Pathogenesis of Allergic Disease

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Lecture 1
An Overview of Allergic Immune Responses
Lecture I

• History & classification of allergic responses
• IgE mediated allergic responses
  • Early and Late Phase Responses
  • Mast cell/basophil responses
  • Soluble mediators of allergic inflammation
• Non IgE mediated allergic responses
• Treatment & regulation of allergic responses
History

• ANAPHYLAXIS
  – First described 2640 BC – pharaoh Menes died after a wasp sting
  – Adverse reactions in dogs to immunisation with *Actinia* extracts (Portier & Richet 1902)

• ALLERGY
  – “state of altered immune reactivity” (von Pirquet 1906)
  – observed that the development of antibodies could alter subsequent responsiveness in an unfavourable fashion
History

• ATOPY
  – First used in 1923 Coca & Cooke
    [Greek *atopos* = “uncommon”]
  – Genetic predisposition to become sensitised and produce IgE antibodies in response to ordinary exposures to allergens

• IgE
  – Identified and named 1968
Classification of Hypersensitivity Reactions  Gell & Coombs  1963

• Type I: Anaphylactic
  – react within minutes of exposure
  – Usually IgE-mediated (can be IgG)

• Type II: Cytotoxic
  – IgG/M antibody binds to tissue-bound antigen
  – triggers complement activation
  – eg Autoimmune haemolytic anaemia
Classification of Hypersensitivity Reactions  

Gell & Coombs  1963

- **Type III: Immune complex mediated**
  - formation of circulating immune complexes
  - eg serum sickness, glomerulonephritis

- **Type IV: Cell mediated**
  - = delayed type hypersensitivity
  - Tcell mediated
  - eg tuberculin test, Graft Versus Host Disease
WAO Nomenclature 2003

• Consensus statement on nomenclature of allergic disease
• Hypersensitivity
  – Objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons

J Allergy Clin Immunol 2004;113:832-6
Allergy 2001;56:813-24
WAO Nomenclature 2003

• Allergic Reactions = Immunologically Mediated
  – IgE Mediated
  – Non IgE Mediated
    • T cell mediated
    • Eosinophil mediated
    • IgG mediated
    • Other
Hypersensitivity Reactions

Allergic
Immunologically mediated

IgE mediated

Non-IgE mediated

Other

Non-Allergic
Non-Immunologically mediated

T-cell mediated

IgG mediated

Eosinophil mediated

Other
Hypersensitivity Reactions

Allergic
Immunologically mediated

- IgE mediated
- Non-IgE mediated
- Other

Non-Allergic
Non-Immunologically mediated

- T-cell mediated
- IgG mediated
- Eosinophil mediated

- contact dermatitis
- allergic alveolitis
- oesophagitis
Hypersensitivity Reactions

Allergic
Immunologically mediated

- IgE mediated
- Non-IgE mediated
- Other

Non-Allergic
Non-Immunologically mediated

- T-cell mediated
- IgG mediated
- Eosinophil mediated

contact dermatitis
allergic alveolitis
oesophagitis
IgE MEDIATED ALLERGIC RESPONSE
IgE Mediated Allergic Response

• Early Phase
  – Wheal and flare/ wheeze/ sneeze & rhinorrhaea
  – Vasoactive Mediators Released
    • Histamine, tryptase, leukotrienes

• Late Phase (peak 6-9 hours)
  – Indurated swelling/ wheeze/ nasal blockage
  – Eosinophil, neutrophil, T helper cell infiltration
IgE Mediated Allergic Response

• Both early & late phases classically described as IgE-dependent
• However late phase can occur in absence of early phase response
  – T cell dependent, MHC restricted

Hypersensitivity Reactions

Allergic Immunologically mediated

IgE mediated

Non-IgE mediated

Other

Non-Allergic Non-Immunologically mediated

T-cell mediated

IgG mediated

Eosinophil mediated
IgE Sensitisation

• Priming
  – through initial allergen exposure
  – May be in utero, via breast milk, environmental
• Antigen presentation to T cells
• B cell class switching to IgE production
• Generation of memory B cell clone
• Antigen specific IgE generated
IgE Sensitisation

