Treatment of elderly patients with IBD

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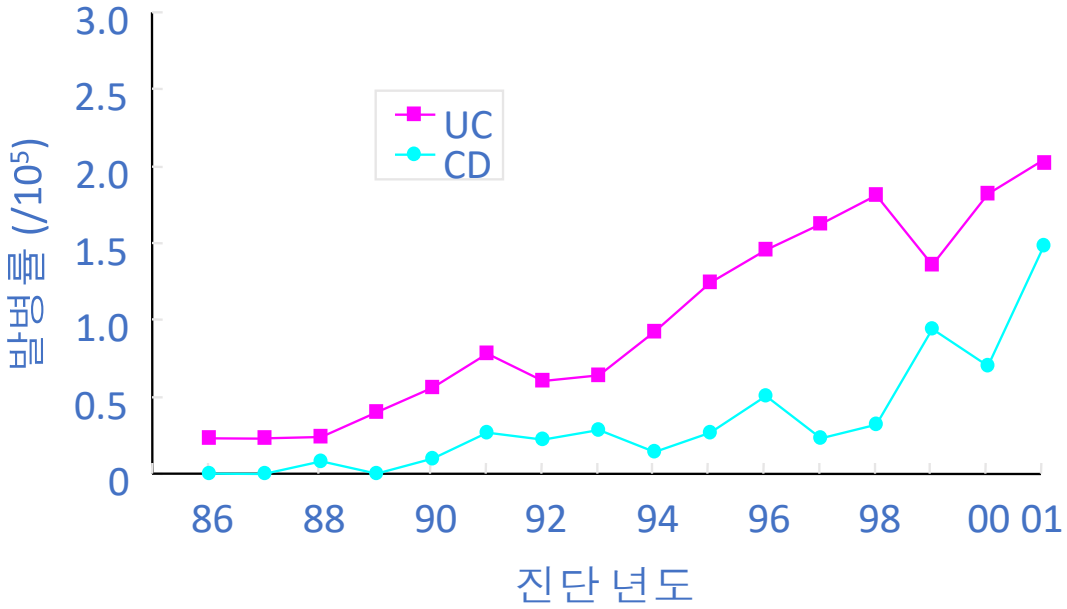
Epidemiology

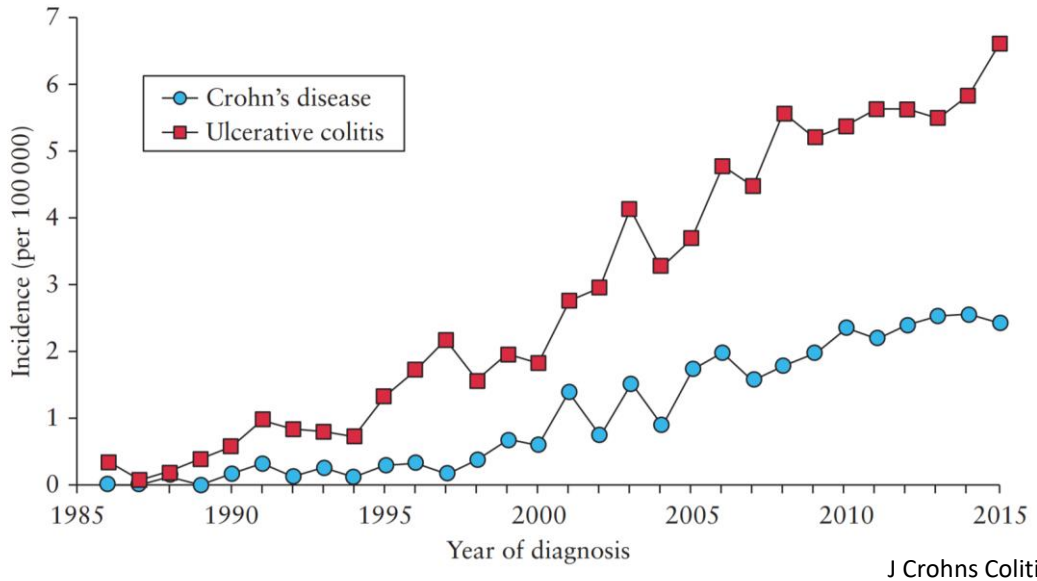
		Incidence	Prevalence
UC	서양	6-12 / 100,000	70-150 / 100,000
	한국	1.73	14.51
CD	서양	3-7 / 100,000	30-100 / 100,000
	한국	0.93	5.30



양석균 2002,
대한소화기학회 추계학술대회

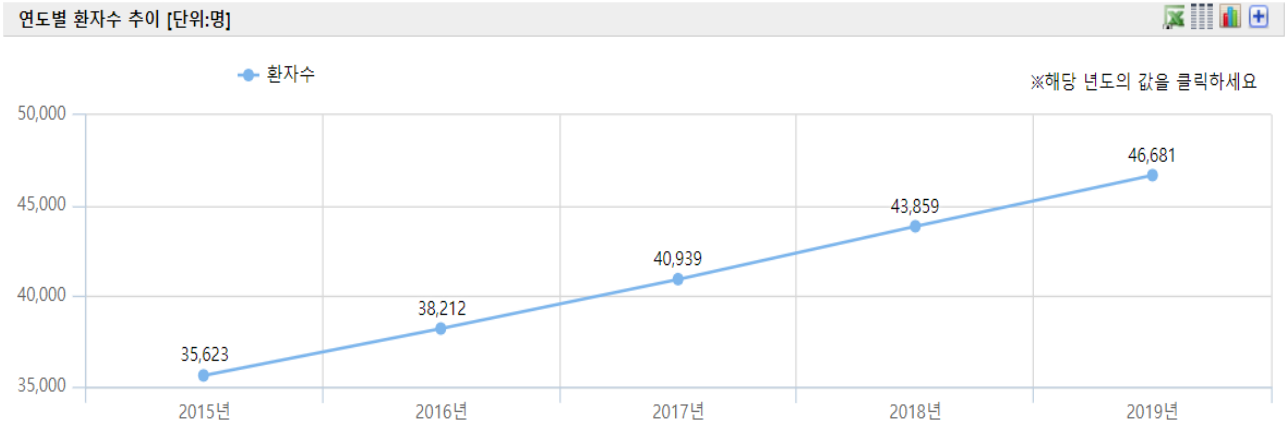
Epidemiology

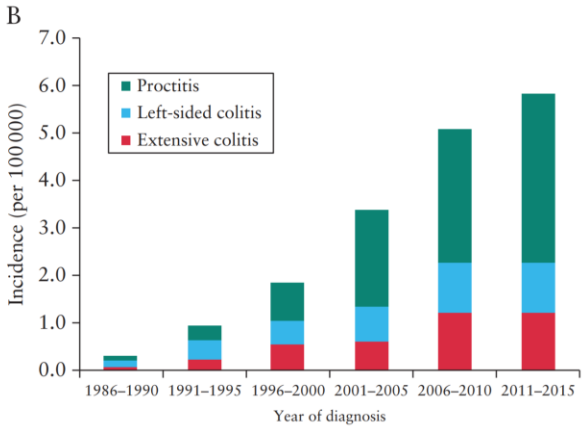
		Incidence	Prevalence
UC	서양	6-12 / 100,000	70-150 / 100,000
	한국	1.73 → 5.82	14.51 → 76.66
CD	서양	3-7 / 100,000	30-100 / 100,000
	한국	0.93 → 2.44	5.30 → 31.59



J Crohns Colitis. 2019 Oct 28;13(11):1410-1417

국내 의료보험 청구 자료 (UC)





3단질병 요양기관그룹별 현황 [단위:명,일,건,천원]

