Looking Back, Moving Forward: Research on Deployment-Related Respiratory Diseases

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Disclosures

• Department of Defense (DoD): Mechanisms and Treatment of Deployment-Related Lung Injury: Repair of the Injured Epithelium
• DoD: Innate Immunity and Deployment-Related Lung Disease
• DoD: Study to Improve Deployment-Related Asthma Using L-Citrulline Supplementation
• Sergeant Sullivan Center
Since 1990, over 3.5 million people deployed to Southwest Asia & Afghanistan.
The first decade (2001 – 2011)

Iraq:
• Operation New Dawn: 2010 – 2011

Afghanistan:
• Operation Enduring Freedom: 2001 - 2014
Early reports of post-9/11 deployment respiratory diseases

- Increased respiratory symptoms

- Acute eosinophilic pneumonia

- New onset asthma/asthma aggravation

- Constrictive bronchiolitis
Deployers reported exposure to multiple, poorly characterized inhalational hazards.

- Burn pit smoke
- Desert dust particulates
- Diesel exhaust
- Industrial fires/pollutants
- Combat dust
- Cigarette smoke
- IED blasts/mortar fire
- Temperate extremes
- Microbial/allergenic agents
- Job-specific VDGF (solvents, welding fumes, concrete, paints)

https://www.military.com/equipment/high-mobility-multipurpose-wheeled-vehicle-hmmwv
Other relevant exposures and outcomes

• First Persian Gulf War
  – Oil well fire smoke, dust storms

• World Trade Center first responders
  – Smoke from smoldering pile, other airborne PM
  – Significant decline in FEV1 in NYC firefighters
  – WTC cough, asthma, COPD, GERD, rhinosinusitis, sarcoidosis, PTSD
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 ug/m3 for PM2.5
- 3 main air pollutants:
  - Geological dust
  - Smoke from burn pits
  - Heavy metals (Al, Cd, Pb in PM2.5 fraction)

2010 IOM Study on burn pits

Multiple studies document increased incidence of respiratory complaints in Veterans of the 1991 Gulf War and post-9/11 conflicts in Iraq and Afghanistan.
An unknown number returned from deployment unable to meet military physical fitness requirements.

- Dyspnea on exertion
- Cough
- Wheezing
- Chest Tightness

https://www.military.com/military-fitness/army-fitness-requirements/army-basic-training-pft
Overview and Recommendations for Medical Screening and Diagnostic Evaluation for Postdeployment Lung Disease in Returning US Warfighters

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Objective: To review inhalational exposures and respiratory disease risks in US military personnel deployed to Iraq and Afghanistan and to develop consensus recommendations for medical screening and diagnostic referral. Methods: A Working Group of physicians and exposure scientists from academia and from the Departments of Defense and Veterans Affairs was convened in February 2010. Results: Despite uncertainty about the number of people affected and risk factors for adverse pulmonary outcomes in this occupational setting, the Working Group recommended: (1) standardized approaches to pre- and postdeployment medical surveillance; (2) criteria for medical referral and diagnosis; and (3) case definitions for major deployment-related lung diseases. Conclusions: There is a need for targeted, practical medical surveillance for lung diseases and for a standardized diagnostic approach for all symptomatic deployed personnel.

Learning Objectives
- Become familiar with published data on inhalational exposures and respiratory disease risks in U.S. military personnel deployed to Iraq and Afghanistan, as reviewed by the Working Group.
- Summarize the Working Group’s recommendations on standardized pre- and post-deployment medical surveillance, criteria for medical referral and diagnosis, and case definitions for deployment-related lung diseases.
- Identify areas of disagreement with the Working Group recommendations in the accompanying “clarification” by the Department of Defense.
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.
**Standardized clinical case definitions**

<table>
<thead>
<tr>
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<th>Symptoms</th>
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<tbody>
<tr>
<td><strong>Distal lung disease</strong></td>
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<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>
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<td>• Bronchiolitis, small airways inflammation, peribronchiolar fibrosis</td>
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<td></td>
<td>• Granulomatous pneumonitis</td>
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<td>• Hyperinflation or emphysema</td>
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<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></td>
<td>• Bronchial wall thickening</td>
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<td><strong>Probable</strong></td>
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<tr>
<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>
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<td>• Post-bronchodilator $\uparrow$ in $FEV_1 \geq 12%$ and $\uparrow$ in $FEV_1 \geq 200$ cc</td>
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<td></td>
<td>• Methacholine challenge with $PC_{20}$ $FEV1 \leq 4$ mg/mL</td>
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<tr>
<td><strong>Probable</strong></td>
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<tr>
<td></td>
<td>• Methacholine challenge with $PC_{20}$ $FEV1 &gt;4$ and $&lt;16$ mg/mL</td>
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<tr>
<td><strong>Deployment-Related Rhinosinusitis</strong></td>
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<td>One or more of the following findings:</td>
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<td>• Sinus CT imaging with evidence of mucosal thickening, partial or complete opacification of the paranasal sinuses, rhinitis</td>
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<td>• Physician-diagnosed rhinosinusitis on laryngoscopy</td>
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</table>
GLIDE: Multi-pronged investigation of lung disease mechanisms and prevention
VA Airborne Hazards and Open Burn Pit Registry

Eligible to participate if deployed to Southwest Asia theater of operations any time after August 2, 1990 or Afghanistan or Djibouti on or after September 11, 2001

https://www.publichealth.va.gov/exposures/burnpits/registry.asp
DRRD research: The 1st decade (2001 – 2011)

• Increased respiratory symptoms among previously deployed
• Complex and variable exposures
• General approach to diagnosis
• Standardized clinical case definitions
• Studies begin on mechanisms of airway injury
• VA Airborne Hazards and Open Burn Pit Registry
The second decade (2012 – 2022)

Iraq:
Operation Inherent Resolve: 2014 - present

Afghanistan:
Operation Enduring Freedom: 2001 - 2014
Operation Freedom’s Sentinel: 2015 – 2021
Key Findings:

- Military deployers with combat experience were 24%–30% more likely to develop asthma than those who did not deploy.
- This association was not seen in deployers without combat experience.
Military occupational specialty codes (MOS) assigned to all personnel by Dept. of Defense

Alpha numeric codes to describe job training & duties.

