Stella E. Hines, MD, MSPH is an Assistant Professor of Medicine at the University of Maryland School of Medicine in Baltimore, with appointments both in the Division of Occupational and Environmental Medicine and in the Division of Pulmonary and Critical Care Medicine. She also serves as the Medical Director for Employee Health Services for the University of Maryland outpatient faculty practices. Dr. Hines, a native Texan, received her undergraduate degree in Biochemistry in 1998 at Rice University in Houston, Texas. She completed medical school at Texas A&M College of Medicine in 2002, and then entered Internal Medicine residency at the University of Chicago. She completed Pulmonary and Critical Care fellowship along with public health graduate training and Occupational/Environmental Medicine residency at the University of Colorado, Denver and National Jewish Health. During her time in Colorado, Dr. Hines' research focused on longitudinal pulmonary function analysis in flavor manufacturing workers and surveillance for immune-mediated respiratory health effects in epoxy resin manufacturing workers. She also participated in regional medical surveillance clinics of coal, hard rock, and uranium miners. During her time at the University of Maryland, Dr. Hines has continued in her clinical and research interests in occupational lung disease. Her work has focused on respiratory health effects in military populations, including research focused on health effects in Depleted Uranium-exposed Gulf War Veterans. She is currently funded by CDC-NIOSH to study determinants of elastomeric respirator use in healthcare workers, as an alternative to conventional N95 use. She is the course director of the Pathophysiology and Therapeutics pulmonary unit for the second year medical students at University of Maryland, and is involved with the clinical education of fellows and residents from the University of Maryland, Johns Hopkins and the Uniformed Services University of the Health Sciences. She enjoys group exercise, watching baseball and eating blue crabs on the Chesapeake Bay.
OBJECTIVES:
Participants should be better able to:

1. The listener will learn about new cases reported in the medical literature of constrictive bronchiolitis in flavoring-exposed populations.

2. The listener will learn about the increasing body of medical literature related to pulmonary health in military Service members from combat operations in Southwest Asia.

FRIDAY, MARCH 4, 2016 10:30 AM
Update in Occupational Lung Disease: Constrictive Bronchiolitis in Flavors and War

Stella E. Hines, MD, MSPH
Assistant Professor
The University of Maryland-Baltimore
School of Medicine

Dr. Hines has declared no conflicts of interest related to the content of her presentation.
Disclosures

• Dr. Hines has evaluated patients for flavoring-induced lung disease and provided programmatic advice to flavor manufacturing employee health services within her academic practice at the University of Maryland School of Medicine.

Outline

• Review of nomenclature
• Review and Update on Flavoring-induced Lung Disease
• Review and Update on Deployment-related Lung Disease
• Summary
Constrictive Bronchiolitis/ Obliterative Bronchiolitis

- Bronchiolar disorder
  - Airways < 2 mm
  - Lack of cartilage
- Concentric narrowing of the bronchiolar lumen due to fibrotic changes to the airway wall


Related terms/conditions

- Cellular bronchiolitis
- Follicular bronchiolitis
- Proliferative bronchiolitis
- BO with organizing pneumonia

Examples of exposures associated with bronchiolar disorders

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammonia</td>
<td>Chemical industry, refrigerant</td>
</tr>
<tr>
<td>Benzalkonium compounds</td>
<td>Floor polish spill</td>
</tr>
<tr>
<td>Chlorine</td>
<td>Transportation spill, industrial accident</td>
</tr>
<tr>
<td>Flock (nylon, rayon)</td>
<td>Upholstery</td>
</tr>
<tr>
<td>Humidifier disinfectant</td>
<td>Homes</td>
</tr>
<tr>
<td>Nitrogen oxides</td>
<td>Explosive detonation, silage</td>
</tr>
<tr>
<td>Sulfur dioxide</td>
<td>Sulfur mine fire, paper mill bleaching</td>
</tr>
<tr>
<td>Sulfur mustard</td>
<td>Chemical warfare</td>
</tr>
<tr>
<td>Styrene</td>
<td>Fiberglass-reinforced plastics</td>
</tr>
</tbody>
</table>


- association with constrictive bronchiolitis
Audience Response Question 1

• True/False
  – Flavoring-related Constrictive Bronchiolitis was first recognized as an occupational illness among lollipop factory workers?
  • A. TRUE
  • B. FALSE

Audience Response Question 1

Flavoring-related Constrictive Bronchiolitis was first recognized as an occupational illness among lollipop factory workers?

