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Allergy

Antony Aston ***(Paediatric Allergy Consultant)***

GP Update Course – Royal London

Milk madness?

- Lactose intolerance
- IgE cow's milk allergy
- Non-IgE cow's milk allergy
- Or <u>not</u>

Common food allergies in childhood

- Peanuts
- Tree nuts
- Fish
- Shellfish
- Cow's milk
- Soya
- Egg
- Wheat

90%
of food allergic reactions caused by these
8
foods

Increase in anaphylaxis-related hospitalizations but no increase in fatalities: An analysis of United Kingdom national anaphylaxis data, 1992-2012
Turner, Paul J. et al. Journal of Allergy and Clinical Immunology , Volume 135 , Issue 4 , 956 - 963.e1

Systems/Symptoms

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Gastroenterology

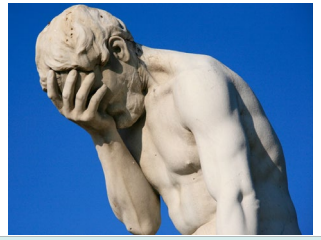
- Pallor / tiredness
- Oral itching
- Angioedema of the lips tongue and palate
- Nausea
- Vomiting
- Reflux
- Food refusal/aversion
- Abdominal pain
- Colic
- Perianal redness
- Diarrhoea
- Constipation
- Flatus
- Blood/mucus in stool

Dermatology

- Eczema
- Erythema
- Itching
- Urticaria
- Angioedema

Respiratory

- Nasal itching
- Sneezing
- rhinorrhoea or congestion
- Cough
- Chest tightness
- Wheezing
- Shortness of breath



Definitions

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- **Intolerance:**
  - difficulty digesting a particular food resulting in physical symptoms (**not generated by the immune system**)
  - nothing to do with eczema
  - nothing to do with respiratory problems

Lactose intolerance

- **Primary:**
  - most common
  - lactase production falls off sharply by *adulthood*
- **Secondary:**
  - decreases lactase production after an *illness*, *injury* or *surgery* involving your small intestine
- **Congenital:**
  - *rare* (most common in Finland - 1 in 60,000)
  - gene defect
  - complete absence of lactase in the child

Definitions

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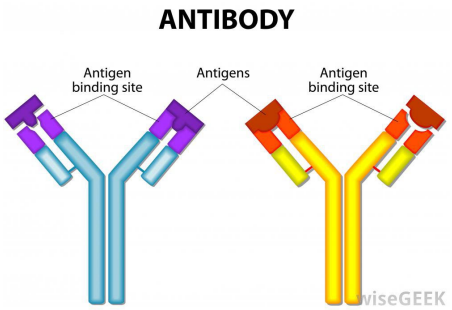
- ***Food allergy*:**
  - **hypersensitivity reaction to a food** via by immunological mechanisms

Definitions

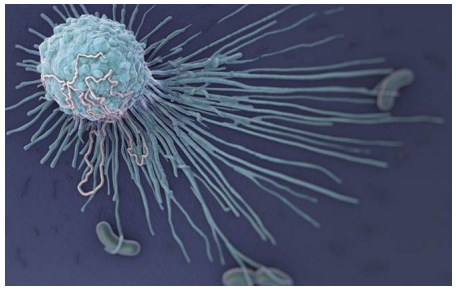
- ***Cow's milk protein allergy (CMPA)*:**
  - **hypersensitivity reaction to a cow's milk protein** via by immunological mechanisms

