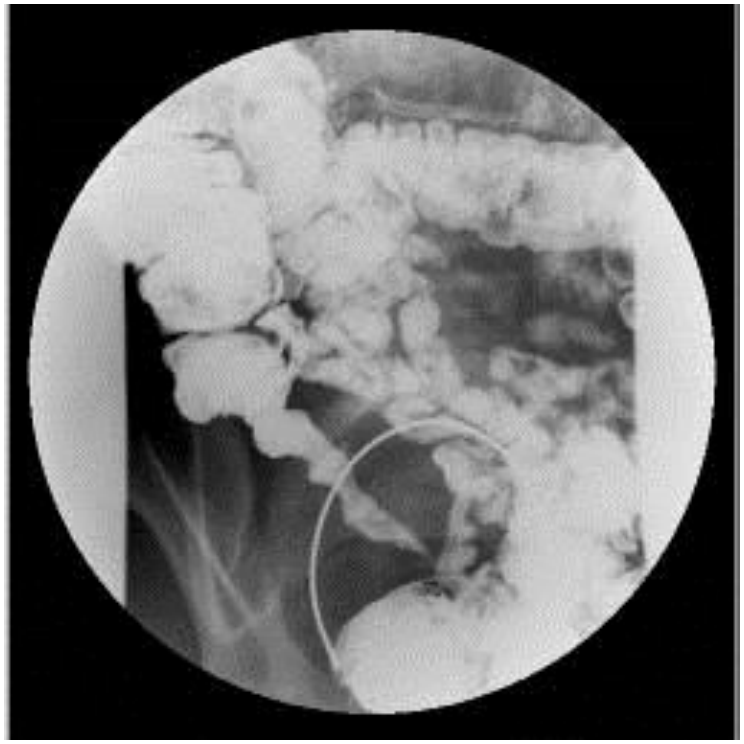
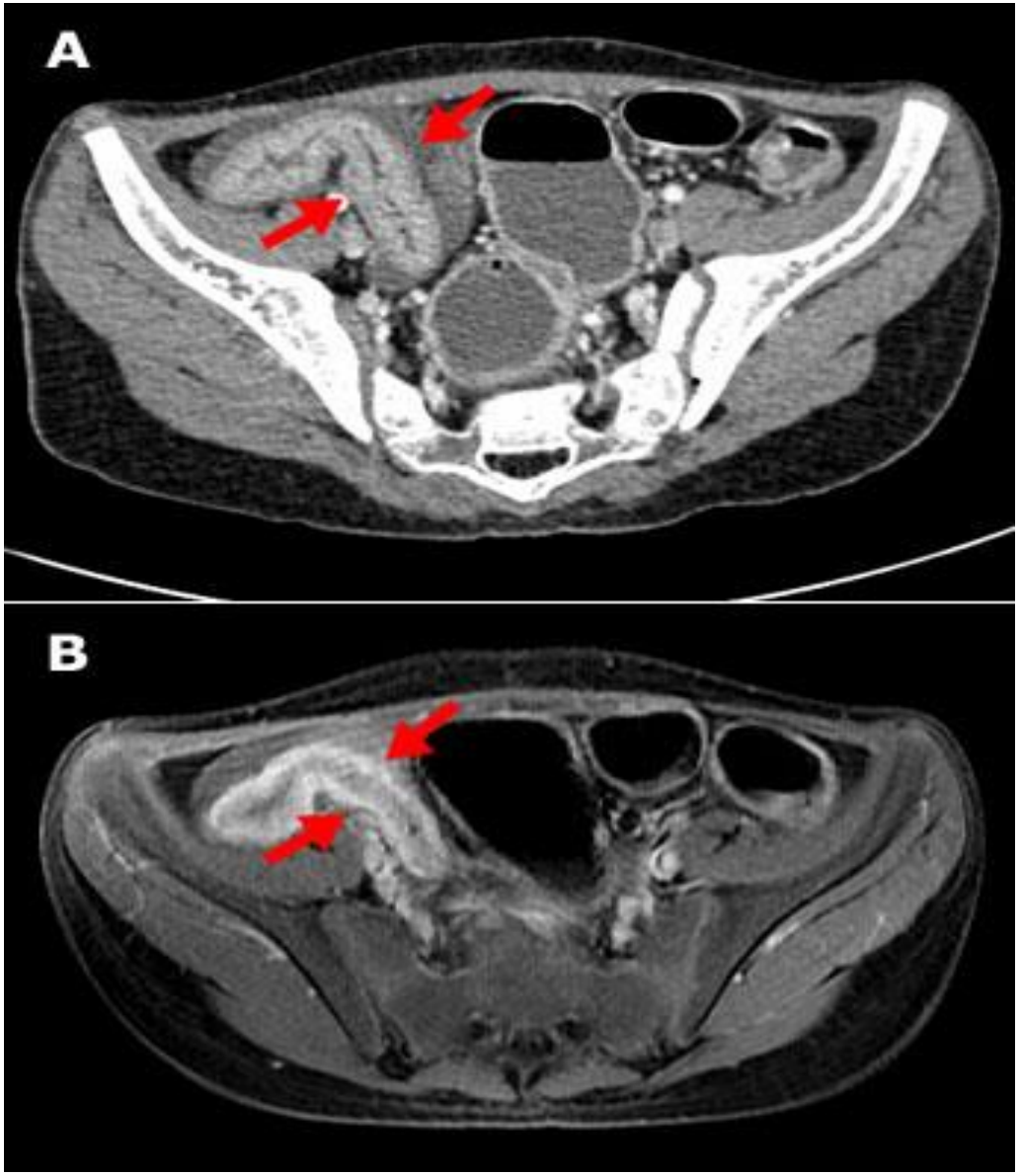
Capsule Endoscopy



