PULMONARY DISORDERS RELATED TO IRAQ AND AFGHANISTAN DEPLOYMENT

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Disclosures

Dr. Rose reports no financial relationships with any ACCME-defined commercial interests* but would like to make the audience aware of her research funding sources:

– Sergeant Sullivan Center: Purchase of LCI equipment

Commercial Interest – Any entity producing, marketing, re-selling or distributing health care goods or services consumed by patients. The ACCME does not consider providers of clinical service directly to patients to be commercial interests. (ACCME Standards for Commercial Support, 2018).
Case #1 presentation

**History:** 29 y/o soldier with exertional shortness of breath and dry cough

- No history of respiratory disease
- Never smoker
- Pre-deployment Army 2 mile run time: 14 min
- Deployed to Joint Base Balad, 2005-2006
- Exposed to burning waste and dust storms
- Post-deployment: Unable to complete the 2 mile run due to shortness of breath
Case #1: Pulmonary physiology

PFTs:
- Normal spirometry
- Elevated RV 169%
- DLCO 84%

Methacholine challenge:
- PC20 FEV1 = 3.2 mg/ml

CPET:
- Reduced VO2max 67%

Source: Nathan S. Webster (2008), www.waronterrornews.typepad.com
Case #1: Imaging features

- Normal chest x-ray
- HRCT scan:
  - Air trapping (mosaic attenuation on expiration)
  - Small centrilobular nodules
Constrictive bronchiolitis and emphysema on VATS biopsy
Overview

- Inhalation exposures
- Spectrum of deployment lung diseases
- Approach to diagnosis
- Lung histology
- Noninvasive markers of distal lung disease
- Future research directions
Since 2001, 3 million military personnel and contractors have deployed to Iraq and Afghanistan.
Military personnel report exposure to multiple inhalational hazards.

- Desert dust
- Burn pit emissions
- Industrial fires/pollutants
- Diesel exhaust
- IED blasts/mortar fire
- Temperature and humidity extremes
- Microbials/allergens
- Job-specific VDGF (e.g., paints, welding fumes)

Enhanced Particulate Matter Surveillance Program

- 15 locations in SWA (Iraq 6, Afghanistan 2)
- >3000 filter samples – TSP, PM10, PM2.5
- All sites exceeded the Military Exposure Guideline (MEG) of 15 $\mu$g/m$^3$ for PM2.5
- 3 main air pollutants:
  - Geological dust
  - Smoke from burn pits
  - Heavy metals (Al, Cd, Pb in PM2.5 fraction)

[Engelbrecht et al, Inhal Tox; 21:2009]
Spectrum of noninfectious post-9/11 deployment-related respiratory diseases

- Acute eosinophilic pneumonia [Shorr 2004]
- Increased respiratory symptoms [Helmer 2007; Smith 2009]
- Allergic rhinitis/allergies [Szema 2010]
- New onset asthma/asthma aggravation [Roop 2007]
- Constrictive bronchiolitis [King 2011]
Constrictive bronchiolitis in soldiers returning from Iraq and Afghanistan


- 80 soldiers with unexplained exertional dyspnea and decreased exercise tolerance
- 49 had surgical lung biopsy
- 38 had constrictive bronchiolitis
- Median age 33 yrs
- 66% never smokers
- PFTs and chest HRCT scans normal or nonspecific

Source: www.marshallthompson.org
Working Group on post-deployment lung disease

- Multi-disciplinary (Pulmary, OEM, Epidemiology, Toxicology, IH, Geology; MD & PhD)
- Military (DoD, VA) and civilian (academic)
- Review current data and knowledge gaps
- Discuss coordinated approach to clinical and research efforts
- Consensus recommendations for medical surveillance, referral, and diagnosis
Recommended approach to diagnosis

- Comprehensive occupational & medical history
- Physical examination
- Complete pulmonary function testing
- Methacholine challenge
- Chest HRCT – prone & supine, expiratory
- Metabolic exercise testing
- Consider surgical lung biopsy for constrictive bronchiolitis

[Rose C et al, JOEM 2012 54;6:746-51]
Indications for surgical lung biopsy

• Unexplained disabling chest symptoms
• Lack of diagnostic clarity
• Empiric treatment unsuccessful
• Patient understands that the procedure is invasive, painful, risky, and that findings may not inform therapy, affect symptoms, or change outcomes.
DoD-funded study: Respiratory Disease Related to Deployment (R2D2)

