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REPORT FROM

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An identity card to effectively detect a COPD exacerbation: The Rome proposal

The current GOLD definition of a chronic obstructive pulmonary disease (COPD) exacerbation (ECOPD) is: *"An acute worsening of respiratory symptoms that results in additional therapy".* The severity of the event is classified based on the treatment the patient received during the episode. This definition is based solely on worsening respiratory symptoms and the severity of the event is classified post hoc. These shortcomings have supported the need of revising the definition.

The Rome Proposal is a manuscript created by a panel of experts using a modified Delphi method to achieve consensus agreement on an ECOPD definition and severity classification. The suggested new definition is:

"In a patient with COPD, an exacerbation is an event characterized by dyspnea that worsens over ≤14 days, frequently accompanied by cough, sputum, tachypnea and/or tachycardia, due to a local and systemic inflammatory burst caused by an infection, pollution, or other insult to the airways. It can be a life-threatening medical condition requiring adequate evaluation and treatment".

The proposal defines three severity categories (mild, moderate or severe) using six measurable variables: dyspnea, oxygen saturation, respiratory rate, heart rate, C-reactive protein, and, if needed, blood gases.

The Rome proposal of ECOPD addresses many of the shortcomings of older definitions:

- It specifies the timespan within which worsening of symptoms define an ECOPD.
- To the subjective worsening of symptoms it adds a series of clinical variables that are objectively measurable and readily available.
- Based on agreed thresholds, it integrates these variables into three mutually exclusive severity categories that can be used to classify the exacerbation severity at initial patient contact.
- This definition aims to facilitate and improve clinical care, research, and health services planning.

The future will show when and how this proposal will be applied into practice.

Suggested reading:

Celli et al., 2021. An updated definition and severity classification of chronic obstructive pulmonary disease exacerbations: The Rome Proposal. American Journal of Respiratory and Critical Care.

Open Access via: https://www.atsjournals.org/doi/10.1164/rccm.202108-1819PP

Supplement: https://www.atsjournals.org/doi/suppl/10.1164/rccm.202108-1819PP/suppl_file/celli_data_supplement.pdf

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New and old tests for asthma diagnosis in primary care: from peak flow to FeNO

On Tuesday morning I attended the session: *"Asthma diagnosis: new and old approaches to increase primary care capability"*. The presentation by David Lo, pediatrician and researcher from UK, covered tests for asthma diagnosis in primary care, how they work and why it is important to get a correct asthma diagnosis.

Misdiagnosis in asthma is very common, up to 50 % of the adults are over- or underdiagnosed, resulting in inappropriate treatment. Therefore, it is of great importance to follow established guidelines such as GINA, ERS and NICE and use the appropriate diagnostic tests that are available to diagnose asthma. Although the guidelines look differently, they show that the diagnosis should be based on thorough clinical assessment and evidence of:

- Obstructive airflow with reversibility +/-
- Airway inflammation +/-
- Airflow variability over time.

The tests which are recommended to use in a primary care setting are spirometry + bronchodilator reversibility (BDR), fraction of exhaled NO (FeNO) and peak flow variability, whereas indirect or direct challenge tests should be performed in secondary care. None of these tests have perfect diagnostic accuracy. They are useful when used in combination and at the right time, since they measure different things.

One of the challenges for implementing different diagnostic tests is costs. Depending on the country, the cost for spirometry + BDR, FeNO and Peak expiratory flow rate can cost up to 100 Euro. Interestingly, when adding FeNO testings to diagnosis health economic calculations have shown savings of 56 Euro/patient (UK) and 63 Euro/patient (Sweden), due to correct and earlier diagnosis, appropriate treatment and reduced heath care utilisation.