Radiology

- X-ray, CT, MRI
- CTE and MRE





Serologies

Test Result

☒ **IBD Predicted**

☐ IBD Not Predicted

☐ Ulcerative Colitis Predicted

☒ **Crohn's Disease Predicted**

PROMETHEUS IBD Serology 7
Overall Performance

	IBD	CD	UC
Sensitivity	93%	88%	93%
Specificity	95%	98%	97%
PPV	96%	96%	89%
NPV	90%	93%	98%

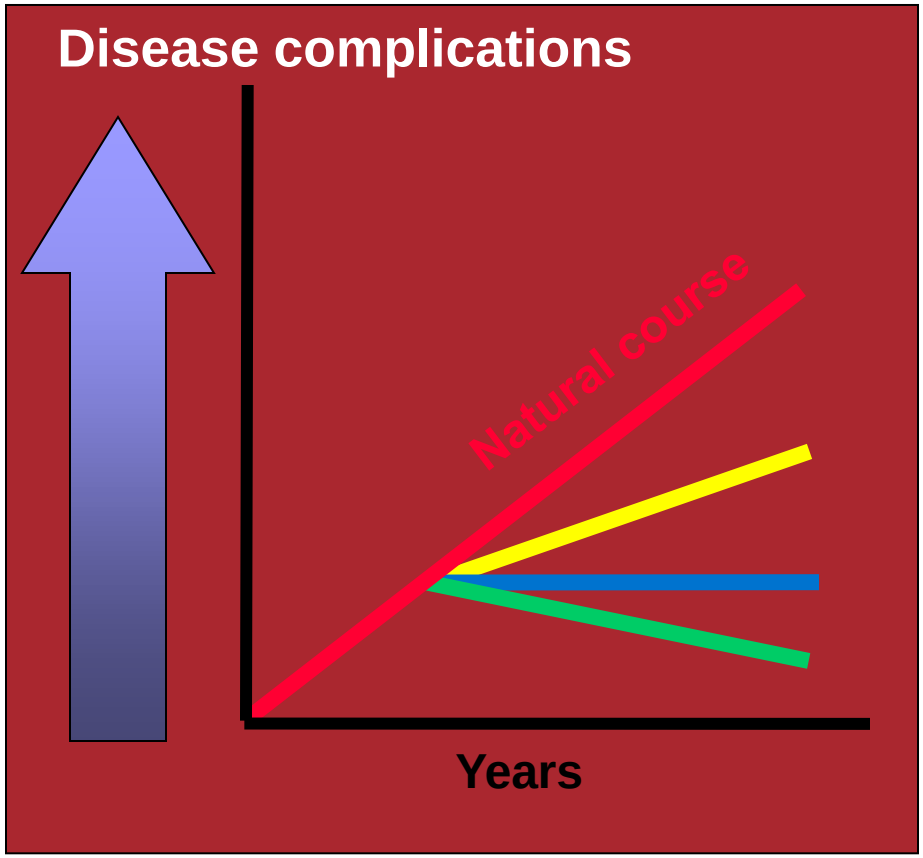
PROMETHEUS™ Predictive Algorithm Description:

- Utilizes Smart Diagnostic Algorithm (SDA) technology to characterize complex relationships between multiple markers to produce a diagnostic prediction with greater accuracy than simple comparison of assay results to a reference range.
- Developed (n=1813; 36% CD, 24% UC, 20% IBS, 20% normal) and validated (n=500; 38% CD, 21% UC, 41% normal) using serology results for samples with a known diagnosis.

