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

Mark S. Dykewicz, MD
Raymond & Alberta Slavin Endowed Chair in Allergy & Immunology
Chief, Section of Allergy & Clinical Immunology
SAINT LOUIS UNIVERSITY

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.

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

Mark S. Dykewicz, MD *Winston-Salem, NC* JACI 2009 (March);123:519-28

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.
PMH: 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

QUESTONS
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?

- DEFINITIONS & IMPORTANCE
- TYPES OF OA
- PATHOPHYSIOLOGY
- EPIDEMIOLOGY AND RISK FACTORS
- DIAGNOSIS
- DIFFERENTIAL DIAGNOSIS
- MANAGEMENT
- PREVENTION AND SURVEILLANCE
- PROGNOSIS AND OUTCOMES

Tarlo SM et al. Diagnosis and management of work-related asthma: American College of Chest Physicians consensus statement. Chest 2008;134(3 Suppl):1S-41S.

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, aeroallergens, 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.

Tarlo SM et al. Chest 2008;134(3 Suppl):1S-41S. **ACCP**
Balmes J et al. . AJRCCM 2003;167:787-97. **ATS**

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

Banauch GI. Curr Opin Pulm Med 2005;11:160-8.

Irritant-induced OA

- Controversy whether chronic lower-level exposure to irritants can cause OA.

Tarlo. Chest 2008;134(3 Suppl):1S-41S.
Mapp CE. AJRCCM 2005;172:280-305.

- Repeated peak exposure to irritant gases in pulp industry increases risk for asthma.

Andersson E. Am J Ind Med 2003;43:532-8.

- 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)

PROTEIN SOURCE	OCCUPATION
Animal & Insect derived	
Snow crab, Sea squirt (oyster parasite)	Seafood processors
Mammalian proteins (dander, urine)	Lab workers, pet care
Vegetable/plant dusts	
Wheat flour	Baker's asthma (flour)
Henna dye	Beauticians
Psyllium	Nursing
Bacterial and fungal–derived	
Bacillus subtilis–derived enzymes	Detergent formulators
Penicillium caseii	Cheese workers

OA from LMW Sensitizers
(only some IgE mediated)

CHEMICAL	OCCUPATION
Persulfates (hair bleaching)	Hairdressers
Metals and metal salts	
Chromium	Miners; cement, electroplating, tanning workers
Platinum	Alloy makers
Organic chemicals	
Acid anhydrides (trimellitic anhydride)	Plastics industry, epoxy resins, dye, insecticide makers
Polyisocyanates (toluene diisocyanate)	Polyurethane, paints, foam coatings, adhesives production

- 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

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.

Grammer LC.J Occup Environ Med 2002;44:1179-81.

Karjalainen A. Chest 2003;123:283-8

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)*

Grammer LC.J Occup Environ Med 2002;44:1179-81.
Karjalainen A. Chest 2003;123:283-8.

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!

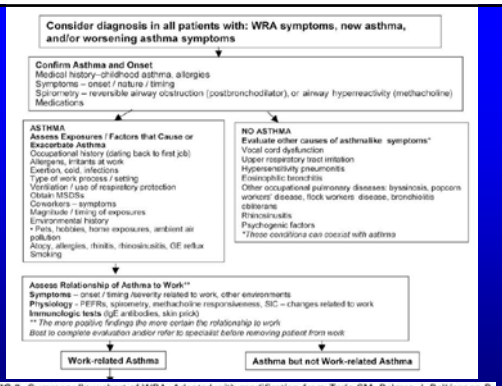


FIG 2. Summary flow chart of WRA. Adapted with modification from Tarlo SM, Balmes J, Balkissoon R, Beach J, Beckett W, Bernstein D, et al. Diagnosis and management of work-related asthma: American College of Chest Physicians consensus statement. Chest 2008;134(3 Suppl):1S-41S.[2] GE, Gastrointestinal.

