Assessing dyspnea

- Is it cardiac versus lung? Job #1 is to try and discern between these two basic causes of the dyspneic applicant
  - Rare causes: Anemia, neuromuscular pathology, occult pulmonary hypertension
  - Common non-cardiac causes: Deconditioning, Occult Obstructive Sleep Apnea Syndrome (OSAS)

- Subjective versus Objective: How to we quantitate dyspnea?
  - Spirometry
  - Complete PFTs
  - Echocardiogram
  - 6-minute walk test
  - Sa02 measurements
  - ETT (Exercise Treadmill Test): METS achieved when study is limited by dyspnea

Assessing smoking (or past smoker) applicants

- Recognition that very early age of onset of smoking (< age 12 v > age 18) AND early age of onset of COPD (< age 50) has adverse correlation with future morbidity/mortality

- Recognition that the adverse lung consequences of smoking is much greater in women than men, especially when the smoking is “casual” or at levels < 1 pack-per-day

- Recognition that former smokers will have some mortality/morbidity that never “expires”

- Recognition that the morbidity/mortality of smoking may be significantly amplified in certain settings
  - History of asbestos exposure, and especially presence of asbestos lung disease
Combination of smoking and reactive lung disease

- Recognition that the mortality/morbidity of smoking may be roughly divided into 3 consequences
  - Cardiovascular, including CAD (Coronary Artery Disease) and ASPVD (Arteriosclerotic Peripheral Vascular Disease – also referred to as PAD – Peripheral Arterial Disease)
  - Cancer (Many types of cancer, with lung cancer being the #1 cause of cancer death in BOTH men and women in the US)
  - COPD

Assessing ASTHMA

- Know that “Mild Intermittent” asthma may be treated with as-needed use of a short-acting MDI (usually albuterol) but if that usage exceeds 2 x per week, they should be treated as “Mild Persistent” and be placed on anti-inflammatory inhaled medication (inhaled corticosteroids)

- Childhood versus Adult onset: generally greater morbidity/mortality in the latter
  - Childhood asthma usually resolves in their teens, rarely to recur
  - Adult-onset asthma usually tends to be worse than “Mild Intermittent”

- Recognition of the HIGH RISK applicant
  - Any prior history of requirement for intubation/mechanical ventilation
  - Frequent hospitalizations or ER visits
  - Non-compliant teens
  - Inner-city applicants, especially children, with limited access to medical care
  - If can be discerned from the medical records, the frequency of refills of short-acting beta-agonist MDIs (ideally 1 per year … Mortality correlates linearly with # of MDI’s)

- “Credits” for asthma
  - Compliance with use of inhaled corticosteroids (Mortality correlates linearly but inversely with # of prescriptions filled – the more, the lower the mortality)
  - ACT (Asthma Control Test) or other questionnaires reflecting good control
  - Normal spirometry
• Recognition that asthma is rarely a cause for significant mortality (especially in children) – childhood mortality in asthma is largely confined to those with limited access to medical care
  o Not to view the use of bolus steroid therapy (prednisone 20-50 mg/day x 3-10 days) as unfavorable, as long as it is used < 3 x per year

• Other factors that could be considered as noteworthy in an applicant with asthma
  o Any applicant with Asthma beyond “Mild Intermittent” who is not on daily inhaled corticosteroids
  o Any applicant with Asthma beyond “Mild Intermittent” who smokes
  o Any applicant with Asthma who undergoes spirometry when they are “asymptomatic” with results showing an FEV1/FCV < 70%
    ▪  This would give them GOLD criteria diagnosis of “COPD”
    ▪  And would imply that their airways have undergone remodeling and that their airway inflammation now more closely mirrors that of COPD rather than Asthma

Assessing COPD

• Remember that COPD is under-diagnosed (only 1 in 2 persons with COPD in US carries diagnosis of COPD). Any applicant who smokes and has symptoms of chronic cough, sputum production, wheezing, or dyspnea-on-exertion probably has COPD, even if not formally diagnosed.

