

# 50<sup>th</sup> Nordic Lung Congress

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PEER-REVIEWED  
CONFERENCE REPORT



## Asthma Increases Risks Around Delivery

A Finnish study showed that asthma is associated with increased risks of perinatal mortality, preterm birth, asphyxia, low birth weight, and foetal growth restriction, which is unaffected by asthma treatment.

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## Social Distancing Reduced Bronchiectasis Exacerbations

Social distancing during the COVID-19 pandemic reduced exacerbations in bronchiectasis patients. However, the daily symptoms commonly experienced by these patients were not substantially reduced.

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## Lung Cancer Screening in Denmark

Systematic lung cancer screening of high-risk groups offers great potential for reducing the disease burden and mortality of lung cancer; the Danish National Board of Health is considering introducing screening.

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## COLOPHON

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Prof. Vibeke Backer

## Biography

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Conflict of Interest Statement:  
Nothing to declare



Prof. Charlotte Suppli Ulrik

## Biography

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Conflict of Interest Statement:  
No COI in relation to the present work.



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## Biography

Dr Ole Hilberg is a professor in respiratory medicine at Southern Danish University, Chairman of the Danish Research Center for Lung Cancer, and former Chairman of the Danish Society of Respiratory Medicine. He has authored more than 200 publications and has been supervisor for more than 20 PhD students.

Conflict of Interest Statement:  
No COI in relation to the present work.

# Introduction

## **Dear Readers,**

The 50<sup>th</sup> Nordic Lung Congress should have been held in 2021 but due to COVID-19, it was postponed to this year. And what a joy it was to be able to welcome all attendees in person again!

This congress showcases the scientific merits of the Nordic countries within the field of respiratory diseases. Although the overall output (in terms of actual numbers of scientific publications) from the Nordic countries is seemingly low, consistent with the relatively small numbers of inhabitants, the quality of research is regarded as outstanding. All 5 Nordic countries rank among the 7 best countries worldwide when it comes to research.

Prof. Thorarinn Gislason (University of Iceland, Reykjavik, Iceland) highlighted the importance of cross-country collaboration. Working together means to be part of the society one lives in, taking into account the characteristics and differences whilst seeking mutual ground.

Prof. Amund Gulsvik (University of Bergen, Norway) added to this by stating that preferably an area of research should be sought which is closely related to the specific natural advantages in a country, its research environment, and authorities. This may give access to local research tools and knowledge.

Prof. Ronald Dahl (Aarhus University, Denmark) emphasised the importance of finding a dedicated team with a clear focus and aim.

The Nordic Lung Congress – with Copenhagen as a home base for 2022 – thus serves as a platform encouraging collaboration, interaction on various topics, initiation of new research projects, as well as networking across all areas of respiratory disease.

We hope you enjoy this summary.



# Respiratory Disease and Physical Activity

## Physical activity improves asthma control

Being active is important for everyone, even more so for people suffering from lung disease. Regular exercise – tailored to the specific needs of patients – can help maintain a good level of overall health and may also improve signs and symptoms of a lung condition. Although it can be challenging to prescribe exercise to asthma patients, physical activity proves to be a valuable intervention as it improves asthma control. However, people should not overdo it, as excessive vigorous training increases the risk of developing asthma and asthma-related conditions – as found among elite athletes.

Dr Morten Hostrup (University of Copenhagen, Denmark) emphasised that people with asthma should be physically active. "A systematic review and meta-analysis of 11 randomised-controlled trials assessing the effects of aerobic exercise training for 8 weeks or longer showed that this type of exercise (including walking, jogging, spinning, and treadmill running) can potentially improve asthma control and lung function. However, it has no effect on airway inflammation [1]." Exercise combined with a high protein/low glycaemic index diet in non-obese asthma patients improves asthma control compared with diet only or exercise only. Nevertheless, this combination does not affect airway hyperresponsiveness or airway inflammation [2]. Dr Hostrup also pointed out that aerobic exercise training effectively improves disease outcomes in obese asthma and that this effect may be more pronounced in women. For those asthma patients wishing to engage in vigorous training such as high-intensity interval training (HIIT), Dr Hostrup stated that they can safely do so, but should keep a short-acting beta-2 agonist nearby. "High-intensity interval training has demonstrated to effectively improve maximal oxygen consumption and peak power output in asthma patients who are untrained, regardless of the individual levels of asthma control, forced expiratory volume in one second (FEV<sub>1</sub>), fraction of exhaled nitric oxide (FeNO), and airway hyperresponsiveness [3,4]."

1. Hansen ESH, et al. Eur Respir J. 2020;56(1):2000146.
2. Toennessen LL, et al. J Allergy Clin Immunol Pract. 2018;6(3):803–811.
3. Toennessen LL, et al. Eur Clin Respir J. 2018;5(1):1468714.
4. Hostrup M. Exercise adaptations and prescriptions in Asthma. Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.

## Tailored exercise needed for COPD patients

Exercise training is a key component in COPD management and can lead to multiple physiological and clinically relevant adaptations and improvements. Different exercise modalities are (likely) needed to manage the disease as it is clear that one-size-does-not-fit-all when it comes to COPD management.

Prof. Andre Nyberg (Umea University, Sweden) discussed various aspects of exercise training for patients with COPD. He stated that low muscle mass in patients with COPD holds a 4-fold increase in mortality risk [1]. "However, we do not really know what happens within the muscle tissue, so we still need to learn which type of exercise is suitable for which patient," he commented. "It is clear though, that exercise training is a cornerstone of COPD management," Prof. Nyberg stated. "Exercise is effective independent of the GOLD stage, symptom severity, or disease control." Referring to the type of exercise, aerobic and resistance training are very effective [2]. "In addition, the type and level of exercise need to be customised for the individual patient according to the disease manifestations and its imposed limitations as well as harmonised with lifestyle adjustments." To this end, new targets have been set by the guidelines, focusing not only on patients who experience reduced strength, but also reduced muscle power, and endurance [3,4]. Prof. Nyberg warned that the response may differ at individual level, and that patients with even mild COPD can experience difficulties in progressing exercise workloads which calls for alternative strategies. Besides, variation is very important to prevent stagnation [5]. "So, though exercise training in patients with COPD is effective, there is still room for improvement at the individual level [6]."

1. Marquis K, et al. Am J Respir Crit Care Med. 2002;166(6):809–13.
2. Nolan CM, et al. COPD. 2019;16(5-6):378–389.
3. Spruit MA, et al. Am J Respir Crit Care Med. 2013;188(8):e13–64.
4. Evans RA, et al. Chest. 2015;147(3):673–684.
5. Klijn P, et al. Am J Respir Crit Care Med. 2013;188(2):193–200.
6. Nyberg A. Exercise adaptations and -prescription in COPD. Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark

## Exercise training for IPF patients is feasible but access needs to be improved

Although exercise training in interstitial lung disease (ILD) has been shown to be both safe and effective, it

**should be customised in the individual patient. Moreover, access to pulmonary rehabilitation for patients with idiopathic pulmonary fibrosis (IPF) needs to improve in the Nordic countries.**

According to Dr Jana de Brandt (Umeå University, Sweden), the ATS/ERS/JRS/ALAT Guideline provides specific recommendations for pulmonary rehabilitation for patients with IPF who have a generally poor prognosis and for whom there is no cure, apart from a possible lung transplantation [1,2]. The aims of exercise training within the relatively short lifespan left for these patients should primarily focus to improve quality of life and, if eligible for lung transplantation, to optimally prepare patients for surgery. Whether pulmonary rehabilitation is effective on different disease parameters in ILD was assessed in a literature review. Randomised controlled trials and quasi-randomised controlled trials implementing pulmonary rehabilitation were compared with no pulmonary rehabilitation or with other interventions in patients with ILD (see Table) [3].

Table: Effectiveness of pulmonary rehabilitation on various disease parameters in ILD [3]

Disease parameter	Effective?	Level of certainty
Exercise capacity	Yes	Moderate
Muscle function	Lack of evidence	--
Dyspnoea	Maybe	Low
Quality of life	Yes	Moderate
Survival	Maybe	Low

A study by Perez-Bogerd et al. demonstrated that it is feasible for ILD patients to undertake pulmonary rehabilitation with 69% of patients with IPF completing the program compared with 63% of patients with COPD [4]. However, some considerations need to be considered when prescribing pulmonary rehabilitation in IPF, Dr de Brandt mentioned. "Early referral, well-trained staff, and comorbidities are important issues, and the training program should be customised accordingly. Also, training does not stand alone; education and self-management are also key components of the program which we offer our ILD patients [5,6]."

Dr de Brandt noted that access to non-pharmacological treatment for IPF patients – including pulmonary rehabilitation – is very patchy across Europe. For instance, Finland has no pulmonary rehabilitation services specialised for ILD patients and pulmonary rehabilitation is even unavailable in some university hospitals. In Denmark, pulmonary rehabilitation is limited and often not designed for patients with ILD [7]. "This means there is a big challenge lying ahead of us," concluded Dr de Brandt [8].

