ATS Conference 2018

American Thoracic Society

18-23 MAY 2018 • SAN DIEGO • USA

PEER-REVIEWED CONFERENCE REPORT

Dupilumab May Reduce the Need for OCS

VENTURE study shows positive effect on OCS dose, severe exacerbations, and long function.

read more on PAGE 4

Immune-Related Adverse Events During PD-1 Immunotherapy

In a US study, 15% of non-small cell lung cancer patients treated with PD-1 inhibitors exhibited adverse events, including pneumonitis.

read more on PAGE 8

Gut Microbiota are Critical Regulator of Intravascular Immunity During Sepsis

MRSA mouse model used to unravel underlying mechanisms.

read more on PAGE 12

MEDICOM MEDICAL PUBLISHERS

Prof. Richard Dekhuijzen, Radboud University Medical Center, Nijmegen, the Netherlands

Contents

COLOPHON

Editor	Prof. P.N. Richard Dekhuijzen, Radboud University Medical Center, Nijmegen, the Netherlands
Editorial Manager	Lisa Colson
Editorial Coordinators	Dr Joery Goossens Nalinee Pathak, MSc
Executive Publisher	Rene Draper, MSc
Medical Writers	Constance de Koning, LLM Prof. Zuzana Diamant
Production Manager	Desiree Heijl
Graphic Design	MOOZ grafisch ontwerp
Layout	Wim Kempink Mayke Putman

MEDICOM MEDICAL PUBLISHERS

Postal address
Medicom Medical Publishers
PO Box 90
Zipcode 3740 AB
City Baarn
Country The Netherlands

Head Office
Medicom Medical Publishers
Faas Eliaslaan 5
3742 AR Baarn
The Netherlands

Telephone +31 85 4012 560
Fax +31 85 4012 569
E-mail publishers@medicom.nl

ISSN 2468-8762 18:7

Letter from the Editor

Prof. Richard Dekhuijzen

Dear Reader,

This year's International Congress of the American Thoracic Society (ATS) was again the place to be to get the most recent update in important areas of pulmonary diseases.
Short- and long-term data on the effects and safety of biological agents are accumulating and may guide to further personalised pharmacological treatment. Modulators of IL-5 and IL-4/IL-13 activity show important effects on exacerbation rates, hospitalisations, and dose of oral corticosteroids. Insights into careful patient selection are increasing.
The main changes in the GOLD 2018 recommendations for COPD have been discussed. The 2017 way to categorise patients by splitting level or airflow limitation and levels of complaints and exacerbations connects better to the daily clinical practice than the previous one. Also, increasing data on LABA/LAMA combinations and when they are preferred to LABA/ICS combinations were presented.
Treatment options in lung cancer are increasingly expanding and provide better outcomes for patients. Data on long-term effects are accumulating. The occurrence of sometimes serious AEs is being more easily recognised. Simultaneously, screening remains an important early stage diagnostic tool. It should be considered in a large number of individuals who may be at high risk of developing cancer.
Respiratory infections remain a burden worldwide, and new therapeutic strategies continue to be investigated. Also, underlying causes and risk factors have been subjected to extensive research, elucidating some of these processes. Interesting data on old and new agents in tuberculosis were presented.
If you have not been able to experience these aspects of the ATS yourself, this report will outline the most significant advancements discussed at the conference, and the practical advice disseminated there. Besides the topics indicated above, interesting findings regarding lung cancer and pulmonary hypertension are also presented. So, we hope that you will enjoy reading this Conference Report!

Kind regards,
Prof. Richard Dekhuijzen

Biography

Prof. P.N. Richard Dekhuijzen (Amsterdam, the Netherlands, 1956) is Professor of Pulmonology at the Radboud University Medical Center in Nijmegen, the Netherlands. His specific area of research interest is in asthma, COPD, and inhalation technology.
He studied medicine at the 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 text book chapters on respiratory medicine. Until 2016, he was chair of the Department of Pulmonary Diseases and chair of the Heart-Lung Centre Nijmegen, and he was Head of Department of Cardiology between 2008-2010. Until 2016, he was chair of the Medical Staff of the 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.

Airway Diseases

Chronic obstructive pulmonary disease (COPD) and asthma treatment options have expanded over the years with a plethora of agents to choose from to suit almost every individual patient. Nevertheless, disease burden remains high, often affecting the quality of life of patients in many different ways. Short- and long-term data on the effects of biological agents are accumulating and may guide to further personalised pharmacological treatment.

