NMDC221 Session 6: Immune System Disease Part I
Recommended Reading
Topic Summary

Immune System

- Introduction – overview of principles and considerations in nutritional management of the immune system
- Immunological basis and nutritional management of food allergies and intolerances
- Therapeutic diets:
  - Elimination diet
  - Low reactive diet
- Relevant nutrient-drug interactions
Overview of the immune system

- The immune system is composed of two major subdivisions, the innate or non-specific immune system and the adaptive or specific immune system.
- The innate immune response is the first line of defence against an invading pathogen. Through specialised receptors, known as pattern recognition receptors, especially Toll-like receptors, specialised cells of myeloid origin, including macrophages and dendritic cells (DCs) are able to phagocytose microorganisms and induce an innate inflammatory response (Harizi & Gualde, 2005).
Overview of the Immune System

- Although B and T lymphocytes recognise tissue antigens with high specificity, they are unable to initiate immune responses. The decision to activate an appropriate immune response is made by unique DC, the antigen-presenting cells (APCs) which control the responses of several types of lymphocytes and play central role in the transition between innate and adaptive immunity (Harizi, & Gualde, 2005).
Overview of the Immune System

(Mayer, 2011)
Immune System

Acts to protect the body from invading organisms, allergens and abnormal host cells

• Non-specific immunity: Physical barriers, secretions, phagocytes, dendritic cells (antigen-presenting cells) NK cells, neutrophils, eosinophils, inflammation, chemical protection

• Specific immunity: lymphocytes – T cells, B cells,
  o The signaling pathway for the immune system relies on many chemicals (PG, LT, hormones, amines etc…)  

(Merck, 2010)
Immune System

The Cells of the Immune System

- Monocytes
- Mast cells
- Neutrophils
- Eosinophils
- Basophils
- Lymphocytes
- Interferon – not a cell but a type of non-specific immunity
Hierarchy (Haemopoiesis schematic representation)

Key:
- Precursor cells or "blasts"
- Formed elements of circulating blood
- Tissue cells

Pluripotent stem cell

Myeloid stem cell

CFU-E
- Proerythroblast
- Nucleus ejected
- Reticulocyte
- Red blood cell

CFU-Meg
- Megakaryoblast
- Megakaryocyte
- Platelets

CFU-GM
- Monoblast
- Myeloblast
- Monocyte
- Neutrophil

Eosinophilic myeloblast
- Eosinophil

Basophilic myeloblast
- Basophil

Pre-B cells

Prothymocyte

Lymphoid stem cell

B lymphoblast
- B lymphocyte
- Plasma cell

T lymphoblast
- T lymphocyte
## Immune System

<table>
<thead>
<tr>
<th>Monocytes</th>
<th>Therapeutic Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Function</strong></td>
<td>Non-specific immunity</td>
</tr>
<tr>
<td><strong>Cofactors</strong></td>
<td>Vitamin B12 and folate</td>
</tr>
<tr>
<td></td>
<td>Glutamine</td>
</tr>
<tr>
<td></td>
<td>Beta-carotene</td>
</tr>
<tr>
<td></td>
<td>Vitamin E</td>
</tr>
</tbody>
</table>

(Tortora & Grabowski, 2014, p. 645; Gropper, Smith & Carr 2016; Shils et al 2006)
## Immune System

<table>
<thead>
<tr>
<th>Macrophages</th>
<th>Therapeutic Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Function</strong></td>
<td>Non-specific immunity</td>
</tr>
<tr>
<td><strong>Co-factors</strong></td>
<td>Vitamin B12 &amp; folate</td>
</tr>
<tr>
<td></td>
<td>Glutamine</td>
</tr>
<tr>
<td></td>
<td>Acetyl-L-Carnitine</td>
</tr>
<tr>
<td></td>
<td>Glucans (β-1,3 &amp; β-1,6)</td>
</tr>
<tr>
<td></td>
<td>CoQ10</td>
</tr>
<tr>
<td></td>
<td>Vitamin B5</td>
</tr>
<tr>
<td></td>
<td>Vitamin D</td>
</tr>
</tbody>
</table>

(Tortora & Grabowski, 2014, p. 645; Gropper et al. 2016; Shils et al 2006)
## Immune System

<table>
<thead>
<tr>
<th>Neutrophils</th>
<th>Therapeutic Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Function</strong></td>
<td>First WBC to reach wounds: Destroy antigens &amp; detrimental bacteria. Principal component of pus</td>
</tr>
<tr>
<td><strong>Co-factors</strong></td>
<td></td>
</tr>
<tr>
<td>Vitamin B12 &amp; Folate</td>
<td>Cofactors in bone marrow for development of stem cells division</td>
</tr>
<tr>
<td>Glutamine</td>
<td>Aids in the ability of neutrophils to destroy antigens</td>
</tr>
<tr>
<td>Acetyl-L-Carnitine</td>
<td>Enhances the function of neutrophils</td>
</tr>
<tr>
<td>Taurine</td>
<td>Improves ability to perform phagocytosis</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>Enhances the function of neutrophils</td>
</tr>
<tr>
<td>Vitamin B6</td>
<td>Improves phagocytosis</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Deficiency = inability to perform phagocytosis</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Improves phagocytosis</td>
</tr>
</tbody>
</table>

(Tortora & Grabowski, 2014, p. 645; Gropper et al. 2016; Shils et al 2006)
**Immune System**

<table>
<thead>
<tr>
<th>Mast Cells</th>
<th>Therapeutic Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Function</strong></td>
<td>Specific immunity</td>
</tr>
<tr>
<td><strong>Co-factors</strong></td>
<td>Vitamin B12 and folate</td>
</tr>
<tr>
<td>Tyramine</td>
<td>Stimulates the release of excessive amounts of histamine from mast cells</td>
</tr>
<tr>
<td>Quercetin</td>
<td>Stabilises the cell membranes of mast cells</td>
</tr>
<tr>
<td>Zinc</td>
<td>Inhibits the release of histamine from mast cells</td>
</tr>
</tbody>
</table>