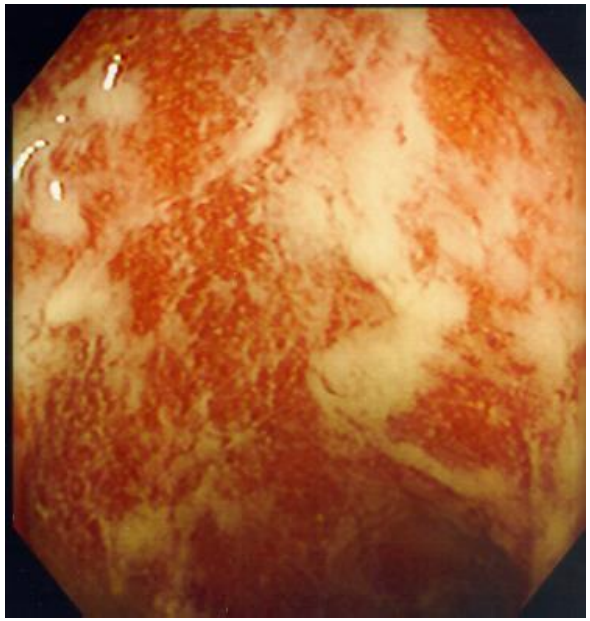
	심사년도	2019년				
코드	요양기관그룹	환자수	내원일수	청구건수	요양급여비용총액	보험자부담금
K51	계	46,681	279,131	248,948	51,154,185	44,728,185
	상급종합병원	19,997	123,600	110,037	29,834,220	26,405,107
	종합병원	12,332	82,351	71,627	15,254,055	13,414,044
	병원급	8,003	31,130	25,444	3,749,780	3,002,272
	의원급	11,194	41,825	41,615	2,314,286	1,905,164
	보건기관등	119	225	225	1,843	1,599

http://opendata.hira.or.kr/

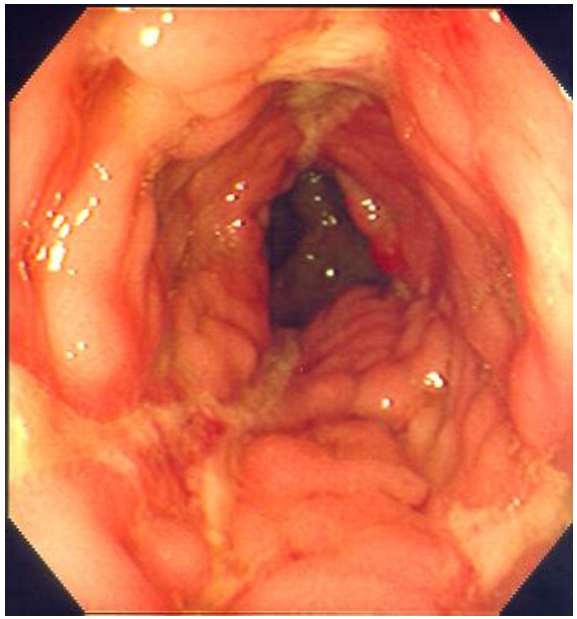
Inflammatory bowel disease

- **Chronic inflammation of the bowel of unknown etiology**

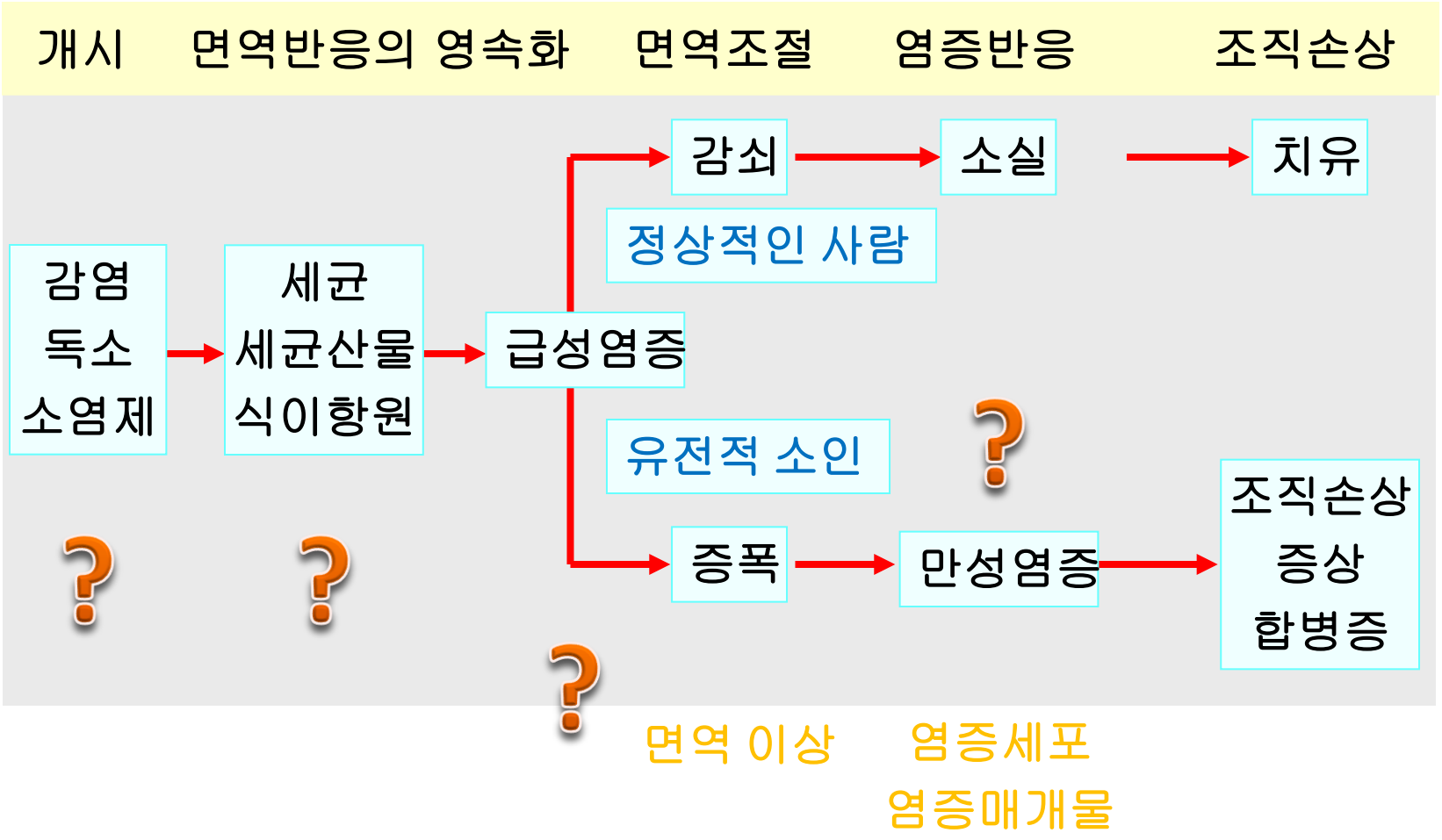
Ulcerative colitis (UC)



Crohn's disease (CD)



Pathophysiology



by Sartor RB (1995)

Genetic factors

Table 1. Genetic Associations with Crohn's Disease and Ulcerative Colitis.*

Gene	Genomic Region	No. of Genes in Region†	Associated with Crohn's Disease	Associated with Ulcerative Colitis
Innate immune responses				
NOD2 (nucleotide-binding oligomerization domain 2)	16q12	1	Yes	No
ATG16L1 (autophagy-related, 16-like)	2q37	1	Yes	No
IRGM (immunity-related GTPase M)	5q33	3	Yes	Equivocal
Interleukin-23–Th17 pathway				
IL23R (interleukin-23 receptor)	1p31	1	Yes	Yes‡
IL12B (interleukin-12B, p40 subunit)	5q33	1	Yes	Yes‡
STAT3 (signal transducer and activator of transcription 3)	17q21	4	Yes	Yes‡
CCR6 (chemokine [C-C motif] receptor 6)	6q27	3	Yes	No
Other genes in association regions				
PTGER4 (prostaglandin E receptor 4)	5p13	0	Yes	No
ZNF365 (zinc finger protein 365)	10q21	1	Yes	No
SLC22A4 (solute-carrier family 22, organic-cation transporter)	5q31	7	Yes	Equivocal
PTPN2 (T-cell protein tyrosine phosphatase)	18p11	1	Yes	No
Major histocompatibility complex (MHC)	6p21	—	Yes‡	Yes
NKX2-3 (NK2–transcription-factor–related, locus 3)	10q24	1	Yes	Yes‡
MST1 (macrophage stimulating 1)	3p21	35	Yes	Yes‡
PLA2G2E (secretory phospholipase A_2)	1p36	0§	No	Yes
IL10 (interleukin-10)	1q32	1¶	Equivocal	Yes
IFNG (interferon-γ)	12q15	2§	No	Yes