Benralizumab improves lung function in severe, uncontrolled, eosinophilic asthma

Benralizumab – a humanised, afucosylated anti-interleukin (IL)-5 receptor alpha monoclonal antibody, which induces direct, rapid, and nearly complete depletion of eosinophils – has been investigated in the ZONDA phase 3 trial. This study included 220 patients (aged 18-75 years) with severe, uncontrolled asthma (eosinophil counts ≥150 cells/μL) who were receiving high-dosage inhaled corticosteroids (ICS) and/or long-acting β2-agonists, and had oral corticosteroids (OCS) titrated to the minimum effective dosage (baseline) without losing asthma control. Patients received benralizumab 30 mg subcutaneously either every 4 weeks (Q4W: n=72) or every 8 weeks (Q8W; first three doses Q4W: n=73), or placebo (Q4W: n=75), for 28 weeks. The treatment period comprised a 4-week induction phase (in which optimised OCS dosage was maintained), a 20-week reduction phase (in which OCS dosage was reduced), and a final 4-week maintenance phase (in which no further OCS dosage adjustment took place). Benralizumab significantly reduced OCS dosages from baseline by 75% vs 25% for placebo (P<0.001), while reducing the annual exacerbation rate by as much as 70% vs placebo (P<0.001) [1]. Now, the impact of benralizumab treatment and reduced OCS use on lung function, as assessed by peak expiratory flow (PEF) was assessed. In this pre-specified analysis, PEF averages over 2-week periods for 28 weeks were estimated. The results showed that morning PEF increases, expressed as least squares mean changes from baseline to week 28, were greater with benralizumab Q8W than with placebo (difference: 30.01 L/min, nominal P=0.023, Table 1) [2].

Table 1 Changes in morning PEF from baseline* [2]

Endpoints	Benralizumab 30 mg Q4W (n=72)	Benralizumab 30 mg Q8W (n=73)	Placebo (n=75)
Week 2			
Patients with Week-2 data, n	72	72	75
Least squares mean change, L/min	23.61	20.26	1.53
Least squares mean difference vs placebo, L/min	22.07	18.73	-
(95% CI)	(7.05, 37.10)	(3.71, 33.74)	
Nominal P-value	0.004	0.015	-
Week 28			
Patients with Week-28 data, n	67	68	67
Least squares mean change, L/min	29.02	39.78	9.77
Least squares mean difference vs placebo, L/min	19.25	30.01	-
(95% CI)	(-6.58, 45.07)	(4.26, 55.76)	
Nominal P-value	0.143	0.023	-

* Baseline was the average of data collected from the evening of study day -14 to the morning of day 1. Averages were calculated over the 2-week period ending at week 2 or week 28.

Morning PEF increases from baseline to week 28 were observed also with benralizumab Q4W. These increases were greater than those observed with placebo, but smaller than those observed with benralizumab Q8W. Greater increases in least squares mean changes from baseline in morning PEF with benralizumab Q4W or Q8W vs placebo were observed during the first 2 weeks (Q8W: difference: 18.73 L/min, nominal P=0.015). Improvements were maintained through week 28. Thus, benralizumab – as an OCS-sparing therapy – improved lung function as assessed by PEF for patients with severe, uncontrolled, eosinophilic asthma [2].

Macrolides can improve asthma control, quality of life, and symptom scores

A meta-analysis of clinical trial results to update the current evidence of macrolides in the management of patients with asthma was performed by Wang et al. [3]. Included in the meta-analysis were randomised controlled trials of macrolides treatment on patients with asthma published up to October 2017 that reported pulmonary function, quality of life scores, symptom scores, and asthma control. A total

of 16 studies involving 1,745 patients were identified. It was shown that macrolides treatment could significantly improve asthma control (standard mean difference: -0.58, 95% CI: -1.15 to -0.01), quality of life (mean difference: 0.16, 95% CI: 0.04 to 0.29), symptom scores (mean difference: -0.76, 95% CI: -1.29 to -0.23), but it was not associated with improvement in forced expiratory volume in one second (FEV_1) (standard mean difference: 0.06, 95% CI: -0.06 to 0.28) and PEF (mean difference: 0.11, 95% CI: -0.02 to 0.24). It was concluded that macrolides treatment seemed to have no effect on lung function (FEV_1 or PEF), but produced significant improvements in asthma control, quality of life, and symptom scores. The researchers stated that further large clinical trials are necessary to measure the clinically relevant outcomes (such as asthma exacerbations, symptom score, and lung function) [3].

