UPDATES IN PULMONARY AND SLEEP MEDICINE

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American College of Physicians – Virginia Chapter
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1. I do not have any potential conflicts of interest to disclose, OR

2. I wish to disclose the following potential conflicts of interest

<table>
<thead>
<tr>
<th>Type of Potential Conflict</th>
<th>Details of Potential Conflict</th>
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<tr>
<td>Grant/Research Support</td>
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3. The material presented in this lecture has no relationship with any of these potential conflicts, OR

4. This talk presents material that is related to one or more of these potential conflicts, and the following objective references are provided as support for this lecture:
OUTLINE

• What Internists Should Know about OSA
  – Improving PAP Adherence
• Assessment of Pulmonary Nodules
• Updates on COPD Management
WHAT THE INTERNIST SHOULD KNOW ABOUT OBSTRUCTIVE SLEEP APNEA
COMMON FEATURES OF OSA

- Habitual snoring
- Daytime somnolence or fatigue
- Witnessed apneas
- Restless or non-refreshing sleep
- Overweight, recent weight gain
- GERD, HTN, DM, Metabolic syndrome, headaches
- Erectile dysfunction
- Depression
- Sweating and dry mouth at night
- Nocturia
RISK FACTORS FOR OSA

• Obesity
• Increasing age, Male gender
• Anatomic abnormalities of upper airway
  – Retro/micrognathia
• Family history of OSA
  – OR 2X for one and 3X for two 1st degree family members
• Alcohol or sedative use
• Certain Medical Conditions
  – Ex: Hypothyroidism, Afib, HTN, CVA, CHF.
**RISK FACTORS FOR OSA**

- Of all risk factors/high-probability features for OSA, BMI (obesity) is the most associated.
- Likelihood for OSA in other common risk factors

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Published associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt;40 independent risk</td>
</tr>
<tr>
<td></td>
<td>odds increase with each decade of life</td>
</tr>
<tr>
<td></td>
<td>11-fold increase from age 20 to 65</td>
</tr>
<tr>
<td>Snoring</td>
<td>67-85% of apneics vs 30-38% of non-apneics</td>
</tr>
<tr>
<td>Witnessed apneas</td>
<td>accuracy 48-52%</td>
</tr>
<tr>
<td></td>
<td>OR 2.09-2.47</td>
</tr>
<tr>
<td>Family History</td>
<td>2-2.5 X with 1st degree relative</td>
</tr>
<tr>
<td></td>
<td>3 X risk with 2 1st degree relatives</td>
</tr>
<tr>
<td>HTN</td>
<td>52% of apneics vs 30-36% of non-apneics</td>
</tr>
<tr>
<td>BMI</td>
<td>BMI&gt;31 - OR of 7.8</td>
</tr>
<tr>
<td></td>
<td>BMI&gt; 32 - OR of 12.8</td>
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<tr>
<td>COMMON COMORBIDITIES AND OSA</td>
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<tr>
<td>-------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>CNS/Behavioral Health</strong></td>
<td></td>
</tr>
<tr>
<td>• Headache disorders</td>
<td></td>
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<tr>
<td>• Fibromyalgia</td>
<td></td>
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<tr>
<td>• Depression</td>
<td></td>
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<tr>
<td>• PTSD</td>
<td></td>
</tr>
<tr>
<td>• ADD/ADHD</td>
<td></td>
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<tr>
<td><strong>Genitourinary</strong></td>
<td></td>
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<tr>
<td>• Nocturia</td>
<td></td>
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<tr>
<td>• Erectile dysfunction</td>
<td></td>
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<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
</tr>
<tr>
<td>• GERD</td>
<td></td>
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<td>• IBS</td>
<td></td>
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<tr>
<td><strong>Respiratory</strong></td>
<td></td>
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<tr>
<td>• Chronic hypoxia</td>
<td></td>
</tr>
<tr>
<td>• Pulmonary HTN</td>
<td></td>
</tr>
<tr>
<td>• DVT/PE</td>
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<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
</tr>
<tr>
<td>• CVA</td>
<td></td>
</tr>
<tr>
<td>• Myocardial infarction</td>
<td></td>
</tr>
<tr>
<td>• Cardiomyopathy/CHF</td>
<td></td>
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<tr>
<td>• Atrial Fibrillation</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td></td>
</tr>
<tr>
<td>• Weight gain</td>
<td></td>
</tr>
<tr>
<td>• Hyperlipidemia, metabolic synd</td>
<td></td>
</tr>
<tr>
<td>• Diabetes</td>
<td></td>
</tr>
</tbody>
</table>
### Screening Tool for OSA

