Agenda

Friday, July 29

9:00 am: **Registration opens**
Sheraton Ballroom Promenade, Level 4

11:00 am: **Exhibits open and Lunch Served**
Sheraton Ballroom IV – V, Level 4

Asthma Inception and Progression
1:00 – 4:30 pm

Moderators: Daniel J. Jackson, MD and David B. Peden, MD MS FAAAAI

Objectives: Describe the mechanistic characteristics of asthma in young children; Identify appropriate treatment methodologies for young children with asthma.

1:00 pm: **Plenary: When and How Does Asthma Begin?**
Sheraton Ballroom I-III, Level 4
Robert F. Lemanske, Jr., MD FAAAAI

1:30 pm: **Symposium**
Sheraton Ballroom I-III, Level 4
- **Basic: Immunology of Childhood Asthma**
  Patrick G. Holt, DSc
- **Translational: Early Life Events in Asthma Expression**
  Fernando D. Martinez, MD
- **Clinical: Treatment Approaches to Preschool Wheezing Illnesses**
  Leonard B. Bacharier, MD FAAAAI

2:30 pm: **Break and Refreshments Served**

3:00 pm: **Discussion Workshops**
- **Group 1:** Sheraton Ballroom I-III, Level 4
  Moderator: Leonard B. Bacharier, MD FAAAAI
- **Group 2:** Sheraton Ballroom I-III, Level 4
  Moderator: James E. Gern, MD FAAAAI
- **Group 3:** Ohio Meeting Room, Level 2
  Moderator: John M. Kelso, MD FAAAAI
- **Group 4:** Mississippi Meeting Room, Level 2
  Moderator: Patrick G. Holt, DSc
- **Group 5:** Arkansas Meeting Room, Level 2
  Moderator: Daniel J. Jackson, MD
- **Group 6:** Colorado Meeting Room, Level 2
  Moderator: Fernando D. Martinez, MD
- **Group 7:** Missouri Meeting Room, Level 2
  Moderator: Stanley J. Szefler, MD FAAAAI

4:00 pm: **Reconvene for Discussion Workshop Summary**
Sheraton Ballroom I-III, Level 4

4:45 pm: **Wine and Cheese Poster Session**
Sheraton Ballroom IV – V, Level 4

Agenda

Saturday, July 30

7:00 am: **Registration Opens**
Sheraton Ballroom Promenade, Level 4
Exhibits Open and Continental Breakfast Served
Sheraton Ballroom IV – V, Level 4

Reducing and/or Eliminating Asthma Exacerbations
8:00 – 11:30 am

Moderator: Jacqueline A. Pongracic, MD FAAAAI

Objectives: Describe the biological characteristics of asthma exacerbations; Outline the appropriate use of biologic therapies to treat asthma exacerbations.

8:00 am: **Plenary: Identifying Biologic Targets to Attenuate or Eliminate Asthma Exacerbations**
Sheraton Ballroom I-III, Level 4
William W. Busse, MD FAAAAI

8:30 am: **Symposium**
Sheraton Ballroom I-III, Level 4
- **Basic: Immunopathologic Features of Asthma Exacerbations**
  Mario Castro, MD MPH
- **Translational: Acute Physiologic Characteristics and Long Term Clinical Consequences of Asthma Exacerbations**
  Stephen P. Peters, MD PhD FAAAAI
- **Clinical: Precision Asthma Therapy: Picking the Right Biologic for the Right Patient**
  Thomas B. Casale, MD FAAAAI

9:30 am: **Break and Refreshments Served**

10:00 am: **Discussion Workshops**
- **Group 1:** Sheraton Ballroom I-III, Level 4
  Moderator: William W. Busse, MD FAAAAI
- **Group 2:** Sheraton Ballroom I-III, Level 4
  Moderator: Thomas B. Casale, MD FAAAAI
- **Group 3:** Ohio Meeting Room, Level 2
  Moderator: Mario Castro, MD MPH
- **Group 4:** Mississippi Meeting Room, Level 2
  Moderator: Monica Kraft, MD FAAAAI
- **Group 5:** Arkansas Meeting Room, Level 2
  Moderator: Robert Lemanske, Jr., MD FAAAAI
- **Group 6:** Colorado Meeting Room, Level 2
  Moderator: Stephen P. Peters, MD PhD FAAAAI
- **Group 7:** Missouri Meeting Room, Level 2
  Moderator: Jacqueline A. Pongracic, MD FAAAAI

11:00 am: **Reconvene for Discussion Workshop Summary**
Sheraton Ballroom I-III, Level 4

11:30 am: **Lunch and Exhibit Visitation**
Sheraton Ballroom IV – V, Level 4

Agenda

Saturday, July 30 (Cont.)

Preventing and Treating Severe Asthma
1:00 – 4:30 pm

Moderators: Lewis J. Smith, MD and Daniel Rotrosen, MD

Objectives: Define the mechanistic and clinical characteristics of severe asthma; Differentiate difficult to treat from severe asthma

1:00 pm: **Plenary: Severe Asthma: Can it be Prevented or Reversed?**
Sheraton Ballroom I-III, Level 4
Sally E. Wenzel, MD FAAAAI

1:30 pm: **Symposium**
Sheraton Ballroom I-III, Level 4
- **Basic: Airway Structural Alterations that Contribute to Severe Asthma**
  Reynold A. Panettieri, Jr., MD
- **Translational: Novel Molecular Targets for Severe Asthma**
  Harald E. Renz, MD FAAAAI
- **Clinical: Differentiating Difficult to Treat from Severe Asthma**
  Monica Kraft, MD FAAAAI

2:30 pm: **Break and Refreshments Served**
Sheraton Ballroom IV – V, Level 4

3:00 pm: **Exhibits Close and Abstract Posters Removed**

3:00 pm: **Discussion Workshops**
- **Group 1:** Sheraton Ballroom I-III, Level 4
  Moderator: Andrea J. Apter, MD MA MSc FAAAAI
- **Group 2:** Sheraton Ballroom I-III, Level 4
  Moderator: Theresa W. Guilbert, MD MS
- **Group 3:** Ohio Meeting Room, Level 2
  Moderator: Monica Kraft, MD FAAAAI
- **Group 4:** Mississippi Meeting Room, Level 2
  Moderator: Reynold A. Panettieri, Jr., MD
- **Group 5:** Arkansas Meeting Room, Level 2
  Moderator: Harald E. Renz, MD FAAAAI
- **Group 6:** Colorado Meeting Room, Level 2
  Moderator: Lewis J. Smith, MD
- **Group 7:** Missouri Meeting Room, Level 2
  Moderator: Sally E. Wenzel, MD FAAAAI

4:00 pm: **Reconvene for Discussion Workshop Summary**
Sheraton Ballroom I-III, Level 4

Agenda

Sunday July 31:

7:00 am: **Registration Opens and Continental Breakfast Served**
Sheraton Ballroom Promenade, Level 4

Asthma and COPD Overlap Syndrome (ACOS)
8:00 – 11:30 am

Moderator: James P. Kiley, PhD

Objective: Compare and contrast the biological and environmental characteristics of asthma and COPD; Define appropriate treatment strategies of ACOS

8:00 am: **Plenary: Moving from the Oslerian Paradigm to the Post-genomic Era: Are Asthma and COPD Outdated Terms?**
Sheraton Ballroom I-III, Level 4
Nicola A. Hanania, MD MS

8:30 am: **Symposium**
Sheraton Ballroom I-III, Level 4
- **Basic: Pathophysiologic Mechanisms of Asthma and COPD**
  Arthur F. Gelb, MD
- **Translational: Influence of Environmental Factors on Asthma and COPD**
  David B. Peden, MD MS FAAAAI
- **Clinical: Precision Therapy for ACOS**
  Joe W. Ramsdell, MD

9:30 am: **Break and Refreshments Served**

10:00 am: **Discussion Workshops**
- **Group 1:** Sheraton Ballroom I-III, Level 4
  Moderator: Thomas B. Casale, MD FAAAAI
- **Group 2:** Sheraton Ballroom I-III, Level 4
  Moderator: Jim Donahue, MD
- **Group 3:** Ohio Meeting Room, Level 2
  Moderator: Arthur F. Gelb, MD
- **Group 4:** Mississippi Meeting Room, Level 2
  Moderator: Nicola A. Hanania, MD MS
- **Group 5:** Arkansas Meeting Room, Level 2
  Moderator: David B. Peden, MD MS FAAAAI
- **Group 6:** Colorado Meeting Room, Level 2
  Moderator: Stokes Peebles, Jr., MD FAAAAI
- **Group 7:** Missouri Meeting Room, Level 2
  Moderator: Joe W. Ramsdell, MD

11:00 am: **Reconvene for Discussion Workshop Summary**
Sheraton Ballroom I-III, Level 4

11:30 am: **Conference summary**
Sheraton Ballroom I-III, Level 4

12:00 pm: **Meeting concludes**

Friday, July 29

This program is not sponsored or programmed by the AAAAI.

Problem-Based Learning: An Interactive Case Discussion of a Patient with Asthma
Friday, July 29, 6:30 to 8:30 pm
Sheraton Grand Chicago, Mayfair, Level 2
Sponsored by Teva Respiratory.

Join us for an interactive case-based presentation delivered in a problem-based learning format, presented by Dr. Ray S. Davis.

Presenter
Ray S. Davis, MD
Professor in Clinical Pediatrics
Division of Allergy Immunology & Pulmonary Medicine
Washington University School of Medicine
St. Louis, Missouri

Saturday, July 30

This program is not sponsored or programmed by the AAAAI.

A Clinical Discussion on Severe Eosinophilic Asthma and Its Management
Saturday, July 30, 4:45 to 6:30 pm
Check in begins at 4:30 pm
Sheraton Grand Chicago, Mayfair, Level 2
Sponsored by Teva Respiratory.

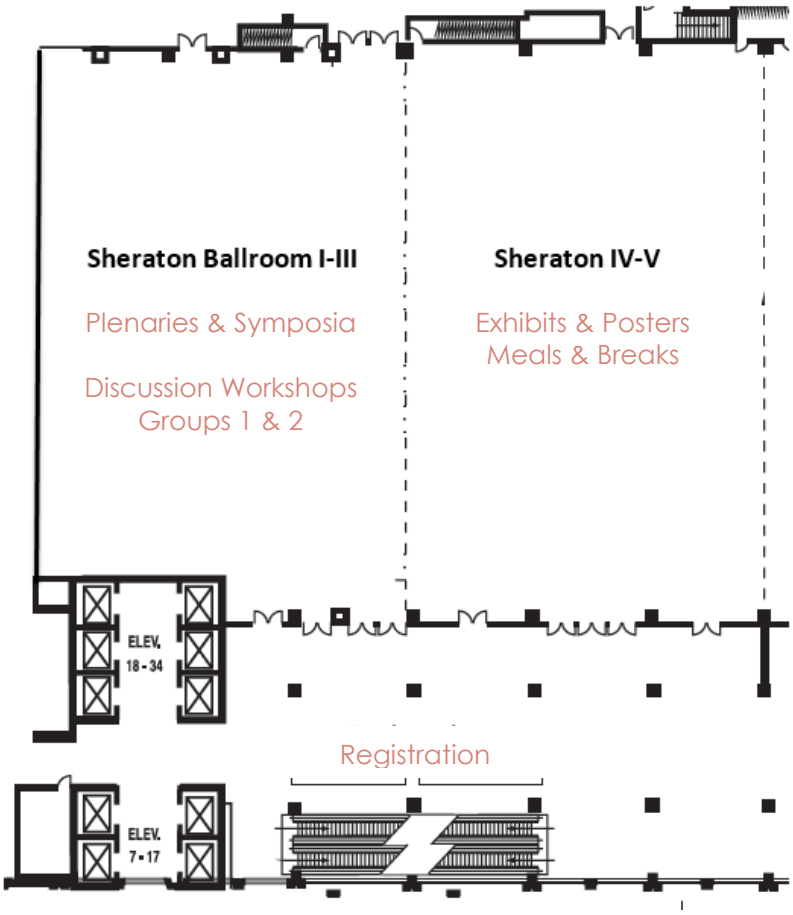
A review of considerations in the diagnosis and management of severe eosinophilic asthma.

Presenters
Mario Castro MD, MPH, FCCP
Alan A. and Edith L. Wolff Professor of
Pulmonary and Critical Care Medicine
Professor of Medicine and Pediatrics
Washington University School of Medicine
St. Louis, Missouri

Flo Deleon, RN, BSN
Manager, Regional Field Nursing
Teva Pharmaceuticals

Floorplans

Sheraton Grand Chicago – 4th Floor



Sheraton Grand Chicago – 2nd Floor

PQRS, MACRA and MOC: The AAAAI has you covered!

The Medicare Access and CHIP Reauthorization Act of 2015 (**MACRA**) establishes new ways to pay physicians for caring for Medicare beneficiaries, and includes opportunities for QCDRs to fulfill the following:

The registry can help you to satisfy the following activities:

- Three Merit-Based Incentive Payment System (MIPS) categories: Starting in 2017, Quality, Advancing Care Information (ACI) and Clinical Practice Improvement Activity (CPIA) compromise 90% of the composite performance score. **The AAAAI QCDR can help you to fulfill these requirements.**
- Physician Quality Reporting System (PQRS) program: **The AAAAI QCDR can still be used for the 2016 PQRS reporting before the 2017 MIPS reporting is in effect.**
- PQRS Reporting Options: **The AAAAI QCDR offers either individual or Group Practice Reporting Option (GPRO) for groups of 2 or more eligible providers.**
- Meaningful Use (MU) public health reporting: **The AAAAI QCDR can be used as a specialized registry for allergen/immunology.**
- **NEW!** MOC Credits for CME Activities: **The AAAAI QCDR has been approved for MOC Part IV for up to 20 AMA PRA Category 1 CME Credits™.**

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General questions about the registry: Email: QCDR@aaaai.org Phone: 414-272-6071
For Technical Support Contact: support@medconcert.com

American Academy of Allergy Asthma & Immunology

CECITYREGISTRY® A CMS Qualified Clinical Data Registry

2016 AAAAI QCDR Measures

www.aaaai.org/QCDR

Allergen Immunotherapy Measures
Allergen Immunotherapy Treatment: Allergen Specific Immunoglobulin E (IgE) Sensitivity Assessed and Documented Prior to Treatment *1
Documentation of Clinical Response to Allergen Immunotherapy within One Year *1
Documented Rationale to Support Long-Term Aeroallergen Immunotherapy Beyond Five Years, as Indicated *1
Achievement of Projected Effective Dose of Standardized Allergens for Patient Treated With Allergen Immunotherapy for at Least One Year *1
Assessment of Asthma Symptoms Prior to Administration of Allergen Immunotherapy Injection(s) *1
Documentation of the Consent Process for Subcutaneous Allergen Immunotherapy in the Medical Record *1
Asthma Measures
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Optimal Asthma Control *3
Assessment of Asthma Control - Ambulatory Care Setting *4
Asthma Control: Minimal Important Difference Improvement *2
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Adult Sinusitis: Computerized Tomography for Acute Sinusitis (Overuse) *5
Adult Sinusitis: More than One Computerized Tomography (CT) Scan Within 90 Days for Chronic Sinusitis (Overuse) *5
General Care Measures
Preventing Care and Screening: Tobacco Use: Screening and Cessation Intervention *4
Tobacco Use and Help with Quitting Among Adolescents *6
Pneumonia Vaccination Status for Older Adults *6
Documentation of Current Medications in the Medical Record *6
Body Mass Index *7
Preventive Care and Screening: Influenza Immunization *4
Additional electronic Clinical Quality Measures (e-CQMs) added to the registry
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Closing the Referral Loop: Receipt of Specialist Report *7
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Appropriate Testing for Children with Pharyngitis *6
Use of High-Risk Medications in the Elderly *6
Childhood Immunization Status *6
Use of Appropriate Medications for Asthma *6

*Measure Steward: 1 (JTF QPM) 2 (AAAAI) 3 (MNCM) 4 (AMA/PCPI) 5 (AAO) 6 (NCQA) 7 (CMS)

JTF QPM (AAAAI/ACAAI Joint Task Force on Quality Performance Measures)
AAAAI (American Academy of Allergy Asthma & Immunology)
MNCM (Minnesota Community Measurement)
AMA/PCPI (American Medical Association/Physician Consortium for Performance Improvement)
AAO (American Academy of Otolaryngology)
NCQA (National Committee for Quality Assurance)
CMS (Centers for Medicare & Medicaid Services)

American Academy of Allergy Asthma & Immunology

CECITYREGISTRY
A CMS Qualified Clinical Data Registry

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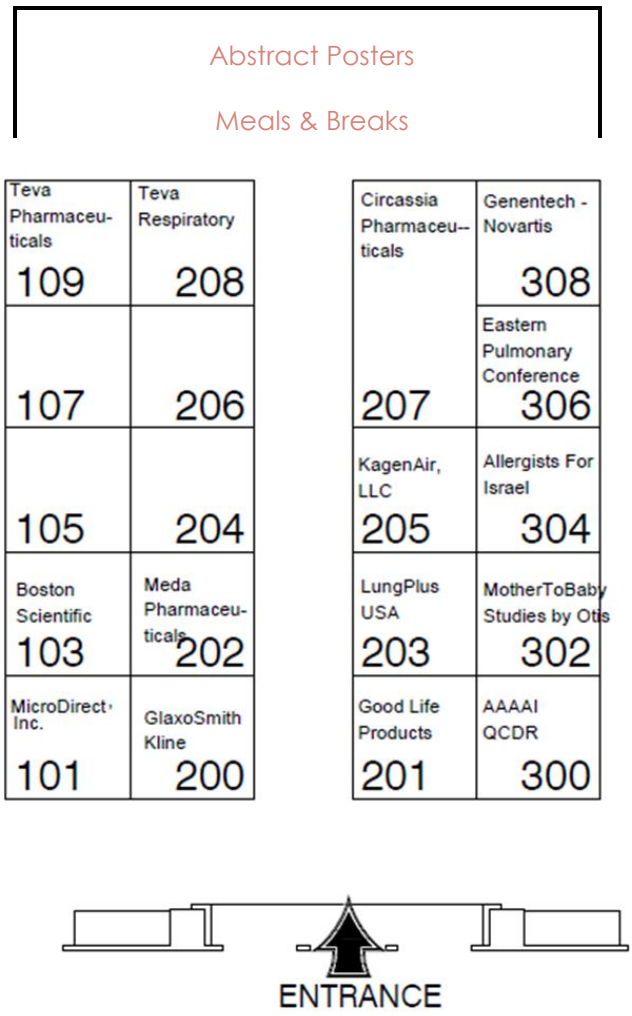

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AAAAI Quality Clinical Data Registry on Allergy and Asthma, in cooperation with CE City
555 E. Wells Street
Suite 1100
Milwaukee, WI 53202
Phone: (414) 272-6071
http://aaaai.org
Booth #300
Physician Education
The AAAAI Quality Clinical Data Registry (QCDR) in collaboration with CECity is a CMS approved registry for the Physician Quality Reporting System (PQRS) program year. The AAAAI QCDR is the only PQRS reporting option with allergen immunotherapy measures available for reporting and is designed as a practice improvement tool.

Allergists For Israel
10464 Stablehand Drive
Cincinnati, OH 45242
Phone: (515) 673-7420
http://allergists4israel.org
Booth #304
Physician Education
AFI is promoting the 2016 WISC Meeting of the WAO to be held in Israel in December. AFI is a mutually collaborating partner with WAO and IAACI.

Boston Scientific
100 Boston Scientific Way
Marlborough, MA 01752
Phone: (888) 272-1001
http://btforasthma.com
Booth #103
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Boston Scientific is dedicated to transforming lives through innovative medical solutions and multi-disciplinary approaches that improve the health of patients. Bronchial Thermoplasty, delivered by the Alair™ System, is a safe, one-time, non-drug intervention for adult patients with severe asthma - clinically proven to provide long-lasting reduction in exacerbations. Visit us at #103 and www.BTforAsthma.com.

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Chicago, IL 60606
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Booth #207
Pharmaceuticals
Leading specialty biopharmaceutical company meeting the needs of patients around the world with our market-leading asthma management products and exciting development pipeline of treatments for allergy, asthma and COPD.

Eastern Pulmonary Conference
450 Veterans Memorial Parkway, Building #15
East Providence, RI 02914
Phone: (401) 223-1309
http://easternpulmonaryconference.org
Booth #306
Physician Education
Eastern Pulmonary Conference (CME program) blends the interactivity characteristic of small regional conferences together with the cutting edge science characteristic of large national meetings. The educational goal is to share clinically relevant information which improves the diagnostic accuracy and the effectiveness of treatments with practitioners who treat pulmonary diseases.

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Phone: (714) 540-5595
http://unimedmassager.com
Booth #201
Other
Digital Massager, TENs unit.

GlaxoSmithKline
2512 S. Tri-Center Blvd.
Research Triangle Park, NC 27709
Phone: (888) 825-5249
http://www.gsk.com
Booth #200
Pharmaceuticals
Nucala - Biological medicine indicated for severe asthma.

KagenAir, LLC
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Appleton, WI 54911
Phone: (920) 739-9100
http://www.KagenAir.com
Booth #205
Computer Hardware/Software
Monitor and communicate with your patients with KagenAir. Designed for Your Successful Practice: KagenAir offers you secure Telemedicine services and validated asthma outcomes questionnaires in a Free App for iPhone and Android smartphones as seen at the AAAAI Annual Meeting in Los Angeles. Download the KagenAir App at: www.KagenAir.com.

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Duluth, MN 55810
Phone: (218) 355-0960
http://lungplususa.com
Booth #203
Equipment/Supplies
Lungplus is a mouthworn humidifier and heat exchanger that helps those with asthma, COPD and other breathing challenges. The unit is easy to use, keeps your face dry and your glasses fog free. After use, clean by rinsing in hot water or putting it in the dishwasher and it will last forever.

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http://meda.us
Booth #202
Pharmaceuticals
Meda is a leading international specialty pharma company with a broad product portfolio and its own sales organizations in almost 60 countries. Meda's product portfolio is divided into three main areas: specialty products, OTCs and branded generics. In the US, Meda has a strong history in respiratory innovation, with a focus in allergy and asthma.

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Lewiston, ME 04240
Phone: (800) 588-3381
http://mdspiro.com
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MotherToBaby Pregnancy Studies conducted by OTIS
9500 Gilman Drive
Mailcode 0828
La Jolla, CA 92093
Phone: (877) 311-8972
http://mothertobaby.org
Booth #302
Patient/Public Education
MotherToBaby, a non-profit service of the Organization of Teratology Information Specialists (OTIS), provides evidence-based information to healthcare professionals, and the public about exposures during pregnancy and breastfeeding. MotherToBaby is conducting an observational research study to evaluate the effects from asthma, and the safety of medications and vaccinations, on pregnancy outcome.

Teva Pharmaceuticals
41 Moores Road
Frazer, PA 19355
Phone: (816) 718-1624
http://tevausa.com
Booth #109
Pharmaceuticals
At Teva, we're passionate about improving quality of life and healthcare globally. This is our ongoing mission as we touch the lives of millions of patients every day, and billions of patients every year.

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Frazer, PA 19355
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http://tevausa.com
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Guidelines for Management of Asthma

https://education.aaaai.org/asthma-education

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https://education.aaaai.org/immunotherapy-education

Contact cme@aaaai.org for more information.

Faculty Biographies

Andrea J. Apter, MD, MSc, MA, FAAAAI
Andrea J. Apter, MD, MSc, MA, FAAAAI, is Professor of Medicine, Chief and Program Director of the Section of Allergy & Immunology at the Perelman School of Medicine of the University of Pennsylvania. Her research focuses on asthma, the environmental and social factors that influence disease, patient-clinician communication including electronic communication, access to care, and the impact of health literacy on health, all with the goal of reducing health disparities. Dr. Apter is the recipient of research awards from the NIH/NHLBI which has included research grants and two career development awards. Currently, she holds an NHLBI grant testing the ability of a patient advocate to improve real-world asthma management for adults with moderate or severe asthma who live in the inner city and one from the Patient-Centered Outcomes Research Institute (PCORI) to assess the ability of the electronic health record and home visits by community health workers to improve access and communication and asthma outcomes for low income urban asthmatic adults. Dr. Apter has served as a director of the American Board of Allergy and Immunology and just completed a term on the AAAAI Board of Directors.

Leonard Bacharier, MD, FAAAAI
Leonard Bacharier, MD, FAAAAI, is Professor of Pediatrics and Medicine and the Harvey R. Colten, MD, Scholar in Pediatrics at Washington University School of Medicine, USA Clinical Director of the Division of Pediatric Allergy, Immunology and Pulmonary Medicine, and Unit Co-Leader for the Pediatric Patient Oriented Research Unit. His research focuses on childhood asthma. Specifically, he is a Principal Investigator in the NHLBI-funded AsthmaNet, a multi-centered network examining therapeutic approaches to childhood asthma. He is an investigator in the NHLBI's Severe Asthma Research Program (SARP) and the NIAID's Inner City Asthma Consortium's URECA study examining the influence of urban environments on the development of asthma and allergic disorders. Dr. Bacharier is also currently investigating the role of early infection with Respiratory Syncytial Virus upon the subsequent development of asthma. These research projects have been published in numerous journals, including the New England Journal of Medicine, The Journal of the American Medical Association, The Journal of Allergy and Clinical Immunology, Pediatrics, and The American Journal of Respiratory and Critical Care Medicine.

William W. Busse, MD, FAAAAI
William W. Busse, MD, FAAAAI, has been a faculty member with the University of Wisconsin Madison since 1974. He was the Chair of the Department of Medicine from 2004 to 2009. He served as AAAAI President from 2000 to 2001 and currently serves as the Chair of the AAAAI Foundation Council. Dr. Busse's research interests have included mechanisms of asthma, in which he has received funding for over 30 years from the National Institute of Health (NIH). In addition, Dr. Busse has served as a NIH advisor and member of the National Heart, Lung and Blood Institute (NHLBI) Council and is currently on the Board of External Experts. He is also an original member of the NIH-sponsored Asthma Guidelines (for which he was chair of the Expert Panel Report 3). He is presently the principal investigator of the NIH supported Inner City Asthma Consortium.

Thomas B. Casale, MD, FAAAAI
Thomas B. Casale, MD, FAAAAI, did an A/I fellowship at the National Institutes of Health, where he was chief medical staff fellow. He then joined the University of Iowa where he attained the rank of Professor of Medicine and Director of A/I. Before joining the University of South Florida Division of Allergy and Immunology as Professor of Medicine and Pediatrics and Chief of Clinical and Translational Research, Dr. Casale was a Professor of Medicine and Medical Microbiology and Immunology and Chief of Allergy/Immunology at Creighton University in Omaha. He is a

past President of the AAAAI and is the current Executive Vice President. Dr. Casale helped developed ASTHMA IQ, which is widely used to improve asthma care by both specialists and primary care physicians. He is a past member of the Board of Directors of the World Allergy Organization and a former chair of the American Board of Allergy and Immunology. Dr. Casale's research interests are directed toward determination and treatment of the pathophysiologic mechanisms involved in asthma and allergic diseases. He has published over 325 scientific papers, reviews and chapters on these topics.

Mario Castro, MD, MPH
Mario Castro, MD, MPH, is the Alan A. and Edith L. Wolff Professor of Medicine and Pediatrics at Washington University School of Medicine in St. Louis, Missouri. He is also Adjunct Associate Professor of Community Health at St. Louis University School of Public Health. He is the Director of the Asthma and Airway Translational Research Unit, Director of the Office for Faculty Development in the Department of Medicine, and Director of Training Grant Programs in the Clinical Research Training Center. On the research side, he is following children from very early in life and looking at how their genetic, biologic and immune responses as well as their environment are coming together to cause some of them to develop asthma (NIH RSV Bronchiolitis in Early Life (RBEL) study). He is also studying what causes asthma through the NIH Asthma and Allergic Disease Clinical Research Center (AADCRC) grant and what makes severe asthma different from milder forms (Severe Asthma Research Program (SARP)). He is the lead investigator for two major asthma networks, which are studying better ways to treat asthma.

James F. Donohue, MD
James F. Donohue, MD is a Professor of Medicine and former Division Chief of Pulmonary Diseases and Critical Care Medicine at the University of North Carolina at Chapel Hill in Chapel Hill, North Carolina. He is presently the Chairman of the Board of the Foundation of the American Thoracic Society and serves on the ATS Board of Directors. Over the years, Dr. Donohue has authored more than 100 articles in such peer-reviewed journals as the American Journal of Respiratory Critical Care, Journal of COPD, Proceeding of the ATS and Chest. He also contributed the COPD section to the ACP's issue of the MKSAP. He is an expert in clinical trials and has participated on steering committees, DSMBS, and presented multiple times to the FDA Pulmonary and Allergy Advisory Committee. Dr. Donohue received the ATS North Carolina Thoracic Society 2009 Outstanding Clinician Award and he has been included yearly in both Castle Connolly American Top Doctors and Best Doctors in America since inception and is listed in the top 1% of all pulmonary doctors in the United States.

Arthur F. Gelb, MD
Arthur F. Gelb, MD, is a Clinical Professor of Medicine at the Geffen School of Medicine at UCLA Medical Center. He also has a pulmonology consulting office in Lakewood, California. Dr. Gelb was trained in clinical pulmonary medicine by Harold Lyons, MD, former Director of the Pulmonary Disease Division at Kings County Hospital in Brooklyn, New York, and in pulmonary physiology by Jay A. Nadel, MD, former Chair of the Pulmonary Division and Chief of the Cardiovascular Research Institute, at UCSF, San Francisco Medical Center in San Francisco, California. His interests are in the pathophysiology of asthma and COPD.

Faculty Biographies

James E. Gern, MD, FAAAAI
James E. Gern, MD, FAAAAI, is a Professor of Pediatrics and Medicine at the University of Wisconsin School of Medicine and Public Health in Madison. He completed pediatric residency training at the State University of New York in Syracuse and at Tufts University in Boston. After serving in the United States Navy for three years, he completed an allergy/immunology fellowship at Johns Hopkins University in 1992, and then joined the faculty at the University of Wisconsin. He is currently the Division Chief for Allergy, Immunology and Rheumatology, and the Vice Chair for Research in the Department of Pediatrics. He serves on the Board of the American Academy of Allergy, Asthma & Immunology, and is the past Chair of the American Board of Allergy and Immunology. Dr. Gern is the PI for the Asthma and Allergic Disease Cooperative Research Center and the NIH-funded Allergy/Immunology Research Training Program at the University of Wisconsin. The goal of his research program is to determine how respiratory viruses and other environmental factors affect the onset and disease activity of asthma.

Theresa Guilbert, MD, MS
Theresa Guilbert, MD, MS, is a Professor in the Pediatric Pulmonary Section at Cincinnati Children's Hospital & Medical Center (CCHMC). She is the Co-Director of the Asthma Center at CCHMC and has 16 years of experience in providing clinical care to asthmatic children and adolescents and conducting clinical and epidemiologic research. Dr. Guilbert has been engaged in teaching, research and clinical roles at the University of Arizona and Arizona Respiratory Center from 1999 to 2006 and at the University of Wisconsin-Madison from 2006 to 2013. Her clinical interests are early childhood wheezing, vocal cord dysfunction, and difficult-to-treat/severe asthma. Dr. Guilbert has research interests in the area of early life risk factors, exposures, and environment interactions that lead to the development of early childhood asthma and recurrent wheezing and the use of electronic medical records in epidemiology and clinical research. She was recently a steering committee member of the NIH sponsored Childhood Asthma Research and Education (CARE), AsthmaNet, and Severe Asthma Research Program (SARP) networks, which were created to develop and execute innovative clinical asthma studies in children.

Nicola A. Hanania, MD, MS
Nicola A. Hanania, MD, MS, is Associate Professor of Medicine in the Section of Pulmonary and Critical Care Medicine and Director of the Asthma and COPD Clinical Research Center at the Baylor College of Medicine in Houston, Texas, USA. He completed his medical training at the University of Jordan followed by residency in internal medicine and a fellowship in pulmonary medicine at the University of Toronto, Canada. He subsequently completed a fellowship in critical care medicine at Baylor College of Medicine, where he later earned a master's degree in clinical investigation. Dr. Hanania's research interests focus on the pharmacology and management of asthma and COPD. He has published more than 200 peer-reviewed papers, book chapters, editorials and reviews on these topics. He is actively involved in clinical trials investigating novel treatments. He is Principal Investigator for the American Lung Association Airway Clinical Research Center at Baylor College of Medicine, as well as Principal Investigator or Co-Investigator in several clinical trials in asthma and COPD. He has been invited and has lectured widely at local, regional, national and international meetings.

Faculty Biographies

Patrick G. Holt, PhD, DSc
Patrick G. Holt, PhD, DSc, FRCPath, is the Head of Division of Cell Biology at the Telethon Kids Institute. Professor Holt established the Division of Cell Biology at the Institute's inception in 1990 with his research group's main focus being on the functioning of the pediatric immune system in relation to asthma and allergy. He has been a Senior Research Fellow with the National Health and Medical Research Council of Australia and is an Adjunct Professor for the Department of Microbiology at the University of Western Australia. In 1999, Professor Holt was presented with the King Faisal International Prize for Medicine, one of the world's pre-eminent scientific awards, in recognition of his significant contribution to the improved understanding of asthmatic disease. His pioneering research on the cellular and molecular basis of respiratory allergies and the mechanisms regulating immunological responses to inhaled allergens provided new perspectives on the causes and genesis of allergic respiratory diseases and the possibility of developing primary strategies for their prevention in childhood.

Daniel J. Jackson, MD
Daniel J. Jackson, MD, is an Assistant Professor of Pediatrics in the Division of Allergy and Immunology at the University of Wisconsin School of Medicine and Public Health. His research interests focus on host-microbe interactions in the inception and exacerbation of asthma. He is an investigator in the National Heart, Lung, and Blood Institute (NHLBI) funded AsthmaNet, National Institute of Allergy and Infectious Diseases (NIAID) funded Inner City Asthma Consortium (ICAC) and is the principal investigator of several clinical within these networks. He was also Co-Chair of the Asthma Workgroup for the NHLBI Primary Prevention of Lung Disease Workshop.

John M. Kelso, MD, FAAAAI
John M. Kelso, MD, FAAAAI, graduated from the University of California at Irvine with a BS in Biological Sciences, and received his MD from Saint Louis University. He completed a residency in Pediatrics at the Naval Medical Center in San Diego, practicing General Pediatrics before going on to fellowship training in Allergy and Immunology at the Mayo Clinic. He was Head of the Allergy Division at Naval Medical Center in San Diego and is now at Scripps Clinic in San Diego. Dr. Kelso has an academic appointment as Clinical Professor of Pediatrics and Internal Medicine at the University of California San Diego School Of Medicine, where he has been recognized as an Outstanding Clinician Educator. He served on the Board of Directors of the American Board of Allergy and Immunology and is currently on the Board of Directors of the American Academy of Allergy, Asthma and Immunology. An active researcher, Dr. Kelso has authored over 90 publications in peer-reviewed journals, covering a broad range of allergy topics with a special interest in vaccine allergy.

James P. Kiley, PhD
James P. Kiley, BS, MS, PhD, serves as the Director of the Division of Lung Diseases at the National Heart, Lung and Blood Institute at the National Institutes of Health (NIH). Prior to this position, he was the Director of the National Center on Sleep Disorders Research at NIH. Dr. Kiley received his education and training at St. Anselm's College, Kansas State University and the University of North Carolina at Chapel Hill. He is a member of a number of professional organizations and has received numerous honors and awards for his outstanding contributions to advancing pulmonary biology in health and disease, sleep research, and public health. His major areas of interest include control of respiration, and the pathophysiology of obstructive airways disease. Dr. Kiley is the author or co-author of over 100 scientific articles.

Monica Kraft, MD, FAAAAI
Monica Kraft, MD, FAAAAI, is an internationally renowned physician-scientist who specializes in translational asthma research. She's a Professor of Medicine and Chair of the Department of Medicine at the University of Arizona College of Medicine-Tucson. She's also the Robert and Irene Flinn Endowed Chair in Medicine. Previously, Dr. Kraft was at Duke University where she served as Chief of the Division of Pulmonary, Allergy and Critical Care and Vice Chair for Research in the Department of Medicine from 2009-2013. Dr. Kraft implemented several initiatives to support the department's research endeavors and was instrumental in the re-submission and renewal of Duke's National Institutes of Health-funded Clinical Translational Science Award. Prior to that, Dr. Kraft had served as Director of the Carl and Hazel Felt Laboratory in Adult Asthma Research and Medical Director of the Pulmonology Physiology Unit at the National Jewish Medical and Research Center in Colorado. Dr. Kraft has more than 150 publications in the areas of adult asthma, the role of infection in asthma and the role of the distal lung in asthma and airway remodeling.

