Asthma/COPD/OSA

Presented by
Stephen Kirtland, MD
Chief of Staff, VM Hospital
Medical Director, Thoracic Oncology Program
Director, Bronchoscopy Services
Virginia Mason Medical Center – Seattle WA

Disclosure: Dr. Kirtland has no significant financial interest in any of the products or manufacturers mentioned.
67 yo male with the following:
Increasing dyspnea on exertion for many years
Panting with one flight of stairs, playing with grandkids
BMI>32
1 ppd for 50 years, D/C 6 months ago on your sage advice!
2 puffs combo inhaler: anticholinergic
and beta-agonist PRN- most days, O2 sat 87%

His PFT’s:

<table>
<thead>
<tr>
<th></th>
<th>Predicted</th>
<th>measured</th>
<th>% m/p</th>
<th>Post</th>
<th>% m/p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>4.10</td>
<td>2.74</td>
<td>67%</td>
<td>3.05</td>
<td>74%</td>
</tr>
<tr>
<td>FEV1</td>
<td>3.08</td>
<td>0.95</td>
<td>31%</td>
<td>1.76</td>
<td>57%</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>75</td>
<td>35</td>
<td>47%</td>
<td>58</td>
<td>78%</td>
</tr>
</tbody>
</table>
What would be the next medication you would add?

A. LAMA
B. LABA
C. LABA/ICS
D. ICS

• Any of above
• A and C
• All but D
Which therapy will lengthen his life?

- LABA/ICS
- LAMA
- LABA
- Oxygen
- Pulmonary rehabilitation
Which step up therapy will most likely improve FEV1 in most patients with asthma?

- PPI
- Anti-IGE
- LAMA
- Breathing exercises
- Bronchial thermoplasty
Causality with OSA has been established in:

- Hypertension
- Congestive Heart Failure
- Pulmonary Hypertension
- Coronary disease
- Stroke
- Motor vehicle accidents
- Atrial fibrillation
CPAP

- Reduces BP in hypertensive patients
- Improves LV function in patients with CHF
- Persistent NSR after cardio-version if PAF
- Improves glucose control
- Reduces cardiovascular events and mortality
- Reduces motor vehicle accidents
- Reduces daytime sleepiness
- Improves quality of life and depression scores
- All of the above
What’s new in Medicine? COPD/Asthma/OSA

Steve Kirtland, MD FCCP
September 9, 2012
Disclosures
My Goal

• Review the outpatient management of COPD, Asthma and OSA
• Review the treatment of Hospitalized patients
• Highlight some advances in 2011-2012
• Solve world peace and find a cure for cancer
• Questions?
Highlights in the Past year

- Azithromycin prevents COPD exacerbations
- CCMP does not prevent hospitalizations
- PPI’s don’t improve asthma control in asymptomatic patients
- FeNo2 may help identify some “allergic” asthmatics but not helpful for management
- Tiotropium has benefit in some asthmatics
- SDB associated with cancer mortality
Others

• Indacaterol causes improved, sustained bronchodilation equivalent to tiotropium
• Home Sleep studies are helpful
• CPAP machines are smaller/lighter
• Provent
• Triple drug therapy in COPD appears beneficial
• Bronchial Thermoplasty improves QOL?
COPD Epidemiology

• Prevalence: 12-24 mill US, 210 mill worldwide
  • 37% undiagnosed (NHANES III)
  • ~15-20% of smokers

• Morbidity:
  ▪ 2004: 461,000 hospitalizations (4th most common)
  ▪ 1.5 million ED visits

• Mortality:
  ▪ 120,000 deaths in 2001 (6th most common and increasing)
    • 90% (3 mill) in low and middle income countries worldwide
  ▪ 1 death every 4 min (14 during this lecture)
  ▪ Only cause of death in top 10 that is rising

• Cost:
  ▪ 6.5 billion
Of the six leading causes of death in the United States, only COPD has been increasing steadily since 1970.

*Source: Jemal A. et al. *JAMA* 2005*
COPD Mortality Worldwide

<table>
<thead>
<tr>
<th>1990</th>
<th>2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic heart disease</td>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>Lower resp infection</td>
<td>Lower resp infection</td>
</tr>
<tr>
<td>Diarrhoeal disease</td>
<td>Diarrhoeal disease</td>
</tr>
<tr>
<td>Perinatal disorders</td>
<td>Perinatal disorders</td>
</tr>
<tr>
<td>COPD</td>
<td>COPD</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Measles</td>
<td>Measles</td>
</tr>
<tr>
<td>Road Traffic Accidents</td>
<td>Road Traffic Accidents</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>Lung Cancer</td>
</tr>
</tbody>
</table>

Definition of COPD

- Chronic Obstructive Pulmonary Disease is a preventable and treatable disease with some significant extrapulmonary effects.

- The pulmonary component is characterized by airflow limitation that is not fully reversible. FEV/FVC < 0.70

- The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.

- Severe COPD leads to respiratory failure, hospitalization and death.
Natural History of COPD

FEV\textsubscript{1} (liters)

Age (years)

Symptoms

Death

Nonsmoker

Average smoker

Susceptible smoker

© 2012 Virginia Mason Medical Center
COPD Limits Daily Activities for Patients Regardless of Age

P17. How much do you feel your respiratory condition limits what you can do in each of the following areas? n=3,265

INFLAMMATION IN COPD

Small airway disease
- Airway inflammation
- Airway remodeling

Parenchymal destruction
- Loss of alveolar attachments
- Decrease of elastic recoil

AIRFLOW LIMITATION
COPD PATHOLOGY

LUNG INFLAMMATION

Cigarette smoke
Biomass particles
Particulates

Dust: (Al-SiO₄), kaolin
Blocked by simvastatin
Related to adenosine receptor affinity/density

Oxidative stress

Anti-oxidants

Proteinases

Anti-proteinases

Host factors
Amplifying mechanisms

PDE 4-dependent

Repair mechanisms

Genetics

Lack of SP-D
Starvation

COPD PATHOLOGY

Peribronchial fibrosis
Loss of alveolar units

Latent viruses
CD8 cells

RSV in 33%
FEV1 decline

TGFB, IL-1B, 5mod 2,3

New Ideas

Pathogenesis of COPD
Pathophysiology of COPD

Structural Changes

Pathophysiology of COPD

Airflow Limitation

Normal

COPD

Parenchymal tethering

Loss of tethering


© 2012 Virginia Mason Medical Center
Normal

Emphysema
Radiographic Changes in COPD

Low, Flattened Diaphragm

Hyperinflation

Increased A-P Diameter
Chronic hypoxia

Pulmonary vasoconstriction

Pulmonary hypertension

Cor pulmonale

Muscularization
Intimal hyperplasia
Fibrosis
Obliteration

Edema

Death

Pulmonary Hypertension in COPD
Risk Factors for COPD

- Cigarette smoke
- Occupational dust and chemicals
- Environmental tobacco smoke (ETS)
- Indoor and outdoor air pollution

Aging Populations

Nutrition

Infections

Socio-economic status
COPD: Genetics

• Gene abnormalities (SNPs)
   Serpina 1 (AAD)
   Metalloproteases (MMP-9)    upper lobe emphysema
   ADAM-33       FEV1 decline, AHR, inflammation
   Elastin  increase proteolysis
   Secretory PLA$_2$, Group IID  ↑ cytokines, ↑ weight loss
Diagnosis of COPD

**SYMPTOMS**
- cough
- sputum
- shortness of breath

**EXPOSURE TO RISK FACTORS**
- tobacco
- occupation
- indoor/outdoor pollution

**SPIROMETRY**
COPD: Diagnosis

- Always suspect in older patient with complaint of dyspnea
- Do not assume that older smoker with dyspnea necessarily has COPD
- Physical exam and chest x-ray are not reliable in establishing diagnosis
- Always confirm diagnosis with spirometry
  - Obstructive pattern - FEV₁/FVC ≤ 0.70
  - Mild % predicted FEV₁ > 80%
  - Moderate % predicted FEV₁ 50-80%
  - Severe % predicted FEV₁ 30-49%
  - Very severe % predicted FEV₁ < 30%
BODE Index

10 point scale
BMI
FEV1
Dyspnea
Exercise capacity

More reliable than FEV1 for risk of death but not used as guide for therapy
Cell, NEJM 2004
50 yo male
FEV1 2.31 58%,
DLCO 48%

59 yo female
FEV1 1.04
45% DLCO 57%
# Differential Diagnosis: COPD and Asthma

<table>
<thead>
<tr>
<th>COPD</th>
<th>ASTHMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset in mid-life</td>
<td>Onset early in life (often childhood)</td>
</tr>
<tr>
<td>Symptoms slowly progressive</td>
<td>Symptoms vary from day to day</td>
</tr>
<tr>
<td>Long smoking history</td>
<td>Symptoms at night/early morning</td>
</tr>
<tr>
<td>Dyspnea during exercise</td>
<td>Allergy, rhinitis, and/or eczema also present</td>
</tr>
<tr>
<td>Largely irreversible airflow limitation</td>
<td>Family history of asthma</td>
</tr>
<tr>
<td></td>
<td>Largely reversible airflow limitation</td>
</tr>
</tbody>
</table>
ASTHMA

Allergens

Ep cells

Mast cell

CD4+ cell (Th2)

Eosinophil

Bronchoconstriction
AHR

COPD

Cigarette smoke

Alv macrophage Ep cells

CD8+ cell (Tc1)

Neutrophil

Small airway narrowing
Alveolar destruction

Airflow Limitation

Reversible

Irreversible

© 2012 Virginia Mason Medical Center
saving American culture and society, one mind at a time.