(Tortora & Grabowski, 2014, p. 645; Gropper et al. 2016; Shils et al 2006)
## Immune System

<table>
<thead>
<tr>
<th>Eosinophils</th>
<th>Therapeutic Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Function</td>
<td>Non-specific immunity</td>
</tr>
<tr>
<td>Co-factors</td>
<td>Vitamin B12 &amp; Folate</td>
</tr>
</tbody>
</table>

(Tortora & Grabowski, 2014, p. 645; Gropper et al. 2016; Shils et al 2006)
# Immune System

<table>
<thead>
<tr>
<th>Basophils</th>
<th>Therapeutic Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Function</strong></td>
<td>Non-specific immunity</td>
</tr>
<tr>
<td><strong>Co-factors</strong></td>
<td>Vitamin B12 and folate</td>
</tr>
<tr>
<td>Iron</td>
<td>Possess the iron portion of the IgE molecule on specific binding sites on the surface membrane</td>
</tr>
<tr>
<td>Heparin</td>
<td>Contained in Basophils which are released to participate in lipid metabolism</td>
</tr>
<tr>
<td>Quercetin</td>
<td>Inhibits the excessive release of histamine by Basophils</td>
</tr>
</tbody>
</table>

(Tortora & Grabowski, 2014, p. 645; Gropper et al. 2016; Shils et al 2006)
# Immune System

<table>
<thead>
<tr>
<th>Lymphocytes</th>
<th>Therapeutic Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Function</strong></td>
<td><strong>Specific immunity</strong></td>
</tr>
<tr>
<td><strong>Co-factors</strong></td>
<td>Vitamin B12 and folate</td>
</tr>
<tr>
<td></td>
<td>Alanine</td>
</tr>
<tr>
<td></td>
<td>Glutamine</td>
</tr>
<tr>
<td></td>
<td>Beta-carotene and Lycopene</td>
</tr>
<tr>
<td></td>
<td>Glutathione</td>
</tr>
</tbody>
</table>

(Tortora & Grabowski, 2014, p. 645; Gropper et al. 2016; Shils et al 2006)
# Immune System

<table>
<thead>
<tr>
<th>Lymphocyte Co-factors</th>
<th>Therapeutic Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMG (Dimethyl glycine)</td>
<td>Stimulates the body’s production of lymphocytes in response to some antigens</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>Increases proliferation of lymphocytes in response to challenges by antigens</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Stimulates the body’s production (blastogenesis) of lymphocytes</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Found in high concentrations and enhances the function of lymphocytes</td>
</tr>
</tbody>
</table>

(Tortora & Grabowski, 2014, p. 645; Gropper et al. 2016; Shils et al 2006)
## Immune System

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Major Sources</th>
<th>Principal Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1</td>
<td>Activated macrophages</td>
<td>IL-1 + antigen = proliferation of antigen specific T cell, leading to the secretion of IL-2.</td>
</tr>
<tr>
<td></td>
<td>&amp; other APC</td>
<td></td>
</tr>
<tr>
<td>IL-2</td>
<td>Activated T Cells</td>
<td>Amplifies T Cell proliferation &amp; production of other cytokines.</td>
</tr>
<tr>
<td>IL-3</td>
<td>Activated T Cells</td>
<td>Stimulates the proliferation of haemopoietic stem cells.</td>
</tr>
<tr>
<td>IL-4</td>
<td>Activated T Cells</td>
<td>Stimulates the proliferation of B cells and promotes Ig isotype switching.</td>
</tr>
<tr>
<td>IL-5 &amp;</td>
<td>Activated T Cells</td>
<td>Stimulate proliferation and differentiation of B to antibody - producing plasma cells.</td>
</tr>
<tr>
<td>IL-6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INF-γ</td>
<td>Activated T Cells</td>
<td>Activates macrophages &amp; neutrophils (increase phagocytic &amp; bacteriocidal activity)</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Activated Macrophages</td>
<td>Cytotoxic to bacteria and tumour cells, but also to normal tissue.</td>
</tr>
</tbody>
</table>

(Gropper et al. 2016; Shils et al. 2006)
Inflammation & Eicosanoids
The impact of eicosanoids on the crosstalk between innate and adaptive immunity

Cytokines are known as key regulators of immunity, eicosanoids, including PGE(2), PGD(2), LTB(4), and LTC(4), may also affect cells of immune system by modulating cytokine release, cell differentiation, survival, migration, antigen presentation, and apoptosis.

By acting on various aspects of immune and inflammatory reactions, these lipid mediators emerge as key regulators of the crosstalk between innate and adaptive immunity (Harizi & Gualde, 2005).
The diverse activities of PGs and LTs are reflected by their involvement in both normal homeostasis (blue) and pathophysiology.
A comparison of the physiological activities between the n-6- and n-3-derived PGs and LTs.

