The Inflamed Truth:
IBD Update for the Frontline

CME

May 2026

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Greenlane
Medical Specialists

Outline

- **IBD Overview**
  - Clinical Features
  - Diagnostic Testing
- **Changing Demographics**
- **Dietary influence?**
- **Management Principles**
  - Immunomodulator Update….
    - NUDT15
    - Tioguanine
  - New Biological Agents
    - Ustekinumab (Stelara)
    - Vedolizumab (Entyvio)
    - Upadacitinib (Rinvoq)
- **Pregnancy/Breastfeeding**
- **The future…**

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What is IBD?

- Chronic inflammatory disorder of the gastrointestinal tract
- Inappropriate inflammatory response to intestinal microbes in a genetically susceptible host
- Ulcerative colitis and Crohn's disease most common

Ulcerative Colitis

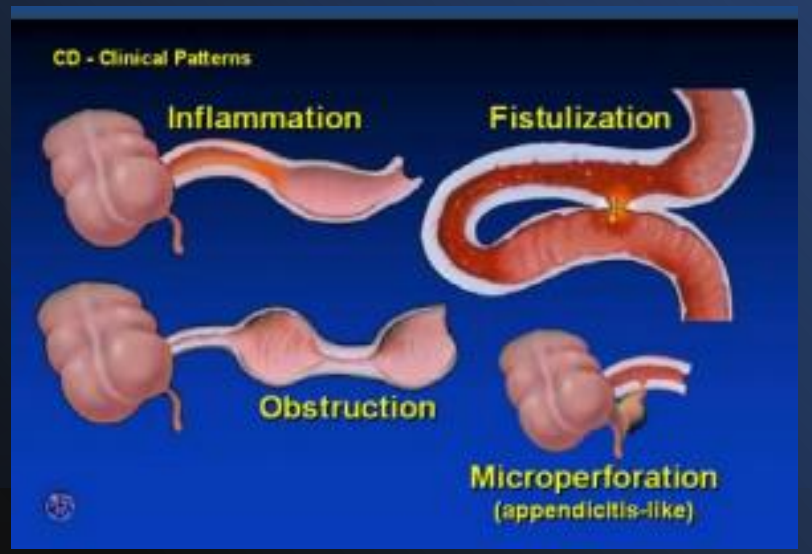
- **Involves submucosa/mucosa only**
- **Characteristically involves rectum**
- Extends proximally in continuous manner
- Limited to colon

Crohn’s Disease:

- **Transmural inflammation**
- **May affect any part of GIT**
- Granuloma’s in ~50% of cases
- Segmental areas of involvement (skip lesions)

Crohn’s Subtypes…

1. **Inflammatory**
2. **Penetrating** (fistulising, perforating)
3. **Stricturing** (fibrotic, inflammatory, mixed)



Establishing a diagnosis…

- History and Examination
  - Depends on disease location, extent and severity
  - Generally 4-6 week duration
  - Bloody diarrhea, diarrhea, abdominal pain

- Lab Tests:
  - CRP, ASCA, p-ANCA, **Faecal Calprotectin**

- **Endoscopy and Histology**

- Imaging:
  - AXR, CT, MRE

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Increasing Worldwide Burden

- Initially confined to western nations only
- Dramatic rise in developing nations over past 20 years
  - Mirroring spread of industrialisation and increased urbanisation
  - Migration effect
- Paediatric disease more common (and aggressive)
- Elderly onset (and prevalence) rising
- More complex phenotypes

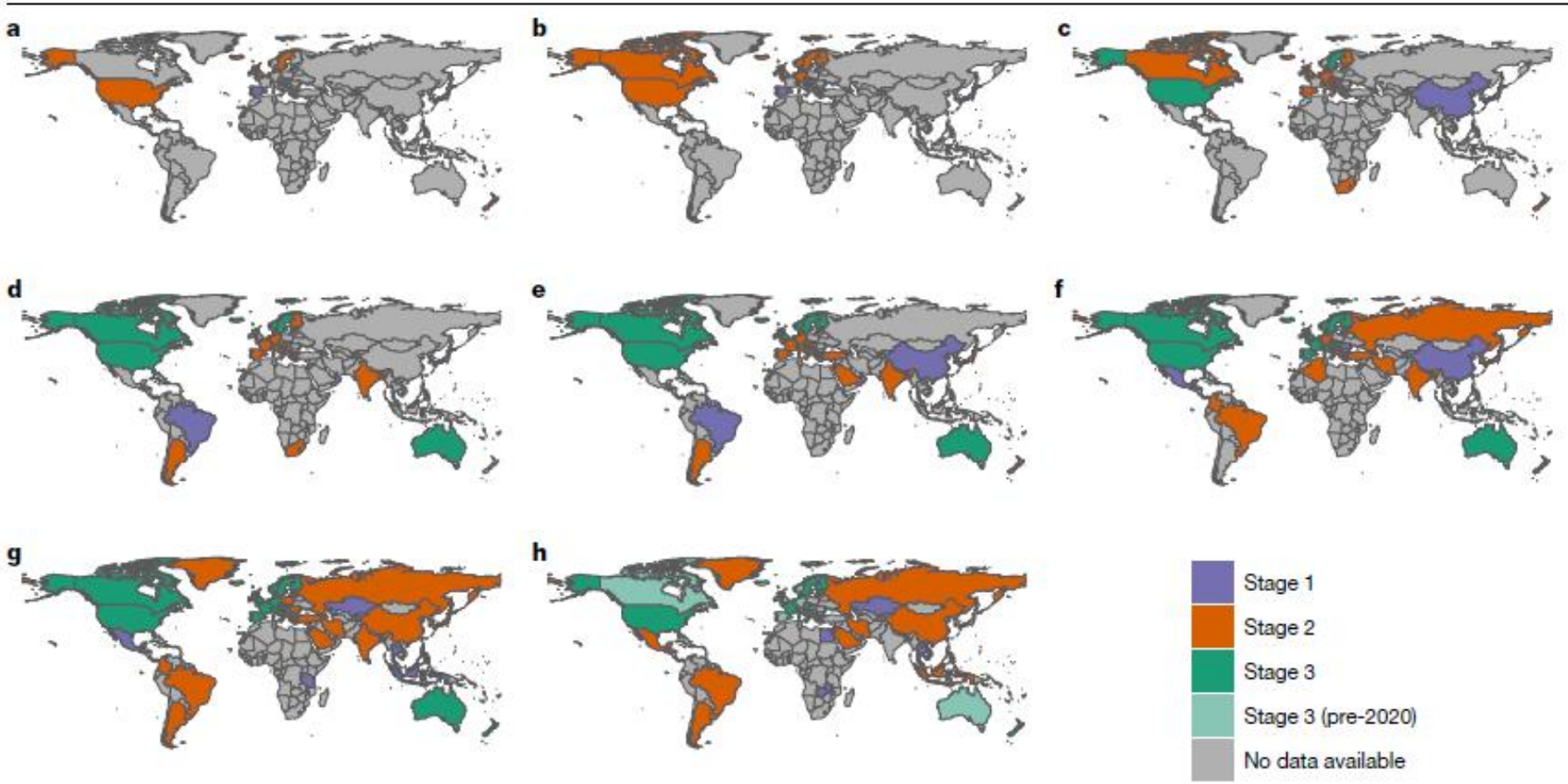


Fig. 3 | Global maps depicting epidemiologic stages of IBD evolution from 1950 to 2024. **a**, Epidemiologic stages from 1950 to 1959. **b**, Epidemiologic stages from 1960 to 1969. **c**, Epidemiologic stages from 1970 to 1979. **d**, Epidemiologic stages from 1980 to 1989. **e**, Epidemiologic stages from 1990 to 1999. **f**, Epidemiologic stages from 2000 to 2009. **g**, Epidemiologic stages from 2010 to 2019. **h**, Epidemiologic stages from 2020 to 2024; because regions cannot regress in stage, regions without data in 2020–2024 but with a previous stage 3 classification are shaded in a lighter green than regions in stage 3 that do have data during this period. Each region is coloured according to its epidemiologic stage as predicted by the random-forest classifier. Interactive maps are available online (https://kaplan-gi.shinyapps.io/GIVES21/).

nature

Article | Open access | Published: 30 April 2025

Global evolution of inflammatory bowel disease across epidemiologic stages

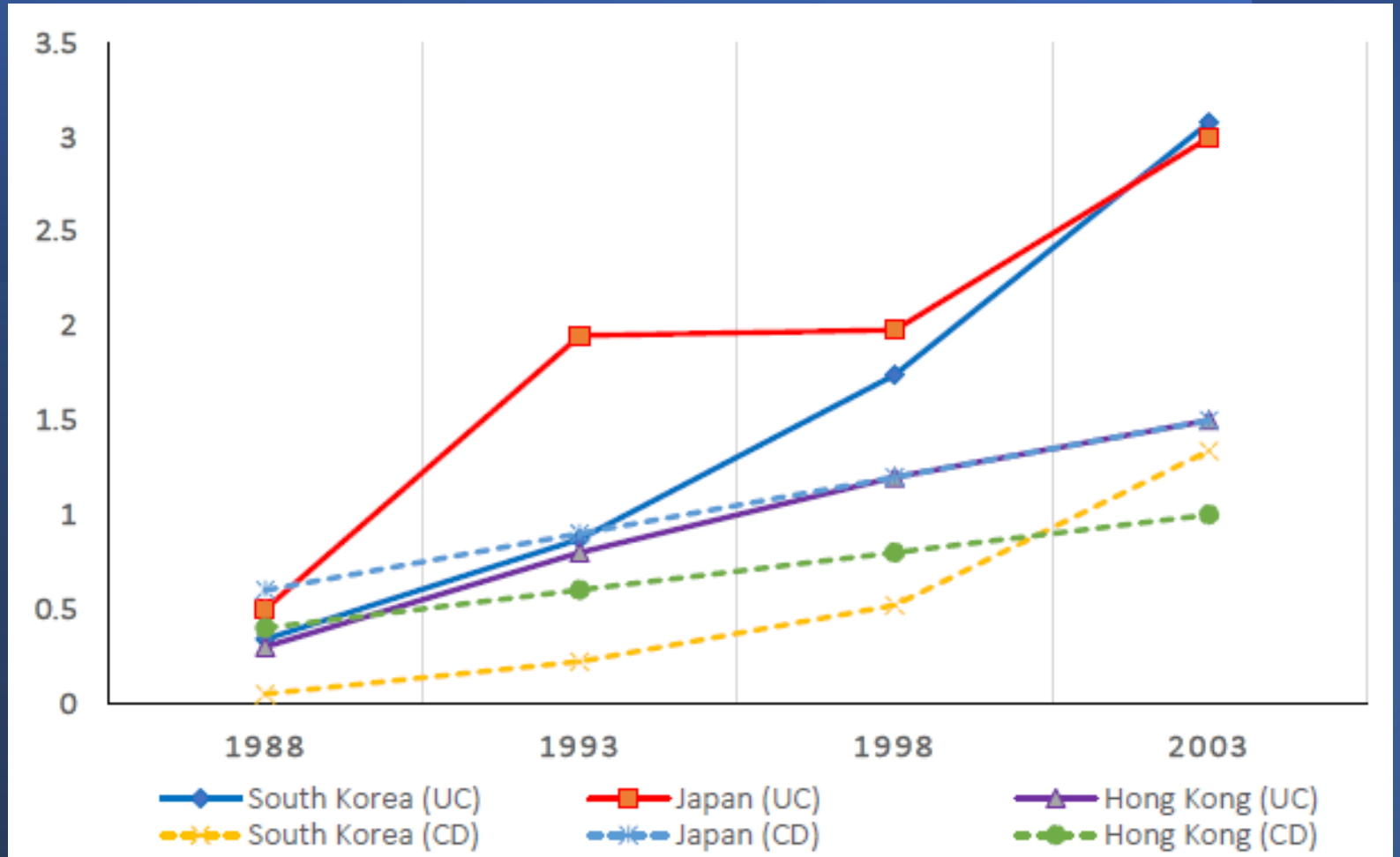


Figure 1. Longitudinal incidence of ulcerative colitis and Crohn's disease per 100,000 individuals in South Korea, Japan and Hong Kong (based on data from Yang et al[71], Yao et al[72], Morita et al[14], Yoshida et al[73], Loc et al[74], Leong et al[60], and Thia et al[75]).

