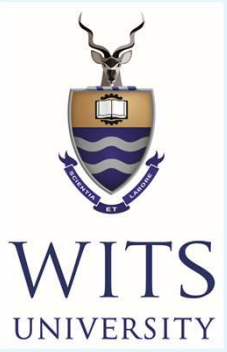
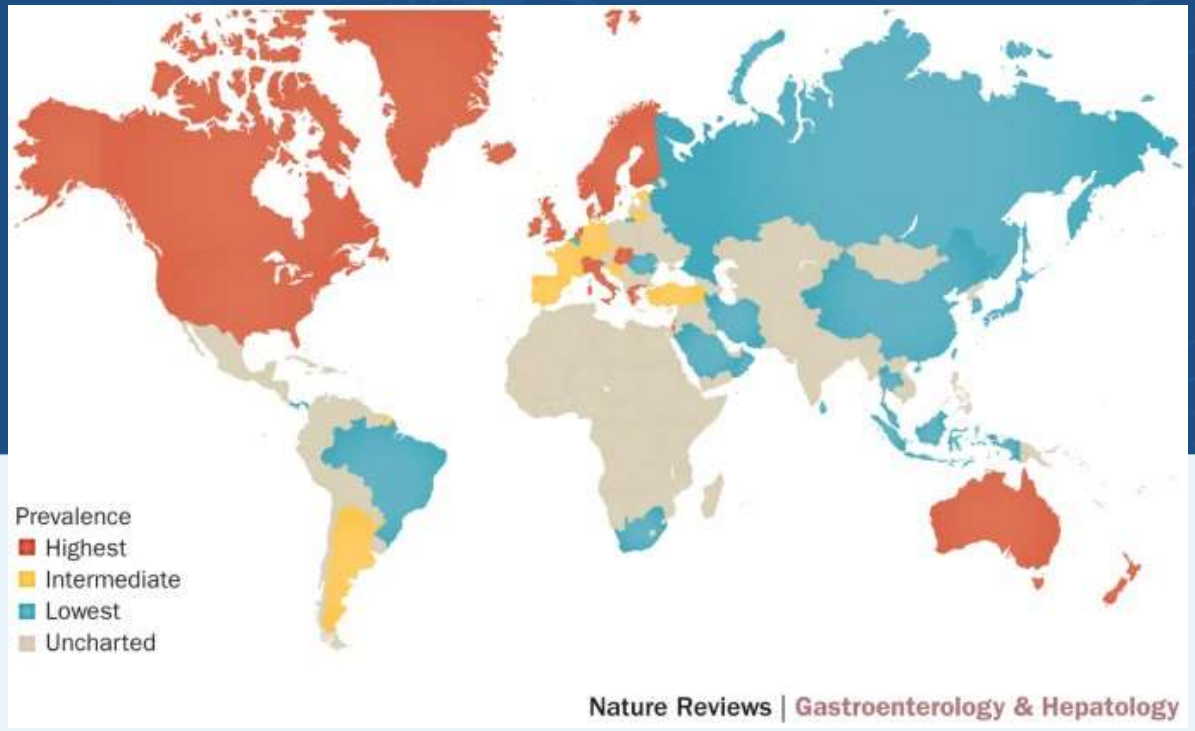
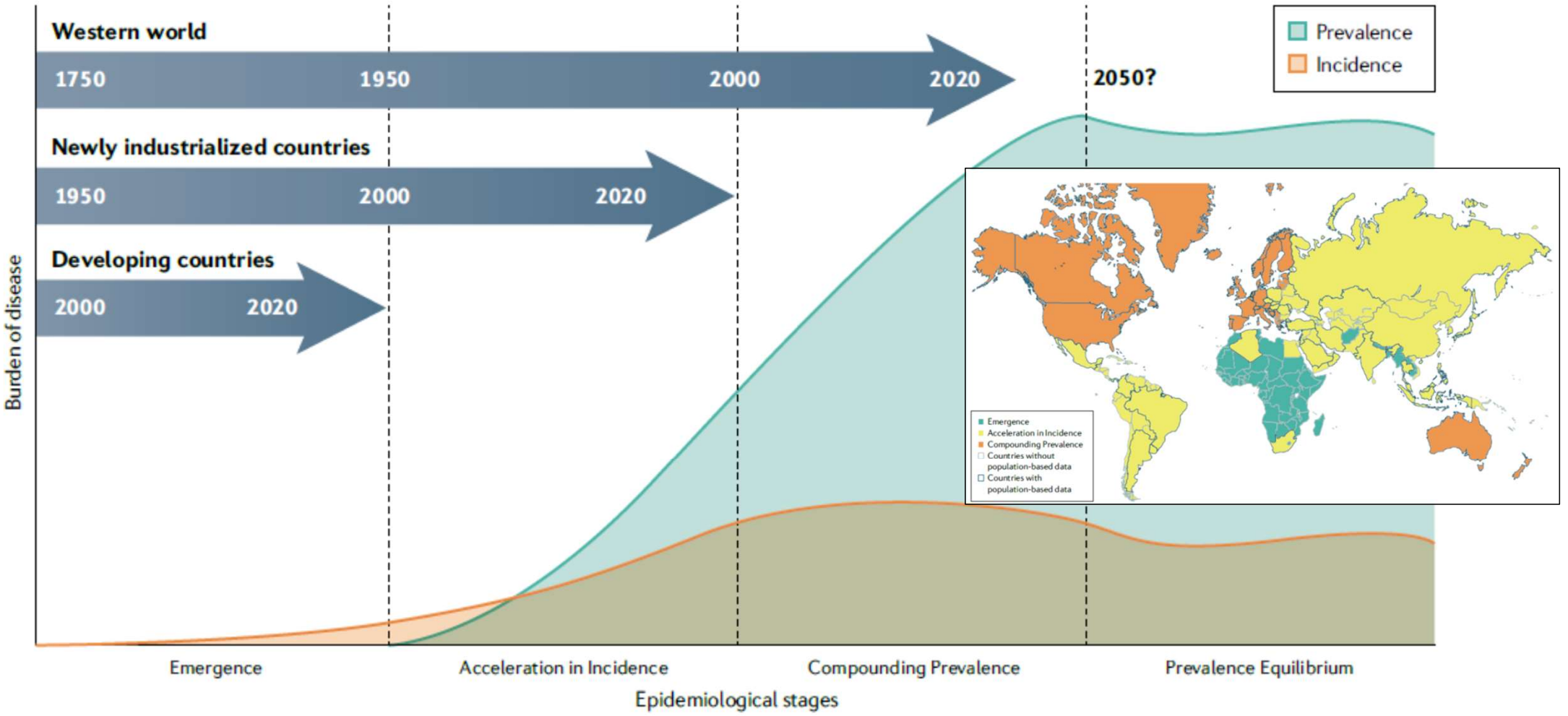
IBD Management in *a* State

Tim De Maayer



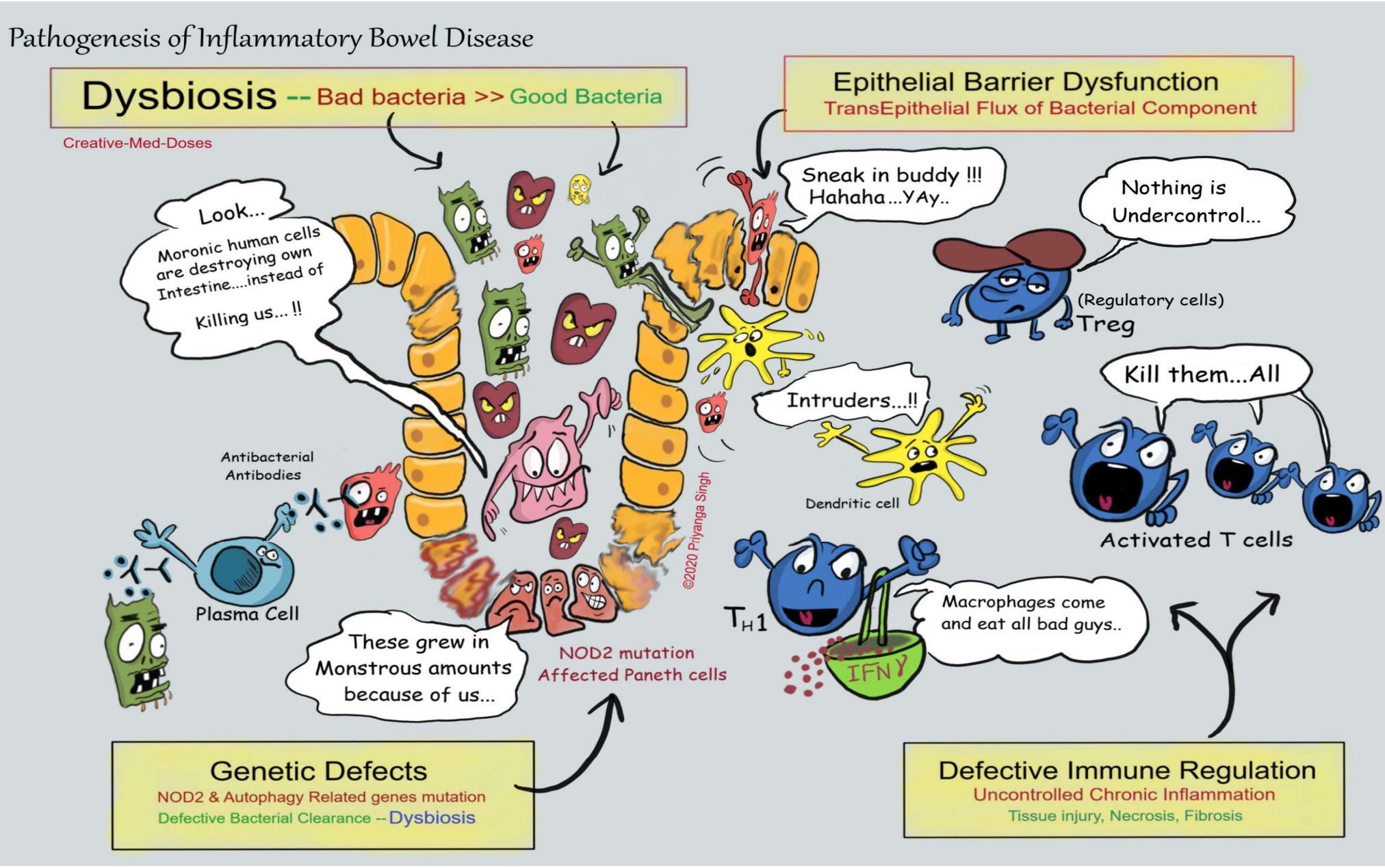
Epidemiology





Kaplan, *Nature reviews,* 2021

Pathogenesis of Inflammatory Bowel Disease



Diet

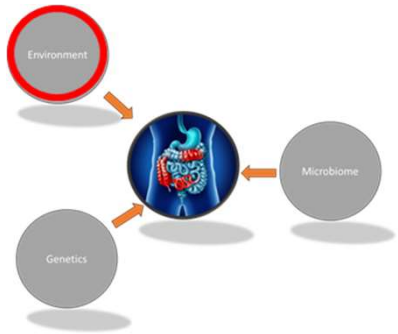
- Emulsifiers
- Ultra-processed foods
- High fibre vs fermented diet