Why crucial decisions can’t be made in the blink of an eye

Michael R. LeGault
Award-winning writer
Asthma

Emphysema

Chronic Bronchitis

Airflow Obstruction

Asthma
Overlap Syndrome

- Current definitions do not fully depict spectrum of disease
- Variable airflow + incompletely reversible airway obstruction
- Increased airway neutrophilia, remodeling
- ~18% of OAD patients, >50% over 70 yo
- M>f, smoking, long duration of disease, intermediate atopy
Overlap Syndrome

• Accelerated decline in lung function
  - Smoking, asthma, BHR, exacerbations

• Incomplete airway growth
  - Maternal smoking, second hand smoke, low birth weight, gender, nutrition, asthma, childhood infections

• Excluded from clinical trials
GOALS of COPD MANAGEMENT

VARYING EMPHASIS WITH DIFFERING SEVERITY

• Relieve symptoms
• Prevent disease progression
• Improve exercise tolerance
• Improve health status
• Prevent and treat complications
• Prevent and treat exacerbations
• Reduce mortality
Treatment for all with COPD

1. Smoking Cessation
   - Commit to quit
   - Nicotine replacement
   - Wellbutrin
   - Varenicline
   - QUIT LINE: 1-800-QUIT-NOW

2. Intermittent bronchodilator therapy
   - Albuterol, ipratropium, or combination

3. Influenza and pneumococcal vaccine
   - Influenza vaccine decreases serious illness and death by 50% (NIHLBI/WHO)

4. Education, exercise, diet

Global Initiative for Chronic Obstructive Lung Disease. Goldcopd.org. NIHLBI & WHO
Pharmacologic Therapy for Stable COPD

- All patients who are symptomatic merit a trial of drug treatment
- Current medications can
  - Reduce or abolish symptoms
  - Increase exercise capacity
  - Reduce number and severity of exacerbations
  - Improve health status
- At present, no treatment has modified the rate of decline in lung function (?)

# Wing Shui Chinese Restaurant

**Free Delivery**

Min. $10.00

Mon. - Thurs.: 11:30 a.m. to 10:30 p.m.
Fri. & Sat.: 11:30 a.m. to 11:30 p.m.
Sun.: 12:00 noon to 10:30 p.m.

**53 NORTH FRONT STREET, KINGSTON, N.Y. 12401**

**TEL.: (845) 339-3397/338-3388**

**PLEASE CIRCLE ITEMS & PRICES DESIRED**

### SOUP (with Wide Noodles)

<table>
<thead>
<tr>
<th>Item</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veg. Soup</td>
<td>$1.70</td>
</tr>
<tr>
<td>wonton soup</td>
<td>$1.70</td>
</tr>
<tr>
<td>wonton Egg Drop Soup Mix</td>
<td>$1.70</td>
</tr>
<tr>
<td>chicken Egg Drop Soup</td>
<td>$1.70</td>
</tr>
<tr>
<td>chicken Rice Soup</td>
<td>$1.70</td>
</tr>
<tr>
<td>chicken Noodle Soup</td>
<td>$1.70</td>
</tr>
<tr>
<td>shrimp Egg Drop Soup</td>
<td>$1.70</td>
</tr>
<tr>
<td>chicken Egg Drop Soup</td>
<td>$1.70</td>
</tr>
<tr>
<td>Roast Pork Yat Gow Mein</td>
<td>$4.75</td>
</tr>
<tr>
<td>Shrimp Tonkay Mein</td>
<td>$4.75</td>
</tr>
<tr>
<td>sweet &amp; Sour Soup</td>
<td>$1.50</td>
</tr>
</tbody>
</table>

### APPETIZERS

<table>
<thead>
<tr>
<th>Item</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg Roll (chuck)</td>
<td>$1.70</td>
</tr>
<tr>
<td>Egg Rolls</td>
<td>$1.70</td>
</tr>
<tr>
<td>Fried Wonton</td>
<td>$1.70</td>
</tr>
<tr>
<td>Roast Pork Egg</td>
<td>$1.70</td>
</tr>
<tr>
<td>Bar-B-Q Spare Ribs</td>
<td>$1.70</td>
</tr>
<tr>
<td>Beef &amp; Green Eggs</td>
<td>$1.70</td>
</tr>
<tr>
<td>Beef &amp; Pepper &amp; Sauce</td>
<td>$1.70</td>
</tr>
<tr>
<td>Beef &amp; Chinese Vegetable</td>
<td>$1.70</td>
</tr>
<tr>
<td>Shrimp &amp; fried Vegetable Dumpling</td>
<td>$1.70</td>
</tr>
<tr>
<td>Fried Chicken Wings</td>
<td>$1.70</td>
</tr>
<tr>
<td>Fried Shrimp</td>
<td>$1.70</td>
</tr>
<tr>
<td>Sesame Oil Noodles</td>
<td>$1.70</td>
</tr>
<tr>
<td>Spring Rolls</td>
<td>$1.70</td>
</tr>
</tbody>
</table>

### FRIED RICE

<table>
<thead>
<tr>
<th>Item</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vegetable Fried Rice</td>
<td>$1.70</td>
</tr>
<tr>
<td>Roast Pork Fried Rice</td>
<td>$1.70</td>
</tr>
<tr>
<td>Beef Fried Rice</td>
<td>$1.70</td>
</tr>
<tr>
<td>Shrimp Fried Rice</td>
<td>$1.70</td>
</tr>
<tr>
<td>Chicken Fried Rice</td>
<td>$1.70</td>
</tr>
<tr>
<td>Lobster Fried Rice</td>
<td>$1.70</td>
</tr>
</tbody>
</table>

### LO MEIN

<table>
<thead>
<tr>
<th>Item</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>vegetable Lo Mein</td>
<td>$1.70</td>
</tr>
<tr>
<td>Roast Pork Lo Mein</td>
<td>$1.70</td>
</tr>
<tr>
<td>Beef Lo Mein</td>
<td>$1.70</td>
</tr>
<tr>
<td>Shrimp Lo Mein</td>
<td>$1.70</td>
</tr>
<tr>
<td>House Special Lo Mein</td>
<td>$1.70</td>
</tr>
<tr>
<td>Lobster Lo Mein</td>
<td>$1.70</td>
</tr>
</tbody>
</table>

### CHOW MEIN (with Rice & Noodles)

<table>
<thead>
<tr>
<th>Item</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vegetable Chow Mein</td>
<td>$1.70</td>
</tr>
<tr>
<td>Roast Pork Chow Mein</td>
<td>$1.70</td>
</tr>
<tr>
<td>Beef Chow Mein</td>
<td>$1.70</td>
</tr>
<tr>
<td>Chicken Chow Mein</td>
<td>$1.70</td>
</tr>
<tr>
<td>Plain Broccoli</td>
<td>$1.70</td>
</tr>
<tr>
<td>Chicken &amp; Green Vegetables</td>
<td>$1.70</td>
</tr>
<tr>
<td>Roast Pork Chow Mein</td>
<td>$1.70</td>
</tr>
<tr>
<td>Lobster Chow Mein</td>
<td>$1.70</td>
</tr>
<tr>
<td>Chicken &amp; Green Vegetables</td>
<td>$1.70</td>
</tr>
<tr>
<td>Shrimp &amp; Chinese Vegetable</td>
<td>$1.70</td>
</tr>
<tr>
<td>Roast Pork Chow Mein</td>
<td>$1.70</td>
</tr>
<tr>
<td>Lobster Chow Mein</td>
<td>$1.70</td>
</tr>
</tbody>
</table>

### HAPPY FAMILY

<table>
<thead>
<tr>
<th>Item</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>BBQ Pork &amp; Green Peppers</td>
<td>$1.70</td>
</tr>
</tbody>
</table>

### SPECIAL PRICE FOR LUNCH

Served with Roast Pork Fried Rice

$4.25, 11:30 a.m. to 2:30 p.m.

### NEW LUNCH SPECIAL

Served with Roast Pork Fried Rice

<table>
<thead>
<tr>
<th>Item</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orange Chicken</td>
<td>$4.05</td>
</tr>
<tr>
<td>Sesame Chicken</td>
<td>$4.05</td>
</tr>
<tr>
<td>Honey Cheese Chicken</td>
<td>$4.05</td>
</tr>
<tr>
<td>Roast Pork Egg Foo Young</td>
<td>$4.05</td>
</tr>
<tr>
<td>Peas &amp; Egg Foo Young</td>
<td>$4.05</td>
</tr>
<tr>
<td>Beef &amp; Chinese Vegetable</td>
<td>$4.05</td>
</tr>
<tr>
<td>Shrimp &amp; fried Vegetable Dumpling</td>
<td>$4.05</td>
</tr>
<tr>
<td>Beef &amp; Green Eggs</td>
<td>$4.05</td>
</tr>
<tr>
<td>Beef &amp; Pepper &amp; Sauce</td>
<td>$4.05</td>
</tr>
<tr>
<td>Beef &amp; Chinese Vegetable</td>
<td>$4.05</td>
</tr>
<tr>
<td>Shrimp &amp; fried Vegetable Dumpling</td>
<td>$4.05</td>
</tr>
<tr>
<td>Beef &amp; Chinese Vegetable</td>
<td>$4.05</td>
</tr>
<tr>
<td>Shrimp &amp; fried Vegetable Dumpling</td>
<td>$4.05</td>
</tr>
</tbody>
</table>

