Fever related to chemical inhalation: mechanisms and outcome

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Calls due to inhalational exposures

- represent only about 5% inquiries to TIC in the Czech Republic, mostly involve adults (82%)

- calls with a difficult estimation of severity of exposure, causality and prognosis
Causality?

- No symptoms: 50%
- Mild: 19%
- Severe: 10%
- Medium: 9%
- Not announced: 2%
- Probably unrelated: 2%
- Unrelated: 8%
Prognosis at the time of the call?

- 38% Good
- 40% Probably good
- 21% Uncertain + unknown
- 1% Probably severe
What are the causes?

- Home work: 35%
- Occupational: 16%
- Unintentional: 13%
- Accident, fire: 6%
- Abuse: 1%
- Aggression: 9%
- Other: 20%
What agents did the subjects inhale?

- Cleaning Products: 28%
- Gases: 18%
- Solvents: 18%
- Pesticides: 15%
- Metals: 13%
- Other: 8%
INHALATION FEVERS

Several syndromes characterized by short-term but intense flulike symptoms after exposure to inorganic and organic dusts and fumes

1) METAL FUME FEVER - benign inhalation fever syndromes
   - Zn, Cu, Mg, polymers, ...

2) METAL-INDUCED LUNG DISEASE - potentially severe -
   Cd, Co, Cr, Hg, Mn, Ni, Vn, ZnCl₂,...

3) EAA/HYPERSENSITIVITY PNEUMONITIS - potentially severe - organic and inorganic dusts
Metal fume fever – most frequent acute complaint in welders

5 million persons occupationally exposed to welding fumes worldwide

fumes and particles of the respirable size

mostly from the rod/wire – oxidized metal
1. BENIGN METAL FUME FEVER
oxides of Zn, Cu, Mg, Teflon

Acute febrile illness with good prognosis

First described in the mid 1800s – in brass foundry workers
1900s in welders of galvanized steel

Associated with welding, melting, flame-cutting galvanized metal of brass, foundry works

Wrong practice
1. BENIGN METAL FUME FEVER
oxides of Zn, Cu, Mg, Teflon

- Self-limited flulike illness:
  - fever
  - shaking chills
  - sweet/metallic taste
  - generalized body aches – myalgias, arthralgias
  - malaise.
- Frequently also: headache, sore throat, chest pain, cough, mild dyspnoe.
1. BENIGN METAL FUME FEVER

oxides of Zn, Cu, Mg, Teflon

- Timing - within a few hours after exposure or during it
- resolves within 1 day
- no residual effects
- intensity of symptoms increases with exposure dose
- Repeated exposures cause "desensitization" or tachyphylaxis – within subsequent 1-2 days – have no symptoms (Monday fever)
- then the tolerance is lost
1. BENIGN METAL FUME FEVER
Mechanism – cytokine mediated

- **ZINC**
  - Boiling Point: 907.0 °C i.e. 1664.6 °F

- Immunological reaction in the alveolus
- leading to release of ENDOGENOUS PYROGENS
- Welding exposures in humans ↑ levels of cytokines in BAL:
  - TNF (3 h post exposure), IL-8, (8 h) IL-6 (22 h) - (Blanc 1993, Kuchner et al. 1995, 1997, Fine 1997, Kelleher et al. 2000)
  - Small decrease of lung functions – FEV₁ still on the following day (Pasket et al. 1997)
  - ZnO in vitro ↑ release of TNF from monocytes/alveolar macrophages in a dose-dependent manner (Kuschner et al. 1998)
1. BENIGN METAL FUME FEVER

- COPPER
  
  - relatively high boiling point 2562°C (4644°F)
  - in copper refinery – no elevation of respiratory diseases
  - Metal fume fever – benign - without severe injury
  - Fever, cough
  - Experiments: ROS generation in vitro (*Drozdz 1998*)
1. BENIGN METAL FUME FEVER

- **MAGNESIUM**

- boiling point 1090°C, i.e. 1994°F
- Metal working industry
1. BENIGN FUME FEVER
frying pan

TEFLON resins (*polytetrafluoroethylene*) combustion products

- Polymer fume fever – benign - without severe injury

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melting point 327 °C (621 °F), but already above 300°C (572 °F) degradation products – polymer fumes are created
2. METALS LEADING TO MORE SEVERE ACUTE LUNG INJURY

- TYPE OF METALS IS IMPORTANT
- Cd, Hg, Cr, Ni (stainless steel), Mn, Co, Vn, ZnCl, ....
  BROADER SPECTRUM OF METALS – RARE EXPOSURES