**STOP BANG**

<table>
<thead>
<tr>
<th>S</th>
<th>Snoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>Tired</td>
</tr>
<tr>
<td>O</td>
<td>Observed Apnea</td>
</tr>
<tr>
<td>P</td>
<td>Pressure-HTN</td>
</tr>
<tr>
<td>B</td>
<td>BMI &gt; 30</td>
</tr>
<tr>
<td>A</td>
<td>Age &gt; 50</td>
</tr>
<tr>
<td>N</td>
<td>Neck &gt; 17”</td>
</tr>
<tr>
<td>G</td>
<td>Gender (M)</td>
</tr>
</tbody>
</table>

*STOP BANG* is a screening tool used to identify individuals at risk for obstructive sleep apnea (OSA). A positive screening result indicates a need for further evaluation by a healthcare professional.
Numerous studies have concluded

- Moderate to Severe OSA shortens life expectancy
- Risk of Fatal CV events increases with increasing OSA severity
BENEFITS OF TREATING OSA

• Improved QoL
• Reduced daytime somnolence
• Improved neurocognitive function
• Reduces BP
• Reduces CV events, improves all-cause mortality
• Improved control/outcomes of several comorbid conditions
  – Afib, CHF, DM, Headaches, Behavioral health disorders, GERD, HTN, chronic pain
ADHERENCE IN PAP THERAPY

• Despite its benefits, PAP adherence remains problematic
• Largely related to PAP intolerance (or unwillingness)
• 20% do not initiate therapy
• Approx 30% discontinue in first month
• By 3 years, only ¼ are “regular users” of CPAP

Numerous interventions to improve acceptance and use of PAP therapy
• Adherence still a problem
• Large demand for CPAP alternatives
• Some beneficial, others potentially harmful
TECHNOLOGY AND ADHERENCE

• PAP platforms (CPAP vs APAP vs BIPAP vs VPAP)
  – None shown to significantly improve adherence
• Integrated heated humidifies
  – Improved comfort, minimal impact on adherence
• Expiratory pressure relief
  • Improved comfort, minimal impact on adherence
• Mask interfaces
  • Improved comfort, minimal impact on adherence
IMPROVING PAP ADHERENCE

• Simple interventions can improve initial tolerance and long-term use of PAP
• Several common, predictable barriers to PAP
• Largely related to patient buy-in and initial experiences with PAP
• Education
• Treatment of rhinitis
• Proper mask selection and pressure settings
• Short-term sedative hypnotics
• PAP remains the most common and most efficacious treatment for OSA
• Other beneficial treatment options
  – Forced positional therapy
  – Oral Appliances/Mandibular Advancement Devices
  – Surgery
  – Hypoglossal nerve stimulation
EVALUATION OF PULMONARY NODULES
PULMONARY NODULES

- Incidence
  - 0.2% of all CXRs, 13% of CTs, 31% Cardiac CTs
- Majority are benign
  - 2-15% of nodules are malignant
- Given risk for CA, all must be evaluated
- Evaluation and need for follow-up depends on nodule features and individual risk factors
  - Size, density, shape, location, doubling time
# Evaluation of the Solitary Pulmonary Nodule

Radiologic Features Suggestive of Benign or Malignant Solitary Pulmonary Nodules

<table>
<thead>
<tr>
<th>Radiologic Feature</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>&lt; 5 mm</td>
<td>&gt; 10 mm</td>
</tr>
<tr>
<td>Border</td>
<td>Smooth</td>
<td>Irregular, spiculated</td>
</tr>
<tr>
<td>Density</td>
<td>Dense, solid</td>
<td>Nonsolid, “ground glass”</td>
</tr>
<tr>
<td>Calcification</td>
<td>Typically benign</td>
<td></td>
</tr>
<tr>
<td>Doubling time</td>
<td>&lt;1 month; &gt;1 year</td>
<td>1 month – 1 year</td>
</tr>
</tbody>
</table>
## Risk for Malignancy