Dysbiosis

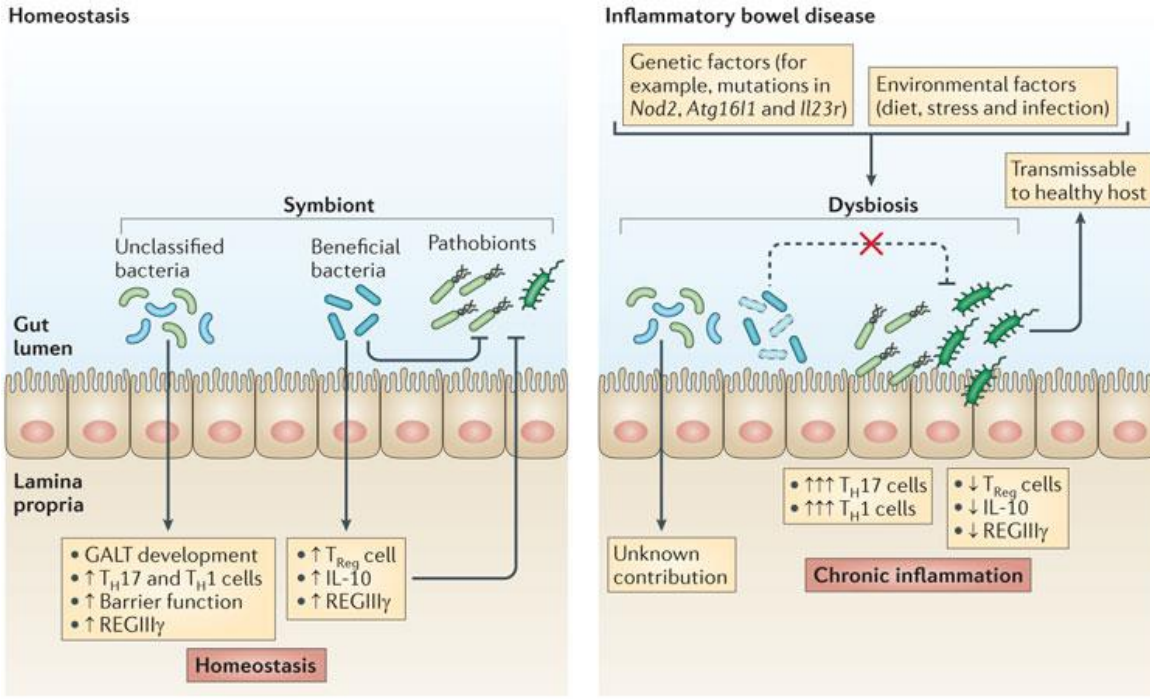
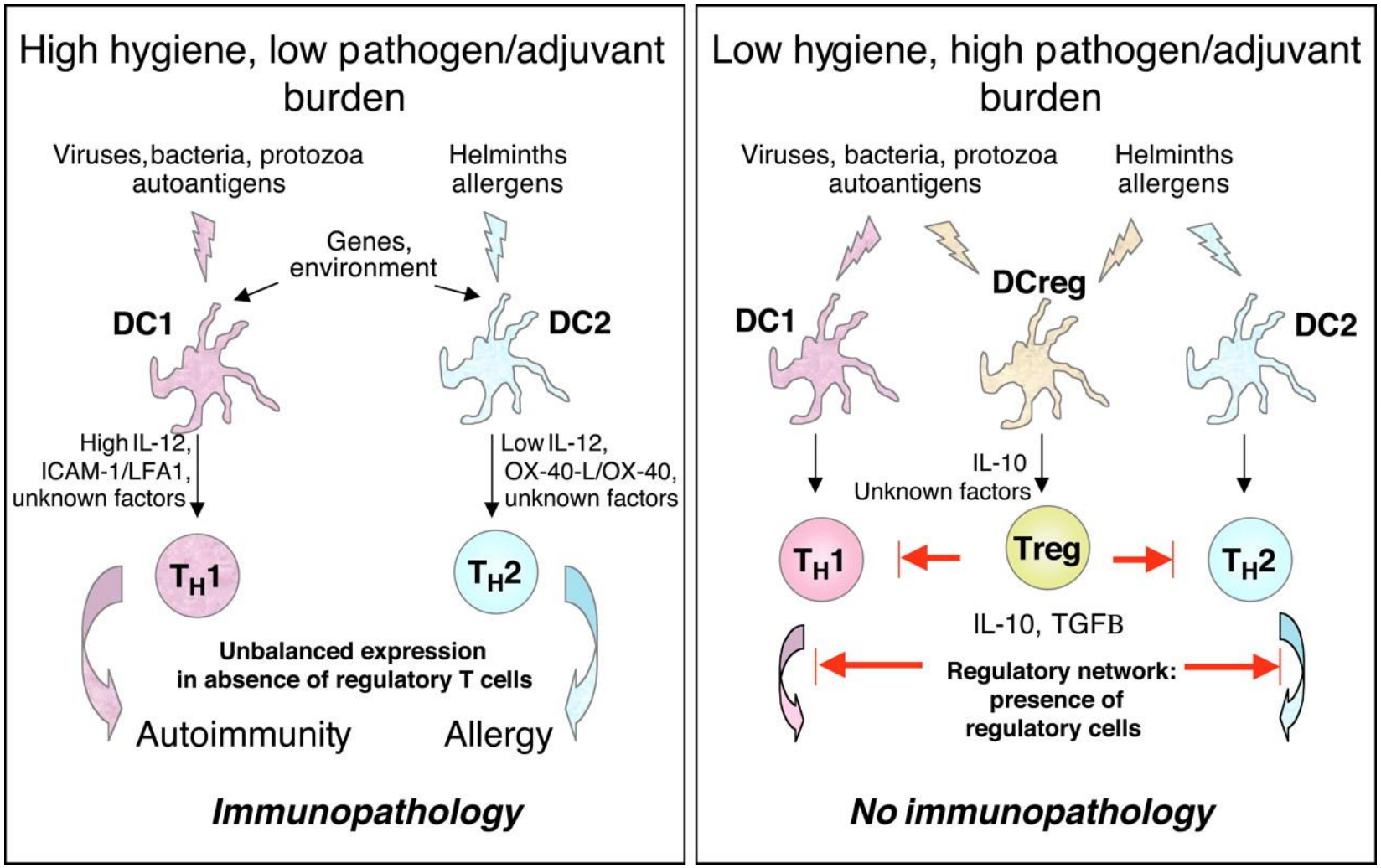