Key take-home message from the speaker is: *"Objective testing should be attempted in all patients to confirm a diagnosis of asthma".*

Jenny Johansson
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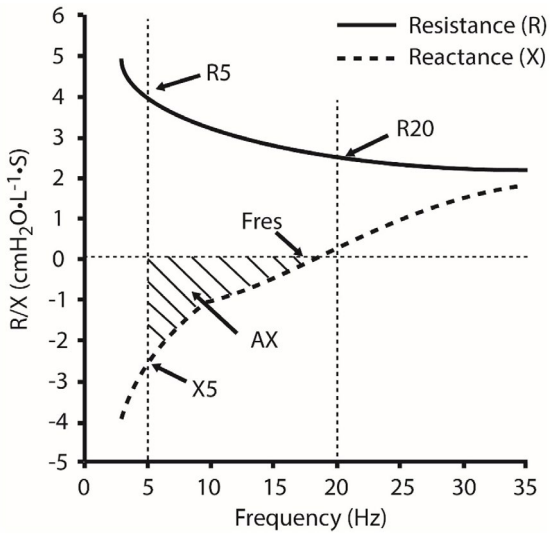
A need for improvement of asthma diagnosis – is Oscillometry the way to go?

The complexity in both, asthma disease understanding and treatment is *"continuously increasing leading to a demand for better and more precise diagnosis"*. This is in particular evident from numerous studies showing that misdiagnosis in asthma is an established phenomenon, ranging in adults from 26-56% and 19-70% for over- and underdiagnosis, respectively, depending on the country in question, (Backer et al., 2007; Aaron et al., 2008; Heffer et al., 2015, among others).

International Asthma Guidelines agree that diagnosis should be based on thorough clinical assessment and evidence of obstructed airflow with and without reversibility, plus/minus airway inflammation and airflow variability over time. The above is usually established through, but not limited to, spirometry + bronchodilator reversibility, Peak Flow, FeNO and/or eosinophil count.

To reduce misdiagnosis more objective tests are required and oscillometry could be the way to go!

Oscillometry is an acoustic test of airway function based on low range (5-35 Hz) soundwaves superimposed on tidal breathing patterns, at a duration of ~30 seconds. Although easy to perform, the data generated can be difficult to understand and interpret. The figure below and the following text give a crash course in understand oscillometry readouts.



R5 (resistance at 5 Hz) measures the total airway resistance, R20 reflects the resistance of the proximal airways, and R5–R20 is the resistance of the small airways and ventilation inhomogeneities. An R5-R20 close to zero indicate absence of small airway disease. Contrary, an increased positive R5-R20 indicate increased probability of small airways obstruction. X5 and AX reflects lung stiffness and heterogeneous ventilation. More negative X5 and increased AX indicate loss of elastic recoil and thus stiffness of the lung.

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Of clinical relevance, the ATLANTIS study has demonstrated that oscillometry is a key measurement to detect small airways disease, and changes in oscillometry are independent risk factors for asthma exacerbations (Postma et al., 2019; Kraft et al., 2022).

With the above in mind, I believe that oscillometry should be considered as a valuable adjunction to spirometry providing extra information needed to diagnose asthma patients correctly.

Recommended readings:

Lundblad et al, 2019. Applications of oscillometry in clinical research and practice. Canadian Journal of Respiratory, Critical Care, and Sleep Medicine. Open Access on: https://doi.org/10.1080/24745332.2019.1649607

Thamrin et al, 2022. Technical standards for respiratory oscillometry and bronchodilator response cut-offs. European Respiratory Journal; DOI: 10.1183/13993003.02663-2021

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Pearls in airway immunology and novel mechanisms in asthma and COPD

On Monday I had the pleasure to attend several sessions covering novel mechanisms in asthma and COPD, and research on potential new targets for the treatment of obstructive lung disease.

At the session named *"Pearls in immunology: from mouse to man"*, we were presented data on the differences in profiles of Innate Lymphoid Cell (ILC) between COPD, asthma, smoking controls and non-smoking healthy controls. In particular, analyses presented by Cathelijne M. Van Zeist, The Netherlands revealed significant differences in the ILC profiles of COPD patients compared to asthma patients and smoking controls. This indicates that ILC subsets in peripheral blood can discriminate between COPD inflammation and exposure to smoking.