Encyclopaedia of Human Nutrition 2013
## Eicosanoids

<table>
<thead>
<tr>
<th>Eicosanoid</th>
<th>Pathway By-Products</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thromboxane A₂</strong> COX path</td>
<td>From platelets. Causes thrombosis, Stimulates platelet aggregation, causes vasoconstriction &amp; bronchoconstriction, Promotes angiogenesis</td>
</tr>
<tr>
<td><strong>Prostacyclin PGI₂</strong> COX path</td>
<td>From vascular endothelial cells. Causes thrombolysis, Inhibits platelet aggregation, Causes vasodilation, Reduces angiogenesis</td>
</tr>
<tr>
<td><strong>Prostaglandin E₂F₂D₂</strong> COX path</td>
<td>Increases smooth muscle contraction (vaso &amp; bronchoconstriction). Decreases platelet aggregation, lymphocyte migration, interleukin 1 &amp; 2</td>
</tr>
<tr>
<td><strong>5 &amp; 12 HETE</strong> Lipoxygenase path</td>
<td>Promotes metastasis. Increases adhesive factors, stimulates proteolysis enzymes &amp; vasodilation. Suppresses apoptosis</td>
</tr>
<tr>
<td><strong>Leukotrienes (LTC₄ &amp; LTD₄)</strong> Lipoxygenase path</td>
<td>Increases inflammation, vascular permeability, T-cell proliferation, leukocyte aggregation, INF-γ, IL-1, IL-2. Stimulates bronchoconstriction</td>
</tr>
</tbody>
</table>

(Shils et al 1999; Gropper, et al. 2016)
Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators

Serhan, CN et al 2008 [http://www.nature.com/nri/journal/v8/n5/fig_tab/nri2294_F3.html]
# Inflammation & Eicosanoids

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Arachidonic Acid Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E</td>
<td>Inhibits the excessive production of endogenous arachidonic acid from its precursor PUFA's.</td>
</tr>
<tr>
<td>PGE 1</td>
<td>Inhibits the release of arachidonic acid from cell membranes (thereby preventing arachidonic acid from stimulating the production of (usually toxic) PGE 2 and Leukotriene 4).</td>
</tr>
<tr>
<td>PGE 3</td>
<td>Inhibits the endogenous production of arachidonic acid and also inhibits the activity of arachidonic acid (to an even greater extent than does PGE1).</td>
</tr>
<tr>
<td>Docosa-hexaenoic Acid (DHA)</td>
<td>Inhibits the release of arachidonic acid from cell membranes and competes with arachidonic acid for incorporation into phospholipids.</td>
</tr>
</tbody>
</table>

(Gropper et al. 2016; Shils et al. 2006)
## Inflammation & Eicosanoids

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Arachidonic Acid Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eicosapentaenoic Acid (EPA)</td>
<td>Inhibits the release of arachidonic acid from cell membranes and competes with arachidonic acid for incorporation into phospholipids. EPA competes with arachidonic acid as the substrate for cyclooxygenase. Instead of cyclooxygenase catalysing the production of detrimental PGE 2 and thromboxanes 2 from arachidonic acid, EPA “redirects” cyclooxygenase into catalysing the production of beneficial PGE 3 and leukotrienes 3 from EPA.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Leukotriene Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutathione</td>
<td>Glutathione Peroxidase inhibits the production Series 4 Leukotrienes.</td>
</tr>
<tr>
<td>DGLA</td>
<td>Inhibits the production of Series 4 Leukotrienes.</td>
</tr>
<tr>
<td>Quercetin</td>
<td>Inhibits the manufacture of Series 4 Leukotrienes.</td>
</tr>
</tbody>
</table>

(Gropper, et al. 2016; Shils et al. 2006)
# Inflammation & Eiosanoids

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Cyclooxygenase Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melatonin</td>
<td>Inhibits the production of cyclooxygenase.</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Inhibits the production of cyclooxygenase (COX – 2).</td>
</tr>
<tr>
<td>Oligomeric Proanthocyanidins (OPC’S)</td>
<td>Down regulate the activity of cyclooxygenase.</td>
</tr>
<tr>
<td>Ginger</td>
<td>Inhibits the production of cyclooxygenase</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Inhibits the production of cyclooxygenase – 2.</td>
</tr>
<tr>
<td>Resveratol</td>
<td>Inhibits the production of cyclooxygenase 2 without inhibiting the production of cyclooxygenase 1.</td>
</tr>
</tbody>
</table>

(Gropper et al. 2016; Shils et al. 2006)
Inflammation & Eicosanoids

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Cofactors Involved with Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta-5-desaturase</td>
<td>Zinc, B3, C</td>
</tr>
<tr>
<td>Delta-6-desaturase</td>
<td>Magnesium, zinc, B6 (PLP)</td>
</tr>
<tr>
<td>Delta-9-desaturase</td>
<td>Iron</td>
</tr>
<tr>
<td>Cyclooxygenase</td>
<td>Molybdenum</td>
</tr>
<tr>
<td>Elongase</td>
<td>Molybdenum</td>
</tr>
<tr>
<td>Lipoxygenase</td>
<td>Molybdenum</td>
</tr>
</tbody>
</table>

(Gropper et al. 2016; Shils et al. 2006)
# Anti-inflammatory Nutrients

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Dosage</th>
<th>Therapeutic Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>1000-5000 iu</td>
<td>Activates T &amp; B lymphocytes, lipid antioxidant, controls gene expression</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>1000-5000 mg divided doses</td>
<td>Anti-inflammatory, antioxidant, connective tissue synthesis &amp; maintenance</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>1000-3000 iu</td>
<td>Anti-proliferative, aids in the conversion of monocytes to macrophages, regulates T-cell mediated immune responses</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>100-1000 iu</td>
<td>Anti-inflammatory, Anti-oxidant, enhances T helper cell synthesis, stabilizes cell membranes</td>
</tr>
<tr>
<td>Selenium</td>
<td>50-200mcg</td>
<td>Anti-oxidant, anti-tumour, recycles antioxidants</td>
</tr>
<tr>
<td>Zinc</td>
<td>10-50mg</td>
<td>Involved in the enzymatic control of anti-oxidant system, wound healing, white blood cell control and is anti-viral</td>
</tr>
</tbody>
</table>
## Anti-inflammatory Nutrients