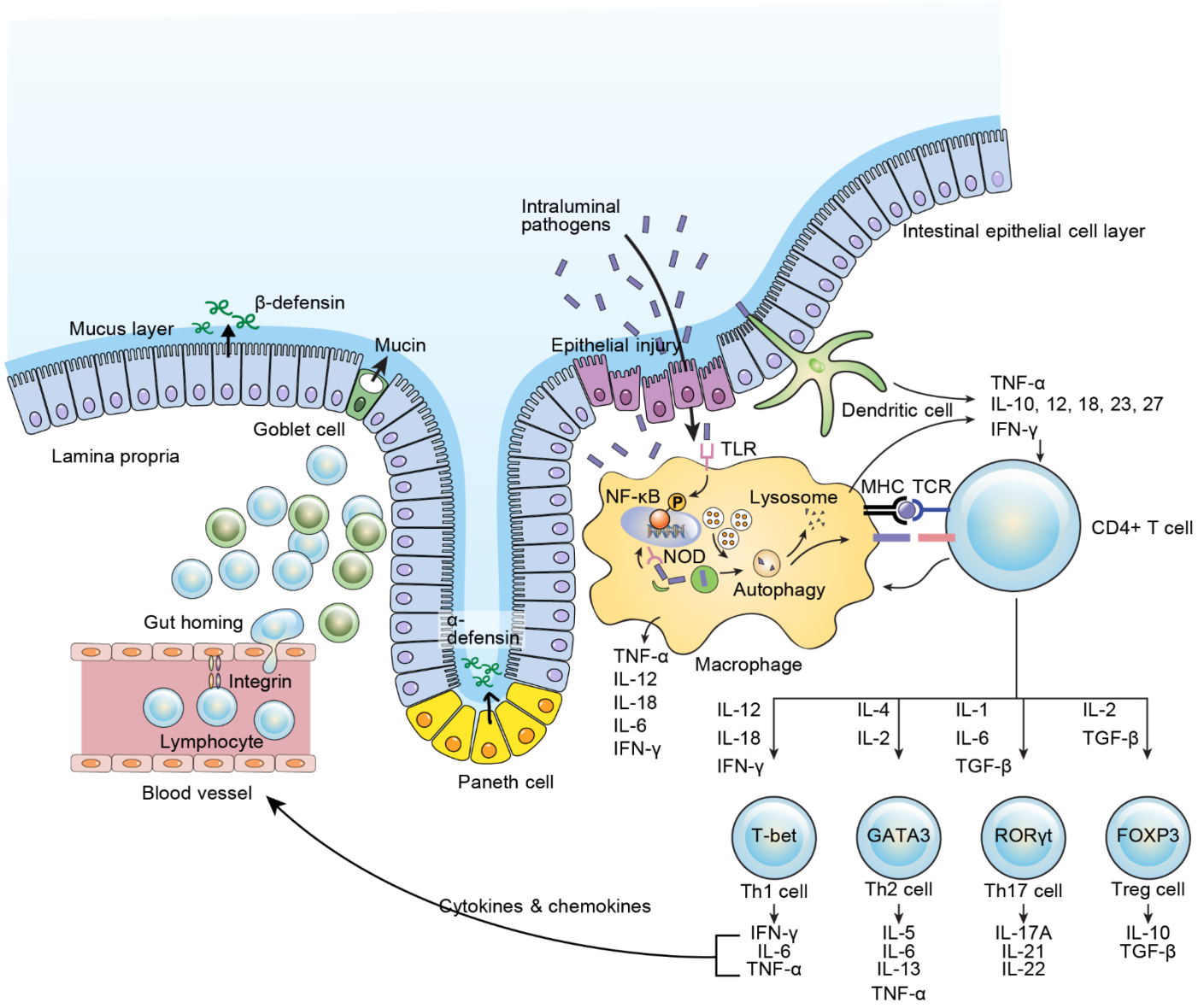
Table 1. Changes in the Microbiome Linked to IBD

Microbial composition	Decrease in α diversity
	Decrease in *Bacteroides* and Firmicutes
	Increase in Gammaproteobacteria
	Presence of *E coli*, specifically adherent-invasive *E coli*
	Presence of *Fusobacterium*
	Decrease in Clostridia, Ruminococcaceae, *Bifidobacterium*, *Lactobacillus*
	Decrease in *F prausnitzii*
Microbial function	Decrease in SCFAs, butyrate
	Decrease in butanoate and propanoate metabolism
	Decrease in amino acid biosynthesis
	Increase in auxotrophy
	Increase in amino acid transport
	Increase in sulfate transport
	Increased oxidative stress
	Increase in type II secretion system, secretion of toxins