Indacaterol/glycopyrrolate significantly improves COPD

The impact of reversibility on lung function, health status, and dyspnea in COPD patients treated with indacaterol/glycopyrrolate 27.5/15.6 mg twice-daily vs placebo was assessed in a pooled analysis of the FLIGHT1 (NCT01727141) and FLIGHT2 (NCT01712516) studies [4]. These were 12-week, randomised studies including 2,043 patients with moderate-to-severe COPD. The study compared indacaterol/glycopyrrolate vs placebo by reversibility for the following endpoints: FEV_1 area under the curve (AUC) from 0-12 hours, St. George's Respiratory Questionnaire (SGRQ) total score, and Transition Dyspnea Index (TDI) score. Patients with any history of asthma were excluded. FEV_1 reversibility was calculated as percentage increase of FEV_1 after sequential inhalation of short-acting (anticholinergic and β2-agonist) bronchodilators. Reversibility was defined as a post-bronchodilator increase of ≥12% and ≥0.200 L in FEV_1. Results from the pooled analysis showed that the overall mean reversibility was 22.8% (standard deviation 17.6%); 54.5% of patients met the reversibility criteria. Indacaterol/glycopyrrolate showed statistically significant improvements compared to placebo in FEV_1 AUC 0-12h at day 85 regardless of reversibility status (least squares mean treatment difference: reversible 0.308 L, P<0.001; non-reversible 0.170 L, P<0.001). Significant reductions in the SGRQ total score vs placebo were also observed, with greater reductions in the reversible group than in the non-reversible group (-6.3, P<0.001 and -3.5, P=0.001, respectively). Significant increases in TDI score compared to placebo were seen in reversible and non-reversible groups with greater improvements in the reversible group (1.93, P<0.001 and 1.29, P<0.001, respectively). These findings show that indacaterol/glycopyrrolate significantly improves lung function, SGRQ total score, and TDI score compared to placebo, regardless of reversibility status. Greater improvements were observed in reversible patients. It was emphasised that the effect of reversibility on the response to bronchodilator therapy should be explored in future studies [4].

Dupilumab may reduce the need for OCS

Dupilumab – a monoclonal antibody directed against the alpha subunit of the IL-4 receptor that inhibits IL-4 and IL-13 signalling – has been approved in several countries for treatment of adults with inadequately controlled moderate-to-severe atopic dermatitis. However, it has also shown to significantly reduce severe exacerbations and improved lung function in patients with uncontrolled persistent asthma (NCT01854047) [5]. The LIBERTY ASTHMA VENTURE is a phase 3 study (NCT02528214) that evaluates efficacy and safety of dupilumab for OCS reduction in patients with corticosteroid-dependent severe asthma [6]. A total of 210 patients aged ≥12 years received (1:1) subcutaneous dupilumab 300 mg (600 mg loading dose on day 1) or placebo every 2 weeks (Q2W) for 24 weeks as add-on therapy. After completing an 8-10-week optimisation period, OCS dose was down-titrated from week 4 to week 20, then maintained for 4 weeks. The primary endpoint of this study was the percentage reduction in OCS dose at week 24. Secondary endpoints included absolute reduction of OCS dose, proportion of patients achieving ≥50% reduction in OCS dose, proportion of patients achieving reduction in OCS dose to <5 mg/day, proportion of patients no longer requiring OCS, and proportion of patients achieving maximum OCS dose reduction at week 24. The results showed that in dupilumab-treated vs placebo-treated patients, OCS dose at week 24 was reduced by 70.1% vs 41.9% from baseline (P<0.0001). Also, 80% of dupilumab-treated patients at week 24 achieved ≥50% reduction in OCS (50% for placebo), 69% vs 33% achieved reduction to <5 mg/day, 48% vs 25% no longer required OCS, and 48% vs 26% achieved their maximum OCS dose reduction. Dupilumab reduced severe exacerbations by 59.3% (P<0.0001) and improved FEV_1 by 0.22 L vs placebo at week 24 (P<0.001). Its efficacy was observed regardless of baseline blood eosinophils. Adverse events (AEs) most frequently occurred at higher rates in dupilumab-treated vs placebo-treated patients. These included eosinophil count increase (6.8% vs 0%), eosinophilia (6.8% vs 0.9%), bronchitis

(6.8% vs 5.6%), and sinusitis (6.8% vs 3.7%). Conjunctivitis AEs were similar between treatment groups (1.0% vs 0.9%) [6].

