Asthma Treatment

Standard Therapy, Biologics, Bronchial Thermoplasty, and Beyond

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Asthma Definition

• No clear and unified definition exists

• Chronic inflammatory disorder of the airways

• Mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells play a role

• In susceptible individuals, inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning
Pathophysiology – brief primer

- Asthma is multifactorial in origin
- Inflammation is the cornerstone of pathology
  - Immune system
  - Cytokines
  - Epithelium
Risk factors

• Hygiene hypothesis
• Atopy
• Infections (RSV, rhinovirus)
• Obesity (adipokines, TNF-α, IL-6, leptin)
• Tobacco use
• Genetics
• Environmental exposure
Airway remodeling

• Structural alteration of the airway
• Feature of chronic asthma
• Pathophysiology
  – Deposition of collagen in sub-epithelium
  – Airway smooth muscle (ASM) hyperplasia
  – Proliferation of submucosal glands
• Leads to permanent airflow limitation
The epithelial-mesenchymal trophic unit in asthma

Environmental agents
Inflammatory cell products

Th-2 and Th1 cytokines

Dendritic cell

Th-2 cell
IL-9, IL-3, IL-4
IL-3, IL-5, GM-CSF

Mast cell
TNF

Eosinophil

Neutrophil

(Myo) fibroblasts

Mucus
Initiation

Amplification

Propagation

Smooth muscle
Blood vessels

Chemoattractants eg IL-8, proinflammatory mediators

THE EPITHELIAL-MESENCHYMAL TROPHIC UNIT IN ASTHMA
Diagnosis of asthma

• History
  – Personal (wheezing, cough, dyspnea)
  – Family history of asthma
  – Presence of triggers
    • Environmental
    • Work related
Diagnosis of asthma

• Spirometry
  – FEV1 – forced expiratory volume during 1st second
  – Most standardized test of airflow obstruction
    • Objective
    • Non-patient-reported (if good effort)
  – Increase of 12% AND 200cc after bronchodilator
    • Indicates reversible airflow obstruction
    • Suggestive but not diagnostic of asthma
Diagnosis of asthma

• Accepted approach when evidence VERY convincing
  – History
  – Response to bronchodilator on PFTs

• Bronchoprovocation challenge can be used when diagnosis unclear
Airway hyperresponsiveness

- AHR to environmental stimuli = hallmark of asthma
- Patients who have normal PFTs but are suspected of asthma will develop bronchoconstriction in response to a stimulus (provocative challenge)
Provocative challenge

• Direct stimulation of the airways with an agent that is known to provoke bronchoconstriction via direct action on airway smooth muscles

• Agents
  – Methacholine
  – Mannitol
  – Histamine
  – Adenosine
Methacholine

- A longer-acting derivative of acetylcholine
- Standard agent of choice in the US and Europe
  - ATS (American Thoracic Society)
  - ERS (European Respiratory Society)
Methacholine inhalation challenge

• Inhalation solutions from 0.03mg/ml to 16 mg/ml

• Test:
  – Diluent inhaled
  – FEV1 measured x 2 at 30 and 90 seconds
  – Increased concentration is delivered

• **PC20**: concentration at which FEV1 decreases by 20%

• Positive test = PC20 of 8 mg/ml or less

• Negative test = PC20 of 16 mg/ml
  – Convincingly rules out asthma

• PC20 concentration is associated with asthma severity
Severity of asthma

• Mild intermittent
• Mild Persistent
• Moderate Persistent
• Severe Persistent
Mild intermittent asthma

- Normal spirometry
- Symptoms < 2 / week
- Night symptoms < 2 / month
- Albuterol use < 2 / week
- 0-1 asthma exacerbations / year
  - Requiring prednisone
Persistent asthma

• 2 or more exacerbations / year
  – Requiring prednisone
  – ER visit or hospitalization
  – Missed school / work
Mild persistent asthma

• Normal spirometry
• Symptoms > 2 / week but not every day
• Night symptoms 3 - 4 / month
• Albuterol use > 2 / week but not every day
• >2 asthma exacerbations / year
Moderate persistent asthma