### SIDE ORDER

<table>
<thead>
<tr>
<th>Item</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fried Noodles</td>
<td>$0.30</td>
</tr>
<tr>
<td>Fried Chicken</td>
<td>$0.30</td>
</tr>
<tr>
<td>Beef Chow Mein</td>
<td>$0.30</td>
</tr>
<tr>
<td>Shrimp &amp; Sour Pork or Chicken</td>
<td>$0.30</td>
</tr>
</tbody>
</table>

### HOT & SOUR (with Rice) Order

<table>
<thead>
<tr>
<th>Item</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweet &amp; Sour Pork</td>
<td>$1.50</td>
</tr>
<tr>
<td>Sweet &amp; Sour Beef</td>
<td>$1.50</td>
</tr>
<tr>
<td>Sweet &amp; Sour Wonton</td>
<td>$1.50</td>
</tr>
</tbody>
</table>

### SWEET & SOUR

<table>
<thead>
<tr>
<th>Item</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pork Chow Fun</td>
<td>$1.50</td>
</tr>
<tr>
<td>Beef Chow Fun</td>
<td>$1.50</td>
</tr>
<tr>
<td>Shrimp Chow Fun</td>
<td>$1.50</td>
</tr>
</tbody>
</table>

### SPECIAL COMBINATION PLATES

Served with Roast Pork Fried Rice

<table>
<thead>
<tr>
<th>Item</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orange Chicken</td>
<td>$4.05</td>
</tr>
<tr>
<td>Sesame Chicken</td>
<td>$4.05</td>
</tr>
<tr>
<td>Honey Cheese Chicken</td>
<td>$4.05</td>
</tr>
<tr>
<td>Roast Pork Egg Foo Young</td>
<td>$4.05</td>
</tr>
<tr>
<td>Peas &amp; Egg Foo Young</td>
<td>$4.05</td>
</tr>
<tr>
<td>Beef &amp; Chinese Vegetable</td>
<td>$4.05</td>
</tr>
<tr>
<td>Shrimp &amp; fried Vegetable Dumpling</td>
<td>$4.05</td>
</tr>
<tr>
<td>Beef &amp; Green Eggs</td>
<td>$4.05</td>
</tr>
<tr>
<td>Beef &amp; Pepper &amp; Sauce</td>
<td>$4.05</td>
</tr>
<tr>
<td>Beef &amp; Chinese Vegetable</td>
<td>$4.05</td>
</tr>
<tr>
<td>Shrimp &amp; fried Vegetable Dumpling</td>
<td>$4.05</td>
</tr>
<tr>
<td>Beef &amp; Chinese Vegetable</td>
<td>$4.05</td>
</tr>
<tr>
<td>Shrimp &amp; fried Vegetable Dumpling</td>
<td>$4.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Item</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fried Chicken</td>
<td>$0.30</td>
</tr>
<tr>
<td>Beef Chow Mein</td>
<td>$0.30</td>
</tr>
<tr>
<td>Shrimp &amp; Sour Pork or Chicken</td>
<td>$0.30</td>
</tr>
</tbody>
</table>

### DIET FOOD

<table>
<thead>
<tr>
<th>Item</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed Vegetable</td>
<td>$0.25</td>
</tr>
<tr>
<td>Mixed Vegetable</td>
<td>$0.25</td>
</tr>
</tbody>
</table>

### TEAM MEDEICINE

**MT 0967**
Table 3. Commonly Used Formulations of Drugs for COPD

<table>
<thead>
<tr>
<th>β₂-agonists</th>
<th>Anticholinergics</th>
<th>Glucocorticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting</td>
<td>Short-acting</td>
<td>Inhaled</td>
</tr>
<tr>
<td>- Salbutamol</td>
<td>- Ipratropium bromide</td>
<td>- Beclomethasone</td>
</tr>
<tr>
<td>- Terbutaline</td>
<td>- Long-acting</td>
<td>- Budesonide</td>
</tr>
<tr>
<td>Long-acting</td>
<td>- Tiotropium</td>
<td>- Fluticasone</td>
</tr>
<tr>
<td>- Formoterol</td>
<td></td>
<td>- Triamcinolone</td>
</tr>
<tr>
<td>- Salmeterol</td>
<td></td>
<td>Systemic</td>
</tr>
<tr>
<td>- Arformoterol tartrate</td>
<td></td>
<td>- Predisone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Methylprednisone</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Combination β₂-agonists/Anticholinergics</th>
<th>Combination β₂-agonists/Grucocorticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salbutamol/ipratropium</td>
<td>Salmeterol/fluticasone</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Methylxanthines
- Aminophylline
- Theophylline

ATS/ERS Algorithm for Pharmacologic Treatment in COPD

Confirm Dx of COPD

Intermittent Sx (cough, wheeze, dyspnea)

SA-BD p.r.n.

Persistent Sx (dyspnea, pm awakenings)

LA-BD/SA-BD q.i.d. with rescue

Limited Benefit?

Yes

Alternative class/combination (LA-BD/ICS)

Limited Benefit? AE?

Yes

Add/substitute oral theophylline

ICS: inhaled corticosteroid
LA-BD: long-acting bronchodilator
SA-BD: short-acting bronchodilator


© 2012 Virginia Mason Medical Center
Which is best?

- Tio vs Fp/Sal: all things being equal Tio
- Improved Fev1, symptoms
- Inspire = equivalent, ? Mortality, pneumonia
- Personalize
- ?Indacaterol
Combination

- Tio + LABA $\geq$ Tio
- LABA + Tio $>$ LABA + ICS
- ICS + LABA $>$ separate

- Triple inhaler therapy
  - LABA + ICS + Tio $>$ LABA + ICS
  - LABA + ICS + Tio $>$ Tio
Risks

- Tremor
- Hypokalemia
- Tachycardia (vasodilation)
- Desensitization
- Glaucoma
- Urinary retention
- Other
### Therapy at Each Stage of COPD

<table>
<thead>
<tr>
<th>Stage</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁/FVC</td>
<td>&lt; 70%</td>
<td>&lt; 70%</td>
<td>&lt; 70%</td>
<td>&lt; 70%</td>
</tr>
<tr>
<td>FEV₁</td>
<td>≥ 80% predicted</td>
<td>50% ≤ FEV₁ &lt; 80% predicted</td>
<td>30% ≤ FEV₁ &lt; 50% predicted</td>
<td>FEV₁ &lt; 30% predicted or FEV₁ &lt; 50% predicted plus chronic respiratory failure</td>
</tr>
</tbody>
</table>

**I: Mild**

- Active reduction of risk factor(s); influenza vaccination

**II: Moderate**

- Add regular treatment with one or more long-acting bronchodilators (when needed);
- Add rehabilitation

**III: Severe**

- Add inhaled glucocorticosteroids if repeated exacerbations

**IV: Very Severe**

- Add long term oxygen if chronic respiratory failure.
- Consider surgical treatments
**ABSTRACT**

**BACKGROUND**

Previous studies showing that tiotropium improves multiple end points in patients with chronic obstructive pulmonary disease (COPD) led us to examine the long-term effects of tiotropium therapy.

**METHODS**

In this randomized, double-blind trial, we compared 4 years of therapy with either tiotropium or placebo in patients with COPD who were permitted to use all respiratory medications and to adjust tiotropium doses as needed. From the David Geffen School of Medicine at the University of California, Los Angeles (D.P.T.); Caritas St. Elizabeth’s Medical Center, Boston (B.C.); Glasgow University, Glasgow, Scotland (S.S.); Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT (D.B., S.K., S.M.); and the University of Leuven, Leuven, Belgium (M.D.). Address reprint requests to Dr.

**UPLIFT: Understanding Potential Long-Term Impacts on Function with Tiotropium**

- 5993 patients, 4 years, FEV1 <70%, mean 48%
Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease

Peter M.A. Caiverly, M.D., Julie A. Anderson, M.A., Bartolome Celli, M.D., Gary T. Ferguson, M.D., Christine Jenkins, M.D., Paul W. Jones, M.D., Julie C. Yates, B.S., Jørgen Vestbo, M.D., for the TORCH investigators

TORCH: Towards a Revolution in COPD Health

6112 patients, 42 countries, 444 centers
3 years
FEV1 <60% mean 44%
Inhaler Devices

• Up to 75% errors with use
• CFC-free propellants (HFA) feel and taste different
• 10/80 rule (can reduce 10 fold with spacer)
• Actuation-inhalation coordination
• Observe, teach, practice
• Priming, creaming, determining when out
Management of Stable COPD

Other Pharmacologic Treatments

- **Antibiotics**: Only used to treat infectious exacerbations of COPD???

- **Antioxidant agents**: No effect of n-acetylcysteine on frequency of exacerbations, sputum volume, or airflow (bronchoconstriction)

- **Mucolytic agents, Antitussives, Vasodilators**: Not recommended in stable COPD

- **Nutrition**: 30% (severe) malnourished, but?
Management of Stable COPD

Non-Pharmacologic Treatments

- **Rehabilitation**: All COPD patients benefit from exercise training programs, improving with respect to both exercise tolerance and symptoms of dyspnea and fatigue (Evidence A).

- **Oxygen Therapy**: The long-term administration of oxygen (> 15 hours per day) to patients with chronic respiratory failure has been shown to increase survival (Evidence A).
What does Pulmonary Rehabilitation Involve?

- Evaluation
- Education
  - COPD causes and pathology
  - Medications, and rescue therapy
- Breathing exercises
- Endurance and resistance training
- Nutrition
- Stress and anxiety management
Do home based programs work?

