Viral infections and their role in wheezing disorders and development of asthma.
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Virus and bronchiolitis

- Respiratory syncytial virus (RSV)
- Human rhinovirus (HRV) especially the C
- Many others
Virus and future asthma

- Whether these infections are causal in asthma development
- Or simply identify predisposed children – controversial
- Hygiene hypothesis proposed that respiratory infections in early life were protective towards the development of asthma.
- Contrary to the concept that link infections in early life with subsequent wheezing,
Respiratory epithelial cells are the initial site of viral inoculation
Serve as the primary site of viral replication.
Influenza and RSV - cytopathic damage
Can affect the function of the epithelium and airway smooth muscle.
Disturbing the integrity of the epithelial layer
Enhance mucosal permeability
Increase exposure of inflammatory and antigen-presenting cells to allergens, other infections, and irritants.
Dendritic cells

- Airway mucosa dendritic cells - potent antigen presenting cells and mediators of the synergistic inflammation
- Upregulation and cross linking of the Fc-Epsilon receptor on lung dendritic cells may promote Th2 inflammation
- Induction of high-affinity IgE receptor on lung dendritic cells during viral infection leads to mucous cell metaplasia.

Increased immunoglobulin E (IgE)

- Experimental HRV infection: Increased IgE levels those with allergic rhinitis, but not in those with nonallergic rhinitis
- RSV and parainfluenza virus: can stimulate total IgE and virus-specific IgE in children
- The development of virus-specific IgE levels correlates with the probability of recurrent episodes of wheeze.
Exposure to viruses

- Airflow limitation
- AHR
- ↓ Antiviral activity
- Poor regulation of inflammation

Wheezy LRI

Lung factors

- Airway remodeling
- ↓ Alveolarization

Recurrent wheeze and asthma

Immune factors

- Epithelial reprogramming
Virus and future asthma PRO

- Severe RSV bronchiolitis was associated with an increased risk of asthma at 13 years of age Sigurs et al
- Large retrospective cohort study in Tennessee supported a causal role for RSV bronchiolitis during infancy
- Treatment of otherwise healthy preterm infants with palivizumab to prevent severe RSV infection was associated with a decreased rate of recurrent wheeze vs placebo group (11% vs 21%, respectively) in a RCT of 429 high-risk infants

Virus and future asthma PRO

- A longitudinal data from the Tucson Children's Respiratory Study suggested that RSV - LRTI during the first 3 years of life were associated with subsequent wheezing and asthma in early childhood, but not beyond age 11 years.

- Relationship between severe RSV infection and development of asthma based on a registry-based twin study in Denmark, and found that severe RSV infection does not cause asthma but is an indicator of the genetic predisposition to asthma Thomsen et al.
Increased LTC4 in nasal secretions of children with wheezing during RSV infections

Suggests that eosinophil recruitment to the airway - related to RSV

Virus and future asthma PRO

- A systematic review of 28 articles - asthma risk after RSV hospitalization during infancy.
- Prevalence estimates of asthma among those hospitalized for RSV in infancy:
  - 8% to 63% (at ages <5), 10% to 92% (5 – 11 yrs) and 37%, (12 years)
  - These rates were higher than those among non-hospitalized comparisons.
- The attributable risk of asthma due to RSV ranged from
  - 13% to 22% (at ages <5), and 11% to 27%, (5 – 11 yrs) was 32% (12 years)
- Despite variability in asthma prevalence available data suggest a link between severe RSV infection in infancy and childhood asthma.

- Elevated risk of asthma after hospitalization for respiratory syncytial virus infection in infancy
- Shelagh M. Szabo
- Paediatric Respiratory Reviews 13(S2) (2012) S9–S15
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Rhinoviruses

- Do not damage the epithelium.
- Activates epithelial cells to upregulate the expression of ICAM-1 receptors, enhancing replication of HRV.
- Induce epithelial cells to secrete a wide variety of chemokines and cytokines IL-6, IL-8, IL-11, and RANTES (regulated upon activation, normally T expressed),
- Chemoattractant for eosinophils, monocytes, and T cells.
- Release of epithelial mediators such as thymic stromal lymphopoietin (TSLP), IL-25, and IL-33, which promote T helper cell type 2 (Th2) inflammation
- Promotes lower airway inflammation to allergen and can thereby enhance existing allergic inflammation.
Human Rhinovirus (HRV) PRO

- Stronger predictor of developing asthma than RSV
- Especially if the infection is in the LOWER airways as against the upper airways
- HRV-induced wheezing episodes in infancy were highly predictive of subsequent asthma, and this relationship persisted at least through the late teen years. Kotaniemi-Syrjänen et al.
- The Childhood Origins of Asthma (COAST) study, a high-risk birth cohort identified HRV wheezing illnesses during the first year of life as significant risk factors for wheezing at 3 years and asthma at 6 years.
Epidemiologic studies suggested that frequent respiratory infection during infancy may protect against the later development of asthma.

Remote islands whose population has both a very low incidence of respiratory infections and strikingly high prevalence rates of asthma and atopy.

Development of asthma, hay fever, or eczema has been shown to be inversely related to the number of older siblings or participation in day care.

Respiratory infections early in life somehow delay or prevent the expression of allergic diseases later in life.
There are no conclusive epidemiologic data linking infections to causation of asthma in previously normal adults.

RSV prophylaxis decreased the risk of recurrent wheezing in children without a family history of atopy, but had no effect in children from atopic families.

Virus and asthma exacerbations

- Respiratory syncytial virus (RSV)
- Rhinovirus is the predominant pathogen identified in school-aged children and adult patients with acute asthma exacerbations.
- HRV- C associated with more severe disease in children admitted for asthma exacerbations
- Viral infections trigger up to 85% of asthma exacerbations in school-aged children
- Up to 50% of exacerbations in adult
Asthma is a complex disease
Genetic
Environmental interactions e.g. rural / urban
Epigenetic regulation is also a major contributor.
Interface between prenatal and early postnatal environmental exposure
Epigenetic changes can occur throughout life, but much of the epigenome is established during early development of the fetus.
FINALLY

- Several prenatal environmental exposures such as maternal smoking, dietary pattern, and microbial exposure have been shown to modify fetal immune function.
- Recent studies - exposure to non-pathogenic rather than pathogenic microbes would be more important in reducing the risk for asthma.
SUMMARY

- WE ARE NOT SURE

- SO YOU WILL **NOT** BE GETTING AN MCQ QUESTION IN YOUR EXAMS
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Photo: H. Fiebig / 50 Treasures of Kenya