Occupational asthma: Current concepts in pathogenesis, diagnosis, and management

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The conference is aimed toward a gap in knowledge regarding occupational asthma with...

Objectives
1. To recognize and describe the revised classification and nomenclature for work-related asthma (WRA), occupational asthma (OA) and work-exacerbated asthma (WEA) outlined in recent consensus guidelines.
2. To recall and describe current theories of the pathogenesis and risk factors of WRA.
3. To describe evidence-based recommendations for diagnosis and management of OA.
4. To describe prognostic indicators of OA.
CASE
A 47 y.o. man is referred for possible occupational asthma. He reports that he developed dyspnea and wheezing in the spring of 2010, several months after he began working in a new workplace environment. He reports symptoms were worse at work and improved after being away from work for several days. With a prescribed inhaled corticosteroid/long acting beta agonist regimen, he reports getting only incomplete improvement.

He stopped taking his controller inhalers 1 mo. ago, and is taking only albuterol PRN. He has now been off work for 6 weeks – P.C.P. advised that pt. stay off work until evaluated by you. Employer is pressuring pt. to return to work, and pt. is concerned about being fired.

Work environment: spray painting in work area
Home environment: 2 dogs. 20 P.Y. smoker.
P.M.H: mild PAR some SAR worsening, treated with OTC antihistamines. No family hx asthma.
Phys Exam: edema nasal mucosa; lungs CTA
ACT 15/25
FEV1/FVC 0.70.
Skin tests: + trees, ragweed, dog, house dust mites
Record review:
April, 2010: Seen by P.C.P. for severe URI
Sept 2010: CXR WNL, Spiro (on ICS+LABA):
FEV1/FVC 0.76

QUESTIONS
What additional information would you want?
What additional testing would you order?
What would be your recommendations about when he can return to work?

If he returns to work at some point, how should he be monitored?
What should be done to assess if this patient has work related asthma (WRA), work exacerbated asthma (WEA) or occupational asthma (OA) – and what difference would that make?
Work-related asthma (WRA): exacerbated or induced by inhalation exposures in workplace.

A. OA: de novo asthma or the recurrence of previously quiescent asthma induced either (1) by sensitization to a workplace substance, termed sensitizer-induced OA, or (2) by exposure to an inhaled irritant at work, termed irritant-induced OA.

NB: Previously, OA defined only as sensitizer-induced OA.

B. Work-exacerbated asthma (WEA): in workers with pre-existing or concurrent asthma, triggered by work-related factors (eg, allergens, irritants, or exercise)....not considered OA

Importance of WRA

• At least 9-15% of adult asthma has been attributed to workplace exposures, although recent data indicate that 25% or more of de novo asthma may have an occupational basis.
Importance of WRA

- **WRA** results in considerable morbidity to affected individuals, but also results in tremendous costs to society.
- Failure to recognize OA in a timely fashion can lead to *permanent respiratory impairment*; need early diagnosis and intervention.

DEFINITIONS

TYPES OF OA
- Sensitizer-induced OA
- Irritant-induced OA

PATHOPHYSIOLOGY

EPIDEMIOLOGY AND RISK FACTORS

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

MANAGEMENT

PREVENTION AND SURVEILLANCE

PROGNOSIS AND OUTCOMES

Occupational Asthma from Sensitizers

- Latent period of immunologic sensitization
  - Can range from months to decades
- Low levels cause symptoms
- Sensitivity increases with continued exposure
- Usually only in minority of workers
• > 250 reported workplace sensitizers
• Categorized on basis of molecular weight.
• High-molecular weight (HMW) sensitizers: >10 kd
  – e.g. inhaled protein agents
  – IgE mediated mechanisms
• Low molecular-weight (LMW) sensitizers
  – often reactive chemicals, act as haptens, ie only
    induce adaptive immune response and recognized
    as antigens after combining with self-proteins to
    form immunogenic conjugates.
  – Some LMW agents cause sensitization via IgE
    mechanisms, whereas others do not

