Chiesi

REPORT FROM

ERS Satellites 2023

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COPD

Disease mechanisms

Early life origins vs accelerated decline: are these types of COPD the same?

The first talk of the COPD session was presented by Rosa Faner Canet from Barcelona, Spain. She presented the similarities and the differences between two types of the disease: early life origins versus accelerated decline of COPD. As COPD is a serious and complex disease and the third leading cause of death, there is a high wish for earlier diagnosis, a better understanding of the heterogeneity as well as the mechanisms behind the disease to find better cure.

What are the different vital lung trajectories that might be associated with the development of COPD later in life? There is growing evidence that lung function in early life predicts later lung function. Around 4-12 % of the population have an abnormal lung function in early adulthood. This abnormal lung function may or may not be followed by an early accelerated decline and lead to the development of COPD later in life. Also, genetic and environmental factors over the lifespan might influence an individual's lung function trajectory, resulting in poor respiratory health. There are three phases of the lung function trajectory; a growth phase (from birth to early adulthood), a plateau (peak) phase (that lasts for a few years), and a phase of decline.

In young adulthood the lung function (FEV1) peaks. After the peak, the lung function declines naturally with age, but some people experience a more accelerated decline, leading to poorer lung function and e.g., COPD.

Some examples of phenotypes, biomarkers and genetics that are associated with COPD related to age:

- In older people with COPD (age over 50 years) several phenotypes have been identified such as persistent inflammation, comorbidities, co-existing asthma, emphysema, and exacerbations. Also, several biomarkers have been associated with COPD in elderly people such as smoking, emphysema, exacerbations, poor FEV1, increase of sputum neutrophils, eosinophils, CRP, and a decrease of CC18 and sRAGE.
- In persons younger than 50 years of age, COPD is associated with e.g. emphysema, low levels of hematocrit, neutrophils, increased visits to GPs at a younger age, low educational level and working status (unemployment).

- In persons 25-35 years of age, who have low peak lung function and have not yet been diagnosed with COPD, it has been shown that they tend to have a shorter duration of pregnancy, increased occurrence of wheezing, and an abnormal lung function. A similar pattern in biomarkers as for the older COPD patients can be found; an increase in CC19 and CCL2 and a decrease in sRAGE and CC16. When markers for ageing, such as telomer length and mitochondrial DNA are measured, no changes are detected compared to healthy subjects.

Accelerated ageing is implicated in the pathogenesis of respiratory diseases. Hallmarks of accelerating ageing, such as methylation, were associated with aged COPD, whereas shortening of telomers was associated in both young and old persons living with COPD.

Genetic susceptibility has age-dependently been associated with the risk of developing COPD.

In conclusion:

- A life course perspective is needed for COPD.
- Similar pattern in biomarkers has been found in both young and older persons with COPD.
- COPD biomarkers are present in young adults with abnormal peak lung function.
- The genetics of COPD are related to early onset of disease.
- Accelerated aging has a role in severity of the disease, independent of the patient's age.

Suggested reading:

Agusti A, Faner R. Lung function trajectories in health and disease. Lancet Respir Med. 2019 Apr;7(4):358-364.

Brugel et al., Clinical COPD phenotypes: a novel approach using principal component and cluster analyses, European Respiratory Journal 2010 36: 531-539.

Vanfleteren et al., Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive. 2013 Apr 1;187(7):728-35.

Cosio B, Faner R et al. Phenotypic characterisation of early COPD: a prospective case–control study. ERJ Open 2020 6: 00047-2020.

Olvera et al. Circulating Biomarkers in Young Individuals with Low Peak FEV1, Am J Respir Crit Care Med. 2023 Feb 1;207(3):354-358.

Casas-Recasens et al Frontiers Medicine Telomere Length but Not Mitochondrial DNA Copy Number Is Altered in Both Young and Old COPD, Front Med, 2021 Nov 24;8:761767.

Sakornsakolpat P et al., Genetic landscape of chronic obstructive pulmonary disease identifies heterogeneous cell-type and phenotype associations, Nat Genet. 2019 Mar;51(3):494-505; Zhang J et al., A polygenic risk score and age of diagnosis of COPD, Eur Respir J. 2022 Sep 15;60(3):2101954.