• Role of spirometry in assessing severity: GOLD criteria
  o COPD defined as FEV1/FVC ratio ≤ 70%
  o With severity defined by the FEV1 % predicted
    ▪  > 80% predicted       “Mild”                  Stage 1
    ▪  50-79% predicted     “Moderate”               Stage 2
    ▪  30-49% predicted     “Severe”                 Stage 3
- < 30% predicted “Very Severe” Stage 4
  
  o Value of Flow-Volume loop
    - “Visual” estimation of severity of airflow obstruction
    - Potential implications of an abnormal inspiratory limb of flow-volume loop ("plateauing" of the inspiratory limb of the FVL as a possible indication of upper-airway obstruction: vocal cord paralysis, tumor, tracheal stenosis)

- “Red Flags” for increased morbidity/mortality in the applicant with diagnosed COPD
  
  o Continuance of smoking (with cessation of smoking being the only intervention proven to alter mortality)
  
  o Quantity of smoking’s role in morbidity/mortality (increasing # pack-years correlates with increasing morbidity and mortality)
  
  o Presence of prominent reactive airways disease (Copenhagen hypothesis) as part of their COPD
  
  o Frequency of AECOPD (Acute Exacerbation of COPD)
    - Especially those requiring ER or hospital interventions
  
  o Lack of compliance with available interventions
    - Pneumovax immunization
    - Yearly influenza vaccinations
    - Being on anti-inflammatory corticosteroids + LABAs
      - Currently fluticasone + salmeterol (Advair), budesonide + formoterol (Symbicort), or nebulizer therapy with budesonide 0.5 mg + aerosolized LABA (Brovanna, Performist)
  
  o If done, testing for alpha-1-anti-trypsin revealing mz or zz phenotype
  
  o Implications of diagnosis of or clinical findings (physical exam, CXR, echocardiogram) of cor pulmonale

- Role of Complete Pulmonary Function Testing
  
  o Lung volume measurement to quantify hyperinflation
  
  o Lung diffusion study (DLCO) to diagnose emphysema
- Arterial blood gas analysis (especially measurement of pCO2 to define hypercapnic respiratory failure)

**Medical Mortality Assessment of Mild-to-Moderate COPD**

- **Lung Health Study**: evaluated 5887 smokers ages 36-60 with mild to moderate COPD by GOLD criteria (mean FEV1 %predicted 78%) for 14.5 years and assessed death as the primary outcome.
  - Deaths occurred in 731 of the 5887 subjects (12%) over 14.5 years
    - Lung cancer accounted for 33% of deaths
    - Cardiovascular disease accounted for 22% of deaths
    - Cancers other than lung cancer accounted for 21% of deaths
    - Respiratory failure accounted for 8% of deaths

**Medical Mortality Assessment of Severe COPD**

- **TORCH** (Towards a Revolution in COPD Health) Study: evaluated the effect of inhaled/combined salmeterol and fluticasone propionate on COPD mortality over 3-year period in 6112 subjects with mean age 65 and mean FEV1 44% of predicted.
  - 875 of the 6112 (14%) died over the 3-year study
    - Respiratory failure accounted for 35% of deaths
    - Cardiovascular disease accounted for 27% of deaths
    - Cancer (2/3 lung and 1/3 “other”) accounted for 21% of deaths
    - The remaining 17% of deaths were from “other” causes

**BODE Index**

**Computation of the BODE Index**

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<thead>
<tr>
<th>Variable</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
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<tbody>
<tr>
<td>FEV1 % predicted</td>
<td>≥65</td>
<td>50-64</td>
<td>35-49</td>
<td>≤35</td>
</tr>
<tr>
<td>Distance walked in 6 min (m)</td>
<td>≥350</td>
<td>250-349</td>
<td>150-249</td>
<td>&lt;149</td>
</tr>
<tr>
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<td>0-1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>BMI</td>
<td>&gt;21</td>
<td>≤21</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


- “We do not need to add up the “BODE points” as if we are doing clinical research, but we do need to search the attending physician’s statement for each of these characteristics, and then
piece them together into a global view of the applicant. If the proposed insured is losing weight, has a reduced FEV1, is dyspneic, and is unable to exert himself, then our job is easy."


