UNIVERSITA' DEGLI STUDI DI PERUGIA
DIPARTIMENTO DI MEDICINA E CHIRURGIA
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# Reazioni avverse agli alimenti e patologie gastrointestinali correlate

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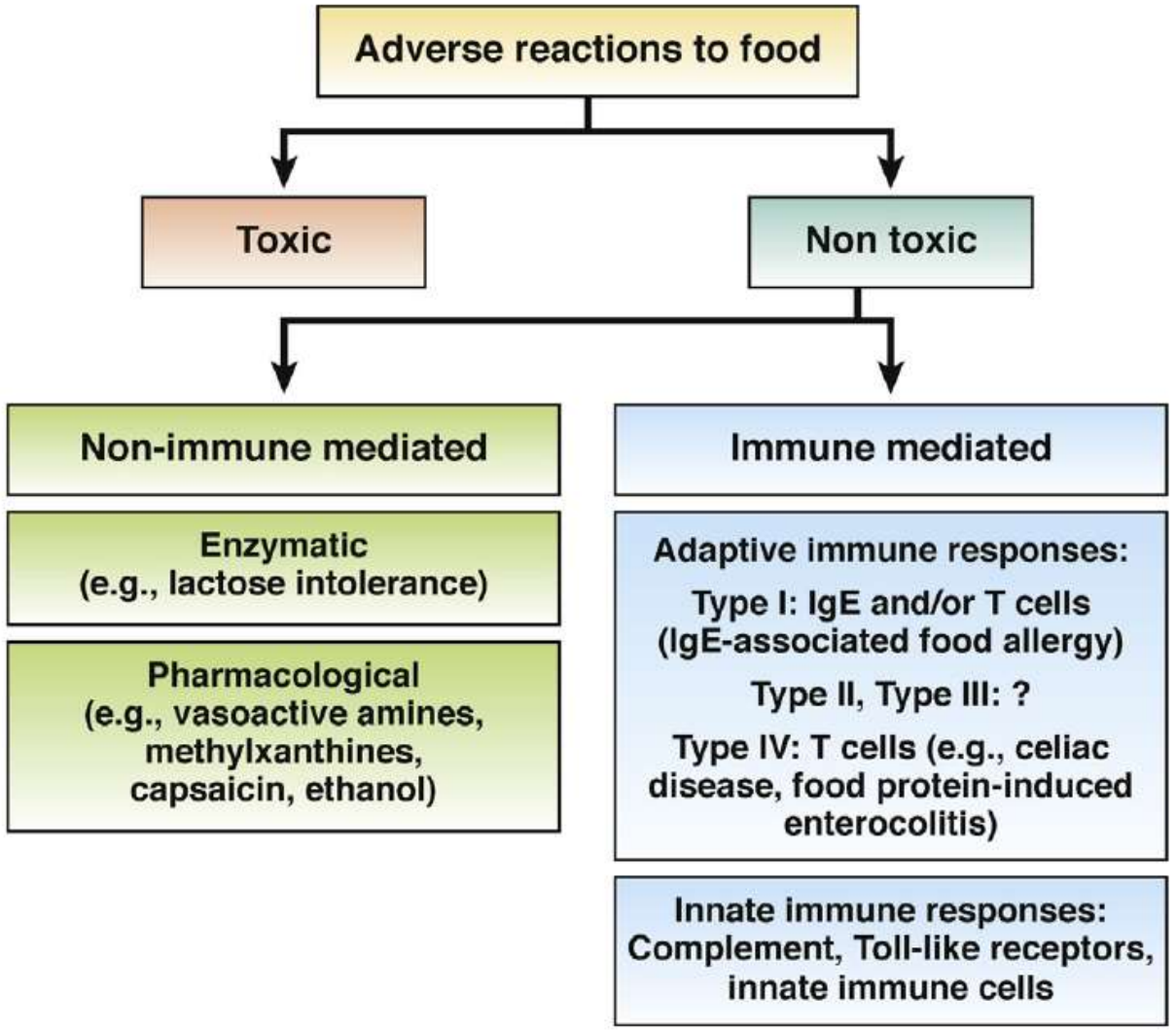



Figure 1. Classification of food intolerance. Adverse reactions to food can be classified as toxic or nontoxic reactions.

Nontoxic reactions are categorized further as immune-mediated or non–immune-mediated. The most common adverse reactions are based on non–immunemediated mechanisms such as enzyme defects as observed in lactose intolerance. Hypersensitivities involving the adaptive immune system can be subdivided into 4 categories (types I–IV). Type I reactions are always associated with the formation of IgE against food allergens and therefore can be called IgE-associated food allergies. There is firm evidence for an involvement of IgG in type II or type III reactions in immune-mediated adverse reactions to food, whereas type IV reactions, which involve T cells, have important roles in disorders such as celiac disease. There is evidence that the innate immune system, which includes complement, Toll-like receptors, and innate immune cells, also mediates immune reactions against certain food components.

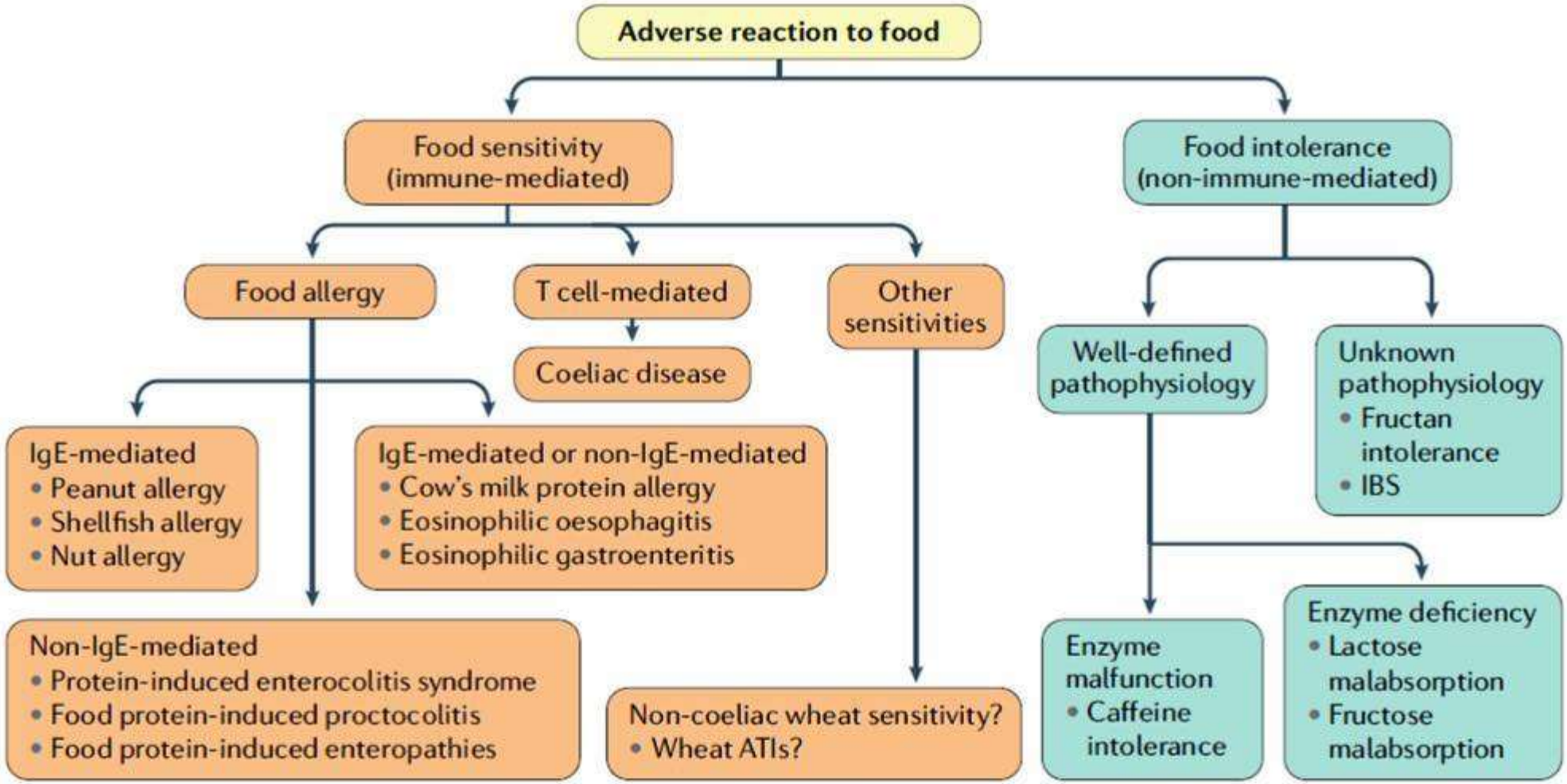
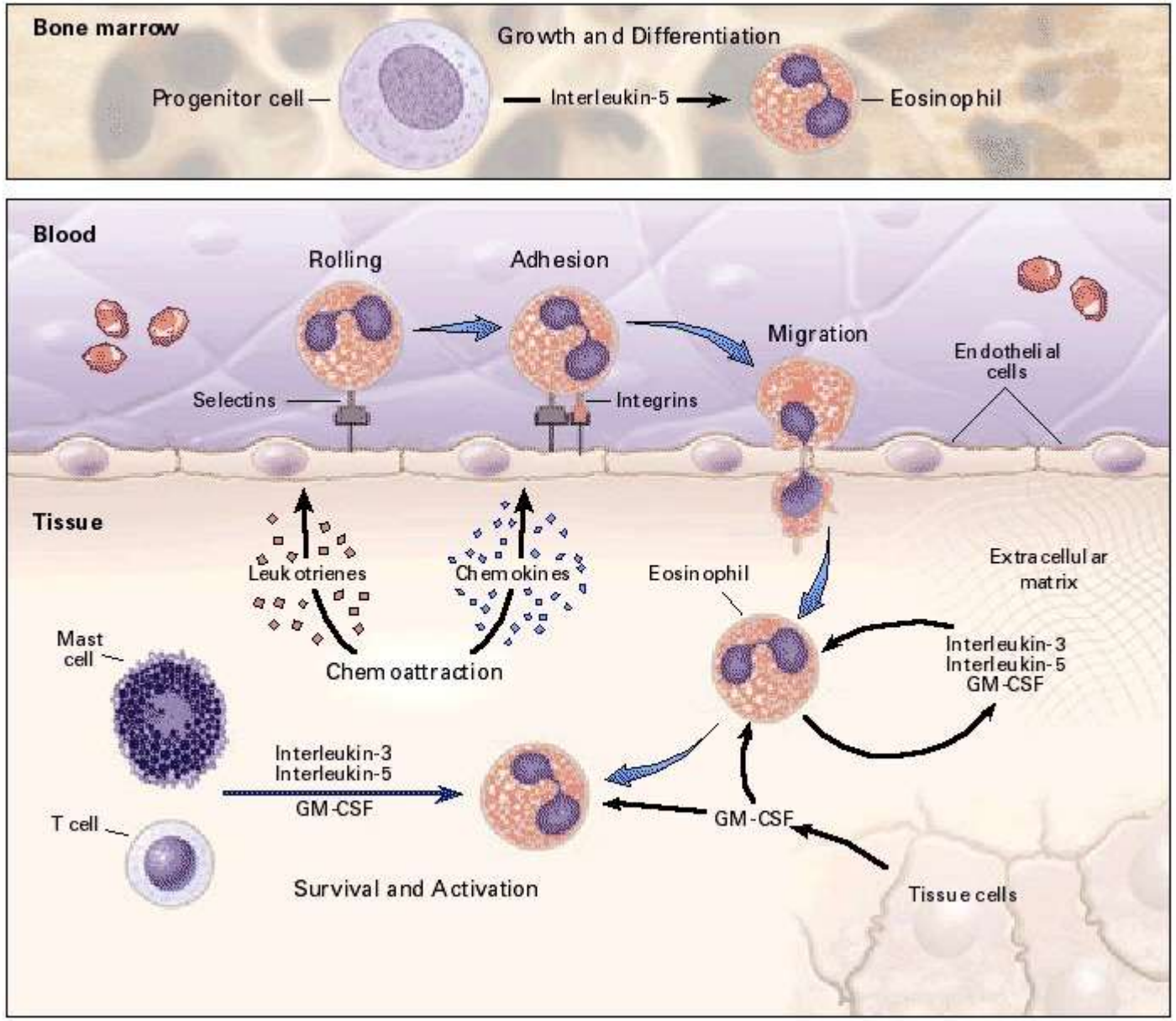


