Medicom International Conference Series in Pulmonology

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PEER-REVIEWED CONFERENCE REPORT

Antibody Cocktail Successful in Treating COVID-19

Results from REGN-COV 2067 showed that the combination of casirivimab and imdevimab reduced the risk of all-cause death by 71% in patients with lab-confirmed disease and at least 1 risk factor for severe disease.

read more on PAGE 3

IL-4/13 Blocker Effective in Children with Moderate-to-Severe Asthma

In VOYAGE, dupilumab reduced annualised exacerbations in children with uncontrolled asthma by more than 50% and led to a rapid and sustained improvement of lung function.

read more on PAGE 8

Biomarkers for Acute Exacerbation in COPD Patients – What Can You Expect?

D-dimers have shown to be useful in differentiating exacerbations from pulmonary embolism. The lung microbiome might be a promising future tool to identify patients with poor prognosis.

read more on PAGE 14

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Editor Prof. Richard Dekhuijzen, Radboudumc, the Netherlands

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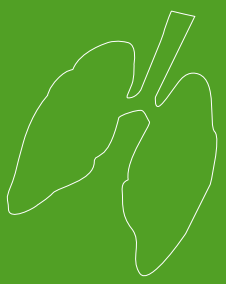

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Letter from the Editor

Prof. Richard Dekhuijzen

Dear colleagues,

As expected, the ATS 2021 was held online, due to the COVID-19 pandemic. Again, numerous speakers were able to present the most recent updates in important areas of pulmonary diseases. Some of these studies and findings are highlighted below.

The casirivimab and imdevimab combination comprises 2 potent neutralising monoclonal antibodies that bind non-competing epitopes on the SARS-CoV-2 spike protein. In patients with mild-to-moderate COVID-19, this combination showed a risk reduction for death of over 70%, and also a 4-day reduction of disease duration.

Air pollutants increase the fatality of viral infections. In a Chinese study during the SARS epidemic, the fatality rate increased with the increment of the air pollution index. This was now also demonstrated in the COVID-19 pandemic. Healthcare workers (HCW) are more likely to get infected (7.3%) compared with non-HCW (0.4%). Duration of symptom prevalence was additionally followed, and even though most subjects were not hospitalised, some of their symptoms were longer lasting.

The GINA guidelines no longer recommend short-acting β2-agonists (SABA) as needed as sole treatment. As-needed ICS-formoterol reduces the risk of exacerbations compared with as-needed SABA.

The VOYAGE trial showed that the IL-4/13 blocker dupilumab reduced exacerbations in schoolchildren with uncontrolled moderate-to-severe asthma by >50% compared with placebo. The safety profile was similar to that seen in adolescents and adults.

An observational study assessed the influence of earlier versus later therapy with the tyrosine kinase inhibitor nintedanib in patients diagnosed with idiopathic pulmonary fibrosis. Early therapy was associated with less hospitalisations and a reduction of all-cause medical costs.

This report outlines the most significant advancements discussed at the ATS conference. So, we hope that you will enjoy reading this Conference Report!

Stay healthy and kind regards,
Prof. Richard Dekhuijzen

Biography

Prof. P.N. Richard Dekhuijzen is Professor of Pulmonology at the Radboud University Medical Center in Nijmegen, the Netherlands. His specific area of clinical and research interest includes asthma, COPD, and inhalation technology. He studied medicine at VU Amsterdam and completed his training in pulmonology at the Onze Lieve Vrouwe Gasthuis in Amsterdam and in the Academic Hospital Nijmegen. In 1989, he finished his PhD thesis on training of the respiratory muscles in COPD, followed by a PhD thesis on steroid induced myopathy of the diaphragm in 1994 at the Catholic University Leuven (Belgium). He is author/co-author of over 330 peer-reviewed papers and many textbook chapters on respiratory medicine. From 2008-2010, he was Head of the Cardiology Department at Radboudumc. Until 2016, he chaired the Department of Pulmonary Diseases, the Heart-Lung Centre Nijmegen, and the Medical Staff at Radboudumc. He is the scientific chair of the Aerosol Drug Management Improvement Team (ADMIT) and chair of the Dutch Inhalation Technology Working Group. Currently, he is chair of the Medical Ethical Committee of the Radboudumc.

Conflict of Interest Statement:
In the last 3 years, Richard Dekhuijzen and/or his department received research grants, unrestricted educational grants, and/or fees for lectures and advisory board meetings from AstraZeneca, Boehringer-Ingelheim, Chiesi, GSK, Mundipharma, Novartis, Sandoz, Teva, and Zambon.

Listen to the Interview with Prof. Richard Dekhuijzen

LISTEN TO THE INTERVIEW

ATS meeting 2021 addresses health disparities in respiratory disease

Interview with ATS past president
Prof. Juan C. Celedón, MD, DrPH,
conducted June 2021 by Dr Susanne Kammerer

Prof. Juan C. Celedón is Immediate Past President of the American Thoracic Society (ATS) and the Niels K. Jerne Professor of Paediatrics and Professor of Medicine, Epidemiology, and Human Genetics at the University of Pittsburgh and Division Chief of Pulmonary Medicine at UPMC Children's Hospital of Pittsburgh, PA, USA.

What are the advantages of an online congress and what do you miss compared with the classic on-site event?

The obvious advantage of the virtual format is that one can reach a larger international audience as it is easier for people from abroad to participate. Last I checked, we had about 47% of international registrants. The second advantage is the on-demand feature. If you are attending an in-person meeting, either you attend a session, or you don't. In contrast, with most of the sessions available on demand until 2 July, people can watch whichever sessions they are interested in on their own schedule.

Of course, what the majority of participants look forward to the most, is the in-person interaction. We made a great effort to provide this possibility on the virtual format as much as we could (e.g, with question-and-answer sessions and possibilities for interactions with the speakers), but I would say it is not the same as an in-person meeting.

What have been the most interesting sessions at ATS 2021 for you?

My entire career has been on research in minority populations and so I was very pleased to see the number of sessions about issues related to disparities in respiratory diseases. When you look at the programme, there was a high number of sessions addressing racism, health disparities related to race or ethnicity, the role of gender and sex, and research in those fields. This was all quite interesting to me.

What do you think are/were the biggest challenges for clinicians during the pandemic?

I think that at the height of the pandemic, depending on where you were in the world, you dealt with a tremendously increased workload and in some settings with limited resources, whether in staffing, supplies, or treatment. I think it was devastating for many of our colleagues to lose patients to COVID-19 in an intensive care unit (ICU) without their family around or, if possible at all, only by zoom. Moreover, clinicians were socially isolated, which added to their toll, particularly for those working in ICUs. Besides, everybody but particularly women and younger people have had to deal with the closure of in-person attendance at schools and thus increased pressure at home, while also having to manage an increased clinical workload. For physician-scientists, all the pressures posed by the pandemic may have negatively impacted their time for research.

How do you reach your patients with chronic diseases in this difficult time?

I would be afraid to generalise, but some hospitals have switched to virtual consults relatively quickly. Even as conditions improved, patients were still reluctant to take in-person visits because of their fear of COVID-19. Thus, I think in many countries, regions, and cities, patients and physicians have tried to do telemedicine appointments. This has been necessary and has worked to some extent, particularly for routine and non-complex visits. However, many patients miss face-to-face contact with their physicians.

So, what is your opinion on virtual contact/telemedicine?

COVID-19 has been a great accelerator in clinical care and education, including the broader adoption of telemedicine. Early in the pandemic, the ATS co-led a series of webinars with our peer societies around the world, which had a very high attendance because clinicians wanted to have the latest information on the prevention, diagnosis, and management of COVID-19. Indeed, the virtual (webinar) format for education has been very valuable to clinicians worldwide during the pandemic. As noted above, telemedicine has gained its rightful place in patient care and consultation work, allowing discussion of cases with our colleagues around the globe.

COVID-19
What Pulmonologists Need to Know

Antibody treatment for COVID-19: a combination is successful

Dual therapy with casirivimab plus imdevimab was investigated as treatment for patients with mild-to-moderate COVID-19. The results not only showed a risk reduction for death of over 70%, but also a 4-day reduction of disease duration. This was found in the adaptive phase 1/2/3 REGN-COV 2067 trial.

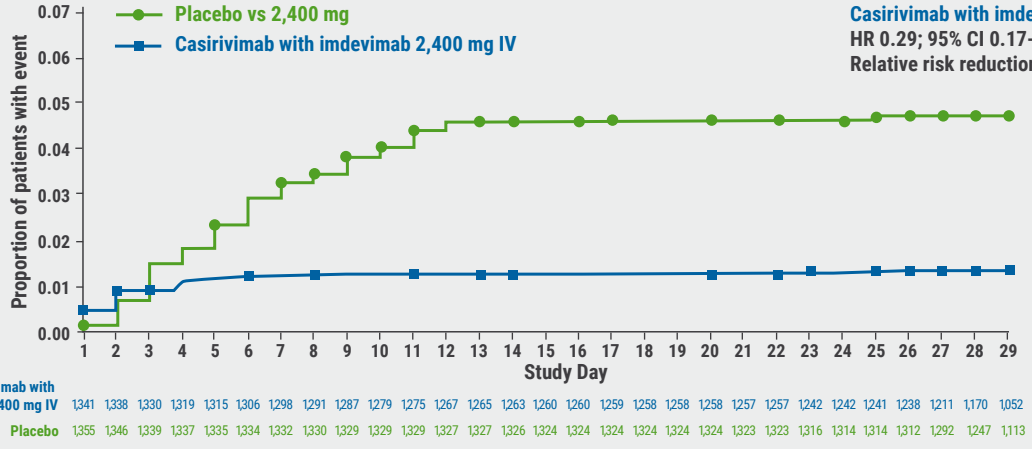
As a high viral load of SARS-CoV-2 was linked to worse outcomes of COVID-19, monoclonal antibodies with the ability to counteract the virus have come into focus for possible treatment [1]. Research results for antibody treatment of other viral infections such as Ebola led Dr Julie V. Philley (University of Texas Health Science Center, USA) and colleagues to hypothesise that a treatment approach with combined antibodies could be beneficial [2]. "The casirivimab and imdevimab combination comprises 2 potent neutralising monoclonal antibodies that bind non-competing epitopes on the SARS-CoV-2 spike protein," Dr Philley described in her talk presenting results from the REGN-COV 2067 clinical trial (NCT04425629) [3].

The adaptive phase 1/2/3 study tested dual therapy with casirivimab and imdevimab in outpatients with mild-to-moderate COVID-19. Among the prerequisites for study subjects were central lab-confirmed disease <72 hours and appearance of symptoms ≤7 days prior to randomisation. Initially, randomisation was performed 1:1:1 to 8,000 mg, 2,400 mg, and placebo, but after the analysis of phase 1/2, the protocol was changed with a re-randomisation to 2,400 mg, 1,200 mg, or placebo, eligible only for patients with ≥1 risk factor for severe disease. After a single infusion with casirivimab/imdevimab or placebo on day 1, patients were followed until day 29. The primary endpoint was defined as the proportion of patients with ≥1 hospitalisation or all-cause death, whereas the timespan until COVID-19 symptoms resolved was among the secondary endpoints.

"Patients were well matched across the treatment and the placebo groups: median age was 48.5 years, 58% were obese, 49% were men, and approximately one-third were Hispanic or Latino. Medium viral load was approximately 7 log10 copies and 69% had a negative baseline SARS-CoV-2 serum antibody status," Dr Philley described the study cohort. She also remarked that the presence of risk factors was well balanced between the study arms.

In the group receiving 2,400 mg of casirivimab/imdevimab, the relative risk of all-cause death decreased by 71% (P<0.0001) (see Figure). Concerning subgroups, COVID-19-related

Figure: Comparison of casirivimab/imdevimab versus placebo for all-cause death and COVID-19-induced hospitalisations [3].