- Mild drop in FEV1 (still more than 60% predicted)
- Symptoms: daily
- Night symptoms > 1 / week but not every night
- Albuterol use: daily
- >2 asthma exacerbations / year
Severe persistent asthma

- FEV1 moderately reduced (<60% predicted)
- Symptoms: many times / day
- Night symptoms: nightly
- Albuterol use: many times / day
- >2 asthma exacerbations / year
Standard treatment of asthma

• Depends on asthma severity
• Stepwise approach
  – Short acting bronchodilator (SABA)
  – Inhaled corticosteroid (ICS)
  – Long acting bronchodilator (LABA)
  – Leukotriene antagonist (LTRA)
• Systemic glucocorticoid during exacerbations
  – Prednisone 40mg x 5 days
  – No need for taper
Standard treatment of asthma

• Most asthmatics can be well controlled on SABA + ICS
• Most asthmatics are unnecessarily on SABA + ICS/LABA
Stepwise approach for managing asthma in youths greater than or equal to 12 years of age and adults

**Intermittent asthma**

Persistent asthma: daily medication
Consult with asthma specialist if step 4 care or higher is required.
Consider consultation at step 3.

**Mild**

- **Step 1**
  Preferred: Low-dose ICS
  Alternative: SABA PRN

- **Step 2**
  Preferred: Low-dose ICS + LABA or Medium-dose ICS
  Alternative: Cromolyn*, LTRA, or Theophylline

**Moderate**

- **Step 3**
  Preferred: Medium-dose ICS + LABA
  Alternative: Medium-dose ICS + either LTRA, Theophylline, or Zileuton

- **Step 4**
  Preferred: High-dose ICS + LABA
  Consider Omalizumab for patients who have allergies

- **Step 5**
  Preferred: High-dose ICS + LABA + oral corticosteroid
  AND
  Consider Omalizumab for patients who have allergies

- **Step 6**
  Preferred: High-dose ICS + LABA + oral corticosteroid
  AND
  Step up if needed (first, check adherence, environmental control, and comorbid conditions)

**Assess control**

- **NHLBI 2007**
Standard treatment of asthma

• Once patient is treated, their asthma severity commonly decreases
Novel therapies

• Bronchial thermoplasty
• Biologics
• Future
Bronchial thermoplasty

- Asthma is a disease of inflammation first and foremost
- Asthma exacerbation causes contraction of airway smooth muscles (ASM)
  - Airways narrow $\rightarrow$ Increased airflow obstruction
Bronchial thermoplasty

- BT aims at disrupting ASM
  - Radiofrequency energy is delivered into the wall of the airway, heating it up
  - Cartilage has minimal water content – little effect
  - Airway smooth muscle proteins coagulate
    - Disruption of sarcomeres
    - Impeded ability to contract
    - Thinning of muscle over time
Bronchial Thermoplasty
Airways Before and After Bronchial Thermoplasty Treatment

Airway of Person without Asthma

- Normal band of airway muscle
- Open airway where air travels

Airway of Person with Severe Asthma

- More airway muscle causes airway to narrow
- This is where the device applies heat to the airway wall during BT treatment

Airway of Person with Severe Asthma after Treatment

- Reduced airway muscle after BT treatment
- After BT, the inside airway wall and other tissue heals, but airway muscle is reduced
Bronchial thermoplasty

• Procedure
• 3 bronchoscopies
  – At least 6 weeks apart (allows healing)
    • #1 RLL
    • #2 LLL
    • #3 RUL and LUL
Bronchial thermoplasty

- Follow up studies now of 7 years
- Decreased number of asthma exacerbations
- Decreased number of severe asthma exacerbations
- Less missed days at work / school
Bronchial thermoplasty

• What BT is not
• It is not a cure for asthma
• Patients still need:
  – Asthma action plan (home Rx for prednisone)
  – SABA
  – Maintenance inhaler
Biologics

