Occupational asthma

DR. AMIT RAODEO

DM SEMINAR

Introduction

- Occupational asthma is the most prevalent form of occupational lung disease in industrialized nations
- Occupational asthma caused by more than 250 chemicals
- With the introduction of new organic and inorganic chemicals, the list continues to grow
- About 15% of adult-onset asthma attributed to occupational exposure to irritants.
- Finds mention even in Hippocratic era
- Poorly recognized entity

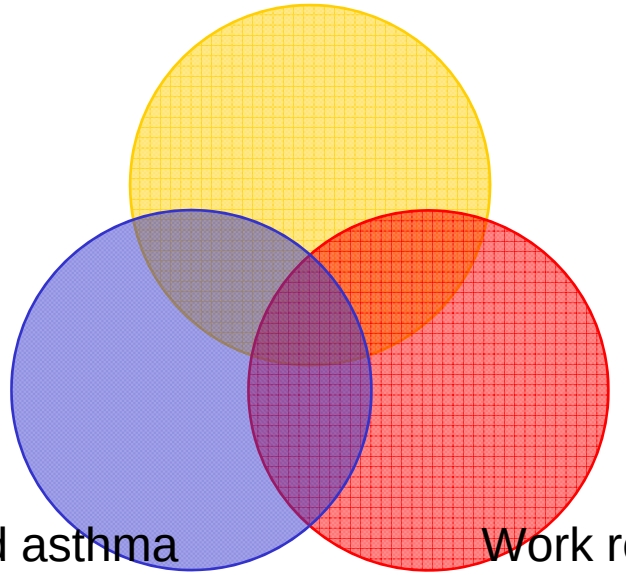
Definition

- Variable airflow limitation, bronchial hyperresponsiveness, or both, due to exposures in a particular workplace separate from those outside the work environment
- Controversial issues

- whether to include work aggravated asthma
- how many objective tests should be positive

