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The human microbiome company

Getting to the guts of histamine intolerance

The role of the gut microbiome

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Histamine Intolerance (HIT)

- Histamine intolerance (HIT) is defined as an intolerance to dietary histamine
- Originally known in it's worst form as scombroid fish poisoning or scombrotoxicosis
- It is thought to develop due to an enzyme deficiency, resulting in the inability to break dietary histamine down quick enough, giving a higher overall load
- The majority of dietary histamine is broken down in the digestive system and the gut wall
- Histamine intoxication, a kind of food poisoning, may occur after the consumption of foods with an unusually high histamine content that overpowers the degradation mechanisms

So where does histamine come from?

- Most of the foods we consume contains varying amounts of histamine
- Histamine mainly comes from the bacterial fermentation of histadine
- The amount we do eat a day is very hard to estimate, as the amount in food can vary wildly, due to things like the manufacturing process, the cleanliness of materials, the microbial composition, the ripeness of the food and the amount of bacterial fermentation it has undergone
- Histamine is the most common food poisoning from fish products – fresh fish has very little, but bacteria in the gut and gills of the fish start begin to decompose the proteins in the fish as it ages
- Heating, canning and freezing does not reduce levels, but can stop more from being made by halting bacterial fermentation

(Visciano et al., 2014)

So where does histamine come from?

- Foods high in histamine are ones that are more prone to bacterial fermentation – dried, aged or fermented meats, fish, fruits
- OR are foods that are high in naturally occurring amino acid histadine or other biogenic amines, that in turn be metabolised into histamine
- Another source of histamine can be endogenous production and release by mast cell degranulation – in response to allergic reactions
- Histamine contents of more than 40 mg per meal (0.75 mg/kg body weight) increases the risk of scombroid poisoning, but some individuals are much more sensitive than others to the impacts of it
- Biogenic amines such as monoamine tyramine, diamines histamine, putrescine and cadaverine, as well as the polyamines spermine and spermidine can also play a role in HIT symptoms

Symptoms of histamine intolerance – normally 20 mins post exposure

Respiratory and cardiovascular system

- Shortness of breath, cough, asthma, nasal or sinus congestion, sinus issues, sore throat, post-nasal drip, throat clearing, palpitations, syncope, POTS, low blood pressure

Digestive system

- nausea, vomiting, diarrhoea, constipation, stomach pain, bloating, and acid reflux

Nervous system

- headaches, migraines, vertigo, dizziness, insomnia, fatigue, and anxiety

Musculoskeletal system

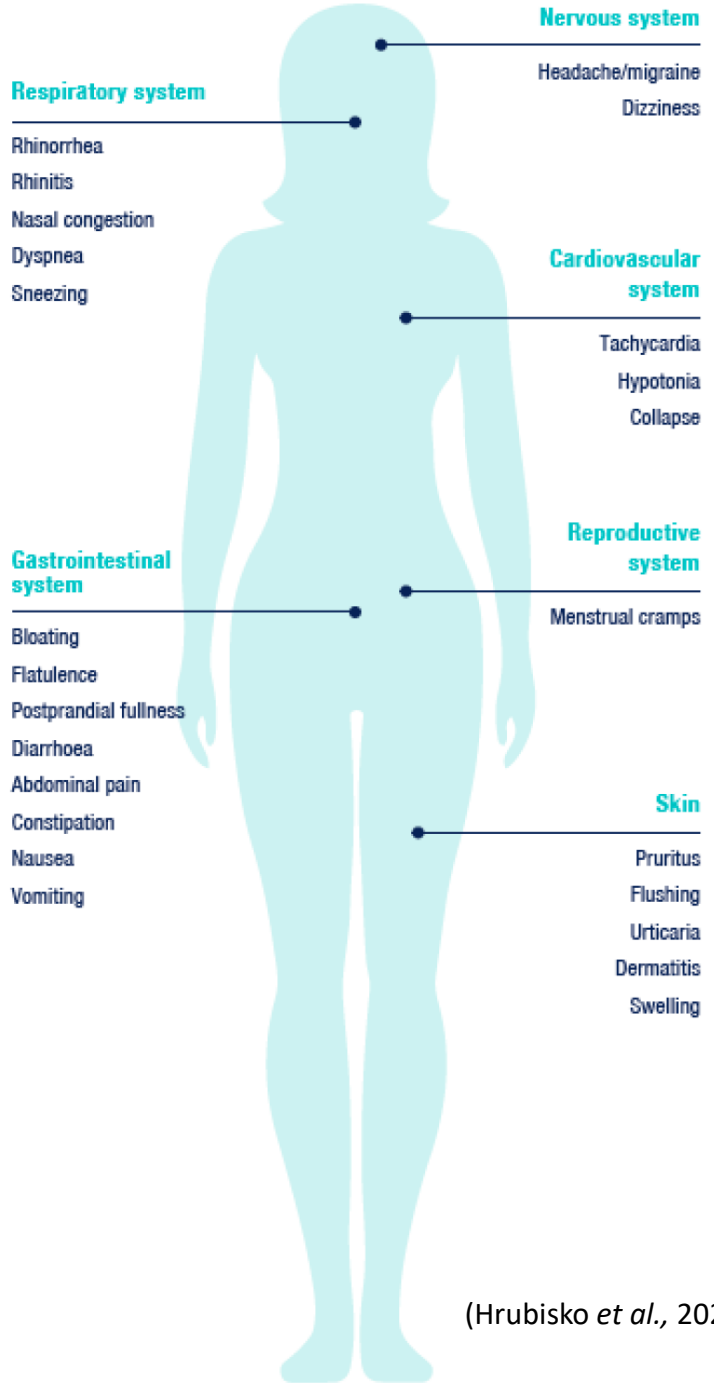
- muscle twitches, myalgia, joint pain and fibromyalgia.

