FACT

FICTION

SORTING OUT COMMON MISCONCEPTIONS ABOUT ULCERATIVE COLITIS TO IMPROVE PATIENT CARE

Friday, January 19, 2018
6:00 AM – 7:30 AM

Aria Hotel, Pinyon 7-8
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CONTINUING MEDICAL EDUCATION

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Disclosures

- ***Research/Grants:*** AbbVie Inc.; Genentech, Inc./Roche; Janssen Pharmaceuticals, Inc.; Prometheus Laboratories Inc.; Takeda Pharmaceuticals U.S.A., Inc.; UCB, Inc.

- ***Consultant:*** AbbVie Inc.; AbGenomics; Allergan; Amgen Inc.; Celgene Corporation; Forward Pharma; Genentech, Inc./Roche; Janssen Pharmaceuticals, Inc.; Merck & Co., Inc.; Miraca Life Sciences, Inc.; Napo Pharmaceuticals, Inc; Pfizer Inc.; Salix Pharmaceuticals; Samsung Bioepsis; Sandoz; Shire; Takeda Pharmaceuticals U.S.A., Inc.; TARGET PharmaSolutions, Inc.

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Learning Objective 1

Recognize the complex nature of UC that requires risk stratification to drive treatment decisions.

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Learning Objective 2

Integrate a steroid-sparing management strategy into treatment planning to minimize long-term steroid dependence and associated side effects.

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Learning Objective 3

In patients with moderate to severe UC, initiate early, top-down treatment aligned with the AGA UC Clinical Care Pathway to achieve remission and improvement in endoscopic appearance of the mucosa.

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The Natural History of Ulcerative Colitis

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# General Public Myths and Misconceptions about IBD

- In an internet survey of 1,200 individuals:
  - Familiarity with IBD self-reported at an average of 5.54 (1 = not at all familiar, 10 = extremely familiar)
  - IBD ranked as having greater social stigma than genital herpes, alcoholism, cancer, diabetes, obesity, and HIV/AIDS
  - Visible conditions contributing to stigma: presence of a stoma, bloody diarrhea, excessive weight gain, body odor, restroom proximity, sudden dizzy spells, skin sores, acne and gas
  - Knowledge of IBD low: 86% of respondents answered majority of questions pertaining to IBD causes, symptoms and possible cures incorrectly
    - Web-based content and social media sites significantly contributed to this lack of knowledge

Grosbeck J, et al. *J Med Internet Res*. 2017;19(12):e403.

Appropriate Treatment Is Important – Unfavorable Disease Course in ~50% of UC Patients
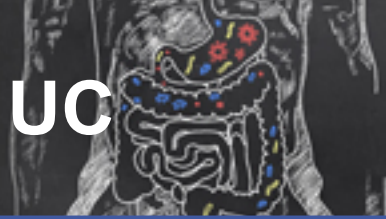
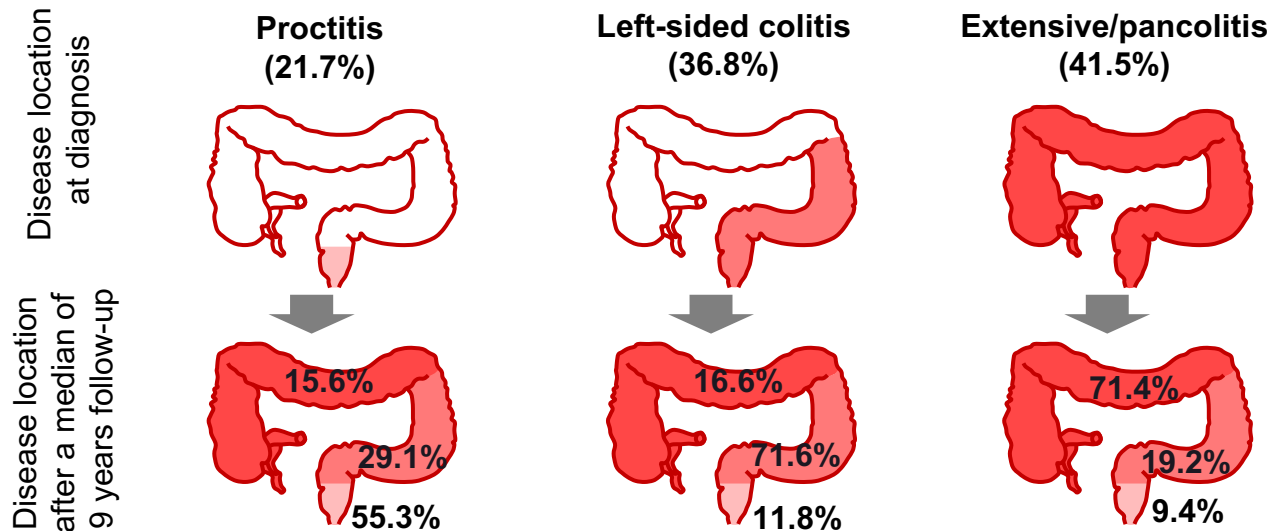IBSEN study*: Clinical course of UC over 10 years follow-up (N = 423)

Diagnosed 1990 to 1994
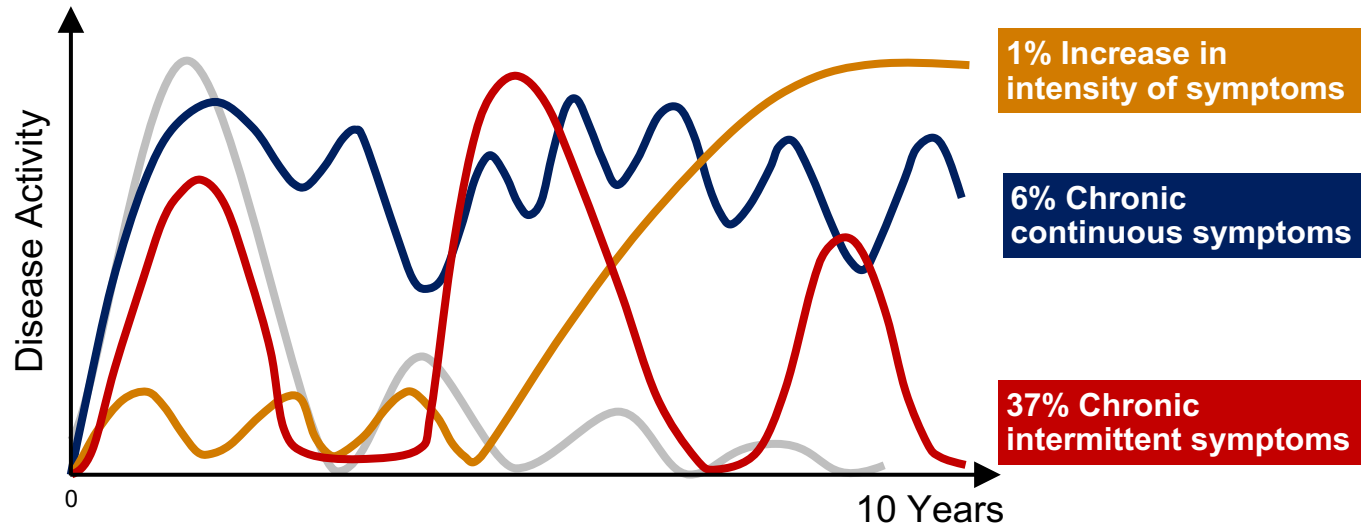
1% Increase in intensity of symptoms

6% Chronic continuous symptoms

37% Chronic intermittent symptoms

*From 1990 to 1994, patients with inflammatory bowel disease were enrolled in South-Eastern Norway and systematically followed-up for up to 10 years after diagnosis. Grey line: 55% decrease in intensity of symptoms or remission over time. Adapted from: Solberg IC, et al. *Scand J Gastroenterol*. 2009;44:431-440.

Ulcerative Colitis Is a Progressive Disease: How Do We Measure Progression — Proximal Extension?

Swiss IBD cohort study: Evolution of disease extent over a median disease duration of 9 years, from 2006 (N = 918)
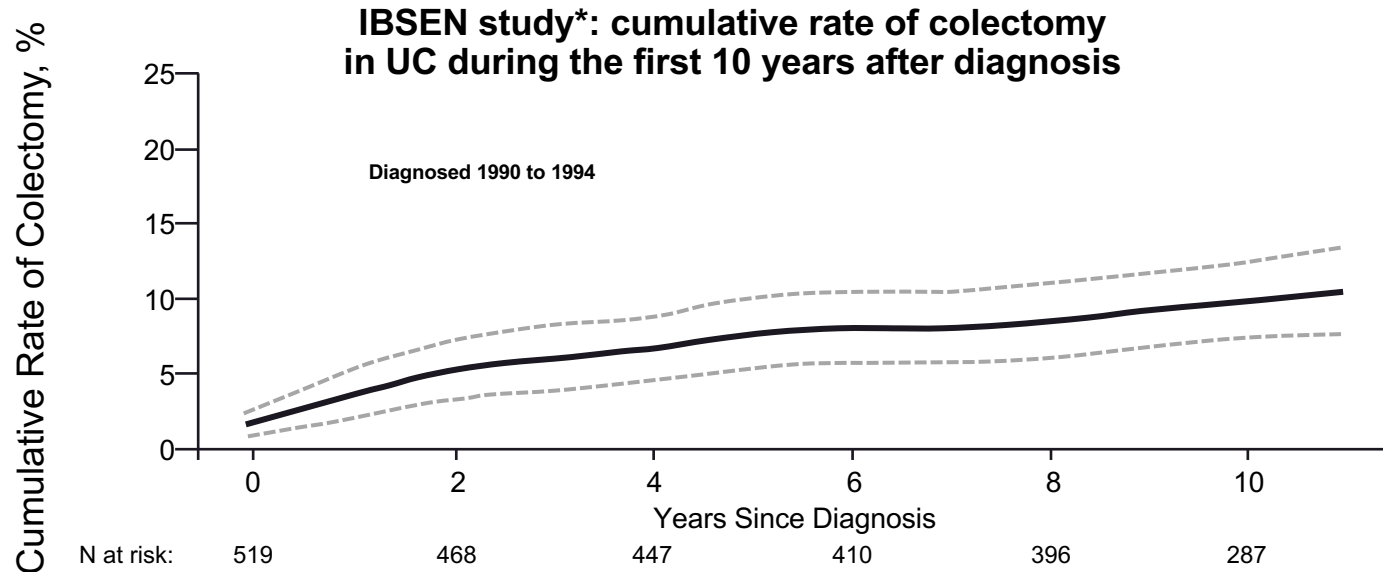
Disease duration at study inclusion: Median 6 years, IQR 2-13 years, Range 0-46 years

Disease location at diagnosis

Proctitis (21.7%)

Left-sided colitis (36.8%)

Extensive/pancolitis (41.5%)

Disease location after a median of 9 years follow-up

15.6% / 29.1% / 55.3%

16.6% / 71.6% / 11.8%

71.4% / 19.2% / 9.4%

~15% of UC patients experienced proximal disease extension over 9 years

Safroneeva E, et al. *Aliment Pharmacol Ther*. 2015;42:540-548.

Ulcerative Colitis Is a Progressive Disease: How Do We Measure Progression — Colectomy?

IBSEN study*: cumulative rate of colectomy in UC during the first 10 years after diagnosis

Diagnosed 1990 to 1994

Cumulative Rate of Colectomy, % (y-axis: 0, 5, 10, 15, 20, 25)

Years Since Diagnosis (x-axis: 0, 2, 4, 6, 8, 10)

N at risk: 519   468   447   410   396   287

~10% of patients with UC required colectomy over 10 years

*From 1990 to 1994, patients with inflammatory bowel disease were enrolled in South-Eastern Norway and systematically followed-up for up to 10 years after diagnosis.