Assay Information

Assay	ASCA IgA ELISA	ASCA IgG ELISA	Anti-OmpC IgA ELISA	Anti-CBir1 ELISA	Neutrophil-Specific Nuclear AutoAntibodies (NSNA) (IBD specific pANCA)		
					AutoAntibody ELISA	IFA Perinuclear Pattern	DNAse Sensitivity
Assay Value	109.4 EU/ml	113.8 EU/ml	26.0 EU/ml	50.2 EU/ml	< 12.1 EU/ml	Not Detected	Not Detected
Note: *Test result determined by the PROMETHEUS Predictive Algorithm without direct consideration of assay values relative to reference values. However, interpretation of prognostic information should be made based on relative differences between assay values and reference values.*							
Reference Value	< 20.0 EU/ml	< 40.0 EU/ml	< 16.5 EU/ml	< 21.0 EU/ml	< 12.1 EU/ml	Not Detected	Not Detected

Can therapy safely alter the natural history of IBD?



- Induce and maintain gastrointestinal healing
- Prevent need for steroids
- Prevent strictures and penetrating complications
- Prevent extra-intestinal complications
- Decrease hospitalization/surgery
- Decrease long-term cost of care

Slide courtesy of Stephen B. Hanauer, MD.

Crohn's and Colitis Foundation of America 2008 Advances in Inflammatory Bowel Disease.

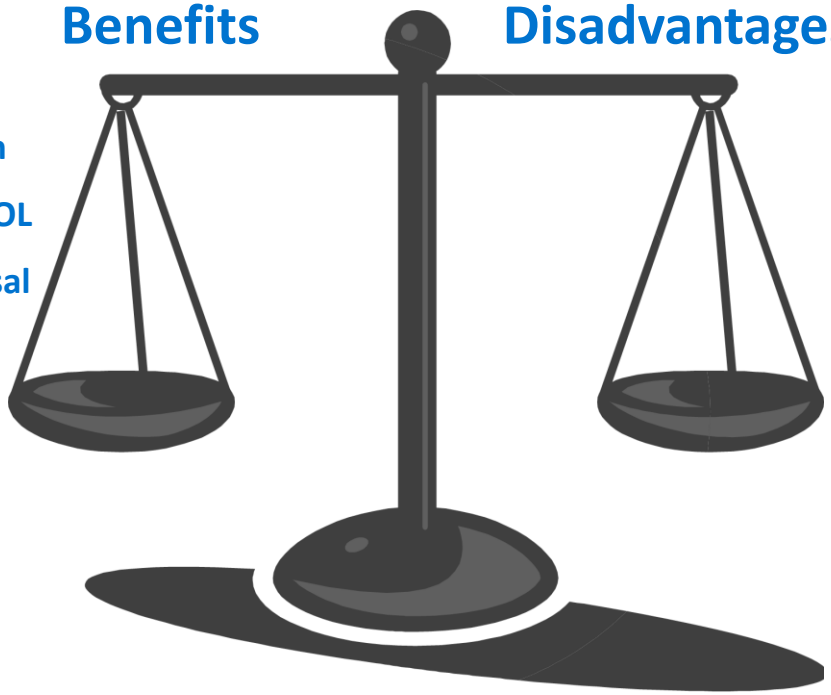
IBD Therapy in 2015

Antibiotics	Ciprofloxacin Metronidazole	Immunomodulator	6 MP Azathioprine Methotrexate Tacrolimus Thalidomide
Mesalamine	Apriso Pentasa Asacol Sulfasalazine Lialda Colazal Rowasa Canasa	Anti-TNF	Infliximab Adalimumab Certolizumab Golimumab
		Anti-integrin	Natalizumab Vedolizumab
Steroids	Entocort/Uceris Prednisone Hydrocortisone enemas Cortifoam	Surgery	

Risk Versus Benefit of Therapy

Benefits

- Maintenance of remission
- Improved function and QOL
- Early promotion of mucosal healing to prevent complications
- Decrease rate of hospitalizations, surgery, less steroid exposure



Disadvantages

- Side effects
- Cost
- Majority of patients may not require more potent treatments initially
- Risk of untreated disease

Lichtenstein GR, et al. *Inflamm Bowel Dis*. 2004;10:S2–S10.
Caprilli R, et al. *Digestive Liver Dis*. 2005;37:973–979.