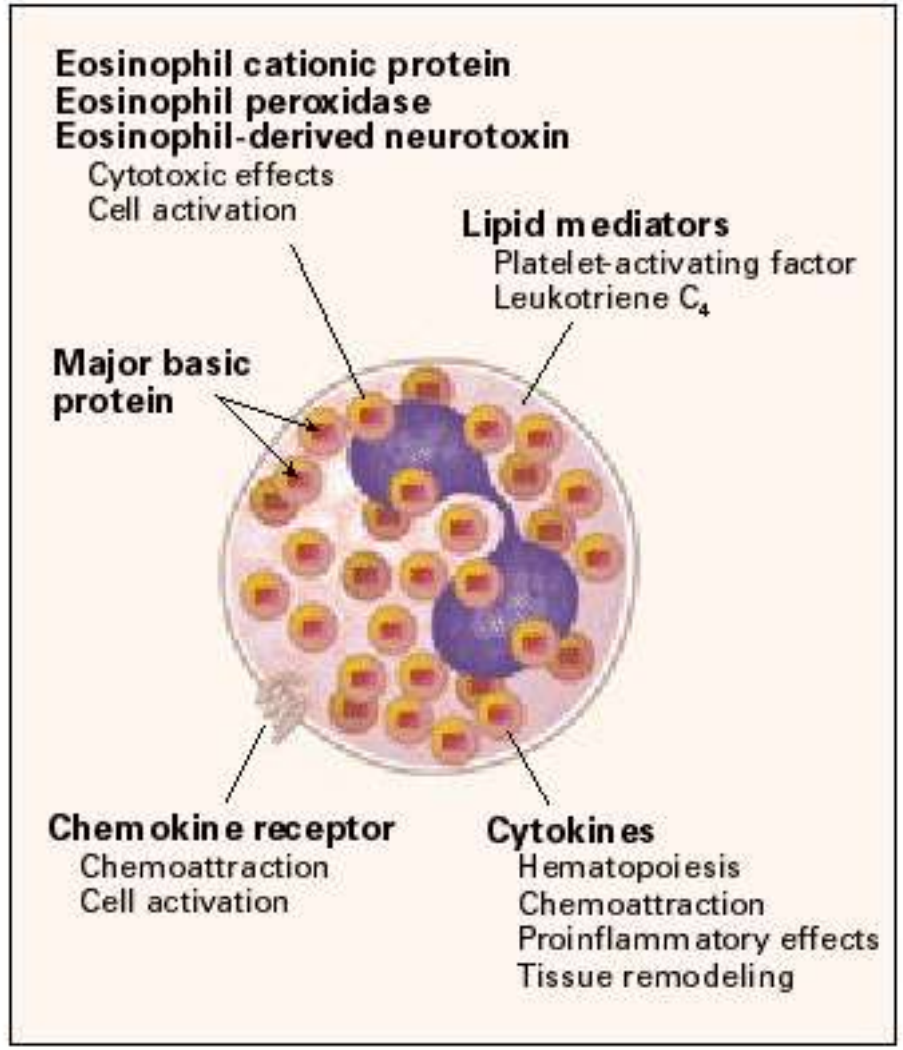

Fig. 1 | **Classification of adverse reaction to food according to underlying pathophysiology.** Adverse reactions to food can be divided into food intolerances (non-immune mediated) and food sensitivities (immune mediated) according to their underlying pathophysiology. Both types can be subclassified into specific diseases on the basis of their pathophysiology. ATI, α-amylase-trypsin inhibitor; IgE, immunoglobulin E.

# Food allergy and intollerance

Food *allergy (hypersensitivity)* is a general term--it includes food anaphylaxis and is used to denote an immunologic reaction to food, whether it is IgE-mediated or the result of some other immune mechanism

*Food intolerance* is a general term describing an abnormal physiologic response to an ingested food or food additive that is not proven to be immunologic in nature. This term encompasses idiosyncratic, metabolic, pharmacologic, or toxic responses to a food or food additive.


Bone marrow
Growth and Differentiation
Progenitor cell
Interleukin-5
Eosinophil
Blood
Rolling
Adhesion
Migration
Endothelial cells
Selectins
Integrins
Tissue
Leukotrienes
Chemokines
Chemoattraction
Eosinophil
Extracellular matrix
Mast cell
Interleukin-3
Interleukin-5
GM-CSF
T cell
Interleukin-3
Interleukin-5
GM-CSF
GM-CSF
Survival and Activation
Tissue cells


Eosinophil cationic protein
Eosinophil peroxidase
Eosinophil-derived neurotoxin
Cytotoxic effects
Cell activation
Lipid mediators
Platelet-activating factor
Leukotriene $C_4$
Major basic protein
Chemokine receptor
Chemoattraction
Cell activation
Cytokines
Hematopoiesis
Chemoattraction
Proinflammatory effects
Tissue remodeling

# Food Allergy: IgE and non-IgE

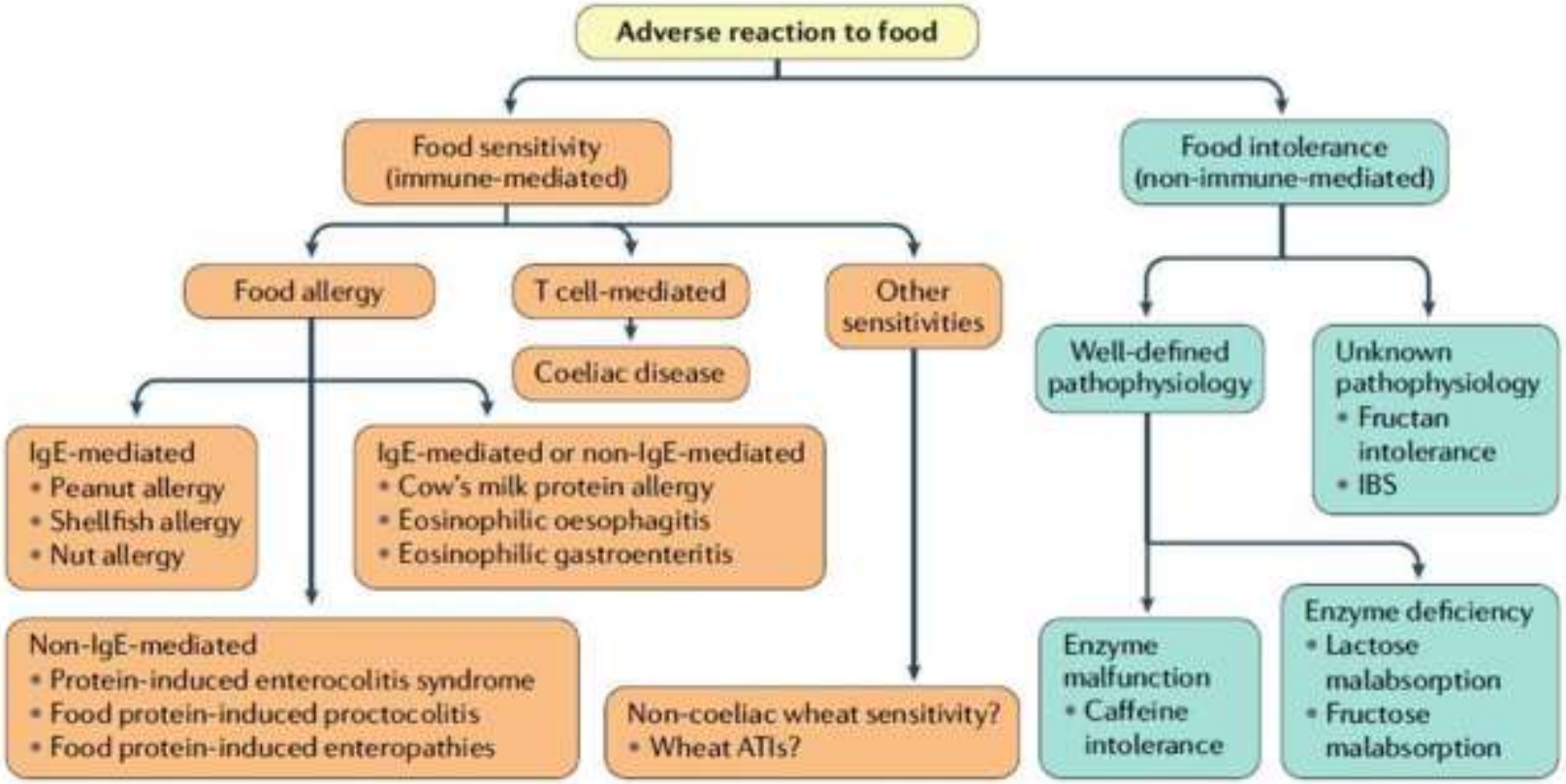



Fig. 1 | **Classification of adverse reaction to food according to underlying pathophysiology.** Adverse reactions to food can be divided into food intolerances (non-immune mediated) and food sensitivities (immune mediated) according to their underlying pathophysiology. Both types can be subclassified into specific diseases on the basis of their pathophysiology. ATI, α-amylase-trypsin inhibitor; IgE, immunoglobulin E.

# Food allergy and intollerance

| | Food allergy | Coeliac disease | Food intolerance |
|---|---|---|---|
| **Presentation** | • Infantile eczema (particularly facial)<br>• Acute reactions<br>– rash around mouth<br>– urticaria<br>– angioedema<br>– vomiting<br>– breathing difficulty<br>– anaphylaxis | • Fatigue<br>• Gastrointestinal symptoms<br>– bloating<br>– cramps<br>– diarrhoea<br>– constipation<br>• Anaemia<br>• Osteoporosis<br><br>NB: May have no symptoms | • Episodic/recurrent/chronic<br>– hives/swellings<br>– stomach/bowel irritation<br>– headaches/migraine<br>– fatigue/aches/pains<br>– mouth ulcers<br>– sinus congestion/polyps<br>• In children:<br>– irritable behaviour ('colic', 'screaming', disturbed sleep, leg aches and pains, ADHD)<br>– reflux (from birth)<br>– eczema/itchy rashes<br>– nappy rash |
| **Age of onset** | Infants and toddlers (mostly) | Any age | Any age |
| **Family history** | • Atopic<br>– asthma<br>– eczema<br>– hay fever | • HLA gene association<br>– coeliac disease<br>– type 1 diabetes<br>– thyroid disease | • Commonly<br>– irritable bowel<br>– hives<br>– headaches |

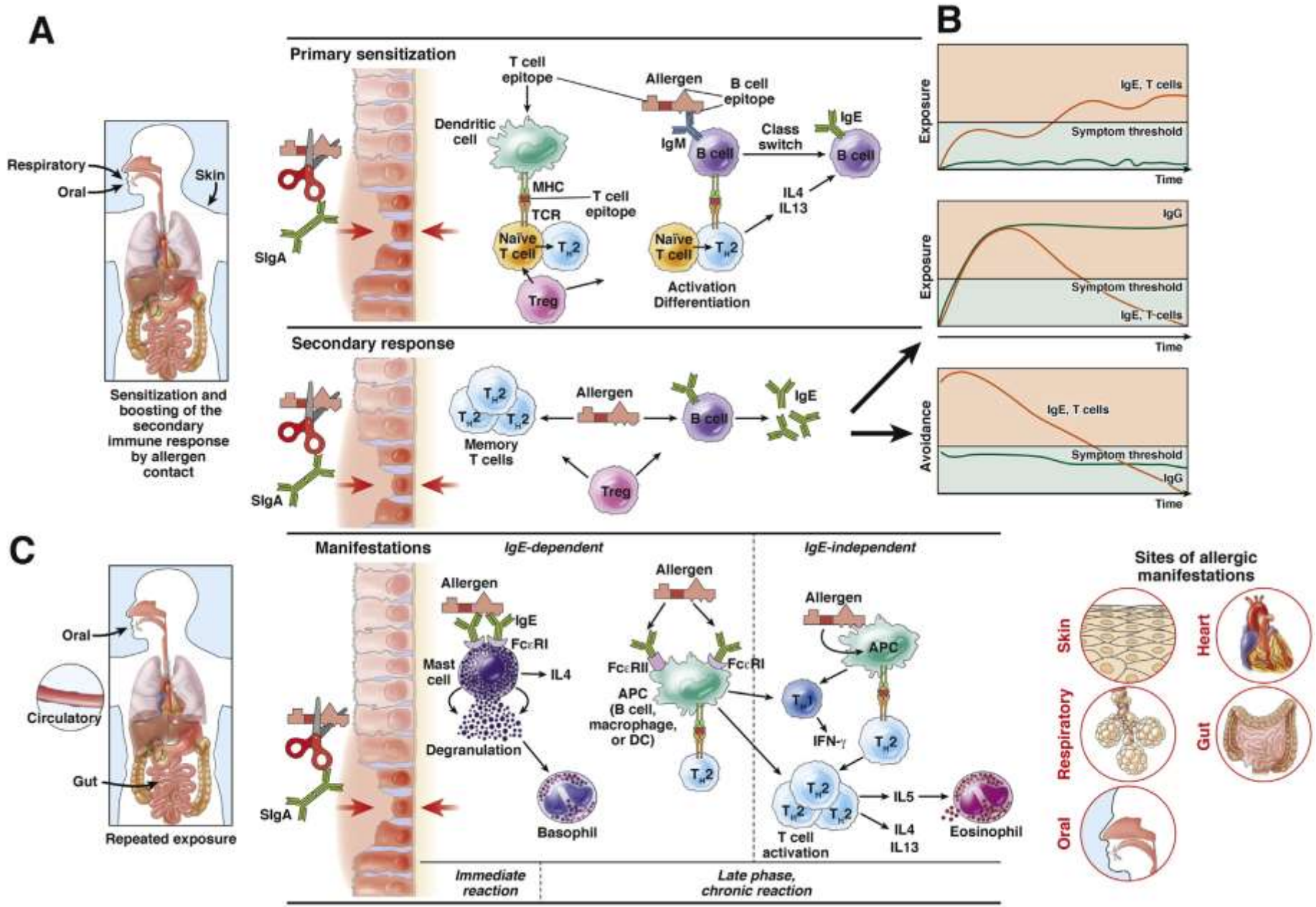
# Food allergy and intollerance

| | | | |
|---|---|---|---|
| | | | – mouth ulcers |
| **Reaction timing** | Immediate (minutes → 1–2 hours) | Hours → days | Hours → days |
| **Reaction reproducibility** | Reproducible | Reproducible | Variable |
| **Mechanism** | Immune<br>(IgE antibodies) | Immune<br>(inflammatory T-cells) | Nonimmune<br>(irritation of nerve endings) |
| **Food triggers** | Specific food proteins: egg, milk, peanut, tree nuts, sesame, fish, crustaceans, wheat, soy | Gluten (wheat, triticale, rye, barley) | • Natural food chemicals: salicylates, amines, monosodium glutamate (MSG)<br>• Food additives: preservatives and artificial food colours<br>• Some cereals<br>• Dairy products |
| **Tests** | • Skin prick tests<br>• Blood tests (RAST) – measure IgE to specific allergens | • Antibodies to tissue transglutaminase (must be eating gluten at time of testing)<br>• Small bowel biopsy | • Elimination diet<br>• Food chemical challenges |
| **Dietary management** | Complete avoidance of identified food proteins | Gluten free diet (strict) | Comprehensive dietary modification: maintain overall chemical intake below reaction threshold |
| **Outcome** | • Egg, milk, wheat and soy (usually outgrown)<br>• Peanut, tree nuts, seafood (often persists) | • Life long immune reactivity<br>• Bowel pathology and antibodies usually return to normal on gluten free diet | • Life long susceptibility<br>• Variable tolerance<br>• Symptoms can come and go |