IgE mediated



Non-IgE mediated

CELL



IgE mediated reaction

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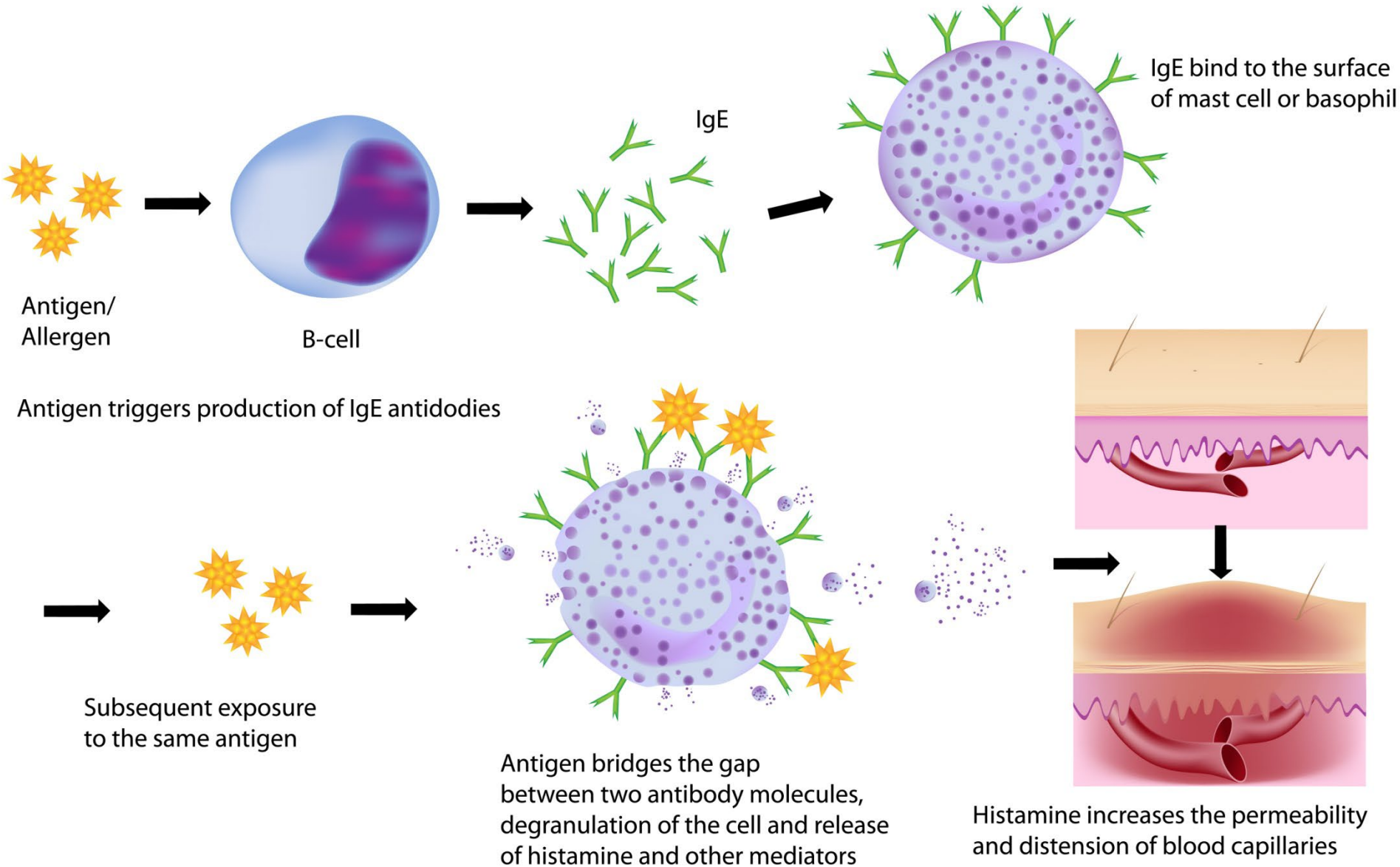

IgE mediated reaction

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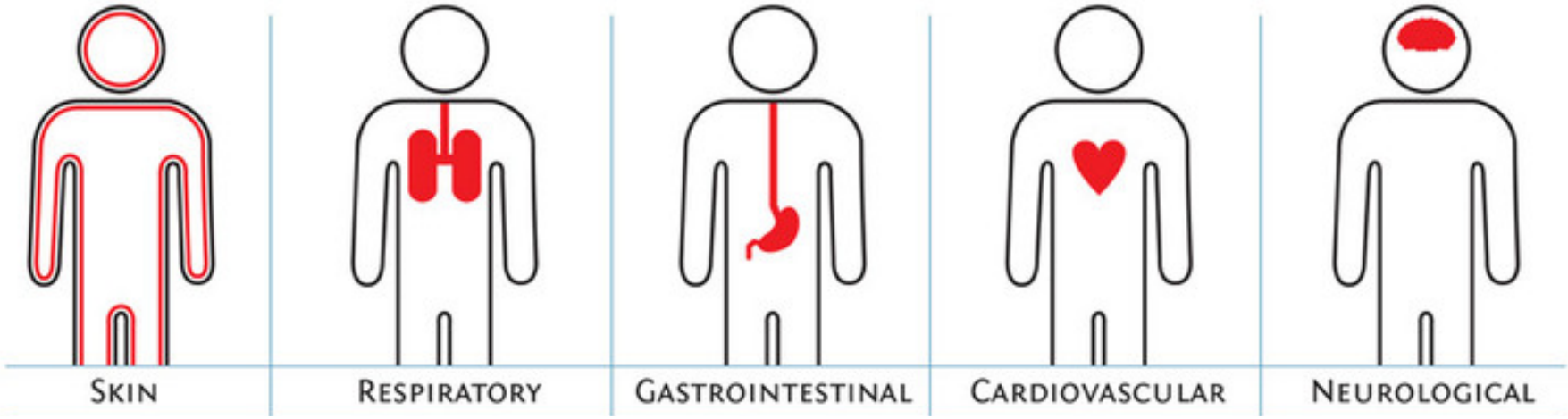

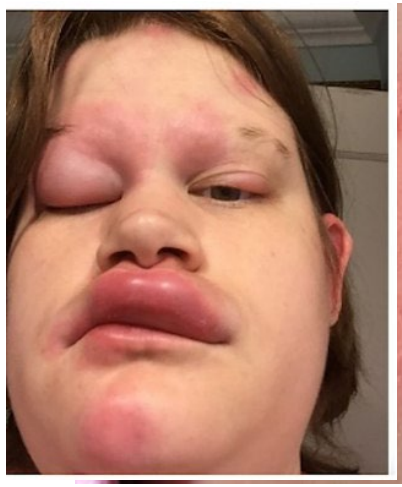

*** *Single or Multi-system reaction* ***

Non-IgE mediated reaction

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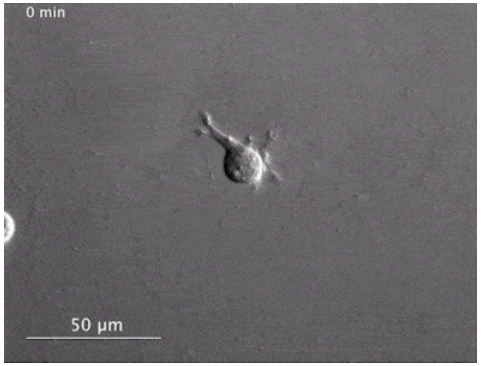

- Cell-mediated reaction (type IV hypersensitivity)
- Slow (at least > 3-4 hours after exposure)
- Different symptoms compared to IgE reactions as histamine not involved

Non-IgE mediated allergy ?