Jenny Johansson
PhD, Medical Advisor, Sweden

State of the art treatment

Dealing with biology to behavior. David M. G. Halpin (Exeter, GB)

All people living with COPD are different and all of them have different behaviors. All this needs to be considered when we treat these persons, says Prof David Haplin, who is holding the next presentation. He is a member of the GOLD Science Committee and involved in the work around the GOLD report. In the presentation he highlights the main recommendations in the GOLD report and how they will relate to clinical cases.

The importance of having the correct diagnosis was addressed, where symptoms, risk factors and spirometry need to be considered. In confirming the COPD diagnosis, it is also of high importance to rule out other diagnosis, e.g. heart conditions. Here it is important to pay attention to the comorbidities and not only to focus on COPD.

He also mentions the importance of being aware of people living with so called Pre-COPD. These people are at risk of developing COPD and therefore in need of monitoring. It is also of importance to get an early diagnosis, to prevent the loss of lung function and achieve a better outcome and reduce mortality *(Stolz et al., Towards the elimination of chronic obstructive pulmonary disease: a Lancet Commission, Lancet 2022 Sep 17;400(10356):921-972).*

Once the COPD diagnosis is established by spirometry, the severity of airflow limitation (GOLD 1-4) is assessed, followed by the clinical assessment. Depending on the clinical assessment - magnitude of current symptoms (MRC and CAT-score), previous history of exacerbations and multimorbidity - patient will be placed into one of three classification groups, group A, B or E. Group E (≥ 2 moderate exacerbations or 1 ≥ exacerbation leading to hospitalization, regardless of the symptoms) was previously Group C and D which have now been merged. The initial management will then depend on which group the person living with COPD is placed into. In the Group A “A bronchodilator”, Group B “LABA+LAMA” and in Group E “LABA+LAMA or LABA+LAMA+ICS if blood eosinophils ≥ 300 cells/µL” are recommended.

The goals for treatment of COPD are to reduce symptoms and reduce risk of disease progression, exacerbations and ultimately, mortality.

As the disease progresses, the treatment is revised and assessed by adjusting pharmacological and non-pharmacological interventions such as inhalation technique, smoking cessation, vaccination, and exercise. If there is a need for pharmacological adjustments the algorithm presented in the GOLD document shows how to change the pharmacological treatment depending on if the person living with COPD is experiencing dyspnea or exacerbations.

Prof Haplin also addresses when to consider initiating ICS treatment. Use of ICS is advised when people living with COPD have experienced exacerbations, have higher levels of blood eosinophils (100 to < 300 cells/µL or ≥ 300 cells/µL) and a history of asthma. The use of ICS is not advised if the person has experienced pneumonias, has low levels of blood eosinophils (≤ 100 cells/µL) and a history of mycobacteria infections.

I my opinion, this was an interesting and fruitful presentation, covering the most important parts of GOLD 2023. To get a deeper understanding of this summary I highly recommend to also look at the GOLD 2023 report (GOLD 2023, https://goldcopd.org/2023-gold-report-2/).

Jenny Johansson
Medical Advisor, Sweden

Clinical approach
Implementing rehabilitation in the real life

Thierry Troosters (Leuven, BE)

The presentation handled the issues of COPD patient rehabilitation in the real life.

Rehabilitation is an integral part of therapy together with pharmacotherapy, but several aspects remain to be defined: Why, how long and where? What can be expected from the rehabilitation?

How is rehabilitation anchored in the care pathway? Certain is, that it needs to be implemented instead of having it on paper- this is the biggest challenge today.

How many subjects are prescribed to a program? When prescribed, are the patients using this option? Less and less patients are included in the programs. Around 15% are referred, 10% will take the offer and 70% of these will complete the rehabilitation program. Patients are lost along the line, and this is a big challenge to clinicians and community.

Terms that are related to rehabilitation are physical activity, exercise training or pulmonary rehabilitation. All of them fit in the same melting pot. Physical activity is everything that is done during a regular day, i.e., walking. Exercise training is more purposeful, an intervention that comes with a given dose, frequency, and duration. It is like a “medicine”, if you stop exercising you lose the benefit. Pulmonary rehabilitation is an individually tailored program, which gives the person living with COPD the tools to go on with his/her life. Overall, the goal of all measures is to improve the person´s physical and mental health and to help the subject to adhere to more to long term health-enhancing behaviours.

