“The Wind in the Willows”

Dr Ramesh J Kurukulaaratchy DM FRCP
(with apologies to Kenneth Grahame)

A Difficult Case

- Bradford Royal Infirmary.
- SpR asked to review a patient on the AMU as no one knows what is wrong with her.
- “AD”.
- 34 ♀ repeatedly admitted over past 6 months with “allergic reactions”.
- “I’ve not spent more than 10 days out of Hospital in that time”.

Presenting History… Allergic Reactions

- **Recurrent widespread itchy rashes – "welts".**
- **Intense sensation of body heat.**
- **Intermittent, increasingly frequent episodes of facial/tongue swelling.**
- **More recently associated throat closure & wheezing; sometimes abdo pain.**

- Worse with heat & pressure on the skin.
- Other triggers unclear -?? related to diet on some occasions.
- Tried changing washing powder, taking wheat & dairy produce out of diet, plus antihistamines.
- Getting worse – multiple admissions; frequent short courses of Oral Steroids [OCS].
- Admitted to ICU twice [not intubated] recently.

- **Referred to Clinical Immunologists at Leeds – diagnosed as CHRONIC IDIOPATHIC URTICARIA & ANGIOEDEMA.**

Some Background History

- No childhood asthma, eczema, food allergy or rhinitis.
- No family history of allergy either.
- No other significant medical problems.

- **Over past 10-years persistent RHINITIS with nasal congestion/intermittent sinusitis.**

- No seasonality to rhinitis.
- No obvious triggers for rhinitis.
- Nasal decongestant/antihistamine.

Some More Background History

- **Last 12 months also getting intermittent wheeze, chest tightness, SOB & cough.**
- **GP diagnosed ASTHMA & commenced on inhaled corticosteroid.**
- **Using salbutamol 2-3x/day, 1-2x nocturnal awakenings per week.**
- **x2 courses of OCS in past year for asthma.**

- Asthma triggers – LRTI's, strong fragrances, ? worse after certain foods.
- Smoker 10 pk-yrs.

Drug History

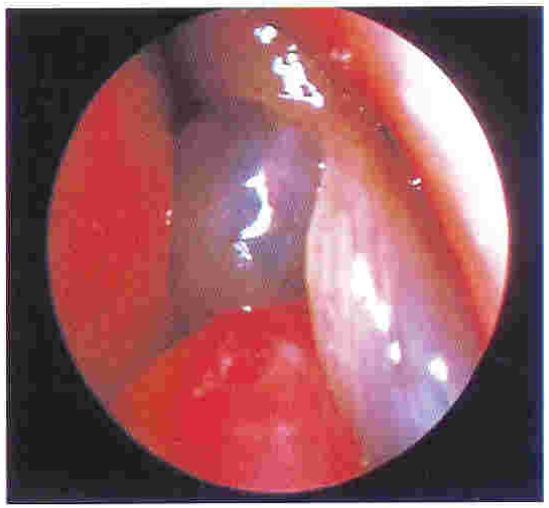
- Becloforte 250 2 puffs bd.
- Salbutamol 100 2 puffs prn.
- Nasal decongestant.
- Certirizine 10 mg od.
- Epipen as needed.
- No known drug allergies.
- (Has never taken NSAID's).

General Examination & Test Results

- Urticaria.
- Angioedema.
- Eosinophilia [0.9].
- Raised total IgE [130].
- **Negative specific IgE to common food & aeroallergens.**
- Normal Hb, U&E, LFT, TFT, Ig's, C3/4, CINH,ANA, & ANCA.

Respiratory Examination

- **Bilateral swollen nasal turbinates.**
- **Bilateral nasal polyps.**
- **Mild wheeze.**
- FEV1 72% predicted.
- FEV1/FVC = 65%.
- FEF25-75 = 43% predicted.
- PEF diurnal variability.
- 15% bronchodilator reversibility in FEV1.