Table 2 Key efficacy outcomes from VENTURE [6]

Outcome	Placebo (n=107)	Dupilumab 30 mg q2w (n=103)	Difference vs placebo (95% CI)*	P-value vs placebo
Primary endpoint				
Percentage reduction of OCS dose (mg/day) at week 24				
Baseline dose, mean (SD)	11.75 (6.31)	10.75 (5.90)		
Percent reduction at Week 24, least squares mean (SE)	41.85 (4.57)	70.09 (4.90)	28.24 (15.81-40.67)	<0.0001
Secondary endpoint				
Reduction of OCS dose (mg/day) vs baseline			-	
Baseline dose, mean (SD)	11.75 (6.31)	10.75 (5.90)		
Absolute reduction at Week 24, least squares mean (SE)	4.77 (0.54)	7.58 (0.58)	2.81 (1.33-4.29)	0.0002
Proportion of patients achieving a reduction of ≥50% in their OCS dose vs baseline at Week 24				
Adjusted probability of achieving a reduction, estimate (95% CI)	0.50 (0.40-0.61)	0.80 (0.70-0.87)	3.98 (2.06-7.67)	<0.0001
Proportion of patients achieving a reduction of OCS dose to <5 mg/day at Week 24				
Adjusted probability of achieving a reduction, estimate (95% CI)	0.33 (0.24-0.44)	0.69 (0.58-0.79)	4.48 (2.39-8.39)	<0.0001
Proportion of patients no longer requiring OCS at Week 24				
Adjusted probability of achieving a reduction, estimate (95% CI)	0.25 (0.17-0.35)	0.48 (0.36-0.59)	2.74 (1.47-5.10)	0.0015
Proportion of patients achieving their maximum possible OCS dose reduction at Week 24				
Adjusted probability of achieving a reduction, estimate (95% CI)	0.26 (0.18-036)	0.48 (0.36-0.59)	2.57 (1.40-4.73)	0.0024
Other endpoints				
Adjusted annualised severe exacerbation events during the 24-week treatment period				
No. patients with ≥1 event, n (%)	53 (49.5)	23 (22.3)		
Estimate (95% CI)	1.597 (1.248-2.043)	0.649 (0.442-0.955)	0.407 (0.263-0.630)	<0.0001
Percent reduction vs placebo			59.3 (37.0-73.7)	
Pre-bronchodilator FEV_1 (L)				
Baseline, mean (SD)	1.63 (0.61)	1.53 (0.53)		
Change from baseline to Week 12, least squares mean (SE)	0.05 (0.04)	0.22 (0.04)	0.17 (0.06-0.29)	0.0035
Change from baseline to Week 12, least squares mean (SE)	0.01 (0.05)	0.22 (0.05)	0.22 (0.09-0.34)	0.0007

* For the continuous endpoints, differences are expressed as least squares mean difference. For the binary endpoints, differences are expressed as odds ratio. For the event rate endpoint, differences are expressed as relative risk and percentage reduction.

Thus, dupilumab 300 mg Q2W significantly reduced the use of OCS while reducing severe exacerbations and improving FEV_1 in patients with corticosteroid-dependent severe asthma regardless of baseline blood eosinophils. The agent was generally well tolerated. Researchers added that these findings may pave the way for patients reducing or even getting off steroid use, which would be highly beneficial [6].

Mepolizumab reduces exacerbations in COPD and an eosinophilic phenotype

Treatment with mepolizumab – an anti-IL-5 monoclonal antibody – has shown to be beneficial for reducing exacerbations in patients with COPD and an eosinophilic phenotype who receive inhaled triple therapy. This was demonstrated by a pre-specified meta-analysis of this particular patient subset in the METREX and METREO studies [7]. These studies were phase 3, placebo-controlled, randomised, double-blind, multicentre trials. Patients were enrolled if aged ≥40 years with COPD and a history of ≥2 moderate and/or ≥1 severe exacerbations in the prior year despite ICS-based triple maintenance therapy. Patients received subcutaneous mepolizumab (100 mg [METREX], 100 or 300 mg [METREO]) every 4 weeks for 52 weeks as add-on therapy to inhaled triple therapy, consisting of ICS, a long-acting β2-agonist, and a long-acting muscarinic-receptor antagonist. There were two treatment comparisons performed (mepolizumab 100 mg vs placebo and mepolizumab all-doses [100 and 300 mg]) vs placebo. Primary endpoint was annual rate of moderate (requiring systemic corticosteroids and/or antibiotics) and/or severe (leading to hospitalisation/death) exacerbations. Secondary endpoints included time to first moderate or severe exacerbation, annual rate of exacerbations requiring emergency department/hospitalisation, and annual rate of severe exacerbations. A total of 1,136 patients were included in the meta-analysis (mepolizumab 100 mg: n=456; mepolizumab 300 mg: n=225, placebo: n=455). Of these, 95% of patients were classified as Global Initiative for Chronic Obstructive Lung Disease (GOLD) group D. Mean annual exacerbation rate (prior year) was 2.6 events/year for both groups. Mepolizumab (100 mg)-treated patients had an 18% significantly lower mean annual rate of moderate and/or severe exacerbations vs placebo (rate ratio: 0.82; 95% CI: 0.71-0.95; P=0.006). Furthermore, mepolizumab 100 mg vs placebo increased time to first moderate or severe exacerbation (hazard ratio: 0.80; 95% CI: 0.68-0.94; P=0.006). Mean annual rates of exacerbations requiring emergency department/hospitalisation were reduced by 15% and annual