After the diagnosis and the initial assessment of the patient, advising towards active life and exercise and self-management are indicated early as part of the initial management. If this does not resolve the symptoms, adjustment of the pharmacological and non-pharmacological therapy should be made, and the person living with COPD should be offered a full rehabilitation program.

Pulmonary rehabilitation improves the subject´s health dramatically. A Cochrane review of several studies on rehabilitation shows that it works. For example, in 6-minute walking test, there is an improvement of 40-50 meters by the intervention, whereas 30 meters improvement already constitutes a clinically important benefit. When combining exercise with pharmacotherapy, constant working test results (CWT) are improved significantly compared to pharmacotherapy alone.

From a large group of patients at Leuven who were offered rehabilitation, 85% had improvement both in functional exercise capacity and health-related quality of life to a clinically meaningful extent.

Rehabilitation also benefits persons living with COPD with impaired mental health and those who suffer from anxiety and depression. In patients with severe exacerbations, it improves survival and reduces re-admission rates.

Offering an exercise training program to a patient is not enough, because its only goal is to improve the patient's physiology and not to change the patient's behaviour. Interventions for behavioural changes should also be provided. These include for example setting an exercise goal to a patient or offering motivating applications (step counter etc).

How is rehabilitation anchored in the care pathway? Three things to think about:

1. The right patient should have the right rehabilitation program.

- Optimal bronchodilator therapy should be offered so that the person living with COPD can breathe as much as possible
- Change in behaviour by defining an exercise goal to achieve
- Suitable training program should be selected for each diseased person

2. Need to address the full scope of the problems experienced by the person living with COPD

- Targeting as much as possible the treatable traits that the person might have
- Almost all rehabilitation programs try to improve the physical fitness of the person
- Other treatable traits such as nutritional problems, smoking cessation, non-adherence to treatment or mental health issues are not picked up in the offered programs and hinder from getting the full benefits of the programs.
- Rehabilitation teams could do better targeting all the extra-pulmonary treatable traits

3. Ensuring the continuity after rehabilitation program

- Rehabilitation is offered only as package for a couple of weeks
- Continuation of exercise in clinical care after rehabilitation is important, for example supervised exercise once a week

The real problem is the access to rehabilitation. There are several issues, for example:

- Rehabilitation centre is not close to the patient
- Rehabilitation programs are not prescribed as much as they should be

Rehabilitation can take different shapes and forms and may require efforts from occupational therapist, nurse, physiotherapist, and exercise physiologist. It may be done in inpatient setting or outpatient setting and it can be done, whether the patient stable or not. Exercise can take many forms.

Suggested reading:

McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2015, Issue 2. Art. No.: CD003793. DOI: 10.1002/14651858.CD003793.pub3.

Pekka Ojasalo
Medical Advisor, Finland

Horizon scanning

Horizon scanning in COPD: wholistic care

Judith Garcia Aymerich (Barcelona, ES)

Horizon scanning is a technique for detecting early signs of potentially important developments through a systematic examination of potential threats and opportunities, with emphasis on new technology and its effects on the issue at hand (OECD 2019).

Dr Aymerich selected three areas that in her opinion constitute major challenges in the next decade in general as well as related to COPD. In her talk, she presented her thoughts on how and why they are going to modify the trends in COPD research and impact medical care.

1. Ageing

Life expectancy has increased and the number of people older than 60 years is going to increase dramatically. Healthcare professionals will face new problems with diseases, of which multimorbidity will be the most important. It is estimated that 25% of the population suffers from more than one disease and this proportion is going to increase with age. The problem with the current medical practice is that it under-recognizes, under-diagnoses and under-treats multimorbidity. Some multimorbid patients, including people living with COPD suffer from over-treatment and lack of knowledge of drug interactions.

Dr Aymerich started a poll and asked the audience how ageing is going to affect COPD?

The majority (96%) answered that the prevalence of COPD will increase and that COPD patients will suffer more comorbidities.

It is known that people living with COPD have more concomitant chronic diseases than patients with other chronic conditions.