Robert F. Lemanske, Jr., MD, FAAAAI
Robert F. Lemanske, Jr., MD, FAAAAI, is a Professor of Pediatrics and Medicine at the University of Wisconsin School of Medicine and Public Health (UWSMPH) in Madison, where he is the Head of the Division of Pediatric Allergy, Immunology, and Rheumatology. He received his MD from the University of Wisconsin in 1975 and completed his pediatric residency training at the University of Wisconsin Hospitals from 1975 to 1978. His allergy/immunology training was performed at the University of Wisconsin from 1978 to 1980 and the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, from 1980 to 1983. He is board certified in both pediatrics and allergy/immunology. He is Immediate Past-President of the AAAAI and previously served as Director and Chair of the American Board of Allergy and Immunology. Dr. Lemanske is currently the Chair of the Allergy and Immunology Conjoint Program at UWSMPH and the Director of the Morris Institute for Respiratory Research. He is a Principal Investigator of the NHLBI-funded AsthmaNet Network and the National Heart, Lung, and Blood Institute (NHLBI) funded Childhood Origins of ASThma (COAST) study.

Fernando D. Martinez, MD
Fernando D. Martinez, MD, is Regents' Professor, Swift-McNear Professor of Pediatrics, Director of the Arizona Respiratory Center, and Director of the Asthma and Airway Disease Research Center at the University of Arizona. Dr Martinez is a world-renowned expert, and one of the most highly regarded researchers, in the field of childhood asthma. His primary research interests include the natural history of childhood asthma, and the role of genetic, physiological, immunological and environmental factors as determinants of the risk for asthma in early life. Dr Martinez is a member of the National, Heart, Lung and Blood Institute (NHLBI) Advisory Council and member of the National Scientific Council on the Developing Child. He has been a member of the Board of Extramural Advisors of the NHLBI, and of the Pulmonary and Allergy Drug Advisory Committee of the Food and Drug Administration. He was also a member of the National Asthma Education and Prevention Program's Expert Panel, which developed the last two versions of the NHLBI Guidelines for the Treatment of Asthma.

Reynold A Panettieri, Jr., MD
Reynold A. Panettieri, Jr., MD, is the Director of the Institute for Translational Medicine and Science and Vice Chancellor for Translational Medicine and Science at Rutgers University. He's interested in the cellular and molecular mechanisms that regulate airway smooth muscle cell growth and the immunobiology of airway smooth muscle. Dr. Panettieri's lab also focuses on cytosolic signaling pathways that mediate gene expression and alter myocyte function. Dr. Panettieri also served as the Deputy Director of the Center of Excellence in Environmental

Toxicology. He directed the human exposure chamber that defines the molecular mechanisms regulating ozone and particulate matter-induced airway hyperresponsiveness. In parallel with his basic science interests, he's managed the comprehensive clinical program for the care of patients with asthma and is actively involved in clinical investigations into the management of asthma and COPD. Dr. Panettieri has also served as chairperson of the NIH Lung Cellular, Molecular, and Immunobiology Study Section, is a member of the NIH Distinguished Editorial Panel, and is a member of the American Society for Clinical Investigation and Association of American Physicians.

David B. Peden, MD FAAAAI

David B. Peden, MD, FAAAAI, completed medical school and pediatric residency at West Virginia University and allergy/immunology fellowship at the National Institutes of Health (NIH). He joined the University of North Carolina where he is now Andrews Professor of Pediatrics, Senior Associate Dean for Translational Research, Director of the Division of Allergy, Immunology and Rheumatology and Director of the Center for Environmental Medicine, Asthma and Lung Biology. He leads an Environmental Protection Agency (EPA) and NIH funded research program focused on air pollution effects in asthma and inflammation, authoring 160 research articles and book chapters on this topic. Dr. Peden is an Associate Editor of The Journal of Allergy and Clinical Immunology and is currently the President-Elect of AAAAI. He has also chaired the American Board of Allergy and Immunology and is listed in Best Doctors and Top Doctors for A/I.

Stokes Peebles, Jr., MD FAAAAI

Stokes Peebles, Jr., MD, FAAAAI, is the Elizabeth and John Murray Professor of Medicine at Vanderbilt University Medical School. He graduated from Davidson College and Vanderbilt University School of Medicine. Dr. Peebles completed a residency in internal medicine at Vanderbilt, was Chief Resident at the Nashville VA Medical Center, and was elected to the Alpha Omega Alpha Honor Medical Society. He completed a four year fellowship in allergy/clinical immunology at Johns Hopkins and a three year fellowship in pulmonary/critical care medicine at Vanderbilt. Dr. Peebles is board certified in internal medicine, allergy/immunology, pulmonary, and critical care medicine. Dr. Peebles has a very active research program investigating lung inflammation and is currently principal investigator of a U19 Asthma and Allergic Diseases Cooperative Research Center, an NIH R01, and a Veterans Administration Merit Award.

Stephen P. Peters, MD PhD FAAAAI

Stephen P. Peters, MD, PhD, FAAAAI, holds the Thomas H. Davis Chair in Pulmonary Medicine; is Chief of the Section on Pulmonary, Critical Care, and Allergy & Immunologic Diseases; is Professor of Internal Medicine, Pediatrics, and Translational Science; and Associate Director of the Center for Genomics and Personalized Medicine Research at Wake Forest University School of Medicine, Winston-Salem, North Carolina. He is also Executive Director of the Respiratory Service Line in Wake Forest Baptist Health. Current research includes pulmonary inflammation and fibrosis in human asthma and COPD, the genetics/pharmacogenetics of asthma and personalized approaches for treating patients with asthma and COPD. Dr. Peters is involved in the National Heart, Lung, and Blood Institute (NHLBI) Severe Asthma Research Program (SARP), NHLBI-supported genetic studies of asthma, the NHLBI SPIROMICS COPD Program, and is PI of a clinical consortium performing asthma clinical trials sponsored by the NHLBI (ACRN 1 and 2, AsthmaNet). He is also an Executive Committee member of the American Lung Association and advisor to the data coordinating center of the ALA Airway Clinical Research Centers.

Jacqueline A. Pongracic, MD FAAAAI
Jacqueline A. Pongracic, MD, FAAAAI, is a Professor of Pediatrics and Medicine at the Feinberg School of Medicine of Northwestern University and Division Head of Allergy and Immunology at Ann and Robert H Lurie Children's Hospital of Chicago. Dr. Pongracic received both her bachelor's degree in medical science and her medical degree from Northwestern University. She completed an internship and residency in internal medicine at North Shore University Hospital in Manhasset, New York, and Memorial Sloan-Kettering Cancer Center in New York City. She completed training in allergy and immunology at The Johns Hopkins University School of Medicine in Baltimore, Maryland. Dr. Pongracic is board certified by the American Board of Internal Medicine and the American Board of Allergy and Immunology. With support from the National Institutes of Health, Dr. Pongracic is researching the factors which contribute to inner-city asthma and its greater morbidity/mortality as compared to non-inner city populations (Inner City Asthma Consortium or ICAC). She is especially interested in the relationships between allergen sensitization, exposure and morbidity for cockroach, rodents and fungi.

Joe W. Ramsdell, MD
Joe W. Ramsdell, MD, is a Distinguished Professor of Medicine at the University of California, San Diego School of Medicine. He graduated from Indiana University School of Medicine and joined the faculty in the Department of Medicine at UCSD. He is board certified in internal medicine and pulmonary medicine and internationally known for his research in asthma and COPD. Dr. Ramsdell is the Division Chief of General Internal Medicine. He is also the Director for the UC San Diego CREST (Clinical Research Enhancement through Supplemental Training) Program data management module and serves as a research mentor to several students, residents, interns, fellows and junior faculty. Dr. Ramsdell serves as the Director of the UC San Diego Clinical Trials Center/Airways Research Center and serves as the principal investigator on several NIH grants focusing on asthma and COPD gene studies.

Harald Renz, MD FAAAAI
Harald Renz, MD, FAAAAI, is a Professor of Laboratory Medicine at the Philipps University of Marburg, Germany, and is sub-specialized in Clinical Immunology and Allergology. He is also the Head of the Institute of Laboratory Medicine and Pathobiochemistry-Molecular Diagnostics of the University Hospital Giessen and Marburg. He is currently the president of the German Society of Allergology and Clinical Immunology. Since 2005, Dr. Renz has coordinated the interregional Research Consortium of Allergies and Asthma, which is funded by the German Research Council; since 2010 he has served as vice-speaker of the Universities of Giessen and Marburg Lung Center (UGMLC). Dr, Renz has made major contributions in the field of the origin of asthma, with regard to the prenatal and postnatal environment, as well as to the development of animal model systems representing different phenotypes of allergies and asthma. He is co-founder of sterna biologicals, a biotech start-up company, aimed at developing DNA enzymes against key transcription factors involved in T-cell development and differentiation.

Daniel Rotrosen, MD
Daniel Rotrosen, MD, serves as Director of the Division of Allergy, Immunology and Transplantation (DAIT) for the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH). Dr. Rotrosen completed his internship, residency and fellowship training at Harbor-UCLA Medical Center in Los Angeles and is board certified in Internal Medicine and Infectious Diseases. He has received numerous awards for scientific management and leadership, including two U.S Department of Health and Human Services (HHS) Secretary's Awards for Distinguished Service, the HHS Secretary's Outstanding Team Performance Award and the NIH Director's Group Award. Under his leadership, DAIT has developed transformative approaches to data transparency and public access. Two open-access data portals, TrialShare

and ImmPort, enable users to view and download complete data sets used in published manuscripts and provides tools for data visualization, re-analysis and alternative hypothesis generation. Dr. Rotrosen served as co-chair of the Immunity and Inflammation Steering Committee of the Foundation for NIH Biomarkers Consortium. He also is a member of the Steering Committee of the Federation of Clinical Immunology Societies.

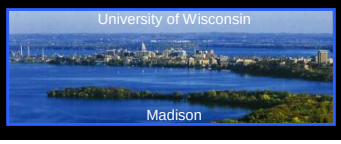
Lewis J. Smith, MD
Lewis J. Smith, MD, is Professor of Medicine, Director of the Center for Clinical Research in the Northwestern University Clinical and Translational Sciences Institute, and Associate Vice President for Research at Northwestern University. He has had active laboratory-based and clinical research programs with funding from the Department of Veterans Affairs, the NIH, foundations and industry. For the past 30 years he has studied various aspects of asthma pathogenesis and treatment. He has been the Chicago site PI for the American Lung Association's Asthma (now Airways) Clinical Research Centers (ALA-ACRC) program since its inception in 1999, corresponding PI for the Chicago center of the NHLBI-supported AsthmaNet program, and PI of a multicenter NIH-funded study exploring the role of soy isoflavones for the treatment of patients with poorly controlled asthma. He chairs the Pulmonary Committee of the longitudinal Coronary Artery Risk Development in Young Adults (CARDIA) study. He is currently leading an initiative to expand and enhance clinical research support throughout Northwestern and its clinical affiliates.

Stanley J. Szefler, MD FAAAAI
Stanley J. Szefler, MD, FAAAAI, is currently the Research Medical Director and Director of the Pediatric Asthma Research Program in the Breathing Institute of the Pediatric Pulmonary Section at Children's Hospital Colorado. He is also Professor of Pediatrics at the University of Colorado Denver School of Medicine. Dr. Szefler's major contributions are directed toward the individualized use of asthma therapy. He has identified biomarkers and asthma characteristics that are associated with asthma exacerbations and response to asthma therapy. Since 1997, he has been the Deputy Editor for The Journal of Allergy and Clinical Immunology. For the past ten years, he has developed a school-centered asthma program funded by the Colorado Department of Public Health and Environment Cancer, Cardiovascular and Pulmonary Disease Program and Glaxo Smith Kline. This program identifies those students most significantly affected by asthma, establishes lines of communication between schools, primary care physicians, and specialists to assure that these children have consistent medical care. As Director of the AAAAI Office of School Based Management of Asthma and Allergies, his goal is to make this program available to schools with limited resources for supporting children with asthma.

Sally Wenzel, MD FAAAAI
Sally Wenzel, MD, FAAAAI, completed her MD degree at the University of Florida. Following her residency in internal medicine at Wake Forest University and her fellowship in pulmonary and critical care medicine at Virginia Commonwealth University, she spent 19 years at National Jewish and the University of Colorado where she rose to the rank of Professor of Medicine. During her years at National Jewish, she served on the Pulmonary–Allergy Advisory Committee to the FDA, was Assembly Chair for the American Thoracic Society (ATS) section on Allergy, Immunology and Inflammation and chaired the ATS International Conference Committee. Dr. Wenzel served as Deputy Editor for the American Journal of Respiratory and Critical Care Medicine and served on the LCMI Study Section for NIH grant reviews. She moved to the University of Pittsburgh in 2006 to take a position as director of the Asthma Institute. In relation to her clinical interest in asthma, Dr. Wenzel has developed a strong translational program to study the pathobiology and mechanisms of the human disease. She is one of seven NHLBI funded investigators in the Severe Asthma Research Program (SARP) network.

When and How Does Asthma Begin?

Robert F. Lemanske, Jr., M.D.
Professor of Pediatrics and Medicine



Precision Medicine

- ***Precision medicine*** can be defined as the tailoring of preventive measures and medical treatments to the characteristics of each patient to obtain the best clinical outcome for each person while ideally also enhancing the cost-effectiveness of such interventions for patients and society.
- ***Clearly, the best clinical outcome for allergic diseases and asthma is not to get them in the first place.***

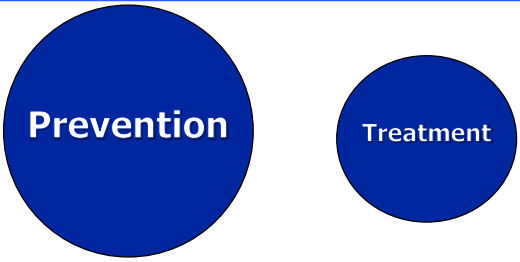
Galli, SJ. JACI 137:1289, 2016

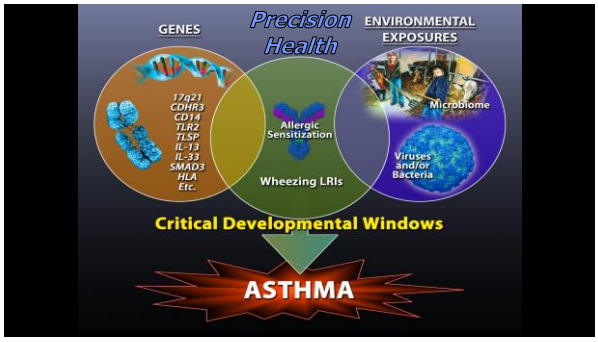
Precision Health

- ***Precision health***, which can be defined as the use of all available information pertaining to specific subjects (including family history, individual genetic and other biometric information, and exposures to risk factors for developing or exacerbating disease), as well as features of their environments, to sustain and enhance health and prevent the development of disease

Galli, SJ. JACI 137:1289, 2016

Precision Health in Asthma





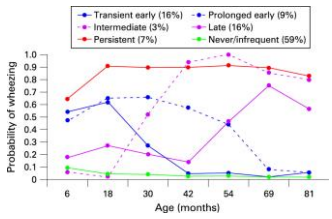
When does asthma begin in childhood?

Asthma Inception

- Wheezing phenotypes
- Airway inflammation
- Alterations in lung function
- Environmental factors (infections & allergens)
- Genetic contributions

Wheezing Phenotypes

Estimated prevalence of wheezing identified by latent class analysis in 6265 children



Henderson, J et al. Thorax 63:974, 2008

Airway Inflammation

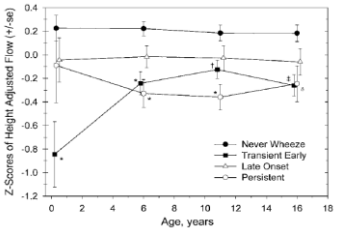
Pathologic Features in Preschool Wheezing Children

- In infants, eosinophilic inflammation and reticular basement membrane (RBM) thickening NOT yet present despite presence of reversible airflow obstruction
- At 3 years of age, both are present in children with severe persistent wheezing
- Increased angiogenesis and epithelial shedding also reported
- Markers of airway wall remodeling may not differ between episodic versus multiple trigger wheezers
- Airway smooth muscle (ASM) increased only in atopic wheezers (differences not seen with other features of remodeling)
- Increased ASM mass only reported feature to be a predictor of future asthma

Saglani, S and Bush, A AJRCCM 192:121, 2015
Lezmi G, et al. AJRCCM 192:164, 2015

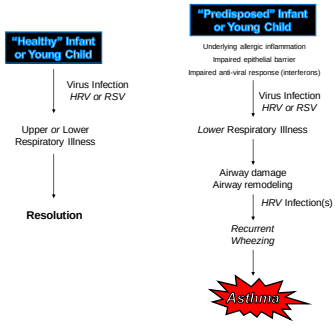
Alterations in Lung Function

Persistent Wheezing & Lung Function

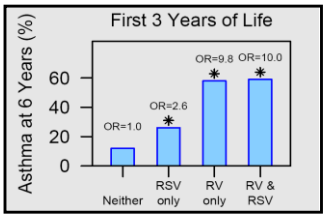


Morgan, *AJRCCM* 2005

Environmental Factors

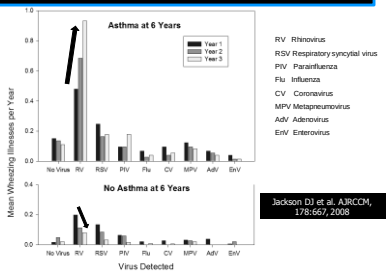


RV Wheezing vs. RSV Wheezing in First 3 Years and Asthma at Age 6 Years



Jackson DJ et al. AJRCCM, 178:667, 2008

Etiology of Wheezing Illnesses in Early Childhood



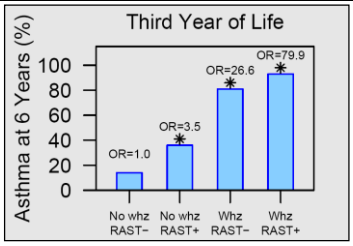
Jackson DJ et al. AJRCCM, 178:667, 2008

Persistence of Asthma Risk following Early Life RV vs RSV Wheezing Illnesses

Rubner FJ, et al. JACI, in press

What influence does allergic sensitization have on asthma risk?

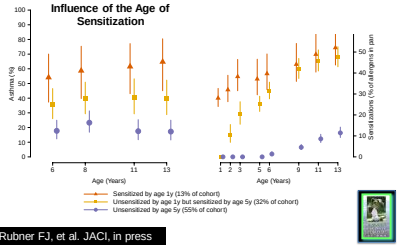
RV Wheezing & Allergic Sensitization in Year 3 and Asthma at Age 6 Years



Jackson DJ et al. AJRCCM, 178:667, 2008

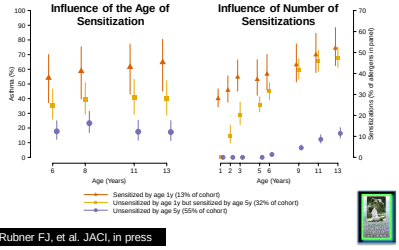
What influence does age and the magnitude of sensitization have on future asthma risk?

Early Life Rhinovirus Wheezing, Allergic Sensitization and Asthma Risk at Adolescence



Rubner FJ, et al. JACI, in press

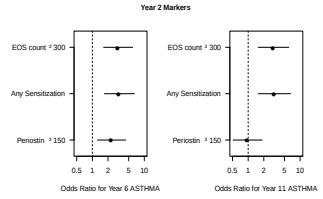
Early Life Rhinovirus Wheezing, Allergic Sensitization and Asthma Risk at Adolescence



Rubner FJ, et al. JACI, in press

Type 2 Inflammatory Markers in Early Life

Relationships among peripheral eosinophil counts, aeroallergen sensitization, and serum periostin on the development of childhood asthma



Anderson H. et al. JACI in press 2016

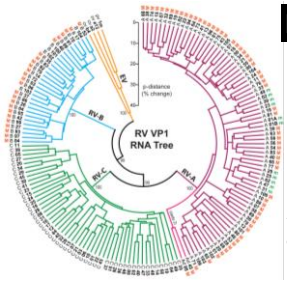
Influence of more than one factor at various ages on future asthma risk at age 11 years

Asthma at age 6					
		Asthma		OR(95% CI)	
	N(%)	6	N(%)	vs. None	vs. *Only* one
None	68(35%)	Yes	14(21%)	Ref	
		No	54(79%)		
Only one	90(46%)	Yes	20(22%)	1.1 (0.5, 2.4)	Ref
		No	70(78%)		
Any two or more	38(19%)	Yes	24(63%)	6.6 (2.7, 16.0)	6.0 (2.6, 13.7)
		No	14(37%)		
Asthma at age 11					
		Asthma		OR(95% CI)	
	N(%)	11	N(%)	vs. None	vs. *Only* one
None	58(34%)	Yes	15(26%)	Ref	
		No	43(74%)		
Only one	78(46%)	Yes	20(26%)	1.0 (0.5, 2.2)	Ref
		No	58(74%)		
Any two or more	34(19%)	Yes	18(53%)	3.2 (1.3, 7.9)	3.3 (1.4, 7.6)
		No	16(47%)		

Anderson H. et al. JACI in press 2016

HRV Strain

Virulence



RV Species

RV-A 78 types
RV-B 30 types
RV-C 51 types

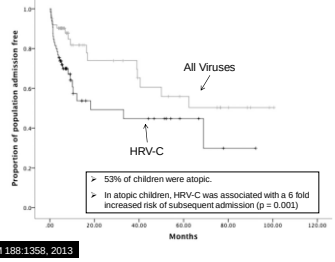
Receptors

A and B = ICAM-1 and LDL

C = ?

Palmenberg A et al, Molecular Protocols, 2014

Time to First Admission: HRV-C vs All Viruses



Cox DW et al. AJRCCM 188:1358, 2013

Identification of the RV-C Receptor

- **RV-A, RV-B**
  - ICAM-1 – expressed by 2-4% of cultured epithelial cells
  - LDLR
- **RV-C**
  - Unique receptor
  - Not expressed on undifferentiated epithelial cells, and most cell lines
  - Expressed on fully differentiated epithelial cells

Yury Bochkov

nature genetics

A genome-wide association study identifies *CDHR3* as a susceptibility locus for early childhood asthma with severe exacerbations

Klaus Bonnelykke[1,24,25], Patrick Sleiman[2,24], Kasper Nielsen[3,24], Eskil Kreiner-Moller[1], Josep M Mercader[4], Danielle Belgrave[5,6], Herman T den Dekker[7–9], Anders Husby[1,10], Astrid Sevelsted[1], Grissel Faura-Tellez[11,12], Li Juel Mortensen[3], Lavinia Paternoster[13], Richard Flaaten[1], Anne Mølgaard[1], David E Smart[10], Philip F Thomsen[14], Morten A Rasmussen[15], Silvia Bonàs-Guarch[4], Claus Holst[16], Ellen A Nohr[17,18], Rachita Yadav[2], Michael E March[2], Thomas Blicher[19], Peter M Lackie[11], Vincent W V Jaddoe[7,9,20], Angela Simpson[5], John W Holloway[21], Liesbeth Duijts[8,9,21], Adnan Custovic[5], Donna E Davies[10], David Torrents[4,22], Ramneek Gupta[3], Mads V Hollegaard[23], David M Hougaard[23], Hakon Hakonarson[2,25] & Hans Bisgaard[1,25]

Severe exacerbations occurring between 2 and 6 years of age in a total of 1,173 cases and 2,522 controls.

NATURE GENETICS VOLUME 46 | NUMBER 1 | JANUARY 2014

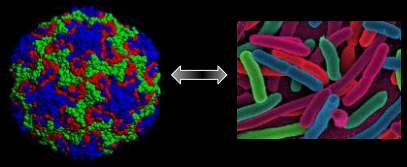
Cadherin-related family member 3, a childhood asthma susceptibility gene product, mediates rhinovirus C binding and replication

Yury A. Bochkov[a,1], Kelly Watters[b], Shamaila Ashraf[a,2], Theodor F. Griggs[a], Mark K. Devries[a], Daniel J. Jackson[a], Ann C. Palmenberg[b,3], and James E. Gern[a,c,3]

Proc Nat Acad Sci 112:5485, 2015

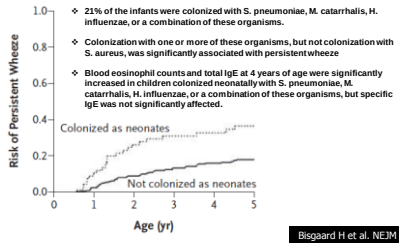
- CDHR3 is a transmembrane protein with as yet unknown function
- Enables RV-C binding and replication
- A coding SNP in CDHR3, previously linked to wheezing illnesses and hospitalizations for childhood asthma, also mediates enhanced RV-C binding and progeny yields in vitro
- Within domains 1 and 2 of the CDHR3 molecule, there are potential binding sites for viral capsid surface regions that are highly conserved among RV-C types

Interactions between Viruses and Bacteria



Asthma Inception

Bacterial Colonization at One Month of Life Increases Risk for Persistent Wheezing



- 21% of the infants were colonized with S. pneumoniae, M. catarrhalis, H. influenzae, or a combination of these organisms.
- Colonization with one or more of these organisms, but not colonization with S. aureus, was significantly associated with persistent wheeze
- Blood eosinophil counts and total IgE at 4 years of age were significantly increased in children colonized neonatally with S. pneumoniae, M. catarrhalis, H. influenzae, or a combination of these organisms, but specific IgE was not significantly affected.

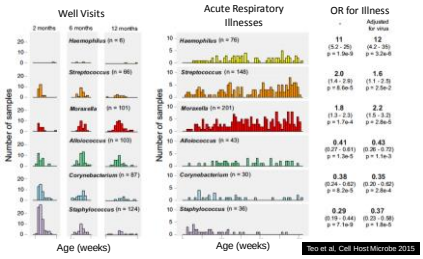
Bisgaard H et al. NEJM 357:1487, 2007

Environment: Viral Infections and Airway Microbiome

- Birth cohort (n = 234)
- Year 1 nasal secretions (2, 6, and 12 months
  - 487 healthy
  - 534 sick
- Microbiome analyzed with 16S gene deep sequencing
- Virology and RV typing
- Illness characteristics
  - Febrile

Teo M et al, Cell Host & Microbe 2015

Nasopharyngeal Microbiome in Infants & Risk of Respiratory Illnesses



Teo et al, Cell Host Microbe 2015

Risk Factors for Future Asthma

- Early colonization with Streptococcus
- Febrile illness
- HRV-C

Gene by Environment Interactions

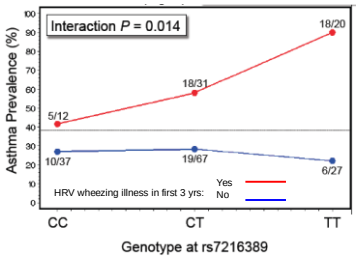
GWAS and 17q21

•Variation at a locus spanning five genes on chromosome 17q21, including the *ORMDL3* gene has yielded the most significant association in two asthma GWAS evaluations

•The 17q21 locus is the most replicated asthma locus and represents the *most significant genetic risk factor for childhood asthma* known to date

Gene by Pathogen Interactions

Caliskan M et al. NEJM 368:1398, 2013



This SNP is located in an intron of GSDML and is an eQTL for both ORMDL3 and GSDML.

Asthma prevention: Is it possible?

- Target IgE
- Target IL-5 (? IL-4, IL-13, or receptor)
- Target genotype
- Prevent infection with respiratory pathogens
  - RSV (palivizumab), (vaccine)
  - RV (vaccine), (block RV-C receptor)
- Alter microbiome
  - Target pathogenic bacteria
  - ORBEX study (Broncho-Vaxom)
    - lyophilized bacterial lysates of Haemophilus influenzae, Streptococcus [pneumonia, pyogenes and sanguinis (viridans)], Klebsiella (pneumoniae and ozaenae), Staphylococcus aureus and, Moraxella catarrhalis

Precision Health in Asthma

- Who is the right patient?
- What is the correct treatment?
- When is the right time to treat?
- How long to treat and what to monitor?
- Cost of therapy and side effects?

Immunology of Childhood Asthma

Patrick G. Holt PhD DSc
Telethon Kids Institute, University of Western Australia

Translational: Early Life Events in Asthma Expression

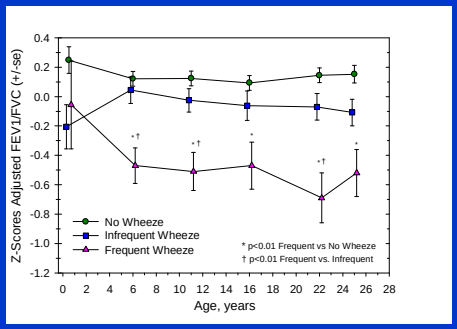
Fernando D. Martinez, M.D.

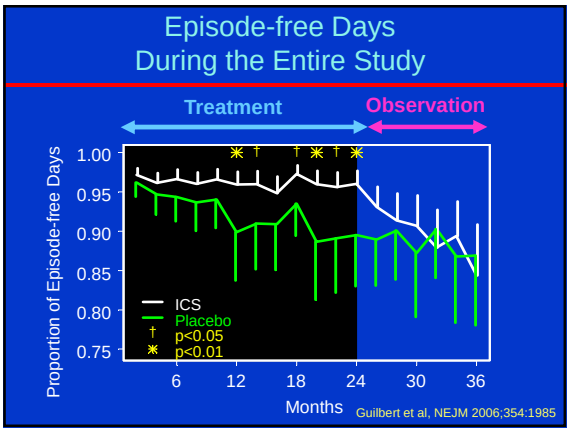
Asthma and Airway Disease Research Center
The University of Arizona

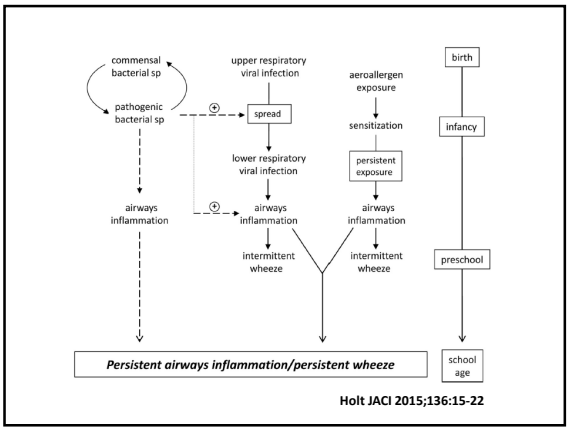
Disclosures

- Recipient of a contract with Johnson and Johnson to assess asthma preventive compounds in farm dust

Lung Function from Birth by Wheezing at Age 24-26 Yrs




Episode-free Days
During the Entire Study
Treatment
Observation
Proportion of Episode-free Days
1.00
0.95
0.90
0.85
0.80
0.75
ICS
Placebo
† p<0.05
* p<0.01
6
12
18
24
30
36
Months
Guilbert et al, NEJM 2006;354:1985


commensal bacterial sp
pathogenic bacterial sp
upper respiratory viral infection
spread
lower respiratory viral infection
airways inflammation
airways inflammation
intermittent wheeze
aeroallergen exposure
sensitization
persistent exposure
airways inflammation
intermittent wheeze
birth
infancy
preschool
school age
Persistent airways inflammation/persistent wheeze
Holt JACI 2015;136:15-22

Microbial Diversity, Living on a Farm, and Asthma

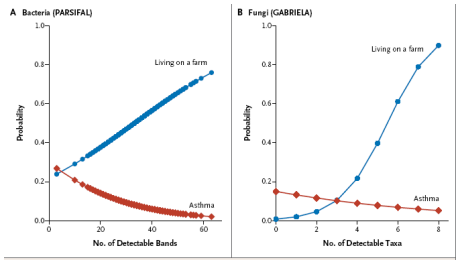
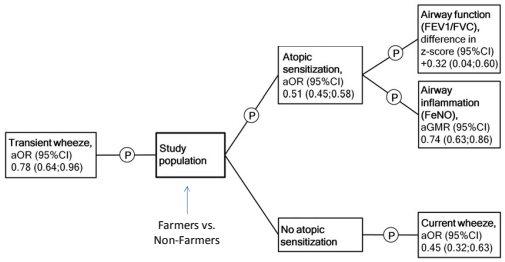


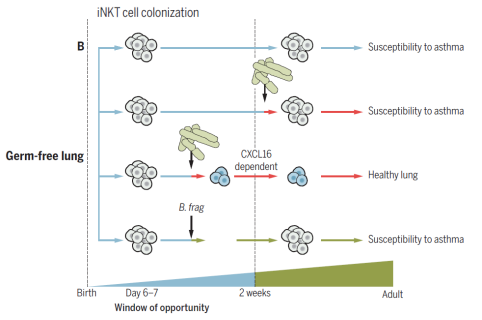
Figure 3. Relationship between Microbial Exposure and the Probability of Asthma.
In both the PARSIFAL study and GABRIELA, the range of microbial exposure was inversely associated with the probability of asthma.

Ege et al, N Engl J Med 2011;364:701-9.

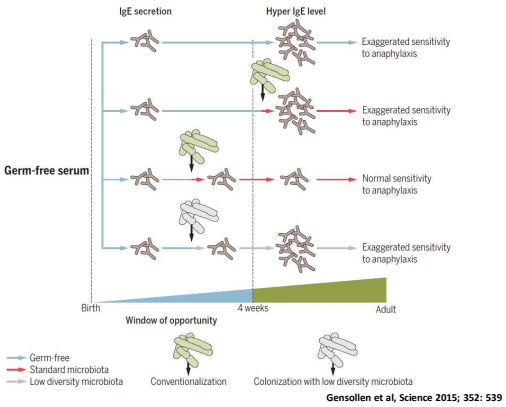
Farming Environment Protects Against All Forms of Early Wheeze



Fuchs et al, JACI 2012;130:382-8.

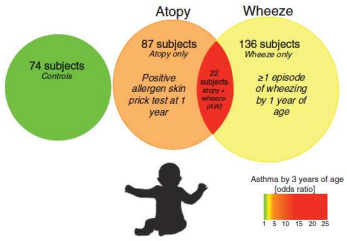


Gensollen et al, Science 2015; 352: 539



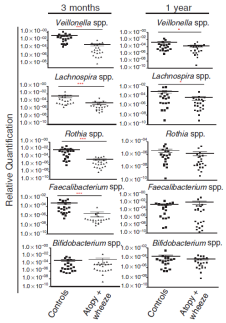
Gensollen et al, Science 2015; 352: 539

Intestinal Microbiome and Atopy/Wheeze: The CHILD Study



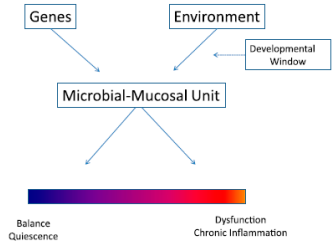
Arrieta et al, Sci Transl Med 2015; 7: 52

Intestinal Microbiome and Atopy/Wheeze: The CHILD Study



Arrieta et al, Sci Transl Med 2015; 7: 52

The Microbial-Mucosal Unit



Ann Am Thorac Soc. 2014;11 Suppl 1:S7-S12

Intestinal Microbes and Allergic Asthma

- Several investigators have used live oral probiotics to treat and prevent many diseases including eczema and asthma
- Results of a recent review: "We found no evidence to support a protective association between perinatal use of probiotics and doctor diagnosed asthma or childhood wheeze" (Azad et al, BMJ 2014; 347:f6471).
- Biochemical complexity of live probiotics poses great challenges re: drug regulation/standardization
- Investigators have thus explored the possibility that bacterial extracts could be used as a surrogate

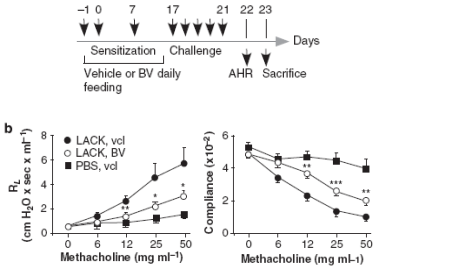
Bacterial Extracts

- Bacterial extracts (OM-85BV) are lyophilized fractionated alkaline extracts of H. influenzae, D. pneumonia, K. ozaenae, K. pneumoniae, S. aureus, S. pyogenes, S. viridans, and N. catarrhalis
- It is a mixture of acidic proteins, peptides and amino acids, with minor components of detoxified LPS and lipoteichoic acids

Clinical Use of Bacterial Extracts

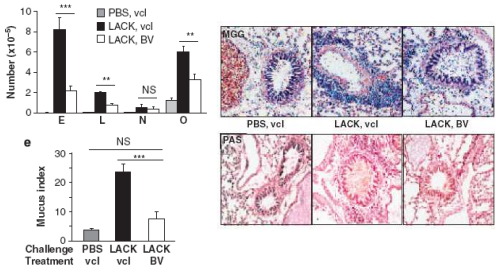
- Bacterial extracts have been widely used in Europe for the last 2-3 decades in children and adults as oral medicines to reduce the frequency and duration of URIs
- They have also been used in the prevention of exacerbations in CF and COPD

Prevention of BHR by Oral Administration of Bacterial Extracts



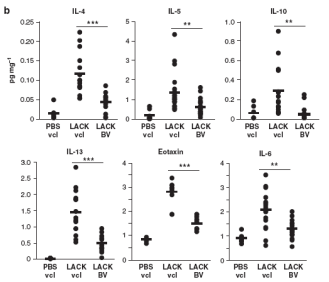
Navarro et al, Mucosal Immunol 2011; 4:43

Decreased Airway Inflammation by Oral Administration of Bacterial Extracts



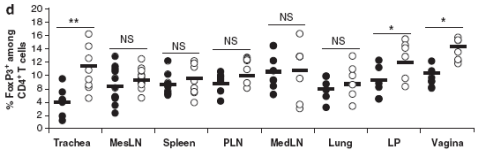
Navarro et al, Mucosal Immunol 2011; 4:43

Decreased BAL Cytokines by Oral Administration of Bacterial Extracts



Navarro et al, Mucosal Immunol 2011; 4:43

Increased Tracheal Treg Cells by Oral Administration of Bacterial Extracts



Navarro et al, Mucosal Immunol 2011; 4:43

Activation of Treg in Airway Mucosa by Oral OM-85BV in Rats

- Oral pretreatment of sensitized rats with OM-85BV strikingly accelerated the resolution of AHR that is triggered by aeroallergen exposure.
- The kinetics of the AHR response in treated animals closely mirrored associated CD86 expression on airway mucosal dendritic cells
- The principal feature distinguishing OM-85BV treated rats from controls was their markedly increased (2 ×) baseline numbers of airway mucosal Tregs.