OXIDATIVE DAMAGE – lipid peroxidation, $\text{H}_2\text{O}_2$ generation in the cells, DNA damage
Stainless steel fumes, containing also Cr and Ni have higher ROS –related damage capacity than mild steel *(Leonard et al. 2010)*

- Irritation of the airways
- Metal pneumonitis
- Lung edema
- Bronchial asthma

Exposure factors – air concentration, duration of exposure, scenarios, mixtures of agents,...
2. METALS LEADING TO MORE SEVERE ACUTE LUNG INJURY

• MECHANISMS

ROS generation in the cells of the airways and alveoli
Oxidant injury, oxidation of lipids, proteins and nucleic acids, DNA damage
Depletion of thiol reserves
Apoptosis,
Impaired macrophage cell function
Replacement of alveolar structure by a thickened extracelular matrix, etc. (Kelleher 2000, Yoshida 2011)

Many factors – air concentration, duration of exposure, scenarios, mixtures of agents
Individual factors – disposition - not fully understood
Chemicals have the potential to function as either **ANTIGENS** or **IRRITANTS** or **BOTH** to APS (dendritic cells), alveolar macrophages and/or epithelial cells.

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**Yoshida et al. 2011**

- **Chemicals**
  - **(Antigens)**
  - **(Irritants)**
  - **Cytotoxicity**
  - **Inflammation**

**Diagram:**
- Treg
- APC
- T cell
- TNF-α
- IFN-γ
- IL-2
- MIP-1α
- MCP-1/3/5
- Eotaxin-1
- TARC
- MDC
- ELIC
- SLC
- Macrophage
- PMN
- T/B cell
- Bone marrow
- Fibrocyte
- Fibroblast
- Myofibroblast
- Granuloma

- **Bone morphogenetic proteins:**
  - BMP
  - Gremlin
  - TGFβ
  - PP1A
  - PTEN
Costello et al. 2010 High **gremlin expression** in the lung inhibits epithelial regeneration and **blocks apoptosis of myofibroblasts**
2. DISORDERS DUE TO SOME METALS CAUSING ACUTE LUNG INJURY

- **CADMIUM** - pneumonitis, lung oedema, emphysema
- **MERCURY** - pneumonitis, tracheobronchitis, lung oedema
- **COBALT** - pneumonitis, lung oedema
- **CHROMIUM** - pneumonitis, lung oedema
- **NICKEL** - pneumonitis, lung oedema, pulmonary hemorrhage, asthma
- **MANGANESE** - pneumonitis
- **VANADIUM** - bronchitis
- **ZINC CHLORIDE** - pneumonitis, lung oedema
2. METALS LEADING TO SEVERE ACUTE LUNG INJURY

• CADMIUM –
  • low boiling point (767°C i.e. 1413°F),
  • high vapor pressure during welding, soldering
  • Acutely: Toxic effect on alveolar epithelium + endothelium
  • latency - 24 h – dyspnoea, fever, fatigue, may progress to lung oedema, death
  • Survivors: fibrosis, emphysema
  • Experimentally:
    - ROS -induced cytotoxicity, inhibition of repair, ↓collagen, elastin
      (Chambers 1998)
2. METALS LEADING TO SEVERE ACUTE LUNG INJURY - Hg

- MERCURY
- **Melting Point:** -38.87 °C (-37.966 °F)

- MECHANISMS

Hg covalently binds + reduces SH groups on proteins/enzymes → cells unprotected against oxidant injury

*apoptosis* → decreased number of cell thiols and free SH groups able to reduce ROS *(Kelleher 2000)*
2. Acute inhalational injury – mild lung edema due to Hg vapours

Exposure 10 h – confined space, chills, fever, cough, dyspnea, treated symptomatically without antidotal treatment. No neuro or nephrotoxicity.
Subacute Hg vapours exposure in a family

Father, mother, 2 children found a carpet at garbage
Father was cleaning Hg spot during about 5 hours
Inhaled Hg vapors
All stayed in the apartment for 3 more days
Symptoms of the father

- PNEUMONITIS
- Fever, chills, dry cough, wheezing
- INCREASED BRONCHOVASCULAR LININGS –
  - very mild interstitial oedema
- GINGIVITIS 2\textsuperscript{nd} - 3\textsuperscript{rd} day inflammation and pain
- TREMOR
- 5\textsuperscript{th} day polakisuria and lumbar pain
Neurological symptoms - Hg

ERETHISM – duration about 2 weeks
anxiety, depression, concentration impaired, tiredness, inversed sleeping pattern
Antidote treatment
unithiol –DMPS, Heyl

• Urine concentration 1.86 mg/g creatinine,
• 20x exceeding the limit for workers
• 180 x after DMPS