1. Strongman H. et al. *Adv Ther*. 2018 May;35(5):724-736.
2. Raghu G. et al. *Adv Ther*. 2022;205(9):e18–e47.
3. Dowman L. et al. *Cochrane Database Syst Rev*. 2021 Feb 1;2(2):CD006322.
4. Perez-Bogerd S. et al. *Respir Res*. 2018 Sep 2019(1):182.
5. Matsuo S. et al. *J Clin Med*. 2021;10(14):3153.
6. Wickerson L. et al. *J Cardiopulm Rehabil Prev*. 2018 Nov;38(6):419-424.
7. EU-IPFF. <https://www.eu-ipff.org/who-we-are>
8. De Brandt J. Exercise adaptations and -prescription in IPF. Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.

# Respiratory Disease and Reproduction

## Asthma increases risks around delivery

Asthma is associated with increased risks of perinatal mortality, preterm birth, asphyxia, low birth weight, and foetal growth restriction (small for gestational age [SGA]), Dr Paula Kauppi (University of Helsinki, Finland) explained in her lecture. Asthma treatment reduces the risk of preterm delivery, but it does not seem to reduce other complications (esp. not the perinatal mortality rate).

A Finnish study aimed to assess the association between maternal asthma and the perinatal risks as well as the possible impact of asthma medication on these risks. The study included 962,405 singleton live and stillbirths in which 93.3% of pregnancies were in mothers with neither confirmed asthma nor use of asthma medication and 2.8% pregnancies in mothers who had confirmed maternal asthma. Main outcome measures were premature birth, low birth weight, SGA, and neonatal death. Maternal asthma was associated

with an adjusted odds ratio (aORs) for perinatal mortality of 1.24 (95% CI 1.05–1.46), preterm birth 1.18 (95% CI 1.11–1.25), low birth weight 1.29 (95% CI 1.21–1.37), foetal growth restriction (SGA) 1.32 (95% CI 1.24–1.40), and asphyxia 1.09 (95% CI 1.02–1.17). Although asthma treatment (based on filled prescriptions) was associated with a reduced risk of preterm birth aOR 0.85 (95% CI 0.76–0.96), mothers who received asthma treatment had higher risks of foetal growth restriction (SGA): aOR 1.26 (95% CI 1.10–1.45) and asphyxia aOR 1.37 (95% CI 1.17–1.61) compared with mothers with untreated asthma [1,2]. This study did not investigate/report the actual adherence to asthma medication nor provided data on asthma control (pre-post treatment).

1. [Kempainen M, et al. PLoS One. 2018 May;13\(5\):e0197593.](#)
2. Kauppi P. Fertility and airway diseases-Why is there an association? Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.

## PRO-ART study: unravelling the link between asthma and subfertility

The association between asthma and decreased fertility is currently being investigated in the PRO-ART study. The outcomes are expected to provide insights into the underlying mechanism and help to increase our understanding of this complex relationship.

Asthma and sub-/infertility are among the most common chronic disorders in young adults [1]. Moreover, women with asthma seem to experience a prolonged time of unwanted non-conception [2]. Despite a possible association between asthma and decreased fertility, the underlying mechanisms are presently unknown. Possibly, the asthma-associated systemic inflammation may affect the reproductive organs and/or the germ cells thereby reducing fertility.

The primary objective addressed in the PRO-ART study is to investigate whether systemic treatment with omalizumab (aimed at controlling systemic asthma-related inflammation as well as at improving asthma control) may improve the pregnancy rate/outcomes in women with type2-asthma ([NCT03727971](#)). Secondary objectives include, among other, local and systemic inflammatory biomarkers and asthma control. This multicentre study has a randomised, 2-arm parallel, placebo-controlled design. The study started in January 2019, aiming to include 180 women, with the estimated study completion date of 31 December 2024 [3]. Dr Anne Hansen (Copenhagen University Hospital, Denmark) pointed out that "The role of the men should also be

considered as over the last decades the overall sperm quality has been decreasing globally. Could systemic asthma-related inflammation play a role in this decline? To get a more complete picture, further research is needed [4]."

1. Nielsen HS, et al. Forebyggelse af nedsat frugtbarhed. København: Vidensrådfor Forebyggelse. 2016:1–152.  
[http://www.vidensraad.dk/sites/default/files/vidensraad\\_nedsatfrugtbarhed\\_digital\\_update-1.pdf](http://www.vidensraad.dk/sites/default/files/vidensraad_nedsatfrugtbarhed_digital_update-1.pdf)
2. Gade EJ, et al. Eur Respir J. 2016 Apr;47(4):1144-51.
3. Tidemandsen C, et al. BMJ Open. 2020;10(11):e037041.
4. Hansen HV. Asthma and fertility treatment. Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.

## Early-onset and uncontrolled asthma: strong association with recurrent pregnancy loss

A Danish study investigated the association between asthma-onset and asthma control (based on asthma medication prescriptions) and pregnancy loss. Dr Casper Tidemandsen (Copenhagen University Hospital, Denmark) explained that there appears to be a stronger association between early-onset and/or uncontrolled asthma and (repeated) pregnancy loss compared with later-onset cohorts and controlled asthma, respectively.

The aim of this nationwide study was to investigate whether increased/repeated pregnancy loss in asthma was associated with the age of onset (early-onset: 6–15 y; adult-onset: 16–39 y; late-onset: 40–45 y); i.e. onset of asthma before or during the fertile age. A total of 128,553 women with asthma and 1,297,233 women without asthma in the age of 6 to 45 years were identified in the national health registers. Logistic regression analysis (adjusted for year of birth and educational level) showed that as compared with non-asthmatic women, women with asthma had odds ratios (ORs) of 1.05 (95% CI 1.03–1.07), 1.09 (95% CI 1.05–1.13), and 1.18 (95% CI 1.11–1.24) for 1, 2, and 3 or more pregnancy losses, respectively. The OR for recurrent pregnancy loss was 1.19 (95% CI 1.12–1.27). Subgroup analyses of the respective age-cohorts showed that women with early-onset asthma had an OR of 1.47 (95% CI 1.24–1.72) for ≥3 pregnancy losses. For women with uncontrolled asthma (defined as ≥400 doses of short-acting beta<sub>2</sub> agonist per year) versus controlled asthma, a significant OR of 1.60 (95% CI 1.16–2.16) was found for ≥3 pregnancy losses [1,2].

1. [Tidemandsen C, et al. J Allergy Clin Immunol Pract. 2022 May;25:S2213-2198\(22\)00499-8.2022.](#)
2. Tidemandsen C. Asthma and recurrent pregnancy loss. Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.

## **Round-up of respiratory disease and reproduction topics**

**This summary features the most important outcomes of 4 separate sessions which formed part of the topic 'Respiratory diseases and reproduction'.**

Fathers who are overweight before puberty, negatively influence forced expiratory volume in 1 second (FEV<sub>1</sub>) and forced vital capacity (FVC) in their sons (lower capacity), and a lower adult height in their offspring. No associations have been identified before the age of 30 years, the FEV<sub>1</sub>/FVC ratio, or in the maternal line [1].

Maternal asthma may be associated with several pregnancy complications. If expecting mothers experience asthma exacerbations, the risk of the baby being small for gestational age (SGA) and the need for a caesarean section increase [2]. Another interesting pattern is seen in pre-eclampsia; regardless of familial factors and confounders, severe pre-eclampsia is associated with the development of asthma in childhood [3,4].

To assess reproductive ageing in a simple manner, researchers have developed and validated a new reproductive ageing score (RAS). This tool consists of 3 questions and is able to distinguish non-menopausal women from peri-

and postmenopausal women (area under the ROC curve 0.91). Distinguishing postmenopausal women from non-menopausal and perimenopausal women resulted in an area under the ROC curve of 0.85 [5,6].

Despite large individual variations, a clear association exists between reproductive factors and asthma/lung function as well as an interplay between endocrine and metabolic factors. Thus, it is not surprising that maintaining adequate levels of sex hormones has (overall) positive effects on lung function. Many associations between sex, reproduction, and airway function/disease need to be elucidated in the coming years, such as the role of different sex hormones on fertility and respiratory health, the interaction between hormones and hormonal status and metabolism and lifestyle and environment and chemicals/hormonal disruptors [7].

1. Lønnebotn M. Parental overweight and off-spring asthma and lung function. Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark
2. [Robijn AL, et al. ERJ Open Res. 2020 Dec 21;6\(4\):00295-2020.](#)
3. [Byberg KK, et al. Int J Epidemiol. 2022 Jun 13;51\(3\):749-758.](#)
4. Almqvist Malmros C. Maternal asthma, pregnancy-related complications, and asthma in the off-spring. Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.
5. [Triebner K, et al. PLoS One. 2020 Jun 30;15\(6\):e0235478.](#)
6. Triebner K. Reproductive Ageing and the Lungs. Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.
7. Gomez Real F. Research on Gender, Reproduction and the Lungs-Overview and way forward. Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.