Reproductive system

- irregular periods, period cramps/pain, endometriosis

Skin

- Hives, pruritis, swollen eyes, redness, eczema, atopic skin



(Hrubisko *et al.,* 2021)

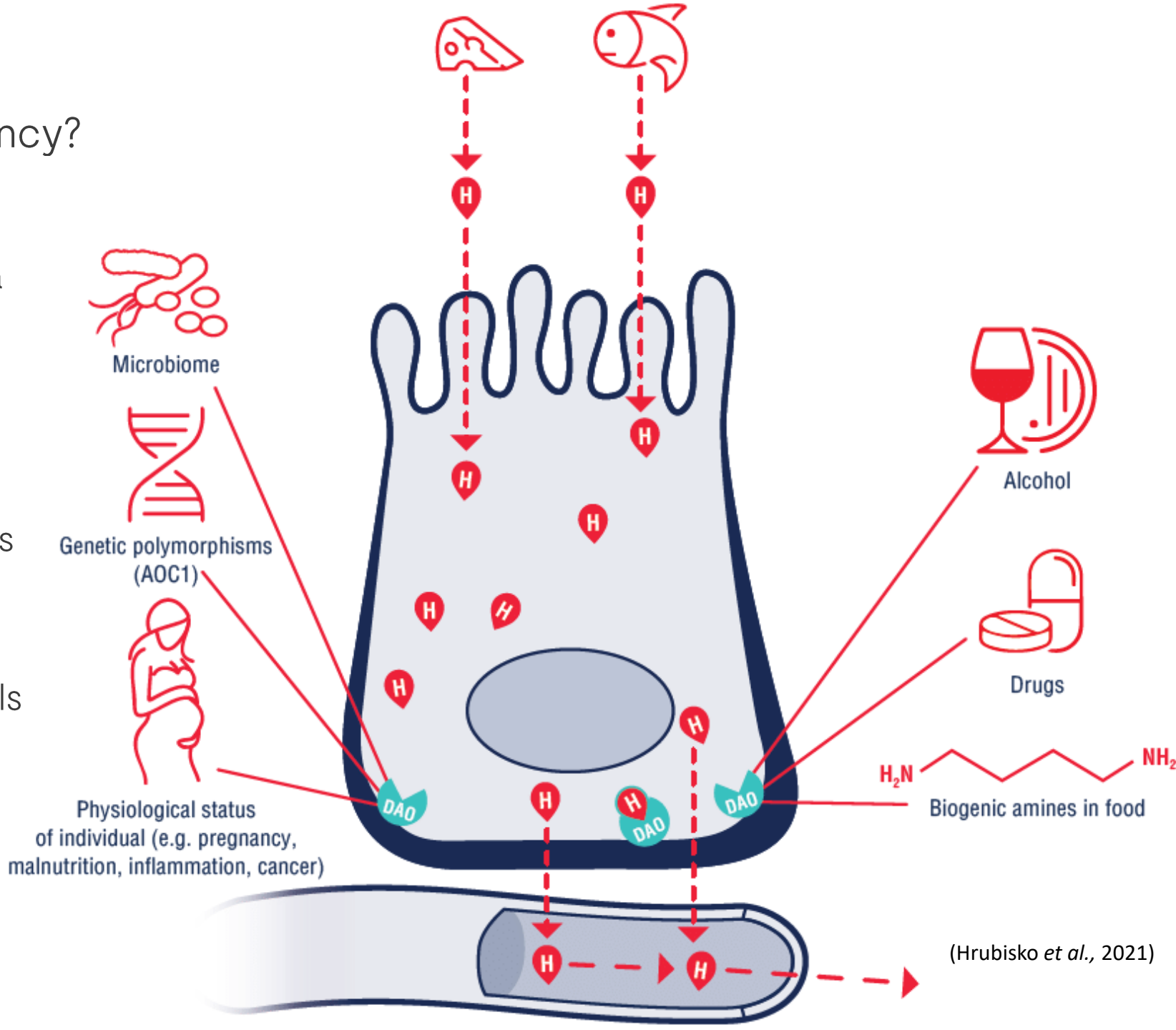
Histamine intolerance, or DAO deficiency?

- The 2 main enzymes that degrade histamine are the predominant intestinal **diamine oxidase** (DAO), and **N-methyl transferase** (HMNT).
- DAO is the most important for dietary/gut degradation of histamine
- DAO is in it's highest concentration in the gastric mucosa, as well as kidneys, placenta, thymus and seminal vesicles
- DAO is produced by mature intestinal enterocytes and is constantly released from the intestinal mucosa into the gut as well as into the blood circulation, during digestion
- Histamine intolerance is said to occur when the level of histamine we ingest/produce overpowers the number of enzymes that we produce

What causes DAO deficiency?

- DAO deficiency may have a genetic origin and has been associated with single nucleotide polymorphisms (SNP's)
- Impaired DAO activity can occur as a side effect of some pharmacological drugs
- Many gastrointestinal disorders impact our ability to make DAO, due to the damage to the epithelial cells
- The production of DAO enzyme fluctuates with oestrogen in the menstrual cycle

(Comas-Basté *et al.*, 2020)



(Hrubisko *et al.*, 2021)

Medications that cause DAO deficiency

Pharmacological indication	Active Principle	Pharmacological indication	Active principle
Analgesics	Metamizol, Acetyl salicylic acid	Diuretics	Amiloride, Furosemide
Antihistamines	Diphenhydramine, Climetidina Promethazine	Expectorants	Ambroxol (Mucosán)
Anti-arrhythmic drugs	Propafenone, Quinidine	Mucolytics	Acetilcysteine (Fluimicil, Frenacil)
Anti-asthmatics	Theophylline	Antipmalarials	Chloroquine
Antidepressants	Amitriptyline, Tranylcipromine	Antibiotics	Clavulanic acid, Isoniazid (Augmentine, Amoxiplus)
Anti-hipertensive drugs	Dihidralazina, Verapamil	Antiemetics	Metoclopramide (Primperan)
Antirheumatics	Acemetacina	Neuroleptics	Haloperidol
Antiseptics	Acriflavine	Prokinetics	Metoclopramide
Antituberculosis	Isoniazid	Tranquilizers	Diazepam
Bronchiolitics	Aminophylline	Muscle relaxants	Pacuroni
Cardiotonics	Dobutamine		

Medications that increase endogenous histamine production

Pharmacological Indication	Active Principle
Analgesics	Acetylsalicylic acid, Meclofenamic acid, mefenamic acid, Diclofenac, Infometacina, Ketoprofen, Meperidine, Morphine of animal origen
Anestesics	Thiopental, Prolocaina, Barbiturates
Antitussives	Codeine
Cytostatics	Cyclophosphamide
Expectorants	Ambroxol
Mucolytics	Acetylcysteine
Muscle relaxants	D-tubocurarine, Alcuroni
Anti-inflamatory	Naproxen

Picture source: https://www.deficitdao.org/en/dao-deficiency/origin-of-dao-deficiency/pharmacological-factors/

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How to put together a clinical picture of HIT