Solberg IC, et al. *Scand J Gastroenterol.* 2009;44:431-440.

Ulcerative Colitis Is a Progressive Disease: How Do We Measure Progression — Hospitalization?

Cumulative probabilities of hospitalization in patients with UC
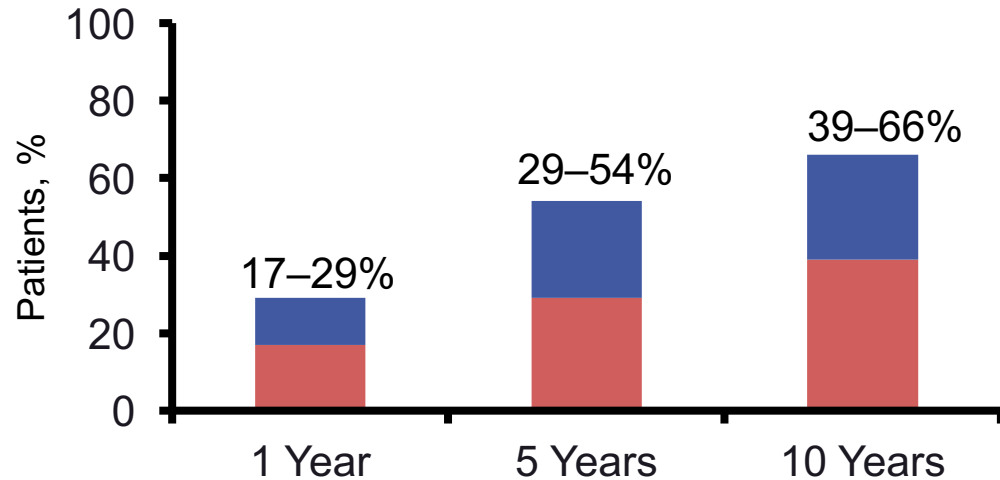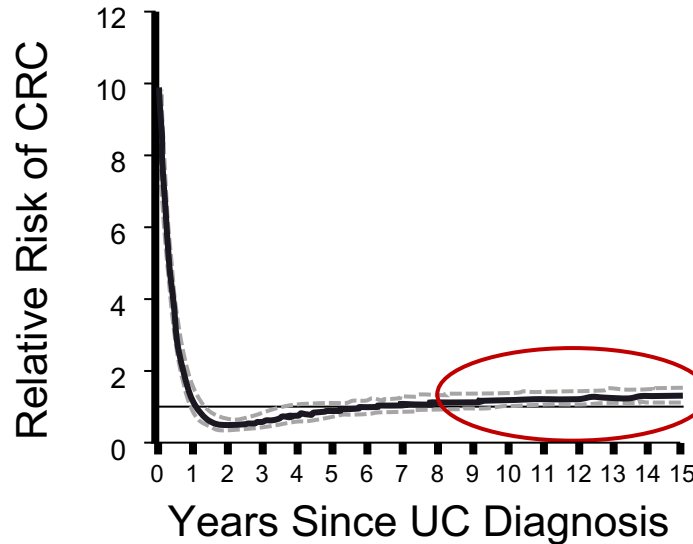

~50% of patients with UC required hospitalization at some point during disease course

Fumery M, et al. *Clin Gastroenterol Hepatol.* 2017;15:665-674.

Ulcerative Colitis Is a Progressive Disease: How Do We Measure Progression — Colorectal Cancer?

Risk of colorectal cancer in a nationwide cohort of Danish patients with UC > 30 yrs (N = 32,911)

Relative risk adjusted for sex, age, calendar time.
Dotted lines indicated 95% confidence intervals.

Subgroups of patients with UC were at increased risk for colorectal cancer

Jess T, et al. *Gastroenterology*. 2012;143:375-381.

Ulcerative Colitis Is a Progressive Disease: How Do We Measure Progression — Bowel Damage?

Local Complications of Ulcerative Colitis: Stricture, Pseudopolyposis, and Carcinoma of Colon and Rectum*

F. T. DE DOMBAL,† M.B., B.CHIR.; J. McK. WATTS,‡ M.B., F.R.A.C.S.; G. WATKINSON,§ M.D., F.R.C.P.
J. C. GOLIGHER,‖ CH.M., F.R.C.S.

Brit. med. J., 1966, 1, 1442–1447

Part of the notoriety which ulcerative colitis enjoys is derived from the diversity of complications accompanying this disease. We have reported elsewhere on the rectal and perirectal com... ...bal, Watts, Watkinson, and ...colon (de Dombal...

extent of colitis was repeatedly estimated by means of barium enema and by sigmoidoscopy. Both the severity and extent of disease were reassessed each year on the basis of information available in that year.
...follow-up...

Other damage
- Dysmotility
- Anorectal dysfunction
- Impaired permeability

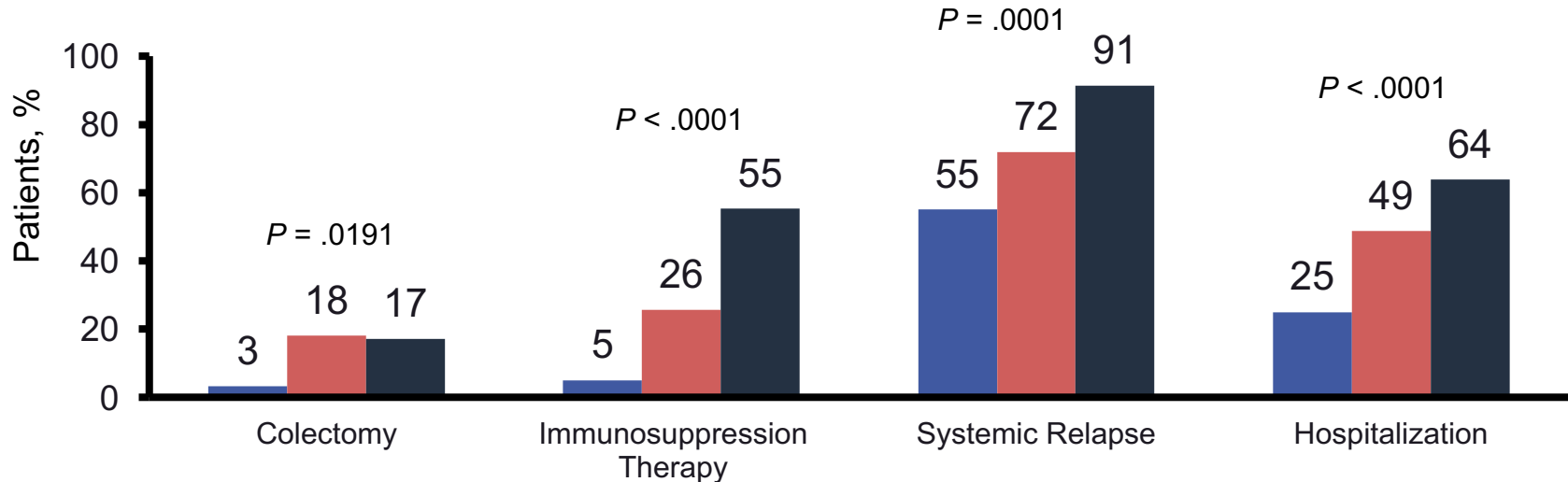Torres J, et al. *Inflamm Bowel Dis.* 2012;18:1356-1363.

Early, Lasting Clinical and Endoscopic Remission Predicts Better Long-term Outcomes in UC

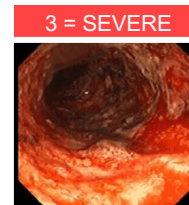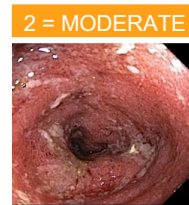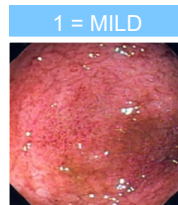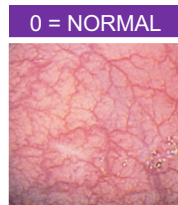Outcome at 5-year follow-up according to early response to steroids

- Clinical and endoscopic remission at month 3 (n = 60)
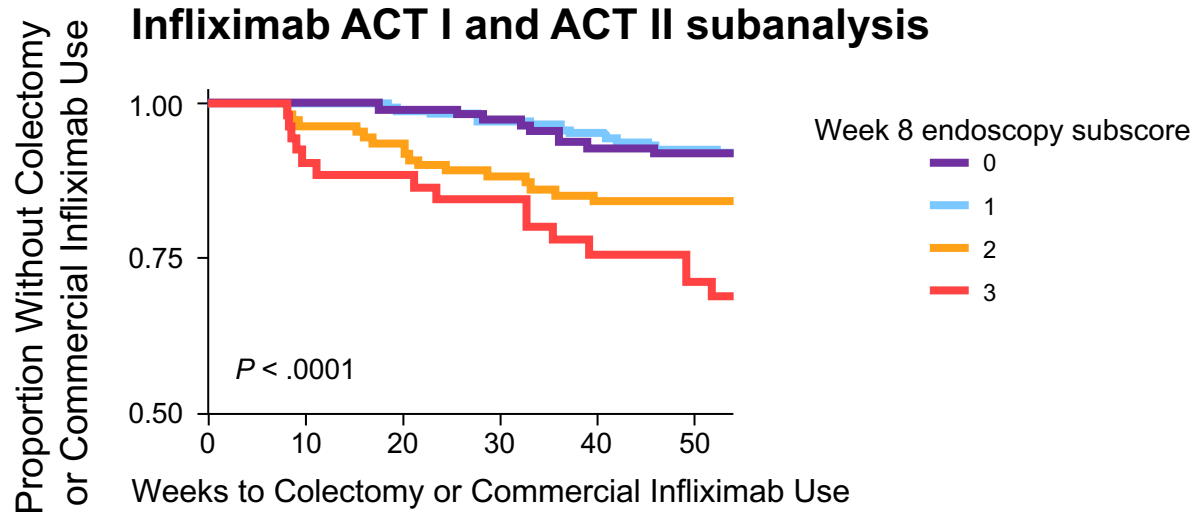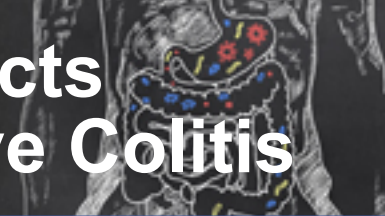- Clinical but no endoscopic remission at month 3 (n = 39)
- No clinical and endoscopic remission at month 3 (n = 58)

N=157 patients with moderate-to-severe newly diagnosed UC; 5-year follow-up after first course of steroids; classified according to remission at 3 months; mean follow-up 51 (4−60) months.
Ardizzone S, et al. *Clin Gastroenterol Hepatol*. 2011;9:483-489.e3.

Greater Endoscopic Improvement Predicts Better Long-term Outcomes in Ulcerative Colitis

Infliximab ACT I and ACT II subanalysis

Week 8 endoscopy subscore
- 0
- 1
- 2
- 3

P < .0001

0 = NORMAL 1 = MILD 2 = MODERATE 3 = SEVERE

Colombel JF, et al. *Gastroenterology*. 2011;141:1194-1201.