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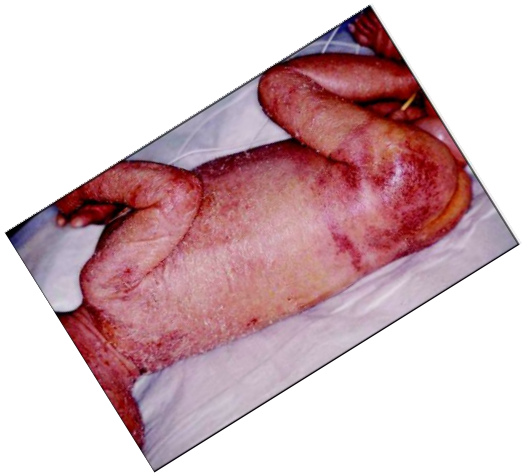
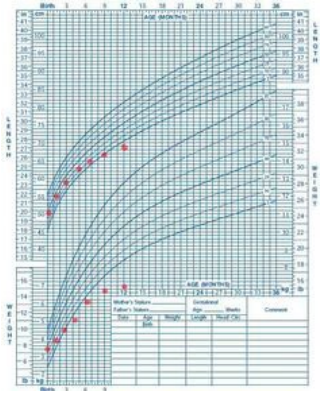
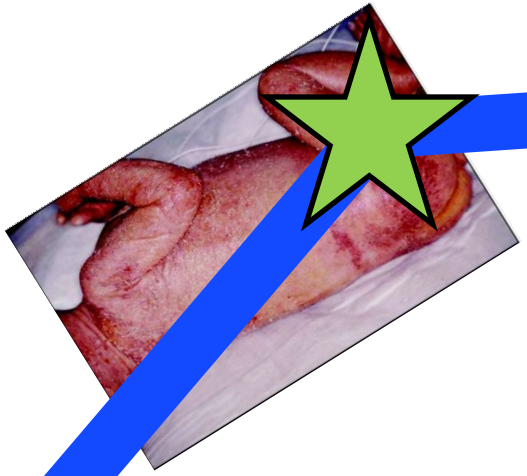
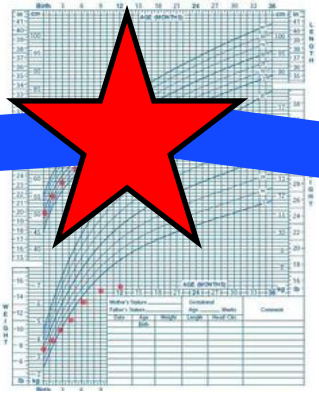
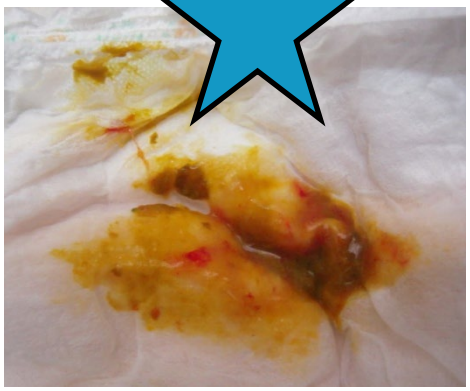




Non-IgE mediated allergy

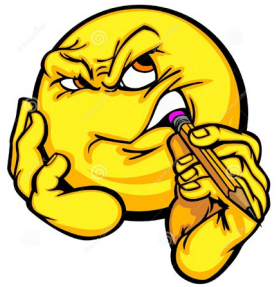






More likely if several symptoms present

History is essential



"I already diagnosed myself on the Internet.
I'm only here for a second opinion."

Conditions & Symptoms

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IgE mediated	Non-IgE mediated
Itching	
Diarrhoea	
Abdominal pain/Colic	
Vomiting	
Anaphylaxis	Faltering growth
Acute rhinitis/conjunctivitis	Blood/mucus in stool
Angioedema	Constipation
Urticaria	Food aversion
	Eczema

Conditions & Symptoms

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IgE mediated	Non-IgE mediated
	Itching Diarrhoea Abdominal pain/Colic Vomiting
Anaphylaxis Acute rhinitis/conjunctivitis Angioedema Urticaria	Faltering growth Blood/mucus in stool Constipation Food aversion Eczema

History is essential

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Skin

IgE- mediated	Non-IgE-mediated
Pruritus	Pruritus
Erythema	Erythema

mins

> 2 hours

BUT……

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Skin

IgE- mediated	Non-IgE-mediated
Pruritus	Pruritus
Erythema	Erythema

Continuously eating an allergic food will produce constant symptoms

BUT……

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Skin

IgE- mediated	Non-IgE-mediated
Acute urticaria – localised or generalised	Atopic eczema
Acute angioedema – most commonly of the lips, face and around the eyes	

