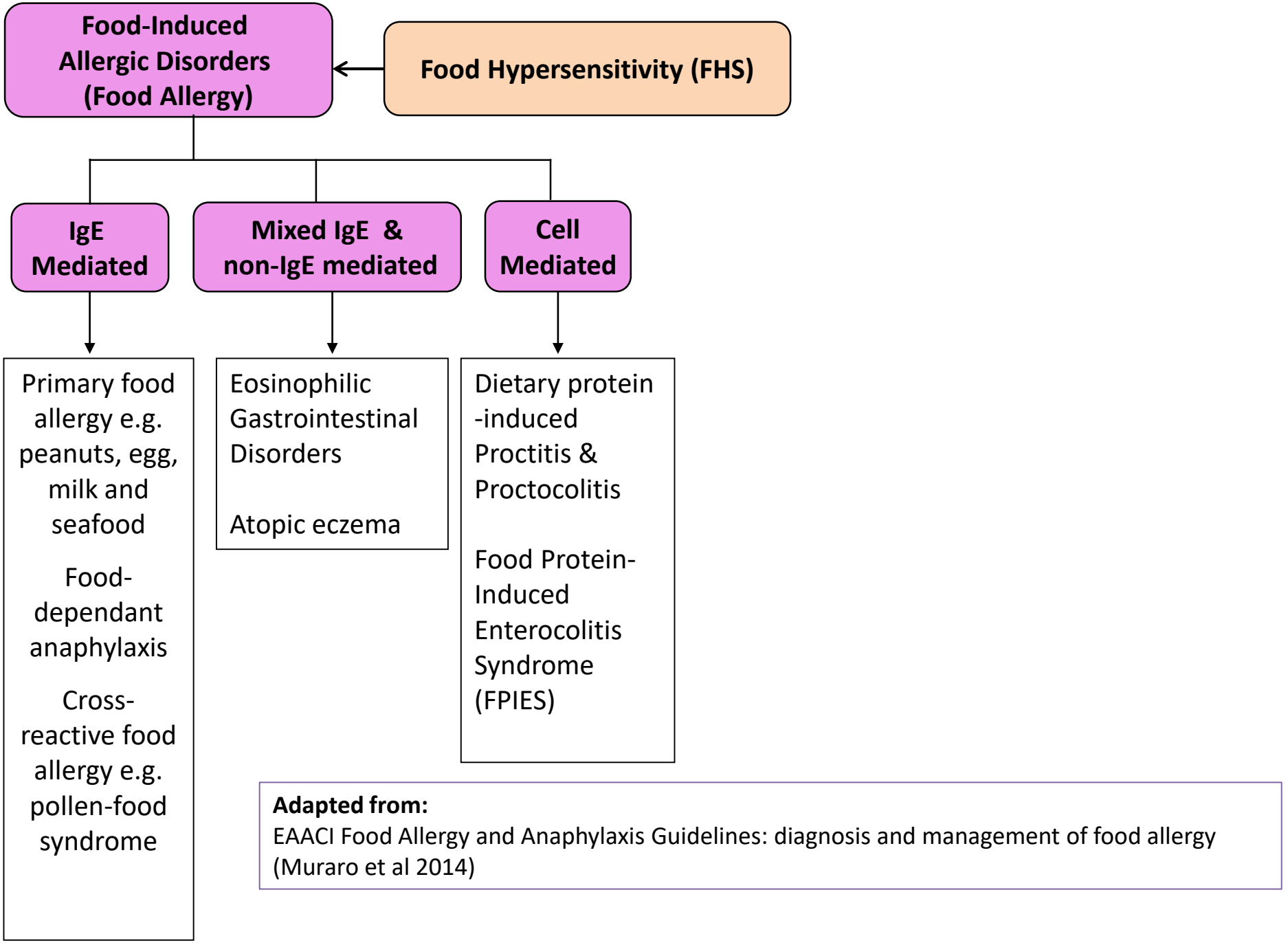
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