A subtype of COPD exists, which is characterized by systemic problems, inflammation, cardiovascular problems, and obesity. These comorbidities can start early in life. There is a need to change the paradigm from “a COPD patient with comorbidities” to “a patient with multimorbidity”. Focusing on multimorbidity instead of the existence of single conditions has allowed the identification of biological pathways that are relevant for understanding the etiology and mechanisms of some diseases. It has also allowed identifying causes for individual diseases. More research is needed in the area of COPD. Also, healthcare professionals and healthcare services need to adapt to these changes more efficiently. Also training on multimorbidity is needed.

2. Climate change

Climate change is the single biggest health threat facing humanity. It will affect our demographic structure, socio-economy, and politics. It will eventually have effect on human health.

Poll: How is climate change going to affect COPD?

The majority (94%) answered: We don’t know, but it’s likely to increase the frequency of exacerbations.

It is difficult to predict if global warming will have an effect on the disease COPD, although there are some indications that climate change may have a negative effect, particularly on the risk of exacerbations. The calculations of the effect on COPD have only started.

Other factors related to climate change are still unknown. It is likely that higher temperatures, air pollution and extreme weather events will change the amount and allergen-content of pollen. This will certainly have an impact on exacerbations in patients with an allergic component. Also, emerging infectious agents combined with the loss of biodiversity will affect the number of infections and again have an effect on COPD exacerbations.

COPD may worsen climate change. It is estimated that more than 4% of carbon footprint is caused by healthcare activities and most of it comes from hospitals and long-term care, where COPD is included. Some inhalers used to treat asthma and COPD release greenhouse gases which makes it necessary to balance between individual patients´ and collective environmental needs. In the coming years there is a need to investigate more of the effects, mechanisms, and interventions to mitigate the impact of climate change on COPD.

3. Patients' voice

The traditional paternal relation between physician and patient during medical visits can risk the success of actions by healthcare professionals.

Patient involvement in healthcare has increased and patients are more active in making decisions concerning their health.

Poll: How often do you ask open questions to your COPD patients and include patients' voice into your COPD research?

The Majority (59%) answered: Often but less than I'd like to.

32% answered: Always, and 17%: Rarely.

Patients and caregivers are often well-organized. Patient organizations have become real professionals of advocacy. They should not be ignored at any level of healthcare.

Nowadays the regulatory agencies such as EMA and FDA require clear reporting of patient experiences and preferences in approval processes for all kinds of medical interventions.

In conclusion: The future is unknown, but in COPD

1. Multimorbidity will likely be important.
2. Climate change will affect patients (and vice versa).
3. Patients' voice will be needed to be heard (more).

Pekka Ojasalo
Medical Advisor, Finland

Asthma

Disease mechanisms

Understanding and assessing patients with asthma from basic to deep medicine

The asthma session started off with Prof. Lena Uller from Lund University talking about asthma from its basic clinical characteristics to different underlying disease phenotypes and mechanistic endotypes, also covering some key cell types involved in the pathogenesis.

It is a growing consensus that asthma is not just one disease, it is a syndrome being described as an umbrella diagnosis comprising several subgroups and clinical phenotypes of asthma. Using this umbrella diagnosis, we have learnt that asthma is a heterogenous disease consisting of different clinical phenotypes which are based on observable clinical characteristics, i.e., late onset eosinophilic asthma, very late onset asthma in women, allergic asthma, exercise-induced asthma, aspirin-exaggerated respiratory disease (AERD), obesity-associated asthma, smooth muscle-mediated paucigranolytic asthma, smoking-related neutrophilic asthma. These clinical phenotypes can be further divided into inflammatory phenotypes describing the particular inflammatory pathway being involved, i.e., eosinophilic, mixed eosinophilic neutrophilic, paucigranulytic and neutrophilic inflammation. We can further distinguish the inflammatory phenotypes into asthma endotypes, which describe the distinct pathophysiological mechanisms that work at the cellular and molecular level. The best understood endotypes of asthma today are T2 high and T2 low asthma.