**IC/TLC Index**

- IC/TLC < 25% was found to be as good a predictor for all-cause and respiratory mortality in COPD as FEV1 %predicted and BODE index on basis of ROC-Type II curves

**Interventions that alter mortality in COPD**

- Smoking cessation is the only intervention that unequivocally impacts future mortality in COPD
- Appropriate anti-inflammatory medicines (steroids+ long-acting bronchodilator combination inhaled medicines and inhaled tiotropium) probably have an effect on mortality. The TORCH study failed to “prove” a mortality improvement by 0.005 in a study made difficult by the huge drop-out rate in the placebo group – a not-unexpected event given the severity of the placebo groups’ lung disease.
The frequency of exacerbations may be an obtainable marker (from medical records) suggesting earlier mortality in COPD.

Supplemental oxygen for persons having an SaO2 < 89% on room air (or pO2 < 55 ABG on room air) improve mortality but this applies to end-stage COPD

**Assessing Interstitial Lung Diseases**

- Often initially misdiagnosed as CHF
- Recognition of key findings in ILD
  - Generally non-productive coughing
  - Worsening Dyspnea-on-Exertion (DOE)
  - Interstitial (or reticulonodular) lung infiltrates on CXR radiology report
    - Presence of pleural effusion(s) argues AGAINST ILD
  - Oxygen desaturation on 6-minute Walk Test (if report available); desaturation with exercise is a hallmark of interstitial lung disease
  - Spirometry revealing normal or near-normal FEV1/FVC ratio with decreased FVC % predicted
  - Complete Pulmonary Function Testing showing combination of:
    - Decreased measured lung volume (Functional Residual Capacity – FRC)
    - Decreased lung diffusion (DLCO % predicted < 70%)
  - Worsening of symptoms over time
- Key co-morbidities
  - Present or past smoking history
  - Industrial exposure history (especially beryllium, asbestos, sandblasting)
  - Collagen vascular disease (especially scleroderma, SLE, rheumatoid arthritis)

**Overview of the Interstitial Lung Diseases**

- Idiopathic interstitial pneumonias (AIP, UIP, COP, NSIP, DIP, LIP)
• Chronic interstitial pneumonias secondary to systemic collagen vascular diseases
• Chronic eosinophilic pneumonia
• Granulomatous interstitial lung diseases (Sarcoidosis, Berylliosis, Hypersensitivity Pneumonitis)
• Chronic drug reactions (Amiodarone, methotrexate, macrodantin)
• Miscellaneous diseases: Langerhan cell histiocytosis, Lymphangioleiomyomatosis (LAM), Pulmonary Alveolar Proteinosis (PAP), Amyloidosis, etc
• Lymphangitic carcinomatosis

Recognizing the Idiopathic Interstitial Lung Diseases

• AIP – Acute Interstitial Pneumonitis
  o Essentially this is ARDS (Adult Respiratory Distress Syndrome) of unknown etiology with high mortality
  o This will rarely be encountered in an insurance applicant pool
• UIP – Usual Interstitial Pneumonitis
  o Precursor to IPF – Idiopathic Pulmonary Fibrosis
  o Median survival 2.4 years
• COP – Cryptogenic Organizing Pneumonitis
  o Also commonly referred to as BOOP – Bronchiolitis Organizing Pneumonitis
  o Usually is responsive to corticosteroids but relapse often occurs
• DIP – Desquamative Interstitial Pneumonitis
  o Usually quite responsive to corticosteroids
  o Appears to be caused by cigarette smoking, and this disease will relapse and progress to irreversible disease and even death if the person fails to abstain completely from future smoking
  o RBILD – Respiratory Bronchiolitis Interstitial Lung Disease – is a precursor of DIP
• NSIP – Nonspecific Interstitial Pneumonitis
  o Although this sounds like a “waste basket” diagnosis it is actually a specific histologic entity
  o Predominantly cellular form on lung biopsy may be responsive to corticosteroid therapy. Predominantly fibrotic change on lung biopsy is generally unresponsive to corticosteroid therapy
• LIP – Lymphocytic Interstitial Pneumonitis
  o Most controversial of the idiopathic interstitial pneumonias – with many pathologists arguing that this entity is actually a lymphoproliferative disease involving the lung and others consider it a variant of NSIP
  o Usually responsive to corticosteroids

