Work-Related Asthma: An Overlooked Asthma Trigger

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OBJECTIVES

• Highlight the Importance of Considering Occupational and Environmental Exposures in Diagnosis and Treatment of Adult Onset Asthma

• Discuss Approaches to Diagnosing Work-Related Asthma
Work-Related Asthma Death

• 50 year old white male
• Smoker since age 16
• No personal or family hx of allergies
• Blind right eye
• Began working 12/01
• Company makes adhesives from isocyanates and epoxies
• Small facility of large company – 21 production workers
• Per next-of-kin and fiancée – symptoms associated with work – no symptoms prior
Work–Related Asthma Death

- December 2005 - Collapsed at work
- CPR immediately, EMS 5 minutes later
- Never regained consciousness
- Died 6 days later in hospital

- Autopsy
  - Anoxic encephalopathy
  - Agonal myocardial infarction
  - Lung: “bronchial basement thickening and bronchiolar goblet cell metaplasia with hyperplasia”
  - No evidence non-agonal myocardial infarction or pulmonary emboli
### Chronology of Medical Care

<table>
<thead>
<tr>
<th>Date (MM/DD)</th>
<th>Company Screening</th>
<th>Urgent Care</th>
<th>Primary Care</th>
<th>Pulmonologist</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/01</td>
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<td>01/02</td>
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<td>12/05</td>
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<td>10/05</td>
</tr>
</tbody>
</table>

**12/01 BEGAN WORK**

**12/05 DIED**
Urgent Care

07/02  “Acute bronchitis with mild bronchospasm”
12/02  “Exposed glue fumes at work”
      “Acute tracheitis with possible reactive airways disease and bronchospasm”
      “Suspect underdiagnosed or occult emphysema”

02/03  COPD

07/03  c/o SOB at work, left work
      COPD exacerbation (initially wrote asthma, then crossed out)

09/04  Acute bronchitis
# Company Medical Screening

<table>
<thead>
<tr>
<th>Date</th>
<th>FEV$_1$</th>
<th>Pred</th>
<th>% Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>January 2002</td>
<td>3.75 L</td>
<td>3.94</td>
<td>95</td>
</tr>
<tr>
<td>September 2002</td>
<td>3.60 L</td>
<td>3.77</td>
<td>96</td>
</tr>
<tr>
<td>October 2003</td>
<td>3.27 L</td>
<td>3.74</td>
<td>87</td>
</tr>
<tr>
<td>October 2004</td>
<td>2.58 L</td>
<td>3.54</td>
<td>73</td>
</tr>
</tbody>
</table>
Company Doctor

- 10/3
  Noted under care for asthma with medication
- 10/4
  “Doesn’t work with isocyanates but when incidentally exposed flares up. Happens every 3 months, own doctor treats antibiotics and bronchodilator”
  Abnormal spirometry – urged to stop smoking
Primary Care Doctor

05/03 “asthma, increase Advair”
07/03 “poorly controlled asthma”, increase Advair dose
09/03 “asthma about the same”
11/03 “He notices chemicals at work seem to trigger his asthma. He does wear a respirator and had talked to the occupational health doctor at the job site. They are monitoring his breathing. He doesn’t seem to have trouble outside the office.”
09/04 “was exposed to chemical at work again”
11/04 “exposed isocyanate”
08/05 “trouble with dyspnea from bronchospasm from occupational exposure to lung irritants. This has been going on for some time. He has been on prednisone, averaging one taper per month. It seems that this is not the best route to go long term. He is considering leaving his work but if he leaves voluntarily on his own he loses his severance pay, so he is wondering if there is any way medical reason for leaving his job might help him to retain his severance. I recommend that we have him see a pulmonologist for further evaluation at this point.”
Number of Years between First Primary Care Contact Concerning Work Related Symptoms and Secondary Care Assessment

Fishwick et al, 2007
Reactive Airways Disease
Ongoing Tobacco Abuse

Peak flow monitoring at home and work
Advair, FEV1 3.37L, 12% improvement Post BD,
No air trapping, Normal diffusing capacity

“Certainly it would be much better if his employer would try and find him a different job, but I do understand that this is going to be difficult”