Diagnosis

- Non-atopic difficult asthma.
- Non-atopic perennial rhinitis with polyps.
- Chronic urticaria & angioedema.
- **Underlying salicylate sensitivity.**

Management

- Add **LABA** [oxis turbohaler – 12 ucg bd].
- Add **Leukotriene Receptor Antagonist** [LTRA – Montelukast 10mg od].
- Add **Nasal Corticosteroid** [Flixonase 100ucg bd].
- Use **H1** [Fexofenadine]/**H2** [Ranitidine] antagonist combination.
- Simultaneously started on a **low salicylate diet**.

Progress

- Settled & went home.
- Asthma control markedly improved.
- Rhinosinusitis persistent.
- Urticaria & Angioedema continued but no longer associated with severe compromise.
- No Hospital admissions for 4 months.
- Went back to Clinical Immunology Clinic in Leeds.
- Salicylate sensitive diagnosis questioned, diet relaxed, & in view of sinusitis referred to ENT and advised to use analgesia for headaches in interim….

Progress

- Took ibuprofen at home.
- **Anaphylactoid reaction.**
- **Peri-arrest.**
- **Admitted to ICU.**
- Recovered.
- **Salicylate sensitivity diagnosis accepted.**
- **Diet resumed & NSAID's avoided.**

Progress over Subsequent Years

- Polypectomy – rhinitis much improved.
- Anaphylactoid episodes rare & urticaria/ angioedema relatively mild.
- Asthma ↑ problem.
- **Now on high dose ICS for increasingly difficult asthma – needed frequent courses of OCS.** ***[Step 4-5 BTS].***
- **2009 Started Omalizumab.**

Salicylate Sensitivity

Salicylate Sensitivity

- What are Salicylates?
- A Brief History of Aspirin.
- Mechanism of Aspirin Activity & Sensitivity.
- Salicylate Exposures.
- **Clinical Features of Salicylate Sensitivity.**
- **Recognising Salicylate Sensitivity.**
- **Treating Salicylate Sensitivity.**

What are Salicylates?

- **Salicin [salicyl alcohol] is a signalling molecule found in plants.**
- Many plant-derived foods contain salicin.
- Salicin possesses a spectrum of biological properties including anti-inflammatory activity.
- Salicin containing herbal preparations were used as anti-inflammatory agents for millennia.
- More recently refined salicin derived medications have been developed for clinical use.

A Brief History of Aspirin

- **Hippocrates: 400 BC**

Used willow bark & leaves (rich in salicin) to treat pain/fever.

- **Raffaele Piria: 1838**

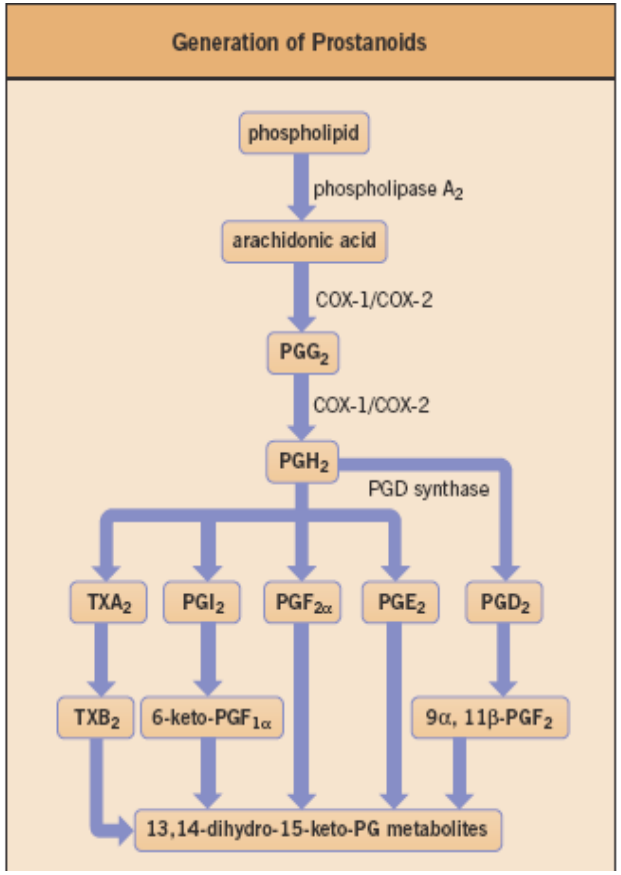
Synthesised salicylic acid from salicin.