Early Intensive Treatment Should be Personalized in Ulcerative Colitis
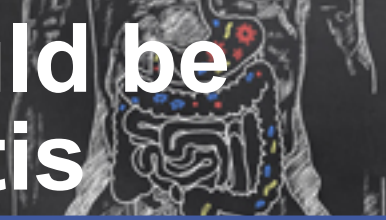
- Early, intensive treatment may not be necessary for all UC patients
- To guide the initiation of appropriate treatment in the right patient at the right time, we need a global evaluation of overall disease severity

IOIBD: UC overall disease severity index

Effects of Disease
- Frequency of loose stools
- Rectal bleeding
- Nocturnal bowel movements
- Anorectal symptoms
- Daily activity impact

Inflammatory Burden
- Anemia
- CRP level
- Albumin level
- Mucosal lesions

Disease Course
- Steroid use
- Biologics use
- Disease extent
- Recent hospitalization

Siegel CA, et al. *Gut*. 2018;67(2):244-254.
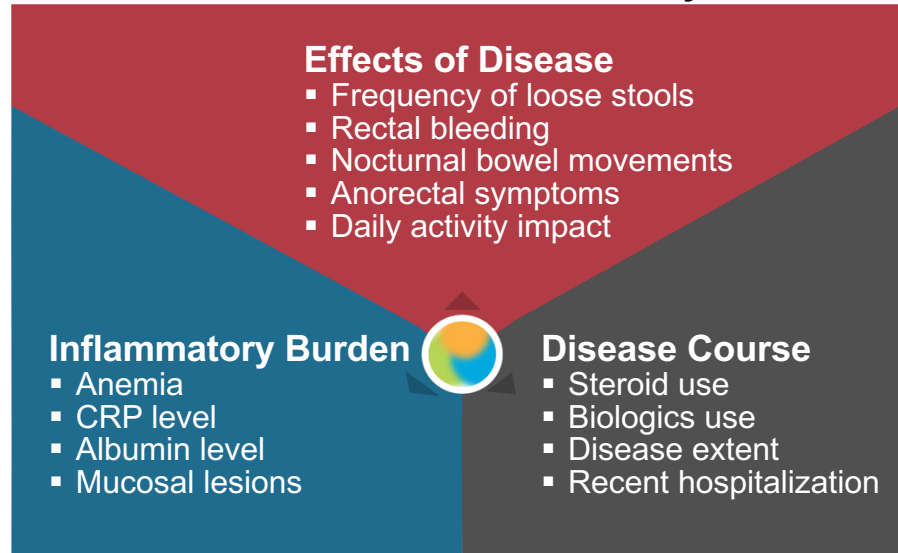
IOIBD: Ulcerative Colitis Overall Disease Severity Index

Effects of disease		Score
Frequency of loose stools	▪ No change in frequency of loose stools compared with baseline	0
	▪ Increase in frequency of loose stools by 1 per day compared with baseline	4
	▪ Increase in frequency of loose stools ≥2 per day compared with baseline	5
Rectal bleeding	▪ No rectal bleeding	0
	▪ Rectal bleeding	3
Nocturnal bowel movements	▪ No nocturnal bowel movements	0
	▪ Nocturnal bowel movements	4
Anorectal symptoms	▪ None of the following: anorectal pain, bowel urgency, incontinence, discharge, tenesmus	0
	▪ ≥1 of the following: anorectal pain, bowel urgency, incontinence, discharge, tenesmus	4
Daily activity impact	▪ Disease does not significantly impact daily activities	0
	▪ Disease significantly impacts daily activities	14

IOIBD: Ulcerative Colitis Overall Disease Severity Index

Inflammatory burden		Score
Anemia	▪ Not anemic (according to WHO criteria) ▪ Anemic (according to WHO criteria)	0 5
CRP level	▪ Normal CRP levels (1–3 mg/L) ▪ Slightly elevated CRP levels (3–5 mg/L) ▪ Elevated CRP levels (above 5 mg/L)	0 4 11
Albumin level	▪ Normal albumin level (>3.5–5.0 g/dL) ▪ Low albumin level (<3.5 g/dL)	0 5
Mucosal lesions	▪ No active erosions or ulcers ▪ Active erosions confirmed by endoscopy ▪ Active ulcers confirmed by endoscopy	0 14 18

IOIBD: Ulcerative Colitis Overall Disease Severity Index

Disease course		Score
Steroid use	▪ No steroid use within the past year ▪ Steroid use within the past year	0 8
Biologics use	▪ Never used biologics/immunomodulators ▪ Experienced some symptom improvement with use of biologics/immunomoduators ▪ No symptom improvement with use of biologics/immunomodulators	0 4 10
Disease extent	▪ Distal colitis (inflammation potentially treatable using enemas) ▪ Extensive colitis (inflammation extending beyond reach of enemas)	0 5
Recent hospitalization	▪ No disease-related hospitalization within last 12 months ▪ Disease-related hospitalization within last 12 months	0 8

Siegel CA, et al. *Gut*. 2018;67(2):244-254.

Disease Severity Components Differ According to Individual's Disease State

Asymptomatic left-sided colitis and moderately active endoscopic lesions
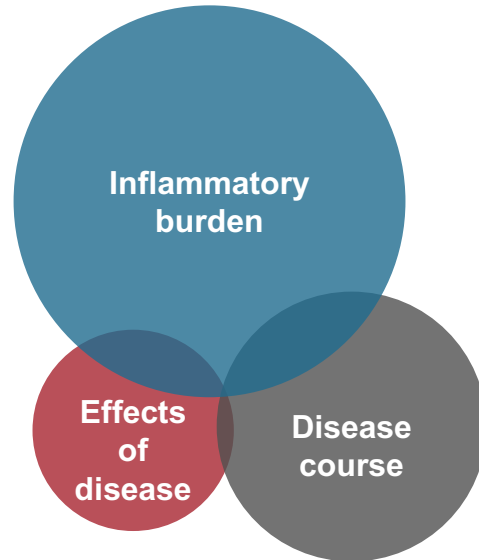
Anorectal dysfunction causing distressing symptoms of urgency, tenesmus, and incontinence

Adapted from Peyrin-Biroulet L, et al. *Clin Gastroenterol Hepatol*. 2016;14:348-354.
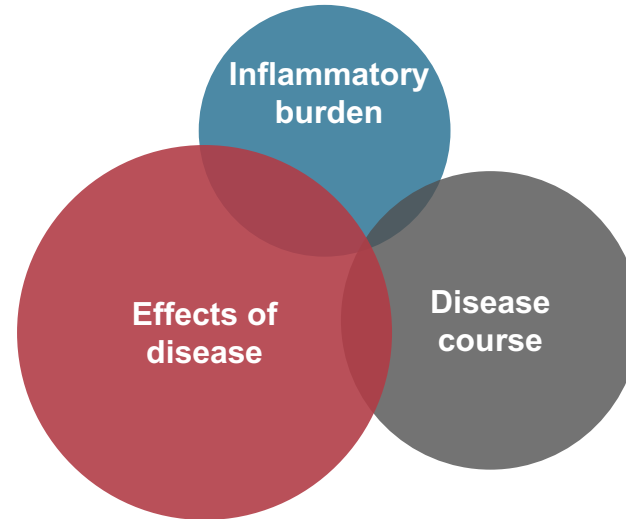
Treatment Strategy Should Take Into Account Patients' Perception About Their Disease

UC CARES Study: Patients' Perception of Disease

Peyrin-Biroulet L, et al. *Dig Liver Dis.* 2016;48:601-607.
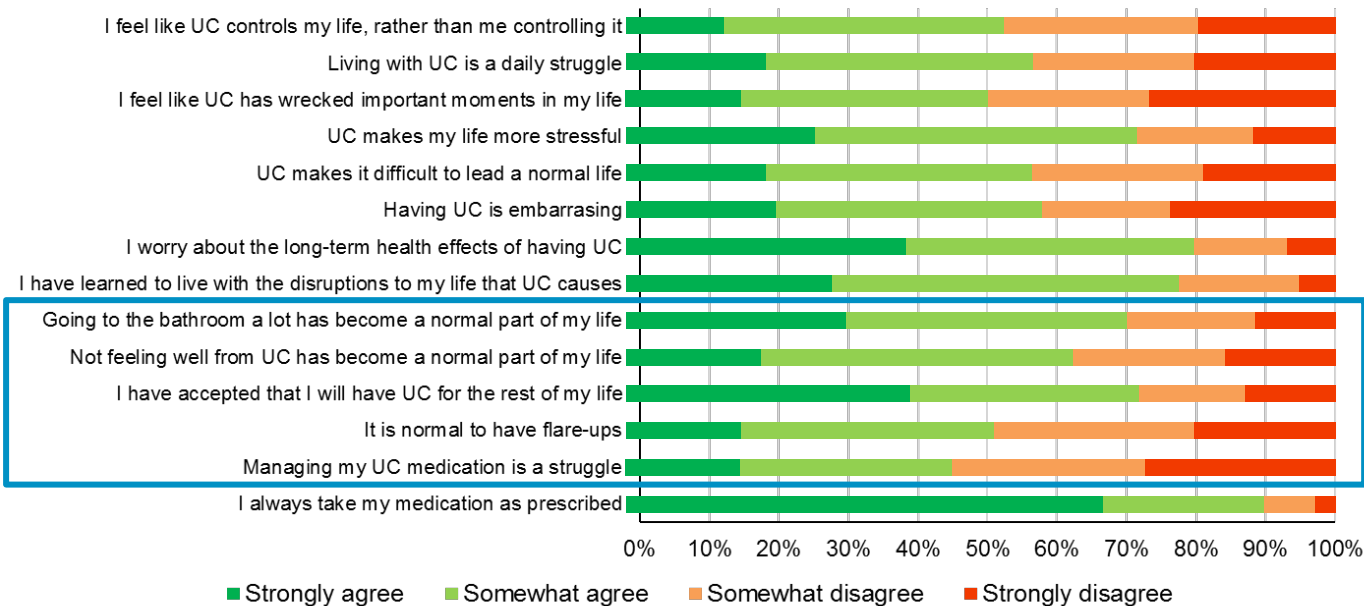
Conclusions

- UC is a chronic and progressive disease, but lack of direct, operational measures for disease progression may have contributed to suboptimal management of UC

- Early, lasting remission is associated with improved long-term outcomes in UC and therefore warrants early intensive therapy in appropriate patients

- Patients desire a medical therapy with
  - Rapid onset
  - High efficacy
  - Long-lasting action
  - Favorable safety

- Risk stratification is important for making treatment decisions

Steroid Fact or Fiction: Before You Reach for the Prednisone… Again

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Mortality From a Severe Ulcerative Colitis Attack
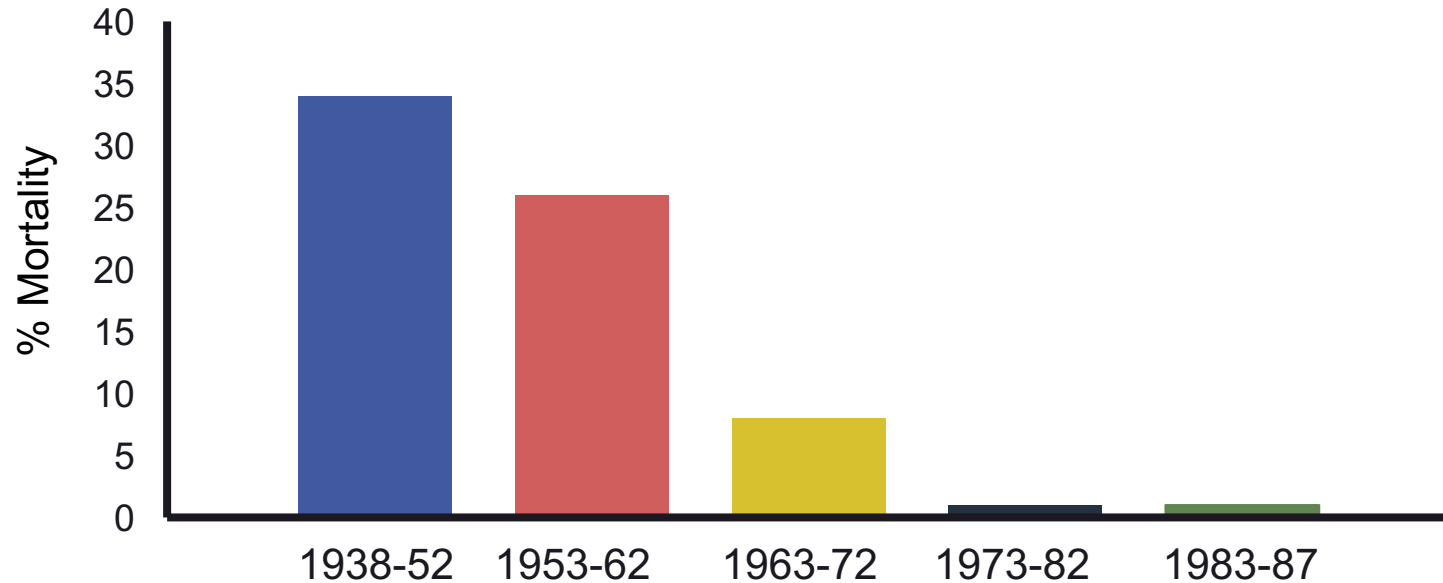
Edwards FC, et al. *Gut*. 1963;(4):299-315.
Daperno M, et al. *Aliment Pharmacol Ther.* 2002;16(4):7-12.