- **Allergen**
- **APC**
- **Th2 cell**
- **B cell**
- **IgE**
- **IL4**
- **IL13**
IgE Sensitisation
IgE Receptors

• Cell receptors for IgE are of low affinity..
  – Found on lymphocytes, eosinophils, platelets, macrophages $\text{Fc}_\varepsilon\text{RII}$
• ..Or of high affinity $\text{Fc}_\varepsilon\text{RI}$
  – Found on mast cells and basophils
  – Very high affinity binding through Fc portion of IgE
• Antigen binding to surface bound IgE leads to crosslinking of IgE, internalisation of $\text{Fc}_\varepsilon\text{RI/II}$ molecules and activation of cell
Early Phase IgE Allergic Response

**Preformed Mediators**
- Histamine
- Tryptase [20% protein product]
- Heparin

**Newly generated Mediators**
- Leukotrienes eg LTC4
- Prostaglandin D2

**Cytokines** eg IL-4, TNFα

Histamine – bronchospasm, vasodilatation, permeability post capillary venules

Leukotrienes – bronchoconstriction, mucus secretion, eosinophil recruitment, vascular permeability, reduced cardiac contractility, peripheral vasoconstriction
Early and Late Phase IgE responses

Immediate response:
- Preformed mediators
- Newly formed mediators
- Cytokines

Late response:
- Th2 cell
- APC
- IL5
- Eos
- MBP
- ECP

Cytokines
Late Phase IgE Allergic Response

• Cutaneous
  – Can be induced with early phase reaction using anti IgE antibody
  – Not induced by histamine alone
  – Other mediators stimulate cellular recruitment etc eg leukotrienes, PGD$_2$, PAF, cytokines
  – Mixed cellular infiltrate.. Neutrophils, monocytes then CD4 lymphocytes, eosinophils, basophils
  – Dense perivascular infiltrate
  – Indurated swelling for up to 48 hours
Late Phase IgE Allergic Response

• Pulmonary
  – Associated with more persistent and severe airway hyperresponsiveness
  – Mediated by PGD$_2$, leukotrienes, cytokines
  – BAL shows neutrophilia early, then eosinophilia and CD4+ T cells
  – Airway oedema/obstruction, mucus secretion
Late Phase IgE Allergic Response

• Nasal Airway
  – Early.. Sneezing, rhinorrhea, pruritis
  – Late.. Congestion
  – Mediators of late phase response
    • Kinins, histamine, ECP, MBP, cytokines
  – Cells of late phase response
    • Eosinophils, then neutrophils, lymphocytes also
MAST CELL/BASOPHIL RESPONSES
Mast cell/basophil biology

- Haematopoietic stem cell origin
- Circulating basophils vs tissue bound mast cells
  - $T^{1/2}$ shorter for basophils
- Distinction between mucosal (gastrointestinal) and connective tissue mast cells
- Different responses in rats
  - eg bee venom peptide induces histamine release from connective tissue but not mucosal mast cells
- Responses modulated by microenvironment, and maturation stage of mast cells
Mast cell/basophil biology

• Differences in response patterns
  – eg Mucosal mast cells don’t respond to morphine
  – Dexamethasone inhibits basophil mediator release, but not mast cell mediator release

• Differences in secretion patterns
  – eg mast cells release PGD$_2$, IL5; basophils don’t

• Despite these differences, little evidence in humans that mast cell/basophil secretory process differs markedly
Non-IgE mediated Mast Cell/Basophil Activation

• IgG receptor mediated
  – low affinity
  – IgG/antigen complexes can bind and trigger degranulation
  – More common in rodents
  – Seen in humans in serum sickness, dextran reactions

• Complement mediated
  – C5a and C3a major complement derived anaphylatoxins
  – Specific receptor for C5a

• Other mechanisms
  – morphine, contrast media
Enhancement of Mast Cell/Basophil Activation

• Cytokines
  – eg IL-3 enhances induced basophil histamine release
  – GSCF/IL-1 enhance IgE mediated histamine release from basophils