IgE reactions can also exacerbate existing eczema

What this is not

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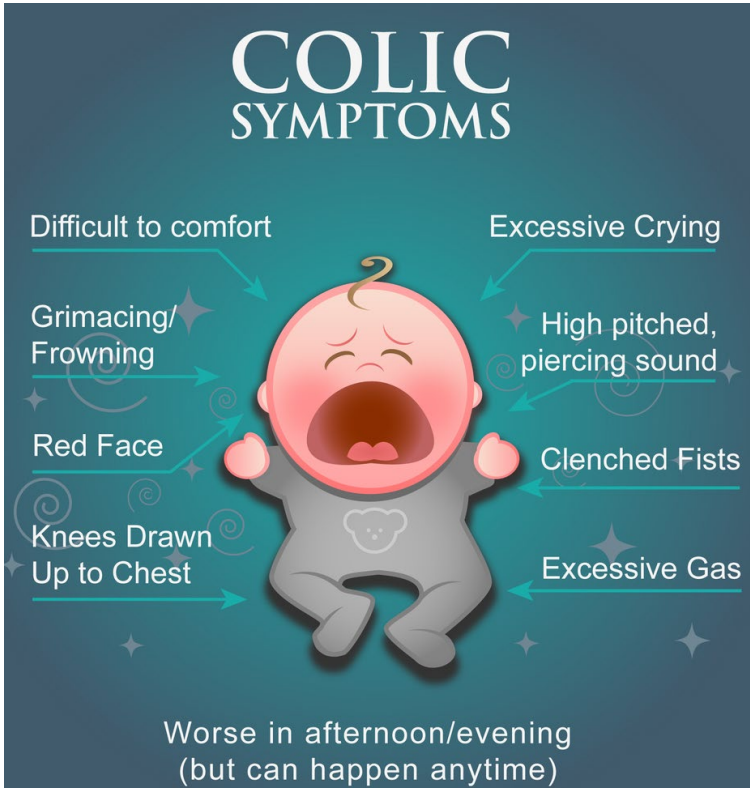
Not the diagnosis or answer to all complaints of **colic** or **reflux**



These can be part of the differential

You can test by ***appropriate*** dietary exclusion BUT…….

What this is not

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BUT -

beware of this leading to wide ranging unnecessary restriction of maternal and/or baby's diet

(no evidence base)

AND -

like a trial of a medication

if exclusion doesn't work stop and reassess

(non-IgE - 2 week minimum and up to 4-6 weeks for a trial)

Remember:

Reflux can improve with solids

Birth | 1 m | 2 m | 3m | 4 m | 5 m | 6 m

Reducing colic numbers

Lactose intolerance tests

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- Hydrogen breath test
- Lactose tolerance test (bloods after consuming lactose)
- Stool sugar chromatography
- Stool acidity
- Small bowel biopsy

Lactose intolerance tests

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Exclusion

Most feasible and accessible test

Exclusion – *diagnosis & treatment*

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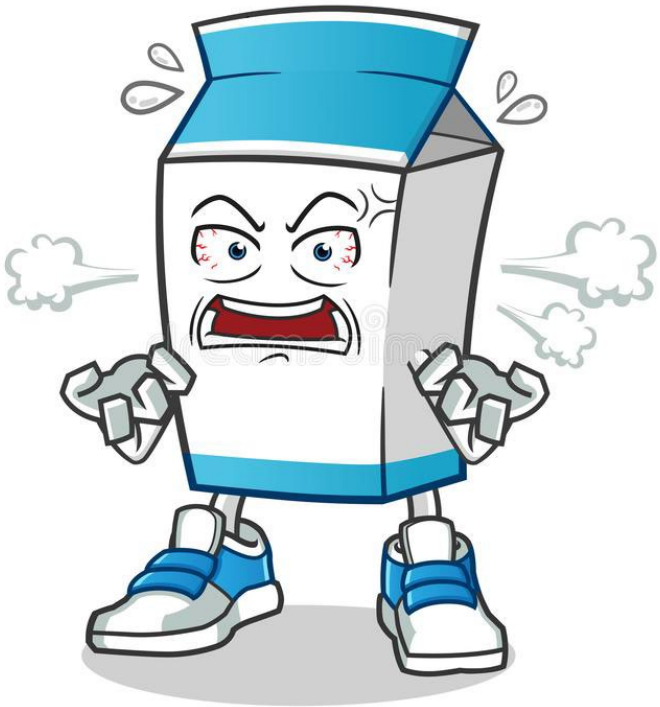
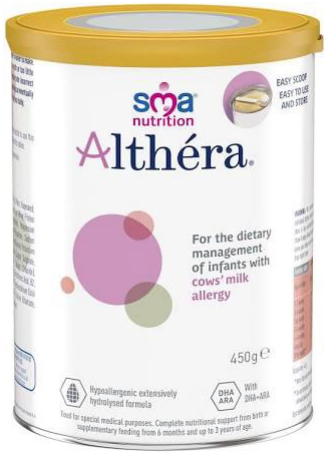
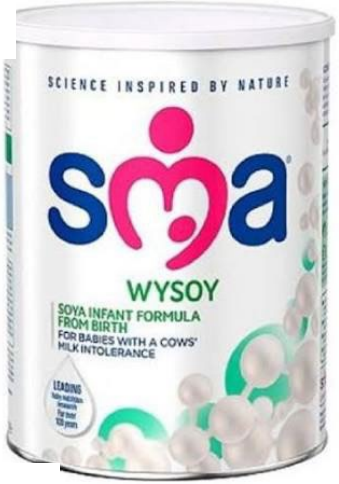