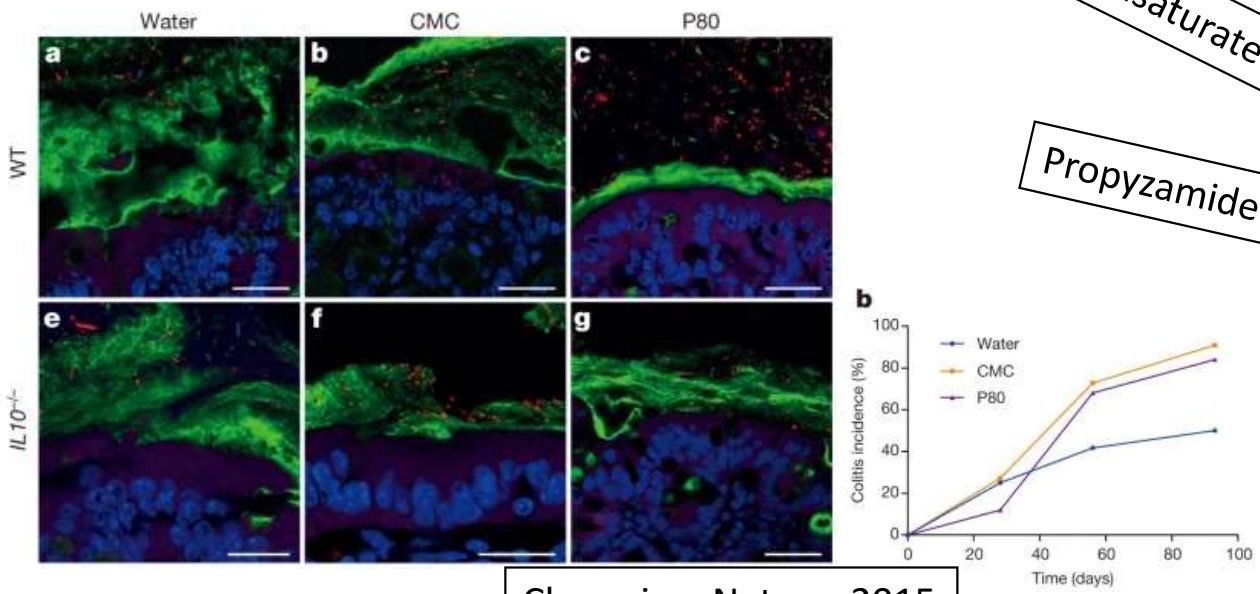
Debaryomyces hanseii

Artificial sweeteners

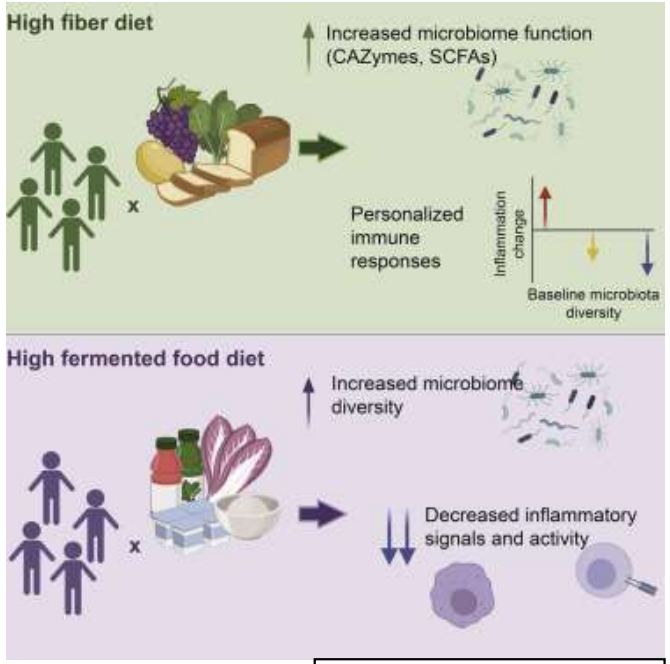
Polyunsaturated fats

Propyzamide

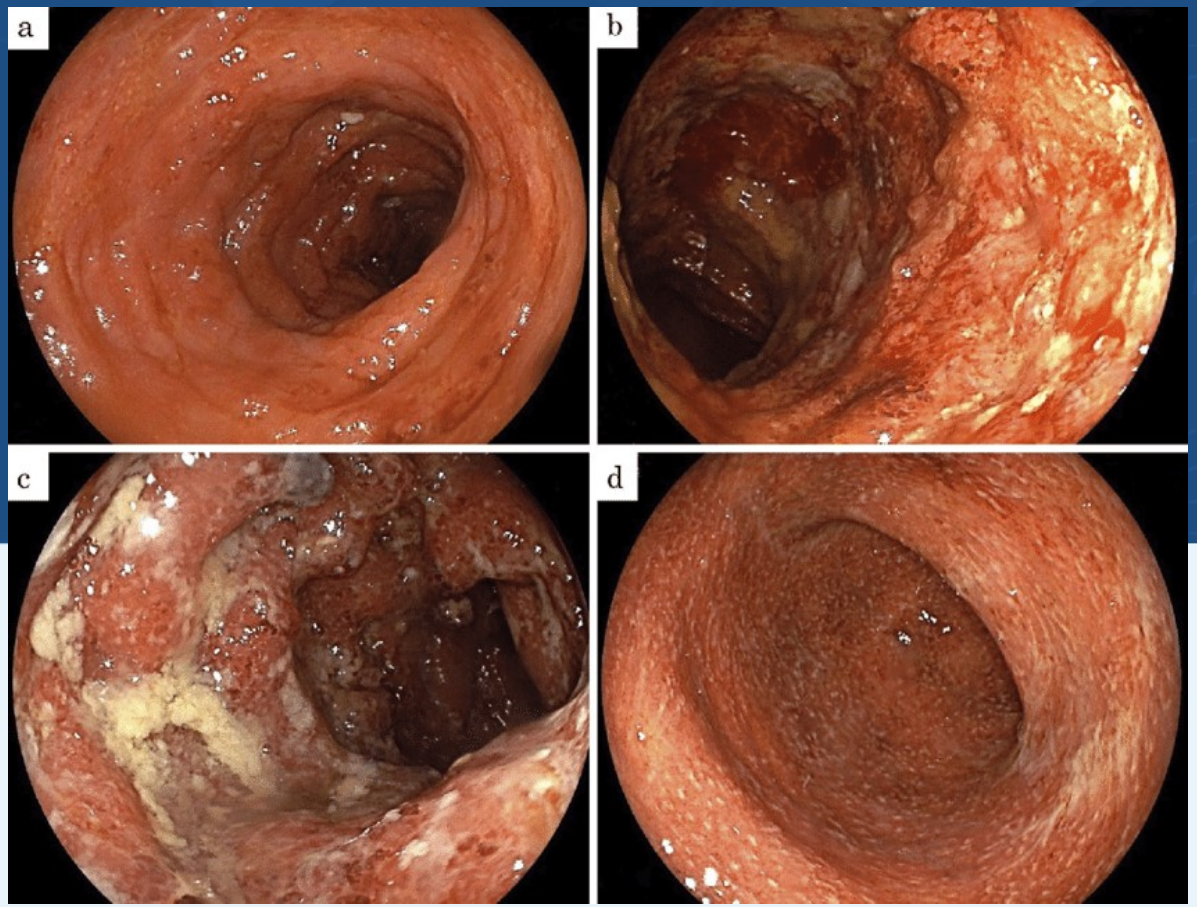




Chassaign, Nature, 2015

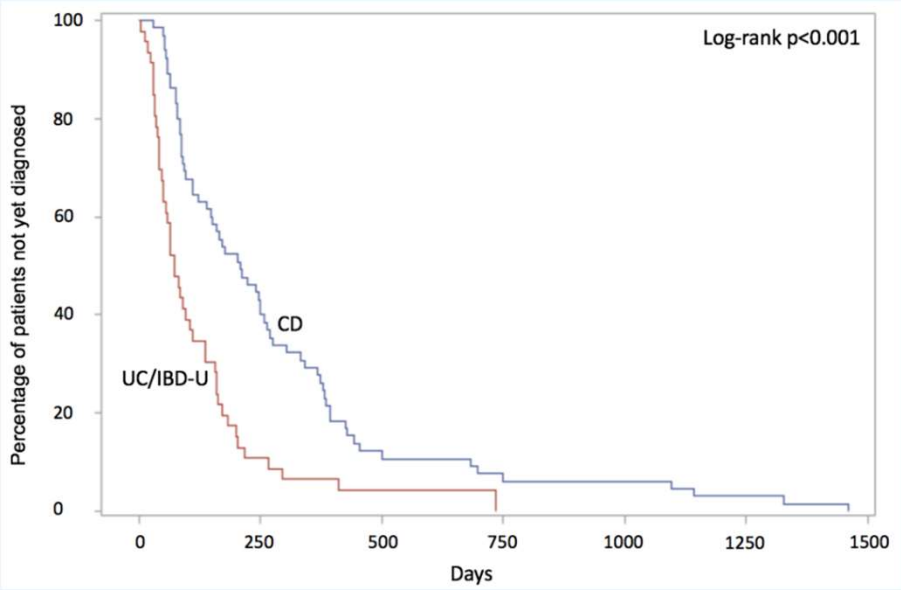


Wastyk, Cell, 2021



Diagnosis

Diagnostic delay



Ricciuto A, et al. *Arch Dis Child* 2018

- Delayed Growth & Development
- Disease complications
- Decreased effectiveness of treatment