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Dosage</th>
<th>Therapeutic Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential fatty acids</td>
<td>1000-6000mg</td>
<td>Cell tissue communication and modulator of leukotriene synthesis, maintains cell membranes</td>
</tr>
<tr>
<td>Glutamine</td>
<td>0.5-3gm</td>
<td>Ammonia detoxification, energy for enterocytes, lymphocytes, macrophages, promotes healing</td>
</tr>
<tr>
<td>Bioflavonoids</td>
<td>600mg-3gm</td>
<td>Immune stimulator, anti-inflammatory, induces apoptosis of tumour cells</td>
</tr>
</tbody>
</table>

(Osiecki, 2014)
Vitamin D Sunlight Activity
## Recommendations for Vitamin D

Source: http://www.osteoporosis.org.au/vitamin-d

<table>
<thead>
<tr>
<th>Skin Type</th>
<th>Season</th>
<th>Skin Exposed</th>
<th>Recommended time of day</th>
<th>Sun Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderately Fair</td>
<td>Winter</td>
<td>Arms or equivalent</td>
<td>midday</td>
<td>7 – 30 minutes*</td>
</tr>
<tr>
<td>Darker skin</td>
<td>Winter</td>
<td>Arms or equivalent</td>
<td>midday</td>
<td>20 min – 3hrs*</td>
</tr>
</tbody>
</table>

*depends on location within Australia and type of skin

<table>
<thead>
<tr>
<th>Skin Type</th>
<th>Season</th>
<th>Skin Exposed</th>
<th>Recommended time of day</th>
<th>Sun Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderately Fair</td>
<td>Summer</td>
<td>Arms or equivalent</td>
<td>mid morning or mid afternoon</td>
<td>5 – 10 minutes</td>
</tr>
<tr>
<td>Darker skin</td>
<td>Summer</td>
<td>Arms or equivalent</td>
<td>mid morning or mid afternoon</td>
<td>15 – 60 minutes*</td>
</tr>
</tbody>
</table>

*depends on location within Australia and type of skin
Vitamin D Sunshine Map, recommended sun exposure based on location

Source: http://www.osteoporosis.org.au/vitamin-d
Immunological basis of food allergy and intolerance
Immunological Basis Of Food Allergy And Intolerance

Food Intolerance - *Cell Mediated Immunity*

- Abnormal physiological response to the presence of certain food chemicals.

Food Intolerance may be mediated by:
- T lymphocyte T helper (Th) cells
- The Th cells differentiate depending on the presence of the cytokine series that the antigen cell produces due to the presence of the food protein.

(Mahan & Escott-Stump, 2008, p. 742)
Aetiology

Risk Factors for Food Allergies and Intolerances:

- Genetics
- Epigenetics
- Intestinal barrier integrity
- Microbiome status
- Maternal and infant factors – Caesarean, infant feeding (Breast feeding versus bottle feeding), stress, hormonal fluctuations
- Psychological factors
- Environmental

(Mahan & Raymond, 2014)
Immunological Basis Of Food Allergy And Intolerance

Food Intolerance - *Cell Mediated Immunity*

**Immediate Hypersensitivity Reaction**

- Th2 cells = cytokines that make B cells produce IgE. This then attaches to a mast cell & with re-exposure the mast cells degranulate and release chemical mediators of food allergy.

- Reaction can occur within seconds but may take up to 2 hours.
  - E.g. Hay fever, anaphylaxis, food allergies, atopic dermatitis and asthma responses.

(Mahan & Escott-Stump, 2008, p. 742)
Review: Functions of the Immune System

Immunological Basis Of Food Allergy And Intolerance

Antigen-Antibody complex
- Occurs in some food reactions
- IgG & IgM form a precipitating antibody complex.
- Reactions usually take 6+hours and may take several days for symptoms to become apparent.
  - E.g.: chronic respiratory infections, gastroenteropathy.

(Mahan & Escott-Stump, 2008, p. 743)
Immunological Basis Of Food Allergy And Intolerance

Delayed Hypersensitivity
- T cells interact directly with the antigen.
- Delayed reaction
- Contact dermatitis, food protein induced enterocolitis

(Mahan & Escott-Stump, 2008, p. 743)
Immunological Basis Of Food Allergy And Intolerance

Immune Responses

- The gut mucosa is the major site of contact with antigens.
- It holds the largest mass of lymphoid tissue in the body.
- Under physiological conditions, microbiota and dietary antigens are the natural sources of stimulation for the gut associated lymphoid tissue (GALT) and for the immune system as a whole.

(Faria et al. 2012, p. 1)
Immunological Basis Of Food Allergy And Intolerance

- Normal antigenic contact through the gut mucosa induces two major non-inflammatory immune responses:
  - Oral tolerance
  - Production of secretory IgA.

- However, under pathological circumstances mucosal homeostasis is disturbed resulting in inflammatory conditions such as food hypersensitivity and inflammatory bowel diseases (IBDs).

(Faria et al. 2012, pg1)
Immunological Basis Of Food Allergy and Intolerance

Mucosal Barrier
http://www.elsevierimages.com/image/24730.htm
Immunological Basis Of Food Allergy And Intolerance

Food Allergy – Humoral Immunity

- Antibody mediated responses include:
  - IgA – predominant antibody reaction immunoglobulin
  - IgE – systemic hypersensitivity reaction
- Prevalence under 3 yo.
  - Is 5-8% after 3yo, improving to 2-4% after 5+yo (40% subside by this age)
- Most food allergies are outgrown by early childhood – exceptions are peanuts, nuts, fish & shellfish.
- Re-challenge is warranted after one to two years of exclusion. Exception is nuts, peanuts & seafood – re-challenge at 4-8 year intervals

