Infection and acute exacerbations of Asthma and COPD

Prof Peter Wark
Centre for Asthma and respiratory Disease HMRI, University of Newcastle
Outline

1. Innate and adaptive immune responses in the airways
2. Infection as a causative factor in chronic airways disease
3. Why are those with chronic airways disease susceptible to infections?
4. What can we do to improve outcomes?
INNATE AND ADAPTIVE IMMUNE RESPONSES IN THE AIRWAYS
Pathology of asthma

- Airway smooth muscle hypertrophy
- Basement membrane thickening
- Airway inflammation
Innate immune recognition

- **PAMPS (exogenous)**
  - Viral RNA, dsRNA
  - Bacterial molecules, LPS, flagellin
  - Fungal, β glucan

- **DAMPs (endogenous)**
  - Uric acid and ROS
  - Low molecular weight hyaluronan
  - Lysophosphatidic acid
Epithelial innate immune surveillance-DC immune activation

- TLRs (2,3,4,5)
- RIG-I like helicases
- NOD like receptors
- C-type lectins
- Protease activated receptors
The role of the airway epithelium in innate immunity

- Barrier function
  - Mucociliary clearance
  - Collectins/ defensins
- Surveillance
- Recruitment and activation of effector cells and antigen presenting cells

Schleimer et al JACI 2010
Reducing the AEC activation threshold, leads to an maladaptive innate immune response

Wark et al Exp Rev Respir Med 2014

Disease Risk → Disease Induction → Disease Consolidation → Disease Progression

- TH2 bias
- Innate immune response
- Low level PAMP
- TH2, TH17, TH9
- Maladaptive Innate immune response
- Injury DAMPs/PAMPs
- Remodelling

Genes → Epigenetics → Maternal exposure

Injury Virus → Injury Allergen
Asthma pathogenesis

• Asthma is a disease of the airways, leading to variable airflow obstruction, with:
  – Airway hyperresponsiveness
  – Airway inflammation

• Asthma a chronic cycle of inflammation leading to persistent pathological change/remodelling

Holt & Sly Nat Med 2012
Asthma and the “Hygiene hypothesis”

- Prevalence of asthma has increased in the last 50 years in western societies
- Children growing up on farms in Europe\(^1\)
  - OR for asthma 0.62
  - Exposure to a broader range of microbial agents reduced asthma risk
- Protection even more marked during pregnancy the mother works on a farm or drinks unpasteurised milk\(^2\)

1. Ege NEJM 2011
2. Ege JACI 2007
Farm dust and endotoxin protect against allergy through A20 induction in lung epithelial cells

Schuijs Science 2015
Key role of the innate immune response in leading to asthma

Sly & Holt NEJM 2015
Allergen sensitisation primes early innate immune responses

- HDM (proteolytic allergens and microbial PAMPs)
- Recognised PAR2/TLR4
- EC release TSLP GMCSF
- Primes DC to present Ag TH0 and induce TH2
- TH2 release IL13, IL4 induce EC release TSLP & GMCSF
Epithelial activation of DCs → Asthma


DCs only migrate in response to AEC TLR4 activation

IT LPS only induces response in TLR4 expressing airways
The response to House dust mite allergen, important role for DCs

- DCs depleted from the airways sensitised mice, allergic inflammation did not develop\(^1\)
- DC from sensitised mice → naïve mice → TH2
- Repeated exposure of naïve mice to sensitised DC induce “asthma” \(^2\)

2. Van Rijk AMJRCCM 2011
TH-2 High Asthma

Allergens

TH-2

APC

ILC2

TSLP IL33, IL25

INOS, periostin, eotaxin,

IL-5, IL-13

IL-4, IL-13

IL-5

IL-4

TH-2

B cell

eosinophil

Mast cell

IL-4, IL-13

IL-5

IL-13

IgE

Isotype

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Hunter Medical Research Institute

Hunter New England

NSW Health

THE UNIVERSITY OF NEWCASTLE

Australia
What comes first?

Virus infection?  Allergic sensitisation?
INFECTION AS A CAUSATIVE FACTOR IN CHRONIC AIRWAYS DISEASE
RV induced wheeze in early life leads to asthma at 6 years
Lemanske JACI 2005

- Cohort of children at high risk for asthma
- Viruses identified in 90% wheezing episodes (most RV)
- Asthma at 6 years
  - RV (OR 26)
  - Aeroallergen sensitisation (OR 3.4)
Any airway infection can be associated with early life wheeze and asthma at 7 years.