CI, confidence interval; HR, hazard ratio; IV, intravenous; mFAS, modified full analysis set.

hospitalisations and all-cause death were also significantly reduced. This included patients with high viral loads and high or low baseline seropositivity. The duration of symptoms also decreased by 4 days under casirivimab/imdevimab at both dosages and, again, the result was consistent across the subgroups.

In terms of safety, casirivimab/imdevimab was well tolerated with more fatal outcomes in the pooled placebo groups (0.3%) than in the casirivimab/imdevimab arms (0.1% with 1,200 mg; <0.1% with 2,400 mg; and 0% with 8,000 mg).

1 Fajnzylber J, et al. Nat Commun. 2020;11(1):5493.
2 Mulangu S, et al. N Engl J Med. 2019;381(24):2293-2303.
3 Philley JV, et al. Casirivimab with Imdevimab, a cocktail of two antibodies against SARS-CoV-2, in the outpatient setting: phase 3 efficacy and safety results. Session B007: Breaking news: clinical trial results in pulmonary medicine. ATS 2021 International Conference, 14-19 May.

Air pollution: an underestimated negative prognostic factor for COVID-19

Air pollution is a driver of both COVID-19 morbidity and mortality. Different modes of action are discussed, including impairment of immune response, thus facilitating viral penetration and replication.

Even with air pollution levels decreasing during the lockdowns, the COVID-19 pandemic has highlighted adverse health impacts of air pollution. The best data exists for particulate matter (PM), nitrogen dioxide (NO_2), ozone (O_3), and sulphur dioxide (SO_2). The deposition of PM in the lungs can cause pulmonary injuries such as asthma, pulmonary dysfunction, pneumonia, and lung cancer. As Prof. Meredith McCormack (John Hopkins University, MD, USA) pointed out, the size of particles is directly linked to their potential for causing harm to the airways: particles that are smaller than 2.5 µm ($PM_{2.5}$) can reach the terminal bronchioles and enter alveoli [1].

Air pollutants do not only impair the health of the respiratory system directly but can also increase the fatality of viral infections. In a Chinese study during the SARS epidemic, the fatality rate increased with the increment of the air pollution index [2]. This was also demonstrated in the COVID-19 pandemic [3]. Target organs of both COVID-19 and air pollution are the central nervous system, lungs, and heart. Different mechanisms can explain the detrimental effect of air pollution on a SARS-CoV-2 infection. Air pollutants impair the immune response, thus facilitating viral penetration and replication [3]. Furthermore, they exaggerate inflammatory and oxidative stress responses. Viruses may persist in air through complex interactions with particles and gases [3]. "In addition, PM and NO_2 exposures *in vitro* lead to overexpression of angiotensin-converting enzyme (ACE)2, a cellular target of SARS-CoV-2 that can lead to enhanced entry, infection, and replication," Prof. McCormick said. There are estimates that particulate pollution from anthropogenic sources contributes to 15% of COVID-19 mortality worldwide [4].

According to another study, an increase of 1 µg/m^3 in the long-term average $PM_{2.5}$ is associated with an 11% increase in the COVID-19 mortality rate [5]. "We will see more studies like this. Moreover, air pollutants do not only influence mortality, but also morbidity," Prof. McCormack said. Only recently the American Lung Association published the report 'State of the air 2021'; according to this statement, even in the USA, more than 4 in 10 inhabitants live in places with unhealthy levels of air pollution [6]. "Air pollution does not affect all persons in the same way; poor people live in regions with higher air pollution. Accordingly, we have seen high death tolls of Latinos living in areas with higher air pollution," Prof. McCormick explained.

Vice versa, cleaner air is a strategy to improve outcomes and reduce the impact of COVID-19. Maintaining and strengthening air quality standards is important to improve health around the globe. "Areas of improvement in air quality are opportunities to address health disparities. COVID-19 provides a lens to reconsider air quality as a potential means to improve health," concluded Prof. McCormack.

1. McCormack M, et al. Learning from our past and forging new frontiers in the COVID 19 era …air pollution exposure as a susceptibility factor for COVID 19 infection. Session A009: From dawn to dusk: pollutant exposures and susceptibility to respiratory infections. ATS 2021 International conference, 14-19 May 2021.
2. Cui Y, et al. Environ Health 2003;20:2:15.
3. Bourdrei Th, et al. Eur Respir Rev 2021;30(159):200242.
4. Pozzer A, et al. Cardiovasc Res 2020;116(14):2247-53.
5. Wu X, et al. Sci Adv 2020;6(45): eabd4049.
6. Report of the American Lung Association. Retrieved from https://www.lung.org/media/press-releases/sota-2021 on 18 May 2021.

Healthcare workers vulnerable to SARS-CoV-2 infections

Cohort data shows a substantial risk of being infected with SARS-CoV-2 not only for nurses, people working in the emergency department, or in operating rooms, but also for employees such as those in housekeeping and nutrition. Even in COVID-19 patients with non-severe disease, post-acute sequelae play an important role.

The current presentation covered the risk situation of healthcare workers during the pandemic concerning infection prevalence and risks according to specific occupations [1].

"New Jersey ranked second of the 50 US states with regard to infection," Prof. Reynold A. Panettieri Jr (Rutgers Institute for Translational Medicine and Science, NJ, USA) described the setting of the research. A screening of nearly 4,000 employees of the Robert Wood Johnson teaching hospital (RWJ) included 74% women, 68.8% had direct patient contact, 44.1% were 20–39 years old, and 12.2% ≥60 years of age [2]. Markers of ongoing or previous SARS-CoV-2 infection were detected in about 10%. However, when looking further at the different occupations within the hospital, the rate varied. Being a phlebotomist carried the highest risk of a positive COVID-19 test with a proportion of 23.9%. Corresponding percentages in other occupations included maintenance/housekeeping 17.3% and food services 16.9%. Interestingly, rates of positive testing were 9.1% in nurses and 7.2% in doctors.

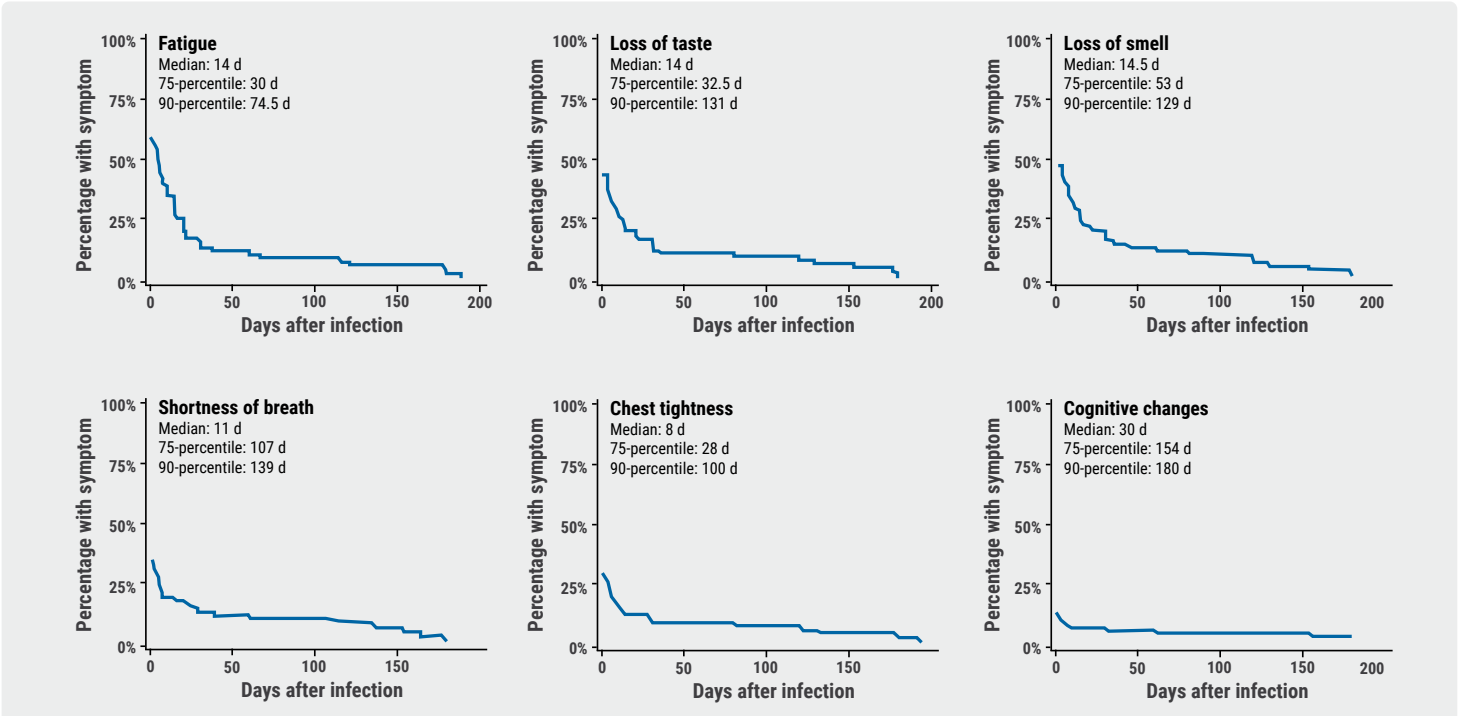
The Rutgers Corona Cohort consists of 548 healthcare workers (HCW) and 283 non-HCW. HCW from this cohort had regular patient exposure and worked at least 20 hours per week in the hospital [3]. Non-HCW included faculty, staff, and students. All participants had no prior history of a COVID-19 diagnosis. The proportion of positive tests for COVID-19 showed differences between hospital sites but, overall, HCW had higher rates of infection (7.3%) than non-HCW (0.4%). "So, the takeaway is, if you work in a hospital, you are more likely to get infected," commented Prof. Panettieri.

When evaluating factors that might be associated with SARS-CoV-2 infection in HCW, working in an intensive care unit appeared protective, as was having diabetes, whereas working as a nurse, being obese, or being Hispanic increased the likelihood of infection [1]. "For nurses, working in an emergency room or on a medical floor rendered greater susceptibility to SARS-CoV-2 infection," Prof Panettieri specified. Also, being staff of an operating room was a significant factor. Another interesting result was that among the HCW who were infected, those with the most severe disease had the highest IgG antibody titres.

Duration of symptom prevalence was additionally followed, and it was observed that even though most patients were not hospitalised, some of their symptoms were longer lasting. "Fatigue and body aches were symptoms that persisted in almost 20% of positive cases of HCW," Prof Panettieri said, "fatigue lasted for 30 days in the 75-percentile, chest tightness nearly 30 days for the 75-percentile, and cognitive changes almost half a year. Hence, long haulers or long-haul symptoms persisted in HCW in those individuals who had mild disease without hospitalisation or ER visits" (see Figure).

1. Panettieri RA. Lessons Learned from a Large, Prospective COVID-19 Occupational Exposure Cohort. Session C026: Occupational COVID-19 exposure: risks and mitigation. ATS 2021 International conference, 14-19 May 2021.
2. Barrett ES, et al. Open Forum Infect Dis. 2020;7(12):ofaa534.
3. Barrett ES, et al. BMC Infect Dis. 2020;20(1):853.

Figure: Duration of symptoms in infected participants of the Rutgers Corona Cohort [1]



Genetic risk variants responsible for COVID-19 predisposition

The susceptibility and severity of a SARS-CoV-2 infection are determined by a complex interaction of genetics and environmental exposures. A study that combined genetic information with gene expression and proteomic datasets identified genetic risk variants in the *ABO* gene that might significantly increase the chances of a SARS-CoV-2 infection.