A. True
B. False
**Original Cases in Microwave Popcorn Workers**

- **2000:**
  - 9 former workers of a microwave popcorn plant in rural Missouri dx with Bronchiolitis Obliterans
  - Non-smokers
  - Spirometry: fixed airflow obstruction
    - FEV1 ranged 14-67% predicted
  - HRCT: mosaic attenuation, air trapping
  - Surgical lung bx: bronchiolitis obliterans
  - All had worked in production areas of the plant


**Additional Cases in Flavor Manufacturing Workers - 2007**

- **Diacetyl Manufacturer in Netherlands**

**MMWR**

*April 27, 2007: Fixed Obstructive Lung Disease Among Workers in the Flavor-Manufacturing Industry --- California, 2004–2007*

- 2 cases in California flavor companies
  - 29 yo M; fixed airflow obstruction, typical HRCT
  - 40 yo W; fixed airflow obstruction; bx with peribronchial inflammation, interstitial fibrosis, granulomas

**Van Rooy et al, AJRCCM, 3007**
2007 - Consumer Case brings “Popcorn Lung” to national attention

• 53 y.o. never smoker c/o shortness of breath & cough
• Spiro: Fixed obstruction
• VATS Bx: bronchiolitis obliterans (& granulomas)
• SHx: Consumes 2 bags/day microwave popcorn x 10 years

Industry Response to Consumer Case

• Change in formulation & advertising
  Press Releases
  AMERICAN POP CORN COMPANY, MAKERS OF JOLLY TIME POP CORN,
  STATEMENT ON THE BUTTER FLAVORING AGENT DIACETYL
  September 5, 2007
  America’s first brand name of popcorn, JOLLY TIME, will remove all added diacetyl from their microwave popcorn products within the next 90 days.

• Change to different flavoring agents
  • Butter starter distillate, Acetoin, 2,3-pentanedione
Diacetyl substitutes still induce epithelial toxicity in rat & mouse models

- Inhalation of 2,3-pentanedione
  - Upper airway epithelial necrosis (*Hubbs 2010, Morgan 2010*)
  - Extra & intraluminal airway fibrosis (*Morgan 2012*)

- Intratracheal administration of 2,3-pentanedione
  - Bronchiolar epithelial inflammation & necrosis + intramural fibrosis (*Flake 2010*)

Morgan et al, Tox Path, 2012. Figure: Constricted bronchiolar lumen lined by irregular epithelium.

Audience Response question 2

- TRUE/FALSE

- No additional cases of biopsy-proven constrictive bronchiolitis have been published among flavor-exposed populations since the report of the consumer case.
  - A. TRUE
  - B. FALSE
Audience Response Question 2

No additional cases of biopsy-proven constrictive bronchiolitis have been published among flavor-exposed populations since the report of the consumer case.

A. True
B. False

Additional Cases – Consumers

• 47 yo F, non-smoker
  – Worked at video store x 4 years, popped 30 bags of popcorn/weekend
  – Consumed 3-5 bags/day popcorn 1996-2004

• 43 yo F, non-smoker
  – Consumed 1-2 bags/day from 1989-2000, and sporadically thereafter
  – NSIP + bronchiolitis obliterans

Additional Cases – Food Production

• Cookie manufacturing in Brazil
  – 4 male, non-smokers, exposed to artificial butter flavoring

Cavalcanti et al, J Bras Pneumol. 2012

Additional Cases – Coffee Production

2 Cases

• 34 yo Hispanic F, nonsmoker
  • Initially worked in QC, then housekeeping, then flavoring room
  • Operated grinding and packing machines for flavored beans for 1 year
  • Moved to similar job in unflavored coffee area for another 2.5 years
  • Initially diagnosed and treated for asthma, worsened

• 39 yo Hispanic M, nonsmoker
  • Initially worked as green coffee bean unloader, then maintenance, then mixer in flavorings room x 19 months
  • Symptoms noted after 18 months at this job
  • Initially diagnosed and treated for bronchitis
Cases and Surveillance from Coffee Production (same facility)