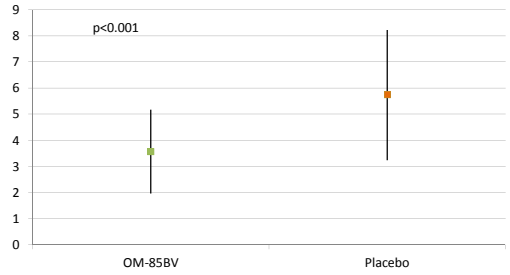
Strickland and Holt, Mucosal Immunol. 2011;4:43-52

The Study by Razi et al

- This study was a randomized, double-blind, placebo-controlled, parallel group study with OM-85 BV in patients with recurrent wheezing in Ankara, Turkey
- 75 (40 OM-85BV, 35 placebo) 1-6 yr old children with recurrent wheezing
- Participants were randomly assigned to groups given either OM-85 BV or placebo (1 capsule per day for 10 days each month for 3 consecutive months) at the start of the trial.

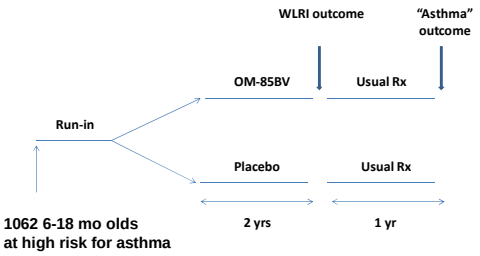
J Allergy Clin Immunol 2010;126:763-9

Cumulative Yearly Number of Wheezing Episodes per Participant



J Allergy Clin Immunol 2010;126:763-9

ORBEX Trial Schematata



1062 6-18 mo olds at high risk for asthma

Participants in ORBEX

DCC: Dave Mauger, Penn State Hershey
CCC: Fernando Martinez, University of Arizona

Clinical Centers
- Wanda Phipatanakul, Boston Children's
- Dan Jackson, UW Madison
- Meyer Kattan, Columbia University NYC
- Anne Fitzpatrick, Emory University Atlanta
- Len Bacharier, Washington University S. Louis
- Steve Teach, Children's National DC
- Wayne Morgan, University of Arizona

Disclosures

- Employment
  - Washington University
- Financial Interests
  - Consultant: DBV, Merck, Boehringer Ingelheim, Vectura, Sanofi, Genetech/Novartis
  - Honoraria/Speakers Bureau: Teva, BI, Astra Zeneca, Genentech
  - Research Support: None
- Research Interests
  - NIH/NHLBI, NIAID
- Organizational Interests
  - AAAAI Annual Meeting Planning Committee
  - Director, ABAI
- Gifts
  - Nothing to Disclose
- Other Interests
  - Nothing to Disclose

Learning Objectives

- Examine strategies for the management of acute severe wheezing illnesses in preschool children.
- Explore the role of azithromycin in the prevention and attenuation of wheezing illnesses.

Background

- Severe episodes of lower respiratory tract symptoms are common in early childhood
- Disproportionate healthcare resource utilization in this age group
- Viral infection most common trigger, but bacteria have an emerging role in illness pathogenesis
- More evidence is needed to guide practitioners for episode management and prevention

Are Oral Corticosteroids Effective in Episodes of Wheezing in Preschool Children?

Oral Corticosteroids (OCS) for Acute Wheezing Episodes

- Recommended by asthma guidelines for asthma exacerbations: children and adults[1]
- Efficacy is well proven for acute asthma exacerbations among school-age children and adolescents (acute care setting):
  - Lower risk of relapse, fewer hospitalizations, and less need for β_2-agonist treatments[2]
- OCS have traditionally been used for treatment of acute episodic wheezing in preschool children, mainly based on their benefits in older children with asthma

1. NAEPP. *Expert Panel Report III : Guidelines for the diagnosis and management of asthma.* 2007.
2. Rowe BH. Cochrane Database Syst Rev 2007;(3):CD000195.

Systemic Corticosteroids in Preschool Children

- Early parent-initiated OCS treatment (home)
  - Does not prevent urgent visits[1]
    - Potentially higher rate of urgent visits[2]
  - Does not improve respiratory symptoms[1]
  - Low compliance[1]
- Emergency Department
  - Reduced rate of hospitalization (approx 50%)[3]

[1] Oommen A, *Lancet.* 2003; 362:1433-1438.
[2] Grant C, *Pediatrics.* 1995; 96:224-229.
[3] Tal A, *Pediatrics.* 1990; 86:350-356.

Oral Prednisolone for Preschool Children with Acute Virus-Induced Wheezing

Jayachandran Panickar, M.D., M.R.C.P.C.H., Monica Lakhanpaul, M.D., F.R.C.P.C.H., Paul C. Lambert, Ph.D., Priti Kenia, M.B., B.S., M.R.C.P.C.H., Terence Stephenson, D.M., F.R.C.P.C.H., Alan Smyth, M.D., F.R.C.P.C.H., and Jonathan Grigg, M.D., F.R.C.P.C.H.

- 700 preschool children (10-60 mo) hospitalized for acute wheezing episode preceded by viral URI symptoms
  - ~30% were first time wheezers
- RDBPC: 5-day course of oral prednisolone vs. placebo
  - 10 mg daily for children 10-24 months
  - 20 mg daily for older children
- Primary outcome: duration of hospitalization

Panickar J et al. *NEJM* 2009;360:329-38.

No Significant Reduction in Episode Severity

- No significant difference in duration of hospitalization (or time until ready for discharge) - 11.0 hrs vs. 13.9 hrs (p=0.18)

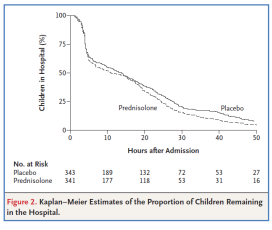


Figure 2. Kaplan–Meier Estimates of the Proportion of Children Remaining in the Hospital.

No difference between groups in:

- **Use of albuterol**
- **Rescue open-label OCS**
- **PRAM score at 4, 12, 24 hrs**
- **Rate of readmission**

No difference in outcomes based on API status

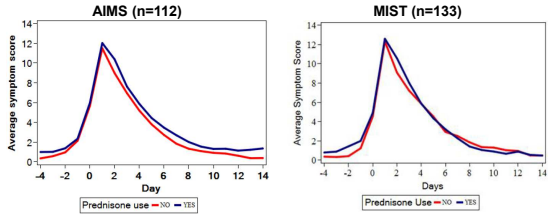
Panickar J et al. *NEJM* 2009;360:329-38.

Do Oral Corticosteroids Reduce Severity of Acute LTRI in Preschool Children?

- *Post hoc* analyses[1] in 2 outpatient cohorts of preschool children participating in Childhood Asthma Research and Education (CARE) Network clinical trials
  - Initial cohort (AIMS study[2]) & validation cohort (MIST study[3])
- Participants: 1-5 y/o children with history of episodic wheezing in the context of RTIs
- Prednisolone (4 days): rescue treatment (protocol criteria)
  - Significant lower respiratory tract illness (LRTI) after consultation with study physician

[1]Beigelman A, for the CARE Network. *JACI.* 2013;131:1518-25.
[2]Bacharier L, for the CARE Network. *JACI* . 2008; 122:1127-1135.
[3]Zeiger R, for the CARE Network. *NEJM.* 2011; 365:1990-2001.

Total Symptom Scores Were Not Lower Among Episodes Treated With OCS



No significant difference in cough score, wheeze score, trouble breathing score, or interference with activity score

Beigelman A, for the CARE Network. *JACI.* 2013;131:1518-25.

Summary: Uncertain Efficacy of OCS in Preschool Children with Episodic Wheezing

- Outpatient (home) setting
  - Did not improve respiratory symptoms
  - Potentially associated with higher rates of ED visits
- ED setting
  - One study showed reduced rate of hospitalization
- Hospital setting
  - Did not reduce duration of hospitalization or improve respiratory symptoms
- Very little evidence to support the efficacy of OCS in preschool children with episodic wheezing

Potential Explanations for OCS Findings in Preschool Children

- Different wheezing/asthma phenotypes with potentially different mechanisms and thus response to interventions
- Episodic/"severe intermittent" wheezing
  - Dominance of the "risk domain"
    - Significant morbidity during acute wheezing episodes
    - Minimal persistent asthma symptoms
  - Potentially more background and acute neutrophilic[1,2] and less eosinophilic airway inflammation

1. Le Bourgeois M. *Chest.* 2002;122:791-7.
2. Saglani S. *Am J Respir Crit Care Med.* 2007;176:858-64.

Potential Role of Macrolides for the Prevention of Acute Wheezing

- Antibiotic use in wheezing illnesses is not recommended by national guidelines
  - Antibiotics are commonly prescribed in clinical practice (1/6 US ambulatory visits for asthma)*
- Viral infections are the most common trigger for acute wheeze, but bacteria have an emerging role in illness pathogenesis
- Macrolides antibiotics have shown to provide benefits in other inflammatory airway diseases (e.g., CF)
  - Anti-bacterial and anti-inflammatory properties

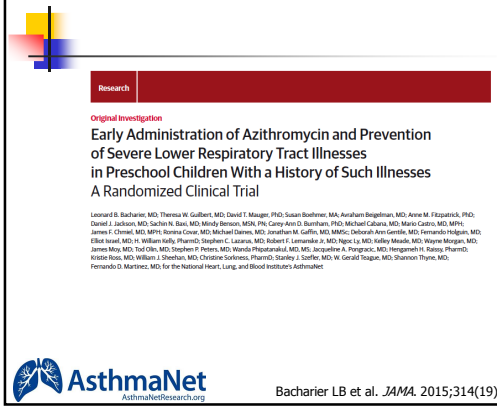
*Paul IM et al. *Pediatrics* 2011:127:1014-21

ARS SLIDE #1

For preschool children with recurrent severe lower respiratory tract illnesses, the NAEPP Guidelines do not recommend antibiotics as a component of episode management. How often do you prescribe an antibiotic for significant lower respiratory tract illnesses in this population?

A. Never, ever, under any circumstances
B. <25% of the time
C. 25-50% of the time
D. 50-75% of the time
E. >75% of the time

Would early administration of azithromycin, started prior to the onset of severe lower respiratory tract symptoms, in preschool children with history of recurrent severe lower respiratory tract illnesses, prevent the progression of these episodes?


Research

Original Investigation

Early Administration of Azithromycin and Prevention of Severe Lower Respiratory Tract Illnesses in Preschool Children With a History of Such Illnesses

A Randomized Clinical Trial

Leonard B. Bacharier, MD; Theresa W. Guilbert, MD; David T. Mauger, PhD; Susan Boehmer, MA; Avraham Beigelman, MD; Anne M. Fitzpatrick, PhD; Daniel J. Jackson, MD; Sachin N. Baxi, MD; Mindy Benson, MSN, PN; Carey-Ann D. Burnham, PhD; Michael Cabana, MD; Mario Castro, MD, MPH; James F. Chmiel, MD, MPH; Ronina Covar, MD; Michael Daines, MD; Jonathan M. Gaffin, MD, MMSc; Deborah Ann Gentile, MD; Fernando Holguin, MD; Elliot Israel, MD; H. William Kelly, PharmD; Stephen C. Lazarus, MD; Robert F. Lemanske Jr, MD; Ngoc Ly, MD; Kelley Meade, MD; Wayne Morgan, MD; James Moy, MD; Tod Olin, MD; Stephen P. Peters, MD; Wanda Phipatanakul, MD, MS; Jacqueline A. Pongracic, MD; Hengameh H. Raissy, PharmD; Kristie Ross, MD; William J. Sheehan, MD; Christine Sorkness, PharmD; Stanley J. Szefler, MD, W. Gerald Teague, MD; Shannon Thyne, MD; Fernando D. Martinez, MD; for the National Heart, Lung, and Blood Institute's AsthmaNet

AsthmaNet AsthmaNetResearch.org

Bacharier LB et al. *JAMA.* 2015;314(19):2034-2044

Study Design & Protocol Treatments

- Randomized, double-blind, parallel group trial
- Azithromycin (AZM) 12mg/kg (maximum 500mg/d) or Placebo once daily for 5 days
  - Begin at onset of each RTI when patient developed signs or symptoms that parents defined as the patient's usual starting point before development of LRT symptoms
  - Albuterol 4 times daily for 48 hours and as needed
- Duration - 52 weeks (3 treated RTIs), extended to 78 weeks (4 treated RTIs)

AsthmaNet AsthmaNetResearch.org

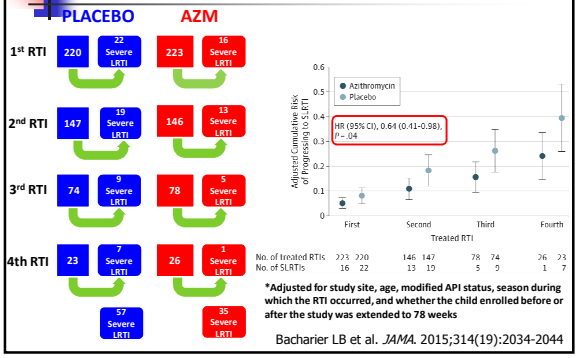
Bacharier LB et al. *JAMA.* 2015;314(19):2034-2044

Primary Outcome

- **The number of respiratory tract illnesses (RTIs) not progressing to severe lower respiratory tract illness (LRTI)**
  - >6 albuterol treatments over a 24 hour period, OR
  - If symptoms are more than mild and not improved after 3 albuterol treatments in 1 hour, OR
  - Require albuterol more often than every 4 hours on 2 consecutive occasions, OR
  - Moderate-severe cough or wheeze for ≥5 days during which study therapy was used, OR
  - Need for acute/urgent/emergency care for respiratory symptoms, OR
  - Physician discretion

Bacharier LB et al. *JAMA*. 2015;314(19):2034-2044

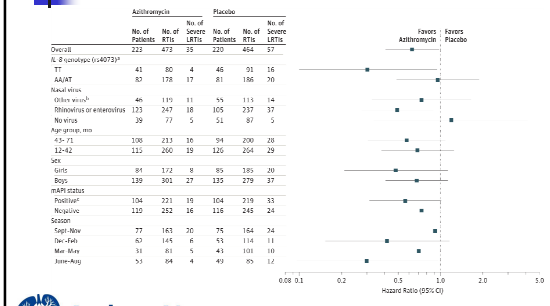
Reduction in Risk of Progression to Severe LRTI



***Adjusted for study site, age, modified API status, season during which the RTI occurred, and whether the child enrolled before or after the study was extended to 78 weeks**

Bacharier LB et al. *JAMA*. 2015;314(19):2034-2044

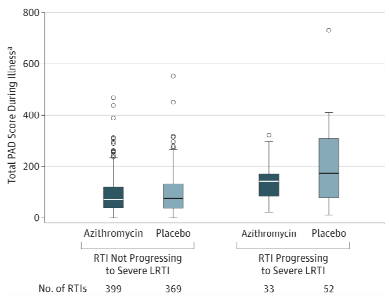
Subgroup Analyses



AsthmaNet
AsthmaNetResearch.org

Bacharier LB et al. *JAMA*. 2015;314(19):2034-2044

Reduction in Albuterol Use During Severe LRTIs



AsthmaNet
AsthmaNetResearch.org

Bacharier LB et al. *JAMA.* 2015;314(19):2034-2044

Summary

- Azithromycin, started at the earliest signs of RTIs, was effective in reducing the risk of experiencing episodes of severe lower respiratory tract illnesses
- Symptoms significantly less severe
- No difference in response by API status
- Well-tolerated with low rates of adverse effects

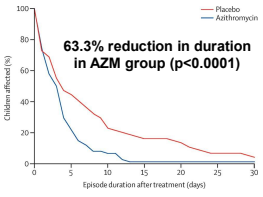
AsthmaNet
AsthmaNetResearch.org

Bacharier LB et al. *JAMA.* 2015;314(19):2034-2044

Azithromycin for episodes with asthma-like symptoms in young children aged 1–3 years: a randomised, double-blind, placebo-controlled trial

Jakob Stokholm, Bo L Chawes, Nadja H Vissing, Elin Bjarnadóttir, Tine M Pedersen, Rebecca K Vinding, Ann-Marie M Schoos, Helene M Wolsk, Sunna Thorsteinsdóttir, Henrik W Hallas, Lambang Arianto, Susanne Schjørring, Karen A Krogfelt, Thea K Fischer, Christian B Pipper, Klaus Bønnelykke, Hans Bisgaard

- Double blind placebo controlled trial among COPSAC2010 1-3yrs with recurrent asthma-like symptoms (n=72)
- After >3 days of asthma-like symptoms, AZM 10mg/kg/d or placebo for 3 days
  - Concurrent ICS in 82% of episodes, LTRA in 60%
- Primary outcome: duration of episode after start of therapy



Stockholm J et al. *Lancet Resp Med* 2016;4: 19-26

Azithromycin for episodes with asthma-like symptoms in young children aged 1–3 years: a randomised, double-blind, placebo-controlled trial

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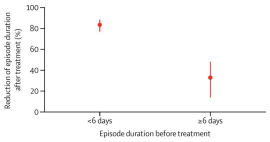
- Greater effect when AZM started before day 6 of episode



- No differential effect if:
  - Evidence of pneumonia
  - Detectable wheezing
  - Use of ICS or LTRA
  - Presence of bacteria (other than was more effective if *H. influenzae* detected in hypopharyngeal aspirate)
  - No difference based upon presence or absence of viral infection
- No effect on time to next episode

Stockholm J et al. *Lancet Resp Med* 2016;4: 19-26

Summary: Preschool Children with Severe Wheezing Episodes

- A therapeutic trial of azithromycin, early in the course of respiratory tract illnesses (RTI), should be considered to prevent progression to severe lower-RTI and need for OCS
  - Children who demonstrate an azithromycin response (less severe episodes of RTI) may benefit from repeating azithromycin with subsequent illnesses
  - Concern of antimicrobial resistance – monitor frequency of RTIs prompting azithromycin use and response to the intervention
    - More information is needed regarding the development of antibiotic resistant pathogens with this strategy
- Unknown: efficacy of this prevention approach compared to the efficacy of daily (or intermittent) ICS therapy or role in patients already receiving controller therapy

Asthma Inception and Progression

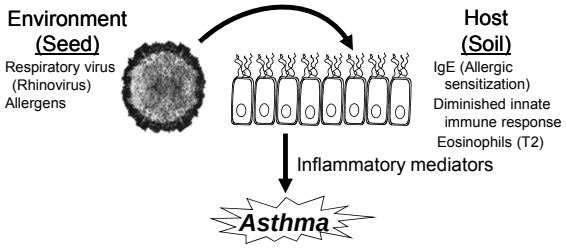
Friday, July 29 at 3:00 pm

Major discussion question:
In an 18-month old male child (RFL) who has experienced four episodes of wheezing, the last of which was severe enough to require evaluation in an urgent care clinic, nebulized bronchodilator, and a 5-day course of oral glucocorticoids (has a + API), how would you counsel the parents who want to do everything possible to prevent RFL from developing asthma (if he doesn't have it established already) and/or preventing him from developing more severe manifestations of lower airway involvement?

Identifying Biologic Targets to Attenuate or Eliminate Asthma Exacerbations

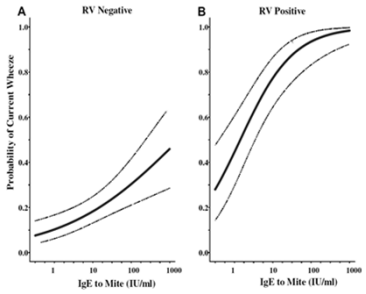
Asthma exacerbations are a major cause of disease morbidity and costs. For both children and adults, viral respiratory infections are the major cause of these exacerbations. The mechanisms underlying these episodes are complex and involve multiple cells and factors. With the use of biologics to treat more severe asthma and exacerbation-prone patients, greater insight has been gained into the targets, and consequently, the mechanisms by which respiratory viruses, particularly the common cold virus – rhinovirus, lead to exacerbations. The following discussion on biologic targets for exacerbations will focus on major risk factors in this process: IgE, allergic sensitization, deficiencies in innate immunity, particularly interferon generation, and the multiple cells and pathways involved. The unfolding of this new information has not only provided greater insight to this major cause of asthma morbidity, and its loss of control, but also is identifying new targets whose targeted control promises to lead to improved outcomes and the attenuation or prevention of exacerbations.

What are key biologic targets in asthma exacerbations?



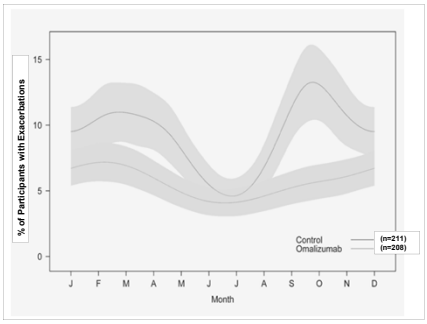
What role does IgE play in asthma exacerbations?

What is the effect of IgE antibody to dust mite allergen and risk for wheezing among asthmatic children infected with rhinovirus?



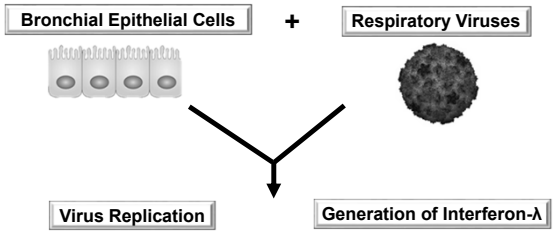
Soto-Quiros, *et al. J Allergy Clin Immunol* 2012;129:1499–1505

What is the effect of omalizumab on asthma exacerbations on a seasonal basis?



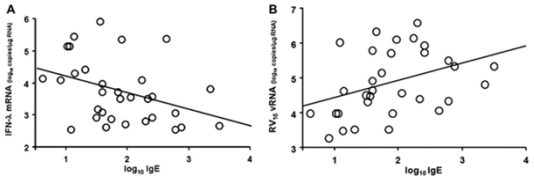
Busse WW and Morgan WJ, et al. N Engl J Med 2011;364:1005-159

What role do innate immune responses play in asthma exacerbations?



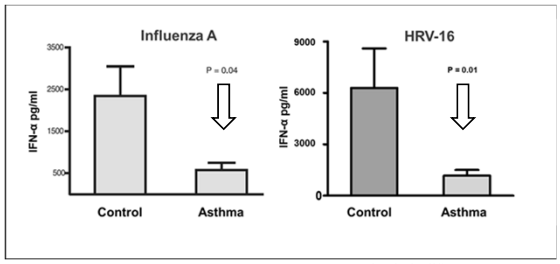
Baraldo et al. J Allergy Clin Immunol 2012; 130:1307-1314.

Total Serum IgE Levels



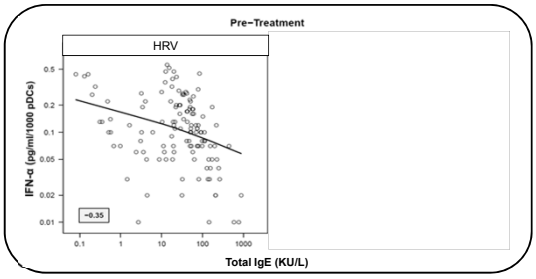
Baraldo et al. J Allergy Clin Immunol 2012; 130:1307-1314.

Is dendritic cell (pDC) generation of IFN-α antiviral impaired in patients with allergic asthma?

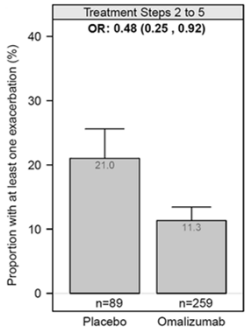


J. Immunol., 2010, 184 (11), 5999-06.

What is the relationship between IgE and virus-induced IFN-α generation?

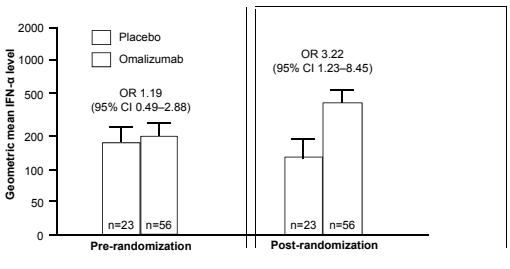


What effect does omalizumab have on seasonal exacerbations of asthma in PROSE?



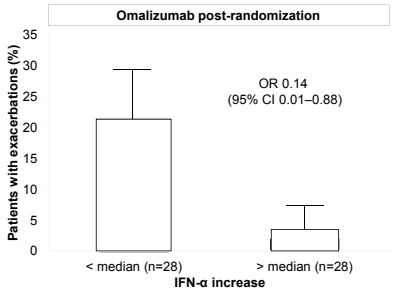
Teach, SJ et al. J Allergy Clin Immunol 2015; 136:1476-1485

What effect does omalizumab treatment have on *in vitro* generation of IFN-α from isolated PBMC incubated with RV?



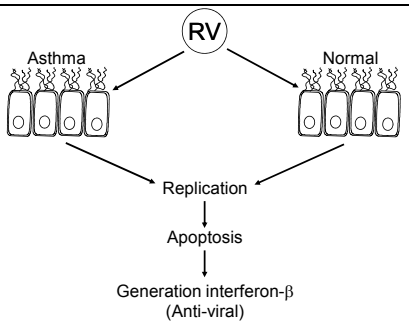
Teach, SJ et al. J Allergy Clin Immunol 2015;136:1476-1485

What is the effect of restoring IFN-α generation to asthma exacerbations?



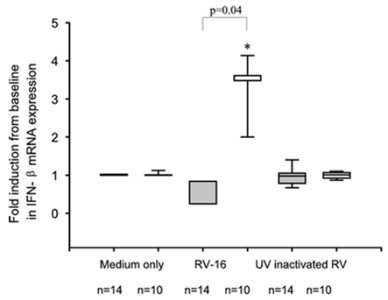
Teach, SJ et al. J Allergy Clin Immunol 2015;136:1476-1485

Is there a difference in bronchial epithelial cell generation of interferon between normal and asthma?



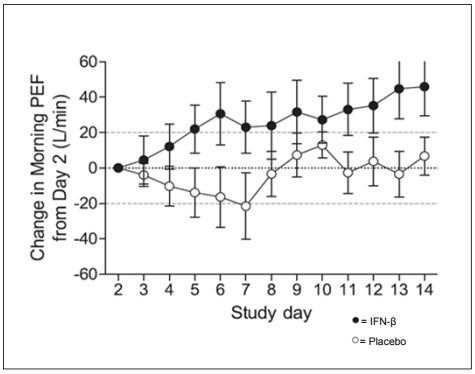
Wark et al. J Exp Med 2005; 201:937-947.

Impaired IFN-β production in asthma

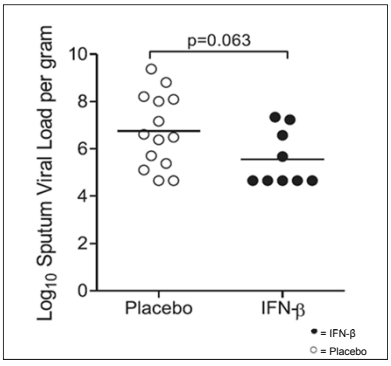


Wark et al. J Exp Med 2005; 201:937-947.

Djukanović R, et al. The effect of inhaled IFN-β on worsening of asthma symptoms caused by viral infections. Am J Respir Crit Care Med 2014;190:145-154.

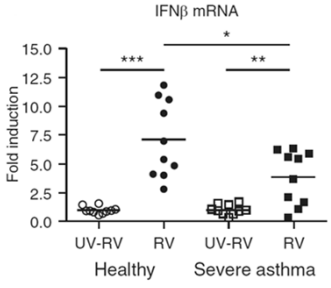


Djukanović et al. Am J Resp Crit Care Med 2014;190:145-154.



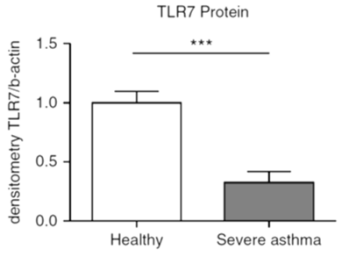
Djukanović et al. Am J Resp Crit Care Med 2014;190:145-154.

What is the alveolar macrophage expression of interferon-β to RV in severe asthma?



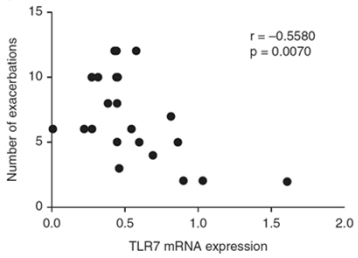
Rupani H., et al. Am J Respir Crit Care Med 2016;194:26-37.

What is the comparative of TLR7 protein generation by AM to RV in severe asthma?



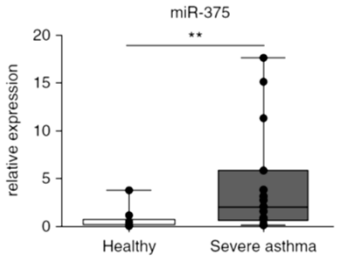
Rupani H., et al. Am J Respir Crit Care Med 2016;194:26-37.

Is there a relationship between TLR7 expression by AM and frequency of exacerbation in severe asthma?



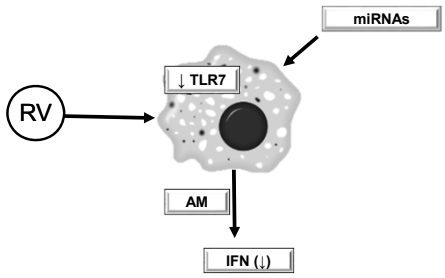
Rupani H., et al. Am J Respir Crit Care Med 2016;194:26-37.

What is the comparative AM expression of miRNAs in healthy and severe asthma subjects?

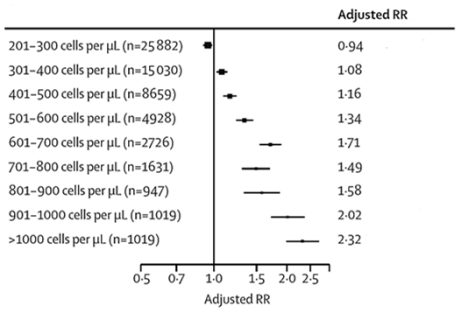


Rupani H., et al. Am J Respir Crit Care Med 2016;194:26-37.

Alteration of alveolar macrophage generation of interferons



What is the relationship of blood eosinophils to severe asthma exacerbations?

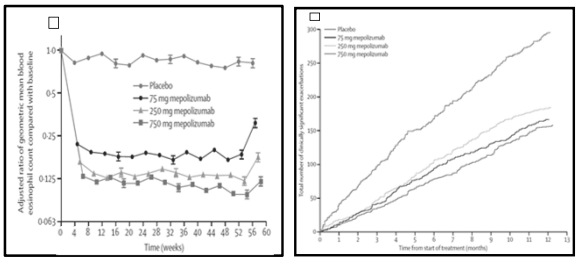


Price DB, et al. Lancet Respir Med 2015;3:849-58.

Pavord ID, et al. Mepolizumab (anti-IL-5) for severe eosinophilic asthma (DREAM). Lancet 2012;380:651-59.

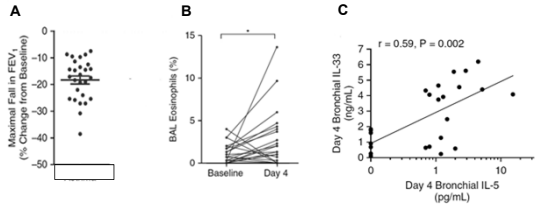
- Evaluated mepolizumab (75, 250 and 750 mg) vs. placebo
- 621 adult patients on high doses of ICS and with one or more of the following
  - 2 or more exacerbations in previous year
  - Sputum eosinophils ≥3%
  - FeNO ≥50 ppb
  - Blood eosinophils ≥300/microliter

Increased susceptibility factors for exacerbations



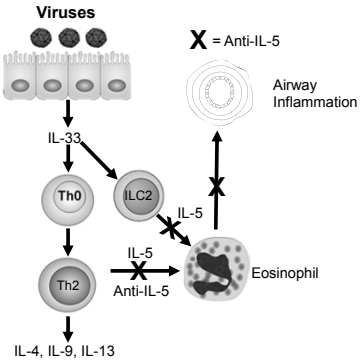
Pavord ID, et al. Lancet 2012;380:651-659.

What is the effect of a RV infection on asthma, eosinophils, IL-33 and IL-5?

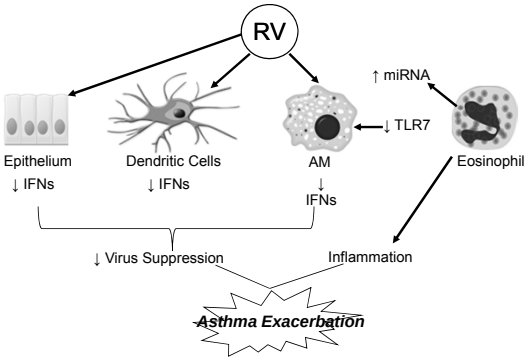


Jackson DJ, et al. Am J Respir Crit Care Med 2014;190:1373-1382

How may anti-IL-5 affect virus-induced asthma exacerbations?



What are key biologic targets that may promote asthma exacerbations?



AAAAI The Life Spectrum of Asthma 2016

Reducing/Eliminating Asthma Exacerbations: Immunopathologic Features of Asthma Exacerbations

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School of Medicine

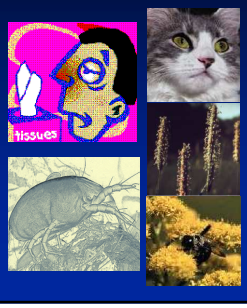
Disclosures

Mario Castro, M.D., M.P.H.

