A gyulladásos bélbetegségek a klinikus szemével

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IBD jellemző tünetei

- **Colitis ulcerosa**

  Általában típusos
  - Véres, nyákos hasmenés
  - Tenezmus
  - Általános tünetek kiterjedt betegségnél: anaemia, fogyás

- **Crohn-betegség**

  Gyakran atípusos
  - Nem véres hasmenés
  - Hasi fájdalom
  - Fogyás
  - Tapintható terime
  - Fistula
  - Hiánytünetek
  - Extraintestinalis tünetek

IBD diagnosztikája

- **Diagnózis**
  - jellemző klinikum
  - klinikai, endoszkópos, radiológiai, mikrobiológiai kritériumok
  - lehetséges, valószínű, biztos esetek
- **Differenciáldiagnózis**
  - egyéb gyulladásos bélbetegségektől, daganattól
  - irritábilis bél szindrómától
  - egymástól (UC, CD)

IBD diagnosztikája

- Panaszok, klinikai tünetek
- Tenyésztéses vizsgálatok
- Laboratóriumi vizsgálatok
- Endoscopia
- Képalkotó vizsgálatok
  - Irrigoscopia
  - Enterographia
  - UH
  - CT, MRI
  - Leukocyta scintigraphia

Colitis ulcerosa és Crohn betegség klinikai elkülönítése

	UC	CD
Fogyás	(+)	++
Hasi fájdalom	(+)	++
Hasmenés	+++	++
Véres széklet	+++	(+)
Tenezmus	++	(+)
Tapintható rezisztencia	-	++
Láz	(+)	++
Nyák, genny ürítése	+++	(+)
Perianális laesio	-	++

+++ típusos ++ gyakori + időnként (+) ritkán - nincs

Colitis ulcerosa osztályozása

Természetes lefolyás

- Acut
- Remittáló
- Krónikusan aktív

Súlyosság

- Enyhe
- Középsúlyos
- Súlyos/fulmináns

Kiterjedés, lokalizáció

- Proctitis
- Baloldali colitis
- Pancolitis

Megjelenés

- folyamatos
- felületes

Crohn-betegség osztályozása

Természetes lefolyás

- Krónikus relapsusos
- Krónikusan aktív
  - Steroid dependens
  - Steroid resistens
- Krónikus agresszív

Szövődmények szerint

- Fibrostenoticus (stenosisra hajlamos)
- Perforáló (tályog, fistulaképződésre hajamos)

Lokalizáció

- Vékonybél
- Vékony- és vastagbél
- Vastagbél
- Perianalis

Megjelenés

- ugráló léziók
- transmurális

A Crohn betegség Bécsi osztályozása (1998)

Életkor a diagnóziskor

- A1: <40 év
- A2: >40 év

Viselkedés

- B1: nem strictura képző, nem penetráló
- B2: strictura képző
- B3: penetráló

Lokalizáció:

- L1: terminális ileum
- L2: colon
- L3: ileocolon
- L4: felső gastrointestinális tractus

IBD szövődményei

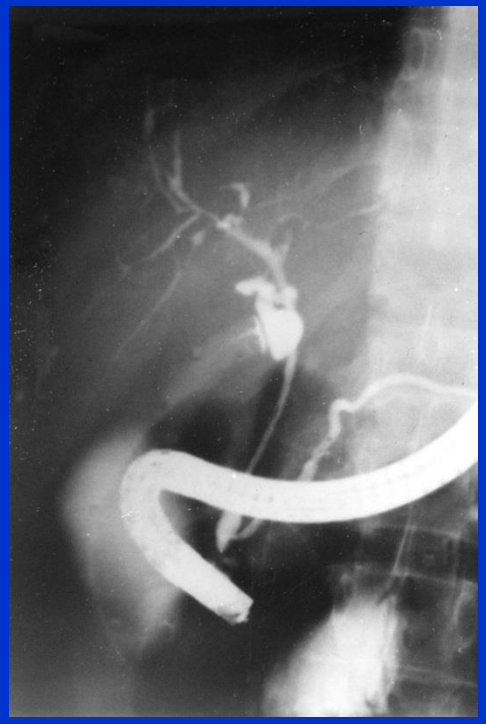
Intestinalis

- Súlyos vérzés
- Toxicus megacolon
- Perforáció
- Stenosis- ileus
- Tályog
- Fistula (külső- belső)
- Malignus elfajulás (tumor surveillance !)

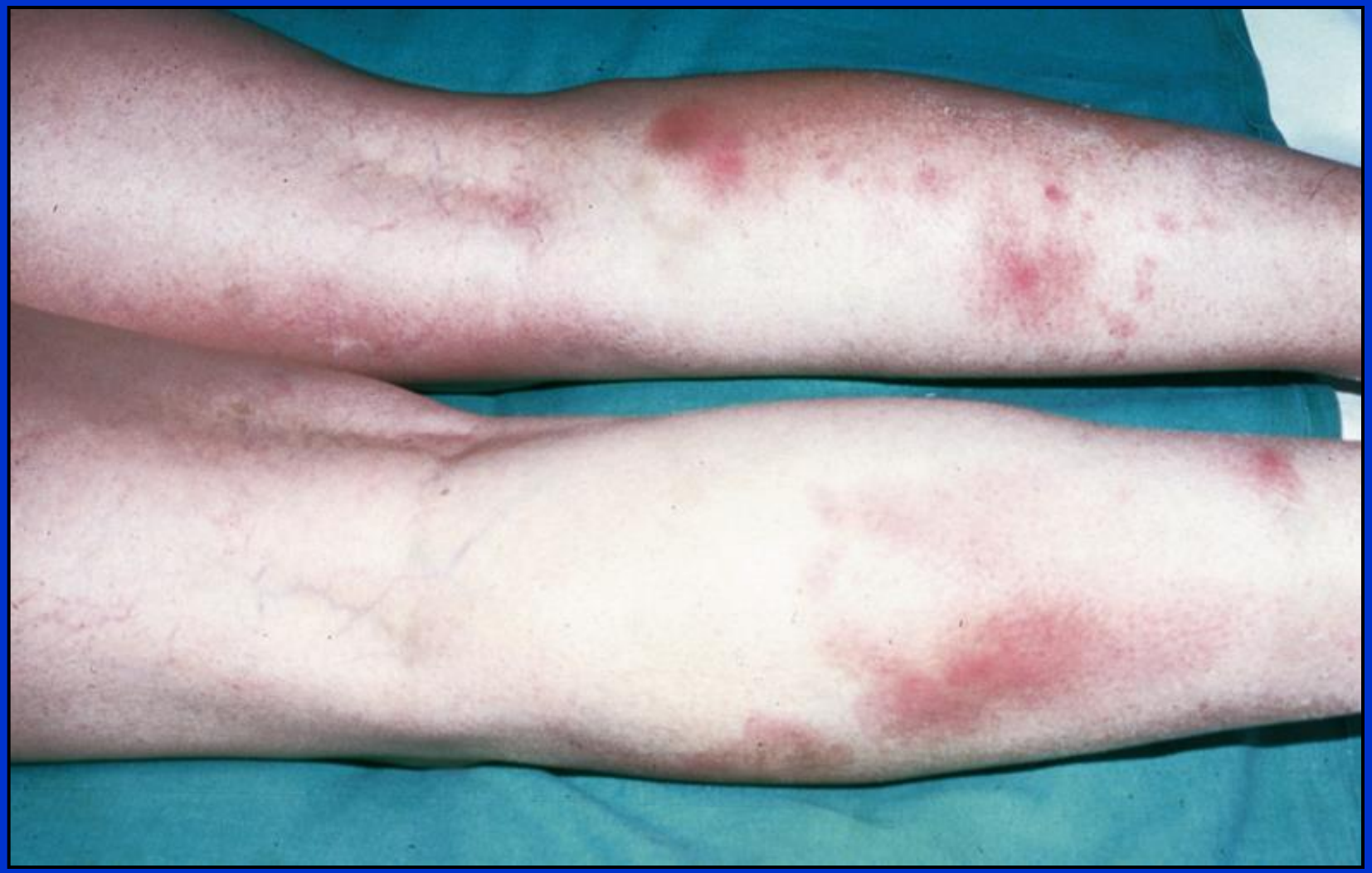
IBD szövődményei

Extraintestinalis

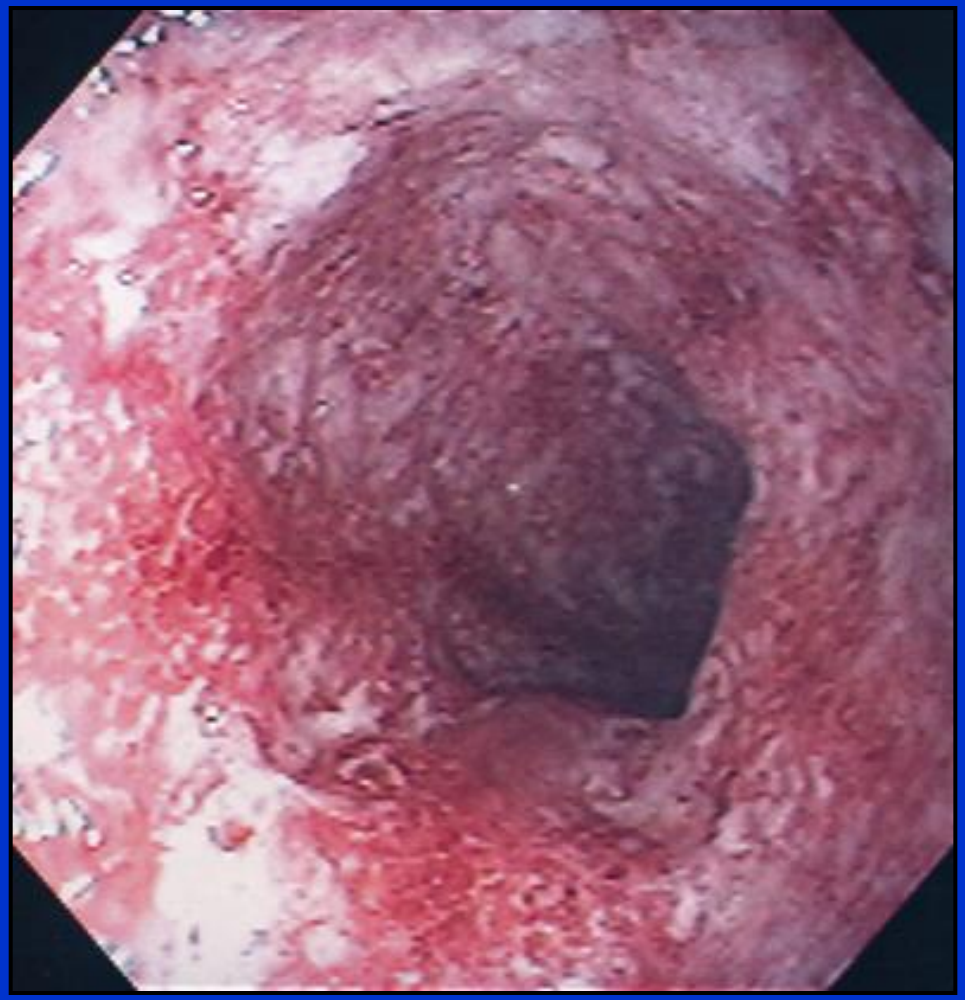
- **Hepatobiliaris** (PSC, steatosis, CAH)
- **Izületi** (sacroileitis, polyarthritis, spondylarthritis)
- **Szem** (episcleritis, uveitis, iridocyclitis)
- **Bőr** (erythema nodosum, pyoderma gangraenosum)
- **Haematologiai** (anaemia, thrombosis, haemolysis)



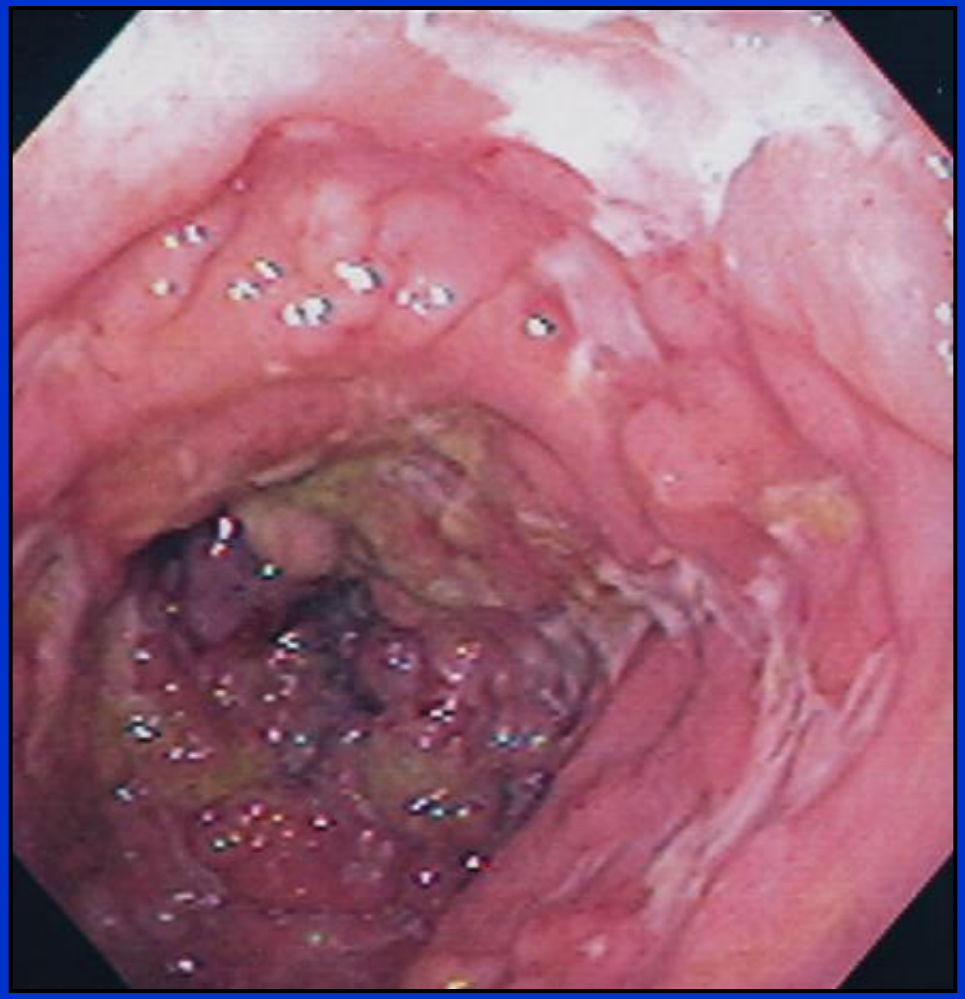
Erythema nodosum IBD-ben



Súlyos colitis ulcerosa endoscopos képe

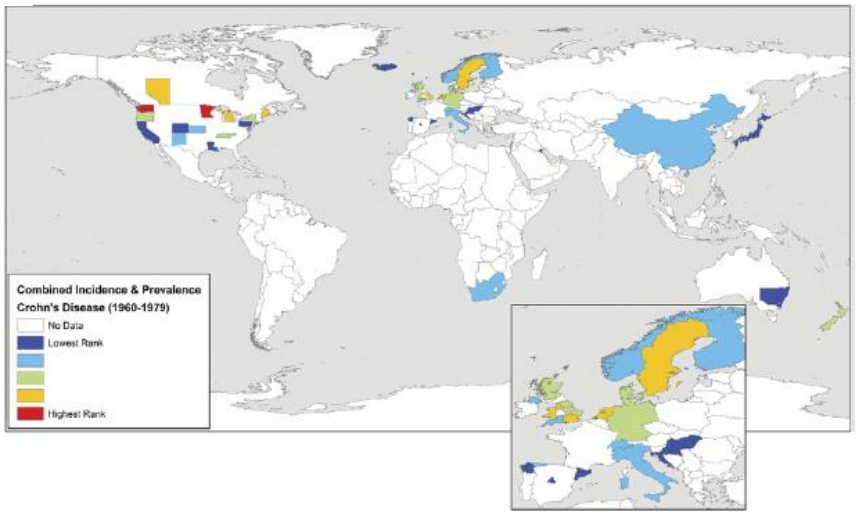


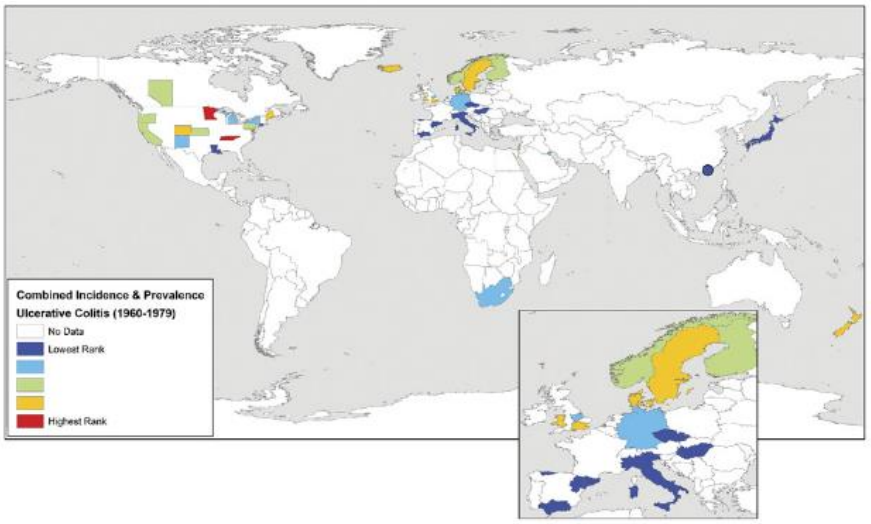
Súlyos Crohn-colitis endoscopos képe

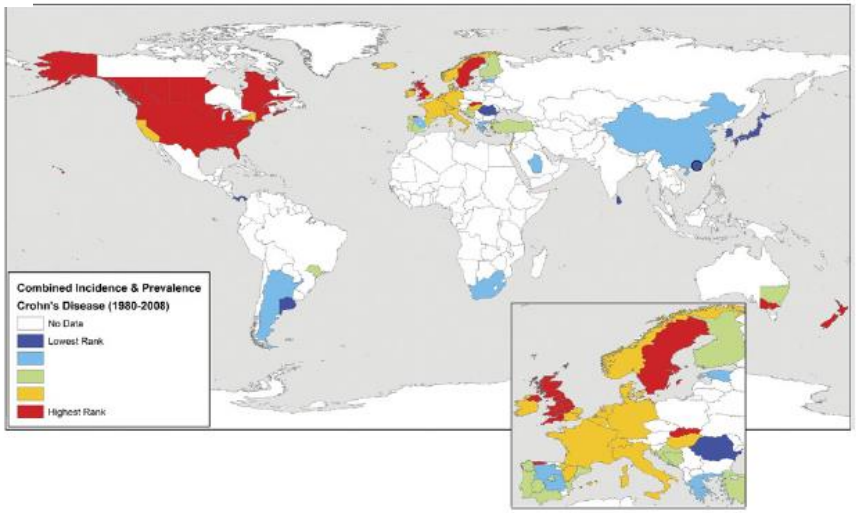


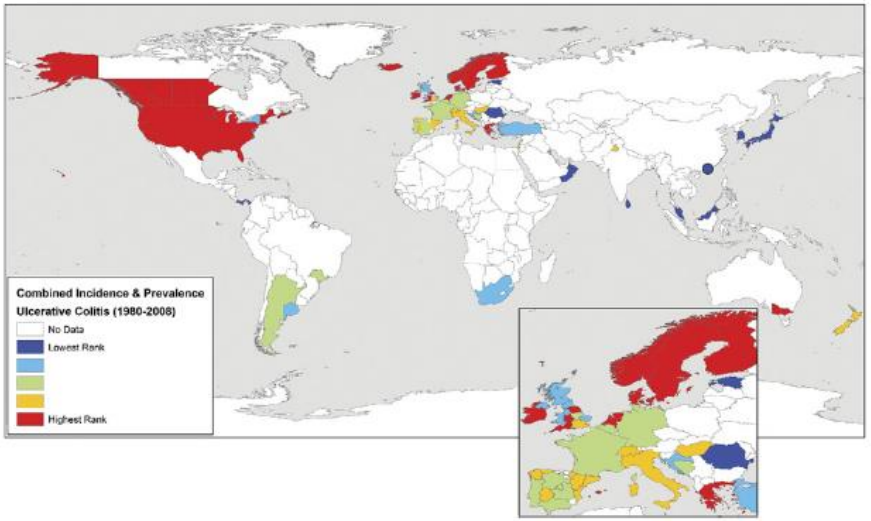
Do IBD patients progress: „natural history”