Reproduced from: the RPAH Elimination Diet Handbook with modifications from the DAA Food Allergy and Intolerance Interest Group and with kind permission from the

# Food allergy: epidemiology

- For reasons that are not entirely understood, the diagnosis of food allergies has apparently become more common in Western nations in recent times.
- In the United States food allergy affects as many **as** **5% of infants less than three years** of age and **3% to 4% of adults**. There is a similar prevalence in Canada.
- The most common food allergens include **peanuts, milk, eggs, tree nuts, fish, shellfish, soy, and wheat** - these foods account for about 90% of all allergic reactions


A
Respiratory
Oral
Skin
Sensitization and boosting of the secondary immune response by allergen contact
Primary sensitization
T cell epitope
Allergen
B cell epitope
Dendritic cell
IgM
B cell
Class switch
IgE
B cell
MHC
T cell epitope
TCR
IL4
IL13
Naïve T cell
$T_H2$
Treg
Activation Differentiation
SIgA
Secondary response
$T_H2$
Memory T cells
Allergen
B cell
IgE
Treg
SIgA
B
Exposure
IgE, T cells
Symptom threshold
Time
IgG
IgE, T cells
C
Oral
Circulatory
Gut
Repeated exposure
Manifestations
IgE-dependent
IgE-independent
Allergen
IgE
FcεRI
Mast cell
IL4
Degranulation
Basophil
FcεRII
APC (B cell, macrophage, or DC)
APC
$T_H1$
IFN-γ
IL5
Eosinophil
T cell activation
IL4
IL13
Immediate reaction
Late phase, chronic reaction
Sites of allergic manifestations
Skin
Heart
Respiratory
Gut
Oral

Time course, pathogenesis, and manifestations of food allergies. IgE-associated food allergies appear to develop early in childhood. This process is termed allergic sensitization. (A) Allergen contact via the gastrointestinal tract, via the respiratory tract, and eventually via the skin induces IgE production (primary sensitization) in genetically predisposed individuals.

Repeated allergen contact activates allergen-specific T cells and induces IgE responses during the secondary immune response. Factors that affect the epithelial barrier (red arrows) and the extent to which allergens are digested or degraded are important for primary sensitization and boosting of secondary immune responses. SIgA and T-regulatory cells may be important for exclusion of allergens from the intestinal lumen and induction of tolerance, respectively. (B) The balance between allergen-specific IgE and blocking IgG helps determine whether or not a patient will develop symptoms. Allergen avoidance could reduce levels of allergen-specific IgE to below the threshold for symptom induction (lower panel), whereas exposure could increase production of IgE, leading to symptoms (upper panel). If allergen exposure induces allergen-specific IgG, which blocks the interaction between the allergen and IgE, then symptoms might be reduced (middle panel). (C) Allergy symptoms are caused by repeated contact with the oral allergen, via the immediate allergic reaction (allergen-induced crosslinking of mast cell–bound IgE by allergen and then activation of allergen-specific T cells), and then by other inflammatory cells, such as eosinophils and basophils, during late-phase and chronic inflammation. Factors that affect the epithelial barrier and the extent of allergen degradation affect the amount of allergen intrusion and the magnitude and type of inflammation. After allergen ingestion, inflammation develops not only in the intestine, but in other organs, such as the skin, respiratory tract, and circulatory system (right). These allergens and allergen fragments are internalized and distributed throughout the body (left).

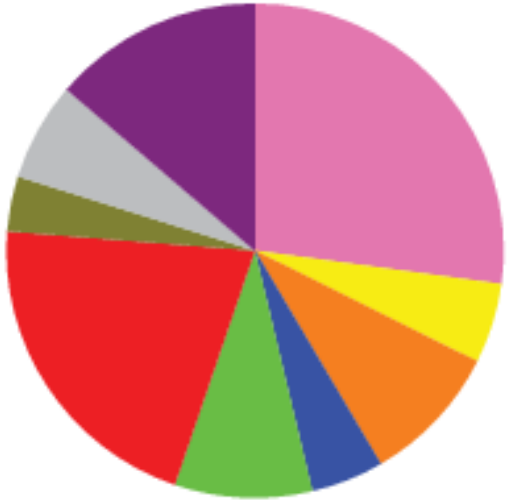
MHC, major histocompatibility complex; T-reg, T-regulatory cell; TCR, T-cell receptor.

# Food allergy

**Children**

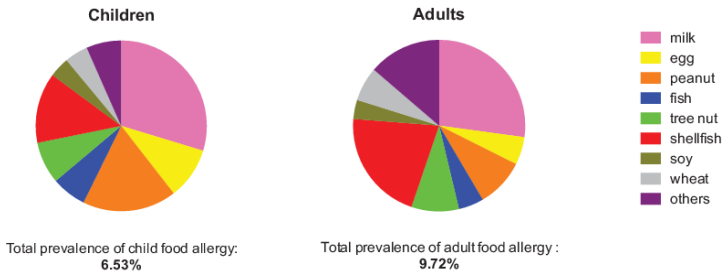
Total prevalence of child food allergy:
**6.53%**

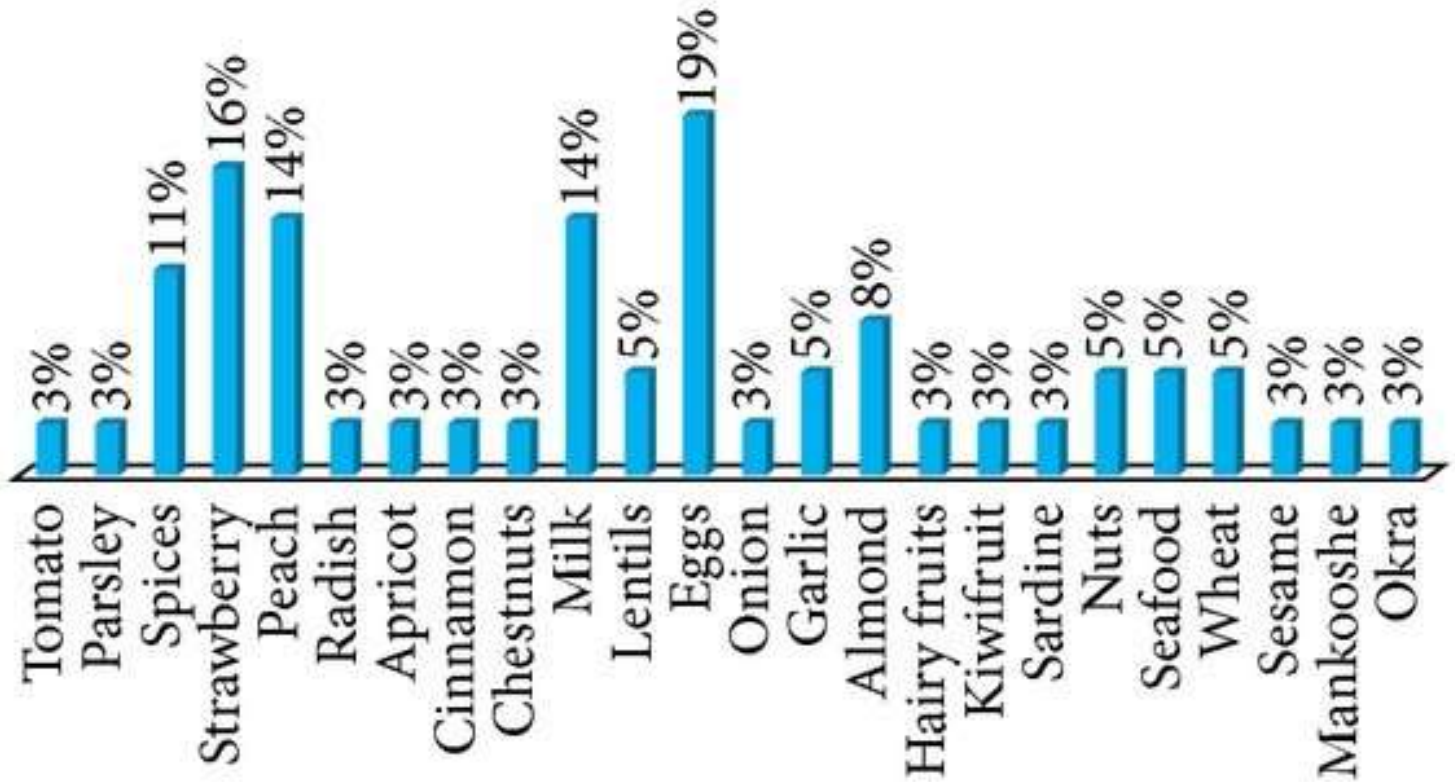
**Adults**



Total prevalence of adult food allergy :
**9.72%**

# Food allergy



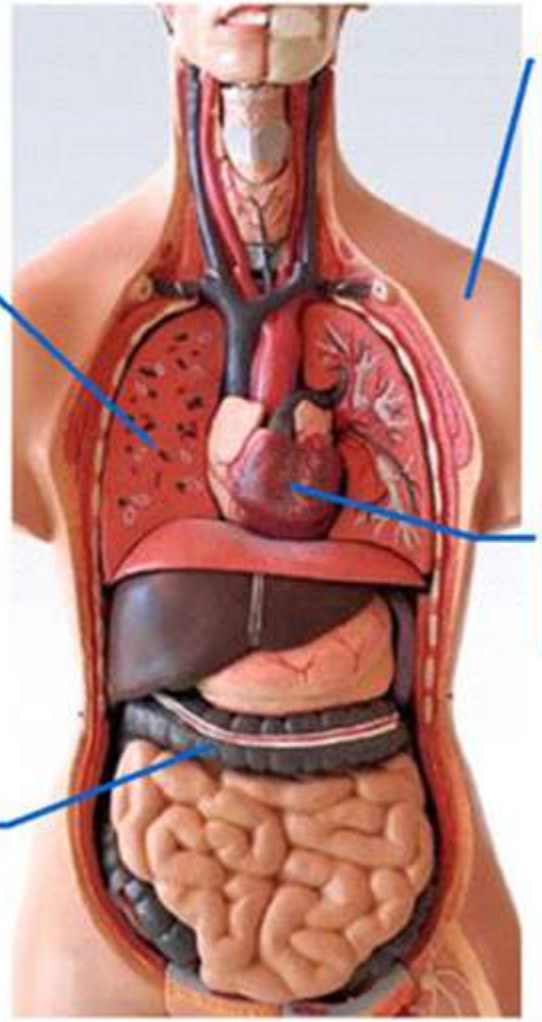



# Food allergy: symptoms

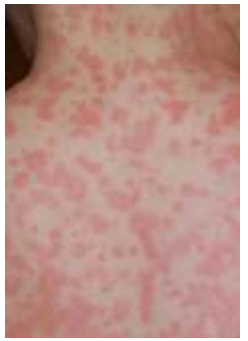
**Table 1**
**Symptoms of an immunoglobulin E–mediated allergic reaction**

| | |
|---|---|
| Cutaneous | Urticaria, angioedema, pruritus, flushing, morbilliform rash |
| Respiratory | Upper airway: rhinorrhea, nasal pruritus, nasal congestion, sneezing, hoarseness, stridor<br>Lower airway: cough, wheeze, dyspnea, cyanosis |
| Cardiovascular | Increased heart rate, low blood pressure, pallor, dizziness, shock, loss of consciousness |
| Gastrointestinal | Swelling of lips/tongue/uvula, nausea, vomiting, abdominal cramps, diarrhea |
| Neurologic | Anxiety, headache, seizure, altered mental status, feeling of impending doom |
| Ocular | Conjunctival erythema and tearing |

# Food Allergy: Symptoms

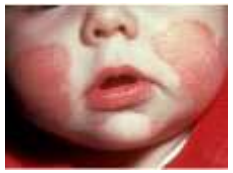


Skin / mucous membrane symptoms:
- urticaria
- angio-oedema
- rhinitis
- conjunctivitis