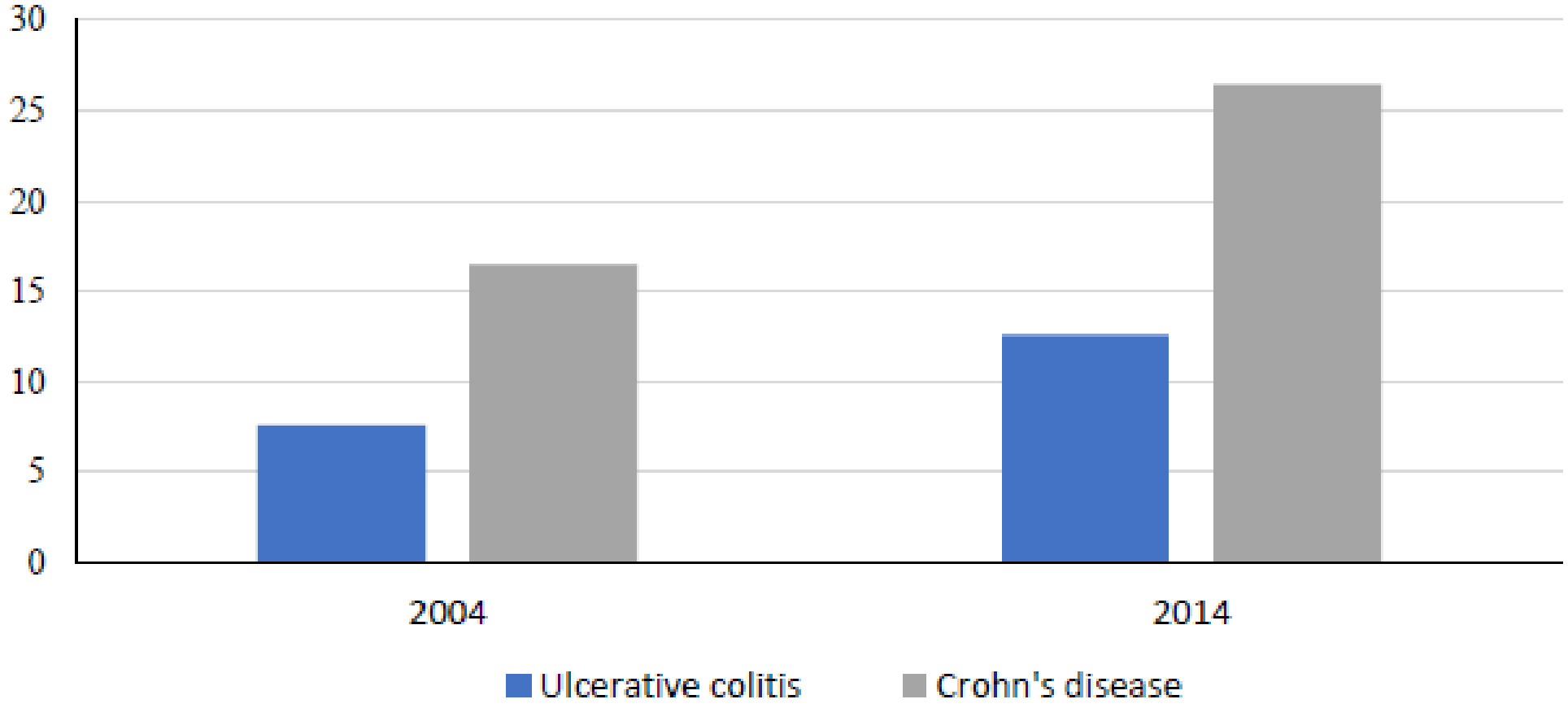


Figure 2. Temporal increase in ulcerative colitis and Crohn's disease incidence within the Canterbury region of New Zealand per 100,000 individuals (based on data from Gearry et al[81] and Su et al[82]).

Drivers for increasing disease burden?

- Mirrored spread of industrialization

- Shift in lifestyle and exposures which promote development of IBD
  - Increased cigarette smoking
  - Sedentary occupations
  - Lower rates of breast feeding

- Hygiene hypothesis:
  - Largely retrospective data, prone to recall bias

- Microbiome changes?

Migration increases incidence of IBD:

Table 1. Cases and Incidence of Ulcerative Colitis by Ethnic Origin in Leicester City, 1991–1994 (Crude Incidence)*

	European		South Asian	
Year	n	Incidence†	n	Incidence†
1991–92	9	4.6 (95% CI 2.1–8.8)	9	14 (95% CI 6.4–26.8)
1992–93	16	8.2 (95% CI 4.7–13.4)	11	17.1 (95% CI 8.6–30.8)
1993–94	16	8.2 (95% CI 4.7–13.4)	13	20.3 (95% CI 10.8–34.8)
1991–94	41	7.0 (95% CI 5.0–9.5)	33	17.2 (95% CI 11.8–24.3)

* Cases were identified from a wide range of sources. There was a variation in incidence in the European population but the incidence in the South Asian population was high and continued to rise in the 3 yr of the study.

† Per 10^5 population/yr.

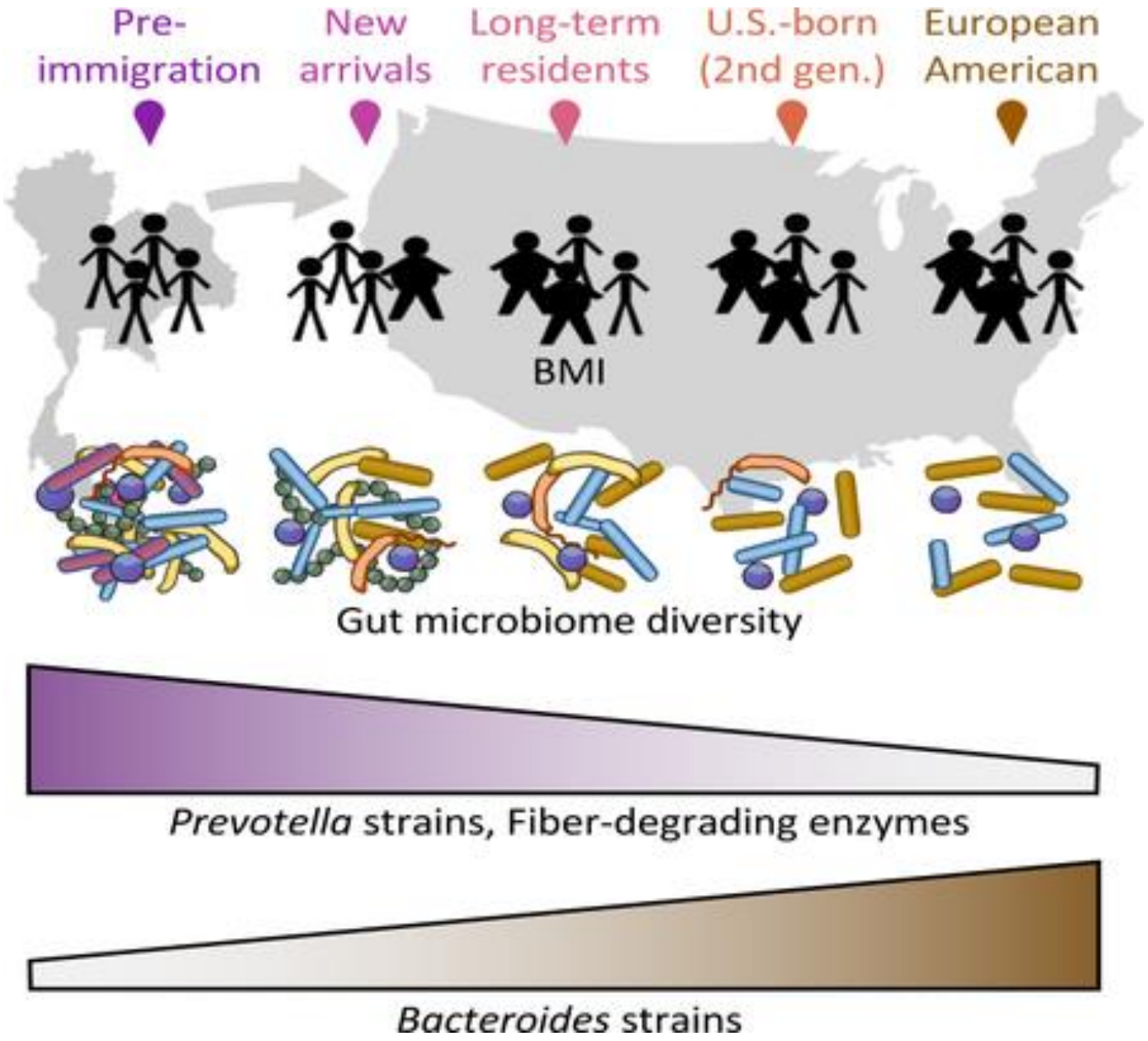
CI = confidence interval.

AJG The American Journal of GASTROENTEROLOGY

The Effects of Migration on Ulcerative Colitis: A Three-Year Prospective Study Among Europeans and First- and Second-Generation South Asians in Leicester (1991–1994)

Irene Carr, R.G.N., and John F. Mayberry, M.D., F.R.C.P.
Gastrointestinal Research Unit, Leicester General Hospital NHS Trust, Leicester, United Kingdom

Microbiome changes with immigration



Cell

US Immigration Westernizes the Human Gut Microbiome

Authors

Pajau Vangay, Abigail J. Johnson, Tonya L. Ward, ..., Purna C. Kashyap, Kathleen A. Culhane-Pera, Dan Knights

How is this relevant for us?

- Relatively high migrant population in Auckland
- High IBD incidence
  - Crohn's and UC
- Often presenting in 20's
- Aggressive phenotype common
- **If clinically suspicious:**
  - **Calprotectin**
  - **Refer for review or Colonoscopy**

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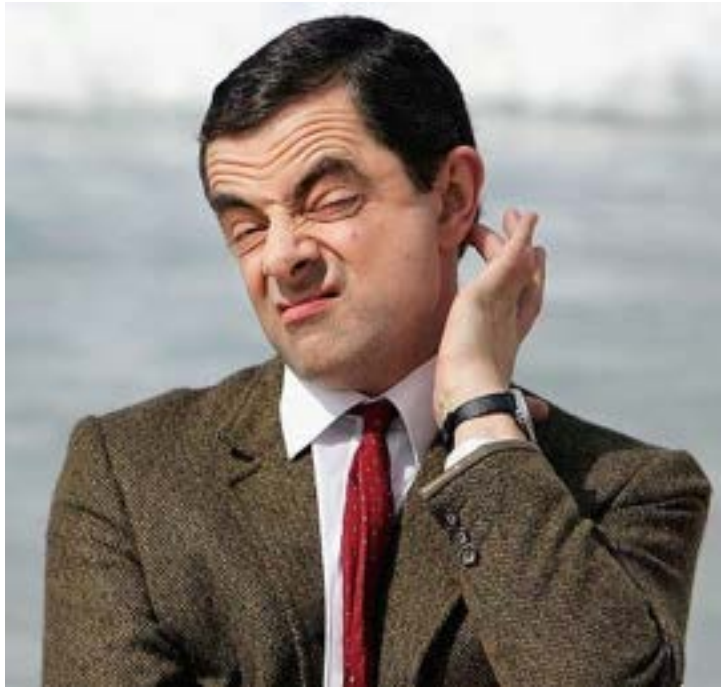
Common Question!

“Doctor, what foods should I eat or avoid?”



Ultra-processed foods (UPFs):

- Undergone multiple industrial processes
- Often containing:
  - Additives (emulsifiers, sweeteners, colours, preservatives)
  - Refined sugars/fats
  - Generally low in fibre
  - Ready meals, packaged snacks, sugary drinks, processed meat
- Growing data suggest association with increased risk of IBD development and adverse outcomes
- Hot topic!