Epidemiology of IBD: evolution of epidemiology research



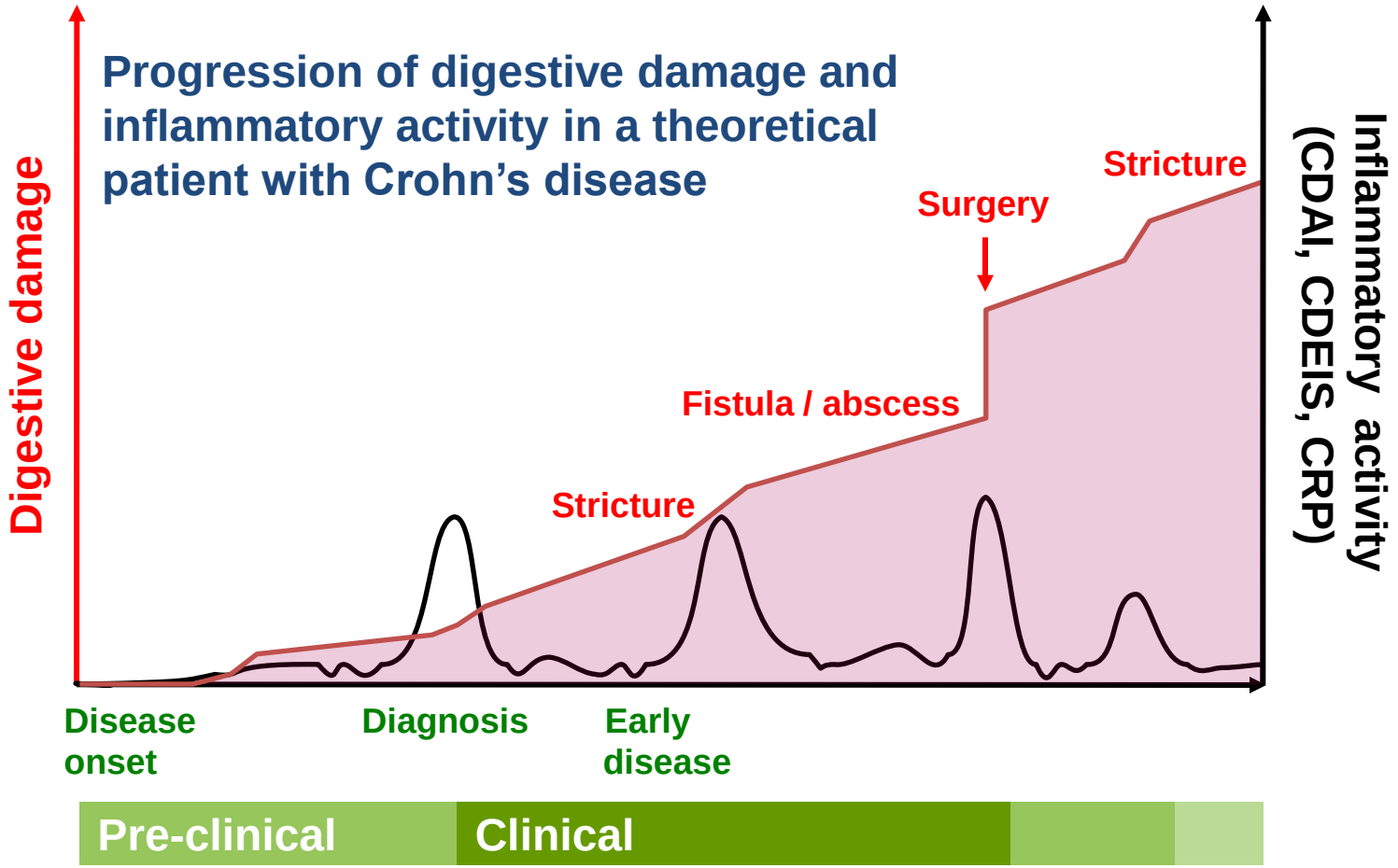






Molodecky Gastroenterology2012

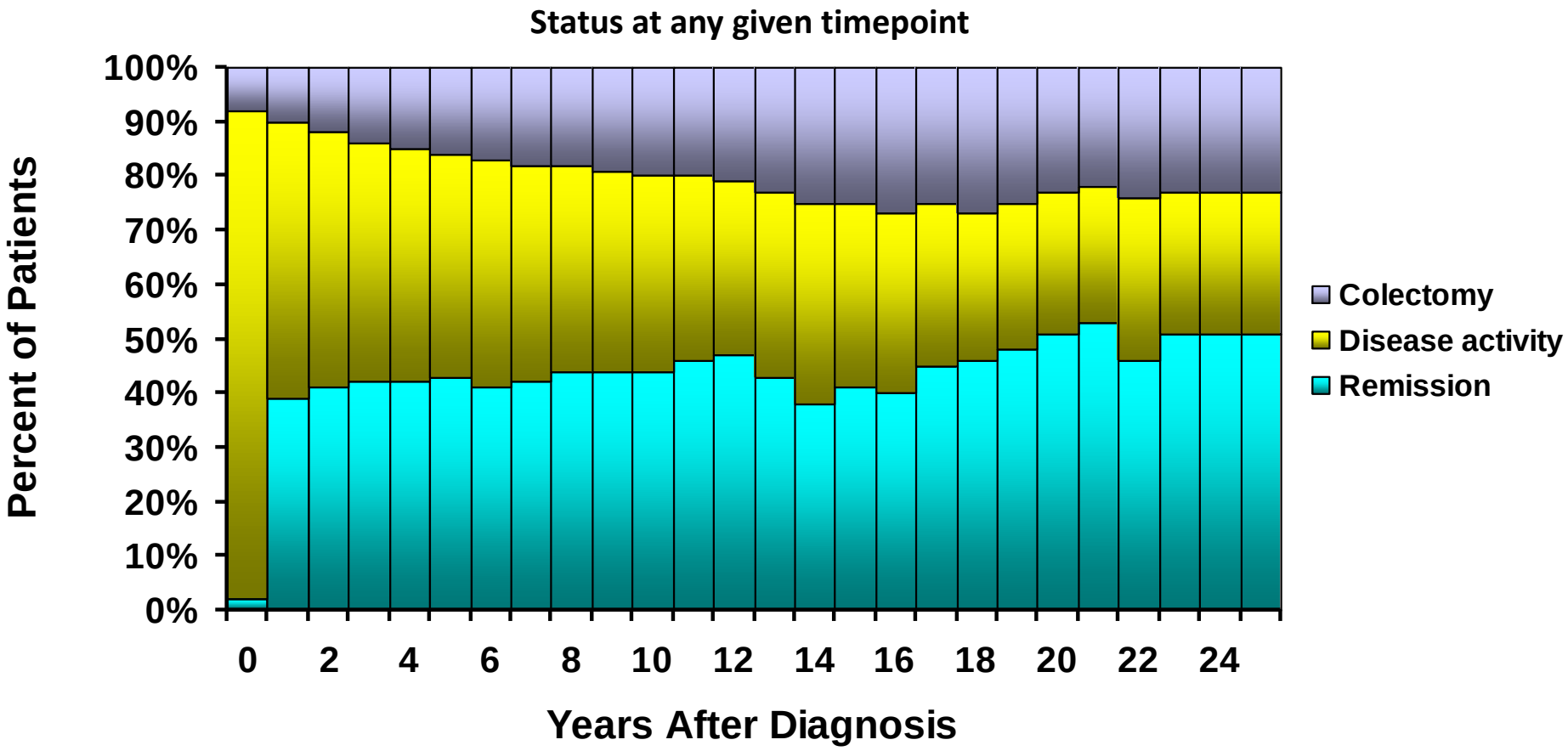
Inflammation is ongoing and resulting tissue damage is cumulative



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

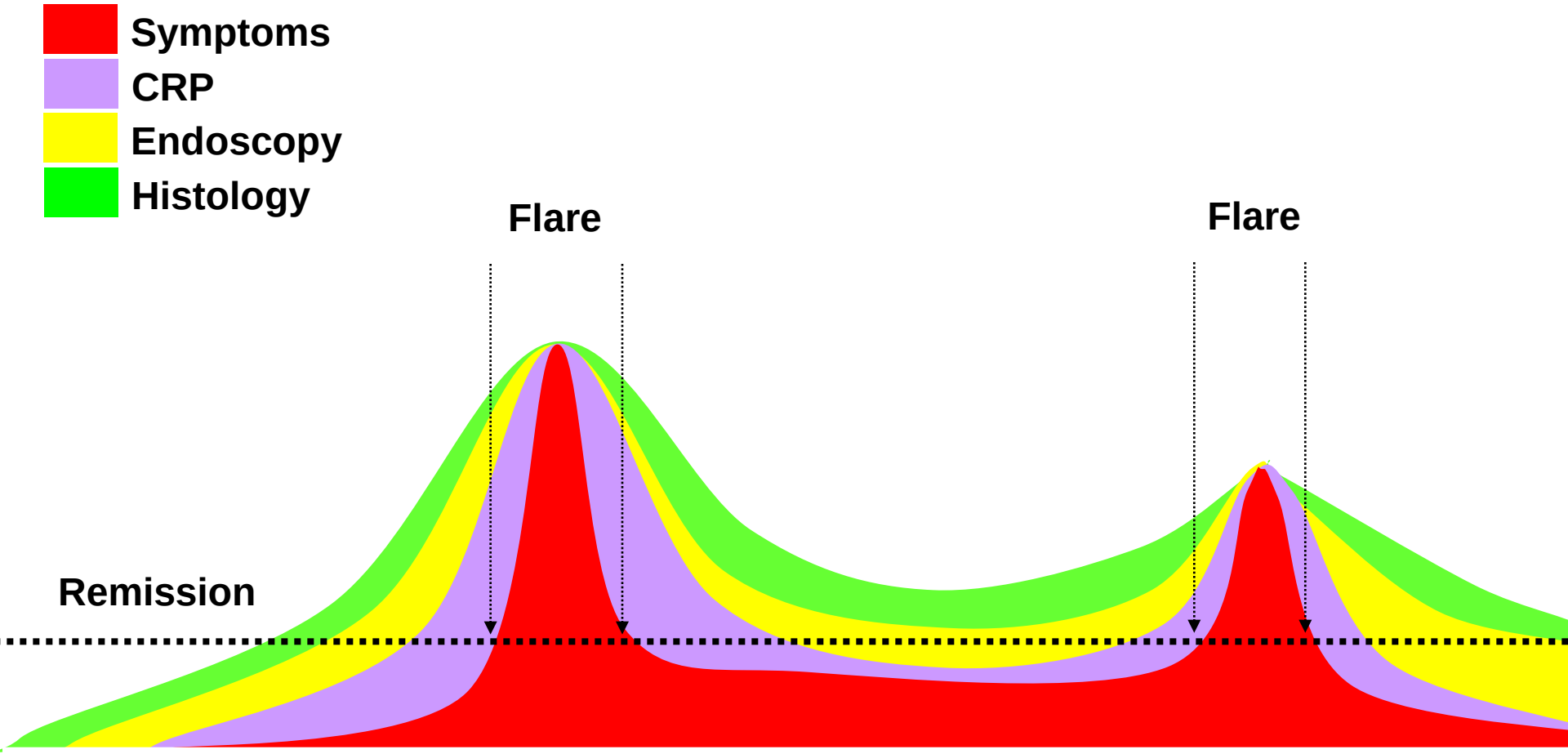
Natural History of Ulcerative Colitis*



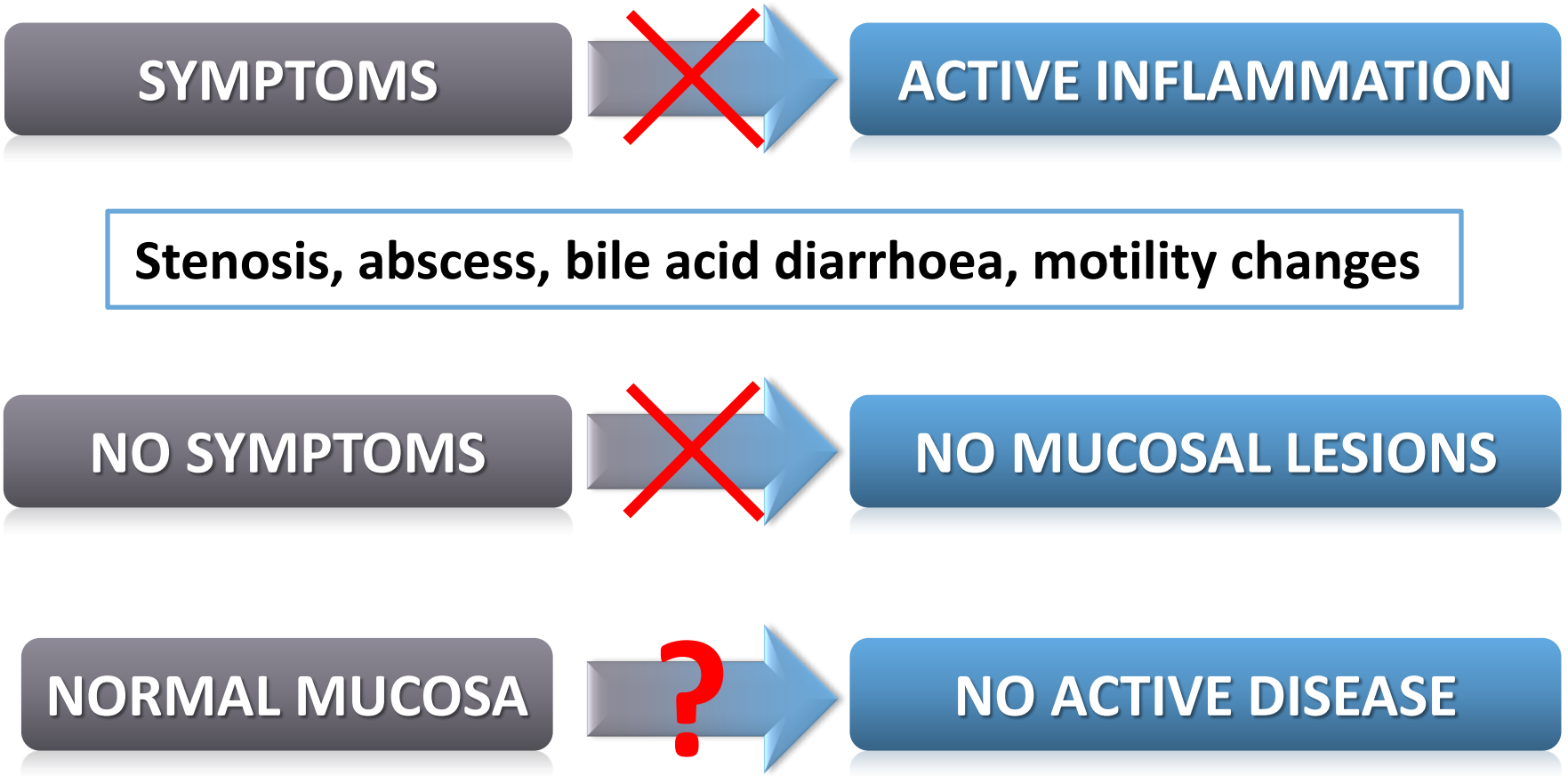
Langholz E et al. Gastroenterology. 1994;107:3.

Patient profiles: who is at risk for progression/complications?

IBD severity assessment



Lessons learned in clinical practice

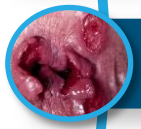


PREDICTORS: Possible factors associated with severe course of Crohn's disease have been proposed

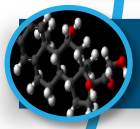
Young-adult age (Beaugerie L, *et al. Gastroenterology* 2006;130:650–6; Franchimont DP, *et al. Eur J Gastroenterol Hepatol* 1998;10: 821–5)

Smoking (Franchimont DP, *et al. Eur J Gastroenterol Hepatol* 1998;10: 821–5; Lakatos P, *et al. Inflamm Bowel Dis* 2013;19:1010–7)

Extensive small bowel disease (Munkholm P, *et al. Gastroenterology* 1993;105:1716–23)

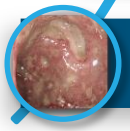


Perianal disease (Beaugerie L, *et al. Gastroenterology* 2006;130:650–6; Loly C, *et al. Scand J Gastro* 2008;43:948–54)



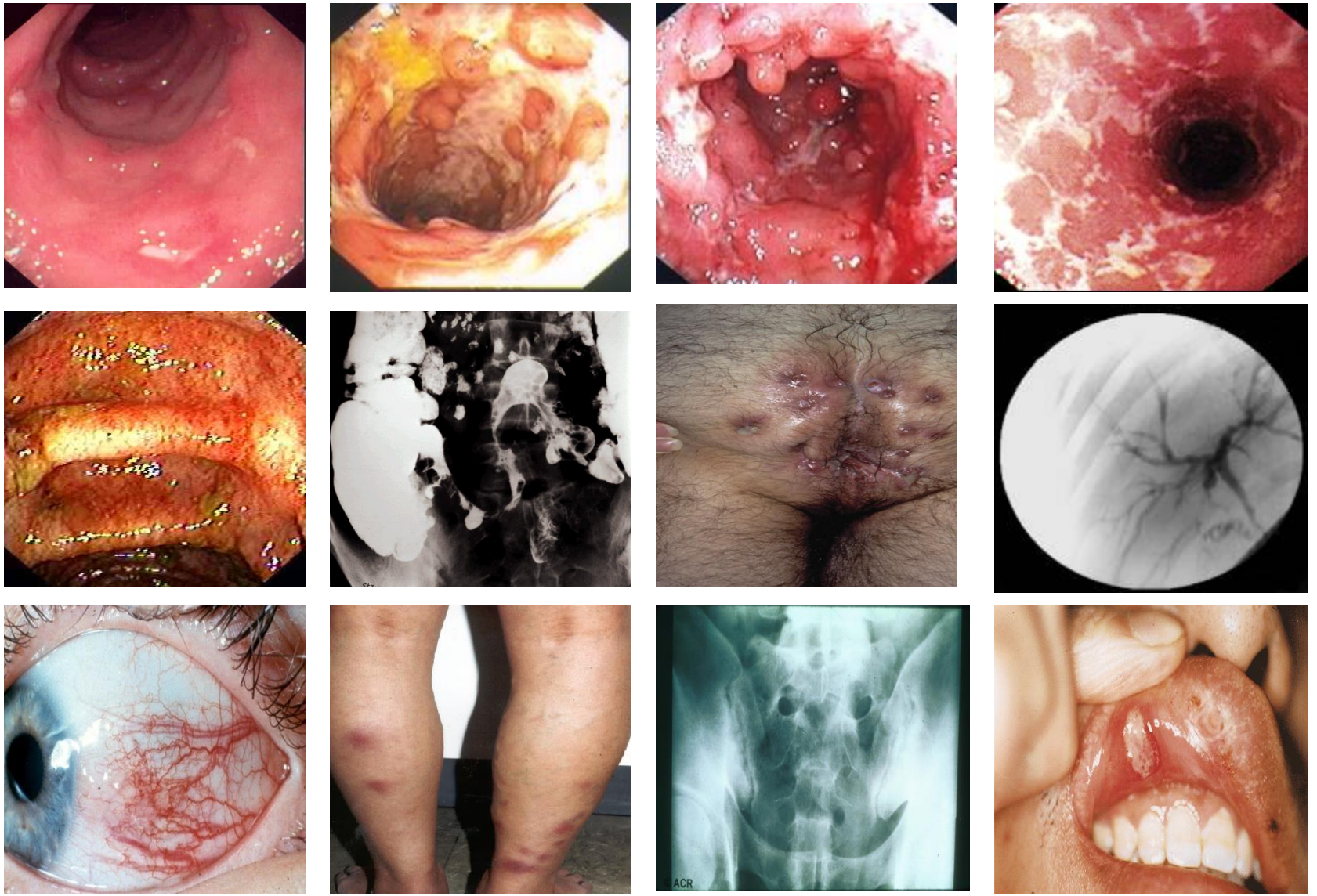
Steroids at diagnosis (Beaugerie L, *et al. Gastroenterology* 2006;130:650–6; Loly C, *et al. Scand J Gastr* 2008;43:948–54

Weight loss (Loly C, *et al. Scand J Gastro* 2008;43:948–54)



Deep ulcerations at endoscopy (Allez M, *et al. Am J Gastroenterol* 2002;97:947–53)

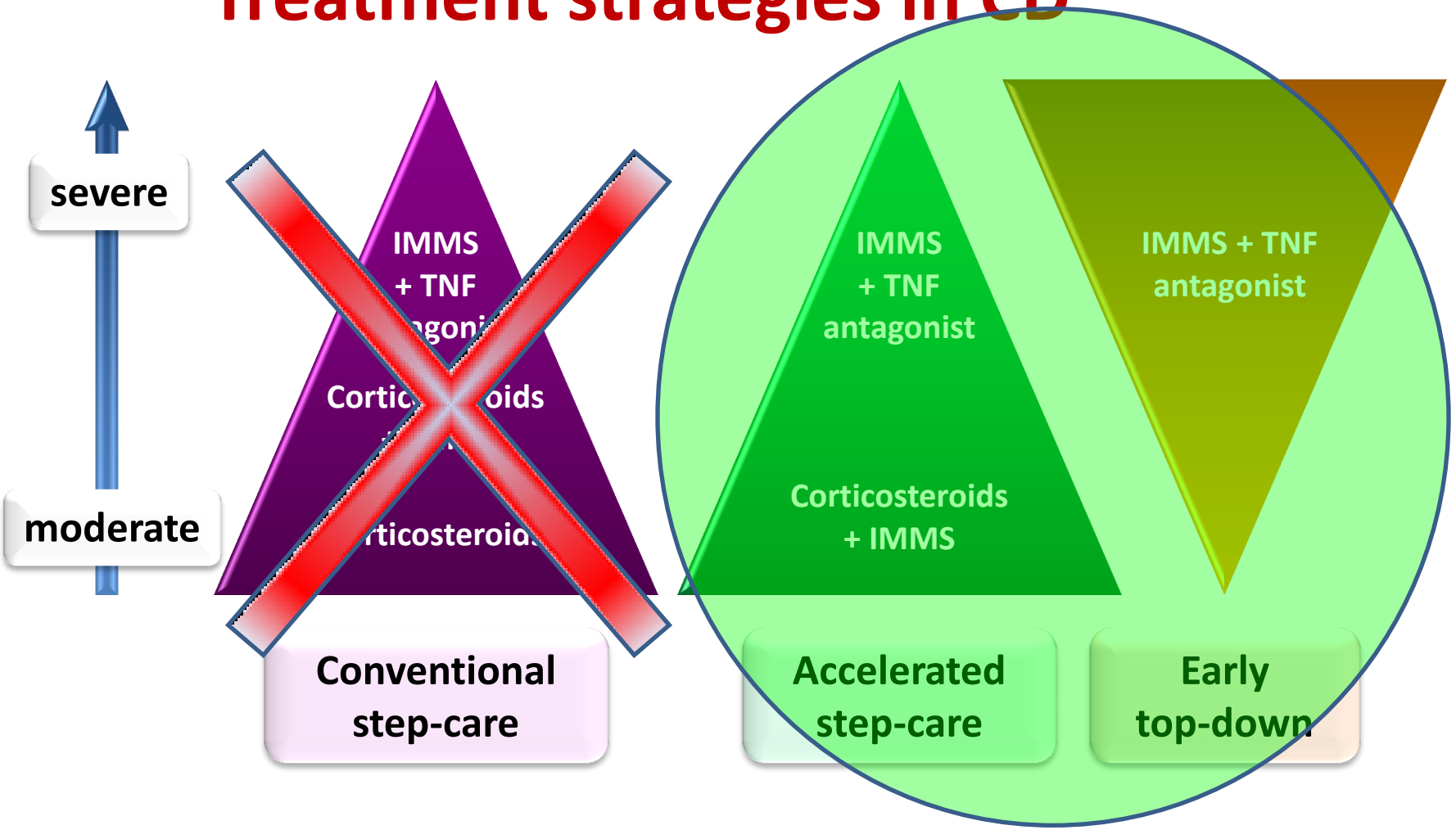
IBD… a complex phenotype: GI ± EIMs



GI, gastrointestinal; EIMs, extraintestinal manifestations

Set treatment goals!!