# **Palliative Care in Respiratory Diseases**

## **Advance care planning**

**The topical symposium 'Palliative care in respiratory diseases' addressed advance care planning, lessons to be learned by specialists, and integration of palliative care in clinical practice in non-malignant respiratory diseases: challenges and opportunities.**

Instead of more studies on barriers and views on advance care planning, better evidence is needed to decrease barriers in advance care planning, with a clear need for randomised controlled trials addressing advance care planning in patients with respiratory diseases. "These randomised controlled trials should deliver realistic and clinically relevant outcomes, containing simple advance care planning-

conservations. Relevant specialists should be involved," Prof. Mette Asbjørn Neergaard (Aarhus University, Denmark) pointed out. "Furthermore, an international consensus guideline is needed [1]." Pulmonologists can learn valuable lessons from palliative care specialists, said Dr Reeta Piili (Tampere University, Finland). "Palliative care offers realistic opportunities aimed at the reduction of the overall symptom burden, and consequently enhancing the quality of life and increasing the patient-care giver satisfaction [2]. It is important to inquire about the patient's expectations in this critical phase of life and hence, a smooth and clear communication is vital in this aspect of care. Topics to discuss can include defining goals of care and making an appropriate advance care plan [3-5]."

To successfully integrate palliative care in clinical practice in non-malignant respiratory diseases, various recommendations can be made. Firstly, palliative care needs to be accessible (including home visits) as well as flexible (over the disease trajectory including multidisciplinary involvement), and affordable. Regarding the latter aspect: limited resources usually urge the patient to stick to (standard) treatment/conditions, whereas in palliation, the treatment/conditions should suit the patient. Secondly, palliative care should be integrated into routine care: the balance between active disease management and palliation should be regarded as complementary, not opposing. Also, a multidisciplinary holistic assessment of physical, psychological, social, and spiritual needs using both

objective measures and conversations on goals of care and timely advance care planning should be made. Cooperation/integration to specialist palliative care is important, as are the relationships with a very few trusted health care professionals which enable continuity of care. Finally, bereavement and caregiver support should not be forgotten amongst all other items as an integral part of good palliative care [6].

1. Asbjørn Neergaard M. Advance care planning in chronic respiratory diseases – Does it matter? Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.
2. [Maddock M, et al. Lancet. 2017;390:988-1002.](#)
3. [Au DH, et al. Chest. 2012 Mar; 141\(3\):726–735.](#)
4. [Curtis JR, et al. Eur Respir J. 2008;32:796-803.](#)
5. Pilii R. What can pulmonologists learn from palliative care specialists? Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.
6. Marsaa K. Integration of palliative care in clinical practice in non-malignant respiratory diseases-challenges and opportunities. Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.

# Biologics in Asthma

## Severe asthma in the spotlights

According to more recent insights, bronchial epithelium plays a key role in the immunopathogenesis of severe asthma. Within the affected airways, epithelial cells can be triggered by e.g. viruses, allergens, or other irritants, causing a subsequent release of pro-inflammatory cytokines, called alarmins, which subsequently induce innate and adaptive immune responses.

Prof. Lena Uller (Lund University, Sweden) explained that novel biologicals targeting the epithelium cell-derived alarmins, i.e. TSLP, IL-33, and IL-25, can inhibit multiple downstream inflammatory pathways, thus offering a broad anti-inflammatory potential for patients with severe uncontrolled asthma. "In the recently published phase 3 study of tezepelumab, targeting TSLP, clinical effectiveness has been shown across both the type2 as well as the non-type2 asthma endotypes [1]." Although the most pronounced clinical improvements occurred in the type2-subpopulation, further research into anti-TSLP effects also includes patients with type2 low (or non-type) asthma [2,3]. Prof. Uller also pointed out that tezepelumab is the first available anti-alarmin biological (in the USA) and that the currently available biologicals in the Nordic countries (and other Western countries) only target more downstream mechanisms of type2-asthma [4].

1. [Menzies-Gow A, et al. N Engl J Med. 2021;384:1800-1809.](#)
2. [Wechsler ME, et al. Lancet. 2022;10\(7\):650-660.](#)
3. [Menzies-Gow A, et al. Respir Res. 2020 Oct 21;21\(1\):279.](#)
4. Uller L. Asthma immunopathology as the determinant of biologic target therapy in severe asthma. Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.

## Common comorbidities in severe asthma

Patients with severe asthma often harbour comorbidities. Atopic dermatitis and chronic rhinosinusitis with nasal polyps (CRSwNP) are common comorbidities of severe type2 asthma which respond well to treatment with biologicals targeting the underlying inflammation.

Dr Asger Sværild (Bispebjerg Hospital, Denmark) summed up the most common comorbidities in patients with severe asthma. "CRSwNP occurs in 30 to 50% of patients with severe asthma, for which the standard of care consists of intranasal steroids, systemic corticosteroids, and/or sinus surgery. Around 10–30% of patients with severe asthma have concomitant atopic dermatitis. One both FDA- and EMA-approved biological targeting the underlying type2-inflammation is currently available for the treatment of atopic dermatitis (dupilumab), and this may also be used for the treatment of asthma and/or CRSwNP. Importantly, dupilumab allows tapering off systemic corticosteroids in severe asthma (approx. 25–45 % of whom receive systemic corticosteroids maintenance therapy) [1]. A less

common pulmonary comorbidity in severe asthma is allergic bronchopulmonary aspergillosis (ABPA), with an estimated prevalence <5% of patients [2].

1. [Domingo C, et al. J Allergy Clin Immunol Pract. 2022;10:1835-43.](#)
2. Sverrild A. Define the right T2 endotype as the right target for biologics - The role of comorbidities and chronic OCS use. Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.

### Switching biologicals in severe asthma

Switching between biologicals in patients with severe asthma can be considered in case of poor response to treatment (including exacerbations, symptom control, and lung function), side effects, and if patients are pregnant or breastfeeding. With the increasing number of available products, switching between biologicals will become part of common daily clinical practice and so far, combining type2-targeted biologicals seems safe and effective [1]. With increasing insights, more differentiated treatment algorithms and long-term safety and efficacy evaluations will follow in the near future.

Currently, 5 biologicals are available for the treatment of severe asthma: omalizumab (anti-IgE), mepolizumab, reslizumab, and benralizumab (anti-IL-5/5Ra), and dupilumab

(anti-IL-4Ra). Possible switches include switching to another biological with a similar or different mode of action or to combine two different modes of action following case reports showing a good clinical response without safety issues. It is important to check that patients fulfil eligibility criteria for a new biological either on or before the current biological if a switch is considered. Most likely, a wash-out period is not necessary when switching biologicals. It needs to be noted that in earlier days only omalizumab was available; many patients who would have been better candidates for anti-IL-5/5R/4R were treated with omalizumab. Presently, these patients may qualify for switching to another biological (e.g. anti-IL-5/5Ra or anti-IL-4Ra). Regarding benralizumab, this biological induces a more complete depletion of eosinophils than mepolizumab which may offer superior clinical effectiveness in some patients with pronounced eosinophilia. However, this requires close monitoring given the potential downside of eosinophil depletion. Furthermore, physicians need to be aware of possible (often transient) increases in blood eosinophils when patients are switched from anti-IL-5/5R to dupilumab [2].

1. [Ortega G, et al. Ann Allergy Asthma Immunol. 2019 Sep;123\(3\):309-311.](#)
2. Lehtimäki L. Switching biologics, how and when? Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.

# Treatable Traits in Obstructive Airway Diseases

## Targeting treatable traits allows a personalised approach to management of (severe) asthma

The concept of targeting “treatable traits” allows for a more holistic management of complex conditions. More recently, an expert panel proposed several pulmonary and extra-pulmonary treatable traits for (severe) asthma and COPD [1]. Dr Florence Schleich (University of Liège, Belgium) pleaded for a treatable traits approach to be applied more broadly in uncontrolled asthma. To avoid corticosteroids overtreatment and associated side effects, pheno/endotyping should be performed. Type 2/eosinophilic inflammation should be

treated with targeted biologics and prominent airflow obstruction in the absence of inflammation should be adequately addressed with long-acting muscarinic antagonists [LAMA]/long-acting beta2-agonists [LABA], and/or thermoplasty. Lifestyle adjustments should be implemented: e.g. smoking cessation for smokers, weight loss and physical activity for overweight/obese patients.

By identifying treatable traits in individual patients, a personalised medicine approach may be developed which can help improve outcomes for the individual patient [1,2].

In patients with uncontrolled or severe asthma, pulmonary treatable traits include blood and sputum eosinophils, FeNO, allergy, fixed airflow limitation, small airway dysfunction, airway infections, as well as extrapulmonary treatable traits such as chronic rhinosinusitis (CRS) with or without nasal polyps, gastroesophageal reflux disease (GERD), obesity, metabolic and cardiovascular disease, and behavioural traits: especially anxiety and depression [3-5]. Dr Schleich showed results from a small study (n=55) with a duration of 16 weeks in which the feasibility and effects of a multidisciplinary treatment plan targeted at predefined treatable traits was compared with usual care in patients with uncontrolled severe asthma. The primary endpoint was the patient-reported outcome of health-related quality of life. Patients presented with on mean 10.44 traits per individual patient (3.01 pulmonary and 4.85 extrapulmonary

traits, and 2.58 behavioural/risk factors). Researchers showed that an individualised treatment strategy aimed at treatable traits of individual patients was feasible in a clinical setting and significantly improved health-related quality of life as measured by the Asthma Quality of Life Questionnaire (AQLQ) (0.86 units, P<0.001) and asthma control according to the Asthma Control Questionnaire (ACQ) (0.73, P=0.01). Thus, in patients with uncontrolled asthma, identifying and targeting of treatable traits may offer a clinically useful approach to effectively deal with the complexity of the disease in individual patients [6,7].