Subgroups of occupational asthma

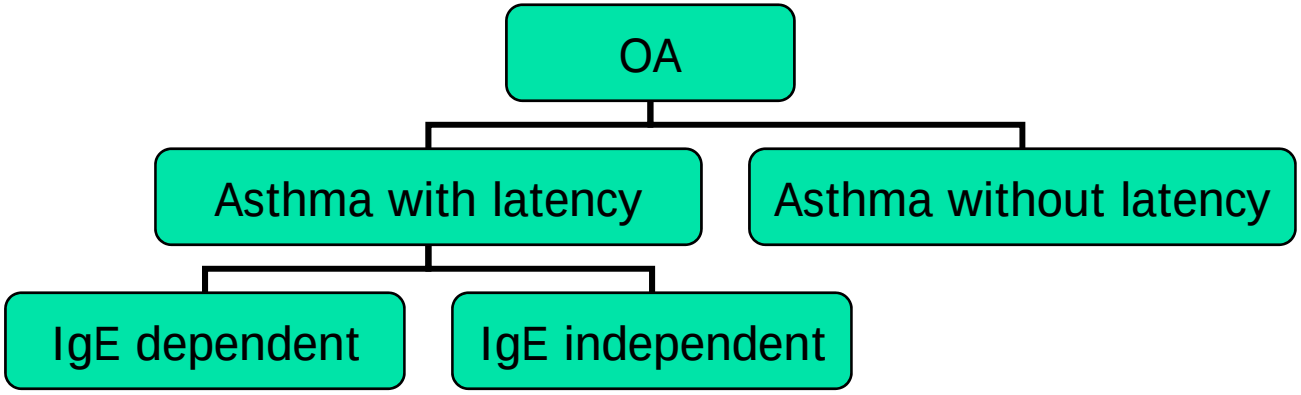
RADS



Work aggravated asthma

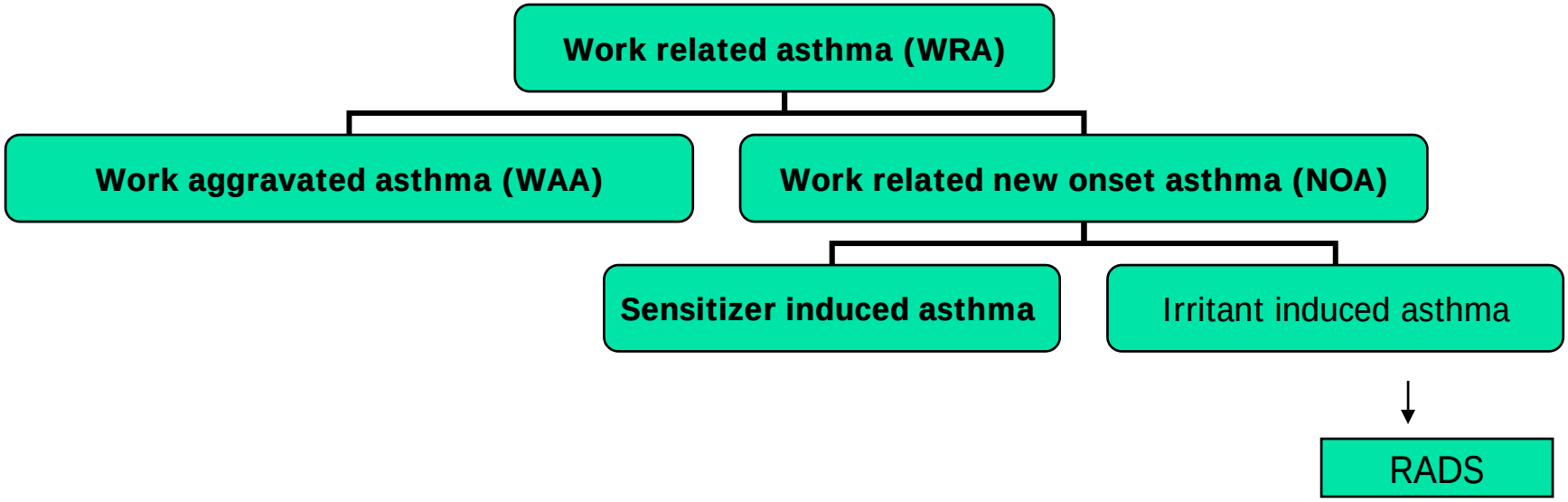
Work related asthma

Subgroups of occupational asthma

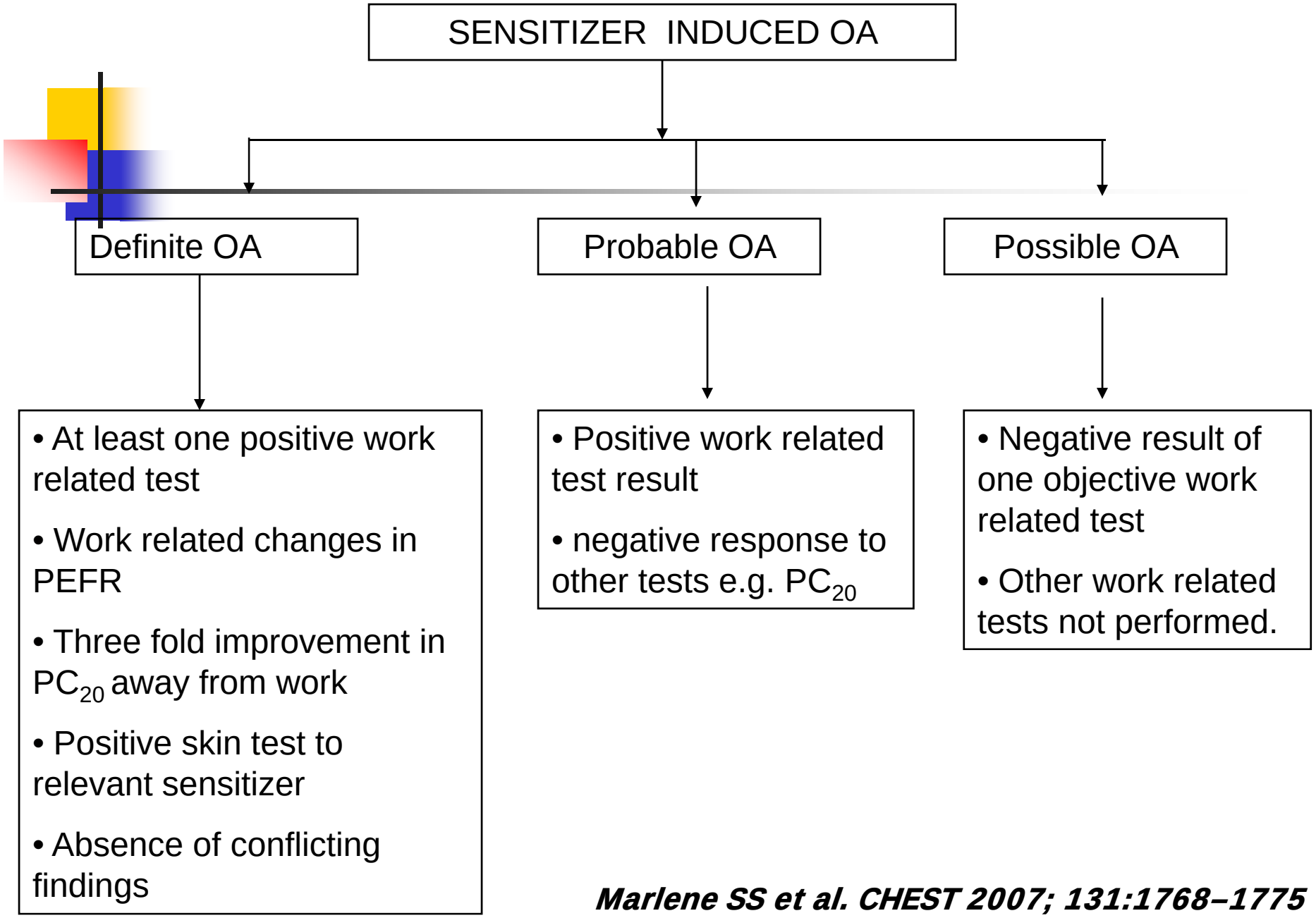


Chan-Yeung et al. N Engl J Med 1995; 333:107–112

Subgroups of occupational asthma



***S K Goe et al. Occup. Environ. Med.* 2004;61;512-517**



Marlene SS et al. CHEST 2007; 131:1768–1775

RADS

- Controversial – subgroup of irritant induced asthma or a separate entity
- Initial description was persistent asthma syndrome after high level irritant exposures.

Brookes SM et al. Chest 1985;88:376–384.

- Essential criteria-strong temporal association between inhalation exposure and the rapid onset of asthmatic symptoms
- Few authors believe, it should never be diagnosed in patients with preexisting asthma
- Others disagree
- Vandenplas et al suggested that, although widely used, the term “RADS” should be replaced “acute irritant induced asthma” or “sudden-onset irritant-induced asthma” to avoid confusion

Eur Respir J 2003;21:706–712

Epidemiology

- Data largely based on surveys in individual workplaces
- Few population based studies
- Limitations

- survivor bias effect- most important drawback
- large discrepancy in reporting
- information bias
- lack of uniform definition
- controversy regarding work aggravated asthma
- most epidemiological studies of occupational asthma cross-sectional in type
- no validated tool for OA

Gautrin D et al. Eur Respir J 2003; 22: 551–559

Epidemiology

- Study by Brisman et al tackled most of these issues
- Retrospective cohort design among bakers in 1959–1989 (n=2,923)
- Two different reference groups, one comprising persons who followed another programme in the trade school and another randomly selected from the population register.
- The RR for bakers was 1.8 (95% CI 1.3–1.6), whereas there was no difference in the prevalences.