- “A Morphometric Approach to Quantification of Small Airways Disease and Particulate Matter Exposure Profiles in Lung Biopsies of Deployed US Military Personnel”
- Collaborators at Vanderbilt (Dr. Robert Miller)
- Characterize histologic abnormalities in lung tissue samples from deployed personnel compared to normal lungs (negative control) and autoimmune bronchiolitis samples (positive control).
Summary: Lung biopsy findings

- Lung biopsies of deployers statistically significantly more likely to have findings of respiratory and constrictive/obliterative bronchiolitis compared to normals.
- Controlling for age and smoking, deployers more likely than normals to have emphysema.
Clinical Center for Deployment Lung Disease at National Jewish Health
Center for Deployment-Related Lung Disease

Since 2001, more than 3 million United States military personnel and contractors have deployed to Iraq, Afghanistan and other sites in southwest Asia. In-theatre exposure to open air burn pits, sandstorms, combat dust, diesel exhaust and other workplace hazards may place deployers at risk for disabling respiratory symptoms and lung diseases. Our program at National Jewish Health is focused on diagnosis and treatment of deployers with these lung conditions and on research into their causes and prevention, identifying new and better diagnostic tools, and developing more effective treatment options.
# Diagnostic approach

## Testing on all patients

- Questionnaire
- 90 minute history & physical exam
- Review of outside records
- PFTs, pre- and post-bronchodilator
- High resolution chest CT
- Cardiopulmonary exercise testing

## Additional studies considered based on clinical findings

- Methacholine challenge
- Laryngoscopy
- Sinus CT
- Laboratory studies
- Cardiology
- Sleep
- GI
- Surgical lung biopsy
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Distal lung disease</th>
<th>Symptoms</th>
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</thead>
<tbody>
<tr>
<td><strong>Deployment Distal Lung Disease (DDLD)</strong></td>
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<tr>
<td><strong>Definite</strong></td>
<td>One or more of the following surgical lung biopsy findings:</td>
<td>Cough</td>
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<tr>
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<td>• Bronchiolitis, small airways inflammation, peribronchiolar fibrosis</td>
<td>Shortness of breath</td>
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<td>• Granulomatous pneumonitis</td>
<td>Chest tightness/ wheezing</td>
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<td>• Hyperinflation or emphysema</td>
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<td></td>
<td><strong>Probable</strong></td>
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<td>Two or more of the following chest CT findings:</td>
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<td>• Centrilobular nodularity</td>
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<td>• Air trapping or mosaicism</td>
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<td>• Bronchial wall thickening</td>
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<td><strong>Proximal respiratory diseases</strong></td>
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<td><strong>Deployment-Related Asthma (DRA)</strong></td>
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<td><strong>Definite</strong></td>
<td>One or more of the following findings:</td>
<td>Cough</td>
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<td>• Post-bronchodilator ↑ in FEV₁ ≥ 12% and ↑ in FEV₁ ≥ 200 cc</td>
<td>Shortness of breath</td>
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<td>• Methacholine challenge with PC&lt;sub&gt;20&lt;/sub&gt; FEV₁ ≤ 4 mg/mL</td>
<td>Chest tightness/ wheezing</td>
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<td><strong>Probable</strong></td>
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<td>• Methacholine challenge with PC&lt;sub&gt;20&lt;/sub&gt; FEV₁ &gt;4 and ≤16 mg/mL</td>
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<td><strong>Deployment-Related Rhinosinusitis</strong></td>
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<td>One or more of the following findings:</td>
<td>Cough</td>
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<td>• Sinus CT imaging with evidence of mucosal thickening, partial or complete</td>
<td>Runny Nose</td>
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<td>opacification of the paranasal sinuses, rhinitis</td>
<td>Rhinorrhea</td>
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<td>• Physician-diagnosed rhinosinusitis on laryngoscopy</td>
<td>Sinus congestion</td>
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<td>Sinus headache</td>
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<td>Post nasal drip</td>
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<td><strong>Deployment-Related Laryngeal Dysfunction (VCD)</strong></td>
<td>One of more of the following findings:</td>
<td>Cough</td>
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<td>• Positive for vocal cord dysfunction on direct laryngoscopy</td>
<td>Shortness of breath</td>
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<td>• Consistent truncation of the inspiratory limb of flow-volume loop on</td>
<td>Chest tightness/ wheezing</td>
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<td>spirometry efforts</td>
<td>Hoarseness</td>
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<td>Throat fullness</td>
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<td>Trailing voice</td>
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Characteristics of 171 cases