1. Agusti A, et al. *ERJ*. 2017;50:1701655.
2. McDonald VM, et al. *ERJ*. 2019;53:1802058.
3. Couillard S, et al. *Thorax*. 2022;77:199–202.
4. Duncan EM, et al. *J Clin Invest*. 2018 Mar 1;128(3):997-1009.
5. Gibson PG, et al. *Lancet*. 2017;390(10095):659-668.
6. McDonald VM, et al. *ERJ*. 2020;55:1901509.
7. Schleich F. Asthma. Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.

# Bronchiectasis

## Social distancing led to a reduced number of exacerbations in bronchiectasis patients

Social distancing during the COVID-19 pandemic reduced the exacerbation risk in bronchiectasis patients. However, the daily symptoms commonly experienced by these patients, including chronic cough and sputum production, were not substantially reduced. In addition, patients did not perceive increased anxiousness as a result of social distancing.

The COVID-19 pandemic highly influenced the lives of everyone, and in particular of patients with chronic pulmonary disease. In a nationwide observational study in Denmark, social distancing, which was introduced to curb the spread of COVID-19, substantially reduced the risk of severe exacerbations, intensive care admissions, and all-cause mortality in COPD patients [1]. Social distancing was also shown to decrease hospital admissions for exacerbations due to common respiratory virus infections in this patient population [2]. Despite these beneficial effects of social distancing, the downside was that many patients experienced an increased sense of loneliness due to the imposed measures [3]. If this was the case for COPD patients, what would the effect of the pandemic and its measures be in patients with bronchiectasis?

Vestergård et al. conducted a study in 306 Danish patients

using the Bronchiectasis Health Questionnaire, which consists of 10 questions. The median age of the participants was 68 years and 68% of participants were women. The period covered by the study was divided into 5 segments: December 2020–February 2021, March–May 2021, June–August 2021, September–November 2021, December 2021–February 2022, and March–May 2022.

The mean number of exacerbations declined from December 2020 to February 2021 to rise again in the period between September and November 2021, increasing until May 2022. Differences in the number of antibiotic courses used for the past 12 months – with December 2020–February 2021 being the reference group – showed a higher number of antibiotic courses used in September–November 2021 and December 2021–February 2022 (2.502 and 4.695, respectively). Regarding the daily symptoms (coughing bouts and sputum production), no significant differences have been observed across the various periods. Furthermore, in this study population, no correlation was found between social distancing and the sense of anxiousness [4].

1. Saeed MI, et al. *Epidemiol*. 2022;191(5):874–885.
2. Tan JY, et al. *Thorax*. 2021;76(5):512–513.
3. Kusk KH, et al. *COPD*. 2021;18(5):549–556.
4. Vestergård C. Exacerbations in bronchiectasis during and after COVID-19 lockdown. Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.

# Challenges in Upper Airway Diseases

## Exercise-induced laryngeal obstruction (EILO) is often misdiagnosed

Exercise-induced laryngeal obstruction (EILO) is often mistaken for asthma. In fact, it is a very different condition that needs a specific management strategy mainly focused on patient awareness. Respiratory and speech training may also prove beneficial, but an inhaler should not be part of therapy (unless the patient has concomitant asthma).

Dr Emil Walsted (Bispebjerg Hospital, Denmark) explained that EILO is caused by narrowing of the laryngeal structures (at the level of the vocal cords or in the supraglottic area) which occurs during vigorous exercise. "This phenomenon leads to exertional breathlessness, coughing during or after exercise, a (high-pitch or) wheezing sound on inspiration, and throat tightness. These symptoms resemble those of asthma, hence the frequent misdiagnosis. EILO is most frequently diagnosed in adolescents, with more young women than men presenting with the condition," Dr Walsted added. "As it is often diagnosed as asthma, patients are prescribed asthma medication such as inhalers. These do not alleviate their symptoms and thus, patients are still limited regarding sports and exercise [1]."

Dr Walsted recommended taking a detailed history when patients present with the above-mentioned symptoms. "This includes a detailed description of episodes of dyspnoea, triggers such as exercise, irritants as well as localisation of the complaints (neck or chest), and presentation (symptoms' onset, characteristics, duration, frequency, etc.). Comorbidities should also be considered, such as asthma, dysfunctional breathing, psychiatric disorders (in particular anxiety), gastroesophageal reflux disease (GERD), and cardiac disease."

EILO should be considered when asthma-like respiratory symptoms do not become manifest on objective (lung function) tests, when there is inspiratory stridor or 'snoring' (the patient may be able to present a video or sound recording), if 'exercise-induced asthma' is suspected and asthma-reliever medication has little or no effect, or when sets in at moderate/high exercise intensity. While correct diagnosis is key, reassurance of the patient is equally important. "Experiencing EILO can be

scary," explained Dr Walsted. "When EILO is demonstrated during the medical examination, patients might be able to understand the mechanism and that they will not suffocate, this can help them to accept and deal with EILO." Unnecessary therapy should be stopped, according to Dr Walsted. "Patients often receive asthma medication which they do not need." Treatments for EILO include respiratory training, speech therapy, inspiratory muscle training, and surgery in patients with predominantly supraglottic obstruction who have failed conservative therapy [2,3].

1. [Walsted ES, et al. ERJ Open Research. 2021;7:00195–2021.](#)
2. [Clemm H, et al. Front Pediatr. 2022;10:817003.](#)
3. Walsted E. EILO. Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.

## CRSwNP outlined

Chronic rhinosinusitis with nasal polyps (CRSwNP) and non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (NERD) occur more often than previously assumed. A lack of knowledge as well as limited nasal endoscopy facilities/access are likely explanations for the underdiagnosis of both conditions in the general population.

CRS – with or without nasal polyps – is defined as the presence of two or more symptoms lasting for over 12 weeks, i.e. obstruction OR drainage +/- loss of smell, facial pain/pressure AND endoscopic polyps/mucus/oedema OR mucosal change on CT sinus scans [1]. The estimated prevalence of chronic rhinosinusitis without nasal polyps (CRSsNP) is 90/1000 individuals, for asthma: 100/1000 and for CRSwNP: >10/1000; NERD has a prevalence of <10/1000 . It needs to be noted that accurate diagnostics are often lacking [1,2]. "Therefore, the true number may be higher," Dr Sanna Toppila-Salmi (University of Helsinki, Finland) explained. "CRSwNP, NERD, and CRSsNP are chronic recurrent conditions and in patients with concomitant lower airway involvement all associate with uncontrolled disease and, hence, impose a substantial burden on health care resources," Dr Toppila-Salmi explained [2–5].

1. [Fokkens WJ, et al. Rhinology. 2020 Apr 1;58\(2\):82-111.](#)
2. [Toppila-Salmi S, et al. BMC Pulmon Med. 2021;214\(21\).](#)
3. [Penttilä E, et al. Asian Pac J Allergy Immunol. 2021 Sep 5. doi: 10.12932/AP-310321-1102.](#)
4. [Lilja M, et al. Allergy Rhinol \(Providence\). 2021 Apr 26;12:21526567211003844.](#)
5. Toppila-Salmi S. Prevalence and predictive factors for CRSwNP and ASA-intolerance. Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.

## The role of biologics in CRSwNP

Currently, 4 biologics targeting type2 inflammatory mechanisms have been approved for the treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) and available in many Western countries, i.e. omalizumab, mepolizumab, benralizumab, and dupilumab. Their future positioning and use as non-surgical treatment for CRSwNP will heavily rely on their cost-effectiveness. "For a more accurate assessment of cost-effectiveness, both direct and indirect costs should be included in health-economic evaluations (including risks and side effects of current treatment options: corticosteroids and surgery) as well as concurrently treated comorbidities (e.g. asthma)," Prof. Lars-Olaf Cardell (Karolinska Institute, Sweden) explained.

A review by Patel et al., which involved omalizumab (n=12), mepolizumab (n=42), benralizumab (n=44), reslizumab (n=6), and dupilumab (n=61), demonstrated that type2-targeting biologics can reduce the use of medication (corticosteroids/antibiotics) for acute exacerbations of chronic rhinosinusitis (AECRS) in patients with asthma and CRSwNP (70% of patients) or chronic rhinosinusitis without nasal polyps (CRSsNP) (30% of patients). The estimated yearly rate for the use of systemic corticosteroids for AECRS decreased from 1.69 (95% CI 1.42–2.02) to 0.68 (95% CI 0.53–0.88), which translates into a reduction of 60% ( $P<0.001$ ). The yearly rate for antibiotic use for AECRS following implementation of biologics decreased from 1.34 (95% CI 1.12–1.59) to 0.68 (95% CI 0.52–0.88); i.e. a 49% reduction ( $P<0.001$ ). These findings suggest that these biologics may offer an effective therapeutic option for patients with type2 disease with frequent AECRS [1]. In this respect, Prof. Cardell also referred to the EPOS 2020 treatment scheme for diffuse/bilateral type2 CRS in which type2 inflammation targeting biologics have been allocated as add-on treatment [2].