- Secondly, they also studied nonrespondent and found that the bakers had changed work significantly more often than controls

Brisman et al .Scand J Work Environ Health 1995;21: 487–494.

Epidemiology

Medical, medicolegal and compensation data

- Many developed countries have registration systems
- Some of them have mandatory reporting e.g. FROD (Finnish Register of Occupational Diseases)
- In others, it is based voluntary reporting e.g. SRROD(Swedish Register of Reported Occupational Diseases)
- Medicolegal statistics can also be useful and devoid of significant ascertainment and selection biases
- Data from compensation claims is unsatisfactory because all patients may not apply

Epidemiology

Sentinel programmes

- Voluntary reporting scheme.
- In UK, two voluntary reporting schemes have proved effective since 1989.
- The Surveillance of Work-Related and Occupational Respiratory Disease (SWORD) draws on reports of newly diagnosed occupational lung disease from specialists in occupational or respiratory medicine
- The other voluntary scheme, Midland Thoracic Society Rare Respiratory Disease Registry Surveillance Scheme of Occupational Asthma (SHIELD)
- The recent figures show stabilisation in the number of new cases with limited variation in the number of cases due to specific agents

Epidemiology

- Similar programme in the USA, the Sentinel Event Notification System for Occupational Risks (SENSOR)
- The objectives of SENSOR are

  - to identify potentially dangerous sentinel cases in the work environment

  - initiate investigations

  - implement interventions.
- Data from SENSOR, exposure to irritants are reported as frequently as that of sensitizers as cause of new onset asthma

Jajosky RA et al. MMWR Morb Mort Wkly Rep 1999, 48 (SS-3):1-20

How much adult asthma is attributable to occupational factors ?