Medical Mortality Assessment of the Idiopathic Interstitial Lung Diseases

• A major problem will be that many applicants who might carry these diagnoses may not have undergone confirmative VATS (video-assisted thoracoscopy) or open lung biopsy. These conditions are rarely confirmatory by fiberoptic bronchoscopy with transbronchial lung biopsy
• AIP will rarely if ever be encountered as an underwriting issue. Survival may be associated with decreased lung function, a morbidity and possible mortality issue
• UIP/IPF has high mortality
• COP usually requires long and slow corticosteroid taper but eventual recovery is the rule
• DIP (and RBILD) carry no morbidity or mortality concerns if there is complete resolution of lung disease with corticosteroid therapy and if the applicant truly and permanently quits smoking
• NSIP that is predominantly cellular (possibly evident by excellent response to long-term, slow tapering corticosteroids) usually has little long-term mortality. Predominantly fibrotic NSIP has morbidity and mortality implications approaching UIP/IPF

Assessing applicants with Sarcoidosis

• Staging of Sarcoidosis (based on CXR, not lung CT)
  o Stage I: Hilar/mediastinal lymphadenopathy
    o Spontaneous regression occurs in 1-3 yrs in 60-90%
  o Stage II: Hilar/mediastinal lymphadenopathy + reticulonodular lung involvement
    o 25% of cases present as Stage II disease
    o 66% will spontaneously remit without intervention, but if symptoms require intervention (invariably corticosteroids) remission commonly occurs but relapse is common after steroids are weaned off. Take-away point: Stage II applicant with spontaneous remission is viewed much more favorably than a Stage II applicant in remission induced by steroids.
  o Stage III: Reticulonodular or interstitial lung involvement without hilar/mediastinal lymphadenopathy
    o Predominantly reticular opacities with shrinkage of hilar lymph nodes
    o Reticular opacities are predominantly in the mid-to-upper lung zones
    o Permanent remission occurs in only 10-20%
  o Stage IV: End-stage fibrotic lung disease
    o Fibrotic lung disease with traction bronchiectasis and bullae formation – again, predominantly in mid-to-upper lung zones
    o NO REMISSION
<table>
<thead>
<tr>
<th>Stage</th>
<th>Remission (%)</th>
<th>Asymptomatic at 5 years (%)</th>
<th>CXR clearing (%)</th>
<th>5 yr Mortality</th>
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<tr>
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</tr>
<tr>
<td>Stage IV</td>
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<td>n/a</td>
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</tr>
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</table>

**Major Considerations in Underwriting Sarcoidosis**

- Presentations suggesting favorable risk (i.e. low mortality risk)
  - Löfgren’s syndrome: symptoms of fever, bilateral hilar lymphadenopathy, polyarthralgias (common in Scandinavians, rare in African-Americans and Japanese)
  - Erythema nodosum: lower extremity erythematous painful shin nodules

- Mild-to-moderate liver function abnormalities, in the absence of symptoms or hypercalcemia, has low mortality risk

- Mortality < 5% in untreated persons
  - Correlates to extent of lung disease in US
  - Correlates to presence of cardiac sarcoidosis in Europe and Japan