Poor access

- Appropriate investigations & timeous referral
- Paediatric GIT
- Quality endoscopy (upper & lower), adequate biopsies
- Histopathologists
- Capsule endoscopy / MRE

Entamoeb
Strongyloid
Schistoson

	Features favouring Crohn's disease	Features favouring intestinal tuberculosis
Clinical	Positive IBD family history; perianal disease; diarrhoea; haematochezia; extra-intestinal manifestations	Previous tuberculosis; positive tuberculosis contact; night sweats; swinging fever; ascites
Laboratory	NA	Positive tuberculin skin test; positive interferon-γ release assay; positive tissue polymerase chain rection; positive HIV test; positive urinary lipoarabinomannan
Endoscopic	Left colonic involvement; longitudinal ulcers; aphthous ulcers; cobblestoning; skip lesions	Transverse ulceration; patulous ileocaecal valve; tumour-like lesions
Radiographic	Involvement of the left colonic segment; long-segment involvement; skip lesions; presence of the comb sign; mesenteric fibro-fatty proliferation; visceral fat	Chest x-ray showing active or healed pulmonary tuberculosis; involvement of ileocaecal area; shorter length of involvement; presence of lymph nodes larger than 1 cm; lymph nodes with necrosis
Histological	Small granulomas; ill-defined and sparse granulomas; architectural distortion distant to granulomatous inflammation; focal enhanced colitis	Large granulomas; confluent and dense granulomas; submucosal granulomas; granulomas with surrounding cuffing lymphocytes; ulcers lined by a band of epithelioid histiocytes; disproportionate submucosal inflammation

Table: **Features differentiating Crohn's disease from intestinal tuberculosis**

Watermeyer, *Lancet Gastroenterol Hepatol*, 2022

Index of suspicion

Symptoms:

- Diarrhoea (>2/52, nocturnal, tenesmus)
- Bloody diarrhoea (exclude constipation!)
- Weight loss
- Abdominal pain > 2/52 (esp. nocturnal)
- Family history

Signs:

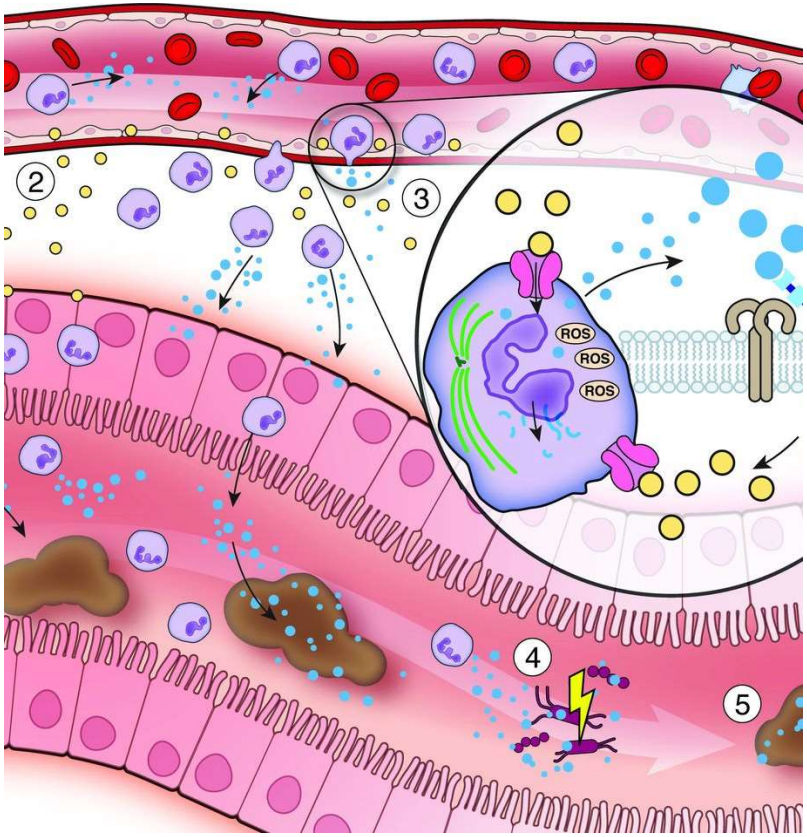
- Perianal disease (fistulae, fissures, tags)
- Frequent severe mouth ulcers
- Extraintestinal manifestations (arthritis, uveitis, erythema nodosum)

Investigations:

- Stool MCS and C diff
- Bloods: FBC, CRP/ESR, Albumin
- Faecal calprotectin

Faecal calprotectin

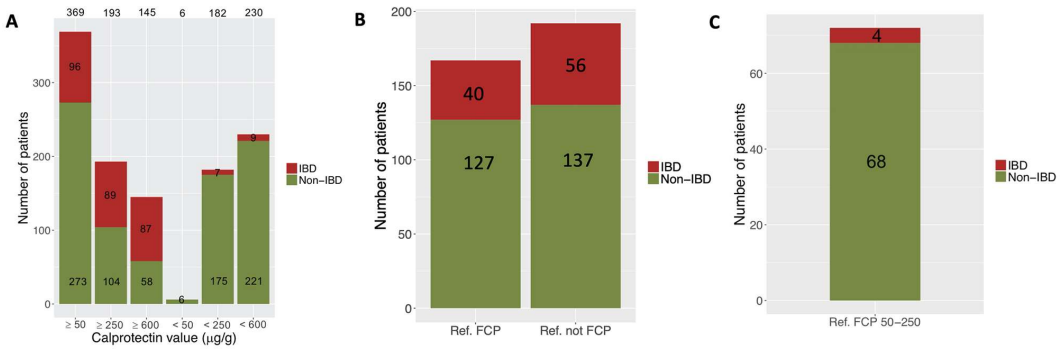
- Inflammatory protein secreted by intestinal leucocytes
- Beware its pitfalls!
  - False positives in NSAID use, haemorrhoidal bleeding, polyps…
  - High variability in young children:
    - Don’t use in infants
    - Adult levels reached 5 to 6 years
- In IBD:
  - Can help distinguish functional disease from IBD
  - Good tool for monitoring IBD (if you can afford it)
    - Combination of low CRP and FC correlates well with endoscopic healing
    - Rise in FC precedes clinical relapse 2 to 3 months

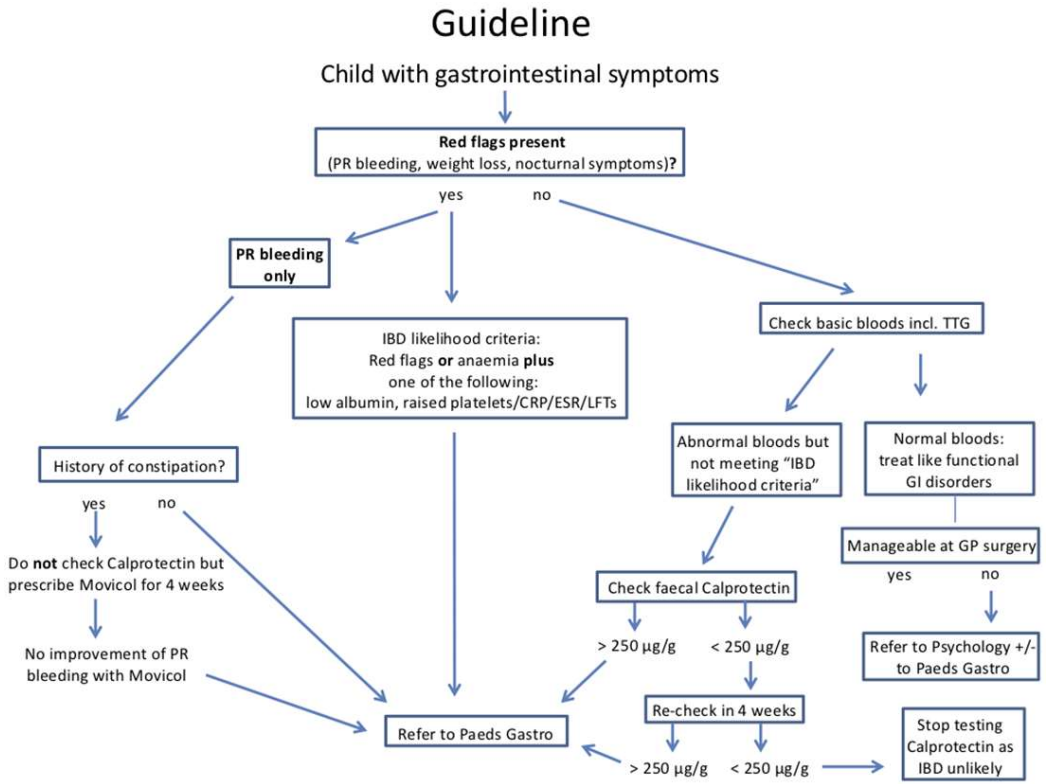


Age group	Number of patients	Median FCP (μg/g)	Interquartile range	p value
< 1y	n = 34	205	498	p < 0.001 compared to all other age groups
1-5y	n = 582	55	120	p < 0.001 compared to 6-14y
6-14y	n = 1598	41	80	p = 0.080 compared to 15-16y
15-16y	n = 579	47	113	p = 0.099 compared to 1-5y

