Occupational Asthma: what occ docs need to know

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Outline

1. Occupational asthma
   - Epidemiology
   - HMW vs. LMW sensitizers
     - Agents and industries
   - RADS and work-aggravated asthma
   - Diagnosis and treatment
     - Patterns of response
2. Occupational COPD/chronic bronchitis
Definition:

“Occupational asthma (OA) is a disease characterized by variable airflow limitation* and/or airway hyperresponsiveness** due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace.”

Editorial consensus *Asthma in the workplace* 3rd edition 2006

*Change in FEV1 by ≥ 12% and 200 mL in response to bronchodilator

**Methacholine Challenge PC20 FEV1 ≤ 4 mg/mL
What portion of adult asthma is attributable to work?

- Population attributable risk of asthma caused by occupation.
- Reviewed 21 studies of adult asthma.
- PAR % ranged from 4 to 58%, with a median value of 15%.

ATS statement: AJRCCM 2003; 167: 878-797
Categories & Prevalence of OA:

• Immunologic (Asthma with latency)
  – High-molecular weight (>5,000 daltons)
    • Prevalence 10-15% in lab animal workers
  – Low-molecular weight (<5,000 daltons)
    • 10% isocyanate workers, 12% anhydride workers

• Non-immunologic (Asthma without latency)
  – Reactive Airways Dysfunction Syndrome (RADS)

• Work-aggravated asthma
Immunologic OA: Pathogenesis

High Molecular Weight Agents
• IgE dependent allergic asthma
• Induce Th2 cytokines and pathways

Low Molecular Weight Agents
• Some act as haptens – platinum, acid anhydrides, isocyanates
• Others, mechanism is unknown – plicatic acid, abietic acid
HMW agents: most are biological

- Bakers in small bakeries
- Farmers
- Greenhouse workers
- Grain workers – plant analysis, animal feed, soy processing plant

Other HMW biological exposures

- Textile workers – cotton, wool, flax, jute, synthetic fibers, latex, cellulase
- Health care workers – latex, enzyme cleaning solutions, (glutaraldehyde or Cidex is LMW)
- Scientists, vets - animal allergens, latex
Exposure to other biological agents (may be HMW or LMW)

- Metal working fluids: machinists
  - Bacterial and fungal growth at the fuel-water interface in gasoline, jet fuel etc.
- Contaminated water mists and vapors: swamp coolers, pools, hot tubs.
- Animal proteins: meat cutters, carcass renderers, feathers and blood.
Other LMW biological agents

- **Plicatic acid**: from Western Red Cedar *Thuja plicata*, an evergreen coniferous tree in the cypress tree family.
- **Abietic acid**: or rosin, derived from coniferous tree sap.
- **Colophony**: used as glue, solder in computer and circuit boards.
- **Antibiotics**: most derived from fungi
Some LMW agents are reactive chemicals

- **Isocyanates**: car paints, truck bed liners

- **Trimellitic anhydrides**: curing agent for epoxy & other resins, in vinyl plasticizers, paints, dyes, etc.

- **Two-part epoxy glues & fillers in auto body work (bondo)**, Bisphenol A (BPA) in polycarbonate plastics and epoxy resins.

![Chemical structure of isocyanate](image1)

![Chemical structure of trimellitic anhydride](image2)
LMW: metals

- Metals – especially vapors (electroplating, foundries)
- Hexavalent Chromium\(^{(6+)}\)
- but not Cr\(^{(3+)}\)
- Platinum
- Cobalt
- Nickel
“Reactive airways dysfunction syndrome is new asthma occurring as the aftermath of an acute inhalation injury caused by irritant exposures.”

(ATS, 1993)
RADS: Causative Agents

- Acids, heated
- Ammonia
- Bleaching agents
- Chlorine gas
- Drain cleaners
- Diesel exhaust
- *Fire/smoke
- *Floor sealants (aromatic hydrocarbons)
- *Fumigating fog
- Glacial acetic acid
- Hydrogen chloride

- *Hydrazine \((N_2H_4\) - emergency and jet fuel)
- Isocyanates
- *Metal coat remover
- Paint fumes
- Perchlorethylene
- Propylene glycol
- Sodium hydroxide
- *Spray paint
- Sulfur dioxide
- *Uranium hexafluoride
- Welding fumes (MFF)

RADS: Diagnostic Criteria

1. Absence of prior respiratory complaints.
2. Onset of symptoms after a single acute respiratory tract irritant exposure.
3. Exposure to very high concentrations of a gas, smoke, fume, or vapor with irritant properties.
4. Symptom onset within 24 hours of exposure and persistence for at least 3 months.
5. Symptoms similar to asthma.
6. Airflow limitation.
8. Exclusion of other types of lung disease.