• Eosinophil major basic protein
  – 50% of eosinophil granule protein
  – Activates basophil/mast cell histamine release
Inhibition of Mast Cell/Basophil Activation - 1

- Also express FcγRIIb, a low affinity IgG receptor
- Activation of either FcγRIIb or FcεRI can lead to degranulation
- BUT...
- Co-activation by IgG/allergen complexes inhibits degranulation
- Aggregation of FcγRIIb to FcεRI leads to inhibition of FcεRI signalling
Inhibition of Mast Cell/Basophil Activation - 2

• ‘Desensitisation’ - in vitro phenomenon
• Thought to underlie some forms of clinical desensitisation
• FCεRI crosslinking leads to secretion of some mediators which inhibit degranulation = ‘desensitisation’
• May be induced using Ag without Ca++, or with v.high dose antigen
Inhibition of Basophil/mast cell Activation – clinical implications

- Penicillin oral and iv desensitisation regimens – need to be repeated if there is a break between doses

- Immunotherapy – associated with increased specific IgG production

- May explain refractory period after major anaphylaxis

- May be exploited for immunotherapy
MEDIATORS OF IgE ALLERGIC RESPONSES
Early and Late Phase IgE responses

**Immediate response**
- Preformed mediators
- Newly formed mediators
- Cytokines

**Late response**
- Th2 cell
- Cytokines
- IL5
- APC
- Eos
- MBP
- ECP
Preformed Mediators

- **Histamine**
  - Potent vasodilator/bronchoconstrictor
  - Metabolised within minutes

- **Proteases**
  - Tryptase, chymase
  - Indirect actions

- **Proteoglycans**
  - Heparin, chondroitin sulphate
  - Storage/stabilising function?
Newly formed mediators

- Lipid derived mediators
  - Platelet Activating Factor
    - Vascular and smooth muscle effects
  - Prostaglandins esp PGD2
    - Bronchoconstriction, chemotaxis, cerebral effects
  - Leukotrienes esp LTC4 (mast cells)
    - Bronchoconstriction, vascular permeability
Cytokines – soluble mediators of inflammation

- Interleukins
  - produced by leukocytes
- Lymphokines
  - produced by lymphocytes
- Monokines
  - produced by mononuclear phagocytes
- Chemokines
  - chemotactic cytokines
- Colony Stimulating Factors
  - proliferation/differentiation of immature hematopoietic cells
Cytokines in Allergic Inflammation

- Produced by lymphocytes, eosinophils, mast cells, structural cells e.g. fibroblasts
- Regulate cellular differentiation, recruitment, adhesion molecule expression, antigen presentation
- Pro-inflammatory cytokines
  - IL1, IL6, TNFα
- Th1 cytokines
  - IFNγ, IL2
Cytokines in Allergic Inflammation

• Th2 cytokines important in allergic inflammation
  – IL4, IL5, IL13
• IL4/IL13 mainly from T cells
• Early IL4 expression critical for development of a Th2 response
• IL4 has a dominant effect
• IL4/IL13 important in B cell class switch to IgE production
Cytokines in Allergic Inflammation

- IL5
- From T cells, eosinophils, mast cells
- Effects
  - Release of bone marrow eosinophils
  - Terminal differentiation of eosinophils
  - Chemotaxis of eosinophils
  - Blocks eosinophil apoptosis
  - Activates mature eosinophils
Regulatory Cytokines IL10

- Source T & B lymphocytes, mast cells, eosinophils, monocytes, macrophages and keratinocytes
- Major regulatory cytokine
- Inhibits T cell cytokine/proliferative responses
- Can induce T cell anergy
- Inhibits eosinophil survival, and mast cell/eosinophil induced inflammation
NON IgE MEDIATED ALLERGIC RESPONSES
T Cell Mediated Allergic Inflammation

- Depends on Antigen presentation to effector T cells
- CD4+ antigen-specific T cells recruited
- Non-specific inflammatory cells [mast basophils, macrophage, neutrophil] also recruited
- Mediated by soluble factors (cytokines etc)
- Inhibited by azathioprine, calcineurin inhibitors
Eosinophilic Allergic Inflammation