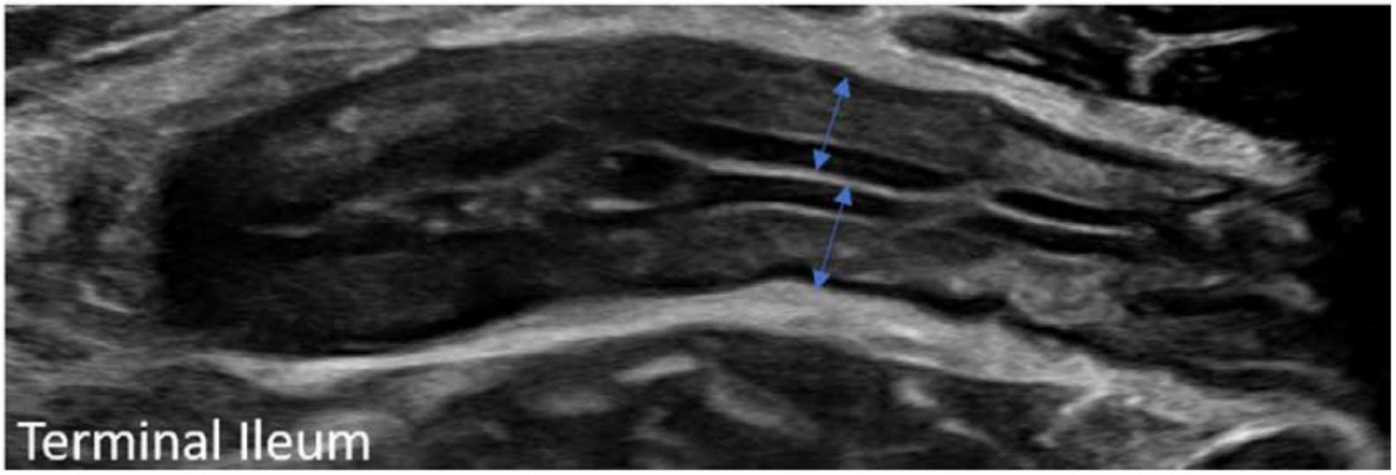
FCP: Faecal Calprotectin.

https://doi.org/10.1371/journal.pone.0246091.t002

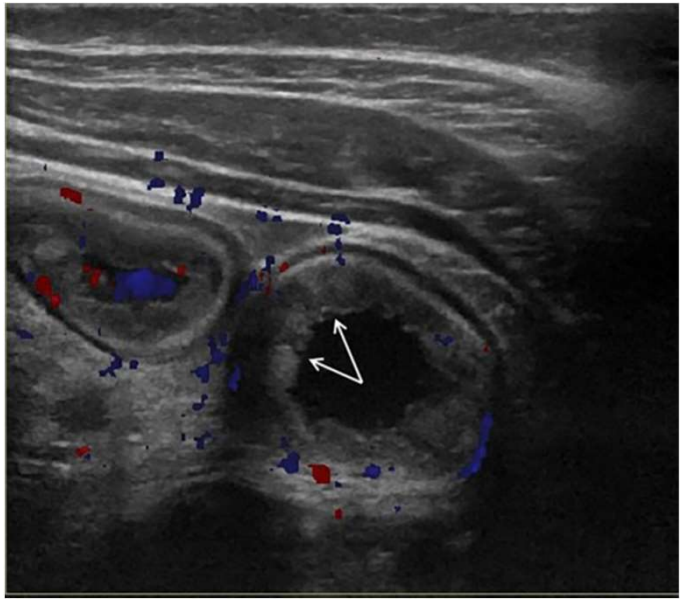


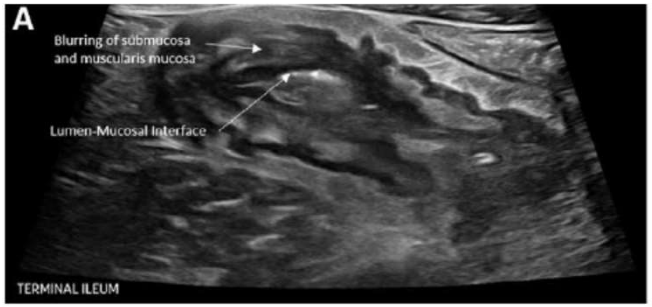


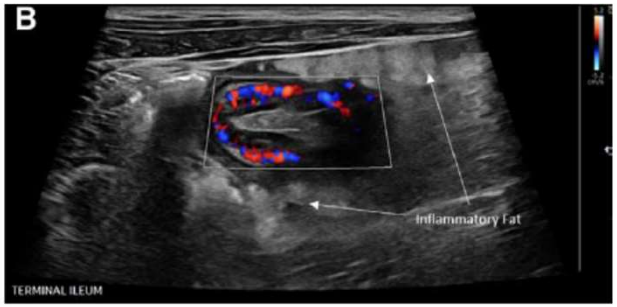
Orfei et al. *PLOS ONE*. 2021

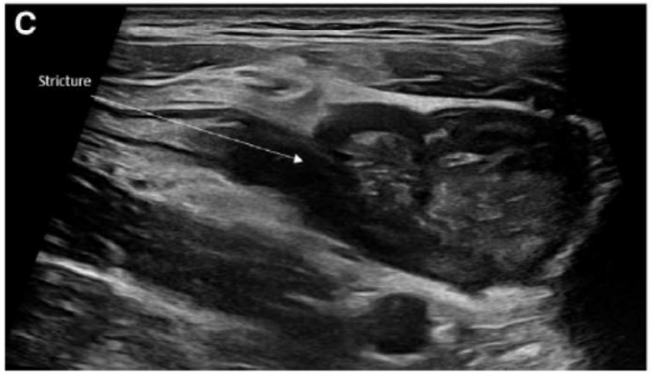


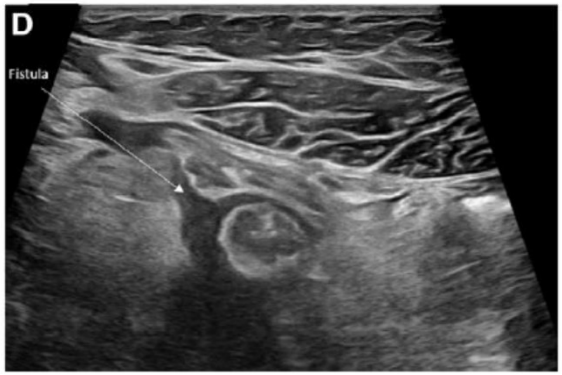
Intestinal ultrasound












Treatment

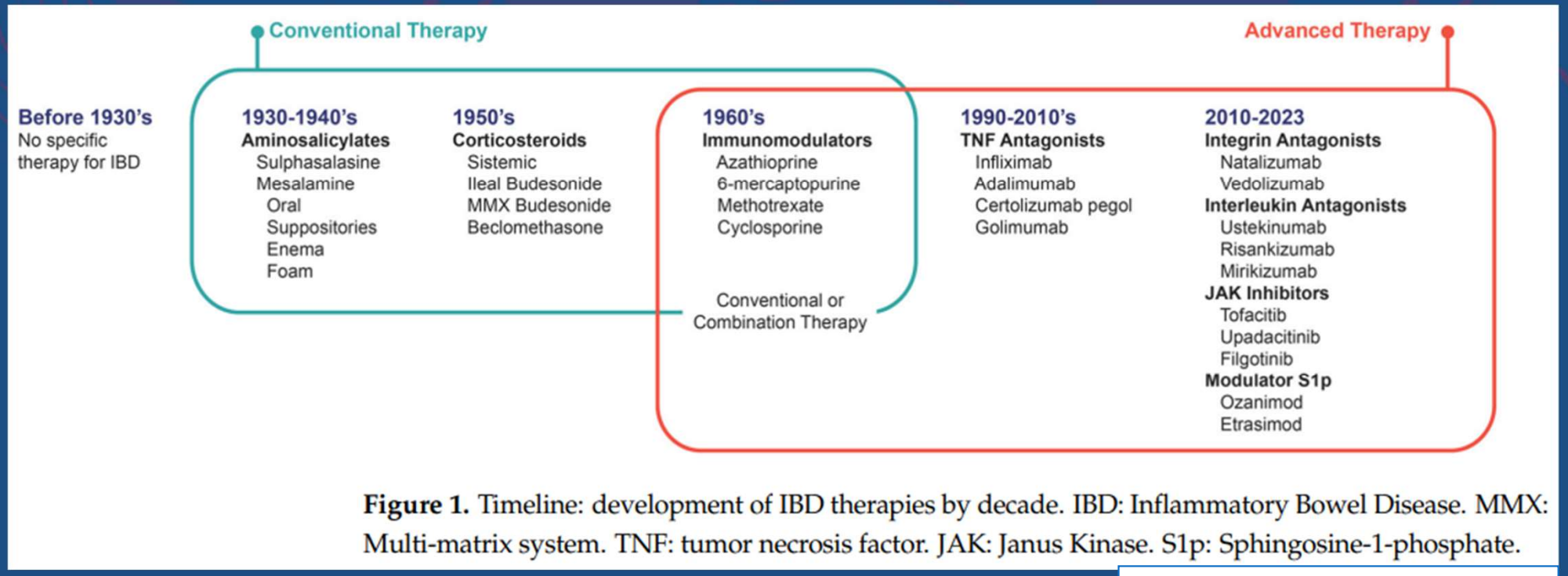


Figure 1. Timeline: development of IBD therapies by decade. IBD: Inflammatory Bowel Disease. MMX: Multi-matrix system. TNF: tumor necrosis factor. JAK: Janus Kinase. S1p: Sphingosine-1-phosphate.