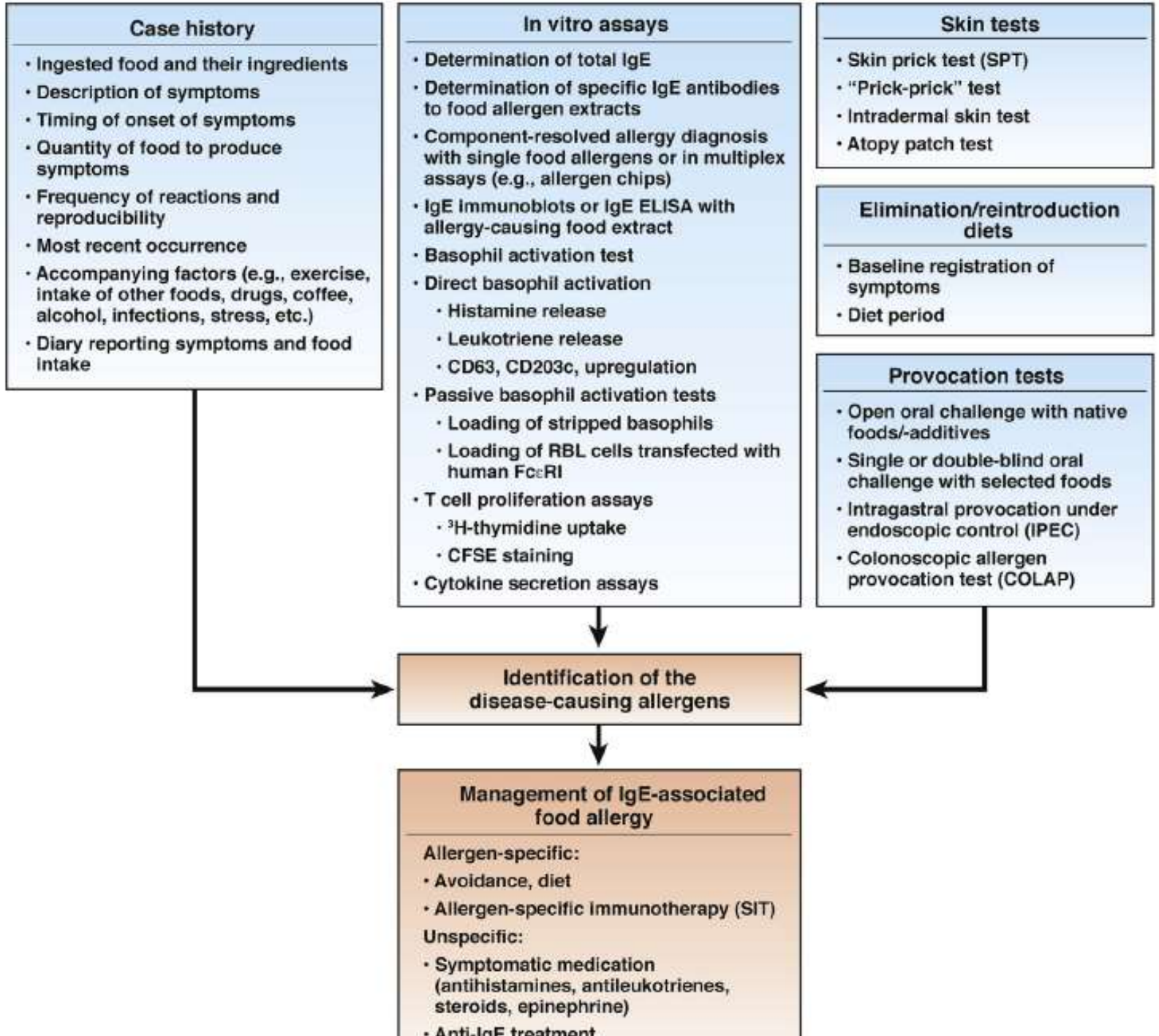


Respiratory symptoms:
- asthma
- hoarseness

Cardiovascular symptoms:
- anaphylactic shock



Gastrointestinal symptoms:
- abdominal pain
- vomiting
- diarrhea


Case history
• Ingested food and their ingredients
• Description of symptoms
• Timing of onset of symptoms
• Quantity of food to produce symptoms
• Frequency of reactions and reproducibility
• Most recent occurrence
• Accompanying factors (e.g., exercise, intake of other foods, drugs, coffee, alcohol, infections, stress, etc.)
• Diary reporting symptoms and food intake
In vitro assays
• Determination of total IgE
• Determination of specific IgE antibodies to food allergen extracts
• Component-resolved allergy diagnosis with single food allergens or in multiplex assays (e.g., allergen chips)
• IgE immunoblots or IgE ELISA with allergy-causing food extract
• Basophil activation test
• Direct basophil activation
• Histamine release
• Leukotriene release
• CD63, CD203c, upregulation
• Passive basophil activation tests
• Loading of stripped basophils
• Loading of RBL cells transfected with human FcεRI
• T cell proliferation assays
• $^{3}$H-thymidine uptake
• CFSE staining
• Cytokine secretion assays
Skin tests
• Skin prick test (SPT)
• "Prick-prick" test
• Intradermal skin test
• Atopy patch test
Elimination/reintroduction diets
• Baseline registration of symptoms
• Diet period
Provocation tests
• Open oral challenge with native foods/-additives
• Single or double-blind oral challenge with selected foods
• Intragastral provocation under endoscopic control (IPEC)
• Colonoscopic allergen provocation test (COLAP)
Identification of the disease-causing allergens
Management of IgE-associated food allergy
Allergen-specific:
• Avoidance, diet
• Allergen-specific immunotherapy (SIT)
Unspecific:
• Symptomatic medication (antihistamines, antileukotrienes, steroids, epinephrine)
• Anti-IgE treatment

# Testing for allergy

The most commonly used in vivo allergenicity tests are the **Skin-prick test (SPT) and direct IgE** measurement tests

Based on the principle that allergic conditions are accompanied by elevated levels of IgE antibodies specific to the allergy-triggering molecule.

Histamine-release tests determine the capability of an antigen to trigger degranulation of basophils isolated from sensitized individuals.

## Skin-prick test (SPT)

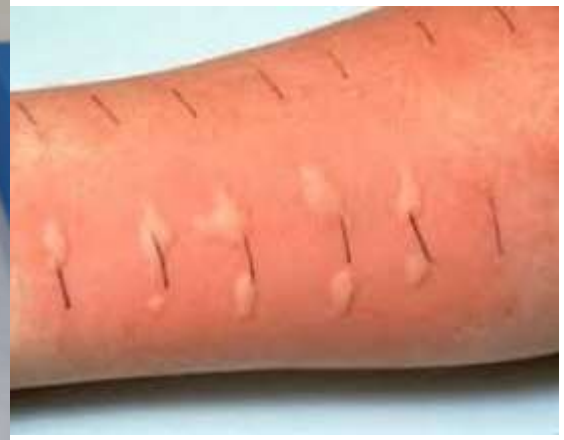
In the SPT, a drop of dilute allergen-containing extract is placed on the skin of the forearm or back of the subject, and a small needle is then used to gently prick the skin through the drop of extract.

The results are then recorded after 10–15 min. The SPT is considered positive when the skin around the prick becomes red with the development of a wheal, whose diameter provides a semiquantitative measure of the level of allergen-specific IgE.

## Serological IgE measurement

Patient blood samples are used to detect and quantify allergens specific to circulating IgE. These tests involve incubating the serum of an allergic patient with allergens immobilized on a solid matrix, followed by detection of the bound IgE with labelled anti-human IgE antibodies. The RAST (Radio AllergoSorbent Test) uses radiolabelled secondary antibodies, whereas the ELISA (Enzyme-Linked ImmunoSorbent Assay) test uses enzyme labelled anti-human IgE antibodies.

# Testing for allergy



# Testing for allergy

Table 3
Predictive values for food allergen–specific immunoglobulin E ($kU_A/L$) and skin prick test wheal size (millimeters)

| | Milk | Egg | Soy | Wheat | Peanut | Tree Nuts | Fish |
|---|---|---|---|---|---|---|---|
| Likely Reactive if ≥ | 15 (95%)<br>≤2 y: 5 (95%)<br>SPT: ≥8 (95%)[20] | 7 (98%)<br>≤2 y: 2 (95%)<br>SPT: ≥7 (95%)[20] | 65 | 80 | 14 (100%)<br>1 y: 34 (95%)<br>4 y: 2.1<br>SPT: ≥8 (95%)[20,65] | 15 (95%) | 20 (100%) |
| Possibly Reactive | — | SPT ≤3 (50%)[20] | 30 (73%) | 26 (74%) | SPT ≤3 (50%)[20] | — | — |
| Unlikely Reactive if < | 0.35 | 0.35 | 0.35 | 0.35 | 0.35 | 0.35 | 0.35 |

Positive predictive values are indicated in parentheses.

*Adapted from* Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. JACI 2001;107:891-6. Other references are noted in the table or text.

# Food allergy diagnosis (2)

**3. FOOD CHALLENGE** , especially double blind placebo-controlled food challenges (DBPCFC), are the gold standard for diagnosis of food allergies, including most non-IgE mediated reactions.  Due to the risk of anaphilaxis , food challenges are usually conducted in a hospital environment in the presence of a doctor.

# Le reazioni avverse al cibo e le intolleranze alimentari

Le **intolleranze alimentari** possono essere definite come tutte quelle reazioni avverse **al cibo non mediate dai meccanismi di ipersensibilità immediata tipici delle allergie alimentari**

# Intolleranze alimentari

Malgrado esistano  test di  valutazione delle intolleranze (a scientificità molto dubbia) che promettono di verificare la sensibilità dell'organismo nei confronti di centinaia di alimenti, esistono solamente **4 sostanze in grado di provocare intolleranze**, i cui effetti sono stati sufficientemente studiati, e quindi riconosciute dalla comunità scientifica:

- **intolleranza al lattosio**
- **intolleranza al fruttosio**
- **intolleranza al al sorbitolo**
- **intolleranza al glutine**

# Le reazioni avverse al cibo e le intolleranze alimentari

- In genere, una intolleranza alimentare si presenta con le seguenti caratteristiche

  1) è solitamente dose dipendente, ovvero la gravità dei sintomi aumenta all'aumentare della quantità di sostanza assunta;
  2) può coinvolgere o meno il sistema immunitario del soggetto colpito;
  3) può avere un effetto ritardato, ovvero l'ingestione della sostanza a cui si è intolleranti può scatenare una reazione anche a distanza di ore dall'assunzione;
  4) può avere una soglia di tolleranza, ovvero può esistere una soglia quantitativa al di sotto della quale la molecola incriminata non causa alcun sintomo.

# Le reazioni avverse al cibo e le intolleranze alimentari

L'**intolleranza agli zuccheri** (lattosio, fruttosio e sorbitolo) è dovuta a un **deficit enzimatico.**

I disaccaridi (zuccheri composti dall'unione di 2 zuccheri semplici) non vengono scissi nei loro costituenti monosaccaridi e quindi non vengono assimilati, richiamano liquidi per effetto osmotico e vengono fermentati dalla flora batterica intestinale con una forte produzione di gas che causa tutta una serie di disturbi intestinali: diarrea, flatulenza, sindrome del colon irritabile, ecc.

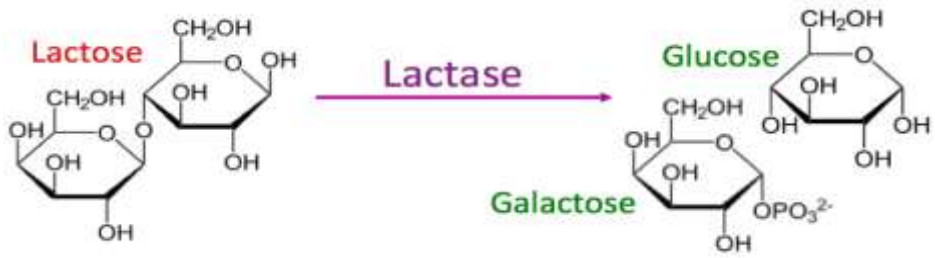
Queste intolleranze alimentari sono piuttosto diffuse e sono spesso la causa di problemi intestinali cronici come la sindrome del colon irritabile .

# Lactase gene

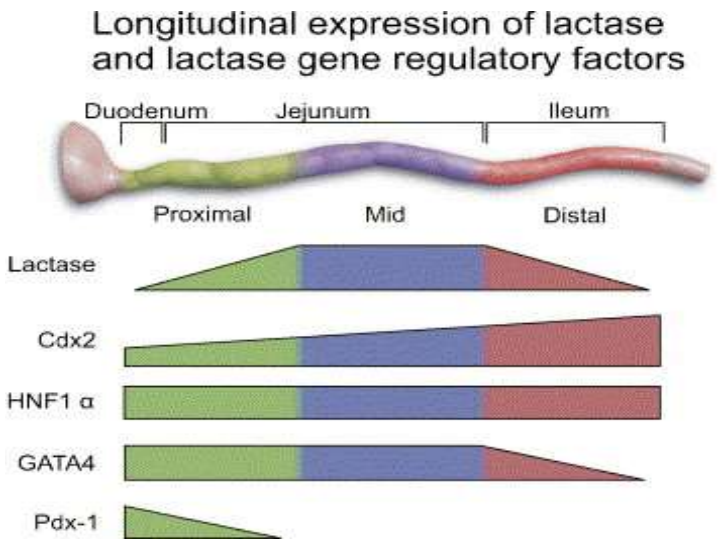
*Gene: LCT*

**The lactase i**s responsible for the hydrolysis of **lactose** into **glucose and galactose**, which can then be absorbed across the intestinal epithelium.

The lactase activity also cleaves other substrates (cellobiose, cellotriose, cellotetrose, and, to a certain extent, cellulose).



# Lactose and lactase




The lactase can be found on the upper surface of enterocytes on the microvilli of the small intestine, and it is maximally expressed in the medium jejunum (where the bacterial concentration is low and, therefore, little fermentation occurs). It hydrolyses a lactose molecule in two monosaccharides, **glucose and galactose**, which, upon digestion, are rapidly absorbed by enterocytes and then used; the glucose is used as a source of energy, while the galactose is used as a part of glycoproteins and glycolipids.
In the case of lactase deficiency, the disaccharide is not properly digested (**lactose maldigestion)** and therefore cannot be absorbed in an undigested form **(lactose malabsorption**) and is fermented by the gut microbiota.