- Randomized controlled trial in Canada
- Trained case manager
- **Living Well with COPD** program
- 8 individual sessions to develop skills to manage COPD symptoms daily
- Home exercise program 3 times/week
- Monthly phone follow up
- Decreased hospitalizations at 1&2 yrs

Long-term Oxygen for COPD
NOTT Trial

Survival proportion

Months on study

O₂ - 18 hours/day

O₂ - 12 hours/day

P = 0.01

Long-term Oxygen for COPD
Downside

- Restricted mobility
- Sense of invalidism
- Nasal drying, irritation, bleeding
- Cost
  - Estimated 800,000 patients in USA
  - Estimated annual cost $1.8 billion in USA
COPD EXACERBATIONS

• COPD exacerbations defined:

“An event in the natural course of the disease characterized by a change in the patient’s baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD.”
Manage COPD Exacerbations

Key Points

- Inhaled bronchodilators (particularly inhaled $\beta_2$-agonists with or without anticholinergics) and oral glucocorticosteroids are effective treatments for exacerbations of COPD (Evidence A).
Antibiotics in Exacerbations

• Moderate to severe: 2/3 (dyspnea, sputum volume or purulence), or hospitalization
• No benefit of sputum culture
• Generally generic: doxy, tmp/smz, not amox
• Broader for sicker or at > risk
• Duration: 3-7 days
• No overall benefit to prophylactic use?
Management COPD Exacerbations

Key Points

- Noninvasive mechanical ventilation in exacerbations improves respiratory acidosis, increases pH, decreases the need for endotracheal intubation, and reduces PaCO$_2$, respiratory rate, severity of breathlessness, the length of hospital stay, and mortality (Evidence A).

- Medications and education to help prevent future exacerbations should be considered as part of follow-up, as exacerbations affect the quality of life and prognosis of patients with COPD.
Pulmonary Embolism in “Unexplained” AECOPD

- Spiral CT and US
  - 211 pts with AECOPD
    - Not requiring mechanical ventilation
    - No acute bronchitis
    - Disparity between CXR and ABG’s
  - 49/197 (25%) positive for PE
    - 43 by CT (19 pos US)
    - 6 by US
- Associations:
  - Prior PE, malignancy, drop of 5 mmHg CO₂

COPD: Novel Therapies

- Macrolides!!!
- Long-acting anticholinergics
- Long-acting corticosteroids
- PDE-4 inhibitors
- Leukotriene modifiers
- TNF-alpha blockers
- Anti-interleukin-8 kinase
- Antiproteases
Phosphodiesterase-4 inhibitors

Roflumilast: improved FEV1, dec exacerbations alone or in combination with LABA

Cilomilast: improved FEV1, dyspnea scores, dec exacerbations

**magnitude is modest, unclear if added benefit to standard therapy

Lung Volume Reduction

• Surgical
  - NETT: Improves health status, exercise capacity, and survival in a selected group
  - 4 year f/u confirms prior results

• Bronchoscopic
  - Multiple one-way valves
  - 11% FEV1 improvement, 23% improvement in walk distance
  - Improved QOL
ASTHMA
Definition of Asthma

- A chronic inflammatory disorder of the airways
- Many cells and cellular elements play a role
- Chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing
- Widespread, variable, and often reversible airflow limitation
Asthma Inflammation: Cells and Mediators

- Allergen
  - Macrophage/Dendritic cell
  - Th2 cell
  - Mast cell
  - Neutrophil
  - Eosinophil

- Mucus plug
- Nerve activation
- Epithelial shedding
- Plasma leak
- Edema
- New vessels (angiogenesis)
- Subepithelial fibrosis

- Sensory nerve activation
- Cholinergic reflex
- Bronchoconstriction
- Hypertrophy/hyperplasia

Airway smooth muscle

Source: Peter J. Barnes, MD
Pathogenesis
Fig. 14.34 Inflammatory and remodelling responses in asthma with activation of the epithelial mesenchymal trophic unit. Epithelial damage alters the set point for communication between bronchial epithelium and underlying mesenchymal cells, leading to myofibroblast activation, an increase in mesenchymal volume, and induction of structural changes throughout airway wall. Adapted from Holgate ST, Polosa R. The mechanisms, diagnosis, and management of severe asthma in adults. Lancet 2006; 368: 780–793 with permission from Elsevier.
ASTHMA: COMPLEX, HETEROGENOUS DISEASE

CHEST 2011; 139; 640-647
Asthma Overview: Prevalence, Morbidity and Mortality

- 24.6 million People diagnosed with asthma
- 12.8 million People experience asthma attacks
- 1.8 million Emergency room visits
- 456,000 Hospitalizations
- 3,447 Asthma-related deaths

TOTAL COST ~6 billion dollars

Approximately 9 People Die From Asthma Each Day in the U.S.

Annual incidence, based on 2007 data

Asthma in Washington

- 400,000 adults (9%), 120,000 children (7-10% of HS; 1/10 households)
- 1/10 women, 1/14 men (69%)
- 100 deaths, 5,000 hospitalizations
- Cost: 240 million, 400 million
- 75% symptomatic this past month
- Native Americans, low income, inhalents
Is it Asthma?

- Recurrent episodes of wheezing
- Troublesome cough at night
- Cough or wheeze after exercise
- Cough, wheeze or chest tightness after exposure to airborne allergens or pollutants
- Colds “go to the chest” or take more than 10 days to clear
Definition and Diagnosis of Asthma

• John Floyer, 1698 defined asthma as:
  ▪ “laborious respiration with lifting of the shoulders and wheeze”

• He understood that it was intermittent and episodic and treatment needed to consistent of both rescue and controller therapy
  ▪ “both in fit and out of it”
Asthma Diagnosis

- History and patterns of symptoms
- Measurements of lung function
  - Spirometry
  - Peak expiratory flow
- Measurement of airway responsiveness
- Measurements of allergic status to identify risk factors
- Extra measures may be required to diagnose asthma in children 5 years and younger and the elderly

• Episodic sx of airflow obstruction or airway hyperresponsiveness
  ▪ Obstruction partially reversible
  ▪ Alternative dx excluded

• Methods to establish dx:
  ▪ Detailed hx, PE
  ▪ Spirometry to demonstrate reversibility
    • “although asthma is typically associated with an obstructive impairment that is reversible, neither this finding nor any other single test is adequate to diagnose asthma”
Typical Spirometric (FEV\textsubscript{1}) Tracings

Note: Each FEV\textsubscript{1} curve represents the highest of three repeat measurements.
Measuring Variability of Peak Expiratory Flow
Measuring Airway Responsiveness

Histogram (mg/ml)
Methacholine (mg/ml)

% Fall in FEV

PC_{20}

Normal

Mild AHR

Moderate AHR

Severe AHR
Diagnostic accuracy of spirometry

- 219 adult patient c/o obstructive lung disease
- Sensitivity for diagnosing airflow obstruction in asthmatics 29%, specificity 90%; + PV 77%, neg PV 53%
Fraction of exhaled Nitric Oxide (Fено) in the Dx of Asthma

• Fено felt to reflect airway inflammation
• Non-invasive, can be quantitated
• Cochrane meta-analysis of 6 studies concluded that benefit of a Fено-based approach to guide treatment was modest at best
Feno: Role in ID a severe asthma phenotype?

- Patients with asthma and increased Feno
  - Greater airway reactivity
  - Increased sputum eosinophils
  - More evidence of atopy
  - More pulmonary hyperinflation
  - Decreased awareness of their sx
  - Persistently high levels, most frequent use of emergency care

Dweik et al  Am J Respir Crit Care Med 2010; 181:1033
Asthma Treatment

• General approach to treatment described in Stedman’s “Twentieth Century Practice” published in 1896:

  The treatment of asthma involves the treatment during fits and between fits. The general indications are:

  1. To allay the spasm during the paroxysm
  2. To find out and remove the exciting cause…
  3. To treat complications and sequelae and to improve the general health”
TREATMENT 1990

- Asthma medication and equipment from 1990.
- Graphs showing the use of cortisone and ACTH in 1950 and 1951.
- Aerosol steroid dosage comparisons.
Asthma Management and Prevention Program

Goals of Long-term Management

- Achieve and maintain control of symptoms
- Maintain normal activity levels, including exercise
- Maintain pulmonary function as close to normal levels as possible
- Prevent asthma exacerbations
- Avoid adverse effects from asthma medications
- Prevent asthma mortality

© 2012 Virginia Mason Medical Center
# Levels of Asthma Control

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controlled</th>
<th>Partly controlled (Any present in any week)</th>
<th>Uncontrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime symptoms</td>
<td>None (2 or less / week)</td>
<td>More than twice / week</td>
<td>3 or more features of partly controlled asthma present in any week</td>
</tr>
<tr>
<td>Limitations of activities</td>
<td>None</td>
<td>Any</td>
<td></td>
</tr>
<tr>
<td>Nocturnal symptoms / awakening</td>
<td>None</td>
<td>Any</td>
<td></td>
</tr>
<tr>
<td>Need for rescue / “reliever” treatment</td>
<td>None (2 or less / week)</td>
<td>More than twice / week</td>
<td></td>
</tr>
<tr>
<td>Lung function (PEF or FEV$_1$)</td>
<td>Normal</td>
<td>&lt; 80% predicted or personal best (if known) on any day</td>
<td></td>
</tr>
<tr>
<td>Exacerbation</td>
<td>None</td>
<td>One or more / year</td>
<td>1 in any week</td>
</tr>
</tbody>
</table>
Component 4: Asthma Management and Prevention Program

Controller Medications

- Inhaled glucocorticosteroids
- Leukotriene modifiers
- Long-acting inhaled $\beta_2$-agonists
- Systemic glucocorticosteroids
- Theophylline
- Cromones
- Long-acting oral $\beta_2$-agonists
- Anti-IgE
- Systemic glucocorticosteroids
## Treatment Steps