The aim of the study presented by Dr Ana Hernandez Cordero (Centre for Heart Lung Innovation, University of British Columbia, Canada) was to use integrative genomics to combine gene expression and proteomic information with COVID-19 susceptibility [1]. Genomic research identifies specific genes that may play a role in biological processes such as the development of disease, while proteomics does the same for proteins. The combination of both approaches allows researchers to get a fuller picture of disease processes. "Genetic associations alone cannot pinpoint the exact gene responsible for COVID-19," said Dr Hernandez. "However, by combining COVID-19 genetic information with gene expression and proteomic datasets, we can figure out which genes are driving the relationship with COVID-19."

The COVID-19 Host Genetics Initiative has been founded to identify genetic determinants of COVID-19 susceptibility and severity and share the results from such activities [2]. The researchers combined genetic information with an examination of lung gene expression to identify genetic variants which control gene expression in the lung that were responsible for COVID-19. They identified specific gene markers that share their effects on gene expression and protein levels with COVID-19 susceptibility. For the analysis, the following bioinformatics were integrated:

- a genomic dataset obtained from patients who were infected with SARS-CoV-2 as well as non-infected individuals (controls);
- lung and blood tissue gene expression datasets from clinical populations (non- COVID-19); and
- a proteome dataset obtained from blood donors (non-COVID-19).

With this method, it was found that several genes responsible for the immune system's response to COVID-19 are also involved in COVID-19 susceptibility. These findings were in line with previous research.

By exploring candidate genes in blood proteins, the effects of genes could be connected to susceptibility to COVID-19. Blood proteomics can also identify markers in the blood that can be easily measured to indicate disease status and, potentially, monitor the disease. "By harnessing the power of genomic information, we identified genes that are related to COVID-19," said Dr Hernandez. Increased levels of ABO in plasma were associated with an increased risk of COVID-19, whereas the blood group O appeared protective against COVID-19.

In addition to the *ABO* gene, people carrying certain genetic variants for *SLC6A20*, *ERMP1*, *FCER1G*, and *CA11* had a significantly higher risk of contracting COVID-19. "These individuals should use extreme caution during the pandemic. These genes may also prove to be good markers for disease as well as potential drug targets," Dr Hernandez concluded.

Several of the genes identified in this analysis have already been linked with respiratory diseases. For example, *ERMP1* has been associated with asthma and *CA11* may also elevate COVID-19 risk for people with diabetes.

1. Al Hernandez Cordero. Integrative genomic analysis highlights potential genetic risk factors for Covid-19. TP91: Lung infection (Non-mycobacterial, i.e., bacterial, viral, fungal, HIV, etc). ATS 2021 International conference, 14-19 May 2021.

Asthma
A Treatment Update

"As-needed" inhaled corticosteroid therapy for mild asthma – what is the evidence?

Several recent studies assessed the benefit of as-needed inhaled corticosteroid (ICS) treatment for mild asthma. An advantage of this approach is the ICS sparing effect, which was evident both in randomised clinical trials and practice studies.

The traditional management of persistent asthma consists of a controller medication daily and reliever medication as needed. "This procedure was the guideline´s first choice over 3 decades," Prof. Kaharu Sumino (Washington University School of Medicine, MO, USA) said in her introduction [1]. However, delivery of daily ICS therapy has been challenging, especially due to adherence of <50%. Obviously, enforcing daily ICS when symptoms are not severe is difficult. "Mild asthma can be associated with significant morbidity and mortality," Prof. Sumino said. A total of 16% of near-fatal asthma and 15% of adults dying from asthma had less than weekly symptoms 3 months before the event [2]. This is the rationale to use non-regular ICS therapies in treating mild asthma, which affects the majority of patients (50–70%) [2]. Potential benefits of as-needed ICS application include a higher sense of self-management by patients. Currently, more evidence is available on as-needed ICS in mild asthma. This reflects in landmark changes in the Global Initiative for Asthma (GINA) guideline in 2019 and the National Asthma Education Prevention Program (NAEPP) guideline in 2020.

Prof. Anne Dixon (University of Vermont, MA, USA) discussed as-needed ICS therapy in adults with mild asthma. In both the GINA and NAEPP guidelines, mild asthma is defined as asthma controlled on step 1 or step 2 treatment, but there are slight differences (see Table) [3]. "What they have in common is the use of as-needed ICS," Prof. Dixon said. As-needed ICS is what patients do already – they use an inhaler when they have symptoms. Another advantage of providing ICS at the time of symptoms is that anti-inflammatory therapy is given when it is most needed.

Only data for the combination budesonide-formoterol

As-needed ICS-formoterol for mild asthma was only studied as budesonide-formoterol combination, a combination that was not yet addressed in the NAEPP update. In the SYGMA 1 trial (NCT02149199) including 3,849 patients with mild asthma that needed step 2 treatment, as-needed budesonide-formoterol provided superior asthma-symptom control to as-needed terbutaline, assessed using electronically recorded weeks with well-controlled asthma for a period of 52 weeks [4]. "Budesonide maintenance was slightly better," Prof. Dixon said. In the SYGMA 2 trial (NCT02224157), a similar patient population was included (n=4,215) [5]. In this 52-week, non-inferiority trial, budesonide–formoterol used as needed was non-inferior to twice-daily budesonide concerning the rate of severe asthma exacerbations but was inferior in controlling asthma symptoms. Another advantage of the as-needed approach was the median daily dose of ICS being 75% lower in the budesonide–formoterol group. These results are backed by 2 studies reflecting a real-life scenario. In the 52-week, real-world, open-label superiority study PRACTICAL (U1111-1174-2273), 890 patients were included and treated with budesonide–formoterol reliever therapy compared with maintenance budesonide plus as-needed terbutaline. Severe exacerbations per patient per year were lower with as-needed budesonide–formoterol than with maintenance budesonide plus terbutaline as needed. In addition, asthma control did not differ between treatment groups. Again, patients treated with as-needed ICS-formoterol had an ~50% lower ICS dose versus budesonide maintenance [5].

Table: Mild asthma treatment options in the NAEPP 2020 update versus GINA 2020 [1]

Mild asthma treatment options	NAEPP 2020 update	GINA 2020
As-needed SABA only	Step 1 treatment for mild intermittent asthma (step 1 controller therapy not part of 2020 update)	No longer recommended as monotherapy for adults and adolescents
Daily low dose ICS (maintenance) plus SABA as reliever	Step 2 for all ages	Age 0–4: step 1 and 2 preferred; Age 6–11 and ≥12: step 2 preferred
As-needed low dose ICS plus SABA at the same time	Step 2 option for age ≥12	Age 6–11 and ≥12: step 1 and step 2 other option
As-needed low dose ICS plus formoterol	Not addressed in the 2020 update	Age 6–11: not included; Age ≥12: step 1 and step 2 preferred

GINA, Global Initiative for Asthma; NAEPP, National Asthma Education Prevention Program; SABA, Short-acting β-agonists; ICS, inhaled corticosteroids.

The START trial (2015-002384-42) had a similar result: in this 52-week, real-world, open-label study, 668 asthma patients were either treated with albuterol, budesonide plus as-needed albuterol (budesonide maintenance group) or budesonide-formoterol [6,7]. The annualised exacerbation rate in the budesonide–formoterol group was lower than that in the albuterol group (P<0.001) and did not differ significantly from the rate in the budesonide maintenance group (P=0.65). In both trials, ICS–formoterol-treated patients needed an ~50% reduced ICS dose.

"In conclusion, we have less data regarding as-needed ICS-formoterol for step 1, but very compelling data for step 2," Prof. Dixon said. As-needed ICS-formoterol reduces the risk of exacerbations compared with as-needed short-acting beta-agonists. In real-world studies, it also reduced severe exacerbations and had a similar effect on symptom scores compared with regularly scheduled ICS, with a lower ICS dose.

1. Sumino KC. Introduction of symposium: as-needed ICS therapy in mild asthma, case presentation and guidelines. Session C006: Are we ready for "as-needed" inhaled corticosteroid therapy for mild asthma? Different patients, different perspectives. ATS 2021 International Conference, 14-19 May.
2. Dusser D, et al. Allergy 2007;62(6):591-604.
3. Dixon A. Adult perspectives of as-needed ICS therapy in mild asthma. Session C006: Are we ready for "as-needed" inhaled corticosteroid therapy for mild asthma? Different patients, different perspectives. ATS 2021 International Conference, 14-19 May.
4. O'Byrne PM, et al. N Engl J Med 2018:378(20):1865-76.
5. Bateman ED, et al. New Engl J Med 2018;378:1877-87.
6. Hardy J, et al. The Lancet 2019;394:919-28.
7. Beasley R, et al. New Engl J Med 2019;380:2020-30.

IL-4/13 blocker successful in treatment of paediatric moderate-to-severe asthma

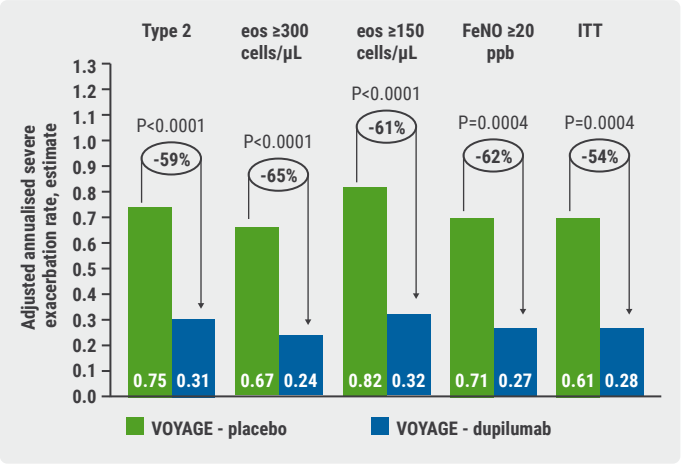
Dupilumab reduced annualised exacerbations in schoolchildren with uncontrolled moderate-to-severe asthma by >50% compared with placebo. The safety profile was similar to that seen in adolescents and adults. These were the results of the VOYAGE trial.

Despite optimised standard-of-care therapy, children with moderate-to-severe asthma may continue to have uncontrolled disease. The IL-4/13 blocker dupilumab has previously been shown to be effective and has a demonstrated favourable safety profile in adolescents and adults with moderate-to-severe asthma [1]. Prof. Leonhard B. Bacharier (Vanderbilt University Medical Center, TN, USA) presented results of the VOYAGE trial (NCT02948959) and pointed out that type 2 inflammation underlies most cases of asthma in children [2]. The VOYAGE trial aimed to assess the efficacy of dupilumab in children aged 6–11 with uncontrolled moderate-to-severe asthma. Enrolled in the trial were 408 children. Patients receiving high-dose inhaled corticosteroids (ICS) alone or a medium-to-high dose ICS with a second asthma controller were randomised 2:1 to receive 100 mg (body weight ≤30kg) or 200 mg (>30 kg) subcutaneous dupilumab or a matched placebo for up to 52 weeks.

The researchers performed pre-specified primary analyses in 2 populations in the study: 350 patients with markers of type 2 inflammation (baseline blood eosinophils ≥150 cells/µL or fractional exhaled nitric oxide (FeNO) ≥20 ppb) and 259 patients with baseline blood eosinophils ≥300 cells/µL.

At the end of the trial, dupilumab significantly reduced the annualised rate of severe exacerbations versus placebo by 59.3% in the type 2 inflammation phenotype and by 65% in the population with baseline blood eosinophils ≥300 cells/µL (P< 0.0001 for both comparisons; see Figure). In addition, the treatment improved the pre-bronchodilator forced expiratory volume in the first second (FEV_1) percent of predicted at week 12, a key secondary endpoint, in both populations and reduced FeNO significantly at 12 weeks compared with placebo. The biologic led to rapid and sustained lung function improvement over the entire treatment period in both populations. At week 24, patients treated with dupilumab showed greater improvement in asthma control scores as compared with the placebo group.

Figure: Dupilumab significantly reduced the annualised rate of severe exacerbations versus placebo [2]0.75



eos, eosinophils; FeNO, fractional exhaled nitric oxide; ITT, intention-to-treat.

