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Abstracts' Service

Microbiological Criteria in Non-tuberculous Mycobacteria Pulmonary Disease: A Tool for Diagnosis and Epidemiology

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Setting. The value of microbiological criteria in diagnosing non-tuberculous mycobacteria pulmonary disease (NTM-PD) and monitoring its epidemiology is unknown.
Objectives. To correlate the rate of NTM-PD based on microbiological criteria (American Thoracic Society/Infectious Diseases Society of America [ATS/IDSA] or stricter microbiological criteria) compared with the full ATS/IDSA criteria, to assess the positive predictive value (PPV) of different microbiological criteria in predicting NTM-PD, and to evaluate the clinical relevance of different NTM species.
Design. Retrospective study of all patients with pulmonary NTM isolates in Croatia during an 8-year period. NTM species were divided into low, intermediate and high clinical relevance groups for additional analyses.
Results. Good correlation between both microbiological and full ATS/IDSA criteria was observed. The PPV of stricter and ATS/IDSA microbiological criteria was respectively 93.3% and 59.8%. The usefulness of microbiological criteria varied between groups. ATS/IDSA microbiological criteria had a PPV of 89.8% in the high relevance group, while in the intermediate relevance group, the PPV of stricter and ATS/IDSA microbiological criteria was respectively 94.3% and 63.4%.
Conclusions. Microbiological criteria are useful in detecting NTM-PD, allowing laboratory-based monitoring. Stricter criteria should be used for species of low clinical relevance, and less stringent criteria for species of high relevance in the local setting.

Usefulness of Bronchoscopic Probe-Based Confocal Laser Endomicroscopy in the Diagnosis of *Pneumocystis jirovecii* Pneumonia

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Background. Probe-based confocal laser endomicroscopy (pCLE) is a novel technique that provides in vivo microscopic imaging of the distal lung. We hypothesized that the intra-alveolar exudates characterizing *Pneumocystis jirovecii* pneumonia (PJP) can be identified by pCLE in vivo and help in its diagnosis.
Objectives We aimed to assess the usefulness of pCLE for the in vivo diagnosis of PJP.
Methods. Thirty-two human immunodeficiency virus (HIV)-positive patients with new pulmonary infiltrates and fever were studied using pCLE. Real-time alveolar images were recorded during the bronchoscopy for off-line analysis by two independent observers. Bronchoalveolar lavage samples were also obtained and processed for microbiology and cytological evaluation, including Grocott stain for *P. jirovecii*. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of pCLE for the diagnosis of PJP in these patients were calculated.
Results. Fourteen patients (44%) were confirmed to have PJP by cultures/staining. pCLE was well tolerated in all patients. It identified intra-alveolar exudates in 13 of them (41%), where 11 of them (85%) had positive Grocott stain for *P. jirovecci*, with 93% concordance between observers. Sensitivity, specificity, PPV and NPV of pCLE for the diagnosis of PJP were 79, 89, 85 and 84%, respectively. In smokers, these figures improved to be 92, 88, 85 and 94%.
Conclusions. pCLE is a quick and safe procedure for on-site diagnosis of PJP in HIV+ patients with excellent specificity and sensitivity mainly in smokers.

A Blood RNA Signature for Tuberculosis Disease Risk: A Prospective Cohort Study

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Background. Identification of blood biomarkers that prospectively predict progression of *Mycobacterium tuberculosis* infection to tuberculosis disease might lead to interventions that combat the tuberculosis epidemic. We aimed to assess whether global gene expression measured in whole blood of healthy people allowed identification of prospective signatures of risk of active tuberculosis disease.

Methods. In this prospective cohort study, we followed up healthy, South African adolescents aged 12-18 years from the adolescent cohort study (ACS) who were infected with *M tuberculosis* for 2 years. We collected blood samples from study participants every 6 months and monitored the adolescents for progression to tuberculosis disease. A prospective signature of risk was derived from whole blood RNA sequencing data by comparing participants who developed active tuberculosis disease (progressors) with those who remained healthy (matched controls). After adaptation to multiplex quantitative real-time PCR (qRT-PCR), the signature was used to predict tuberculosis disease in untouched adolescent samples and in samples from independent cohorts of South African and Gambian adult progressors and controls. Participants of the independent cohorts were household contacts of adults with active pulmonary tuberculosis disease.

Findings. Between July 6, 2005, and April 23, 2007, we enrolled 6363 participants from the ACS study and 4466 from independent South African and Gambian cohorts. 46 progressors and 107 matched controls were identified in the ACS cohort. A 16 gene signature of risk was identified. The signature predicted tuberculosis progression with a sensitivity of 66·1% (95% CI 63·2-68·9) and a specificity of 80·6% (79·2-82·0) in the 12 months preceding tuberculosis diagnosis. The risk signature was validated in an untouched group of adolescents (p=0·018 for RNA sequencing and p=0·0095 for qRT-PCR) and in the independent South African and Gambian cohorts (p values <0·0001 by qRT-PCR) with a sensitivity of 53·7% (42·6-64·3) and a specificity of 82·8% (76·7-86) in the 12 months preceding tuberculosis.

Interpretation. The whole blood tuberculosis risk signature prospectively identified people at risk of developing active tuberculosis, opening the possibility for targeted intervention to prevent the disease.