Association of ultra-processed food intake with risk of inflammatory bowel disease: prospective cohort study

Neeraj Narula,[1,2] Emily C L Wong,[1] Mahshid Dehghan,[2] Andrew Mente,[2] Sumathy Rangarajan,[2] Fernando Lanas,[3] Patricio Lopez-Jaramillo,[4] Priyanka Rohatgi,[5] P V M Lakshmi,[6] Ravi Prasad Varma,[7] Andres Orlandini,[8] Alvaro Avezum,[9] Andreas Wielgosz,[10] Paul Poirier,[11] Majid A Almadi,[12] Yuksel Altuntas,[13] Kien Keat Ng,[14] Jephat Chifamba,[15] Karen Yeates,[16] Thandi Puoane,[17] Rasha Khatib,[18] Rita Yusuf,[19,20] Kristina Bengtsson Boström,[21] Katarzyna Zatonska,[22] Romaina Iqbal,[23] Liu Weida,[24] Zhu Yibing,[24] Li Sidong,[24] Antonio Dans,[25] Afzalhussein Yusufali,[26] Noushin Mohammadifard,[27] John K Marshall,[1] Paul Moayyedi,[12] Walter Reinisch,[28] Salim Yusuf[2]

the bmj | *BMJ* 2021;374:n1554 | doi: 10.1136/bmj.n1554

Table 3 Association between total ultra-processed food intake and risk of inflammatory bowel disease. Values are hazard ratios (95% confidence intervals) unless stated otherwise

	Ultra-processed food intake			
	<1 serving/day	1-4 servings/day	≥5 servings/day	P trend
Inflammatory bowel disease				
No of participants	76 415	25 453	11 742	
No (%) of events	199 (0.26)	134 (0.53)	95 (0.81)	
Unadjusted model	1 (ref)	2.20 (1.77 to 2.74)	3.18 (2.49 to 4.07)	<0.001
Minimally adjusted model*	1 (ref)	1.41 (1.11 to 1.79)	1.42 (1.07 to 1.90)	0.01
Fully adjusted model†	1 (ref)	1.67 (1.18 to 2.37)	1.82 (1.22 to 2.72)	0.006
Fully adjusted plus AHEI score model	1 (ref)	1.75 (1.23 to 2.50)	1.92 (1.28 to 2.90)	0.004
Sensitivity analysis using multiple imputation‡	1 (ref)	1.54 (1.21 to 1.84)	1.71 (1.22 to 2.37)	<0.001
Crohn's disease				
No of participants	76 415	25 453	11 742	
No (%) of events	34 (0.04)	23 (0.09)	30 (0.26)	
Unadjusted model	1 (ref)	2.19 (1.29 to 3.72)	5.84 (3.57 to 9.54)	<0.001
Minimally adjusted model*	1 (ref)	1.15 (0.64 to 2.06)	1.92 (1.05 to 3.49)	0.07
Fully adjusted model†	1 (ref)	2.72 (1.06 to 6.97)	4.50 (1.67 to 12.13)	0.01
Fully adjusted plus AHEI score model	1 (ref)	2.93 (1.13 to 7.60)	4.90 (1.78 to 13.45)	0.008
Sensitivity analysis using multiple imputation‡	1 (ref)	1.30 (0.71 to 2.37)	2.83 (1.45 to 4.65)	0.40
Ulcerative colitis				
No of participants	76 415	25 453	11 742	
No (%) of events	165 (0.22)	111 (0.44)	65 (0.55)	
Unadjusted model	1 (ref)	2.20 (1.73 to 2.80)	2.63 (1.97 to 3.51)	<0.001
Minimally adjusted model*	1 (ref)	1.48 (1.13 to 1.93)	1.27 (0.91 to 1.77)	0.02
Fully adjusted model†	1 (ref)	1.55 (1.06 to 2.28)	1.46 (0.93 to 2.28)	0.08
Fully adjusted plus AHEI score model	1 (ref)	1.61 (1.09 to 2.38)	1.52 (0.96 to 2.41)	0.06
Sensitivity analysis using multiple imputation‡	1 (ref)	1.59 (1.23 to 1.98)	1.45 (0.96 to 2.12)	<0.001

AHEI=Alternate Healthy Eating Index.
Heterogeneity of results from Crohn's disease and ulcerative colitis: χ^2 P=0.595; I^2=0%.
* Adjusted for age, sex, and geographical region.
† Adjusted for age, sex, geographical region, education, alcohol intake, smoking status, body mass index, total energy intake, and location.
‡ To account for participants with missing data on food frequency questionnaire.

Study population

Diet

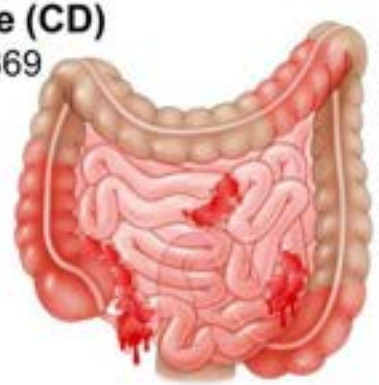
Ultra-processed foods

245,112 participants
5,468,444 person-years of follow-up

Nurses' Health Study
Nurses' Health Study II
Health Professionals Follow-up Study

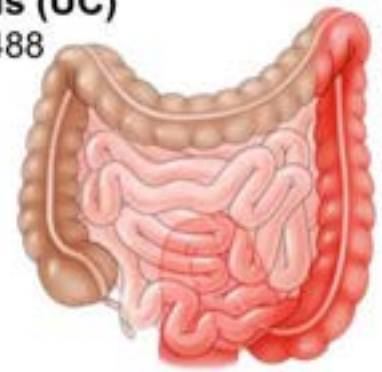
Outcome

Crohn's disease (CD)
Incident cases = 369



Increased risk of CD
Highest vs lowest quartile
HR, 1.70
95% CI, 1.23-2.35
P_{trend} = 0.0008

Ulcerative colitis (UC)
Incident cases = 488



No increased risk of UC
Highest vs lowest quartile
HR, 1.20
95% CI, 0.91-1.58
P_{trend} = 0.25

Clinical Gastroenterology and Hepatology

UPFs increases risk of flares in Crohn's disease

Journal of Digestive Diseases

High Ultra-Processed Food Consumption Is Associated with Clinical Exacerbation in Patients with Crohn's Disease in Remission: A Prospective Cohort Study

Chen Sarbagili-Shabat[a, b] Shira Zelber-Sagi[a, c] Naomi Fliss Isakov[a, d] Ayal Hirsch[a, b] Yulia Ron[a] Laura Sol Grinshpan[c] Nathaniel Aviv Cohen[a, b] Haim Leibovitzh[a, b] Tamar Thurm[a, b] Nitsan Maharshak[a, b]

Dig Dis 2025;43:466–475
DOI: 10.1159/000546486

Received: February 8, 2025
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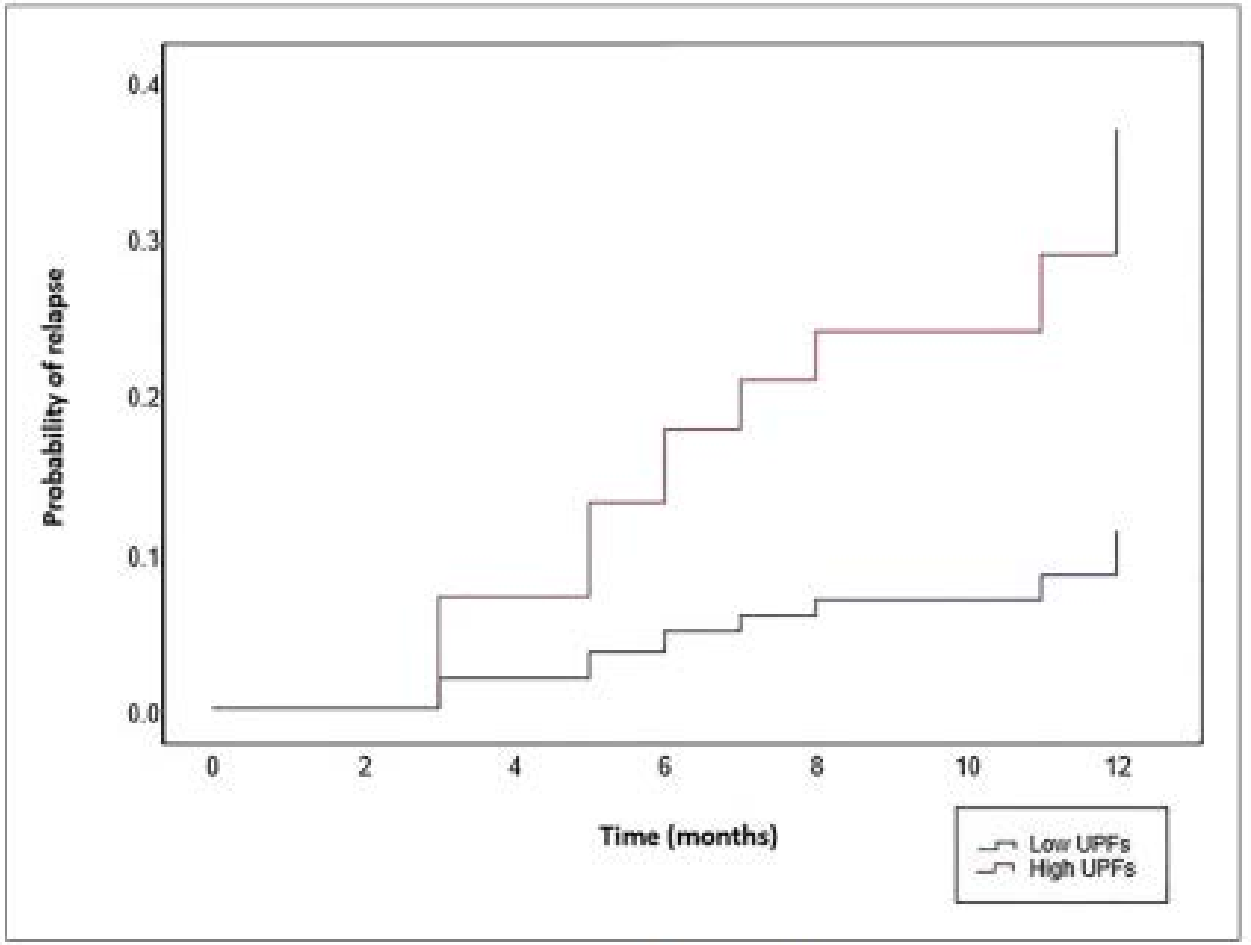


Fig. 2. Comparison of time to clinical relapse in patients with CD stratified by ultra-processed foods consumption. The cut-off for low and high ultra-processed food consumption was determined by the median number: 3.6 servings/day.

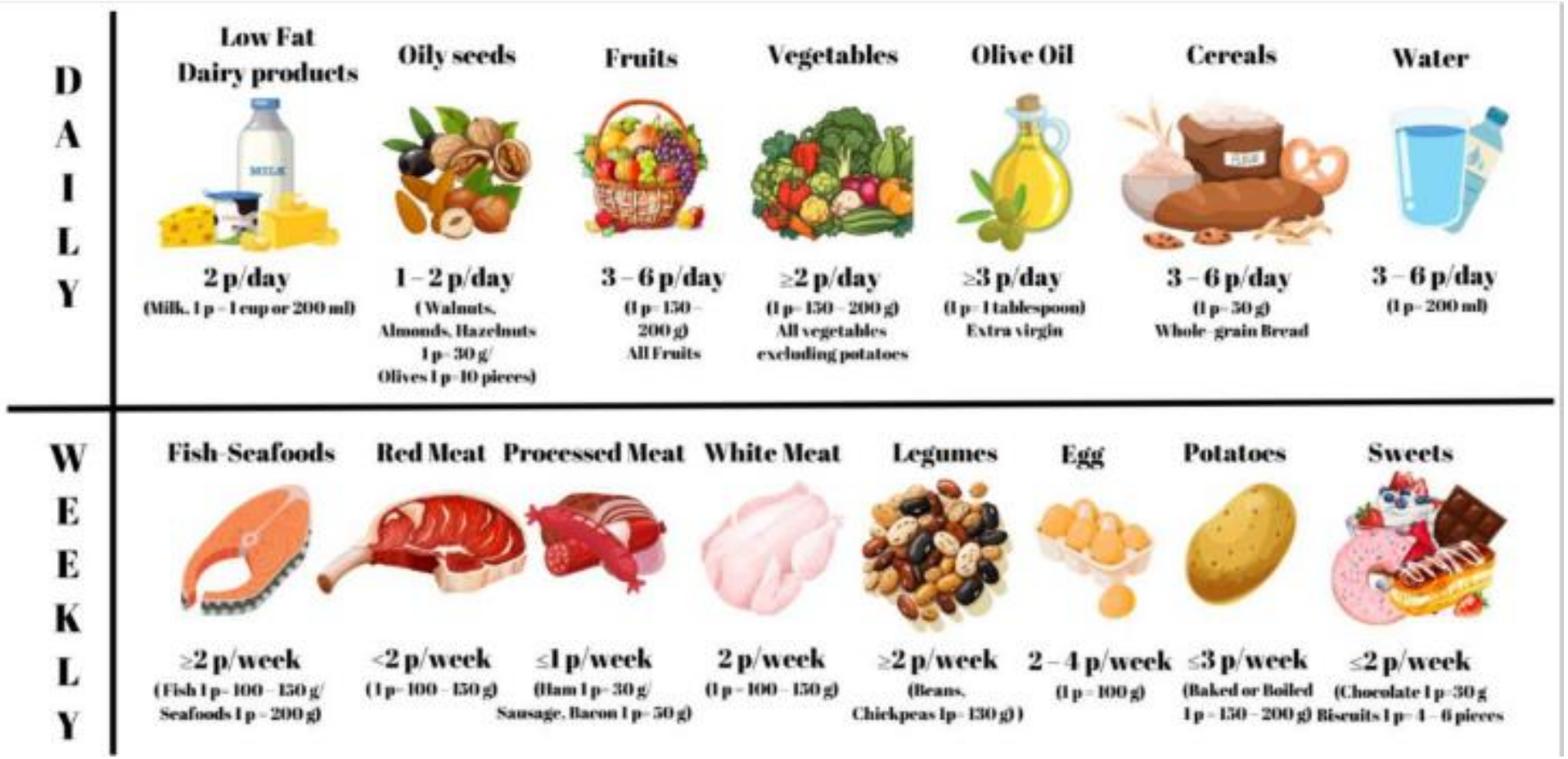
UPF Summary:

- Causality not established but **consistent Crohn's disease signal** over many studies