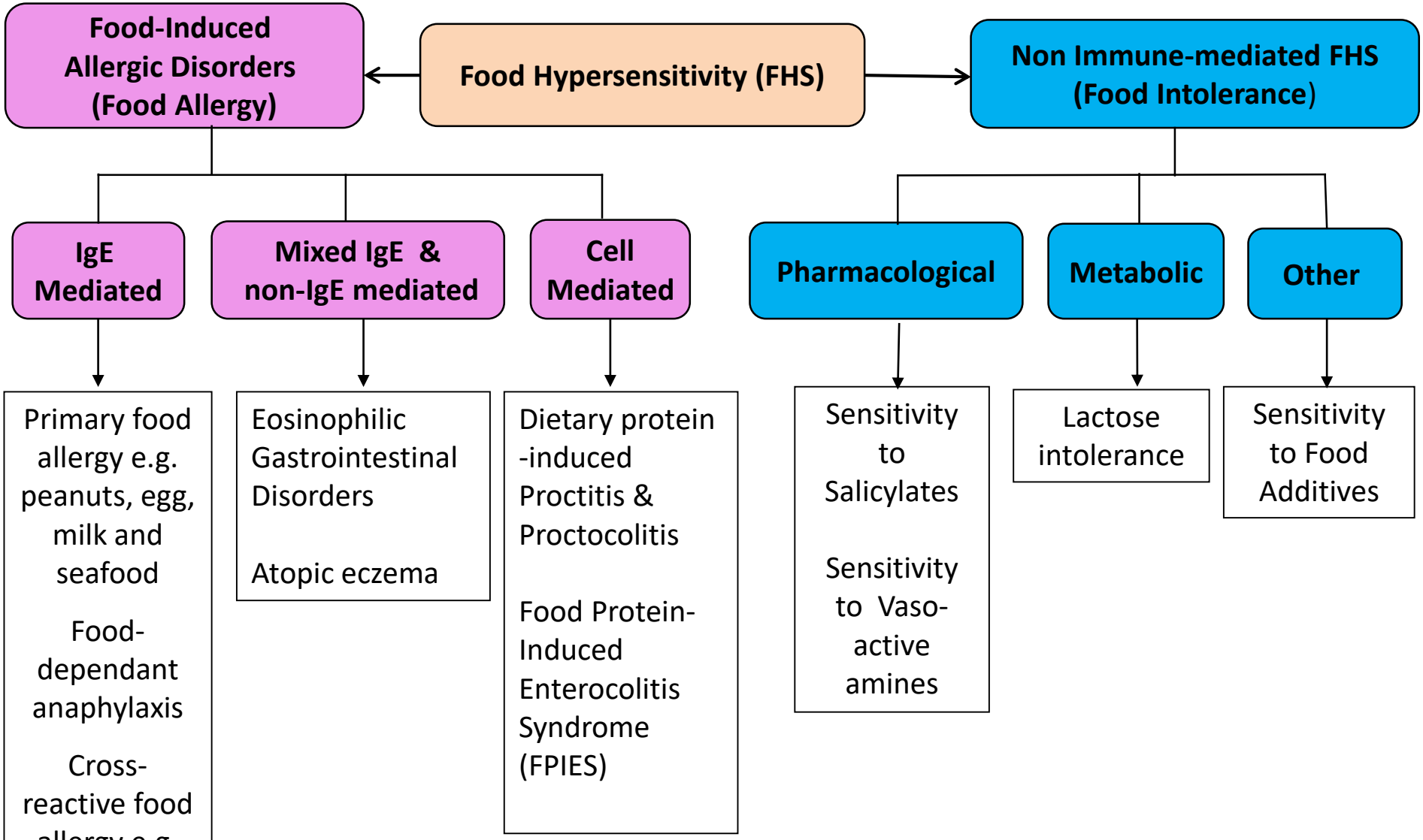
Royal Brompton & Harefield NHS Foundation Trust