# Glossary with definitions related to lactase deficiency, lactose malabsorption and lactose intolerance

| Concept | | Definition |
|---|---|---|
| **CONGENITAL LACTASE DEFICIENCY** | CLD | Very rare genetic disorder (typically frameshift mutations) leading to lack of expression of lactase and severe symptoms immediately after birth |
| **LACTASE NON-PERSISTENCE** | LNP | Decrease of intestinal lactase expression in the first two decades of life. Phenotype in most individuals worldwide (biological wildtype) |
| **LACTASE PERSISTENCE** | LP | Continued expression of intestinal lactase expression beyond infancy; dominant phenotype in Western countries. |
| **LACTASE DEFICIENCY** | LD | Inability to digest large amounts of lactose due to low lactase expression in the small intestine |
| **LACTOSE MALABSORPTION** | LM | Passage of lactose into the large intestine as a consequence of LD or other pathology (eg, rapid transit) |
| **PRIMARY LACTOSE MALABSORPTION** | | Lactose malabsorption due to lactase non-persistence (dominant phenotype worldwide). |
| **SECONDARY LACTOSE MALABSORPTION** | | Lactose malabsorption due to lower lactase expression, typically in the setting of intestinal inflammation (may be reversible). |
| **LACTOSE INTOLERANCE** | LI | Appearance of typical intestinal symptoms such as abdominal pain, bloating, diarrhoea in individuals with LM after lactose ingestion determined by appropriate testing (ideally blinded testing). |
| **FUNCTIONAL LACTOSE INTOLERANCE** | | Symptoms of LI on lactose challenge in individuals without lactose malabsorption. |
| **SELF-REPORTED LACTOSE INTOLERANCE** | SLI | History of LI symptoms without formal testing of either LM or LI. |

# In sumamry :

**Congenital lactase deficiency** (alactasia), **which is extremely rare**, is due to the inheritance of 2 defective alleles of the LCT gene.

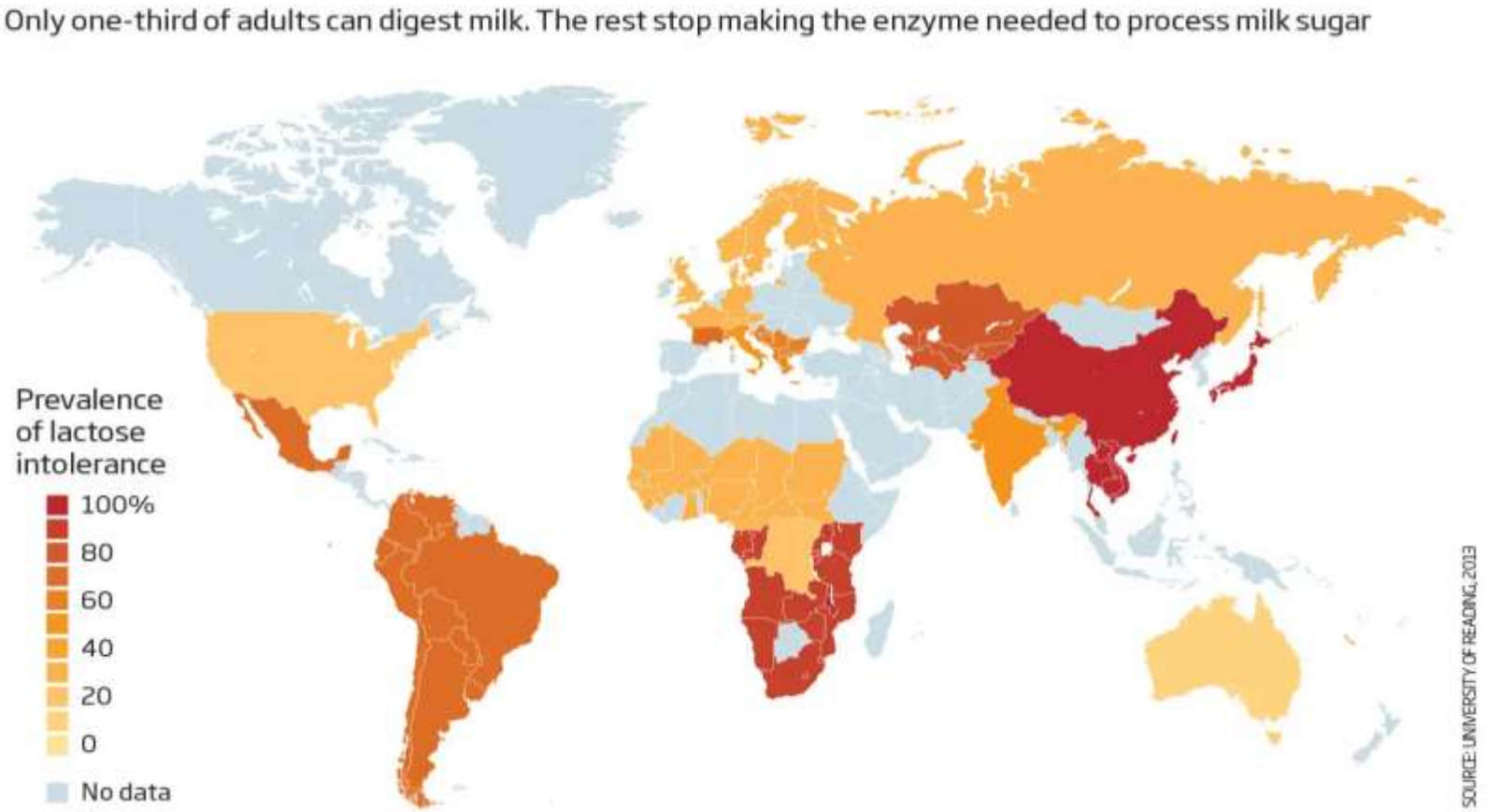
The infant can suffer from watery diarrhoea after being fed with breast milk or food containing milk, and it can become a severe condition, as the shortage of nutritive ingredients can lead to growth delay, dehydration, and alkalosis; infants with congenital lactase deficiency were not expected to survive before the 20th century, when adequate lactose-free milk substitutes were not readily accessible.

**Primary lactase deficiency (adult-type hypolactasia) is caused by the non-persistence of lactase, with enzyme levels progressively reducing starting from the age of 2–5 years, depending on ethnicity**

**Secondary hypolactasia** involves the loss of the lactase enzyme due to other clinical conditions affecting the intestinal tract. Since this enzyme is found on the apex of the duodenal villus, all pathological conditions involving the microvilli can result in the reduction of lactase. Once the primary problem is resolved, lactose-containing products can often be consumed normally. Clinical conditions leading to secondary hypolactasia include:

- *severe malnutrition*
- *celiac disease*
- *inflammatory bowel diseases (Crohn's disease, ulcerative colitis)*
- *bacterial or viral enteritis (e.g., rotavirus), and parasitic disease (e.g., giardiasis, cryptosporidiosis)*
- *actinic enteritis*
- *some pharmacological treatments (kanamycin, neomycin, polymycin, tetracycline, colchicine, and other chemotherapeutic drugs)*
- *some post-surgical conditions, such as stagnant loop syndrome or short bowel syndrome*

# Lactose intollerance




A recent meta-analysis estimated the prevalence of LM worldwide at 68% with higher rates reported for genetic tests than hydrogen breath tests (HBTs). LM is lowest in Nordic countries (<5% in Denmark) and highest in Korean and Han Chinese populations (approaches 100%).

Testing for LI is more complex and would require standardised hydrogen breath testing in large, carefully selected populations and, for this reason, the prevalence of LI is unknown.

# Lactose intollerance

The ability to digest lactose during the period of breast-feeding is essential to the health of the infant as demonstrated by congenital lactase deficiency that is fatal if not recognized very early after birth.

However, following the first few months of life, **lactase activity starts to decrease (lactase non-persistence**).

In most humans, this activity declines following weaning to undetectable levels as a consequence of the normal maturational down-regulation of lactase expression

# Lactose intollerance

The exceptions to this rule are the descendants of populations that traditionally practice cattle domestication maintain the ability to digest milk and other dairy products into adulthood.

The frequency of this "**lactase persistence trait**" is high in northern European populations (>90% in Scandinavia and Holland), decreases in frequency across southern Europe and the Middle East (~50% in Spain, Italy and pastoralist Arab populations) and is low in Asia (~1% in China) and most of Africa (~5%–20% in West African agriculturalists); although it is common in pastoralist populations from Africa (~90% in Tutsi, ~50% in Fulani)

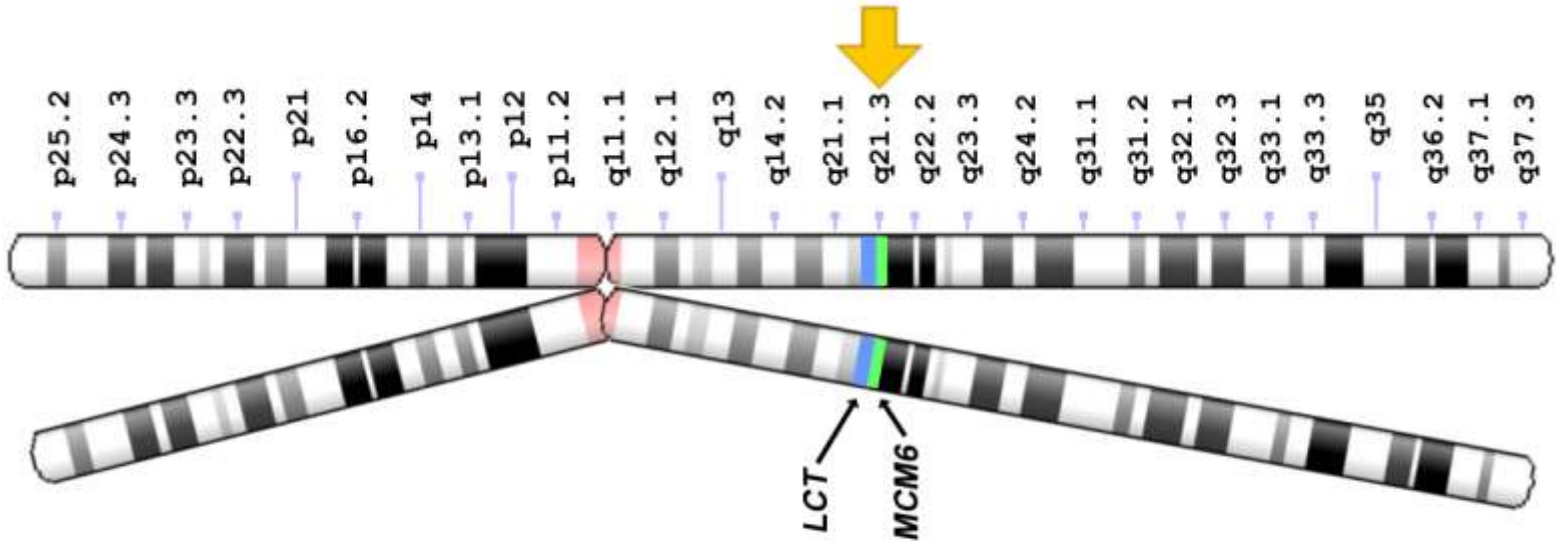
# Lactose intollerance

The molecular mechanism causing lactase reduction is unknown.

**It is not attributable to polymorphisms within the lactase gene itself or within its promoter (55 kb within 70 kb, long arm of chromosome 2 (2p.21q) 17 exons).**

However, there is a close correlation between lactase persistence and two polymorphisms, $C/T_{13910}$ and $G/A_{22018}$ upstream from the lactase gene, in the minichromosome **maintenance complex component 6 (MCM6) gene**. Further on the CC/GG being associated with lactase non-persistence and lactose intolerance.