• Monoclonal antibodies designed to interrupt inflammatory cascade in asthma

• Binding
  – Inflammatory cytokine (IgE, Interleukins)
  – Receptor
Pathogenesis of asthma

antigen

naive T-lymphocyte

IL-12

Th-0

Th-2 response

IL-4, IL-13

IL-9

IL-3

GM-CSF

IL-3, IL-5

Th-1 response

IFN-γ, lymphotoxin, IL-2

Cell mediated immunity and Neutrophilic inflammation

IgE

Mediators of inflammation (eg. histamine, prostaglandins, leukotrienes, enzymes)

Asthma symptoms

Bronchial hyperresponsiveness

Airway obstruction

Mast cells

Basophils

Eosinophils
Pathogenesis of asthma

- Antigen
- Naive T-lymphocyte
- Dendritic cell
- IL-12

Th-1 response:
- (IFN-γ, lymphotoxin, IL-2)
- Cell mediated immunity and Neutrophilic inflammation

Th-2 response:
- IL-4, IL-13
- IL-9
- IL-4
- IL-3
- IL-3, IL-5
- GM-CSF
- IgE
- Mast cells
- Basophils
- Eosinophils
- Mediators of inflammation (e.g., histamine, prostaglandins, leukotrienes, enzymes)
- Bronchial hyperresponsiveness
- Airway obstruction

Asthma symptoms
Biologics

• Anti IgE
  – Omalizumab
  – Ligelizumab (under research)
Pathogenesis of asthma

antigen → naive T-lymphocyte

- IL-12 (Th-0) → IL-12
- IL-12 (Th-1) → Th-1 response (IFN-γ, lymphotoxin, IL-2)
  - Cell mediated immunity and Neutrophilic inflammation
  - Asthma symptoms

- IL-4, IL-13 → IL-4
- IL-9, IL-4 → IL-3
- IL-3, IL-5, GM-CSF → IgE
- IgE → Mast cells → Basophils → Eosinophils
  - Mediators of inflammation (eg. histamine, prostaglandins, leukotrienes, enzymes)
  - Bronchial hyperresponsiveness
  - Airway obstruction

Th-2 response
Biologics

• Anti IL-5
  – IL-5 recruits eosinophils to airways

• Drugs binding IL-5
  – Mepolizumab (Nucala)
  – Reslizumab (Cinqair)

• Drug blocking IL-5 receptor
  – Benralizumab (Fasenra)
Pathogenesis of asthma

Antigen → Naive T-lymphocyte → Th-0 → Th-1 response
- IL-12+ → IL-4, IL-13, IL-9 → IL-4 (IL-13)
  - IgE → Mast cells, Basophils, Eosinophils
  - Mediators of inflammation (e.g., histamine, prostaglandins, leukotrienes, enzymes)
  - Asthma symptoms

Th-2 response
- IL-12- → IL-4 (IL-13)
  - IL-3, IL-5, GM-CSF
  - Bronchial hyperresponsiveness
  - Airway obstruction
Biologics

• Anti-IL4 receptor Antibody
  – Dupilumab (Dupixent)
Future

- Additional agents in development for multiple cascade targets
- Research is difficult
  - Injectables $\rightarrow$ systemic side effects
Pathogenesis of asthma

Antigen → Dendritic cell

Naive T-lymphocyte → Th-0

IL-12

Th-1 response

(IFN-γ, Lymphotoxin, IL-2)

Cell mediated immunity and Neutrophilic inflammation

Th-2 response

IL-4, IL-13 → IL-9, IL-4, IL-3 → GM-CSF

IgE → Mast cells → Basophils → Eosinophils

Mediators of inflammation (e.g., histamine, prostaglandins, leukotrienes, enzymes)

Asthma symptoms → Bronchial hyperresponsiveness → Airway obstruction
Future

• Anti-IL2 antibody – Daclizumab
  – Not on the market
    • Autoimmune hepatitis
    • Autoimmune colitis
Future

• AZD5423
  – SGRM - selective glucocorticoid receptor modulator
    • Binds receptor in a novel way
    • Proposed to reduce inflammatory response without other effects
  – Inhaled
    • When inhaled, less systemic effects found compared with inhaled steroids
  – Undergoing Phase II trial
Thank you

• Questions?