- **Felix Hoffman: 1897**

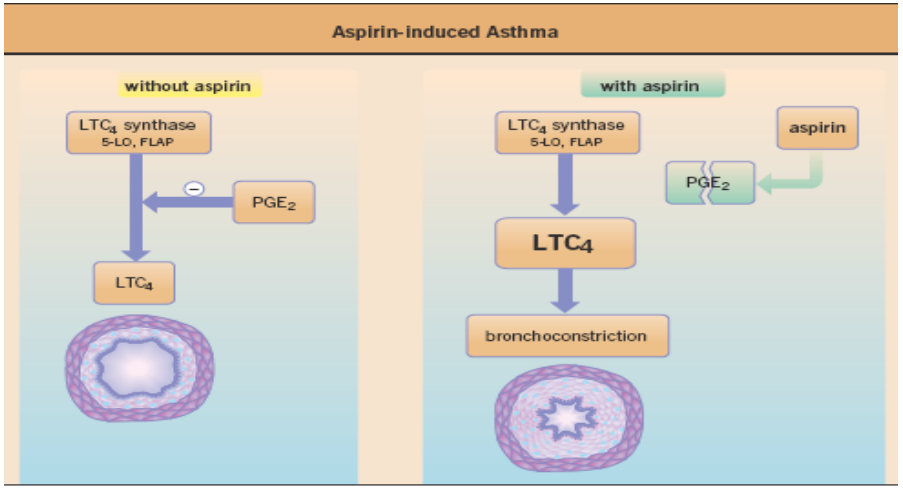
Created acetylsalicylic acid [aspirin] as a refined anti-inflammatory drug.

Mechanism of Aspirin Activity

- Prostanoids synthesised from arachidonic acid.
- Cellular messengers.
- Synthesis catalysed by cyclooxygenases [COX-1 & COX-2].
- Downstream production of bioactive prostaglandins [TXA_2, PGD_2, PGE_2, PGI_2, $PGF_{2\alpha}$].
- PGD_2 & TXA_2 particularly relevant to allergic inflammation.
- PGE2 regulates leukotriene synthesis.
- **Aspirin blocks COX activity.**



Mechanism of Aspirin Sensitivity



Holgate, Church and Lichtenstein: Allergy 3rd edition © 2006 Elsevier Ltd

Aspirin Causes: "block or shunt" through COX inhibition

- **BLOCK:** ↓ production of PGE2/release of "brake" on leukotriene synthesis.
- **SHUNT:** Switch in arachidonic acid metabolism from Prostanoid to leukotriene synthesis.
- **Leukotriene synthesis** ↑ → bronchoconstriction.

Salicylate Exposures

- **Plant Derived Foods:** Fruit, Vegetables, Nuts, Cereals, Drinks. Highest in skin, near surface of food.
- **Medications/ Ingredients:** Aspirin, diclofenac, ibuprofen, naproxen, indomethacin, salicylic acid, magnesium salicylate, menthol, mint, oil of wintergreen.

- **Flavoured Products:** Chewing gum, toothpaste, mouthwash, lozenges.
- **Cross Reacting Substances:** Benzoates, azo-dyes, ? prednisolone, ?hydrocortisone & succinate salts of cortisone.

Samter's Triad:
Aspirin Sensitive Asthma

- **Widal (1922):**

Identified the first case of aspirin sensitivity, rhinitis with nasal polyps, and asthma.

- **Samter & Beers (1967):**

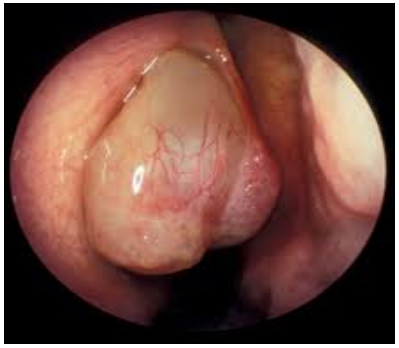
Characterised the "aspirin triad" of above clinical features.