- Clinical picture is most important – pharmaceutical use history, food poisoning history and any GIT insult (including viral infections) may all be important triggers
- Checking for IgE mediated allergic reactions and mast cell activation- Testing may include IgE or tryptase serum testing
- Ruling out sulphite and benzoate allergies
- Keeping a food diary to link with offending foods to see if there is a pattern relating to histamine rich foods
- Testing for serum histamine, and/or serum DAO
- Functional testing once HIT is suspected – microbiome and gut barrier analysis, SNP analysis, oestrogen detoxification

Mast Cell Activation Disorders (MCAS)

- Mast cells release endogenous histamine and increase the inflammatory response
- In certain GIT diseases they can migrate to the GIT and also contribute to the level of histamine, and therefore inflammation, and gut damage, which in turn will worsen exogenous histamine intolerance
- These are known as MCAS, or eosinophilic gastroenteritis
- These conditions can be associated with hypermobility spectrum disorder, Ehlers-Danlos syndrome, and the postural tachycardia syndrome

How the gut and the microbiome contribute to HIT

+ The epithelial barrier is where DAO is produced by mature epithelial cells.
+ It is then released into the mucosal barrier as well into the blood circulation
+ **Damage to the gut barrier, and the subsequent mucosal barrier can therefore reduce the level of DAO being produced** – in IBD we see lowered levels of DAO
+ The undegraded levels of histamine can then contribute to more local inflammation, and therefore more food antigen reactions
+ The microbiome of the gut is important for maintaining gut and mucosal barrier integrity
+ Commensal bacteria also play an important role in immune signalling and immune tolerance

Gastrointestinal disorders are associated with DAO deficiency

DAO deficiency is highly associated with any gastrointestinal disorder where there is mucosal and/or epithelial damage

+ Gastroenteritis and post infection
+ IBD – Crohn's and UC
+ Colon cancer
+ IBS, short bowel syndrome or gastrointestinal surgery
+ Non-coeliac gluten sensitivity
+ Alteration to the composition of the gut microbiota
+ COVID has been found to stay in the gut mucosa for up to 7-9 months post infection, and in some long COVID cases may present with HIT symptoms

Immunotolerance and the microbiome

- The development of the gut microbiome has a major impact on the development and maturation of immune tolerance in individuals
- This is very much linked to developmental stages in association to microbes
- Dysbiosis in paediatric populations has been linked with allergy susceptibility
- The gut microbiome plays an important role through pattern recognition receptors in supporting the maturation/composition of the gut-associated lymphoid tissues (GALT) and mucosal associated lymphoid tissues (MALT)
- It also helps to regulate basophil populations, and promote healthy intestinal barrier function in key developmental periods
- In children, there are differences in the microbial signatures associated with allergies, such as high *Ruminococcus gnavus* as well as lower levels of *Bifidobacterium longum*, *Bacteriodes dorei, B. vulgatus, Ruminococcus bromii* and of several other fibre-degrading species compared with healthy controls (De Filippis et al., 2021)

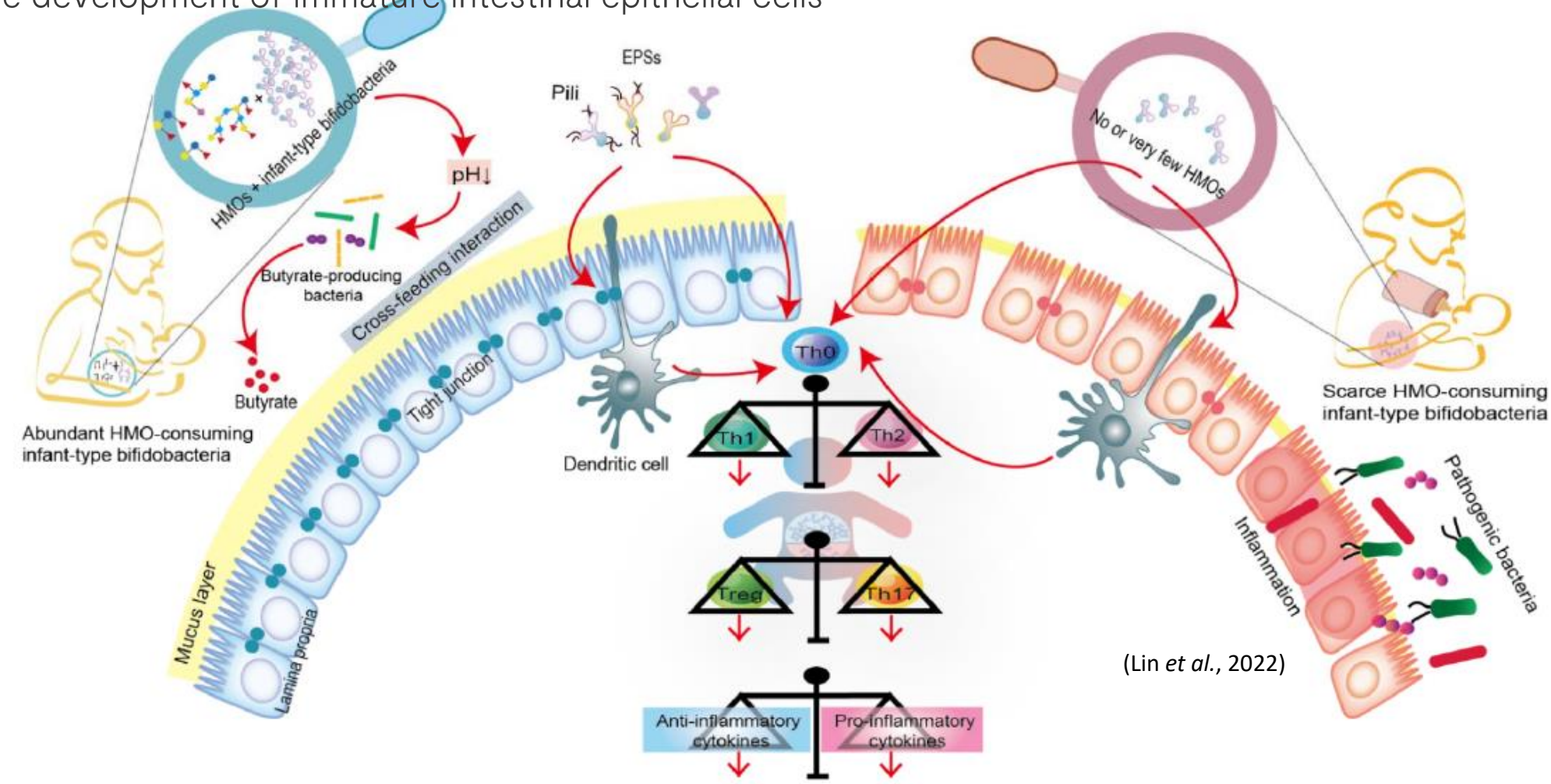
(De Filippis et al., 2021)