Dykewicz MS. JACI 2009;123:519-28

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)

- DEFINITIONS
- TYPES OF OA
- PATHOPHYSIOLOGY
- EPIDEMIOLOGY AND RISK FACTORS
- DIAGNOSIS
  - History
  - Objective medical testing
    - Workplace challenges.
      - Spirometry and peak expiratory flow rates
      - Induced sputum cell counts.
      - Exhaled nitric oxide.
      - Nonspecific airway hyperresponsiveness
    - Specific inhalation challenge
    - Immunologic testing
- DIFFERENTIAL DIAGNOSIS
- MANAGEMENT
- PREVENTION AND SURVEILLANCE
- PROGNOSIS AND OUTCOMES

Beyond History: Objective Testing for OA

- History alone insufficient for diagnosis

  Malo JL, Chan-Yeung M. JACI 2001;108:317

- 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

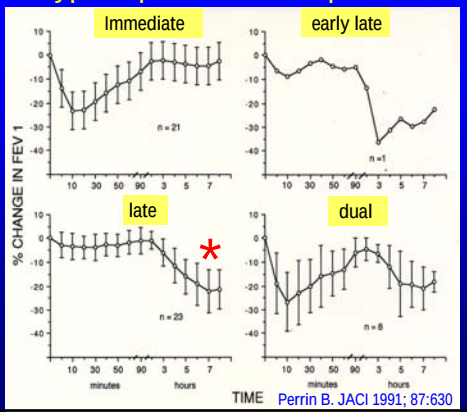
In individuals with suspected WRA *who are currently working at the job in question*,

"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

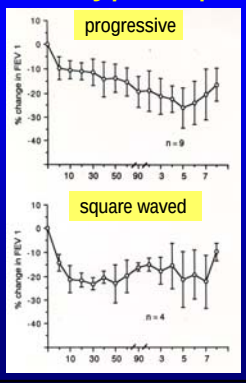
ACCP 2008

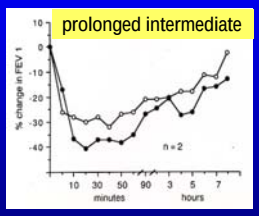
Typical patterns of response



Perrin B. JACI 1991; 87:630

Also *atypical* patterns of response!





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.

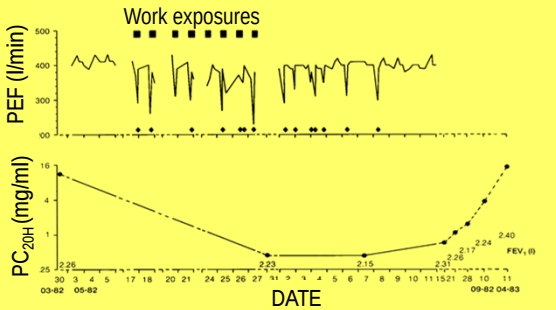
Anees W. Thorax 2002;57:231-6.

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 & PC_{20}

to confirm objectively exacerbation of asthma at work



Cartier A. JACI 1984;74;261

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

Beach J. et al. Diagnosis and management of work-related asthma. summary, evidence report/technology assessment. Rockville (MD): Agency for Healthcare Research and Quality, Department of Health and Human Services; October 2005. Publication no. 06-E003–1.

- DEFINITIONS
- TYPES OF OA
- PATHOPHYSIOLOGY
- EPIDEMIOLOGY AND RISK FACTORS
- DIAGNOSIS
- DIFFERENTIAL DIAGNOSIS
- MANAGEMENT
- PREVENTION AND SURVEILLANCE
- PROGNOSIS AND OUTCOMES

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.

- DEFINITIONS
- TYPES OF OA
- PATHOPHYSIOLOGY
- EPIDEMIOLOGY AND RISK FACTORS
- DIAGNOSIS
- DIFFERENTIAL DIAGNOSIS
- MANAGEMENT
- PREVENTION AND SURVEILLANCE
- PROGNOSIS AND OUTCOMES

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.

- DEFINITIONS
- TYPES OF OA
- PATHOPHYSIOLOGY
- EPIDEMIOLOGY AND RISK FACTORS
- DIAGNOSIS
- DIFFERENTIAL DIAGNOSIS
- MANAGEMENT
- PREVENTION AND SURVEILLANCE
- PROGNOSIS AND OUTCOMES

- 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

- DEFINITIONS
- TYPES OF OA
- PATHOPHYSIOLOGY
- EPIDEMIOLOGY AND RISK FACTORS
- DIAGNOSIS
- DIFFERENTIAL DIAGNOSIS
- MANAGEMENT
- PREVENTION AND SURVEILLANCE
- PROGNOSIS AND OUTCOMES

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 sensitizer 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

Breton C et al. Occup Environ Med 2006;63:411-5.

Lemiere C et al. JACI 2013;131:704-10.

- 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