Know your milks





Soy formula

- Not recommended < 6 months *(phytoestrogen)*
- Up to 50% non-IgE CMPA also allergic to soy

  (10-14% in IgE mediated CMPA)

BDA Position Statement, 2010

Animal milks:

- Many have very similar proteins

  (e.g. goat milk protein has 92% homology to cow's milk)

- Lactose-free products still have milk protein

Prescribed milks

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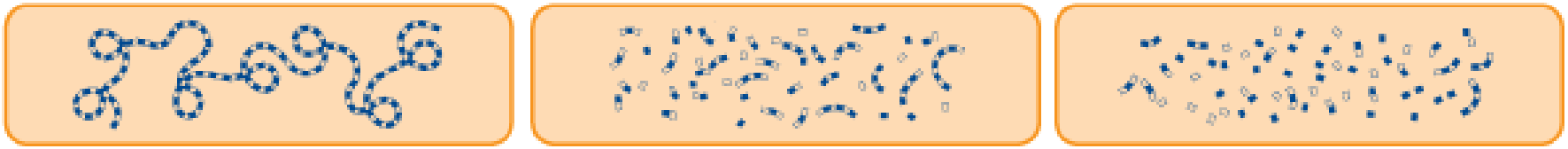
The smaller the protein fragments, the less potential they have for triggering an immune reaction



Lowest allergenic potential

Whole protein	63% of protein < 1000 Daltons	95% of protein < 1000 Daltons
Cow's milk formula	**EXTENSIVELY HYDROLYSED**	**AMINO ACID BASED**
	90% CMPA children tolerate	All milk protein broken down to **amino acids**
	<1% immunoreactive protein	

Breast feeding should always be supported before starting formula unless medically indicated

Extensively hydrolysed

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- Mild to moderate non-IgE *(solely formula fed or mixed)*
- Mild to moderate IgE

Pepti & Althera

– contains lactose

– to make it taste nicer

All other prescribed milks have no lactose

Amino acid based

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- Severe non-IgE / IgE
- Acute reactions with breast feeding
- Failure of initial trial of extensively hydrolysed
- Faltering growth

Prescribing

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- iMAP guidelines for choice between eHF & AAF
- Consider local prescribing guidelines when choosing specific brand
- Approximate monthly requirements:
  - < 6 months: 13 x 400g tins
  - 6 - 12 months: 7-13 x 400g tins
  - Less if top-up feeds in breastfed child

Palatability & Acceptance: Tips

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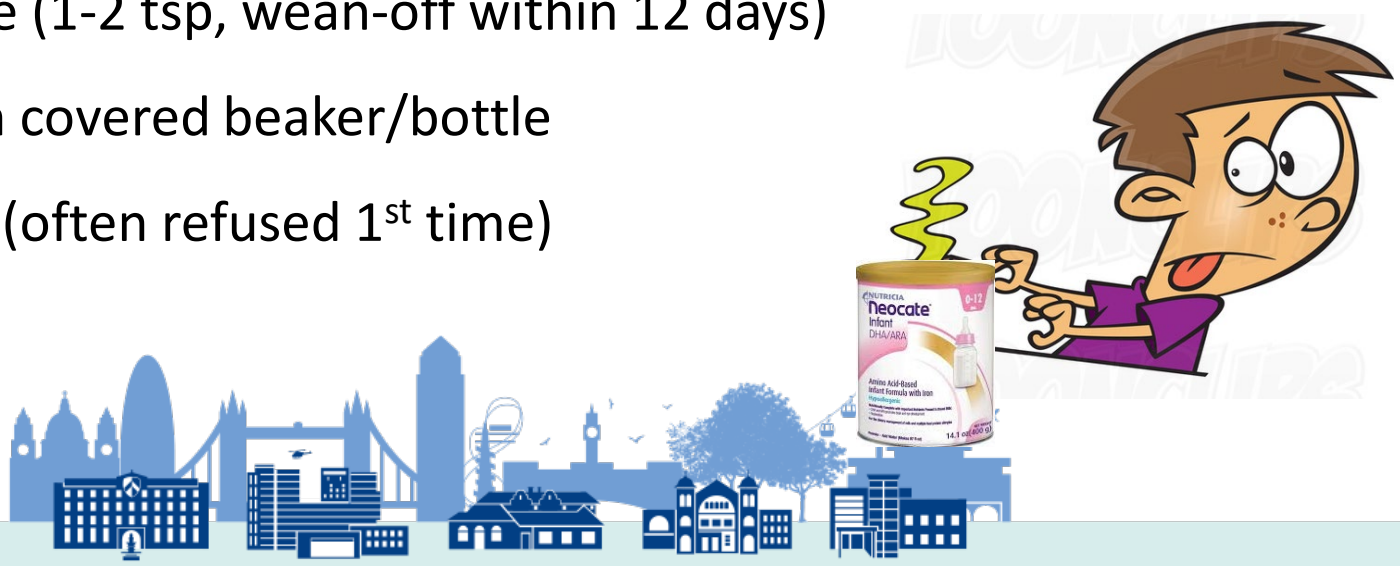
- Consider titrated introduction
  - ❑ mix with EBM/current formula

    try ¼ new formula : ¾ current milk for 3-4 days then increase to ½ : ½, etc.
  - ❑ Can't do this if having immediate severe reactions
- If topping –up ask father or other family-member to offer
- Non-alcoholic vanilla extract
- Apple juice (1-2 tsp, wean-off within 12 days)
- Offer from covered beaker/bottle
- Persevere (often refused 1st time)