For example, Army 11 Bravo = Infantry

Job Duties
• Perform as a member of a fire team during drills and combat
• Aid in mobilization of vehicles, troops and weaponry
• Assist in reconnaissance missions
• Process prisoners of war and captured documents
• Use, maintain and store combat weapons (rifles, machine guns, antitank mines, etc.)

Combat MOS codes are linked to higher exposure risk, but have limitations.

- *Combat MOS codes* linked to the highest mean respiratory hazard exposure intensities and to likelihood of having undergone clinical evaluation for respiratory symptoms.
- Military deployment exposures may be related to variables such as deployment *location* (e.g., presence/absence of a burn pit), *timing* (before/after the drawdown), *season* (e.g., seasonal dust storms), and *job duties* during deployment (e.g., chaplain) that are not reflected in MOS code.

Spectrum of lung histopathologic abnormalities

- Mod/severe emphysema/hyperinflation (46%)
- Constrictive/obliterative bronchiolitis (18.5%)
- Granulomatous pneumonitis (46%)
- Peribronchiolar metaplasia (68%)
- Pleuritis

Noninvasive tests of distal lung disease

Multiple Breath Washout (MBW) Testing
Deployers with DRA and DDLD significantly more likely than controls to have abnormal MBW/LCI.

- MBW/LCI is useful to detect global ventilation inhomogeneity from airways disease in symptomatic deployers.
- Deployers who reported more frequent exposure to explosive blasts had significantly higher LCI scores.

Chest imaging in proximal & distal DRRD


Expanding spectrum of deployment-related respiratory diseases

- Rhinitis and sinusitis
- Eosinophilic syndromes
- New onset asthma/aggravation of pre-existing asthma
- Bronchiolitis, granulomatous pneumonitis and emphysema
- Expiratory central airways collapse
- Intermittent laryngeal dysfunction


- Mitochondrial dysfunction as a cause of dyspnea

VA Centers of Excellence

Post-Deployment Cardiopulmonary Evaluation Network (PDCEN)
2020 NASEM Report

• Insufficient evidence of association
• Lack of good exposure characterization
• DoD-VA partnership ‘with free flow of information’
Emerging consensus on DRRD

- 3-tiered approach to diagnosis
- Injury in multiple lung compartments
- Terminology: DRRD
DRRD research: The 2nd decade (2012 – 2022)

• Expanding spectrum of deployment-related respiratory diseases
• Combat related risks
• Lung histopathology
• Noninvasive diagnostic tests
• VA Centers of Excellence
• PACT Act [Sergeant First Class Heath Robinson Honoring our Promise to Address Comprehensive Toxics Act]
PACT Act covered nonmalignant respiratory illnesses (‘presumptive’) • Asthma that was diagnosed after service • Chronic bronchitis • Chronic obstructive pulmonary disease (COPD) • Chronic rhinitis • Chronic sinusitis • Constrictive bronchiolitis or obliterative bronchiolitis • Emphysema • Granulomatous disease • Interstitial lung disease (ILD) • Pleuritis • Pulmonary fibrosis • Sarcoidosis
Moving forward: 2023 and beyond

“Scientific findings do not fall on blank minds that get made up as a result. Science engages with busy minds that have strong views about how things are and ought to be.”

Sir Michael Marmot, 2004, Professor of Epidemiology at University College London
Research needs and priorities

• Exposure assessment
• Large epidemiologic studies of respiratory outcomes
• Standardized questionnaires in multi-center studies
• Further validation of noninvasive markers of lung disease – eg, iOS, LCI, quantitative imaging
• Better understanding of DRRD pathogenesis to inform treatment
• Longitudinal follow up to assess prognosis
• Linkage of exposures to health outcomes
• Prevention: Targeting high risk settings for realistic exposure control
Longitudinal outcomes

• More intense deployment inhalational exposures linked with lower post-deployment lung function: *Significantly lower mean FEV1pp (88.8%) in highest vs lowest (97.2%) exposure tertile (p=0.004) [adjusted for cigarette smoking and family history asthma/COPD]*

• Consider baseline spirometry for those likely to face combat and those involved in infrastructure (burn pit duties) where risks appear highest.
Evidence-based treatment

SEALS: L-citrulline supplementation for deployment-related asthma
Exposure assessment and control

• Exposure assessment in military theaters
  – Portable, real-time, mixed/variable
  – Biomarkers

• Exposure priorities for PACT Act research
  – PM2.5, burn pit smoke, jet fuels, DEP, allergens/bioaerosols
  – Occupational VDGF
  – Effect modifiers (eg, noise, stress, temperature extremes)

• Linkage of exposures to health outcomes
  – ILER (Individual Exposure Record)
  – VA Asthma Study
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