“Reactive airways disease which is likely occupationally-related, though I do stop short at this time of calling it occupational asthma”
“I do think that it is going to become necessary for them to try and minimize his exposure to isocyanates, since I do feel that he most likely having flare from his work environment. Certainly, if they cannot do this, then we will proceed down the road to spirometry before work and spirometry after work to document changes in his flows and proceed down that road if becomes necessary.”
“Return in 2 months time for clinical reevaluation and spirometry.”
Work-Related Asthma

- Work-Related Asthma (WRA)
  - New-Onset Work-Related Asthma (NOA)
    - Occupational Asthma
  - Work Aggravated Asthma (WAA)
    - Irritant-Induced Asthma Reactive Airways Dysfunction Syndrome (RADS)
Causes of Occupational Asthma

ANIMAL
Animal hair, epidermal cells, insects, mold, dander, bacterial and protein dusts
  Animal Handlers
  Entomologists
  Antibiotic Workers
  Detergent Enzyme Manufacturers

CHEMICALS ("Micromolecular" chemicals)
chloromine, ethylenediamine, formaldehyde, chromium, platinum, gum arabic, anhydrides, isocyanates
  Chemical Workers
  Platinum Refiners
  Epoxy Resin Workers
  Polyurethane Foam Manufacturers

VEGETABLE
Woods, cotton, flax, hemp, grain, flour, maiko, mold, castor, and green coffee beans, garlic
  Cotton Mill Workers
  Wood Workers
  Bakers
  Grain Elevator Operators
Examples of Known Allergens in Health Care Setting

- Vegetable
  - Latex
  - Psyllium
- Chemicals
  - Glutaraldehyde
  - Formaldehyde
  - Subtilisins (enzymatic cleaners)
  - Cleaning agents
    - Quaternary ammonium compounds
    - Diethanolamine
  - Isocyanates
  - Methylacrylates
  - Antibiotics
  - Aerosolized medications
    - Pentamidine
    - Ribavirin
  - Radiograph developing compounds
Clean as a Whistle, But What about that Wheeze?

American Journal Respiratory Critical Care Medicine 2007; 176: 731–734
DOSE–RESPONSE RELATIONSHIPS BETWEEN THE USE OF HOUSEHOLD CLEANING SPRAYS AND THE INCIDENCE OF ASTHMA (n =3,484)

<table>
<thead>
<tr>
<th>Category</th>
<th>Frequency, n (%)</th>
<th>Current Asthma RR (95% CI)</th>
<th>Current Wheeze RR (95% CI)</th>
<th>Physician-Diagnosed Asthma HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of sprays &lt; 1 d/wk</td>
<td>2,016 (57.9)</td>
<td>1.00 (referent)</td>
<td>1.00 (referent)</td>
<td>1.00 (referent)</td>
</tr>
<tr>
<td>Use of sprays 1-3 d/wk</td>
<td>933 (26.8)</td>
<td>1.36 (0.99-1.89)</td>
<td>1.55 (1.17-2.06)</td>
<td>0.93 (0.51-1.67)</td>
</tr>
<tr>
<td>Use of sprays 4-7 d/wk</td>
<td>535 (15.4)</td>
<td>1.75 (1.21-2.54)*</td>
<td>1.08 (0.73-1.59)</td>
<td>2.11 (1.15-3.89)*</td>
</tr>
<tr>
<td>One type of spray used &gt; 1 d/wk</td>
<td>913 (26.2)</td>
<td>1.37 (0.99-1.90)</td>
<td>1.25 (0.92-1.69)</td>
<td>0.97 (0.53-1.77)</td>
</tr>
<tr>
<td>Two types of sprays used &gt; 1 d/wk</td>
<td>355 (10.2)</td>
<td>1.45 (0.92-2.27)</td>
<td>1.63 (1.10-2.41)</td>
<td>1.47 (0.70-3.06)</td>
</tr>
<tr>
<td>Three or more types of sprays used &gt; 1 d/wk</td>
<td>200 (5.7)</td>
<td>2.40 (1.47-3.91)*</td>
<td>1.80 (1.11-2.94)*</td>
<td>2.96 (1.33-6.56)*</td>
</tr>
</tbody>
</table>

*linear trend <p.05

Adapted, Zock et al, 2007
DIAGNOSIS AND MANAGEMENT OF WORK-RELATED ASTHMA: ACCP CONSENSUS STATEMENT

Diagnosis and Management of Work-Related Asthma
American College of Chest Physicians
Consensus Statement

