IRRITANT-INDUCED ASTHMA
(I-IA)

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Occupational asthma or work-related asthma

1. Sensitization: allergic or immunologic with latency: IgE or non-IgE

2. Acute exposure to high concentration of irritant (RADS) without latency

3. Exacerbation or aggravation of preexisting asthma

4. The gray zone: low-dose RADS?
Occupational asthma

1. 469 accepted compensation claims, Ontario: 1984-88
2. Non-irritant exposure: 380 (81%)
3. Accidental high exposure: 89 (19%)
   1. RADS: 12 (13%) or 12/489 (2%)
   2. Exacerbation: 68 (76%)
   3. Irritant-induced?: 9 (10%)

Work-exacerbated asthma

1) 18% of all adults with asthma
2) 25% of working adults with asthma
3) 45% of all work-related asthma

Henneberger PK. 2007; Curr Opinion Allergy Clin Immunology;7:146-51
RADDS (reactive airways dysfunction syndrome) criteria:

- No previous asthma complaints
- Onset of asthma after a single exposure/accident
- High irritant concentrations
- Asthma onset within 24 hours
- Definite asthma diagnosis: e.g. positive methacholine, mannitol, exercise test
- Exclude other respiratory diagnoses
Irritant exposure: consequences

<table>
<thead>
<tr>
<th>SINGLE HIGH-LEVEL EXPOSURE</th>
<th>REPEATED MODERATE EXPOSURE</th>
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</thead>
<tbody>
<tr>
<td>Upper airway edema and obstruction</td>
<td>Upper airway irritation symptoms, Vocal cord dysfunction (VCD)</td>
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<tr>
<td>RADS</td>
<td>Irritant-induced asthma (IIA)</td>
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<tr>
<td>Adult respiratory distress syndrome</td>
<td>Bronchiolitis obliterans (popcorn lung)</td>
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<tr>
<td>Bronchiolitis obliterans</td>
<td>Increased airway hyperresponse</td>
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Inhalation accident prognosis

1) SWORD surveillance 1989-94: England in GPs
2) 383 inhalation accidents
3) 70% recovered within 1 week
4) 10% persistent respiratory symptoms
5) 3% persistent asthma (RADS)

RADS outcome

1) Median symptom duration 51 work-related: 13 months (interquartile range 6.5-43.5)
2) 35 RADS cases after 13.6 years:
   - all symptoms
   - 68% ICS
   - 17/23 positive metacholine
   - 12 depression

Malo JL. Am J Respir Crit Care Med 2009;179:923-8
Pathology of RADS: non-immunologic

1) Epithelial cell injury
2) Bronchial wall inflammation
3) Lymphocytes and plasma cells, no eosinophils
4) Rapid denudation of mucosa
5) Fibrohemorrhagic exudates
6) Regeneration: basal and parabasal cell proliferation over months
Possible RADS mechanism

1) Special airway nociceptors: detect noxious stimuli
2) Transient receptor potential vaniloid-1 (TRPV$_1$). Transient receptor potential cation channel, subfamily A, member 1 (TRPA$_1$)
3) Activated by capsaicin, associated with chronic cough
4) Heightened TRPV$_1$, TRVA$_1$ sensitivity
## Common causes of irritation

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Agent or process</th>
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<tbody>
<tr>
<td>Acids</td>
<td>Sulfuric, hydrochloric, hydrofluric, glacial acetic</td>
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<tr>
<td>Alkali</td>
<td>Bleach, sodium hydroxide, calcium oxide, WTC dust</td>
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<tr>
<td>Gases</td>
<td>Chlorine, ammonia, sulfur dioxide, phosgene, mustard</td>
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<tr>
<td>Sprays</td>
<td>Paints, coatings</td>
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<tr>
<td>Explosion</td>
<td>Irritant gases, vapors, fumes released under pressure</td>
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<tr>
<td>Fire or pyrolysis</td>
<td>Combustion products, PVC pyrolysis, burning paint fumes</td>
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<tr>
<td>Confined spaces</td>
<td>Acrolein, biocides, fumigating aerosol, drain-cleaning agents</td>
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<tr>
<td>Workplace</td>
<td>Popcorn flavoring, Al smelting (potroom), shoe manufacture (solvents), tunnel construction, food industry cleaners</td>
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</tbody>
</table>
Irritation