- Studies from U.S. and Japan, estimated to be 15%.
- Values from 3-20% has been reported in literature.
- In a systematic review by Toren et al (included 43 attributable risk estimates from 19 different countries), median attributable risk of occupationally associated asthma was 9% (25th to 75th interquartile range 5%-19%)
- These estimates included both new onset asthma and work aggravated asthma

Toren et al. Am. J. Med.1999;107:580-587

How much occupational factors contribute to adult asthma?

- In a recent international prospective population based study (n=6837), relative risk was found to be 1.6% (95% CI 1·1–2·3, p=0·017)
- Risks were highest for asthma defined by bronchial hyper-reactivity in addition to symptoms (2·4, 1·3–4·6, p=0·008)
- Asthma risk was also increased in participants who reported an acute symptomatic inhalation event such as fire, mixing cleaning products, or chemical spills (RR=3·3, 95% CI 1·0–11·1, p=0·051) irrespective of whether they develop immediate symptoms.

Kogevinas M et al. Lancet 2007; 370: 336–41

WAA asthma prevalence among OA

No	Prevalence	No. of patients studied	reference
1	27%	71	Wheeler S et al. West J. Med. 1998;48:98-104
2	18%	55	Gassert TH et al. J. Occ. Environ. Med. 1998;48:481-91
3	49%	51	Tarlo SM et al. Chest 2000;178:1309-14

Risk factors

- Level of exposure- most common and universal risk factor

***Chan-Yeung M et al. N Engl J Med 1995; 333:107–112*.**

- For isocyanate-induced asthma, one study has suggested that peak exposures could be more relevant than the cumulative dose of exposure.

Leroyer C et al,Thorax 1998;53:152–153

- H/o atopy
- Cigarette smoking - increases the risk of sensitization to high-molecular-weight agents that cause OA through an IgE mechanism

Pathophysiology

Pathogenetic factor	Occupational asthma	Non-occupational asthma
Predominent T lymphocyte subtype	CD8+ Tcells or CD4-/CD8- Tcell	CD4 T cell
HLA association	HLA-BQ1 and HLA-AQ1	No definite HLA association
Genetic mutation	Glutathione-S transferase gene mutation	Usually multifactorial single gene mutation not seen

Pathophysiology of irritant induced asthma

- Definite pathophysiologial mechanism not known due to lack of animal models
- Hypothesis- epithelial damage followed by activation of nonadrenergic, noncholinergic pathway (NANC) via axon reflexes
- Pathologically similar apart from excess of subepithelial fibrosis
- There is still controversy about whether intermittent high level exposure and chronic low-level exposure to irritants can cause OA

Tarlo et al. Ann Allergy Asthma Immunol 2003;90:19–23.

Aetiology

- The occupations with the greatest statistically significant increase in the odds ratio for asthma relative to the reference group were farmer (odds ratio, 2.6), painter, and cleaner.

  Susan M. et al. Curr Opin Pulm Med 2000, 6:145–150

- In a study by Toren et al (n=321) in a Swedish city, highest-risks were from exposures to grain dust and flour dust.

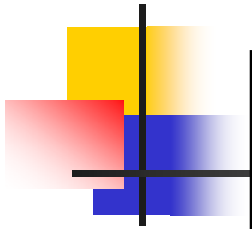
  Toren K et al. Eur Respir J 1999, 13:496–501

Diagnosis

- Grossly under-diagnosed disease
- Definitive confirmation of diagnosis is essential for compensation and rehabilitation purposes
- Difficulties in the diagnosis

  - presence of preexisting asthma
  - exposure to multiple substances at workplace
  - exposure to substances outside the workplace
  - significant latency period between exposure and symptoms
- Two step process