Breast feeding & elimination

Humans make lactose

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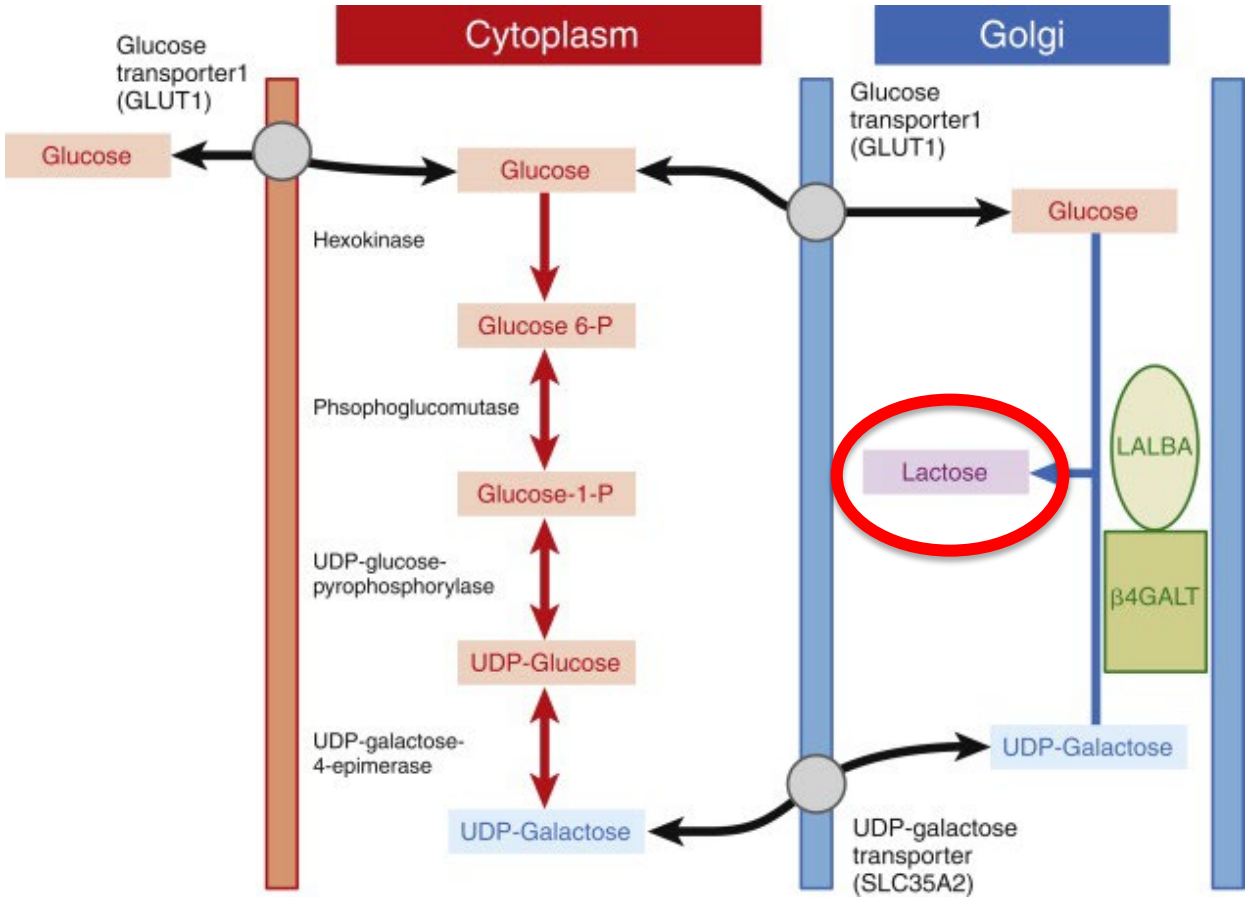

Pathway of lactose synthesis in the epithelial cells of the breast alveoli

Glucose transporter 1 (GLUT1) brings glucose into the cell and also transfers it into the Golgi. In the cytoplasm, glucose is converted to UDP-galactose, a process requiring energy input. UDP-galactose is actively transported into the Golgi by a specific transporter, where the complex of lactalbumin (LALBA) and β4-galactosyl transferase (β4GALT) catalyzes the formation of the disaccharide lactose

Urgent cases

- Is there any evidence of failure to thrive?

- Is there any history consistent with anaphylaxis?

Guidelines

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Milk Allergy in Primary Care (MAP) Guideline 2019

GP Infant Feeding Network (UK) (gpifn.org.uk)

https://gpifn.org.uk/imap/

UK Adaptation of iMAP Guideline for Primary Care and 'First Contact' Clinicians

Presentation of Suspected Cow's Milk Allergy (CMA) in the 1st Year of Life

Having taken an Allergy-focused Clinical History and Physically Examined

Apr 2019

Less than 2% of UK infants have CMA . There is a risk of overdiagnosis of CMA if mild, transient or isolated symptoms are over-interpreted or if milk exclusion diets are not followed up by diagnostic milk reintroduction. Such situations must be avoided. There should be increased suspicion of CMA in infants with multiple, persistent, severe or treatment-resistant symptoms. iMAP primarily guides on early recognition of CMA, emphasizing the need for confirmation of the diagnosis, either by allergy testing (IgE) or exclusion then reintroduction of dietary cow's milk (non IgE). Breast milk is the ideal nutrition for infants with CMA and any decision to initiate a diagnostic elimination diet trial must include measures to ensure that breastfeeding is actively supported. Refer to accompanying leaflet for details of supporting ongoing breastfeeding in milk allergic infant. Firststepsnutrition.org is a useful information source on formula composition.