Susan M. Tarlo, MBBS, FCCP; John Balmes, MD, FCCP;
Ronald Balkissoon, MD; Jeremy Beach, MD; William Beckett, MD, MPH, FCCP;
David Bernstein, MD; Paul D. Blanc, MD, FCCP; Stuart M. Brooks, MD;
Clayton T. Cowl, MD, MS, FCCP; Feroza Daroowalla, MD, MPH, FCCP;
Philip Harber, MD, MPH; Catherine Lemiere, MD, MSc;
Gary M. Liss, MD, MS; Karin A. Pacheco, MD, MSPH;
Carrie A. Redlich, MD, MPH, FCCP; Brian Rowe, MD, FCCP;
and Julia Heitzer, MS

CHEST / 134 / 3 / SEPTEMBER, 2008 SUPPLEMENT 1s-41s
What Percentage of Asthma is Work-Related?


21 asthma cohort or population based studies range 4-58%, 15% median
1. “In all individuals with new-onset or worsening asthma, take a history to screen for WRA (OA and WEA). Then confirm the diagnosis of asthma and investigate to determine whether the patient has WRA, performing these tests, whenever possible, prior to advising the patient to change jobs.”
2. “In all individuals with suspected WRA, obtain a history of job duties, exposures, industry, use of protective devices/equipment, and the presence of respiratory disease in coworkers, and consult material safety data sheets (MSDSs), which list many recognized hazardous agents. Document the onset and timing of symptoms, medication use, and lung function, and their temporal relationship to periods at and away from work.”
3. “In individuals who have asthma not caused by work but that subsequently worsens while working, consider the diagnosis of WEA, which is usually based on changes in symptoms, medication use, and/or lung function temporally related to work.”
Medical History

- African American female in late teens
- Dx asthma as toddler
  - (ICU twice, intubated age 3)
- Health insurance up to 6 weeks prior to death
- 4 visits to PCP and allergy specialist in year before death
- ED 2-3 times in year before death
- Nebulizer 3-4x/week
- Proventil, Advair, Singulair
- Peak flow meter, allergy testing, PFTs
- School in AM, 2 jobs afternoon and evening
- Breathing problems once per week
- BMI = 30
- NHLBI = moderately persistent
Restaurant/Bar

- Arrived at work at bar at 9:45 PM
- Co-workers and bar owner indicated no problems
- 30 people in bar
- Owner – bar was not “overly smoky”
- Became acutely SOB, did not have inhaler with her
- EMS called at 10:06 PM
Autopsy Findings

Cause of Death – “Asphyxia secondary to acute asthma attack. No evidence of acute or chronic cardiac or neurologic disease was found.”

Lung Pathology
- Mild chronic bronchiolitis with a focal moderate interstitial eosinophilic infiltrate
- Goblet cell hyperplasia and a distinctive ‘saw-tooth’ luminal morphology of some of the bronchiolar mucosa
- Bronchiolar lumens are variably filled with fibrinous exudates, small mucous plugs and foamy macrophages
- Congestion in the surrounding alveolar parenchyma
- No smooth muscle hyperplasia or bronchiolar fibrosis
Health Studies Among Asthmatic Bar and Restaurant Workers Pre/Post Smoking Ban

• Scotland
  Quality of Life 2 months Post Ban +7.3 points (p=.049)
  1 month Post Ban FEV₁ +15.7% (p=.008) and NO -20% (p=.04)
  2 months Post Ban FEV₁ +10.2% (p=.046) and NO -19%(p=.12)

Menzies D et al. Respiratory symptoms, pulmonary function and markers of inflammation among bar workers before and after a legislative ban on smoking in public places. JAMA 2006; 296: 1741-1748

• Norway
  Before Ban FEV₁ - Cross Shift Change - 122ml (- 3.6%)  
  After Ban FEV₁ – Cross Shift Change + 12ml (+0.2%)  
  (p=.02)

Skogstad M et al. Cross shift changes in lung function among bar and restaurant workers before and after implementation of a smoking ban. Occup Environ Med 2006; 63: 482-487
Exposures in Bars and Restaurants Pre/Post Smoking Ban