More explicit guidance on the use of biologics in CRSwNP has been recently defined by expert panels [2,3]. "In these patients, specific criteria are required and should be at least 3 of the following: evidence of type2 inflammation, the need for systemic corticosteroids or a contraindication to systemic steroids, significantly impaired quality of life, loss of smell, or a diagnosis of comorbid asthma." Response to biological treatment in CRSwNP is defined by evaluation of 5 outcome criteria (i.e. reduced nasal polyp size, reduced need for systemic

corticosteroids, improved quality of life, improved sense of smell, and reduced impact of co-morbidities). If a patient fits all 5 criteria, this is considered an excellent response; 3-4 criteria is moderate response, 1-2 criteria is defined as poor response, and 0 criteria equals no response [2–4].

1. Patel G, et al. *Allergy Asthma Proc.* 2021;42:417-424.
2. Fokkens WJ, et al. *Rhinology.* 2020 Apr 1;58(2):82-111.
3. Hellings PW, et al. *Rhinology.* 2020 Dec 1;58(6):618-622.
4. Cardell L-O. CRSwNP and biologic treatment. Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark. Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.

## The ULANC Group: working together in CRSwNP/asthma

Prof. Vibeke Backer (Rigshospitalet/Copenhagen University, Denmark) addressed collaboration opportunities in the field of global airway disease and pointed out the work of the ULANC Group. This European consortium – in which pulmonologists and ear-nose-throat (ENT) specialists are represented – aims to optimise management of airway disease in the broadest sense of the word for the benefit of both patients and healthcare providers.

"Objectives of the ULANC group are 4-fold," Prof. Backer explained, "firstly, to build a consensus of expert opinion on practical ways to identify patients needing a global airways approach; secondly, to enhance cross-specialty collaboration and referral. Thirdly, to widen the knowledge to support the diagnosis and management of patients with CRSwNP and asthma, and finally, to suggest ways to integrate these suggestions within existing care pathways, and supplement existing guidelines." The underlying hypotheses which the ULANC Group thoroughly explored, feature the idea that improving global airways knowledge among specialists will facilitate timely and adequate treatment, and that systematic assessment of both the upper and lower airways increases the likelihood of discovering global airways disease [1]. "Also, collaboration between upper and lower airway physicians will improve treatment and disease control in patients with global airways disease," Prof. Backer pointed out. "Collaboration across all treating physicians is vital. Hopefully, ULANC stimulates reflection, prompts cross-functional discussion, and renews the focus on improving care for patients with global airways disease."

1. Backer V. Collaboration opportunities in global airway diseases. Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.

# Interstitial Lung Diseases (ILD)

## No oral corticosteroids before a confirmed diagnosis of ILD

Data from a Finnish study assessing the pre-operative risk factors for transbronchial lung cryobiopsy (TBLC) complications in patients with interstitial lung disease (ILD) showed that patients should refrain from oral corticosteroids before a confirmed diagnosis. Also, severe cough should be considered before TBLC is considered.

Not much is known about the pre-operative risk factors associated with TBLC complications. Therefore, a study evaluating the pre-operative risk factors of clinically relevant complications of TBLC in patients with ILD was initiated [1]. Apart from complication rates, the study also aimed to describe the Finnish TBLC procedure and to report the diagnostic yield of the procedure.

Between January 2015 and December 2019, 100 patients (60 men) with a median age of 66.1 years were recruited from two Finnish hospitals (Kuopio University Hospital and Tampere University Hospital). The inclusion criteria consisted of a referral for a suspected ILD and a requirement of a histological investigation to confirm the diagnosis. Patients with a BMI >30 kg/m<sup>2</sup>, a history of an acute myocardial infarction or another acute or untreated cardiovascular disease, or active tuberculosis were excluded from the study, as were patients who were on anticoagulation treatment that could not be withheld, and those with abnormal bleeding history or abnormal clotting parameters. High-resolution CT (HRCT) scans and Leicester Cough Questionnaire were obtained before the TBLC; current medication use (including oral corticosteroid use within 30 days before the TBLC) was recorded. TBLC and bronchoalveolar lavage (BAL) were performed in an operating room in an outpatient setting and the obtained samples were subsequently analysed. Following the procedures, of the 100 participants, 68 had no or only mild complications, whereas 32 experienced clinically significant complications (i.e. clinically significant bleeding and/or pneumothorax, ICU admission or death within 90 days). Two patients died within 90 days of the procedures (suspected acute exacerbation of ILD, acute cardiac arrest); none of the patients died within 30 days of the procedures.

The diagnoses were concluded in a multidisciplinary meeting. The diagnostic yield was 87% and interobserver agreement on honeycombing was  $\kappa=0.66$ , on emphysema  $\kappa=0.70$ , and on traction bronchiectasis  $\kappa=0.44$ . Regarding (post-operative) complications: a history of severe cough was associated with pneumothorax; also oral corticosteroid use within 30 days of the TBLC seemed to associate with complications. According to the researchers, limitations of the study include a rather small population and the use of the backward stepwise elimination method which can be considered hypothesis-generating. However, the covariates in this model were carefully selected before the analysis to increase the reliability of the model and to reduce noise variables [1,2].

1. [Mononen M. et al. Resp Med. 2022;200:106922.](#)
2. Mononen M. Risk factors associated with clinically significant complications in transbronchial lung cryobiopsy in ILD patients. Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.

## Rheumatoid arthritis-associated ILD

Rheumatoid arthritis (RA)-associated interstitial lung disease (ILD) is a largely under-diagnosed, serious manifestation of RA which accounts for a high mortality rate in affected patients. In recent years, more insight has been obtained regarding triggers, risk factors, and underlying mechanisms enabling more effective treatment of the condition.

Dr Phuong Phuong Diep (Oslo University Hospital, Norway) explained that data on the prevalence of ILD in RA (RA-ILD) widely vary – partly attributable to underdiagnosis. The lifetime risk of developing RA-ILD for RA patients is 3.6% and it appears that the MUC5B promoter variant is a strong risk factor. Patients with RA harbouring MUC5B have an increased lifetime risk of developing ILD of 16.8% (95% CI 13.1–20.2) versus 6.1% (95% CI 5.0–7.2) for those without MUC5B. The difference between these risks starts to become evident when patients reach the age of 65 years, with men being more at risk than women [1]. Based on high-resolution computed tomography (HRCT) findings in 1,138 patients from 12 studies, several subtypes of RA-ILD can be distinguished. These include: usual interstitial pneumonia (UIP; affecting 43% of RA-ILD patients), non-specific interstitial pneumonia (NSIP; affecting 17%), organising pneumonia (occurring in

2%), and other (seen in 6% of RA-ILD patients) [2]. Based on 7 histopathological studies (n=161), the proportion of affected patients shows a considerable variability: UIP 35%, NSIP 34%, organising pneumonia 18%, diffuse alveolar damage 2%, and unclassifiable disease 3% [3]. Patients with RA-ILD have a significantly higher morbidity and mortality compared with RA patients without ILD [4]. Based on radiological patterns, Yunt et al. showed that patients with definite or possible UIP usually have worse survival rates compared with patients with NSIP [5]. This study comprised 158 patients of whom 63% had definite UIP, 15% had possible UIP, and 22% had NSIP [5]. No survival difference was seen between patients with definite and possible UIP [5]. Dr Diep mentioned the risk factors for progressive pulmonary fibrosis (including related mortality): i.e. older age, male sex, honeycombing or UIP pattern on HRCT, reduced forced vital capacity, and reduced diffusing capacity [6,7].

1. Palomäki A, et al. Ann Rheum Dis. 2021 Dec;80(12):1530-1536.
2. Bendstrup E, et al. J Clin Med. 2019 Nov 21;8(12):2038.
3. Kim E, et al. Chest. 2009 Nov;136(5):1397-1405.
4. Hyldgaard C, et al. Ann Rheum Dis. 2017 Oct;76(10):1700-1706.
5. Yunt ZX, et al. Respir Med. 2017 May;126:100-104.
6. Wijzenbeek M, et al. N Engl J Med. 2020 Sep 3;383(10):958-968 2020.
7. Diep PP. Disease characteristics and risk of progression and mortality in rheumatoid arthritis-associated ILD. Nordic Lung Congress 2022, 01–03 Jun, Copenhagen, Denmark.

## Update on treatment of fibrotic ILD

The definition of progressive fibrotic-interstitial lung disease (PF-ILD) has been replaced by the more adequate definition of progressive pulmonary fibrosis (PPF). Antifibrotic therapy has shown to benefit patients with idiopathic pulmonary fibrosis (IPF)/PPF; and with an increasing number of new treatment modalities currently in the pipeline, outcomes for patients will – hopefully – continue to improve in the future.

The ATS/ERS/JRS/ALAT Clinical Practice Guidelines have proposed a new definition of PPF which requires at least two of three criteria within the past year without an alternative explanation in a patient with an ILD other than IPF (see Table) [1].