Mild to Moderate Non-IgE-mediated CMA

Mostly 2-72 hrs. after ingestion of Cow's Milk Protein (CMP)

Usually formula fed, at onset of formula feeding.
Rarely in exclusively breast fed infants

Usually several of these symptoms will be present. Symptoms persisting despite first line measures are more likely to be allergy related e.g. to atopic dermatitis or reflux. Visit gpifn.org.uk for advice about other infant feeding issues.

Gastrointestinal

Persistent Irritability - 'Colic'
Vomiting - 'Reflux' - GORD
Food refusal or aversion
Diarrhoea-like stools – abnormally loose +/- more frequent
Constipation – especially soft stools, with excess straining
Abdominal discomfort, painful flatus
Blood and/or mucus in stools in otherwise well infant

Skin

Pruritus (itching), Erythema (flushing)
Non-specific rashes
Moderate persistent atopic dermatitis

The symptoms above are very common in otherwise well infants or those with other diagnoses, so clinical judgement is required. Trial exclusion diets must only be considered if history & examination strongly suggests CMA, especially in exclusively breastfed infants, where measures to support continued breastfeeding must be taken.

Cow's Milk Free Diet

Exclusively breast feeding mother*

Trial exclusion of all Cow's Milk Protein from her own diet and to take daily Calcium and Vit D

Formula fed or 'Mixed Feeding'*

If mother unable to revert to fully breastfeeding, trial of Extensively Hydrolysed Formula - eHF

See Management Algorithm

Severe Non-IgE-mediated CMA

Mostly 2-72 hrs. after ingestion of Cow's Milk Protein (CMP)
Usually formula fed, at onset of mixed feeding.
Rarely in exclusively breast fed infants

One but usually more of these **severe, persisting & treatment resistant** symptoms:

Gastrointestinal

Diarrhoea, vomiting, abdominal pain, food refusal or food aversion, significant blood and/or mucus in stools, irregular or uncomfortable stools
+/- Faltering growth

Skin

Severe atopic dermatitis +/- Faltering Growth

Cow's Milk Free Diet

Exclusively breast feeding mother*

If symptomatic, trial exclusion of all Cow's Milk Protein from her own diet and to take daily Calcium & Vit D

Formula fed or 'Mixed Feeding'*

If mother unable to revert to fully breastfeeding, trial of replacement of Cow's Milk formula with Amino Acid Formula (AAF). If infant asymptomatic on breast feeding alone, do not exclude cow's milk from maternal diet.

Ensure:

Urgent referral to local paediatric allergy service

Urgent dietetic referral

Severe IgE CMA

ANAPHYLAXIS

Immediate reaction with severe respiratory and/or CVS signs and symptoms.
(Rarely a severe gastrointestinal presentation)

Emergency Treatment and Admission

Mild to Moderate IgE-mediated CMA

Mostly within minutes (may be up to 2 hours) after ingestion of Cow's Milk Protein (CMP)
Mostly occurs in formula fed or at onset of mixed feeding

One or more of these symptoms:

Skin – one or more usually present

Acute pruritus, erythema, urticaria, angioedema
Acute 'flaring' of persisting atopic dermatitis

Gastrointestinal

Vomiting, diarrhoea, abdominal pain/colic

Respiratory – rarely in isolation of other symptoms

Acute rhinitis and/or conjunctivitis

Cow's Milk Free Diet

Support continued breast feeding where possible.
If infant symptomatic on breast feeding alone, trial exclusion of all Cow's Milk Protein from maternal diet with daily maternal Calcium & Vit D as per local guidance.
If infant asymptomatic on breast feeding alone, do not exclude cow's milk from maternal diet.

Formula fed or 'Mixed Feeding'*

If mother unable to revert to fully breast feeding
1st Choice -Trial of Extensively Hydrolysed Formula – **eHF**
Infant soy formula may be used over 6 months of age if not sensitised on IgE testing

If diagnosis confirmed (by IgE testing or a Supervised Challenge in a minority of cases) :
Follow-up with serial IgE testing and later Planned Challenge to test for acquired tolerance

Dietetic referral required

UK NICE Guidance - If competencies to arrange and interpret testing are not in place - early referral to local paediatric allergy service advised

*** Actively support continued breastfeeding (see over)**

iMAP was developed without any funding or support from industry but note that authors do make declarations of interest.

UK Adaptation of iMAP Guideline for Primary Care and 'First Contact' Clinicians

Management of Mild to Moderate Non-IgE Cow's Milk Allergy (CMA)

(No initial IgE Skin Prick Tests or Serum Specific IgE Assays necessary)

May 2019

Exclusively Breastfeeding [UK Recommendation 1st 6 months]

Strict elimination of cow's milk containing foods from maternal diet

Maternal daily supplements of Calcium and Vit D according to local recommendations
Refer to dietitian - a maternal substitute milk should be advised
An agreed Elimination Trial of up to 4 weeks - with a minimum of 2 weeks.
If severe atopic dermatitis or more severe gut symptoms – consider soy/egg avoidance as well, only with specialist advice
Mothers should be actively supported to continue to breastfeed through this period*.