- Common in gastrointestinal disorders, also asthma and rhinitis
- IL5 critical for eosinophil production in bone marrow and traffic to effector site
- Eotaxins critical for tissue recruitment
- Release leukotrienes, PAF, cytokines, ECP and MBP
- MBP increased smooth muscle contractility, degranulates mast cells/basophils
Eosinophil → Bronchial hyperreactivity → Bronchospasm → Leukotrienes, PAF, MBP, EPO → Increased vascular permeability → MBP, ECP, EPO ($\pm H_2O_2 + X^-$), (EDN)

Basophil → Bronchospasm → Leukotrienes and histamine

EBP, EPO ($\pm H_2O_2 + X^-$), ECP

Epithelial damage
Treatment of Allergic Inflammation

- **Antihistamine**
  - Effective in EPR
  - Weak inhibition of cutaneous and pulmonary LPR
- **Mast cell stabilisers**
  - Cromoglycate, ketotifen
  - Inhibit pulmonary LPRs
- **Corticosteroids**
  - Effective inhibition of pulmonary/cutaneous/nasal LPR, without inhibiting EPR
- **Leukotriene antagonists**
  - Effective in EPR and LPR
Treatment of Allergic Inflammation

• Anti IgE therapy
  – Inhibits both EPR and LPR

• Calcineurin Inhibitors
  – Inhibit LPR

• Immunotherapy
  – Inhibits both EPR and LPR

• Anti IL5
  – Inhibits eosinophilic inflammation
Regulation of Allergic Immune Responses

• Clonal Deletion ‘central tolerance’
  – Thymic (central) esp in early life
  – Also seen in lymph nodes (peripheral) eg after organ transplants
  – Works best if lots of antigen and few reactive T cells
  – Principal mechanism in prevention of autoimmunity

• Peripheral Tolerance Mechanisms
  – Important in protection against environmental antigens
  – Anergy – antigen presentation in absence of adequate costimulation
Two signals for lymphocyte activation

- Antigen acquisition by BCR
- Antigen processing
- Signal 1
  - Activation

MHC-restricted antigen-recognition by TCR
- Signal 1
  - Activation

Costimulation
- Signal 2

The B cell

The T cell
Regulation of Allergic Immune Responses

• Regulatory T cells
  – Innate – CD4+25+ act by cell/cell contact
  – Antigen specific – eg Tr1 act via IL10
    • IL10 inhibits costimulatory molecule expression
  – Others eg NK regulatory cells, γδT cells

• Mast cell/basophil specific mechanisms
  – Desensitisation
  – Combined FcγRIIb/FcεRI signalling

• Others
  – Regulatory Dendritic Cells
  – Other cytokines eg TGFβ
  – Histamine receptor 2 agonism
Allergic Inflammation – putting it all together!
Regulatory Mechanisms

HR 2 activation

Th0 cell

APC

IL10

CD4+25 + Treg

CD4+25 + Treg

Mast

FCγIIb activation

IL10

Tr1

CD4+25

Treg

Treg

Treg
Pharmaceutical Actions

- Th2 cell
- APC
- Immunotherapy
- IL4
- IL13
- IL5
- Mast cell
- B cell
- IgE
- Anti IgE
- Anti IL5
- Corticosteroids
- Calcineurin inhibitors
- Mast cell stabilisers
- LTR/H1 Antagonists
Lecture 2
Aetiology & Natural History of Allergic Immune Responses
Lecture II

- Characteristics of Allergens
- Routes of sensitisation
- Ontogeny of allergic immune responses
- Natural history of allergic sensitisation
- Aetiology of allergic disease
- Opportunities for prevention
CHARACTERISTICS OF ALLERGENS
What makes an antibody ligand

- Antibodies can bind antigens in solution, independently of any other molecule
- Most antigens are proteins/peptides
- Binding epitopes for antibodies are usually conformational, i.e., destroyed by denaturing of the protein
- T cell binding epitopes are usually linear, i.e., not destroyed by denaturing protein
Conformational Epitope