Intolerance to food additives and natural food components – what is the evidence?

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Adapted from:
EAACI Food Allergy and Anaphylaxis Guidelines: diagnosis and management of food allergy (Muraro et al 2014)



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Guidelines for the Diagnosis and Management of Food Allergy in the United States (Boyce et al 2010)

Food Intolerance

Covers a broad spectrum of conditions

No validated tests

Complex presentation:

- Report multiple symptoms
- Often excluding many foods
- Usually seen other specialists
- Have reduced quality of life
- Often undertaken their own extensive research

Food Additives:

- Natural and artificial colourings
- Preservatives
- Flavour enhancers

Natural Food 'Chemicals':

- Vaso-active amines – histamine
- Salicylates

FOOD ADDITIVES

Artificial food colourings

Azo dyes - tartrazine (E102), Quinoline yellow (E104), Sunset Yellow (E110), Azorubine or Carmoisine (E122), Amaranth (E123), Ponceau 4R (E124) and Allura red (E129)

60-70% of all dyes used in food and textile manufacture

Tartrazine – linked to asthma but poor evidence (Juhlin et al 1972, Nettis et al 2003)

A diet free of additives could help in the treatment or prevention of hyperactivity in children (Feingold 1975)

Mix of sodium benzoate and food colourings including tartrazine shown to increase hyperactivity in some children (McCann et al 2007)

Natural Food Colourings

- **Cochineal** (E120) or carmine – manufactured using the female insect *Dactylopius coccus*
- Commercial carmine retains insect derived proteins which can cause IgE-mediated food allergy

- 26 year old MSc student
- Ate red velvet cupcake in café
- 30 minutes later developed itching on hands and feet, followed by orbital and facial swelling
- Eating eggs, milk, wheat
- Now avoiding all food colourings
- SPT in clinic positive to HDM (15mm) and cochineal (9mm)
- Diagnosis – cochineal allergy

Natural Food Colourings

- **Annatto** (E160b) - extracted from the seeds of *Bixa Orellana,* present in cheese, margarine, butter, smoked fish
- case report of a severe reaction to Gouda cheese precipitated by Annatto (Ebo et al Allergy 2009)
- **Turmeric** (E100) - extracted from *Curcurma longa*, (ginger family), present in curry powder, mustard and other foods
- Curcumin, the active ingredient in tumeric, has been reported to cause contact dermatitis

Food Preservatives – sulphites (E220-227

Control browning, reduce microbial spoilage, bleaching agent, control black spot in shrimps

- EU Maximum Permitted Level (MPL) - dried fruit 600-2000mg/kg, wine 200mg/litre and horseradish pulp 800mg/kg
- Acceptable Daily Intake (ADI) 0.7mg/kg: 40-60mg
- Typical daily intake 54.5mg including 20.2mg from wine (Manzi et al 1992)
- Up to 123mg/day could be consumed by adults – wine, dried fruit and salt fish (Leclercq et al 2000)

MPL	Fruit ,Vegetables & nuts	Sulphite (mg)
351	500ml cider	100
2000	5 dried apricots (40g)	80
2000	1 tablespoon sultanas (30g)	60
2000	3 prunes (30g)	60
450	1 meat burger (less than 100% meat)	45
2000	1 fig (20g)	40
300	1 small jar shrimps (100g)	30
210	1 standard glass white/rose wine (150 mls)	30
50	500ml beer	25
160	1 standard glass red wine (150 mls)	25
1000	10 slices dried banana (13g)	25
1000	1 tbsp candied/crystallised/glace fruit (25g)	25
200	1 portion dried salted fish (120g)	25
200	1 Quorn fillet (100g)	20
100	1 portion frozen chips/potatoes (165g)	17
162	Lemon or lime cordial (50mls)	13
164	1 glass grape juice (160mg)	11
800	1 sachet horseradish sauce (12g)	10

Does sensitivity to sulphites really exist?