Ireland

Before Ban PM$_{2.5}$ 35.5µg/m$^3$, Benzene 18.8µg/m$^3$
After Ban PM$_{2.5}$ 5.8µg/m$^3$ (p<.01), Benzene 3.7µg/m$^3$ (p<.01)


Norway

Before Ban Total Dust 275 (81-506) µg/m3, Nicotine 28 (3-65) µg/m3
After Ban Total Dust 77 (17-170) µg/m3, Nicotine 0.6 (ND-1) µg/m3

Skogstad M et al. Cross shift changes in lung function among bar and restaurant workers before and after implementation of a smoking ban. Occup Environ Med 2006; 63: 482-487
Most Cases Go Unrecognized As Work-Related Asthma

Approx. 300 confirmed cases

2001 surveillance data (incidence in CA, MA and MI)

239,000 adults with WRA

2001 BRFSS data (prevalence in CA, MA and MI)
Estimates of Current Asthma Attributable to Work by Selected Definitions, Adults (≥18 Years) with Current Asthma: MI, MN, & OR

1. Yes to at least one of questions 1, 2, 3, or 4
2. Yes to at least one of questions 5 or 6
3. Yes to at least one of the 6 questions

(Lutzer et al., J Asthma 2010)
For Adults with Lifetime Asthma who Report Asthma was Caused/Aggravated by Any Job, the Proportion who Discussed with a Health Professional that Their Asthma was Work-Related: MI, MN, & OR

(Lutzer et al., J Asthma 2010)
Prevalence of Having Nighttime Awakenings (30 days) by Work-Relatedness, Adults (≥18 Years) with Current Asthma: MI, MN, & OR

(Lutzer et al., J Asthma 2010)

*p<0.001
**Yes to at least one of the 6 questions
Prevalence of $\geq 1$ Asthma ED/UC Visit (1 year) by Work-Relatedness, Adults ($\geq 18$ Years) with Current Asthma: MI, MN, & OR

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<th>WRA**</th>
<th>Non-WRA</th>
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<tbody>
<tr>
<td>MI</td>
<td>19.4</td>
<td>12.4</td>
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<tr>
<td>MN</td>
<td>14.7</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>11</td>
<td>9</td>
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* $p<0.0001$
** Yes to at least one of the 6 questions
§ Data suppressed due to estimate stability.
ED=Emergency Department; UC=Urgent Care

(Lutzer et al., J Asthma 2010)
4. “In individuals with suspected sensitizer-induced OA, in addition to carefully documenting the occupational history, perform additional objective tests when feasible (eg, serial peak flow recordings, serial methacholine challenges, immunologic assessments, induced sputum testing, and SICs) to improve the diagnostic probability.”

5. “In individuals with suspected WRA who are currently working at the job in question, record serial measurements of peak flow as part of the diagnostic evaluation and ask the patient to record these optimally a minimum of four times daily, for at least 2 weeks at work and 2 weeks off work. “

6. “In individuals with suspected sensitizer-induced OA, working at the job in question, perform a methacholine challenge test or obtain comparable measurements of nonspecific airway responsiveness during a working period, and repeat it during a period (optimally, at least 2 weeks) away from the work exposure to identify work-related changes.”

7. “In individuals with suspected sensitizer-induced OA, perform immunologic tests (skin prick testing or in vitro specific IgE assays) to identify sensitization to specific work allergens when these tests are technically reliable and available. “

8. “In individuals with suspected sensitizer-induced OA, conducting an SIC (where available) is suggested when the diagnosis or causative agent remains equivocal; however, this testing should only be performed in specialized facilities, with medical supervision throughout the testing. “
Change in FEV₁ After Challenge to Control Lactose, Fresh Sugar Beet Pulp and Moldy Sugar Beet Pulp

![Graph showing the change in FEV₁ over time for different substances.](image-url)

- **Lactose**
- **Fresh Sugar Beet Pulp**
- **Moldy Sugar Beet Pulp**

- **Baseline**
- **Exp #1**
- **Exp #2**
- **Exp #3**
- **Exp #4**

- **Time**
  - 20 min
  - 30 min
  - 40 min
  - 50 min
  - 1 hr
  - 2 hr
  - 3 hr
  - 4 hr
  - 5 hr
  - 6 hr
  - 7 hr
  - 8 hr
  - 24 hr

- **17% Drop**
- **23% Drop**
Compatible clinical history and exposure to possible causal agents