# Lactase gene




**2q21.3 = Chromosome 2, long arm, position 21.3**

**_LCT_ gene, from base pair 135,787,840 to 135,837,195**

**_MCM6_ gene, from base pair 135,839,626 to 135,876,477**

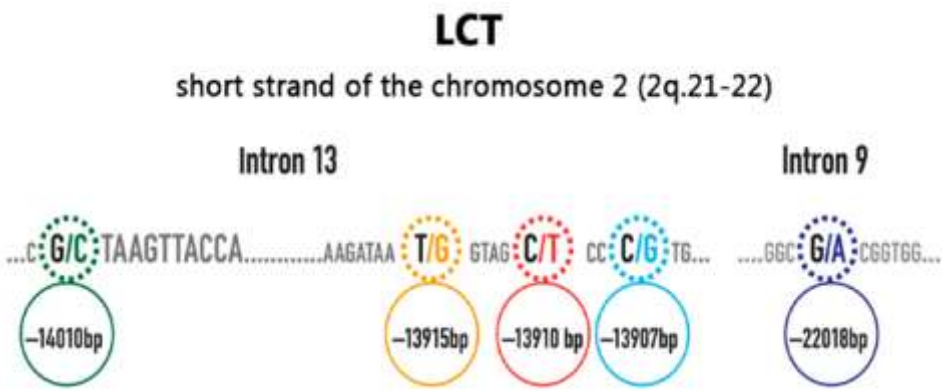
# Genetics of lactose intollerance

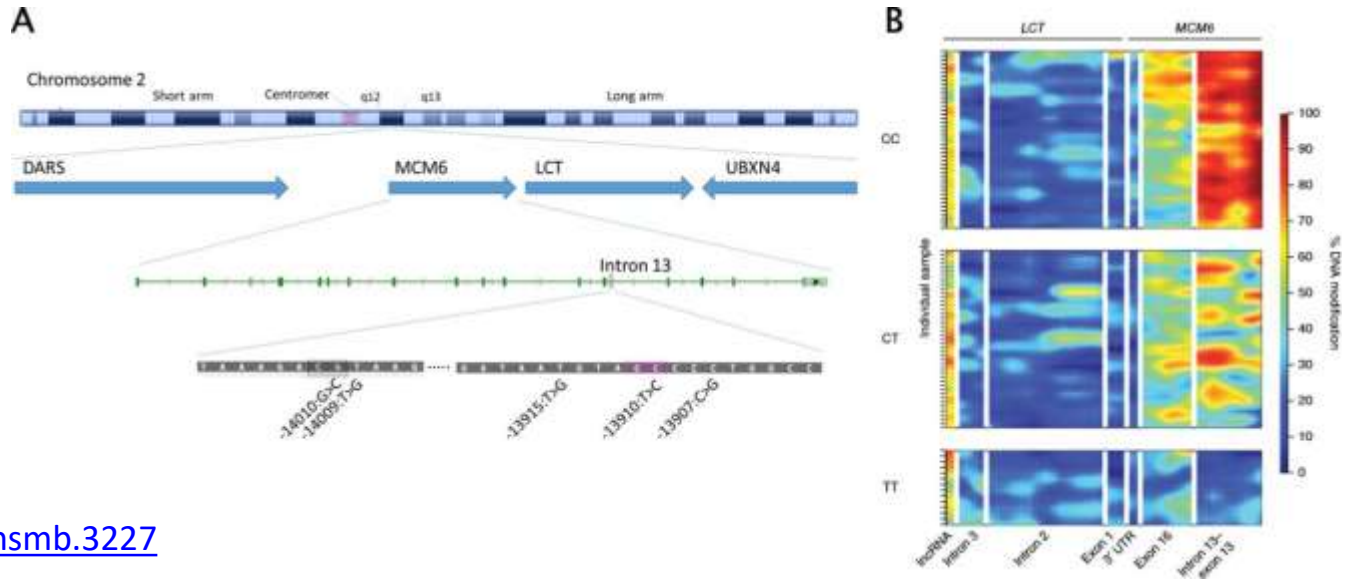
(A) Organisation of the lactase genetic locus on chromosome 2. The positions of the lactase gene (LCT) and the neighbouring genes aspartyl-tRNA synthetase (DARS), minichromosome maintenance complex component 6 (MCM6) and UBX domain-containing protein 4 (UBXN4) are indicated.

**(B) Polymorphisms relevant for lactose malabsorption are located within intron 13 of the MCM6 gene, upstream of the lactase gene.**

(C) (B) Differential levels of methylation of intron 13 of MCM6 and the LCT gene in individuals with genetic lactose malabsorption (LCT −13910:**C/C**), lactose tolerance (LCT −13910:**T/T)** and the clinically silent, physiologically intermediate genotype LCT −13910:**C/T**.

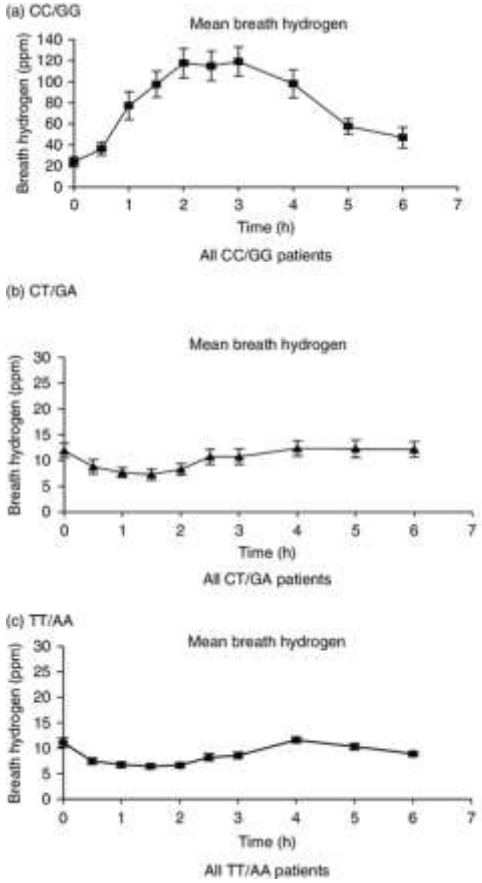
**Hypermethylation (red colour) results in genetic silencing of the respective gene.** (Labrie *et al 2016* ).




Nat Struct Mol Biol 2016;**23**:566–73.doi:10.1038/nsmb.3227

# Lactose intollerance




**CC hypolactasia (non-persistent LCT)**

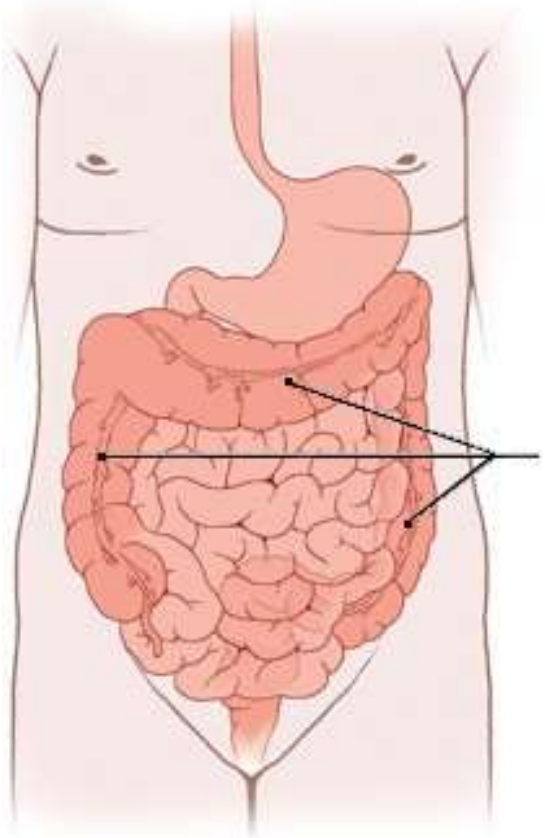
**CT Intermediate**

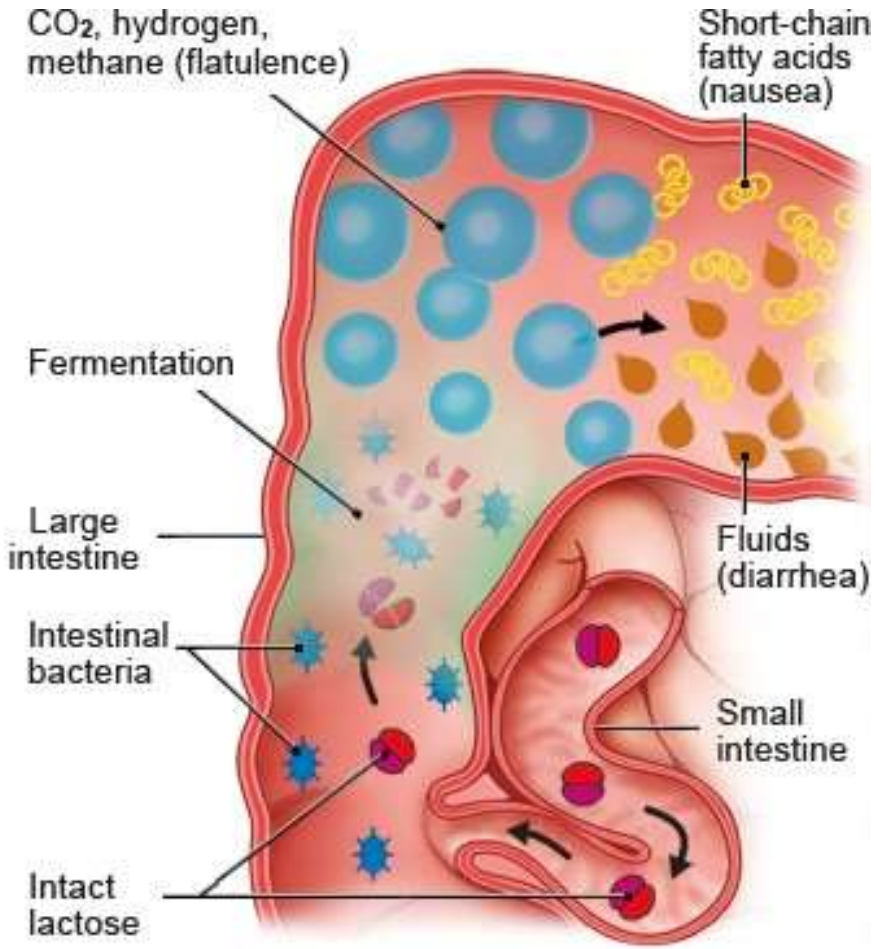
**TT persistent LCT**

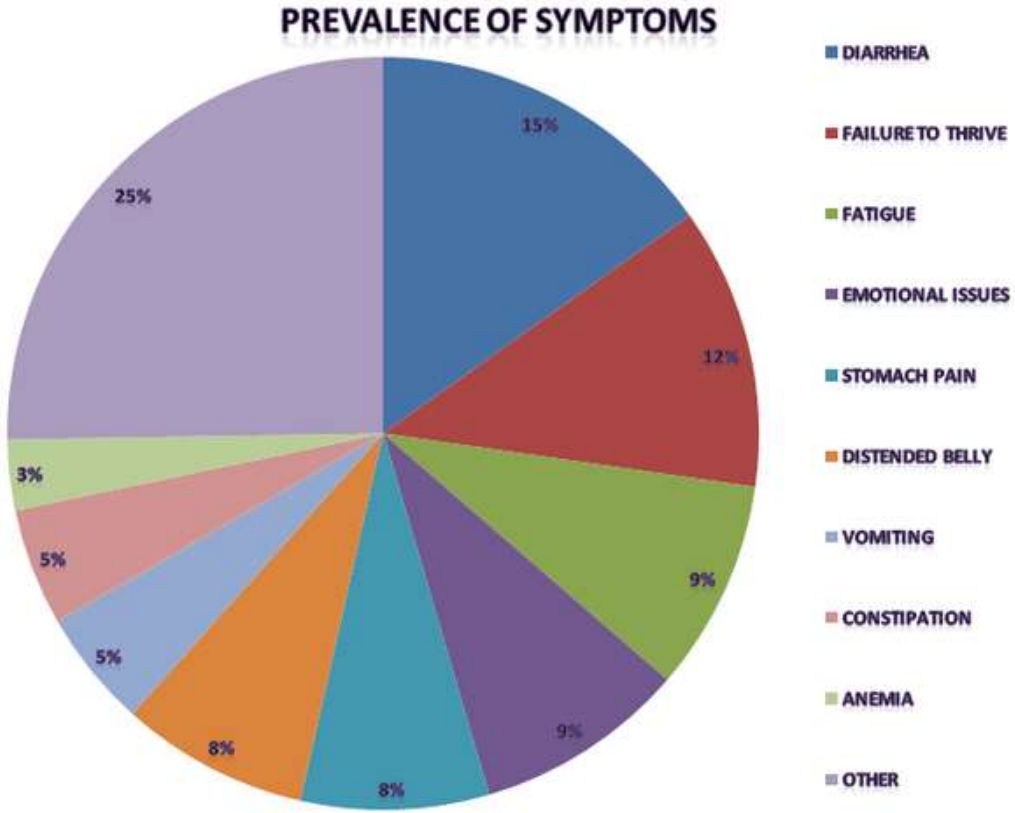
Effect of 50 g lactose on breath hydrogen in the three principal genetic groups.

Boxes represents CC/GG lactase non-persistent genotype, breath hydrogen >20 ppm above the nadir at 30 minutes and continues throughout the testing period. Triangles represent CT/GA heterozygous lactase persistent genotype showing a rise in breath hydrogen >20 ppm above the nadir after sampling above 300 minutes. Diamonds represent **TT/AA homozygous lactase persistent genotyped patient** in which the breath hydrogen does not rise above 20 ppm throughout the testing period of 360 minutes.

