Asthma and the Airway Microbiome: New Insights and Hypotheses

Yvonne J. Huang, MD
Division of Pulmonary and Critical Care Medicine
Department of Internal Medicine
University of Michigan, Ann Arbor

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Objectives

- Asthma Overview
- Origins of childhood asthma (microbiome)
- Adult asthma and the importance of phenotypes
- Adult asthma and the airway microbiome
- Unanswered questions, new lines of investigation
Global Prevalence of Asthma

- 300 million globally have asthma; 22 million in U.S.
- In 2013, asthma-related medical costs and lost days of productivity in the U.S. amounted to $56 billion.

Masoli et al. Allergy 2004; Science 2011
Links between the microbiome and development of allergy or asthma

Shaping of gut and airway microbiota, Immune development

Marsland, Annals ATS 2013
GINA 2014 new definition:
“Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.”
Asthma Susceptibility Genes

Microbial recognition, Immunoregulation

Epithelial cells: Chemokines, antimicrobial peptides

Type 2 effector functions

Asthma has many different phenotypes

- Onset/triggers  
- Clinical severity  
- Airway inflammation  

Disease control  
Disease risk  
Response to therapy
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- Onset/triggers
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Disease control
Disease risk
Response to therapy

Wenzel, Nature Medicine 2012

Haldar et al. Am J Respir Crit Care Med 2008
Relevance of type 2-“high” vs. type 2-“low” inflammatory phenotypes in asthma

Woodruff et al, Am J Respir Crit Care Med 2009
A large subgroup of mild-moderate asthma is persistently non-eosinophilic

ICS-negative

ICS-positive

Mcgrath et al, AJRCCM 2012
A significant proportion of adult asthmatics do not have type 2-driven asthma (50%).

Inhaled corticosteroids (ICS) and newer biologics (type 2-targeting) do not work as well in type 2-“low” asthma.

A survey of 1000 patients indicated 86% of asthmatics on controller therapies (i.e. ICS) still had sub-optimal or poor asthma control. (Colice et al. Annals Allerg Asthma Immunol 2012)

What are the drivers of type 2-”low” asthma?
Adult Asthma and Potential Influence of the Microbiome

What are the known relationships between asthma, the airway microbiome, and inflammation?
1. Does lower airway microbiota composition differ between asthmatic and healthy adults?

- Some asthmatics harbor higher bacterial burden and diversity in the lower airways.
In mild asthma, the lower respiratory tract is enriched in certain bacteria (Proteobacteria) compared to healthy controls.

Sputum

Marri et al. JACI 2013
2. Are patterns of lower airway microbiota composition associated with phenotypic features of asthma?

- In mild-moderate asthma, greater diversity (β- and γ-Proteobacteria) is correlated with more severe airway hyper-responsiveness.

β- and γ-Proteobacteria = 60% of taxa correlated with worse airway hyper-response.

Huang et al. JACI 2011
Characteristics of the airway microbiota may play a role in asthma therapeutic response (example: macrolide).

Huang et al. JACI 2011
In severe asthma, bacterial microbiota patterns are differentially associated with phenotypic features.

Obese severe asthmatics demonstrate increased bronchial abundance of certain bacteria.

**Bacteroidetes**
- Prevotella
- Flavobacteria

**Firmicutes**
- Clostridiales
- Lachnospiraceae
- Fusobacteria

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**Phylum (Family)**
- Bacteroidetes (Flavobacteriaceae)
- Bacteroidetes (Prevotellaceae)
- Bacteroidetes (Rikenellaceae II)
- Chlorobi (OPB56)
- Firmicutes (Clostridiales Family XI. Incertae Sedis)
- Firmicutes (Clostridiales Family XIII. Incertae Sedis)
- Firmicutes (Lachnospiraceae)
- Fusobacteria (Fusobacteriaceae)
- Proteobacteria (Desulfobacteraceae)
- Proteobacteria (Helicobacteraceae)
- Spirochaetes (Spirochaetaceae)
- Tenericutes (Erysipelotrichaceae)
- Tenericutes (Mycoplasmataceae)

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**Severe Asthma**

**BMI (severe asthma grp)**

$R_s = 0.61, p < 0.05$
Worse symptom control in severe asthma is correlated with greater abundance of predominantly Proteobacteria members.

448 taxa; R = 0.5 – 0.8, FDR-adj p < 0.05
Better symptom control in severe asthma is correlated with greater relative abundance of Actinobacteria

362 taxa; $R = -0.5$ to $-0.8$, FDR-adjusted $p < 0.05$
Expression levels of a steroid-responsive gene in airway epithelial cells correlate with greater bacterial diversity, mostly Actinobacteria.

83 taxa, FDR-adjusted q-value < 0.10

Huang et al. *JACI* in press
A distinct group of bacteria are associated with airway epithelial expression of genes related to Th17 inflammation.
Asthma

Observable characteristics

Phenotypes

“Endotypes”

Microbiome

Condition subtype defined by distinct functional or pathophysiological mechanism
NIH AsthmaNet Microbiome Proof-of-Concept study (NCT01537133)

1. Allergic, Asthmatic
2. Allergic, Non-asthmatic
3. Healthy

- Oral wash
- Sputum
- Bronchoscopy
- Stool

Airway microbiome analysis
Effect of inhaled steroids
Immune profiling (blood, lung)
University of Michigan
Characterization of Adults for Asthma Microbiome Research Studies (CAARS)

Key: ICS = inhaled corticosteroid; Q, questionnaires; S, spirometry; MC, methacholine challenge; AR, airway reversibility; IS, induced sputum; Stl, stool sample.

- Asthmatics on ICS
- Asthmatics, ICS-naive
- Healthy controls

Visit 1
Screen (Q, Bld, S, MC, IS, Stl)
Visit 2
Phone call (Q, S, AR, IS, Stl)

Screen

Visit 1

Visit 2

Prospective observational, longitudinal
Detailed subject characterization and sample/data collection:
- Lung function assessments
- Multiple questionnaires (asthma control, sino-nasal symptoms, environmental microbial exposures, detailed dietary history)
- Sputum, oral wash, stool, blood, urine
Some Research Questions (clinical)

1. Is airway enrichment in specific bacteria predictive of worse asthma outcomes?
   - Bacterial biomarkers in clinically accessible sample types?

2. What is the stability of the airway microbiome in adult asthma, and its relationship to environmental exposures, even diet?

3. Does the respiratory microbiome differ between obese and non-obese individuals, with or without asthma?

4. Does the gut microbiome differ in adults with asthma?

5. Are patterns of gut dysbiosis associated with phenotypic features of asthma, including worse outcomes?
• What is the impact of pulmonary therapeutics on the microbiome?
• Do the above result in treatment-refractory asthma subtypes?
  ➢ Mechanisms?
• Does the respiratory microbiome play a role in therapeutic response?
  ➢ Biomarkers? microbial-derived therapeutics?
• Alveolar macrophage responses to steroids may be altered in the presence of specific bacteria (*H. parainfluenzae*)

Goleva et al. AJRCCM 2013

• Steroids (beclomethasone) can alter behavior of *H. influenzae*

Earl et al. EMBO Mol Med 2015
Summary

1. Mounting evidence implicates a role for the respiratory microbiome in the phenotypic heterogeneity of adult asthma.

2. Despite the known influence of gut microbiota in early life susceptibility to allergy or asthma, little is known about the GI microbiome in relation to adult asthma.

1. Potentially important interactions may exist between the respiratory microbiome and treatments used for asthma and other chronic airway diseases.
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yvjhuang@umich.edu

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