- 250 cases of sulphite-related adverse effects in the USA in the 1980s (Yang and Purchase 1985)
- Predominant symptom is bronchoconstriction but has also caused anaphylaxis (Jamieson et al 1985)
- May affect up to 5% of asthmatics - range 3.9% to 8.4% if steroid-dependant (Buckley et al. 1985, Bush et al. 1986)
- Sulphites are the only food additive that has to be declared - Sulphur dioxide and sulphites at concentrations of more than 10mg/kg or 10mg/litre

Wine reaction = sulphite sensitivity?

- Added to control mildew in grapes and oxidation in the wine
- Champagne bottle fermented so less added sulphite
- 122/366 adult asthmatic subjects reported reactions to alcohol but no difference in asthmatic response to high and low sulphite wine (Vally et al 2000/2007)
- 43% subjects reporting reaction to white wine had positive DBPCFC to sodium metabisulphite capsules (Skypala et al unpublished)

Is asthma the only condition involved?

- Sulphites can cause urticaria and angio-oedema both through topical and/or ingested sulphite (Vally et al 2009)
- In Korea 2 phenotypes of sulphite sensitivity reported:

  66% - sulphite sensitive asthma

  33% sulphite-sensitive urticaria (Ban et al 2014)

- About 4% of contact dermatitis due to occupational exposure to sodium metabisulphite, but these patients can also have systemic symptoms (Madan et al 2007, Garcia Galvin et al 2012)
- Sulphites can non-specifically activate mast cells, releasing small amounts of histamine which can cause gut symptoms and soft stools

Diagnosing sulphite sensitivity

History – foods reported to provoke symptoms, time from ingestion to symptoms, presence or absence of asthma

Other tests – not validated

Oral Food Challenge – best method but not without risk

Materials

- Food - only 50% subjects with a confirmed sulphite sensitivity responded to a variety of sulphite foods – (Taylor et al 1988)
- Capsules or solutions of sodium/potassium metabisulphite (Bush et al 1986, Taylor et al 2003, Ban 2014)

Dosage

- 40mg sulphite precipitated reactions (Vally)
- Challenge dose 20mg and 50mg in capsules precipitated reactions (Skypala et al unpublished)

Beware the internet

- 54 year old male
- Reports that he has linked facial ezcemetous patches and extreme lethargy to eating high sulphite foods 24 hours previously
- Now avoiding most fruits/vegetables, also nuts, meat, shellfish, eggs, all alcohol and tap water
- Eating milk, fresh fish, chicken, rice, oats, apples, green beans, cucumber
- Dietary information has come from ‘Dr Google’
- Has unstable asthma
- Given correct food list and strongly advised to reintroduce foods not on the list
- Advised cannot challenge due to asthma

Benzoates (E210-219)

- Added to some foods to retard the growth of bacteria
- Occurs naturally in other foods e.g. cinnamon
- Parabens - esters of para-hydroxybenzoic acid – found in cosmetics and drugs

- Preserved salted fish 75.4 mg
- Cinnamon - 33.6 mg
- Soft drinks - 14.4 mg
- Ice cream 10.7 mg
- Cranberry 8.9 mg
- Jams 7.1 mg
- Soy sauce 5.1 mg
- Nutmeg 4.41 mg
- Dried apricots 3.04 mg

Campbell et al 2013

Link to Allergy?

- Allergic dermatitis - DBPCFC to a mixture of food additives including benzoates was negative (Wuthrich 1998, Van Bever and Stevens 1989, Park et al 2008)
- Asthma - only 2-4% of patients with asthma reacted on challenge and this was not reproducible on re-testing or on dietary exclusion (Weber et al 1979, Tarlo et al. 1981)
- Perennial rhinitis - 9% of subjects reacted on DBPCFC and improved on an additive-free diet (Pacor et al. 2004)
- Urticaria - 0.7-2% of those with chronic urticaria and angiooedema are reactive to sodium benzoate (Ortalani 1984, Nettis 2004, Di Lorenzo 2005)
- Oro-facial granulomatosis (a rare chronic granulomatous inflammatory disease of the lips, face and mouth) - 54-78% with this condition improved on a cinnamon and benzoate-free diet (White 2006, Campbell 2011)

Monosodium Glutamate (E621)

Flavour enhancer - savoury snacks, crisps, soups, stock, gravy, rubs, coatings, ready-meals, black bean sauce, oyster sauce, tomato sauce, marmite

Natural sources - Fish Sauce, Parmesan cheese, mushrooms, spinach, soy sauce, miso, ripe tomatoes, cured meat

Intake - 0.5g (USA) - 1.6g (Korea) -⅓ comes from added MSG

Does MSG provoke food intolerance?