Bønnelykke et al JACI 2015
RV wheeze does not induce allergic sensitisation

Jackson et al AMJRCM 2012

Viral wheeze leading to allergic sensitisation HR = 0.76 (0.5, 1.1)
The airway microbiome early life infection and asthma at 5yrs  Teo et al  Cell Host Microbe 2015

In partnership with our community

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![Image of the airway microbiome study](image.png)

**C** Healthy samples

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B: Wheezy HRV C LRI

P-value: 0.039 (142)

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VIRAL INFECTION TRIGGERS ACUTE ASTHMA
Seasonal variation in hospital separations for asthma, by age

Source: AIHW National Hospital Morbidity Database 2007 and 2008

Hospital admissions for asthma per 100,000 population

Children

- 0–23 months
- 2–4 years
- 5–14 years

Adults

- 15–34
- 35–64
- 65 and over
Viral infection and acute asthma

Johnston 1995
Freymuth 1999
Rakes 1999
Nicholson 1995
Wark 2001

% acute asthma


Children
Adults
Rhinovirus C dominant in preschool children

Bizzintino ERJ 2011

In partnership with our community

THE UNIVERSITY OF NEWCASTLE AUSTRALIA
HUNTER NEW ENGLAND NSW HEALTH

CENTRE OF EXCELLENCE IN SEVERE ASTHMA
Innovative solutions for severe asthma
Older age more diverse viruses, still lead to more severe disease

LOS increased
• Presence virus
• Lower FEV1

Wark et al Respirol 2013
Reducing the AEC activation threshold, leads to an maladaptive innate immune response

Wark et al Exp Rev Respir Med 2014

Disease Risk  |  Disease Induction  |  Disease Consolidation  |  Disease Progression

- TH2 bias
- Innate immune response
- Low level PAMP
- Injury
- Virus
- Allergen
- Maladaptive innate immune response
- TH2
- TH17
- TH9
- Remodelling
- Injury DAMPs/PAMPs
WHO IS AT RISK OF ACUTE ASTHMA
Epidemiology of acute asthma hospitalisation

1. Age, the very young and the very old
2. Sex
3. Socioeconomic status
4. Indigenous populations, but the pattern is different?
5. Seasonal variation, driven by viral RTI
Predicting exacerbations in asthmatics 6-20yrs  Teach et al JACI 2015

• 400 Inner city US asthmatics
• 37.5% had exacerbations, the majority (28%) in the fall

Multivariate predictive model
Risk of severe asthma exacerbations in optimally treated adult asthmatics?

Bateman et al JACI 2014

- Poor Asthma control
- More severe asthma
- Smoking
- High BMI
Poor asthma control leads to acute asthma.

Does infection worsen asthma?

Does poor asthma control impair antiviral immune responses?
Does viral infection worsen asthma?
Virus infection as a cause of acute asthma

<table>
<thead>
<tr>
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<th>Infection &amp; acute asthma</th>
<th>Non-infective acute asthma</th>
<th>Analysis</th>
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<tbody>
<tr>
<td>Mean FEV&lt;sub&gt;1&lt;/sub&gt; % predicted</td>
<td>63.6</td>
<td>84.6</td>
<td>p = 0.02</td>
</tr>
<tr>
<td>Proportion admitted to hospital %</td>
<td>78</td>
<td>36</td>
<td>p = 0.03</td>
</tr>
<tr>
<td>Median length of stay (days)</td>
<td>2</td>
<td>0</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Median Sputum Neutrophils x10&lt;sup&gt;6&lt;/sup&gt;/ml</td>
<td>5.1</td>
<td>0.8</td>
<td>p &lt; 0.05</td>
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<tr>
<td>Median Sputum Neutrophil elastase μg/ml</td>
<td>3129</td>
<td>169</td>
<td>p &lt; 0.05</td>
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1. Wark et al Eur Resp J 2002; 19: 68
Airway inflammation in experimental RV infection

1 Message et al PNAS 2008;105:13562

(a) BAL Cells (10^6/L)
- Lymphocytes
  - Normal
  - Asthmatic
  - P=0.06
- Eosinophils
  - Normal
  - Asthmatic
  - P=0.004
- Neutrophils
  - Normal
  - Asthmatic
  - P=0.07

(b) Total chest symptom score
- Asthmatics alone
  - r=-0.79, P=0.01

(c) Maximum change in morning PEF (%)
- Asthmatics alone
  - r=-0.74, P=0.021

Day 4 BAL neutrophils (x10^6/L)
RV infection of asthmatic epithelium activates IL-25 and type 2 immunity?

Beale, Bartlett et al. Science TM, 2014
IL-33 and type 2 inflammation during RV infection  

Jackson et al AMJRCCM 2014

Worse symptoms

Increased eosinophils

Increased IL-13, 5, 33
Blocking IL-33 prevents type 2 inflammation during RV infection

Jackson et al AMJRCCM 2014
DOES POOR ASTHMA CONTROL IMPAIR ANTIVIRAL RESPONSES?
RV replicates more efficiently in asthma AECs and this is linked to a reduced Type I IFN response

- RV replicates faster on asthmatic BEC
- Linked to deficient IFN-β response from asthmatic BEC in response to RV

In-vivo IFN-λ production in asthmatics and severity of symptoms


- Significant inverse correlations between IFN-λ
  - BAL virus load
  - Recruitment of inflammatory cells
  - Severity of symptoms
Asthmatic AEC express innate immune triggers

Parsons et al Clin Exp Allergy 2014
Impaired antiviral response in asthma independent of MDA-5 expression

Parsons et al Clin Exp Allergy 2014
But not all asthmatics have impaired antiviral responses?
Interferon (IFN)-λ2/3 mRNA induction after rhinovirus (RV)-1B and RV16 was not different in subjects with mild controlled asthma compared with healthy controls.