(Katz, 2008, pp 275-276)
# Classes of Immunoglobulins

## Table 17.1: A Summary of Immunoglobulin Classes

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>IgG</th>
<th>IgM</th>
<th>IgA</th>
<th>IgD</th>
<th>IgE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structure</strong></td>
<td>Monomer</td>
<td>Pentamer</td>
<td>Dimer (with secretory component)</td>
<td>Monomer</td>
<td>Monomer</td>
</tr>
<tr>
<td><strong>Percentage of Total Serum Antibody</strong></td>
<td>80%</td>
<td>5–10%</td>
<td>10–15%*</td>
<td>0.2%</td>
<td>0.002%</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Blood, lymph, intestine</td>
<td>Blood, lymph, B cell surface (as monomer)</td>
<td>Secretions (tears, saliva, mucus, intestine, milk), blood, lymph</td>
<td>B cell surface, blood, lymph</td>
<td>Bound to mast and basophil cells throughout body, blood</td>
</tr>
<tr>
<td><strong>Molecular Weight</strong></td>
<td>150,000</td>
<td>970,000</td>
<td>405,000</td>
<td>175,000</td>
<td>190,000</td>
</tr>
<tr>
<td><strong>Half-Life in Serum</strong></td>
<td>23 days</td>
<td>5 days</td>
<td>6 days</td>
<td>3 days</td>
<td>2 days</td>
</tr>
<tr>
<td><strong>Complement Fixation</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No¹</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Placental Transfer</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Known Functions</strong></td>
<td>Enhances phagocytosis; neutralizes toxins and viruses; protects fetus and newborn</td>
<td>Especially effective against microorganisms and agglutinating antigens; first antibodies produced in response to initial infection</td>
<td>Localized protection on mucosal surfaces</td>
<td>Serum function not known; presence on B cells functions in initiation of immune response</td>
<td>Allergic reactions; possibly lysis of parasitic worms</td>
</tr>
</tbody>
</table>

*Percentage in serum only; if mucous membranes and body secretions are included, percentage is much higher.

¹May be yes via alternative pathway.

Source: Open Source Public Domain_Adaptive Immune System, Midlands Technical college
Immunological Basis Of Food Allergy And Intolerance

Risk factors

Prenatal
- Genetic predisposition
- Diet during pregnancy
- Intrauterine sensitisation
- Race and Gender
- Number of pregnancies
- Mothers age
- Caesarean section

Postnatal
- Age of food introduction
- Maternal latency
- Exposure to allergens
- Exposure to pollutants

(Kumawat & Jha, 2011, p 41)
Therapeutic Considerations

- Although food allergy can arise to any food, the allergens responsible for more than 85% of food allergy are:
  - Milk
  - Egg
  - Peanut
  - Tree nuts
  - Shellfish
  - Fish
  - Gluten
  - Wheat
  - Sesame seed
  - Soy

- It is the protein component, not the fat or carbohydrate component, of these foods that leads to sensitisation and allergy.

(Waserman & Watson, 2011, pg1)
Therapeutic Considerations

- Allergic sensitisation begins early in life and occurs primarily in high risk infants, who have a parent with underlying allergic disease.
  - Initial sensitisation is usually to foods such as egg or milk.

- This sensitisation may lead to clinical symptoms, but by 3–5 years of age, tolerance to foods has often developed.

(Busse, 2011, p1)
Therapeutic Considerations

- Allergen sensitisation results in immunoglobulin E (IgE) antibody production to specific allergens and their attachment to populations of IgE-receptor bearing cells such as mast cells or basophils.

- Following sensitisation, re-exposure to the antigen results in a recognition by specific IgE antibodies and a rapid activation of sensitised mast cells and basophils with release of mediators, which then account for or contribute to clinical reactions.

(Busse, 2011, p1)
Immunological Basis Of Food Allergy And Intolerance

- Maternal use of probiotics during lactation has been shown to offer protection.

(Katz, 2008, pp. 275-276)
WHY ARE FOOD ALLERGIES ON THE RISE?

- LEAP (Learning Early About Peanut Allergy)
  

  https://www.youtube.com/watch?v=tn8OGPC65gk
Therapeutic Considerations

Symptoms Of Food Allergy (IgE)

- Clinical symptoms of adverse food reactions typically involve:
  - **Skin** (most common)
    Eg: Urticaria, angioedema, atopic dermatitis, dark circles under the eyes, recurrent ear infections, pruritus,
  - **GIT**
    Eg: nausea, vomiting, pain, and/or blood in the stool are common & occur within one hour of ingestion, oral; and pharyngeal pruritus.
  - **Respiratory system**
    Eg: oropharynx contact hypersensitivity (fresh fruits & vegetables). Other symptoms include redness, itchiness, increased mucous, wheeze, coughing, sneezing, asthma and anaphylaxis

(Kumawat & Jha, 2011, p. 40)
Therapeutic Considerations

Food Intolerance – *Pseudo-allergy (Non-Immune mediated)*

- Release of histamine due to large exposure to food chemicals
- **NOT immunoglobulin driven**
  - Key difference between an *intolerance* and *allergy* and are **much more common**

- Common foods within this class include:
  - Caffeine
  - Vasoactive amines in deli meats (*ham, bacon, salami etc.*)
  - Tyramine in cheese, chocolate & red wine
  - Mono-sodium glutamate (*MSG*) & sulphites used to preserve wine & dry fruits

(Katz, 2008, p. 276)
Therapeutic Considerations

- Respiratory allergy to birch pollen implicates potatoes, carrots, celery, hazelnuts and apples.
- Respiratory allergies to ragweed pollen allergies implicates melons & bananas.

- These symptoms can occur alone or in combination, with more than one symptom occurring at one time; and in some cases there can be generalised anaphylaxis.

(Kumawat & Jha, 2011, p. 40)
Assessment Of Food Allergy, Intolerance And Reaction

Classification of adverse food reactions (Kumawat & Jha, 2011, p. 41)
Biochemical Markers & Testing

Identification of Inappropriate Food Responses

- Diagnostic imaging procedures, endoscopy, histology, and stool examinations can assist in diagnosing diseases of structural aetiology.