1. Somesthesia, chemesthesia, chemical nocioception
2. Eye, nose and throat: trigeminal nerve (CN V)
3. Pulmonary irritation: vagus nerve (CN X)
4. Odor: olfactory nerve (CN I)
5. Toxicity: Odor ≠ irritation
Preexposure to irritant enhances airway responsiveness to allergens

1. Th₂ cytokine-producing cell recruitment
2. Amplifying Th₂ inflammation through thymic stromal lymphopoiten
3. Allergen enzymes cause mucosal irritation enhancing immunological response
4. Dust mite proteolytic allergens (Der 1 p and Der 9) dose-dependent release IL-6, IL-8 and granulocyte-macrophage colony-stimulating factor (in-vitro)
Asthma-like symptoms and odor

1) Airway sensory hyperreactivity
2) 15-30%??
3) Upper or lower airway symptoms induced by odor
4) Increased cough sensitivity to capsaicin-challenge
5) Normal methacholine
6) Poorer quality of life
Asthma and construction work

1) Finnish registry linkage study
2) 2,548 incident cases
3) Increased RR
   - Welders, flamecutters: 2.34 (1.79-3.06)
   - Asfalt roofers: 2.04 (1.02-4.09)
   - Plumbers: 1.90 (1.63-2.21)
   - Brick layers: 1.83 (1.46-2.28)
4) New welding asthma: 7.0 (1.2-41.6)

Karjallainen A. J Occup Envirom Med 2002;44:752-7
Omland O. J Allergy Clin Immunol 2011;128:761-5
Calcium carbonate

Burge PS. 2011: doi.1093/occmed/kqr211
Asthma and cleaners: a prospective study

1) Cleaners, nurses, homemakers
2) Increased risk of new-onset asthma
3) Incidence: 2.2/1000 person-years
4) Ammonia, bleach, cleaning sprays

Swimming pool asthma

1) Chlorine + sweat, urine
2) Chlorination products: trichloramine (nitrogen trichloride)
3) Children swimmers (Belgian, 2003)
   - Increased lung epithelium permeability
   - Increased asthma prevalence
   - Chlorine-atopy interaction
Swimming pool asthma (2)

4) **Elite swimmers**: increased prevalence of rhinitis and asthma. Biopsies similar to mild asthma: +/- airway hyperresponsiveness (2012)

5) **Chlorine-free pools** (copper-silver ionization method): asthma prevalence 2-3 times reduced (2009)

6) A solid hypothesis?
Sodium hypochlorite

Nitrogen trichloride

Thickett KM. Europ Resp J 2002;19:827-32
Asthma: highest vs lowest swimming
5738 kids 10y follow-up

Font-Ribera L. Am J Respir Crit Care Med 2011;183:582-8
New irritants

1) Alcohol hand gels: denatonium (a quaternary ammonium, quat)
2) Robertsen A. ERS 2011 Poster 4948, Birmingham Chest Clinic
3) Controlled provocation
   - A midwife: OASYS score 3.43 (<2.5), dual asthmatic reaction
   - A nurse: OASYS score 3.93, prolonged immediate reaction

Quirce S. Immunol Allergy Clin N Am 2011;31:677-98
http://www.occupationalasthma.com
Summary

1) Work-exacerbation is very common
2) Demonstrate work relation
3) Peak flow (OASYS: http://www.occupationalasthma.com/oasys.aspx)
4) Evaluate atopy and specific allergens
5) Consider irritant-induced asthma
6) Consider irritant-allergen interaction
7) Causation: non-specific chronic irritation or a specific non-IgE reaction