Bifidobacterium and immune tolerance

- *Bifidobacteria* is an important species required in the early colonisation of the infant microbiome to educate the neonatal immune system
- It is the predominant intestinal microbiota in infants and are abundant also in the adult population comprising up to 6% of the normal intestinal microbiota
- *Bifidobacteria* metabolise human milk oligosaccharides (HMO's), as they possess glucosidase, which we do not
- The metabolites liberated by HMO degradation generate more diverse growth of different species *of Bifidobacterium*, and also the metabolites contribute to infant immune, gut and nervous system development

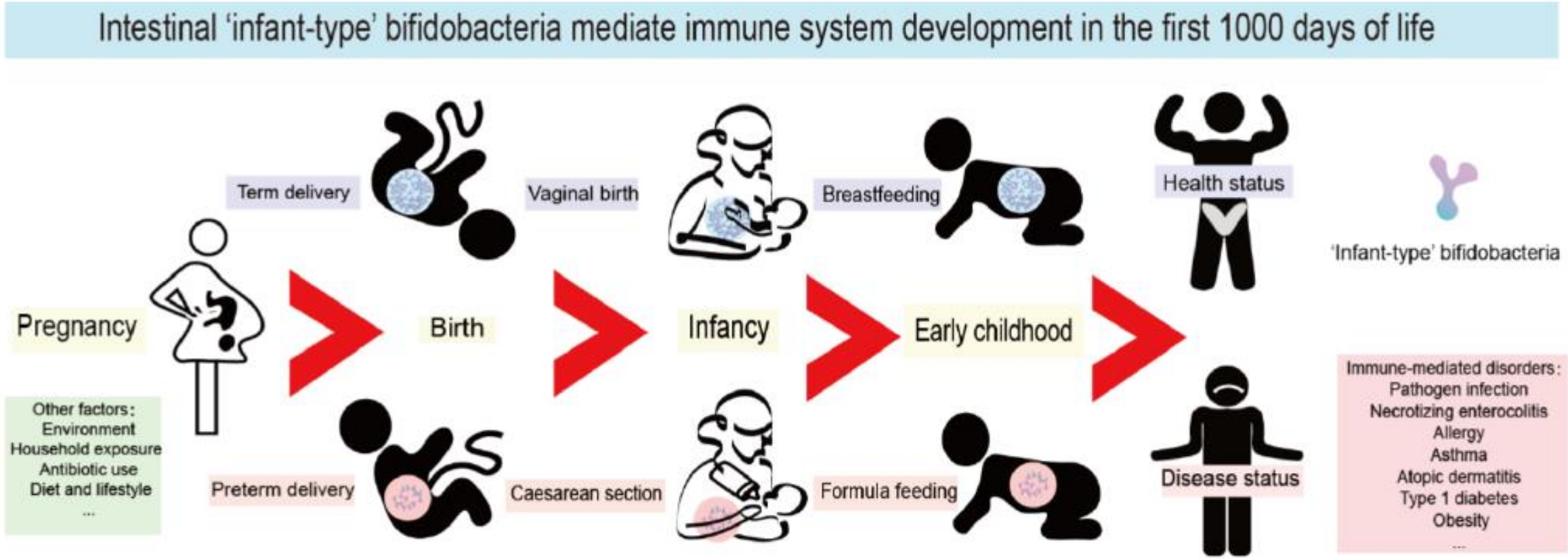
(Lin *et al.*, 2022)

- *Bifidobacteria* represent one of the earliest antigens to activate the host defence mechanism, which helps to promote immune development and prime the anti-inflammatory gene pool
- Metabolites such as tryptophan-derived indole-3-lactic acid (ILA) have been shown to regulate the response of monocytes to lipopolysaccharides, modulate T helper cell 2 (Th2) and Th17 immune responses that are required to induce immune tolerance, inhibit intestinal inflammation and promote the development of immature intestinal epithelial cells



(Lin *et al.*, 2022)

Bifidobacterium and immune tolerance



(Lin *et al.*, 2022)

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FUT2 gene, ABH antigens and the microbiome

- The enzyme fucosyltransferase 2, is responsible for the expression of ABH antigens that are secreted into the intestinal mucosa of the gut
- The gene, **FUT2,** is responsible for the production of the this enzyme.
- In people with SNPs on the FUT2, they end up not secreting these antigens
- These antigens can be found in mucosal secretions, and also breast milk, so secretors vs non-secretors can have different linkages to their HMO's
- These antigens are an energy source and adhesion receptors for many microbes, so different linkages patterns can impact microbiome development

FUT2 gene, ABH antigens and the microbiome

- Non-secretors have been shown to possess lower bifidobacterial diversity richness and abundance when compared with those that are secretors (Wacklin et al., 2011)
- Non-secretors may have higher susceptibility to *Candida albicans* and *Streptococcus pneumoniae*
- Non-secretors may also have a higher risk of autoimmune diseases such as IBD, type 1 diabetes, coeliac disease
- However secretors may have a higher risk of *H.pylori* infections
- Non-secretors may have more immunity to noroviruses, and a slower HIV-1 virus progression
- In adults though, the correlation between stool microbial profiles and FUT2 status seems to be less clear, and there may be many other SNP's and factors at play here

(Bordoni et al., 2020, Wacklin et al., 2011)