- PI (University Grant Funding): AsthmaNet, American Lung Association, Severe Asthma Research Program
- PI (Pharmaceutical Grant Funding): Amgen, Boeringer-Ingelheim, Boston Scientific, Genentech, Gilead, GSK, Invion, Johnson&Johnson, Kalabios. Medimmune, Novartis, Sanofi Aventis, Teva, Vectura
- Consultant: Boston Scientific, Genentech, GSK (DSMC), Holaira, Neostem, Roche
- Speaker: Boeringer-Ingelheim, Boston Scientific, Genentech, Teva
- Royalties: Elseiver
- Stock Options: Sparo, Inc

Causes of Asthma Exacerbations

- Poor underlying control
- Environmental factors
  - VRIs
  - Allergen exposure
  - Air pollution
  - Bacterial infections
  - Stress
  - Exercise/cold air
  - Occupational exposure



Asthma Exacerbations

- Viruses cause asthma exacerbations in adults and children
- RVs cause ~60% of virus-induced exacerbations of asthma
- The response to viral infection is shaped by the host's antiviral response
- Worsening of airway inflammation during exacerbations may be related to accelerated loss of lung function and structural changes

Viruses Detected During Asthma Exacerbations in Children

	Method of detection				
Virus	PCR	Culture	Immuno-fluorescence	Antibody rise by ELISA	Total
Picornaviruses	146	47			147*
Coronavirus	17	14		21	38
Influenza viruses		14	10	20	21
Parainfluenza viruses 1, 2, and 3		6	6	18	21
RSV		6	6	12	12
Other		2	1	2	3

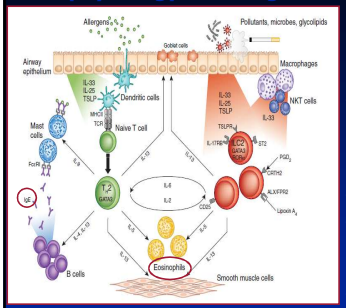
*108 school age children; viruses detected 80% of exacerbations; 84 of 147 picornaviruses identified as RV on further testing.
ELISA=enzyme-linked immunosorbent assay.
Reprinted from *BMJ*. 1995;310:1225-1229, with permission from the BMJ Publishing Group.

Viruses Detected in Symptomatic Asthma Exacerbations in Adults

Pathogen	Number	Percent of all episodes
RV	76	33.2
HCV OC43	21	9.2
HCV 229E	15	6.6
Influenza B	2	0.9
Parainfluenza	5	2.2
RSV	2	0.9
Chlamydia psittaci	3	1.3
Dual infection	5	2.2

138 adults with 280 exacerbations
RV=rhinovirus; HCV=human coronavirus; RSV=respiratory syncytial virus.
Nicholson KG et al. *BMJ*. 1993;307:982.

Pathophysiology of T2-High Asthma



High eosinophil levels cause[1–4]:

- Recruitment and activation of immune and structural cells
- Airway inflammation
- Airway wall fibrosis, thickening, and remodeling
- Inadequately controlled asthma symptoms and increased

ALX/FPR2 = receptor for lipoxin A4; CRTH2 = chemoattractant receptor-homologous molecule Th2; FcεRI = high-affinity receptor for IgE; GATA3 = GATA-binding protein 3; Ig = immunoglobulin; IL = interleukin; NKT = natural killer T; PGD_2 = prostaglandin D_2; RORα = retinoic acid receptor–related orphan receptor α; TSLP = thymic stromal lymphoprotein.

1. Brusselle GG. *Nature Med.* 2013;19(8):977-979. **2.** Walford HH. *J Asthma Allergy.* 2014;7:53-65. **3.** Jackson DJ. *Immunol Allergy Clin North Am.* 2014;34:e1-e22. **4.** National Heart, Lung, and Blood Institutes. National Asthma Education and Prevention Program (NAEPP). August 2007.

ICS Withdrawal in Moderate Persistent Asthma

	(n=27)
Age - mean (yrs)	41 ± 14
Male/Female	8/19
Atopy	18
FEV_1 L	2.60 ± 0.83
% pred	106 ± 13
PC_{20} (mg/ml)	1.4 ± 2.0
Met criteria for exacerbation	13 (52)

Castro et al AJRCCM 2004:169:842-849

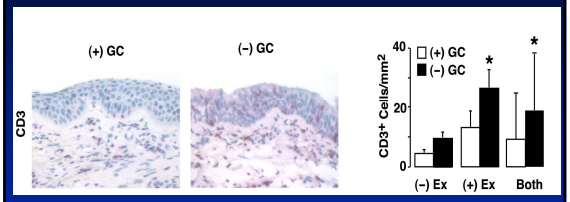
Physiologic Changes With ICS Withdrawal

	No Exacerbation (N=12)		Exacerbation (N=13)	
	(+) GC	(-) GC	(+) GC	(-) GC
AM PEF (L/min)	407 ± 107	389 ± 107†	429 ± 103	374 ± 125†
PM PEF (L/min)	451 ± 125	425 ± 105	424 ± 88	387 ± 125
FEV_1 (L)	2.89 ± 0.83	2.80 ± 0.82	2.91 ± 0.75	2.16 ± 0.99†
% Pred	87 ± 12	84 ± 13	94 ± 13	74 ± 24†
Range	63 - 107	61 - 107	71 - 111	32 - 114
FEV_1 PC_{20} (mg/ml)	3.7 ± 5.8	2.2 ± 4.5	3.4 ± 4.9	1.7 ± 3.5†
Range	0.13 - 16	0.16 - 16	0.05 - 16	0.03 - 12

†Value significantly different (P<0.05) from value for asthma subjects (+) GC.

Castro et al AJRCCM 2004:169:842-849

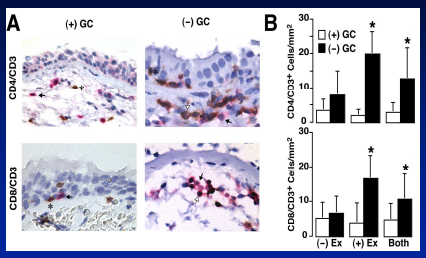
Inflammatory Responses During an Asthma Exacerbation



Corr with increase in β-agonist r = 0.55, p = 0.03 and reactivity r = -0.41, p = 0.04

Castro et al AJRCCM 2004:169:842-849

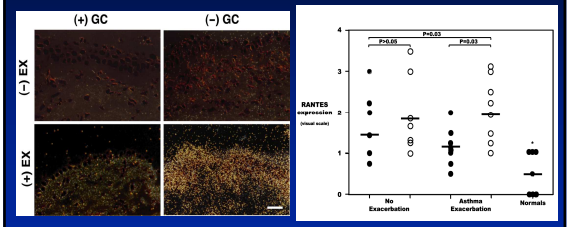
T cell subsets in the Airway During an Asthma Exacerbation



CD8 corr with decrease in FEV_1, r = -0.76, p = 0.02 and reactivity r = -0.66, p = 0.05

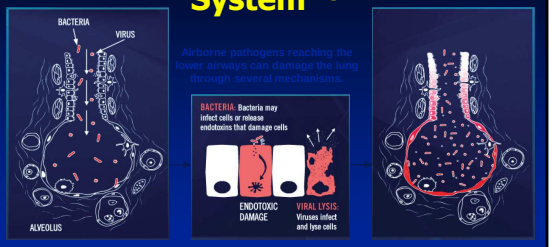
Castro et al AJRCCM 2004:169:842-849

RANTES Expression in the Airway Epithelium following Steroid Withdrawal



Castro et al AJRCCM 2004:169:842-849

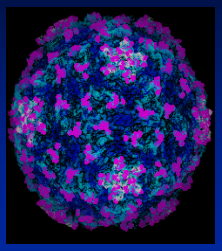
The Role of the Respiratory Immune System[1-3]



1. Sadikot et al. *Am J Respir Crit Care Med.* 2005;171(11):1209-1223.
2. Nalkein et al. Vaccine. 2008;26(Suppl 4):D50-D60.
3. Curtis JL. *Proc Am Thorac Soc.* 2006;3(5):412-416.

Mechanisms of VRI-Induced Asthma Exacerbations

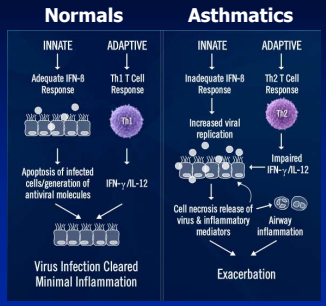
- Viral infections (esp. RV) frequently cause exacerbations of asthma
- Possible mechanisms
  - Extension into the lower airway[1-3]
  - Inflammation with lymphocytes, eosinophils, neutrophils [2,3]



1. Gern JE et al. *Am J Respir Crit Care Med.* 1997;155:1159.
2. Gern JE, Busse WW. *J Allergy Clin Immunol.* 2000;106:201.
3. Fraenkel DJ et al. *Am J Respir Crit Care Med.* 1995;151:879.

Poor Viral Clearance May Also Lead to Exacerbations

- A Th2 bias may also limit the respiratory immune system's ability to effectively clear virus
- This may lead to greater viral replication, lysis of epithelial cells, airway inflammation, and asthma exacerbations[1]

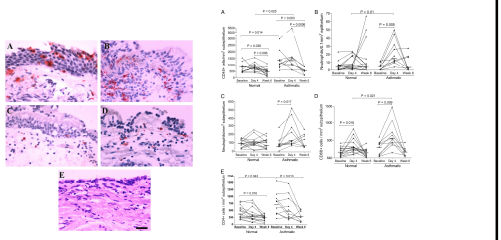


Malia et al. *Chest.* 2006;130:1203-1210.

CHEST

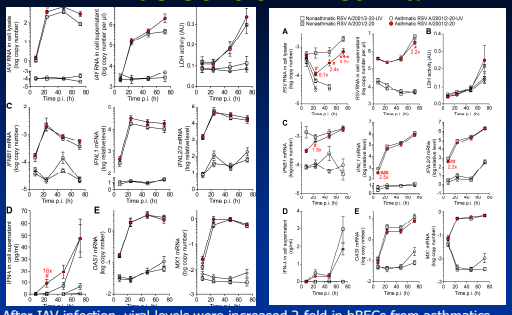
From: Airway Inflammation and Illness Severity in Response to Experimental Rhinovirus Infection in Asthma

Chest. 2014;145(6):1219-1229. doi:10.1378/chest.13-1567



Cell counts in bronchial biopsy specimens of subjects with and without asthma at baseline and days 4 and 6 of rhinovirus 16 infection. A, CD45+ cells. B, Epithelial neutrophils. C, Subepithelial neutrophils. D, CD68+ cells. E, CD4+ cells. Data are presented as the number of positive cells per square millimeter of subepithelium or per 0.1 mm² of epithelium. ▲ and ▲ show individual counts, and horizontal bars show median values (Wilcoxon matched pairs and Mann-Whitney U tests).

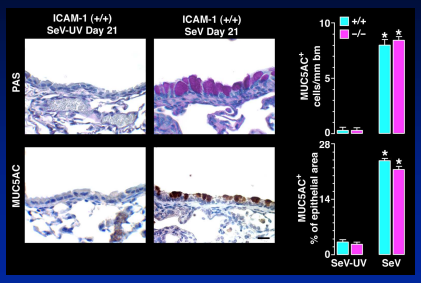
Interferon Response & Respiratory Virus Control in Asthma



After IAV infection, viral levels were increased 2-fold in hBECs from asthmatics compared to controls (P < .05) but not following RSV infection.

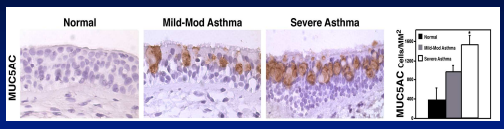
Patel, DA et al JACI 2014; 134(6):1402-1412.

Virus-induced Goblet Cell Hyperplasia



Walter M et al J Clin Invest 2002;110:165-75.

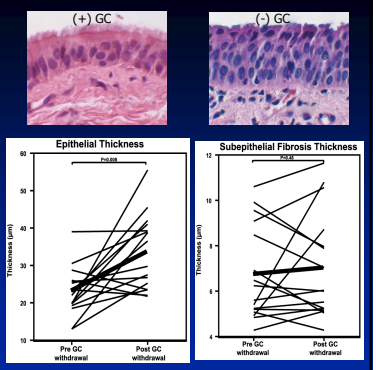
Mucin Products and Goblet Cell Hyperplasia



- Increase in mucin products have been described in mild- moderate asthma - MUC2, MUC5B, and MUC5AC (Ordonez AJRCCM 2001;163:517)
- In severe asthma, there appears to be a marked increase in goblet cells and mucin products as well

Christie et al PATS 2007:175:A837

Airway Epithelial Remodeling with Steroid Withdrawal

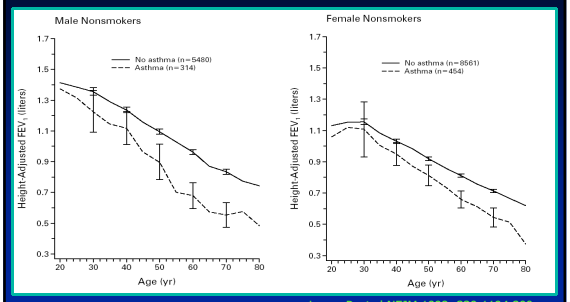


Castro et al AJRCCM 2004:169:842-849

Airway Remodeling in Asthma

- Individuals with asthma have a more rapid decline in FEV_1 with age than normals
- Despite long term therapy with steroids, some asthmatics develop irreversible airflow obstruction and persistent airway hyperreactivity
- Repetitive injury and repair of airways caused by chronic inflammation results in structural changes
- Healing of the airways involves replacement with normal cells or replacement by connective tissue/scar

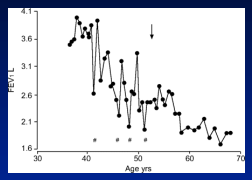
Decline in Lung Function in Asthma
(15 years follow up)



Lange P. et al NEJM 1998; 339:1194-200

Exacerbations -Leads to Remodeling?

- Bai et al. studied 93 asthmatics prospectively for ≥5 yrs (median 11 yrs)
- 60% experienced at least one severe exacerbation*
- Exacerbators experienced greater decline in FEV_1 - difference 16.9 ml/yr
- One exacerbation per yr associated with 30 ml greater decline in FEV_1



*Hospitalization or ≥20% and ≥500 ml drop in FEV1

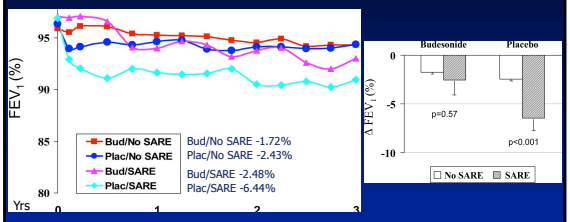
Bai et al ERJ 2007;30:452-6

Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START)

- 7,165 patients (5-66 yo) with persistent asthma <2 yrs randomized to budesonide vs. placebo for 3 yrs
- Mean followup: 2.47 yr Bud; 2.44 yr placebo
- Drop-out rates: 27.5% Bud; 28.6% placebo
- Added ICS: 12.5% Bud; 23.6% placebo

O'Byrne et al AJRCCM 2009;179:19-24

Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START)



- Mean yr decline in FEV_1 in placebo grp with SARE vs w/o: 66 vs 34 ml
- Mean yr decline in FEV_1 in Bud grp with SARE vs w/o: 27 vs 21 ml

O'Byrne et al AJRCCM 2009;179:19-24

Exacerbations and Airway Remodeling

- Viruses are a common cause of asthma exacerbations leading to AHR and GCM
- Exacerbations are associated with the influx of CD4 and CD8 lymphocytes
- Worsening of airway inflammation during exacerbations may accelerate loss of lung function
- ICS may prevent progressive loss of lung function in those with severe exacerbations
- Promising therapy such as biologics and thermoplasty may modify airway remodeling

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Washington University in St. Louis School of Medicine

Acute Physiologic Characteristics and Long Term Clinical Consequences of Asthma Exacerbations

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Thomas H. Davis Chair in Pulmonary Medicine
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Stephen P. Peters, MD, PhD Disclosure

- **Basic and Clinical Research**
  - NHLBI (AsthmaNet, SARP, SPIROMICS)
  - ALA (ACRC)
- **Book Chapters**
  - UpToDate
- **Pharmaceutical Trials**
  - Actelion, Amgen, Astra-Zeneca, Boehringer-Ingelheim, Centocor, Cephalon, Genentech, GlaxoSmithKline, Forest, Medimmune, Sanofi
- **Advisory Boards**
  - Array Biopharma, AstraZeneca, Aerocrine, Airsonett AB, Boehringer-Ingelheim, Experts in Asthma, Gilead, GlaxoSmithKline, Merck, Novartis, Ono Pharmaceuticals, Pfizer, PPD Development, Quintiles, Sunovion, Saatchi & Saatichi, Sanofi Regeneron, Targacept, TEVA, Theron
- **Speakers' Bureaus**
  - Integrity CE
- **Editorial Boards**
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  - Resp Research, Assoc Ed
  - J Allergy
  - Case Reports in Medicine
  - US Resp Disease
  - J Pulm Resp Medicine
  - Clin Exp Med Sciences
  - JACI: *In Practice*

Goals and Learning Objectives

- Discuss Acute Asthma Exacerbations with Respect to
  - Risk Factors and Associations for Exacerbations
    - Frequent Exacerbator Phenotype
  - Kinetics and Physiology of Manifestations
  - Impact on Patients and Long Tern Consequences

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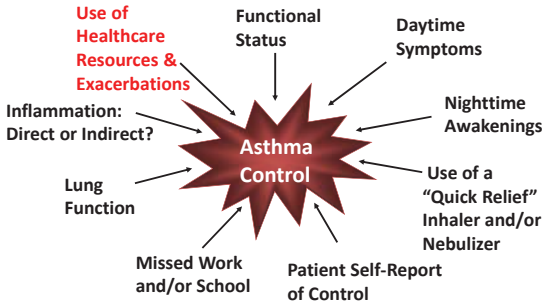
How Should Control of Asthma Be Assessed?



Adapted from Chipps BE, Spahn JD. J Asthma 2006; 43:567-572

Factor Analysis in Asthma

Juniper, et al., Eur Resp J 2004; 23:287-291

	Week			
	0	4	8	12
Quality of Life	1	1	1	1
	1	1	1	1
	1	1	1	1
	1	1	1	1
Airway Caliber	2	2	2	2
	2	2	2	2
	2	2	2	2
	2	2	2	2
	2	2	2	2
	3	3	3	3
Nighttime Symptoms	3	3	3	3
	3,4	3,4	4,3	4,3
	3	3	3	3
	3	3	3	3
	4	4	4	4
	4	4	4	4
Daytime Symptoms	4	None	None	None
	4	4	4	4
	4	4	4	4
	4	4	4	4
	None	4	4	4

Baseline Characteristics Patients 6 Omalizumab Trials

Chipps, et al. Curr Med Res Opin 206; 22:2201-2208

Characteristic	Omalizumab (n = 1342)	Control (n = 1206)
Females, n (%)	808 (60.2)	714 (59.2)
Mean age, years (range)	40.1 (12–79)	40.1 (12–74)
Mean serum total IgE, IU/mL (SD)	211.6 (166.9)	210.8 (165.2)
Mean ICS dose, µg/day (SD)*	1534 (1191)	1463 (1070)
LABA use, n (%)	543 (40.5)	433 (35.9)
Mean FEV_1, % predicted (SD)	69.5 (17.3)	70.2 (17.2)
Severe persistent asthma, n (%)†	1287 (95.9)	1165 (96.6)
Mean duration of asthma, years (range)	21.0 (1–72)	21.3 (1–66)
Mean AQLQ domain scores (SD)		
Activities	4.2 (1.2)	4.2 (1.1)
Emotions	4.3 (1.4)	4.3 (1.5)
Symptoms	4.2 (1.1)	4.2 (1.1)
Environmental exposure	4.0 (1.4)	4.0 (1.4)
Total score	4.2 (1.1)	4.2 (1.1)

Risk Factors for Asthma Exacerbations

- **Recent Exacerbations - OR 6.33 (4.57, 8.76)**
  Adjusted OR 3.77 – 5.62 (Resp Med 2007; 101:481-489)
- **Bateman** (JACI 2015; 135:1457-1464)

Variable	HR (95% CI)
– BMI	1.10 (1.04, 1.17)
– GINA Step (4 vs 3)	1.60 (1.40, 1.83)
– ACQ-5 Score	1.08 (1.04, 1.13)
– SABA Use	1.15 (1.10, 1.21)
– Post BD FEV1	1.11 (1.06. 1.16)

- **Similar Findings TENOR** (Ann Allergy Asthma Immunol 2012; 108-81-87)

BIOAIR – Risk Factors for Exacerbations

Kupczyk, et al., Thorax 2013; 68:611–618

Factor	OR	95% CI	p Value
Severe exacerbations			
Juniper ACQ >1.36 (median)	3.61	1.7 to 7.65	0.001
Sputum eosinophils ≥3%	3.27	1.13 to 9.42	0.028
BMI >25	2.9	1.3 to 6.5	0.01
SGRQ >34.6 (median)	2.22	1.03 to 4.8	0.042

Frequent Exacerbator (≥ 3/yr) Phenotype in SARP Denlinger, SARP, et al., AJRCCM (In press)

Unpublished SARP Data to be Presented Here

Frequent Exacerbator Phenotype (≥ 2/yr) in BIOAIR Kupczyk, ett al., Clin Exp Allergy 2013; 44:212-221

Variable	OR (95% CI)
FeNO > 45 ppb	4.32 (1.02, 18.31)
Smoking	2.90 (1.15, 7.35)

Goals and Learning Objectives

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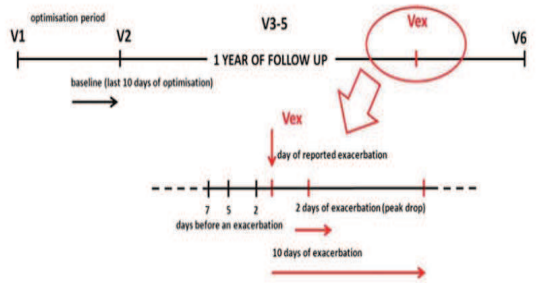
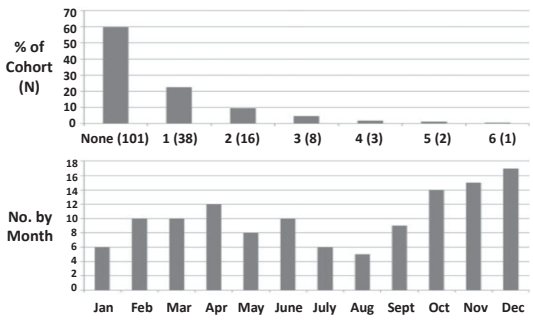
BIOAIR – Physiology of Exacerbations - 1

Kupczyk, et al., Thorax 2013; 68:611–618



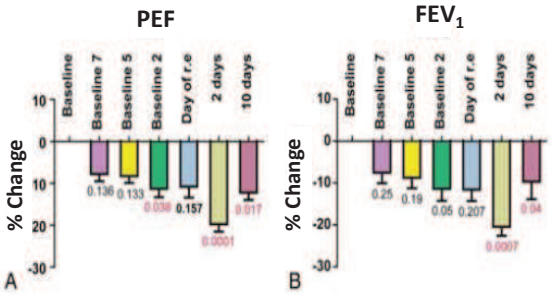
BIOAIR – Frequency of Exacerbations

Kupczyk, et al., Thorax 2013; 68:611–618



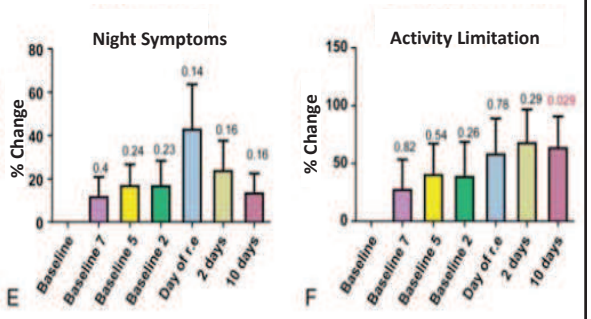
BIOAIR – Physiology of Exacerbations - 2

Kupczyk, et al., Thorax 2013; 68:611–618



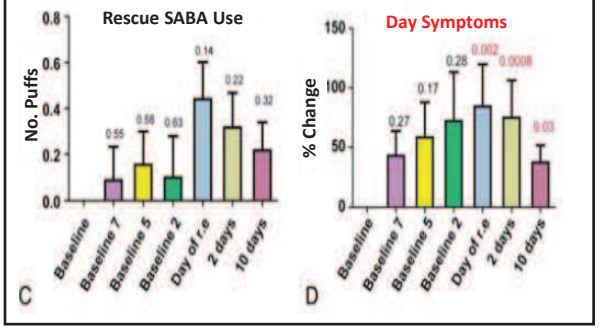
BIOAIR – Physiology of Exacerbations - 3

Kupczyk, et al., Thorax 2013; 68:611–618



BIOAIR – Physiology of Exacerbations - 4

Kupczyk, et al., Thorax 2013; 68:611–618

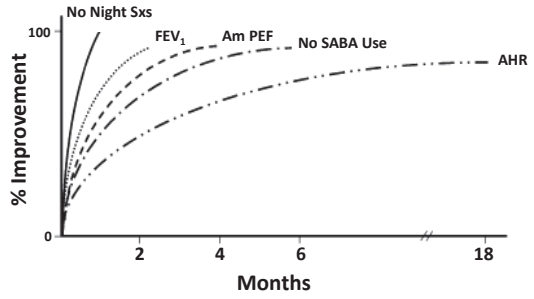


Symptoms: Portend Impending Exacerbation and Drive Treatment

- BIOAIR – increased symptoms preceeded lung function changes and increased rescue β-agonist use (Thorax 2013; 68:611–618)
- Chan-Yeung – symptoms started to increase 2 days before
- the first day of exacerbation and that this occurred before the
- PEF fell (AJRCCM 1996;154:889-893)
- Dennis – "of all the diary card variables an increase in daytime symptoms is strongly predictive of additional oral or increased inhaled corticosteroid usage" (Clin Exp All 2005; 35:308-312)
- FACET - 73% of FACET exacerbations resulted in treatment with oral corticosteroids in response to increasing symptoms rather than a fall in morning PEF (AJRCCM 1999; 160:594–599)

Kinetics of Improvement after ICS

Reddell, et al., AJRCCM 2009; 180:59-99



BIOAIR – Detecting Exacerbations

Kupczyk, et al., Thorax 2013; 68:611–618

Table 3 Sensitivity and specificity of combined parameters to detect severe exacerbations

	Severe exacerbations in the whole asthma cohort	
Definition of exacerbation	Sensitivity (%)	Specificity (%)
20% decrease in PEF on 2 consecutive days and 20% increase in day symptoms on 2 consecutive days	13.3	99.5
20% decrease in PEF on 2 consecutive days or 20% increase in day symptoms on 2 consecutive days	65.0	94.9
20% decrease in FEV_1 on 2 consecutive days and 20% increase in day symptoms on 2 consecutive days	13.2	99.3
20% decrease in FEV_1 on 2 consecutive days or 20% increase in day symptoms on 2 consecutive days	60.4	94.8

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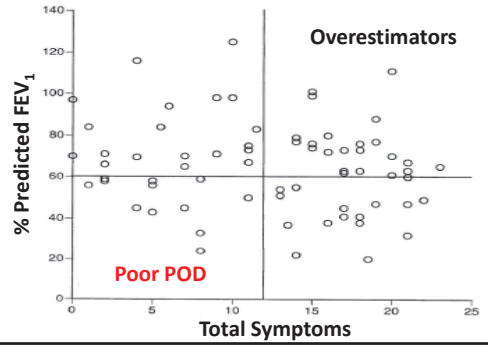
Perception of Airway Obstruction

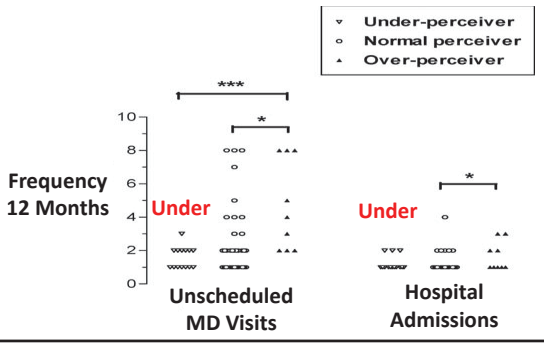
Teeter and Bleecker, CHEST 1998; 113:272-77



Insert "Perception of Dyspnea" Question Here

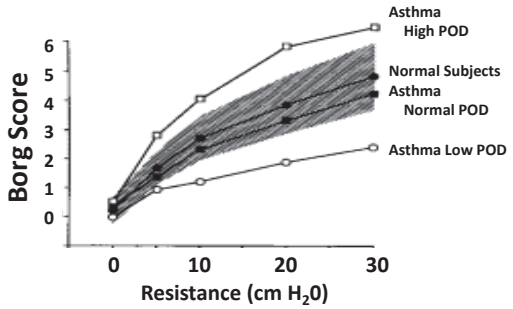
Perceptions of Dyspnea – 1

Loh and Teh, J Asthma 2009; 46:529–534



Perceptions of Dyspnea – 2

Magadle, et al., CHEST 2002; 121:329–333



Perceptions of Dyspnea – 2

Magadle, et al., CHEST 2002; 121:329–333

ED Visits, Hospitalizations, Near Fatal Asthma, Deaths in 113 Patients with Asthma

	Low POD n = 29	Normal POD n = 67	High POD n = 17
ED Visits	32	8	14
Hospitalizations	22	4	3
Near-Fatal Asthma	13	2	1
Deaths	6	1	0

Data are Number of Events; Patients may have had more than one episode.

Recurrent Exacerbations and Enhance Airway Closure

Johannes, et al., AJRCCM 2000; 161:1902–1906

Parameter (% *pred*)	Difficult-to-control Asthma	Stable Asthma	p Value
FEV_1	89.0 ± 4.6	92.9 ± 4.3	0.54
TLC	106.7 ± 4.0	101.7 ± 4.3	0.40
FRC	98.6 ± 6.6	98.7 ± 4.5	0.99
RV	113.1 ± 7.8	100.9 ± 7.1	0.26
RV/TLC	103.5 ± 4.7	95.8 ± 3.8	0.21
dN_2	142.7 ± 16.3	116.0 ± 20.2	0.23
CV/VC	159.5 ± 26.8	98.8 ± 12.5	0.024
CC/TLC	114.0 ± 6.4	99.9 ± 3.6	0.030

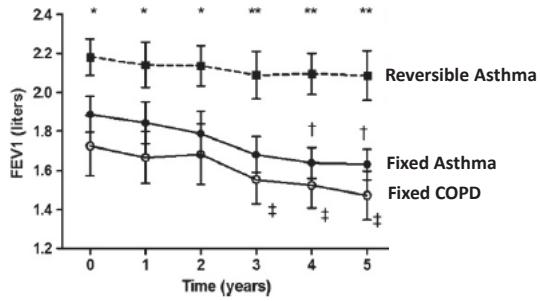
Definition of abbreviations: CC/TLC = ratio of closing capacity to total lung capacity; CC/VC = ratio of closing volume to vital capacity; RV/TLC = ratio of residual volume to total lung capacity; dN_2 = slope of Phase 2 of the nitrogen expiration curve.

All values (% predicted) are expressed as mean ± SEM. RV/TLC = RV as ratio of TLC; dN_2 = slope of phase 3; CV/VC = closing volume as ratio of vital capacity; CC/TLC = closing capacity as ratio of TLC).

Insert "Lung Function Decline and Exacerbations: Cause and Effect?" Question Here

Fixed Airflow Obstruction* and Lung Function Decline Over 5 Years

Cantoli, et al., J Allergy Clin Immunol 2010; 125:830-837



*FEV1/FVC < 70% after albuterol and prednisolone

Fixed Airflow Obstruction* and Lung Function Decline Over 5 Years

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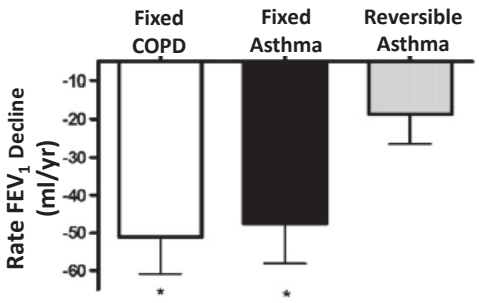
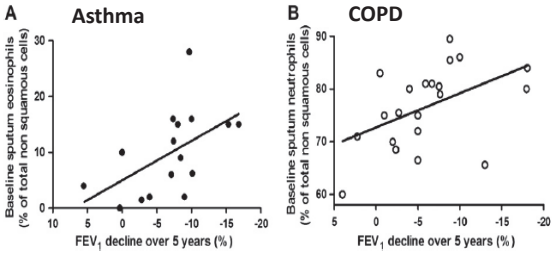


*FEV1/FVC < 70% after albuterol and prednisolone

Fixed Airflow Obstruction* and Lung Function Decline - Inflammation

Cantoli, et al., J Allergy Clin Immunol 2010; 125:830-837



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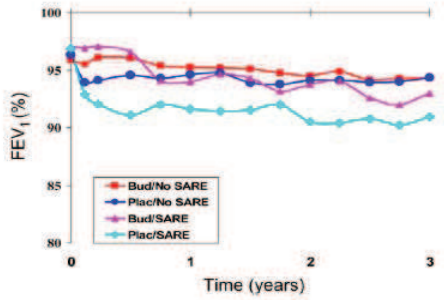
Severe Asthma Exacerbations and Lung Function Decline (3 yrs, post-BD) - START

O'Byrne, et al., AJCCM 2009; 179:19-24



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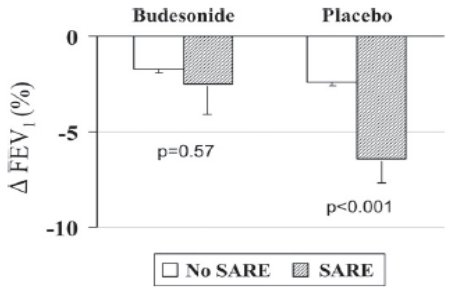
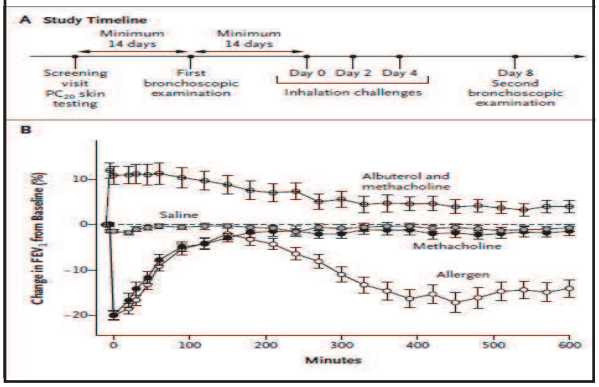


Bronchoconstriction and Airway Remodeling

Grainge, et al., NEJM 2011; 364:2006-2015



Bronchoconstriction and Airway Remodeling

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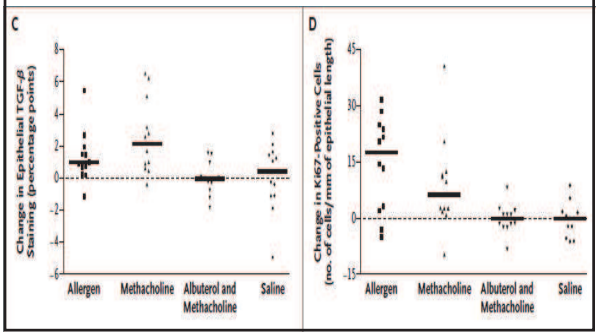


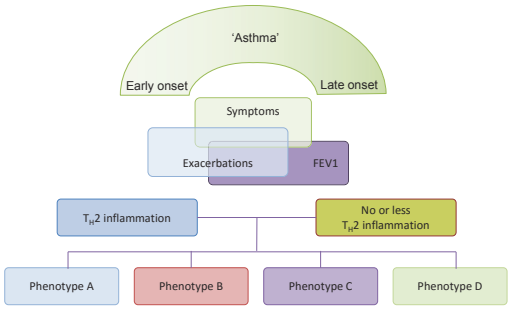
Summary and Conclusions

- Risk Factors for Exacerbations include Recent Prior Exacerbations, More Severe Asthma, High BMI, Poor Symptom Control and Excess β-Agonists Use, and Airflow Limitation
- Exacerbations are a Major Cause of the Morbidity Associated with Asthma
- Airflow Limitation and Decrease in Lung Function Appear to be Both Risk Factors for Exacerbations and a Result of Them

Precision Asthma Therapy:
Picking the Right Biologic for the Right Patient

Thomas B. Casale, MD
Professor of Medicine and Pediatrics
University of South Florida Morsani College of Medicine
Tampa, FL USA

The Asthma Umbrella



Wenzel S. Nature Medicine 18, 716–725 (2012)

Precision Asthma Therapy: The Path Forward

Clinical phenotypes

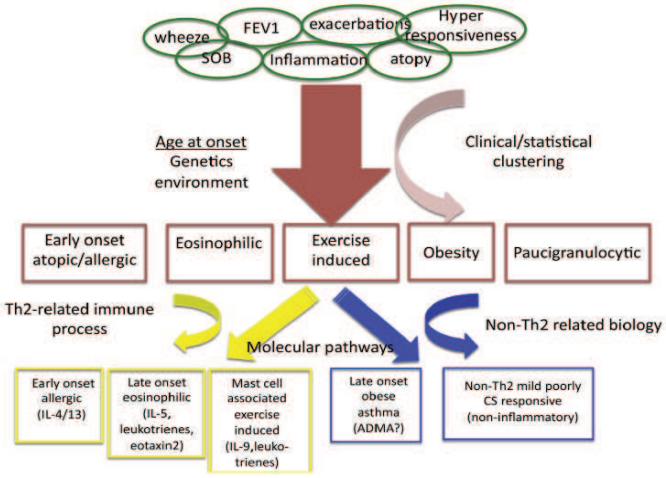
Treatable traits

Molecular endotypes

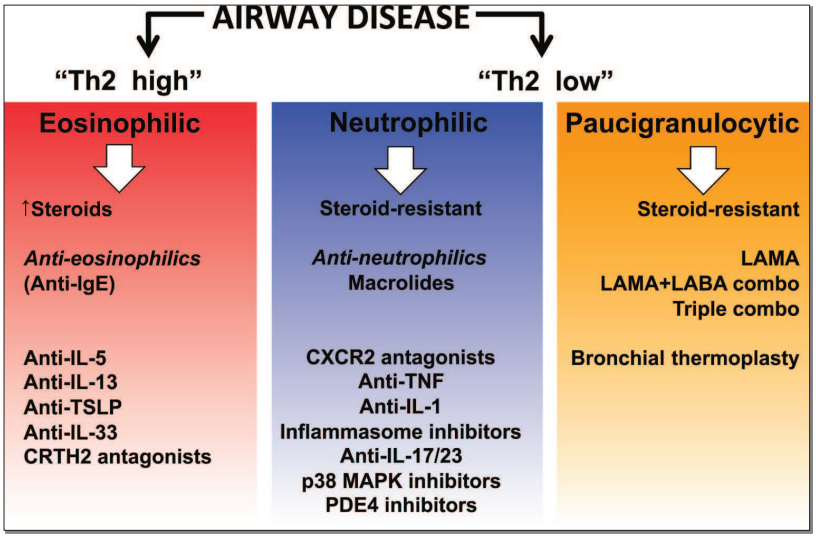
Precision medicines

Remissions and cures

Phenotypes to Endotypes



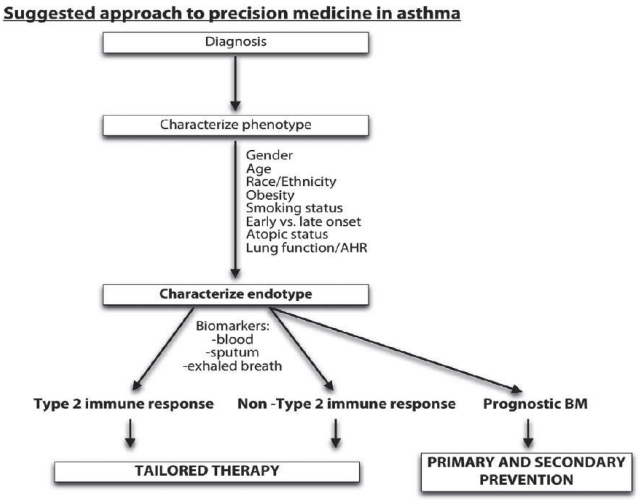
Wenzel SE. *Pulm Pharmacol Ther.* 2013;26:710-715.