- Presumed mechanisms:
  - Microbiome changes: reduced diversity
  - Barrier dysfunction (additives, emulsifiers etc): increase permeability allowing antigens to promote immune response
  - Pro-inflammatory pathway stimulation: refined sugar, saturated fat, certain additives

- Limitations:
  - Most studies are observational
  - Self-reported dietary data: potential recall bias or measurement error
  - Confounding
  - Differences between Crohn's disease and UC not always consistent

Mediterranean Diet:



Mediterranean Diet:


Impact of diet on inflammatory bowel disease risk: systematic review, meta-analyses and implications for prevention

THE LANCET

Study	Participants	CD cases	Weight	aHR [95%CI]
Mediterranean diet				
Racine, 2016	366,351	117	21.9%	0.90 [0.45; 1.77]
Khalili, 2023	83,147	164	28.6%	0.58 [0.32; 1.06]
Xia, 2024	197,391	260	49.4%	0.49 [0.31; 0.77]
Total (95% CI)			**100.0%**	**0.59 [0.43; 0.81]**

Heterogeneity: $Tau^2 = 0.0005$; $Chi^2 = 2.1$, df = 2 (P = .35); $I^2 = 4.9\%$

Test for overall effect: Z = −3.24 (P = .001)

Study	Participants	UC cases	Weight	aHR [95%CI]
Mediterranean diet				
Racine, 2016	366,351	256	14.5%	0.79 [0.48; 1.32]
Khalili, 2023	83,147	395	29.6%	1.00 [0.70; 1.42]
Xia, 2024	197,391	601	56.0%	0.82 [0.64; 1.07]
Total (95% CI)			**100.0%**	**0.86 [0.71; 1.05]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.94$, df = 2 (P = .63); $I^2 = 0\%$

Test for overall effect: Z = −1.48 (P = .14)

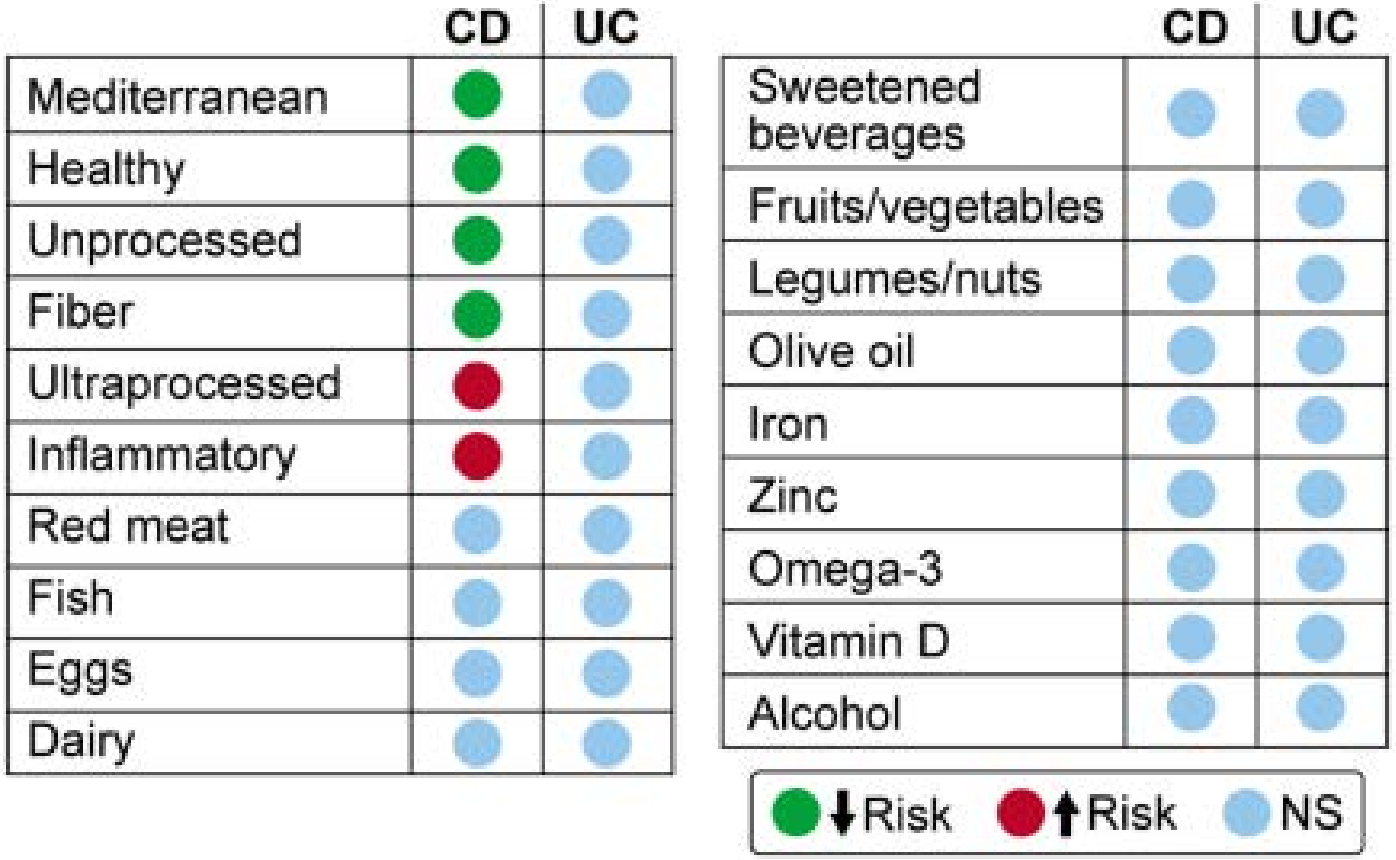
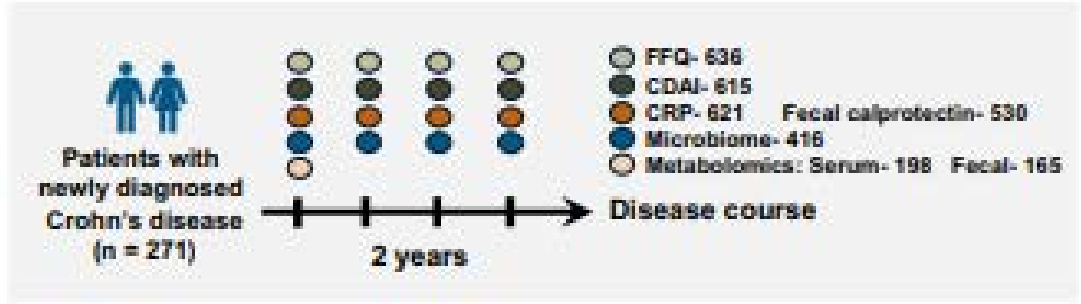
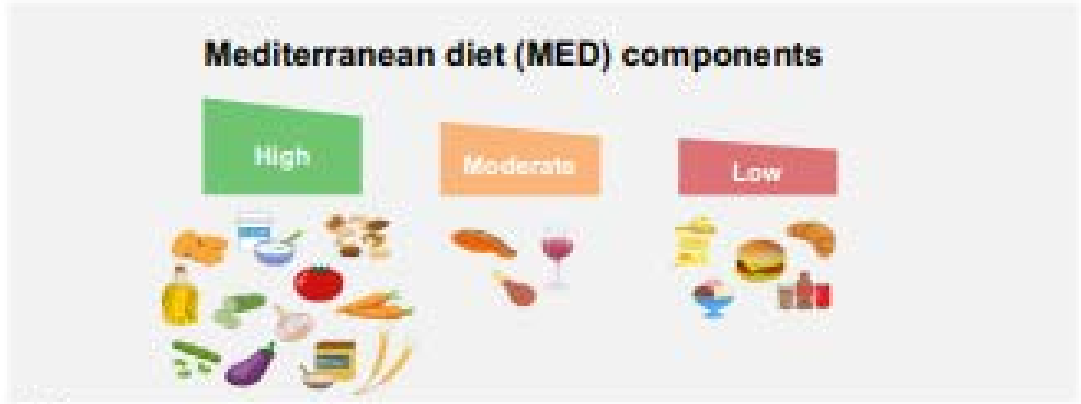


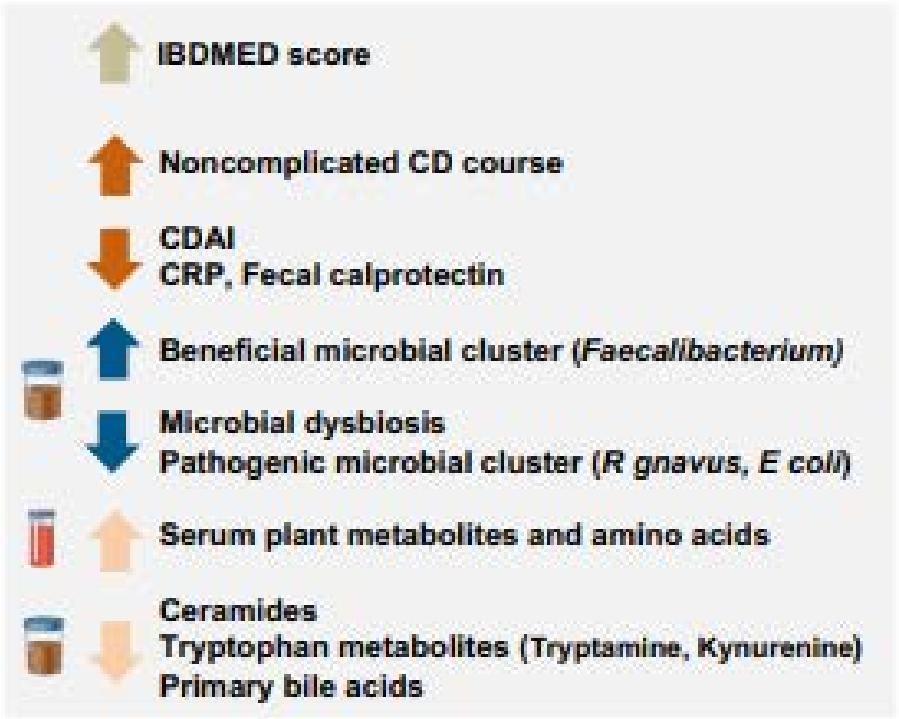
Fig. 6: Summary of the meta-analyses of 64 prospective cohort studies which examined the association between pre-disease diet and risk of Crohn's disease (CD) and ulcerative colitis (UC).

Mediterranean Diet:


Mechanistic Implications of the Mediterranean Diet in Patients With Newly Diagnosed Crohn's Disease: Multiomic Results From a Prospective Cohort







Gastroenterology

“Doctor, what foods should I eat or avoid?”

➢AGA/ECCO Guidelines:

- Mediterranean diet recommended
- Low UPF consumption

➢Stricturing Crohn’s disease:

- May not tolerate fibrous, plant-based foods
- Emphasis on careful chewing and cooking to a soft consistency may help
- Protein-calorie supplements (Ensure/Fortisip) helpful

