

# Do we know the cause of asthma?



# Asthma

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Asthma and COPD (smoker's lung) are the most prevalent chronic inflammatory diseases of the lung all over the world. The WHO (World Health Organization) estimated in 2015 that both diseases together affect more than 400 million people with increasing incidences. The available data from Europe implied that asthma and COPD are largely under- or wrongly diagnosed and therefore many patients receive inadequate treatment.

New epidemiologic studies suggested that in Europe and the Americas the increase of asthma and COPD is slowing down, while it is rapidly increasing in Asian countries. The data published from Africa reflects mainly the situation in the Republic of South Africa, and the other countries shows a high variability of prevalence which may be due to missing data or that chronic "coughing" is not regarded as a major problem by many. The causes of the increasing prevalence of asthma and COPD over the past decades are unclear.

Major problems with asthma and COPD are:

- Insufficient understanding of the events initiating the pathogenesis;
- No clear diagnostic marker(s) for either disease, thus lengthy and repetitive assessments of lung function under different conditions are needed;
- Acute attacks and inflammation can be controlled by anti-inflammatory and muscle relaxing drugs, but there is no lasting cure available; and
- Airway wall remodelling is irreversible and does not respond to any known drug.

Asthma is a disease of the airways which limits breathing. The global initiative for asthma (GINA 2017) defined asthma as follows: "Asthma is a heterogeneous disease usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and intensity together with variable expiratory airflow limi-



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tation”. This definition is open to interpretation and reflects how little we know about the disease. The fundamental initiating cause(s) of the pathogenesis of asthma is unknown. New studies imply that the long prevailing assumption that chronic inflammation of the airway is the major cause of all other asthma pathologies has to be revised, and the American Thoracic Society stated in 2016 that asthma may only become curable after understanding the cause of airway tissue remodelling.

Different types of asthma have been defined, such as allergic asthma, which develops often together with other atopies of the patient. Seasonal asthma, when a patient is allergic to a natural allergen such as grass pollen that occurs only during a limited period during the year. Occupational asthma, a type of allergic asthma, is caused by repetitive exposure to chemical, drugs, or agricultural products. Patients with allergic asthma have often increased IgE and humanized anti-IgE-antibodies are an effective new form of therapy. Anti-IgE-therapy effectively reduces inflammation, and it

was suggested that it also reduces airway wall remodelling. However, there are insufficient clinical data available to prove a benefit of anti-IgE antibodies on airway wall remodelling.

Non-allergic asthma accounts for approximately 40% of all patients and can be caused by inhaling cold/hot air, psychologic stress, or exercising. Exercise-induced asthma is known from many Olympic athletes, especially those performing in water or winter sports. It is estimated that more than 50% of these athletes suffer from asthma during training. But the mechanism how changes of the water content in the inhaled air lead to an asthma attack remains unknown. Epi-genetic mechanisms are currently investigated but it is too early to draw conclusions.

Less well understood is the pre-condition for asthma, why do not all allergic people develop asthma? For sure hormones affect the susceptibility to asthma, but how they do it is not well investigated. Hormonal changes as they occur during puberty, menopause or as reduced



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androgens in men often affect the course of asthma in both ways: (i) during puberty many children lose their asthma; while (ii) later in life hormonal changes often lead to more severe types of asthma. Thus, the pathogenesis of asthma has to be re-investigated.

COPD is defined as: "common preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases." In Europe and the Americas cigarette smoking is the major cause of COPD, which develops in 20% of smokers. The fact that "only" a fifth of smokers develop COPD raises the question of a pre-condition, which is largely unknown. Some studies imply that the stage of lung maturation may set the lung to develop COPD like symptom later in life. Two percent of COPD patients develop the disease as the result of a genetic disorder, alpha1-antitrypsin deficiency.

In other areas of the world open fire cooking

and heating is the major cause of COPD, often combined with cigarette smoking. However, earlier this year it was reported that additional causes of COPD have been identified, especially compounds contained within ordinary household cleaners. This topic was picked up by many daily newspapers and stirred a discussion how serious the underlying investigation had been. Such reports should be taken with care, since there is no information available how many cleaners suffer from this type of COPD and how frequent the exposure to cleaning detergent has to be to cause COPD. Another question is if the symptoms were correctly diagnosed and not be confused with occupational asthma. Inhaled vaporized chemicals or aerosols are assumed to damage the airways, but the type of damage and how it occurs has to be investigated in more detail.