PRACTALL consensus report

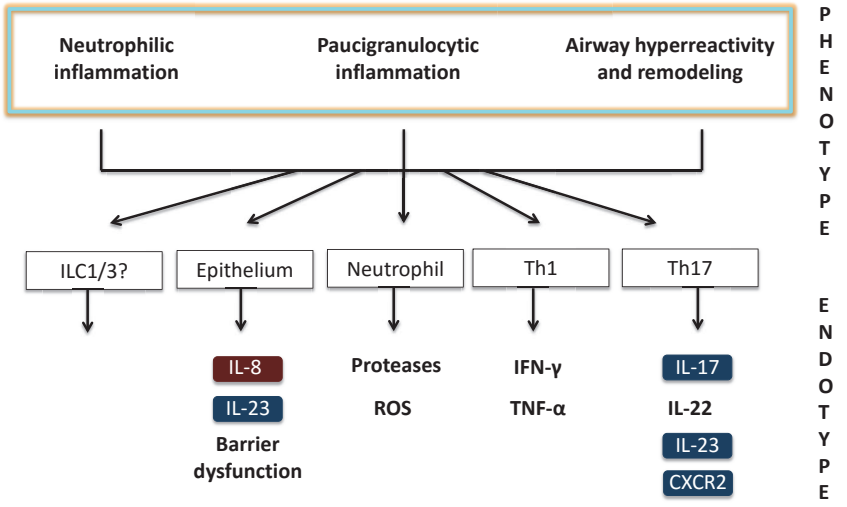
Precision medicine in patients with allergic diseases: Airway diseases and atopic dermatitis—PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology

Antonella Muraro, MD,[a] Robert F. Lemanske, Jr, MD,[b] Peter W. Hellings, MD,[c] Cezmi A. Akdis, MD,[d] Thomas Bieber, MD,[e] Thomas B. Casale, MD,[f] Marek Jutel, MD,[g] Peck Y. Ong, MD,[h] Lars K. Poulsen, PhD,[i] Peter Schmid-Grendelmeier, MD,[j] Hans-Uwe Simon, MD,[k] Sven F. Seys, PhD,[l] and Ioana Agache, MD[m] *Padua, Italy, Madison, Wis, Leuven, Belgium, Davos and Bern, Switzerland, Bonn, Germany, Tampa, Fla, Wroclaw, Poland, Los Angeles, Calif, Copenhagen, Denmark, and Brasov, Romania*



JACI, May 2016

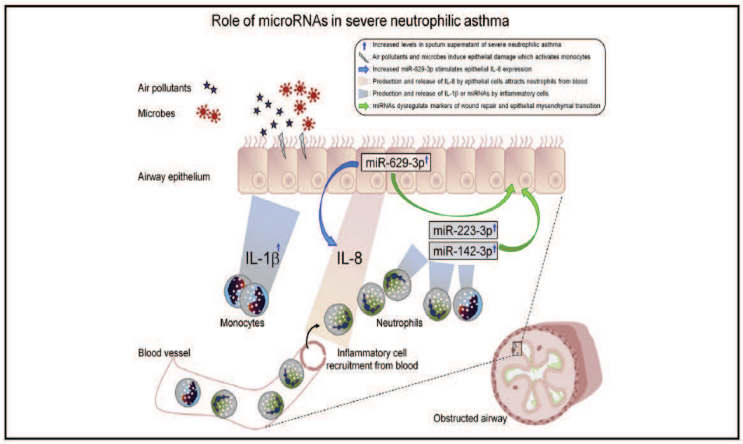
Type 2 Low Asthma



JACI, May 2016

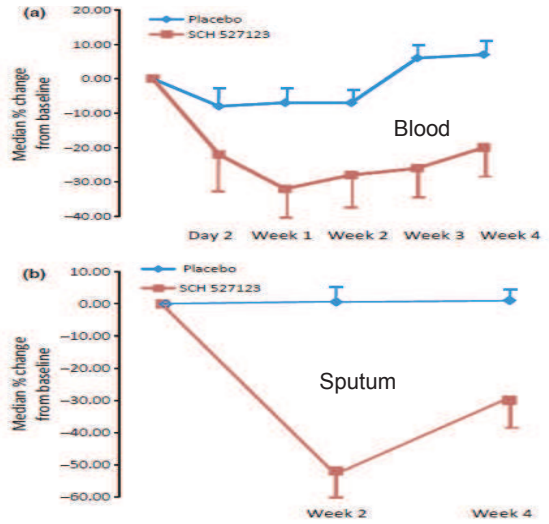
Approved treatment targets | Under investigation treatment targets | Potential treatment targets

Neutrophilic Asthma: A Potential Biomarker for Disease



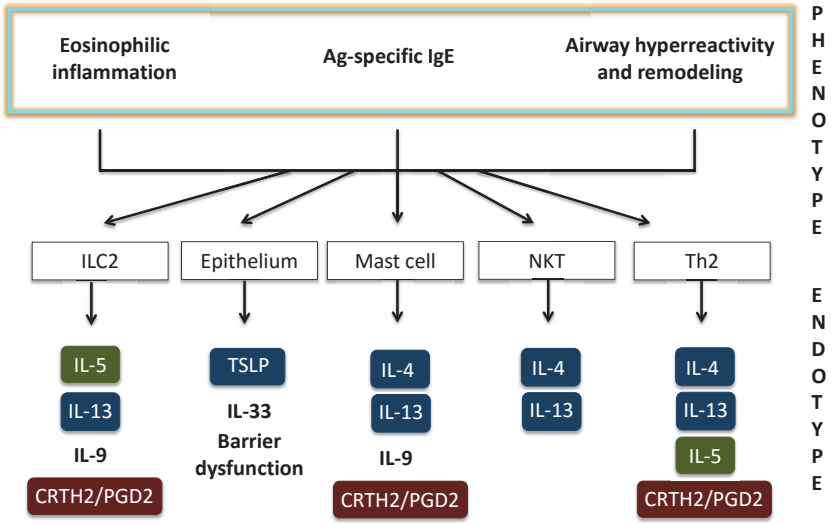
Maes et al, JACI, May, 2016

Efficacy Of A CXCR2 (IL-8) Antagonist In Severe Asthma With Sputum Neutrophils



Nair P, et al. Clin Exp Allergy. 2012 Jul;42(7):1097-103.

Type 2 Hi Asthma



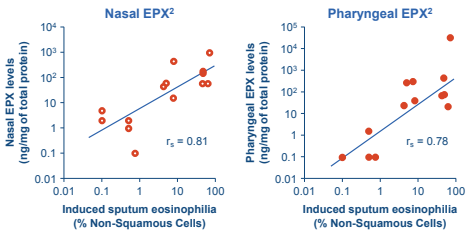
JACI, May 2016

Approved treatment targets | Under investigation treatment targets | Potential treatment targets

Biomarker	Treatment expected to produce a response	Associations	Comments (point of care, variability/fluctuation)
BLOOD			
Eosinophil	Anti-IL5 Anti -IgE Anti- IL-4/IL-13 Corticosteroids (CS) CRTH2 antagonists	Exacerbations LF decline Fixed airway obstruction	Easily available Significant fluctuation
Specific IgE	Anti-IgE AIT	Exacerbations AHR (AIT)	
Periostin Dipeptidyl peptidase-4 (DPP-4)	Anti-IL-13	LF decline Exacerbations	Research type Assay dependent
INDUCED SPUTUM			
Eosinophils	Anti IL-5 ICS	Exacerbations	Research type Significant fluctuation
IL-13	Anti IL-13	?	Research type
EXHALED BREATH			
FeNO	Anti IL-5 Anti IgE Anti IL-13 ICS	Exacerbations, LF decline	Easily available Point of care Significant fluctuation
Metabolomics (VOC)	ICS	?	Research type

Novel Ways to Measure Eosinophils in Clinical Practice

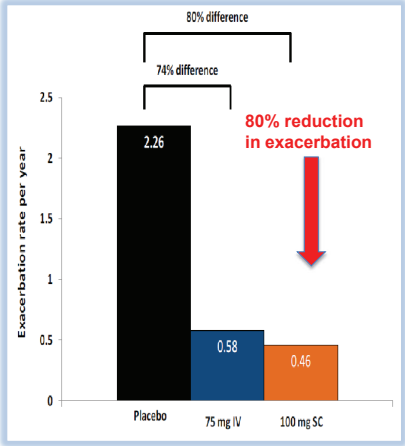
- Inexpensive, point-of-care diagnostic tools being developed to improve management of patients with respiratory diseases
- Bioactive paper[1]
  - "Bio-inks" on paper strip measures quantity of eosinophil peroxidase (EPX) in sputum
- Throat or nasal swabs[2]
  - Strong association between nasal and pharyngeal EPX levels and percentage of induced sputum eosinophils
  - Potentially clinically relevant diagnostic metric; simplicity of use provides potential novel point-of-care assay for management of poorly controlled patients

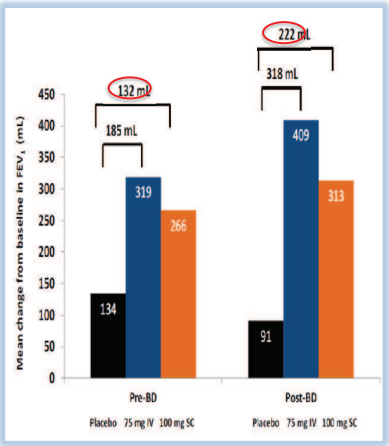


1. Bioactive Paper Will Revolutionize Point-of-Care Diagnostics. http://dailynews.mcmaster.ca/article/bioactive-paper-will-revolutionize-point-of-care-diagnostics/. March 7, 2016. 2. Rank MA et al. *Allergy*. 2016;71(4):567-570.

Potential for application in doctor's offices, outpatient clinics, and by patients themselves for self-management[1]

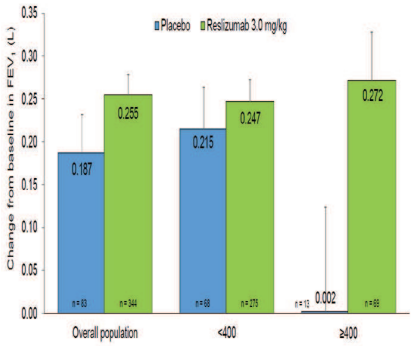
Subgroup Analysis Of 177 Patients With Blood Eosinophils ≥500 Cells/mL From MENSA Population

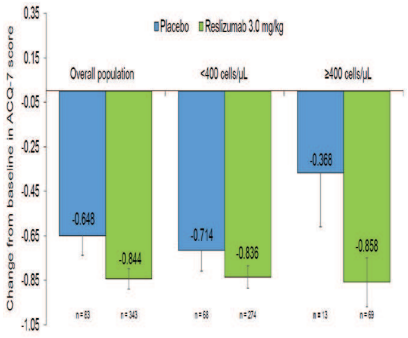




Source: Ortega et al . N Engl J Med 2014; 371:1198-1207

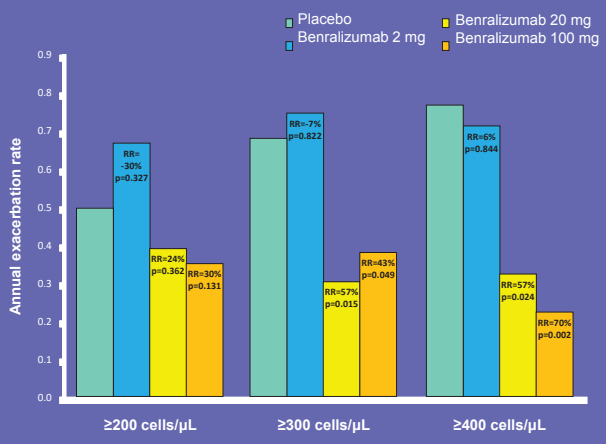
Reslizumab Effects on FEV1 and ACQ Based On Bld Eos: 16-Week Studies





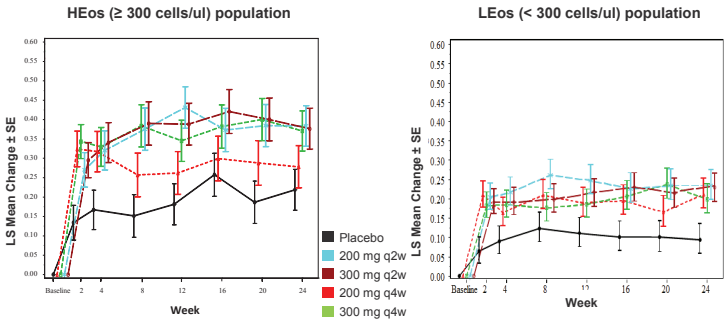
Corren et al, Chest, 2016, In Press

Benralizumab's Effects on Annual Exacerbation Rate By Eosinophil Level



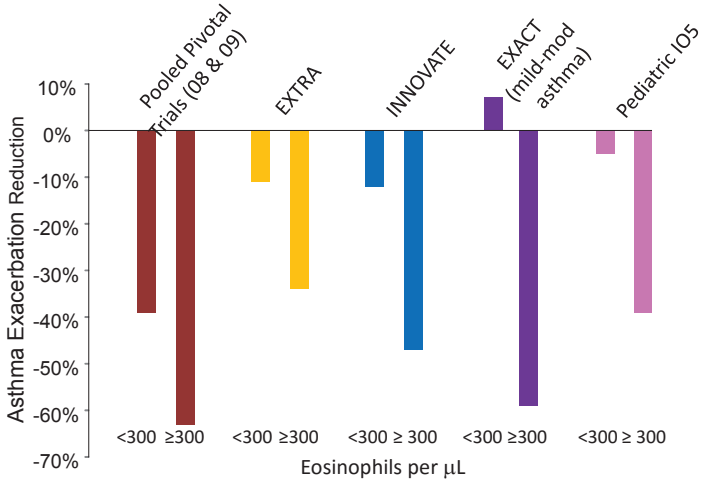
RR, rate ratio
Castro et al. Lancet Resp Med 2014; 2: 879–90

Dupilumab-Induced Changes From Baseline in Absolute FEV_1 By Eosinophils



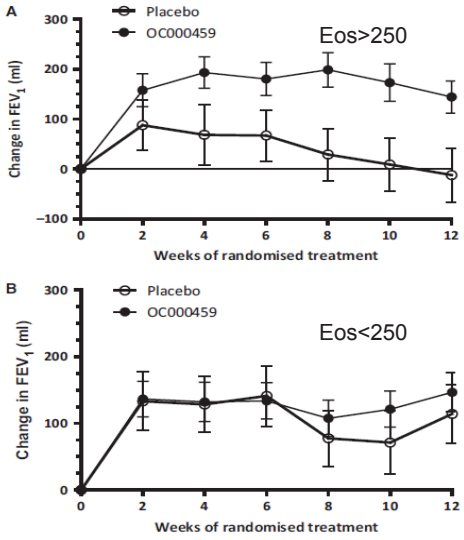
Wenzel, et al, Lancet, 2016

Asthma Exacerbation Reductions in Omalizumab Clinical Trials by Eosinophil Strata



Sources: Hanania et al. *AJRCCM* 2013; Busse et al. *JACI* 2013; Genentech and Novartis Data on File

Heightened Response Of Eosinophilic Asthmatics To CRTH2 Antagonist OC000459



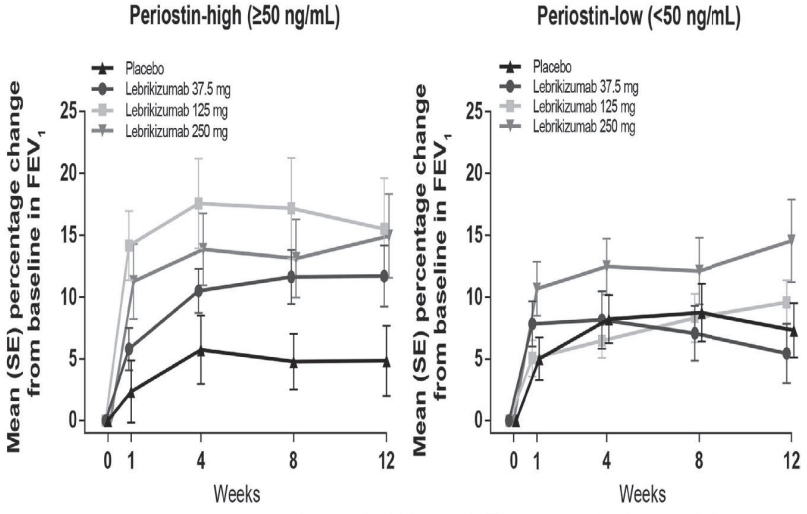
Pettipher R, et al. Allergy. 2014 Sep;69(9):1223-32.

Endotype-Driven Treatment In T2 Asthma

Predictive biomarker	Drug	Target	Effects
Blood eosinophils Periostin FENO	Omalizumab	IgE	Reduces exacerbations Improves symptoms and quality of life
Blood/sputum eosinophils FENO	Mepolizumab	IL-5	Reduces eosinophil counts, exacerbations, and OCS Improves FEV_1
Blood eosinophils	Reslizumab	IL-5	Reduces eosinophil counts, exacerbations Improves FEV_1
Blood eosinophils	Benralizumab	IL-5Rα	Reduces eosinophil and basophil counts, exacerbations Improves FEV_1
Blood eosinophils	Dupilumab	IL-4Rα	Reduces exacerbations Improves FEV_1 Improves symptoms and quality of life
Periostin DPP-4	Tralokinumab	IL-13	Reduces eosinophil counts and exacerbations Improves FEV_1
Periostin	Lebrikizumab	IL-13	Reduces exacerbations Improves FEV_1

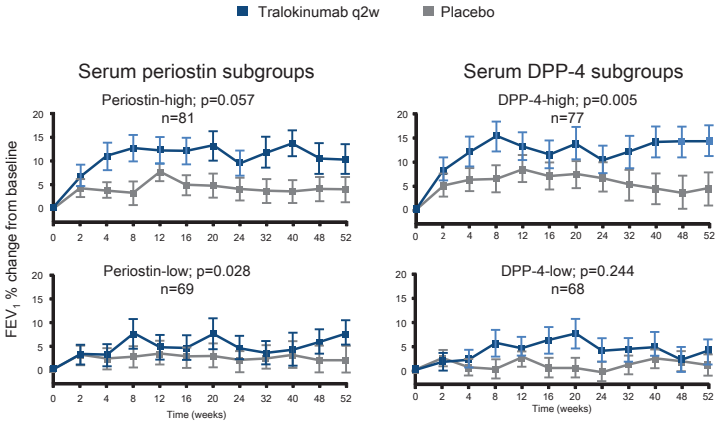
JACI, May 2016

52-Week Replicate Lebrikizumab Trials in Adults with Asthma



Hanania NA, et al. Thorax. 2015 Aug;70(8):748.

Changes In FEV_1 In Subgroups Treated With Tralokinumab for 52 Weeks



Brightling CE, et al. Lancet Respir Med 2015;DOI:10.1016/S2213-2600(15)00197-6

Critical Issues /Questions for Th2 Blockers

- Many options for similar patient populations.
  - Phenotype/Endotype (Biomarker) driven choices overlap: *No specific biomarkers*
- Optimal treatment goals have not yet been met:
  - True Immunomodulation: prevent/alter disease course
- Th2 blockers likely have favorable risk/benefit ratio

Why Precision Medicine is Important

Reducing and/or Eliminating Asthma Exacerbations

Saturday, July 30 at 10:00 am

Major discussion question:
What therapeutic intervention(s) should be considered to reduce both the frequency and severity of exacerbations in a teenager on Step 3 care using high dose LABA/ICS combination therapy who has 3 or more asthma exacerbations/year requiring OCS, but normal daily activities and spirometry between episodes?

Severe Asthma(s): Can THEY be prevented or reversed?

Sally Wenzel, MD
Professor of Medicine
UPMC Chair in Translational Airway Biology

Disclosures

- Sally Wenzel, M.D.
  Grant/Research Support: Boehringer-Ingelheim, Sanofi, GSK, Genentech, AstraZeneca
  Consultant: Knopp, Aerocrine

Umbrella Definition: Severe Asthma *Chung et al ERJ 2014*

- …requires treatment with high dose inhaled corticosteroids (ICS) (≥1000 µg fluticasone propionate or equivalent) plus a second controller (and/or systemic CS) to prevent it from becoming "uncontrolled" or remains "uncontrolled" despite this therapy

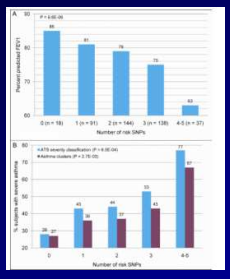
The Severe Asthmas

- Severe asthma not a single disease
- Most clear phenotypes:
  - Childhood onset allergic
    - Always severe
    - Worsening in adulthood
      - Uncommon to slowly progress to severe asthma
  - Adult onset/nasal polyposis
  - Comorbidity associated
  - Autoimmunity/asthmatic granulomatosis
- Each may require different approaches to prevention/reversal

Common Elements of Prevention

- Have normal lung function at birth and during infancy
  - Pick your parents wisely
    - Genetics of asthma/lung function
    - Make sure Mom doesn't smoke during pregnancy
  - Avoid certain viruses (RSV/RV), especially if you're premature

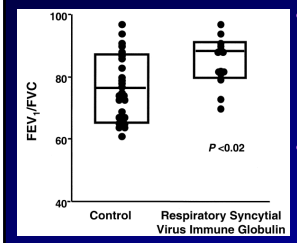
Pick your parents wisely: Genetics of lung function



- Select mutations in HHIP, PTCH1, FAM13A1, PID1, NOTCH4 associated with lower FEV1
- Additive effect of mutations in all 5 associated with lowest FEV1 and highest % severe dz

Li, X….E. Bleecker J Allergy Clin Immunol 2011

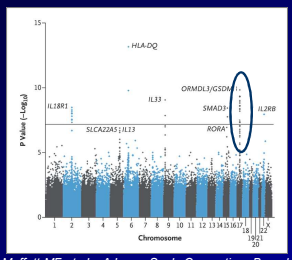
Avoid viral infections (or get preventive immunizations)



Fewer asthma attacks, school days missed Wenzel Am J Med 2002

- Severe bronchiolitis associated with asthma risk, esp in those with asthma FH
  - Sigurs et al AJRCCM 2005
- Premature infants at risk for RSV and treated with RSV immunoglobulin had less asthma/better lung function 10 yrs later

Childhood onset allergic asthma: Genetics and presence of asthma

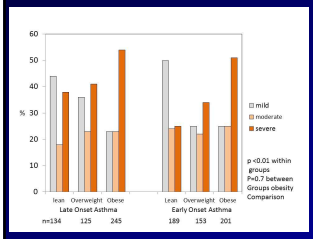


- >10,000 asthma/16,000 controls
- Highest p-values for any region were in 17q12-21 in association with CHILDHOOD onset asthma (<16 yrs old)
- Not seen with adult onset asthma
- Gene x environment interactions: Dogs protective

Moffatt MF et al. A Large Scale Consortium-Based Genomewide Association Study of Asthma N Engl J Med 2010;363:1211-1221

The NEW ENGLAND JOURNAL of MEDICINE

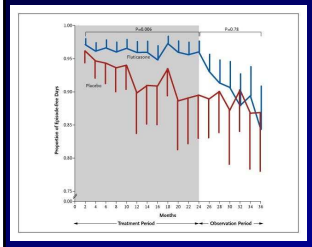
Avoid comorbid conditions



Holguin F, J Allergy Clin Immunol 2011

- Adult onset disease associated with both smoking and obesity
  - Obesity in adult onset asthma not associated with disease duration (as it is in childhood onset) *Holguin JACI 2011*
- Obesity associated with poorly controlled asthma
- Both "preventable"

Can any treatment *prevent* severe asthma?



- Early ICS Rx does not prevent asthma progression in children
  - Those who best responded to ICS suffered the most on withdrawal
- Trials of specific biologics at very early age are needed

Guilbert TW et al. N Engl J Med 2006;354:1985-1997.

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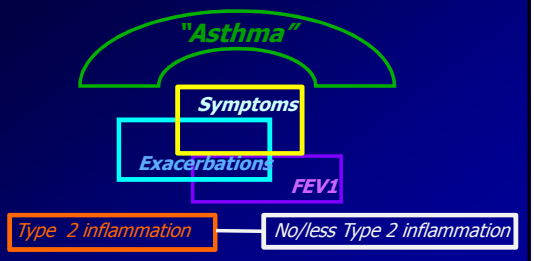
Reversal: Type-2 Hi vs Not?



The promise of biologics?

What does it mean to reverse?

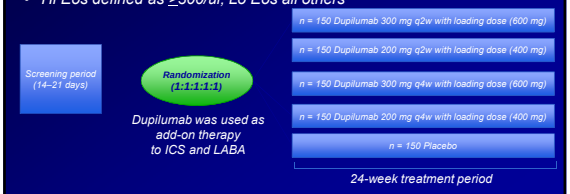
- Prevent progression
- Bring poorly controlled asthma back to well controlled asthma
- Permanently improve lung function or remodeling elements
- Improve asthma control AND reduce medication requirements

Likely only modest evidence to suggest can bring poorly controlled asthma back to well controlled

Anti-IL-4Rα in Eos/T2Hi Asthma

Multinational, randomized, placebo-controlled study in patients with uncontrolled asthma despite background therapy with medium- to high-dose ICS and LABA

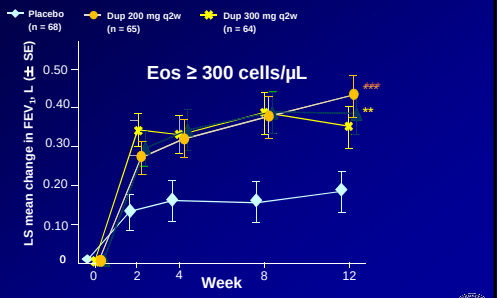
- *Patients stratified by blood eosinophil count*
- *Hi Eos defined as ≥300/ul, Lo Eos all others*



Dupilumab was used as add-on therapy to ICS and LABA

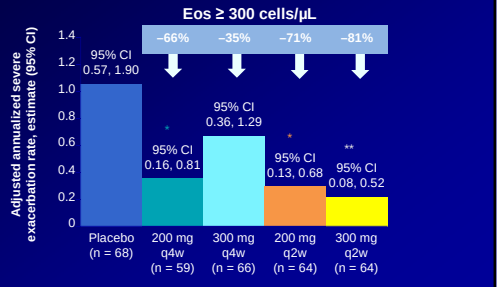
Wenzel, Castro, Corren et al Lancet e-pub 2016

Primary endpoint: Change in FEV1 in patients with ≥300 eos/µL



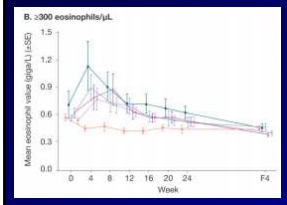
Wenzel, Castro, Corren et al Lancet e-pub 2016

~75% reduction in steroid requiring asthma exacerbations (6mos)



Wenzel, Castro, Corren et al Lancet e-pub 2016

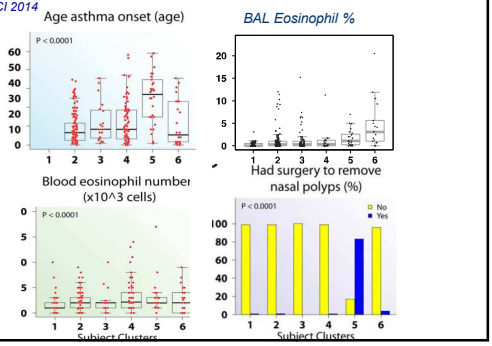
Could there be immune modification as well?



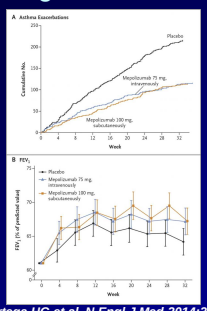
- Dupilumab increases blood eos, esp in those with high #s
- However, after 4-5 mos on Rx, they are back to baseline and perhaps even lower
  - Associated decrease in T2 biomarkers
- *Could* inhibition of IL-4R reduce T2 activity?

Alternative Type-2: adult onset-nasal polyp/eosinophilic disease

Wu, JACI 2014



Mepolizumab consistently effective in 3 large trials of eosinophilic patients

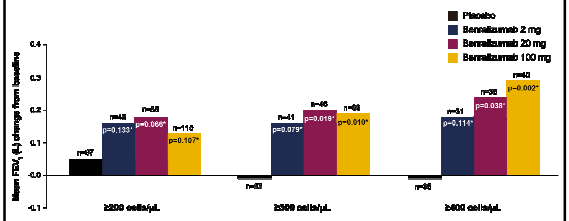


- Targeted patients with blood eosinophils >~280/ml
- Reductions in exacerbations of 40-50%
- Recent studies show impact on FEV1/ACQ as well
- Responses improve with increasing eosinophils (and likely nasal polyposis/sinus dz)
- Recently approved by FDA
- Similar data with reslizumab, benralizumab (anti-IL5Receptor antibody) *Castro Lancet Resp Med 2014 and 2015*

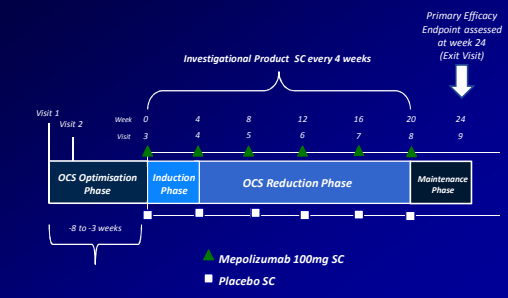
Ortega HG et al. N Engl J Med 2014;371:1198-1207.

THE NEW ENGLAND JOURNAL of MEDICINE

The more blood eos present the better the response (anti-IL5R)

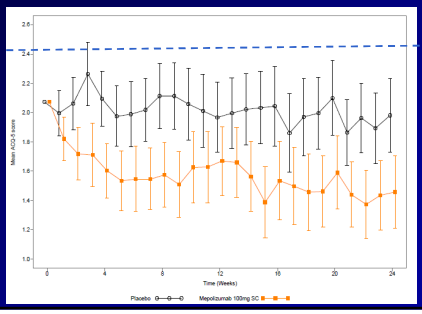


Anti-IL-5 as CS sparing agent



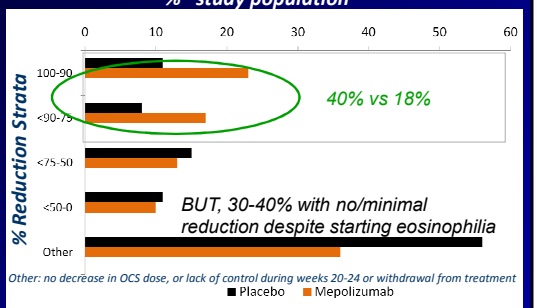
Bel E, et al, N Engl J Med Sept 2014

Improvement in asthma control *despite* reduction in corticosteroids

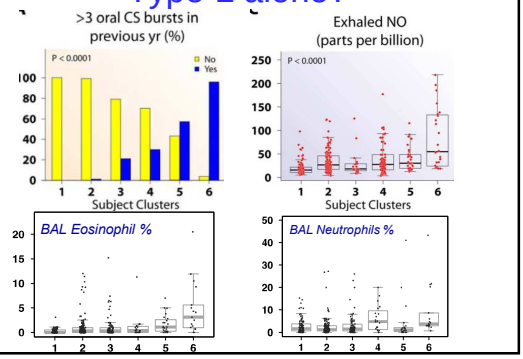


p=0.004

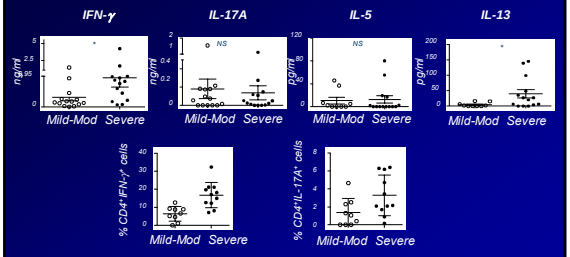
Despite persistent eos, >1/3 of SA could not reduce CS dose



Very severe disease: *Beyond* Type-2 alone?