(Brooks, 1985)
RADS due to alkaline particulates

- “Bronchial hyperreactivity and other inhalation lung injuries in rescue/recovery workers after the World Trade Center collapse”
- Sample FDNY workers n=179, highly exposed during the collapse, and moderately exposed 1-2 days after collapse.
- $\text{BHR} = \text{PC}_{20} \text{FEV1} < 8 \text{ mg/mL}$

Significantly higher rates of RADS in highly exposed workers (p=0.009)

Workers with no prior respiratory symptoms, no history asthma or allergies, never smokers.
RADS vs. Immunologic OA

- Latency
- Pathogenesis: both may involve both the upper and lower airway
- Outcome
Outcome of occupational asthma after cessation of exposure: complete symptomatic recovery

Outcome of occupational asthma after cessation of exposure: persistent BHR

Figure 4. Determinants of persistent non-specific bronchial hyperreactivity at follow-up. HMW, high molecular weight; LMW, low molecular weight.

Long-term pathologic consequences of acute irritant-induced asthma


FIG 1. Examples of H and E staining in bronchial biopsies from healthy subject (A) and subject with RADS (B). Graph C shows ↑ thickness of basement membrane, and (D) epithelial cell detachment in bronchial biopsies from 10 subjects with RADS compared with 10 healthy controls and 10 subjects with mild asthma. Mean follow-up was 11 yrs.

BAL: ↑ eosinophils and PMNs in RADS vs. asthma or controls
Work exacerbated asthma

- More common than sensitizer induced OA
- “The occupational contribution to severe exacerbations of asthma”

- 966/9,812 eligible participants of ECRHS study 1998-2003 with MD dx asthma, > 2 yrs duration, worked in past year, completed Q.
- Main outcome => severe exacerbations (ER, hospital, or course of steroids)
- Exposure assessed for biological dusts, mineral dusts, and gases and fumes.
Occupational contribution to severe exacerbations of asthma ~15%

- Analysis: population attributable risk percentage (PAR%) for occupational contribution to severe exacerbation
- More common in women
- Current smokers (10.6% vs 4.1% in former p=0.008)
- Occupations: Nurses RR=1.7 (.99-2.9), Bakers RR=7.9 (5.1-12.2), Drivers RR=2.3 (1.03-5.0), other Blue Collar workers RR=2.7 (1.4-5.1).
Risk Factors for OA

1. What are some of the determinants of sensitization and disease?
   • Exposure
   • Co-exposures
   • Host risk factors:
     • atopy, cigarettes, genetics

2. Does skin sensitization play a role in respiratory illness?
Dose Response of Sensitization and Symptoms

Baur. Clinical and Experimental Allergy 1998;28:537-44

Houba, et al. AJRCCM 1996;154:130-6


IAS=initial asthma-like sx
FAS=follow-up asthma-like sx
NAS=new onset asthma-like sx
Role of Skin Exposure

- Developed colorimetric wipe test for isocyanates.
- Detected on many workplace surfaces: painters' workbenches, spray equipment, cleaning tools.
- Frequent on painters’ skin.
- Latex gloves showed significant penetration.

What is the role of rhinitis?

“Occupational rhinitis is an inflammatory disease of the nose, which is characterized by intermittent or persistent symptoms (i.e. nasal congestion, sneeze, rhinorrhea, itching) and/or variable nasal airflow limitation and/or hypersecretion due to causes and conditions attributable to a particular work environment and not to stimuli encountered outside the workplace”.


- Rhinitis frequently precedes the onset of OA
- HMW and LMW agents, irritants (RUDS)
How do you diagnose OA?

**Preliminary Evaluation**
1. Suspect the diagnosis - especially new onset in adults.
2. Confirm asthma by bronchodilator response or bronchial hyperresponsiveness.

**Confirmatory Evaluation**
3. Obtain objective evidence of a workplace association: serial peak flows, changes in PC20, SIC.
4. Determine the specific causative agent, if possible.
1: When to Suspect OA

- New-onset adult asthma:
  - Think of the Link to the Workplace
- Accurate occupational history
  High risk occupation – job title/job duties
  Use of known sensitizer
  Previous work history
  Has the patient moved out of exposure due to sx?
  Are coworkers sick?
  Review material safety data sheets (MSDS)
Take an occupational history

Helpful questions to start:

- What is your job title?
- Where do you work?
- What products are made?
- Describe a typical day's work.
- How long did it take for you to develop symptoms?
- Is there any job or part of the plant where your symptoms are worse?
- Is anyone else affected at work?
- How long did it take for you to develop symptoms?
- Draw a map of the work flow.

Take an occupational history
2: Confirm Asthma

• Methacholine Challenge or bronchodilator response
• A negative test in a subject **who is still in the workplace** may rule out OA
  – (may be exceptions with variable exposure to the causative agent).
  – AJRCCM 2000 Sep;162(3 Pt 1):976-80. Persistent specific bronchial reactivity to occupational agents in workers with normal nonspecific bronchial reactivity.

• The positive predictive value for asthma in this population is about 85-90%.