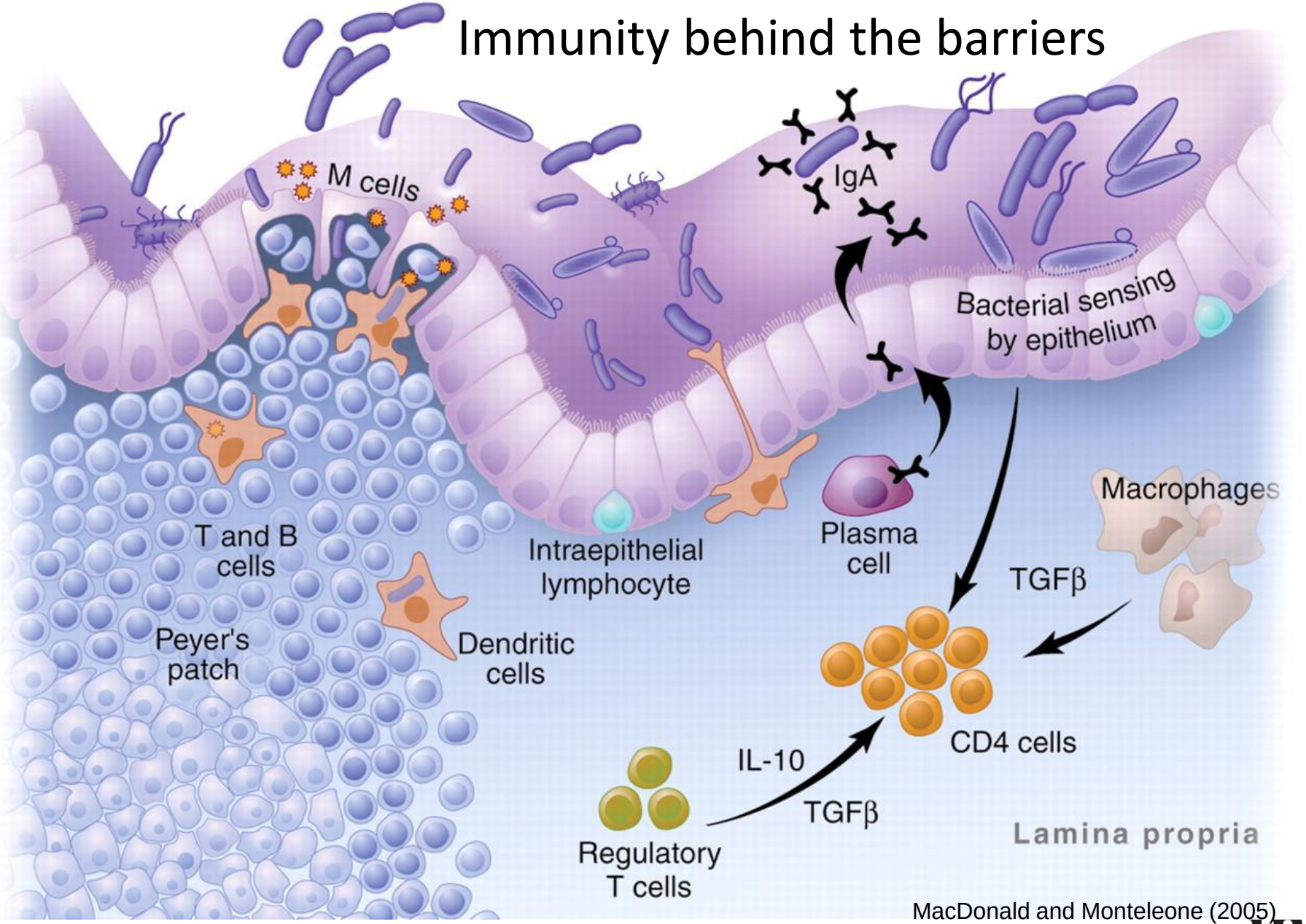
Mucus and bacteria

- Mucus has a dual role in relation to the microbiota:
  - it protects the underlying cells from undesired interactions with microbes such as pathogens
  - it also provides an initial adhesion site, nutrient source, and matrix in which commensal bacteria can proliferate and thrive
- Certain commensal bacteria specialise in degrading the mucin glycans and utilise the energy to feed themselves and their host
- Production and degradation of mucin is usually stable in healthy individuals, leading to a dynamic mucus-layer with a stabile thickness, composition and consistency

Pathogenic bacteria and mucin

- Many pathogenic bacteria have learnt how to navigate the mucin lining – either by adhering to the mucin, and/or using strong flagella to swim through the mucous to get to the epithelial cells – where they induce inflammation
- *E. coli, C. jejuni, C. difficule, H. pylori* are all examples of pathogens that possess mucin binding and/or degrading enzymes to use to their own advantage
- Hence why a passing infection can cause temporary HIT

Immunity behind the barriers



MacDonald and Monteleone (2005)

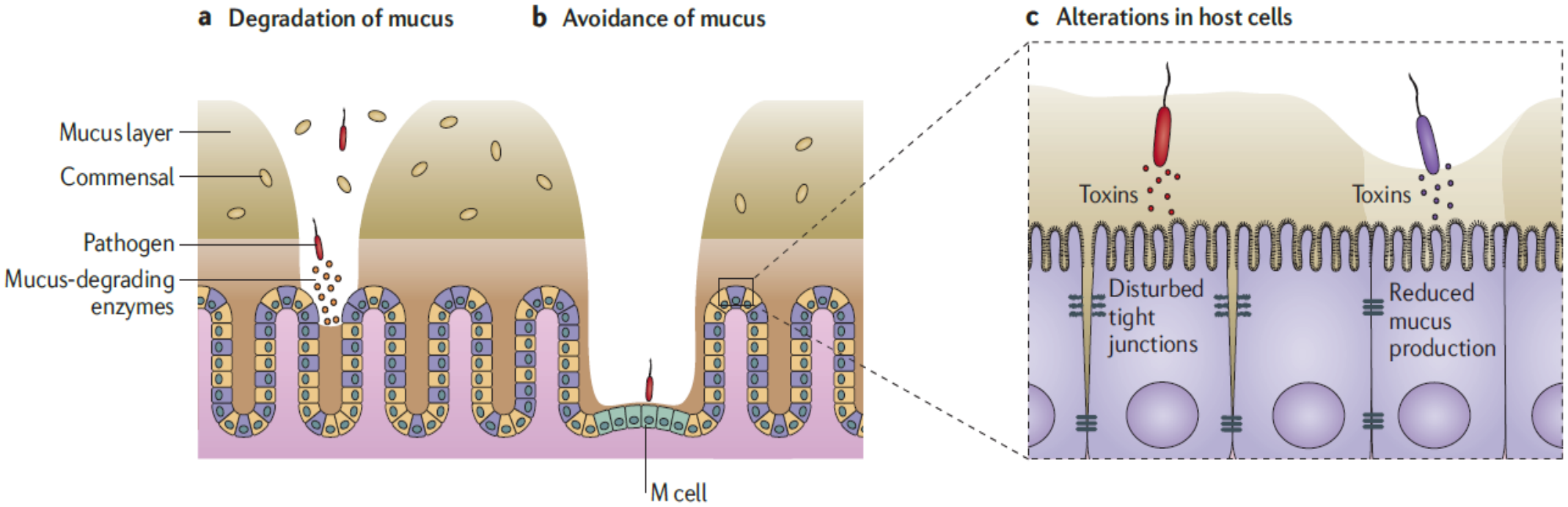


Figure 4 | **Pathogen strategies to subvert the mucus barrier. a** | Pathogens can penetrate the mucus barrier physically, through flagella-mediated motility or through enzymatic degradation of the mucus. This can result in both pathogens and commensal bacteria reaching the epithelium. **b** | Microfold (M) cells in the small intestine sample the commensal microbiota to control the specificity of non-inflammatory, secretory immunoglobulin A-dominated immune responses to the normal microbiota. The M cells are found in the dome epithelium, which is not covered by a thick mucus layer; thus, pathogens can avoid the mucus barrier by entering via the M cells. **c** | Many pathogens secrete toxins that can diffuse through the mucus. These can disrupt the tight junctions between the epithelial cells, block epithelial cell growth and disrupt mucus production. The reduction in mucus levels will allow pathogens to reach the cell surface.