Treatment strategies in CD



- **Tailured therapy!**
- Smoking cessation
- Appropriate timing of elective surgery

Ordas I Gut 2011

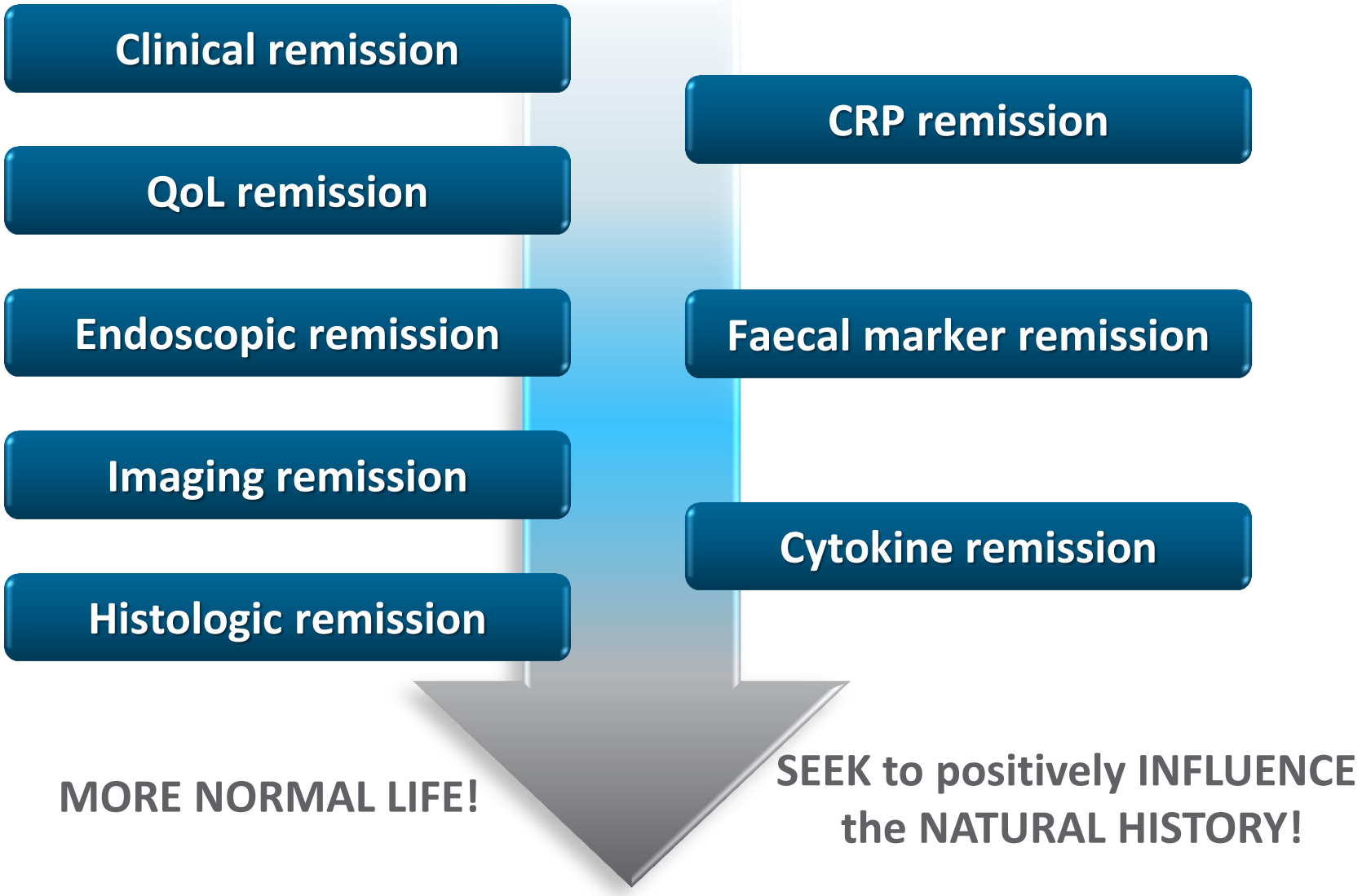
Where do we want to be? Optimal use of therapy for IBD

- The right time
  - not too early, not too late
  - earlier is better but understanding of prognosis is necessary
- The right dose
  - not too little
  - not too much (?)
- The right interval
  - no breakthrough between doses
- The right duration
  - not too short
  - not too long (?)
- The right efficacy: safety
  - disease control, no AEs
- The right cost!

How can we optimize treatment strategy in CD to DECREASE or STOP disease progression?

- **Appropriate timing and re-assessment!**
- **Do not waste time if the therapy is unsuccessful**
  - **Avoid multiple courses or prolonged use of steroids**
  - **Proceed if „conventional IS" is ineffective after 3-6 months**
  - **BUT re-evaluate patients by using objective measures of inlfammation! & do NOT aggravate therapy if there is a complication that needs a different therapy!**

Remission: but what is the definition?



What is the consensus target?

Crohn's Disease	Ulcerative Colitis
The consensus target is a combination of:	
Clinical / PRO remission defined as resolution of abdominal pain & diarrhoea / altered bowel habit which should be assessed at a minimum of 3 months during the active disease **and** **Endoscopic remission defined as resolution of ulceration at ileocolonoscopy** (or resolution of findings of inflammation on cross-sectional imaging in patients who cannot be adequately assessed with ileocolonoscopy) **which should be assessed at 6–9 month intervals during the active phase**	**Clinical / PRO remission defined as resolution of rectal bleeding & diarrhoea / altered bowel habit which should be assessed at a minimum of 3 months during the active disease** **and** **Endoscopic remission defined as resolution of friability and ulceration at flexible sigmoidoscopy or colonoscopy† which should be assessed at 3–6 month intervals during the active phase**
Adjunctive measures of disease activity that may be useful in the management of selected patients but are not a target include:	
• **CRP** • **Faecal calprotectin**	• **CRP** • **Faecal calprotectin** • **Histology**
Measures of disease activity that are not a target:	
• **Histology** • **Cross-sectional imaging§**	• **Cross-sectional imaging**

STRIDE
Selecting targets of remission in inflammatory bowel disease

* STRIDE initiated and under the auspices of the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD).
† While Mayo subscore of 0 may be defined as the target, there is currently insufficient evidence to recommend it in all patients; only Mayo subscore of 0–1 can be systematically recommended in practice.
§ When endoscopy cannot adequately evaluate inflammation, resolution of inflammation as assessed by cross-sectional imaging is a target

PRO: patient-reported outcomes

Peyrin-Biroulet L, *et al*. *Am J Gastroenterol* 2015;110:1324–38

AND: goals may be different in different stages of the disease

Disease stage	Biological remission (Inflammation control)	Clinical remission (Symptom control)	Outcomes
Early disease	**Mucosal healing; colonoscopy: no ulcers** (with the exception of a certain number of aphthous ulcers <5 mm in diameter) **Improvements in serum and faecal biomarkers of active inflammation: CRP: <5 mg/L; faecal calprotectin: <250 µg/g**	**Clinical practice: complete absence of symptoms; 1–2 formed stools per day without abdominal pain/cramping** **Clinical trials: CDAI <150 points**	**Complete absence of symptoms; no disease progression; no complications; no disability; normal quality of life**
Late disease	**Mucosal healing; colonoscopy: no ulcers** (with the exception of a certain number of aphthous ulcers <5 mm in diameter) **Improvements in serum and faecal biomarkers of active inflammation: CRP: <5 mg/L; faecal calprotectin: <250 µg/g**	**Clinical practice: inflammatory symptom improvement** (may experience residual symptoms of pain or diarrhoea because of previous surgical treatment or intestinal damage) **Clinical trials: CDAI 150–220 points**	**Stabilisation of noninflammatory symptoms; no progression of structural damage; no progression of disability; improved quality of life**

Panaccione R, *et al. Inflamm Bowel Dis* 2013;19:1645-53

Setting treatment goals – our practice

In the last several years we have embarked on tight monitoring and objective outcome assessment in our unit:

Continuous access:

- **We provide 24/7 access** (email and daytime phone reply within 1 day)

Emergency appointments:

- **For patients with symptomatic relapse within the next 1–2 days**
- **Objective evaluation: laboratory-US same day, endoscopy-MRI maximum 2–4 days**

Close monitoring in patients in remission

- **Every 3–6 months follow-up, clinical/laboratory**
- **Every 12 month imaging/endoscopy: US/MRI/endoscopy**

Regular interdisciplinary meetings

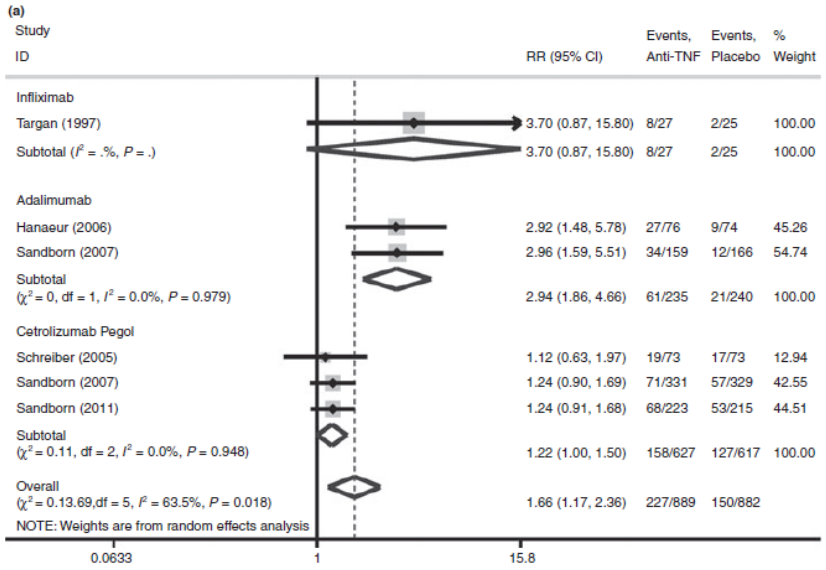
- **With radiologists, surgeons and pathologists**
  (patients can attend if they will be discussed)

Close cooperation with other biological centers

- **2nd opinion if needed**

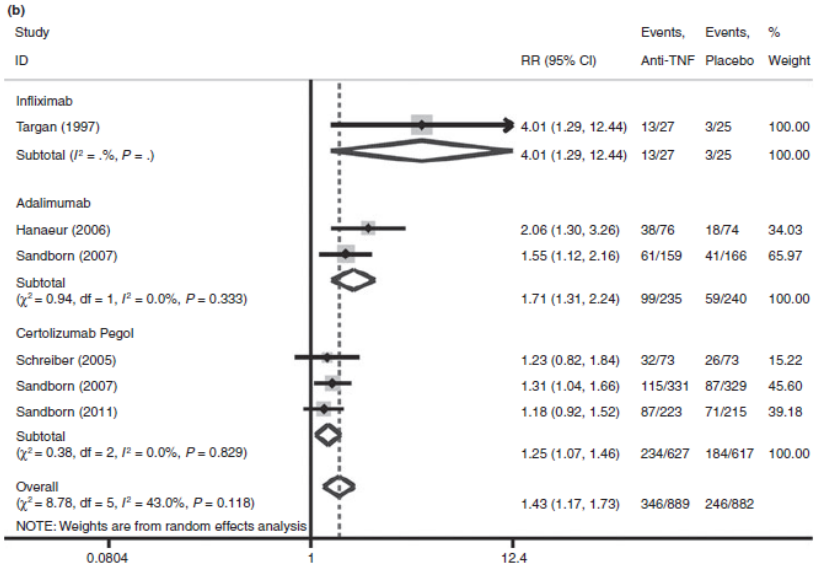
The current era: Efficacy of Anti TNF drugs

Anti-TNFs, Metaanalysis of efficacy: induction



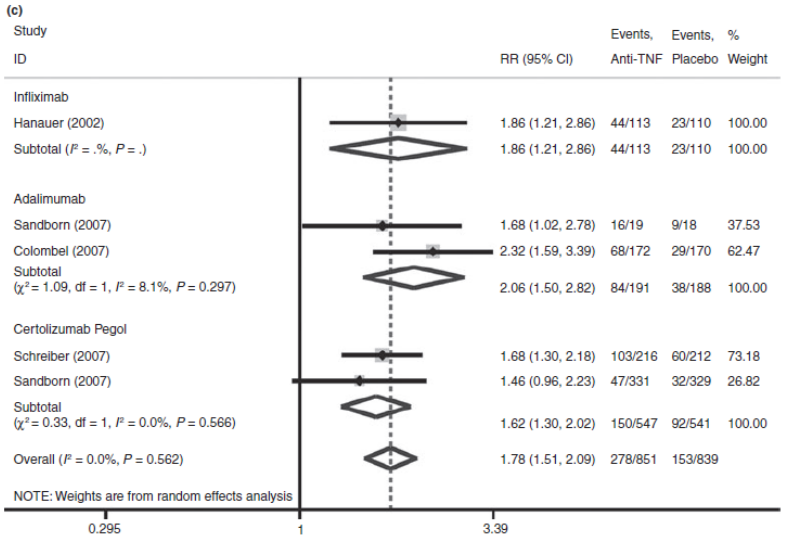
Remission

Response



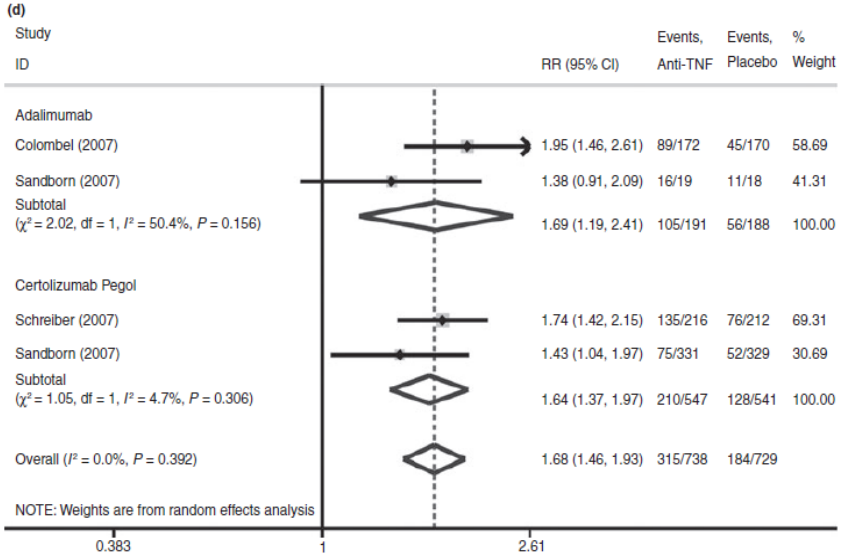
Stidham RW, et al. *APT* 2014;39:1349-62

Anti-TNFs, Metaanalysis of efficacy: maintenance



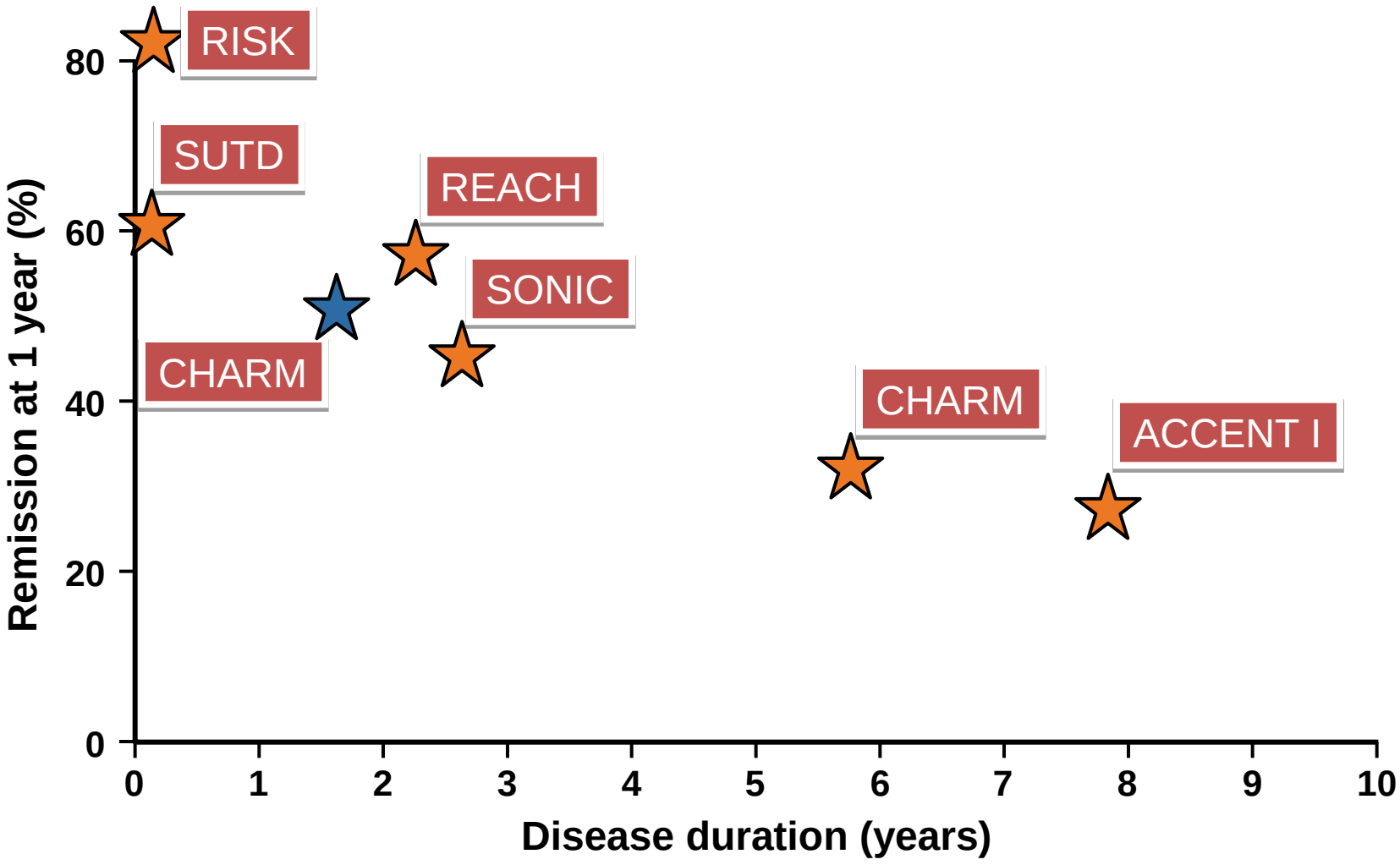
Remission

Response



Stidham RW, et al. *APT* 2014;39:1349-62

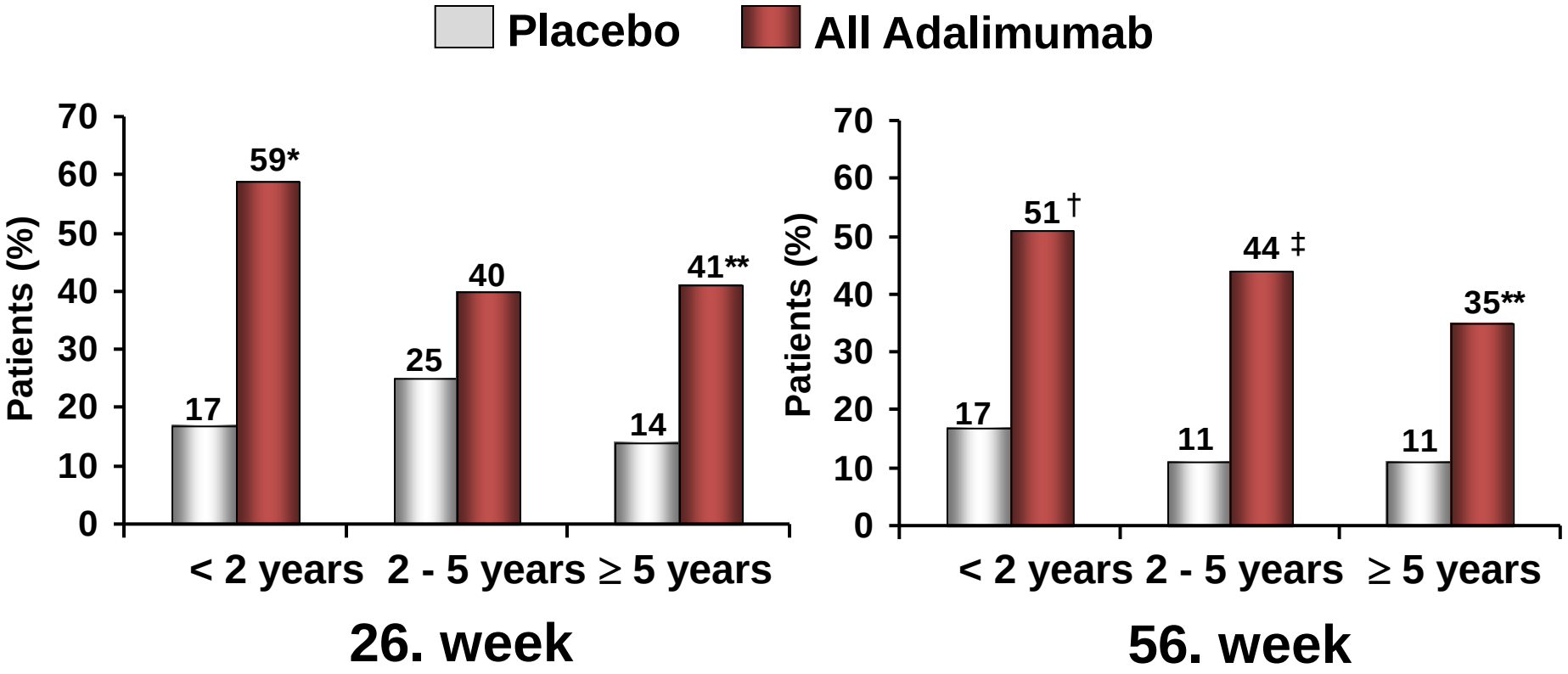
Anti-TNF therapy is most effective in early Crohn's disease



CHARM subanalysis

D'Haens G, *et al. Lancet* 2008;371:660–67; Hyams *et al. Gastroenterology* 2007;132(3):863–73; Walters TD *Gastroenterology* 2013 Oct; Sandborn WJ, *N Engl J Med* 2010 362;15; Hanauer S, *et al. Lancet* 2002;359:1541–49; Schreiber S, *et al. Gastroenterol* 2007;132:A-147; Colombel JF, *et al. Gastroenterology* 2007;132:52–65.