Linear Epitope
What makes a T cell receptor ligand

- MHC Class II antigens elicit helper T cell responses
- Antigens are 15 to 20 amino acid peptides
- Lipids can occasionally act as T cell antigens
- Class II molecules can bind to epitopes before proteolysis
Aeroallergens

- Proteins associated with 2-60µm particles
- Particles over 18µm mostly trapped above the carina
- Particles under 5µm readily reach terminal bronchioles
- Certain groups of proteins are
  - 1. determinants of human allergic responses
  - 2. have high enough exposure levels to be a problem
Outdoor Aeroallergens

• Pollens
  – Tree pollens – usually local effects
  – Grass/weed pollens – carry long distances
  – Grass pollen season September to February

• Fungal spores
  – Understudied area
  – Spore levels peak in late summer
  – eg Cladosporium, Alternaria
Indoor Aeroallergens

• House Dust Mites
  – eg Der.pteronyssinus, Der.farinae
  – 24,000 kD glycoprotein in feces
  – Dominant aeroallergens in non-arid areas

• Pet dander
  – From dead skin
  – Cat allergen more prevalent than dog allergen

• Cockroach
  – Common in deprived inner city areas
Ingested Allergens

• IgG antibody responses are normally made to food proteins
• Heterogeneity in antibody responses elicited by different foods
• Not clear why some foods are common food allergens
• But food allergens are usually...
Ingested Allergens

• Glycoproteins
  – 14-40 kD
  – heat resistant, acid stable
• Proteins
  – Heat sensitive, acid labile
• Commonly egg, milk, wheat, fish, soy, peanut, tree nuts
Injected Allergens

• Insect Stings
  – IgE mediated usually
  – Non-IgE mediated

• Drugs
  – Monoclonal antibodies
  – Other drugs often haptens
  – eg penicillin
What is a hapten?

• Almost any chemical moiety can be a hapten eg lipids, sugars, nucleic acid, synthetic compounds

• Haptens are too small/simple to induce T cell responses

• Haptens are coupled to a carrier eg a plasma protein to induce T cell response
Neoantigens created by sensitizing agents bound to self-proteins

Penicillin G

\[ \text{β-lactam ring} \]

\[ \text{CH}_2 \text{-CO-NH-CH-CH-S-C-C=CH}_3 \]

\[ \text{Nucleophilic attack} \]

\[ \text{NH}_3^+ \]

Native self-protein

Adduct formation

Modified peptide epitope

Modified self-protein
ROUTES OF SENSITISATION
Routes of sensitisation to allergens

- Many food allergic reactions occur on first known exposure
- In utero sensitisation
  - Derp1 has been detected in amniotic fluid from 16/40
  - In vitro work shows 1/1000 proteins from egg allergen cross the placenta
  - Allergen-specific IgE to cow’s milk has been detected in cord blood in some studies
Routes of sensitisation to allergens

• Breast milk
  – Well established that most food antigens are expressed in breast milk
  – Can lead to allergic sensitisation/responses in infant
  – Importance less well established for aero-allergens
Routes of sensitisation to allergens

• Ingested
  – High density of APCs in intestine
  – Phenomenon of neonatal tolerance
  – Hyporesponsiveness to alloantigens if exposed in utero or neonatal period
    • Murine work – 1mg/g for tolerance
  – Clinical relevance variable in allergic disease in humans
    • Nickel allergy less common in those who had braces
    • Single high dose exposure to cow’s milk in neonatal period – no protective effect
Routes of sensitisation to allergens

• Inhaled
  – Likely primary mechanism for aeroallergens

• Cutaneous
  – Likely mechanism for latex, nickel, ?peanut

• Hidden exposures
  – eg β-lactams in meats
  – cross reactive allergens eg oral allergy syndrome – birch pollen & apple/pear/peach
ONTOGENY OF ALLERGIC IMMUNE RESPONSES
Human Thymic Development

• Thymic cortex/medulla present from 12/40
• Thymic cellularity increases ++ in 2\textsuperscript{nd}/3\textsuperscript{rd} trimesters
• May be transient thymic involution in late 3\textsuperscript{rd} trimester due to high steroid levels
• Grows again by 1 month postnatal age, diminishes over first year
• Thymus involutes after puberty
• Retains capacity to produce Ag-naïve cells
T cell repertoire development