Irritant-induced OA

• Not previously considered a form of
  occupational asthma
• De novo asthma caused by exposure to
  inhaled irritants at work now commonly termed
  "irritant-induced OA"

Reactive Airways Dysfunction Syndrome (RADS)
• No previous history of asthma
• Acute, high level exposure to toxic/irritant
  agents
• Respiratory symptoms within 24 hours
• Persistent respiratory symptoms, non-specific
  bronchial hyperreactivity
• Pulmonary functions normal or show reversible
  obstruction
  – Obstruction less reversible than asthma
• Eosinophilic infiltration not characteristic
  
  Brooks SM. Chest 1985; 88:376
• Now considered form of irritant induced OA
### RADS: causal agents

- Chlorine gas, hydrochloric acid, anhydrous ammonia, hydrogen sulfide, fumigating fog, heated acids, smoke by inhalation.
- In 1984, Bhopal, India, chemical plant, toxic cloud of methyl isocyanate gas, killed thousands, survivors with RADS.
- 9/11/01, terrorist attacks on World Trade Center towers in NYC, collapse caused airborne dusts and pollutants; RADS in exposed rescue workers and residents.


### Irritant-induced OA

- Controversy whether chronic lower-level exposure to irritants can cause OA.
  - Tarlo. Chest 2008;134(3 Suppl):1S-41S.
- Repeated peak exposure to irritant gases in pulp industry increases risk for asthma.
- 2008 ACCP: “irritant induced asthma” includes cases that do not meet RADS criteria (eg, when several-day lag before sx onset, or when no single massive exposure but rather repeated exposures over days or weeks).
  - Ex: meat wrapper’s asthma

### DEFINITIONS

- TYPES OF OA
- PATHOPHYSIOLOGY
  - Sensitizer-induced OA
    - OA from HMW sensitizers
    - OA from LMW sensitizers
  - Irritant-induced OA
- EPIDEMIOLOGY AND RISK FACTORS
- DIAGNOSIS
- DIFFERENTIAL DIAGNOSIS
- MANAGEMENT
- PREVENTION AND SURVEILLANCE
- PROGNOSIS AND OUTCOMES
### OA from HMW Sensitizers
(IgE mediated)

<table>
<thead>
<tr>
<th>PROTEIN SOURCE</th>
<th>OCCUPATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal &amp; Insect derived</td>
<td></td>
</tr>
<tr>
<td>Snow crab, Sea squirt (oyster parasite)</td>
<td>Seafood processors</td>
</tr>
<tr>
<td>Mammalian proteins (dander, urine)</td>
<td>Lab workers, pet care</td>
</tr>
<tr>
<td>Vegetable/plant dusts</td>
<td></td>
</tr>
<tr>
<td>Wheat flour</td>
<td>Baker’s asthma (flour)</td>
</tr>
<tr>
<td>Henna dye</td>
<td>Beauticians</td>
</tr>
<tr>
<td>Psyllium</td>
<td>Nursing</td>
</tr>
<tr>
<td>Bacterial and fungal–derived</td>
<td></td>
</tr>
<tr>
<td>Bacillus subtilis–derived enzymes</td>
<td>Detergent formulators</td>
</tr>
<tr>
<td>Penicillium casei</td>
<td>Cheese workers</td>
</tr>
</tbody>
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### OA from LMW Sensitizers
(only some IgE mediated)

<table>
<thead>
<tr>
<th>CHEMICAL</th>
<th>OCCUPATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persulfates (hair bleaching)</td>
<td>Hairdressers</td>
</tr>
<tr>
<td>Metals and metal salts</td>
<td></td>
</tr>
<tr>
<td>Chromium</td>
<td>Miners; cement, electroplating, tanning workers</td>
</tr>
<tr>
<td>Platinum</td>
<td>Alloy makers</td>
</tr>
<tr>
<td>Organic chemicals</td>
<td>Plastics industry, epoxy resins, dye, insecticide makers</td>
</tr>
<tr>
<td>Acid anhydrides (trimellitic anhydride)</td>
<td>Polyurethane, paints, foam coatings, adhesives production</td>
</tr>
<tr>
<td>Polysiocyanates (toluene disocyanate)</td>
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</table>
Factors Modifying Risk for OA

Other than intrinsic physicochemical and immunogenic properties of agents, most important risk for developing OA is the level and duration of exposure to agents.