- 2/130 responded to a large dose given without food, with no responses noted when MSG was given with food (Geha et al 2000)
- Most commonly reported symptom is pressure headache, paraesthesia, neuralgic-like pain in the neck and chest.
- More research needed before establishing cause and effect between MSG and migraine (Obayashi and Nagamura 2016)

Multiple food additive removal in chronic spontaneous urticaria– is it effective?

- ☐ 140 subjects went on a 3 week pseudoallergen-free diet
- ☐ Eliminated all processed food, artificial substances, food additives, dyes, antibiotics, preservatives, phenols, foods naturally rich in aromatic compounds, alcohol, spices and herbs, sweets, eggs, seafood, most fruits and vegetables
- ☐ 20 (14%) strong responders and 19 (19%) partial responders

Mageri et al Allergy 2010

- 100 patients challenged to 11 additives (tartrazine (FD&C Yellow 5), potassium metabisulfite, monosodium glutamate, aspartame, sodium benzoate, methyl paraben, butylated hydroxy anisole, butylated hydroxy toluene, FD&C Yellow 6, sodium nitrate, sodium nitrite)
- 2/100 had a positive urticarial response on single-blind challenge not reproducible on DBPCFC
- Sensitivity to any of the 11 food and drug additives occurs in fewer than 1% of patients

Rajan et al 2014

NATURAL FOOD CHEMICALS

Biogenic or vaso-active amines

- Histamine, beta-phenylethylamine, tyramine, tryptamine, putrescine, cadaverine, spermine and spermidine
- Produced during fermentation, storage or decay with variation in levels due to type of bacteria, food composition and conditions for fermentation (Bodmer et al 1999, Jansen 2003, Yang 2014)

	Gouda	Camembert	Emmenthal
Maintz & Novak 2007	Histamine 900mg/kg Tyramine 900mg/kg	Histamine 1000mg/kg Tyramine 4000mg/kg	Histamine 2500mg/kg Tyramine 700mg/kg

Fish and Alcohol

Fresh 2.6mg/kg, Frozen 5.8, Canned 3.1, Dried 104.0

Sea Bass - Fresh – 0.0,16 days old 0.0

Herring - Fresh 0.0, 16 days old 271.0

Tuna -Fresh/Canned 0.2/0.4 -Unspecified - 2,967

Choi et al 2007, Visciano et al 2012, Yesudhason et al 2013

Alcohol	Amines mg/L	Reference
Cider	5.94-8.42	Garai et al 2006
Red/white wine	287/162	Choi et al 2007
Red/white wine	10/30	Maintz and Novak 2007
French/Italian/Spanish wine	3.63/2.19/5.02	Bodmer et al 1999

Alcohol contains histamine, and Acetaldehyde, a by product of alcohol metabolism, can release histamine

Histamine Reactions

Scombroid poisoning - severe pseudo-allergic reactions usually caused by toxic levels of histamine in seafood due to bacterial conversion of histidine to histamine

- Normal plasma histamine concentrations 0.3 - 1ng/mL
- 1-2 ng/mL -increased gastric acid secretion and heart rate
- 3-5ng/mL - flushing, headache, urticaria, pruritus, tachycardia
- 7-12ng/mL - bronchospasm and 100ng/mL – cardiac arrest
- (Maintz and Novak 2007)