- When corticosteroid intervention is mandated by stage or symptoms, continuous corticosteroid administration with tapering has overall superior results long-term than repeated short bursts of high-dose steroids. Methotrexate may be used as a steroid-sparing agent in some persons (usual dose ≤ 20 mg/week, with monthly monitoring of CBC and liver function studies)

- Skin involvement (Lupus pernio), neurologic/CNS involvement, cardiac involvement: all carry increased risk for morbidity/mortality

**Additional Information on Extrathoracic Sarcoidosis**

**Extrathoracic Sarcoidosis with little or no mortality implication**

- Extrathoracic Lymphadenopathy (occurs in 15-33%)
- Eye (occurs in 12%)
- Liver (occurs in 12%)
Cutaneous Sarcoidosis

- Occurs in 9-15% of all cases of sarcoidosis
- Erythema nodosum – painful inflammatory plaques or nodules on shins – excellent prognosis
- Lupus pernio – violaceous or erythematous papules, plaques, or nodules of central face (especially nasal alae), eyes, ears – associated with more significant intrathoracic disease and worse long-term prognosis

Renal/Electrolyte manifestations of Sarcoidosis

- Defect in calcium metabolism due to extrarenal production of calcitrol by activated macrophages
- Manifestations include:
  - Increased intestinal calcium absorption
  - Hypercalciuria (occurs in up to 50% of all cases of Sarcoidosis)
  - Hypercalcemia (occurs in 10-20% of cases of Sarcoidosis)
  - Nephrocalcinosis (may result in ESRD)
- Although granulomatous infiltration of the kidney is rare, it can cause membranous nephropathy or a proliferative or crescentic glomerulonephritis or focal segmental glomerulosclerosis with high morbidity/mortality

Cardiac Involvement

- Clinically present in 5% of cases (but autopsy studies reveal subclinical involvement in 20-30% of cases)
- Most commonly seen is complete heart block (usually occurring in much younger individuals than would be expected)
- Next most common are Ventricular Dysrhythmias – Ventricular Tachycardia or Multifocal PVCs
  - These two manifestations account for 25-65% of deaths due to cardiac sarcoidosis
- Myocardial sarcoidosis may cause CHF accounting for the rest of the deaths
- Mortality of cardiac sarcoidosis is strikingly higher in Japan than in the US.
- Mortality is significantly increased in symptomatic disease (see above) and the majority of applicants will eventually die of sarcoid cardiac disease.

Neurologic Involvement

- Seen in 5% of cases of sarcoidosis
- There is a predilection for the base of the brain, with cranial nerve involvement (especially facial palsy) and hypothalamic and pituitary lesions common. These lesions respond favorably to treatment.
- Space-occupying masses, peripheral neuropathy, and neuromuscular involvement portend chronic disease with considerably increased morbidity and mortality.
Assessing Obstructive Sleep Apnea (OSA)

- Abnormal morbidity/mortality in MILD OSA without symptoms or signs (daytime somnolence, obesity, hypertension, etc) has not been proven.

- AHI is the number of Apneas + Hypopneas per hour of sleep (averaged: total number of events divided by total number of hours of sleep).

- “Normal” AHI is < 5 events per hour but there is increasing evidence in the sleep literature that this definition of “normal” should be increased to < 10 events in the elderly (age 70+).

- Morbidity/mortality of OSA best correlates with severity of derangement of AHI
  - AHI 5-15: “Mild”
  - AHI 16-30: “Moderate”
  - AHI 30+: “Severe”

- Other findings on a typical Overnight Polysomnogram (PSG) that have relevance include:
  - Sleep efficiency
  - Severity of derangement of sleep architecture (especially the lack of Stage III restorative sleep and Rapid Eye Movement (REM) sleep)
  - Time the subject is breathing < 89% on room air
  - The nadir of hypoxemia
  - The presence of cardiac events
    - Tachycardia, bradycardia
    - Occurrence of supraventricular tachyarrhythmias (SVT) or premature ventricular contractions (PVCs) or bursts of ventricular tachycardia (VT)