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current or past smoking</td>
<td>7.9</td>
</tr>
<tr>
<td>Patient age (per 10-year increment)</td>
<td>2.2</td>
</tr>
<tr>
<td>Nodule diameter (per mm)</td>
<td>1.1</td>
</tr>
<tr>
<td>Time quit smoking (/10-year increment)</td>
<td>0.6</td>
</tr>
<tr>
<td>History of extrathoracic cancer</td>
<td>3.8</td>
</tr>
<tr>
<td>Spiculated morphology</td>
<td>2.8</td>
</tr>
<tr>
<td>Upper lung location</td>
<td>2.2</td>
</tr>
</tbody>
</table>
PULMONARY NODULE GUIDELINES

- 2012 Fleischner Society Nodule Guidelines
- 2013 American College of Chest Physicians Evidence-Based Clinical Practice Guidelines: Diagnosis and Management of Lung Cancer, 3rd ed

- Recommendations based on size and density of nodule
  - Ground glass (< or > 5 mm)
  - Solid (< or > 8 mm)
Features that increase concern for malignancy

- Current or former smoking
- Older age
- Upper lobe
- Sub-solid nodule
- Size > 8mm
- Associated adenopathy
- Irregular or spiculated border
- Lack of calcification
• Smoking is not consistently differentiated from ex-smokers or never smoked
  – Increasing incidence of adenocarcinomas in younger and nonsmoking individuals
  – Smokers have a greater likelihood of cancer and worse prognosis, there are insufficient data to influence guidelines based solely on smoking history
• However, both Guidelines define
  – low risk patients: minimal or absent history of smoking and or other known risk factors
  – high risk patients: history of smoking or of other known risk factors
• Always review prior films when available
  – Lesions stable for >2 yrs do not need further evaluation
Ground Glass Opacities/Nodules (non-solid)
- <5mm: No further evaluation-follow-up needed (Grade 1C)
  - Very low probability these are, or will develop into adenocarcinomas with doubling time < 3-5 years (i.e. even if it is a malignancy it is more likely to be very slow growing)
- >5 mm: Follow-up CT in 3 months to determine persistence, followed by yearly CT for 3 years if persistent and unchanged (Grade 1B)
  - Likelihood for pre-invasive AAH or AIS high enough to warrant long-term CT surveillance
  - Lack of evidence showing that resection is beneficial and potentially harmful
Consider short follow-up CT in 3 months
  – Any increase on follow-up CT should be considered malignant until proved otherwise
  – no resolution should also be considered potentially malignant

Unlike pure GGNs, partially solid GGNs have a sufficiently greater likelihood of being malignant and warrant an aggressive diagnostic approach
• Multiple well-defined GGNs
• If all < 5 mm - conservatively managed with follow-up CT at 2 and 4 years
  – Low likelihood for evolving into an invasive adeno-carcinoma
• Follow guidelines based on the largest nodule (ie. If one is >5mm use those recs)
• If 1+ is >5mm
  – CT in 3 months, then yearly for at least 3 years regardless of smoking history (Grade 1B)
  – Invasive carcinomas more likely to arise in larger
• **No risk factors** for lung cancer - frequency and duration of CT surveillance based on size of the nodule (Grade 2C)
  – < 4 mm – no further evaluation required
  – 4-6 mm repeat CT in 12 months
  – 6-8 mm repeat CT in 6-12 months and again at 18-24 months if unchanged

• **Multiple solid nodules** - follow-up based on the size of the largest lesion
SOLID NODULES < 8MM – HIGH RISK

• Risk factors for lung cancer < 4 mm – no further evaluation required
  – <4 mm - repeat CT in 12 months, stop if unchanged
  – 4-6 mm repeat CT in 6-12 months and again at 18-24 months if unchanged
  – 6-8 mm repeat CT in 3-6 months, again at 9-12 months, and again at 24 months if unchanged

• Remark: CT surveillance should use thin section, low-dose, non-contrast techniques (Grade 2C).
For larger nodules - estimate risk of malignancy

- Very low probability of malignancy (<5%)- Repeat CT in 3-6/9-12 and 24 months (Grade 2C).
- Low-mod probability of malignancy (5%-65%)- obtain functional imaging (PET or dynamic contrast CT) (Grade 2C)
  - PET negative: Repeat CT in 3-6/9-12 and 24 months
  - PET positive: Resection
- High probability of malignancy (>65%)- biopsy or resect (Grade 2C)
CHANGES ON F/U CTs

• Growth on serial imaging – high probability for malignancy
  – biopsy and/or surgical resection unless specifically contraindicated (Grade 1C).