No Clear Improvement

But - CMA still suspected:

Refer to local paediatric allergy service

Consider excluding other maternal foods eg soy, egg only with specialist advice

CMA no longer suspected:

Return to usual maternal diet
Consider referral to local general paediatric service if symptoms persist. Visit gpifn.org.uk for advice about other infant feeding issues.

Clear Improvement - need to confirm Diagnosis

Home Reintroduction: [NICE Quality Standard]
Mother to revert to normal diet containing cow's milk foods over period of 1 week - to be done usually between 2-4 weeks of starting Elimination Trial

No return of symptoms **NOT CMA** - normal feeding

Return of symptoms

Exclude cow's milk containing foods from maternal diet again
If symptoms clearly improve:
CMA NOW CONFIRMED
If top-up formula feeds should later be needed - eHF may well be tolerated. If not - replace with AAF

Symptoms do not settle

As likelihood of sufficient cow's milk protein passage into breast milk to trigger reactions is low, in breast fed cases, complete milk exclusion may not be required.

Formula Feeding or 'Mixed Feeding' [Breast and Formula]

Strict cow's milk protein free diet

If symptoms only with introduction of cow's milk-based feeds – encourage & support return to breastfeeding*. Mother can continue to consume cow's milk containing foods in her diet.
If symptoms settle on return to full breast feeding, reconsider diagnosis if symptoms return on future milk exposure. If symptoms suspected from breastfeeding alone, see Box left.
If **any** formula feeds are required, advise an eHF. Agree an Elimination Trial of up to 4 weeks (minimum of 2 weeks) and assess improvement. **Reintroduction of cow's milk is required to confirm diagnosis.** If weaned - may need advice & support from dietitian. Only follow algorithm further in infants receiving eHF/on diagnostic elimination diet trial.

Clear Improvement - need to confirm diagnosis

Home Reintroduction: [NICE Quality Standard]
Using cow's milk formula
To be done usually between 2-4 weeks of starting Elimination Trial. Refer to iMAP reintroduction leaflet.

Return of symptoms

Support breastfeeding or if not possible, return to **eHF** again
If symptoms clearly improve:
CMA NOW CONFIRMED
Ensure support of dietitian

No return of symptoms **NOT CMA** - normal feeding

Symptoms do not settle

No Clear Improvement

But - CMA still suspected:

Consider initiating a trial of an Amino Acid Formula (AAF)

Refer to local paediatric allergy service

CMA no longer suspected:

Unrestricted diet again
Consider referral to local general paediatric service if symptoms persist

Cow's milk free diet until 9-12 months of age and for at least 6 months – with support of dietitian
A planned Reintroduction or Supervised Challenge is then needed to determine if tolerance has been acquired
Performing a Reintroduction versus a Supervised Challenge is dependent on the answer to the question:
Does the child have **Current Atopic Dermatitis** or **ANY history at ANY time of immediate onset symptoms ?**

No Current Atopic Dermatitis
And no history at any time of immediate onset symptoms
(No need to check Serum Specific IgE or perform Skin Prick Test)
Reintroduction at Home – using a MILK LADDER
To test for Acquired Tolerance

Current Atopic Dermatitis

Check Serum Specific IgE or Skin Prick Test to cow's milk

Negative **Positive**

And still no history at any stage of immediate onset symptoms
Reintroduction at Home - using a MILK LADDER
To test for Acquired Tolerance

History of immediate onset symptoms at any time
Serum Specific IgE or Skin Prick Test needed

Negative
Liaise with local Allergy Service Re: Challenge

Positive or Tests not available

Refer to local paediatric allergy service
(A **Supervised Challenge** may be needed)

*Breast milk is the ideal nutrition for infants & hence continued breastfeeding should be actively encouraged as far as is possible. WHO recommends breastfeeding until 2 years and beyond. Mothers should be offered support of local NHS breastfeeding support services & signposted to further support. Please refer to iMAP patient information leaflet on supporting breast feeding.

Summary

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	IgE	Non-IgE	Lactose intolerance
Symptoms	Skin, respiratory, cardiovascular, gastrointestinal, other	Gastrointestinal or skin	Bowel only *(e.g. pain, flatulence, diarrhoea)*
Mechanism	Acute immune reaction to milk protein	Delayed immune reaction to milk protein	Non-immune Reduced ability to digest lactose
Tests	sIgE or skin prick testing	Exclusion diet (NO MILK PROTEIN) symptoms improve & then reintroduce (symptom reoccur) May take 4–6 weeks for symptoms to improve	Exclusion diet (LOW LACTOSE) symptoms improve & then reintroduce (symptom reoccur) Usually improve within 48 hours of exclusion

* IgE & Lactose intolerance do not present with rectal bleeding

Summary

- Lactose intolerance
  - *rare in babies*
  - *practically diagnosed with a short lactose dietary exclusion and re-introduction*
- non-IgE cow's milk allergy
  - *diagnosed with a cow's milk protein dietary exclusion and re-introduction*
- IgE cow's milk allergy
  - *diagnosed on history +/- allergy tests*
- Be aware of your local guidelines around prescribing milks
- Consider re-introduction in non-IgE
  (see MAP guidelines)