T2 high and T2-low asthma

Prof. Uller gave us a comprehensive overview of the immuno-pathophysiology of T2 high and T2 low asthma. Clinically, T2 high asthma is associated with increased levels of eosinophils, elevated IgE and FeNO, whereas for T2 low asthma there are no reliable biomarkers, hence this endotype is usually defined as “lack of T2 high biomarkers”. T2 high asthma can further be divided into allergic eosinophilic asthma and non-allergic eosinophilic asthma. Taking a closer look at allergic eosinophilic asthma we learnt that for this pathway allergens induce the inflammatory response through the release of key alarmins TSLP, IL-33 and IL-25 from the bronchial epithelium. These alarmins activate ILC2 (innate lymphoid cells type 2) and prime dendritic cells which drive Th2-cell differentiation leading to production of the key T2-inflammatory cytokines IL-4, IL-5 and IL-13. IL-4 stimulates immunoglobulin class switch in B cells for production of IgE, IL-5 acts as a key regulator of eosinophilia and IL-13 contributes to airway remodelling and mucus production. IgE, on its side, activates mast cells leading to release of leukotrienes and histamines. Looking into the other T2 high endotype, non-allergic eosinophilic asthma, we learnt that this endotype is also driven by T2 cytokines and share many of the biomarkers of allergic asthma. However, for this pathway there are no allergic components involved. Instead, this endotype is speculated to be driven by environmental triggers such as viruses, bacteria, smoke, and air pollution. The bronchial epithelium plays a key role also in non-allergic eosinophilic asthma by releasing the alarmins TSLP, IL-33 and IL-25 upon challenge to triggers. The alarmins interact with receptors on ILC2 cells which in turn produce the key T2 inflammatory cytokines IL-4, IL-5 and IL-13 which elicit the same functions as described for allergic eosinophilic asthma. In T2 low asthma on the other hand, eosinophils are lacking, and the underlying pathophysiology is less known. It is believed that irritants, viruses, and bacteria stimulate the epithe-

lium to release TSLP, which can directly influence mast cells to release leukotrienes and histamine, and prime dendritic cells to drive Th1/Th17-cell differentiation which in turn leads to production of TNF-alpha and IFN-gamma that might promote neutrophilia. Prof. Uller emphasized that it is important to keep in mind that even if we tend to classify patients into these distinct endotypes (i.e., T2 high and T2 low), the inflammation in asthma is heterogenous and dynamic. In that regard a study showed that one year after classification into one endotype the allocation to inflammatory clusters was changed in 23.6% of all asthma patients when defined by physiological phenotypes and, remarkably, in 42.3% of the patients when stratified according to sputum cellularity (Kupczyk M. et al., Allergy 2014).

The role of the bronchial epithelium in asthma

Further, Prof. Uller highlighted the key role of the bronchial epithelium in asthma, acting as a physiological and immunological barrier to the outer world. The bronchial epithelium is central for initiating innate and adaptive immune responses and is the major cell type in the lung being infected by rhinovirus and bacteria. It is also a major producer of mediators that can induce structural changes leading to remodelling. Interestingly, multiple features of asthma are associated with epithelial cytokines, including decline in lung function, airway hyperresponsiveness, airway remodelling, asthma severity and increased risk of exacerbations. Immunohistology reveals that the bronchial epithelium in asthma compared to the healthy lung shows clear pathological changes including goblet cell hyperplasia and mucus production, thickened epithelium, and basal membrane inflammatory infiltrates and sometimes subepithelial fibrosis with collagen deposition. Interestingly, Prof. Uller reports from her own work a skewed bronchial epithelial immune response to common triggers such as allergens and viruses. We know that respiratory viral infections are a major cause of asthma exacerbation. However, molecular mechanisms are unknown and efficient treatment is lacking. Importantly, exacerbations are associated with a decline in lung function over time, so it is crucial to limit the number of exacerbations with proper treatment. Research from Prof. Uller`s group shows that in atopic asthma patients the production of antiviral interferon upon viral stimulation decreases with severity and eosinophilia (Porsbjerg C. et al., European Respir J. 2022), indicating that the antiviral response might be attenuated in these patients. Another study by Uller and colleagues showed that the epithelial alarmin TSLP is overexpressed in asthma patients in response to viral stimulation (Uller L. et al., Thorax 2010), suggesting that this cytokine has a certain role in driving asthma immuno-pathogenesis during viral-induced exacerbations.