Efficacy of aTNFs and disease duration in CD



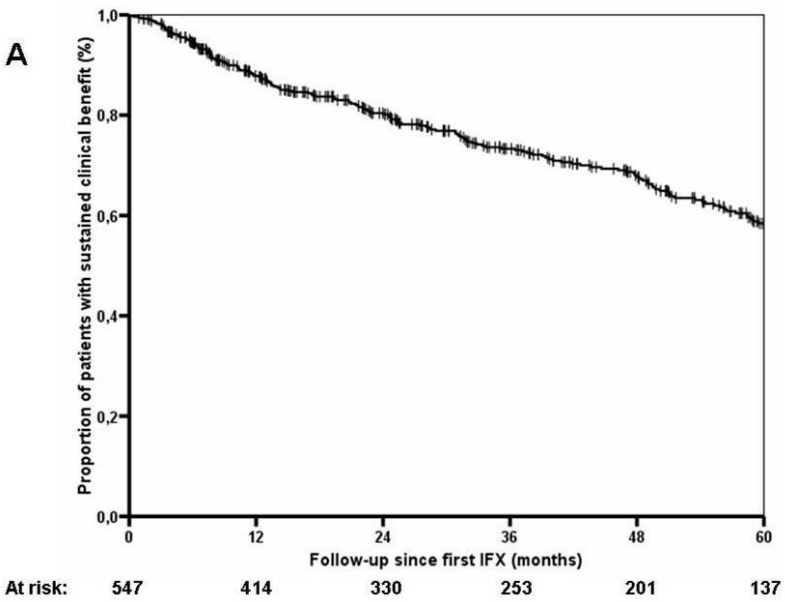
PBO n = 111, Adalimumab n = 233

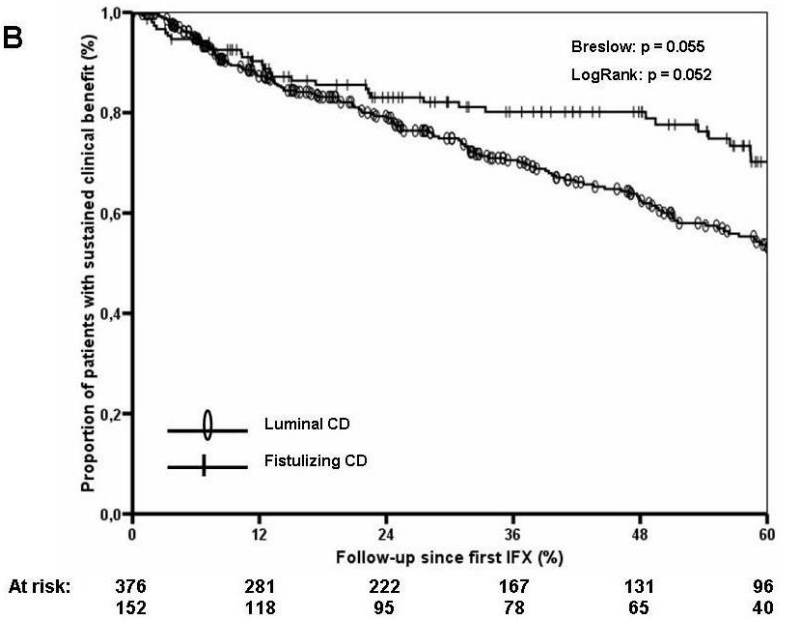
*p=0.002, **p<0.001, †p=0.014, ‡p=0.001 vs placebo

Schreiber S, et al. *Gastroenterology* 2007;132(4 Suppl 2):A-147.

How long can we sustain remission?

Real life experience from Leuven





Of the 547 initial responders, 50% (n=273) did not need any intervention, whereas 26% (n=143) needed 1 intervention, 10% (n=56) needed 2 and 14% (n=75) needed 3 or more interventions.

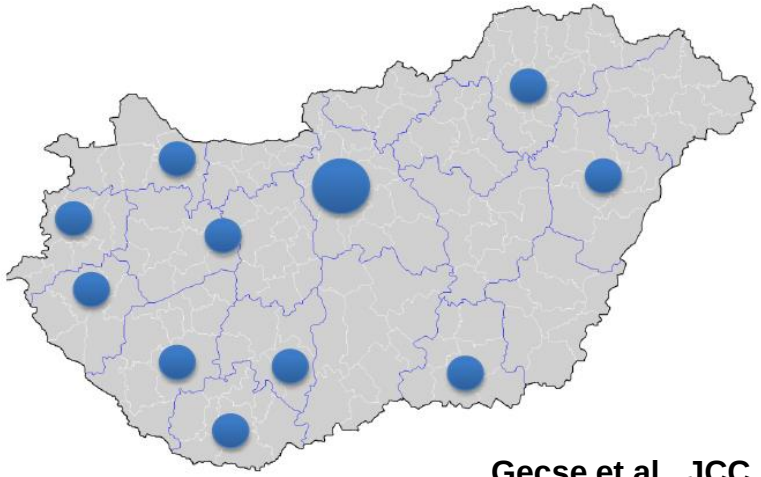
Schitzler F Gut 2009

Background-Hungary

National IBD centers for anti-TNF treatment

- 16 IBD centres are entitled to administer anti-TNF for IBD in Hungary
  - 4 university centers
  - 12 county hospitals

- **Harmonized monitoring strategy is mandatory as requested by the National Health Fund**



Hungarian IBD Study Group

Gecse et al., JCC in press (2015)

Results

Baseline charecteristics

	CD (N = 184)	UC (N= 107)
Male/Female	**82 / 102**	**62/45**
Age at Onset, Median (IQR)	**23 (19-34) yrs**	**28 (22-39) yrs**
Duration, Median (IQR)	**5 (2-11) yrs**	**4 (2-11) yrs**
Baseline activity, Median (IQR)	**CDAI:** 321 (301-352) n=145 **PDAI:** 10 (IQR: 6-11) n=56	**MAYO:** 9 (IQR: 7-11) n=107 **pMAYO:** 7 (IQR: 6-9) n=107
Location (L1/L2/L3/L4/all L4)	**16.8%/32.4%/ 49.1%/1.7%/7.9%**	-
Extent of Colitis (E1/E2/E3)	-	**8.4% / 32.7% / 51.1%**
Behavior (B1/B2/B3)	**58.7% / 21.2% / 20.1%**	-
Perianal	**35.0%**	-
Previous Surgery	**22.5%**	-

Results

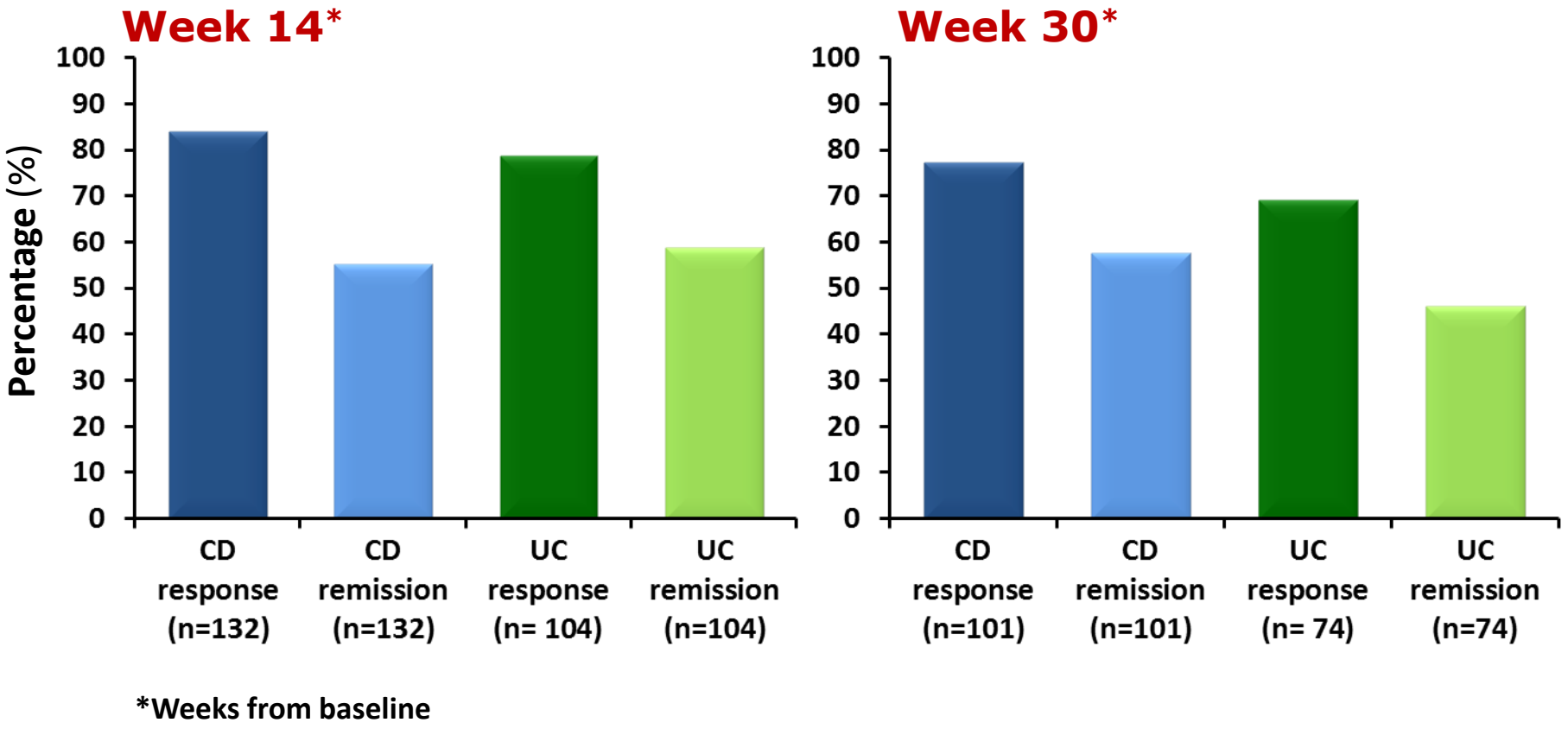
Prior and Concomitant Use of Anti-inflammatory and Immunomodulatory Agents

	CD (N = 184)	UC (N = 107)
Prior Treatments		
5ASA	84.6%	92.3%
Steroids	81.0%	90.9%
AZA	87.4%	74.5%
CSA	-	7.3%
Anti-TNF	24.5%	14.0%
Concomitant Immunomodulators		
Steroids	44.2%	66.4%
AZA	60.3%	51.4%

Lakatos, ECCO 2016

Results

Clinical remission and response



*Weeks from baseline

Definitions:

Response CD: CDAI Δ>70points or fistula drainage Δ>50%, pMAYO Δ>3

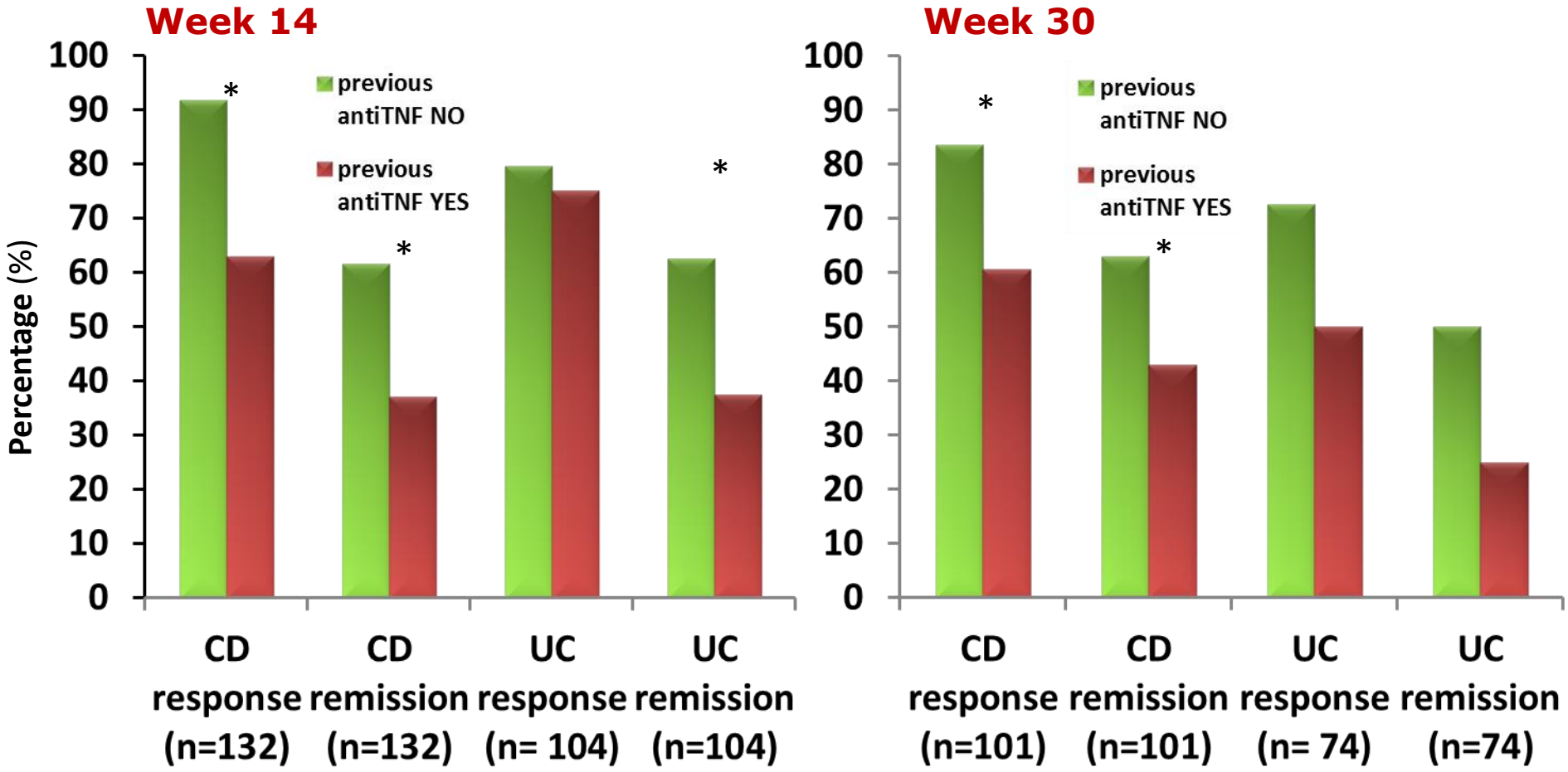
Remission: CD: CDAI <150 or no fistula drainage reported at the visit, UC: pMAYO <3

Hungarian IBD Study Group

Lakatos, ECCO 2016

Results

Clinical remission and response



*p<0.05

Definitions:

Response CD: CDAI Δ>70points or fistula drainage Δ>50%, pMAYO Δ>3

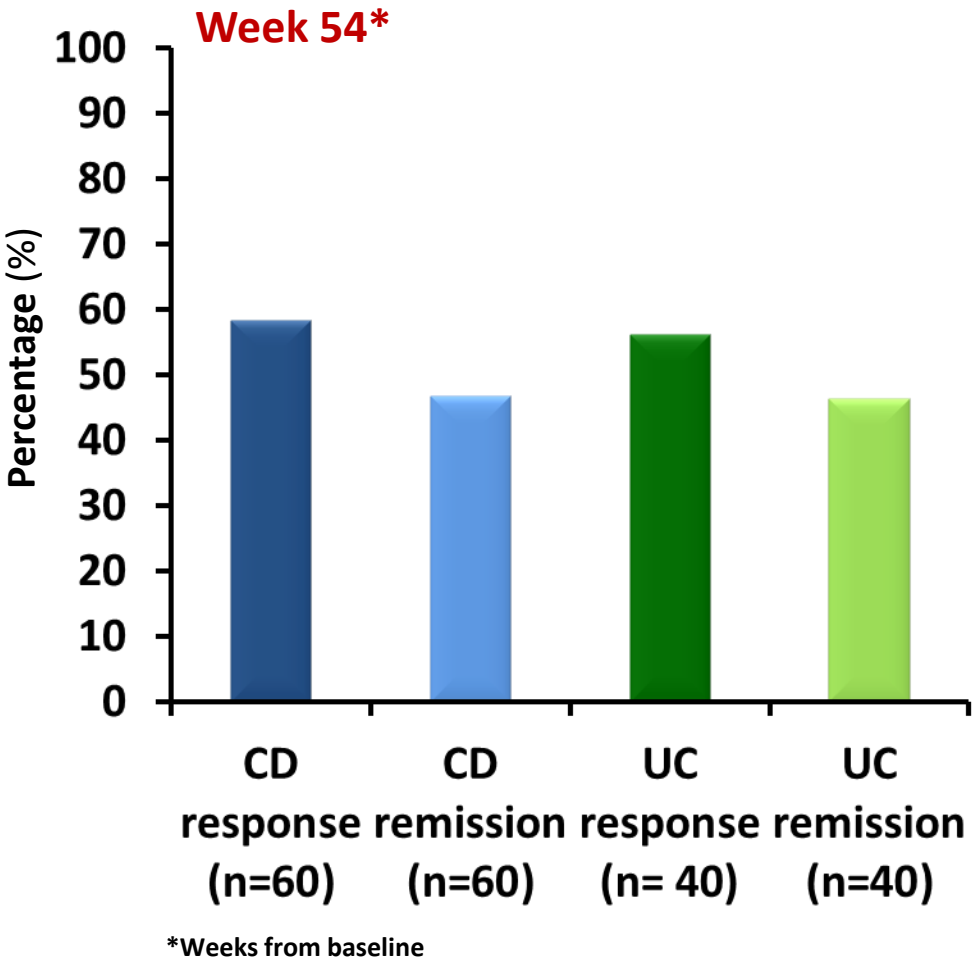
Remission: CD: CDAI <150 or no fistula drainage reported at the visit, UC: pMAYO <3

Hungarian IBD Study Group

Lakatos, ECCO 2016

Results

Clinical remission and response



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Hungarian IBD Study Group

Lakatos, ECCO 2016

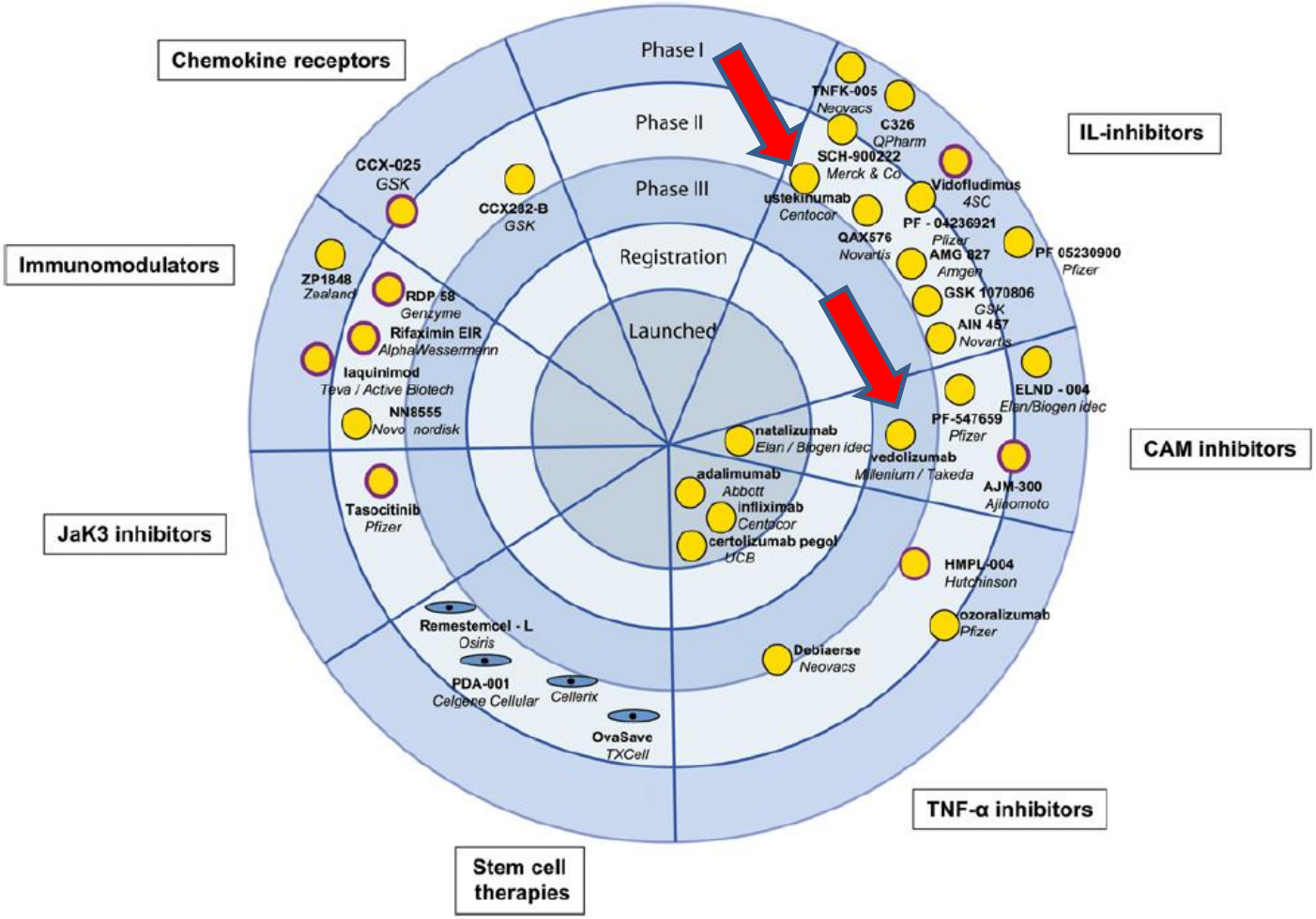
Results

Adverse events by w30 (through Oct 2015)