Corticosteroids

Event	Estimated Frequency
Any side effect leading to the d/c of prednisone	55%
Ankle swelling	11%
Facial swelling	35%
Easy bruising	7%
Acne	50%
Memory problems	7%
Psychosis	1%
Infections	13%
Cataracts	9%
Increased intraocular pressure	22%
HTN	13%
Osteoporosis	33%
Diabetes	10 X increased risk

Adverse Effects Associated With Oral 5-ASAs

Sulfasalazine

- Headache
- Nausea/vomiting
- Dyspepsia
- Anorexia
- Rash
- Bone marrow suppression
- Interstitial nephritis
- Megaloblastic anemia
- Apparently reversible oligospermia
- Folate malabsorption
- Connective tissue disease
- Pancreatitis
- Pericarditis
- Hepatitis
- Paradoxical exacerbation of colitis

Olsalazine, Balsalazide, Mesalamine

- Headache
- Nausea
- Rash
- Hair loss
- Interstitial nephritis
- Pericarditis
- Pneumonitis
- Hepatitis
- Pancreatitis
- Paradoxical exacerbation of colitis
- Secretory diarrhea (olsalazine)

Kornbluth A, Sachar DB. *Am J Gastroenterol*. 2010;105:501.
Sands B. *Gastroenterology*. 2000;118:S68.
Azulfidine (sulfasalazine) [package insert]. New York, NY: Pfizer; August 2006.

AZA/6MP: Adverse Effects

Direct toxicities:

- Pancreatitis (3.3%)
- BM suppression (2%)
- Hypersensitivity reaction (2%)
- Hepatitis (0.3%)
- Nausea (1.3-6%)

Monoclonal Antibodies, Fusion Proteins and Fc-Free Fab' Fragments Against TNFα

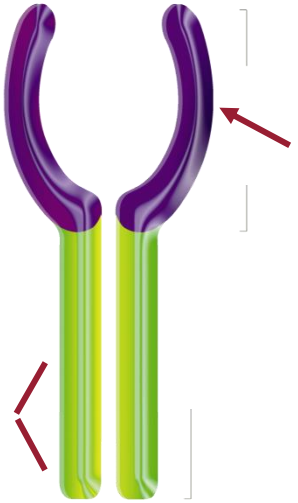
Chimeric monoclonal antibody

Infliximab (Remicade®)

Human monoclonal antibody

Adalimumab (Humira®)

Human recombinant receptor/Fc fusion protein



Etanercept (Enbrel®)

Humanized Fc-Free Fab' fragment

Certolizumab pegol (Cimzia®)

Anti TNF Agents: Safety Information

Risk of serious infections such as sepsis

Tuberculosis (TB), invasive fungal infections, and other opportunistic infections

Malignancies

Hypersensitivity

Hepatitis B reactivation

Hepatitis

Neurologic reactions

Hematologic reactions

Congestive heart failure

Autoimmunity

Drug interactions

Lupus-like reaction

Psoriasis-like reaction

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Meta-analysis of lymphoma rate associated with anti-TNF agents

Event	Estimated Frequency (annual, pt-years)
Non-Hodgkin Lymphoma (baseline)	2/10,000
Non-Hodgkin Lymphoma (on IM)	6/10,000
Non-Hodgkin Lymphoma (on anti-TNF)	6/10,000
Hepatosplenic T-cell Lymphoma	Unknown
Death from sepsis	4/1000
Tuberculosis	5/10,000

Ries LAG, et al (eds). SEER Cancer Statistics Review, 1975-2005, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2005/, based on November 2007 SEER data submission, posted to the SEER web site, 2008. Kandiel A, et al. Gut 2005;54(8):1121-1125 Siegel CA, et al. Gastroenterology 2008;134(4):A144. Abstract 970. Siegel CA, et al. Clinical Gastroenterology and Hepatology. 2006;4:1017-1024. Wolfe F, et al. Arthritis Rheum 2004;50(2):372-379.

Risk factors for Opportunistic Infections in IBD: a Case-Control Study (100 cases, 1983-2003)

Drug	Odds Ratio (95% CI)	p value
		Overall p<0.0001
Steroids alone	2.2 (1.1–4.8)	0.037
6MP/AZA alone	2.5 (1.2–5.1)	0.015
IFX alone	11.2 (0.8–153.3)	0.07
6MP/AZA – steroids	15.7(4.1–59.5)	<0.0001
6MP/AZA – IFX	1.6 (0.1–18.7)	0.71
6MP/AZA – IFX – steroids	Infinite	0.0003

1 medication	2.7 (1.5–4.8)	0.0014
2 medications	9.7 (3.3–28.2)	<0.0001
3 medications	Infinite	

Toruner, et al. Gastroenterology. 2008

Follow-Up

Assessing Response

- Clinical
- Biochemical
- Radiographic
- Endoscopic

Assessing Side Effects

Ultimate Goal: Get our patients well and keep them well

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