Higher IFN-γ/Th1 protein in Severe Asthma Compared to Milder Asthma



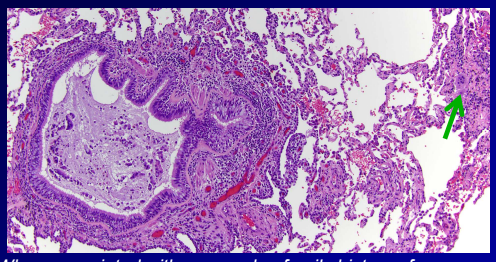
Voraphani Mucosal Immunol 2013, Raundhal et al J Clin Invest 2015

Complex (Autoimmune?) Type- 2 reactive airway disease

- First reported “Asthmatic Granulomatosis” 2012
- 10 “severe asthma” pts (now ~35) who met asthma diagnosis (reversibility or + methacholine)
  - All on systemic corticosteroids (10 mg or above)
- Often adult onset or adult worsening
- Modest obstruction with decrease in FVC and DLCO
- Hi FeNO (and blood eos) despite systemic CSs
- Associated with autoimmune family history in ~70%
- All underwent VATS surgical biopsies

Wenzel Am J Resp Crit Care Med 2012

Small airway inflammation and granulomas: complex immunity



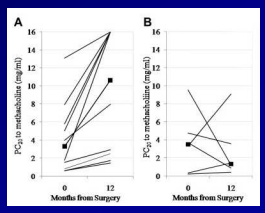
When associated with personal or family history of autoimmunity respond well to azathioprine *Doberer ATS 2015*

“Type 2-Lo Asthma”

- Much less well defined than Type-2 HI
  - Defined as “apparent” absence of Type 2
  - No definite endotypes, but many confounders including obesity, post infectious, smoking, long disease duration likely to play a role
  - ‘omics may provide some clues
- *All* associated with poor CS response
  - Macrolides, thermoplasty, weight loss

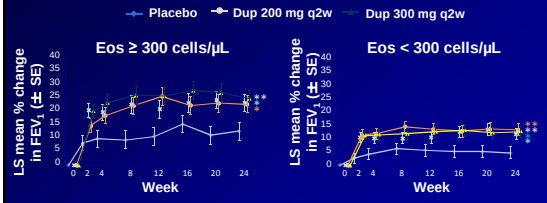
Type 2-Lo late onset obese asthma "reverses" to weight loss

- 23 obese asthmatics evaluated before and 12 mos after bariatric surgery
- Roughly phenotyped patients by median IgE levels (25 vs 305 IU/ml)
  - Late onset asthma=Lower IgE
- Later onset/low IgE obese asthmatics improved PC20 while no effect seen in low IgE/early onset
- Suggest weight loss will be more effective in some phenotypes



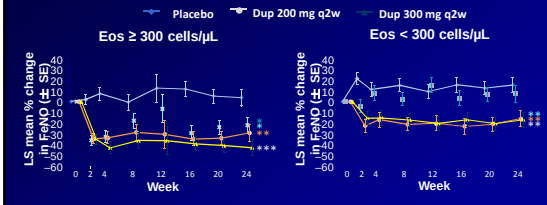
Dixon AE et al J Allergy Clin Immunol 2011

Unlike anti-IL5, anti-IL-4Rα effective in those with low eos…"low" Type-2??



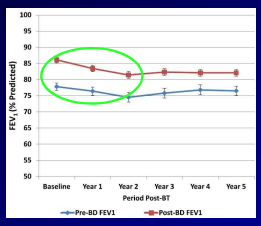
Efficacy of to IL-4Rα blockade in absence of Type-2 biomarker suggests better biomarkers required!!

Reduction in FeNO, even in low eos patients on ICS, supports suppression of ongoing Type-2 inflammation



Suggests residual, corticosteroid responsive Type-2 inflammation in large % of patients

Thermoplasty: Disease modifying?



Wechsler JACI 2013

- Short term data reports improvement in AQLQ, possibly exacerbations
- Longterm data without control group
- FEV1 *declines* in 1st 2 yrs (no statistics given for decline from Baseline to Year 2)

Conclusions

- Prevention of severe asthma(s) is likely dependent on aspects that are difficult to control although maintaining healthy weight in adult hood and never smoking are likely to be helpful
- Reversal depends on definition
- Biologics may get us closer by greatly improving outcomes, but ultimate disease modification not yet observed

Airway Structural Alterations that Contribute to Severe Asthma

Reynold A. Panettieri, Jr., M.D.
Rutgers University

Novel Molecular Targets for Severe Asthma

Harald E. Renz, MD FAAAAI
Philipps University of Marburg

Differentiating Difficult to Control vs. Severe Asthma

Monica Kraft, M.D.
Robert and Irene Flinn Professor of Medicine
Chair, Department of Medicine
University of Arizona Health Sciences Center
Tucson, Arizona

Disclosures

Research (funds paid to U of A):
NIH, Roche, Sanofi, Chiesi
Consulting: TEVA, Astra-Zeneca, Genentech
Royalties: Elsevier

HPI: 38 year old female with severe persistent asthma on chronic oral steroid therapy p/w increasing SOB and worsening wheezing.

Asthma history

Diagnosed with asthma at age 13

30-40 hospitalizations for asthma throughout her life

Endotracheal intubation X 1 for status asthmaticus

Chronic steroid dependence since 2003

Has been treated for contributing diseases

- *GERD, Allergic rhinitis (h/o nasal polyps)*

Current status:

- *Daily symptoms of shortness and wheezing, limited activity*
- *Use of rescue inhalers 6-8x/day*
- *Adherent with her medical regimen*
- *Treated with omalizumab for six years with reduction but not resolution of exacerbations*

Past Medical History:

1.Severe Persistent Asthma
2. Allergic rhinitis
3. GERD
4. Fibromyalgia
5.Major Depressive Disorder

Allergies:

ASA- causes rash and wheezing

Medications:

1.Methylprednisolone 16 mg daily
2.Fluticasone/Salmeterol 500/50 mcg inhalation b.i.d.
3. Montelukast 10 mg daily
4. DuoNebs as needed
5. Albuterol INH 3-4 times daily
6. Omeprazole 20 mg twice daily
7. Loratadine 10 mg daily
8. Fluticasone Nasal 1 puff twice daily
9.Calcium/Vitamin D
10. Alendronate 70 mg weekly
11. Xolair 300 mg SQ q 2 weeks

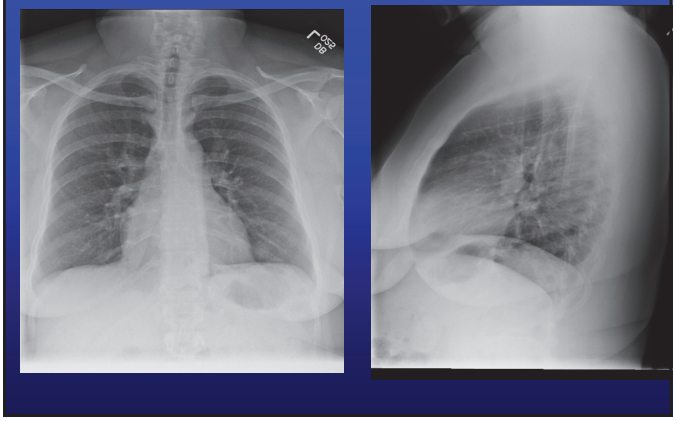
Social History: Married with 3 children and husband, 2 dogs, outside cats, office work with no exposures, non-smoker.

Family History:

mother with asthma and atopic dermatitis

Physical Exam:

Pulmonary- prolonged expiration with moderate air movement and diffuse expiratory wheezing.



Pulmonary Function Testing:

	Ref	Best	% Pred
FVC	3.05	2.40	78%
FEV1	2.65	1.27	48%
FEV1/FVC	86	53	
FEF 25-75%	3.28	0.58	18%
PEF	5.78	2.89	50%
MVV	109	45	41%

What is Asthma?

Asthma is a chronic disease characterized by recurrent episodes of:

- wheezing,
- shortness of breath, and
- cough 2º to reversible airflow obstruction.

Bronchial Hyperresponsiveness &

Airway Inflammation are hallmarks of asthma.

Definition of Severe Asthma > age 6

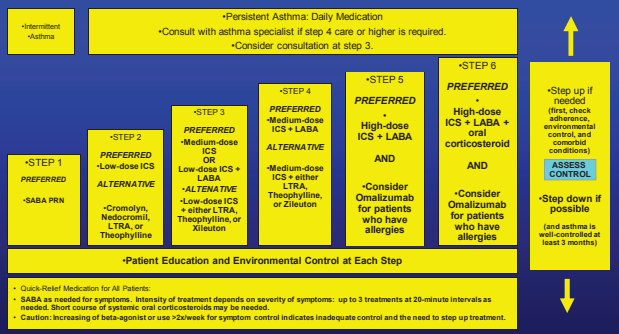
(ATS/ERS Guidelines; ERJ 2014;43:343)

Asthma which requires treatment with guidelines suggested medications for GINA steps 4–5 asthma (high dose ICS and LABA or leukotriene modifier/theophylline) for the previous year or systemic CS for > 50% of the previous year to prevent it from becoming ‘‘uncontrolled’’ or which remains ‘‘uncontrolled‘‘ despite this therapy

Assessing Asthma Control in Patients ≥12 Years of Age

Components of Control		Classification of Asthma Control (Youths ≥12 years of age and adults)		
		Well-Controlled	Not Well-Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	≤2x/month	1-3x/month	≥4x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting beta$_2$-agonist use for symptom control	≤2 days/week	>2 days/week	Several times per day
	FEV_1 or peak flow	>80% predicted/ personal best	60-80% predicted/ personal best	<60% predicted/ personal best
	Validated questionnaires ATAQ ACQ ACT	 0 ≤0.75 ≥20	 1-2 ≥1.5 16-19	 3-4 N/A ≤15
Risk	Exacerbations	0-1 per year	2-3 per year	>3 per year
	Reduction in lung growth	Evaluation requires long-term follow-up care.		
	Treatment-related adverse effects	Medication side effects vary in intensity. Level of intensity does not correlate to specific levels of control but should be considered in overall assessment of risk.		

Stepwise Approach for Managing Asthma in Patients ≥ 12 Years of Age



NHLBI. National Asthma Education and Prevention Program. Full report of the Expert Panel: Guidelines for the diagnosis and management of asthma (EPR-3) DRAFT, page 517. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/epr3/index.htm. Accessed February 9, 2007.

Challenges with Definition

ERS/ATS Severe Asthma Guidelines (ERJ 2014;43:343)

- Inherent in the definition of severe asthma is the exclusion of individuals who present with ‘‘difficult’’ asthma in whom appropriate diagnosis and/or treatment of confounders vastly improves their current condition.
- Therefore, it is recommended that patients presenting with ‘‘difficult asthma’’ have their asthma diagnosis confirmed and be evaluated and managed by an asthma specialist for more than 3 months.
- Thus, severe asthma according to the ATS/ERS definition only includes patients with refractory asthma and those in whom treatment of comorbidities such as severe sinus disease or obesity remains incomplete.

Contribution of Asthma Control to Definition of Severe Asthma

ERS/ATS Severe Asthma Guidelines (ERJ 2014;43:343)

Uncontrolled asthma defined as at least one of the following:

1) Poor symptom control: ACQ consistently > 1.5, ACT < 20 or "not well controlled" by NAEPP/GINA guidelines
2) Frequent severe exacerbations: two or more bursts of systemic corticosteroids (> 3 days each) in the previous year
3) Serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the previous year
4) Airflow limitation: after appropriate bronchodilator withhold FEV1 < 80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal)

Controlled asthma that worsens on tapering of these high doses of ICS or systemic CS (or additional biologics)

Poor Control vs Severe Asthma

- Evidence of any one of these four criteria while on current high-dose therapy identifies the patient as having "severe asthma".
- Patients who do not meet the criteria for uncontrolled asthma, but whose asthma worsens on tapering of corticosteroids, will also meet the definition of severe asthma.
- Fulfilment of this definition predicts a high degree of future risk both from the disease itself (exacerbations and loss of lung function), as well as from side-effects of the medications.

Approach to Management/Contributing Factors/Co-Morbid Conditions

- **Examine for concomitant medical disorders, i.e. sinusitis/rhinitis, nasal polyps – 75-80% prevalence**
- **Obstructive Sleep Apnea**
- **Vocal Cord Dysfunction**
- **GERD - acid and non-acid reflux – 60-80% prevalence**
- **Obesity**
- **Steroid insensitivity – can be affected by co-morbidities or asthma itself**

Approach to Management/Contributing Factors/Co-Morbid Conditions

- Atopy/Environmental exposures
- Ongoing smoking vs. Asthma/COPD overlap
- Alternative diagnoses
- Psychological factors – Anxiety/ Depression – 25-49% prevalence
- Non-adherence
- Drugs: aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), ß-adrenergic blockers, ACE inhibitors

Diagnoses Masquerading as Asthma in Adults

- Dysfunctional breathlessness/vocal cord dysfunction
- Chronic obstructive pulmonary disease
- Hyperventilation with panic attacks
- Bronchiolitis obliterans
- Congestive heart failure
- Adverse drug reaction (e.g. angiotensin-converting enzyme inhibitors)
- Bronchiectasis/cystic fibrosis

Diagnoses Masquerading as Asthma in Adults

- Hypersensitivity pneumonitis
- Hypereosinophilic syndromes
- Pulmonary embolus
- Herpetic tracheobronchitis
- Endobronchial lesion/foreign body (e.g. amyloid, carcinoid, tracheal stricture)
- Allergic bronchopulmonary aspergillosis
- Acquired tracheobronchomalacia
- Churg–Strauss syndrome

Diagnoses Masquerading as Asthma in Children

- Dysfunctional breathing/vocal cord dysfunction
- Bronchiolitis
- Recurrent (micro)aspiration, reflux, swallowing dysfunction
- Prematurity and related lung disease
- Cystic fibrosis
- Congenital or acquired immune deficiency
- Primary ciliary dyskinesia
- Central airways obstruction/compression

Diagnoses Masquerading as Asthma in Children

- Congenital malformations including vascular ring
- Tracheobronchomalacia
- Carcinoid or other tumor
- Mediastinal mass/enlarged lymph node
- Congenital heart disease
- Interstitial lung disease
- Connective tissue disease
- Foreign Body

Key Concepts

- Control: Significant activity of known disease
- If control poor on high dose medication, likely to have severe asthma
- Difficult asthma can suggest asthma or another diagnosis worsened by key co-morbid conditions

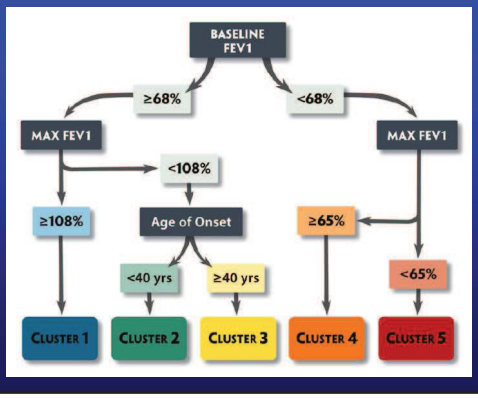
We have now moved to defining phenotypes of this heterogeneous disease

Clinical:
- Fixed obstruction
- Obese
- Adult onset
- Exacerbation prone
- Treatment resistant

Pathologic:
- Eosinophilic
- Non-eosinophilic
- Pauci-granulocytic

Triggers
- Occupational
- Aspirin
- Exercise
- Menses

Severe Asthma Clusters



Moore et al. AJRCCM 2010;181:315-323

Asthma Clusters

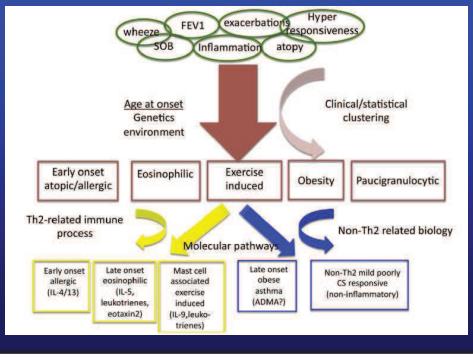
- Cluster 1: early onset, atopic, nl lung fxn ≤ 2 controllers, minimal healthcare utilization
- Cluster 2: early onset, atopic, ≥ 2 controllers, nl lung fxn, significant health care utilization
- Cluster 3: adult onset, obese woman with low lung fxn, high medication requirement and healthcare utilization
- Cluster 4: early onset, atopic, severe obstruction with some reversibility (FEV1: 57% to 76% pred), high healthcare utilization
- Cluster 5: early onset, severe obstruction, 66% atopic; less reversibility (FEV1: 43% to 58%), high health care utilization

Moore et al. AJRCCM 2010;181:315-323

Phenotype to Endotype?

- Phenotype suggests a clustering of characteristics, but may not describe underlying pathobiology that create these characteristics
- Endotype: underlying biologic or pathobiologic mechanism

Phenotypes to Endotypes



Pathological Phenotypes: Can they determine therapeutic choices?

- Eosinophilic/TH2 (IL-4, IL-5 and IL-13)
- Non-eosinophilic (sputum eos < 2%, or peripheral blood eos < 200/μl)

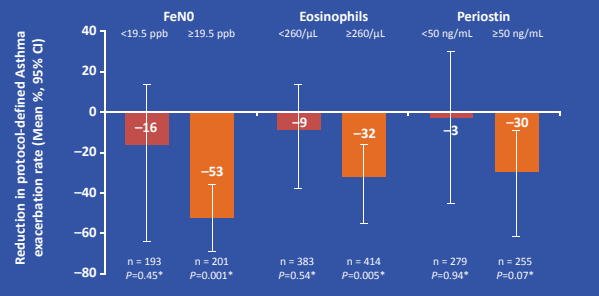
Biomarkers to identify the type 2 asthma phenotype

- Sputum eosinophils
- Exhaled nitric oxide
- Circulating eosinophils
- Periostin
- IgE
- Allergen skin testing
- Eosinophil Peroxidase?

Once we have identified a potential phenotype, what choices do we have?

How Does Omalizumab Compare With New Biologics In Similar Patients?

Effect of omalizumab based on type 2 inflammatory biomarkers



*Exacerbation reduction *P*-values; omalizumab versus placebo in each biomarker subgroup.

Hanania NA et al. *Am J Respir Crit Care Med.* 2013;187:804-811.

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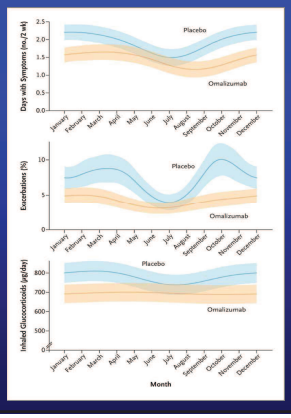
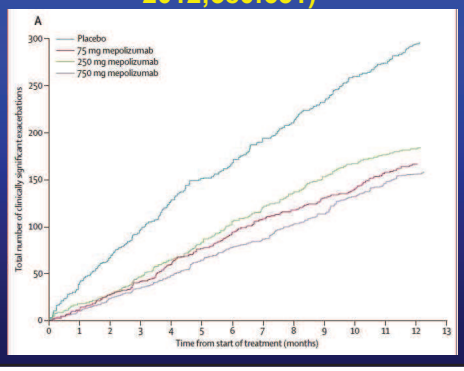
Seasonal Variation in Days with Symptoms, Frequency of Exacerbations, and Dose of Inhaled Glucocorticoids.



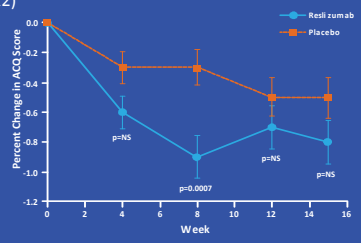
Busse WW et al. N Engl J Med 2011; 364:1005-1015

Mepolizumab (anti-IL-5) in Severe, Eosinophilic Asthma (Pavord et al. Lancet 2012;380:651)



Reslizumab for Poorly Controlled Eosinophilic Asthma

- 106 patients randomized to reslizumab 3 mg/kg vs. placebo (IV dosing at weeks 0, 4, 8, and 12)
- Sputum eosinophil count reduced by 95.4% in reslizumab group vs. 38.7% in placebo group (*P*=0.0068)
- Mean change in FEV1 was –0.08 in the placebo group versus +0.18 in reslizumab group (*P*=0.0023)
- Exacerbations reduced (*P*=0.08)
- Greater change from baseline in patients with nasal polyps –1.0 vs. –0.1 with placebo (*P*=0.012)



Castro M et al. *Am J Respir Crit Care Med.* 2011;184:1125-1132.

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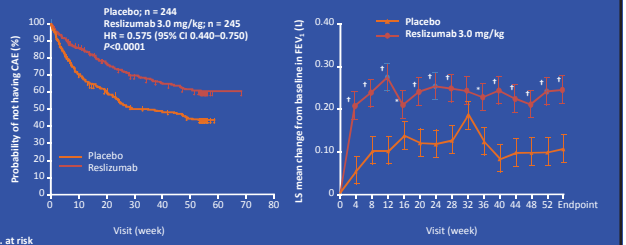
Reslizumab—Effects on Exacerbations and Lung Function



No. at risk

Placebo	244	169	138	112	107	97	0	0	0
Reslizumab	245	207	177	158	146	136	1	0	0

HR = hazard ratio; CI = confidence interval; LS = least square (mean).

Castro M et al. *Lancet Respir Med.* 2015;3:355-366.

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Treatment options for the non-eosinophilic phenotype

- Macrolides
- Tiotropium – perhaps agnostic?
- Bronchial thermoplasty

Conclusions

- Severe asthma is a spectrum of disease, with different pathologic and clinical phenotypes.
- Determining the presence of difficult to control asthma is important as it can be driven by co-morbid conditions that require attention
- Individualizing therapy in asthma to achieve control, decreased exacerbations and high quality of life is the ultimate goal for our patients.

Preventing and Treating Severe Asthma

Saturday, July 30 at 3:00 pm

Major discussion question:
What therapeutic strategies should be considered to improve airway obstruction and relieve symptoms in an adult with severe asthma manifested by low FEV1 (60% predicted) and symptoms requiring rescue bronchodilator 1 to 3 times daily who is adherent with a daily high dose ICS/LABA combination?

Moving from the Oslerian Paradigm to the Post-genomic Era: Are Asthma and COPD Outdated Terms?

Nicola A. Hanania, MD MS
Baylor College of Medicine

ASTHMA-COPD OVERLAP SYNDROME (ACOS) IN SMOKERS and NON-SMOKERS

DUTCH vs BRITISH HYPOTHESIS

Arthur F Gelb MD FACP FCCP
Lakewood Reg Med Ctr
Lakewood, CA
Clin Prof Medicine
Geffen School of Medicine at UCLA Med Ctr
afgelb@msn.com

POTENTIAL CONFLICTS OF INTEREST

- Advisor to Boehringer Ingelheim, Astra Zeneca
- Received funding for participating in clinical trials for Boehringer Ingelheim/Pfizer, Forest, GSK, Pearl Therapeutics/Astra Zeneca and Novartis
- Speaker for Boehringer Ingelheim, Astra Zeneca, GSK, Forest

Dutch Hypothesis

- During the First Bronchitis Symposium held in Groningen, the Netherlands in 1961, the intuitive Orie and colleagues hypothesized that the various forms of airway obstruction, such as asthma, chronic bronchitis, and emphysema, should be considered, as different clinical and phenotypic expressions of one common disease origin. They named this entity "chronic nonspecific lung disease (CNSLD)". They proposed that multiple exogenous and endogenous factors including atopy and hyperresponsiveness influenced pathogenesis. Subsequently, at the Third International Bronchitis Symposium in the Netherlands in 1969, Fletcher and Pride suggested the term "Dutch hypothesis" for the original proposal of Orie and colleagues.

British Hypothesis

- Alternatively, in 1991 Vermeire and Pride emphasized that despite common clinical and phenotypic features in COPD and asthma, the origins were distinctly different. In 2006, Kraft and Barnes debated the clinical and pathophysiologic similarities (Dutch Hypothesis) versus differences (British Hypothesis) between asthma and COPD.

Dutch vs British Hypothesis

- Orie NGM et al. *Bronchitis* Assen the Netherlands Royal Van Gorcum 1961; 43-59
- Fletcher CM and Pride NB 1969 Ciba Symposium. Thorax 1984; 39: 81-85
- Vermeire PA Pride NB ERJ 1991; 4: 490-496
- Kraft M AJRCCM 2006; 174: 238-240
- Barnes PJ AJRCCM 2006; 174: 240-243

Postma DS et al. JACI 2015; 136: 521-529

Postma DS Rabe KF. N Engl J Med 2015; 373: 1241-1249

Barnes PJ Chest 2016; 149: 7-8

Asthma-COPD Overlap Syndrome (ACOS) in Smokers

- Former or current chronic cigarette smokers with persistent expiratory airflow limitation, partial reversibility
- Hyperresponsive airways
- History of preceding asthma before smoking and COPD
- Increased blood/sputum eosinophilia and serum IgE, Type 2 inflammation
- More frequent exacerbations and hospitalizations than COPD without ACOS
- Treatment emphasis on asthma paradigm: ICS, SABA, SAMA, LABA, LAMA, oral CS, omalizumab(IgE)

ACOS IN SMOKERS

Postma and colleagues recently provided an in-depth analysis of the multiple endogenous and exogenous factors that influence the phenotypic homogeneity and heterogeneity in asthma versus COPD and the Asthma-COPD Overlap Syndrome (ACOS).

Postma DS et al. JACI 2015; 136: 521-529

Postma DS, Rabe KF. NEJM 2015; 373: 1241-1249

Augusti A et al ERJ 2016;47: 410-419

Sterk P. ERJ 2016; 47: 359-361

ACOS IN SMOKERS

Gibson PG, McDonald VM. ACOS 2015;Thorax 70; 683-691

Barrecheguren M, et al. ACOS COPM 2015; 21(1): 74-79

Cosio BG, et al. ACOS. Chest 2016; 149: 45-52

Nielsen M, et al. ACOS Int J COPD 2015; 10:1443-1454

Bujarski S, et al. ACOS Curr Allergy Asthma Rep. 2015;15:509

Bateman ED, et al. ACOS Lancet Respir Med. 2015; 3: 719-728

Soler X, Ramsdell JW. ACOS JACI Pract. 2015; 3(4): 489-495

de Marco R et al. ERJ 2015; 46: 671-679

Miravitlles M et al.Int J Chron Obsruct Pulm Dis 2015;10: 321-330

Aalbers R, van den Berge M. J Asthma Allergy 2016; 9: 27-35

Lange P et al. TheLancet Resp Med 2016 (online)

Barnes PJ. Chest 2016; 149: 7-8

Genomic Signatures of Type 2 Inflammation in Asthma vs COPD vs ACOS

Similar airway gene expression alterations can co-occur in asthma and copd and acos

Christenson SA et al. AJRCCM 2015; 191: 758-766

- Ghebre MA et al. JACI 2015; 135: 63-72

Genetic components different in asthma vs copd

Hardin M et al. Eur Respir J 2014; 44: 341-350

- Smolonska J et al. Eur Respir J 2014; 44: 860-872

ACOS JACI 2015; 136: SEPTEMBER

Postma DS et al Revisiting the Dutch Hypothesis 521-529

Reddel HK Treatment of ACOS-guidelines 546-552

Barnes PJ Therapeutic approaches to ACOS 531-545

Gelb AF and Nadel JA ACOS Commentary 553-555

"ACOS" in Non-Smoking Chronic Asthmatics

- Type 2 inflammation, eosinophils, IgE
- Despite treatment have persistent expiratory airflow limitation, with partial reversibility, and who
- Develop a COPD phenotype with loss of lung elastic recoil, and
- Normal or mildly abnormal high resolution-thin section (1mm) CT lung with normal voxel quantification (<10% -950HU) and
- Maintain normal diffusing capacity
- Unsuspected mild diffuse centrilobular emphysema in all 4 autopsied asthmatics and 1 asthmatic post lung transplant presumably due to proinflammatory pathway and proteolytic cascade

"ACOS" IN NON-SMOKERS

Gelb AF, Christenson SA, Nadel JA. Review of ACOS Curr Opin Pulm Med 2016; 9:100-105

Gelb AF Nadel JA ACOS Commentary JACI 2015; 136: 553-555

Gelb AF et al. ACOS in Non-Smokers Chest 2015; 148: 313-320

Rabe KF. Editorial in Chest 2015; 148: 297-298

Gelb AF et al. JACI 2014; 133: 263-265, Erratum 1232

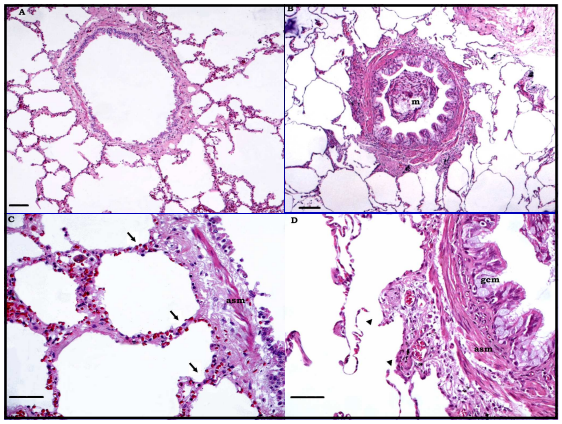
Arthur F. Gelb MD, Noe Zamel MD
Unsuspected Pseudo-Physiologic Emphysema in Chronic Persistent Asthma
Am J Respir Crit Care Med
162: 1778-1782, 2000

Demonstrated loss of lung elastic recoil and its significant contribution to expiratory airflow limitation. Both high resolution-thin section lung CT (1 mm) and diffusing capacity were normal

PATHOLOGY BACKGROUND

Mauad T Silva LFF Santos MA Grinberg L
Bernardi FD Martins MA Saldiva PH Dolhnikoff M
Abnormal Alveolar Attachments with Decreased Elastic Fiber Content in Distal Lung in Fatal Asthma
AJRCCM 2004; 170: 857-62

Localized *peribronchiolar* parenchymal emphysema in fatal asthmatics but no overt emphysema. Decreased elastic fiber content in small airway adventitial layer, and in peribronchial alveoli but not in distal alveoli.
(No imaging and lung function studies included)



UNSUSPECTED MILD EMPHYSEMA IN NON-SMOKING PATIENTS WITH CHRONIC ASTHMA WITH PERSISTENT AIRWAY OBSTRUCTION

- ARTHUR F GELB MD Pulm Div Lakewood Reg Med Ctr Lakewood, CA.,Geffen School of Medicine at UCLA Medical Ctr
- ALFRED YAMAMOTO MD Pathology Dept Lakewood Reg Med Ctr
- THAIS MAUAD MD PhD Pathology Dept Sao Paulo University Medical School, Sao Paulo, Brazil
- JOZEF KOLLIN MD Pathology Dept Lakewood Reg Med Ctr (ret)
- MARK J SCHEIN MD Radiology Dept Lakewood Reg Med Ctr
- JAY A NADEL MD Cardiovascular Research Institute and Dept Medicine, Physiology and Radiology, University of California, San Francisco Medical Center, San Francisco, CA

- JACI 2014; 133: 263-265 Erratum JACI 2014; 133: 1232

ACKNOWLEDGEMENT

- PATHOLOGY: Ranna Patel BS, HT, ASCP LRMC Dept Pathology
  Tracy Dyer MD Pathologist at Dallas County Southwestern Institute of Forensic Sciences, Dallas, Texas
- PFT: Colleen Flynn Taylor MA Lakewood
- Christine Fraser RCP, CPFT Lakewood
- Randy Newsom RCP CPFT Lakewood
- GRAPHICS: Jennifer Klotchman PhD
- Bob Ward BS, MS (EE) Dept Computer Science CSULB
- LUNG CT VOXEL QUANTIFICATION: Ouided Rouabhi and Susan Wood PhD
  Vida Diagnostics Inc, Cupertino, CA and Coralville, Iowa

and

PHYSIOLOGY COLLABORATION: Professor Noe Zamel MD Pulm Div Mt. Sinai Hosp University of Toronto, Toronto, Ontario, Canada

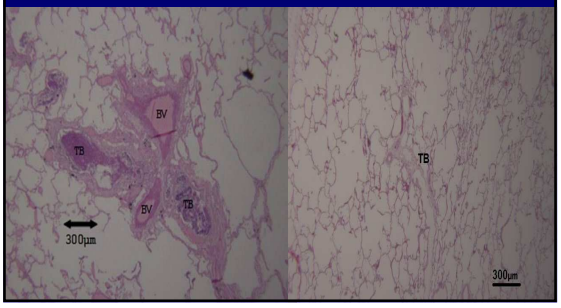
RESULTS

- Asthma Control Test 16-19
- Total blood eosinophils 206(131-260) cells/μL (median, 1-3 IQ) (normal <300)
- Serum IgE 280(31-500) kμ/L (normal <100)
- Thurlbeck lung CT emphysema score ≤10 in 9 asthmatics (2 died) and 15 and 20 in 2 asthmatics who died consistent with mild emphysema
- Voxel quantification ≤-950 HU: nl or trivial emphysema/hyperinflation

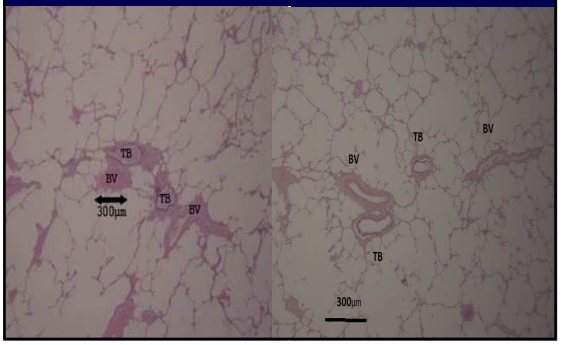
RESULTS

- FEV_1 2.5±0.4L (mean±SD) (69±14)% pred (post 270µg albuterol sulfate MDI with spacer)
- FVC 4.0±1.0L (88±13) %pred
- FEV_1/FVC 63±9%
- SGaw 0.06(0.05-0.09)(median 1-3 IQ) lps/cmH_2O/L 24(23-37)% pred
- RV 3.4(2.8-3.5)L 143(141-176)%pred
- FRC 4.3(3.5-4.4)L 123(109-142)%pred
- TLC 7.3(6.8-7.5)L 110(108-119)%pred
- D_LCO/V_A 5.5(4.6-6.0) ml/min/mmHg/L 130(112-141)%pred

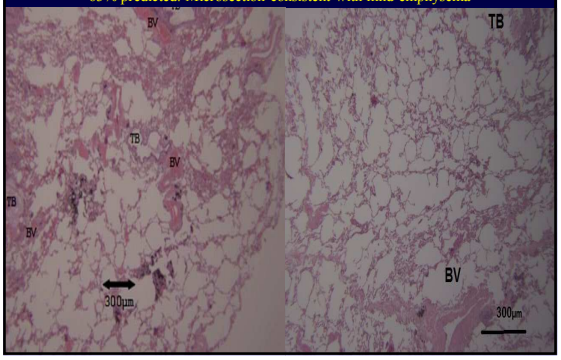
SENTINEL CASE: RUL(left) Case #9 72 yr F with lung CT and autopsy lung macrosection Thurlbeck Emphysema Score 20 (mild) and FEV_1 (L) 42%pred. Microsection: mild emphysema
Control Case: RUL(right) 82 yr old F asthmatic with ***normal*** PFT, lung CT, macrosection and voxel quantification. Microsection: mild to moderate alveolar duct ectasia consistent with aging lung and no emphysema
(Verbeken EK et al Chest 1992; 101: 793-9 and 800-9)



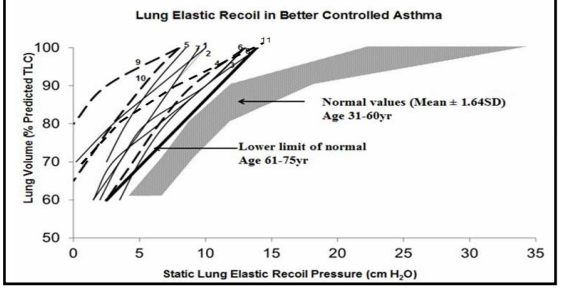
LUL (left) and RLL (right) in Case #10, 82yr old F
Lung CT and autopsy lung macrosection Thurlbeck Emphysema Score 10 (very mild) with normal voxel quantification and FEV_1 (L) 52% predicted.
Microsection with borderline-to-mild emphysema and hyperinflation



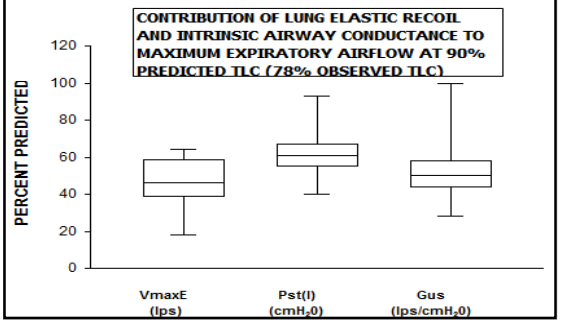
LUL (left) and RLL (right) in Case #4 42yr old M
Lung CT and lung macrosection Thurlbeck Emphysema Score 15 (mild) and FEV_1 (L) 63% predicted. Microsection consistent with mild emphysema



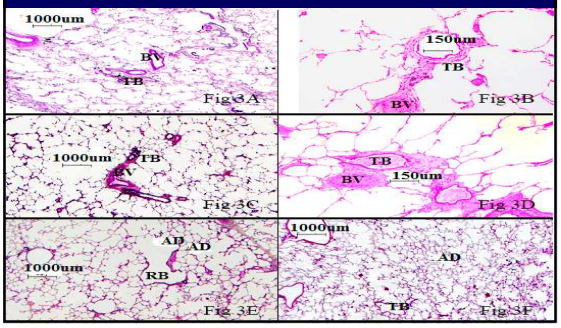
Loss of Lung Elastic Recoil in All 11 Asthmatics Including 4 Who Died (Dashed Line)
(Normal data from Gelb AF and Zamel N Chest 1975; 68: 538-41)



LOSS OF LUNG ELASTIC RECOIL CONTRIBUTES SIGNIFICANTLY TO EXPIRATORY AIRFLOW LIMITATION
Vmax= Pst (l) X Gus (Mead J. JAP 1967; 22: 95-108)



Gelb AF, Yamamoto A, Verbeken EK, Nadel JA
Unraveling the pathophysiology of the ACOS
CHEST 2015, 148: 313-320
Figs 3AB and 3CD:asthma+emphysema,3E: asthma, no emphysema, 3F: nl control



CONCLUSION

- We believe there is pathologic evidence for diffuse lung tissue breakdown of terminal bronchiolar-alveolar attachments within the lung matrix (Mauad T et al AJRCCM 2004;170:857-62) ***and mild diffuse centrilobular emphysema.*** This may be responsible for the heretofore unexplained loss of lung elastic recoil in non-smoking asthmatics with chronic expiratory airflow limitation. A proinflammatory pathway and proteolytic cascade may be operant. Additional on-going and future patho-imaging-physiologic correlative studies will be needed for confirmation.