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Idiopathic Pulmonary Fibrosis: Novel Concepts of Proton Pump Inhibitors as Antifibrotic Drugs

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The prevalence of abnormal acid gastroesophageal reflux (GER) is higher in patients with idiopathic pulmonary fibrosis (IPF) than in matched control subjects. Several studies demonstrated that more than one-third of patients with IPF have abnormal esophageal acid exposures. In addition, many of these studies indicate that the majority of patients with IPF have silent reflux with no symptoms of GER. Findings of abnormal reflux persist in a large proportion of patients with IPF placed on antacid therapy such as proton pump inhibitors (PPIs). This seemingly paradoxical observation suggests that either patients with IPF are somehow resistant to PPI-based intervention or PPIs are inherently unable to suppress acid GER. By contrast, patients with IPF who undergo Nissen fundoplication surgery are effectively relieved from the complications of GER, and retrospective studies suggest improved lung

function. Retrospective, anecdotal data suggest a beneficial role of PPIs in IPF including stabilization of lung function, reduction in episodes of acute exacerbation, and enhanced longevity. The recent evidence-based guidelines for treatment of IPF approved conditional recommendation of PPIs for all patients with IPF regardless of their GER status. Recently, we have reported that PPIs possess antiinflammatory and antifibrotic activities by directly suppressing proinflammatory cytokines, profibrotic proteins, and proliferation of lung fibroblasts. Our study provides an alternative explanation for the beneficial effect of PPIs in IPF. In this Perspective, we reviewed emerging progress on antifibrotic effect of PPIs using IPF as a disease model. In addition, we summarized surgical and pharmacological interventions for GER and their downstream effect on lung physiology.

Delayed Microvascular Shear Adaptation in Pulmonary Arterial Hypertension: Role of Platelet Endothelial Cell Adhesion Molecule-1 Cleavage

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Rationale. Altered pulmonary hemodynamics and fluid flow–induced high shear stress (HSS) are characteristic hallmarks in the pathogenesis of pulmonary arterial hypertension (PAH). However, the contribution of HSS to cellular and vascular alterations in PAH is unclear.
Objectives. We hypothesize that failing shear adaptation is an essential part of the endothelial dysfunction in all forms of PAH and tested whether microvascular endothelial cells (MVECs) or pulmonary arterial endothelial cells (PAECs) from lungs of patients with PAH adapt to HSS and if the shear defect partakes in vascular remodeling *in vivo*.
Methods. PAH MVEC (n = 7) and PAH PAEC (n = 3) morphology, function, protein, and gene expressions were compared with control MVEC (n = 8) under static culture conditions and after 24, 72, and 120 hours of HSS.
Measurements and Main Results. PAH MVEC showed a significantly delayed morphological shear adaptation (P = 0.03) and evidence of cell injury at sites of nonuniform shear profiles that are critical loci for vascular remodeling in PAH. In clear contrast, PAEC isolated from the same PAH lungs showed no impairments. PAH MVEC gene expression and transcriptional shear activation were not altered but showed significant decreased protein levels (P = 0.02) and disturbed interendothelial localization of the shear sensor platelet endothelial cell adhesion molecule-1 (PECAM-1). The decreased PECAM-1 levels were caused by caspase-mediated cytoplasmic cleavage but not increased cell apoptosis. Caspase blockade stabilized PECAM-1 levels, restored endothelial shear responsiveness in vitro, and attenuated occlusive vascular remodeling in chronically hypoxic Sugen5416-treated rats modeling severe PAH.
Conclusions. Delayed shear adaptation, which promotes shear-induced endothelial injury, is a newly identified dysfunction specific to the microvascular endothelium in PAH. The shear response is normalized on stabilization of PECAM-1, which reverses intimal remodeling *in vivo*.

Hypothyroidism during Second-line Treatment of Multidrug-resistant Tuberculosis: A Prospective Study

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Setting. Hypothyroidism is an adverse effect of certain anti-tuberculosis drugs.
Design. This is a prospective study of the frequency and possible pathomechanisms associated with hypothyroidism due to second-line treatment of multidrug-resistant tuberculosis. Fifty human immunodeficiency virus negative patients and 20 controls were included. All participants underwent ultrasonography of the thyroid and measurement of thyroid stimulating hormone (TSH). TSH levels were

checked every 3 months. If hypothyroidism was present, T3, T4 and thyroid peroxidase autoantibodies were measured, and imaging extended to scintigraphy and repeated ultrasonography.

Results. Before treatment, 7 patients (14%) and 1 control (5%) were hypothyreotic. During the first 6 months of treatment, TSH levels increased in 41 patients (82%), 39 (78%) had values above the normal range and 19 (38%) had overt hypothyroidism. As none of the patients had signs of autoimmune thyroiditis, interaction with anti-tuberculosis drugs was assumed to be the cause of hypothyroidism. Nine patients died during treatment, all of whom had developed hypothyroidism. In seven, the metabolic situation at their death was known, and they had become euthyreotic following levothyroxine substitution.

Conclusion. TSH levels should be checked before initiating anti-tuberculosis treatment and after 3 and 6 months to start timely replacement of levothyroxine. Further studies are needed to elucidate the exact pathomechanism involved in hypothyroidism and whether hypothyroidism can be used as predictor of treatment failure.