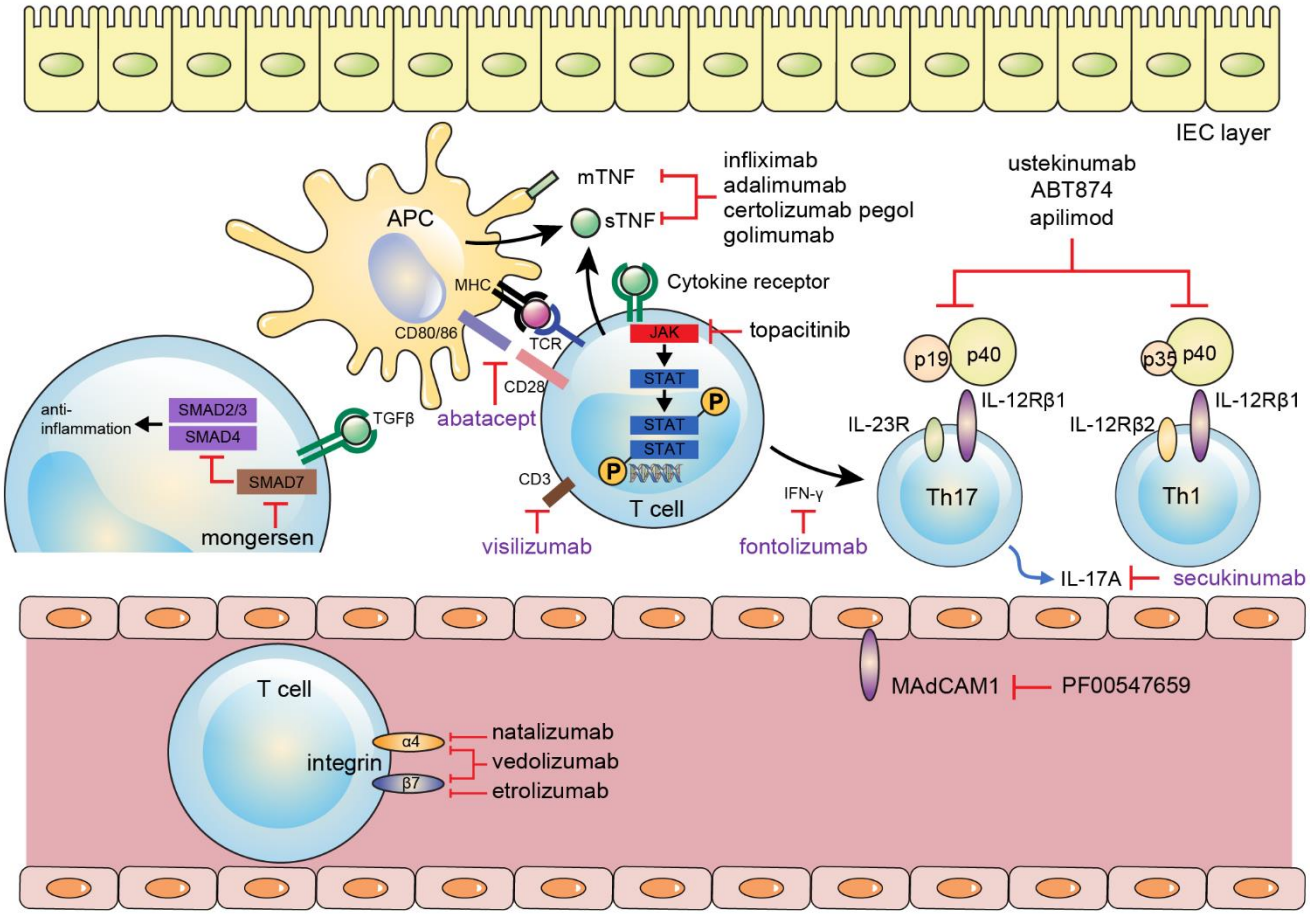
Nature Reviews | Immunology

Hygiene hypothesis



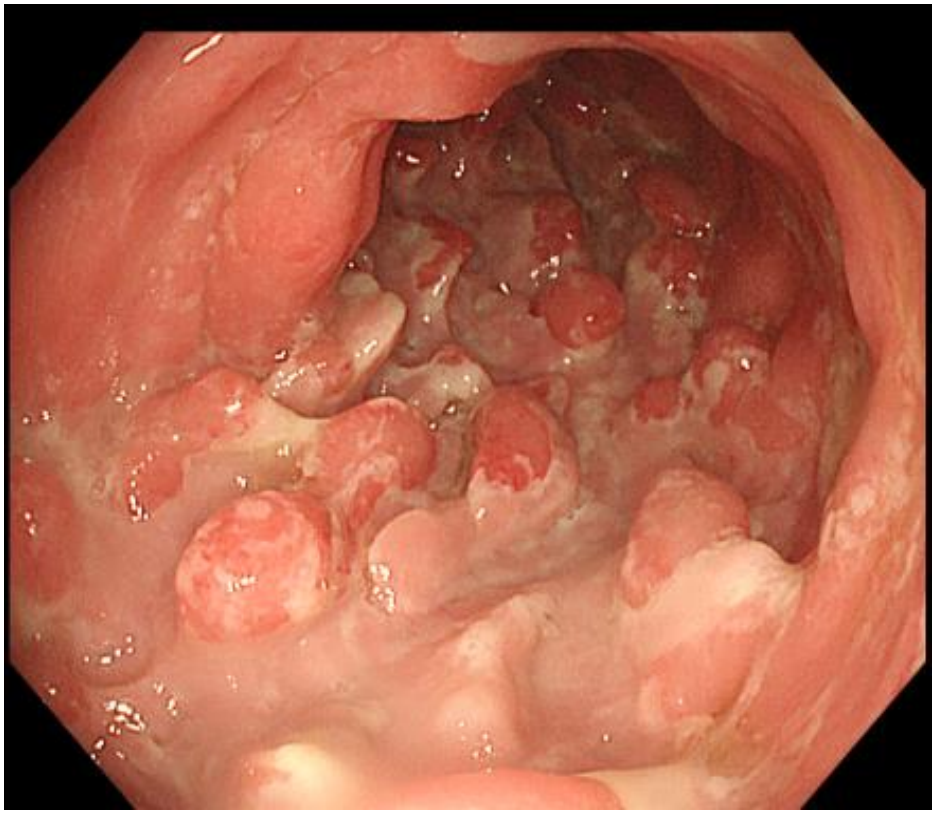


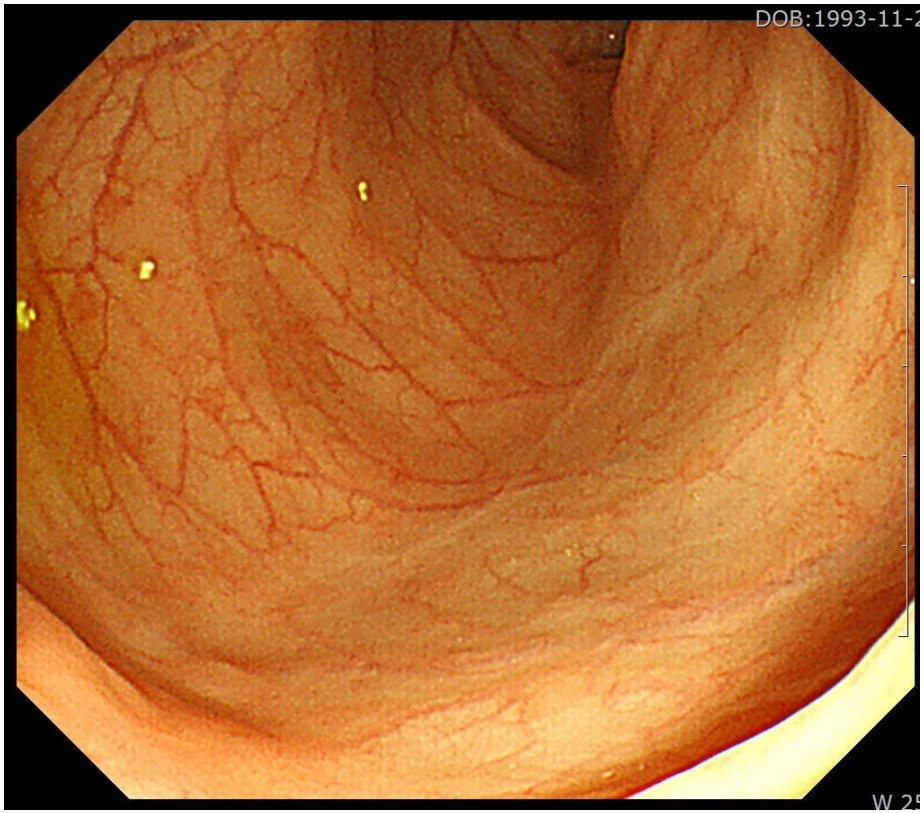
DH Kim and JH Cheon, immune network, 2018



DH Kim and JH Cheon, immune network, 2018

Disease modifying drugs





2014년 5월

2015년 8월

Elderly IBD patients

코드	성별구분	심사년도 연령구분 10세	2019년 환자수					
K51	계	계	46,681					
K51	남	소계	27,408	여	소계	19,273	계	46,681
K51	남	0_9세	31	여	0_9세	33	0_9세	64
K51	남	10_19세	809	여	10_19세	500	10_19세	1,309
K51	남	20_29세	3,798	여	20_29세	2,314	20_29세	6,112
K51	남	30_39세	4,530	여	30_39세	3,181	30_39세	7,711
K51	남	40_49세	5,551	여	40_49세	3,916	40_49세	9,467
K51	남	50_59세	6,128	여	50_59세	4,491	50_59세	10,619
K51	남	60_69세	5,010	여	60_69세	3,417	60_69세	8,427
K51	남	70_79세	2,436	여	70_79세	1,811	70_79세	4,247
K51	남	80세이상	585	여	80세이상	601	80세이상	1,186

60세 이상의 국내 UC 환자 수 13860명 (29.6%)

http://opendata.hira.or.kr/

Elderly IBD patients (western)

- 25%-30% of the IBD population are aged sixty or older.

- Prevalence of IBD in the elderly increased by 5.8% between 1999 and 2008, compared to 3.9% in the non-elderly population.

  → d/t elderly-onset IBD

World J Gastroenterol. Aug 14, 2019; 25(30): 4158-4171

Elderly peak of IBD patients

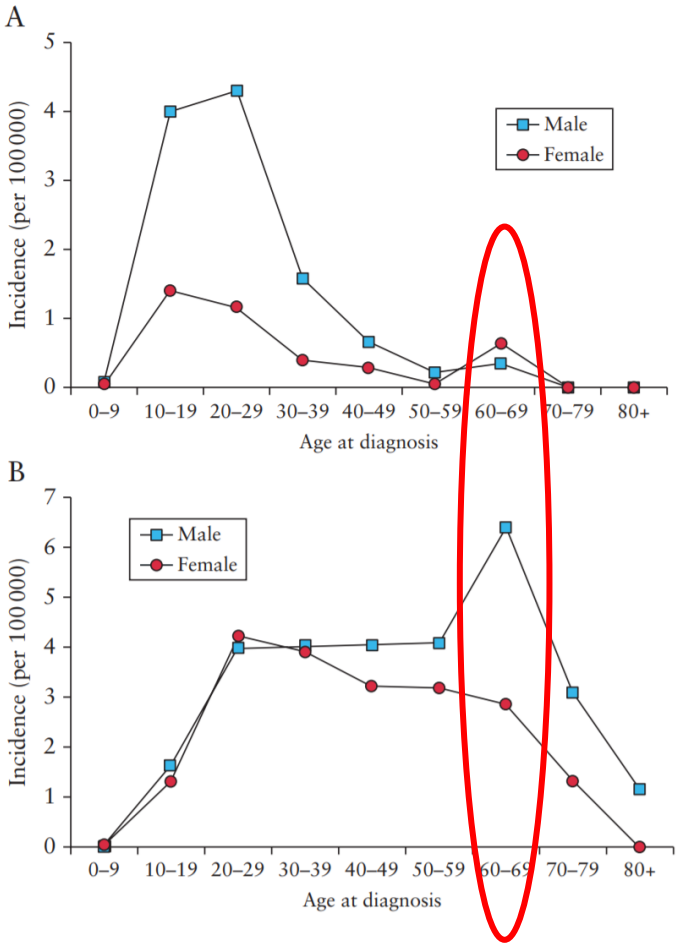


Figure 1. Age-specific incidence of Crohn's disease [A] and ulcerative colitis [B] in the Songpa-Kangdong district, Seoul, 1986–2015.