Prof. Uller ended the lecture by discussing why TSLP is an interesting epithelial target. One central aspect is the fact that the receptor for TSLP is expressed on a wide range of different cell types, not only immune cells but also structural cells, meaning that TSLP potentially can orchestrate airway inflammation across several asthma phenotypes independent on the underlying inflammation.

Suggested reading:

Lambrecht BN, Hammad H. The immunology of asthma. Nat Immunol. 2015 Jan;16(1):45-56. doi: 10.1038/ni.3049. PMID: 25521684.

Porsbjerg C, Melén E, Lehtimäki L, Shaw D. Asthma. Lancet. 2023 Jan 19:S0140-6736(22)02125-0. doi: 10.1016/S0140-6736(22)02125-0. Epub ahead of print. PMID: 36682372.

Kupczyk M, Dahlén B, Sterk PJ, Nizankowska-Mogilnicka E, Papi A, Bel EH, Chanez P, Howarth PH, Holgate ST, Brusselle G, Siafakas NM, Gjomarkaj M, Dahlén SE; BIOAIR investigators. Stability of phenotypes defined by physiological variables and biomarkers in adults with asthma. Allergy. 2014 Sep;69(9):1198-204. doi: 10.1111/all.12445. Epub 2014 Jul 8. PMID: 25039610.

Porsbjerg C, Nieto-Fontarigo JJ, Cerps S, Ramu S, Menzel M, Hvidtfeldt M, Silberbrandt A, Frøssing L,

Klein D, Sverrild A, Uller L. Phenotype and severity of asthma determines bronchial epithelial immune responses to a viral mimic. Eur Respir J. 2022 Jul 28;60(1):2102333. doi: 10.1183/13993003.02333-2021. PMID: 34916261.

Uller L, Leino M, Bedke N, Sammut D, Green B, Lau L, Howarth PH, Holgate ST, Davies DE. Double-stranded RNA induces disproportionate expression of thymic stromal lymphopoietin versus interferon-beta in bronchial epithelial cells from donors with asthma. Thorax. 2010 Jul;65(7):626-32. doi: 10.1136/thx.2009.125930. PMID: 20627922.

Ingvild Bjellmo Johnsen
Medical Advisor, Norway

State of the art treatment
Is stepwise medication adjustment really the only way to manage asthma?

The second lecture of the asthma session was given by Prof. Guy Brusselle from Ghent University Hospital who talked about the management of asthma.

He started out discussing current GINA guidelines including the two tracks of stepwise medication adjustment, i.e., "controller and preferred reliever" and "controller and alternative reliever". Coming to the asthma management cycle, where we currently tend to focus on symptoms, exacerbations and lung function, Prof. Brusselle clearly claimed that this management cycle is lacking clinical and inflammatory phenotypes. He finds the type of inflammation and especially the severity of inflammation important for adjusting the treatment for people living with asthma.

Building on this, he went on talking about asthma phenotypes and the importance of distinguishing between T2 high versus T2 low inflammation considering the future risk of asthma exacerbations. Prof. Brusselle and colleagues recently published a concise guide for asthma management, titled A^2BCD, focusing on phenotypes of asthma and going beyond asthma control, but instead aiming for asthma remission (Lommatzsch M. et al., Lancet RM, 2023). The A^2BCD guide builds on four components: dual assessment (A^2) of asthma (i.e., diagnosis and phenotype + asthma control and future risks); basic measures (B: eg. education, self-management skills, regular physical activity, and avoidance of asthma triggers); identification and treatment of comorbidities (C) of asthma (eg. chronic rhinosinusitis, obesity, or sleep apnea); and phenotype-specific, individually targeted treatment with disease-modifying anti-asthmatic drugs (D).

Elaborating further on inflammatory phenotypes, Prof. Brusselle shared his view on T2 high versus T2 low inflammation. He presented a graph where the x-axis represents blood eosinophils which are increased in the presence of systemic IL-5 and the y-axis represents FeNO which is regulated by the presence of airway IL-13. If one or both are increased the patient has T2 high asthma, if both are low the patient has T2 low asthma (lower left square). The importance of distinguishing between T2 high and T2 low asthma was demonstrated by data from a study looking at predictors of future asthma attacks showing that there is a four-fold increased risk of future asthma attacks if the patient has a blood eosinophil level above 300 and a FeNO above 50 ppb (T2 high) as opposed to FeNO below 25 ppb and blood eosinophil level below 150 (T2 low). Based on this and other studies, the top five most important determinants of future asthma attack risk according to Prof. Brusselle are **1)** history of asthma attacks, **2)** current asthma control, **3)** lung function, **4)** FeNO levels and **5)** blood eosinophil levels.