Reduction in Mortality Rate in Patients with Severe Ulcerative Colitis
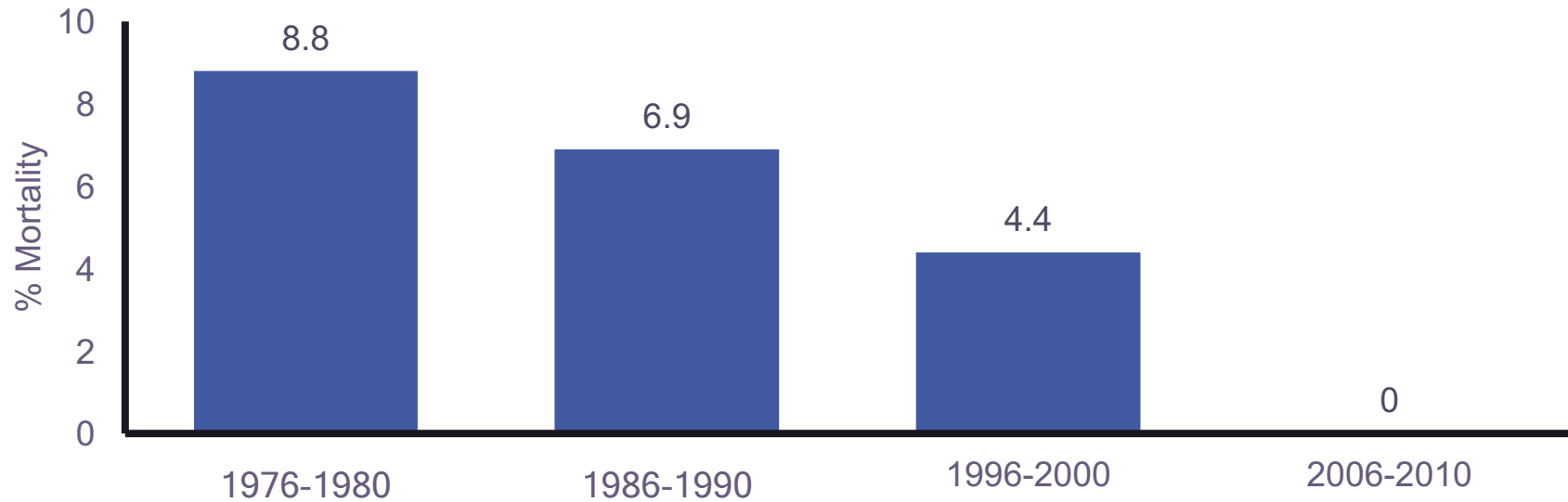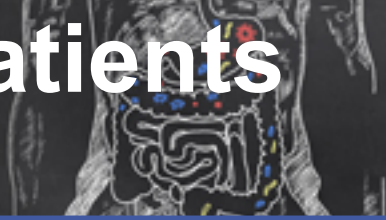
Clemente V, et al. *Dig Liver Dis*. 2016;48:371-375.

Immediate and Prolonged Outcomes of Corticosteroid Therapy* in UC

Responses

| Complete 54% (n = 34) | Partial 30% (n = 19) | None 16% (n = 10) |

1-Year Responses (n = 63)

| Steroid Dependent 22% (n = 14) | Prolonged Response 49% (n = 31) | Surgery 29% (n = 18) |

Faubion WA, et al. *Gastroenterology.* 2001;121(2)255-260.
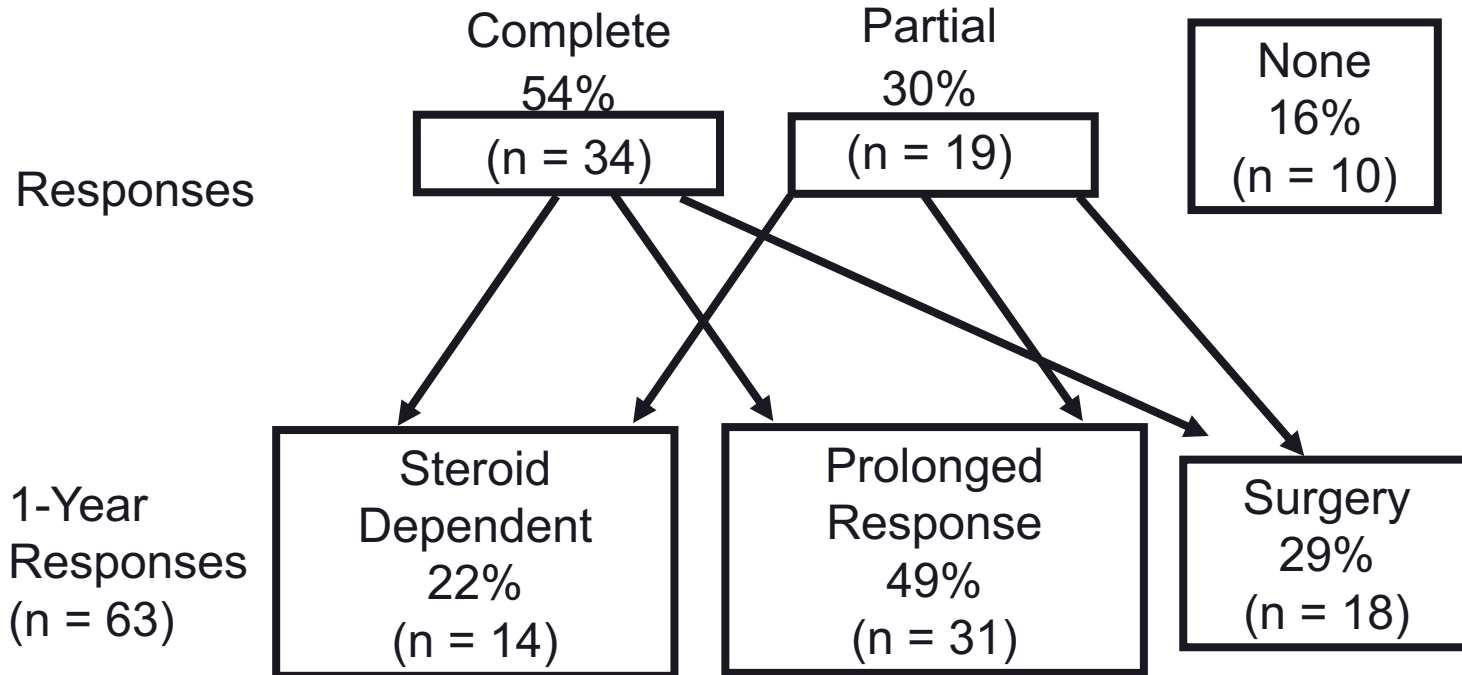
Corticosteroid Toxicity
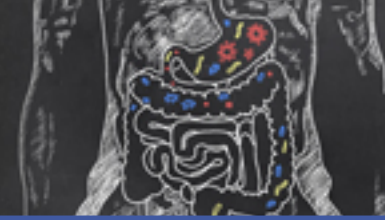
- Diabetes
- Infection
- Osteonecrosis
- Osteoporosis
- Myopathy
- Cataracts
- Glaucoma
- Psychosis

- Moon face
- Acne
- Ecchmoses
- Hypertension
- Hirsutism
- Petechial bleeding
- Striae

Sandborn WJ. *Can J Gastroenterol*. 2000;14(Suppl C):17C-22C.

Mortality Associated with Current and Recent Corticosteroid Use – Adjusted HR (95% CI)
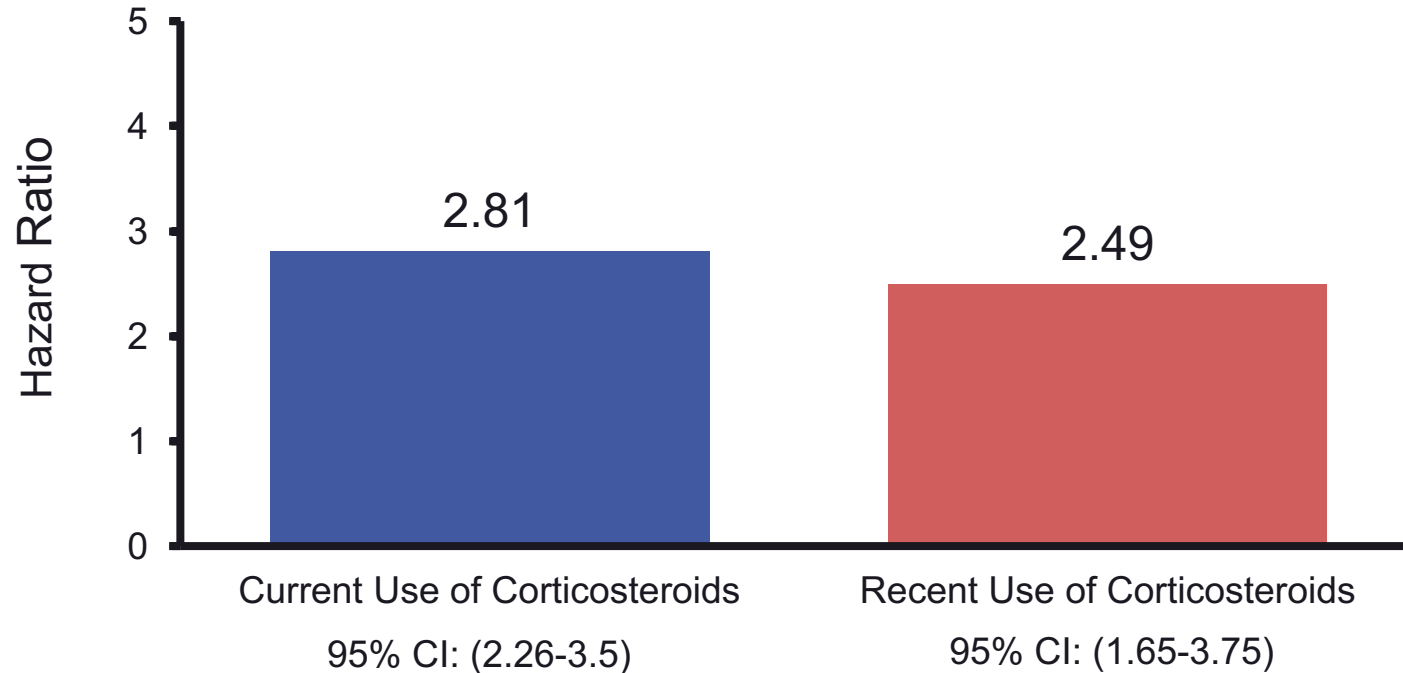
Lewis JD, et al. *Am J Gastroenterol*. 2008;103:1428-1435.