<table>
<thead>
<tr>
<th>Step</th>
<th>Controller Options</th>
<th>Select One</th>
<th>Select One</th>
<th>Add One or More</th>
<th>Add One or Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>as needed rapid-acting $\beta_2$-agonist</td>
<td>low-dose ICS*</td>
<td>low-dose ICS plus long-acting $\beta_2$-agonist</td>
<td>medium- or high-dose ICS plus long-acting $\beta_2$-agonist</td>
<td>oral glucocorticosteroid (lowest dose)</td>
</tr>
<tr>
<td>2</td>
<td>leukotriene modifier**</td>
<td>medium- or high-dose ICS</td>
<td>leukotriene modifier</td>
<td>anti-IgE treatment</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>low-dose ICS plus leukotriene modifier</td>
<td>sustained-release theophylline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>low-dose ICS plus sustained-release theophylline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Inhaled glucocorticosteroids
**Receptor antagonist or synthesis inhibitors
Treatment

**Interruption Asthma**
- **Preferred:** SABA PRN
- **Alternative:** Cromolyn, LTRA, Nedocromil, or Theophylline

**Step 1**
- **Preferred:** Low-dose ICS
- **Alternative:** Medium-dose ICS

**Step 2**
- **Preferred:** Medium-dose ICS + LABA
- **Alternative:** Low-dose ICS + LABA

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

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

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

**Step 6**
- **Step up if needed**
  - (first, check adherence, environmental control, and comorbid conditions)
  - Assess control
  - **Step down if possible**
    - (and asthma is well controlled at least 3 months)

Each step: Patient education, environmental control, and management of comorbidities.

Steps 2–4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes).

*Quick-Relief Medication for All Patients*

- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.
Severe Asthma

• Refractory
• Poorly controlled
• Resistant
• Uncontrolled
• Brittle
• Steroid resistant
Definition

• “I shall not today attempt further to define the kinds of material I understand to be embraced within that shorthand description and perhaps I could never succeed in intelligibly doing so. But I know it when I see it....”

Justice Potter Stewart, Jacobellis vs Ohio, 1964
Severe Asthma—ATS/SARP

Major criteria
To achieve control to level of mild-moderate persistent asthma:
1. Treatment with continuous or near continuous (≥50 percent of year) oral glucocorticoids
2. Treatment with high-dose inhaled glucocorticoids:
   - Beclomethasone >1260 mcg/day
   - Budesonide >1200 mcg/day
   - Fluticasone >880 mcg/day

Minor criteria
1. Requirement for additional daily treatment with a controller medication, eg, long-acting β-agonist, theophylline, or leukotriene antagonist
2. Asthma symptoms requiring short-acting β-agonist use on a daily or near daily basis
3. Persistent airflow limitation (FEV1 <80 percent predicted; diurnal peak expiratory flow variability >20 percent)
4. One or more urgent care visits for asthma per year
5. Three or more oral glucocorticoid bursts per year
6. Prompt deterioration with ≤25 percent reduction in oral or inhaled glucocorticoid dose
7. Near-fatal asthma event in the past
Severe Asthma Epidemiology

- 5-10% of asthmatics
  - Leading cause of hospitalization in Canada
- Ethnic variations (52% of NA asthmatics)
- Increased risk of dying (SMR 865%)
- Increased health care costs $2500 vs $140
- Female, obese
- Adult onset (more rapid decline of FEV1)
- Heterogenous

Eur Resp J 2003;22:479
CLUSTER ANALYSIS AND CLINICAL ASTHMA PHENOTYPES

CLUSTER ANALYSIS: 5 CLUSTERS

<table>
<thead>
<tr>
<th>Cluster 1 n=110</th>
<th>Cluster 2 n=321</th>
<th>Cluster 3 n=59</th>
<th>Cluster 4 n=120</th>
<th>Cluster 5 n=116</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Corticosteroid Use (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>None</td>
<td>45%</td>
<td>31%</td>
<td>14%</td>
<td>15%</td>
<td>5%</td>
</tr>
<tr>
<td>Low-moderate dose ICS</td>
<td>38%</td>
<td>40%</td>
<td>37%</td>
<td>18%</td>
<td>16%</td>
</tr>
<tr>
<td>High dose ICS*</td>
<td>10%</td>
<td>28%</td>
<td>49%</td>
<td>63%</td>
<td>78%</td>
</tr>
<tr>
<td>Oral or Systemic CS**</td>
<td>11%</td>
<td>10%</td>
<td>17%</td>
<td>39%</td>
<td>47%</td>
</tr>
<tr>
<td><strong>Total Controllers(%)†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>None</td>
<td>41%</td>
<td>26%</td>
<td>10%</td>
<td>12%</td>
<td>4%</td>
</tr>
<tr>
<td>≤ 2</td>
<td>41%</td>
<td>46%</td>
<td>35%</td>
<td>33%</td>
<td>28%</td>
</tr>
<tr>
<td>≥ 3</td>
<td>19%</td>
<td>29%</td>
<td>54%</td>
<td>56%</td>
<td>67%</td>
</tr>
<tr>
<td><strong>Health Care Utilization Pst Yr†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>None</td>
<td>67%</td>
<td>61%</td>
<td>41%</td>
<td>38%</td>
<td>32%</td>
</tr>
<tr>
<td>≥ 1 Urgent Visit and/or ED</td>
<td>20%</td>
<td>25%</td>
<td>34%</td>
<td>39%</td>
<td>42%</td>
</tr>
<tr>
<td>≥ 3 Oral CS burst/yr</td>
<td>11%</td>
<td>19%</td>
<td>36%</td>
<td>46%</td>
<td>42%</td>
</tr>
</tbody>
</table>
| Hospitalization | 7%              | 9%             | 15%             | 23%             | 28%     

Severe Asthma Research Program; ACRCCM 2010; 181:315
The Asthma Syndrome
Symptoms of asthma, variable airflow obstruction

Asthma phenotype characteristics
Observable characteristic with no direct relationship to a disease process. Includes physiology, triggers, inflammatory parameters

Asthma Endotypes
Distinct disease entities which may be present in clusters of phenotypes, but each defined by a specific biological mechanism

Endotype 1 | Endotype 2 | Endotype 3 | Endotype 4 | Endotype 5

Source: Journal of Allergy and Clinical Immunology 2011; 127:355-360 (DOI:10.1016/j.jaci.2010.11.037)
Phenotypes

• Early vs late onset
  • 2/3 early, atopic, exzema, FH
  • FEV1 worse in late, heterogenous

• Persistent Airway eosinophilia 50-60%
  • Lower FEV1, inc near-fatal events
  • Inc TGF-B, thicker SBM

• Neutrophillic (w/ or w/o eos)

• Pauci-inflammatory

• Poor steroid responsiveness (MAPK)

*Jaci 2004;113:101
AJRCCM 2005;172:149
Severe Asthma Evaluation

• Is it really asthma?
• Are you really taking your meds?
• Are you taking enough?
• What is making it worse?
Severe Asthma Evaluation

• Confirm that the disease is asthma (12%)
  • PFTs, blood tests, HRCT, laryngoscopy
• ? exacerbating factors/comorbidities
  • pH probe, sinus CT, IgE, skin test, PSG, Am cortisol, persistent exposure
• Evaluate phenotype
  • Age of onset
  • Allergic sensitivity, respiratory infection relation
  • Aspirin sensitivity
  • Sputum analysis, exhaled nitric oxide
  • Bronchoscopy

Eur Resp J 2003;22:479
CT findings in severe asthma

- Right upper lobe apical wall thickening correlation with BM thickening and airflow limitation
- Airway wall remodeling can quantify response to therapy
- Assessment needs to be standardized
- Air trapping/heterogeneity of lung attenuation on exhalation correlates with lung function, hospitalization, duration

Thorax 2010;65:775. CHEST 2009;135:48
Non-adherence

• Median adherence of ICS in mod-severe asthmatics was 40%
  • 2-4 ICS cannisters/year across all severities
• 50% of severe asthmatics on 15mg of prednisolone daily had non-detectable levels or normal cortisol levels
• Respond if confronted with objective measurements
  • Rx refill records, urinary cortisol levels

NEJM 2011;364:1695
Eur Resp J 2003;22:479
Mimics

• Vocal Cord dysfunction
• Central Airway dysfunction
• COPD
• Bronchiectasis (ABPA)
• Bronchiolitis
• Hypersensitivity pneumonitis
• Hypereosinophillic syndromes (CEP)
• Churg-Strauss syndrome
• Sarcoidosis
• Cardiac disease
Vocal Cord Dysfunction

- 1951 - the lying patient
- 1983 National Jewish description
- Many triggers (exercise, gerd, sinus, irrit, meds)
- 20-40yo, female*
- Co-occurs with asthma 40%
- Generally inhalation symptoms*
- “chinking” of the cords
VCD Treatment

• Acute: breathing exercise, heliox, CPAP

• Chronic:
  ▪ Speech therapy
  ▪ Botox
  ▪ Treat underlying conditions
  ▪ Removing triggers
  ▪ Inhaled ipratropium
  ▪ Tracheostomy
Central Airway Obstruction
Bronchiectasis

- Prevalent in severe asthma (40%)
- Associated with longer duration poorer lung function
- Unclear if a comorbidity or represents a structural change
- Daily productive cough, dyspnea, hemoptysis, classic CT findings
- Distribution can be helpful
Bronchiectasis Etiologies