- ❖ Symptoms shortly after eating a meal of spiced fresh tuna fish; nausea, flushing profuse diarrhoea, throat swelling, tongue and lip tingling, headache and whole body pruritis
- ❖ 3 weeks later, lip tingling and a sensation of oral swelling when eating corn on the cob, next to a chicken with a spice rub (cinnamon, coriander, clove, pimiento, ginger and nutmeg) all of which were in tuna meal
- ❖ SPT/SIgE -ve tuna, cinnamon, coriander, clove, pimiento, ginger, nutmeg
- ❖ Eating canned tuna but avoiding sweetcorn, cinnamon and nutmeg
- ❖ Challenge negative to sweetcorn on the cob, nutmeg and cinnamon
- ❖ Likely diagnosis – scombroid poisoning – advised to avoid fresh tuna

Histamine Intolerance

Suggested 1% of the population might be affected - 80% of whom will be middle-aged (Missbuchler 2004)

Impaired histamine catabolism due to diamine oxidase (DAO) deficiency
BUT this causal link yet to be proven (Reese et al 2018)

Related to particular conditions?

Irritable Bowel Syndrome - 58% of IBS patients reported complaints after ingestion of histamine releasing food items or foods rich in biogenic amines (Smolinska 2013)

Non-coelic gluten sensitivity - intestinal and extra-intestinal symptoms similar to those in histamine intolerance (Schnedl et al 2018)

Chronic spontaneous urticaria - 2/157 patients improved on low histamine diet and had positive DBPCFC with histamine. Avoidance diets low in pseudo-allergens can improve urticaria symptoms, but probably not due to the absence of dietary histamine (Siebenhaar et al 2016)

Migraine - DAO activity from 137 migraine sufferers significantly lower than that obtained from 80 healthy volunteers, although 44% of controls also had low levels. One month of DAO supplementation showed a positive trend in the improvement of migraine (Izquierdo-Casas et al 2018)

Symptoms and Dose

- Migraine and headache
- Cutaneous - erythema, pruritus, flushing, urticaria
- Gastrointestinal - nausea, vomiting, flatulence, colic, diarrhoea
- Respiratory - nasal obstruction, rhinorrhoea, asthma
- Cardiac including arrhythmia
- Fatigue

- **36-250mg histamine (100g Emmenthal = 250mg) but reactions to 2.5mg reported (Malone et al 1986, Morrow et al 1991**
- **5/10 healthy volunteers challenged with 75mg histamine experienced immediate and delayed symptoms (Wöhrl et al 2004)**
- **39 patients reacted to 75mg liquid histamine although single symptoms were not reproducible in a placebo-controlled challenges (Komericki et al 2011)**

Diagnosis

DAO Levels

- Patients with typical symptoms had highly reduced serum DAO activity compared to controls (Mušič et al 2013, Manzotti et al 2016)
- BUT –DAO found in various tissues, but not in relevant quantities in the serum (Schwelberger et al 2013)

SPT with Histamine

Wheal size of a histamine SPT greater than 3mm, 50 minutes after test but doubt cast upon this method as not validated (Kofler et al 2011)

Urine/Stool Analysis

- Determination of histamine and methylhistamine in urine (Comas-Basté et al 2017)
- Methylhistamine levels affected by protein content of foods and histamine is a metabolite of intestinal bacteria, so found in stools (Keyser et al 1984, Reese et al 2018)

Determination of DAO levels or histamine in serum/ plasma or stools not recommended (Reese et al 2018)

Diagnosis and Management

- Diagnosis may be considered when >2 typical symptoms of histamine intolerance occur and improvement following a low histamine diet leads to resolution of symptoms with or without concomitant use of antihistamines (Raithel et al)
- 3 step dietary adjustment – diet and symptom diary +/- pragmatic use of H1/H2 receptor blockers (Reese et al 2018)

- Improvement - challenge with histamine 0.5mg/kg, 0.75mg/kg and 1.0mg/kg (Reese et al 2018)

Foods high in histamine

Fresh pork, cured meat e.g. ham, salami, pepperoni, game, bacon, sausages,, Fresh or canned tuna, canned sardines, anchovies, mackerel, salmon, herring, processed fish products (fish pastes, smoked, dried or pickled fish), fish sauce
Blue cheese, Parmesan, Brie, Camembert, Emmental, old Gouda, Cheddar cheese
Oranges bananas, tangerines, pineapple, grapes, strawberries
Tomatoes, pickled cabbage, aubergine, spinach, broad beans, peanuts, tree nuts,
Fermented soy products including miso and tempeh
Green tea, champagne, coffee, Cocoa, Chocolate, wine, beer, fresh fruit juices, smoothies,

What about medication?