• Solid nodules that decrease in size but do not resolve should be followed to resolution or lack of growth over 2 years

• Factors that predispose to interval growth
  – nodule size >10 mm and a history of lung cancer
## Nodule Follow-Up Summary

<table>
<thead>
<tr>
<th>Type</th>
<th>Initial Follow-Up</th>
<th>Continued Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>GGN &lt;5mm</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>GGN &gt;5mm</td>
<td>Repeat CT in 3 months</td>
<td>Establish stability for 3 years</td>
</tr>
<tr>
<td>Partial solid &gt; 5mm</td>
<td>Repeat CT in 3 months</td>
<td>Continue short interval f/u x 2-3 years</td>
</tr>
<tr>
<td>SPN &lt;4mm, Low-risk</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>SPN 4-6mm, Low-risk</td>
<td>Repeat CT in 12 months</td>
<td></td>
</tr>
<tr>
<td>SPN 6-8, Low Risk</td>
<td>Repeat CT in 6-12 months</td>
<td>Repeat CT in 18-24 months</td>
</tr>
<tr>
<td>SPN &lt;4mm, High Risk</td>
<td>Repeat CT in 12 months</td>
<td></td>
</tr>
<tr>
<td>SPN 4-6mm, High-risk</td>
<td>Repeat CT in 6-12 months</td>
<td>Repeat CT in 18-24 months</td>
</tr>
<tr>
<td>SPN 6-8mm, High-risk</td>
<td>Repeat CT in 3-6 months</td>
<td>Repeat CT 9-12 and 24 months</td>
</tr>
<tr>
<td>SPN &gt;8mm</td>
<td>Requires risk stratification</td>
<td>Repeat CT at 3, 9, and 24 months</td>
</tr>
</tbody>
</table>
UPDATES IN THE MANAGEMENT OF COPD
COPD

- 27-32 million persons in the United States
- 3rd leading cause of death in this country
- Major cause of long-term disability
- Largely under-diagnosed
- Majority not receiving treatment according to published guidelines
  - GOLD; ATS/ERS/ACCP
TREATMENT BASED ON DISEASE SEVERITY

- Stage I (mild): FEV$_1$ 80% or greater of predicted
- Stage II (moderate): FEV$_1$ 50-79% of predicted
- Stage III (severe): FEV$_1$ 30-49% of predicted
- Stage IV (very severe): FEV$_1$ < 30% predicted or FEV$_1$ <50% and chronic respiratory failure

- Continued re-assessments needed to ensure treatment endpoints met
TREATMENT GOALS

• Improve (normalize) spirometry/lung function
• Improve functional capacity
• Minimize exacerbations
• Do so with as few medications as possible (mitigate drug toxicity)
# COPD Treatment Recommendations

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>• PRN short-acting bronchodilators</td>
</tr>
</tbody>
</table>
| II    | • long-acting bronchodilator(s)  
    | • cardiopulmonary rehab |
| III   | • long-acting bronchodilator(s)  
    | • cardiopulmonary rehab  
    | • ICS if repeated exacerbations |
| IV    | • long-acting bronchodilator(s)  
    | • cardiopulmonary rehab  
    | • ICS  
    | • long-term oxygen therapy  
    | • consider surgical options: LVRS and transplantation |
Most Patients Are Not on Maintenance Therapy

Commercially Insured (n=42,565)
66.3% no long-term pharmacotherapy
70.9% no long-term pharmacotherapy

Medicare (n=8507)
66.3% no long-term pharmacotherapy
70.9% no long-term pharmacotherapy

- Inadequate therapy risk for exacerbation and hospitalization
- 52.5 – 79% not treated per guidelines at discharge
- 17.9% readmitted within 30 days, 4X higher if not on maintenance therapy

LABAs

- Long-standing efficacy in sustained improvements in FEV$_1$, symptoms and QoL
- Several new agents in past 6 years
  - salmeterol, formoterol, arformoterol, olodaterol, vilanterol, indacaterol
- Likely not as efficacious as LAMAs
- Concerns for increased mortality likely limited to asthmatics using LABAs as monotherapy (not well-reported in COPD)
- Best option – add to LAMA for persistent symptoms for dual long-acting bronchodilation
LAMA: TIOTROPIUM