- These are useful in the detection and identification of different types of food Intolerances, such as fat intolerance in patients with gallstones, reflux esophagitis, or pancreatic insufficiency.

  (Zopf, Baenkler, Silbermann, Hahn, & Raithel 2009, p.363)
Biochemical Markers & Testing

Laboratory Tests

- Used to identify variations in ‘normal ranges’ for a variety of different endogenous agents within the body.

Eg:

- Inflammatory bowel disease (IBD) is an autoimmune disease characterised by a chronic inflammation of the gastrointestinal tract mucosa and is related to an abnormal immune response to commensal bacteria. There is high antibody auto reactivity in IBD and research has found high levels of IgA in sera of IBD patients, whereas IgG levels appear the same as normal controls.

(Hevia et al 2014)
Distribution of the specific anti-cell wall hydrolases (CWH) titres (IgG and IgA) of all the sera divided into two groups (HC: healthy controls, IBD) (**P < 0.01).

Hevia et al 2014
Biochemical Markers & Testing

IgG, IgA, IgE Assessment: *Blood test*

- Assesses a range of foods (4 – 90) to see if there is a reaction.
  - The blood of the person is tested with the food to see if there is an IgG and/or IgE reaction.
  - Normally IgG is used as it has a delayed action, whereby IgE shows an immediate response to the food so is only normally tested on common food allergies.
  - They are given a scale of 0 to 4, with 4 being the most reactive.
Biochemical Markers & Testing

IgG, IgA, IgE Assessment: *Serum Test*

**IgG**
- ↑ IgG (polyclonal) – chronic liver disease, chronic infection or parasitic infestation
- ↓ IgG – protein loss from the bowel, malnutrition (can also be due to burns, nephrotic syndrome or an inherited condition)

**IgM**
- ↑ ↓ IgM – protein loss from the bowel, immune suppression
Biochemical Markers & Testing

*Serum Test Indications continued*

**IgA**
- \(\uparrow\) IgA (polyclonal) – chronic infections of the gut, (or airways), chronic liver disease, cancer of the bowel, or inflammatory bowel disease
- \(\downarrow\) IgA – recurrent gut infection, milk protein intolerance, persistent gastrointestinal problems or food allergy or sensitivity

**IgE**
- \(\uparrow\) IgE – allergy reactions
Biochemical Markers & Testing

Skin Prick Tests
- Excludes IgE mediated food allergy quickly.
- Tested allergens are placed in the skin & the histamine response (wheal, red, itch) indicates allergy.

Radioallergosorbent tests (RAST)
- Serum is mixed with suspected food to identify IgE responses

*No laboratory tests are available for the detection of non-IgE mediated food allergies.*

(Katz, 2008, p. 277)
Therapeutic Considerations

Identification of Inappropriate Food Responses

Food history review with timeline (food diary) to identify point of contact, reaction time & symptom presentation

- Histamine responses usually occur within 30 minutes of ingestion (Payne & Barker, 2010, p. 62)

- Familial links are strong indicators of the types of foods to first start reviewing (Katz, 2008, p. 277)
Therapeutic Considerations

Milk & Egg allergy

- Most common causes of allergy & food intolerance in children but usually resolves by age 5.
- Individuals that have been milk and/or egg free for 1-2 years should be re-assessed for response.

Lactose Intolerance

- Most common non-immune hypersensitivity reaction. Milk consumption is linked to IBS and respiratory conditions.

(Payne & Barker, 2010, p. 67)
Seafood Allergy

- Fish and shellfish are common causes of food allergy
  - Crustaceans and finned fish can especially cause anaphylaxis reactions.
- Fish allergy does not usually resolve.
- Cod, salmon & herring are the most reactive fish but cross-reaction with other species is common.
- Crustacean allergenic proteins are similar to house dust mites and cockroaches.
- No cross reactivity presents between crustaceans and finned fish.

(Payne & Barker, 2010, p. 67)
Therapeutic Considerations

Peanuts
- Presents in early childhood; low incidence of resolution.

Legumes
- Peanuts are within the legume family so co-sensitivities can commonly present to soy, chickpea, lupin and lentils.

Tree Nuts
- There can be a cross-reactivity with peanuts (50% allergic to peanuts will be allergic to tree nuts).
- Low incidence of resolution

Seeds
- Sesame & mustard seeds are the most common
  (Payne & Barker, 2010, p. 68)
Therapeutic Considerations

Fruits & Vegetables

- Allergy to fruits and vegetables is either a primary sensitisation to a plant allergen or a secondary reaction caused by cross-reactions between plant food allergen and an antibody to pollen or latex.

- Most common foods involved in primary fruit or vegetable allergy are apples, peaches, grapes, kiwi fruit, celery & carrots.

(Payne & Barker, 2010, p. 69)
Therapeutic Considerations

Fruits & Vegetables

- Secondary cross-reactions are linked to oral allergy syndrome (OAS)
  - Immediate response (within 30 minutes of consumption) of numb, itchy lips, palate, and ears. Swelling may present. This usually only occurs when the raw food is eaten. Rapid spread of symptoms from the point of contact.
  - OAS is caused by cross-reaction to pollens or latex.

- Latex is linked to food allergies to chestnuts, avocado, banana & kiwi fruit

(Payne & Barker, 2010, p. 69)
Therapeutic Considerations

Food Responses

- Inappropriate food responses may be:
  - IgE mediated (causing immediate symptoms & possible anaphylaxis)
  - Non-IgE mediated (cell-mediated reactions with more delayed symptoms)
  - A combination of both.

- Although these different forms of inappropriate food responses have varying clinical presentations, they likely share a common pathophysiology, with food antigen sensitisation and Th2 skewing of the immune system.