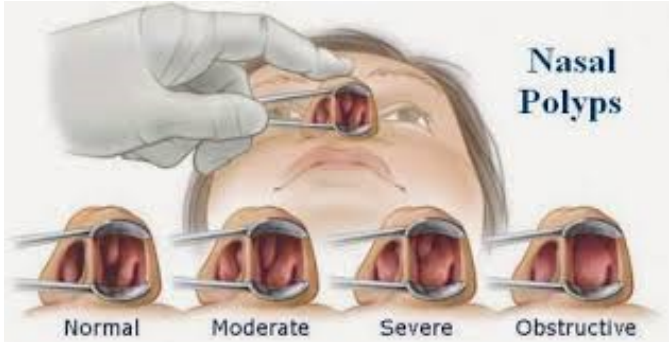
Identified as a "non-immunological" disease.

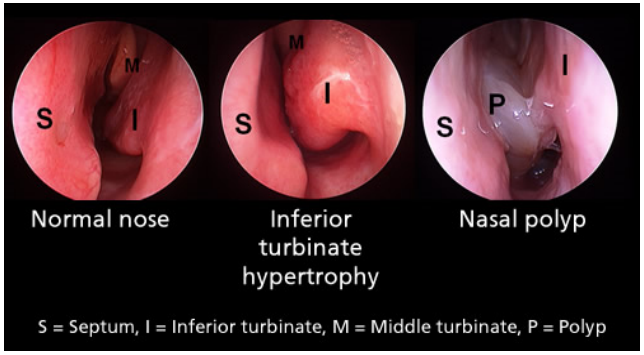
Samter M, Beers RF. Concerning the nature of intolerance to aspirin. J Allergy 1967; 40: 281-93.

Natural History of Aspirin Sensitivity

- Initial watery rhinitis (onset after viral URTI).
- Increasingly chronic nasal congestion, sinusitis, anosmia, nasal polyps.







Natural History of Aspirin Sensitivity

- Development of increasingly treatment dependent asthma.
- Development of "idiopathic" urticaria & angioedema.
- Apparent food related worsening [acute/delayed].
- Development of acute reactions on NSAID exposure Progression rate variable [months→years].
- **Adverse drug reactions usually years after onset of respiratory disease.**
- **Can be FATAL.**

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CASE REPORT

Recognising the risk of aspirin-sensitive respiratory disease in a patient with asthma who has previously tolerated aspirin

Damita Abayaratne[a], *Ramesh J Kurukulaaratchy[b,c]

Clinical Features of Salicylate Sensitive Asthma

- Occurs in ~ 5% of all asthmatics.
- Seen in ~ 30-40% “severe asthmatics”.
- *Under diagnosed* by history; aspirin challenges identify higher prevalence.
- ♀>♂.
- Onset 3rd-4th decade.
- Non-atopic.
- May develop earlier in atopic subjects.
- ?Genetic basis: HLA-DQW2.
- ?Association with infection.

