

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,

Epithelial cells



- 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

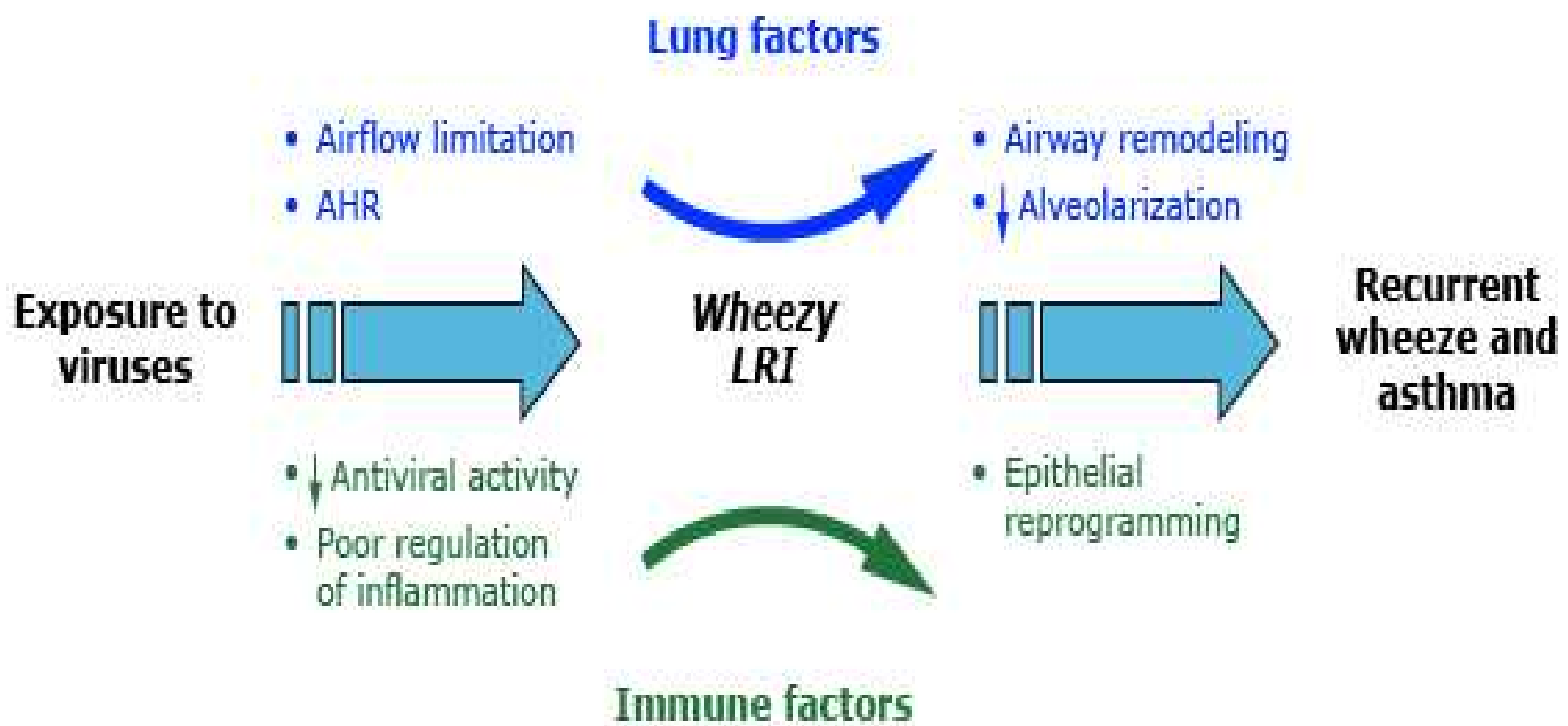


- Airway mucosa dendritic cells - potent antigen presenting cells and mediators of the synergistic inflammation
- Upregulation and cross linking of the Fc-Epsilon receptor on lung dendritic cells may promote Th2 inflammation
- Induction of high-affinity IgE receptor on lung dendritic cells during viral infection leads to mucous cell metaplasia.
- Grayson MH, Cheung D, Rohlfing MM, Kitchens R, Spiegel DE, Tucker J, Battaile JT, Alevy Y, Yan L, Agapov E, Kim EY, Holtzman MJ *J Exp Med.* 2007;204(11):2759.

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.
- The development of respiratory syncytial virus-specific IgE and the release of histamine in nasopharyngeal secretions after infection. Welliver RC, Wong DT, Sun M, Middleton E Jr, Vaughan RS, Ogra PL *N Engl J Med.* 1981;305(15):841.
- Role of parainfluenza virus-specific IgE in pathogenesis of croup and wheezing subsequent to infection. Welliver RC, Wong DT, Middleton E Jr, Sun M, McCarthy N, Ogra PL *J Pediatr.* 1982;101(6):889.



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
- Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. Blanken MO, Dutch RSV Neonatal Network N Engl J Med. 2013 May;368(19):1791-9.

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.

Virus and future asthma PRO



- Increased LTC₄ in nasal secretions of children with wheezing during RSV infections
- Suggests that eosinophil recruitment to the airway - related to RSV
- The release of leukotrienes in the respiratory tract during infection with respiratory syncytial virus: role in obstructive airway disease. Volovitz B, Welliver RC, De Castro G, Krystofik DA, Ogra PL *Pediatr Res.* 1988;24(4):504.

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 lymphopietin (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.
- Respiratory syncytial virus infection of human respiratory epithelial cells up-regulates class I MHC expression through the induction of IFN-beta and IL-1 alpha. Garofalo R, Mei F, Espejo R, Ye G, Haeberle H, Baron S, Ogra PL, Reyes VE J Immunol. 1996;157(6):2506.

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.
- Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. Jackson DJ *Am J Respir Crit Care Med.* 2008;178(7):667.

Virus and future asthma CON



- 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

Virus and future asthma CON



- 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
- The effect of respiratory syncytial virus on subsequent recurrent wheezing in atopic and nonatopic children. Simões EA, Palivizumab Long-Term Respiratory Outcomes Study Group *J Allergy Clin Immunol.* 2010;126(2):256.

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
- Community study of role of viral infections in exacerbations of asthma in 9-11 year old children. Johnston SL, BMJ. 995;310(6989):1225.

FINALLY



- Asthma is a complex disease
- Genetic
- Environmental interactions eg 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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