- Infections (aspiration)
- PCD
- Cystic Fibrosis
- Alpha-1 antitrypsin deficiency
- RA and Sjogren’s
- Young’s syndrome
- Immunosuppression
- ABPA
ABPA

- Asthma
- Skin test reactivity to aspergillus antigens
- Aspergillus precipitants positive
- Elevated IgE (>1000 ng/ml)
- Elevated IgE and IgG to A. fumigatus
- Central bronchiectasis
- eosinophilia
Severe Asthma Treatment

- Optimizing bronchodilation
- Reducing airway smooth muscle reactivity
- Reducing inflammatory cell number and/or function
- Targeting specific airway effector mediators
Treatment
Early Onset atopic asthma

• IgE dependent mechanism
• Omalizumab reduces frequency and occurrence of exacerbations, dec steroids
• Lebrikizumab (anti-IL 13) improves lung function in some patients with periostin
• Fluconazole, itraconazole in specific patients sensitized to fungus (ABPA-like)

AJRCCM 2011;183:1007
NEJM 2006;354:2689, NEJM 2011;365:1088
Late onset non-atopic asthma

- Rhinosinusitis/nasal polyposis +/- asa sensitivity
- Medical/surgical treatment of sinuses
- LRA’s/5-LPI’s in asa sensitive
- Airway eosinophilia is marker of disease
- Prone to distal airway trapping, more severe
- Steroids
- ? Theophylline to potentiate steroids
- Mepolizumab (anti-IL-5) reduces eosinophils, exacerbations, improves symptoms, and QOL

NEJM 2009:360:973
Late onset obese female

- Increasing prevalence
- Pro-inflammatory effects of adipose
- Co-morbidities (OSA, GERD)
- Weight reduction, gastric surgery
- CPAP
- ?PPI—mixed results, treat only if GERD
Neutrophilic asthma

- dec eos, inc pmn’s, inc IL-8 in airways
- Less small airways involvement
- Older, chronic persistent airflow limitation
- ICS have limited efficacy
- ? Associated with C. and M. pneumoniae
- ? Macrolides dec IL-8, improve symptoms

Clin Exp All 2012;42:693
Treatment
Outpatient

Controller (ICS/LABA)
Steroids
Antileukotrienes
5-lipoxygenase inhibitors
Macrolides
Omalizumab, Imitinib, mepolizumab, reslizumab
Approaches to immunosuppression in hard to treat asthma

- Blockade of IgE
  - Omalizumab
- Targeting the Th2 pathway
  - Monoclonals against CD4, CD25, CCR4, CTLA4, OX40L
- Targeting the IL-4/IL-13 pathway
- Targeting Eosinophils
  - Anti-IL5
- Anti-IL9, TNF-alpha
Bronchial thermoplasty

- A procedure that delivers thermal (RF) energy to the airways via a bronchoscope reduce excess airway smooth muscle and limit its ability to constrict the airways
- 65 degrees for 10 seconds in lobar and segmental airways
- 3 separate treatment sessions 3 weeks apart (RLL, LLL, bilateral UL)
Application of RF Energy

- Temperature controlled heat ($65^0 \text{C}$) is delivered to airway wall for 10 seconds per activation – no permanent damage to epithelium
Reduced Airway Smooth Muscle

- 3 years post-treatment (canine model)

Masson’s Trichrome stain
Airway Responsiveness to Local Methacholine Challenge

Canine Model: Airway on left treated with bronchial thermoplasty. Airway on right was not treated.

Clinical Outcomes: Bronchial Thermoplasty Clinical Studies

- Over 800 Procedures Performed
- 3 Randomized Controlled Studies
- Over 10 Publications

Pivotal Study
AIR2: n=190 treated patients at 30 sites
(Castro, AJRCCM, 2010)¹
(Castro, AAAI, 2011)⁵

RISA: n=15
(Pavord, AJRCCM, 2007)²

AIR: n=55
(Cox, NEJM, 2007)³

Feasibility: n=16
(Cox, AJRCCM, 2006)⁴

AIR = Asthma Intervention Research Study
RISA = Research in Severe Asthma Study

© 2012 Virginia Mason Medical Center
AIR2 Trial

- Multicenter (30) RDB-Sham controlled trial
- 297 pts, 2:1 randomization
- Severe persistent asthma (ICS + LABA)
- 3,6,9,12 mo follow-up
- Primary outcome: AQLQ score
- Secondary: PEF, symptom free days, rescue medication use, FEV1
AQLQ

A

Average Score *

5.80

BT
(N=173)

5.68

5.71

5.71

5.40

5.49

5.48

5.56

3 Mon 6 Mon 9 Mon 12 Mon

AQLQ Score

B

**

Sham
(N=95)

80.9

63.2

16.2

29.5

7.4

0 10 20 30 40 50 60 70 80 90 100

Percent of Subjects

Change from Baseline in Average AQLQ Score

≤ - 0.5 > - 0.5 to < 0.5 ≥ 0.5
Health Care Utilization for Respiratory Symptoms During Post-Treatment Period

- 6 weeks after the last bronchoscopy procedure to 12 month follow-up

* Posterior Probability of Superiority = 95.6%
** Posterior Probability of Superiority = 99.9%

Events / Subject/ Year

- Severe Exacerbations (Steroid): 0.7 (35% decrease over Sham)
- Unscheduled Physician Office Visits: 0.36 (22% decrease over Sham)
- Emergency Room Visits: 0.43 (84% decrease over Sham)
- Hospitalizations: 0.13 (73% decrease over Sham)


© 2012 Virginia Mason Medical Center
Risk of Respiratory-Related Hospitalization Following Procedure¹

<table>
<thead>
<tr>
<th>Respiratory-Related Hospitalizations during Treatment Periodᵃ</th>
<th>BT (N=190)</th>
<th>Sham (N=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events / Subject (%)</td>
<td>19/190 (10%)*</td>
<td>2/98 (2.0%)</td>
</tr>
<tr>
<td>Events / Bronchoscopy (%)</td>
<td>19/558 (3.4%)</td>
<td>2/292 (0.7%)</td>
</tr>
</tbody>
</table>

* 10/19 (53%) in the BT group occurred on the day of the procedure.

ᵃ/ Time period beginning at first bronchoscopy to 6 weeks after the third bronchoscopy (approx. 12 week period)


© 2012 Virginia Mason Medical Center
### Persistence of Effect at Two Years

#### Proportion of Subjects Reporting Severe Exacerbations and Healthcare Resource Utilization

<table>
<thead>
<tr>
<th>Percent of Subjects (Number of Subjects)</th>
<th>Year Prior to Study Entry(^a) (n=288)</th>
<th>Year 1 BT (n=181)</th>
<th>Year 2 BT (n=166)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Exacerbations</td>
<td>53.4 (154)</td>
<td>30.9 (56)</td>
<td>23.0 (38)(^b)</td>
</tr>
<tr>
<td>ED Visits</td>
<td>29.8 (86)</td>
<td>5.0 (9)</td>
<td>6.6 (11)(^b)</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>4.9 (14)</td>
<td>3.3 (6)</td>
<td>4.2 (7)(^b)</td>
</tr>
</tbody>
</table>

\(^a\): Includes all patient subjects (BT + Sham) prior to study entry  
\(^b\): Year 2 BT comparison to Year 1 BT is not significant by Fisher’s Exact Test
Questions and Concerns

• QOL improvement not clinically significant
• Sham and BT had improvement in QOL
• No change in FEV1, PEF, symptom-free days, use of rescue medications
• What is the mechanism?
  • No histological studies
• Who does it benefit?
  • Which phenotype?
Treatment
Inpatient

- B-agonists repeatedly but not continuous
- Steroids oral or IV
- Theophylline not helpful
- Magnesium as adjunct in severe cases
- Helium best as nebulizing gas
- BIPAP
Unconventional treatments

- Methotrexate
- Cyclosporine
- Gold
- IVIG
- Azathioprine
- Colchicine
- Dapsone
- Hydroxychloroquine

- Anti-tnf α
- Heparin
- Furosemide
- High-altitude treatment
Future treatments

- Ultra long-acting B-agonists (indacaterol)
- Once daily ICS
- Combinations
- LAMAs (aclidinium)
- PDE4 inhibitors
- FLAP inhibitors
- Statins

- Many more biologics
Severe Asthma Summary

• Development/Pathogenesis is complicated
• Mix of various syndromes/phenotypes
• Must be aware of mimics and poor adherence
• Personalized treatment
• Much more ahead for the next generation
Sleep Disordered Breathing

- Obstructive Sleep Apnea
- Central Sleep Apnea
- Nocturnal Hypoventilation
  - Obesity, COPD, Neuromuscular disease
- Nocturnal exacerbation of a cardiopulmonary illness
  - COPD, Asthma, CHF
Obstructive Sleep Apnea
Definition and Consequences

Repetitive closure of the pharyngeal airway during sleep that leads to……..