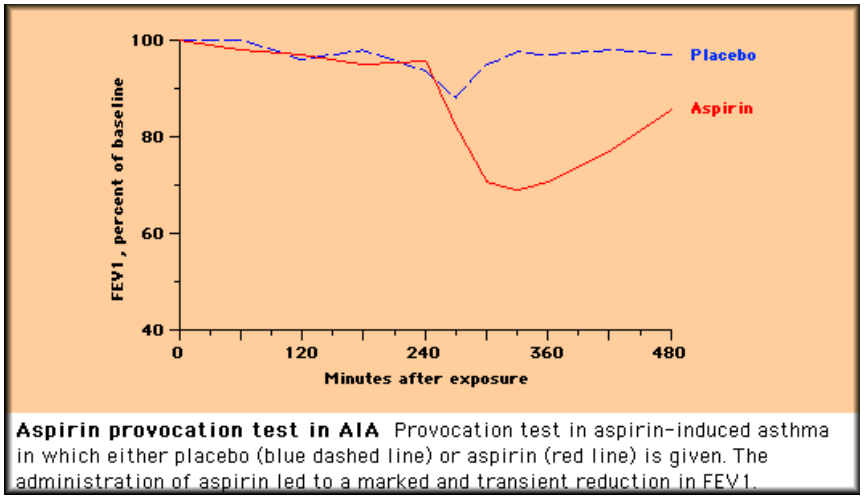
Diagnosing Salicylate Sensitive Disease

- **Clinical diagnosis.**
- **No simple diagnostic test.**
- **Challenge procedures:**

  Oral.

  Nasal.

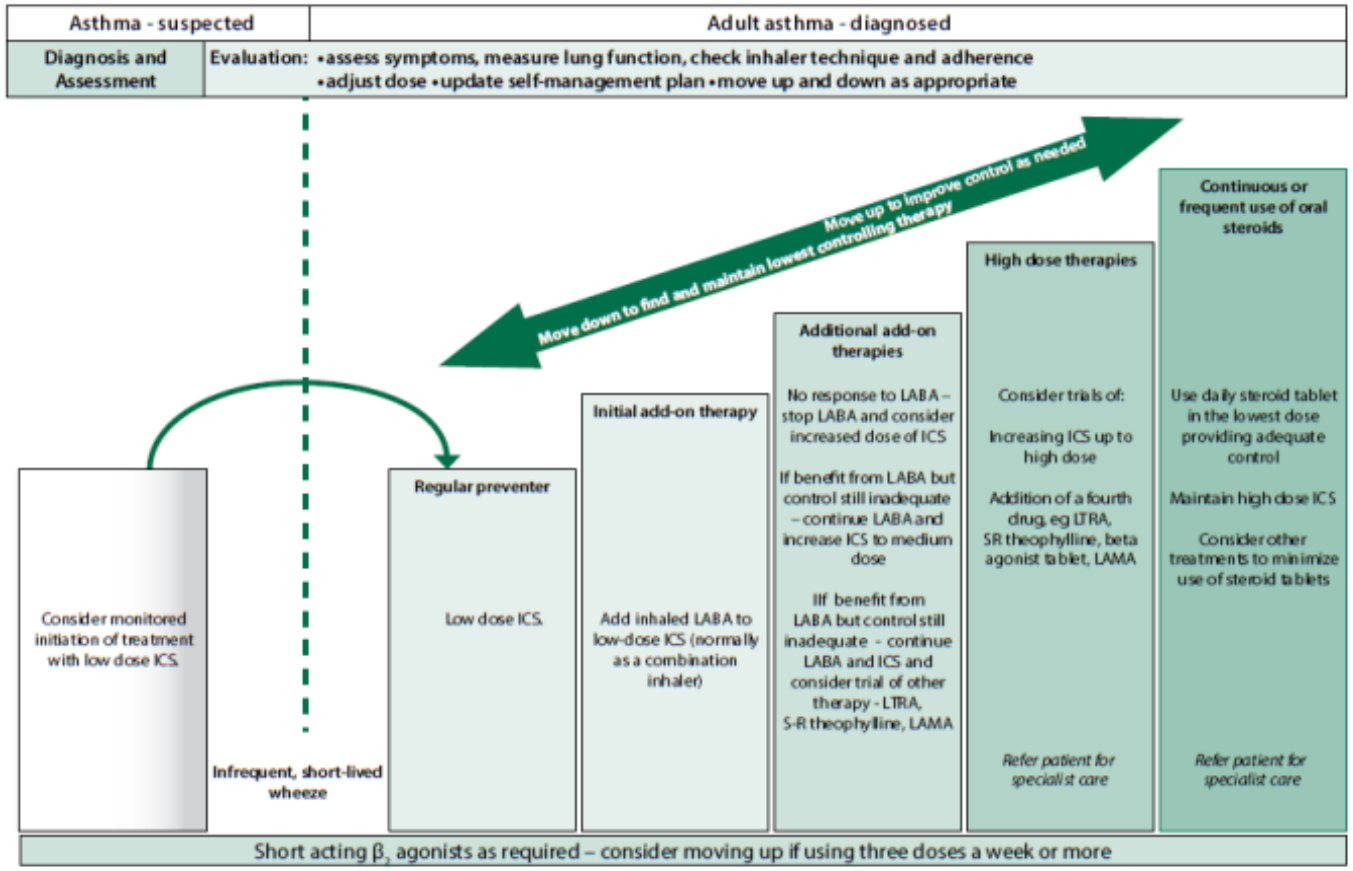
  Inhalation.