Imbrizi et al. *Pharmaceuticals.* 2023

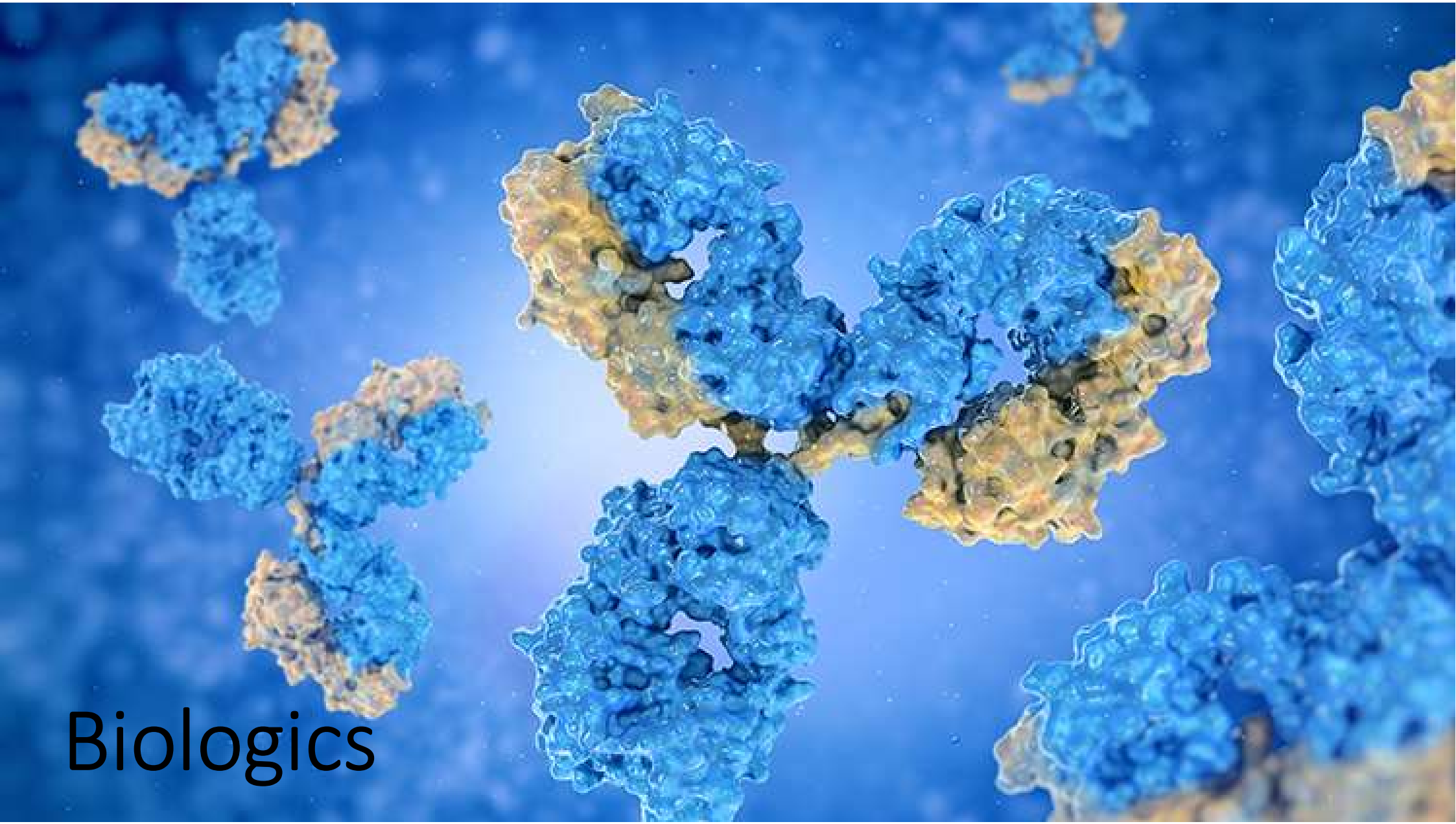
Paediatric IBD EMA approvals

IFX CD 2007 → IFX UC 2010 → ADA CD 2012 → ADA UC 2019

SA EDL Tertiary/Quaternary Approval:

IFX/ADA Fistulising CD March 24 → IFX/ADA luminal CD May 24

Most cost-effective
Not for UC
Not First-line


Biologics

Biologics & biosimilars

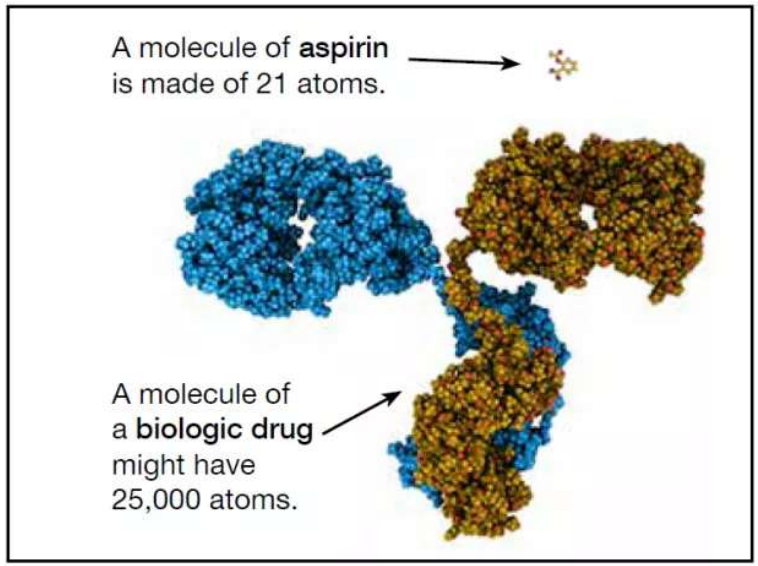
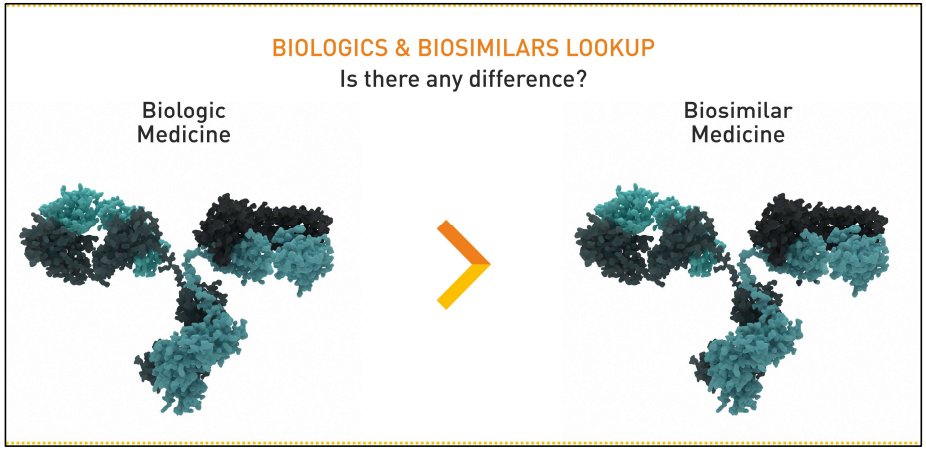
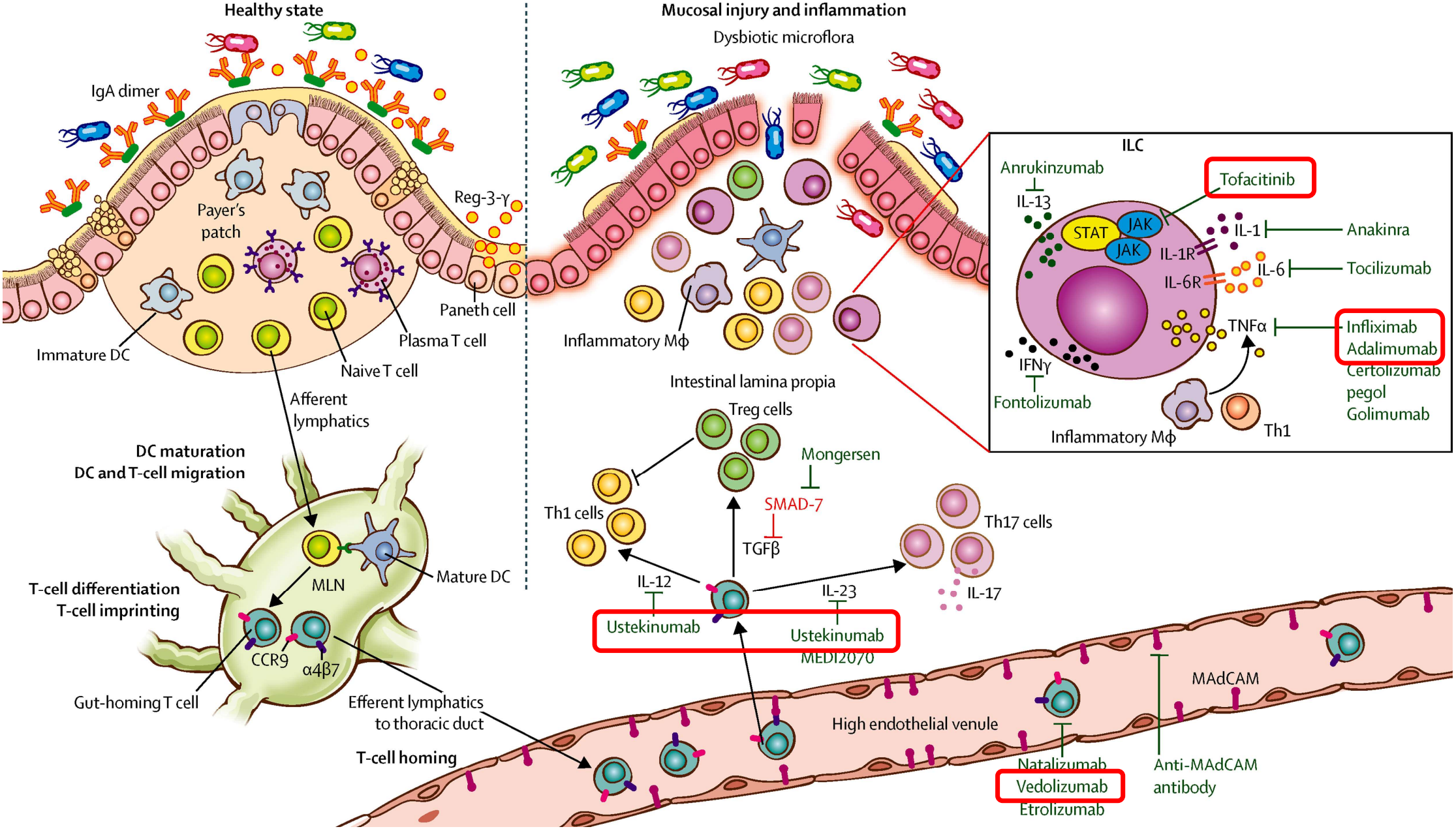


Table 1: Overview of the main differences between chemical and biological drugs

Chemical	Biological
Produced by chemical synthesis	Produced by living cell cultures
Low molecular weight	High molecular weight
Well-defined structure	Complex, heterogeneous structure
Mostly process-independent	Strongly process-dependent
Completely characterised	Impossible to fully characterise the molecular composition and heterogeneity
Stable	Unstable, sensitive to external conditions
Mostly non-immunogenic	Immunogenic




Healthy state
IgA dimer
Payer's patch
Reg-3-γ
Paneth cell
Plasma T cell
Immature DC
Naive T cell
Afferent lymphatics
DC maturation
DC and T-cell migration
MLN
Mature DC
T-cell differentiation
T-cell imprinting
CCR9
α4β7
Gut-homing T cell
Efferent lymphatics to thoracic duct
T-cell homing
Mucosal injury and inflammation
Dysbiotic microflora
Inflammatory Mϕ
Intestinal lamina propia
Treg cells
Mongersen
SMAD-7
TGFβ
Th1 cells
Th17 cells
IL-12
IL-23
IL-17
Ustekinumab
Ustekinumab
MEDI2070
High endothelial venule
MAdCAM
Natalizumab
Vedolizumab
Etrolizumab
Anti-MAdCAM antibody
ILC
Anrukinzumab
IL-13
Tofacitinib
STAT
JAK
JAK
IL-1R
IL-1
Anakinra
IL-6R
IL-6
Tocilizumab
TNFα
Infliximab
Adalimumab
Certolizumab pegol
Golimumab
IFNγ
Fontolizumab
Inflammatory Mϕ
Th1

DECISIONS!