1. Snoring
   – bothersome to bed partner

2. Asphyxia
   – hypoxemia and hypercarbia

3. Negative intra-thoracic pressure
   – CV stress

4. Arousal from sleep
   – daytime sleepiness
Pathophysiology of OSA

• Pharyngeal obstruction occurs when the forces that lead to collapse are greater than the forces that keep the airway open

• Factors that favor pharyngeal collapse:
  - Anatomic narrowing
    - Nasal or pharyngeal
  - Supine position
  - Advancing age
  - Obesity
  - Sleep
  - Drugs
  - Alcohol
  - Altered consciousness
Sagital view of upper airway
Fat in Tongue

A

B

10-12% Fat

28-33% Fat

28-32% Fat
Prevalence of OSA
Sleep apnea is common

Wisconsin Sleep Cohort 402 state employees
• AHI > 5: 24% of men 9% of women
• AHI > 5 & sleepy: 4% of men 2% of women


Current evidence suggests 17% of population
Obstructive Sleep Apnea
A broad clinical spectrum

Presentation depends on:

- degree and location of airway closure
- number of breathing cessations per hour of sleep
- degree of hypoxemia
- biologic susceptibility to sleep fragmentation
Prevalence of OSA in Populations

- 75% of obese type II Diabetics
- 95% of patients with resistant hypertension
- 37% of NFL football players
- 65% of patients with CHF
Mortality Associated with OSA
Sleep apnea shortens life

He et al, Chest Vol. 94(1) pp 9-14, 1988

© 2012 Virginia Mason Medical Center
Diseases Associated with Obstructive Sleep Apnea

Causality established
- Hypertension
- Congestive heart failure
- Coronary artery disease
- Impaired glucose tolerance
- Motor vehicle accidents

Causality not established
- Diabetes mellitus
- Metabolic syndrome
- Weight gain
- Stroke
- Atrial fibrillation
- Glaucoma
- Fatty liver
- Pulmonary hypertension
Cardiac Consequences of an Obstructive Apnea

- Mueller Maneuver
  - More negative intra-thoracic pressure
    - Increased Pre-load
      - Increased Left Ventricular After-load
        - Decreased Cardiac Output
      - Hypoxemia and Hypercarbia
        - Bradycardia/tachycardia
          - Increased sympathetic tone
            - Increased Blood Pressure

- Asphyxia

- Arousal from sleep
Systemic Blood Pressure Response to OSA

Stradling & Davies, Breathing Disorders in Sleep, Saunders 2002
Cardiovascular Consequences of Obstructive Sleep Apnea

- **Acutely**
  - Bradycardia – tachycardia
  - Nocturnal hypertension
  - Elevated PAP & PCWP
  - Increased LV after-load
  - Decreased myocardial oxygen delivery
  - Increased myocardial oxygen demand

- **Chronically**
  - Diurnal hypertension
  - Congestive heart failure
  - Coronary artery disease
  - Cerebrovascular accidents
Sleep Apnea and CVD

1. Hypoxia
2. Arousal
3. Negative thoracic pressure

Intermediary Mechanisms
- Increased platelet adhesion
- Increased fibrinogen & CRP
- Endothelial dysfunction
- Oxidative stress

Hypertension
Diabetes Mellitus
Metabolic Syndrome

Co-morbidities
- Obesity
- Genetics

Cardiovascular Disease
Cardiovascular Disease & OSA

• If you have OSA, more likely to have CVD
  ▪ Prevalence: Odds ratio 1.42¹

• If you have OSA without CVD, you are more likely to get CVD if OSA is untreated
  ▪ Incidence: 36.7% vs. 6.6%²

• If you have CVD, you will do less well if OSA is untreated
  ▪ 56.8% vs. 6.7%²

Sahar, et al, Am J Respir Crit Care Med, 2001¹
Peker, et al, Am J Respir Crit Care Med Vol 166. pp 159-165, 2002²
Hypertension and OSA

- If you have OSA, more likely to have HTN
  - Prevalence: Odds ratio 3.07
    - Young, et al, Arch Intern Med 1997;157:1746-1752
- If you are on ≥ 3 drugs for HTN, you have OSA
- If you have OSA without HTN, you are more likely to get HTN if OSA untreated
  - Incidence: Odds ratio 2.89
    - Peppard, et al, NEJM 2000;342:1378-84
- Treatment with CPAP reduces BP
  - Faccenda et al, AJRCCM 2001;163:344-348
  - Pepperell et al, Lancet 2002;359:204-210
  - Hui et al, Thorax 2006;61:1083-90
Coronary Disease and OSA

• If you have OSA, more likely to have CAD
  ▪ Prevalence: Odds ratio 1.27

• OSA predicts increased mortality if CAD present
  ▪ 37.5% vs. 9.3%, p=0.018
    • Peker, et al, Am J Respir Crit Care Med, 2000

• CAD & OSA, worse long term prognosis
  ▪ Odds ratio 1.62 for death, CVA or MI
    • Mooe, et al., Am J Respir Crit Care Med, 2001

• CPAP treatment delays & reduces new CV events
Congestive Heart Failure & OSA

• If you have OSA, more likely to have CHF
  • Prevalence: Odds ratio 2.38
    • Sleep Heart Health Study

![Bar chart showing the percentage of patients with CSA and OSA across different studies.](chart.png)
Congestive Heart Failure & OSA

• PAP to normalize AHI < 15 increases transplant free survival

• Adaptive servo-ventilation, oxygen and titrated CPAP in Cheyne Stokes CSA
  ▪ Improve quality of life
  ▪ Improve LVEF
  ▪ Normalize AHI
    ▪ CSA Practice Parameters SLEEP 2012; 35(1):17-40
Stroke and OSA

• If you have OSA, more like to have CVA
  ▪ Prevalence Odds ratio 1.58
    • Sleep Heart Health Study

• If you have a CVA, increased risk of death if you have OSA
  ▪ Odds ratio 1.76
    • Sahlin et al, Arch Intern Med 2008;168;297-301

• Patients with CVA may develop acute OSA or CSA
Pulmonary Hypertension & OSA

- OSA is associated with mild pulmonary hypertension
- Most are obese and have daytime hypoxemia and hypercapnea
- Limited evidence OSA causes clinically significant pulmonary hypertension
- Not clear CPAP reduces pulmonary artery pressure
Atrial Fibrillation and OSA

- If you have OSA, you are more likely to have A-Fib
  - Prevalence: Odds ratio 4.02
    - Sleep Heart Health Study
- If you have paroxysmal A-Fib and OSA, you are more likely to stay in sinus rhythm after a cardioversion if OSA is treated
Diabetes Mellitus and OSA

- OSA impairs glucose metabolism
- OSA is associated with diabetes
  - Not enough evidence to establish causality
- OSA is very common in diabetics
  - Diabetics should be screened for OSA
- CPAP may improve glucose control in diabetics
  - No evidence to suggest CPAP prevents the emergence of diabetes
- Encourage CPAP in diabetics with OSA
  - Improved cardiovascular risk profile
Obesity ↔ Sleep Apnea

- Inactivity from daytime sleepiness/fatigue
- “feed fatigue” - eating to rouse
- Hypoxemia/intermittent arousals cause insulin resistance
- Elevated ghrelin levels (appetite stimulant)
- Leptin resistance (appetite suppressant)
- Change in food preferences - fatty carbs
Patients at risk for Obstructive Sleep Apnea

- Morbid obesity with BMI > 30
- Cardiovascular or Metabolic Disease
  - Congestive heart failure
  - Resistant hypertension
  - Coronary artery disease
  - Atrial fibrillation
  - Diabetes mellitus
  - Metabolic syndrome
- Chronic pain or fatigue syndromes
  - Fibromyalgia/chronic pain
  - Chronic fatigue syndrome
  - Chronic headaches, nocturnal/AM

- Neck size > 17 inches
- Craniofacial abnormalities
- Ethnic sub groups
- Psychiatric disease
  - Depression
  - ADHD, ADD
- Sleep symptoms
  - Insomnia
  - Daytime sleepiness
  - Disruptive snoring
- Pre-op evaluation for general anesthesia
Sleep Apnea

Who needs to be screened?

• Routine Review of Systems
• Target special groups
  ▪ Obese
  ▪ Hypertension
  ▪ Diabetics
  ▪ Coronary disease
  ▪ Congestive heart failure
  ▪ Fatigue
  ▪ Chronic pain
  ▪ Depressed
Virginia Mason Sleep Apnea Screening Tool

Please check all that apply

Category I: Snoring  (If you check any 2 of statements 2-6, you are at high risk.)
• 1. You have a bed partner who can reliably observe your sleep.
• 2. You have been told that you snore.
• 3. You snore more than 3 times per week.
• 4. You snore as loud as someone talking.
• 5. Your snoring bothers other people.
• 6. You have been told that you have pauses in your breathing while sleeping and these occur more than 3 times per week.

Category II: Daytime sleepiness or fatigue  (If you check one you are at high risk.)
• 1. You are still tired after sleeping for 8 hours on more than 3 days per week.
• 2. You are tired during the wake time more than 3 days per week.
• 3. You have fallen asleep while driving.
• 4. You do things to keep yourself from falling asleep during the day.

Category III: Body measurements  (If you check one or more you are at high risk.)
• 1. You have high blood pressure.
• 2. Your shirt collar size is greater than 16 inches or
• 3. Your dress size is larger than 14.
• 4. You weigh more than 220 lbs.

DO NOT WRITE BELOW THIS LINE.  FOR CLINIC PROVIDER USE ONLY.