Aspirin provocation test in AIA Provocation test in aspirin-induced asthma in which either placebo (blue dashed line) or aspirin (red line) is given. The administration of aspirin led to a marked and transient reduction in FEV1.

Standard Treatment

- **Asthma: As per chronic asthma [ICS, LABA] with emphasis on also including LTRA in regime. Often oral steroid dependent.**
- **Rhinitis: Nasal steroids +/- surgery.**
- **Urticaria & Angioedema: Antihistamines.**
- **Novel Strategies: Doxycycline, Omega-3-fish oils & desensitisation.**
- **CONSIDER EPIPENS.**
- **Dietary Trial: 4/52 trial of avoidance followed by relaxation to assess impact. Dietetic guidance invaluable.**


Asthma - suspected
Adult asthma - diagnosed
Diagnosis and Assessment
Evaluation: •assess symptoms, measure lung function, check inhaler technique and adherence •adjust dose •update self-management plan •move up and down as appropriate
Move up to improve control as needed
Move down to find and maintain lowest controlling therapy
Consider monitored initiation of treatment with low dose ICS.
Infrequent, short-lived wheeze
Regular preventer
Low dose ICS.
Initial add-on therapy
Add inhaled LABA to low-dose ICS (normally as a combination inhaler)
Additional add-on therapies
No response to LABA – stop LABA and consider increased dose of ICS
If benefit from LABA but control still inadequate – continue LABA and increase ICS to medium dose
IIf benefit from LABA but control still inadequate - continue LABA and ICS and consider trial of other therapy - LTRA, S-R theophylline, LAMA
High dose therapies
Consider trials of:
Increasing ICS up to high dose
Addition of a fourth drug, eg LTRA, SR theophylline, beta agonist tablet, LAMA
Refer patient for specialist care
Continuous or frequent use of oral steroids
Use daily steroid tablet in the lowest dose providing adequate control
Maintain high dose ICS
Consider other treatments to minimize use of steroid tablets
Refer patient for specialist care
Short acting β2 agonists as required – consider moving up if using three doses a week or more

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Novel Treatments

- **Omega-3 –Fish Oils:**

  Augments anti-inflammatory activities on leukotriene mediated pathways?

  Maximum of 10 x 1000mg capsules a day!

- **Doxycycline:**

  Patients with nasal polyps show increased **staphylococcal nasal colonisation.**

  Staph. Enterotoxins can act as a *superantigen* for local IgE production with ↑IL-5, and eosinophilia.

  Perpetuates local inflammation.

  ? Both secondary & direct effects on lower airways.

  Doxycycline 100-200mg bd for 3 month trial.

Aspirin Desensitisation

- Sensitive patients show “Refractory period” for 2-5 days after aspirin ingestion.
- Opportunity for desensitisation?
- Under medical supervision as an inpatient.
- Significant risk of adverse reaction.
- Where benefits outweigh risks (eg coronary artery disease).
- **Pretreat with OCS & LTRA for ≥ 48 hours.**
- **Varying dosing schedules.**
- **Administer incrementally increasing doses of aspirin at 2 hourly intervals over 2-3 days to a final dose of 325mg.**
- **Then take aspirin 325mg od long-term.**
- **Maximum dosing interval of 48 hours.**
- **Complete sensitivity returns within 7 days of last dose.**
- 67% show improvement in rhinitis.
- Can give significant ↑in asthma control.