Demographics:

- 86% Male
- 83% Caucasian
- Mean age 39 years (range 23-69)
- Smoking: 37% former, 61% never, 2% current
- Service branch: 67% Army/Marines
- 48% Iraq, 24% Afghanistan, 23% both
- Mean deployment duration: 19 months (2-120)
- Mean deployment frequency: 2 times (1-7)
Exposures and symptoms

- **Exposures:**
  - Daily burn pit exposure: 71%
  - Weekly or bi-weekly sandstorms: 70%

- **Symptoms:**
  - Dyspnea: 82%
  - Chest tightness: 75%
  - Wheezing: 68%
  - Cough: 64%
Lung function and imaging

- Pulmonary function testing:
  - 19.5% restrictive pattern (FVC < LLN)
  - 18% DLCO < 80%
  - 44% RV > 140%
- Positive methacholine challenge: 41%
- Reduced exercise tolerance (VO2max < 84%): 48%
- Chest HRCT scan: Most common abnormalities are air trapping/mosaic attenuation (52%) and centrilobular nodularity (36%)
Spectrum of deployment-related respiratory disorders

- Rhinosinusitis (14%)
- Laryngeal dysfunction (15%)
- Expiratory dynamic airways collapse (EDAC)/tracheobronchomalacia (TBM)
- New onset asthma or aggravation of pre-existing asthma
- Eosinophilic syndromes
- Bronchiolitis
- Other histologic abnormalities: hyperinflation, granulomata, pleuritis
Hematoxylin and eosin staining of surgical lung biopsy shows the spectrum of histologic abnormalities in those with deployment distal lung disease including constrictive bronchiolitis (A), emphysema (B), and granulomatous pneumonitis (C).
THE GLIDE STUDY

- DOD funded study, 2016 - 2021
- 4 projects: Rose, Downey, Chu/Day, Seibold
GLIDE Project 1: Specific Aims

1. Determine the utility and sensitivity of the lung clearance index (LCI) as a marker of deployment-related distal lung disease (DDLD) in symptomatic deployers compared to non-deployed adults matched for age and smoking.

2. Determine the utility and sensitivity of isovolumetric chest CT enhanced with quantitative pulmonary and textural analysis as noninvasive markers of DDLD.
Aim 1: What is Lung Clearance Index (LCI) testing?

- Multiple breath washout (MBW) performed during tidal breathing to measure rate of clearance of an inert gas.
- Sensitive, noninvasive test of small airways disease.
- Studies in patients with CF show that LCI is more sensitive than spirometry (FEV1) at detecting early lung disease across a wide range of ages (Gustafsson 2003; Aurora 2005; Fuchs 2001).
Pilot study found LCI scores were higher in deployers than controls.

**TABLE 2. LCI Results in Controls and Deployers**

|                      | Controls (n = 24) | Deployers (n = 28) | P *  
|----------------------|------------------|--------------------|------
| Mean LCI, unadjusted (95% CI) | 6.95 (6.73–7.17) | 7.76 (7.34–8.17) | 0.001 |
| Mean LCI, adjusted (95% CI) | 7.06 (6.74–7.39) | 7.42 (7.13–7.71) | 0.10 |
| Percent LCI >7 | 54% | 82% |

95 CI, 95% confidence interval; LCI, lung clearance index.

*Note: P value of 0.001 reported is unadjusted; t test adjusted for covariates of age, smoking status, and BMI demonstrates no significant difference (P = 0.10) between mean LCI of controls (7.06) and deployers (7.42).

[Kreft et al, JOEM, 2017]
Distribution of LCI score by diagnosis

- P-value = 0.0003 via ANOVA test
- Tukey test detects significant differences between DDLD & DRA and DDLD alone from controls
Deployment lung: 
CT features

- Centrilobular nodularity reflects small airway thickening
- Bronchial wall thickening
- Expiratory gas trapping
- CT may be normal
Deployment lung: quantitative CT evaluation

- Textural analysis of centrilobular nodularity
- Classification of regions of interest: normal, emphysema, CLN
- Approach has been shown to identify small airways injury in smokers
- Develop algorithm to apply to CT scans of deployed subjects

Future directions

• Linkage of exposure data to health outcomes
• Standardized questionnaires for use in clinical diagnosis, multi-center studies
• Noninvasive markers of lung disease
• Better understanding of disease pathogenesis to inform treatment
• Longitudinal follow up to assess prognosis
• Prevention
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Questions?