What is the role of acute and chronic exposure to irritants in the development of asthma?

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Outline

- Asthma and work
- Asthma after an acute exposure to irritants
- Asthma and chronic exposure to irritants

Asthma and work

Definitions

- Occupational asthma
  Asthma that is caused (specifically) by exposure to an agent present at work
- Work-aggravated / work-exacerbated asthma
  Pre-existing asthma that is aggravated (non-specifically) by work (cold, exercise, irritants)

Work-aggravated asthma

- Exposures at work are frequently evoked as causes of exacerbations
  - Henneberger *et al.* OEM 2006, 63, 551-7
    - 598 adult asthmatics (HMO), telephone questionnaire
    - workplace exacerbation in 23%
  - Berger *et al.* JOEM 2006, 48, 833-9
    - 301 working asthmatics (low-income minority, NY)
    - workplace exacerbation of respiratory symptoms reported by 51% (current job) - 71% (ever)

Henneberger *et al.* The occupational contribution to severe exacerbation of asthma. *ERJ* 2010, 36, 743-50
- ECRHS-I & II
- 966 working adults with current asthma
- 74 (7.7%) at least 1 self-reported severe exacerbation in past year
- If high exposure to dust, gas or fumes: RR 3.1 → PAR 14.7% among workers with asthma
Work-aggravated asthma (WEA)

- Median prevalence: 21.5% among adults with asthma
- “WEA should be considered in any patient with asthma that is getting worse or who has work-related symptoms”
- “Management of WEA should focus on reducing work exposures and optimizing standard medical management, with a change in job only if these measures are not successful”

**Occupational asthma**

**Types**

1. Occupational asthma caused by immunological sensitisation to a workplace agent (i.e. allergy)

2. Occupational asthma not caused by immunological sensitisation

**Asthma and work**

**Epidemiology**

- Literature-based estimation of population attributable risk (PAR) for asthma «due» to occupational exposures: median 15%
  (21 studies: 4% to 58%)
How much asthma is work-related?

• Karjalainen et al. AJRCCM 2001, 164, 565-8
  • 3 cohorts of all employed Finns (25 - 59 y) without pre-existing asthma in 1985, 1990, 1995
  • followed for incident asthma for 4 years
  • 49,575 incident cases of adult asthma in Finland
  • 1.65 (M) - 2.47 (F) / 1,000 / year
  • 2,464 cases of recognized occupational asthma

How much asthma is work-related?

• Karjalainen et al. AJRCCM 2001, 164, 565-8
  • attributable fraction of occupation for adult-onset asthma (controls = administrative workers):
    • 29 % (men) - 17 % (women)
    • not confounded by smoking
    • known sectors (agriculture, manufacture, services) and occupations (bakers, …), but also less known jobs (cleaners, …)
  • share of recognised cases of OA << 50 %

How much asthma is work-related?


• ECRHS-I (1990-95), 28 centres, 13 countries, 20-44 y
• ECRHS-II (1998-2003): follow-up of 6,837 subjects without asthma or respiratory symptoms
  • New-onset asthma (symptoms or medication): n=134
  • Occupational exposures (high-risk job; job-exposure matrix; inhalation accidents)
  
  ➢ PAR due to occupation: 10-25% (250-300 cases/10^6/y)

How much asthma is work-related?

Astma severity and occupation

  • Retrospective study of tertiary referral centres (France): 148 asthmatics
  • 8 grade score of severity (frequency of attacks, persistence of symptoms, hospitalizations)
  • Asthma more likely to be "severe" if exposure to known occupational asthmogens (HMW & LMW sensitizers; irritants)

Irritant-induced asthma after acute exposure

RADS ("Reactive Airways Dysfunction Syndrome")