Gaps in the Care of Ulcerative Colitis

- Do not know the cause of and do not have a medical cure for UC
  - Clinical and epidemiologic observations and associations
  - Many theories
  - Patients often have their own thoughts about it
- Large primary non-response rate
- Large secondary loss of response
- Fear of adverse events (by patients and clinicians)
  - Therapies
  - Disease-related (cancer, surgery)
- Surgery has its downsides
- Mismatched expectations and confusion between patients and providers

Goals of Treatment for IBD

Induction of Deep Remission	• Turning "off" the inflammation • Feeling well • Normalization of labs, growth, development and nutrition • Healing of the bowel
Maintenance of Remission	• Stable disease control and optimization of therapy • NO STEROIDS • Prevention of relapse over time • Changing the natural course of the disease
Disease Monitoring and Prevention	• Monitoring for early relapse • Monitoring therapies • Prevention of infections • Cancer prevention

Current Medications for Ulcerative Colitis

5-ASA	Sulfasalazine Mesalamine Oral/Enema/suppository
Corticosteroids	Prednisone Budesonide MMX Foams/Enemas/suppository
Immunomodulators	Azathioprine/6-MP* Cyclosporine* Tacrolimus*
Biologics	Infliximab Adalimumab Golimumab Vedolizumab

*azathioprine, 6-MP, cyclosporine, and tacrolimus are not FDA-approved for UC.
[Package Insert]. Drugs@FDA Website.

Historical Treatment Strategies for IBD: Symptom-Based, Short-Term Goals

Disease severity at presentation?

Severe

Moderate

Mild

Pyramid levels (top to bottom):
- Anti-TNF / Cyclosporine / Anti-Adhesion
- AZA/6-MP / Methotrexate
- Prednisone / Budesonide-MMX / 5-Aminosalicylates

Step-up sequence:
- Aminosalicylate
- Aminosalicylate (ASA)
- Corticosteroids
- Aminosalicylate (UC)/ Thiopurine/MTX (CD)
- Anti-TNF
- Anti-TNF (UC)/ Thiopurine/MTX (CD)
- Cyclosporine/Tacrolimus Natalizumab

Induction
Maintenance

time

"Step-Up" and "Dirty Therapy" Strategies are Flawed

Azathioprine (AZA), 6-mercaptopurine (6-MP), methotrexate (MTX), cyclosporine, and tacrolimus are not FDA-approved for UC or Crohn's disease (CD).

Inherent Problems with Step-Up and Expectant Management

- Don't accurately reflect heterogeneity of patient types

- "Reactive" rather than "proactive"
  - Require failure of one step or class before moving onto another
  - Imply static treatment levels and do not address or anticipate changes over time

- New therapies tend to be added to the end of the line

Induction Treatment with Anti-TNFα in UC
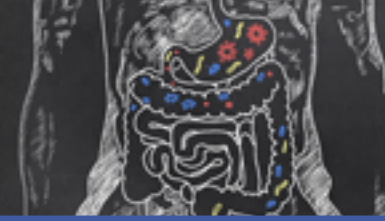
Infliximab

Response at Week 8

Remission at Week 8

Rutgeerts P, et al. *N Engl J Med*. 2005;353(23):2462-2476.
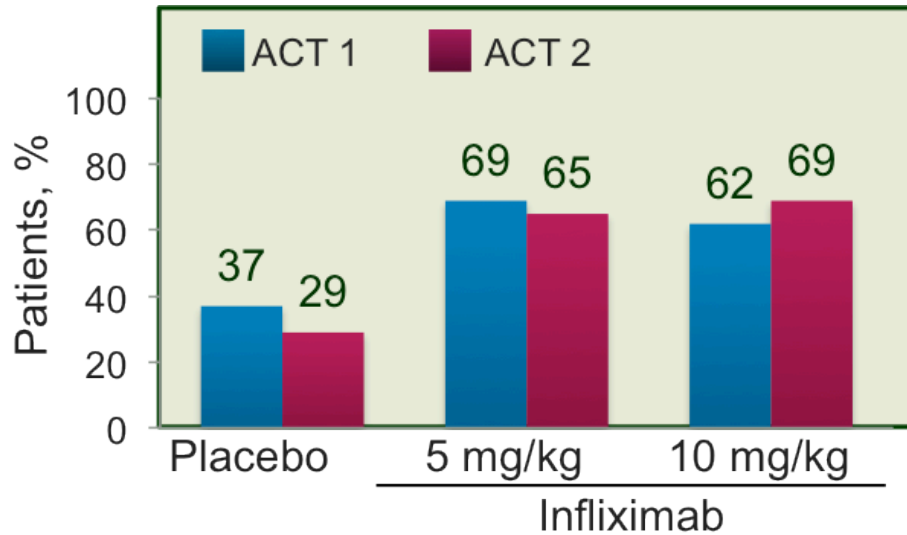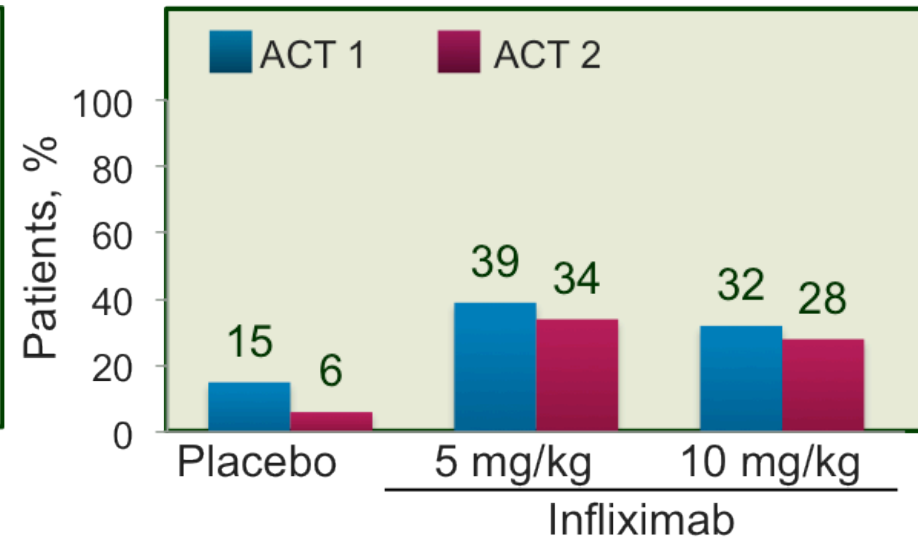
Induction Treatment with Anti-TNFα in UC

Adalimumab Outcomes at Week 8[1]

Legend:
- Placebo (n = 130)
- 80/40/40/40 (n = 130)
- 160/80/40/40 (n =130)

Proportion of Patients

Remission: 9.2, 10, 18.5 (*)
Response: 44.6, 51.5, 54.6 (P = NS)
Mucosal Healing: 41.5, 37.7, 46.9 (P = NS)

* p < .05; **p < .001

Golimumab Outcomes at Week 6[2]

Legend: Response, Remission

Patients, %

Placebo (n=256): Response 30, Remission 6
200/100 mg (n=257): Response 52 (**), Remission 19 (**)
400/200 mg (n=258): Response 55 (**), Remission 18 (**)
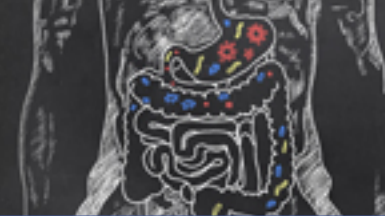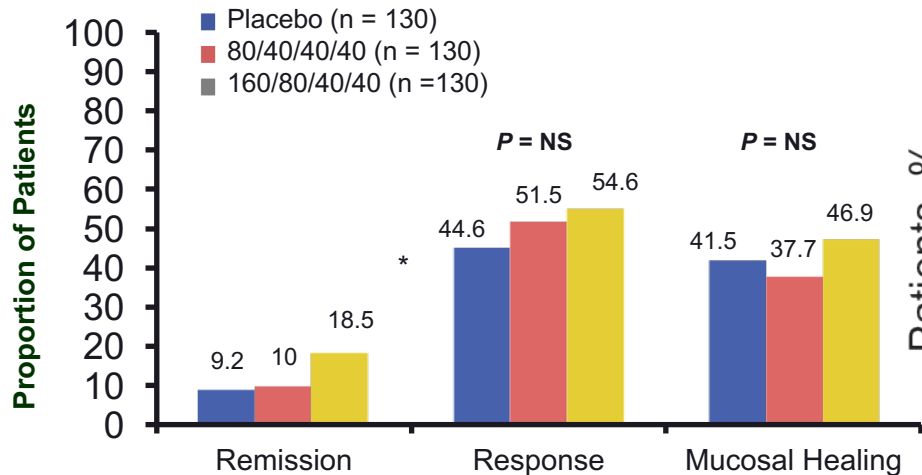
Golimumab
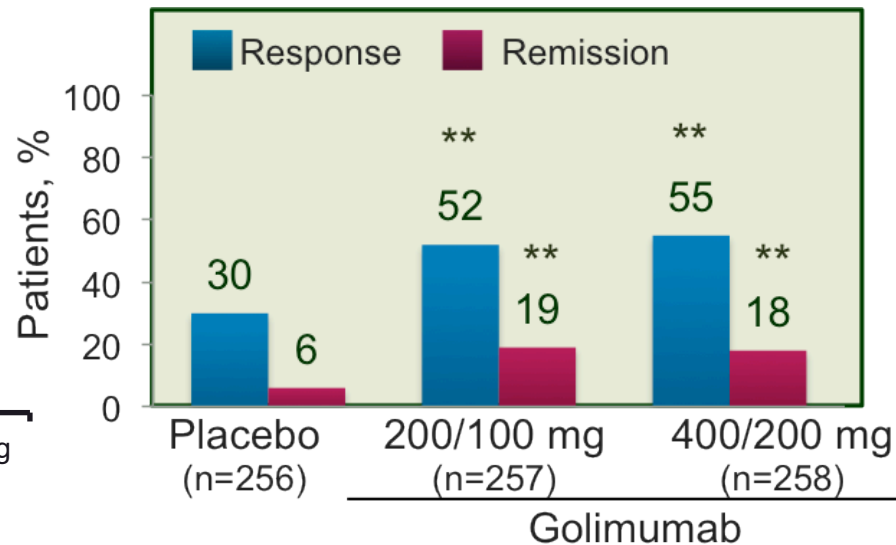
[1]Reinisch W, et al. *Gut*. 2011;60(6):780-787.
[2]Sandborn WJ, et al. *Gastroenterology*. 2014;146(1):85-95.