Annemarie Sykes et al. Thorax 2014;69:240-246
Impaired innate interferon induction in severe therapy resistant atopic asthmatic children

Mucosal Immunology (2013) 6, 797-806;
doi:10.1038/mi.2012.118
Uncontrolled allergic asthma impairs antiviral responses

- Mice with impaired antiviral responses (TLR7 knockout) had increased viral replication
- Mice with allergic inflammation induced had
  - Eosinophilic inflammation and AHR
  - Impaired antiviral TLR7 expression
  - Increased RV replication

Hatchwell et al Thorax 2015
Uncontrolled eosinophilic airway inflammation is associated with impaired antiviral immune (TLR7) responses

Hatchwell et al Thorax 2015
Allergen induced IL-33 impairs antiviral responses

Lynch et al  JACI 2016

Sensitization impairs antiviral response

IL-33 reduces pDC recruitment and antiviral responses
IgE cross linking on pDCs impairs antiviral responses via FcεRI Gill et al JI 2010

- pDCs express sense virus via TLR7/9 and release IFNα
- Allergic asthma pDCs also express FcεRIα and present Ag to T cells
- pDCs from allergic asthmatics and controls, cultured with influenza asthmatics reduced IFN, inverse to serum IgE

Cross linking IgE on pDCs reduced IFNα to Flu and TLR7 agonist
IgE cross linking on pDCs impairs antiviral responses via FcεRI  

- Durrani et al JACI 2012: RV induces less IFN-α and IFN-λ1 from pDCs
- Pritchard et al JI 2012; pDCs should constrain TH2 responses to RV
TREATMENT THAT TARGETS INFLAMMATION, IMPROVES ASTHMA OUTCOMES, AND REDUCES EXACERBATIONS
Treatment and asthma mortality

Deaths per 100,000 population

- Beclomethasone

Year:
- 1911 to 2006

Population groups:
- All ages
- 5 to 34 years
Omalizumab for asthma
Normansell et al Cochrane Database Syst Rev 2014

- Moderate to severe allergic asthma
- 10 trials, n=3261
- >6 years
- Reduced
  - Exacerbations requiring OCS
  - Hospitalisations
Randomized Trial of Omalizumab (Anti-IgE) for Asthma in Inner-City Children
Busse et al NEJM 2011

- 490, 6-20yr with asthma
- Guideline therapy and then either Omalizumab or placebo
- Omalizumab
  - Reduced exacerbations
  - Improved symptom scores
  - Greatest reduction was seen in fall
  - No difference in RV isolation or colds
• 319 Asthma with history of cold induced exacerbations

• Control
  – ACQ 1.6
  – FEV190%
  – 58 BTS step 4-5

• 147 randomised
Inhaled interferon for acute virus asthma

Djukanovic et al

AMJRCM 2014

A

Change in ACQ-6 from Treatment Baseline

difference 0.11, p=0.469

Clinically relevant difference

No change

Placebo IFN-β

B

Change in ACQ-6 from Treatment Baseline

difference 0.63, p=0.004

Clinically relevant difference

No change

Placebo IFN-β

C

Change in Morning PEF from Day 2 (L/min)

-60 0 20 40 60

2 3 4 5 6 7 8 9 10 11 12 13 14

Study day

D

Change in Morning PEF from Day 2 (L/min)

-60 0 20 40 60

2 3 4 5 6 7 8 9 10 11 12 13 14

Study day
Conclusions

• Acute asthma remains an important clinical challenge;
  – especially in the young and the old
  – Seasonal variation linked closely to viral infection
• Asthma control is crucial in preventing acute exacerbations, achieved by controlling asthmatic inflammation
• In those with severe uncontrolled asthma important questions remain
  – What is the link between asthmatic inflammation and impaired antiviral responses?
  – Can the addition of nebulised interferon prevent virus asthma exacerbations
Acknowledgments

• University of Newcastle
  – Mrs Kristy Nichol
  – Mr Prabuddha Pathinyake
  – Dr Nathan Bartlett
  – Prof Phil Hansbro
  – Prof Darryl Knight
  – Prof Peter Gibson

• Prof Seb Johnston, Imperial College London

• Prof Donna Davies, Prof Ratko Djuknaovic, Prof S Holgate Synairgen and University of Southampton.