The major problem for such studies is the use of household cleaners. Most often a cleaning person will use different cleaner types for different tasks on one job. This opens the possibility that the COPD causing effect will only



happen when different cleaning detergents are inhaled in a certain pattern. The chemicals will then react in the airway and damage the epithelium and the tissue beneath.

COPD shares many pathologies with asthma and at early stages shows chronic inflammation and airway wall remodelling. However, remodelling is found more in the small airways while in asthma this feature occurs in the large-medium sized airways. At late stages of COPD the lung structure disintegrates which led to the hypothesis that COPD is the result of an imbalance between tissue building and degrading enzymes.

Similar to asthma, it has been postulated that exposure to risk factors during late pregnancy and/or early childhood pre-dispose the lungs to develop COPD later in life, but a final proof of such an epi-genetic pre-dispositioning will be difficult to prove. It is also indicated that COPD is not as specific for the lung, which is the just the organ where it manifests first. Therefore, new studies on the interaction

between the different lung tissue forming cells and the immune system have to be undertaken, as well as studies that take the response of other organs with the lung into account.



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# Severe asthma shows the tip of the iceberg of personalised medicine

**Isabel Proaño Gómez, Communications Manager at European Federation of Allergies and Airways Diseases Patients' Associations (EFA) explores the issue of severe asthma and how our understanding of it is evolving**

"I knew it!". This is what many adult asthma patients are thinking today. They knew there was something wrong with the way their lungs behave, despite their asthma medication. Science is not knowledge set in stone, and the patient community knows it very well: their daily burden is and should be at the heart of medical research developments.

Patients with what we know today as severe asthma suffer from aggressive and sudden symptoms. No matter how hard they try to control it, asthma attacks, coughing and wheezing surprise them in the middle of something, ruining their day, week, month and their life.

Patients whose asthma is severe relate this kind of experiences very often go to their doctors. Although asthma is a well-known chronic disease, which in its allergic form can even disappear in childhood with the correct treatment, asthma touches 30 million Europeans below 45 years old. The minority of patients with severe asthma (10%) suffer a real burden, with acute symptoms that can lead to a deadly asthma attack.

## **Severe asthma requires accurate diagnosis and research**

Our understanding of asthma is evolving at a quicker pace now. A century ago, asthma was divided between allergic and non-allergic asthma, but this classification has significantly changed, and physicians are referring now to the genotypes and phenotypes (the genes and

environmental factors that explain the existence of a disease). On top of that, thanks to new recent laboratory techniques, researchers are now looking for biomarkers, which are specific chemicals in our blood, urine and sputum that could tell us more about who is at risk of developing what type of asthma.

Although no specific biomarker has been defined for asthma yet, the asthma patient community is expecting to participate in new research following up on what we have. At European Federation of Allergies and Airways Diseases Patients' Associations (EFA), we took part in the U-BIOPRED research project, a multi-year Innovative Medicines Initiative project working on the biggest European asthma patient data cohort and highlighted what we already felt: asthma is definitely more complex than expected and we need to define different types of severe asthmas more precisely.

## **Delayed diagnosis undermines self-confidence and health**

In the meantime, severe asthma diagnosis has to rely on the patients' experience more than on innovative tests. In the last decades, the concept of asthma severity has progressed from the classification by lung function, to the patients' degree of asthma control. In my opinion, this evolution is already showing that care for asthma patients is shifting towards the priority that matters: to what extent can patients cope with asthma? The response to the question has already enabled the commercialisation of new



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treatments, but is knowledge distilling across countries and healthcare professionals?

The good news is that things are shifting with precision medicine or, more preferably, P4 medicine; predictive, preventative, personalised and participatory. People with severe asthma need personalisation and to be able to set their own goals to live and plan this life healthier. When it comes to diagnosis and management, we might be adopting the “one patient, one asthma” approach.

The bad news is that many patients are right now fighting their asthma without having a proper diagnosis on its severity. In severe asthma, the patients’ response to treatment is irregular and to define it, doctors look at elements like the number of hospitalisations and long-term use of oral corticosteroids in high doses, which have severe secondary effects. Asthma severity is defined by medication. Even with that, patients need to wait approximately a decade to get a proper diagnosis of their asthma, which undermines their trust in finding a solution but also their self-confidence.

### **Asthma demonstrates trust in patients is key**

As we have captured in our “Severely, asthma” video series, people with severe asthma have been pointed by the finger of a wrong inhaler technique or not following the prescribed treatment. Yet their experience with asthma can be a source of knowledge and innovation for researchers and healthcare systems. People

with severe asthma are determined for health. The experience of severe asthma diagnosis is, therefore, the tip of an iceberg that we need to confront for the 21st-century personalised healthcare era.

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