Diamine Oxidase capsules

- Intake of Diamine oxidase capsules compared to placebo - significant reduction of total symptom scores (Komericki et al 2011)
- 20/54 had a reduction in symptoms and a significant increase in serum DAO activity values ($P < 0.0001$) when adopted histamine-free diet (Mušič et al 2013)
- 13/14 symptomatic subjects had mean DAO 7.04U/mL compared to 39.50U/mL in healthy controls, felt better when supplemented with DAO (Manzotti et al 2016)

Anti-Histamine Tablets

- No studies on the efficacy of H1 and H2 receptor blockers in patients but might work in the treatment of flushing (H1 blockers) or nausea/vomiting (H2 blockers) (Reese et al 2018)

A useful dietary intervention?

- 64 year old female patient developed flushing, itching, gut symptoms 20 minutes after eating
- She decided to cut out milk and dairy products as she thought symptoms due to lactose intolerance
- Worse after Italian foods (is still eating Parmesan cheese as low in lactose)
- Rash and flushing with alcohol
- Plan – 4 week avoidance of high histamine foods
- Result – feeling much better but diet very restricted
- Advised managing the diet by avoiding eating high histamine foods together
- Advised trying anti-histamine or diamine oxidase replacements if eating out or taking alcohol at home

Capsaicin

- Paprika, chili pepper and spices can cause non-specific gastritis, abdominal pain, diarrhoea or IBS exacerbation after 15-20 minutes
- Capsaicin intolerance causes numbness, paraesthesia, oral burning, flushing, abdominal cramps, or diarrhoea due to the activation of transient potential vanilloid 1 receptors (TRPV1) in the gut
- Single or intermittent capsaicin ingestion has been shown to worsen symptomatology in IBS patients
- Large doses desensitize the TRPV1, and may improve functional symptoms.
- (Esmaillzadeh 2013, Gonlachanvit et al 2009)

Salicylates

- White willow has a pain relieving effect
- 1828 – effect due to salicin, which is converted into salicylic acid during digestion
- 1853 – salicin extracted, oxidised and hydrolysed to make salicylic acid
- 1899 - acetyl salicylic acid was commercially launched and called aspirin

How does aspirin work?

- The enzyme cyclo-oxygenase (COX) enables the conversion of arachidonic acid to cyclic prostenoids which are further processed into prostaglandins
- There are two isoforms of COX: COX-1 is inhibited by Aspirin and COX-2 by Ibuprofen

Aspirin Hypersensitivity

- Prevalence 0.6% to 2.5%
- Increases to 4.3-11% in asthmatics
- Aspirin-sensitive asthmatics may also have nasal polyps - Samter's triad (Samter and Beers 1967)
- **Can salicylate in plant foods also provoke a reaction?**

- A nonspecific antigen-induced pseudo-allergic hypersensitivity reaction to salicylic acid, affects 2-7% of those with food allergy and IBS (Raithel et al 2005)
- 2.6mg of salicylate reported to elicit a 15% decrease in FEV1 in sensitive asthmatics (Corder and Buckley 1995)
- 2.5% of Europeans may have salicylate sensitivity (Baenkler 2008)
- **BUT - no published studies demonstrating efficacy of salicylate avoidance in gut disease or asthma (Dahlén et al1994, Gibson 2011, Barrett and Gibson 2012)**

Which foods contain salicylate?