Maintenance Treatment with Anti-TNFα in UC
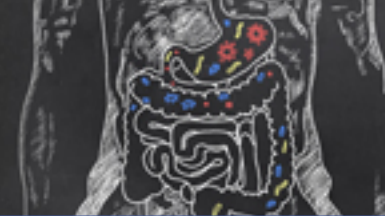
Remission Rates Achieved with Anti-TNF Agents

Infliximab[1]

- Placebo
- Infliximab 5 mg/kg
- Infliximab 10 mg/kg

Weeks 8 and 30: 8.3, 23.1 (P=0.001), 26.2 (P<0.001)
Weeks 8, 30, and 54: 6.6, 19.8 (P=0.002), 20.5 (P=0.002)

Adalimumab[2]

- Placebo
- Adalimumab

Week 8: 9, 17 (P=0.002)
Week 52: 9, 17 (P<0.01)
Weeks 8 and 52: 4, 9 (P<0.05)

Golimumab[3]

- Placebo
- Golimumab 50 mg
- Golimumab 100 mg

Weeks 30 and 54: 15.6, 23.2 (P=0.122), 27.8 (P=0.004)
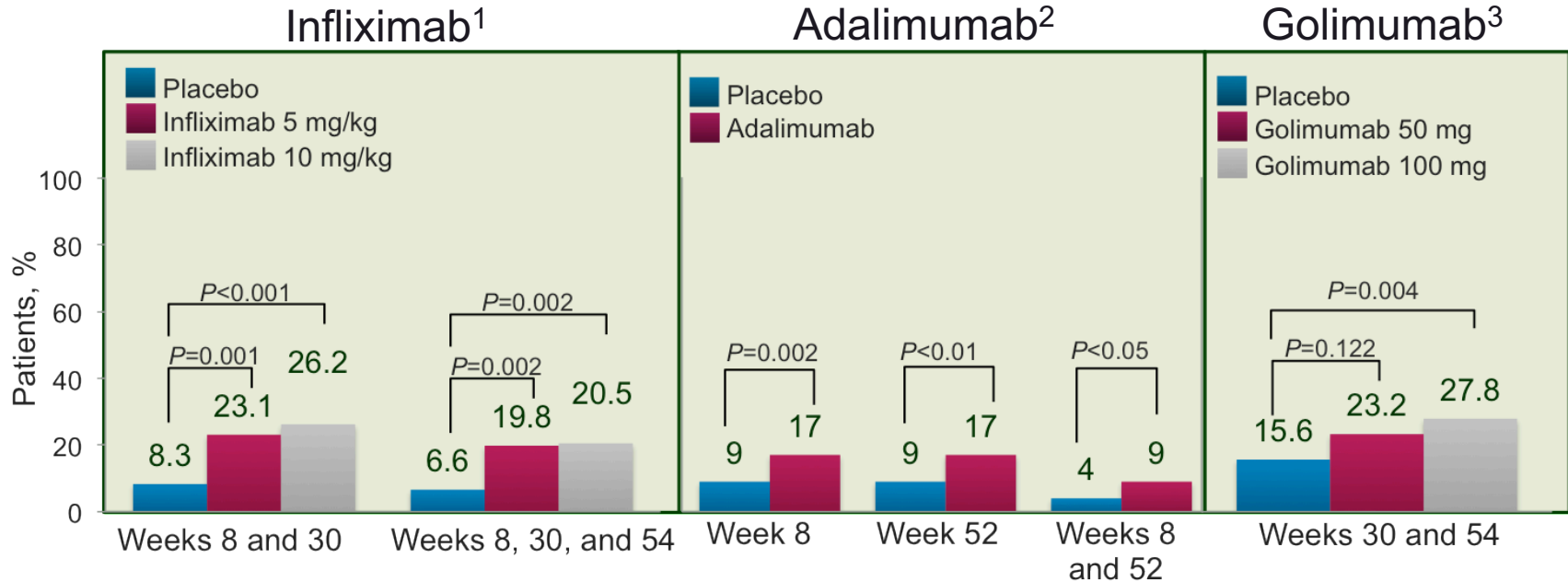
Patients, %

[1]Rutgeerts P, et al. *N Engl J Med*. 2005;353(23):2462-2476.; [2]Sandborn WJ, et al. *Gastroenterology*. 2012;142(2):257-265.; [3]Sandborn WJ, et al. *Gastroenterology*. 2014;146(1):96-109.

Proportion of Patients Achieving Clinical Remission by Serum Infliximab (IFX) Concentration: ACT 1 and 2

- At weeks 8, 30 and 54, the proportion of patients achieving clinical remission increased with increasing quartiles of IFX concentrations.

IFX Conc. (% patients)	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile	*p*-values
Week 8	26.3% (<21.3µg/mL)	37.9% (≥21.3-<33µg/mL)	43.9% (≥33-<47.9µg/mL)	43.1% (>47.9µg/mL)	*p* = .0504
Week 30	14.6% (<0.11µg/mL)	25.5% (≥0.11-<2.4µg/mL)	59.6% (≥2.4-<6.8µg/mL)	52.1% (>6.8µg/mL)	*p* < .0001
Week 54	21.1% (<1.4µg/mL)	55.0% (≥1.4-<3.6µg/mL)	79.0% (≥3.6-<8.1µg/mL)	60.0% (>8.1µg/mL)	*p* = .0066

Adedokun OJ, et al. *Gastroenterology*. 2014;146(6):1296-1307;
Reinisch W, et al. *Gastroenterology*. 2012;142 (5; Suppl 1):S-114.

Vedolizumab (VDZ) for Induction of Remission in UC (GEMINI I)

- PBO (N = 149)
- VDZ (N = 225)

Clinical Response — $p < .0001$; PBO 25.5, VDZ 47.1
Clinical Remission — $p = .0009$; PBO 5.4, VDZ 16.9
Mucosal Healing — $p = .0012$; PBO 24.8, VDZ 40.9

Patients (%)

95% CI:	Clinical Response	Clinical Remission	Mucosal Healing
	Δ21.7	Δ11.5	Δ 16.1
	11.6, 31.7	4.7, 18.3	6.4, 25.9

Feagan BG, et al. *N Engl J Med*. 2013;369:699-710.
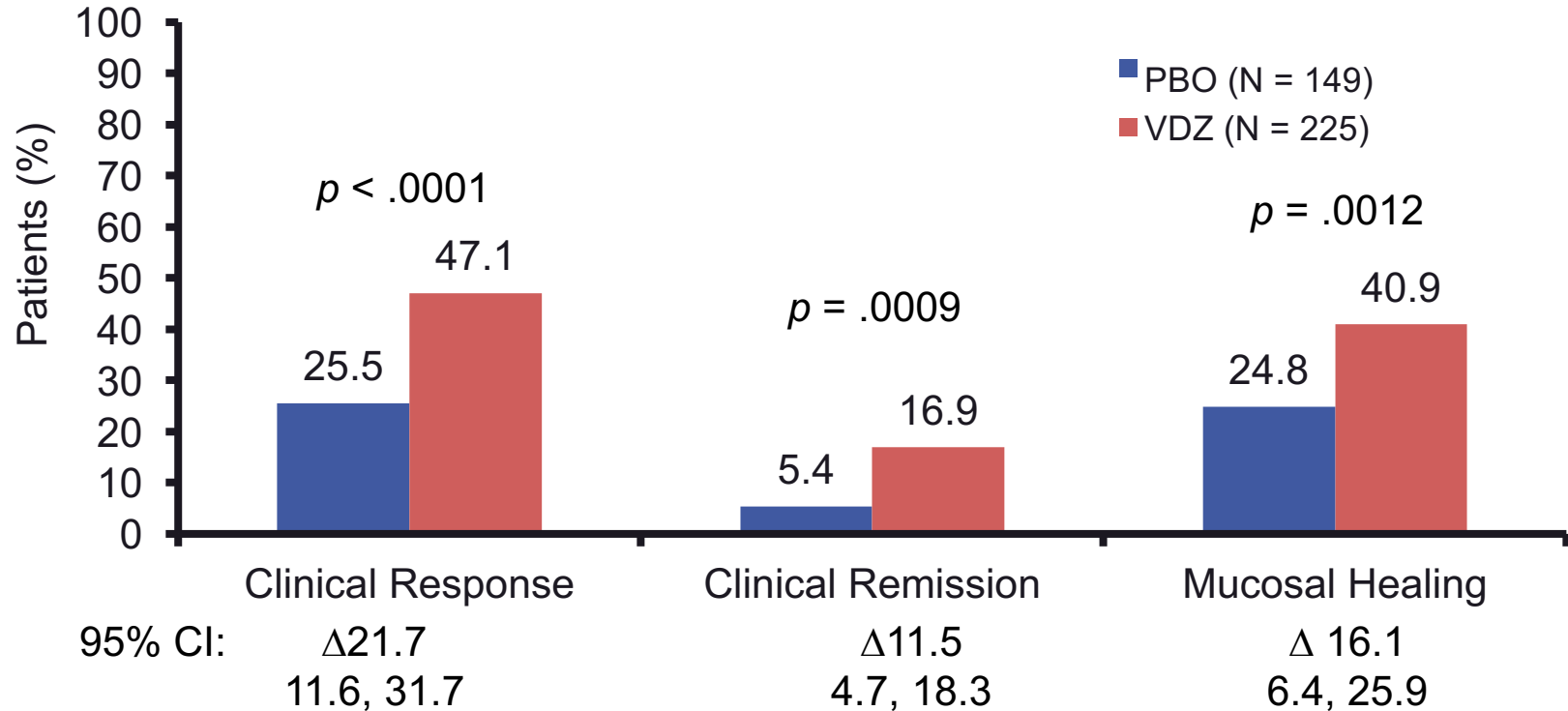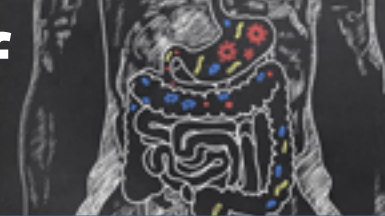
Vedolizumab for Maintenance of Remission in UC (GEMINI I)

Legend:
- ■ Placebo n = 126
- ■ VDZ Q8 wks n = 122
- ■ VDZ Q4 wks n = 125

Clinical Response
- Placebo: 15.9
- VDZ Q8 wks: 41.8 ***
- VDZ Q4 wks: 44.8 ***

Durable Clinical Response
- Placebo: 23.8
- VDZ Q8 wks: 56.6 ***
- VDZ Q4 wks: 52.0 ***

Mucosal Healing
- Placebo: 19.8
- VDZ Q8 wks: 51.6 ***
- VDZ Q4 wks: 56.0 ***

Durable Clinical Remission
- Placebo: 8.7
- VDZ Q8 wks: 20.5 **
- VDZ Q4 wks: 24.0 **

CS-Free Remissions
- Placebo: 13.9
- VDZ Q8 wks: 31.4 *
- VDZ Q4 wks: 45.2 ***

Y-axis: % (0 to 60)
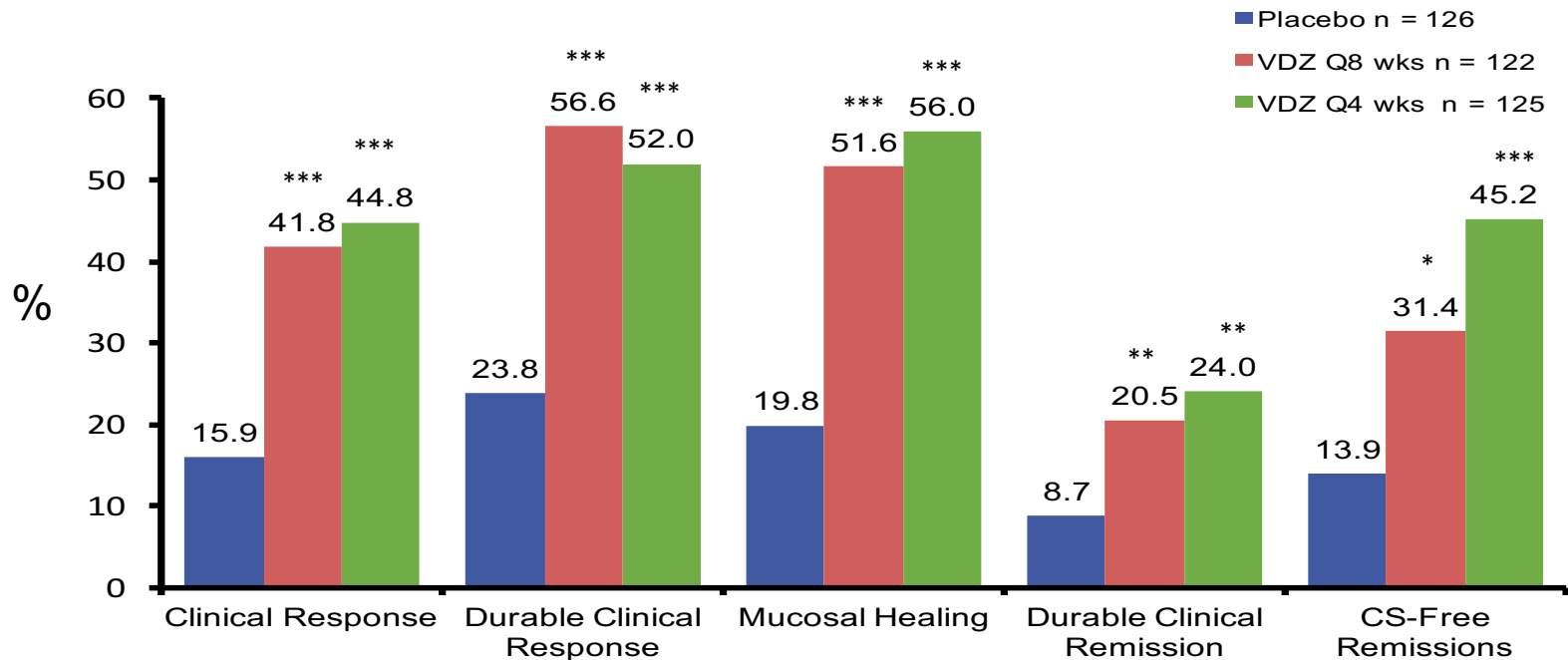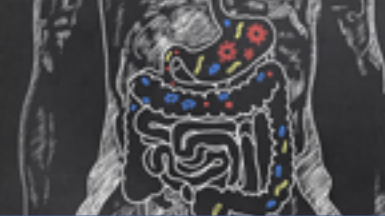
*p < .05   **p < .01   ***p < .001

Feagan BG, et al. *N Engl J Med*. 2013;369:699-710.