?Role for Biologics

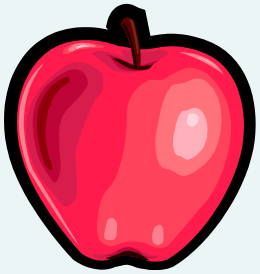
- These patients often have OCS dependent poorly controlled asthma.
- Anti-IgE (Omalizumab)?
- Anti-IL5 (Mepolizumab/Reslizumab)?

Is Diet Relevant to Aspirin Sensitive Patients?

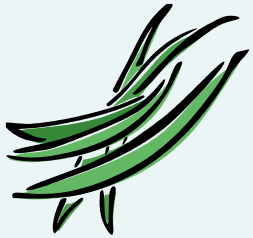
- Considerable debate.
- Several studies have quantified salicylate content in foods; variable findings.
- Consistently highest foods include herbs, spices, & loose leaf tea.
- Food related reactions often seem dose-dependent.
- 2.6mg salicylate mean intake invoking a 15% in ↓FEV1 in aspirin sensitive asthmatics.

Food sources of salicylate - fruit

Low Salicylate	Medium Salicylate	High Salicylate
Apples – golden delicious Figs – fresh Kiwi Pear – peeled Pomegranate	Apples – red Avocado Banana Lychee Mandarin Mango Papaya/pawpaw Passionfruit Peach Watermelon	Apples—green Apricot All Berries Cherry Currants Grapefruit Grapes Guava Lemon Loganberry Nectarine Orange Peach Pineapple Plum Prunes Raisins and Sultanas Rhubarb Tangerines



Food sources of salicylate - vegetables

Low Salicylate	Medium Salicylate	High Salicylate
Bamboo shoots	Beetroot	Alfalfa sprouts
Bean sprouts	Broccoli	Artichoke
Brussels sprouts	Carrot (cooked)	Aubergine
Cabbage	Chinese leaves	Broad beans
Cauliflower	Lettuce (other)	Carrot (raw)
Celery	Mange tout	Chicory
Green beans	Marrow	Chilli peppers
Leek	Parsnip	Courgette
Lettuce: iceberg	Potato (new)	Cucumber
Onion	Pumpkin	Endive
Potato peeled	Snow peas	Gherkins
Pulses (lentils, chick peas etc.)	Spinach	Mushrooms
Swede	Sweetcorn	Okra
Turnip	Sweet potato	Olives
	Turnip	Peas
		Peppers
		Radishes
		Tomatoes
		Water chestnut
		

Food Sources of Salicylates

- **Nuts and Snacks:**
  - Almonds.
  - Peanuts.
  - Water chestnut.
  - Flavoured crisps/snacks.
  - Muesli/cereal bars.

- **Sweets:**
  - Chewing gum.
  - Honey.
  - Jams.
  - Liquorice.
  - Marmalade.
  - Mint flavoured sweets.

Food Sources of Salicylates

- **Drinks:**
  - Coloured fizzy drinks.
  - Fruit cordials, Fruit squashes, Fruit juices.
  - Peppermint tea, Camomile tea, Tea.
  - Champagne, Liqueurs, Port, Rum, Sherry, Wines.
  - Can have Gin & Tonic, Vodka, Whisky

- **Herbs and Spices:**
  - Large amounts of all herbs and spices.

- **Fats and oils:**
  - Coconut oil.
  - Creamed coconut.
  - Olive oil.

Low Salicylate Foods

- All fresh meat, fish, shellfish, poultry, eggs, dairy produce (milk, butter, plain yoghurts and cheese), plain cereals and breads are low in salicylates and may be eaten in normal amounts.

SUMMARY

- **Aspirin/Salicylate sensitivity may be a cryptic diagnosis.**
- **Not unusual in difficult asthma/rhinitis.**
- **Consider if associated urticaria & angioedema +/- possible food related reactions.**
- **Often signals a difficult disease.**
- **Several useful/novel therapeutic options.**