ECCO European Crohn’s and Colitis Organisation

aga American Gastroenterological Association

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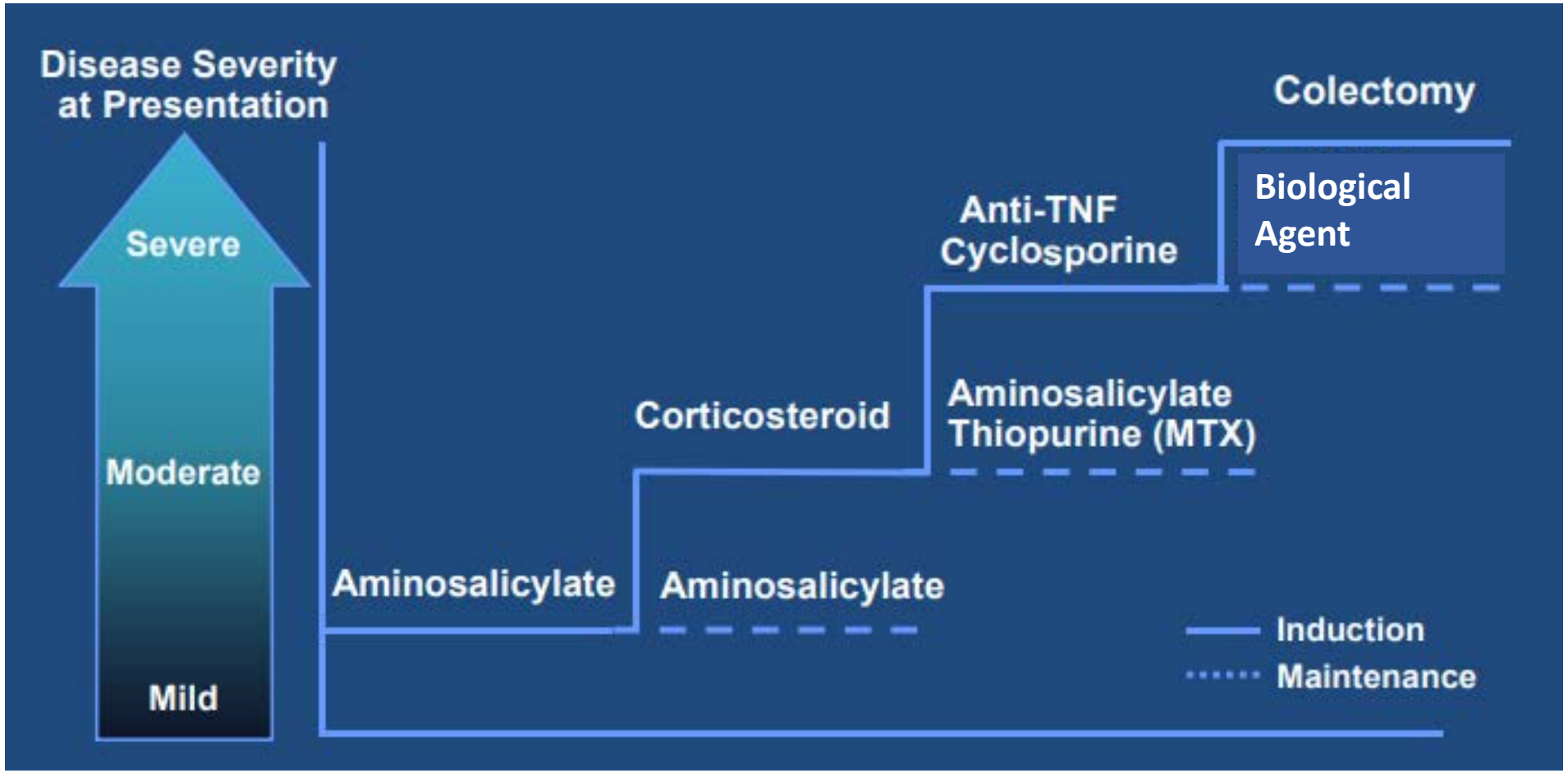
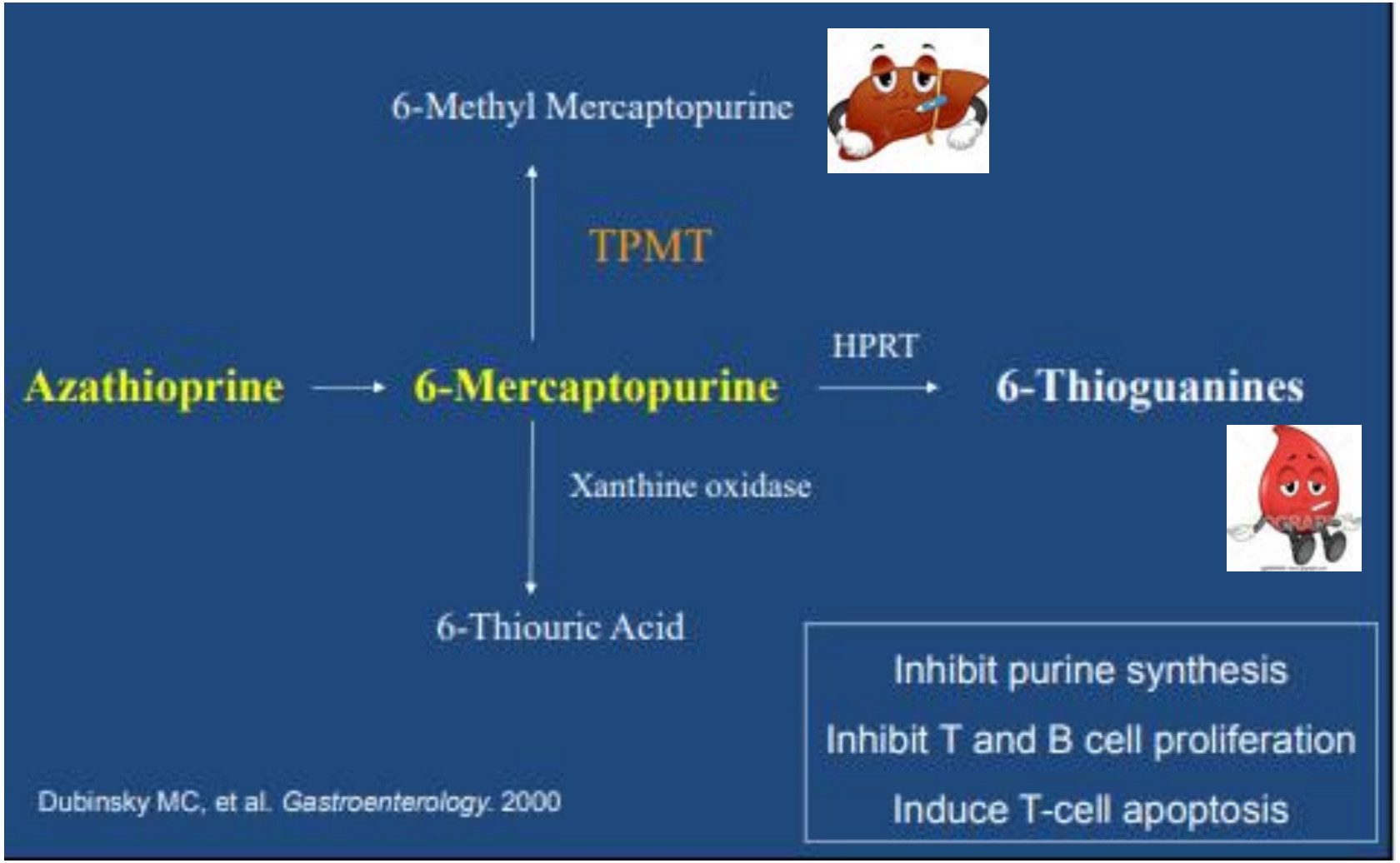
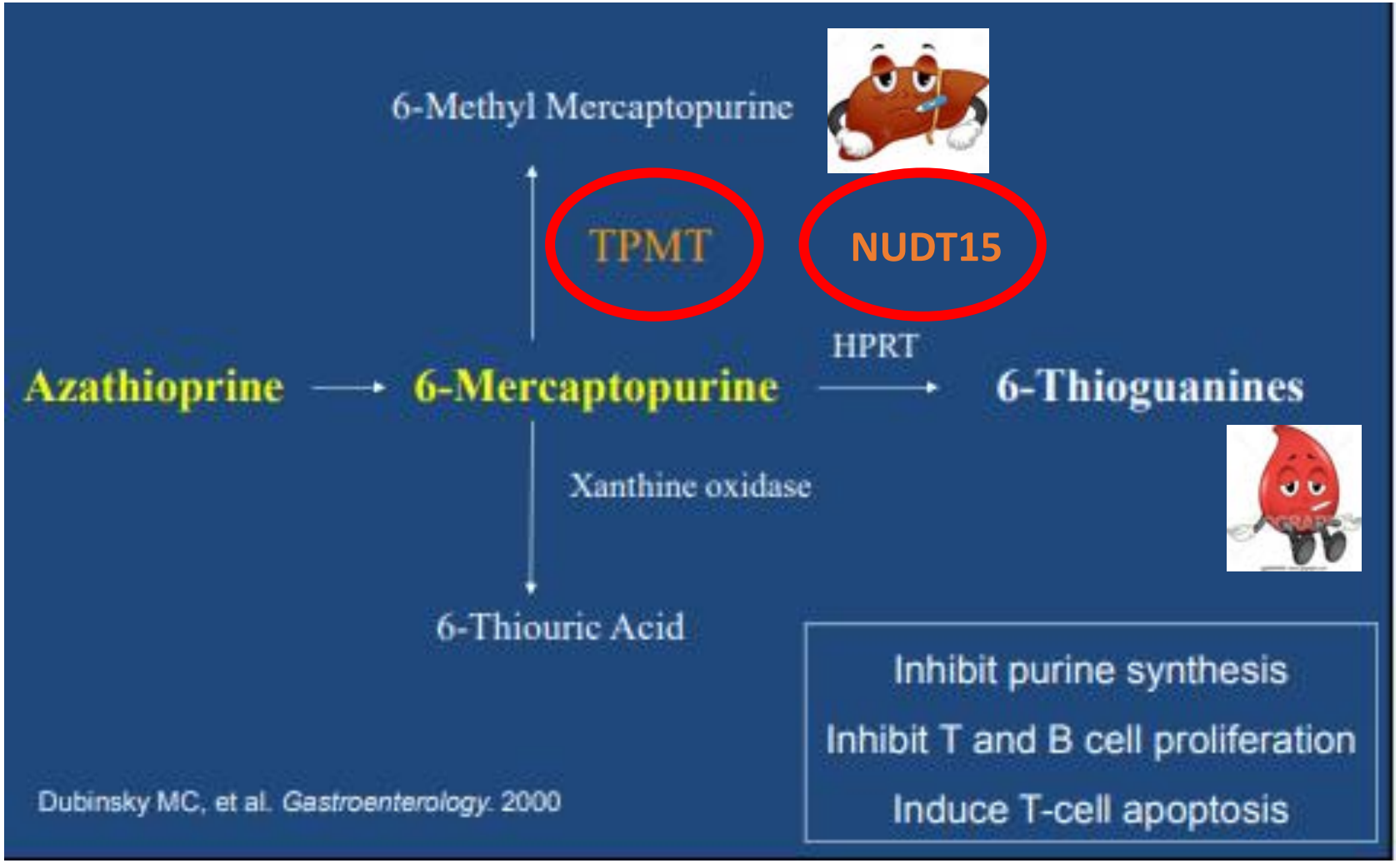
Overview of IBD Management



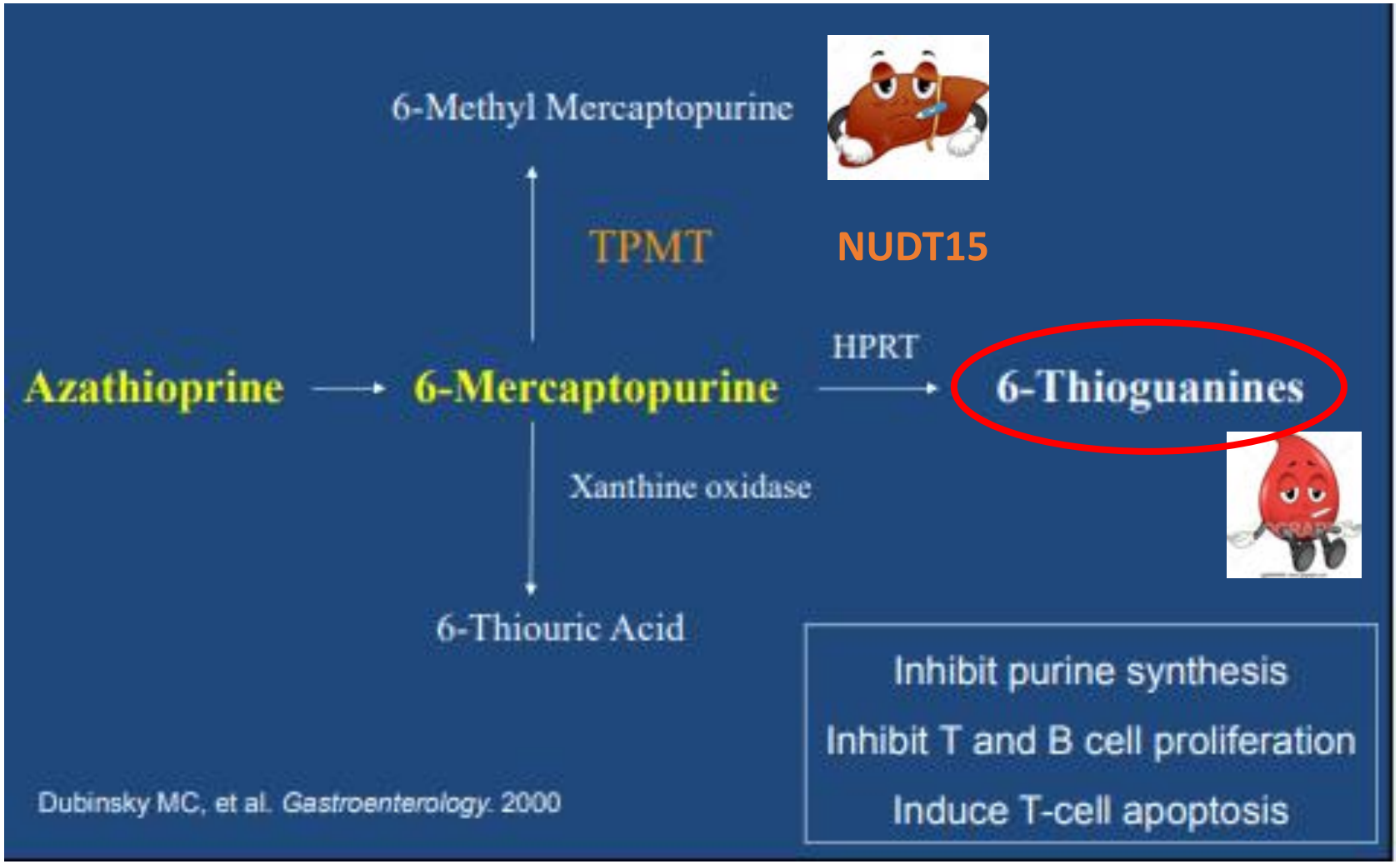
Thiopurine Updates…



Thiopurine Updates…



Tioguanine


6-Methyl Mercaptopurine
TPMT
NUDT15
Azathioprine
6-Mercaptopurine
HPRT
6-Thioguanines
Xanthine oxidase
6-Thiouric Acid
Inhibit purine synthesis
Inhibit T and B cell proliferation
Induce T-cell apoptosis
Dubinsky MC, et al. Gastroenterology. 2000

Tioguanine

➢Traditional Thiopurines (AZA/6-MP)

- Limited by metabolite variability and toxicity

➢Why Tioguanine?