SAE/AE	Patient (n/%)
Death	1/0.3%
Infections	
• Sepsis/invasive fungal infection	1/0.3%
• Pneumonia	1/0.3%
• Upper respiratory tract infection	8/2.5%
• Tuberculosis	0
• Gastroenteritis (salmonellosis)	6/1.9%
• C.difficile	2/0.6%
• Urinary tract infection	1/0.3%
• Viral infections (influenza, herpes, varicella)	3/0.9%
Allergy	
• Infusion reaction	21/7.2%
• Anaphlylaxis	1/0.3%
Others	
• Delayed hypersensitivity	7/2.2%
• Arthralgia	10/3.1%
• Malignancy	0

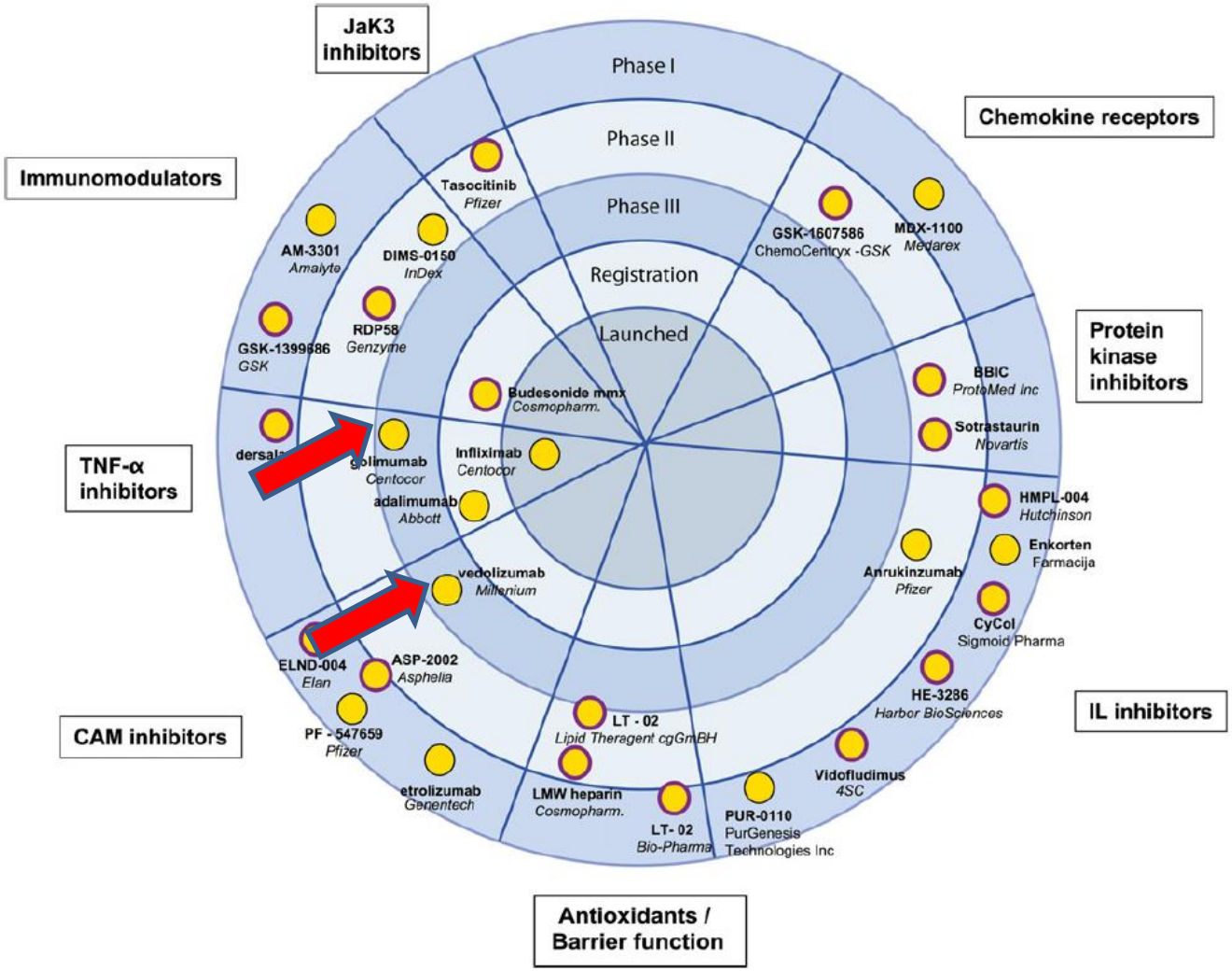
Lakatos, ECCO 2016

New agents and mechanisms in CD



Danese S GUT 2012;62:618

New agents and mechanisms in UC



Danese S GUT 2012;62:618

How to monitor/engage our patients?

The impact of patient involvement

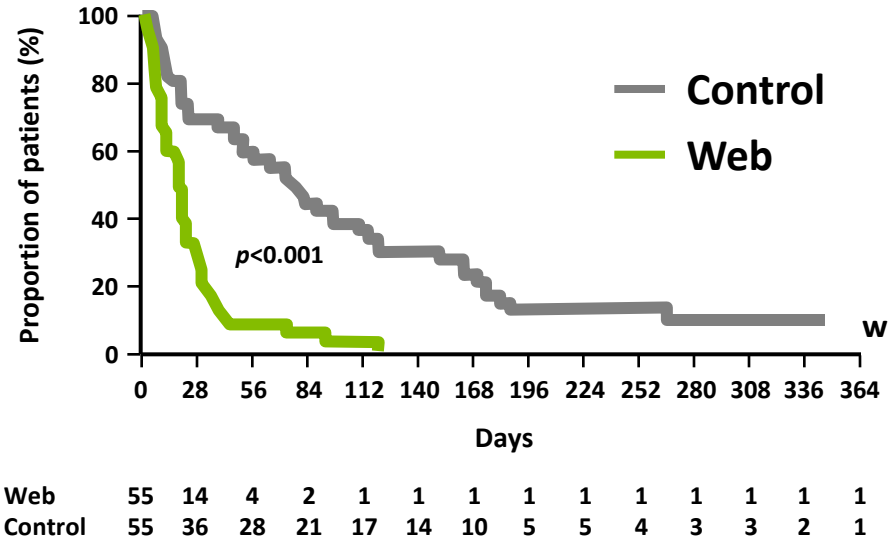
Acceptance → **Adherence** → **Improved outcomes**

333 UC on 5-ASA

Education & self-management via http://www.constantcare.dk

Adherence to treatment increased by 30–40%

Controls



Time (days) from the first relapse to remission in web and control patients during 1 yr of follow-up

We have 24/7 email access….

Randomized controlled trial in 333 mild/moderate UC patients in Denmark and Ireland.

Elkjaer M *et al. Gut* 2010;59:1652–61; WHO2003. Adherence to long-term therapies. http://www.who.int/chp/knowledge/publications/adherence_report/en (Last accessed Sept 2015)

What are the clinical activity indices – validated and used in CD?

- IOIBD Position papers –"guidance"

GASTROENTEROLOGY 2002;122:512–530

SPECIAL REPORTS AND REVIEWS

A Review of Activity Indices and Efficacy Endpoints for Clinical Trials of Medical Therapy in Adults With Crohn's Disease

WILLIAM J. SANDBORN,*,† BRIAN G. FEAGAN,§ STEPHEN B. HANAUER,*,† HERBERT LOCHS,* ROBERT LÖFBERG,* ROBERT MODIGLIANI,*,‖ DANIEL H. PRESENT,*,† PAUL RUTGEERTS,* JURGEN SCHÖLMERICH,* EDUARD F. STANGE,* and LLOYD R. SUTHERLAND*

*The Clinical Trials Task Force of the International Organization of Inflammatory Bowel Disease (IOIBD), †The Clinical Alliance of the Cr and Colitis Foundation of America, the §Clinical Network of the Crohn's and Colitis Foundation of Canada, and the ‖Groupe d'Etude Therapeutique des Affections Inflammatoires Digestives. See Appendix I for institutional affiliations for each author and for the comple membership of the IOIBD Clinical Trials Task Force

CDAI

Table 1. Crohn's Disease Activity Index

Variable no.	Variable description	Multiplier	Total
1	No. of liquid or soft stools (each day for 7 days)	×2	
2	Abdominal pain, sum of 7 daily ratings (0 = none, 1 = mild, 2 = moderate, 3 = severe)	×5	
3	General well-being, sum of 7 daily ratings (0 = generally well, 1 = slightly under par, 2 = poor, 3 = very poor, 4 = terrible)	×7	
4	Number of listed complications (arthritis or arthralgia, iritis or uveitis, erythema nodosum or pyoderma gangrenosum or aphthous stomatitis, anal fissure or fistula or abscess, other fistula, fever over 37.8°C [100°F])	×20	
5	Use of diphenoxylate or loperamide for diarrhea (0 = no, 1 = yes)	×30	
6	Abdominal mass (0 = no, 2 = questionable, 5 = definite)	×10	
7	Hematocrit (males, 47-Hct [%], females, 42-Hct [%])	×6	
8	Body weight (1-weight/standard weight) × 100 (add or subtract according to sign)	×1	
CDAI score			

Adapted with permission from Best WR, Becktel JM, Singleton JW. Rederived values of the eight coefficients of the Crohn's Disease Activity Index (CDAI). Gastroenterology 1979;77:843–846.

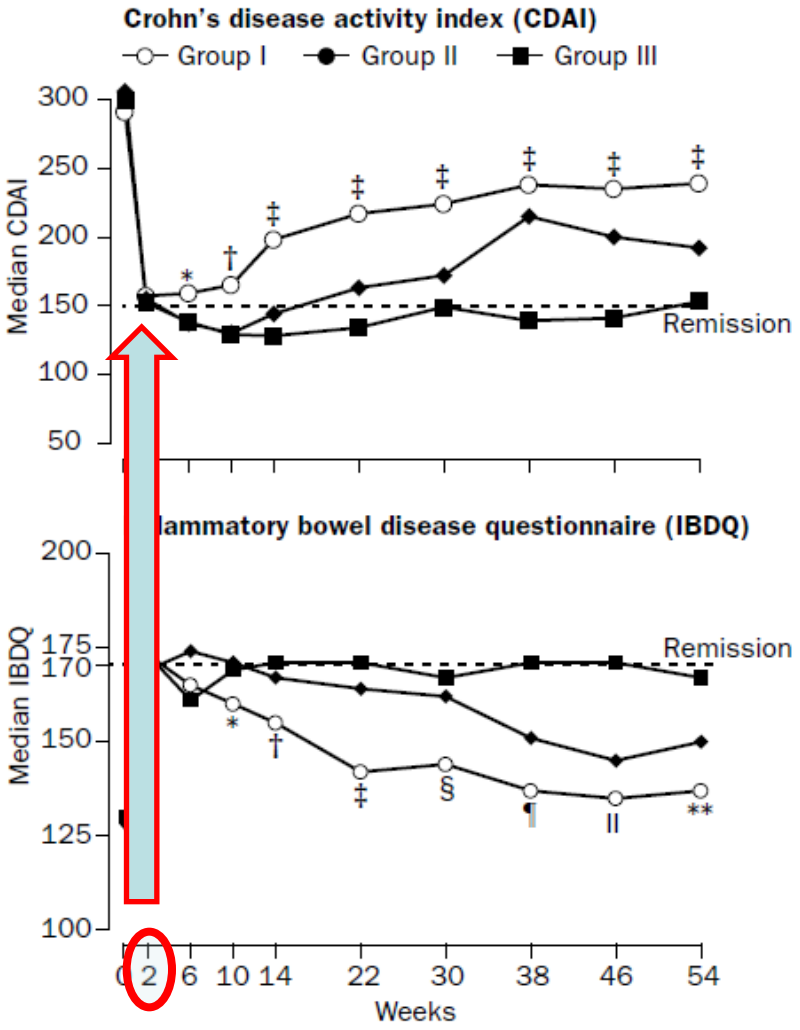
HBI

Table 2. Harvey Bradshaw Index (HBI, Simple Index)

Variable no.	Variable description	Total
1	General well being (0 = very well, 1 = slightly below par, 2 = poor, 3 = very poor, 4 = terrible)	
2	Abdominal pain (0 = none, 1 = mild, 2 = moderate, 3 = severe)	
3	Number of liquid stools daily	
4	Abdominal mass (0 = none, 1 = dubious, 2 = definite, 3 = definite and tender)	
5	Complications: arthralgia, uveitis, erythema nodosum, apthous ulcer, pyoderma gangrenosum, anal fissure, new fistula, abscess (score 1 per item)	
HBI Score		

Adapted with permission from Harvey RF, Bradshaw JM. A simple clinical index of Crohn's disease activity. Lancet 1980;1:514.

How-quickly are they changeing meaningfully??



Hanauer Lancet 2002 ACCENT I

Activity indices for UC

1.	Truelove and Witts'	*BMJ* 1955;2:1041-8
2.	Powell Tuck/St Marks	*Scand J Gastro* 1978;13:833-7
3.	Sutherland/DAI/UCDAI	*Gastroenterology* 1987;92:1894-8
4.	Mayo/Disease Activity Index	*NEJM* 1987;317:1625-9
5.	Clinical Activity Index/CAI/Rachmilewitz	*BMJ* 1989;298:82-6
6.	Lichtiger/Modified T&W Severity Index	*Lancet* 1990;336:16-9
7.	Activity Index/Seo	*Am J Gastro* 1992;87:971-6
8.	Simple Clinical Colitis Index/Walmsley	*Gut* 1998;43:29-32
9.	Ulcerative Colitis Clinical Score	*NEJM* 2005;352:2499-507

Number of different indices:

9 Clinical and biochemical activity

9 Endoscopic activity

4 Clinical and endoscopic

2 Quality of life

9 Histological activity

D'Haens & Sandborn et al Gastroenterology 2006

Assess inflammation objectively!

Endoscopy / imaging

- Colonoscopy / ileoscopy / Enteroscopy / CE
- CT enterography / MR enterography
- Doppler / contrast enhanced ultrasonography

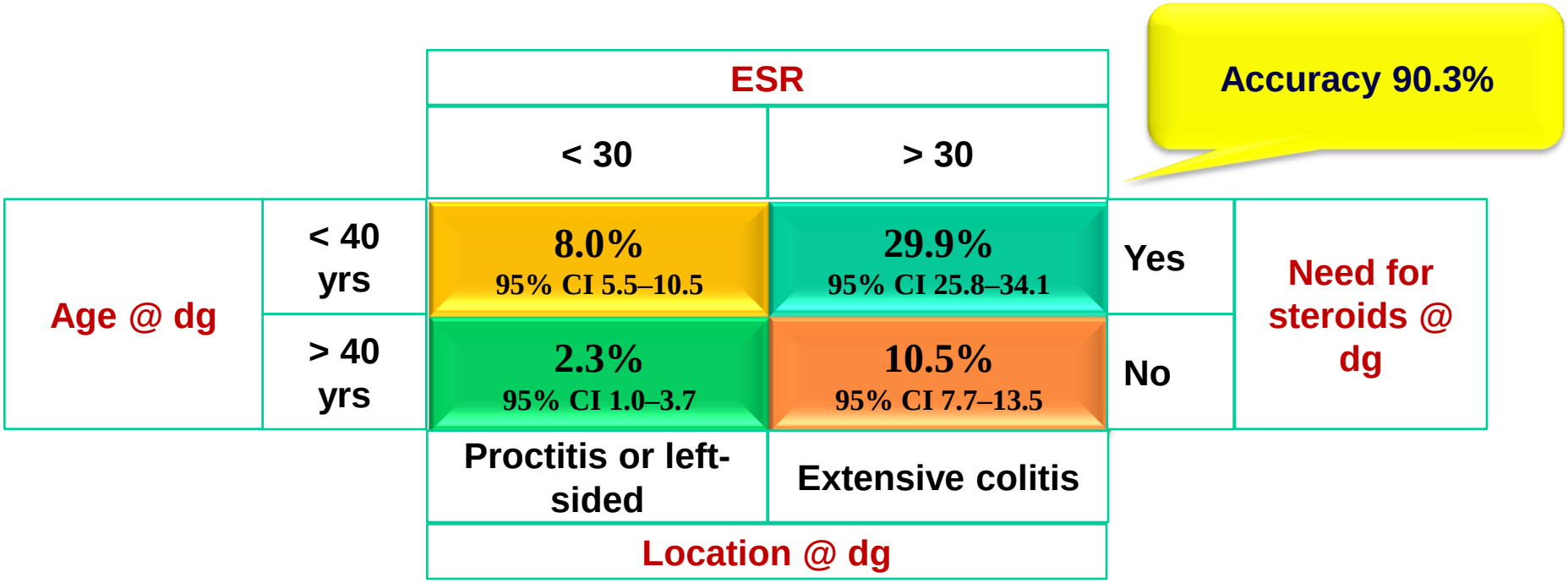
Biomarkers

- CRP
- Faecal calprotectin, lactoferrin, S100A12

CE: capsule endoscopy

Mulivariate model to predict Risk of Colectomy

IBSEN



ESR = Erythrocyte sedimentation rate; HR = hazard ratio

Solberg IC, et al. *Scan J Gastroenterol* 2009;44(4):431–440

What are the endoscopic activity indices – validated and used in CD?

- IOIBD Position papers –"guidance"

GASTROENTEROLOGY 2002;122:512–530

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CDEIS-Rutgeerts score

Table 5. Crohn's Disease Endoscopic Index of Severity

Variable no.	Variable description	Weighing factor	Total
1	Number of rectocolonic segments (rectum, sigmoid and left colon, transverse colon, right colon, ileum) that deep ulcerations are seen in divided by the number of segments examined	12	
2	Number of rectocolonic segments (rectum, sigmoid and left colon, transverse colon, right colon, ileum) that superficial ulcerations are seen in divided by the number of segments examined	6	
3	Segmental surfaces involved by disease. The degree of disease involvement in each segment is determined by examining each segment for the following 9 lesions (pseudopolyps, healed ulcerations, frank erythema, frank mucosal swelling, aphthoid ulcers, superficial ulcers, deep ulcers, nonulcerated stenosis, ulcerated stenosis) and estimating the number of cm of involvement (1 or more lesions present) in a representative 10 cm portion from each segment. The average segmental surface involved by disease is calculated by dividing the sum of each of the individual segmental surfaces involved by disease by the number of segments examined	1	
4	Segmental surfaces involved by ulcerations. The degree of ulceration in each segment is determined by examining each segment for ulceration (aphthoid ulcers, superficial ulcers, deep ulcers, ulcerated stenosis) and estimating the number of cm of intestine involved by ulceration in a representative 10 cm portion from each segment. The average segmental surface involved by ulceration is calculated by dividing the sum of each of the individual segmental surfaces involved by ulceration by the number of segments examined	1	
5	Presence of a nonulcerated stenosis in any of the segments examined	3	
6	Presence of an ulcerated stenosis in any of the segments examined	3	
Total CDEIS			

Adapted with permission from Groupe D'Etudes Therapeutiques Des Affections Inflammatories Du Tube Digestif (GTEAID) presented by Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Gut 1989;30:983–989.

PDAI

Table 3. Perianal Crohn's Disease Activity Index

Categories affected by fistulas	Score
Discharge	
No discharge	0
Minimal mucous discharge	1
Moderate mucous or purulent discharge	2
Substantial discharge	3
Gross fecal soiling	4
Pain/restriction of activities	
No activity restriction	0
Mild discomfort, no restriction	1
Moderate discomfort, some limitation of activities	2
Marked discomfort, marked limitation	3
Severe pain, severe limitation	4
Restriction of sexual activity	
No restriction sexual activity	0
Slight restriction sexual activity	1
Moderate limitation sexual activity	2
Marked limitation sexual activity	3
Unable to engage in sexual activity	4
Type of perianal disease	
No perianal disease/skin tags	0
Anal fissure or mucosal tear	1
<3 Perianal fistulae	2
≥3 Perianal fistulae	3
Anal sphincter ulceration or fistulae with significant undermining of skin	4
Degree of induration	
No induration	0
Minimal induration	1
Moderate induration	2
Substantial induration	3
Gross fluctuance/abscess	4

Reprinted from Irvine EJ. Usual therapy improves perianal Crohn's disease as measured by a new disease activity index. McMaster IBD Study Group. J Clin Gastroenterol 1995;20:27–32.