• DMPS = unithiol - (Dimaval) cps.
• 600 mg 2 weeks, then 300 mg 3 weeks
• No residues of lung or renal impairment
Hg in urine during DMPS treatment

Non-exposed population 0.005 mg/g creatinine

Limit for workers 0.1 mg/g creatinine

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<th>Day after cleaning</th>
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3. EXTRINSIC ALLERGIC ALVEOLITIS
(Hypersensitivity pneumonitis, Farmers´ lung)

- FEVER in the acute stage
- due to exposure to biological antigens
- or chemical factors (incomplete antigens)
- frequently overlooked
- Due to REPETITIVE inhalation of antigen (or haptene)
- small enough to reach lower respiratory tract

Moldy hay, moldy feedstuff, isocyanates, insulation foam
EXTRINSIC ALLERGIC ALVEOLITIS (Hypersensitivity pneumonitis, Farmers’ lung)

- immunologically mediated LUNG FIBROSIS
- typically type III (humoral - immune complex-mediated)
- alveolitis - inflammatory reaction and thickening of the alveolar wall – impaired diffusion (DLCO), lung fibrosis
- cor pulmonale

moldy hay-  
moldy feedstuff-  
isocyanates insulation foam
Acute form

- 4-6 h after exposure to antigens
- Flu-like symptoms – fever, chills, malaise, cough, dyspnoea, tiredness, rhinitis,
- lasting 1-2 days
- Good prognosis
- Frequently overlooked

- Tolerance does not occur.
- After several attacks irreversible changes occur
Pathophysiology

• Immune complex deposition in the lungs,
• release of immune mediators and cytokines,
• infiltration with lymphocytes

• Individual sensitivity - only a small percentage of individuals develop symptoms and signs

• Hypothesis: subjects with immunoregulatory defect are sensitive (Schreiber J, Eur Respir J 2008)
EAA – Farmer’s lung

Acute form with infiltrate and resolution
Natural antigens – bacteria, molds, proteins

A) Plant products- contaminated with antigens:
• Farmer´s lung (moldy hay)
• Malt worker´s lung (contaminated barley)
• Mushroom worker´s lung (mouldy compost)
• Hot tub lung

*(Thermophilic actiomycetes, Faenia rectivirgula, Aspergillus spp., Cladosporium spp., etc.)*
B) Animal antigens:
• Bird-breeder’s lung
  avian protein in feathers, droppings, urine, serum
• Furrier’s lung (animal fur)
C) Chemicals - haptenes – Isocyanate lung

Highly reactive chemicals for production of polyurethane (PUR) materials.

- HEXAMETHYLENE DIISOCYANATE (HDI)
- TOLUENE-2,4-DIISOCYANATE (TDI)
- DIPHENYL METHANE- 4,4-DIISOCYANATE (DMDI),...

- Manufacture of flexible and rigid foams, fibers, glues
- Automobile industry, car seats, spraying paints and varnishes for truck beds, trailers, boats
- Foam mattresses, shoes, carpets
- Building insulation materials and sprays
- Heating of PUR – release of isocyanates
Chronic form

• Increasing dyspnea on exertion,
• cough
• bi-basilar crepitation (velcro rales)

X-ray:
• interstitial fibrosis
• honeycombing

(Lacasse + HP Study Group 2003)
(Fenclova, Ind Health 2009)
(Flors, AJR 2010)
Biopsy – rarely performed

Thickening of the alveolar wall, granulomas with giant cells, diffuse collagenous fibrosis of the interstitium, oedematous fluid with monocytes, lymphocytes, plasma cells, histiocytes,..
Diagnosis supported by:

- **Laboratory:** IgG antibodies in blood-serum precipitins against *Saccharopolyspora, rectivirgula, Thermoactinomycetes, Aspergillus, ....*)

- Proof of repeated exposure, not of disease.

- **History of symptoms** after exposure to known antigens
EAA/HP - challenge for physicians and PCC staff

- **Early diagnostics** is highly important,
- **Repeated exposures** lead then to irreversible fibrotic changes of the lungs.
- Usually removal from the workplace necessary.
Take home message for PC detectives

• Fever due to inhalation
• Activities few hours before the fever
  • at work
  • at home
• may help to solve the puzzle
• predict prognosis
• decide management
• infectious causes must be ruled out
Take home message for PC detectives

FEVER due to METAL FUME – most frequently caused by Zn, Cu, polymere - good prognosis

FEVER related to Hg, Cd, Co, Cr, Ni, Mn, Vn may be a sign of severe delayed lung damage after ACUTE high exposure

FEVER related to antigens in organic material or material releasing isocyanates – REPEATED exposure is dangerous and leads to lung fibrosis
Thank my colleagues:
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