- VDJ recombination leads to up to $10^{15}$ types of T cell receptor (TCR)
- Occurs from 8/40 onwards
- Circulating T cells present from 13/40
- Full repertoire present at birth
- % T cells in circulation peaks at 6/12 age
Ontogeny of Peripheral T cells

- Peripheral T cells in fetus/neonate express CD38 – probable marker of immaturity
- Also CD45ROneg/low ie haven’t been activated by foreign antigens
- Reduced DC function in neonate
- Reduced cytokine responses esp Th1 – Similar to adult naïve CD45ROneg/low T cells
Other Immune Differences in Neonates

- Low induced CD40ligand expression to 3-4 weeks age
- Increased spontaneous apoptosis during in vitro culture
- Alloantigens induce anergy in neonatal CD4+ T cells, in the absence of strong costimulation. Neonatal Tolerance mechanism
- Limited ability of activated neonatal T cells to traffic to sites of inflammation
- NK cells immature & at low numbers
Early T cell Function & Allergic Sensitisation

- T cell function in fetus/neonate is impaired
- Cytokine responses mainly IL10
  - IFNγ>IL4, but ratio reduced compared to adults ie not classical Th2 response to allergens
- T cell proliferative response to environmental antigens is seen but at low levels
  - Significance of this is not clear
Ontogeny of Peripheral B cells

- From 10/40 B cells express IgM (but not IgD)
  - IgM+IgD- B cells respond to antigen exposure with clonal anergy
- This may account for lack of antibody response after some forms of congenital infection [at times despite persistent T cell responses]
- Marrow B cells express all Ig isotypes by 16/40
- By 22/40 similar B cell no. s in many tissues to adult
- Germinal centres appear in first months of life (after antigenic stimulation)
Ontogeny of Ig Repertoire Development

- VDJ recombination more limited than for TCR in 1\textsuperscript{st}/2\textsuperscript{nd} trimesters
- IgG/A produced by 20/40
- Neonatal B cells express activation markers CD80 and CD27
- Neonatal antibody responses/isotype switching/ Tcell help are reduced
- B cell proliferation in response to CD40ligand is normal
Early B cell Function & Allergic Responses

- Direct immunisation of fetal monkeys results in effective antibody priming and secondary IgG antibody response from about 2nd trimester equivalent. This is true for both particulate and cellular antigens. Response to some antigens seems to develop earlier than others.
- Fetal response to tetanus toxoid vaccine in 3rd trimester found in some but not other studies (ie IgM at birth, and enhanced response to 2nd jab).
- IgE to toxoplasma, schistosoma found in infants born to infected mothers at time of birth.
- Fetal IgE synthesis from 11/40, but cord levels are 0.5% of maternal levels.
NATURAL HISTORY OF ALLERGIC SENSITISATION
Prenatal immune changes in allergic children

• Raised cord blood IgE [PPV 35-72%]
• Reduced cord blood IFNγ responses to allergen/mitogen
• Reduced soluble CD14 in amniotic fluid
• Decreased HLA-DR expression on unstimulated cord blood monocytes
Development of Allergic Sensitisation

• At birth
  – Some authors have reported allergen-specific IgE

• At age 1
  – 11% of infants are sensitised to an environmental allergen

• At age 6
  – 30% of children are sensitised to an environmental allergen

JACI 1999:103;1173-9
Point prevalences of sensitization

A

- Hen's egg
- Cow's milk
- Wheat
- Soy

B

- Birch
- Grass

C

- Cat
- Mite
- Dog
Resolution of allergic sensitisation

• To most foods in first 5 years of life
• To insect stings, drugs, occupational exposures
  – May occur with strict avoidance
• To nuts, fish, aeroallergens
  – Resolution unusual
AETIOLOGY OF ALLERGIC DISEASE
Increasing Burden of Allergic Disease

- ¹Wheezing in Aberdeen schoolchildren – 10% 1964; 20% 1989; 25% 1994; 28% 1999
- ²7-fold increase in UK hospital admissions for anaphylaxis 1990/1 – 2000/1
- ³2-fold increase in self-reported nut allergy in US 1997-2002