Case A

• previously healthy woman (50 y) exposed accidentally to "chlorine" fumes when opening a flask containing a few "bleach tablets" (dichloroisocyanic acid) + moisture
<table>
<thead>
<tr>
<th>Case A</th>
<th>Case B</th>
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<tbody>
<tr>
<td>- previously healthy woman (50 y) exposed accidentally to</td>
<td>- Man, 32 y, never smoker</td>
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<tr>
<td>“chlorine” fumes when opening a flask containing a few “bleach</td>
<td>- No atopy, no previous respiratory disease</td>
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<tr>
<td>tablets” (dichloroisocyanic acid) + moisture</td>
<td>- Security agent: transport of bank notes</td>
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<td>- immediate cough, dyspnea, retrosternal pain</td>
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<td>- hospitalization: hypoxemia, normal chest x-ray</td>
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<td>- budgerigar later found dead</td>
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<td>- mild obstruction when discharged after 2 days</td>
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<tr>
<td>- severe asthmatic symptoms, airway obstruction &amp; hypoxemia</td>
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<td>- persistent labile asthma and airway hyperresponsiveness (= RADS)</td>
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<td>Case B</td>
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<td>• 28.05.2004: accidental collision</td>
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<td>- automatic lock of all doors of van</td>
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<td>+ security cases triggered to release fumes</td>
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<td>+ security cases triggered to release fumes</td>
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<td></td>
<td>- Sustains mild traumatic injuries</td>
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<td></td>
<td>+ helps his two more severely injured colleagues to escape</td>
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<td>through a manhole in roof of cabin</td>
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<td></td>
<td>Case B</td>
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<tr>
<td>In hospital:</td>
<td>RADS</td>
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<tr>
<td>• intubated + ventilated (24h)</td>
<td>Brooks SM, Weiss MA, Bernstein IL. Reactive airways dysfunction</td>
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<tr>
<td>• no x-ray changes</td>
<td>syndrome (RADS): persistent asthma syndrome after high level</td>
</tr>
<tr>
<td>• discharged after 3 days</td>
<td>irritant exposure. Chest, 1985, 8, 376-84</td>
</tr>
<tr>
<td>After discharge:</td>
<td>= de novo asthma caused by an acute</td>
</tr>
<tr>
<td>• cough persisting for 6 months</td>
<td>inhalation injury</td>
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<td>• “normal” pulmonary function, but decreased exercise capacity</td>
<td></td>
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<tr>
<td>• bronchial hyperreactivity = RADS</td>
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</table>
RADS – criteria

1. Documented absence of preceding respiratory complaints
2. Onset of symptoms after a single specific exposure incident
3. Exposure to gas, smoke, fume or vapour present in very high concentration and with irritant properties
4. Onset of symptoms within 24 h after exposure
5. Persistence of symptoms for at least 3 months
6. Symptoms simulate asthma (cough, wheezing, dyspnoea)
7. Pulmonary function tests may show airflow obstruction
8. Positive methacholine/histamine test
9. Other disease ruled out

RADS

- Many case reports or case series of RADS following a wide variety of inhaled agents
  - chlorine
  - inorganic gases & vapours (HCl, SO\textsubscript{2}, NO\textsubscript{2}, NH\textsubscript{3}, H\textsubscript{2}S, …)
  - organic chemicals (isocyanates, acids, aldehydes, tear gas, pesticides, solvents, …)
  - poorly defined mixtures (fire smoke, welding fumes, diesel exhaust, irritant aerosols, …)


RADS – epidemiology

- Jajosky et al. MMWR CDC SS, 1999, 48, 1-20
  - USA, SENSOR (CA, MA, MI, NJ), 1993-95
  - 1101 cases of work-related asthma
    - work-aggravated asthma: 210 (19.1%)
    - new-onset asthma: 891 (80.9%)
      - occupational asthma: 768 (89.8%)
      - RADS: 123 (11.2%)

RADS – epidemiology

- Kopferschmitt-Kubler et al. ERJ, 2002, 19, 84-9
  - France, ONAP, 1997
  - 559 cases of occupational asthma
    - typical occupational asthma: 460 (82%)
    - “atypical asthma syndrome”: 71 (13%)
    - RADS: 26 (5%)

RADS – epidemiology

- Ross & McDonald. AOH 1996, 40, 645-50
  - England, SWORD, 1990-93
  - follow-up of 734 reported inhalation accidents
  - 50/683 (9%) had asthma symptoms > 1 month
  - 34/47 of these were compatible with RADS
  - chest physicians: 27/214 accidents (13%)
  - occupational physicians: 7/406 accidents (2%)
  - various causes (including known sensitizers, such as isocyanates, glutaraldehyde)
RADS – criteria (3’)
3. Exposure to gas, smoke, fume or vapour present in very high concentration and with irritant properties
   • yes, in typical cases
     • inhalation injury requiring medical treatment (emergency room admission, infirmary, ...)
   • some cases do not appear to involve “very high” concentrations, nor clinically severe injury needing (immediate) medical attention