The safety profile of dupilumab was generally consistent with the known safety profile of dupilumab in patients aged ≥12 years with moderate-to-severe asthma. "There were 7 parasitic infections, 5 of those were enterobiasis, but they were not serious and did not lead to treatment discontinuation," Prof. Bacharier explained.

"The effect of dupilumab on improving lung function in these children was particularly impressive," noted Dr Bacharier. "Decreased lung function is associated with an increased risk of future asthma exacerbations. In addition, impaired lung function may result in abnormal lung growth," he concluded.

1. Castro M, Corren J, Pavord ID, et al. N Engl J Med 2018;378(26):2486-96.
2. Bacharier LB, et al. Dupilumab efficacy and safety in children with uncontrolled, moderate-to-severe asthma: The phase 3 VOYAGE study. Session B007: Breaking news: clinical trial results in pulmonary medicine. ATS 2021 International conference, 14-19 May.

Benralizumab lives up to its phase 3 results in real-world findings

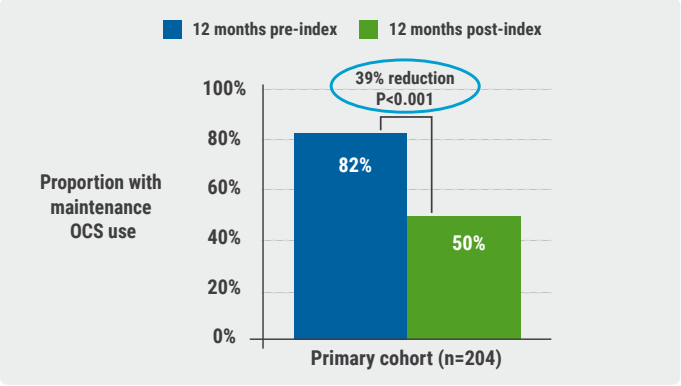
The efficacy of benralizumab for severe eosinophilic asthma was confirmed in a retrospective cohort trial utilising US claims data. Exacerbation rates and the use of controller medication were significantly diminished with benralizumab treatment.

After demonstrating significant results in phase 3 trials, the anti-IL-5 antibody benralizumab has been approved by the EMA as add-on maintenance medication in adult patients with severe eosinophilic asthma insufficiently controlled by a combination of inhaled corticosteroids and long-acting beta-agonists [1,2]. This new analysis assessed whether the rates of 51% decreased exacerbations observed in phase 3 would be confirmed in real-world data [3]. The presented retrospective cohort study included patients from medical claims who started benralizumab between 2017 and 2019 [1]. The index date in this pre-post study was the first day after the drug was taken for the first time. Data from 12 months before this day was compared with that of 12 months after the index date. The participants of the primary and secondary cohort were all naïve to biologic treatment and had suffered from ≥2 exacerbations in the pre-index course. The 204 patients of the primary cohort all had ≥2 records of benralizumab, while the secondary or persistent group contained 103 subjects with ≥6 records. Moreover, 114 patients switching from omalizumab and 97 changing from mepolizumab to benralizumab were analysed.

Mean age in the primary cohort was 45.3, 68.6% were women, 77.5% had comorbidity of allergic rhinitis, 45.1% gastroesophageal reflux disease, and 45.6% hypertension. Asthma exacerbation rates were calculated per person-year (PY). The results revealed a 55% reduction (3.25 vs 1.47 per PY) for the benralizumab users within the primary and 62% (3.23 vs 1.23 per PY) in the persistent cohort. Both differences were significant with a P<0.001 for pre- and post-index comparisons.

Of note, 41.2% and 42.7% under benralizumab in the primary and persistent cohort, respectively, did not experience any exacerbations during the post-index period. The outcomes for the switch cohorts were similar: 54% reduction when changing from omalizumab and a 34% drop in exacerbations with previous mepolizumab. The ameliorations were also consistent with a decrease in cumulative dosage of oral corticosteroids in the post-index period: in the primary cohort, 82% received steroid maintenance pre-index, but only 50% post-index (P<0.001) (see Figure). "Additionally, rescue medication use, commonly prescribed controllers, and antibiotics also decreased in the post-index period," Dr Donna Carstens (AstraZeneca, Wilmington, DE, USA) pointed out with regard to significance for short-acting beta-agonists (P<0.001) and the combination of inhaled corticosteroids (ICS), with long-acting β2-adrenergic receptor agonists (P<0.001). In view of the study design that lacked a control arm, further research confirming the results is desirable. "Patients treated with benralizumab in this real-world analysis experienced a significant reduction in asthma exacerbations consistent with pivotal trials, as well as those who switched from other biologics," concluded Dr Carstens.

Figure: Reduction of oral corticosteroid use among benralizumab receivers [1]



OCS, oral corticosteroids.

1. Carstens D, et al. Real-World Effectiveness of Benralizumab on Asthma Exacerbations: Results from the ZEPHYR 1 Study. Session TP015: Updates in Adherence and treatment of lung disease. ATS 2021 International Conference, 14-19 May.
2. https://www.ema.europa.eu/en/medicines/human/EPAR/fasenra
3. Bleecker ER, et al. Lancet. 2016 Oct 29;388(10056):2115-2127.

Tezepelumab – good success rates in various types of severe asthma

Tezepelumab showed convincing results for the treatment of severe asthma. Besides significantly reducing exacerbation rates in many different inflammatory profiles, the first-in-class TSLP blocker also improved asthma control and quality of life.

Tezepelumab is a monoclonal antibody with specific inhibition of thymic stromal lymphopoietin (TSLP) resulting in hindering TSLP to cooperate with its receptor thus acting upstream of various cytokines involved not only in type 2 inflammation, but also in neutrophil activation and mast cell effects [1,2]. So, why is this so interesting for the treatment of asthma? "Inflammation in asthma remains a complex heterogeneous and dynamic process and even with biologic treatment, 60% of US patients with severe asthma have suboptimal controlled disease and there is a need for alternative treatments for severe asthma that treat a wider spectrum of inflammation," Prof. Michael E. Wechsler (National Jewish Health, Denver, CO, USA) described the current situation [3].

The results of the phase 3 NAVIGATOR (NCT03347279) study were one of breaking news of the ATS 2021 congress [3]. NAVIGATOR included patients with severe, poorly controlled asthma and ≥2 exacerbations in the last 12 months. Among the study participants were equal rates of patients with blood eosinophil counts <300 cells/µL and ≥300 cells/µL at screening. Over 1,000 patients were randomised to receive either 210 mg of tezepelumab or placebo every 4 weeks over 52 weeks while continuing their background controller medication. They were followed for 12 more weeks thereafter. The study met its primary endpoint by a significant reduction of 56% in the annualised asthma exacerbation rate (AAER): 2.10 and 0.93 in the placebo and the tezepelumab arm, respectively (P<0.001). "Exciting about the NAVIGATOR study was that tezepelumab reduced exacerbation in the overall population and in patients with a broad range of inflammatory profiles," stated Prof. Wechsler. Among those groups were patients with high and low eosinophil counts, high and low exhaled nitric oxide levels, as well as positive and negative perennial-specific IgE status. AAER leading to hospitalisation or emergency room visits were significantly reduced by 79%. Lung function improved overall, with greatest differences to placebo in those with eosinophils ≥300 cells/µL. The efficacy of tezepelumab also resulted in significant amelioration in asthma control (P<0.001), asthma symptom diary score (P=0.002), and asthma quality of life (P<0.001). "Importantly, tezepelumab also reduced blood eosinophil counts, exhaled nitric oxide, and IgE levels over the 52 weeks of this treatment study," emphasised Prof. Wechsler.

Overall, adverse events were more frequent in placebo patients than in the tezepelumab receivers (80.8% vs 77.1%) [4]. Most common in both groups were nasopharyngitis, upper respiratory tract infection, and headache. Serious adverse events also occurred more often in the placebo group compared with the tezepelumab arm (13.7% vs 9.8%). Discontinuation of treatment was induced by adverse events in 3.6% (placebo) and 2.1% (tezepelumab).

1. Gauvreau GM, et al. N Engl J Med. 2014;370(22):2102-10.
2. Corren J, et al. N Engl J Med. 2017;377(10):936-46.
3. Wechsler ME. Latest clinical evidence from phase 3 tezepelumab trials in severe asthma. Session B007: Breaking news: clinical trial results in pulmonary medicine. ATS 2021 International Conference, 14-19 May.
4. Menzies-Gow A, et al. N Engl J Med. 2021;384(19):1800-09.

Sleep Disorders
An Underestimated Problem

OSA: A risk factor for earlier cognitive decline

Increasing evidence indicates that obstructive sleep apnoea (OSA) is associated with cognitive decline. Therapy with continuous positive airway pressure (CPAP) has demonstrated not only to improve various cognitive tests, but also to reduce biomarkers associated with Alzheimer´s disease (AD).

Neuropathologic hallmarks of AD are abundant amyloid plaques containing β amyloid, neurofibrillary tangles, and dystrophic neurites containing hyperphosphorylated tau. How sleep-disordered breathing might impact cognition was assessed in the ADNI cohort, an active cohort including 2,470 subjects with an average follow-up of 2–3 years. A subset of 767 subjects was available for sleep analysis. They

completed sleep questionnaires, were asked whether they have sleep apnoea and if yes, whether they use CPAP. In this subset of patients, age of mild cognitive impairment (MCI) diagnosis could be determined. "One of the advantages of this cohort is that these subjects were followed closely with progressive neuropsychological tests, so exact stages of transition from low cognition to MCI, an early stage of AD, could be precisely determined," said Prof. Andrew W. Varga (Mount Sinai Integrative Sleep Center, NY, USA) [1]. A previous study examined whether the presence of OSA is associated with an earlier age at MCI or AD onset in this cohort [2]. Results indicated that the age of onset of MCI was reduced in older subjects with sleep-disordered breathing. "There was a marked difference of 11 years," Prof. Varga explained. "However, those treated with CPAP had a much later onset," he said. Their risk of MCI was comparable to those who did not have sleep-disordered breathing.

CPAP use improves memory tests

A positive influence of CPAP on memory deficits could also be demonstrated in a second case-control study including 36 patients with newly diagnosed OSA and 36 matched healthy controls [3]. Primary outcome was improvement in a declarative memory test (verbal paired-associate task [VPA]). The overnight testing included a training session of the task in the evening followed by a polysomnogram and a VPA recall test in the morning. The groups had similar performances in the evening. The following morning, patients with OSA correctly completed on average 74.1% of the word pairs, a 7.1% increase from the evening before, compared with 82.4% in the healthy controls, a 13.9% increase – almost twice that of the OSA group [3]. Subjects with OSA were then randomly assigned to a CPAP group and a no-CPAP group. After 3 months, both groups returned for overnight testing, including evening training and morning recall. The polysomnogram revealed that the CPAP group had more than twice as much stage 3 (N3) sleep compared with the non-CPAP group. In addition, the CPAP group achieved test results similar to healthy controls and significantly better than the no-CPAP group. Between the CPAP and no-CPAP group was a mean difference of 6.21% (95% CI 1.08–11.34). "These results demonstrated that the deficit in remembering words is a result of OSA and this can be reversed by CPAP," Prof. Varga commented. Increases in N3 sleep from the baseline night predicted the increase in overnight VPA memory improvement between the 2 test sessions (r=0.34; P=0.04). A similar study performed by Prof. Varga and co-workers demonstrated that OSA alters morning performance in spatial navigation memory processing (tested with a 3D maze environment) [4]. In the evening, no difference was observed between participants with and without OSA. However, OSA altered the morning performance independent of deleterious effects on morning vigilance or evening navigation.

OSA severity is associated with increases in cortical amyloid deposits

Another trial tested the hypothesis that there is an association between severity of OSA and longitudinal increases in amyloid burden in cognitively normal elderly [5]. Data were derived from a 2-year prospective longitudinal study. All subjects were healthy and cognitively normal volunteers aged 55–90. Cerebrospinal fluid (CSF) amyloid β was measured using ELISA and positron emission tomography (PET). A subset of 34 subjects completed a second amyloid PET scan at 2.5 years.