rates of severe exacerbations by 12% with mepolizumab 100 mg vs placebo (rate ratios: 0.85; 95% CI: 0.61-1.18; P=0.328 and 0.88; 95% CI: 0.62-1.25; P=0.475, respectively). Similar results to mepolizumab 100 mg were observed in the mepolizumab all-doses group. Thus, mepolizumab significantly improved the annual rate and time to first occurrence of moderate or severe exacerbations vs placebo in patients with COPD and an eosinophilic phenotype. Also, reductions in exacerbations requiring emergency department/hospitalisation and rate of severe exacerbations were apparent with mepolizumab 100 mg relative to placebo [7].

Results from IMPACT: once-daily single-inhaler triple therapy beneficial in COPD

The IMPACT study compared single-inhaler triple therapy fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI) (100/62.5/25 µg) with FF/VI (100/25 µg) and UMEC/VI (62.5/25 µg), randomised 2:2:1 for 52 weeks in patients with symptomatic COPD and a history of exacerbations [8]. Primary endpoint of the study was the annual rate of moderate and/or severe exacerbations with FF/UMEC/VI vs FF/VI and UMEC/VI. A total number of 10,355 patients was treated (FF/UMEC/VI: n=4,151; FF/VI: n=4,134; and UMEC/VI: n=2,070). The results showed a statistically significant reduction in the annual rate of moderate and/or severe exacerbations for FF/UMEC/VI (0.91 annual exacerbation rate) vs FF/VI (1.07; rate reduction 15%; P<0.001) and vs UMEC/VI (1.21; rate reduction 25%; P<0.001). Annual moderate and/or severe exacerbation rates were lower with FF/UMEC/VI vs either dual combination regardless of eosinophil level, though a greater reduction was seen in patients with higher levels vs UMEC/VI (eosinophils <150 cells/µL: FF/UMEC/VI: 0.85/year; FF/VI: 1.06; UMEC/VI: 0.97, and ≥150 cells/µL: FF/UMEC/VI: 0.95/year; FF/VI: 1.08; UMEC/VI: 1.39). Annual rate of severe (hospitalised) exacerbations was 0.13 with FF/UMEC/VI, 0.15 with FF/VI (13% reduction; not significant) and 0.19 with UMEC/VI (34% reduction; P<0.001). Risk of on-treatment moderate or severe exacerbation was reduced by 14.8% for FF/UMEC/VI vs FF/VI (P<0.001) and by 16.0% vs UMEC/VI (P<0.001); based on time to first event. Difference in change from baseline trough FEV_1 at week 52 for FF/UMEC/VI was 97 mL (P<0.001) vs FF/VI and 54 mL (P<0.001) vs UMEC/VI. The change from baseline in SGRQ at week 52 was an improvement of -5.5 units for FF/UMEC/VI with a difference of -1.8 units vs both FF/VI and UMEC/VI (both P<0.001). The most frequent on-treatment serious AEs in FF/UMEC/VI, FF/VI and UMEC/VI treatment arms were COPD exacerbation (11%, 11%, 13%) and pneumonia (4%, 4%, 3%), respectively. Safety data were consistent with the known safety profiles of the individual components. Thus, use of the once-daily single-inhaler triple therapy FF/UMEC/VI reduced the rate of moderate and/or severe exacerbations, COPD hospitalisations, and improved trough FEV_1 and health status vs dual therapy with FF/VI or UMEC/VI in patients with symptomatic COPD with a history of exacerbations. No unexpected differences in AE profile between triple and dual therapy groups were observed [8].