Skin testing and/or specific IgE assessment (if possible)

Assessment of bronchial responsiveness to pharmacologic agents

- Normal
- Increased

- Subject still at work
- Subject no longer at work

(Laboratory challenges with the suspected occupational agent)*

- Positive
- Negative

Workplace (or laboratory*) challenges with the suspected occupational agent, peak expiratory flow monitoring, or both

- Positive
- Negative

Consider return to work

- No
- Yes

Clinical judgement

Review previous breathing test results in relationship to work

- (Not possible or not clinically advisable)

No asthma

Occupational asthma

Nonoccupational asthma

*Not available (Adapted from NEJM 1995:333:107-112, dashed lines and boxes added)
Sensitivity and Specificity of Diagnostic Tests For Work-Related Asthma

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
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</thead>
<tbody>
<tr>
<td>Clinical History</td>
<td>94%</td>
<td>33-45%</td>
</tr>
<tr>
<td>Pre-Post Work Change in FEV$_1$ (5-10%)</td>
<td>22-85%</td>
<td>56-89%</td>
</tr>
<tr>
<td>Serum IgE Tests</td>
<td>17-72%* (90%)**</td>
<td>60-85%</td>
</tr>
<tr>
<td>Peak Flow (q2h)</td>
<td>73%</td>
<td>74-100%</td>
</tr>
<tr>
<td>Serial Methacholine</td>
<td>62-67%</td>
<td>54-78%</td>
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</table>

The range of percentages for the sensitivity and specificity reflect the results from different studies.

*Low molecular weight (chemical)
**High molecular weight (animal, plant)
9. “For all individuals with WRA, attempt better control of exposures. Remove patients with sensitizer-induced OA from further exposure to the causative agent in addition to providing other asthma management.”
Severity of Asthma Symptoms by Duration of Exposure to Allergenic Substance

Severity of Symptoms

Duration of Exposure

WE=Weekend

WE
Duration of Exposure and Symptoms of 43 Subjects Who Moved Away from Exposure to TDI After Diagnosis, according to Their Outcome at the Time of Follow-up Examination

<table>
<thead>
<tr>
<th></th>
<th>Recovered Subjects (Group 1, n=12)</th>
<th>Improved Subjects (Group 11, n=10)</th>
<th>Non-improved Subjects (Group 11, n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of exposure to TDI (y)</td>
<td>6.3*</td>
<td>10.0</td>
<td>15.9</td>
</tr>
<tr>
<td>Duration of symptoms before diagnosis (y)</td>
<td>1.6**</td>
<td>2.8</td>
<td>5.4</td>
</tr>
</tbody>
</table>

(Adapted from Pisati et al BJIM, 1993;50:60)
10. “In individuals with irritant-induced asthma or WEA, the panel advises optimizing asthma treatment and reducing the exposure to relevant workplace triggers. If not successful, change to a workplace with fewer triggers is suggested in order to control asthma.”
12. “An individual diagnosis of OA represents a potential sentinel health event:
– Evaluate the workplace to identify and prevent other cases of OA in the same setting; and
– For work environments with potential exposure to sensitizers, the Panel advises secondary preventive measures including medical surveillance using tools such as questionnaires, spirometry, and, where available, immunologic tests. “
<table>
<thead>
<tr>
<th>All</th>
<th>Symptoms of Daily or Weekly S&amp;B, Wheezing or Chest Tightness</th>
<th>Injury Illness Log with Asthma or Asthma-Like Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fellow Workers</td>
<td>8,683</td>
<td>1,438 (17%)</td>
</tr>
<tr>
<td>Companies</td>
<td>487</td>
<td>342 (70%)</td>
</tr>
</tbody>
</table>

*8 workers among 1,438 on Injury and Illness Log.
11. “For workers who are potentially exposed to sensitizers or uncontrolled levels of irritants, the panel advises primary prevention through the control of exposures (e.g., elimination, substitution, process modification, respirator use, and engineering control).”
Summary

• WRA is Common (15-50%)
• Health Care Providers Not discussing with their Patients (≤ 25%)
• Consequences of Not Considering or Delay in Considering
  - Death
  - Increased Morbidity
  - Missed Opportunity for Primary Prevention
www.oem.msu.edu then click on resources


http://www.remcomp.com/asmanet/asmapro/asmawork.htm