  1) confirmation of asthma
  2) prove occupational association



? Occupational Asthma

Establish relationship of symptoms to workplace exposure

Look for other cause of Asthma

- **Symptom occurrence at work place**
- **Symptomatic** improvement **at week ends**
- **Symptoms occurring regularly office work shift**
- **Symptoms progressively increasing over work week**
- **Symptoms improve after change in work environment**

- **H/o Atopy**
- **Hobbies**
- **Drug history**
- **H/S/O GERD**
- **H/o Cardiac Symptoms**

If any one present

No

Non occupational asthma

yes

Detail Occupational History

Objective Tests

Specific diagnostic tests

N0.	Diagnostic test	Advantages	Disadvantages
1	SIC	-Gold standard -Can differentiate between WEA and WRA	-false negative can occur -expensive -Availability limited
2	Single or serial NSBP	-Relatively simple -Sensitive	-Nonspecific
3	Serial PEFR	-Relatively simple -Inexpensive -Good sensitivity and specificity	-measurement bias -compliance problems -limitation in recording devices -Unable to diagnose of multiple substances exposure
4	SPT	-Highly sensitive - Good negative predictive value for natural proteins	-Nonspecific -Special reagents not routinely available -Only useful in HMW compounds
5	Specific IgE	Higher specificity compared to SPT	Less sensitive for screening

Newer diagnostic modalities

- Induced sputum
- Eosinophilia is a reasonably good noninvasive index of airway inflammation
- In one study, sputum eosinophils, eotaxin, and IL-5 were elevated after exposure to LMW agents

  Lemiere CJ Allergy Clin Immunol 2000;106:1163–1170.
- The addition of sputum cell counts to monitoring of PEFR increased the specificity of this test by 18 to 26.8%

  Girard F et al. Am J Respir Crit Care Med 2004;170:845–850.
- Sputum may be particularly helpful in differentiation between work-aggravated asthma and superimposed OA due to a workplace sensitizer

  Obata H et al. Eur Respir J 1999;13:489–495
- Also helpful in monitoring OA

Newer diagnostic modalities

- Exhaled nitric oxide (eNO)
- Gives measure of airway inflammation
- Measurements are confounded by use of ICS and smoking
- Also, it is produced in high amounts in paranasal sinus and stomach epithelial cells
- A few occupational studies have investigated the role of eNO in assessing OA, but with inconsistent results
- The sensitivity of this measurement is high but specificity is low.
- Currently can not be recommended for diagnosis or monitoring of OA

Other investigational modalities

- Exhaled breath condensates
  - Isoprostanes and aldehydes
  - Mediators like prostaglandins and leukotrienes
- Nasal lavage fluid eosinophils and basophils
- Rhinomanometry

Role of diagnostic tests in OA

	ROLE IN DIAGNOSIS	DIAGNOSTIC TEST
1	Diagnosis of asthma	-Nonspecific airway hyperreactivity -Reversibility of airflow obstruction
2	Association with workplace exposure	Serial PEFR at workplace
3	For sensitization to environmental antigen	-Skin prick testing -Specific IgE serum testing
4	determining a specific causal etiology of asthma	- Specific inhalational challenge (SIC)

Factors associated with delay in the diagnosis of OA

- In a study from Ontario, the mean time of diagnosis was 4.9 years.
- On average, patients waited 7.4 months before discussing the work-relation of symptoms with a physician.
- Main self-reported reasons for delay were lack of enquiry about work relatedness by the primary care physician (41%) and fear of losing work time (37%).
- Reported increases in time during secondary care were related to difficulties associated with completion of investigations (35%).
- Lower education level ($p = 0.04$) and household income ($p = 0.03$) were significantly associated with an increased time to diagnosis

Poonai N. et al. Can. J. Public Health 2005;96(3):230-233

Factors associated with delay in the diagnosis of OA

Sensitizer induced OA

- Old age (p=0.009)
- Male sex (p=0.002)
- Sole income earner (p=0.05)
- Lack of knowledge of workplace hazards (p=0.06)

WEA

- Physicians not asking about work association with asthma (p-0.009)
- Travel distance > 60 km to reach specialist (p=0.08)
- More dependents (p=0.04)
- Longer period of working (p=0.06)