- Adult-onset elderly IBD
  - higher risk of disease progression in UC (28% *vs* 16% at ten years)
  - increased prevalence of perianal disease upon follow-up in CD (27% *vs* 17%, average follow-up of 6 years)
- Elderly-onset IBD
  - milder, colonic disease

J Crohns Colitis. 2019 Oct 28;13(11):1410-1417

Past reports of elderly IBD pts.

- 60세를 기준으로 볼 때 양군은 치료 반응에 있어 차이가 없다.
  - *Age and Ageing*, Volume 14, Issue 6, November 1985, Pages 366–370

- 노인 UC환자에서 전신적 스테로이드가 필요한 경우가 흔하지만 수술률에는 차이가 없으며 같은 성별 및 연령의 일반인과 비교하여 사망률에 차이가 없다.
  - *Age and Ageing*, Volume 17, Issue 6, 1988, Pages 410–414

Clinical feature of elderly UC

- Males appear to be affected (56%–62%) more often with elderly-onset UC
- The frequency of abdominal pain, weight loss, and fever is lower in elderly-onset disease than in younger-onset disease

- Left sided UC disease was the most common (45%; 95% CI, 40%– 52%), followed by pancolitis (31%), and proctitis (22%).
- Proximal extension was less common (22.9%) elderly-onset UC than in the younger-onset UC (32.0%)

Intest Res. 2018 Apr; 16(2): 194–208.

고령 IBD 환자의 문제점

- 면역체계의 변화
- 감염질환의 위험
- 악성 종양의 고려
- 다양한 동반 만성 질환 (약물)
- 스테로이드 연관 부작용
- 영양 관리
- 수술 등 적극적인 치료의 부작용

Immunosenescence

- Decreased bone marrow production
  - A decrease in hematopoietic stem cells
- Thymic atrophy
  - A decrease in naïve T cells
- Reduced ability of peripheral lymphoid cells to undergo clonal expansion or regeneration

→ an attenuation of cell-mediated immune response, phagocytic activity, and monocyte and macrophage function

Intest Res. 2018 Apr; 16(2): 194–208.

Comorbidities of elderly pts.

- Diabetes and hypertension may not be ideal candidates for steroids
- Anti-TNF therapy is contraindicated in patients with congestive heart failure (NYHA class III/IV)
- A history of recent malignancy (<2 years) may not be suitable candidates for thiopurines where the risk of lymphoproliferative disorders is also higher

Intest Res. 2018 Apr; 16(2): 194–208.

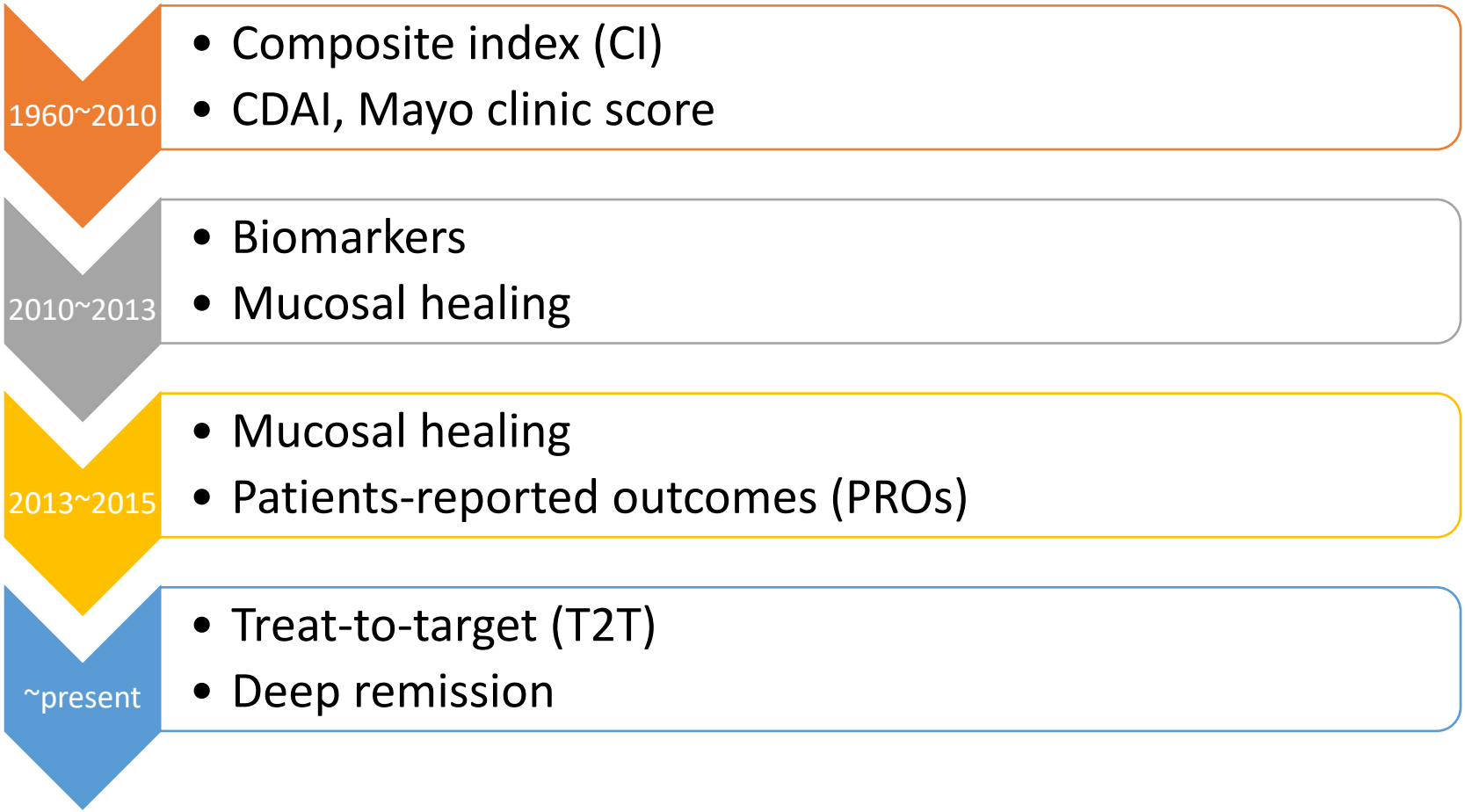
Polypharmacy of elderly pts.

- More than 30% of elderly patients are taking more than 5 prescription medications concurrently in the USA.