• However, a single abnormal test does not confirm an occupational cause.
3: Confirm workplace association

- Peak flow monitoring (at least 4 times/day)  
  Thorax. 1993 Dec;48(12):1211-7
- Cross-shift FEV1 (pre and post, or beginning and end of workweek): least helpful
- Methacholine challenge at and away from work  
  (2 to 3 fold change in PC\textsubscript{20} considered significant)
- Specific inhalation challenges
Peak Flow Monitoring

- Most extensively studied method
- Requires good patient effort and cooperation
- Unit must be able to measure high flows
- Computerized monitor is ideal (PiKO-1)
- Sensitivity – 85-90% Specificity – 85-90%
- Positive >=20% fall in PEFR at or following work:
  Comparison with periods of ≥ 7d off work improves the sensitivity

Occup Environ Med 2010;67:562-7
4: Determine Causative Agent(s)

Immunologic testing
- Skin prick testing better than IgE serology.
- Not useful for most LMW agents.
- Positive results indicate sensitization, not disease: helpful but not definitive.
- Lack of standardized antigens.
- Poor negative predictive value.
Specific Challenge: Indications

- Confirm that a specific agent is cause of OA, or distinguish causal agent from many exposures.
- The diagnosis has significant consequences: removal from the work process or the job.
- Other diagnostic procedures have not established the diagnosis of OA.
- No option to return to workplace to monitor PEFR: too sick, or out of job.
- Distinguish upper from lower airway response.
Specific Challenge: poor indications

- Medical-legal issues
- Patient education

- A patient with a positive methacholine challenge, and evidence of sensitization to a known immunologic agent, has an 80% chance of reacting to a specific agent challenge.

Cockroft 1979, 2005
Specific Challenge: Limitations

• False negatives:
  – Wrong agent
  – Wrong method of delivery
  – Inadequate exposure dose
  – Patient responds to a combination of agents
  – Patient too long out of exposure

• False positives:
  – Irritant reactions
  – Unstable asthma
  – VCD
  – ‘Psychological factors’
Other non-invasive measures

• Sputum for markers of inflammation, changes with exposure  
  – eosinophil counts
  – eosinophil cationic protein (ECP)

• Exhaled nitric oxide (in general, increased after positive challenges to latex, MDI, Western Red Cedar).
  – Used in conjunction with physiologic changes.
Treatment

• The cornerstone of therapy for occupational asthma is removal from exposure.
  – Work with the patient to restrict from exposure by modifying job duties.
  – Severity of disease helps dictate restrictions.
  – Removal from exposure ≠ removal from job.

• Pharmacologic management is the same as for non-occupational asthma.
Prognosis: without removal

• Many patients have persistent disease: colophony, red cedar, isocyanates, flour, psyllium.
• About 1/3 have progression of symptoms and physiologic abnormalities.
• Death may occur despite use of respiratory protection and adequate treatment (isocyanates).
• What about workers with OA who don’t consult a physician?
Prognosis: with removal

- 50% cure rate.
- Improvement in symptoms and pulmonary function is the rule, but it can take years.
- RADS has a poorer prognosis.
Predictors of worse outcome:

- Longer duration of exposure prior to symptom onset.
- Longer duration of symptoms before diagnosis.
- Severity of disease at diagnosis:
  - Abnormal PFT’s
  - Nonspecific bronchial hyperresponsiveness
Public Health Model

A diagnosis of occupational asthma is a sentinel health event.

• Diagnosis of **one** case of occupational respiratory disease offers the opportunity to prevent disease in other exposed workers.

• Work with occupational medicine physicians and industrial hygienists to evaluate work place and institute primary prevention of disease.
Methods of Prevention

• 1 to modify or eliminate the causative agent so that exposure does not occur.
• 2 Periodic medical evaluation of workers for early detection of sensitization, symptoms, or both, with use of data to modify exposures (may not prevent disease).
• 3 Treatment of disease that has already occurred.
Approaches to prevention

• What is the best strategy to reduce OA and allergy in bakers?
  – Modeled effects of different strategies to reduce the burden of occupational respiratory sx & disease.
Approaches to prevention

- **Hygiene intervention** – rigorous exposure control measures.

- **Health surveillance** – reduce exposures of sensitized, or non-sensitized workers with rhinitis.

- **Sector-wide training & education**: inform workers of risk of exposures & describe good exposure control practices.

- **Pre-employment screening** to exclude atopic workers
Best intervention was exposure education

• 6-yr program, outcome parameters:
  – WR sensitization, upper & lower resp sx, work disabling asthma

• Comparing approaches:
  – Hygiene intervention – extremely expensive.
  – Health surveillance – doesn’t prevent disease.
  – Pre-employment exclusion of atopic workers - illegal

*Not ethical to exclude a substantial section of the working population because of ↑susceptibility (atopy), when can adjust exposure and there are other, unknown risk factors as well.*
Can occupation cause COPD?

- ATS Statement 2003: PAR = 15%
- Demonstrated in certain occupations:
  - Coal dust
  - Cadmium fumes
  - Cotton dust (byssinosis)
  - Acute inhalational exposures
  - Welding (recurrent MFF)
  - Silica exposures
Resources

http://www.remcomp.fr/asmanet/asmapro/
http://www.ilpi.com/msds/index.html#General


Websites and Consultants

Top bar: Policies and position statements.
Sidebar: Find an occupational medicine doctor (by city, state)

Sidebar: Access to information – Consultants listing: search by city and state to find a certified IH.

Top bar: Clinical information – environmental and occupational – Clinical cases, EOH statements.
Can’t access membership list if not a member.