Smoking: Not consistent association, may vary by agent
Siracusa A et al. Clin Exp Allergy. 2006;36:577-84

Atopy: risk for OA from HMW, but generally not LMW

Presence of occupational rhinitis and conjunctivitis: may identify patients at greater risk for developing OA (TMA), may precede OA.


So-called ‘allergic march’ not common in bakers
Walusiak J et al. Allergy 2004;59:442

DEFINITIONS
TYPES OF OA
PATHOPHYSIOLOGY
EPIDEMIOLOGY AND RISK FACTORS
DIAGNOSIS
–History
–Objective testing
DIFFERENTIAL DIAGNOSIS
MANAGEMENT
PREVENTION AND SURVEILLANCE
PROGNOSIS AND OUTCOMES

History
The 2008 ACCP guidelines recommend that the following key questions be posed:

1) Were there changes in work processes in the period preceding the onset of symptoms? Increased exposure?

2) Was there an unusual work exposure within 24 hours before the onset of initial asthma symptoms? RADS?

3) Do asthma symptoms differ when away from work such as weekends or holidays? NB: positive response, 26% misdiagnosis

Lemière C. JACI 2002;110:641-6
History
4) Are there symptoms of allergic rhinitis and/or conjunctivitis symptoms that are worse with work?
• These symptoms may start before or have onset concurrent with development of OA, and work-related rhinitis increases probability of OA from HMW (although not consistently from LMW)


Occupational History
• Current and previous jobs
  – Employer, job names and descriptions, duration
• Specific exposures – known to cause asthma?
• Control measures
• Are other workers affected?
• Have workers left because of similar symptoms?

Does History Suggest Non-Occupational Basis?
• No relation between work and symptoms
• Preexisting asthma / respiratory problems
• Upper respiratory infection at onset of symptoms
• Non-occupational allergies
• Smoking

Review medical records!
Additional Information About Suspect Work Exposures

- Information sources: employers, product manufacturers, labor unions,
- Material safety data sheet (MSDS)
  - By law, employer must provide
  - Identity of workplace agents and information about adverse health effects, allowable exposure limits
  - May be incomplete/misleading
  - Contacts for additional information
- Medical literature searches

Occupational Hygiene Assessment

- Occupational/industrial hygienists assess work place environments
- Perform tests to determine if suspect agents exceed permissible levels
- Recommend changes in the work environment (e.g. improved ventilation)
Beyond History: Objective Testing for OA

• History alone insufficient for diagnosis

• Objective testing
  All tests have potential false-positive and false-negative responses, but the more tests positive, the greater the probability of a correct diagnosis of OA.

ACCP 2008

Serial peak flows and spirometry

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.”

– Effort dependent
– Use data logger to prevent fabrication
– Typical pattern: patient better on Mondays, worse as week progresses

ACCP 2008
Typical patterns of response

Immediate early late

late *

dual

Perrin B. JACI 1991; 87:630

Also atypical patterns of response!

progressive square waved

prolonged intermediate

Perrin B. JACI 1991; 87:630

Induced sputum cell counts before and after workplace challenge

- Sputum eosinophils increase after exposure to both HMW agents and some LMW agents, support diagnosis of OA.
- In 1 study, 37% of 38 patients had sputum eos counts of >2.2% while continuing work exposure.
  - High sputum neutrophil counts of >50% occurred in both eosinophilic and noneosinophilic OA groups.