- Simplified metabolism (bypasses TPMT/NUDT15)
  - More predictable levels
- Improved tolerance
  - Easier and fixed dosing
  - Doses of 20mg/day low risk of NRH
- Comparable efficacy
- Therapeutic monitoring available

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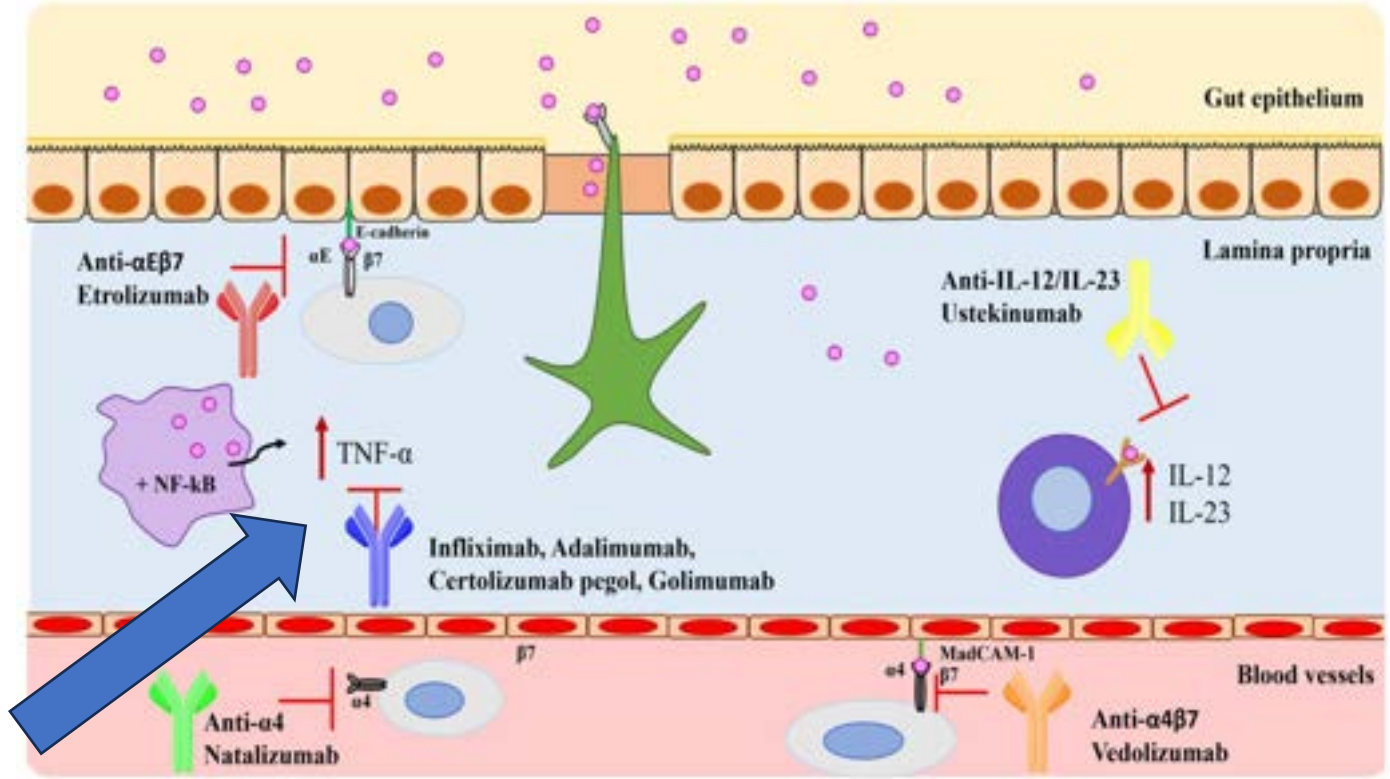
BIOLOGICAL AGENTS FOR INFLAMMATORY BOWEL DISEASE IN NEW ZEALAND

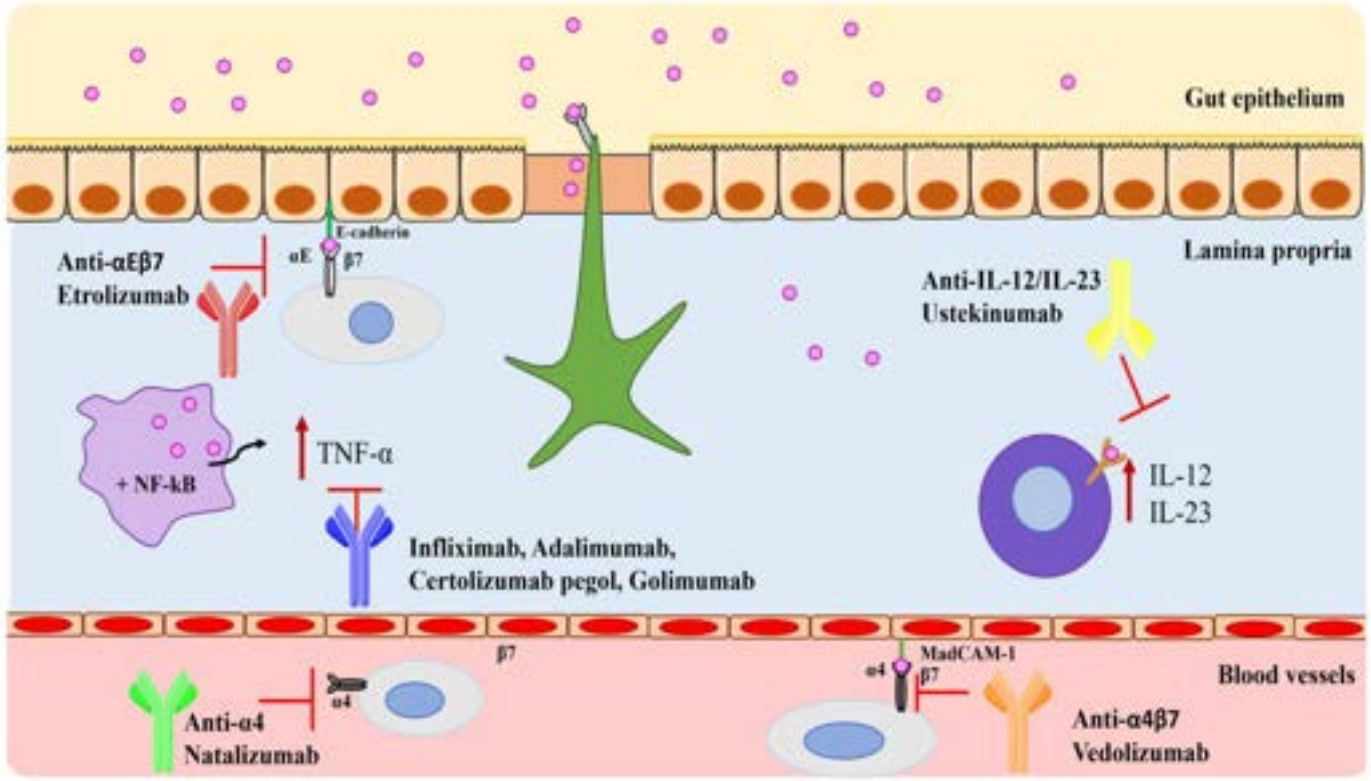
INFLIXIMAB

ADALIMUMAB



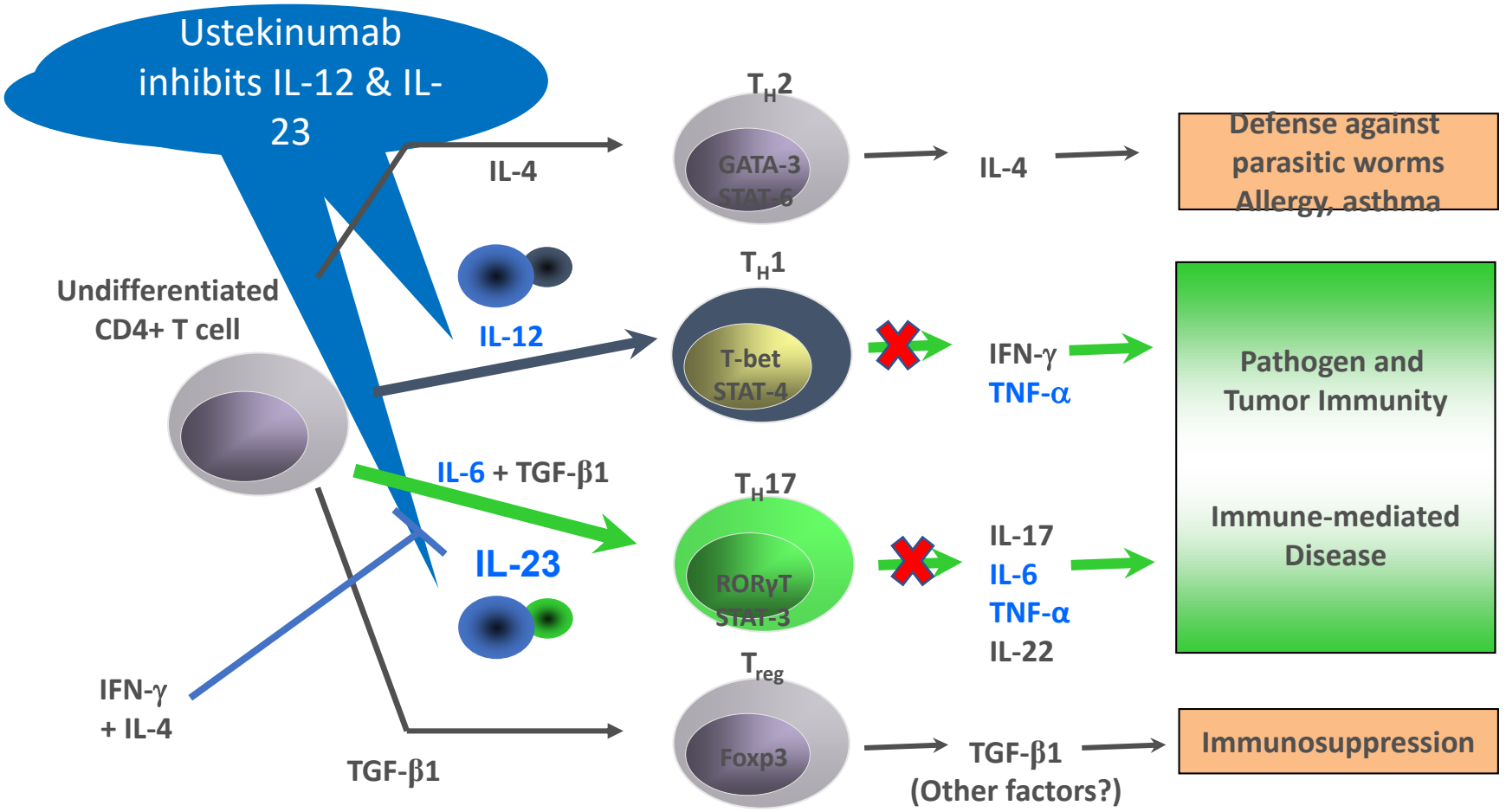
BIOLOGICAL AGENTS FOR INFLAMMATORY BOWEL DISEASE IN NEW ZEALAND

- INFLIXIMAB
- ADALIMUMAB
- USTEKINUMAB
- VEDOLIZUMAB
- UPADACITINIB



Di Rienzo, A.; Marinelli, L.; Dimmito, M.P.; Toto, E.C.; Di Stefano, A.; Cacciatore, I. Advancements in Inflammatory Bowel Disease Management: From Traditional Treatments to Monoclonal Antibodies and Future Drug Delivery Systems. *Pharmaceutics* **2024**, *16*, 1185.

Ustekinumab



Modified from Tato CM, O'Shea JJ. Nature. 2006; 441:166-8.