(McGuckin, 2011)

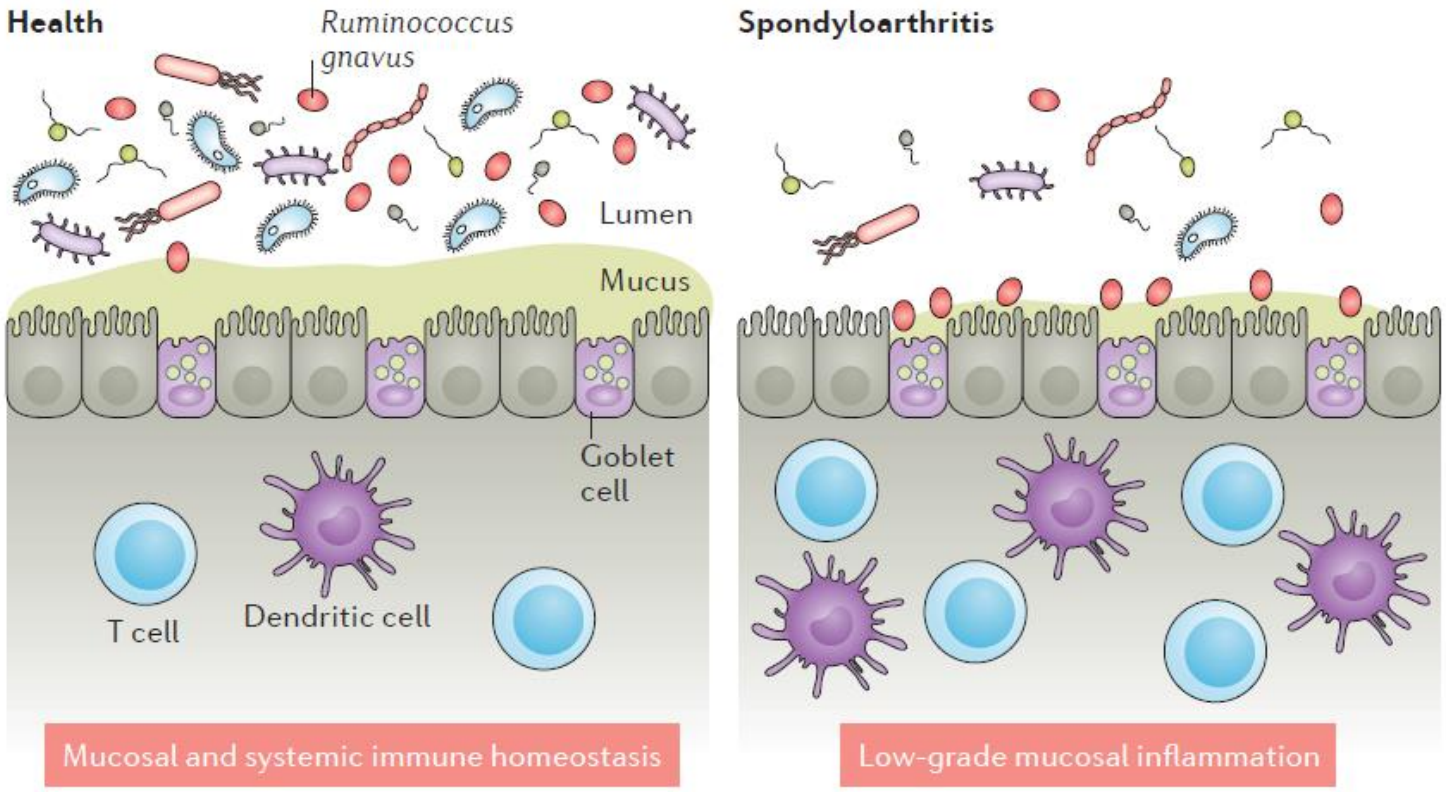


Figure 1 | **Disturbed microbiota–host interactions in spondyloarthritis.** The intestines of healthy individuals have high levels of bacterial diversity with a very low prevalence of *Ruminococcus gnavus*, contributing to a stable intestinal barrier and to homeostasis of the mucosal and systemic immune system. By contrast, the intestines of patients with spondyloarthritis have reduced bacterial diversity and high abundance of *R. gnavus*. This high prevalence of *R. gnavus* is thought to lead to mucus degradation, destabilization of the intestinal barrier, low-grade mucosal inflammation and spondyloarthritis.

Vereecke, L. & Elewaut, D. (2016)

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Microbial and host marker patterns in HIT