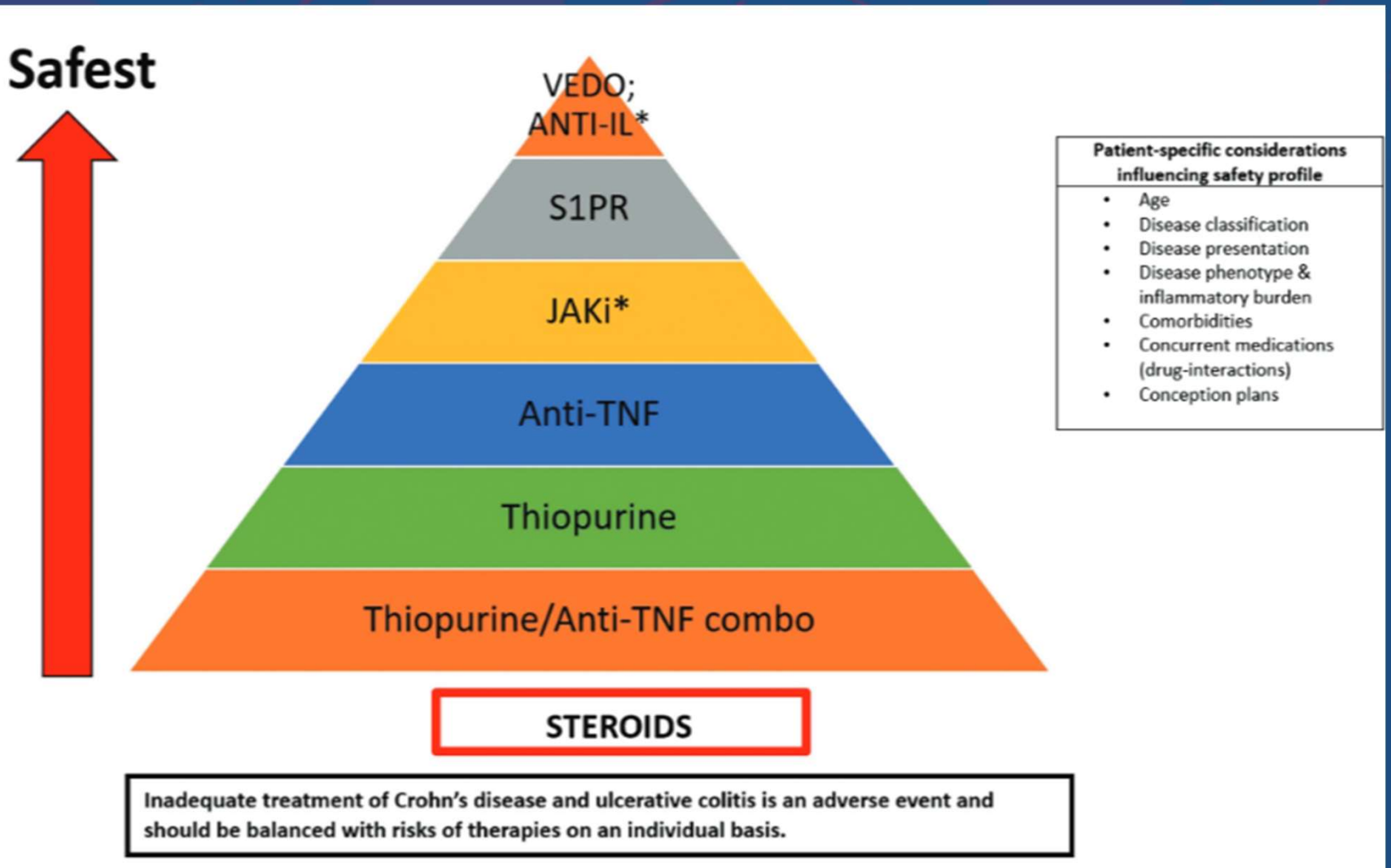
Disease type

Disease Severity / inflammatory burden

Age

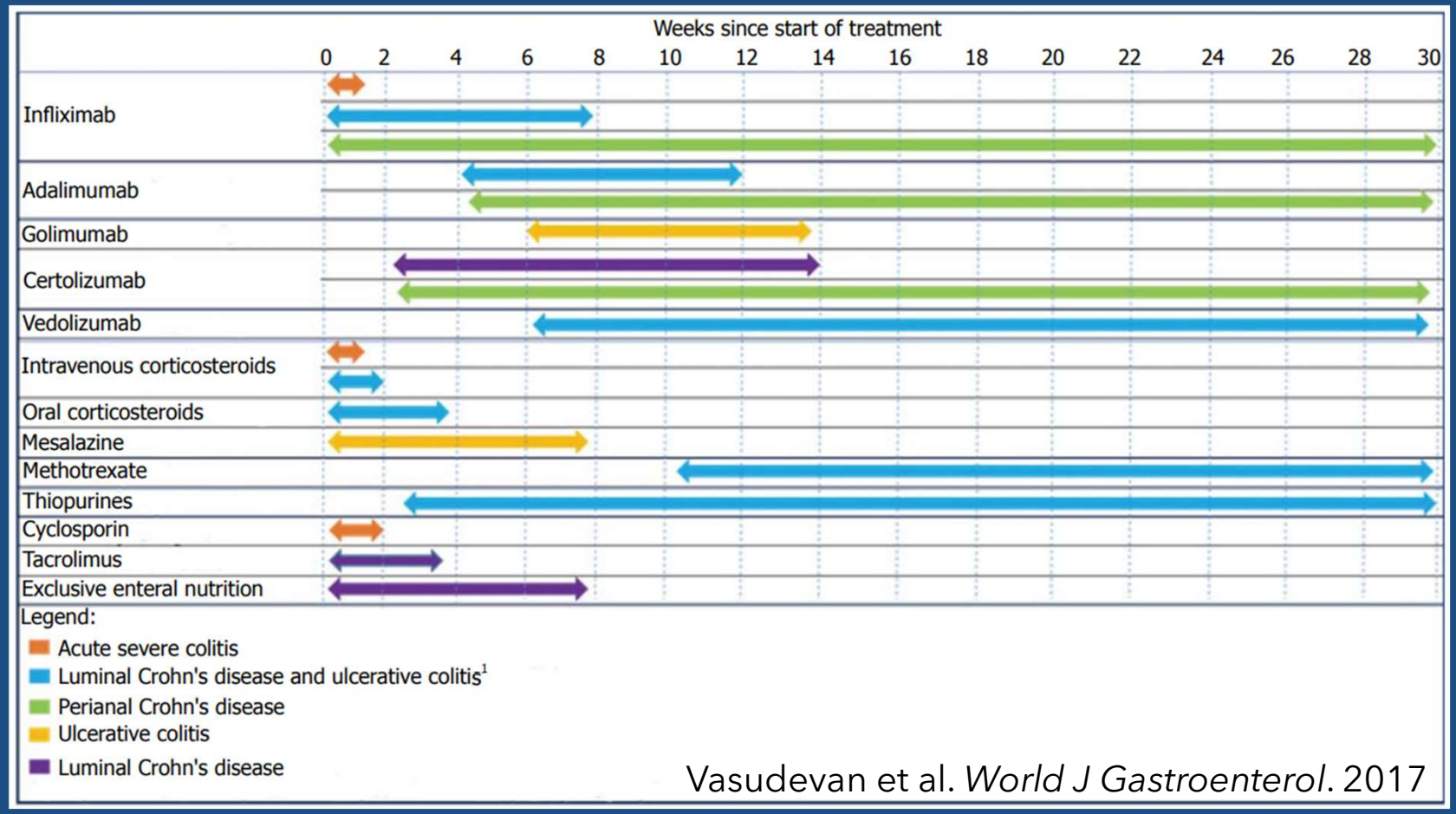
Safety profile

Concurrent medications



Bhat, *Inflamm Bowel Dis*, 2024

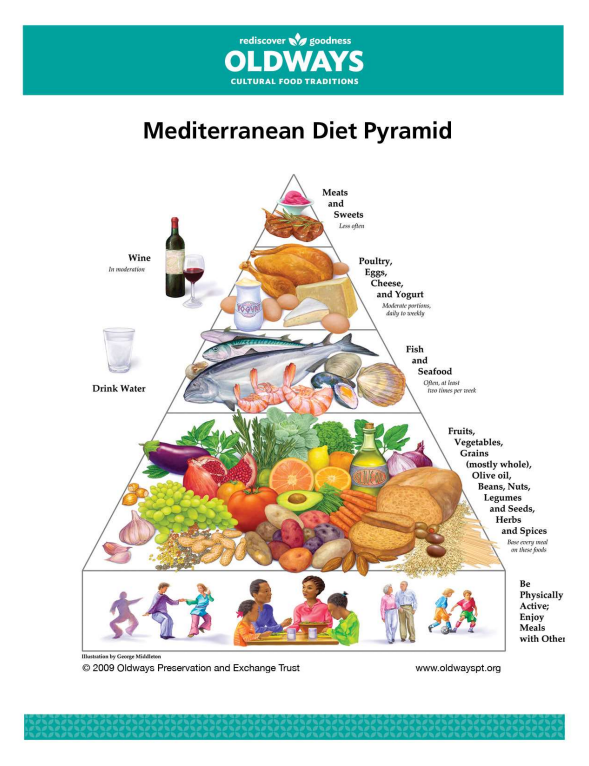
Time to clinical response and remission for therapeutics in inflammatory bowel diseases