Recent reduction in asthma prevalence in many countries

¹BMJ 2004;329(7464):489-90
²BMJ 2003;327(7424):1142-3
³JACI 2003;112(6):1203-7
<table>
<thead>
<tr>
<th>Condition</th>
<th>1993</th>
<th>2002</th>
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<td>Asthma ever</td>
<td>28.6</td>
<td>25.5</td>
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<tr>
<td>Hayfever ever</td>
<td>14.9</td>
<td>19.8</td>
</tr>
<tr>
<td>Eczema ever</td>
<td>22.6</td>
<td>32.3</td>
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MJA 2004;180:273-6
Known Risk factors for Allergic Disease

- Genetic
  - 73% asthma risk *Skadhauge Eur Resp J* 99;13:8-14

- Environment
  - Small family size/low birth order *Strachan DP BMJ* 89;299:1259-60
  - No childcare attendance *Ball TM NEJM* 00;343:538-43
  - Low infection rates in infancy *Illi S BMJ* 01;322:390-5
  - No exposure to stables/farm milk in infancy *Riedler J Lancet* 01;358:1129-33
World Map of the Prevalence of Clinical Asthma

Proportion of population (%) *

- ≥10.1
- 7.6-10.0
- 5.1-7.5
- 2.5-5.0
- 0-2.5
- No standardised data available
Microbial exposures & allergic disease

• Lipopolysaccharide
  – Major component of G neg cell membrane
  – Levels 60% higher in farm environment
  – Murine work to suggest LPS exposure modulates development of allergic immune responses
  – Correlation between low LPS levels in mattress dust and development of asthma/allergic sensitisation/allergic rhinitis
Microbial exposures & allergic disease

• Intestinal Microbiota
  – Greatest microbial exposure in early life
  – Important stimulus for immune development
  – Germ free mice resistant to oral tolerance induction
  – Microbiota different in infants who go on to develop allergic disease
  – One study found probiotic treatment in infancy prevented eczema (RR0.50)
Microbial exposures & allergic disease

• Other microbial exposures
  – Hepatitis A
  – BCG
  – Measles
  – TLR2 mediated microbial signalling
OPPORTUNITIES FOR PREVENTION
Prevention of Allergic Disease

• Primary Prevention
  – Allergen Avoidance
    • Dietary – maternal and/or infant low allergen diet
    • Environmental – dust mite eradication
    • Combined dietary and environmental
  – Other interventions
    • Omega 3 fatty acids
    • Probiotic

Gore C, Custovic A Allergy 2004;59:151-61
Prevention of Allergic Disease

• Secondary Prevention
  – Environmental – mattress covers and advice reduced sensitisation to HDM in 6 yr old children already sensitised to other aeroallergens. NNT 15
  Arshad SH Clin Exp All 2002;32:843-9

  – Allergen Specific Immunotherapy
    • 3 years immunotherapy for pollen sensitised school age children with rhinoconjunctivitis reduced the risk of asthma
    • OR 0.40
      Moller C JACI 2002;109:251-6

  – Pharmacological
    • Cetirizine for 18 months in children with AD – no overall benefit, but some reduction in asthma in grass pollen sensitised children RR
      Warner JO JACI 2001;108:929-37
Primary Prevention of Allergic Disease

• Allergen Avoidance

- Dietary allergen avoidance by pregnant/lactating mothers has not been proven to prevent allergic disease
- Exclusive breast feeding to 4-6 months
Primary Prevention of Allergic Disease

• Allergen Avoidance

- In high risk infants who cannot be breast fed, using hydrolysed formula in place of cow’s milk formula for a prolonged period protects against early childhood allergic disease (RR 0.63) eg cow milk allergy, eczema

Osborn DA, Sinn J. The Cochrane Database of Systematic Reviews 2003, Issue 3
Lecture II

- Characteristics of Allergens
- Routes of sensitisation
- Ontogeny of allergic immune responses
- Natural history of allergic sensitisation
- Aetiology of allergic disease
- Opportunities for prevention