Anti-TNF Naïve Patients Do Better with Vedolizumab (GEMINI I)

Clinical Remission to VDZ in UC

Anti-TNF Naïve: VDZ/Placebo 19%, VDZ/VDZ Q8w 46%, VDZ/VDZ Q4w 48%

Prior Anti-TNF Failure: VDZ/Placebo 5%, VDZ/VDZ Q8w 37%, VDZ/VDZ Q4w 35%

■ VDZ/Placebo ■ VDZ/VDZ Q8w ■ VDZ/VDZ Q4w

Feagan BG, et al. *N Engl J Med*. 2013;369(8):699-710.
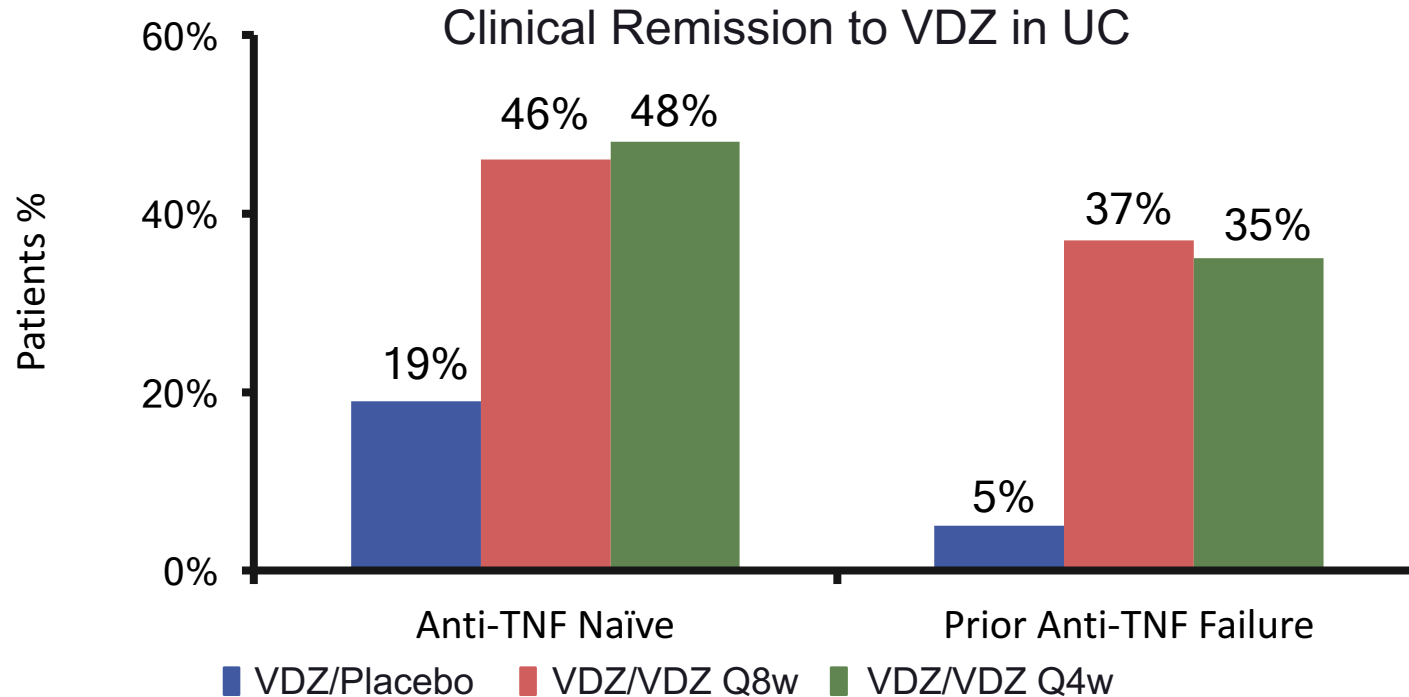
Sub-Optimal Therapy in IBD

- 1,699 UC patients from the Thomson Reuters MarketScan Commercial Database (2005-2013)

- 91% of patients experienced at least one indicator of suboptimal biologic therapy within 36 months of biologic treatment initiation

	12-month rate (%)	36-month rate (%)
Any Indicator of suboptimal therapy	72	91
Dose escalation	28	44
Discontinuation	43	65
Switching	6	11
Augmentation	23	50
Disease-related surgery	8	13
Disease-related urgent care	10	15

Patel H, et al. *PLoS One*. 2017;12(4):e0175099.

Assessment of Disease Risk in Ulcerative Colitis

- Standard assessment of UC activity (mild, moderate, severe) insufficient in guiding selection of therapy

- Need to assess risk of colectomy

Low-Risk for Colectomy	High-Risk for Colectomy	
• Limited anatomic extent • Mild endoscopic disease	• Extensive colitis • Deep ulcers • Age <40 • High CRP and ESR • Steroid-requiring disease	• History of hospitalization • *C. difficile* infection • CMV infection

Ulcerative Colitis Care Pathway
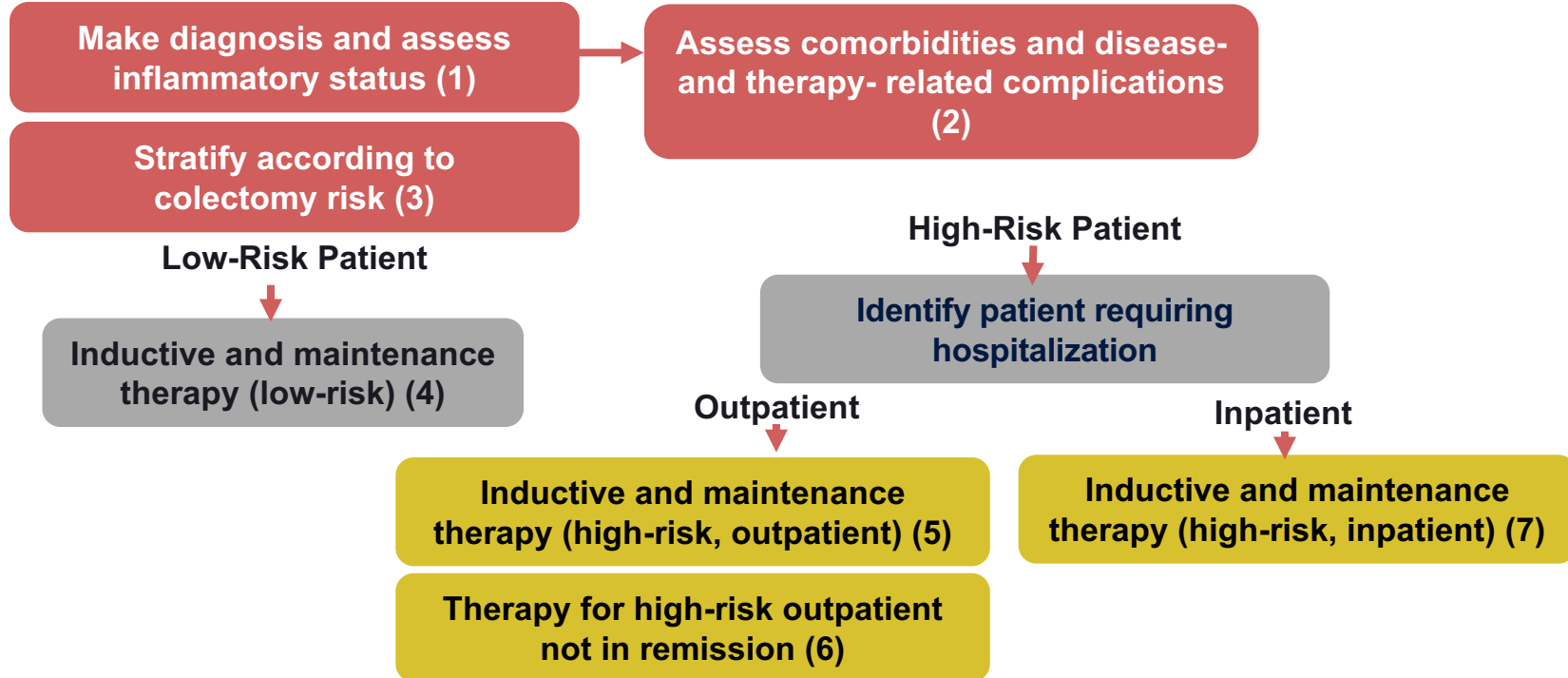
Make diagnosis and assess inflammatory status (1) → **Assess comorbidities and disease- and therapy- related complications (2)**

Stratify according to colectomy risk (3)

Low-Risk Patient

Inductive and maintenance therapy (low-risk) (4)

High-Risk Patient

Identify patient requiring hospitalization

Outpatient

Inductive and maintenance therapy (high-risk, outpatient) (5)

Therapy for high-risk outpatient not in remission (6)

Inpatient

Inductive and maintenance therapy (high-risk, inpatient) (7)

Dassopoulos T, et al. *Gastroenterology*. 2015;149:238-245.

Adverse reaction to medical therapy	→	**Modify therapy**
Thromboembolic complications	→	**Treat DVT/PE**
Colorectal cancer/dysplasia[a]	→	**Colectomy**
Toxic megacolon/ fulminant colitis	→	**Consult surgery**

[a]Colectomy is recommended for: 1) Endoscopically unresectable dysplasia; 2) Invisible high-grade dysplasia; 3) Invisible low-grade dysplasia if multifocal, repetitive, or prevalent
DVT = deep vein thrombosis; PE = pulmonary embolism.
Dassopoulos T, et al. *Gastroenterology*. 2015;149:238-245.