(Wang & Sampson, 2011, p 87)
Therapeutic Considerations

- Birch pollen cross reactions are linked to apples, stone fruit, tree nuts, kiwi fruit, peanuts, soy, bean sprouts, tomatoes, avocados, pear, strawberries, carrots, grapes, capsicum & celery.
  - Itching hands when peeling potatoes or parsnips is a common symptom

- Herbs implicated in reactions include basil, fennel, parsley and coriander.

- Curry powder reaction is linked to coriander, caraway, cayenne, fenugreek, celery seed or mustard.

(Payne & Barker, 2010, p. 69)
Therapeutic Considerations

Wheat & Other Grains

- Wheat can cause reactions via ingestion, inhalation & skin contact.
- Those individuals with IgE mediated responses to grasses usually present with the same reaction to wheat (80%)
- Reaction to gliadin – gluten fraction of wheat is the main cause of coeliac disease.
  - This means exclusion from wheat, rye and barley. Oats may react. Cereals that can be consumed include rice, millet, quinoa & corn
  - Require dietary support of iron, calcium, folic acid and vitamin B12. (Payne & Barker, 2010, p. 70)
Therapeutic Considerations

Food additives

- Food colourings have been linked to urticaria or angio-oedema (small blood vessels leak fluid into tissues causing oedema).

- Sulphites (E220-227) may cause wheeze, bronchospasm, rhinitis and sinusitis and trigger asthma attacks (5% of asthmatics).
  - Found in cider, dried fruit, wine, lager, dried onions, horseradish, lemon & lime juice, frozen or tinned potatoes and frozen beef burgers.

- MSG may cause sweating, tachycardia and irritation.
  - Found in tomatoes, parmesan cheese, yeast extracts, hydrolysed vegetable protein and soy sauce.

(Payne & Barker, 2010, p. 70)
Therapeutic Considerations

- Aspirin (acetyl-salicylic acid) allergy sufferers may benefit from low salicylate diets.
- Look at low salicylate diets for atopy and other immune conditions.
  - Foods implicated include: apples (golden delicious – low salicylate), lemons, coffee, tea, herbs & spices, yeast spreads and tomatoes.
  - Vasoactive amines can create reactions.
  - Histamine containing foods include: parmesan, blue cheese, Roquefort cheese, red wine, spinach, eggplant, yeast extract, tuna & mackerel.
  - Tyramine presents in fermented foods such as cheese, yeast extract, red wine, chicken liver, fermented beans (soy, miso) & rollmops (herrings)

(Payne & Barker, 2010, p. 71)
Nutritional management of food allergies and intolerances
Dietary & Nutritional Prescription

Elimination diets

- Suspected food allergen is eliminated for a period of 2-3 weeks.
- Are diagnostically & therapeutically useful.
- Common food allergens
  - *Children* – dairy, eggs, peanuts (legume & not a tree nut), soy, wheat and/or gluten.
  - *Adults* – fish, shellfish, nuts and peanuts, dairy, wheat and/or gluten.

**Note:** the antigenic proteins to be eliminated from the diet, may present in a number of foods. This needs careful discussion with your patient.

(Kats, 2008, p. 277)
Dietary & Nutritional Prescription

**Food Challenge**

- Confirms or refutes the food component’s response within the client.
- Where the initial response to the food is extreme, the food can be rubbed onto the outer lip and then the mouth mucosa without being swallowed.
- If significant symptoms are associated with the food start with half the usual amount. Fast from midnight and consume the food first thing in the morning in its purest form, ie milk. Additional food can be included in the later meals depending of the degree of symptoms. Symptoms will usually be delayed therefore monitor for 24 hours.

(Payne & Barker, 2010, p. 65-66)
Dietary & Nutritional Prescription

Food Challenge *continued*

- Challenges should only utilise one suspected food at a time.
- If more than one food is implicated, wait three symptom free days before retesting with a new challenge.

(Payne & Barker, 2010, p. 65-66)
Conducting an Elimination Diet with a Patient

**PHASE 1**

- Comprehensive symptom & diet history as part of consultation

  Patient to keep a diet & symptom diary when eating ‘usual diet’

  Practitioner to review

  Assess for commonly consumed foods and timing of symptoms

  Eliminate foods that are suspect

    *Provide patients with alternatives!*

**PHASE 2**

- Patient to keep a diet & symptom diary for at least 21 days

  Practitioner to review

  Reintroduce one eliminated food (continue to keep a food & symptom diary)

  Wait 3 days; Observe reactions

  *No reaction → introduce another eliminated food*

  *Reaction = Intolerance & should be eliminated long term*
Resources:

- NSW Government, Royal Prince Alfred Hospital Allergy Unit, available at:
Low Reactive Diet

- The low reactive diet can be used to assess the impact of common reactive foods in a variety of conditions including allergies and intolerances.

- The diet is designed to eliminate:
  - Cows milk products
  - Gluten
  - Yeasts and moulds
  - Phenols
  - Preservatives such as benzoates, metabisulphite, nitrites
  - Colouring agents tartrazine, erythrosine
  - Flavours such as MSG
  - Biologically active amines – histamine, serotonin, tyramine
  - Caffeine, chocolate, sugar
  - Alcohol
Low Reactive Diet

- **Meat, Fish, Poultry, Legumes**
  - **Allowed:** Red meats, beef, veal, chicken, lamb, turkey, all legumes (including whole Soya bean, dried peas, lentils), cold-water fish (salmon, halibut, cod, tuna, mackerel, trout etc..), processed soya products, soya sausage, soya burger, soya sauce, tempeh, tofu, tamari etc.
  - **Avoid:** Pork, eggs, processed meats: cold cuts, bacon, ham, sausage, frankfurters etc..