In this study, the severity of OSA indices was associated with a longitudinal decrease of cerebrospinal fluid amyloid β_{42} – even after adjustment for confounding risk factors. "Longitudinal decrease in soluble amyloid β_{42} in CSF reflected an increase in insoluble β-amyloid plaques found in the brain," Prof. Varga said. This could be verified in the subset of patients undergoing PET imaging: higher OSA severity at baseline was associated with a longitudinal increase in cortical amyloid deposits.

Finally, Prof. Varga discussed whether chronic OSA treatment can impact AD fluid biomarkers over time. This question was assessed in a study including 35 adults with OSA that were prescribed CPAP [6]. CSF was collected before the start of treatment and 1–4 months after treatment. The analysis was limited to CPAP-adhering subjects (18/35 patients). Overall, no significant differences were observed in the biomarkers tau and total protein pre- and post-treatment. Nonetheless, significant negative correlations were observed in the change of apnoea-hypopnoea index and amyloid β biomarkers. "This suggests that there may be a threshold in the apnoea-hypopnoea index that is needed to detect significant changes in some of these fluid biomarkers of AD chronically over time," Prof. Varga concluded.

1. Varga A. Is OSA a risk factor for cognitive decline and Alzheimer's Disease. Session A025: Sleep disorders: The new risk factor for age-related neurodegenerative diseases. ATS 2021 International Conference, 14-19 May.
2. Osorio RS, et al. Neurology 2015;84(19):1964-71.
3. Djonlagic IE, et al. Am J Resp Crit Care 2021;203(9);1188-90.
4. Mullins AE, et al. J Clin Sleep Med 2021;17:939-48.
5. Sharma RA, et al. Am J Resp Crit Care 2018;197(7): 933-43.
6. Ju YE S, et al. Ann Neurol 2019;85:291-5.

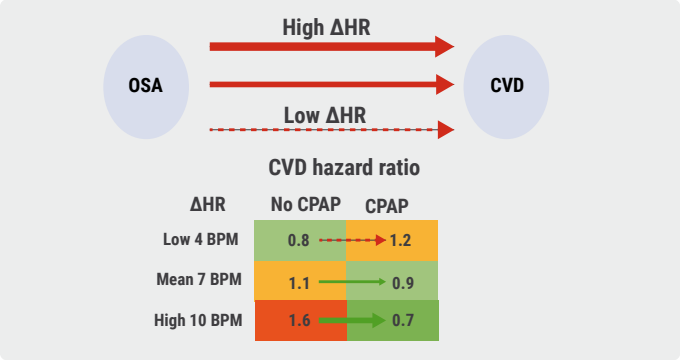
Subgroup of patients with high heart rate response and coronary artery disease benefit from CPAP

Several trials found no protective effect of continuous positive airway pressure (CPAP) on adverse cardiovascular outcomes in patients with coronary artery disease. However, a re-analysis of the RICCADSA trial presented during the ATS 2021 meeting demonstrated that the subgroup of patients with a high heart-rate response to obstructive events experienced a >50% risk reduction for a cardiovascular event when treated with CPAP.

Previous studies have found no protective effect of CPAP on adverse cardiovascular outcomes in patients with coronary artery disease and non-sleepy obstructive sleep apnoea (OSA) [1-3]. "Our previous study showed that those with non-sleepy OSA who demonstrated a greater respiratory event-related pulse rate response (ΔHR) are at increased risk of cardiovascular morbidity and mortality," Prof. Ali Azarbarzin (Harvard Medical School, MA, USA) explained [4]. This was the rationale to test the hypothesis that patients with a higher pre-treatment ΔHR might benefit more from CPAP regarding cardiovascular outcomes. Therefore, Prof. Azarbarzin and his colleagues re-analysed data from the RICCADSA clinical trial (NCT00519597) of cardiovascular risk for non-sleepy OSA patients with heart disease [5]. ΔHR was measured from the oximetry pulse rate signals collected during baseline polysomnography of the RICCADSA trial. The primary outcome of this analysis was a composite of repeat revascularisation, myocardial infarction, stroke, and cardiovascular mortality. In the original study, the OSA effect on cardiovascular disease was similar across subgroups. The researchers now analysed whether the effect of the CPAP treatment on the primary outcome was influenced by ΔHR. "If this were true, then we would expect to see a preferential benefit from using CPAP on cardiac outcomes in those with higher ΔHR," said Prof. Azarbarzin. "Indeed, this is what we found: the greater the ΔHR, the greater the calculated treatment benefit of CPAP."

ΔHR measures were obtained in 92% of patients, and 48 composite events were recorded over a 57-month median follow-up. A significant interaction between treatment and ΔHR was observed. CPAP provided protection from cardiac events in non-sleepy OSA patients whose pulse rates rose significantly during sleep apnoea events. Patients with the highest ΔHR of 10 beats per minute experienced a >50% reduction of risk for a cardiovascular event when treated with CPAP (see Figure).

Figure: Patients with high ΔHR experience a more than 50% risk reduction for cardiovascular events with CPAP [5]



OSA, obstructive sleep apnoea; CVD, cardiovascular disease; ΔHR, pulse rate response.

"Our study provides novel evidence that a greater heart rate responsiveness to obstructive airway events is an identifiable, deleterious, and potentially reversible risk factor that could be used to select patients most likely to exhibit long-term cardiovascular benefit from CPAP therapy," Prof. Azarbarzin concluded.

1. McEvoy RD, et al. New Engl J Med 2016;375:919-31.
2. Peker Y, et al. Am J Respir Crit Care Med 2016;194(5):613-20.
3. Sánchez-de-la-Torre M, et al. Lancet Respir Med 2013;1(1): 61-72.
4. Azarbarzin A, et al. Am J Respir Crit Care Med 2021 Jan 6 [e-pub ahead of print].
5. Azarbarzin A, et al. Cardiovascular benefit of CPAP is modified by the Sleep Apnea related pulse rate response in coronary artery disease patients with nonsleepy OSA: Findings from the RICCADSA randomized controlled trial. Session B14: Pathophysiology, cardiovascular disease, and COVID – what´s happening in sleep research right now. ATS 2021 International conference, 14-19 May 2021.

Association between positive airway pressure treatment adherence and COVID-19 infection rates

A large retrospective study found a higher COVID-19 infection rate in patients with obstructive sleep apnoea (OSA) and lower positive airway pressure (PAP) treatment adherence. However, no association between sleep apnoea and its treatment was found with regard to the necessity of hospitalisation or the use of intensive care.

Within the USA, Kaiser Permanente is a very large non-profit healthcare plan with 12.5 million members that includes a network of sleep centres [1]. The study included 81,932 patients, all of them enrolled with Kaiser Permanente before February 2020 [1]. None of the patients had priors of COVID-19. "We specifically looked at adults and also those with daily PAP therapy data wirelessly transmitted, which we then used to calculate adherence between 1 March and 31 July 2020 coinciding with the pandemic period. We then assessed COVID-19 infection rates and measurements of COVID-19 severity," explained Dr Dennis Hwang (Kaiser

Permanente, CA, USA). The study population was sorted into 4 groups, based on PAP adherence:

- A: patients without OSA;
- B: OSA patients with PAP use ≤2 h/day;
- C: OSA patients with PAP use 2–3.9 h/day; and
- D: OSA patients with PAP use ≥4 h/day.

The mean age of the cohort was 54 and 60.2% were men. "As expected, the OSA cohort was older, more likely to be male, more obese, and had a greater degree of baseline comorbidities," Dr Hwang described the patient characteristics. In numbers, this equalled a mean BMI of 30.4 in the no-OSA group (group A) and 34.3 in group B, a Charlson Comorbidity Index of 1.3 (group A) versus 2.0 (group B), and a percentage of men of 44% versus 60.3%, respectively.

The results showed the highest COVID-19 infection rate of 2.1% in those with OSA, but poor use of PAP (group B). In comparison, 1.7% in group A and group C contracted COVID-19, and OSA patients with the best adherence to their PAP treatment (group D) had the lowest incidence of COVID-19: 1.3%. These findings were corroborated by the results of an adjusted model that calculated the odds ratio (OR) of infection for group A versus group B equalling 0.82. In a comparison of well-treated (≥4 h/day, group D) versus not adequately treated (≤2 h/day, group B) OSA the OR was 0.68. "Clinical factors such as obesity and more comorbidities at baseline were also associated with a higher rate of becoming infected," Dr Hwang said. Unexpectedly, a lower infection likelihood was found for older patients with an OR of 0.88 for every increase of 5 years. "The association of demographic factors with risk suggests social-behavioural influences, while the association of clinical factors could suggest biologic mechanisms. Neither OSA nor PAP was associated with COVID-19 severity outcomes, but the overall incidence rates were small," Dr Hwang concluded.

1. Hwang D. Impact of Obstructive Sleep Apnea and Positive Airway Pressure Therapy on COVID-19 Outcomes. Session B014: Pathophysiology, cardiovascular disease, and COVID-what's happening in sleep research right now. ATS 2021 International Conference, 14-19 May.

Chronic Obstructive Pulmonary Disease What Is New

Does COPD plus COVID-19 equal higher mortality?

The evaluation of chronic obstructive pulmonary disease (COPD) patients with COVID-19 did not find increased mortality, nor a negative impact of exacerbation status. Similar results were found for asthma and COVID-19.

"We sought to assess whether COPD or asthma are risk factors for intubation in COVID-19, as well as mortality in COVID-19," Dr Jacob Schwartz (Lenox Hill Hospital, NY, USA) said [1]. For this analysis, data of 21,865 patients was included after extraction from electronic health records during the pandemic from March to July 2020. Findings from COVID-19 patients who had COPD or asthma were evaluated versus those without obstructive lung disease. Mechanical ventilation served as an indicator of severe COVID-19. The study cohort consisted of 1,370 patients with asthma plus COVID-19, 847 with COPD plus COVID-19, and 19,347 with COVID-19 but no obstructive lung disease.

The results for the COPD patients revealed a greater likelihood for intubation (aOR 1.35 vs controls; P=0.0095), but there was no link between COPD and COVID-19 mortality. On the other hand, patients with asthma and COVID-19 were neither at greater odds for mechanical ventilation nor increased mortality. "Our findings with regard to intubation may be explained by a more aggressive approach to intubate instead of using non-invasive ventilation early in the pandemic," Dr Schwartz explained, "We especially intubated these patients early as they are likely perceived as high risk due to underlying lung disease."

When comparing patients with the combination of COPD plus COVID-19 to those with asthma and COVID-19, the latter were less likely to die from COVID-19 than those with COPD (aOR 0.72; P=0.0329). The authors hypothesised that this disparity could be due to the different underlying pathophysiology of the diseases, as well as the possibility of a small protective impact derived from inhaled steroids. Whether asthma or COPD were exacerbated or stable while having COVID-19 did not augment the risk to die from COVID-19. "It is our hope that this data contributes to the further understanding of the complex relationship of COVID-19 and obstructive lung disease," Dr Schwartz concluded.

1 Schwartz J, et al. COVID-19 and Obstructive Lung Disease: Are COPD and asthma risk factors for severe COVID-19? Evaluating the data from the largest health system in New York State. Session TP3: COVID-19 infections, mechanisms, and clinical implications. ATS 2021 International Conference, 14-19 May.

Possible aetiologies for COPD exacerbations – more evidence is needed

Under-recognised aetiologies for chronic obstructive pulmonary disease (COPD) exacerbations are especially interesting with regard to exacerbations without inflammatory triggers. They include arrhythmias, diastolic dysfunction, psychological distress, and gastroesophageal reflux disease.