QUESTIONS

- 1. Do you accept there is a probable pathophysiologic, generic, and clinical overlap between asthma and copd (ACOS) even in non-smokers?
- A. yes B. no C. maybe
- 2. If you accept ACOS, original credit goes to?
- A. Orie and Dutch Hypothesis B. British Hypothesis
- C. French Hypothesis
- 3. Treatment in symptomatic patients with ACOS with abnormal expiratory spirometry could include?
- A. ICS, SABA, LABA
- B. ICS, SABA, LABA, SAMA, LAMA,
- C. ICS, SABA, LABA, SAMA, LAMA, tapering oral CS, omalizumab

"Influence of Environmental Factors on Asthma and COPD"

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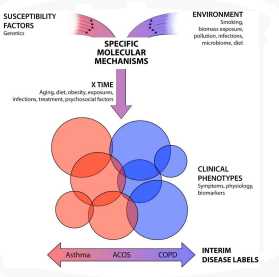
Andrews Distinguished Professor
Departments of Pediatrics & Medicine
Senior Associate Dean for Translational Research
Director, Center for Environmental Medicine, Asthma and Lung Biology

Disclosures

- Research Funding
  - Environmental Protection Agency
  - NIEHS, NCATS
  - NSF
  - Immune Tolerance Network (NIAID)
  - Glaxo Smith Kline (clinical trials)
- Other
  - Editor in Chief, Current Allergy and Asthma Reports
  - Associate Editor, JACI
  - Up To Date

Asthma COPD Overlap Syndrome

- Common biological factors/concepts
  - ACOS represents a continuum in airway endotypes ranging from asthma to COPD
  - Tobacco exposure
  - IgE/TH_2 inflammation
  - Bronchial reactivity
- Environmental exposures-"tobacco-like"
  - Smoking
  - Second-hand smoke exposure
  - Particulate matter from biomass use
    - Household Air Pollution
    - Ambient Air PM



Mechanistic basis of immune response to particulate pollutants

Oxidative stress
Innate immune response
Modification of IgE responses

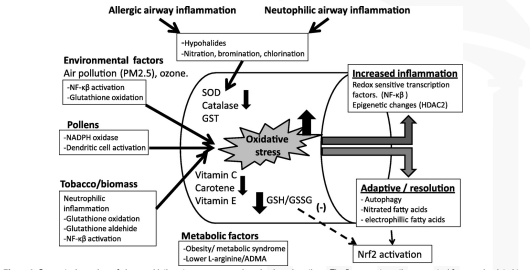
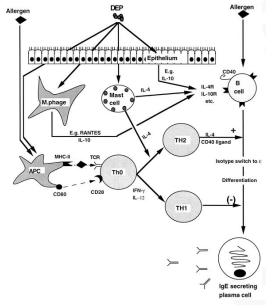


Figure 1. Conceptual overview of airway oxidative stress sources and mechanisms in asthma. The figure captures the conceptual framework related to airway oxidative mechanisms throughout the paper. ADMA = asymmetric dimethylarginine; GSH = reduced glutathione; GSSG = oxidized glutathione; HDAC2 = histone deacetylase–2; NADPH = nicotinamide adenine dinucleotide phosphate; NF-κB = nuclear factor κB; Nrf2 = nuclear factor (erythroid-derived 2)-like 2; PM2.5 = particulate matter < 2.5 μm; SOD = superoxide dismutase.

Annals ATS, 2013
http://www.atsjournals.org/doi/abs/10.1513/AnnalsATS.201305-116AW
Published in: Fernando Holguin; Annals ATS 10, S150-S157.
DOI: 10.1513/AnnalsATS.201305-116AW

Oxidative Stress Mechanisms by which PM, ETS and Biomass impact IgE production



- Initial studies show that DEP associated with IgE production
- Experimental evidence indicates that DEP related ROS from particles drive isotype switch towards IgE
- ROS derives from organic oxidants derived from polyaromatic hydrocarbons
- PAHs and related agents found in most particles produced by low combustion of organic matter-**diesel, tobacco smoke, biomass fuel use**

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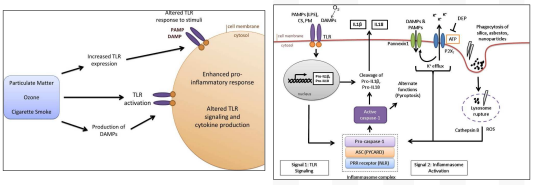
Innate Immune Responses to Environmental Agents



Source: Journal of Allergy and Clinical Immunology 2012; 129:14-24 (DOI:10.1016/j.jaci.2011.11.004)
Copyright © 2012 American Academy of Allergy, Asthma & Immunology

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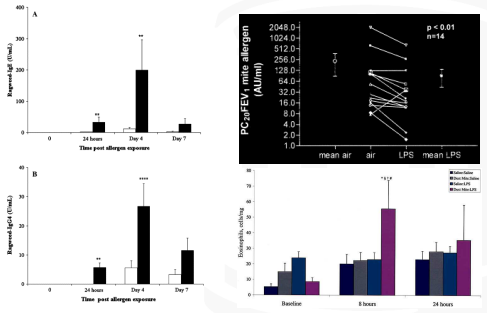
PM exposure enhances response to inhaled allergens

(diesel exhaust to the left, LPS to the right)



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Epidemiological evidence of PM influence in airway disease

Tobacco smoke
Particulate matter
Household air pollution

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Coogan, PF et al "Active and Passive Smoking and the Incidence of Asthma in the Black Women's Health Study", American Journal of Respiratory and Critical Care Medicine, Vol. 191, No. 2 (2015), pp. 168-176.

Table 2. Smoking Status and Incidence of Asthma, Black Women's Health Study, 1995–2011

Smoking Status	Cases	Person-Years	Basic Model (Age and Questionnaire Cycle) [*HR (95% CI)*]	Multivariable Model [*HR (95% CI)*]*
Never active or passive	142	84,071	1.0	1.0
Passive only	677	284,103	1.36 (1.13–1.63)	1.21 (1.00–1.45)
Exposed before age 20 only	225	105,193	1.26 (1.02–1.56)	1.17 (0.94–1.45)
Exposed at age 20 or older only	180	72,745	1.39 (1.11–1.74)	1.24 (0.99–1.56)
Exposed before and after 20	272	106,165	1.43 (1.16–1.75)	1.18 (0.96–1.46)
Former smoker	423	139,885	1.71 (1.41–2.08)	1.36 (1.11–1.67)
Current smoker	281	85,741	1.72 (1.40–2.11)	1.43 (1.15–1.77)

Am J Respir Crit Care Med, 2015 http://www.atsjournals.org/doi/abs/10.1164/rccm.201406-1108OC
Published in: Patricia F. Coogan; Nelsy Castro-Webb; Jeffrey Yu; George T. O'Connor; Julie R. Palmer; Lynn Rosenberg; *Am J Respir Crit Care Med* 191, 168-176.
DOI: 10.1164/rccm.201406-1108OC

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Association between Residential Proximity to Fuel-Fired Power Plants and Hospitalization Rate for Respiratory Diseases

Liu X, Lessner L, and Carpenter DO; Environmental Health Perspectives 120(6), 2012

Table 2. Crude hospital discharge rates for asthma, ARI, and COPD according to age and exposure after excluding extremes of MHI status.

		Hospital discharge rate per 100,000 (95% CI)		
Exposure	Person-years	Asthma	ARI	COPD
Age < 10 years				
Clean	8,661,904	359 (355, 363)	404 (400, 409)	
Fuel only	567,857	381 (365, 397)	414 (397, 431)	
Waste only	8,939,610	452 (448, 457)	474 (470, 479)	
Fuel and waste	3,355,019	509 (501, 517)	551 (544, 559)	
Age ≥ 10 years				
Clean	56,609,900	512 (510, 513)	147 (146, 148)	1,222 (1,219, 1,225)
Fuel only	3,962,094	570 (563, 578)	154 (151, 158)	1,390 (1,379, 1,402)
Waste only	60,539,925	589 (597, 601)	169 (168, 170)	1,401 (1,398, 1,404)
Fuel and waste	21,653,627	672 (669, 676)	192 (191, 194)	1,627 (1,622, 1,633)

Table 3. Adjusted RRs of hospital discharge for asthma, ARI, and COPD as a function of residence in ZIP codes with different exposure status.

	Asthma				ARI				COPD	
	Age < 10 years		Age ≥ 10 years		Age < 10 years		Age ≥ 10 years		Age ≥ 10 years	
Exposure	RR (95% CI)	*p*-Value	RR (95% CI)	*p*-Value	RR (95% CI)	*p*-Value	RR (95% CI)	*p*-Value	RR (95% CI)	*p*-Value
Clean	1.00		1.00		1.00		1.00		1.00	
Fuel only	1.01 (0.91, 1.12)	0.85	1.11 (1.02, 1.20)	0.01	1.03 (0.93, 1.14)	0.56	1.15 (1.05, 1.27)	0.003	1.17 (1.06, 1.29)	0.002
Waste only	1.11 (1.03, 1.19)	0.005	1.07 (1.00, 1.14)	0.04	1.13 (1.05, 1.21)	0.001	1.09 (1.02, 1.17)	0.01	1.16 (1.08, 1.26)	0.0001
Fuel and waste	1.19 (1.11, 1.28)	< 0.0001	1.18 (1.11, 1.26)	< 0.0001	1.24 (1.15, 1.33)	< 0.0001	1.21 (1.13, 1.30)	< 0.0001	1.26 (1.17, 1.37)	< 0.0001

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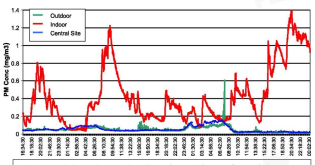
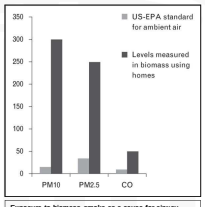
Indoor PM exposure in the US and where biomass is used



Indoor Air Pollution and Asthma in Children. Patrick N. Breysse; Gregory B. Diette; Elizabeth C. Matsui; Arlene M. Butz; Nadia N. Hansel; Meredith C. McCormack. *Proc Am Thorac Soc.* **2010,** 7, 102-106.

Figure 1. Comparison of particulate matter (PM) concentrations simultaneously measured indoors, immediately outdoors, and at a central monitoring site.



Exposure to biomass smoke as a cause for airway disease in women and children. Kodgule, Rahul; Salvi, Sundeep. Current Opinion in Allergy & Clinical Immunology. 12(1):82-90, February 2012.

Figure 3. Comparison of US-EPA standard for ambient air and levels measured air in homes exposed to biomass smoke PM10, PM2.5 and CO. Levels expressed as mcg/m3 x 10 for PM10, mcg/m3 for PM2.5 and ppm for CO.

Exposure to Household Air Pollution and Lower Respiratory Tract Infection

Smith KR, et al, Lancet. 2011 Nov 12;378(9804):1717-26

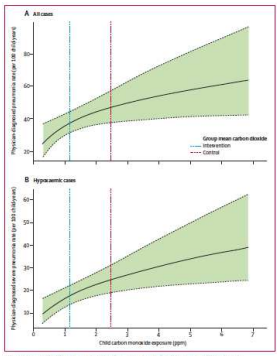
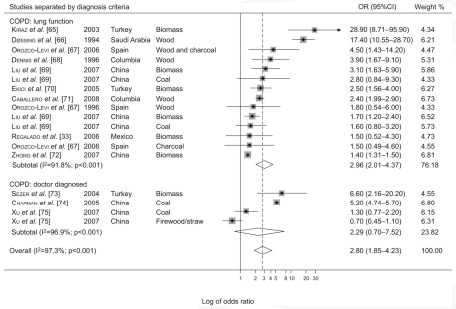


Figure 4: Exposure-response for personal carbon monoxide concentrations in study children for physician-diagnosed pneumonia (A) and physician-diagnosed severe (hypoxaemic) pneumonia (B)

Forest plot showing risk of chronic obstructive pulmonary disease (COPD) in populations exposed to solid fuel smoke.



Om P. Kurmi et al. Eur Respir J 2012;40:239-254

Summary of Epidemiology

- Particulate matter from organic biomass burning similar across several sources
  - Low temperature combustion with polyaromatic hydrocarbons
  - Endotoxins
  - Similar in tobacco smoke, much ambient PM (coal, diesel), and biomass burning
- PM associated with:
  - LRTI
  - COPD
  - Asthma
- Markedly increased levels in indoor environments
  - Seen in US
  - Much greater where biomass is used

Oxidative Stress Genes

GSTM1

Effect of glutathione-S-transferase M1 genotypes on allergen induced responses to diesel exhaust and secondhand smoke

Gilliland FD, Li Y-F, Diaz-Sanchez D. Lancet 2004 (363) 9403, 119-125
Gilliland FD, Li Y-F, Gong H, Diaz-Sanchez D. Am J Respir Crit Care Med 2006, 174, 1335-1341

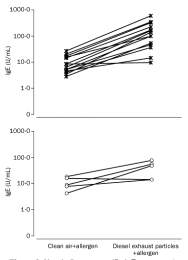


Figure 3. Nasal allergen-specific IgE response to allergens plus clean air and allergen plus diesel exhaust particles for GSTM1 absent (upper) and present (lower) genotypes Y axis is log scale of median IgE concentrations.

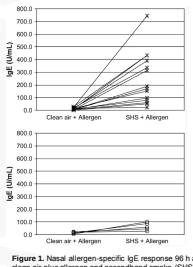
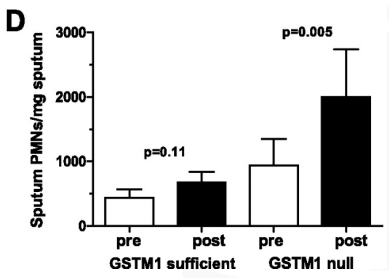


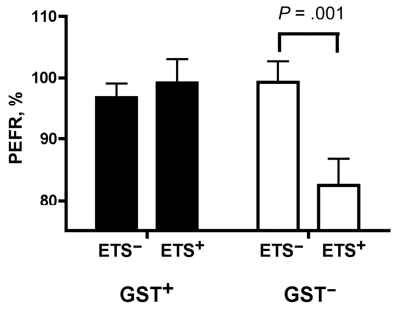
Figure 1. Nasal allergen-specific IgE response 96 h after clean air plus allergen and secondhand smoke (SHS) plus allergen by *GSTM1* genotype. *Asterisks*, *GSTM1* null; *open circles*, *GSTM1* present.

Baseline versus post-CCRE (endotoxin) responses (mean±SEM) in airway sputum (PMNs/mg sputum) in GSTM1 sufficient and GSTM1 null volunteers.



Dillon M A et al. Occup Environ Med
doi:10.1136/oem.2010.061747

Dual GSTM1/GSTP1 genotype and peak expiratory flow in teenagers and young adults with asthma.



Palmer C N et al. Pediatrics 2006;118:710-716

PEDIATRICS

Interventions

Focused on Indoor Interventions

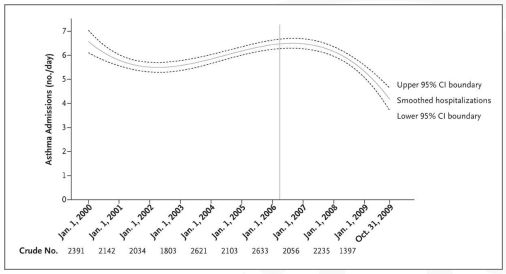
Interventions focused on the environmental causes of disease

- Antioxidant
  - NRF2 based interventions
  - Specific radical scavengers
  - Results of early studies mixed, yet to see significant phase III type studies
- Avoidance of PM
  - Strong evidence that policy measures to decrease ambient air PM related to better health outcomes
  - Indoor biomass use of better cookstove ventilation being studied
  - Decrease of active smoking and second hand tobacco smoke exposure works

21

UNC SCHOOL OF MEDICINE

DAILY HOSPITAL ADMISSIONS FOR ASTHMA AMONG CHILDREN BETWEEN JANUARY 2000 AND OCTOBER 2009



MACKAY D ET AL. N ENGL J MED 2010;363:1139-1145

The NEW ENGLAND JOURNAL of MEDICINE

Clinical: Precision Therapy For ACOS

Joe Ramsdell, M.D.
University of California, San Diego, School of Medicine
The Life Spectrum of Asthma 2016
Chicago, Illinois
July 31, 2016

1

Disclosures

- Institutional grants and contracts:
  - Amgen
  - Astra Zeneca
  - Boehringer Ingelheim
  - Forest
  - Glaxo Smith Kline
  - Novartis
  - Pearl
- Personal Consulting: Boehringer Ingelheim

2

Clinical: Precision Therapy For ACOS

- Point of view: Clinical
  - Decisions must be made based on information readily available in the clinical setting
  - Predictors (e.g., genetic, phenotypic) must be verified (i.e. evidence-based) and have a high predictive value for propose therapy
- What is precision therapy?
- What is the state-of-the-art for (im)precise therapy for ACOS?
  - Genetics
  - Environment–critical element of smoking
  - Pathways
  - Overlap/interaction
  - Problem of normal aging
- What is a busy clinician to do?
  - The GINA/GOLD Recommendations

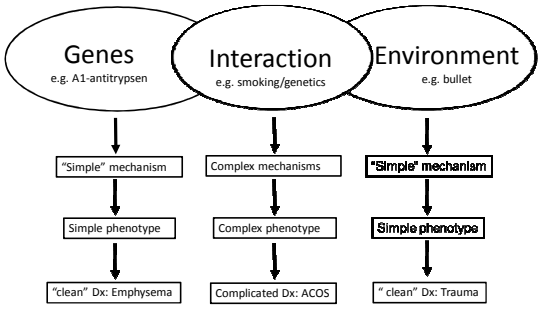
3

Precision Medicine

The NIH Precision Medicine Initiative Cohort Program Definition

"An approach to disease prevention and treatment based on people's individual differences in environment, genes and lifestyle."

4



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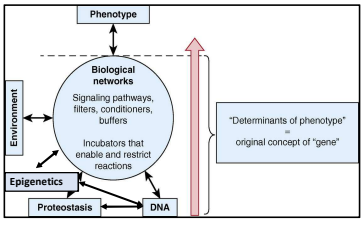
(Complicated) Interactions Of Environment, Genes And Systems To Determine Phenotype



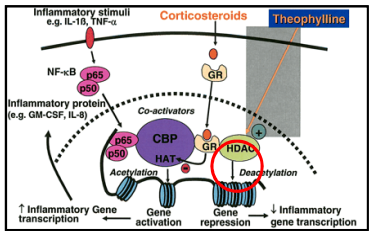
modified from Agusti A et. al. Am J Respir Crit Care Med 2014;191:391-401

Proteostasis: the concept that there are competing and integrated biological pathways within cells that control the biogenesis, folding, trafficking and degradation of proteins present within and outside the cell. The concept of proteostasis maintenance is central to understanding the cause of diseases associated with excessive protein misfolding and degradation leading to loss-of-function phenotypes, as well as aggregation-associated degenerative disorders. May be relevant in cystic fibrosis and other lung diseases.[1]

Epigenetics: the study of cellular and physiological phenotypic trait variations that result from external or environmental factors that switch genes on and off and affect how cells express genes (e.g., histone modification of T_H2 memory cells in asthma).[2]

1. Balch WE, et al. Am J Respir and Crit Care Med 2014
2. Seumois G, et al. Nat Immunol 2014

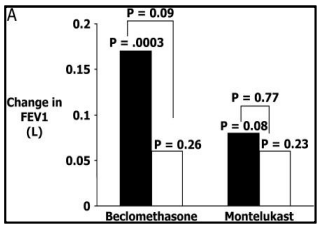
Genetic/environment/pharmacologic interaction: Smoking and Corticosteroids



Barnes PJ. Proc Am Thorac Soc. 2005;334

7

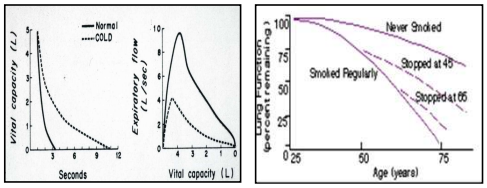
Beclomethasone Not Effective In Smoking Asthmatics (but Montelukast Is)



Lazarus SC. Am J Respir Crit Care Med 2007;175:783–790

8

Don't Forget the Effect of Time: Smoking As Premature Aging



CHRONIC OBSTRUCTIVE PULMONARY DISEASE
NIH Publication No. 95-2020, Reprinted November 1995

9

Precise/Personalized Therapy

- Clean mechanism/diagnoses
- Complicated mechanism/diagnoses
- Straightforward
- Complicated

ACOS is complicated!

10

Is there evidence to support a precision/personalized medicine approach in ACOS treatment?

11

Genetics and ACOS: The COPDGene Analysis

- Single nucleotide polymorphism in CSMD1 and SOX5 (important in lung development) in non-Hispanic whites
- Meta-analysis identified single nucleotide polymorphisms in the gene GPR65 (protein product important in eosinophil activation)
- Suggestive but not clinically actionable

Harden M, et al. Eur Respir J 2014; 44:341–350

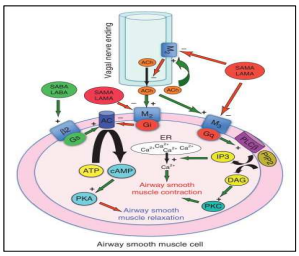
12

Mechanistic and ACOS:
Is there evidence for targeting pathways?

13

LABA and LAMA Non-disease Specific Mechanisms Relevant To Bronchodilation in ACOS

- Both effective in patients with asthma and COPD[1,2]
- Cigarette smoking enhances muscarinic signaling pathways in a rat model[3]
- Mucin gene expression enhanced by cigarette smoke and down regulated by anti-muscarinic stimulation[3]
- No definitive studies in ACOS for either, however



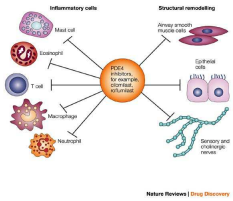
Montuschi, et al. Drug Disc Today 2014;19:1928-35

1. Mangnusen H, et. al. Respir Med. 2008 Jan;102(1):50-6
2. Peters SP et al. N Engl J Med 2010;363:1715-1726
3. Chiba Y. et. al. Am J Respir Cell Mol Biol. 2005; 33:574 – 581
4. Cortijo J, et.al. Eur Respir J. 2011 Feb;37(2):244-54.

14

Phosphodiesterase Pathway Inhibitors

- PDE4 inhibitor, roflumlast, modest clinical benefit in COPD[1,2] and asthma
- Theophylline effective in asthma and COPD[3]
- No studies in ACOS



1 Martinez FJ, et al. Lancet 2015; 385:85 7–66,
2 Azam MA, et al. Sci Pharm 2014; A2: 45 3–81
3 Barnes P.J. J Allergy Clinic Immunol 2015;136:531–45

15

Targeted Anti-inflammatory Mediator Therapy

- Anti-IL5 (benralizumab) not effective in COPD (even with increased eosinophils)[1]
- Anti-TNF antibodies ineffective in COPD or severe asthma[2,3]
- Anti-IL17 ineffective in asthma[4]
- No studies in ACOS

1. Brightling CE, et al, Lancet Respir Med 201
2. Rennard SI, et al, Am J Respire Crit Care Med 2007;175: 926–34
3. Wenzel SE, et al, Am J Respire Crit Care Med 2009;179:549–58, and others
4. Busse WW, et al. Am J Respire Crit Care Med 2013;188:1294–302

16

Antibacterial/Anti-inflammatory(?) Effect Of Antibiotics

- Macrolides (clarithromycin): No clear improvement in asthma but may reduce exacerbations and COPD
- Not studied in ACOS

Sutherland ER, at all J Allergy Clinic Immunol 2010; 1-6:74 7–53,
Ni W, et al. PLoS One 2015; 10:e 012-1257

17

"Untargeted" Anti-inflammatory Therapy: Corticosteroids and ACOS

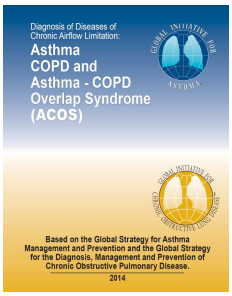
- A retrospective study found no benefit to the use of inhaled corticosteroids on FEV_1 decline, incidence of severe exacerbations or overall mortality in 125 patients with ACOS
- No definitive evidence in ACOS

Lim HS, et al. Annals of **Allergy, Asthma & Immunology**. 2014;113:652-657.

18

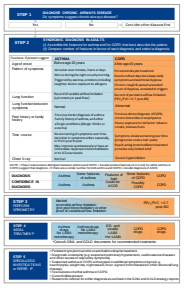
Where Are We Now: What The Guidelines Say.

UPDATED!



19

Stepwise approach to diagnosis and initial treatment of ACOS based on *PHENOTYPE*.



For an adult who presents with respiratory symptoms:

1. Does the patient have chronic airways disease?
2. Syndromic diagnosis of asthma, COPD and ACOS
3. Spirometry
4. Commence initial therapy
5. Referral for specialized investigations (if necessary)

20

GINA 2015, Box 5-4

Step 1 – Does the patient have chronic airways disease?

- Clinical history: consider chronic airways disease if
  - Chronic or recurrent cough, sputum, dyspnea or wheezing, or repeated acute lower respiratory tract infections
  - Previous doctor diagnosis of asthma and/or COPD
  - Previous treatment with inhaled medications
  - History of smoking tobacco and/or other substances
  - Exposure to environmental hazards, e.g. airborne pollutants
- Physical examination
  - May be normal
  - Evidence of hyperinflation or respiratory insufficiency
  - Wheeze and/or crackles

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Step 1 – Does the patient have chronic airways disease?

- Radiology (CXR or CT scan performed for other reasons)
  - May be normal, especially in early stages
  - Hyperinflation, airway wall thickening, hyperlucency, bullae
  - May identify or suggest an alternative or additional diagnosis, e.g. bronchiectasis, tuberculosis, interstitial lung disease, cardiac failure
- Screening questionnaires
  - Designed to assist in identification of patients at risk of chronic airways disease
  - May not be generalizable to all countries, practice settings or patients
  - See GINA and GOLD reports for examples

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Step 2 – Syndromic diagnosis of asthma, COPD and ACOS

- Assemble the features that, **when present**, most favor a diagnosis of typical asthma or typical COPD
- Compare the number of features on each side
  - If the patient has ≥3 features of either asthma or COPD, there is a strong likelihood that this is the correct diagnosis
- Consider the level of certainty around the diagnosis
  - Diagnoses are made on the weight of evidence
  - The absence of any of these features does not rule out either diagnosis, e.g. absence of atopy does not rule out asthma
  - When a patient has a similar number of features of both asthma and COPD, consider the diagnosis of ACOS

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STEP 2 — **SYNDROMIC DIAGNOSIS IN ADULTS**

(i) Assemble the features for asthma and for COPD that best describe the patient.
(ii) Compare number of features in favour of each diagnosis and select a diagnosis

Features: if present suggest -	ASTHMA	COPD
Age of onset	❑ Before age 20 years	❑ After age 40 years
Pattern of symptoms	❑ Variation over minutes, hours or days ❑ Worse during the night or early morning ❑ Triggered by exercise, emotions including laughter, dust or exposure to allergens	❑ Persistent despite treatment ❑ Good and bad days but always daily symptoms and exertional dyspnea ❑ Chronic cough & sputum preceded onset of dyspnea, unrelated to triggers
Lung function	❑ Record of variable airflow limitation (spirometry or peak flow)	❑ Record of persistent airflow limitation (FEV$_1$/FVC < 0.7 post-BD)
Lung function between symptoms	❑ Normal	❑ Abnormal
Past history or family history	❑ Previous doctor diagnosis of asthma ❑ Family history of asthma, and other allergic conditions (allergic rhinitis or eczema)	❑ Previous doctor diagnosis of COPD, chronic bronchitis or emphysema ❑ Heavy exposure to risk factor: tobacco smoke, biomass fuels
Time course	❑ No worsening of symptoms over time. Variation in symptoms either seasonally, or from year to year ❑ May improve spontaneously or have an immediate response to bronchodilators or to ICS over weeks	❑ Symptoms slowly worsening over time (progressive course over years) ❑ Rapid-acting bronchodilator treatment provides only limited relief
Chest X-ray	❑ Normal	❑ Severe hyperinflation

NOTE: • These features best distinguish between asthma and COPD. • Several positive features (3 or more) for either asthma or COPD suggest that diagnosis. • If there are a similar number for both asthma and COPD, consider diagnosis of ACOS

DIAGNOSIS	Asthma	Some features of asthma	Features of both	Some features of COPD	COPD
CONFIDENCE IN DIAGNOSIS	Asthma	Asthma	Could be ACOS	Possibly COPD	COPD

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GINA 2015. Box 5-4 © Global Initiative for Asthma

Step 3 - Spirometry

- Essential if chronic airways disease is suspected
  - Confirms chronic airflow limitation
  - More limited value in distinguishing between asthma with fixed airflow limitation, COPD and ACOS
- Measure at the initial visit or subsequent visit
  - If possible measure before and after a trial of treatment
  - Medications taken before testing may influence results
- Peak expiratory flow (PEF)
  - Not a substitute for spirometry
  - Normal PEF does not rule out asthma or COPD
  - Repeated measurement may confirm excessive variability, found in asthma or in some patients with ACOS

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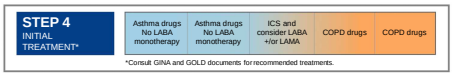
Step 3 - Spirometry

Spirometric variable	Asthma	COPD	ACOS
Normal FEV_1/FVC pre- or post-BD	Compatible with asthma	Not compatible with diagnosis (GOLD)	Not compatible unless other evidence of chronic airflow limitation
Post-BD FEV_1/FVC <0.7	Indicates airflow limitation; may improve	Required for diagnosis by GOLD criteria	Usual in ACOS
FEV_1 ≥80% predicted	Compatible with asthma (good control, or interval between symptoms)	Ccompatible with GOLD category A or B if post-BD FEV_1/FVC <0.7	Compatible with mild ACOS
FEV_1<80% predicted	Compatible with asthma. A risk factor for exacerbations	Indicates severity of airflow limitation and risk of exacerbations and mortality	Indicates severity of airflow limitation and risk of exacerbations and mortality
Post-BD increase in FEV_1 >12% and 200mL from baseline (reversible airflow limitation)	Usual at some time in course of asthma; not always present	Common in COPD and more likely when FEV_1 is low	Common in ACOS, and more likely when FEV_1 is low
Post-BD increase in FEV_1 >12% and 400mL from baseline	High probability of asthma	Unusual in COPD. Consider ACOS	Compatible with diagnosis of ACOS

26

GINA 2015, Box 5-3



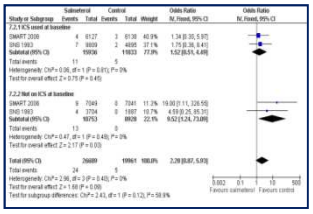
27

GINA 2015

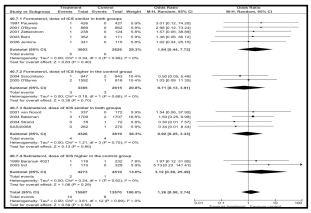
Step 4 – Commence initial therapy

- Initial pharmacotherapy choices are based on both efficacy and safety
  - SABA as needed for symptom relief
- If syndromic assessment suggests asthma as single diagnosis
  - Start with low-dose ICS
  - Add LABA and/or LAMA if needed for poor control despite good adherence and correct technique
  - Do not give LABA alone without ICS
- If syndromic assessment suggests COPD as single diagnosis
  - Start with bronchodilators or combination therapy
  - Do not give ICS alone without LABA and/or LAMA
- If differential diagnosis is equally balanced between asthma and COPD, i.e. ACOS
  - Start treatment as for asthma, pending further investigations
  - Start with ICS at low or moderate dose
  - Usually also add LABA and/or LAMA, or continue if already prescribed

The (“official”) Effects of LABA on Asthma Mortality with and without ICS



Cates CJ, Cates MJ Cochran Database Syst Rev. 2008



Jaeschke R. et.al. Am J Respir Crit Care Med. 2008

Step 4 – Commence initial therapy

- For all patients with chronic airflow limitation:
  - Treat modifiable risk factors including advice about smoking cessation
  - Treat comorbidities
  - Advise about non-pharmacological strategies including physical activity, and, for COPD or ACOS, pulmonary rehabilitation and vaccinations
  - Provide appropriate self-management strategies
  - Arrange regular follow-up
- See GINA and GOLD reports for details

Can we use precision medicine to do better than the guidelines?

Not yet

31

Asthma and COPD Overlap Syndrome

Sunday, July 31 at 10:00 am

Major discussion question:
A 65 year old cigarette smoker with a 20 pack per year smoking history presents with a diagnosis of asthma, exertional dyspnea, and nocturnal shortness of breath several times per week. Spirometry reveals an FEV1 of 65% predicted with 10% and 175 mL reversibility. The patient has had 3 exacerbations requiring oral corticosteroids in the last year despite high dose/LABA used daily. What diagnostic and therapeutic strategies should be considered?

1 A New Patient Operated Sampling Device That Provides Fingerprints of Allergens in Homes to Evaluate Patient Exposure and Improve Asthma Patient Care

Julian Gordon, PhD[1], Prasanthi Gandhi, MBA MPH[1], Andrea Wachter, BS[1] and Paul Detjen, MD FAAAAI[2], [1]Inspirotec Inc, Glenview, IL, [2]Kenilwoth Medical Associates, Kenilworth, IL

Rationale: We developed a device for patients with allergic asthma or rhinitis to run in their own homes so they may establish an allergen exposure profile of their inhalable air for improved asthma and allergy management.
Methods: The device ran for various times and multiple locations within a home in order to assess the dynamic equilibrium of airflow throughout a house. Then patients diagnosed with allergic asthma or rhinitis and possessing cats and/or dogs ran the device in their bedrooms. Aerial load of twelve common household allergens was determined in a laboratory with MARIA™ multiplex immunoassays kits from Indoor Biotechnologies. The utility of the data obtained was then evaluated as part of the complete picture of patient management.
Results: Each home was found to have a unique allergen fingerprint. Results were consistent with patient reports on degree of pet bedroom access. Non-pet allergens: dust mite, mouse, pollens and molds were found in 13 cases. There were no positives for cockroach, rat or birch pollen reflecting socio-economic group and season. Review of fingerprints together with individual medical records showed actionable information in 17 cases. Areas of utility included discovering unanticipated allergens; prioritizing triggers for environmental management; encouraging individualized and targeted allergen avoidance activity; and improving patient compliance.
Conclusions: The capability of patients to run simple allergen exposure fingerprints unsupervised in their own homes provides physicians with individualized data to make evidence based decisions on asthma patient management.

2 Perceived Stress in Adults with Asthma in an Urban Environment

Olabunmi Agboola, MD, Duke University Medical Center, Durham, NC

Rationale: The prevalence of asthma continues to increase with higher rates of asthma morbidity found in urban populations. A number of factors are likely to contribute to the higher morbidity in urban areas including stress. Stress is a widely unmeasured exacerbating factor in asthma. We sought to determine levels of perceived stress in an urban asthma population and its' impact on asthma control.
Methods: We recruited asthma and healthy control subjects, performed spirometry and administered the validated 10 item Perceived Stress Scale (PSS). Asthma subjects were administered the Asthma Control Test (ACT). Basic descriptive statistics were performed, including a Pearson correlation.
Results: Thirteen asthmatics and 11 controls participated in the study. Mean age of the asthma subjects was higher compared to the healthy control group (44.2±15y vs. 31±12 years old; p=0.03). There was no difference in BMI. FEV_1% in the asthma subjects was lower than in the control subjects (75±15% vs. 89±9%, p=0.008). The mean ACT score in our asthma group was 18.6±1.3. Asthma subjects had higher perceived stress scale than the controls (16.86±1.3 vs. 11.9±1.8; p=0.03). Furthermore, the ACT score and the PSS score were inversely correlated, indicating those with higher perceived stress had impaired control of their asthma (p=0.02).
Conclusions: This study revealed that adult asthmatics from an urban environment had higher perceived stress compared to healthy controls. Moreover, we found that the ACT and PSS were negatively correlated which suggests that there is a link between stress and asthma control in asthmatics that reside in urban environments.