What to look for in stool testing

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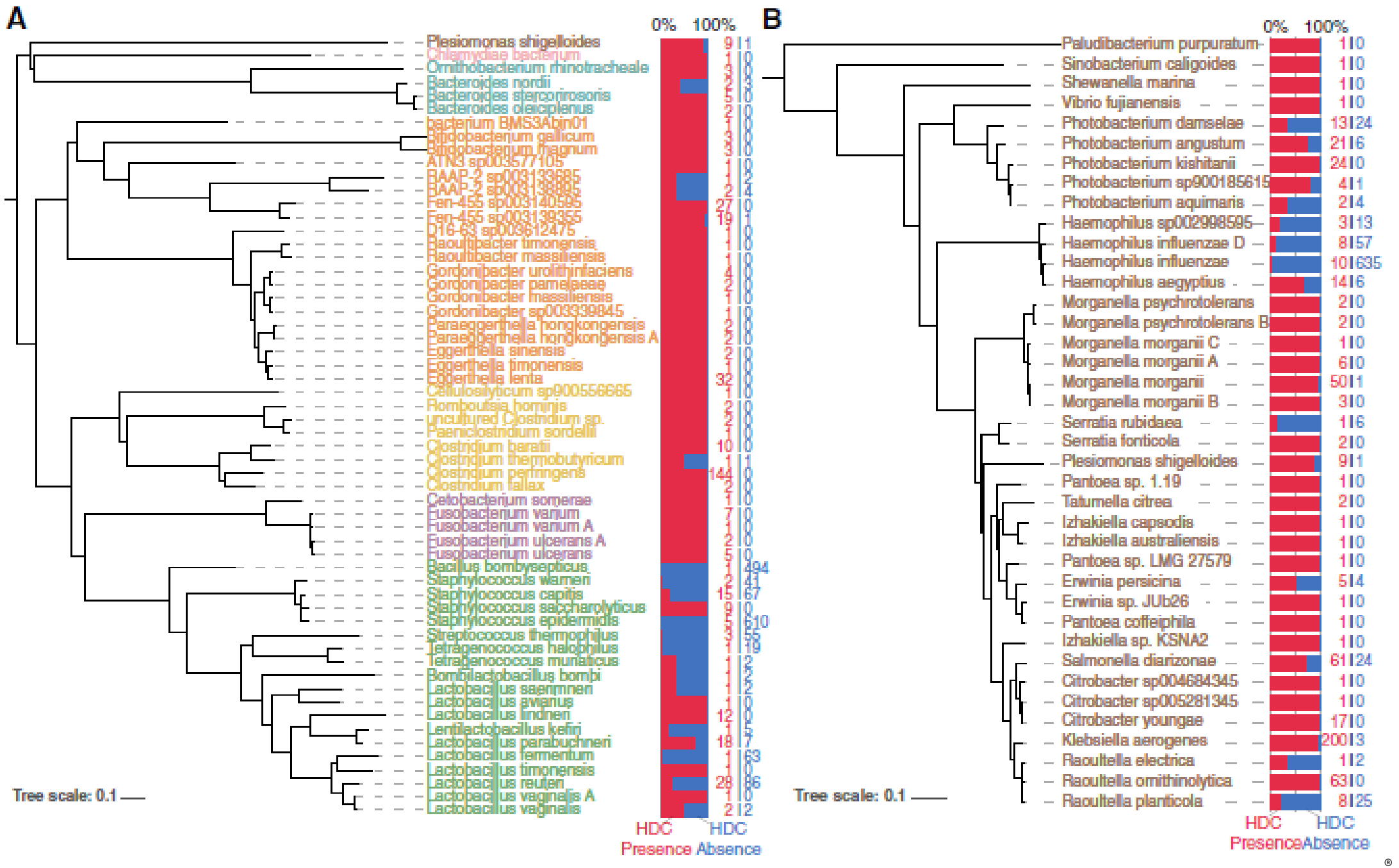
So what microbial and host patterns are we looking for in stool tests?

When looking at a stool test with someone with HIT, we are looking for many different microbiome scenarios that might be associated as a contributing factor:

+ Mucosal barrier disruptions
+ Epithelial barrier disruptions
+ Lack of immunomodulatory commensals
+ Increase in histamine producing bacteria and inflammatory pathobionts
+ SIBO (damages barrier)
+ Helicobacter pylori infections/gastritis

Histamine producing bacteria

- Many bacteria possess the enzymes to produce histamine, this is normal, even in the gut microbiota
- A recent analysis found 117 different microbes in the human gut microbiome possess the genomic potential to secrete histamine
- The ability to produce histamine is very species specific so even within the same
- Species specific bacteria from the families *Lactobacilli spp., Staphlococcus spp. Streptococces spp., Fusobacterium spp., Citrobacter spp., Klebsiella spp., Morganella spp.* are just to name a few
- The histamine producing bacteria shouldn't be singled out in isolation, but looked at in the context of the rest of the microbiome – to see if the balance is skewed in the wrong way
- New research this week though showed that 25% people with IBS have a higher chance of carrying a strong HIT producer – *Klebsiella aerogenes*



Gut Microbial patterns and HIT

- Study of 26 females with HIT
- DNA microbial analysis showed:
  - Higher levels of **proteobacteria** than controls
  - ***Faecalibacterium prausnitzii*** was lower than controls (SCFA producer)
  - lower abundance of ***Prevotellaceae*** **(Bacteroidetes)** was found in the HIT group
  - ***Staphylococcus spp.*** **and** ***Proteus spp.*** were higher in the HIT group
  - ***Enterococcus faecalis, Proteus mirabilis*** **and** ***Escherichia coli*** tended to be higher in the HIT group
  - ***Clostridium perfringens*** occurred much more regularly in the HIT group

(Mou *et al.*, 2021)

Gut Microbial patterns and HIT

+ Bifidobacterium was found to be lower in cases of HIT
+ Proteobacteria were raised
+ SCFA producers were found to be lowered in HIT group (Schink et al., 2018)

+ This shows a similar pattern to other studies conducted

Microbiome or host marker patterns associated with HIT

mucosal barrier disruption

- ↓ Akkermansia muciniphilia
- ↑ Ruminococcus gnavus
- ↑ Ruminococcus torques

Inflammation/epithelial barrier disruption

- ↑ Zonulin
- ↑ Calprotectin
- ↑ FIT

Low immunomodulation potential

- ↓ Bifidiobacterium spp.
- ↓ Lactobacillus spp.

Increase in histamine producers

Hafnia alvei
Klebsiella spp.
Enterococcus faecium
Enterococcus faecalis
E. Coli

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Microbiome or host marker patterns associated with SIBO

Intestinal methanogen overgrowth

↑ Methanobrevibacter smithii

Digestive capacity

↓ Pancreatic elastase

↓ Bile Acids

Hydrogen sulphide gas producers

↑ Desulfovibrio spp.

↑ Bilophilia wadsworthia

↑ Fusobacterium nucleatum

Supporting a healthy microbiome in HIT

+ When it comes to supporting barrier integrity, and diversifying the microbiome in HIT it can be VERY tricky – as often the foods that can really nurture the microbiome, are also the ones that are high in histamine! So it becomes a worrying cycle of food avoidance to reduce symptoms, yet not enough microbial or prebiotic help to diversify the microbiome

+ Everyone has a moving histamine tolerance – it is important at the beginning of the plan to remove histamine/histadine/biogenic amine rich foods – but this should be a short term solution whilst working on the underlying immune, barrier and microbiome imbalances

Probiotics – friend or foe?