Phenotypes of asthma- do they matter for treatment?

Next, Prof. Brusselle asked what the therapeutic implications of clinical and inflammatory phenotypes of asthma are. When dealing with severe asthma, this is particularly important. He presen-

ted the mechanistic action of the 6 monoclonal antibodies that are currently available for treatment of severe asthma and pointed out that it is crucial to be able to distinguish between T2 high and T2 low asthma, as well as allergic and eosinophilic asthma when choosing add-on treatment for this group of patients. Again, using the graph with the x-axis representing eosinophil levels and the y-axis representing the FeNO level, Prof. Brusselle showed that for patients in the upper right corner (both eosinophil and FeNO high) you can use all 6 antibodies for the treatment of uncontrolled T2 high asthma, whereas for patients in the lower left corner only anti-TSLP has been shown to have a minor benefit so far. Moving to the "moderate-to-severe" asthma group, Prof. Brusselle discussed the possible benefit of dual and triple inhalation combinations, focusing on the importance of assessing eosinophilic inflammation and FeNO levels when considering these treatments.

As a concluding remark Prof. Brusselle suggested that for the future, we need to combine the best of two worlds; in addition to the recommended stepwise adjustment in GINA we need to consider the clinical and inflammatory phenotypes to choose the optimal personalized asthma management and aim for asthma remission in addition to asthma control.

Suggested reading:

GINA guidelines 2022, https://ginasthma.org/gina-reports/

Lommatzsch M, Brusselle GG, Levy ML, Canonica GW, Pavord ID, Schatz M, Virchow JC. A2BCD: a concise guide for asthma management. Lancet Respir Med. 2023 Jan 27:S2213-2600(22)00490-8. doi: 10.1016/S2213-2600(22)00490-8. Epub ahead of print. PMID: 36716752.

Ingvild Bjellmo Johnsen
Medical Advisor, Norway

Clinical approach

Asthma and obesity – even minor weight loss matters!

This is the essence of the talk from Professor and Director at Vermont Lung Center, USA, Anne Dixon. Professor Dixon has for decades conducted research into the nexus between asthma and obesity. From recent data, a link between severe asthma and obesity (BMI >30) between the age of 20 and 40 has been established, as the majority of people with severe asthma in this age group are also obese. The link between severity of asthma and being obese declines with increasing age. The reason for this is currently unknown.

Professor Dixon divides patients in two groups: "asthma complicated by obesity" and "asthma consequent by obesity." The latter is more common in women, it usually has a late onset and is manifested with minimal airway inflammation, contrary to asthma in general. Moreover, as the disease is prominent in the lung periphery, these persons can be difficult to diagnose as spirometry may underestimate true mechanical deficits. Professor Dixon´s advice to overcome this diagnostic challenge is to look for bronchodilator response and methacholine reactivity. Interestingly, subjects with the highest symptom burden were shown to have elevated reactance (measured as increased area under the reactance curve; AX) using oscillometry. The reactance reflects the expandability properties of the airways and increased AX indicate loss of elastic recoil and thus stiffness of the lungs. We are awaiting the publication of this this research in Chest soon.

In general, people with asthma and obesity have a reduced response to inhaled controller medication including bronchodilators and ICS. Professor Dixon recommends being aware of comorbidities such as gastroesophageal reflux, obstructive sleep apnoea and depression, which are more common in people with both asthma and obesity. These comorbidities can potentially constitute treatable traits.

Finally, Professor Dixon showed that bariatric surgery very effectively improves asthma control, quality of life and decreases the frequency of exacerbations. Interestingly, and maybe even more relevant for the everyday patient in the clinic, is that **even a minor weight loss matters!** A weight loss of 5% can improve asthma control and quality of life, which are key outcomes for people living with asthma. Facilitating minor changes in lifestyle and diet of the person living with asthma matters, too: low-fat diet increases the responsiveness to bronchodilators while high-fat diet reduces the change in post bronchodilator-FEV1 and increases blood neutrophil counts.