- First approved, and only available LAMA until recently
- Once daily (18 hr efficacy)
- Numerous studies showed improved FEV$_1$ and symptoms
- Improved efficacy vs LABA
- UPLIFT trial
  - Significant reduction in COPD exacerbations and hospitalizations
  - Improved QoL
  - No reduction in the rate of FEV$_1$ decline or mortality
NEW LAMA: GLYCOPYRROLATE

• Glycopyrrolate is a long-acting muscarinic antagonist (LAMA) that produces bronchodilation by inhibiting acetylcholine’s effect on muscarinic receptors in the airway smooth muscle
• FDA approved in 2015 for long-term, maintenance treatment of COPD
• Available alone or in combination with indacaterol (LABA)
**NEW LAMA: Aclidinium**

- Aclidinium: long-acting, antimuscarinic (M3) metered-dose inhaler
- FDA approved in 2012.
- RCTs of 1276 patients
  - FEV1 improvements vs placebo were 0.12 L, 0.07 L, and 0.11 L (P< 0.001)
New LAMA: Umeclidinium

- Umeclidinium bromide
- The first once-daily dual bronchodilator
- Available as a single entity inhaler or combination inhaled powder with vilanterol
- 7 phase III trials w/nearly 6,000 patients
  - Improved exercise capacity and lung function
  - Continued benefits at 52 weeks
  - Safety data similar to other LAMAs
• Current GOLD guidelines
  – maintenance therapy either with a LAMA or LABA
  – When not adequately controlled with a single long-acting bronchodilator, GOLD recommends combining a LAMA with a LABA
• Several new LAMA/LABNA combinations approved
• combination therapy shown to improve lung function, QoL, symptom scores, and exacerbation rates, compared with monotherapies
  – Similar safety outcomes
• Meta-Analysis - *Efficacy and Safety of Long-acting β-agonist/Long-acting Muscarinic Antagonist Combinations in COPD*

• LABA/LAMA combinations associated with
  - greater improvement in lung function, St. George's Respiratory Questionnaire (SGRQ) score, and Transitional Dyspnea Index (TDI) than monotherapies
  - fewer moderate-to-severe exacerbations compared with LABAs (HR 0.82 (95% CrI 0.73–0.93))
  - Concern for increased CV events with LAMA/LABA combinations

LAMA/LABA COMBINATION

• SPARK trial: once-daily fixed-dose combination of indacaterol (LABA) and glycopyrronium (LAMA)
  – improved lung functioning and reduce exacerbations as compared with LAMA monotherapy

• Flight Trials - Two 12-week efficacy studies demonstrated
  – "superior and sustained" improvements in lung function compared with each individual bronchodilator
  – clinically meaningful improvements in health-related QoL and reduced use of rescue medication

SPARK trial; FLIGHT-1 Trial; Flight-2 Trial
• Roflumilast: 2\textsuperscript{nd}-generation, selective phosphodiesterase-4 inhibitors.
• wakefulness-promoting, neuroprotective, antidepressant, and anti-inflammatory effects
• FDA approved for reducing COPD exacerbations among those with severe disease
  — 17\% reduction in exacerbations vs placebo
• Not a bronchodilator, but shown to have modest improvement in lung function
• Gold Guidelines – limit to severe airflow limitation w/high risk of exacerbations, who remain symptomatic after regular use of one or two long-acting bronchodilators
• 2011 ICSI guidelines – appropriate in patients with recurrent exacerbations of COPD and should be added to a regimen that already includes a long-acting bronchodilator.
• Despite guidelines - 70% of patients on ICS
INHALED CORTICOSTEROIDS

- Not recommended as monotherapy
- Do not decrease the decline in FEV
- Do decrease exacerbations and improve QoL
  — for symptomatic patients with an FEV\textsubscript{1} of less than 50%
- TORCH trial – ICS+LABA combination more beneficial than ICS alone
- Well-established increased risk for pneumonia
- Meta-analysis: Stopping ICS in patients using bronchodilators has little effect on symptoms
MACROLIDE ANTIBIOTICS

• Macrolides shown to have anti-inflammatory effects in the airways of COPD patients
• Improve the phagocytic function of pulmonary macrophages
• Chronic therapy shown to reduced the frequency of COPD exacerbations
  – Limited by slight increase in hearing decrements
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