Category IV: Physical examination
• Height: _______inches/cm.  Weight: ____lbs./kg.
• Neck Circumference: _______ cm.
• Body Mass Index: _____kg/m$^2$
(If neck circumference is $> 41$ cm or BMI $> 30$ kg/m$^2$ patient is at high risk)
Symptoms of OSA

**Nocturnal**
- Restless legs and kicking
- Insomnia
- Gasping, choking, snorting
- Nocturia
- Night sweats
- Drooling
- Sleep talking and sleep walking
- Dream enactment behavior

**Daytime**
- Excessive daytime sleepiness
- Fatigue
- Neuropsychiatric abnormalities
- Erectile dysfunction
- Morning headaches
- Morning dry mouth or sore throat
- Peripheral edema
Sleep Apnea and Insomnia

Prevalence of Insomnia Symptoms in Patients with Sleep-Disordered Breathing


• 50% of patients had primary complaints of insomnia and poor sleep quality despite having been referred to a sleep center for “snoring”
Polysomnography
Obstructive Sleep Apnea
Mixed Sleep Apnea
## Central Sleep Apnea

<table>
<thead>
<tr>
<th>BODY POSITION</th>
<th>Supine</th>
<th>Supine</th>
<th>Supine</th>
<th>Supine</th>
<th>Supine</th>
<th>Supine</th>
<th>Supine</th>
<th>Supine</th>
<th>Supine</th>
<th>Supine</th>
<th>Supine</th>
<th>Supine</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3-A2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C4-A1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O1-A2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O2-A1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOC-A2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROC-A1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MENTAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MICRO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTT/F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHEST</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SvO2-A</td>
<td>93%</td>
<td>92%</td>
<td>98%</td>
<td>96%</td>
<td>93%</td>
<td>97%</td>
<td>95%</td>
<td>92%</td>
<td>95%</td>
<td>96%</td>
<td>93%</td>
<td>97%</td>
</tr>
</tbody>
</table>

© 2012 Virginia Mason Medical Center
Home Sleep Apnea Testing
Home Sleep Apnea Testing

• Patients at high risk for sleep apnea
  ▪ Home sleep apnea testing
  ▪ Home CPAP titration
  ▪ Intensive outpatient follow up

• Studies validated in selected patients
  ▪ High risk, caucasian, middle aged men

• Don’t trust a negative home study if patient is at high risk
OSA Treatment Options

“prevent airway collapse during sleep”

• Behavioral
  ▪ Weight loss
  ▪ Position therapy
  ▪ Avoid alcohol near bedtime

• Oral appliances

• Provent

• Surgery
  ▪ Simple - soft tissue
  ▪ Complex - skeletal structures

• Positive pressure therapy
Obstructive Sleep Apnea
Rating the severity

• Severity is based on # of respiratory events/hour
• AHI: apnea - hypopnea index is the number of breathing cessations (complete or partial) per hour of sleep
  • Mild - 5-15, Moderate -15-30, Severe - > 30
  • “enough” or “clinically relevant”
• Severity by AHI correlates with cardiovascular effects, but not with symptoms
## Treatment Efficacy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Snoring</th>
<th>OSA</th>
<th>Side Effects</th>
<th>Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>100%</td>
<td>100%</td>
<td>0</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>CPAP</td>
<td>100%</td>
<td>100%</td>
<td>Reversible</td>
<td>65%</td>
</tr>
<tr>
<td>Soft tissue surgery</td>
<td>75%</td>
<td>40%</td>
<td>2-5%</td>
<td>100%</td>
</tr>
<tr>
<td>Oral Appliance</td>
<td>75%</td>
<td>30%</td>
<td>Reversible</td>
<td>50%</td>
</tr>
<tr>
<td>Skeletal Surgery</td>
<td>95%</td>
<td>95%</td>
<td>Irreversible</td>
<td>100%</td>
</tr>
</tbody>
</table>
**OSA Treatment Plan**

**Presenting complaints:**
- Snoring
- Symptoms
  - Sleepiness
  - Etc.
- Cardiovascular and metabolic disease risk

**Individual factors:**
- BMI
- Upper airway anatomy
- Dentition/Jaw
- OSA severity
- Patient preferences
Sleep Apnea – Clinical Context

- Not everyone needs to be treated
- What are you trying to correct?
  - Snoring
  - Symptoms
  - Cardiovascular and metabolic disease risk
- CVD and metabolic disease risk, but not symptoms correlate with severity (AHI)
Treatment Recommendations

• Weight loss
  • everyone over ideal body weight

• CPAP
  • severe OSA, CVD risks, symptomatic

• Oral Appliance
  • milder OSA, snoring

• Surgery
  ▪ Soft tissue
    • improve CPAP compliance
    • milder OSA, snoring
  ▪ Bi-Max
    • CPAP failure or need orthognathic surgery
CPAP Therapy

- Highly efficacious - “it keeps airway open”
- Reasonably effective - “patients use it”
- Reversible
- Reimbursed
- First line therapy for clinically important sleep apnea
CPAP Devices
CPAP Nasal Interfaces
Outcomes from CPAP Therapy

- Reduced blood pressure in hypertensive patients
- Improved LV function in patients with CHF
- Persistent NSR after cardio-version if PAF
- Improved glucose control
- Reduced cardiovascular events and mortality
- Reduced motor vehicle accidents
- Reduced daytime sleepiness
- Improved quality of life and depression scores
- Improved outcomes in peri-operative period
CPAP Clinic Compliance Data

N = 641 patients

62% use > 4 hours on > 65% of nights
When CPAP is not tolerated…

• Review the treatment plan
• Stop CPAP therapy?
• Weight loss
• Surgery
• Oral appliances
Oral Appliances
OAD - Effectiveness

- 35-40% - AHI less than 5
- 25% get a 50% reduction in AHI but >5
- 35-45% treatment failure
- Less effective than CPAP at PSG improvement but similar symptom response
- 70% tolerate OAD
- Suggestion of improvement in CVD and neuropsychological outcomes
Predictors of a Favorable Response with OAD

- Anthropomorphic
  - Younger
  - Female
  - Thinner
  - Milder
  - Supine only OSA

- Anatomic
  - Shorter soft palate and larger retro-palatal space
OAD - Adverse Effects

• **Short-term**
  - Excessive salivation
  - Mouth dryness
  - Tooth pain
  - Gum irritation
  - Headaches
  - TMJ discomfort

• **Long-term**
  - Reduction in over-jet
  - Increase in facial height
  - Increase in degree of mouth opening
  - Change in inclination of incisors
  - Increase in mandibular plane angle
OAD - AASM Position Paper

• Diagnosis with polysomnography
• Fitted by a dentist
• Treatment goals include:
  • Alternative to CPAP if mild to moderate
  • Use only after CPAP failure in severe
  • Follow up polysomnography with OAD
  • Follow up with dentist and sleep specialist every 6 months
Surgical Therapy for OSA

• Upper airway bypass
  ▪ Tracheostomy

• Simple Surgery – Phase I
  ▪ Palate, Nose, Tongue

• Complex Surgery – Phase II
  ▪ Mandibular and Maxillary advancement
Treatments for Snoring

- Weight loss
- Avoidance of alcohol near bedtime
- Antihistamines, decongestants, nasal steroids
- Semi recumbent position, recliner
- Chin strap
- Soft tissue surgery on upper airway
- Provent
- Nasal strips, cones or stents
- Oral appliances
Treatments for snoring
OSA - Summary

• You don’t have to be short, fat, old, or male
• Sleep testing for prognosis and treatment planning
• CV and metabolic disease risk correlates with AHI
• Symptoms do not correlate with AHI
• Home testing and auto CPAPAP for high risk patients
• Treatment plan requires clinical context
  ▪ Snoring, symptoms, CVD risks
• CPAP and weight loss is first line therapy
  ▪ 65% of patients will wear 4 hours, 5/7 night
• CPAP units are smaller, quieter, more comfortable
Positive Pressure Modalities

- CPAP
  - Fixed pressure
  - CFLEX, EPR
  - Auto-PAP
- Bi-Level PAP
  - With or without back up rate
  - Auto-Bi-Level PAP
- Adaptive servo-ventilation
- Volume cycled - AVAPs
# CPAP mask fitting tips

<table>
<thead>
<tr>
<th>Factor:</th>
<th>Mask fitting tip:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of facial hair</td>
<td>Nasal pillows</td>
</tr>
<tr>
<td>Claustrophobia</td>
<td>Nasal pillows</td>
</tr>
<tr>
<td>Preferred sleep position is prone</td>
<td>Nasal pillows</td>
</tr>
<tr>
<td>Sensitive to straps</td>
<td>Nasal pillows mounted on an oral appliance</td>
</tr>
<tr>
<td>Oral breather</td>
<td>Oral-nasal mask</td>
</tr>
<tr>
<td>Nasal obstruction</td>
<td>Oral-nasal mask</td>
</tr>
<tr>
<td>Dentures</td>
<td>Avoid oral-nasal mask</td>
</tr>
<tr>
<td>Micrognathia</td>
<td>Avoid oral-nasal mask</td>
</tr>
<tr>
<td>Noise sensitivity</td>
<td>Avoid nasal pillows</td>
</tr>
<tr>
<td>Large or asymmetrical nares</td>
<td>Avoid nasal pillows</td>
</tr>
<tr>
<td>Contact skin sensitivities</td>
<td>Avoid gel cushioned masks</td>
</tr>
<tr>
<td>Desire to wear glasses with CPAP</td>
<td>Avoid forehead cushions</td>
</tr>
</tbody>
</table>
Trouble Shooting CPAP Problems

• Snoring
  ▪ Raise pressure, chin strap, replace mask

• Nasal congestion
  ▪ Change humidity, nasal steroids, ENT consult

• Mouth dryness
  ▪ Change humidity, chin strap, oral-nasal mask

• Air swallowing
  ▪ Reduce pressure or change pressure delivery mode

• Condensation
  ▪ Change heat, insulate tubing, lower CPAP unit

• Uncomfortable mask
  ▪ Refit mask
Persistent Sleepiness on CPAP

- Using CPAP enough?
- Correct pressure?
- Equipment in good working order?
- Evidence of oral leakage?
- Other sleep issues?
  - Shift work
  - Sleep restriction
  - PLMS
  - Sleep environment
  - ETOH near bedtime
- Objective sleepiness on MSLT after CPAP PSG?
  - Consider a trial of modafinil (Provigil)