"The majority of COPD exacerbations are due to bacterial or viral infections; some are recognised to be due to environmental pollution and in approximately one-third of cases the aetiology remains unclear," Prof. Surya P. Bhatt (Birmingham School of Medicine, AL, USA) explained [1]. As the current definition of an acute exacerbation of COPD (AECOPD) is based on acute symptom worsening without mentioning aetiologies, 4 clusters of possible phenotypes were distinguished: bacteria-predominant, eosinophil-predominant, virus-predominant, and pauci-inflammatory [2]. All might require different treatment strategies, and this could play a special role in the pauci-inflammatory group constituting about 20% of AECOPD with no clear identifiable cause [1].

Meta-analyses have established an association between COPD and cardiac disease, especially coronary artery disease and cardiac arrhythmias [1]. It has been hypothesised that AECOPD could be linked to unrecognised arrhythmias, and a small study indeed found that p-wave dispersion, a surrogate for atrial arrhythmia, is greater during exacerbation than during the stable phase, hence possibly predating AECOPD [3]. Furthermore, diastolic dysfunction is a point of discussion: Prof. Bhatt presented unpublished data that found a 3-fold increase of severe exacerbations in patients with diastolic dysfunction and evidence of subclinical pulmonary oedema [1].

"Another comorbidity frequently noted in those with COPD is psychological distress in the form of anxiety or depression, which is present in up to 55% of individuals with COPD," informed Prof. Bhatt. Depression carries a higher risk for severe exacerbations as well as short- and long-term readmission to hospital [4,5]. However, anxiety is linked to an amplified risk for mild-to-moderate exacerbations, which could be due to augmented awareness of physical symptoms in anxiety patients [1,4].

Gastroesophageal reflux disease: a novel risk factor for AECOPD

An entirely different condition increasing the likelihood of AECOPD is gastroesophageal reflux disease (GERD). A recent meta-analysis identified that the presence of GERD augmented the odds for exacerbated COPD by 5-fold (OR 5.37; 95% CI 2.71–10.64) [6].

Also, vocal cord dysfunction (VCD) and expiratory central airway collapse were among the under-recognised aetiologies. A small study that included patients with COPD or asthma not only detected that VCD was more common in patients with COPD than with asthma, but also that the frequency of VCD was higher in individuals with (very) severe COPD than in the mild/moderate setting [7]. Furthermore, Prof. Bhatt stated, "Another underappreciated source of dyspnoea in individuals with COPD is that of central airway collapse; it is associated with a high risk of moderate as well as severe exacerbations, but whether this is an indicator of risk or it is causal, is not clear at this time." Prof. Bhatt concluded that even though all these aetiologies are biologically plausible, more data is needed to confirm them.

1. Bhatt SP. Under Recognized Etiologies of Exacerbations. Session B027: Phenotyping acute exacerbations of COPD. ATS 2021 International Conference, 14-19 May.
2. Bafadhel M, et al. Am J Respir Crit Care Med. 2011;184(6):662-71.
3. Chen W, et al. Lancet Respir Med. 2015;3(8):631-9.
4. Laurin C, et al. Am J Respir Crit Care Med. 2012;185(9):918-23.
5. Iyer AS, et al. Ann Am Thorac Soc. 2016;13(2):197-203.
6. Huang C, et al. BMC Pulm Med. 2020;20(1):2.
7. Ruane L, et al. European Respiratory Journal 2019 54 (suppl. 63) OA272.

Biomarkers for acute exacerbations in COPD are required

Currently, C-reactive protein has shown potential for infection triggered exacerbations and D-dimers have great value in differentiating from pulmonary embolism. Analysis of the sputum microbiome opens possibilities for the future.

"Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a heterogeneous disorder; it is not a single entity but made up of many different conditions," stated Prof. Don D. Sin (University of British Columbia, BC, Canada) [1]. They can be grouped by infectious aetiologies resulting from bacterial and/or viral triggers (50–60%) and non-infectious aetiologies such as pulmonary embolism or a lack of compliance. C-reactive protein (CRP) and N-terminal-prohormone of brain natriuretic peptide (NT-proBNP) are the most commonly investigated biomarkers for AECOPD. Nonetheless, even when combined they only achieved 0.8 AUC for discriminating AECOPD from other causes for respiratory distress in COPD patients [2]. For the same purpose, D-dimers have also been tested without providing enough resolution for clinical use, but this biomarker has proved itself valuable for ruling out pulmonary embolism [1]. Using a D-dimer threshold of 500 µg/L demonstrated that over a 3-month period patients below the threshold had a 0.94% risk of venous thromboembolism, whereas the risk of patients with ≥500 µ/L D-dimers was 9.4% [3]. CRP, on the other hand, is interesting to guide antimicrobial therapy. In the outpatient setting, the CRP-based decision-making for or against antimicrobial treatment led to ~20% absolute reduction in the use of antibiotics, compared with the usual approach that is based on clinical appearance [4]. CRP as guidance for antibiotic therapy of AECOPD in the hospital setting also entailed significantly fewer treatments with antibiotics than the Global Initiative for Chronic Obstructive Lung Disease (GOLD)-guided decision-making [5]. In light of these results, it was advocated that the case definition for AECOPD should be altered to become more objective by including values for dyspnoea worsening, oxygen desaturation, and lab results such as CRP, neutrophils, or eosinophils [6]. As the great majority of AECOPD have infectious causes, markers to phenotype the drivers are necessary as well [1].

Lung microbiome: a promising future tool to identify patients with poor prognosis?

Currently, it is known that even in healthy persons the lungs are not sterile. Moreover, molecular testing techniques such as 16S sequencing are used increasingly for pathogen identification. An investigation of the microbiome of the sputum of AECOPD patients at day 1 of hospital admission by 16S rRNA gene sequencing demonstrated that the microbiome profile may identify patients with poor prognosis [7]. The hazard of mortality within 1 year was higher in those who were missing *Veillonella*, a normal commensal in oropharynx and lungs, higher for those positive for *Staphylococcus*, and highest for patients *Veillonella*-negative and *Staphylococcus*-positive versus patients positive for *Veillonella* and negative for *Staphylococcus*. Furthermore, the diversity in the microbiome of survivors was greater than in that of non-survivors.

Concerning virus identification, Prof. Sin also saw future potential: "Going forward, we will have more molecular testing for viruses available to us and we do not have to just say the AECOPD was caused by a virus; we can identify the exact virus that was responsible for the AECOPD and develop a more targeted therapy to that virus.

Prof. Sin summarised: "Biomarkers are urgently needed to segregate the aetiologies into various categories for targeted therapy. Currently, CRP and D-dimers have the most promise. In the future, nevertheless, more molecular testing will be available to phenotype AECOPD and develop targeted therapy."

1. Sin DD. Biomarkers for Acute Exacerbations: Challenges and Promise. Session B027: Phenotyping acute exacerbations of COPD. ATS 2021 International Conference, 14-19 May.
2. Chen YWR, et al. PLoS One 2017;12(3):e0174063.
3. Couturaud F, et al. JAMA. 2021;325(1):59-68.
4. Butler CC, et al. N Engl J Med. 2019;381(2):111-120.
5. Prins HJ, et al. Eur Respir J. 2019;53(5):1802014.
6. Kim V, et al. Eur Respir J. 2018;52(5):1801261.
7. Leitao Filho FS, et al. Am J Respir Crit Care Med. 2019;199(10):1205-1213.

Severe exacerbations: A key driver of all-cause mortality in COPD patients

All-cause mortality increases more than 40-fold in chronic obstructive pulmonary disease (COPD) patients who experience severe exacerbations: this dramatic increase was revealed by a posthoc analysis of the phase 3 IMPACT trial. This result emphasises the need to optimise treatment in patients at risk of exacerbations.

Exacerbations of COPD result in acute worsening of respiratory symptoms, necessitating additional treatment. In particular, severe exacerbations are a key contributor to the clinical and economic burden of COPD. Previously, the IMPACT study (NCT02164513), involving more than 10,000 symptomatic COPD patients, demonstrated that patients treated with 2 bronchodilators that still suffer from exacerbations will benefit from a triple combination: patients treated with the combination of fluticasone furoate, umeclidinium, and vilanterol experienced a 34% reduction in the annual rate of severe exacerbations and a 42% reduction in on-treatment all-cause mortality versus patients treated with the combination of umeclidinium plus vilanterol only [1].

During this year's ATS meeting, a posthoc analysis was presented on the risk of all-cause mortality during and following a moderate or severe exacerbation in patients enrolled in the IMPACT trial [2]. Moderate exacerbations were defined as those requiring treatment with antibiotics or systemic/oral corticosteroids. Severe exacerbations were defined as those resulting in hospitalisation or death.

Overall, 42.5% of patients experienced an on-treatment moderate exacerbation and 11.4% on-treatment severe exacerbations. The most common cause of death in the analysis was cardiovascular in the exacerbation-free period and respiratory during the exacerbation. Moderate exacerbations did not significantly increase the risk of all-cause mortality during an exacerbation. In contrast, this risk increased 41-fold during a severe exacerbation event compared with the exacerbation-free period and decreased thereafter to levels not significantly different from the baseline period. As Prof. Manoj J. Mammen (Jacobs School of Medicine and Biomedical Sciences, NY, USA) pointed out, these results show that severe exacerbations are the driver of mortality risk in these patients. This highlights the importance of the prevention of these events as a COPD treatment goal.

1. Lipson DA et al. N Engl J Med 2018;378:1671-80.
2. Mammen MJ, et al. Risk of all-cause mortality during and after severe exacerbations in patients with chronic obstructive pulmonary disease (COPD): Post hoc analysis of the IMPACT trial. Session TP040: COPD clinical trials and therapies. ATS 2021 International conference, 14-19 May.

Men and women with COPD differ in many ways

The cohort study COSYCONET identified gender-specific differences in certain symptom levels of chronic obstructive pulmonary disease (COPD) and comorbidities and their relationships. Moreover, different predictors for cardiac disease could be identified.

The German COSYCONET cohort strives to investigate the trajectory of COPD with special regard to systemic factors and comorbidity. Dr Franziska Trudzinski (University Hospital Centre Heidelberg, Germany) assessed in a new analysis whether gender-specific differences, when present in symptoms of COPD, could influence the diagnosis of cardiac comorbidities [1]. Included were 2,046 individuals (38.9% women) from COSYCONET with information on clinical history, comorbidity status, and lung function. Also available were results of the 8-item COPD Assessment Test (CAT) and Medical Research Council Dyspnoea Scale (mMRC). Mean age was 65 years, BMI was 26.6 kg/m^2, Global Initiative for Chronic Obstructive Lung Disease (GOLD) classifications 1–4, ratio for forced expiratory volume in 1 second/forced vital capacity ratio (FEV_1/FVC) was 51.6. Smoking status was assessed as well. Using multivariate regression, gender-associated differences in the link between symptoms, functional impairments, comorbidities, and the distinct CAT items were evaluated. Furthermore, data on cardiac disease, represented by coronary artery disease, heart failure, and myocardial infarction, was valued individually for women and men to assess for possible predictors of cardiac comorbidity.

The study discovered noteworthy differences between women and men for certain CAT items, as well as for the majority of functional parameters and comorbidities. Cough (CAT 1), phlegm (CAT 2), and activities (CAT 5) were significantly dissimilar between genders ($P<0.05$). For gender-specific disparities in the relationship of symptoms, functional parameters, and comorbidities, associations were apparent for energy (CAT 8) and activities (CAT 5) in men and chest tightness (CAT 3) in women. These same CAT items per gender were also associated with cardiac disease. The authors deduced that gender-specific differences in COPD not only comprised differences in levels of symptoms, comorbidities, and functional alterations but also differences in their mutual relationships. These findings suggest that diagnostic information should be used differently in men and women.

1. Trudzinski FC, et al. Gender-Specific Differences in COPD Symptoms and Their Impact for the Diagnosis of Cardiac Comorbidities: Results from COSYCONET. Session TP39: COPD Comorbidities. ATS 2021 International Conference, 14-19 May.