Vasudevan et al. *World J Gastroenterol*. 2017

Diet as treatment

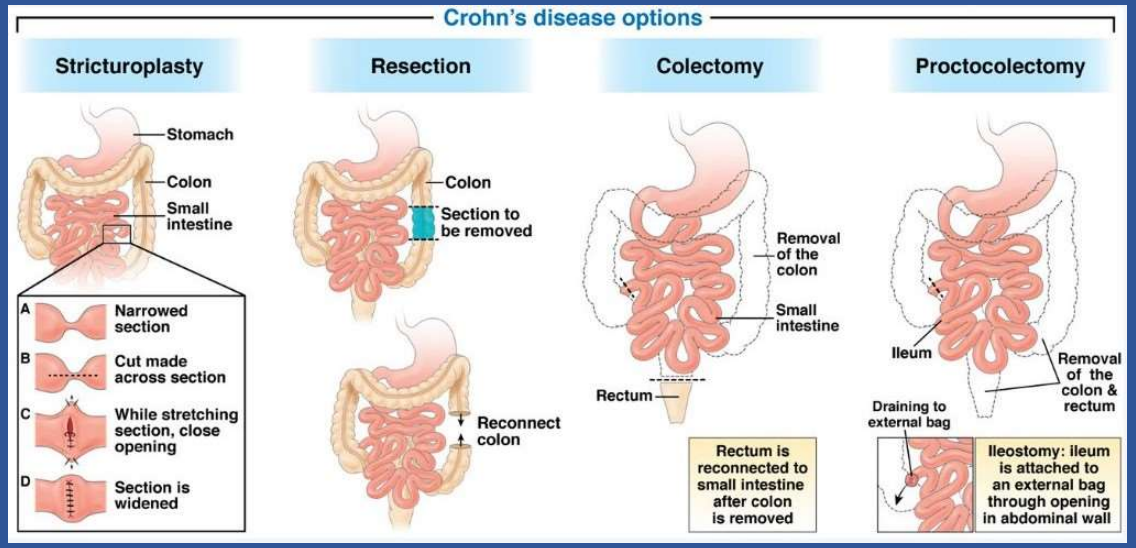
- Exclusive enteral nutrition
- Crohn disease exclusion diet
- CD Treat
- Mediterranean diet
- Specific carbohydrate diet, anti-inflammatory diet, ….



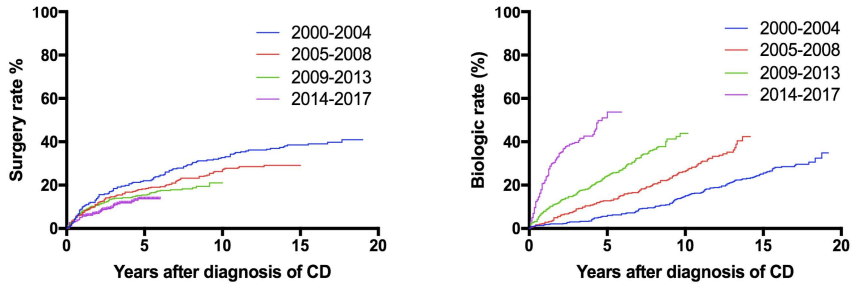
Surgery

- UC + colectomy → curative
- CD surgery 3 main groups:
  - Ileo-caecal resection to achieve remission (Not curative!)
  - Surgery to treat complications: fistulae, collections, strictures
  - Salvage surgery: subtotal colectomy/small bowel resection

Amil-Diaz, JPGN, 2017

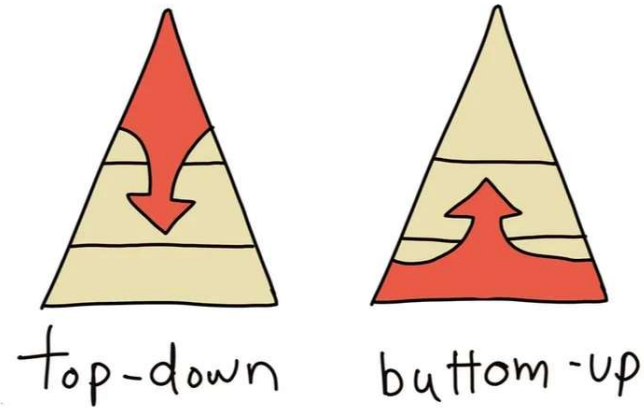


The rates of surgical resection in Crohn's disease have decrease as biologic prescribing has been earlier



Jenkinson P et al *Journal Crohn's Colitis* 2020

Bottom-up approach



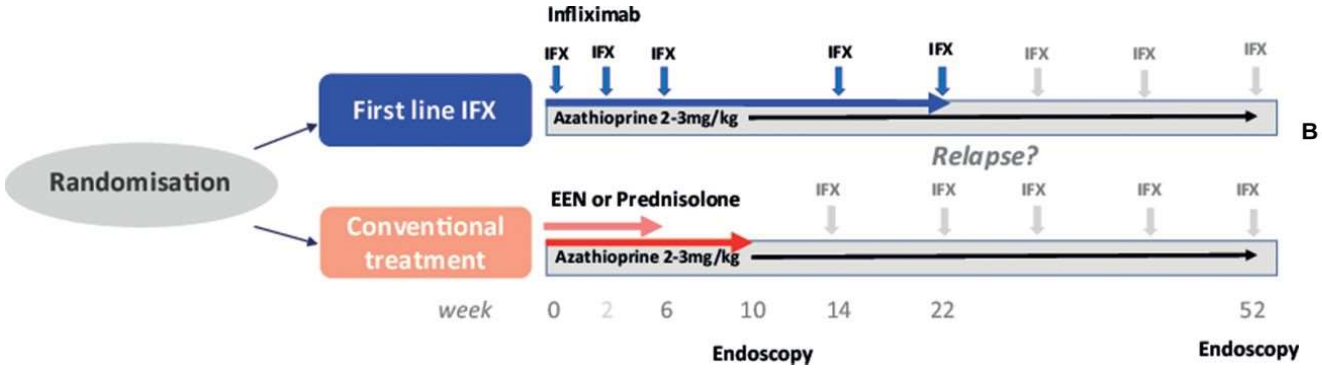
- REACH trial (published 2007):
  - 112 children with active CD despite steroids & immunomodulators
  - Infliximab given 8 or 12 weekly
  - Remission rates 56% vs 23%
- IMAgINE trial (published 2012):
  - 188 children with active CD despite conventional Rx
  - Adalimimab given 2-weekly
  - Remission rate 33.5%