"This new definition ticks all the boxes," according to Dr Elisabeth Bendstrup (Aarhus University Hospital, Denmark). "First of all, this definition takes into account that disease progression is the result of PPF beyond the interstitial space in lung parenchyma. Secondly, disease progression causes a clinical course which is very similar to IPF. Moreover, the definition of PPF is simple and compatible with the broadly used term of pulmonary fibrosis among both clinicians and patients [1]."

Table: New definition of PPF according to ATS/ERS/JRS/ALAT Clinical Practice Guidelines [1]

In a patient with ILD of known or unknown aetiology other than IPF who has radiological evidence of pulmonary fibrosis, PPF is defined as **at least two of the following three criteria** occurring **within the past year** with no alternative explanation\*:

- 1. Worsening of respiratory symptoms**
- 2. Physiological evidence of disease progression (either of the following):**
  - a) Absolute decline in forced vital capacity >5% predicted within 1 year of follow-up
  - b) Absolute decline in diffusing capacity for carbon monoxide (corrected for Hb) >10% predicted within 1 year of follow-up
- 3. Radiological evidence of disease progression (one or more of the following):**
  - a) Increased extent or severity of traction bronchiectasis and bronchiolectasis
  - b) New ground-glass opacity with traction bronchiectasis
  - c) New fine reticulation
  - d) Increased extent or increased coarseness of reticular abnormality
  - e) New or increased honeycombing
  - f) Increased lobar volume loss

\*Although it is critical to exclude alternative factors of worsening in patients with suspected RA-ILD progression, this particularly applies to patients with worsening of respiratory symptoms and/or decline in diffusing capacity for carbon monoxide given the lower specificity of these features for PPF compared with forced vital capacity and chest computed tomography.

"Management of ILD has various aspects," Dr Bendstrup outlined. "It ranges from an 'expectative approach' to anti-fibrotic or immunomodulatory treatment and supportive or palliative care, as well as the treatment of comorbidities and lung transplantation." Increasing insights into the underlying mechanisms of IPF have driven the development of more effective treatment modalities. However, although nintedanib and pirfenidone significantly reduce lung function decline over time, IPF still cannot be cured, underscoring the ongoing unmet need for effective treatment of this disease [2]. "Current guidelines offer a conditional recommendation for the treatment of IPF with both drugs, as well as a conditional recommendation for the treatment of PPF with nintedanib in patients who have failed standard management for fibrotic ILD. Furthermore, the guidelines also advocate further research on effectiveness of pirfenidone in PPF [1]." With regard to new pharmacological treatment modalities, Dr Bendstrup mentioned several classes of candidate drugs currently under investigation aiming at different molecular targets in IPF and/or fibrotic ILD, e.g. endothelin receptor antagonists, angiogenesis inhibitors, cytokine/kinase inhibitors, antioxidants, vasodilators, and anti-inflammatory/immunosuppressive agents [3].

1. Raghu G, et al. Adv Ther. 2022;205(9):e18-e47.
2. Somogyi V, et al. Eur Respir Rev. 2019 Sep 4;28(153):190021.
3. Bendstrup E. Treatment of fibrotic ILD; where are we now and where are we going? Nordic Lung Congress 2022, 01–03 Jun, Copenhagen, Denmark.

## Thoracic ultrasound: a new diagnostic imaging tool in RA-ILD?

The AURORA study aims to determine whether thoracic ultrasound can be used compared with the current reference standard, high-resolution computed tomography (HRCT), to accurately diagnose interstitial lung disease (ILD) in rheumatoid arthritis (RA) patients with respiratory symptoms.

Dr Bjørk Sofíudóttir (University of South Denmark, Denmark) pointed out that point-of-care thoracic ultrasound may offer an interesting option to assess ILD as the current method to diagnose ILD is HRCT (in combination with lung physiological parameters). Dr Sofíudóttir summed up the potential advantages of thoracic ultrasound imaging including the fact that it is radiation-free, minimally time-consuming, as well as cheap and easily applicable during out-patient consultation which allows for feasible implementation and direct read-outs. She also mentioned that there is a strong tradition in rheumatology when it comes to using ultrasound. Potential drawbacks include the highly examiner-dependent nature of the method and limited visualisation of the intra-thoracic structures and hence, more central pathologies may

be missed. Furthermore, the method precludes detection of common chronic airway diseases such as COPD or asthma.

The primary objective of the AURORA study ([NCT05396469](#)) is to assess whether thoracic ultrasound can reliably detect RA-ILD and can serve as a screening tool in the outpatient setting. Using a 14-zone protocol for ILD in RA patients with respiratory symptoms, this study compares diagnostic accuracy of thoracic ultrasound with chest HRCT as the reference standard. Additional study objectives include the assessment of the diagnostic potential of blood biomarkers (surfactant protein-D and microfibrillar-associated protein 4) in the detection of ILD in this study population.

Researchers aim to include 80 RA patients aged  $\geq 18$  years, diagnosed with RA (according to the 2010 ACR criteria for RA) with respiratory symptoms indicative of RA-ILD (i.e. experiencing at least one of the following symptoms: unexplained dyspnoea, unexplained cough, and/or residual pneumonia, or a chest X-ray showing interstitial abnormalities of the lung). The study has just been initiated and it aims to be completed in January 2024 [1].

1. Sofíudóttir B, et al. Detection of rheumatoid arthritis-associated ILD by ultrasound of the lung. Nordic Lung Congress 2022, 01–03 Jun, Copenhagen, Denmark.

# Respiratory Failure

## The role of CPAP and HFNC in COVID-19

Depending on the severity of COVID-19-induced respiratory disease, different treatment modalities can be applied regarding the use of continuously delivered continuous positive airway pressure (cCPAP) and high flow nasal cannula therapy (HFNC).

By using cCPAP, an airflow is delivered to the airways by establishing a positive pressure which is maintained through the respiratory cycle. HFNC consists of warm, humidified oxygen which is being delivered in a high flow by a nasal cannula. In patients with mild to moderate COVID-19, the target is acceptable SpO<sub>2</sub> obtainable with  $\leq 5$  L O<sub>2</sub>/min (FiO<sub>2</sub> 0.4) oxygen therapy delivered by bi-nasal canula or air-entrainment mask. For patients with severe COVID-19, the target is acceptable SpO<sub>2</sub> obtainable with 6–15 L O<sub>2</sub>/min (FiO<sub>2</sub> 0.4–0.6), and the ICU personnel should be advised about the patient's condition.

cCPAP is not contraindicated, whereas intermittent mandatory ventilation (IMV) is not indicated. The initial flow of HFNC is 45 L/min and additional oxygen may be administered to meet the target SpO<sub>2</sub>. In the case of critical COVID-19, the target is acceptable SpO<sub>2</sub> obtainable with  $\geq 15$  L O<sub>2</sub>/min (FiO<sub>2</sub> >0.6); depending on the contraindications to IMV, patients may be intubated, or CPAP and HFNC can be continued at higher flow/higher FiO<sub>2</sub> at intermediate or intensive care unit. Furthermore, bilevel (Bi)PAP at 10/20 cm H<sub>2</sub>O may be used, with the effect evaluated after 2 hours [1].

1. Bertelsen BB. CPAP and HFNC for COVID-19 and hypoxic respiratory failure. Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.

## Hypoxemia and dyspnoea

The relationship between hypoxemia and dyspnoea (which is a sensation of uncomfortable, difficult or laboured breathing, or the experience of breathing discomfort) can be

**quite complex [1]. Hypoxemia per se does not necessarily elicit dyspnoea in healthy condition, despite an increased ventilatory drive and an increased minute ventilation.**

The maximal sustainable ventilation for an average adult varies according to the time frame. The maximal voluntary ventilation (MVV) for 15 seconds is 130 L/min, and 75% of MVV can be maintained for 15 minutes at 100 L/min, whilst 50% of MVV can be maintained for many hours at 65 L/min. Furthermore, 30 L/min can be maintained for an almost indefinite period of time, which does not necessarily elicit dyspnoea. The ventilatory response to hypoxemia can be blunted by a number of factors such as age and diabetes, both imposing a 50% reduction in

ventilatory response to hypoxemia. Similarly, fever causes a right shift in the dissociation curve which results in a lower SaO<sub>2</sub> with preserved PaO<sub>2</sub> (no chemoreceptor response to the low SaO<sub>2</sub>) [2]. Hypoxemia and concomitant hypocapnia favour maintaining an acceptable SaO<sub>2</sub> despite low PaO<sub>2</sub>. The most common reasons for dyspnoea include hypercapnia, increased work of breathing (reduced compliance), and neuromechanical dissociation. In fact, the aetiology of dyspnoea is often multifactorial and hypoxemia can be a contributing factor [3].

1. [Parshall MB, et al. Am J Respir Crit Care Med. 2012 Feb 15;185\(4\):435-52.](#)
2. [Tobin MJ, et al. Am J Respir Crit Care Med. 2020 Jun 1;201\(11\):1319-1320.](#)
3. Frausing Hansen E. Dyspnea and hypoxemia - what is the correlation (including silent hypoxemia). Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.

