Hot Topics from the Assemblies

Rhinovirus detection in symptomatic and asymptomatic children: value of host transcriptome analysis

Authors: Heinonen S, Jartti T, Garcia C, *et al*.

Am J Respir Crit Care Med 2015; [In press DOI: 10.1164/rccm.201504-0749OC]

Summary: The "transcriptome" represents the set of RNA expressed by genes in one cell or a population of cells. Transcriptome analysis could facilitate our understanding of how the body reacts to environmental and infectious triggers. This study used transcriptome analysis to evaluate the effects of rhinovirus infection on the blood transcriptome. In particular, the authors investigated whether a transcriptional pattern exists that could allow differentiation between individuals acutely infected with rhinovirus (active infection) and those who are rhinovirus-positive but have no symptoms (incidental detection).

The authors included 151 previously healthy children aged <2 years and divided them into four subgroups: 37 control rhinovirus-negative children, 14 asymptomatic rhinovirus-positive children, 30 outpatient rhinovirus-positive children with respiratory infection and 70 inpatient rhinovirus-positive children with respiratory infection. The analysis of the transcriptional profiles was made on blood samples and focused on the activation of the immune response: the results show that active rhinovirus infection is characterised by a strong and reproducible transcriptional pattern, with a clear change in the expression of genes involved in the immune response (overexpression of innate immunity and underexpression of adaptive immunity genes), while no significant change was found in asymptomatic rhinovirus-positive children. Specifically, overexpressed transcripts included genes related mostly to interferon (*IFITM3* and *IFI27*; the latter being the most overexpressed transcript), but also to neutrophil function (*DEFA1*, *3* and *4*, *BPI*, *GPR84*, *FCGR1*) and apoptosis (*MMP9*).

This study raises preliminary speculation that transcriptomic analyses could provide a useful clinical tool to differentiate between active infection and incidental pathogen detection. Further studies are now needed.

Reviewed by: Maria Di Cicco (Italy, Assembly 7)

Hypoxic epithelial necrosis triggers neutrophilic inflammation via IL-1 receptor signaling in cystic fibrosis lung disease.

Authors: Fritzsching B, Zhou-Suckow Z, Trojanek JB, *et al*.

Am J Respir Crit Care Med 2015; 191: 902–913

Summary: Neutrophilic inflammation and lung damage begins early in cystic fibrosis (CF), often without any detectable bacterial infection or respiratory symptoms. "Sterile inflammation" has been observed in other organs as an outcome of hypoxic cell death. Thus, hypoxic epithelial necrosis due to airway surface liquid (ASL) dysfunction and mucous obstruction presents a novel mechanism to explain the pathology of early airway inflammation in CF.

To address this hypothesis, Fritzsching *et al.* utilised the *Scnn1b* transgenic (*Scnn1b*-Tg) mouse model of CF, which overexpresses a sodium channel. These mice exhibit characteristics of CF airway disease including ASL dysfunction and mucous plugging in the first days of life followed by neutrophilic inflammation.

Hypoxic cell death in other organs releases interleukin (IL)-1α, that activates IL-1 receptor (IL-1R) to induce inflammation though myeloid differentiation primary gene 88 (*MyD88*), a signalling pathway also utilised by Toll-like receptors. Inactivation of IL-1R in *Scnn1b*-Tg mice, through either genetic deletion or pharmacological inhibition, was protective and significantly reduced neutrophil infiltration, mucous obstruction, emphysema and mortality. The authors also assessed sections of human small airways for epithelial necrosis. Lung sections from patients with CF showed abundant epithelial necrosis, and necrotic cell number correlated with the severity of mucous obstruction.

Together, these important findings implicate hypoxic IL-1α release as a key mediator of early inflammation in CF and present IL-1R inhibition as a potential future therapeutic avenue for reducing lung damage.

Reviewed by: Luke Garratt (Australia, Assembly 7)

Double-blind randomised placebo-controlled trial of bolus-dose vitamin D3 supplementation in adults with asthma (ViDiAs)

Authors: Martineau AR, MacLaughlin BD, Hooper RL *et al*.

Thorax 2015; 70: 451–457

Summary: Preventing exacerbations is a primary aim when treating patients with asthma. Exacerbations are commonly precipitated by viral upper respiratory tract infections (URTIs). Vitamin D insufficiency has previously been shown to be associated with increased susceptibility to URTI with asthma. Vitamin D supplementation has an established role in many diseases. However, prospective data demonstrating the impact of vitamin D_3 supplementation in asthma exacerbation or URTI in adults with inhaled corticosteroid-treated asthma are lacking.

250 adult asthmatics were enrolled in a double blind, randomised controlled trial to receive six 2-monthly oral doses of 3 mg vitamin D_3 (n=125) or placebo (n=125) over 1 year. The aim was to ascertain the effect of bolus vitamin D_3 supplementation on time to first severe asthma exacerbation or URTI (co-primary outcomes).