Ustekinumab Summary:

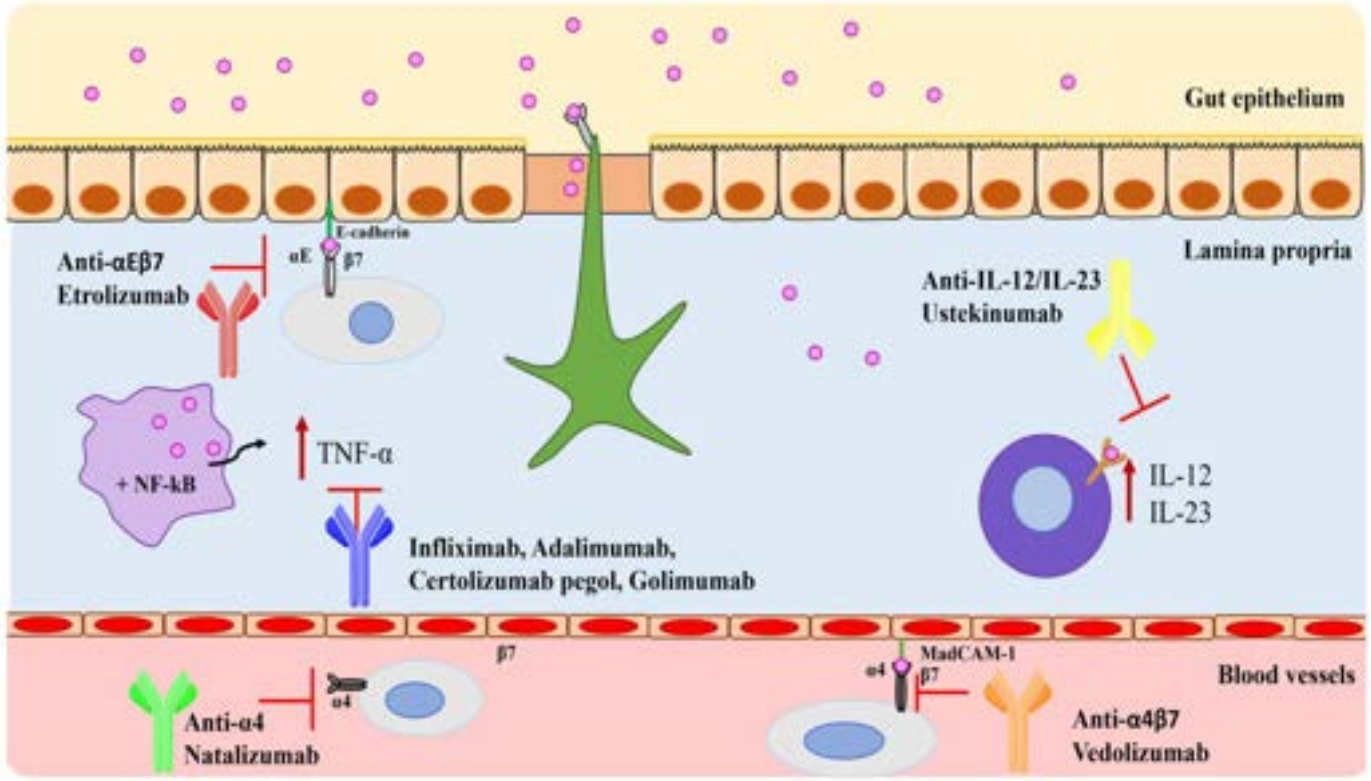
- Indication: Moderate-Severe UC or Crohn's disease
- Pharmac: Second line biologic
- Administration: Single IV infusion then 8wkly SC
- Advantages:
  - Convenient dosing
  - Low immunogenicity
  - Effective for extra intestinal manifestations
  - Excellent safety profile…

Ustekinumab Safety:

- Generally safe
- No anaphylaxis or serious infusion reactions with IV Ustekinumab (n=790)
- Most common adverse reactions
  - Nasopharyngitis and headache (>5%)
  - Mostly mild and drug continued
- Tuberculosis
  - Screen and treat (if latent)
  - Latent TB: no active TB if given isoniazid concurrently

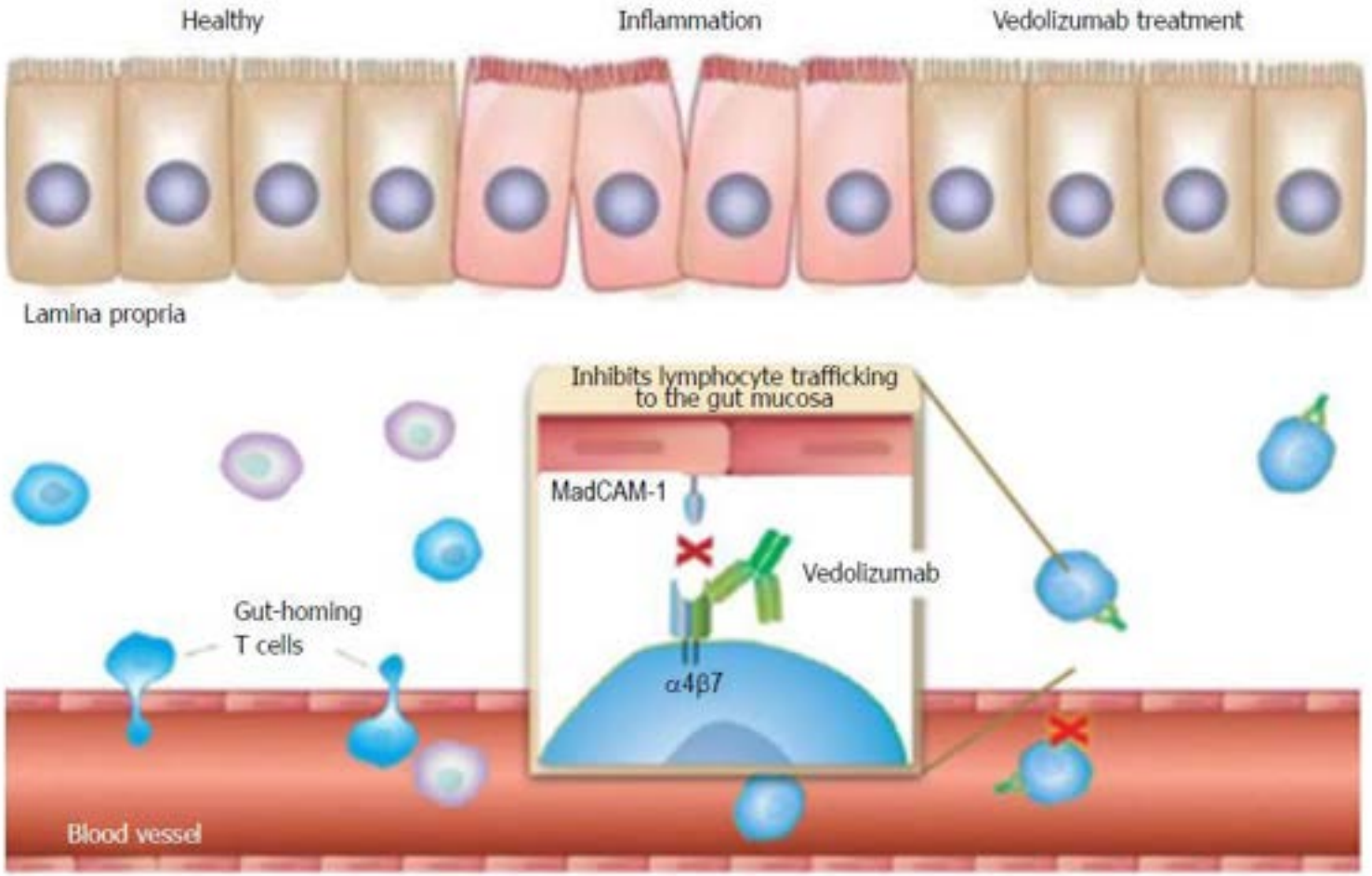
BIOLOGICAL AGENTS FOR INFLAMMATORY BOWEL DISEASE IN NEW ZEALAND

- INFLIXIMAB
- ADALIMUMAB
- USTEKINUMAB
- VEDOLIZUMAB
- UPADACITINIB



Di Rienzo, A.; Marinelli, L.; Dimmito, M.P.; Toto, E.C.; Di Stefano, A.; Cacciatore, I. Advancements in Inflammatory Bowel Disease Management: From Traditional Treatments to Monoclonal Antibodies and Future Drug Delivery Systems. *Pharmaceutics* **2024**, *16*, 1185.

Vedolizumab:



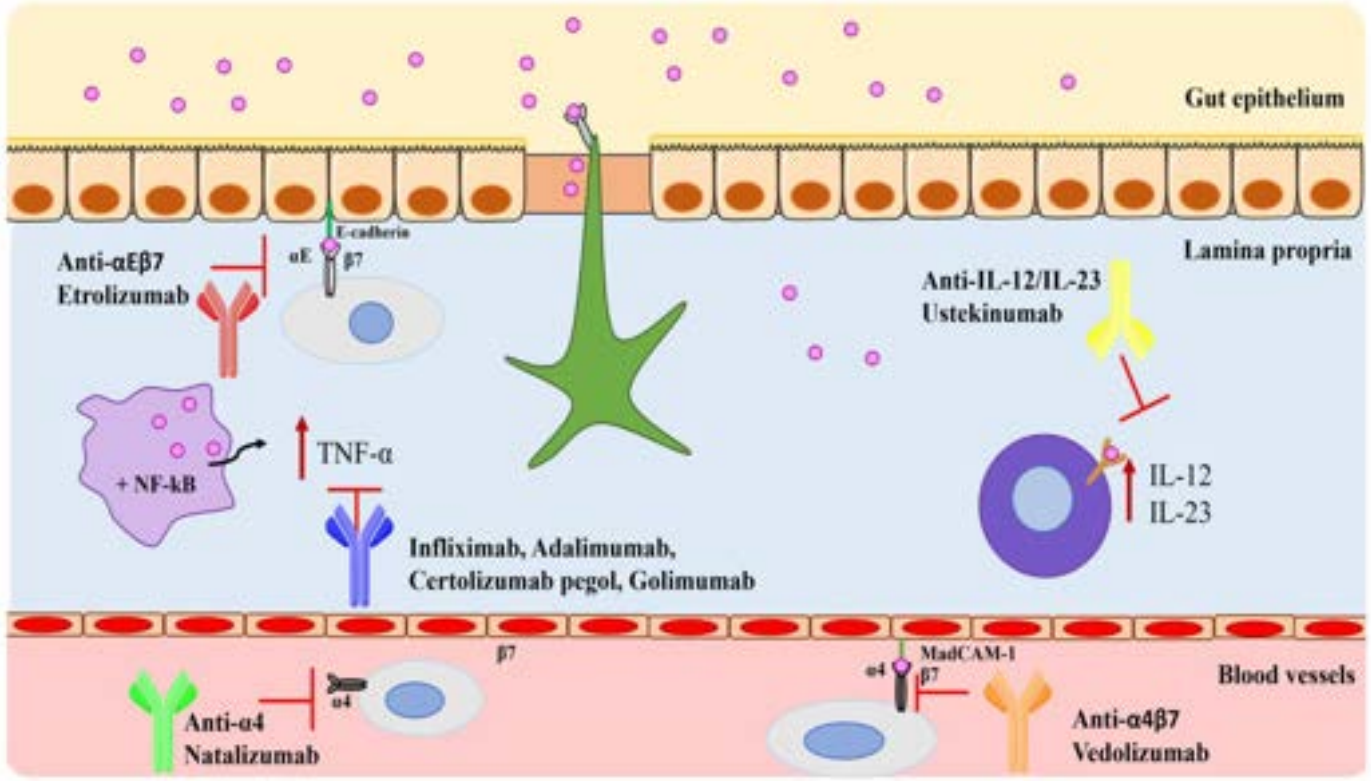
Modified from: Cribano ML. Vedolizumab for inflammatory bowel disease: From randomized controlled trials to real-life evidence. World J Gastroenterol 2018; 24(23): 2457-2467.