→increase the risk of adverse events and drug interactions that could affect the efficacy and safety of IBD medications

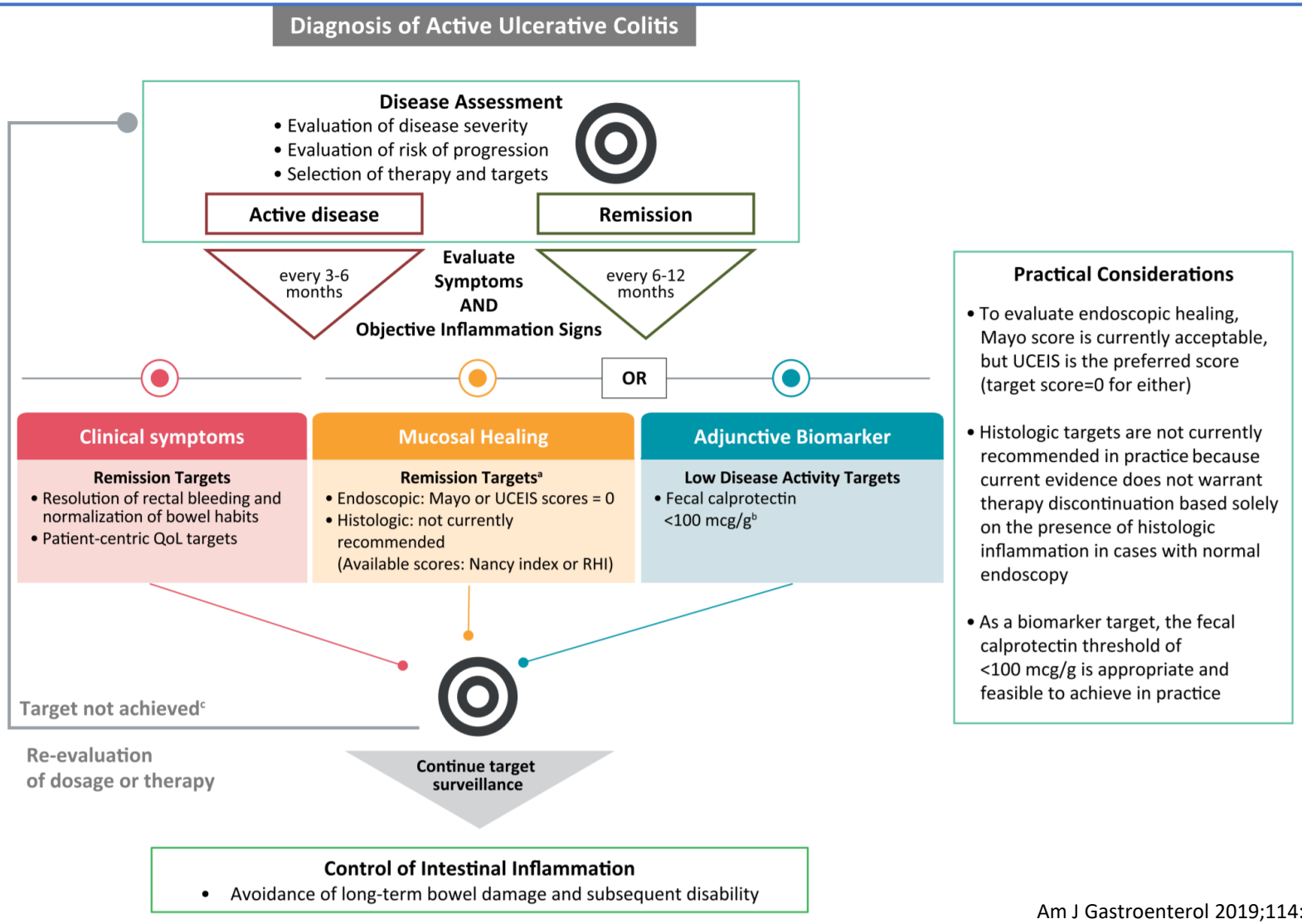
Intest Res. 2018 Apr; 16(2): 194–208.

Selecting therapeutic targets



Korean J Gastroenterol Vol. 71 No. 2, 61-68

T2T in UC



Am J Gastroenterol 2019;114:874–883

T2T in IBD

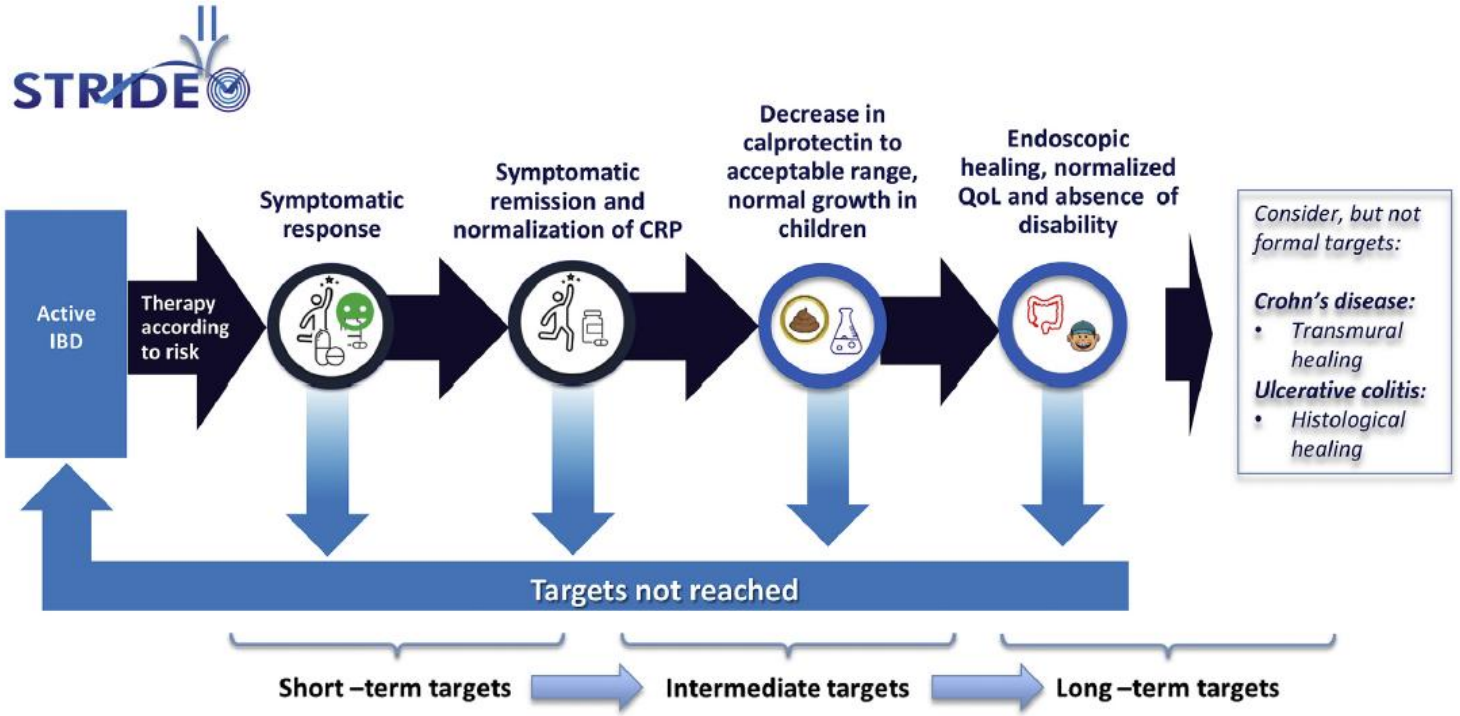


Figure 2. Treatment targets in CD and UC.

Gastroenterology. 2021 Apr;160(5):1570-1583.