- Some species of Lactobacilli can produce histamine, does this mean we shouldn't use them?
- The evidence shows that probiotics on the whole reduce the symptoms of histamine intolerance, but downregulating inflammatory cytokines, and reducing mast cell degranulation
- The ability for probiotics to produce histamine is completely strain specific – you could have 2 exact same species, but 2 different strains where one has the histamine producing enzymes, and the other does not
- In some sensitive individuals, you can concentrate on using strains that have been shown not to produce histamine – the best way is to ask the company if they have been genetically tested to not produce histamine

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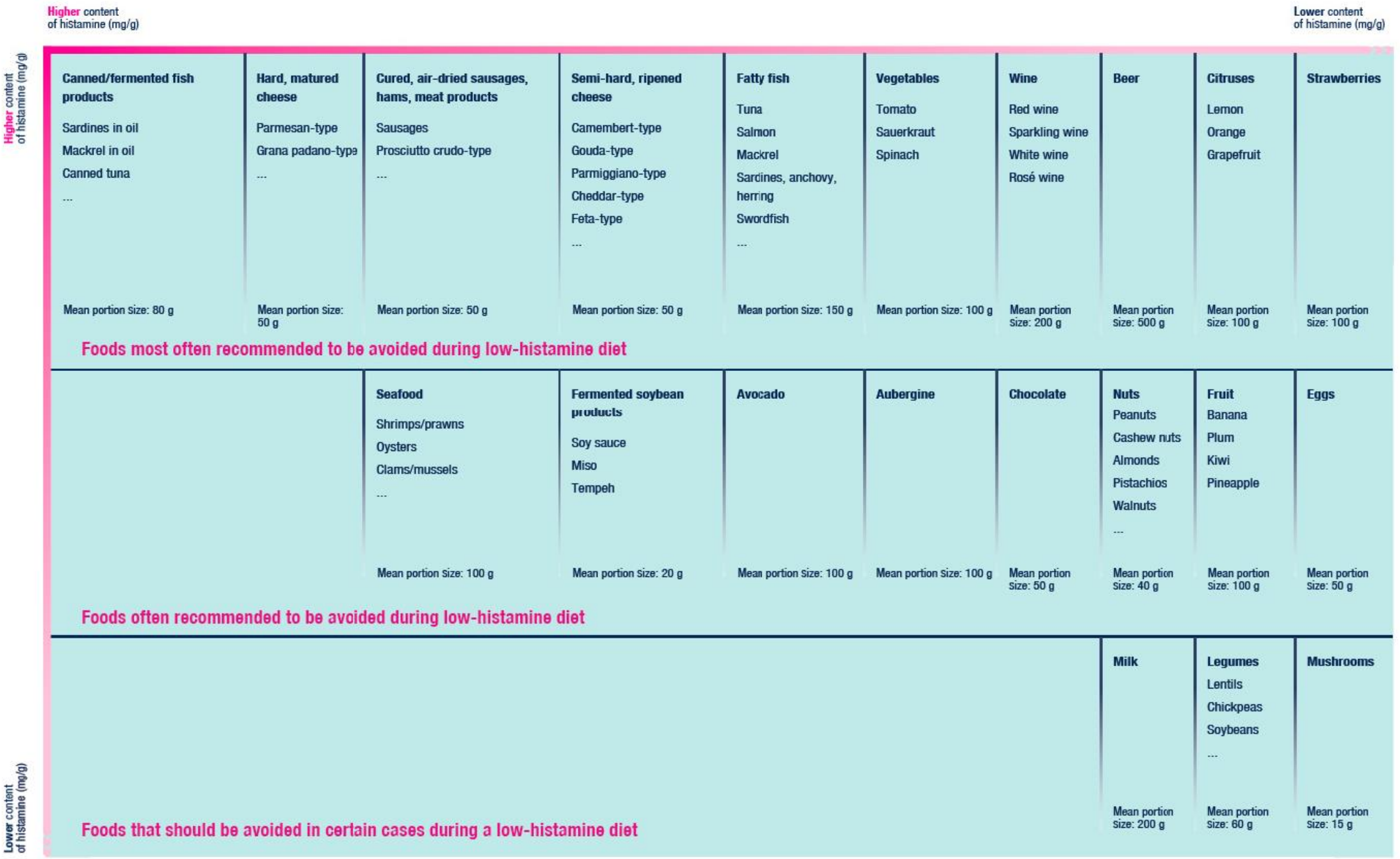

Hrubisko et al, (2021).

Table 5. Phases of dietary measures in patients with suspected HIT. Adapted according to [1].

Phase	Objective	Recommendation	Duration
Phase 1: Elimination phase	Reduction in symptoms to a maximum possible level	• Change in diet composition - introduction of mixed diet measures with accent on fresh vegetables and reduction of biogenic amine intake, in particular histamine • Nutrient optimization	10–14 days
Phase 2: Test phase	Reintroducing foods excluded in Phase 1, after taking into account individual risk factors (stress, menstruation, medication use etc.)	• Targeted gradual reintroduction of suspected foods taking into consideration patient's individual dietary preferences • Assessment of individual sensitivity to ingested histamine	Up to 6 weeks
Phase 3: Long-term diet	Maintenance of high-quality of life Continual balanced diet	• Individual nutritional recommendations based on individual sensitivity to ingested histamine taking exogenous risk factors into consideration	–

Hrubisko et al, (2021).

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Possible nutritional interventions

Symptom control

- Use of exogenous DAO enzymes with meals

Mast cell stabilisation

- Vitamin C
- Quercetin
- Bromelain
- Nettles
- Fish oil (normally low histamine due to histamine not being fat soluble)

Possible nutritional interventions

Gut barrier repair and microbial support

- Vitamin A, Vitamin D3 and Zinc (check SNP's)
- Colostrum (if tolerated)
- Probiotics that are histamine safe – Bio.Me Barrier
- Digestive enzymes to improve digestive breakdown
- Prebiotics for Bifidobacterium – GOS
- Prebiotics for SCFA producers – PHGG
- Fucose rich polysaccharides – fucoidan

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Possible nutritional interventions

Treating dysbiosis or SIBO

- Antimicrobial herbs – dependant on stool test results
- Use of a prokinetic to prevent relapse
- Digestive enzymes
- SIBO safe probiotics –IB+
- SIBO safe prebiotics – PHGG and GOS

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Thank you for your time

Online Resources

- Technical papers for all diagnostics and therapeutics are available when logged in on the relevant product page.
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