- Recognize that Split-Night studies usually underestimate the severity of OSA based on the AHI (because most of the REM events normally occur in the early morning hours, after the subject has been switched to CPAP)

- Recognize that CPAP is the most effective intervention for OSA
  - General consensus that 4+ hours of CPAP use nightly is needed to attain benefit

- CPAP may worsen subjects condition when excessive central apneas are present
Use of BiPAP or ADAPT machines indicated when CPAP fails to lower AHI or causes central apneas

- Confirming compliance with CPAP therapy
  - Compliance testing now mandatory by Medicare and most insurers
  - Follow-up home testing with SaO2 trend studies showing still-existing bursts of desaturations may indicate inadequate CPAP settings
  - Worsening obesity or increasing difficulty with control of BP may be indirect indicators of non-compliance with CPAP

- At this time, ENT surgical interventions (UPPP, “Pilar procedure”) and oral dental “mandible-forward” devices have not been proven to be of benefit in anything beyond snoring or mild OSAS

- Assessment of Daytime Sleepiness (usually with Epworth Sleepiness Scale Score) unfortunately does not reflect correction of OSA. Strangely, up to 50% of persons with Moderate to Severe OSA who are compliant with CPAP continue to have some problems with daytime sleepiness, and often require treatment with stimulants such as Armodafanil (NuVigil®) 150 or 250 mg/day.

- FINALLY: Remember that Sleep-Disordered Breathing (SDB) consists of two major entities:
  - Central Apneas
    - Idiopathic
    - Cheyne-Stokes – associated with CHF (congestive heart failure) or CVA (stroke)
    - Obesity-Hypoventilation Syndrome
    - Induced by high levels of CPAP
  - Obstructive Apneas
    - Overall higher mortality associated with Central Apneas than with Obstructive Apneas

**Assessing Pulmonary Hypertension**

Definition:

- Mean PA pressure ≥ 25 mm Hg
- Most commonly found on echocardiography which is now considered a screening but not diagnostic test for PH
  - RVSP (Right Ventricular Peak Systolic Pressure) > 40
• Any evidence of RA and/or RV enlargement
  • Formal diagnosis requires a Right Heart Catheterization
    o Usually with a Flolan or NO titration

**WHO Classification of Pulmonary Hypertension**

- **Type 1:** Pulmonary Arterial Hypertension **PAH**
  - Idiopathic
  - Collagen-vascular disease related (usually Scleroderma)
  - HIV
- **Type 2:** Pulmonary Hypertension **PH** due to Cardiac Disease
  - Congenital
  - Valvular
  - Ischemic or hypertensive myopathy with failure
    - Systolic Dysfunction
    - Diastolic Dysfunction
- **Type 3:** Pulmonary Hypertension **PH** due to Lung Disease
  - Cor pulmonale
  - Pulmonary fibrosis
  - Sleep-disordered Breathing (SDB)
    - Obstructive Sleep Apnea
    - Central Sleep Apnea
- **Type 4:** Pulmonary Hypertension **PH** due to Pulmonary Thromboembolic Disease
- **Type 5:** Pulmonary Hypertension **PH** due to “Other” causes
  - Portosystemic hypertension

**Treatment of PAH and PH**

- For PH – treat the underlying cause (i.e. – hypoxemia, CHF, etc)
- Phosphodiesterase-5 Enzyme Inhibitors: Sildenafil (Revatio), or Tadalafil (Adcirca)
- Endothelin Receptor Antagonists: Bosentan (Tracleer), Ambrisentan (Letairis)
- Prostacyclins: IV pump infusions or inhaled formulations

**Implications for Life and Disability Applicants**

- Correctly diagnosed and validated PAH or PH usually calls for significant concern as to insurability

**References**


This document is also updated and available online: http://circ.ahajournals.org/content/119/16/2250

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