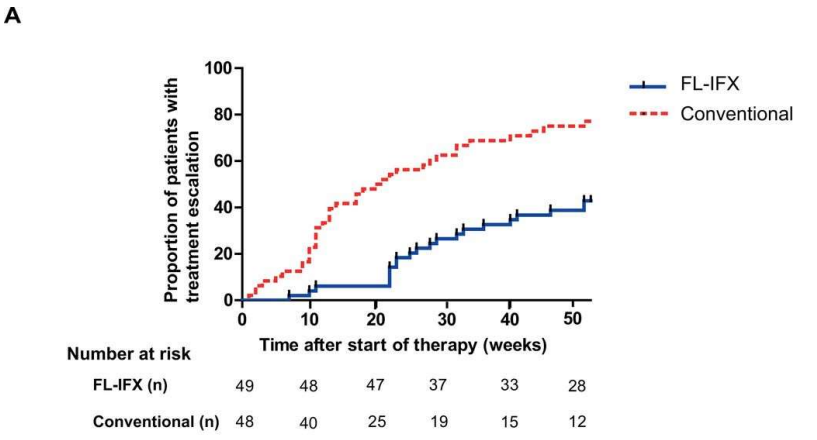
Hyams, Gastroenterology, 2007 & 2012

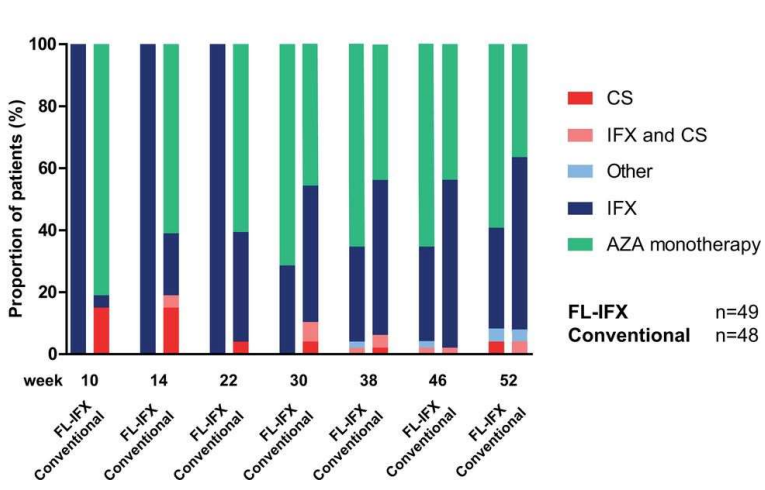
TISKIDS

100 children 3 to 17y old with

Untreated, mod/severe CD





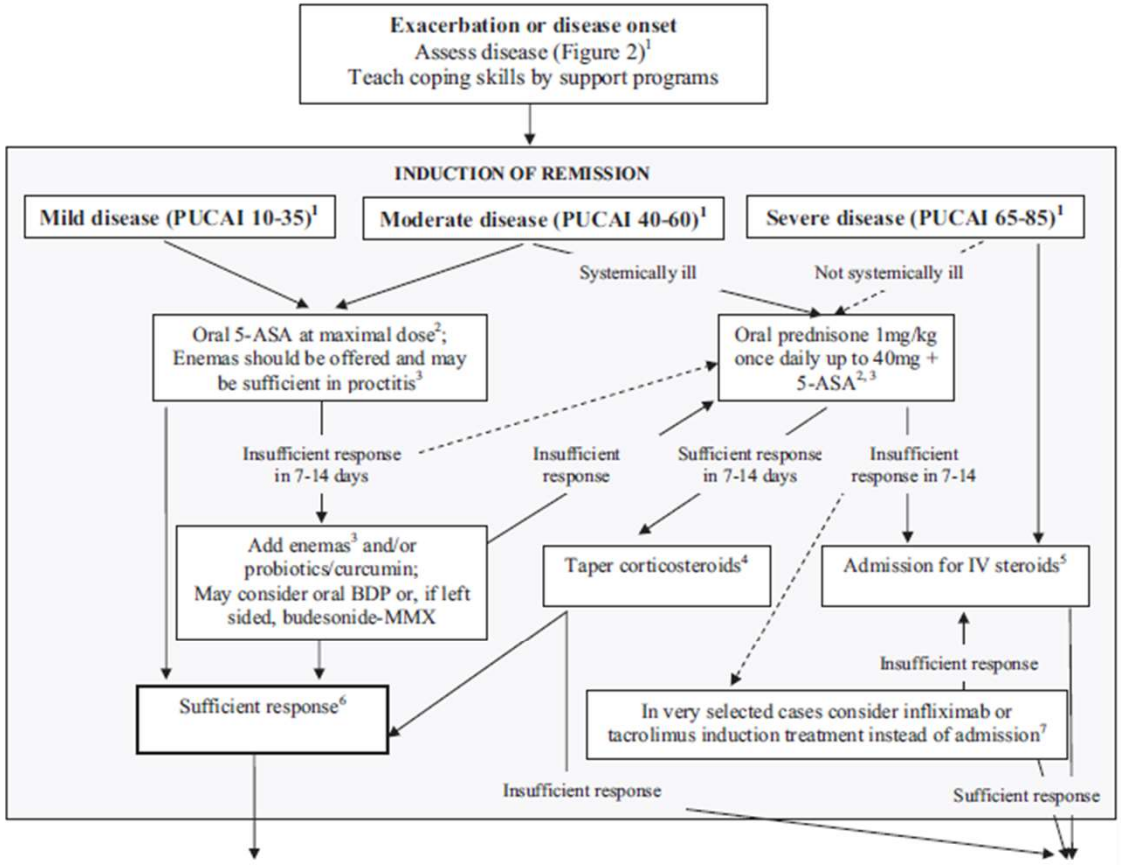


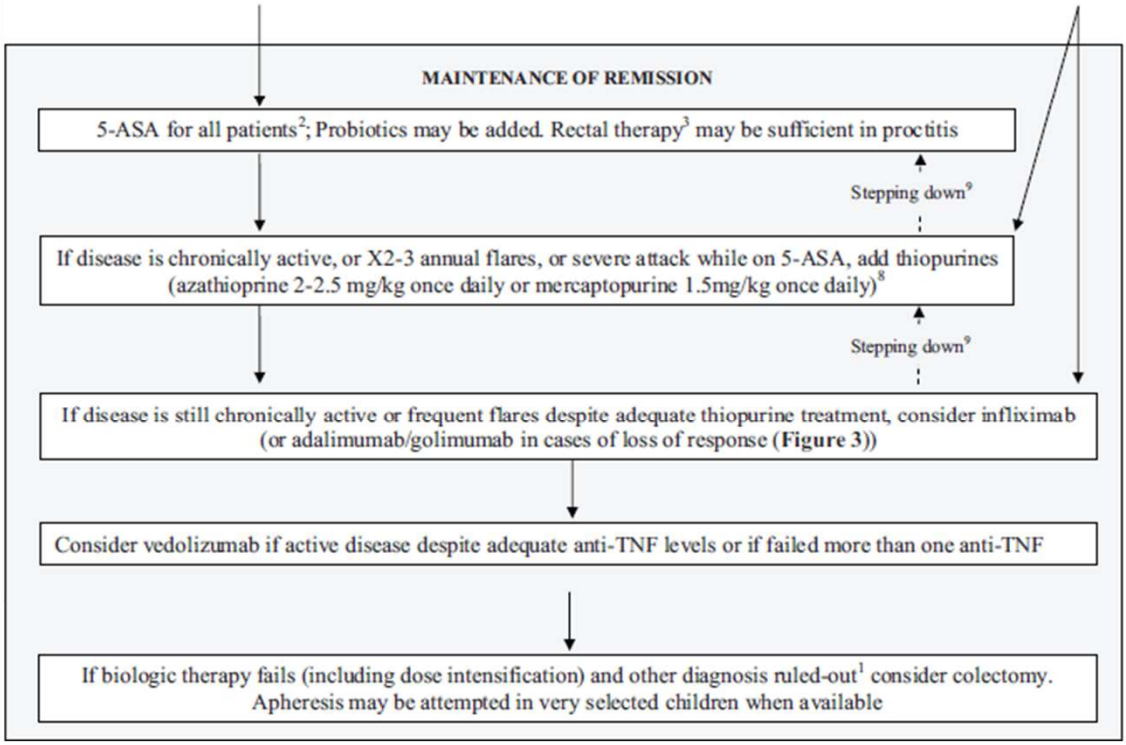
Jongsma, BMJ, 2022

UC – ESPGHAN guideline

INDUCTION
- Steroids
- 5-ASA
- Tacrolimus, cyclosporin
- Anti-TNF
- Colectomy

MAINTENANCE
- 5-ASA
- Topical steroids
- Thiopurines
- IFX, ADA, VEDO
- Tofacitinib



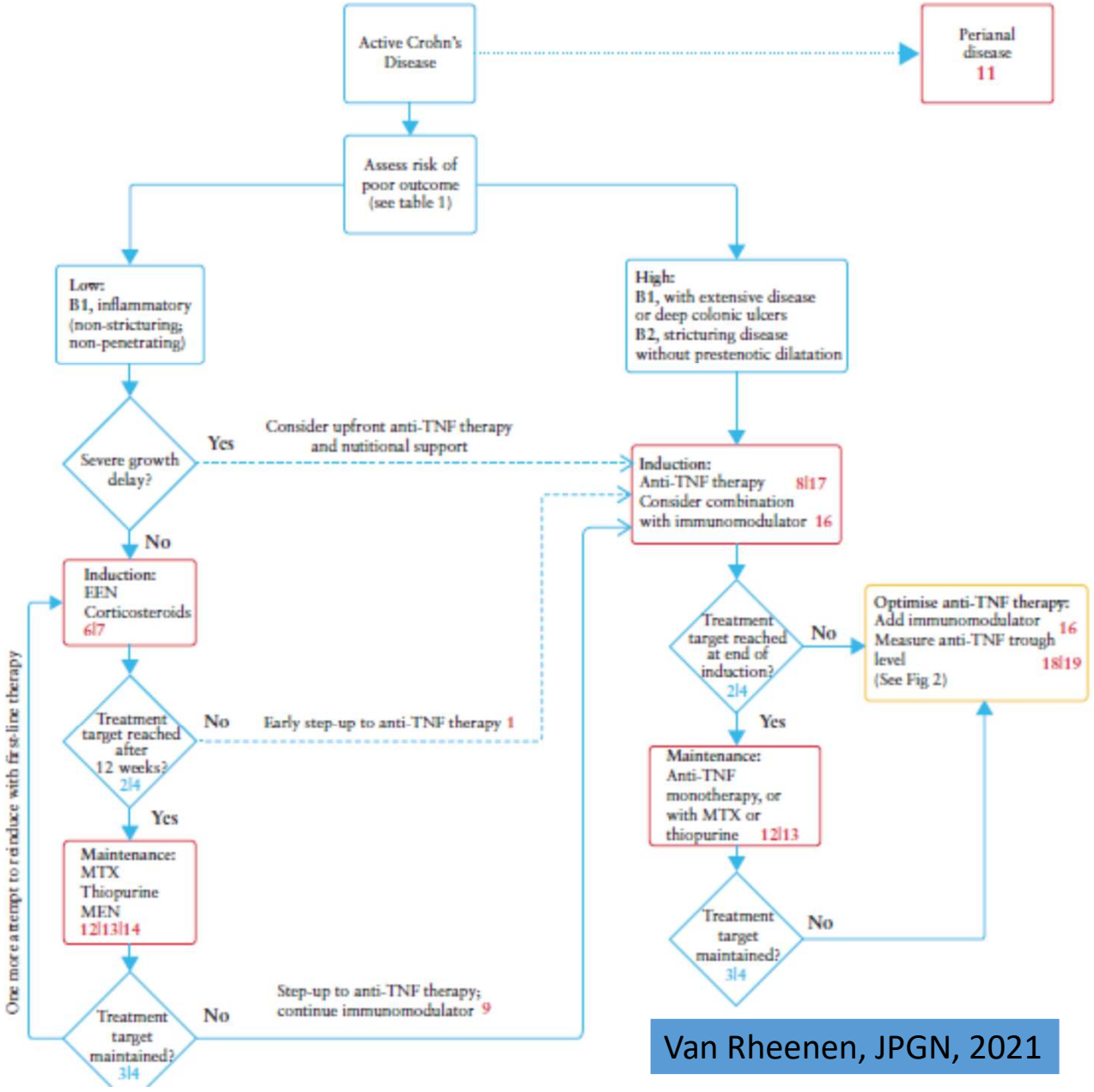


Turner et al. *JPGN.* 2018

Crohn Disease

INDUCTION
- Steroids
- EEN (CDED, CD-treat)
- IFX, ADA, USTE, …
- Surgery

MAINTENANCE
- Methotrexate
- Thiopurines
- PEN
- Biologics



Van Rheenen, JPGN, 2021

Take home message

Prevention

Think IBD!

Use diagnostic tests appropriately

Call your friendly gastroenterologist

Thank you for your attention