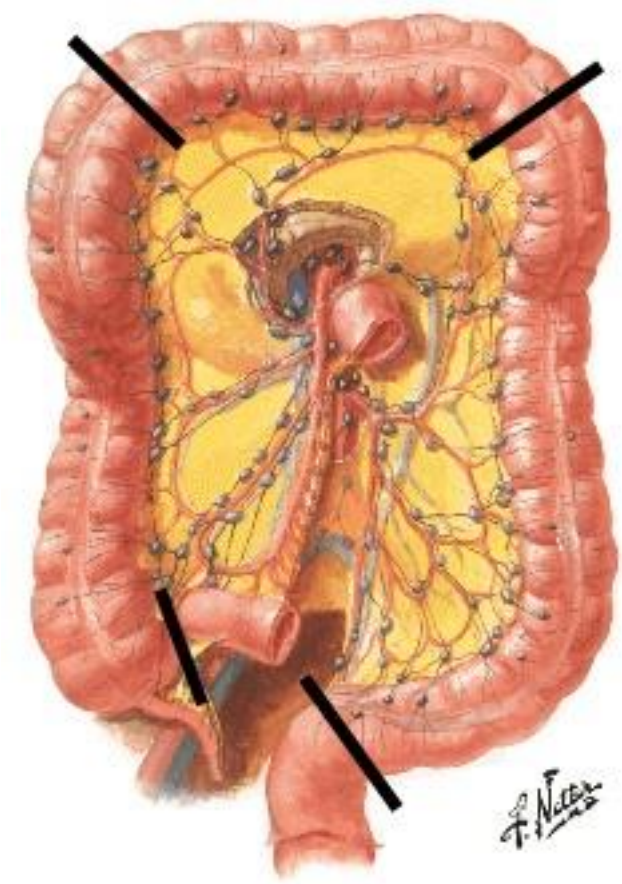
Improvement vs Remission

Table 4. Fistula Drainage Assessment

Endpoint	Definition
Improvement	Closure of individual fistulas defined as no fistula drainage despite gentle finger compression. Improvement defined as a decrease from baseline in the number of open draining fistulas of ≥50% for at least 2 consecutive visits (i.e., at least 4 weeks)
Remission	Closure of individual fistulas defined as no fistula drainage despite gentle finger compression. Remission defined as closure of all fistulas that were draining at baseline for at least 2 consecutive visits (i.e., at least 4 weeks)

Modified with permission from Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med 1999;340:1398–1405.

CDEIS and SES-CD: Ileocolonic segments



The definition of MH is still heterogenous

Crohn's disease

- No mucosal ulceration in any of 5 segments
- Absence of mucosal ulceration
- Disappearance of all ulcerative lesions
- CDEIS ≤2, ≤3, ≤4, ≤6
- SES-CD ≤5
- Rutgeerts score ≤i1

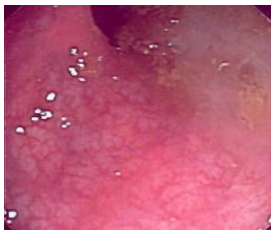
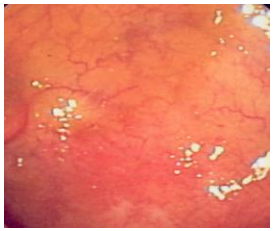
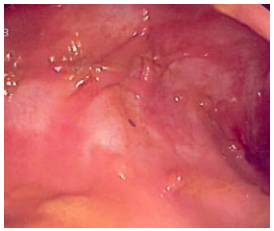
Ulcerative colitis

- Normal, improved, no change or worse
- Severity of bleeding without considering ulcers
- UC-DAI≤1
- Mayo≤1

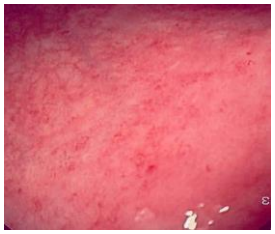
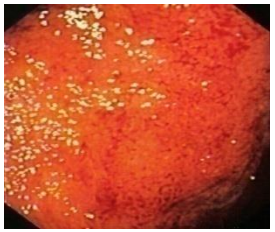
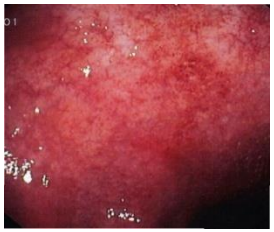
Need for homogenous definition of mucosal healing
No score available for small bowel disease

Mayo sub-Score (DAI)

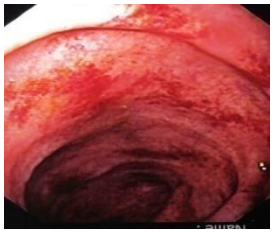
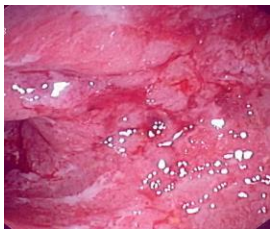
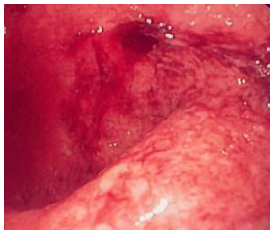
score 0 — normal or healed mucosa

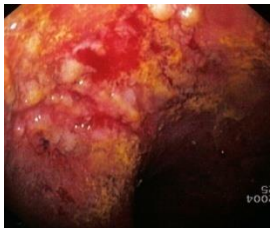
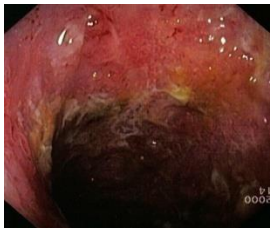
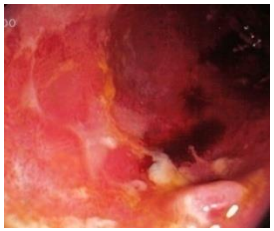
score 1 — faded vascular pattern
mild friability
erythema

score 2 — absent vascular pattern
marked friability
erosions

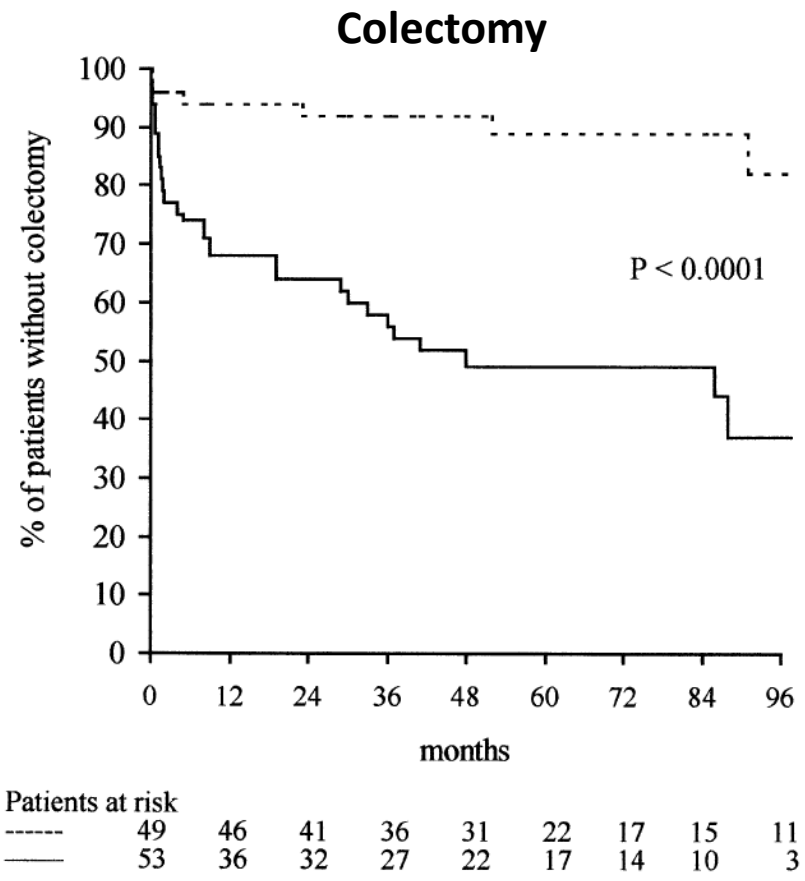




score 3 — spontaneous bleeding
large ulcers

Schroeder KW et al, NEJM, 1987

Severity of Endoscopic Lesions and Long Term Outcome in CD

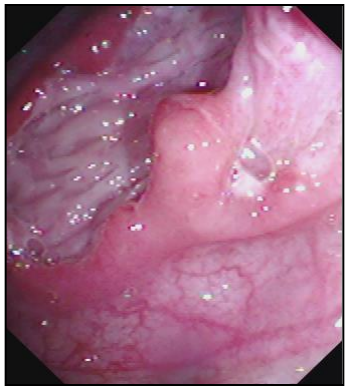


Severe Endoscopic Lesions:
Deep ulcerations > 10% surface of one segment

- **Independent risk factors for colectomy:**
  - **Severe endoscopic lesions RR: 5.43 (2.64 –11.18)**
  - **CDAI > 288**

    RR 2.21 (1.09–4.47)
  - **No immunosuppressive therapy**

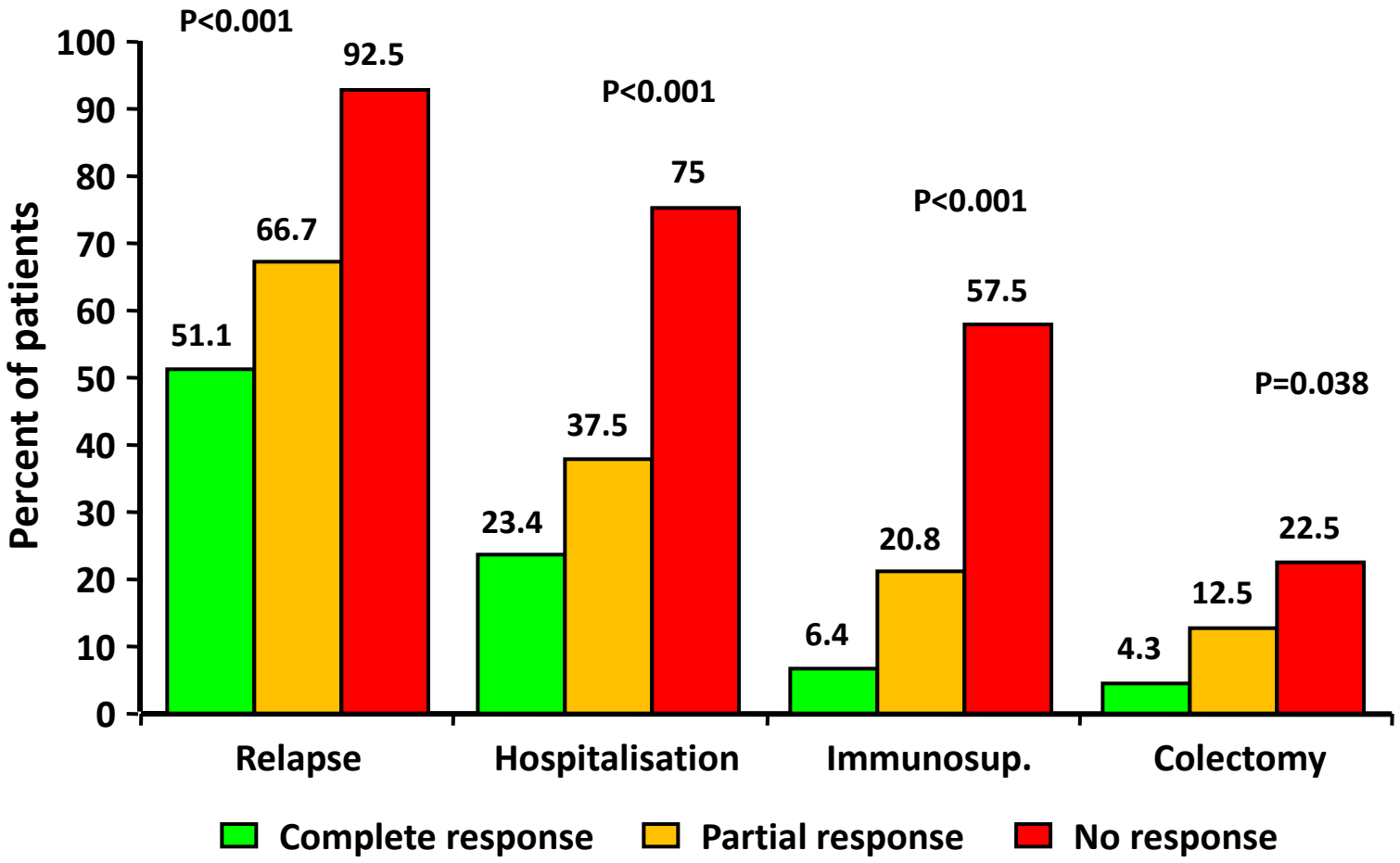
    RR: 2.44 (1.20 –5.00).



Allez M et al. *Am J Gastroenterol* 2002;97:947–53.

UC: Outcomes at 5-Year Follow-up According to Early Response to Steroids

Complete response (PT=0 and Ba=0); **Partial** (PT=0 and Ba=1–3); No response



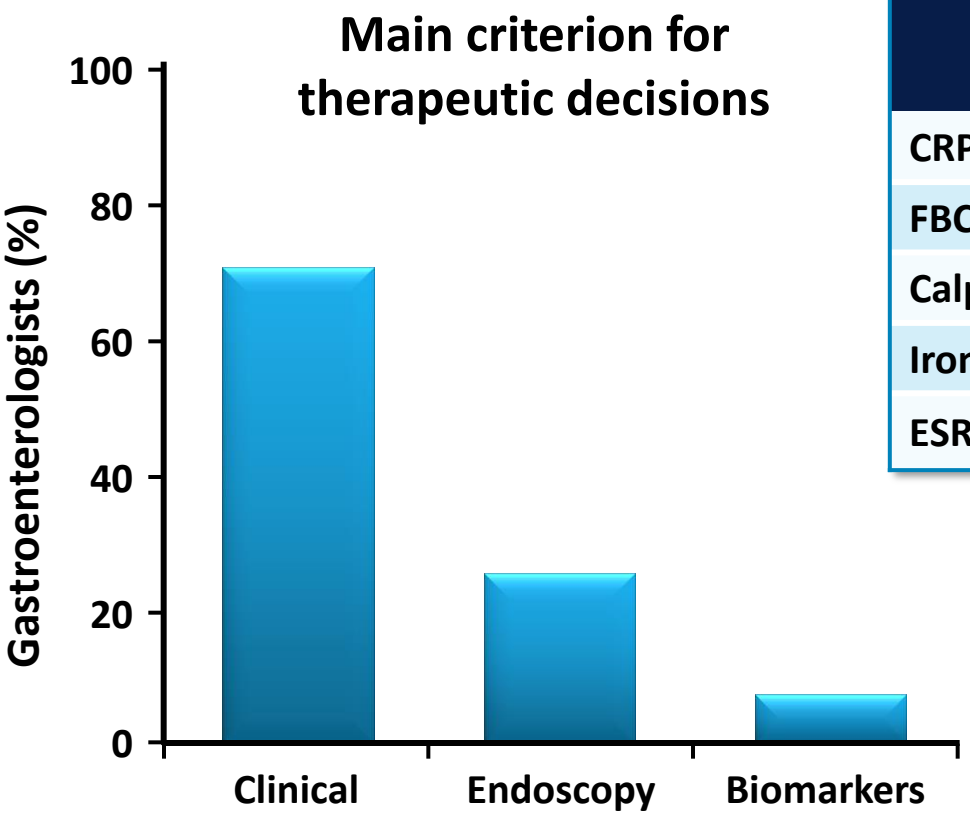
PT = Powell-Tuck index; Ba = Baron score

Ardizzone S, et al. ***Clin Gastroenterol Hepatol*** **2011x**

What are clinicians thinking…?

Clinical criteria are used by gastroenterologists to guide therapeutic decisions

From a survey of 270 Swiss gastroenterologists...



Biomarkers used for IBD activity monitoring	Gastroenterologists (%)
CRP	94
FBC + differential	78
Calprotectin	74
Iron status	63
ESR	3

What we do at Semmelweis?

- **Laboratory every visit** (CRP, FBC, liver enzymes)
- **At relapse or every 12 months imaging/endoscopy: US/MRI/endoscopy**

Schoepfer AM, *et al. J Crohn's Colitis* 2012;6:412–8

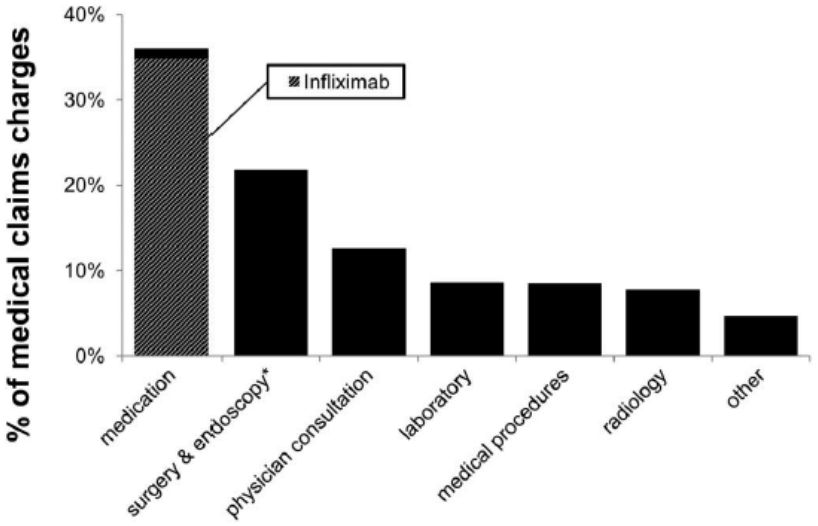
And what about other countries?

Observed average annual rate for hospital visits, endoscopies, surgeries, laboratory investigations, and imaging in US 2010–2012

Healthcare utilisation in 964,633 patients with IBD

	IBD, %	CD, %	UC, %
ER visit	10.7	15.1	4.5
Outpatient visit	93.8	97.4	74.2
Hospitalization	6.5	7.6	4.3
Endoscopy total	42.0	34.1	44.2
Upper GI endoscopy	5.8	6.2	4.7
Colonoscopy	31.3	25.0	33.9
IBD-related surgery total	2.8	3.3	1.6
Resection colon/ileocecal	1.1	1.2	0.8
Fistula/abscess surgery	0.6	0.9	0.1
CBC	32.5	39.5	18.6
CRP	8.8	11.2	4.1
ESR	9.7	12.0	4.8
Liver enzymes	20.4	24.9	11.4
Fecal calprotectin	0.1	0.2	0.1
Fecal lactoferrin	0.1	0.1	0.1
Fecal leukocytes	0.3	0.3	0.3
Influenza vaccination[a]	1.8	1.9	1.3
Pneumococcal vaccination[a]	0.5	0.5	0.4
Hepatitis B vaccination[a]	0.1	0.2	0.1
TB screen[a]	0.8	1.1	0.4
Hepatitis B screening[a]	0.8	1.0	0.4
US/MRI/CT abdomen/pelvis	18.1	22.6	11.3
DXA scan	0.6	0.8	0.3

[a]Might not be billed for independently.
CD, Crohn's disease; CBC, complete blood count; CRP, C-reactive protein; CT, computed tomography; DXA, dual-energy x-ray absorptiometry; ER, emergency room; ESR, erythrocyte sedimentation rate, GI, gastrointestinal tract; MRI, magnetic resonance imaging; TB, tuberculosis; UC, ulcerative colitis, US: ultrasound.