The next session I attended was *"Clinical and translational studies of asthma and COPD: novel mechanisms"*. Here, Lei Fang from Switzerland showed evidence that the chaperone HSP60 induces airway remodelling (AWR) via the Toll-like receptors TLR4 and TLR2 heterodimers in mice. He proposed that circulating HSP60 could be a marker for AWR in asthma and its inhibition might present a novel therapeutic target.

At the same session, Ian C. Scott from UK presented data on tozorakimab, a novel anti-IL33 monoclonal antibody. Of interest, tozorakimab demonstrates dual pharmacology to inhibit IL-33 activities through ST2 and RAGE/EGFR signalling pathways. The data also showed that the antibody was well tolerated demonstrated in a phase 1 study also providing a proof of mechanism. The safety and efficacy of tozorakimab are currently under investigation in phase 2 and 3 studies for COPD, asthma and diabetic kidney disease.

The last talk of this session was given by Fabrizio Facchinetti from Italy. He showed data on a novel inhaled PFE4 inhibitor, tanimilast, with proven anti-inflammatory properties in various inflammatory cells, including leukocytes derived from asthma and COPD patients. Of particular interest, Facchinetti showed that LPS-activated monocyte-derived dendritic cells treated with tanimilast express distinct phenotypical and functional properties characterized by the upregulation of CD141 expression, CD86/80 ratio and the acquisition of Th2-skewing properties.

On this optimistic note on possible future alternatives for treatment of asthma and COPD, we can only look forward to following the research field further.

Ingvild Bjellmo Johnsen
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Towards elimination of COPD

On Tuesday afternoon, The Lancet commission made an urgent call for action. The session not only spoke to my compassion but also engagingly pointed to unacceptable injustice. In addition, it listed concrete actions and measurable goals. I chose to write about this session to support their mission.

I believe we all can do efforts wherever we are to drive a change – join the fight to eliminate COPD!

COPD meets the definition of a pandemic: an outbreak of the disease over a wide geographic area, continuing to "spread". We need to reframe how we think about COPD to enable a change. Today, COPD is diagnosed very late and in a progressed stage of lung function decline, as this is when symptoms occur. Therefore, current treatments concentrate on patients progressed in their disease. Moreover, the access to spirometry is unequal in the world. With this, the COPD pandemic affects the poor and vulnerable over proportionally.

Factors impacting COPD development span over a whole life, from fetus to the elderly. They include:

- Pre-birth exposure to smoking.
- Exposure to indoor smoke from biomass fuels, eg for cooking.
- Air pollution.

The disease looks different in differently parts of our world: While patients in Northern America, Australia and Europe are in their higher ages, patients in Africa, India and China are very young. Moreover, access to COPD care is unequal in the world, both non-pharmacological and pharmacological interventions including rescue inhalers. This also leads to geographical disparities in age-adjusted COPD mortality. COPD mortality is negatively correlated with income.

Funding for research into COPD is low compared to other chronic diseases, and it can be speculated whether this is due to an ethically and factually debateable "COPD only affects smokers"-attitude. This results in too little research and innovation. Since 1969, only two major innovations were made for treatment of COPD: PDE4 inhibitors and endobronchial valves.

The Lancet commission suggests the following:

- Sound the alarm, we need to act.
- Recognise non-smoking risk factors and classify COPD by risk factors causing the disease (genetic, early life events, infections, tobacco smoke exposure, environmental exposure).
- Eliminate well-known and emerging risk factors, spanning from tobacco smoke to prematurity.
- Improve diagnostic tools for early disease and move beyond spirometry.
- Increase treatment efficacy, effectiveness, and push for cure focussing on subtypes of the disease and the related biological processes.

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