Marlene SS et al. CHEST 2007; 131:1768–1775

Factors associated with delay in the diagnosis of OA

- Most patients report symptoms when unbearable.
- A minority of patients referred by workplace screening
- Workplace screening associated with delay and worse outcome.
- Self-reported median time with WRA symptoms significantly shorter in patients with WEA (1 month) vs those with OA (3 months; p=0.0001)

Marlene SS et al. CHEST 2007; 131:1768–1775

Role of physicians in the diagnosis and management of OA

- Delay in the diagnosis is the most important factor responsible for poor outcome in OA(OR = 1.12,95% CI 1.05–1.18, P < 0.001)

Dascatha A et al. Allergy 2007: 62: 795–801

- In an older study, physicians reported seeing on an average 20 patients per year of OA

Harber et al.Chest 1995;107:1156-296 1161.

- In a recent study, similar findings were reported
- Time constraints, forgetting to ask occupational history and lack of availability of specific tests were main factors responsible for under-recognition

Role of physicians in the diagnosis and management of OA

- The most important sources for improving performance of physicians were

  - Educational conferences
  - Journal articles
  - Consultation notes

Holeness DL et al. Chest 2OO6;130:1165-85

Management

- Complete cessation of exposure to irritant or sensitizer is most important step
- Guidelines for management are similar to that of non-occupational asthma
- Atleast a couple of studies have addressed the role of ICS in occupational asthma
- In a double blind crossover study, Malo et al demonstrated that ICS induce a small but significant improvement in patients with sensitizer induced asthma (both due to HMW and LMW) after withdrawal from exposure

  Am. J. Respir. Crit. Care. Med.1996;153:953-960
- In a 3-year longitudinal study of workers with mild to moderate persistent OA who were still exposed at work to the causal agent , it was suggested that regular treatment with ICS+LABA prevent deterioration of lung function

  Marabini et al. Chest 2003;124:2372–2376.

Prevention

- Significant impact on health, work and socioeconomic status
- Potentially preventable disease
- Early diagnosis and removal from exposure is associated with greatest chance of cure
- Majority of patients continue to have symptoms and some worsen

Primary prevention strategies

- Change of process
- Substitute a nonsentizing or less sensitizing product
- E.g. 1) potential use of paints and varnishes without diisocynate
  2) manufacturing detergents without enzymes
  3) encapsulation of enzymes
  4) substituting non NRL (Natural rubber latex) gloves
  - may not always be successful

- Appropriate use of respiratory protection
- Occupational hygienic measures
- Education regarding medical investigation of work related symptoms

Primary prevention strategies

- Reduction of exposure levels for workers

  - increased local ventilation
  - enclosure of processes
  - use robots instead of human workers

- Currently no proven level of exposure has been found to be effective

Secondary prevention strategies

- Goals are early detection of cases or sensitization and prevention of progression by early intervention
- Methods

  - periodic respiratory questionnaire
  - spirometry
  - skin testing – available only for HMW sensitizers
- Used in combination with primary preventive strategies
- In a review of surveillance from one diisocynate using company, questionnaire component was found to be more specific and sensitive than spirometry component.

Tarlo et al. Am. J. Int. Med. 1999;35: 87-91

Secondary prevention strategies

- Only few studies have investigated the impact of such strategies
- In a study of supermarket bakery workers, routine surveillance measures were compared with cross sectional studies.
- The participation was less (72% vs 92%) and number of persons with positive skin test was also less (1% vs. 4%)
- Authors concluded that surveillance measures underestimate the prevalence

Brant et al. Occ. Environ. Med. 2005;62:395-396

- In a report in detergent workers, combination respiratory questionnaire with spirometry led to early detection of cases
- Significant fall in rate of OA was observed when these patients were moved out of workplace

Shweigert et al. Clin. Exp. Allergy2000;30:1511-1518

Tertiary prevention measures

- Early diagnosis and confirmation of cases by physicians
- Intervention by removing patient from further exposure
- Providing good medical management of asthma
- Supporting patient for appropriate compensation
- Advice of future safe workplace
- Notification to appropriate authority to prevent risk of exposure to other workers

Conclusion

- Occupational asthma contributes significant proportion of asthma cases
- Significantly under-recognized disease both among patients and physicians
- Diagnosis of OA has significant impact on health and socioeconomic status of the patient
- Early and confident diagnosis followed by prompt removal of exposure are cornerstone in the management of OA
- Education of both workers and physicians is required to improve outcome of OA