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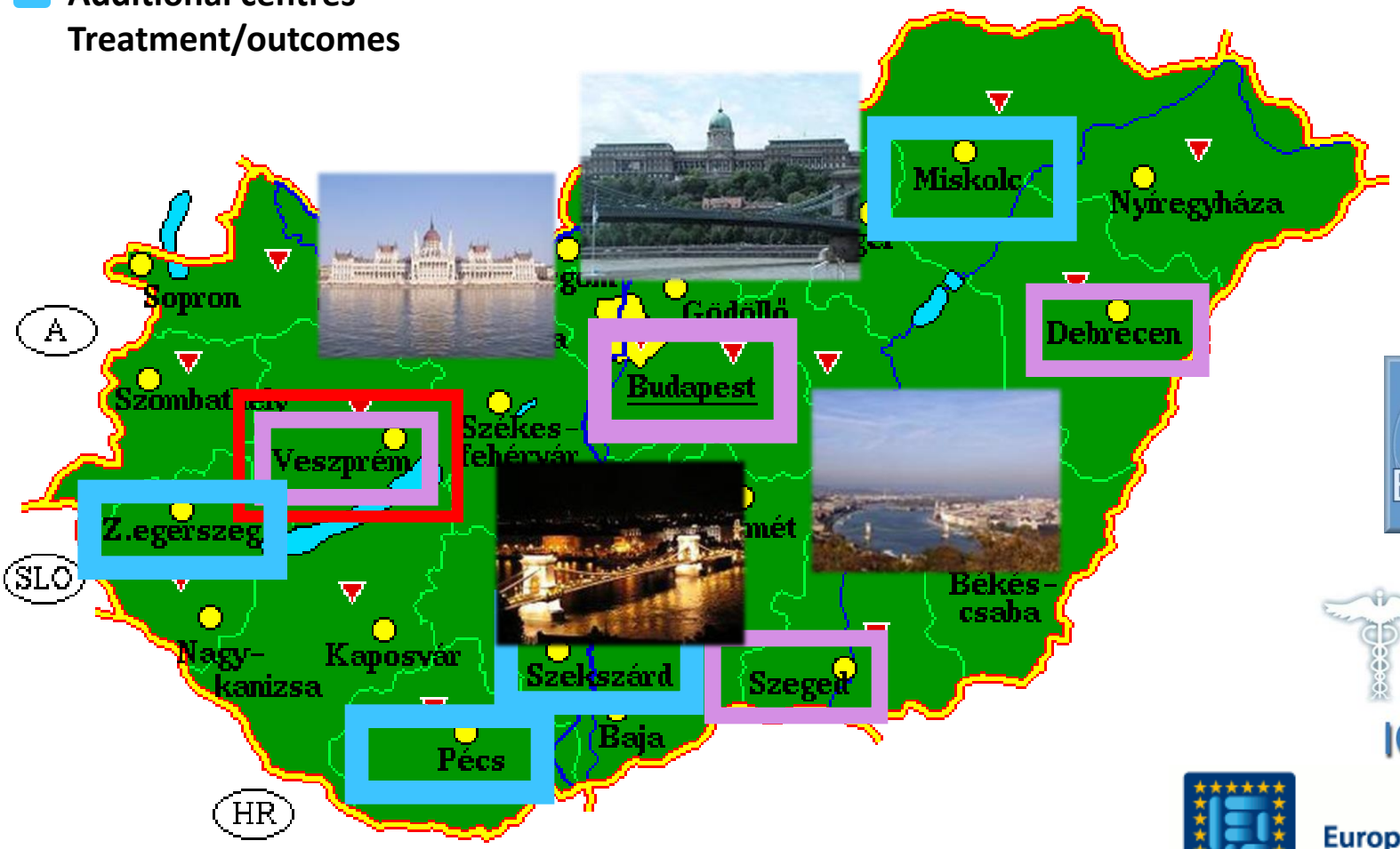
- **At relapse or every 12 months imaging/endoscopy: US/ MRI/endoscopy**

Van Deen WK, *et al. Inflamm Bowel Dis* 2014;20:1747–53

Hungarian IBD Study Group Centres

- Core centres
- Epidemiology
- Additional centres
- Treatment/outcomes



IBD

EpiCom

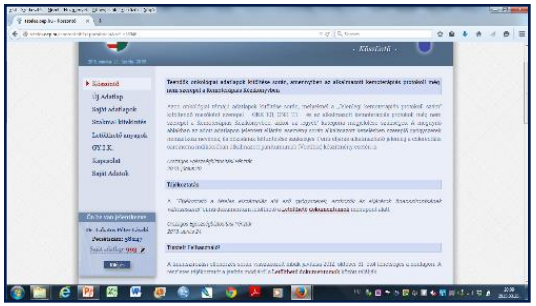
IOIBD

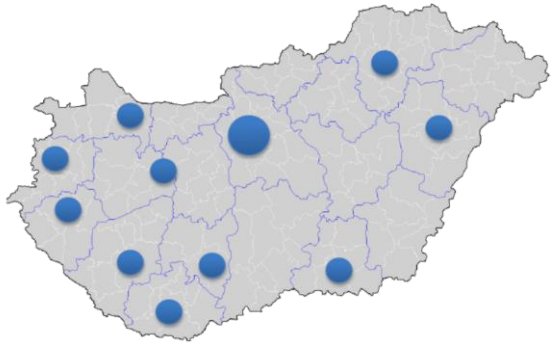
ECCO

European
Crohn's and Colitis
Organisation

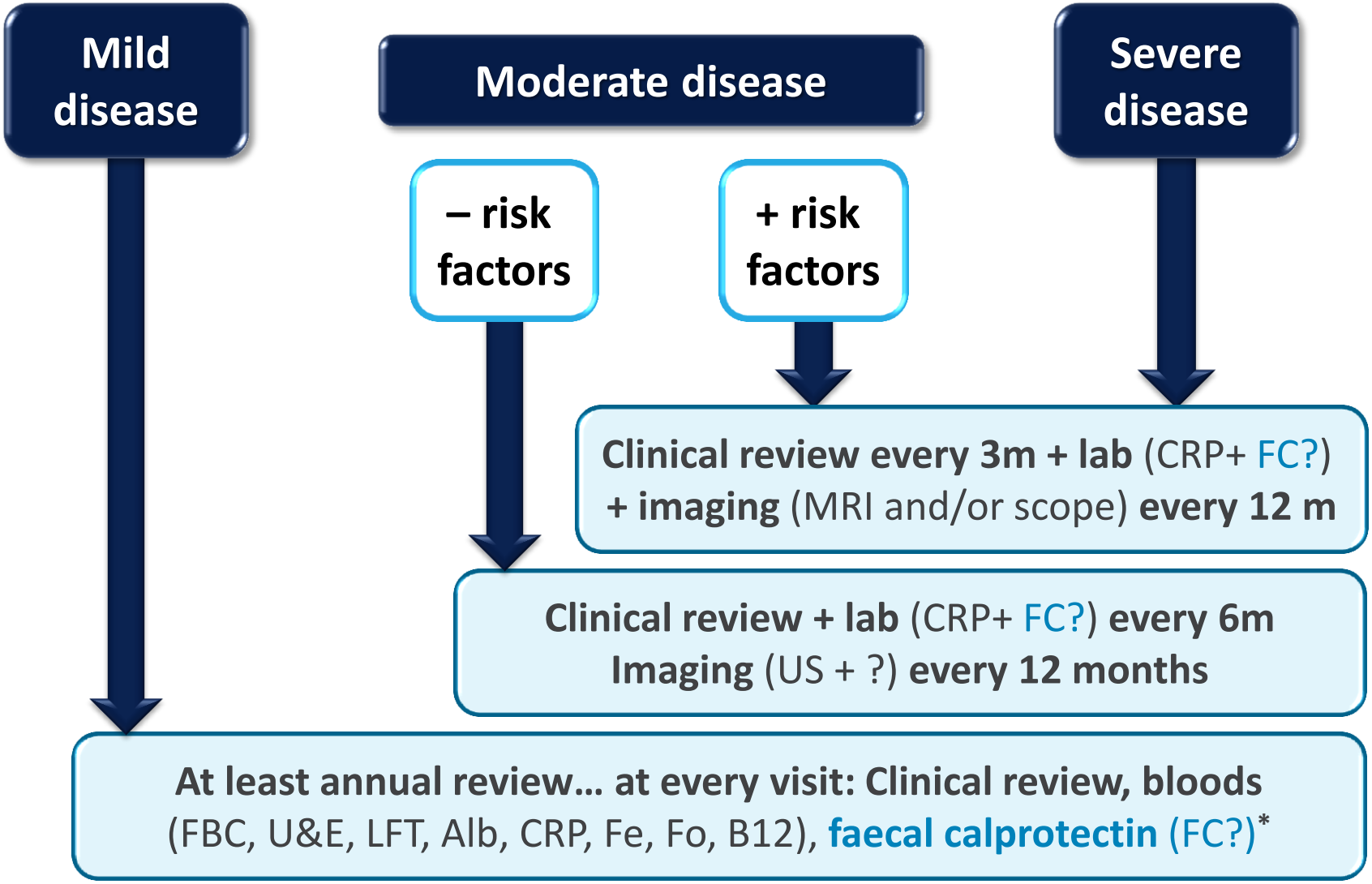
Monitoring of anti-TNF treated patients is harmonised in our center and Hungary

	Baseline	W14	W30	W54
Demographic data	✔			
Medication history	✔	✔	✔	✔
Clinical activity CDAI / PDAI or partial Mayo	✔	✔	✔	✔
Biochemical activity WBC, CRP, ESR, albumin	✔	✔	✔	✔
Endoscopic activity SES-CD or Mayo	✔			✔
Imaging (perianal) MR or CT	✔			✔
Adverse events	✔	✔	✔	✔





Tight monitoring – my practice



U&E: urea and electrolytes

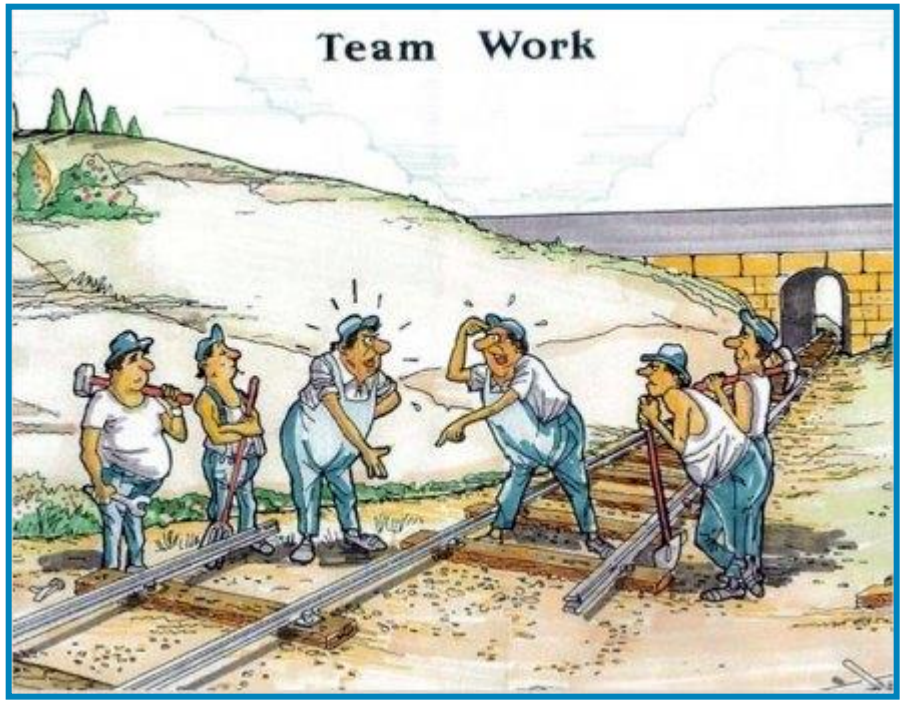
* Colonoscopy and MRE in selected individuals at 12m or if increase CRP / FC indicates active disease

And of course….multidisciplinary approach….

dermatologist

rheumatologist

paediatrician



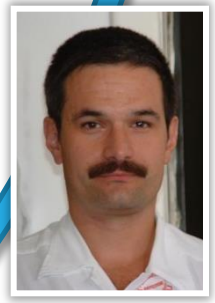
"The main ingredient of stardom is the rest of the team"

John Wooden

dietician/psychologist

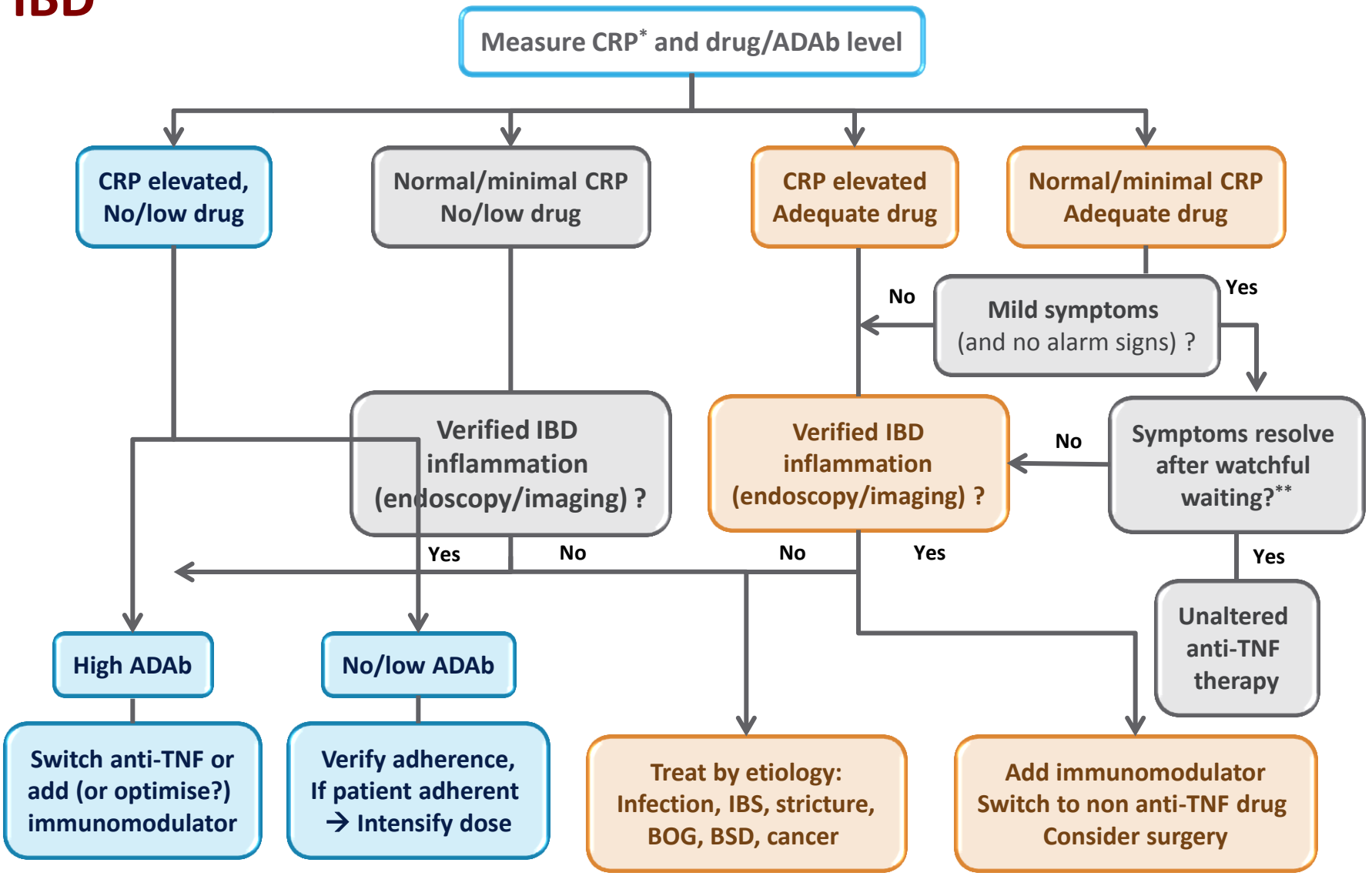
radiologist

surgeon



The NEW „era”:
T(herapeutic) D(rug) M(onitoring) tool or toy?

Tailoring anti-TNF and other biological therapies? in IBD

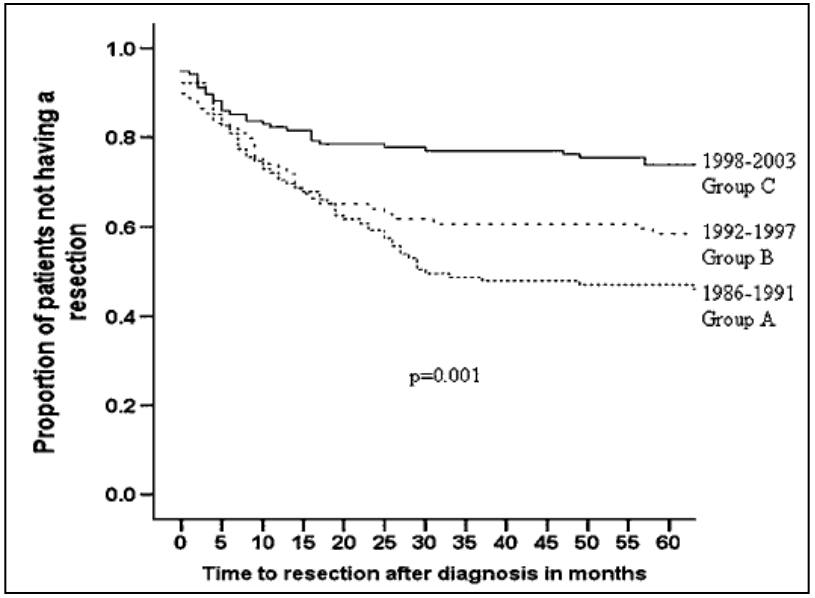


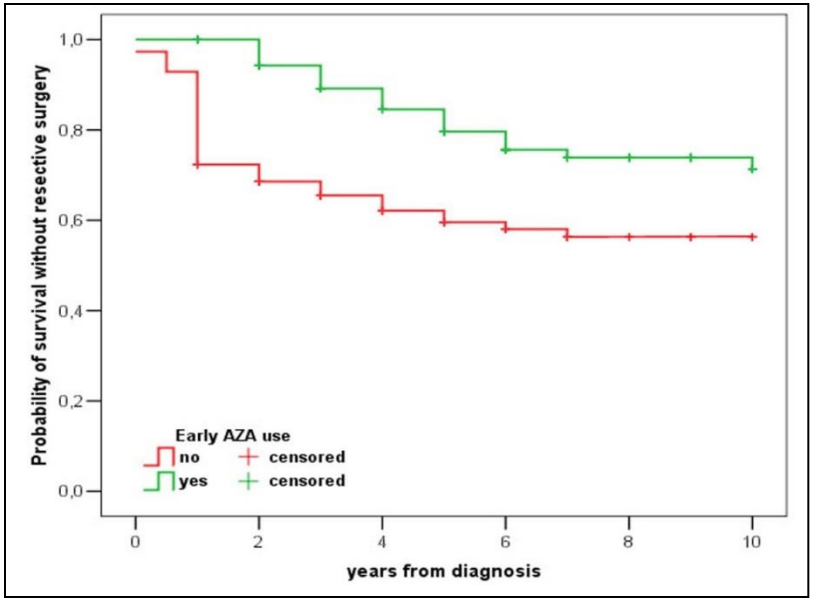
ADAb: anti-drug antibody

Ben-Horin S, Chowers Y. *Nature Rev Gastroenterol* 2014;11:243–55

Does therapeutic strategy modify outcomes?

Early azathioprine use and risk of surgery in Crohn's disease





In a multivariate Cox analysis:

- year of diagnosis
- disease location
- oral corticosteroids within 3 months of diagnosis
- early thiopurine use (within the year of diagnosis)

were all independent factors affecting likelihood of intestinal surgery.

In a propensity score model

	p value	Hazard ratio
early AZA use*	<0.001	0.42 (0.26-0.67)
very early AZA use**	0.023	0.40 (0.18-0.83

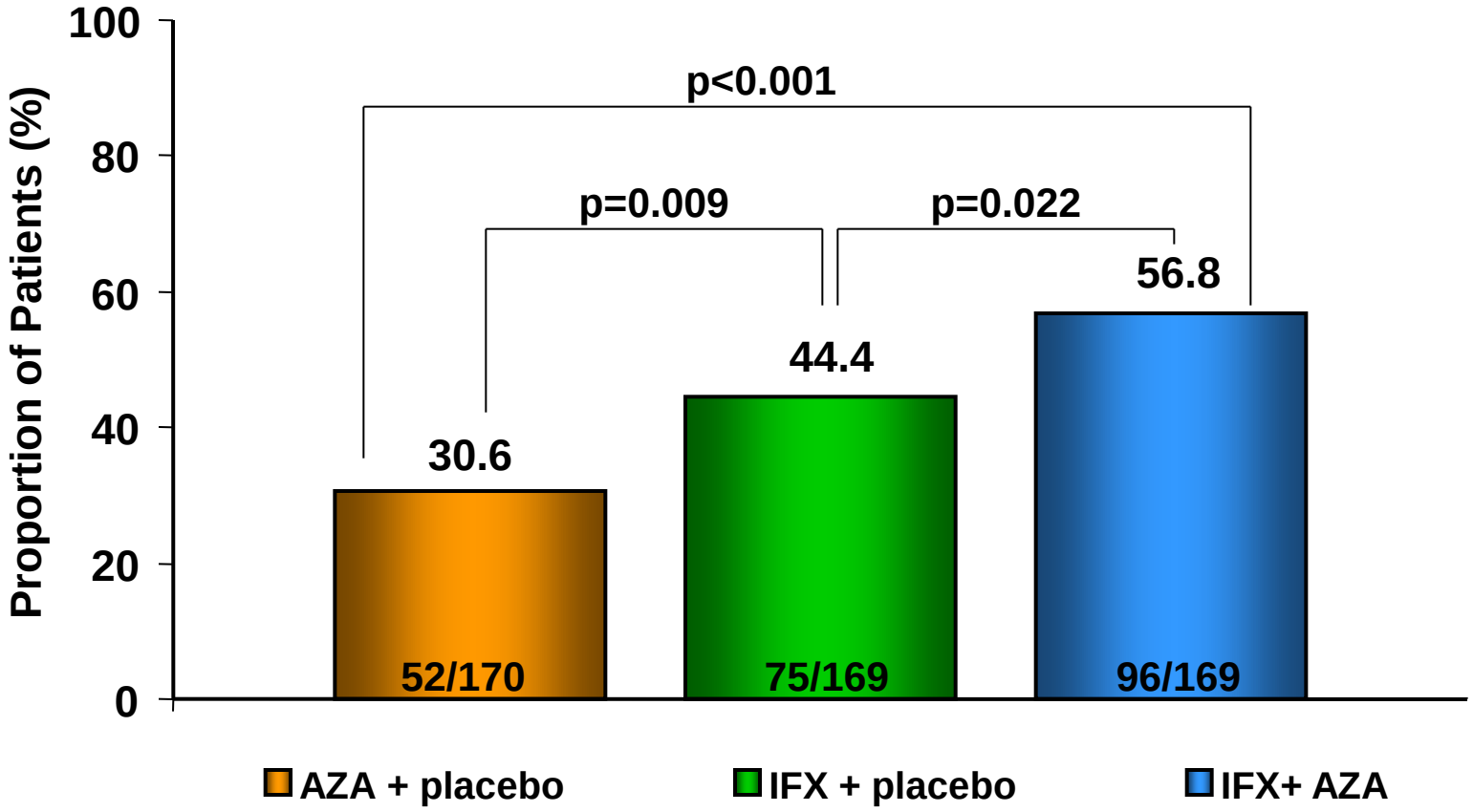
*<3years after diagnosis, **<1.5ears after diagnosis

Ramadas Gut 2010
Lakatos AJG 2012

Combination: Clinical Remission Without Corticosteroids!