# Lactose intollerance





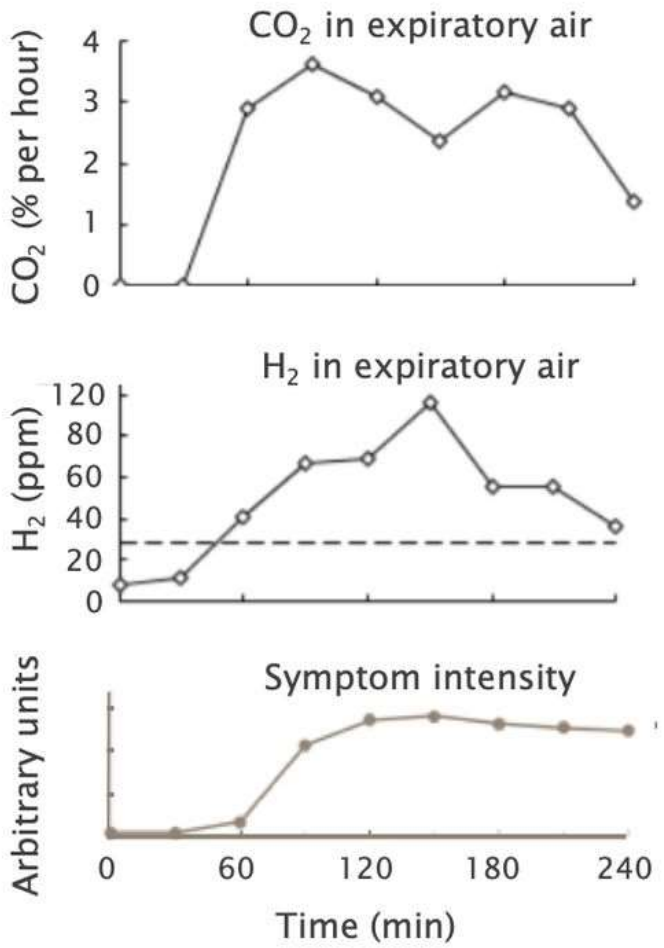
# Most frequently reported gut-related and systemic symptoms in patients with lactose intollerance

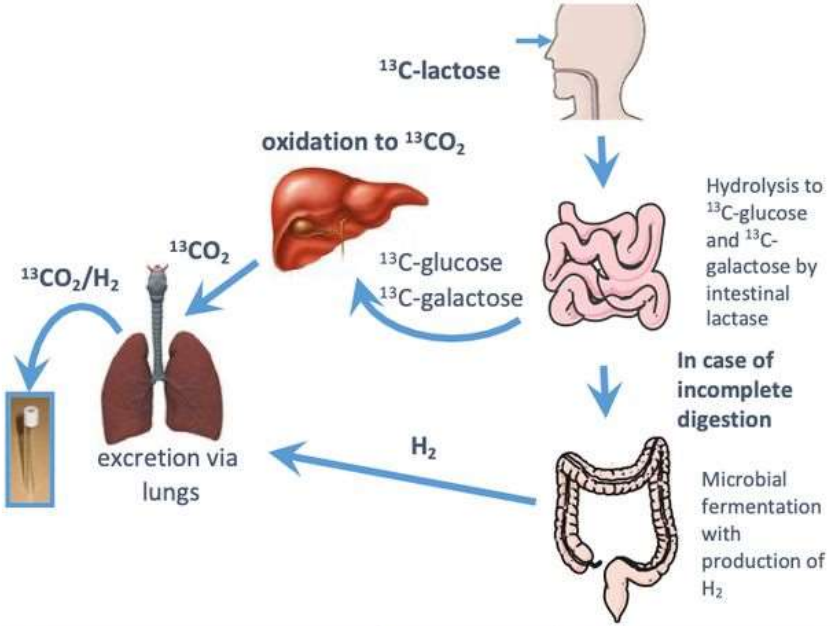
| Symptoms of Lactose Intolerance | | Frequency (% of Total) |
|---|---|---|
| GUT-RELATED SYMPTOMS | Abdominal pain | ~100 |
| | Gut distension | ~100 |
| | Borborygmi | ~100 |
| | Flatulence | ~100 |
| | Diarrhoea | 70 |
| | Constipation | 30 |
| | Nausea | 78 |
| | Vomiting | 78 |
| SYSTEMIC SYMPTOMS | Headache | 86 |
| | Loss of concentration | 82 |
| | Tiredness | 63 |
| | Muscle pain | 71 |
| | Joint pain/stiffness | 71 |
| | Mouth ulcers | 30 |
| | Increased frequency of micturition | <20 |

# Lactose intollerancve: diagnosis

- Diagnosis of lactose malabsorption can usually be made on the basis of the history, supported by dietary manipulation.
- Diagnostic tests range from changes in **breath hydrogen levels** to biopsy of the small bowel.
- The measurement of **breath hydrogen after ingestion of 25 to 50 g of lactose is more sensitive and specific than the lactose tolerance test**

# Test for lactose malabsorption



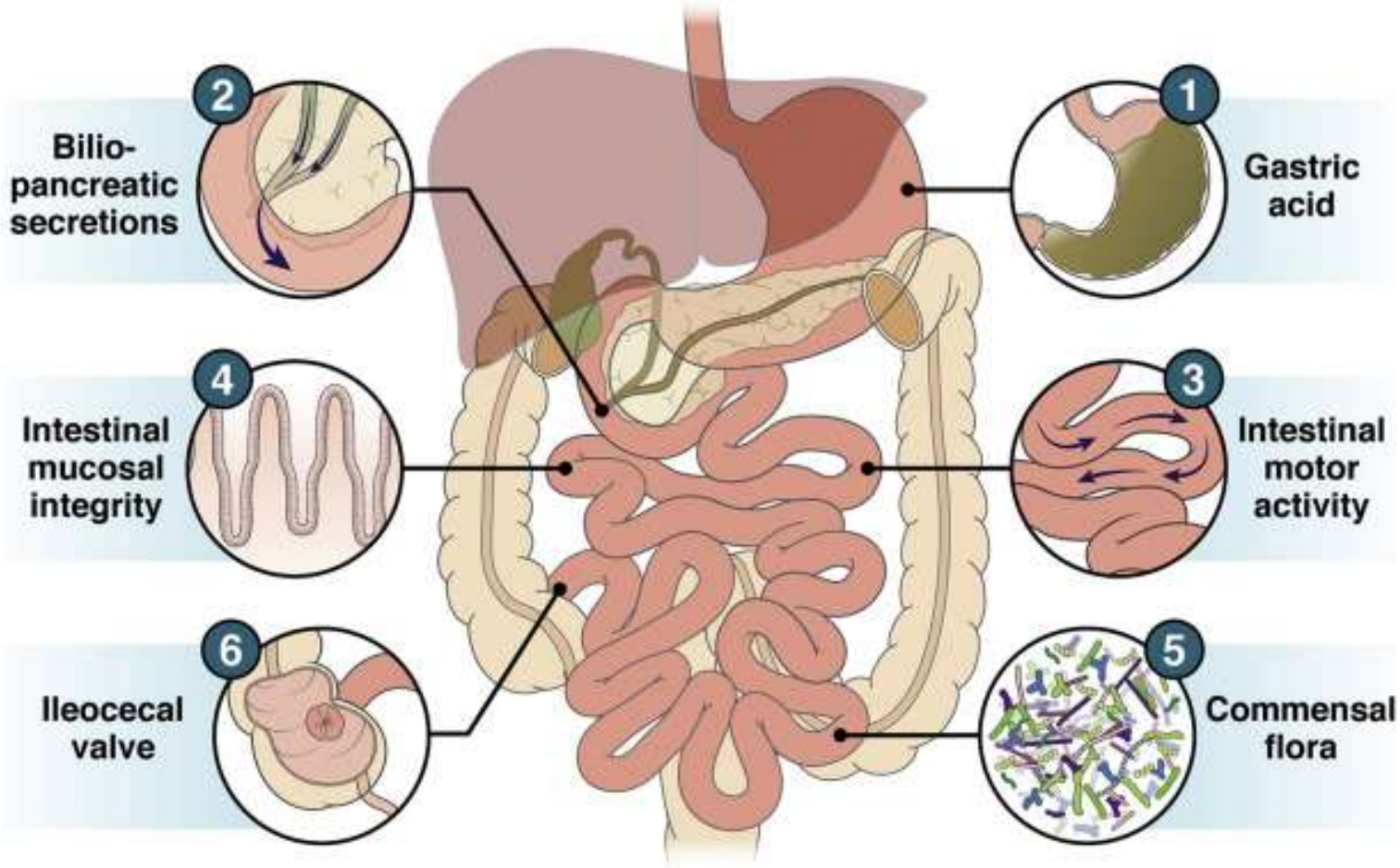

| $^{13}CO_2$-excretion | $H_2$-increase | Interpretation |
|---|---|---|
| > cut-off for normal lactose digestion* | <20 ppm | Normal lactose assimilation |
| > cut-off for normal lactose digestion* | >20 ppm | Lactose malabsorption or SIBO |
| < cut-off for normal lactose digestion* | | Lactase deficiency |

*cut-off for normal lactose digestion : cum $^{13}CO_2$ excretion over 4h >14.5% of administered dose $^{13}$C

# Bacterial overgrowth (SIBO)

- Small intestinal bacterial overgrowth (SIBO) is a condition defined by the excess bacteria or changes in bacterial composition of the small intestine.
- These are associated with various gastrointestinal (GI) symptoms such as bloating, abdominal distension, diarrhea, nutrient deficiencies, and even frank weight loss.
- Small bowel jejunal aspirate of >105CFU/ml has traditionally been considered the gold standard for diagnosis.
- Glucose and lactulose breath testing have become more common in clinical practice as they are noninvasive, easily accessible, and have lower cost.
- Treatment focuses on the eradication of excess bacteria in the small bowel and is traditionally done with the use of oral antibiotics. Other emerging therapies may include probiotics, diet manipulation, and prokinetic agents.

# Bacterial overgrowth (SIBO)



# Bacterial overgrowth (SIBO)

**Table 2.** Disorders Linked to SIBO

| |
|---|
| Abnormal small intestinal motility |
| Diabetic autonomic neuropathy |
| Systemic sclerosis/scleroderma |
| Amyloidosis |
| Hypothyroidism |
| Idiopathic intestinal pseudo-obstruction |
| Acromegaly |
| Gastroparesis |
| Myotonic muscular dystrophy |
| Chronic opiate use |
| Long-standing use of motility-suppressing drugs |
| Anatomic abnormalities |
| Small intestinal diverticulosis |
| Surgically induced alterations in anatomy (Billroth II gastrectomy, end-to-side anastomosis) |
| Strictures (Crohn's disease, radiation, surgery) |
| Blind loops |
| Gastrocolic or jejunocolic fistula |
| Ileo-cecal valve resection |
| Hypochlorhydria |
| Postsurgical |
| Long-term acid suppression |

# Bacterial overgrowth (SIBO)

Immune deficiency
- Inherited immune deficiencies
- Acquired immune deficiency (eg, AIDS, severe malnutrition)

Multifactorial
- Chronic pancreatitis
- Celiac disease
- Tropical sprue
- Crohn's disease
- Cystic fibrosis
- Intestinal failure
- Radiation enteropathy
- Liver disease
- End-stage renal disease

# Bacterial overgrowth (SIBO)

| Process | Mechanisms of action | Clinical consequences |
|---|---|---|
| Mucosal injury induced by bacteria and/or their toxins or products | 1. Loss of brush-border enzymes<br>2. Injury to the epithelial barrier leading to enhanced intestinal permeability<br>3. Inflammatory response generating inflammatory cytokines | 1. Carbohydrate maldigestion<br>2. Protein-losing enteropathy; bacterial translocation and portal and systemic endotoxemia<br>3. Liver injury and inflammation, systemic inflammatory responses |
| Luminal competition with host for nutrients | 1. Consumption of dietary protein<br>2. Consumption of vitamin $B_{12}$<br>3. Consumption of thiamine<br>4. Consumption of nicotinamide | 1. Hypoproteinemia, edema<br>2. $B_{12}$ deficiency, megaloblastic anemia, neurologic symptoms<br>3. Thiamine deficiency<br>4. Nicotinamide deficiency |
| Bacterial metabolism | 1. Fermentation of unabsorbed carbohydrates<br>2. Deconjugation of primary bile acids<br>3. Synthesis of vitamin K<br>4. Synthesis of folate<br>5. Synthesis of D-lactic acid<br>6. Synthesis of alcohol<br>7. Synthesis of acetaldehyde | 1. Bloating, distension, flatulence<br>2. Diarrhea due to effects of deconjugated bile acids in the colon; depletion of the bile acid pool leading to fat and fat-soluble vitamin malabsorption<br>3. Interference with anticoagulant dosing<br>4. High serum folate levels<br>5. D-lactic acidosis<br>6. Liver injury<br>7. Liver injury |

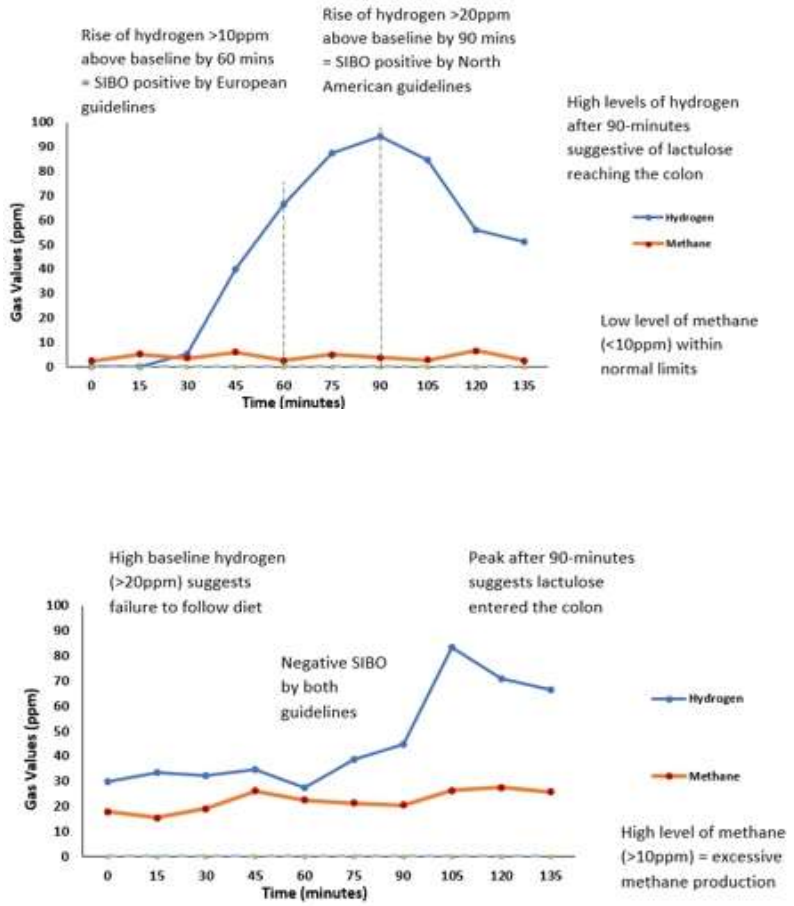
# Bacterial overgrowth (SIBO)

**Table 3.** Identification of small intestinal bacterial overgrowth (SIBO) in a patient.

| | |
|---|---|
| Physical examination | Nonspecific findings: abdominal distension, small intestinal succession splash [Taylor *et al.* 1991], scarring associated with prior surgeries, severe cases may have latent tetany, polyneuropathy and skin manifestations (rosacea) |
| Laboratory tests | Anemia, low vitamin B12, signs of malnutrition (lymphopenia, low serum pre-albumin and transferrin), elevated serum folate and vitamin K levels (bacteria produce these) |
| Direct tests | Quantitative culture of luminal contents |
| Indirect tests | Breath tests: $^{14}C$ d-xylose, hydrogen |
| Other diagnostic tests | Urinary tests, serum test |
| Imaging/colonoscopy | Barium studies, CT enterography to identify mechanical causes of SIBO |

CT, computerized tomography.