To summarize, when facing a person with asthma and obesity, Prof Dixon reminds us to be aware of potential minimal airway inflammation, inconclusive spirometry, and advises us to look for bronchodilator responsiveness, methacholine reactivity and to perform oscillometry to look for increased AX in relation to the symptom burden. Last but not least, it is important to treat comorbidities!

Suggested reading:

Peters U, Dixon AE, Forno E. Obesity and asthma. J Allergy Clin Immunol. 2018 Apr;141(4):1169-1179. doi: 10.1016/j.jaci.2018.02.004. PMID: 29627041; PMCID: PMC5973542.

Nyenhuis SM, Dixon AE, Ma J. Impact of Lifestyle Interventions Targeting Healthy Diet, Physical Activity, and Weight Loss on Asthma in Adults: What Is the Evidence? J Allergy Clin Immunol Pract. 2018 May-Jun;6(3):751-763. doi: 10.1016/j.jaip.2017.10.026. Epub 2017 Dec 6. PMID: 29221919; PMCID: PMC5948112.

Nicolai Krogh
Medical Science Liaison, Denmark

Chiesi

Horizon scanning
Horizon scanning in severe asthma

Professor Liam Heaney at Queen's University Belfast, Northern Ireland, addressed the following questions: What does clinical remission in severe asthma mean, how to achieve it and what are the barriers?

Clinical remission in severe asthma can be defined as:

- Optimization and stabilization of lung function.
- Sustained absence of significant asthma symptoms based on validated tests.
- No use of systemic corticosteroid therapy for exacerbation treatment or long-term disease control.

An agreement regarding disease remission should be established between the person living with asthma and the healthcare professional. The key of reaching clinical remission is sustained treatment effects. Complete remission will be achieved when, in addition to the points above, a normalization of the underlying pathophysiology (e.g. absence of inflammation, normal BHR (bronchial hyperresponsiveness), etc.) is established.

Professor Heaney emphasized that clinical remission in severe asthma is not all about biologics. This is illustrated by the relative high placebo effects seen across multiple studies addressing the effects of various biological treatments for severe asthma. There is no controversy that biologics have a general effect on lung function, asthma control and quality of life, but the striking improvements seen in the placebo groups illustrate that increased awareness and focus on the person living with disease, e.g. when entering a clinical trial, have a significant impact.

One of the major barriers for clinical remission is late intervention with otherwise effective treatments. This is illustrated in the REDES study that confirms that early intervention is needed in order to achieve better results: people living with asthma who achieved clinical remission had less severe asthma compared to those who did not. Another issue is glucocorticoid toxicity that might be established early on and is not necessarily reverted upon treatment with biologics. Although effective reduction in exacerbation rates is seen when treated with biologics, e.g., almost 50% reduction in the DREAM study, we need to establish what is driving the other 50% of the events.

In addition, Professor Heaney listed some of the major barriers to achieve control in severe asthma:

- Behavioural factors (medication non-adherence, smoking and physical deconditioning)
- Airway structural changes (fixed airway obstruction, bronchiectasis and mucus hypersecretion)
- Multiple cause of airway inflammation (T2-pathways, infections and other immunologically active molecules such as IL-17, CXCR2, IL-23 and IL-6)
- Cough reflex hypersensitivity.

Moreover, many common comorbidities such as rhinosinusitis, nasal polyps, psychological factors, vocal cord dysfunction, obesity, obstructive sleep apnoea, hyperventilation syndrome, gastroesophageal reflux, etc. can complicate disease control.

Will it be possible, in the future, to achieve clinical remission in severe asthma or even complete remission?

Suggested reading:

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Domingo Ribas C, Carrillo Díaz T, Blanco Aparicio M, Martínez Moragón E, Banas Conejero D, Sánchez Herrero MG; REDES Study Group. REal worlD Effectiveness and Safety of Mepolizumab in a Multicentric Spanish Cohort of Asthma Patients Stratified by Eosinophils: The REDES Study. Drugs. 2021 Oct;81(15):1763-1774. doi: 10.1007/s40265-021-01597-9. Epub 2021 Sep 29. Erratum in: Drugs. 2021 Oct 21;: PMID: 34586602; PMCID: PMC8550660.

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