Younger adults with COPD at higher health risk than previously thought

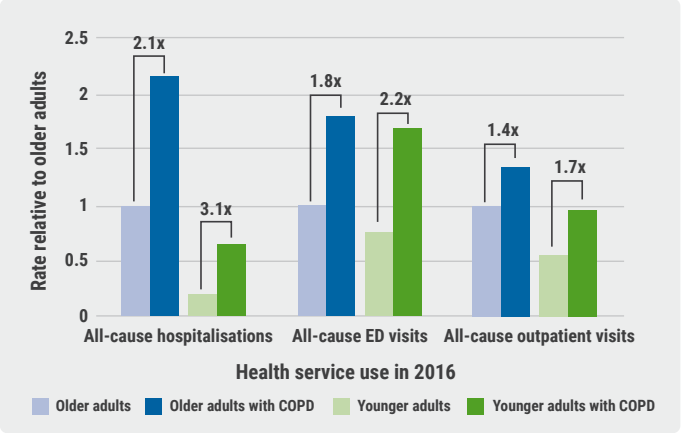
A population-based Canadian study found that younger adults with chronic obstructive pulmonary disease (COPD) needed healthcare much more than expected. Not only did they visit the emergency department almost as often as older COPD patients, but the height of their excess mortality rate was also unanticipated.

COPD is mostly seen as a condition of older individuals, but it is present as well in younger adults [1]. "It is commonly assumed that COPD diagnosed earlier in life equates a milder form of the disease," indicated Dr Alina J. Blazer (University of Toronto, ON, Canada). Dr Blazer and her fellow researchers strove to investigate the burden of disease in terms of

healthcare usage and mortality of younger COPD patients, as currently there is little evidence on this group's real-world clinical features.

Healthcare administrative data from 14 million Ontarians between 2006 and 2016 was screened and all younger adults with COPD (aged 35 to 55) as well as older ones (>65 years) were identified. Furthermore, corresponding rates of individuals without COPD of the same age groups were included. "For comparison of relative differences, the data presented here has been normalised to the rate for older adults without COPD as one," informed Dr Blazer. The findings that both older and younger COPD patients needed healthcare more often than individuals without COPD was not unexpected. "However, we were surprised to find how elevated the rates were among younger adults," said Dr Blazer. Looking at all-cause hospitalisations, older adults with COPD had a ~2-fold increase compared with those without COPD (see Figure). However, in the younger group, the rate was more than 3 times higher for the COPD patients compared with individuals without COPD. Also, for emergency department visits and outpatient visits, the rates of the younger adults with COPD surpassed those of the COPD-free correspondents. Dr Blazer pointed out that the rate of emergency department visits approached that of older adults with COPD. Concerning mortality, the rate of older adults with COPD was 2.5 times higher than in their comparison group. Remarkably, younger adults with COPD had a 5-fold amplified mortality rate when compared to those without COPD.

Figure: Rates of hospitalisation, emergency department, and outpatient visits in the different groups [1]



"This study provided further evidence that so-called early COPD is not necessarily a benign entity and suggests that we should focus clinical efforts on identifying COPD in younger patients in the hope that earlier intervention may improve their current health, reduce resource utilisation, and prevent further disease progression," concluded Dr Blazer.

1. Blazer AJ. Excess Healthcare Utilization and Mortality in Younger Adults with COPD. Session C008: Innovations and updates in the study and management of COPD. ATS 2021 International Conference, 14-19 May.

Metabolic Dysregulation and Lung Disease

Obesity: A risk factor for new-onset asthma and worse asthma control

For at least 2 decades, it has been widely recognised that obesity increases asthma incidence, impairs asthma control, diminishes response to therapy with inhaled corticosteroids (ICS), and increases the chances of an asthma exacerbation. Abdominal obesity appears the most important risk factor.

Obesity stimulates bronchial hyperresponsiveness and leads to a steeper loss of lung function. "While there are varying degrees of strength and consistency in these associations, taken together, they strongly suggest that metabolic dysregulation/obesity can worsen airway function and adversely affect the health of patients with asthma," Prof. Fernando Holguin (University of Colorado Asthma Research and Education, CO, USA) explained [1].

In the longitudinal CARDIA cohort, 4,619 participants were followed for 25 years – 602 developed asthma [2]. Results indicated that metabolic syndrome predicted incident asthma among women but not men. BMI had a similar predictive

association among women but not men. However, in the adjusted model only BMI was significantly associated with future asthma. "BMI is a more significant parameter than metabolic syndrome," Prof. Holguin concluded. In a French study including 121,965 men and women examined between 1999 and 2006, a positive independent relationship between lung function impairment and metabolic syndrome in both sexes was found [3].

Abdominal obesity in women: 50% elevated risk to develop new-onset asthma

In CARDIA, abdominal obesity was the most important risk factor for loss of lung function in both men and women for FEV_1 (OR 1.94; 95% CI 1.80–2.09) and FVC below the lower limit of normal (OR 2.11; 95% CI 1.95–2.29). Another cohort study emphasised the importance of abdominal obesity: in the Nord-Trondelag Health study, 23,191 participants who were asthma-free at baseline were followed for 11 years [4]. During this period, self-reported new-onset cases of asthma were assessed. General obesity was a risk factor for asthma in women and men. In women, after additional adjustment for BMI, abdominal obesity (waist circumference of ≥88 cm) remained a risk factor and was associated with a 50% higher risk to develop asthma [4]. Therefore, Prof. Holguin pointed out that both measures of BMI and waist circumference in women may be a superior clinical assessment for asthma risk than any measure alone.

Metabolic factors are more important than weight loss

An interesting insight on the influence of metabolic factors on asthma development was given by a study on the impact of bariatric surgery on asthma control. Among 2,458 participants of the multi-centre LABS study, change in asthma control was assessed in the 555 participants with an asthma diagnosis [5]. Of these, 78% (n=433) met criteria of metabolic syndrome at baseline. After the procedure, most patients lost weight. The proportion of participants with metabolic syndrome dropped from 78% at baseline to 36% at 1 year of follow-up, and subsequently continued to slowly drop to 30% by 60 months. "Looking at the group of patients that continued to have metabolic syndrome despite weight loss, those patients had a much higher hazard ratio of about 90% to lose asthma control. This is quite striking and suggests that not only one has to lose weight, but one also has to improve some of these metabolic factors," concluded Prof. Holguin. When the researchers assessed the association between the individual components of metabolic syndrome and the risk of uncontrolled asthma, again central obesity turned out to be most important. These patients had a more than 2.5 times elevated relative risk to lose asthma control [5]. In a retrospective cohort of US obese adults with asthma, prediabetes and diabetes were associated with higher rates of asthma exacerbations: compared with individuals with normal HbA1c, those in the prediabetes range had a 27% higher rate (95% CI 5–52%), and those in the diabetes range had a 33% higher rate (95% CI 2–73%) of exacerbations [6].

Diabetes therapeutics can have beneficial effects

Interestingly, therapy of type 2 diabetes can influence the risk of asthma exacerbations. In a study published recently, asthma exacerbations in patients with type 2 diabetes and asthma treated with glucagon-like peptide-1 receptor agonists (GLP-1R) were compared with patients with type 2 diabetes receiving other antidiabetic medications [7]. Patients treated with a GLP-1R had a significantly lower risk of asthma exacerbations within 6 months of drug initiation compared with patients in all comparator groups. "This suggests some protective effect of GLP-1R agonists, which is worth exploring," Prof. Holguin explained. Another antidiabetic that might have a favourable influence on the risk of asthma exacerbations is metformin. In a claims-based cohort study including 23,920 individuals with asthma and diabetes, therapy with metformin was associated with lower hazard of asthma exacerbations, but there were no differences in the use of corticosteroids in patients [8].

One of the mechanisms that could play a role in patients with asthma and metabolic risk factors is a high IL-6 concentration. In a study, exacerbation prone asthma was characterised by lower FEV_1 and a higher prevalence of obesity. High-plasma IL-6 concentrations occurred in these patients, and there was an increased risk of asthma exacerbation of 9% for each 1-pg/µL increase in baseline IL-6 level [9].

Taken together, multiple mechanisms lay behind the detrimental effects of metabolic dysfunction on asthma and other respiratory diseases [10].

1. Holguin F. Metabolic Syndrome and Asthma in Adults. Session A026: Metabolic dysregulation and lung disease: a common thread between children and adults. ATS 2021 International Conference, 14-19 May.
2. Assad N, et al. Am J Respir Crit Care Med 2013;188(3):319-26.
3. Leone N, et al. Am J Respir Crit Care Med 2009;179(6):509-16.
4. Brumpton B, et al. Eur Respir Med 2013;41(2):323-9.
5. Forno E, et al. PLoS One 2019;14(4):e0214730.
6. Wu TD, et al. J Allergy Clin Immunol Pract 2019;7(6):1868-73.
7. Foer D, et al. Am J Respir Med 2020;203 (7):831-840.
8. Wu TD, et al. Ann Am Thorac Soc 2019;16(12):1527-33.
9. Peters M, et al. Am J Respir Crit Care Med 2020;202(7):937-82.
10. Baffi CW, et al. Chest 2016;149 (6):1525-34.

Metabolic dysfunction and lung disease: children are no small adults

Not only in adults but also in the paediatric population obesity is detrimental to respiratory health. Many things are similar to the adult population, including underlying immune mechanisms and inflammatory pathways. But there are also striking differences, especially regarding the anatomy and the development [1].

The extra weight compresses the lung and reduces lung volume and airway diameter. Therefore, it gets more difficult for the airway muscles to relax. Nevertheless, lung function in adults remains the same across a wide BMI spectrum [2]. "However, this is not the case in children; in obese children, FEV_1 decreases rapidly," Prof. Erick Forno (University of Pittsburgh, PA, USA) explained. Another significant difference is airway dysanapsis, the incongruence or asymmetry between the growth of the lung volumes and the calibre of the airways.

"In older adults starting in their 30s and up to their 70s, a restriction is observed following obesity-related lung function. This concept is different in children," Prof. Forno explained. In obese children, airway dysanapsis is present and associated with increased asthma morbidity. The presence of dysanapsis is reflected in greater lung volumes and lesser flows and may partly explain their reduced response to inhaled corticosteroids [3].

In a systematic review, randomised controlled trials that included paediatric asthma patients were analysed [4]. Altogether, 4 trials with a total of 246 patients could be analysed. In these trials, weight loss led to improvements in asthma-related quality of life and, to some degree, asthma control [4]. "Weight loss is important in children. Although we only have small studies, improvements are certainly visible," Prof. Forno concluded.

1. Forno E. Metabolic dysregulation and lung disease: are children small adults? Session A026: Metabolic dysregulation and lung disease: a common thread between children and adults. ATS 2021 International Conference, 14-19 May.
2. Forno E, et al. J Allergy Clin Immunol Pract 2018;6(2):570-81.
3. Forno E, et al. Am J Respir Crit Care Med 2017;195(3):31-23.
4. Okoniewski W, et al. Ann Am Thorac Soc 2019;16(5):613-25.

Best of the Posters

Air pollution in winter linked to more hospital admissions in ILD patients

A study on the effect of air pollution on the hospitalisation rate in patients with interstitial lung disease revealed that elevated nitrogen dioxide concentrations were associated with a 50% increased rate of hospital admissions. The study used 2 models of exposure assessment.

"The body of evidence on the effect of air pollution on pulmonary disease is quite large, but concerning interstitial lung disease (ILD), knowledge on air pollution is still in its infancy," Dr Marya Ghazipura (Marron Institute of Urban Management, NY, USA) said. Today, only 12 studies exist on this topic, with most of them focusing on idiopathic pulmonary fibrosis (IPF), all of them in population-dense regions [1]. Even less is known about the effects of air pollution exposure on non-IPF ILDs in populations that are not in major metropolitan regions.