# Bacterial overgrowth (SIBO)




| What We Can Detect | What It Means |
|---|---|
| High baseline hydrogen (>20ppm) | Patient may not have followed the diet, fast and other preparation correctly |
| Increase of 10ppm hydrogen within 60 minutes | SIBO positive by European Consensus |
| Increase of 20ppm hydrogen within 90 minutes | SIBO positive by North American Consensus |
| Increase in hydrogen after 90 minutes | Normal lactulose fermentation by bacteria in the colon (not found in a glucose breath test) |
| A lack of a peak of hydrogen after 90 minutes | Potential slow gastrointestinal transit, or possible hydrogen sulphide production |
| Presence of methane (>10ppm) | Excessive methane production due to methanogen overgrowth |

| Summary of Available Tests for Assessing Lactose Malabsorption/Intolerance | | | | |
|---|---|---|---|---|
| | **Lactose Tolerance Test** | **$H_2$-Breath Test (HBT)** | **Genetic Test** | **Lactose Activity at Jejunal Brush Border** |
| Test principle | Increase of glycaemia after lactose challenge | Increase of $H_2$ in expirate after lactose challenge | Assessment of 13910C/T polymorphism | Lactase enzymatic activity in bioptic sample |
| Cut-off criterion | <1.1 mmol/L within 3 h | >20 ppm within 3 h | C:C13910<br>Lactase non-persistence phenotype | <17–20 IU/g |
| Availability | Excellent | Good | Good | Rare |
| False positives | Rapid GI-transit, impaired glucose tolerance | Rapid GI-transit, SIBO | Rare (<5%) in Caucasians | Most likely, rare |
| False negatives | Fluctuations in glycaemia | Non-$H_2$-producers, full colonic adaptation | All causes of secondary lactose malabsorption | Patchy enzyme expression |
| Secondary causes | Cannot be excluded | Cannot be excluded, kinetics of $H_2$-increase can be suggestive | Cannot be excluded | Can be excluded (histopathology during same procedure) |
| Symptoms assessment | Possible | Possible | Not possible | Not possible |
| Cost | Lowest | Low | Medium | Highest |
| Comment | Low sensitivity and specificity | Method of choice for assessment of primary and secondary lactose intolerance | Method of choice for assessment of primary lactase deficiency in Caucasians | Invasive and expensive testing |

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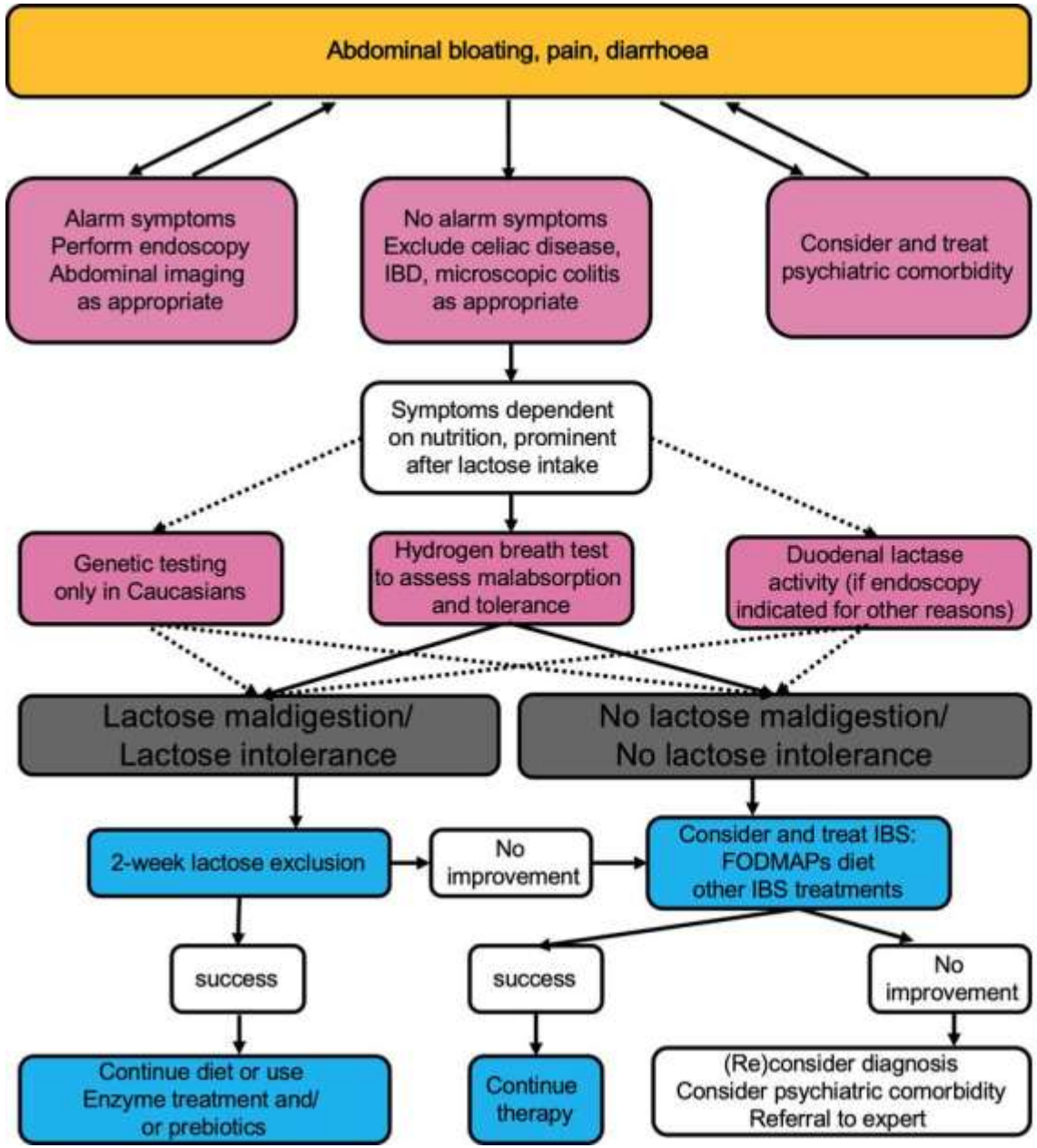
Abdominal bloating, pain, diarrhoea
Alarm symptoms
Perform endoscopy
Abdominal imaging
as appropriate
No alarm symptoms
Exclude celiac disease,
IBD, microscopic colitis
as appropriate
Consider and treat
psychiatric comorbidity
Initial assessment
Symptoms dependent
on nutrition, prominent
after lactose intake
Genetic testing
only in Caucasians
Hydrogen breath test
to assess malabsorption
and tolerance
Duodenal lactase
activity (if endoscopy
indicated for other reasons)
LM diagnostic
+/- symptom
assessment
Lactose maldigestion/
Lactose intolerance
No lactose maldigestion/
No lactose intolerance
2-week lactose exclusion
No
improvement
Consider and treat IBS:
FODMAPs diet
other IBS treatments
Therapy
success
success
No
improvement
Continue diet or use
Enzyme treatment and/
or prebiotics
Continue
therapy
(Re)consider diagnosis
Consider psychiatric comorbidity
Referral to expert

# Lactose intollerance: Therapy

- The treatment for lactose intolerance mainly consists of reducing/eliminating the dietetic amount of lactose until the symptoms disappear.
- Most intolerant patients can tolerate 5 grams of lactose per single dose, with an increase in the tolerance threshold if the lactose is consumed together with other nutrients.

- According to the European regulations for food labelling, the presence of milk or its derivatives—including lactose—should be reported on the label or in the ingredients list for freshly prepared products.
- The absence in many European countries and non-European countries of laws regulating the commercialization of delactosed products—and the consequent lack of a cut-off value for establishing when a product can be labelled “lactose-free”—has resulted in the proliferation of many dairy products claiming the absence or reduction of lactose, despite the presence of a small amount (usually <0.01% or <0.1% and <0.5%, respectively) in such products, which, although reduced, is still enough to induce symptoms in at least a portion of lactose-intolerant patients.
- In Italy, the lactose-intolerant patients’ association, AILI (Associazione Italiana Latto-Intolleranti), has recently asked the Italian Ministry of Health for the definitions of qualitative and quantitative standards for product labelling to be shared by producers, consumers, and institutions for the regulation of the “lactose-free” claim.

# Lactose intollerance :therapy

Patient education is usually highly useful in patients with lactose intolerance

Patients should be informed that having lactose malabsorption does not mean they are allergic to milk, dairy products, or dairy foods.

A milk allergy is related to the proteins in milk rather than the lactose. The degree of lactose malabsorption varies widely among patients, but most patients do not require a totally lactose-free or severely restricted diet.

Dairy products should not be totally eliminated because they provide key nutrients such as calcium, vitamins A and D, riboflavin, and phosphorus.

Diary products provide approximately 75 percent of the calcium available in the food supply.1

Adult patients with lactose intolerance should maintain a calcium intake of 1,200 to 1,500 mg per day, including actual dairy products up to their individual threshold for symptoms.

# Lactose intollerance: Therapy

Patients should also be advised to avoid medications that contain lactose as filler and certain food products that may contain unrecognized lactose .

Patients with mild lactose malabsorption may benefit from using lactase enzyme supplements

The incubation of milk with lactase enzymes may also be helpful.

However, patients should be warned that the lactase enzymes might not completely relieve the symptoms because the digestion of lactose is incomplete or because it is difficult to determine the effective dose of lactase enzyme.

Soy milk and rice milk are also well-tolerated.

# Lactose intollerance: probiotics

*Probiotics as a Future Option in the Management of Lactose Intolerance*

- Recently, the use of specific probiotic strains, in particular those capable of expressing β-galactosidase enzymatic activity, has been proposed as an adjuvant treatment for subjects with lactose intolerance.

- Probiotics are defined by the World Health Organization as live microorganisms, which, when administered in adequate amounts, confer a health benefit on the host.
- Lactase-containing microorganisms in yogurt and fermented milk could hydrolyse lactose, and today, the evidence that probiotics alleviate the clinical symptoms of lactose intolerance is increasing due to a growing number of relevant studies.

- In patients with irritable bowel syndrome (IBS), *Lactobacillus plantarum* has been tested in a four-week treatment and was shown to provide effective symptom relief, with particular efficacy against bloating and abdominal pain . In the same context, *Lactobacillus acidophilus* was associated with reduced scores for abdominal pain and discomfort after a four-week treatment.
- In an observational study with 96 adult IBS patients, a significant decrease in faecal calprotectin levels compared to the baseline was observed after two months of treatment with a multi-strain symbiotic (composed of *Bifidobacterium lactis* W51, *Lactobacillus acidophilus* W22, *Lactobacillus plantarum* W21, *Lactococcus lactis* W19, and inulin).

- In the case of lactose intolerance, the clinical benefit for the host derives from the β-galactosidase activity that strains of both *Lactobacillus* and *Bifidobacterium* have shown in preclinical and clinical settings. A window of opportunity therefore exists to develop probiotic-containing foods and food supplements that can help ameliorate the symptoms of lactose intolerance, and this is considered one of the fields with the most supporting evidence and the strongest potential for the effective use of probiotics

## The β-galactosidase activity of several probiotic strains

| Probiotic Strains | β-Galactosidase Activity Level |
|---|---|
| *Bifidobacterium lactis* W52 | ++++ |
| *Bifidobacterium lactis* W51 | +++ |
| *Lactobacillus acidophilus* W22 | +++++ |
| *Lactobacillus acidophilus* W70 | +++++ |
| *Lactobacillus brevis* W78 | + |
| *Lactobacillus casei* W20 | + |
| *Lactobacillus casei* W79 | ++ |
| *Lactobacillus plantarum* W21 | + |
| *Lactobacillus rhamnosus* W71 | + |
| *Lactobacillus salivarius* W24 | +++++ |
| *Lactococcus lactis* W19 | + |
| *Streptococcus thermophilus* W69 | +++++ |

# Hidden” Sources of Lactose in Food Products

Although milk and foods made from milk are the only natural sources, lactose is often added to prepared foods. People with very low tolerance for lactose should know about the many food products that may contain even small amounts of lactose, including the following:

Bread and other baked goods

Processed breakfast cereals

Mixes for pancakes and cookies

Instant potatoes, soups, and breakfast drinks

Margarine