# Lung Cancer Screening in the Nordics

## Lung cancer screening in Denmark

**Systematic lung cancer screening of high-risk groups offers great potential for reducing the disease burden and mortality of lung cancer. In January 2021, a proposal was submitted to the Danish National Board of Health to introduce this screening modality in Denmark.**

The proposal recommends systematic annual low-dose CT screening of high-risk groups with integrated smoking cessation intervention aimed at individuals aged 55–74 years, who are current or former smokers (>10 cigarettes/day for 30 years or >15 cigarettes/day for 25 years). “Consequently, more lung cancers can be detected in early stages of the disease which helps to decrease the numbers of late-stage cancer with a subsequent reduction in both disease-specific and overall mortality,” Dr Zaigham Saghir (University of Copenhagen, Denmark) explained. However, screening may also induce harmful effects such as false-positive findings as well as overdiagnosis. The Dutch-Belgian NELSON trial showed an excess-incidence overdiagnosis rate of 19.7%. When the follow-up was extended to 11 years post-randomisation, the excess-incidence overdiagnosis dropped to 8.9% [1]. “A lead time of 9–12 years of CT screening should be taken into account,” Dr Saghir said. He also pointed out that psychosocial consequences of CT screening have been extensively studied. “Although some potentially negative short-term effects have been observed, there were hardly any long-term effects

detected.” Another consequence of systematic lung cancer screening may be the considerable number of incidental findings (either thoracic or extra-thoracic). Finally, the radiation dose should always be considered. However, the population that qualifies for annual screening is a high-risk population. Taking into account that screening carries a 0.075% increased lifetime risk of dying from cancer, the benefits of screening clearly outweigh this potential disadvantage [2].

Currently, the Danish National Board of Health and Ministry of Health are considering the proposal and possible funding of a Health Technology Assessment pilot. This pilot would serve as the first step prior to national implementation. “Important in this respect is that we should focus on screening intervals, the use of risk models including biomarkers, recruitment of hard-to-reach groups (socio-economic inequality), and the assessment of the resource burden. It is key to start small and upscale fast,” Dr Saghir emphasised [3].

1. [De Koning HH, et al. N Eng J Med. 2020;382:503–513.](#)
2. [Oudkerk M, et al. Nat Rev Clin Oncol. 2021;18\(3\):135–151.](#)
3. Saghir Z. The planning of lung cancer screening in Denmark. Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.

## Points of interest for radiologists screening for lung cancer

**When screening for lung cancer, the type and position of the nodule offer important information, as do the size of the nodule including volume, benign or malignant**

**features, and its growth pattern. Nevertheless, nodules may be missed for which there are many reasons.**

Dr Michael Brun Andersen (Copenhagen University Hospital, Denmark) pointed out that assessment of CT scans is highly dependent on the observer. "Obviously: the more observers (radiologists), the higher the variability. Sensitivity in detecting 5 mm indeterminate pulmonary nodules at 1 mm slices ranges from 30 to 73%. Double readings, computer-aided diagnosis programs, minimisation of disturbance

and subspecialty all increase the quality and focus of the radiologist," Dr Andersen explained [1]. He briefly discussed the Lung Imaging Reporting and Data System (Lung-RADS) which is a classification system aimed at standardising follow-up and management decisions in low-dose CT screening exams for lung cancer [2,3].

1. [Rubin GD et al. Radiology. 2015 Jan;274\(1\):276-86.](#)
2. [ACR Lung-RADS version 1.1](#)
3. Andersen MB. Lung cancer screening from radiologist's perspective. Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.

# E-cigarettes

## E-cigarettes impose detrimental effects on health

The use of e-cigarettes – which contain harmful substances – is more common in the younger population. Older users are most likely tobacco smokers and, in this population, e-cigarette use is not associated with successful smoking cessation. Furthermore, the use of e-cigarettes is linked to respiratory symptoms and other detrimental health effects.

Dr Linnea Hedman (Umeå University, Sweden) discussed the new tobacco and nicotine products that have become widely available over recent years. She pointed out that the e-liquid used in e-cigarettes consists of various components such as propylene glycol, glycerine, nicotine, flavour components, and other additives, such as preservatives. The aerosol content may include formaldehyde, acetaldehyde, acrolein, diacetyl, and various metals, all of which impose detrimental (often carcinogenic) health effects in users [1–5]. "The use of e-cigarettes has a generally low prevalence in Sweden," Dr Hedman said. "It is most common in individuals aged 16 to 44 years [6]. These products are also openly aimed at children and young individuals as they come in colourful containers and attractive flavours such as fruit, mint, and candy." Although the use of e-cigarettes is often presented as a method to support smoking cessation of 'ordinary' tobacco products and may be perceived as less harmful, recent meta-analyses show an association between e-cigarette use and asthma and COPD diagnosis: for asthma, the pooled

adjusted odds ratio was 1.39 (95% CI 1.28–1.51) and for COPD 1.49 (95% CI 1.36–1.65) [7,8].

1. [Goniewicz ML et al. Tob Control. 2014 Mar;23\(2\):133-139.](#)
2. [Williams M et al. PLoS One. 2013;8\(3\):e57987.](#)
3. [Pankow JF et al. PLoS One. 2017 Mar 8;12\(3\):e0173055.](#)
4. [Eshragain E et al. Tob Prev Cessation. 2021;7\(February\):10.](#)
5. [Taylor A et al. Drug Test Anal. 2021 Feb;13\(2\):242-260.](#)
6. Public Health Agency Sweden.
7. [Wills TA et al. Eur Respir J. 2021;57:1901815.](#)
8. Hedman L. Who are the e-cigarette users and what are the pulmonary effects of e-cigarette vaping? Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.

## Effects of passive vaping in COPD patients

The results from a Danish study point out that exposure to passive vaping from e-cigarettes may induce an acute systemic and airway inflammatory response in COPD patients. This calls for more research to elucidate the impact of passive vaping.

Prof. Torben Sigsgaard (Aarhus University, Denmark) presented the outcomes of a study which aimed to examine acute health effects of passive exposure to aerosol generated by e-cigarettes in individuals with COPD under controlled conditions. The hypothesis was that exposure to passive vaping is associated with inflammation and self-reported respiratory symptoms. This study had a randomised, double-blind, controlled, cross-over design in which participants were exposed to either passive vaping or clean air for 4 hours with a wash-out period of 14 days, followed by a second exposure (4 hours) to either clean air or passive vaping. A total of 16 COPD patients were included of whom 6 women

and 10 men. All were former smokers with a mean age of 67.6 years. The study had some limitations, Prof. Sigsgaard explained: "In the first place, a low power due to the relatively small sample size, but also the vapers used in the study, which resulted in an overall low exposure to the aerosols with a substantial variability and the fact that it was not a real-life simulation, including absence of mixtures of substances with synergistic effects, and repeated exposures." Prof. Sigsgaard emphasised that effective public policies posing restrictive measures on the use of e-cigarettes are very much needed. "Regulatory measures should include prohibiting the use of e-cigarettes at least to the extent that conventional cigarettes are prohibited: hence not allowed in public places. Also, the use of e-cigarettes should be avoided in close proximity to vulnerable populations [1]."

1. Sigsgaard T. Passive vaping in COPD patients. Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.

## Vaping amongst adolescents: an alarming trend

**According to Finnish research, there is a strong need to strengthen preventive policies on e-cigarettes to prevent adolescents to fall prey to the tobacco epidemic. This includes comprehensive and strict e-cigarette regulations, in line with all tobacco regulations.**

E-cigarettes have become increasingly popular, especially among youngsters. "This is definitely a worrisome observation," stated Dr Anu Linnansaari (University of Tampere, Finland). "Exposure to nicotine in adolescence can induce significant long-term deficits in the developing brain with an increased risk of impulsive behaviour, decreased attention, cognitive

impairment, and a negative emotional state. Also, this may impose 3 times increased risk of smoking initiation."

Dr Linnansaari investigated the use and social context of vaping among Danish, Finnish, and Norwegian adolescents aged 15–20 years. Four separate themes were addressed to gain more insights into this practice. The first theme was youth vaping as a social practice, which demonstrated that vaping among youngsters stood as an inherently social practice that was commonly interlinked with experimental and occasional use patterns. Investigating the second theme, appeal of low harm to health, showed that e-cigarettes were perceived as rather harmless, or at least less harmful than ordinary cigarettes and snuff. Occasional use and the so-called 'innocent' flavour additives added to this perception. From the appeal of product innovation, the third theme, it was made clear that innovative features facilitated new and playful use practices, again with the novelty and appeal of flavours playing a key role. Finally, the fourth theme, youths' digital lives offering new arenas for e-cigarettes, demonstrated that the use of e-cigarettes by youngsters was integrated into their digital lives. This is mainly encouraged by various social media channels, digital promotion, and availability as well as self-presentation of youngsters on digital platforms. Dr Linnansaari concluded that "considering youth culture, the innovative characteristics of the products, and the global phenomenon of the tobacco epidemic, it is vital to ensure effective tobacco prevention (including awareness) and healthcare practices such as cessation support [1]."

1. Linnansaari A. E-cigarette use in Nordic adolescents: trends, youth's own reflections and cross-country differences in legislation. Results from the NADNIC study. Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.