RADS and severity of initial injury
• Cohort studies do not indicate that RADS only occurs after a clinically severe inhalation injury *
  • Kern. ARRD 1991, 144, 1058-64
    • spill of glacial acetic acid in hospital
  • Cone et al. Chest 1994, 106, 500-8
    • derailment → metam sodium in river → MITC (CH₃NCS)
  • Banauch et al. AJRCCM 2003, 168, 54-62
    • NYFD after 9/11 WTC collapse

“WTC 9/11”
• Prezant et al. NEJM, 2002, 347, 806-15
  • 11,336 FDNY firefighters
  • 343 died - 10,116/10,993 evaluated
    • 1636 (16%) high exposure (present at WTC collapse)
    • 6958 (69%) moderate exposure (within first 2 days)
    • 1320 (13%) low exposure (3-7 days after collapse)

Bronchial hyperreactivity
\[
\text{PC}_{20} \leq 8 \text{ mg/ml}
\]

RADS at WTC
• RADS = « bronchial hyperreactivity with respiratory symptoms at 6 months »
  • 17/83 (20%) of highly exposed
  • 3/40 (8%) of moderately exposed
  • all nonsmokers, except one
  • no evidence of clinically severe initial injury

RADS – Prognosis
Malo et al. Long-term outcomes of acute irritant-induced asthma. AJRCCM 2009, 179, 923-8
35 subjects with RADS, 13.6 y [4 – 24 y] after accident
   ➢ All had respiratory symptoms (34% inhaled steroids)
   ➢ No improvement in spirometry
   ➢ Methacholine test (n=23): normal or improved in 6+3 (better starting values)
   ➢ Induced sputum (n=27):
     ➢ eosinophils >2% (n=8), pmm >60% (n=8);
     ➢ ↑ mediators of inflammation & remodelling (= occupational asthma)
   ➢ Abnormal depression score: n=12
RADS – research questions

- What proportion of victims of inhalation accidents evolve to RADS?
  - Registration and good follow-up of all victims
- Why do some victims evolve to RADS?
  - Severity of damage (agent, dose, …)
  - Individual predisposition? (pre-existing NSBHR, atopy, abnormal epithelial repair, …)
  - Treatment modalities? (oxygen, steroids, antioxidants, …)
- Role of irritants in (occupational) asthma?

Irritant-induced asthma and repeated/chronic exposure to irritants

RADS – criteria (2’)

2. Onset of symptoms after a single specific exposure incident
   - yes, in typical cases
   - also after repeated high-level respiratory irritant exposures

Tarlo SM, Broder I. Chest, 1989, 96, 297-300

Case C

- male, 47 y
  referred 04/1995 for advice on possible occupational origin of asthma (compensation refused)
- life-long nonsmoker, no atopy
- safety engineer in several companies from 1975
- perfect health until 1989

Clinical history (1)

- 1989: started work in oil refinery:
  - progressive symptoms of
  - rhinitis (→ nasal septum correction + conchotomy)
  - excessive sputum production
  - dyspnea on exercise
  - wheezing at night
  - intolerance to nonspecific irritants

Clinical history (2)

- 10/1994: claimed compensation, left job
  - improvement of symptoms, but persistent asthma needing medication
- 05/04/1995: VC 99%  
  FEV1 97%  
  histamine PC20 1.1 mg/ml
- no identified causes of allergic asthma
Exposure history (safety interventions)

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<tbody>
<tr>
<td>Leaks to process equip.</td>
<td>18</td>
<td>28</td>
<td>52</td>
<td>32</td>
<td>65</td>
<td>72</td>
</tr>
<tr>
<td>Requiring compr. air eq.</td>
<td>66</td>
<td>55</td>
<td>140</td>
<td>55</td>
<td>124</td>
<td>72</td>
</tr>
<tr>
<td>Interv. for gas leaks</td>
<td>4</td>
<td>6</td>
<td>16</td>
<td>13</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>Interv. for fires</td>
<td>19</td>
<td>19</td>
<td>32</td>
<td>26</td>
<td>19</td>
<td>7</td>
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<tr>
<td>Interv. for liquid leaks</td>
<td>15</td>
<td>44</td>
<td>87</td>
<td>135</td>
<td>158</td>
<td>31</td>
</tr>
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</table>

mainly H₂S and S-compounds, some very serious incidents with deaths (n=3) & severe inhalation injuries (n=5)

Previous pulmonary function data?