Salicylates are found in a wide variety of plant foods

Average intake 10-200 mg/day (Swain et al1985) OR 0-5mg (Venema et al 1996)

One aspirin tablet contains 200-500mg of acetyl salicylate

First data published by Anne Swain in 1985 but UK and European studies have published very differing figures (Swain et al 1985, Venema et al 1996, Scotter et al 2007, Wood et al 2011)

Food	Portion size	Salicylic acid mg/kg Scotter/Swain
Lemon	20g	3.2 / 0.18
Currants	25g	<0.01 / 5.8
Tomato ketchup	12g	0.3 / 2.48
Dried Oregano	3g	26.0 / 66.0
Mixed Herbs	3g	22.3 / 55.6
Curry powder	3g	15.2 / 218.0
Coffee	1 mug	6.8 / 0.84
Tea	1 mug	1.06 / 5.57

Dietary Intervention

- Establish tolerance to aspirin and NSAIDS and review current diet and likely levels of salicylate
- 4 week trial of the avoidance of high salicylate foods and advice on cumulative effects of medium salicylate foods
- Remember salicylates may protect against certain cancers, especially colorectal cancer, so make sure you do not leave people on a low salicylate diet indefinitely (Raithel et al 2005)

Fruits	Granny Smith apples, cherries, strawberries, currants, raisins, kiwi, Gala melon, peaches and nectarines, raspberries
Vegetables, nuts, seeds and savoury snacks	Asparagus, sweet corn, raw tomatoes, tomato puree
Condiments & miscellaneous	Ginger, mixed herbs, mustard, oregano, curry powder, black pepper, cardamom pods, cinnamon, cumin, fenugreek, mint, nutmeg, paprika, rosemary, thyme, turmeric, liquorice, peppermint, Worcestershire sauce, honey, tomato ketchup
Drinks	Coffee, pineapple juice, cider, Benedictine liqueur, lemon tea, black tea, apple juice, cranberry juice, orange juice, tomato juice, fizzy drinks, Drambui liqueur, wine, rum

Mitchell and Skypala 2013, Skypala et al 2015

Are some foods high risk?

Food	Amine	Glutamate	Salicylate	Sulphite	Benzoate
Cheese	✓	✓			
Wine	✓		✓	✓	
Soy	✓	✓			✓
Tomatoes	✓	✓	✓		✓
Spinach	✓	✓			✓

Differential diagnosis

- Gut symptoms - Giardiasis, Helicobacter Pylori, Irritable Bowel Syndrome, inflammatory bowel disorders, coeliac disease, carbohydrate malabsorption
- Flushing - Neuroendocrine tumours - flushing
- Itching and rash – non-specific pruritis, chronic spontaneous urticaria +/- angioedema
- Swelling - Angioedema –ACE inhibitors, HAE or acquired C1-esterase deficiency secondary to lymphoma
- Systemic symptoms and a high level of tryptase - Mastocytosis characterised by excessive mast cells in one or more tissues,
- Throat tightness/obstruction - Laryngospasm/Vocal Cord Dysfunction
- Generalised non-specific symptoms – ME, psychosomatic reactions, eating disorders,
- **Food Allergy**

- **History +++++++**
- **Immune system:**
- Allergy (IgE) +/- IgG, IgM, IgA (infection, autoimmunity)
- Inflammatory markers (ESR, CRP)
- Complement C3, C4, C1 Esterase inhibitor, C1 Esterase functional
- **Gut symptoms:**
- Tissue Transglutaminase – Coeliac disease
- Hydrogen breath tests
- Stool cultures to exclude infections (Helicobacter Pylori, Giardiasis), and assess intestinal inflammation (calprotectin)
- **Other** - Liver and kidney function
- **Nutritional status – iron, vitamin D, Folate, B12**

Not a real food allergy?

- Additives and natural food components can induce severe symptoms including anaphylaxis
- Evidence for the efficacy of their removal from the diet is limited but does exist

- Careful history to exclude food allergy, a food allergy linked to a co-factor or a differential diagnosis
- Keep an open mind but don't over exclude foods
- Target the dietary intervention to match the symptoms and foods involved
- Placebo effect of dietary intervention has not been measured but probably significant

THANK YOU FOR LISTENING