AGA Ulcerative Colitis Care Pathway
Induction and Maintenance Therapy in High-risk Outpatients

Induction Therapy

| Short course of steroids with initiation of thiopurine |

Remission →

Maintenance Therapy

- Thiopurine and taper steroids over 60days, or
- Anti-TNF ± thiopurine, or
- Vedolizumab ± thiopurine or methotrexate*

| Anti-TNF ± thiopurine | → | Continue anti-TNF ± thiopurine |

| **Vedolizumab ± immunomodulator** | → | Continue **vedolizumab ± immunomodulator** |

No Remission
Therapy for **high-risk** outpatient not in remission
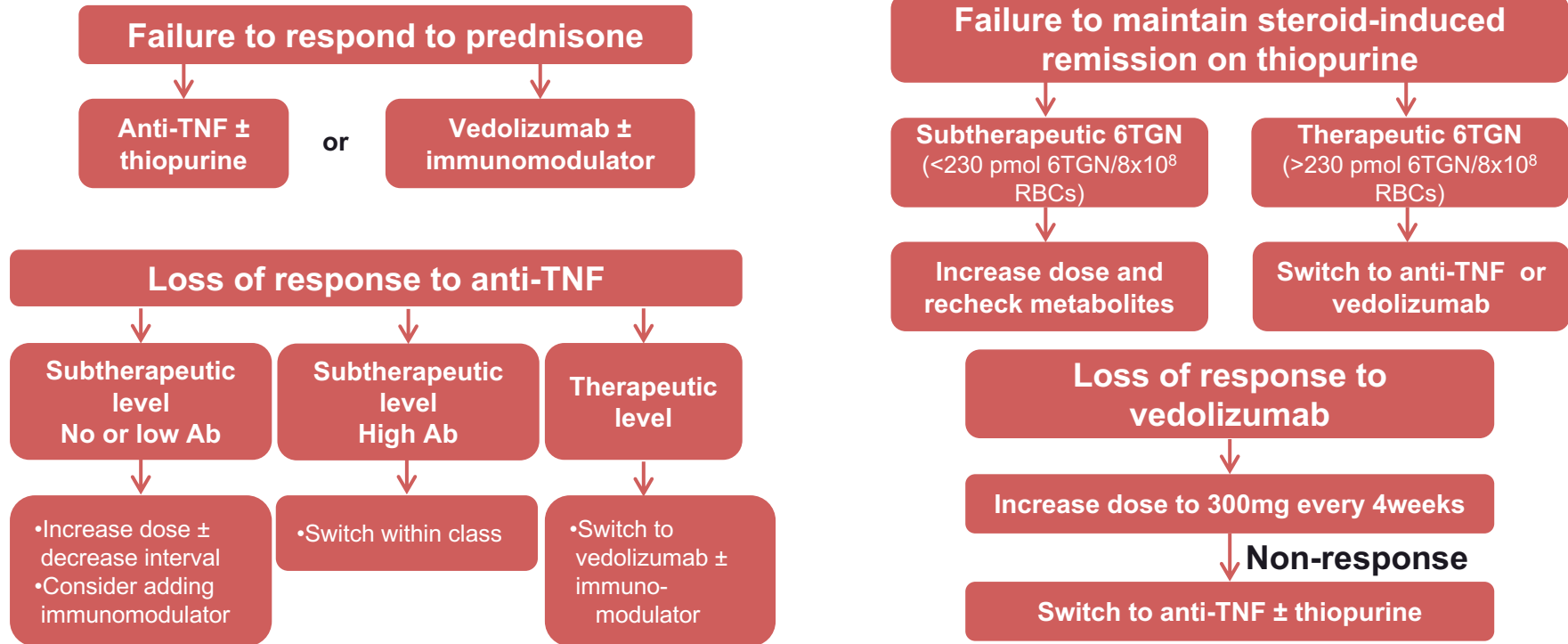
Relapse
Therapy **for** high-risk outpatient not in remission

*Methotrexate not FDA-approved for UC
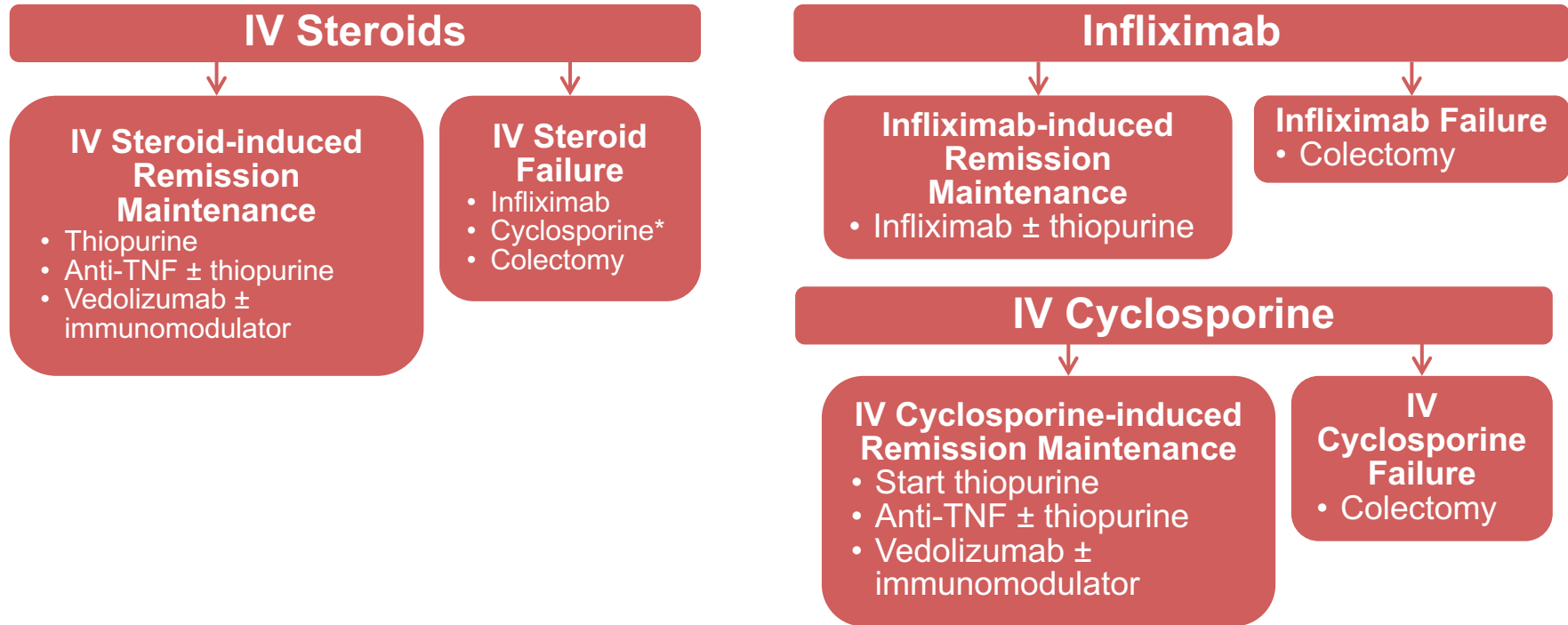Dassopoulos T, et al. Gastroenterology. 2015;149(1):238-245.

AGA Ulcerative Colitis Care Pathway
Therapy in High-risk Outpatients Not in Remission

Failure to respond to prednisone

→ **Anti-TNF ± thiopurine** *or* **Vedolizumab ± immunomodulator**

Loss of response to anti-TNF

- **Subtherapeutic level No or low Ab**
  - •Increase dose ± decrease interval
  - •Consider adding immunomodulator
- **Subtherapeutic level High Ab**
  - •Switch within class
- **Therapeutic level**
  - •Switch to vedolizumab ± immuno-modulator

Failure to maintain steroid-induced remission on thiopurine

- **Subtherapeutic 6TGN (<230 pmol 6TGN/8x10^8 RBCs)**
  - **Increase dose and recheck metabolites**
- **Therapeutic 6TGN (>230 pmol 6TGN/8x10^8 RBCs)**
  - **Switch to anti-TNF or vedolizumab**

Loss of response to vedolizumab

→ **Increase dose to 300mg every 4weeks**

Non-response

→ **Switch to anti-TNF ± thiopurine**

Dassopoulos T, et al. *Gastroenterology*. 2015;149(1):238-45.

AGA Ulcerative Colitis Care Pathway
Induction and Maintenance Therapy in High-risk Inpatients

IV Steroids

IV Steroid-induced Remission Maintenance
- Thiopurine
- Anti-TNF ± thiopurine
- Vedolizumab ± immunomodulator

IV Steroid Failure
- Infliximab
- Cyclosporine*
- Colectomy

Infliximab

Infliximab-induced Remission Maintenance
- Infliximab ± thiopurine

Infliximab Failure
- Colectomy

IV Cyclosporine

IV Cyclosporine-induced Remission Maintenance
- Start thiopurine
- Anti-TNF ± thiopurine
- Vedolizumab ± immunomodulator

IV Cyclosporine Failure
- Colectomy

*Cyclosporine is not FDA-approved for UC
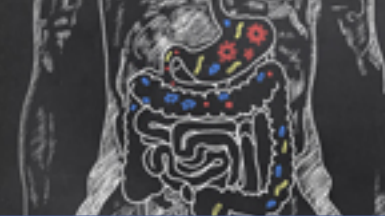Dassopoulos T, et al. *Gastroenterology*. 2015;149(1):238-245.

Considerations of a "Top-Down" Strategy for Managing UC

- May gain control earlier in disease course
- May achieve a greater amount of remission and improved outcomes
- May improve quality of life
- There are no prospective data to support these claims

Treat-to-Target

- Systematic assessment of an identified "target" and serial adjustment of therapy until the target is reached or until the patient refuses or we run out of options

- Primary goal: maximize health-related QoL
  - Control of symptoms
  - Normalization of function and social participation
  - Prevention of progressive structural damage

- Presumption is that achievement of target may improve QoL and changes the natural history of the disease

Sofia MA, Rubin DT. *Therap Adv Gastroenterol*. 2016;9(4):548-559.

SMART Goals

- Incorporate the use of operational measures to assess disease progression – both morphological and functional – in UC to optimize management

- Implement early, intensive therapy to facilitate durable remission
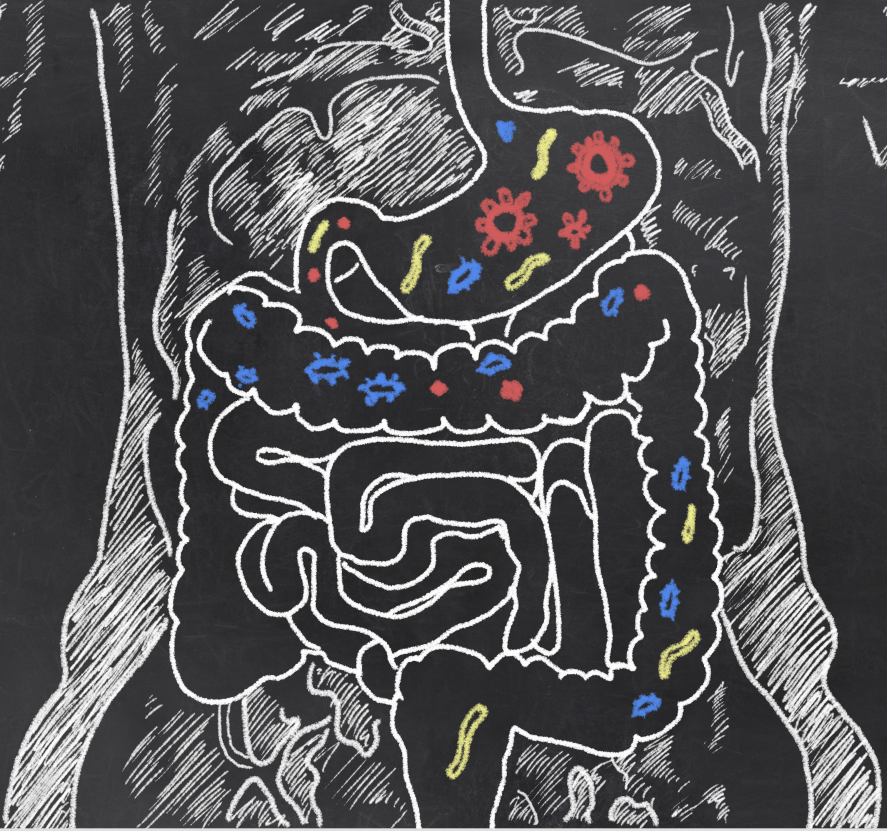
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