- being a safety engineer, he had undergone yearly medical examinations and fitness tests for wearing breathing apparatus

Case C – conclusion

- good documentation of repeated exposure to peaks of respiratory irritants (H₂S, SO₂, ...)
- availability of good longitudinal lung function data
  - confident diagnosis of "irritant-induced asthma"
  - compensation awarded

Non-RADS irritant-induced asthma – own experience

- 2000-02 (Kempeneers, unpublished)
  15 subjects with adult-onset work-related asthma, regularly exposed to excessive levels of irritants, without evidence of acute inhalation injury, nor sensitization (including specific provocation tests in some cases)
  - vegetable industry (metabisulphite + acid → SO₂)
  - rubber industry (HCl)
  - cleaning of silos (HCl)
  - cleaning of metals (H₃PO₄)
  - emptying cess-pits (H₂S)
  - hospital (HClO; formaldehyde)
  - laboratory (photographic emulsion)

Asthma and irritants?
Asthma risk by occupation

- Reinisch et al. AJIM 2001, 39, 72-83
  - California: 945 reported cases of work-related asthma (1993-96) + structured telephone interview (n = 444)
  - 25/1,000,000 workers/y, but actually estimated at 78
  - janitors & cleaners, firefighters, ...
  - mostly no exposure to known sensitizer, probably irritant exposures

- Wang et al. AJRCCM 2010, 182, 1369-76
  - Taiwan, case-control study
  - 504 adult cases of asthma, 504 community controls, 504 hospital-based controls
  - Exposure assessed by asthma-specific JEM
  - Atopic asthma associated with occupational exposure to HMW asthmogens (aOR 4.0)
  - Nonatopic asthma associated with occupational exposure to LMW asthmogens (aOR 2.6), including irritants

Asthma and cleaning agents

- Higher risk of asthma in female cleaners
  - Zock et al. SJWEH 2001; 27: 76-81: P.R. 1.7
  - “hidden sensitizers”?
  - Quaternary ammonium cpds (disinfectants / preservatives)
  - Isothiazolinones (preservatives)
  - ethanol amines (wax-removal agents)
  - d-Limonene, terpenes (perfumes)
  - exposure to irritants and sprays?

Asthma and cleaning agents

Medina-Ramón et al. OEM 2005, 62, 598-606
- (Nested) case-control study of female cleaners (30-65 y)
- 40 cases (asthma or chronic bronchitis) – 155 controls
  - Higher risk of asthma if use of bleach (dose-related)
  - Higher risk of asthma if reported inhalation incident (frequent)
Asthma and cleaning agents

Zock et al. AJRCCM 2007, 176, 735-741

- ECRHS-I → ECRHS-II [+ 9 y]
- N = 3,503 (69% women), 20-48 y [→ 28-57 y]
  - ECRHS-I: free of asthma at baseline
  - ECRHS-II: “doing cleaning at home”
    - face-to-face interview
      - use of 15 products for domestic cleaning and washing?
      - never, <1 d/w, 1-3 d/w, 4-7d/w

- use of cleaning sprays ≥1d/w: RR 1.49 for incidence of asthma symptoms/medication
- use of cleaning sprays ≥4d/w: RR 2.11 for incidence of physician-diagnosed asthma
- sprays for glass-cleaning, furniture and air-refreshing
- no association with cleaning products not applied as sprays
- no modification of risk by atopy

Asthma and irritants?

- Experimental research needed using animal models of asthma
  - which “irritants”? [“inflammagens”]
    - gaseous agents
    - particulates
    - endotoxin
  - role of irritants?
    - in nonspecific bronchial hyperresponsiveness
    - in bronchial inflammation
    - in allergic sensitisation to HMW and LMW agents
How much asthma is work-related?

“In adults, asthma is caused (directly or indirectly) by work in approximately 15% of cases”

- Work-aggravated asthma? some
- Occupational allergic asthma? minority
- Irritant-induced asthma? many??

Thank you for your attention

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