"The aim of our study was to quantify the short-term effects of outdoor air pollution on hospitalisations in a population of patients with ILD in the Intermountain West region of the US," explained Dr Ghazipura. Therefore, a cohort of 1,365 patients with ILD across this region was followed at the University of Utah, with hospitalisation data collected from 2009–2018 [2]. Daily concentrations of major pollutants (atmospheric particulate matter with a diameter of <2.5 micrometres ($PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3) were calculated using 2 models of exposure assessment: one by ground-level monitors, where weighted concentrations of all monitors within a 20 km radius of the patient were obtained, and one optimal interpolation (OI) model, a validated model integrating satellite remote sensing data. A time-stratified, case-crossover study was performed using a 14-day interval to estimate the association between short-term exposure to air pollution and hospitalisations. Results were stratified by high (March to October) and low (April to September) ozone months.

No association was found between concentrations of $PM_{2.5}$ and O_3 and the risk of hospitalisation in both models. In contrast, the OI model found that in the colder season, an interquartile increase in daily average NO_2 exposure was associated with 1.5 times the odds of being hospitalised. This association was significantly more pronounced in men. "We would not have

been able to detect this significant association with NO_2 if we had only relied on the monitors, considering all the monitor gaps in the Intermountain West region. For NO_2, using the OI model was critical," Dr Ghazipura explained. She concluded that further research on this topic will help to give evidence-based guidance regarding air pollution to this already vulnerable patient group.

1. Harai S, et al. Eur Resp Rev 2020;29:200093.
2. M Ghazipura. Impacts of air pollution in patients with interstitial lung disease. Session TP066: Diffuse parenchymal lung diseases: ILD, sarcoidosis, IPF, LAM. ATS 2021 International conference, 14-19 May.

Tobacco biomarkers do not improve prediction of lung cancer risk

Previous studies have demonstrated tobacco biomarkers to be associated with lung cancer. Nonetheless, a case-control study showed that the integration of 3 relevant tobacco biomarkers in the validated lung cancer prediction model PLCOm2012 did not improve the performance of this validated model.

The lung cancer risk prediction model PLCOm2012 is a validated logistic regression lung cancer risk prediction model based on data collected from the control arm of the PLCO trial. This model uses historical and demographic data to identify individuals who should receive cancer screening. Previous studies have shown that biomarkers of tobacco exposure are associated with lung cancer, but they were never used in the prediction of lung cancer risk. Therefore, Dr Christine Lambert (University of Minnesota, USA) and her co-workers created a new lung cancer risk prediction model that incorporated 3 tobacco biomarkers into the PLCOm2012 model: serum cotinine level, NNAL, and PheT [1]. Cotinine is a metabolite of nicotine. Both NNAL and PheT are metabolites of polycyclic aromatic hydrocarbons (PAH), which are believed to be among the principal causative agents for lung cancer in smokers [2]. This case-control study was performed with the aim to assess whether including these biomarkers can improve the prediction of 6-year lung cancer risk.

Lung cancer cases (n=72) diagnosed within 6 years of PLCOm2012 randomisation –to match the prediction time frame of this model– were compared with 115 cancer-free controls drawn from current smokers in the screening arm of PLCO. Smoking-pack years and levels of the 3 tobacco biomarkers were higher in lung cancer cases compared with controls. "In the logistic regression model, the PLCOm2012 was a significant predictor of lung cancer risk," Dr Lambert said. In contrast, all 3 biomarkers did not predict lung cancer risk after accounting for the PLCOm2012 risk score. "The addition of biomarkers did not improve the performance of the prediction model for lung cancer risk compared with the PLCOm2012 model alone," concluded Dr Lambert. Lack of study population diversity and heavy smoking amongst cases and controls may have limited the tobacco biomarker effect and its predictive ability.

1. Lambert C, et al. Use of tobacco biomarkers in lung cancer risk assessment. Session TP136: Thematic Poster session: Lung cancer, thoracic oncology. ATS 2021 International conference, 14-19 May 2021.
2. Yuan JM, et al. Cancer Res 2011;71:6749-57.

Vaping identified as risk factor for asthma

An analysis of Canadian survey data found an association between e-cigarette smoking and asthma. Not only did vaping increase the odds for asthma by 19%; those who had asthma were also more prone to exacerbation.

Every 2 years, the Canadian Community Health Survey gathers health-related data of Canadian inhabitants at the regional level. The 2019 survey in Ontario reported 23% of >14,000 adolescents in student grades 7–12 as e-cigarette (EC) smokers, a marked rise from the previous survey. "Our study asks the following questions: do EC users have an increased risk of asthma, and if so, do they incur higher odds of an asthma attack," Prof. Theresa To (The Hospital for Sick Children, ON, Canada) explained [1]. The new cross-sectional study was based on data from individuals aged ≥12 years partaking in 2 cycles of the Canadian Community Health Survey dated 2015/2016 and 2017/2018 [2]. For the case-control design, cases were defined as those self-reporting EC smoking within the last 30 days. To each case, 5 non-vaping controls were matched by age, sex, BMI, smoking, and socioeconomic status, employing a propensity score. The latter is a common statistic technique to reduce bias due to confounding variables in observational studies.

Together, the study included 17,190 matched subjects of whom 3.1% met the criteria of EC users. Hence, 1 in 32 participants smoked EC within the last 30 days. The logistic regression that controlled for potential confounders associated with asthma, including the variables utilised for the propensity score, identified 19% elevated odds of asthma in EC-using persons. Moreover, EC-vaping individuals with asthma had a 24% higher likelihood of having experienced an asthma attack in the last year. Interestingly, 50% of EC users also smoked cigarettes on a daily basis, whereas only 15% in the group not using EC did. "Of the EC users, about 15% reported fair to poor mental health compared with 7% amongst non-user," Prof. To further

elaborated. "These findings suggest that EC use is a modifiable risk factor for asthma to be considered in the primary care of youths and adults," concluded Prof. To.

1. To T, et al. Does Vaping Increase the Odds of Asthma? A Canadian Community Health Survey Study. Session TP16: Clinical and research updates on tobacco cessation, vaping, and e-cigarettes. ATS 2021 International Conference, 14-19 May.
2. Mehra VM, et al. BMC Public Health 2019;19(1):1208.

Advanced cystic fibrosis – improved lung function with long-term triple therapy

Longer treatment with triple CFTR-modulation resulted in not only FEV_1 but also FVC amelioration in cystic fibrosis patients with high-risk features . This was found in a new study that thus confirmed benefits seen in pivotal trials for advanced disease.

The combination elexacaftor/tezacaftor/ivacaftor has demonstrated benefit in lung function improvement in clinical trials and was approved by the EMA as orphan drug to treat patients with cystic fibrosis (CF) who have at least one F508del mutation in the *CFTR* gene [1]. The currently presented retrospective cohort trial shed light on longer-term efficacy. The study included medical records of 50 adult patients with CF and advanced lung disease. Efficacy and safety of triple combination therapy (TC) with the CFTR-modulators was investigated [2]. A reason for the particular interest in the question is the exclusion of subjects with advanced lung disease from phase 3 trials for CF, resulting in a lack of knowledge about treatment of this patient group in terms of TC. Previously, the group of researchers had already demonstrated short-term outcome improvements with TC for patients with CF and advanced lung disease.

The participants all had a forced expiratory volume in 1 second percent of predicted (FEV_1pp) <40% or other high-risk features before they started TC. Baseline characteristics comprised 52% women, 64% patients who were homozygous for F508de, and a mean age of 32. Pre-treatment mean values were FEV_1pp 33.0, forced vital capacity per cent predicted (FVCpp) 54.3, and BMI 23.2 kg/m^2. TC was started between September 2019 and February 2020. The results of spirometry –performed at 2–12 weeks, 3–9 months, and >9 months after TC commencement– served as markers for treatment response, as did the change in BMI. The longer-term TC therapy resulted in a significant 8.4% increase in FEV_1pp (P<0.001) and a significant amelioration of FVCpp by 9.4% (P<0.001). Furthermore, positive results of TC were noted as increased BMI (25.1 kg/m²) and a reduction of exacerbations from 3.22 in 12 months to 1.25 (p<0.0001). Importantly, after TC, only 22% remained to have a transplant referral; before TC this was 63%. The authors wish for further investigations with data from more centres that contain rates of lung function loss, lung transplantation, and mortality.

1. https://www.ema.europa.eu/en/medicines/human/EPAR/kaftrio, accessed 30 May 2021.
2. Bermingham B, et al. A one-year retrospective analysis of the effect of elexacaftor-tezacaftor-ivacaftor on lung function in cystic fibrosis patients with advanced lung disease. Session TP32: Epidemiology, biomarkers, and therapy in CF and non-CF bronchiectasis. ATS 2021 International Conference, 14-19 May.

IPF patients benefit from early antifibrotic therapy

An observational study assessed the influence of earlier versus later therapy with the tyrosine kinase inhibitor nintedanib in patients diagnosed with idiopathic pulmonary fibrosis. Early therapy was associated with less hospitalisations and a reduction of all-cause medical costs.

Idiopathic pulmonary fibrosis (IPF) is a chronic lung disease characterised by progressive lung function decline and a poor prognosis with a median survival time ranging from 2.5 to 3.5 years [1]. In posthoc analyses of placebo-controlled studies, the tyrosine kinase inhibitor nintedanib consistently decelerated lung function decline by ~50% among patients with preserved or reduced lung function [2,3]. However, the debate is ongoing on when to initiate treatment in a real-life setting. Therefore, a posthoc analysis presented during ATS 2021 assessed medical costs and risk of hospitalisation among patients with IPF by the timing of nintedanib initiation within 12 months after diagnosis [3]. The observational study included administrative claims data on insured patients aged ≥40 years with ≥2 medical claims with an IPF diagnosis on separate dates from 01 Oct 2014 to 30 Jun 2019 [4]. All participants were enrolled for at least 6 months before IPF diagnosis and up to 13 months after for cost analysis, or 12 months after for hospitalisation analysis. The researchers retrospectively analysed data on all-cause 12-month medical costs and all-cause follow-up hospitalisation. As information such as forced vital capacity value is not readily available in claims data, proxies (e.g., oxygen use) were utilised as markers for disease severity and included as confounder in the statistical analysis.

Study cohorts were analysed according to time from IPF diagnosis to treatment initiation (1, 2–3, 4–6, or 7–12 months). The study sample consisted of 449 patients with a mean age of 72 years; the majority were men (68%), as expected in an

IPF population. Baseline all-cause medical utilisation and associated costs were comparable between cohorts.

Adjusted 12-month all-cause medical costs and adjusted all-cause hospitalisation risk differed by the timing of nintedanib initiation (P=0.020 and P<0.001, respectively). All-cause hospitalisation risk was significantly higher among patients who were not yet treated versus patients treated before the end of months 2–3 (P=0.026), 4–6 (P=0.014), and 7–12 (P<0.001). In addition, 12-month all-cause medical costs were 69% higher for patients who initiated treatment in months 2–3 versus month 1. Costs were numerically higher but not statistically different for patients starting therapy in months 4–6 and 7–12 versus month 1.

The authors concluded that early therapy soon after the IPF diagnosis may have reduced hospitalisation risk and was associated with lower medical costs. The reason for the benefit of early treatment might be due to the preservation of lung function in IPF, which obviously translates into a measurable real-world benefit.

1. Ley B, et al. Am J Resp Crit Care Med 2011;183(4): 431-40.
2. Costabel U et al. Am J Respir Crit Care Med. 2016;193(2):178-185.
3. Kolb M et al. Thorax 2017; 72(4):340-346.
4. Singer D, et al. Impact of timing of nintedanib initiation among patients newly diagnosed with idiopathic pulmonary fibrosis. Session TP15: Diffuse parenchymal lung diseases: ILD, sarcoidosis, IPF, LAM, ATS 2021 International conference, 14-19 May 2021.