MOLECULAR ANALYSIS OF ISONIAZID RESISTANT M. TUBERCULOSIS ISOLATES USING A DIRECTED OLIGONUCLEOTIDE ARRAY

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Rationale and Methods In England and Wales the incidence of isoniazid resistant TB has risen from 2.9% to 5.0% in the last decade. MDR TB, although uncommon, remains a concern. Rapid diagnosis of drug resistant isolates ensures appropriate antituberculous chemotherapy from the outset. This study uses pcr /macroarray analysis to identify strains containing the most commonly reported mutations associated with isoniazid resistance in a cohort of isoniazid resistant *M. tuberculosis* isolates identified in England and Wales during 1998, plus 185 randomly selected fully sensitive isolates. IS6110 and LP typing was performed on all isolates. DNA sequencing was carried out on isolates with mutations identified but not characterised by the array.

Results Of the 180 isoniazid resistant isolates, 88.9% had mutations in *katG* (codon 315), the *inhA* promoter region or the *oxyR-ahpC* intergenic region. However, mutations in the latter were present in both sensitive and isoniazid resistant isolates (see table). DNA sequencing confirmed a polymorphism at -46 from the *ahpC* transcription start site

Mutation present	Isoniazid Resistant (n=180)		Fully Sensitive (n=185)	
katG 315	103	(57.2%)	0	(0.0%)
inhA promoter	50	(27.7%)	1	(0.5%)
oxyR-ahpC	51	(28.3%)	26	(14.0%)
katG or *inhA*	150	(83.3%)	1	(0.5%)

Conclusions Analysis of only 3 polymorphic sites (katG 315, inhA –15, inhA –8) using a directed oligonucleotide array identified 83% of unique isoniazid resistant isolates in an population. Mutations in *oxyR-ahpC* intergenic need to be interpreted with caution.

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SYMPTOMS IN ALUMINUM SMELTER WORKERS. H Siahpush, JD Kaufman, K Thomas, M Siadaty, F Daroowalla. University of Washington, Seattle, USA

Background: Predictors of incident respiratory symptoms described in aluminum smelter workers remain unclear. *Method:* We analyzed data from a longitudinal study of naïve aluminum smelter workers. The Venables asthma-like symptom instrument and the ATS respiratory symptom instrument were administered to workers at hire and then several times after work exposure had started. The presence of two or more Venables symptoms (cough, wheeze or breathlessness) defined the asthma-like complex. *Results:* Of the 87 subjects who had valid one-year follow-up assessment; 11 (12.2%) workers developed new asthma-like symptom complex.113 subjects had at least one valid follow-up between 6 months and 2 years after hire; of these 19 (16.9 %) had developed asthma-like symptom complex by their last follow-up interview (mean duration of follow-up = 1.6 yrs). Subjects with $FEV_1/FVC \leq 0.75$ at hire had a 3.7 fold risk (95% CI: 1.7,8.1) of developing a new asthma-like complex by their last follow-up compared to those with higher FEV_1 ratio. Smokers at hire were 2.1 (CI: 0.9,4.7) times more likely to develop asthma-like symptom complex compared to never or ex-smokers. Atopy (measured by skin prick testing) at hire and parental asthma or allergy were not associated with development of the symptom complex. One year after hire 13.0% (12) of workers had developed new phlegm and 10.6% (10) had developed cough (ATS instrument). Smokers at hire had an increased risk for developing incident phlegm production (5.9 [1.4,29.1]). *Conclusions:* Naïve aluminum smelter workers developed asthma-like symptoms within one year of exposure to the potroom. Reduced FEV_1/FVC ratio at hire was associated with increased likelihood for symptom development.

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ACUTE EFFECTS OF NITROGEN TRICHLORIDE ON LUNG EPITHELIUM OF SWIMMERS

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Nitrogen trichloride (NCl_3) is the main chlorination by-product present in the air of indoor chlorinated pools. It is a powerful oxidant that causes acute lung injury at high doses.

We studied the acute effects of chlorination products on the lung epithelium of children (n=16) and adults (n=13) attending for two hours an indoor chlorinated pool. NCl_3 concentration was measured in the air of the pool. The integrity of lung epithelium was assessed by measuring the serum levels of three lung specific proteins: surfactant-associated proteins A and B (SP-A and SP-B) and Clara cell protein (CC16). Serum IgE levels were also measured. Blood was sampled in all subjects before entering the pool, after two hours in water for children, after one hour attendance without swimming and one hour later after swimming for adults.

The mean NCl_3 concentration during the experiment was 0.49 mg/m³. SP-A and SP-B levels and the SP-B/CC16 ratio were significantly increased in both children (p range: 0.034-0.063) and adults (p range: 0.005-0.009). In the latter, the increase was already statistically significant after one hour exposure without swimming (p range: 0.023-0.041). In children, CC16 levels did not show a consistent exposure-response relationship, but in adults, the response of CC16 was clearly biphasic, with a significant decrease after one hour (p=0.028) and a reversal towards normal one hour later. IgE levels were unaffected by pool attendance but they were negatively correlated with CC16 levels (r=0.44, p=0.018) and positively with lung epithelium permeability as assessed by SP-B levels (r=0.36, p=0.062) or the SP-B/CC16 ratio (r=0.53, p=0.0035) (correlations calculated with pre-exposure values).

Short-term exposure to NCl_3 in indoor pools increases lung epithelium permeability, an observation which is consistent with experimental data on the toxicity of NCl_3. Lung hyperpermeability was also found to be correlated with serum IgE. Further research is needed to determine the clinical significance of these findings.

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Upper Airway Dysfunction Associated with Bronchoscopic Proven Lower Airway Inhalation Injury without Bronchial Hyperresponsiveness R. Balkissoon, National Jewish Medical and Research Center, Denver, CO Irritant associated upper airway dysfunction (UAD) is characterized by laryngoscopic evidence of paradc adduction of the vocal cords during inspiration and/or early expiration follo inadvertent repeated high level irritant exposures. Ten non-smoking patients laryngoscopic evidence of UAD who did not meet criteria for Reactive Air Dysfunction Syndrome (RADS) (negative methacholine challenge) have been studied with bronchoscopy with endobronchial biopsies. Four patients were exposed to an alkali soap, 1 patient was exposed to a sterilizing agent containing high levels of phosphoric acid and sodium metasilicate, 2 patients were exposed to chlorine gas and 2 patients to ammonia and 2 patients with smoke inhalation. Lavage fluid showed no characteristic inflammatory pattern with variable elevations of lymphocytes and neutrophils. Endobronchial biopsies revealed bronchial wall thickening, edema and chronic lymphocytic inflammation in all 10 patients. One patient with smoke inhalation revealed evidence of non-caseating granulomas. One patient who had follow up bronchoscopy 6 months after initial biopsies revealed persistent though decreased chronic inflammation. Seven of nine patients had negative pH probes. Six of ten patients had symptoms consistent with postnasal drip. High-level irritant exposures may lead to chronic airway inflammation without bronchial hyperresponsiveness. Vocal cord dysfunction may be an associated complication of airway inhalation injuries.

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ABSTRACTS

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This special supplement of the *American Journal of Respiratory and Critical Care Medicine* contains abstracts of the scientific papers to be presented at the 2002 International Conference. The abstracts appear in order of presentation, from Sunday, May 19 through Wednesday, May 22 and are identified by session code numbers. To assist in planning a personal schedule at the Conference, the time and place of each presentation is also provided.

Respiratory Health in Potroom Work--An Inception Cohort

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