SONIC

Primary Endpoint



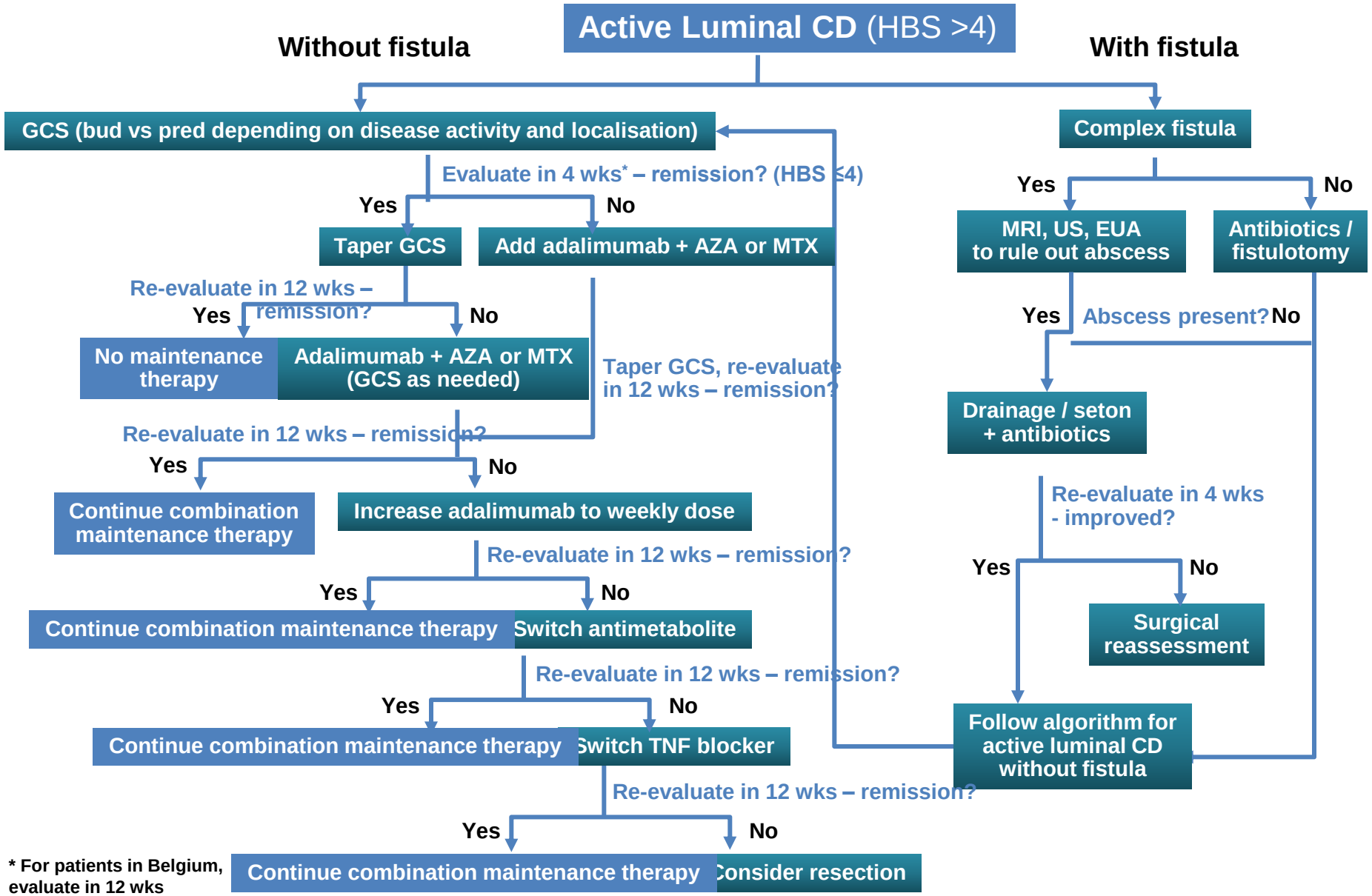
Colombel NEJM 2010;362:1383-95.

REACT: patient level demographics

	Conventional management (n=898)	Early combined immunosuppression (n=1084)
Age, mean (SD)	44.1 (14.5)	44.2 (14.6)
Sex, male	382 (42.5%)	456 (42.1%)
Harvey Bradshaw Index (SD)	4.14 (1.17)	4.03 (1.03)
Smoking status		
Current	163 (18.2%)	271 (25.1%)
Former	278 (31.0%)	301 (27.8%)
Non-Smoker	457 (50.9%)	510 (47.1%)
Site of disease		
Colon	178 (19.9%)	257 (23.9%)
Small bowel	319 (35.6%)	343 (31.9%)
Small bowel and colon	398 (44.5%)	474 (44.1%)
Fistula ever	276 (30.7%)	322 (29.9%)
Current fistula	71 (7.9%)	73 (6.8%)
Corticosteroids	154 (17.2%)	206 (19.0%)
Antimetabolites	367 (40.9%)	489 (45.1%)
TNF antagonist	312 (34.7%)	343 (31.6%)
Combined anti-TNF and anti-metabolite	116 (12.9%)	129 (11.9%)

Khanna R, *et al*. Lancet. 2015;386:1825-34.

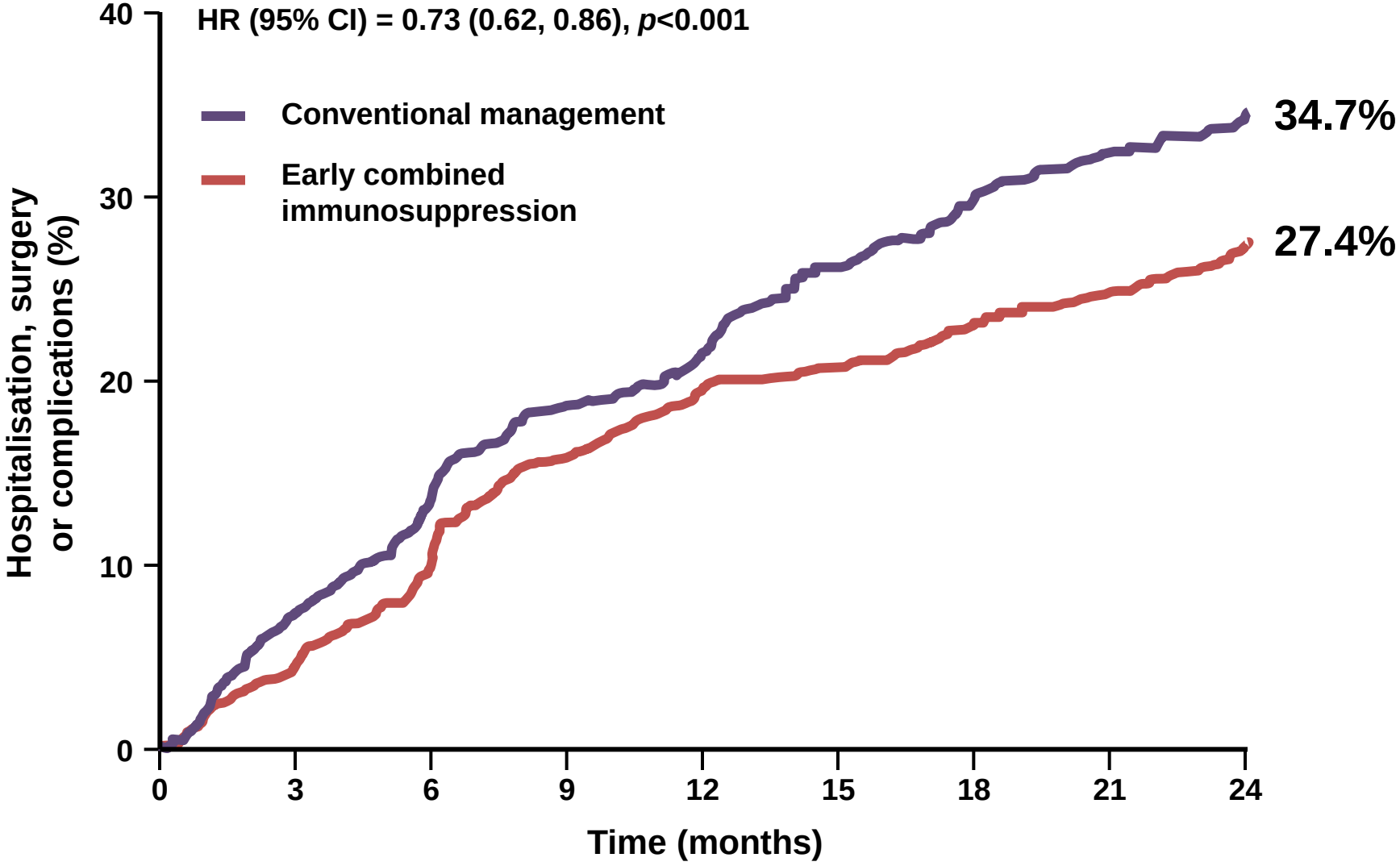
REACT: therapeutic algorithm for Crohn's disease



* For patients in Belgium, evaluate in 12 wks

Khanna R, *et al*. Lancet. 2015;386:1825-34.

REACT: time to first hospitalisation, surgery or complication

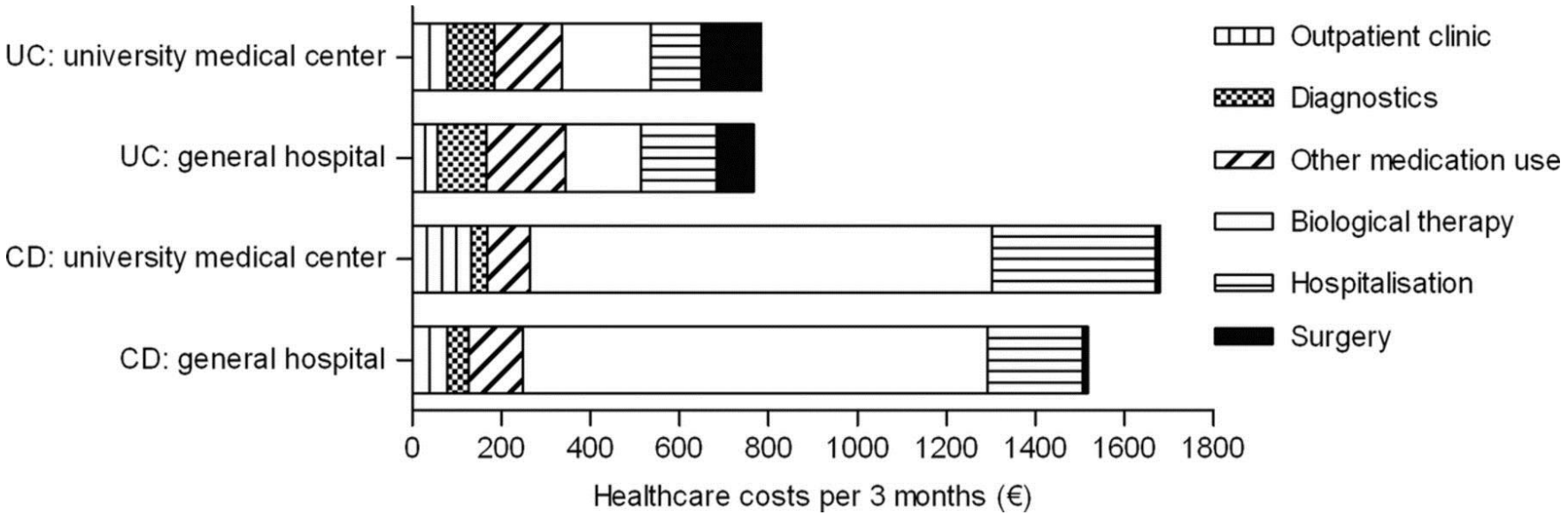


Khanna R, *et al*. Lancet. 2015;386:1825-34.

Exposure to anti-TNFs is rising in IBD
Real life data from The Netherlands

Do we have enough COINs?

1315 CD patients and 937 UC patients



Van der Valk ME, *et al. Gut* 2014;63:72–79

Estimated patient numbers and access to biologics in selected Eastern European countries

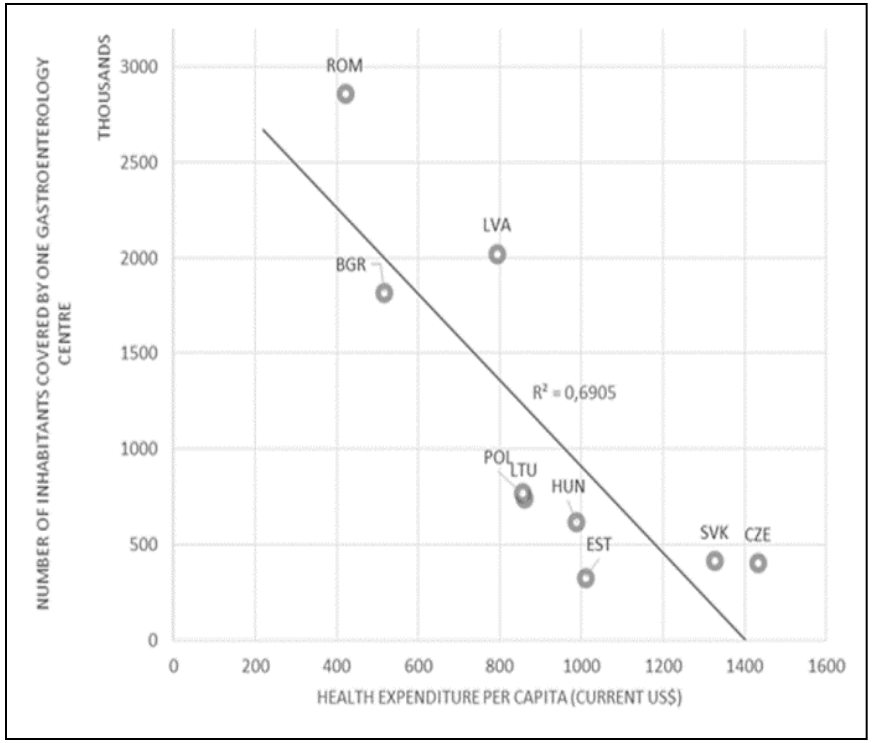
	Number of patients								
	CD[1]			UC[1]				Total	Centres
Country	infliximab	adalimumab	Total	infliximab	adalimumab	golimumab	Total		
Bulgaria	NR	46	46	NR	0	NR	0	46	4
Czech Republic	750	240	990	412	NA	NA	412	1402	26
Estonia	29	13	42	21	5	1	27	69	4
Hungary	970	900	1870	460	170	0	630	2500	16
Latvia	1	2	3	0	0	0	0	3	1
Lithuania	30	43	73	15	31	0	46	119	4
Poland	506	382	888	NA	NA	NA	NA	888	50[2]
Romania	114	139	253	73	540	37	650	903	7
Slovakia	350	340	690	320	110	10	440	1130	13[3]
Total	2750	2105	4855	1301	856	48	2205	7060	125

1. Including paediatric and adult patients
2. Approximately
3. 10 adult and 3 paediatric

National gastroenterology societies, Ministries of Health, IMS data, personal communication.
NA: Not available; NR: Not reimbursed

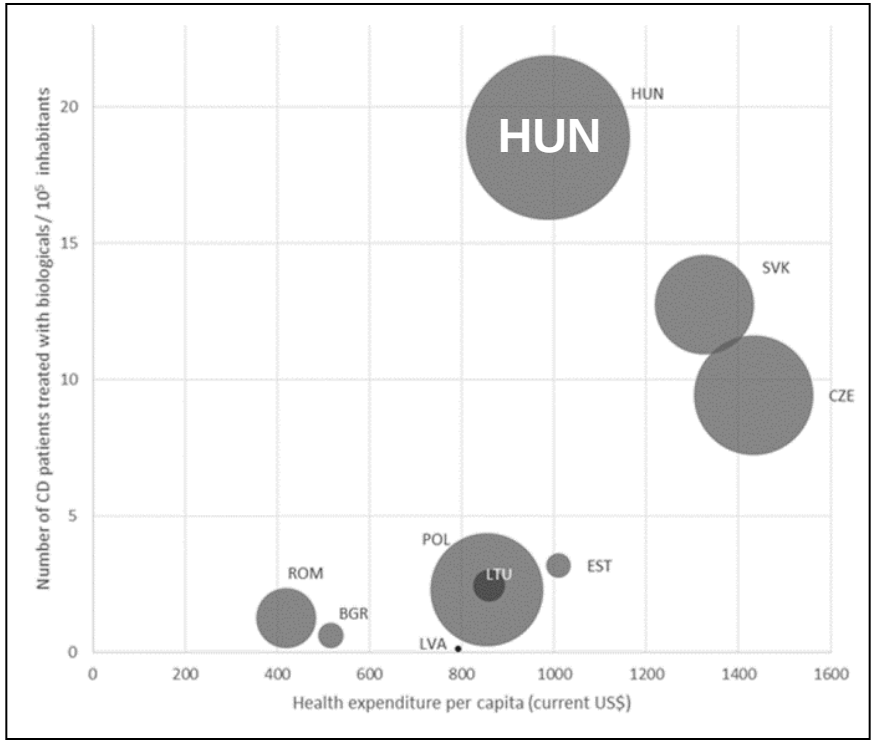
Rencz F, *et al. World J Gastroenterol* 2015;21:1728–37

Estimated patient numbers and access to biologics in selected Eastern European countries



Number of inhabitants covered by one gastroenterology centre entitled to administer biological therapy in 9 selected Central and Eastern European countries, 2014. Population data Eurostat Statistics Database (2013)[34], total health expenditure per capita (2012): World Bank Databank[26].

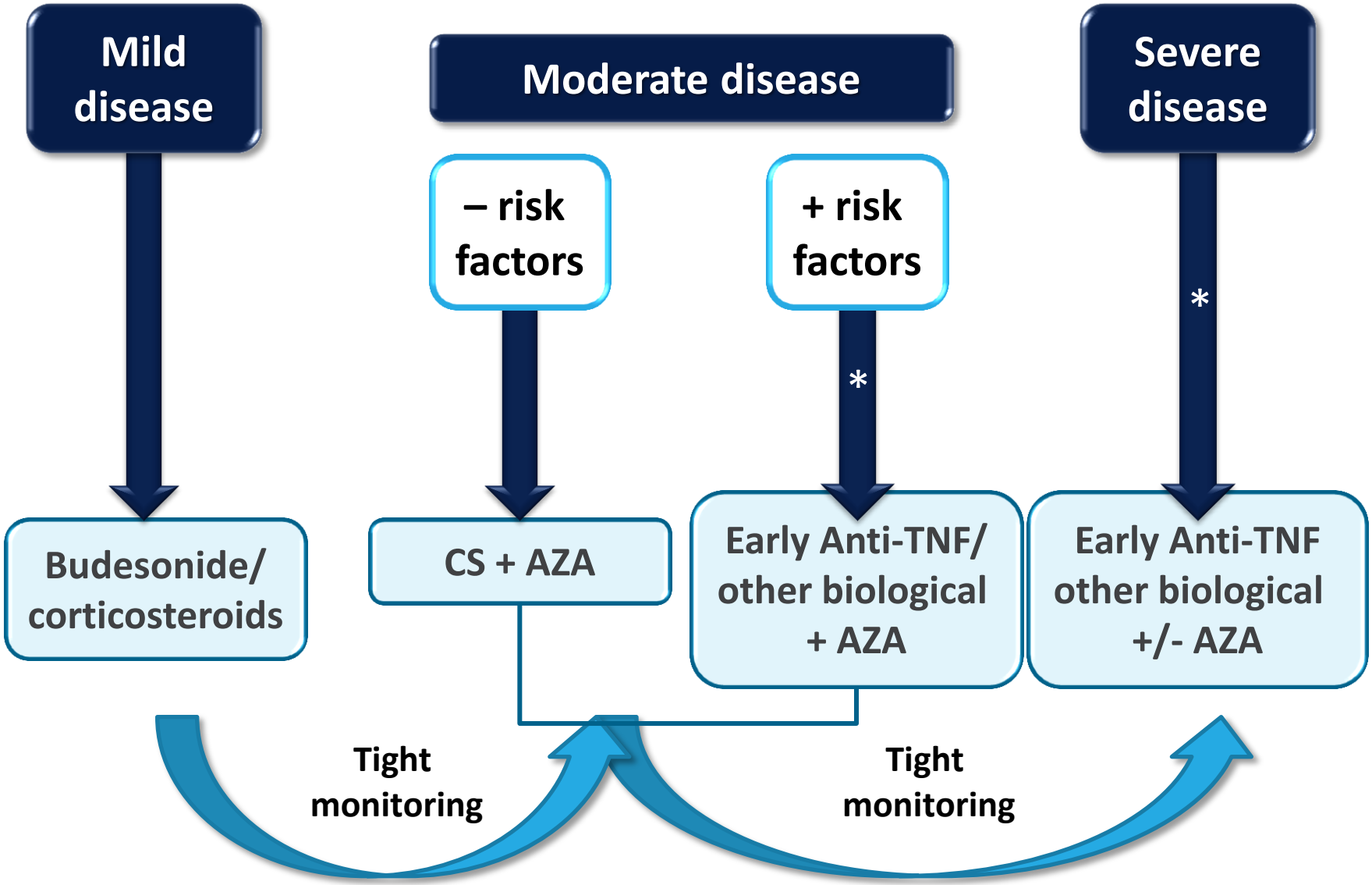
BGR: Bulgaria; CZE: Czech Republic; EST: Estonia; HUN: Hungary; LVA: Latvia; LTU: Lithuania; POL: Poland; ROM: Romania; SVK: Slovakia.



Average number of Crohn's disease patients treated with biologicals per 10^5 inhabitants compared to countries per capita total expenditure on health. Ulcerative colitis would display a similar figure. Sizes of bubbles refer to the absolute number of patients treated with biologicals in each country. Data sources: patient numbers: IMS data (2014 or latest available), population data: Eurostat Statistics Database (2013)[34], total health expenditure per capita (2012):World Bank Databank[26].

Rencz F, *et al. World J Gastroenterol* 2015;21:1728–37

Tailured therapy! at diagnosis and during follow-up in CD



* Anti-TNF labels: indications specify initiation in moderate to severe IBD patients AFTER failure on conventional treatment (CS and/or immunosuppressants).

The art of IBD management today

- Assess patient prognosis objectively at diagnosis and during follow-up: adapt goals and therapeutic strategy if needed
- Discuss and set treatment goals with our patients: be realistic!
- Involve our patients: patient empowerment, shared decision making
- Use MDT approach ensures that we practice ‘tight monitoring’ and optimise therapy as appropriate
- **Patient stratification, appropriate timing and objective re-assessment are key elements of success!**