- **Dairy Products**
  - **Allowed:** Milk substitutes such as rice milk, nut milks, soya beverages - in moderation due to their high carbohydrate content. Dairy alternatives: soya yoghurt, soya cheese.
  - **Avoid:** Milk, yoghurt, cheese, ice cream, cream, non-dairy creamers. Coconut milk or cream.
Low Reactive Diet

- **Grains, starches, breads and cereals**
  - **Allowed:** Whole: grains, rice, buckwheat, millet, soya, amaranth, quinoa, tapioca, arrowroot, their flours and pastas. Potato flour and gluten-free products.
  - **Avoid:** All gluten containing products: wheat, rye, oats, barley, malt. Breads biscuits, crackers, pasta, cereals, etc., including gluten-containing pasta.

- **Soups**
  - **Allowed:** Clear, vegetable-based broth, Homemade vegetarian soups.
  - **Avoid:** Canned or creamed soups.

- **Vegetables**
  - **Allowed:** All vegetables, preferably fresh, frozen or freshly juiced.
  - **Avoid:** Canned, creamed or in casseroles. Pumpkin, squashes, baby marrow, sweet potato, corn, mushrooms.
Low Reactive Diet

- **Beverages**
  - **Allowed**: Pure water, ginger water, freshly prepared fruit or vegetable juices. Herbal teas (excluding citrus and strawberry).
  - **Avoid**: Chilled drinks, milk, coffee, tea, cocoa, alcoholic beverages, soft drinks, sweetened beverages, citrus drinks, and strawberry drinks.

- **Fruits**
  - **Allowed**: Unsweetened fresh, frozen, or water-packed canned fruits (excluding citrus and strawberry), mangoes, rock melon, peeled apples, peeled pears, lychees, paw paw, bananas.
  - **Avoid**: Commercial fruit packed in syrups, citrus fruits, strawberries, avocados and all dried fruit.

- **Sweeteners**
  - **Allowed**: Maple syrup - in moderation due to high carbohydrate content.
  - **Avoid**: Honey, raw/brown-white sugar, artificial sweeteners.
Low Reactive Diet

- **Fats, Oils and Nuts**
  - **Allowed:** Cold/expeller pressed, unrefined, light-shielded flax and walnut oil. Cook with sesame or olive oil. Seeds: sesame, sunflower, or flaxseed. Nuts: walnuts, pecans, and almonds.
  - **Avoid:** Margarine, shortening, unclarified butter, refined oils, coconut, peanuts, salad dressing and spreads.

- **Yeast and Moulds**
  - **Allowed:** All yeast free products, apple cider vinegar.
  - **Avoid:** All packaged and processed foods, refined sugars, all foods from a box, bottle or can, any foods containing yeast, cheeses, commercially prepared condiments, peanuts, vinegar, alcoholic beverages.
Nutritional Supplements
Dietary & Nutritional Prescription: *Prevention*

- Therapeutic objectives in Food Allergies and Intolerances:-
  1. Identify underlying foods and follow dietary advice
  2. Anti-inflammatory – inhibit arachidonic acid
  3. Immune regulation - Stabilise mast cells – anti-histamine
  4. Gut - Reduce reactivity of mucosal surface
    - Reduce gut permeability
  5. Support tissue function - Antioxidants – avert tissue injury
  6. Ensure microbiome health (especially in children)
## Main nutrients to consider

| **Quercetin** | Anti-inflammatory effect due to direct inhibition of several of the initial processes of inflammation, via interaction with calcium channels and/or calmodulin (the intra cellular calcium binding protein). Inhibits mast cell and basophil degranulation, neutrophil and monocyte lysosomal secretion, prostaglandin (most notably leukotriene) formation. Exerts potent antioxidant activity and vitamin C-sparing action. |
| **Probiotics** | 10-40 billion organism day | Adreno-corticoïd function; assist in regulating stress response. |
| **Glutamine** | 300-600mg/day | Down-regulates inflammatory mediators in the GIT by stimulating protective stress response in gut cells and reduces intestinal permeability. Reduces intestinal permeability and is involved in CuZn SOD. |
| **Zinc** | 10-40mg day | Adreno-corticoïd support, immune regulating, stabilise mast cells. |
| **Vitamin C** | 500mg-5,000mg day | Adreno-corticoïd support, immune regulating, stabilise mast cells. |
Anti-histamines and Corticosteroids
## Anti-histamines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Action</th>
<th>Side Effects</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihistamines</td>
<td>Reduces the histamine-induced vasodilation, blood vessel permeability, erythema and oedema. Used for Allergic rhinitis</td>
<td>Dry mouth, Drowsiness, Dizziness GIT symptoms, Blurred vision, confusion</td>
<td>None listed</td>
</tr>
</tbody>
</table>

(Braun & Cohen, 2010; Bryant & Knights, 2011)
# Topical corticosteroids

<table>
<thead>
<tr>
<th>Drug</th>
<th>Action</th>
<th>Side Effects</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topical Corticosteroids:</strong> hydrocortisone, methylprednisolone, betamethasone</td>
<td>Anti-inflammatory, antipruritic, immuno-suppressant action.</td>
<td>Skin atrophy, striae, burning, dryness, itching, loss of pigmentation, hirsutism, folliculitis. Proportion is systemically absorbed (dependent on the size of area and the frequency of application) which may result cortisol excess symptoms.</td>
<td><strong>Aloe vera:</strong> beneficial in combination. <strong>Green tea:</strong> concurrent consumption has presented with significant skin lesion healing <strong>Zinc &amp; Biotin:</strong> Co-administration of oral doses have seen reduced requirements for topical applications of corticosteroids.</td>
</tr>
</tbody>
</table>

(Stargrove et al, 2008, p.635; Bryant & Knight, 2011, p.862)
References


References


References


References