Analysis of the 206 out of 250 (82%) vitamin D deficient participants found there was no influence on time to first severe exacerbation (adjusted HR 1.02,

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95% CI 0.69 to 1.53; p=0.91) or first URTI (adjusted HR 0.87, 95% CI 0.64 to 1.16, p=0.34). Further analysis demonstrated the influence of vitamin D_3 was not modified by baseline vitamin D levels or genotype.
This is the first prospective clinical trial to investigate and demonstrate that vitamin D supplementation in asthmatics has no influence on time to exacerbation or URTI frequency. As such this will better inform clinicians of the role of vitamin D deficiency and treatment of asthma.
Reviewed by: Andrew I Ritchie (UK, Assembly 3)

TOLLIP, MUC5B, and the response to *N*-acetylcysteine among individuals with idiopathic pulmonary fibrosis
Authors: Oldham JM, Ma SF, Martinez FJ, *et al*.
Am J Respir Crit Care Med 2015; 192: 1475–1482
Summary: Idiopathic pulmonary fibrosis (IPF) is an incurable interstitial lung disease associated with a high mortality. Genes encoding Toll-interacting protein (*TOLLIP*) and mucin 5B (*MUC5B*) are believed to play a key role in the lung immune response. Genetic variation within TOLLIP and MUC5B have been associated with IPF susceptibility and mortality in genome wide association studies.
This *post hoc* exploratory analysis studied patients enrolled in the 'Evaluating the Effectiveness of Prednisolone, Azathioprine, and *N*-Acetylcysteine (NAC) in Patients with IPF' (PANTHER-IPF) trial (n=154). The authors investigated the influence of single-nucleotide polymorphisms in *TOLLIP* (rs5743890/rs5743894/rs5743854/rs3750920) and *MUC5B* (rs35705950) on the response to trial interventions. In the analysis, a composite endpoint-free survival was used, the time from trial enrolment to death, transplantation, hospitalisation or a decline of ≥10% in FVC.
A multivariate Cox regression model demonstrated a significant interaction between NAC therapy and rs3750920 (*TOLLIP*) (Pinteraction=0.001). In subjects carrying an rs3750920 (TOLLIP) TT genotype, NAC therapy was associated with a significant reduction in composite endpoint risk (hazard ratio, 0.14; 95% confidence interval, 0.02–0.83, p=0.03). These findings were replicated in an independent cohort. Carriage of the rs3750920 CC genotype was associated with a trend toward harm.
These findings suggest that the efficacy of antioxidant NAC therapy for IPF may be determined by the patient's genetic makeup; a drug–gene interaction and therefore a pharmacogenetic approach to future clinical drug trials may be warranted.
Reviewed by: Richard J Hewitt (UK, Assembly 1)

Hot topics are short (approx. 200 words) summaries of recent important articles in respiratory medicine written by Junior ERS members. To become a hot topic author, please contact Aran Singanayagam: e-mail: aransinga@gmail.com

Early administration of azithromycin and prevention of severe lower respiratory tract illnesses in preschool children with a history of such illnesses: a randomized clinical trial
Authors: Bacharier LB, Guilbert TW, Mauger DT, *et al*.
JAMA 2015; 314: 2034–2044
Summary: Wheeze in children is frequently triggered by viral infection of the lower respiratory tract (LRTI) that is initiated in the upper respiratory tract (URTI). These wheezing episodes represent a significant burden to patients and healthcare systems with randomised controlled trials (RCTs) of existing treatment showing lack of efficacy to prevent these episodes. Recent evidence implicates colonising bacteria in acute exacerbations and raises speculation that antibiotic treatment may be effective in preventing exacerbations.
Bacharier *et al*. performed an RCT of azithromycin treatment to prevent progression from URTI to LRTI with wheeze in 443 children aged 12-71 months. Subjects had a history of recurrent severe wheeze (defined as requiring oral corticosteroids, doctor/ED visit or hospitalisation). Those with the most severe wheezing (multiple oral steroid courses, multiple hospitalisations) were excluded and those receiving low dose corticosteroids or montelukast only had this discontinued at enrolment.
Azithromycin reduced the risk of progression to LRTI relative to placebo HR 0.64 (95% CI 0.41–0.98; p=0.04). The number needed to treat (NNT) varied according to the number of RTIs experienced with NNT of seven for children who had experienced four URTIs.
This is the first study to show that antibiotic treatment of viral induced wheeze can reduce disease severity. If further studies confirm these findings, this is a potentially exciting step forward in the treatment of childhood respiratory tract infections.
Reviewed by: Samuel A Collins (UK, Assembly 7)

Discontinuation on inhaled corticosteroids in COPD and the risk reduction of pneumonia
Authors: Suissa S, Coulombe J, Ernst P.
Chest 2015; 148: 1177–1183
The role of inhaled corticosteroids (ICS) in chronic obstructive pulmonary disease (COPD) is still controversial. In the context of ICS overuse, recent studies have shown that ICS discontinuation does not lead to an increase of COPD exacerbations, although it is unclear if the risk of pneumonia decreases after the withdrawal of the treatment.
In a nested case–control study, the authors assessed the effect of ICS discontinuation in COPD on the incidence of pneumonia-related hospitalisation or death.
Using the Quebec health insurance databases the authors identified 103 386 COPD patients treated with ICS in 1990–2005, of whom 14020 (13.6%) had a serious pneumonia event during 4.9 years of follow-up (incidence rate 2.8% per year). For each case, 10 control subjects were selected from the cohort.
Discontinuation of ICS was associated with a 37% reduction in the rate of serious pneumonia (rate ratio 0.63, 95% CI 0.60–0.66). The risk reduction went from 20% in the first month to 50% in the fourth month after discontinuation, and was more pronounced with fluticasone than with budesonide (rate ratio 0.58, 95% CI 0.54–0.61 for fluticasone *versus* RR 0.87, 96% CI 0.78–0.97 for budesonide). The risk reduction in pneumonia-related adverse events remained consistent after stratification according to previous COPD hospitalisation, recent oral corticosteroid use and the duration of follow-up.
This study highlights the potential benefits of the withdrawal of ICS in COPD patients and suggests that judicious use of ICS may minimise the risks associated with their use.
Reviewed by: M Barrecheguren (Assembly 1)