# Tuberculosis and Sarcoidosis

## Sarcoidosis guidelines update

**Sarcoidosis continues to be a challenging disease for which the indication for treatment is still unclear. The measurements of treatment response are too heterogeneous and single endpoints may not be reliable (enough). There are still many questions to be answered, and for the time being, international guidelines aim to fill in the gaps as much as possible/clinically feasible.**

The ATS guidelines (last update in 2020) state that the diagnosis of sarcoidosis is not standardised, but based on 3 major criteria: a compatible clinical presentation, the histological finding of non-necrotising granulomatous inflammation in  $\geq 1$  tissue samples, and the exclusion of alternative causes of granulomatous disease [1]. Due to a lack of substantial evidence, the guidelines currently offer only 1 strong recommendation (i.e. for baseline serum calcium

testing), whilst 13 conditional recommendations are made [1]. The ERS guidelines (2021) present 12 recommendations for 7 PICOs (patients, intervention, comparison, and outcomes) and state that the major reasons for treating sarcoidosis are to lower morbidity and mortality risk and/or to improve the quality of life [2,3].

1. [Crouser ED, et al. Am J Respir Crit Care Med. 2020 Apr 15;201\(8\):e26-e51.](#)
2. [Baughman RP, et al. Eur Respir J. 2021 Dec 16;58\(6\):2004079.](#)
3. Bock K. Essentials from the European Respiratory Society (2021) and the American Thoracic Society (2020) clinical practice guidelines on the diagnosis and treatment of sarcoidosis. Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.

## New antigens in sarcoidosis

In search of an effective treatment strategy for sarcoidosis, candidate antigens, *Aspergillus Nidulans*, and vimentin (a T-cell autoantigen), have been recently identified. Given the involvement of these antigens in the underlying mechanisms of sarcoidosis, functional analyses are currently ongoing to assess whether targeting these components could offer future therapeutic options.

"The incidence of sarcoidosis in Sweden is 12/100,000 a year with 1,200 new cases a year," explained Prof. Johan Grünewald (Karolinska Institute, Sweden). "Men show an early peak between the age of 30 to 40 years, whereas in women the peak occurs between the age of 50 to 60 years (sex hormones may play a role)." Although the origin of the disease is still largely unknown, it seems to develop as a result of a genetic predisposition in combination with external triggers (viruses, bacteria, etc.). Treatment options are limited, imposing a considerable unmet need. According to Prof. Grünewald, current research is aiming to identify specific sarcoidosis-antigens: i.e. to characterise the function of previously identified antigens and identify new biomarkers (e.g. IGRA). There are many possible antigens in sarcoidosis such as bacteria which prompt research. Recently, vimentin – a cytoskeletal protein – has been suggested to act as a T-cell auto-antigen, as it was identified in human leukocyte antigen molecules of sarcoidosis patients. Another candidate is *Aspergillus Nidulans* which is found in immunosuppressed individuals and is capable of triggering T-cells in sarcoidosis patients [1,2].

1. [Greaves SA, et al. J Exp Med. 2021 Oct 4;218\(10\).](#)
2. Grünewald J. Latest discoveries in the mechanisms of sarcoidosis. Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.

## Fatigue syndrome in sarcoidosis

A new approach to managing sarcoidosis-associated fatigue aims to facilitate increased levels of functioning,

by shifting from targeting just the symptoms to targeting new coping strategies [1].

Sarcoidosis-associated fatigue is very common; it is reported in up to 90% of patients and negatively affects quality of life [2,3]. Even after remission of active disease, fatigue may persist [4]. Fatigue can be assessed by using patient-reported outcome measures (PROMS) as recommended by the guidelines, but it is important to rule out other causes of fatigue before sarcoidosis-associated fatigue can be diagnosed [5]. For patients, key implications are reassurance and to improve acceptance as well as mastery of their fatigue. In this context, exercise training is recommended for sarcoidosis patients, focusing on low-to-moderate intensity exercise as high intensity may worsen patient's fatigue [6,7]. The ERS Guidelines also offer some advice and recommendations on managing fatigue in sarcoidosis patients [8,9].

1. [Kvale D, et al. JMIR Res Protoc. 2021 Oct 7;10\(10\):e32216.](#)
2. [De Kleijn WPE, et al. Curr Opin Pulm Med. 2009;15:499-506.](#)
3. [Voortman M, et al. Lung. 2019;197:155-161.](#)
4. [Korenromp IHE, et al. Chest. 2011;140\(2\):441-447.](#)
5. [Thunold RF, et al. Sarcoidosis Vasc Diffuse Lung Dis. 2017;34\(1\):2-17.2017.](#)
6. [Strookappe B, et al. Lung. 2015 Oct;193\(5\):701-8.](#)
7. [Marcellis RGJ, et al. Sarcoidosis Vasc Diffuse Lung Dis. 2015 Jun 22;32\(1\):53-62.](#)
8. [Baughman RP, et al. Eur Respir J. 2021 Dec 16;58\(6\):2004079.](#)
9. Grongstad A. Fatigue syndrome in sarcoidosis. Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.

## Detection of latent TB infection key to preventing the spread of the disease

As the incidence of tuberculosis (TB) in the Nordic countries is low, the knowledge of the disease in this region of the world is waning both amongst professionals as well as in the general public. Nevertheless, latent TB poses a serious health threat which requires adequate management.

Prof. Tuula Vasankari (University of Turku, Finland) delivered an update on latent TB, which can be defined as a persistent immune response to stimulation by *M. tuberculosis* antigens with no evidence of clinically active TB disease. "TB is very common, as approximately a quarter of the world's population is infected with TB," Prof. Vasankari stated. "It is often hard to identify TB-infected individuals - especially since in latent TB infection there is usually a lack of clinical signs and symptoms." Nevertheless, identification of individuals with latent TB infection is an important goal in TB elimination. "Treatment of latent TB infection can curb the development of active disease and can thus prevent further spread of TB [1]."

Targeted testing for TB can be used as a TB control strategy to identify and treat individuals at high risk for latent TB infection, and those at high risk for developing TB disease once infected with *M. tuberculosis*. "Once you decide to apply targeted testing, then you decide to treat," Prof. Vasankari said. Latent TB infection can be diagnosed by a Mantoux tuberculin skin test and interferon-gamma release assay (IGRA) blood test; both tests assess an individual's immune reactivity to *M. tuberculosis*. "TB testing activities should only be performed when there is a plan for care or follow-up. This means that healthcare workers should only test those individuals who are at high risk for developing TB disease; people not at high risk should generally not be tested." Eligible populations for targeted testing include pregnant immigrant women from highly endemic areas who have a positive IGRA test within 2 years upon arrival in a Nordic country, and/or who have other diseases, and/or pulmonary X-ray indicative of previous TB, and/or who are newly exposed to infectious TB. Patients planned for immunosuppressive treatment or organ transplantation who have a positive purified protein derivative or IGRA test, and/or pulmonary X-ray indicative of previous TB, and/or a suspect medical history or previous exposure also qualify for testing. The same applies for patients with HIV and a positive purified protein derivative or IGRA test.

Prof. Vasankari emphasised that anyone with TB symptoms or a positive Mantoux tuberculin skin test or a positive IGRA blood test should be evaluated for TB disease. "Clinical evaluation of TB includes medical history, physical examination, tests for TB infection, chest X-ray, and bacteriological examination." Regarding pharmacological treatment, the currently approved regimens consist of daily

isoniazid monotherapy for 6–9 months, daily rifampicin plus isoniazid for 3 months, daily rifampicin monotherapy for 4 months, daily rifapentine plus isoniazid for 1 month, and weekly rifapentine plus isoniazid for 3 months [2,3]. In addition, drug-resistance and regular patient monitoring should further guide personalized TB treatment.

1. Sterling TR, et al. MMWR Recomm Rep. 2020;69(1):1-11.
2. WHO. WHO consolidated guidelines on tuberculosis. Module 4: Treatment Drug-susceptible tuberculosis treatment. 2021  
[https://www.tbonline.info/media/uploads/documents/ds-tb\\_who\\_guidelines.pdf](https://www.tbonline.info/media/uploads/documents/ds-tb_who_guidelines.pdf)
3. Vasankari T. Latent tuberculosis—an update. Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.

## TB management update

Current treatment of drug-sensitive tuberculosis (TB) consists of a 6-month regimen (isoniazid, rifampicin, ethambutol, and pyrazinamide). Now, a 4-month treatment regimen with rifapentine-moxifloxacin has been suggested for patients aged 12 years and over [1].

The feasibility of a 4-month regimen in a national TB plan includes the fact that it is a treatment option which can be used in persons with human immunodeficiency virus (HIV) infection who have CD4+ cell counts  $\geq 100$  cells/ $\mu$ L and who are being treated with or are planning to use efavirenz. Rapid drug-susceptibility testing for rifampicin, fluoroquinolones and isoniazid should be performed and absorption of rifapentine in the gut is improved in the presence of high-fat foods. However, the costs may be higher for the rifapentine-moxifloxacin regimen compared with the standard 6-month regimen [2].

1. Carr W, et al. MMWR. 2022;71(8):285-289.
2. Blöndal K. Recent advances and guides for management of tuberculosis. Nordic Lung Congress 2022, 01–03 June, Copenhagen, Denmark.