Vedolizumab Summary:

- Indication: Moderate-Severe UC or Crohn's disease
- Pharmac: First or second line biologic
- Administration: IV infusions, 8wkly maintenance
- Advantages:
  - **Gut-specific mechanism**
  - Very little systemic side effects
  - Suitable for elderly or comorbid patients
  - Suitable in context of infection/malignancy risk
- Disadvantages:
  - Relatively slower onset of action
  - Infusion capacity constraints

BIOLOGICAL AGENTS FOR INFLAMMATORY BOWEL DISEASE IN NEW ZEALAND

- INFLIXIMAB
- ADALIMUMAB
- USTEKINUMAB
- VEDOLIZUMAB
- UPADACITINIB



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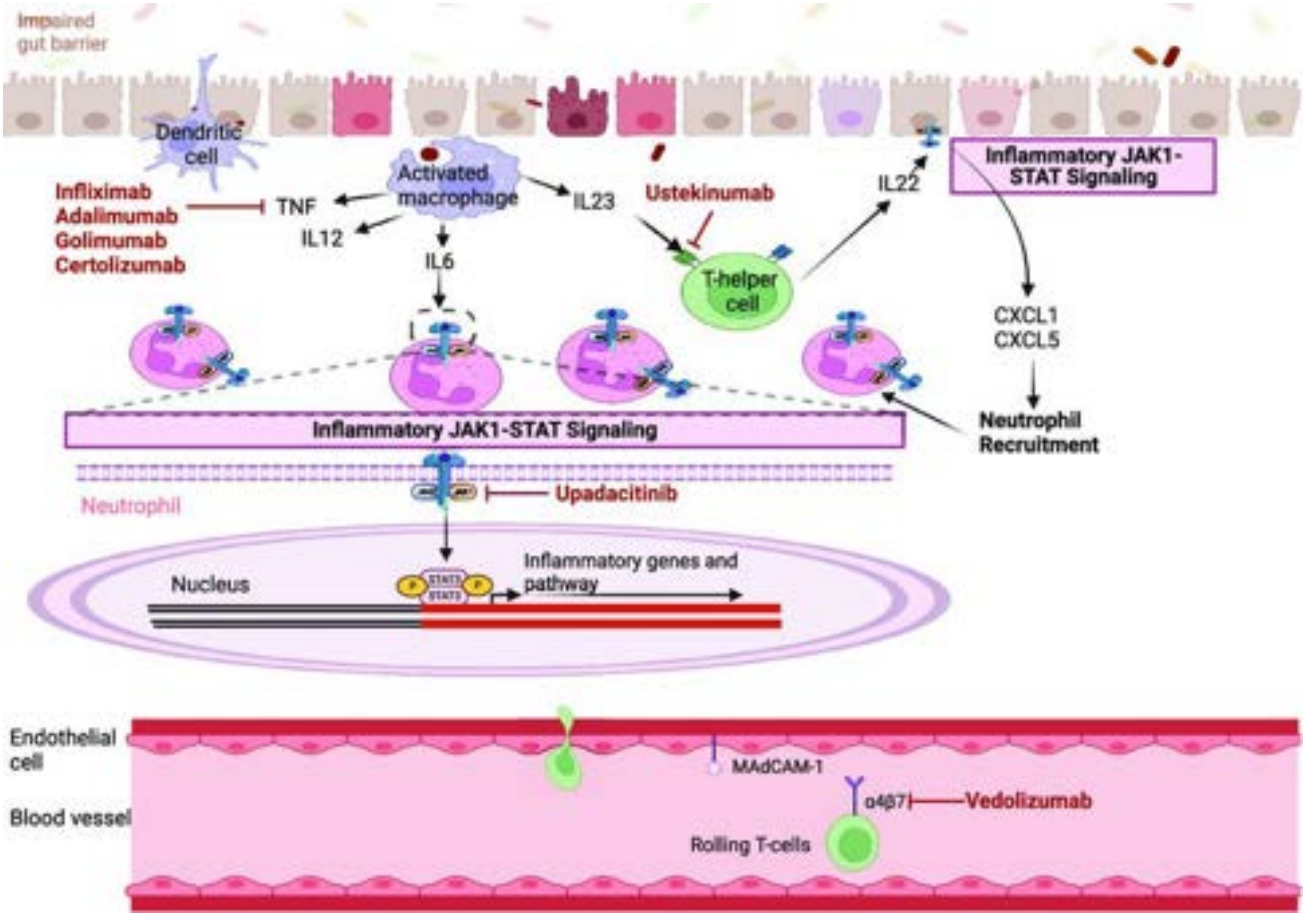
Upadacitinib:



Modified from: Cockburn, Ella & Kamal, Shahed & Chan, Andrea & Rao, Vikram & Liu, Tianwei & Efklides, Joanna & Segal, Jonathan. (2023). Crohn's disease: an update. Clinical Medicine. 23. 549-557

Upadacitinib Summary:

- Indication: Moderate-Severe UC or Crohn's disease
- Pharmac: Second line biologic
- Administration: **oral**, daily dose (45mg induction, 30/15mg maintenance)
- Advantages:
  - Oral administration
  - Rapid symptom onset
  - Effective
  - Can stop immunomodulators
- Disadvantages:
  - Safety issues:
    - Infection risk (e.g Herpes Zoster, respiratory infections, opportunistic infections)
    - Thrombosis
      - Rare but increased risk of VTE/MACE
      - Especially in older patients or those with risk factors
  - Adverse effects affecting adherence:
    - Acne
    - Headache, nausea, fatigue

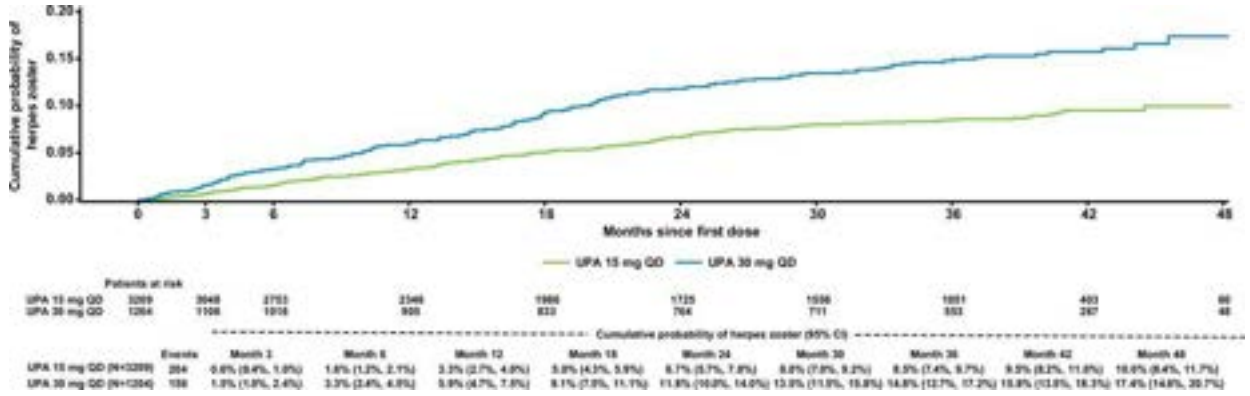
Upadacitinib Issues in Primary Care:

NDC 0074-2306-30

NDC 0074-2310-30

Upadacitinib: Herpes Zoster

- 3-6x increased risk c.f non-JAK inhibitor therapy
- Absolute risk 3-5 per 100 patient-years
- Dose dependent
- Risk Factors:
  - Previous HZ
  - Concomitant corticosteroids
  - Higher dose
  - Older age



Upadacitinib: Herpes Zoster

- Shingrix Vaccine strongly recommended:
  - Recombinant vaccine
  - 2 doses, 6 months apart
  - Ideally administer before starting
  - Can still be administered after commencement
    - Discuss immune response expectations
  - Major barrier in NZ:
    - Cost: $300-400 per vaccine
    - Pharmac funding criteria being reviewed

Upadacitinib: Herpes Zoster

➢ Management of HZ whilst on Upadacitinib:

1. Confirm the diagnosis:
    - Typical features/consider swab for VZV PCR if diagnosis uncertain
    - Assess extent and severity
        - Mild/localised: outpatient management
        - Severe/disseminated/ocular/neurological involvement: inpatient management

2. Prompt antiviral therapy
    - Do not need to wait for confirmation
    - Treatment <72 hours of rash onset reduces duration/complications
    - Aciclovir/Valaciclovir for 7 days

3. Withold Upadacitinib temporarily
    - Reduces risk of dissemination
    - Do not restart until:
        - Vesicles crust
        - Systemic symptoms resolved
        - Green light from specialist

4. Consider vaccination after recovery

Upadacitinib: Thrombosis

- Higher rates of MACE and VTE with Tofacitinib
- Not clearly replicated with Upadacitinib
- Elevated Lipid profile with Upadacitinib
  - Total cholesterol/LDL/HDL
  - Effect on CVS morbidity and mortality not determined
- Caution if ≥65 and/or >1 CVS risk factor

Monitor lipid levels 12 weeks after commencement. Further monitoring and management as per dyslipidaemia guidelines

Upadacitinib: CYP3A4

- Primarily metabolized by CYP3A4
  - CYP3A4 inhibitors:
    - Increase Upadacitinib exposure
    - *"Use with caution"*
    - **e.g Ketoconazole, Clarithromycin**
    - Dose adjustments might be necessary
  - CYP3A4 inducers:
    - "Not advised"
    - Rifampicin

- **No dose adjustment for CYP3A substrates**
  - **e.g Atorvastatin, Rosuvastatin**

- Oral contraceptives OK

Upadacitinib: Acne

- Common (6%)
- Mild-moderate papulopustular acne on face and/or trunk
- Within 2-8 weeks of initiation
- Dose dependent
- Most cases respond to standard acne treatment within 1-2 months
- Pre-emptive education and reassurance important

Outline

- **IBD Overview**
  - Clinical Features
  - Diagnostic Testing
- **Changing Demographics**
- **Dietary influence?**
- **Management Principles**
  - Immunomodulator Shift….
    - NUDT15
    - Tioguanine
  - New Biological Agents
    - Ustekinumab (Stelara)
    - Vedolizumab (Entyvio)
    - Upadacitinib (Rinvoq)
- **Pregnancy/Breastfeeding updates**
- **The future…**

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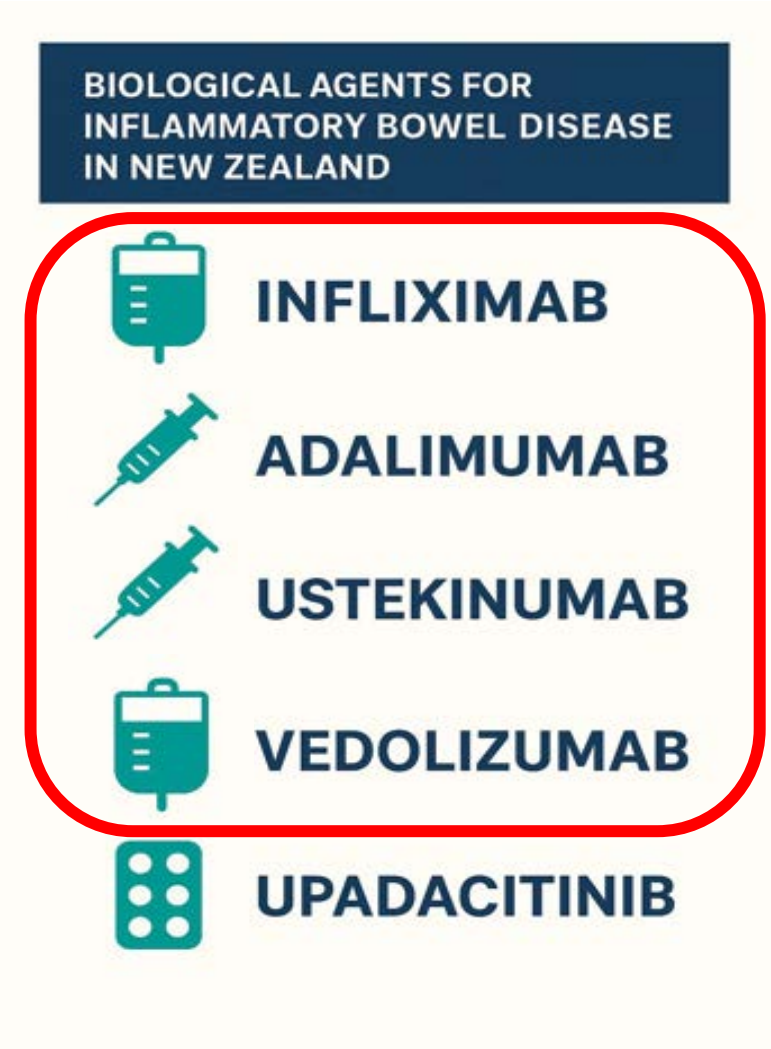
Pregnancy/Breastfeeding Update:



- **Safe during conception, pregnancy and breastfeeding**
- Adjustments to doses/timing of doses no longer recommended
- Pregnancy exposure:
  - No live vaccines for 12 months
- Breastmilk exposure only:
  - Normal vaccination schedule

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Pregnancy/Breastfeeding Update:

- Fetal development affected in animal studies
- No data in humans
- **Avoid in conception and pregnancy**

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The future of IBD management…

- Use of dual Biologics
- Microbiome-based therapies
- Precision medicine
  - Biomarkers and genomics to predict response

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Summary:

- Epidemiology: IBD much more common in migrants
- Diet more relevant in Crohn's disease?
  - UPF: increased incidence and adverse outcomes
  - Mediterranean diet: reduced incidence and symptoms
- Tioguanine gaining popularity as first line immunomodulator
- New biologics are effective, safe, convenient with good persistence
- Upadacitinib issues: HZ risk, Lipids, Interactions, Acne.
- Conception/Pregnancy/Breastfeeding: Upa = bad, Others = good

Thank you!