- 3 additional cases in former workers based on non-invasive testing → **total of 5**
- 2.7 x Increased Airflow Obstruction
- 1.6 x Excess of SOB on mild exertion among current workers compared to NHANES III

*Bailey et al, AJIM. 2015*

New Exposure Data – Coffee production

- High levels of flavoring compounds not just in flavoring rooms, but in areas with unflavored beans

*Bailey et al, AJIM. 2015; Gaffney et al, Tox Reports. 2015*
New Exposure Data – Coffee Shops

- Simulated small coffee shop, preparation & consumption of unflavored coffee
  - Grinding of beans
  - Brewing
  - Pouring into cups
- Compared levels to NIOSH proposed REL of 0.005 ppm over 8 hours

New Exposure Data – Cigarette Smoke

- Diacetyl and 2,3-pentanedione measured in mainstream smoke via standard smoking machine
  - Mean diacetyl: 250-361 ppm
  - Mean 2,3-pentanedione: 32.2-50.1 ppm
- Author Conclusions:
  - Exposures from smoking far exceed occupational exposures;
  - Findings suggest that studies implicating health effects associated with diacetyl exposure have been confounded due to non-occupational exposure to diacetyl from cigarette smoking

New Exposure Data – E-cigarettes

51 types of e-cigs by leading brands, with flavors deemed “appealing” to youth.
- “Cotton candy”
- “Cupcake”

We continue to see this disease in flavor-exposed populations......
We continue to identify new opportunities for exposure but
Is this the same disease being seen in military deployers?

Constrictive Bronchiolitis in Deployers to Middle East and Southwest Asia

- Fort Campbell soldiers referred to Vanderbilt for evaluation of exertional dyspnea
  - Unable to complete 2 mile run
  - Most exposed to large sulfur mine fire in Iraq
  - 80 evaluated
    - 49 referred for VATS
      - 38 had constrictive bronchiolitis
      - Remaining 11: 2 with Respiratory Bronchiolitis, 2 RB-ILD, 2 HP, 2 Sarcoidosis, 2 other

*King NEJM 2011; Miller, ATS 2011*

**Audience Response question 3**

- TRUE/FALSE

*Deployers from the 2011 NEJM report with Constrictive Bronchiolitis showed severe pulmonary functional impairment.*

  A. True
  B. False
Audience Response Question 3

*Deployers from the 2011 NEJM report with Constrictive Bronchiolitis showed severe pulmonary functional impairment.*

A. True  
B. False

![Chart showing 63% and 37%]

PFTs & Imaging not that “impressive”

- **PFTs**
  - **Totally normal in 13**
  - 25 with abnormal gas exchange (low diffusion capacity (DLCO))
  - FEV1, FVC, FEV1/FVC all *significantly different* from controls but still “normal”
    - FEV1 % Pred: 86.7  
    - FVC % Pred: 90.3  
    - FEV1/FVC %: 79.1  
    - TLC % Pred: 96.1  
  
  **But...**
  - DLCO % Pred: 73.4
    - vs. 90.6% in controls

- **High res chest CTs (n=37)**
  - **25 NORMAL**
    - 6 mild air trapping  
    - 1 single nodule  
    - 2 multiple nodules  
    - 1 basilar scarring  
    - 1 pleural thickening  
    - 1 apical bullae

- **Cardiopulmonary Exercise Tests**
  - VO2 max & Anaerobic Thresholds significantly lower than controls
So, clinically this is odd.
Was it really constrictive bronchiolitis?

Subepithelial fibrosis

Fibrosis between epithelium & muscle layer

Smooth muscle hypertrophy

Smooth muscle hypertrophy + intimal fibrosis + PA medial hypertrophy & peribronchial pigment

Polarizable pigment (from E)

King NEJM 2011

Exposures of Concern

Photo credit: R. Teichman, WRIISC conference, Aug 2011
Institute of Medicine Report, released 2011

• VA directed IOM to prepare an evaluation of Burn Pit issues and recommendation back to the VA

• Conclusions
  – Mixture of chemicals from regional bkgrd & local sources that contribute to the high PM
  – Unable to determine whether long-term health effects likely due to burn pit emissions;
    • BUT service in Iraq or Afghanistan might be associated with long-term health effects (mainly b/c of PM from natural & anthropogenic sources)
  – Needs more study