3 Effect of the SQ House Dust Mite Sublingual Immunotherapy Tablet on Rhinitis and Asthma Symptoms in North American Adolescents and Adults: A Randomized, Placebo-Controlled Trial

Susan Lu, PharmD[1], David I Bernstein, M.D.[2,3], Jorgen Kleine-Tebbe, MD[4], Gordon L. Sussman, MD, FAAAAI[5], Dorthe Seitzberg, PhD[6], Dorte Rehm[6], Amarjot Kaur, PhD[1], Ziliang Li, PhD[1], Harold S. Nelson, MD FAAAAI[7] and Hendrik Nolte, MD, PhD[1], [1]Merck & Co., Inc., Kenilworth, NJ, [2]Bernstein Clinical Research Center, Cincinnati, OH, [3]Division of Immunology, University of Cincinnati, Cincinnati, OH, [4]Allergy & Asthma Center Westend, Berlin, Germany, [5]University of Toronto, Toronto, ON, Canada, [6]ALK, Horsholm, Denmark, [7]National Jewish Health, Denver, CO

Rationale: SQ house dust mite (HDM) sublingual immunotherapy (SLIT) tablet (MK-8237; Merck/ALK) was assessed in North American subjects with HDM allergic rhinitis with/without conjunctivitis (AR/C).
Methods: Subjects aged ≥12 years were randomized to daily 12 SQ-HDM or placebo for up to 52 weeks in this double-blinded, multicenter trial (NCT01700192). Included subjects were those with HDM AR/C with or without asthma requiring, at most, medium-dose ICS. A rhinitis daily symptom score (DSS; 4 symptoms, maximum=12) of ≥6, or ≥5 with 1 symptom being severe, on 5 of 7 consecutive days before randomization was required for inclusion. Primary endpoint was the average total combined rhinitis symptom and medication score (TCRS) during the last 8 weeks of treatment. Average asthma DSS (3 symptoms; maximum=9) was an additional endpoint.
Results: Of the 1,482 randomized subjects, 31% had asthma. Treatment with SQ HDM improved TCRS 17.2% vs placebo (95% CI: 25.0%, 9.7%). In the entire trial population, mean asthma DSS was 1.26 with SQ HDM and 1.56 with placebo, corresponding to a 19% improvement vs placebo. In subjects with asthma, mean asthma DSS was 1.37 with SQ HDM and 1.83 with placebo, corresponding to a 25% improvement. No treatment-related serious adverse events were reported. A treatment-related systemic allergic reaction of moderate intensity occurred on day 1 under medical supervision and was treated with epinephrine. Subjects with asthma generally tolerated active treatment well.
Conclusions: This was the first North American trial with SQ HDM SLIT-tablet to demonstrate a significant improvement in HDM AR/C and asthma symptoms. Treatment was well-tolerated.

4 Safetly of Immunotherapy Mix – USP 747 Issues

Joann Catherine Blessing-Moore, MD, Solo Practice, Palo Alto, CA and Tara LaBounty, Joann Blessing-Moore MD, INC

Rationale: We know allergy shots improve patient outcomes and are cost effective. Allergy Immunotherapy mixes are made of the individual allergens to which the patient has proven sensitive. We prepare these mixes in our office and have never had any known problems with infections related to the shots.
Methods: There are 4 dilutions of the mix and treatment is started at the lowest dilution and advanced until a maintenance concentration is reached. We use the standardized preparation technique presented in "Allergen Immunotherapy Extract Preparation Manual from the AAAAI practice Management Resource Guide 2012 edition (Michael Nelson, Linda Cox)". We culture the last dilution.
Results: Since 1991 preparation of these mixes in our office included a culture of the last dilution. We have done test runs with blinded mixes to test for accuracy for reading the cultures. If any positive culture after 3 days the mix would have been remade. No patient cultures have proven positive after 3 days with the presently used method.
Since 1994 as a solo practitioner, we have prepared and tested 760,106 mixes and have not had one contaminated mix after 3 days culture.
Conclusions: Allergy Immunotherapy mixes can be made safely in the office setting. These mixes are essential in the care of our allergy/asthmatic patients and are being prepared in a safe cost effective manner in the allergist's offices. We do not need to revise these present techniques. (USP797)

5 Once-Daily Tiotropium Respimat® Add-on Therapy Improves $FEF_{25-75\%}$ in Children and Adolescent Patients with Persistent Symptomatic Asthma

Stanley Goldstein[1], Stanley J. Szefler, MD FAAAAI[2], Christian Vogelberg[3], George Bensch[4], John Given[5], Georges El Azzi[6], Petra Moroni-Zentgraf[6], Michael Engel[6], Ralf Sigmund[7] and Eckard Hamelmann[8], [1]Island Medical Research, Rockville Centre, New York, NY, [2]Department of Pediatrics, Children's Hospital of Colorado and the University of Colorado Denver School of Medicine, Aurora, CO, [3]University Hospital Carl Gustav Carus, Technical University of Dresden, Dresden, Germany, [4]Bensch Research Associates, Stockton, CA, [5]Allergy and Respiratory Center, Canton, OH, [6]TA Respiratory Diseases, Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim am Rhein, Germany, [7]Global Biometrics and Data Sciences, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany, [8]Evangelisches Krankenhaus Bielefeld, and Allergy Center of the Ruhr University, Bochum, Germany

Rationale: $FEF_{25-75\%}$ may be a more sensitive parameter than FEV_1 to assess changes in small, peripheral airway function. We report $FEF_{25-75\%}$ responses from 5 Phase II and III trials that investigated once-daily tiotropium Respimat® (tioR) add-on to existing therapy, in patients aged 6–11 and 12–17 years with persistent symptomatic asthma.

Methods: Five randomized, double-blind, placebo-controlled trials: 2 Phase II, incomplete-crossover trials of tioR 5µg, 2.5µg, or 1.25µg in children aged 6–11 years and adolescents aged 12–17 years with moderate persistent symptomatic asthma; 3 Phase III, parallel-group trials of tioR 5µg or 2.5µg in children aged 6–11 years with severe persistent symptomatic asthma and adolescents aged 12–17 years with moderate or severe persistent symptomatic asthma. Study medication was delivered as 2 puffs. Primary endpoint: peak FEV_1 change from baseline (response) within 3 hours post-dosing. Mean $FEF_{25-75\%}$ response was a further endpoint.
Results: 1397 patients were randomized across the 5 trials. Baseline demographics and disease characteristics were balanced between treatment groups. TioR improved peak and trough FEV_1 responses versus placebo; the improvement was statistically significant in the majority of cases, more frequently with the 5µg dose. In each trial, $FEF_{25-75\%}$ responses versus placebo were statistically significantly improved at most time points across all doses. In most cases, the 5µg dose corresponded with larger $FEF_{25-75\%}$ responses.
Conclusions: In children and adolescents with persistent symptomatic asthma, once-daily tiotropium Respimat® add-on to ICS or ICS plus other controller medication improves lung function. Improvements in $FEF_{25-75\%}$ responses are consistent and more pronounced than improvements in peak and trough FEV_1 responses.

6 Impact of Asthma Exacerbations on Lung Function in a Large Cohort of Patients with Severe or Difficult-to-Treat Asthma

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Rationale: Asthma exacerbations contribute to morbidity and mortality, but limited evidence exists about the extent to which such exacerbations may lead to worsening airway obstruction.
Methods: Patients with severe or difficult to-treat asthma were followed observationally for three years in The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR). Percent predicted post-bronchodilator forced expiratory volume in one second ($ppFEV_1$) was collected annually, and asthma exacerbations, defined as an overnight hospitalization, emergency room visit, or steroid burst, were assessed bi-annually. Patients with chronic obstructive pulmonary disease and current smokers were excluded from analyses. Annual change in $ppFEV_1$ was modeled using repeated measures as a function of asthma exacerbations during that year, baseline ppFEV1, age, sex, race/ethnicity, and body mass index.
Results: A total of 2,429 patients (n=1,803 adults ≥18 years; n=394 adolescents ages ≥12-17 years; n=232 children ages 6-11 years) met the entry criteria. After adjustment for covariates, the 12-month change in $ppFEV_1$ was lower in patients with any asthma exacerbation compared with those with no asthma exacerbation (-1.27±0.26 vs. 0.70 ±0.22; net difference: 1.97±0.36; $p<0.001$); in adults (-1.14±0.30 vs. 0.68±0.25; net difference: 1.82 ±0.41; $p<0.001$); in adolescents (-2.46±0.74 vs. 0.46±0.59; net difference: 2.92±0.98; $p=0.004$); in children (-1.05±0.79 vs. 0.99±0.76; net difference: 2.04±1.14; $p=0.081$).
Conclusions: Asthma exacerbations are associated with lung function decline in patients with severe or difficult-to-treat asthma. Together with prior evidence, this research suggests that prevention of asthma exacerbations may limit airway remodeling and declines in irreversible airway obstruction.

7 Asthma Carepartners: Embedding an Innovative Community Health Worker Program into Standard Healthcare Delivery

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Rationale: The Asthma CarePartners (ACP) program, an innovative partnership between Sinai Urban Health Institute (SUHI) and a Medicaid managed care organization, aims to improve the health of Chicago children and adults with asthma. Four previous asthma interventions with rigorous results and demonstrated cost savings have proven the effectiveness of SUHI's community health worker (CHW) model, leading to this venture to incorporate the model within standard healthcare delivery.
Methods: ACP utilizes CHWs making home visits to educate patients with poorly controlled asthma about the disease, its triggers and proper management. Participants receive six home visits during the year-long intervention. Education focuses on improving medical management while simultaneously addressing environmental triggers. CHWs conduct

structured home environmental assessments, working collaboratively with families to reduce exposure to home triggers.
Results: Since 8/16/11, 596 participants have completed a baseline visit. Among the 120 participants who completed the 12-month intervention, ED visits were reduced by 71% ($p<0.0001$) between the year prior to and the year following the intervention. Furthermore, nights where sleep was disturbed by asthma decreased from 5.7 nights at baseline to an average of 1.9 over the intervention period ($p<0.0001$). Caregiver Asthma-Related Quality of Life scores improved from 5.4 to 6.6 at the 12-month follow-up ($p<0.05$), a clinically and statistically significant improvement.
Conclusions: Data demonstrate an improvement in asthma control, reduction in symptom frequency and a dramatic reduction in asthma-related health resource utilization. Embedding a CHW home visit asthma intervention into managed care delivery yields cost-savings for the healthcare system and life-changing benefits for participants.

8 Expected Number Needed to Treat with Omalizumab to Prevent an Asthma Exacerbation, Emergency Room Visit, or Hospitalization in Patients with Severe Uncontrolled Asthma

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Rationale: Clinicians use number needed to treat (NNT) to compare therapies. We estimated expected NNT to prevent an exacerbation, hospitalization, or emergency room (ER) visit, if omalizumab was used in patients with severe uncontrolled asthma.
Methods: An anti-IL-5 study in patients with severe asthma and history of 3.6 exacerbations reported background placebo rates of exacerbations (1.74 per year), including those requiring hospitalizations (0.10 per year), and ER visits or hospitalizations (0.20 per year). In omalizumab pivotal trial, relative risk reduction (RRR) for exacerbations (by current ATS guidelines: worsening of asthma symptoms requiring ≥3 days of systemic corticosteroids) was 55% (79% in subgroup of patients on LABA in addition to background therapy). Omalizumab annual RRR for hospitalizations was 84%, a Cochrane meta-analysis) and 56% for hospitalizations or ER visits (systematic literature review).
We calculated expected per-year absolute risk difference: (anti-IL-5 placebo background rates) x (omalizumab RRR)/100. We calculated the expected per-year NNT with omalizumab: 1/(expected absolute risk difference).
Results: For omalizumab, the expected per-year NNT to prevent an exacerbation comprised 1.04 (1/0.957) for all enrolled patients or 0.73 (1/1.375) for only patients treated with LABA. The expected NNT comprised 11.9 (1/0.084) for asthma-related hospitalizations and 8.9 (1/0.113) for asthma-related hospitalizations or ER visits.
Conclusions: With the contemporary definition of an asthma exacerbation and background therapy, clinicians would expect to treat ~1 patient with severe uncontrolled asthma for a year with omalizumab to prevent one asthma exacerbation, ~12 patients to prevent a hospitalization, or ~9 patients to prevent a hospitalization or an ER visit.

10 Burden of Allergic Status in Patients with Severe Asthma: A Matched-Cohort Real-World Evidence Study

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Rationale: Allergic asthma comprises a well-recognized phenotype; the burden of allergic status in severe asthma needs elucidation.
Methods: This propensity-score matched cohort study used insurance claims (Truven MarketScan) to identify 6+ year old patients with severe asthma: 1 inpatient or 2 outpatient claims for asthma plus step 6 NHLBI therapies in baseline year. Evidence of allergic asthma included: ≥1 ICD-9-CM code for extrinsic asthma plus ≥1 code for allergic comorbidity (sinusitis, rhinitis, conjunctivitis, nasal polyposis, anaphylaxis, eczema/dermatitis, food allergy, urticaria/angioedema, atopic dermatitis). Allergic and non-allergic patients were matched 1:1 by baseline characteristics: demographics, provider specialty, year, comorbidities, and asthma medications.
Results: Matched severe asthma patients with (n=1,523) and without (n=1,523) evidence of allergic status [mean (SD) age 36.1 (20.9) years, 62.1% female] were well-balanced at baseline, except more chronic conditions, cough, and upper respiratory infections in the allergic group. Medication use in patients with vs without evidence of allergic

status: LABA (57.1% vs 52.5%; p=0.011), LTRA (46.2% vs 35.1%; p<0.001), and omalizumab (3.4% vs 0.9%; p<0.001). Patients with vs without evidence of allergic status were more likely to experience exacerbations [47.7% vs 43.2% (p=0.012)] and used more annual outpatient visits: all-cause (24.6 [SD 21.0] vs. 16.2 [16.2], p<0.001) and asthma-related (3.2 [4.7] vs 2.1 [2.8], p<0.001). Hospitalization and emergency room use rates were comparable.
Conclusions: Severe asthma patients with evidence of allergic status experience more exacerbations and outpatient visits (overall and asthma-related) than their counterparts without allergic status. Treatments directed at allergic asthma may reduce the burden in this severely-affected population.

11 Montelukast Is a Better Controller in Obese Atopic Asthmatics

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Rationale: The concomitant rise in the prevalence of asthma and obesity has suggested an association between the two. Two phenotypes of obesity-associated asthma exist; early-onset atopic and late-onset non-atopic asthma. Animal and human studies suggest involvement of leptin and leukotrienes in inflammatory pathways. We hypothesized that montelukast is a more effective controller of early-onset atopic asthma in overweight/obese (O) compared to normal (N) weight asthmatics.
Methods: Mild to moderate persistent early-onset asthmatics on inhaled corticosteroids (ICS) were randomized in a double-blind controlled manner to receive montelukast (M) or placebo (P). Active treatment with M was compared to P at week 24 with the primary outcome measure, Asthma Control Test (ACT) scores, and secondary outcome measures (spirometric measures, exhaled nitric oxide, total ICS dose, serum leptin and urinary leukotriene E4 levels). Mean difference was calculated as M group minus P group with corresponding 95% confidence interval.
Results: The two treatment groups were comparable at baseline. At week 24, the O group, but not the N group, treated with M demonstrated a significantly higher ACT score than P (25.0 vs. 15.7 respectively, p<0.01). ACT score differed significantly between M and P groups (24.5 vs. 18.1 respectively, p<0.01), overall, but not for any other clinical or laboratory parameters assessed. There were no significant interactions between treatment group and weight subgroup for the parameters of interest.
Conclusions: Montelukast is a more effective controller medication among obese atopic early-onset asthmatics compared to normal weight asthmatics. These data underscore the need to individualize asthma management in obese asthmatics.

12 A Randomized, Multi-Center, Single Visit Study to Compare Feno Measured with the Niox Mino and the Niox Vero in Subjects with Asthma

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Rationale: Measurement of exhaled Nitric Oxide (FeNO) is useful in the diagnosis and management of asthma. The primary objective of this study was to assess the agreement and repeatability of FeNO measured with NIOX MINO and NIOX VERO.
Methods: Data from two randomized, multi-center, single visit studies were pooled. All Subjects performed two measurements with the NIOX MINO and the NIOX VERO in random order. The primary endpoint was the proportion of subjects with FeNO values within the tolerance limits. The secondary endpoint was to evaluate the agreement of FeNO measured with NIOX MINO and the NIOX VERO.
Results: 109 completed one valid FeNO measurement on each device. 90.8%(99/109) of the subjects were within the tolerance limits for the first valid FeNO measurement. The mean observed paired difference for the first valid FeNO measurement on each device was -4.6 ppb (95% CI: -5.825 to -3.3//; p<0.0001). Weighted Deming Regression Analysis showed slope of 0.842 (95% CI: 0.757, 0.927) and Y-intercept of -0.472 (95% CI: -1.999, 1.055). Paired differences were centered close to 0. Intra-subject repeatability of NIOX VERO was significantly better than NIOX MINO (p= 0.0112).
Conclusions: FeNO measurements using the NIOX VERO were slightly lower than on the NIOX MINO, however, no substantial differences were noted between replicates within age groups, gender groups or randomization sequences and the difference is within the technical specifications of the device. The results support a high degree of intra-

subject repeatability. The same agreement was seen when comparing the first valid measurement and the mean of the two measurements.

13 Pulmonary Embolism Is a Patient with Factor V Leiden Mutation, Presenting with Symptoms of Asthma Exacerbation

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Rationale: The differential diagnosis of asthma is extensive. Pulmonary embolism may present with similar symptoms to asthma. We present a case of pulmonary embolism in a patient with moderate persistent asthma and Factor V Leiden mutation who presented with symptoms of an asthma exacerbation.
Methods: Our patient was referred for evaluation and treatment of moderate persistent asthma.
Results: A 52 year old woman with a Factor V Leiden mutation presented with a history of moderate persistent asthma. Symptoms included cough, wheezing, and shortness of breath. She had been previously treated with montelukast with no significant benefit. She could not tolerate medications with long-acting beta agonists due to anxiety side effects. She was placed on fluticasone proprionate 220 mcg two puffs twice daily with benefit. However, after two months, she developed worsening shortness of breath symptoms with wheezing. On exam, she had normal heart rate (80), respiratory rate (12), and blood pressure (110/70). Lung exam was clear to auscultation without any wheezes, rhonchi, or rales. Fluticasone dose was increased with some benefit in two days, however, mild symptoms still occurred. She then developed chest discomfort, which was exacerbated by arm movement. She was referred to emergency department for further evaluation, and CT pulmonary angiography revealed a pulmonary embolism. She was successfully treated with anticoagulant therapy.
Conclusions: This case demonstrates the importance of considering pulmonary embolism in the differential diagnosis of an asthma exacerbation, especially in a patient with a hypercoagulable state, such as Factor V Leiden.

14 Improving Asthma Outcomes Among Adults through a Community Health Worker Home-Based Intervention

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Rationale: Approximately 7% of the U.S population has asthma. Of these 23 million people, 73% are adults. Asthma prevalence and morbidity are highest among African Americans and those living in poverty. Mount Sinai Hospital, located in Chicago's economically challenged, predominantly African American Westside, sees a disproportionate prevalence of asthma among adults. In 2012, Mount Sinai Hospital's 30-day readmission rate for asthma was 8.1%, or 3.2 times the national rate.
Methods: The Helping Chicago's Westside Adults Breathe and Thrive study is one of the first across the country to test the feasibility and effectiveness of a community health worker (CHW) asthma and healthy homes intervention exclusively with adults. The intervention aims to increase asthma control, improve the home environment, and reduce asthma-related morbidity. CHWs make 5-6 home visits in a year to provide comprehensive, individualized asthma education. They also conduct home environmental assessments to identify in-home asthma triggers, and work closely with participants, landlords and management companies to address them.
Results: Two hundred two adults enrolled in the study. Preliminary results, based on 41 participants who completed the year-long intervention, show a significant reduction in daytime symptoms (65%), nighttime symptoms (55%), and days needing rescue medication (42%). Hospitalizations decreased by 50% and asthma-related Emergency Department visits decreased by 57%.
Conclusions: These results suggest the effectiveness of the CHW model in improving asthma outcomes for adults and that the model translates well. Through home visits, CHWs encourage and empower participants to adopt effective asthma control behaviors, such as addressing in-home triggers to create an asthma-friendly home.

16 Association Between Recent and Future Asthma Exacerbations in Pediatric Patients with Severe or Difficult-to-Treat Asthma

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Rationale: To investigate risk of future severe asthma exacerbations (FSE) in pediatric patients with severe or difficult-to-treat asthma who experience a recent severe asthma exacerbation (RSE).

Methods: Pediatric patients (ages 6-11 years) in the TENOR 3-year observational study were analyzed. A RSE was defined as either an overnight hospitalization or emergency department (ED) visit in the 3 months before baseline; a FSE was defined as either an overnight hospitalization, ED visit, or death between month 6 and month 36. A secondary analysis examined steroid bursts as an independent predictor and outcome measure. Generalized estimating equations repeated measures logistic regression models were used to assess risk of future exacerbations adjusting for demographics, clinical variables, asthma severity, and control.
Results: Compared to patients without a RSE, patients with a RSE were over 3 times (OR=3.8, 95%CI: 2.7, 5.4) more likely to experience a FSE. The association persisted after adjusting for demographic and clinical variables (OR=3.1, 95%CI: 2.2, 4.4), asthma severity (OR=3.4, 95%CI: 2.4, 4.8), and asthma control (OR=4.5, 95%CI: 3.1, 7.0). Patients with a recent steroid burst were over 2 times (OR=2.8, 95%CI: 2.2, 3.7) more likely to experience a future steroid burst after adjusting for demographic and clinical variables (OR=2.6, 95%CI: 2.0, 3.4).
Conclusions: RSE's are an important independent predictor of FSE's in pediatric patients with severe/difficult-to-treat asthma and should be considered when determining asthma action plans. Healthcare providers should question patients regarding recent exacerbation history and adapt treatment plans to reduce future risk.

17 Childhood Obesity in Difficult to Control Pediatric Asthma Patients in a Tertiary Pediatric Subspecialty Clinic

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Rationale: Identifying clinical features associated with difficult to control asthma will help address overall control and more effective asthma management. Our clinical observation suggested that the proportion of overweight/obesity is significantly higher in difficult-to-control (DTC) than in well-controlled asthmatics.
Methods: This was a retrospective chart review of 400 patients, aged 5 to 18 years. Cases (n=200) were identified as 100 subjects with difficult-to-control severe persistent asthma and an inhaled corticosteroids (ICS) dose of ≥1000 mcg/day and 100 subjects with well-controlled mild and moderate persistent asthma and an ICS dose of ≤500 mcg/day. The control group included 200 subjects without asthma. Multivariable logistic regression models were used to assess the relationships between asthma status and weight status, age, race and gender.
Results: The BMI percentile was significantly higher in the difficult-to-control asthma group than in the well-controlled asthma group and in the control group (74.66 ± 28.19 vs. 54.25 ± 29.92 vs. 55.19 ± 32.54, $p<0.001$). 36% of the difficult-to-control asthmatics were obese (vs. 6% of the well-controlled asthmatics, $p<0.001$, vs. 13% of non-asthmatics, $p=0.002$), and 47% normal weight (vs. 79% of the well-controlled asthmatics, vs. 75% of non-asthmatics, $p<0.001$). Mean age and the proportion of African Americans in the difficult-to-control asthmatics were significantly higher than in the well-controlled asthmatics and in the control group ($p<0.001$).
Conclusions: The results of this study demonstrate a significant association between severe persistent DTC asthma and obesity, age and race. Obese difficult-to-control asthmatics need treatment approaches addressing both asthma control and weight management.

18 Characterization of T Cell Reactivity in Cockroach-Allergic Children with Different Disease Severities

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Rationale: German cockroach (Bla g) allergy is commonly defined by IgE titers to Bla g extract or allergens. It is commonly associated with rhinitis and asthma in inner-city children. Studying Bla g T cell response is of great relevance to understand potential differences as a function of allergic disease and for the development of efficacious immunotherapy approaches.
Methods: Using pools of previously identified Bla g-derived T cell epitopes, we characterized the allergen-specific T cell response of children who exhibited 1) early onset atopy (Bla g-sensitized, n=8) 2) late onset atopy (Bla g-sensitized, n=7) or 3) low atopy (not Bla g-sensitized, n=6). PBMC from Bla g-sensitized children from all 3 groups were analyzed ex vivo for Bla g-specific T cell responses based on cytokine production in response to antigen stimulation measured by Flow cytometry. Additionally, bulk frequency of total Th2A cells, a Th2 cell subset that has been associated with the pathogenicity of allergy and asthma, was assessed by flow cytometric analysis.
Results: Analysis of total Th2A cells in three groups revealed a 2-3 fold increase of the Th2A populations in the atopic children compared to children with low atopy (p=0.01). Bla g-specific IL-5 production in CD4 t cells was significantly higher in children with early or late onset atopy (median 0.38 and 0.58%, respectively) than low atopy (median 0.03%) (p=0.009).
Conclusions: Onset of early and late atopy in cockroach allergic children is associated with an increase in frequency of total Th2A cells and allergen-specific IL-5-producing T cells compared to children with low atopy.

19 Neighborhood Deprivation Is Longitudinally Associated with Childhood Asthma

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Rationale: Although longitudinal studies have shown associations between parental income and childhood asthma development, deprivation has been proposed as a more comprehensive measure of childhood socioeconomic status. We determined the associations between material deprivation and childhood asthma.
Methods: Prospectively-collected administrative data housed at the Institute for Clinical Evaluative Sciences were evaluated for the 1997-2003 Toronto birth cohorts. Neighbourhood material deprivation was reported according to the Ontario Marginalization Index criteria, including no high school graduation, lone parent families, government transfers, unemployment, low income, and homes needing major repairs. Incident asthma was defined by the time of entry into the Ontario Asthma Surveillance Information System (OASIS) database, requiring 2 outpatient visits for asthma within 2 consecutive years or any hospitalization for asthma. We measured risk of incident asthma due to high neighborhood deprivation with Cox proportional and discrete-time hazard models and associations between asthma visits and deprivation by year of life with Generalized Estimating Equations and generalized linear mixed models.
Results: OASIS asthma criteria were met for 21% of the 326,383 children. After adjusting for sex, preterm delivery, obesity, and atopic conditions, children with high birth neighborhood deprivation were at increased risk of any (HR 1.11; 95% CI, 1.09-1.13) and currently-symptomatic (HR 1.11; 95% CI, 1.06-1.15) incident asthma. High deprivation in a given year of life was associated with increased odds of asthma in that year of life (OR 1.10; 95% CI, 1.07-1.12).
Conclusions: Children living in high-deprivation neighborhoods are at increased risk of incident asthma, suggesting possible primary asthma prevention strategies.

20 Prevalence of Exercise-Induced Bronchoconstriction Using the 6-Minute Free-Running Test in 5- to 6-Year-Old Japanese Children: A Cross-Sectional Study

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Rationale: Exercise-induced bronchoconstriction (EIB) develops during or after exercise in healthy children, as well as in those with bronchial asthma (BA). However, the definition of EIB varies because of differing criteria among countries, and differences between sexes are poorly understood. This study aimed to investigate the prevalence of EIB using 3 different criteria of positive EIB, taking into account sex, in kindergarteners in Japan.
Methods: Fifty-one 5- to 6-year-old children without BA were enrolled in this cross-sectional study. The children underwent the 6-minute free-running test (6MFRT) for an exercise challenge. Peak expiratory flow rate (PEFR) was measured before exercise and at 0, 3, 10, and 20 minutes after exercise. Positive EIB was defined using 3 criteria: ≥15%, ≥20%, or ≥25% decrease in post-exercise PEFR from pre-exercise PEFR.
Results: Among the children (n=23 boys; n=28 girls), the prevalence of EIB was 54.9% (28/51) in children when a ≥15% decrease in PEFR was used, 41.2% (21/51) when a ≥20% decrease in PEFR was used, and 25.5% (13/51) when a ≥25% decrease in PEFR was used. When EIB was defined as a ≥25% decrease in PEFR, the prevalence of EIB was significantly higher in girls than in boys (39.3% vs 8.7%, p = 0.022).
Conclusions: Regardless of which criteria are used, the prevalence of EIB in Japanese kindergarteners is higher than that observed worldwide, especially in girls. Our results suggest that the criteria for diagnosing EIB in 5- and 6- year-old children should take sex into account.

21 Using Electronic Medical Records (EMR) to Improve Outpatient Quality of Care for Children with Asthma

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Rationale: Poorly controlled asthma is the leading cause of school absenteeism and accounts for billions of dollars in medical costs annually for children. Use of EMR can be helpful with both monitoring asthma control and standardization of care.
Methods: Retrospective chart reviews were completed in two phases. In Phase 1 (2013), outpatient encounters for patients with asthma in general pediatrics and pulmonology were analyzed. Data collected included: severity classification, inhaled corticosteroid (ICS), asthma action plan (AAP) and patient education. Results from Phase 1 were summarized and distributed to attending physicians and residents in individual report cards. Mandatory questions regarding asthma severity and management were added to EMR charts. In Phase 2 (2015), a post-intervention chart review was completed for patients meeting the same inclusion criteria.
Results: In Phase 1, 1229 charts were reviewed and compared to 1672 charts in Phase 2. The rates of documenting severity classification significantly increased from 67.6% (832/1229) in Phase 1 to 91.5% (1530/1672) in phase 2 (p=0.001). Use of ICS significantly improved from 60.1% (739/1229) in Phase 1 to 70.2% (1175/1672) in Phase 2 (p=0.001). Documentation of asthma education improved from 73.1% (898/1229) in Phase 1 to 76.6% (1282/1672) in Phase 2 (p=0.026). The distribution of AAP improved significantly from 48.4% (598/1229) in Phase 1 to 60% (1002/1672) in Phase 2 (p=0.001).
Conclusions: Standardization of documentation in the EMR resulted in significant improvement in documentation of severity classification, utilization of ICS, distribution of AAP and provision of education.

22 Mobile Phone Asthma Action Plan Application; Use in Adolescents

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Rationale: Asthma burden affects mortality, morbidity, quality of life, and the economy. The *British Medical Journal* recently reported that two-thirds of asthma deaths are due to failure to follow recommended guidelines and primary care failings in routine care. Written asthma action plans are standard of care according to national guidelines, but these plans are seldom prescribed. Furthermore, these written care plans are often unavailable at the time of an exacerbation. The purpose of this project was to create an asthma action plan application for smartphones. The goal of the project was improved patient access to their asthma action plan and improved utilization rates among providers.
Methods: A development studio was consulted for support in developing a smartphone application to code the software for the asthma action plan and assist in the design process. Following development of the application, a survey was completed to evaluate design and functionality.
Results: All survey participants agreed that the application was easy to use, could be used without written instruction and was designed for adolescents with asthma of any severity. Patients and providers noted that the app would help provide information about what to do in the event of an asthma exacerbation and that the application would be used frequently.
Conclusions: There was consensus from both patients and providers that this application is not only functional but also helpful in the event of an asthma exacerbation. The project met the goal of creating a mobile phone application that improved patient access to asthma action plans.

23 Inhaled House Dust Programs Pulmonary Dendritic Cells to Promote Type 2 T-Cell Responses By an Indirect Mechanism

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Rationale: The induction of allergen-specific T helper 2 (Th2) cells by lung dendritic cells (DCs) is a critical step in allergic asthma development. Airway delivery of purified allergens or microbial products can promote Th2 priming by lung DCs, but how environmentally relevant quantities and combinations of these factors affect lung DC function is unclear.
Methods: We investigated the ability of house dust extract (HDE), which contains a mixture of environmental adjuvants, to prime Th2 responses against an innocuous inhaled antigen in mice.
Results: Inhalational exposure to HDE conditioned lung conventional DCs, but not monocyte-derived DCs, to induce antigen-specific Th2 differentiation. Conditioning of DCs by HDE was independent of Toll-like receptor 4 signaling, indicating that environmental endotoxin is dispensable for programming DCs to induce Th2 responses. DCs directly treated with HDE underwent maturation but were poor stimulators of Th2 differentiation. In contrast, DCs treated with bronchoalveolar lavage fluid (BALF) from HDE-exposed mice induced robust Th2 differentiation. DC conditioning by BALF was independent of the proallergic cytokines IL-25, IL-33, and thymic stromal lymphopoietin. BALF treatment of DCs resulted in upregulation of CD80 but low expression of CD40, CD86, and IL-12p40, which was associated with Th2 induction.
Conclusions: These findings support a model whereby environmental adjuvants in house dust indirectly program DCs to prime Th2 responses by triggering the release of endogenous soluble factor(s) by airway cells. Identifying these factors could lead to novel therapeutic targets for allergic asthma.

24 Neuronal Nitric Oxide Synthase Plays an Important Role in the Early TLR4-Triggered Inflammatory Response Via the SOCS1-p38-AP1 Signaling Axis

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Rationale: Asthma and chronic obstructive pulmonary disease (COPD) are very common inflammatory diseases of the airways. Proinflammatory cytokines play a key role in symphonizing the chronic inflammation and structural changes of the respiratory tract in both asthma and COPD. Therefore, identifying the regulatory mechanisms of

proinflammatory cytokine expression can be useful clinically to mitigate tissue damage and foment repair caused by dysregulated or persistent inflammatory conditions.
Methods: Mice were procured from Jackson laboratory, USA. Microvessel Kfc was measured to determine the pulmonary microvascular permeability to liquids, as described previously (Vogel et al., 2000). Bioluminescence intravital imaging was performed using an IVIS charge-coupled camera (PerkinElmer). NO concentration in the culture medium was assessed indirectly by measuring NO2 accumulation using a 280i Nitric Oxide Analyzer (Sievers Instruments) and reported as nmol NO per mg protein. Measurement of peroxynitrite production was done using Coumarin-7-boronate (CBA; Sigma-Aldrich). Protein localization was determined by LSM 510 META confocal laser scanning microscope (Carl Zeiss). RT PCR was done using 7500 Real-Time PCR System (Applied Biosystems).
Results: We studied that NOS1 regulation of suppressor of cytokine signaling-1 (SOCS1) stability in macrophages as a critical effector of macrophage derived proinflammatory cytokines. Further, increased amounts of SOCS1 in NOS1-/- macrophages leads to decreased p38MAPK activity and ultimately decreased activity of AP-1 and NFkB transcription factors, which impairs expression of pro inflammatory cytokines.
Conclusions: Our studies suggest that NOS1 is a clinically relevant drug target to suppress inflammatory conditions like Asthma and chronic obstructive pulmonary disease (COPD).

25 Induction of Kruppel-like Transcription Factor (KLF4&5) By Baker's Yeast Mannan in Human Bronchial Epithelial and Smooth Muscle Cells

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Rationale: Mannan derived from *Saccharomyces cerevisiae*(SC-MN) modulates allergic asthma pathogenesis in a mouse model. The purpose of this study is to explore downstream transcription factor(s) involved in SC-MN's beneficial effects in asthma. The KLFs are important transcription factors in epithelial survival, and modulate epithelial mesenchymal transition and smooth muscle proliferation. As KLF4&5 are highly expressed in lung, we hypothesize that SC-MN can induce KLFs in lung cells.
Methods: Primary normal human epithelial cells (NHBEC) and bronchial smooth muscle cells were incubated with SC-MN and examined for KLF4, KLF5, p38MAPK levels and phosphorylation over a time course by Western Blot (WB). Normal human bronchial smooth muscle cells were analyzed for SM22alpha levels by WB and alpha-isoactin by indirect immunofluorescent staining.
Results: Following exposure to SC-MN, protein levels of KLF4 and KLF5 increased in both NHBEC and NHBSM cells over the subsequent 2-18 h. SC-MN–treated bronchial smooth muscle cells, but not in NHBEC, showed biphasic activation of p38MAPK (5-120 min and 8 h) that is known to lead to KLF phosphorylation in vascular smooth muscle cells. In addition, SC-MN increased smoooth muscle specific alpha-isoactin and SM22aαlpha at 24 hrs, consistent with a phenotype change.
Conclusions: SC-MN can induce KLF4 or KLF5, transcription factors that are important in epithelial survival and regulation of smooth muscle proliferation.