Medical treatment of elderly UC

- The most commonly used medications in elderly patients with IBD are 5-ASAs
  - 60% to 90% of patients with UC
- Up to a third of elderly IBD patients receive steroid therapy
  - cumulative probability of steroid use at 10 years being 47% and 40% in elderly patients with CD and UC.
- Overall rates of immunomodulator and biologic use were 17% and 4% in elderly patients with UC

Clinical course of elderly UC

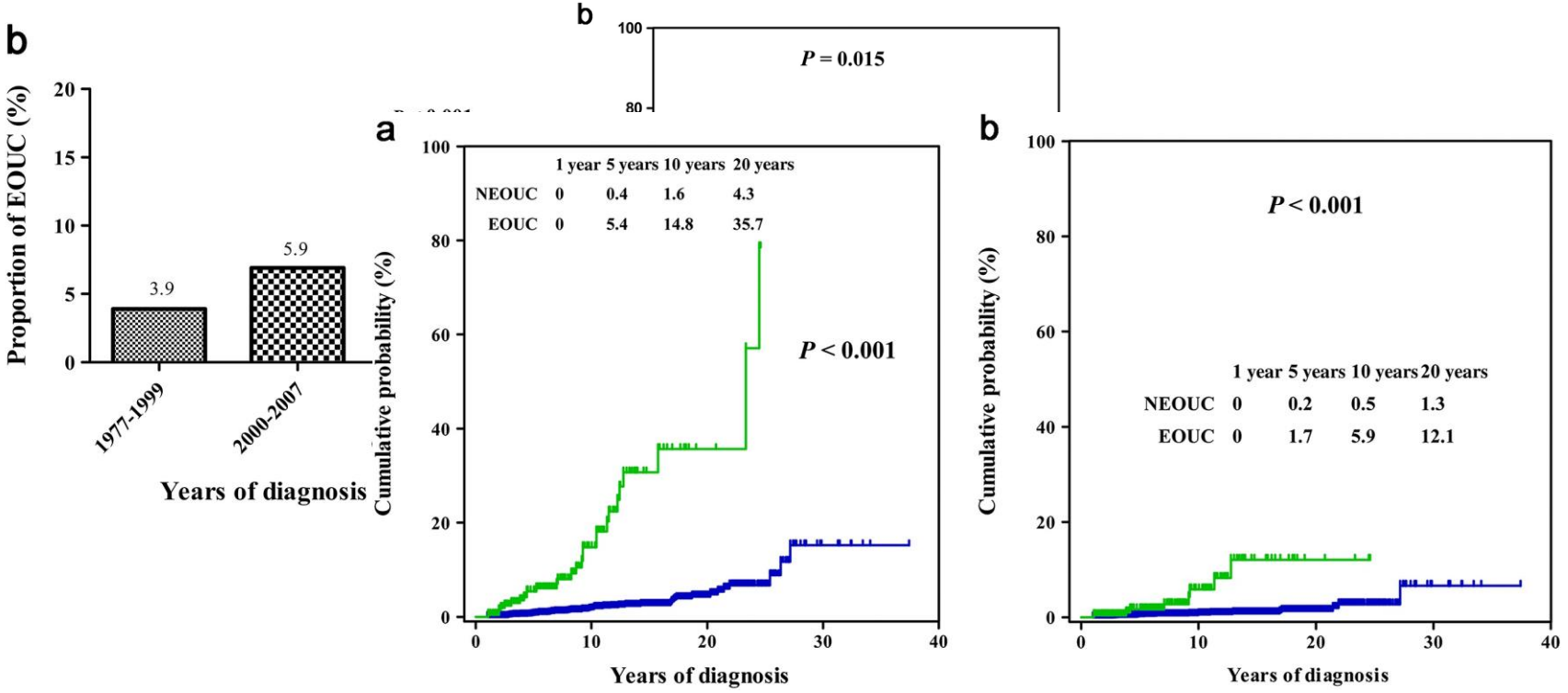
- Overall rates of surgery in patients with UC were 9%.
  - Elderly onset UC were less likely to receive immunomodulators (OR, 0.60; 95% CI, 0.45–0.79) or biologic therapies (OR, 0.41; 95% CI, 0.27–0.62)27 and were more likely to undergo surgery (OR, 1.36; 95% CI, 1.18–1.57; P<0.001).

→ Indolent disease course and fear for drug adverse events

J Crohns Colitis 2016;10:1224-1236.

Clinical course of elderly onset UC

- Among the 3060 patients, 226 were diagnosed with EOUC (7.4%)



J Gastroenterol Hepatol. 2018 Jan;33(1):172-179.

Aminosalicylates

- Complex dosing regimens and polypharmacy could negatively influence compliance
- Reasons for discontinuation of therapy were nausea and/or diarrhea (0.9%), gastrointestinal intolerance (0.4%) and nephritis (0.3%)
- Nephrotoxicity associated with 5-ASA
- 5-ASA has been shown to interact with Warfarin
- Combining antacids and 5-ASA may hinder the therapeutic effects of 5-ASA
- Anorectal dysfunction

Intest Res. 2018 Apr; 16(2): 194–208.

Corticosteroids

- Serious infections (pneumonia, intestinal infections, C. difficile enterocolitis)
- Older patients were found to have a significantly increased fracture risk at 1 year following the initiation of corticosteroids
- Venous thromboembolism was more frequently encountered with corticosteroid users
- 60 years and older treated with corticosteroid monotherapy had significantly worsened depression and anxiety
- corticosteroid use was associated with sleep disturbance, fatigue and worsened anxiety
- Steroids may reduce the activity of drugs such as phenytoin, phenobarbital, ephedrine, rifampicin, and anticoagulant

Intest Res. 2018 Apr; 16(2): 194–208.

Immunomodulators

- Immunomodulators are associated with a higher risk of opportunistic infections and malignancy
  - Lymphoma and non-melanoma skin cancer
- 70% reduced risk of colectomy in those patients treated with thiopurines for more than 12 months in elderly UC patients
- A recent cohort study of elderly-onset IBD found that thiopurine exposure was not associated with an increased risk of developing cancer
- Warfarin, 5-ASAs, and allopurinol

Intest Res. 2018 Apr; 16(2): 194–208.

Biologics (anti-TNF)

- Efficacy of anti-TNF agents in elderly patients are limited and conflicting
  - Same or lower
- Clinical response in the elderly to be significantly lower than in younger patients with IBD (60~70% vs. 80~90%)
- The long-term efficacy (>6 months) was similar between the 2 groups

Intest Res. 2018 Apr; 16(2): 194–208.

- Data on safety of anti-TNF therapy consistently report increased rates of adverse events in elderly patients
- A recently-accepted meta-analysis (elderly patient with auto-immune diseases)
  - 3 times more at risk of infections (OR = 3.48, 95%CI: 1.98-6.14) and malignancy (OR = 3.47, 95%CI: 1.71-7.03)
  - biologic agents were eleven times at higher risk of infections (OR = 11.22, 95%CI: 3.6-34.99)

- Steroids, immune-modulator combination
- Aging factor, comorbidity

Clin Gastroenterol Hepatol. 2019

Biologics (others)

- Anti-TNF vs. vedolizumab in elderly IBD
  - Remission
    - 3 months (50% *vs* 38%, *P* = 0.07), then became comparable at 6 mo (54% *vs* 45%, *P* = 0.23) and 12 mo (58% *vs* 54%, *P* = 0.63)
  - Significant infection
    - 20% for anti-TNF and 17% for vedolizumab
    - *Clostridium difficile* infection and gastrointestinal infections were also similar between groups (21% *vs* 18%, *P* = 0.57)
  - Malignancy
    - 3% of anti-TNF patients and 1% of vedolizumab-treated patients

Aliment Pharmacol Ther. 2019;49:873-879

Surgery

- Elderly age appears to be a predictor of early surgery among patients with UC

- Permanent ileostomy (TPCI)
  - Disturbance of sphincter function and fecal incontinence after surgery in elderly patients (79.9%)
- Odds of 30-day postoperative mortality in elderly patients was 4.4-fold greater in UC (6.1% vs. 0.7%)
- The rates of postoperative complications (34.5% vs. 21.3%, $P<0.001$) was significantly higher

- In a study of 32,833 patients with UC, elective colectomy was associated with better survival than medical therapy (HR, 0.70; 95% CI, 0.54–0.90)

Intest Res. 2018 Apr; 16(2): 194–208.

VACCINATIONS

- Sub-optimal serological responses

- influenza vaccine annually
- pneumococcal vaccine given periodically (5-yearly)
- hepatitis A and B series of vaccinations (if not immune)

- Live vaccines must be avoided in immuno-suppressed patients

Intest Res. 2018 Apr; 16(2): 194–208.

Conclusion

- Concerning elderly UC patients
- Age-specific concerns such as comorbidity, locomotor, and cognitive function, polypharmacy
- Appropriate therapeutic target
- Immunomodulatory and biologics in well-selected patients
- Individualized clinical decisions