New Data on Lung Disease in Military Populations

• Review Articles
    • Recommended diagnostic and management algorithm for deployment-related sx
    • Table of all published data, from case series through cohort studies
New Data on Lung Disease in Military Populations

- Case Reports
  - Zumbrzuskia et al, ATS 2011
    - Pulmonary Fibrosis Presenting At Post-Deployment Health Screening
  - Dhoma et al, ATS 2013
    - Lung Disease in Deployers Returning from Iraq and Afghanistan
  - Sobieszczyk & Holley, ATS 2013
    - Lung Function Testing In Soldiers Serving In Iraq And Afghanistan And Returning With Dyspnea
  - Dhoma et al, ATS 2014
    - Chest Tomography May Predict Histopathologic Abnormalities In Symptomatic Deployers Returning From Iraq And Afghanistan
  - Lowers et al, ATS 2015
    - Lung Biopsies from Symptomatic Military Deployers have Variable Mineral Particle Types and Higher Abundances of Silicon, Aluminum, Cadmium and Vanadium Compared to Controls

STAMPEDE

Figure 1. Frequency of self-reported deployment reported on the follow-up weekly; 3 = daily.

Morris et al, AJRCCM, 2014
Asthma and COPD

• Asthma
  – 400 active duty Army undergoing Medical Evaluation Board for career-limiting asthma
  • No difference in rates of diagnosis or severity based on deployment to Southwest Asia
  • 48% had fixed airflow obstruction
  • 95% had positive Methacholine challenge

• COPD
  – Database review of all active duty with new dx of “emphysema” or “chronic airway obstruction”
  • 371 cases
  • 52% deployed vs. 48%
    – Mean age 40
    – Mean pack-years 19
    – Only 67% obstructed

DelVecchio et al, J Asthma, 2015
Matthews et al, Mil Med, 2014

Exposure and Animal Data

• Compared dust composition & size
  – Camp Victory, Iraq
  – Kuwait
  – Silica (+ control)
  – US Urban Dust (control)

• Similar size fraction

Self-selected Registry Data

VA Airborne Hazards and Open Burn Pit Registry

- 28,426 completed questionnaires as of Dec 2014
  - Most commonly reported provider-diagnosed health conditions:
    - Allergies, asthma, hypertension
  - Burn Pit Exposure
    - More likely to report asthma, hypertension, insomnia, chronic multi-symptom illness
  - Dust Storm Exposure
    - Asthma, COPD associated with exposure

BurnPits360.org Registry

- Published report of 38 Participants
  - 54% nonsmokers
  - 24% worked at burn pits
  - 58% reported general respiratory symptoms
  - 13% have received PFTs
  - 8% have undergone lung biopsy
- Paper references 309 cases of Constrictive Bronchiolitis in Iraq-Afghanistan veterans


Current Recommendations:

Surgical Biopsy?

- Rose et al, 2012
  - “Consider referral for surgical lung biopsy to assess constrictive bronchiolitis on a case-by-case basis.”
- Zacher et al, 2012; Morris et al, 2013
  - “Pulmonologists within the DoD or VA healthcare systems do not advocate surgical lung biopsy in the absence of PFT or CT findings, or without a comprehensive evaluation to eliminate other causes of disease.”
- Cummings and Kreiss, 2015
  - “Given the variable clinical, functional, and radiographic findings in exposure-related bronchiolar disorders, biopsy is warranted for symptoms that remain unexplained after a complete noninvasive evaluation.”
Audience Response question 4

• Multiple Choice
What histopathologic feature continues to show up on the biopsies of flavor- and deployment-exposed military populations *in addition* to constrictive bronchiolitis?

– A. intra-lumenal polypoid tissue
– B. granulomatous inflammation
– C. lymphoid aggregates
– D. emphysema
Spectrum of Hypersensitivity Pneumonitis?

Summary

- Histopathologic nomenclature in occupational bronchiolar disorders should be precise
- New cases of flavoring-related constrictive bronchiolitis continue to be reported
- Since King’s 2011 published case series of constrictive bronchiolitis in deployers, at least 6-10 cases in published conference abstracts
- Non-invasive methods were helpful in flavoring, but perhaps less so in deployment-related cases
Thank you!

Stella E Hines, MD, MSPH
shines@medicine.umaryland.edu
University of Maryland School of Medicine