Nonspecific airway hyperresponsiveness

- Sensitive for diagnosis of asthma, but not specific – if negative proximate to workplace exposure, essentially rules out dx
- Perform toward the end of a work week, with a repeated study at the end of a period (usually >10-14 days) away from the exposure.
- A worsening of PC20 at work versus off work (beyond a 3-fold or greater change in PC20) provides support for OA dx.

Monitoring of PEF & PC20 to confirm objectively exacerbation of asthma at work

Immunologic testing

Nonoccupational allergens
- Perform: may contribute to asthma.

HMW sensitizers
- Negative percutaneous tests to validated occupational protein allergen can exclude OA with high accuracy

LMW sensitizers (IgE mediated only)
- Using protein-LMW chemical conjugates
- Extracts not commercially available for skin testing.
- Limited # in vitro tests for IgE available, typically not good sensitivity, but + results support dx of OA
- Many commercial tests not validated

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DIFFERENTIAL DIAGNOSIS (I)
• Non occupational asthma
• Upper respiratory tract irritation, rhinosinusitis
• Vocal cord dysfunction
• Hypersensitivity pneumonitis
• Psychogenic factors.
• Other occupational lung diseases

DIFFERENTIAL DIAGNOSIS (II)
Other occupational lung disease
• Byssinosis, popcorn workers' disease, flock workers' disease (last two may cause bronchiolitis obliterans)
• Eosinophilic bronchitis:
  – nonproductive cough
  – increased eosinophils in sputum but without evidence of airway obstruction or hyperreactivity
  – Reported from occupational exposure to latex, acrylates, mushroom spores, lysozyme.
Management (I)
In OA from sensitizers
• complete avoidance recommended
• anti-inflammatory agents with continued exposure do not improve overall outcomes.
• exposure reduction by job transfer, more vigorous industrial hygiene measures, or use of respiratory protective devices successful in only several occupational settings, unsuccessful at improving outcomes of OA from TDI and some LMW sensitizers

Management (II)
In irritant-induced OA, may continue in jobs if the risk of a high-level exposure reduced by engineering controls and respiratory protective devices.
Reduce / avoid exposure in work place
- Enhance awareness in workers at risk
- Removal of worker, particularly if sensitizer present
- Surveillance measures
  - Periodic monitoring of work place exposures, spirometry, tests for immunologic sensitization
- Address any non-occupational factors
Prognosis of OA (I)

Depends primarily on 1) cessation of exposure to the offending agent, 2) duration of exposure to sensitizers, and 3) severity of asthma when diagnosed.

Timely removal of workers from exposure to sensitizers caused OA generally associated with favorable outcomes.

Prolonged follow-up may be required to ascertain outcomes in any individual ("maximal medical improvement")

- particularly in OA from sensitizers: may be continued improvement of lung function for 2 years or more after exposure ends.

2001 & 2002 U.S. data: compared to subjects with non-work related asthma (NWRA), subjects with WRA were

- 4.8 times more likely to report having an asthma exacerbation,
- 4.8 times more likely to visit the ED at least once
- 2.5 times more likely to visit their physician for an asthma exacerbation in previous 12 months


- WEA tends to be more severe than OA and is associated with a noneosinophilic phenotype.
- Generally, both subjects with WEA and with OA had to change employment and observed decreased income compared with subjects with NWRA (consistent with previous studies
• Only subjects with OA showed a statistically significant decrease in their health care–related costs during the year after the diagnosis...emphasizes beneficial effect of removal from exposure of subjects with OA.

**Occupational Asthma Summary**

• Take into account your patient's environment – *Hippocrates, c. 400 B.C.*
• To the question recommended by Hippocrates, one more should be added, “What occupation does he follow?” – *Ramazzini, 1713 A.D.*
• History is key to suspecting diagnosis
• Use objective measures to confirm diagnosis
• Focus on prevention