Asthma affects sleep quality across various types of patients

Sleep quality can be affected by asthma and the extent of this relation was investigated by a single-centre cross-sectional study performed between June 2016 and October 2017. It showed that uncontrolled asthma is a predictor of poor sleep, as well as poor sleep quality being associated with worse asthma control and quality of life, which is not uncommon in patients with well-controlled asthma. This study enrolled 101 patients with a mean age of 38 years with physician-diagnosed asthma of at least 6 months (median asthma duration 66 months; range 6-480 months). Patients with acute exacerbation or hospitalisation due to any cause during the preceding 4 weeks, current or former smokers, and those with gastroesophageal reflux disease or high-risk obstructive sleep apnoea (as assessed by Berlin questionnaire) were excluded. Pittsburg Sleep Quality Index (PSQI) cut-off ≥5 was considered as poor sleep. Asthma control and quality of life was assessed by Asthma Control Questionnaire-6 (ACQ6) and Standardised Asthma-related Quality of Life Questionnaire (AQLQ-S), respectively. ACQ6 score of ≥1.5 was defined as uncontrolled asthma. In this population, the mean ACQ6 and AQLQ scores were 1.37 ± 1.00 and 5.30 ± 0.93, respectively. The median PSQI score was 4 (IQR 3-7). Overall, 47.5% of patients had uncontrolled asthma and 48.5% were poor sleepers. Patients with uncontrolled asthma were 3.5 times more likely to have poor sleep quality (odds ratio: 3.54, 95% CI: 1.56-8.0, P=0.002). Also, 34% of patients with controlled asthma reported poor sleep quality. The median PSQI score significantly varied between controlled and uncontrolled asthma (4 vs 6, P=0.003) patients. There was a negative correlation between PSQI and AQLQ (-0.42, P<0.0001) which was even stronger between PSQI and ACQ6 (-0.75, P<0.0001) [9].

Stable COPD patients do not need ICS

Although ICS are recommended for COPD patients who experience frequent exacerbations despite long-acting

bronchodilators, they are discouraged for COPD patients who do not have frequent exacerbations. The SUNSET study assessed efficacy and safety of the switch from long-term triple therapy to indacaterol/glycopyrronium (110/50 µg once-daily) or continuation of triple therapy with tiotropium 18 µg once-daily and salmeterol/fluticasone propionate fixed-dose combination 50/500 µg twice-daily [10]. This was a 26-week, randomised, double-blind, parallel-group multicentre study, which included patients with moderate-to-severe COPD (FEV_1 ≥40% and <80% predicted), no more than 1 exacerbation in the previous year, and the use of triple therapy for at least 6 months prior to study inclusion. The primary endpoint was non-inferiority on change from baseline in post-dose trough FEV_1 (with a non-inferiority margin of -50 mL) after 26 weeks. A total of 1,053 patients were randomised to indacaterol/glycopyrronium (n=527) or triple therapy (n=526). Mean age was 65 years and post-bronchodilator FEV_1 was 1.6 L. ICS withdrawal led to a mean reduction in trough FEV_1 of -26 mL (95% CI: -53 to 1) which exceeded the non-inferiority margin. This difference between treatments on trough FEV_1 was driven by the subset of patients with high blood eosinophil counts at baseline (-68 mL; 95% CI: -125 to -12 for patients with ≥300 cells/µL and -13 mL; 95% CI: -44 to 17 for patients with <300 cells/µL). Both treatments showed similar annualised rates of moderate and/or severe COPD exacerbations (rate ratio 1.08; 95% CI: 0.83-1.40) and all exacerbations (rate ratio 1.07; 95% CI: 0.93-1.22). ICS withdrawal led to a small difference in SGRQ-C (1.4 units; 95% CI: 0.2-2.6 on week 26), but no differences in TDI or use of rescue medication over 26 weeks. Safety and tolerability were balanced across the two treatment groups. Although the withdrawal of ICS in patients on long-term triple therapy and up to 1 exacerbation in the previous year led to a small decrease in lung function, this was not clinically important, and there were no associated differences in the rates of COPD exacerbations, dyspnea, or as-needed bronchodilator use. Thus, switching from triple therapy to indacaterol/glycopyrronium is effective in COPD patients and avoids long-term exposure to ICS [10].

Cachexia in stable COPD outpatients associated with negative outcomes

Cachexia – presenting as weight-loss and altered body composition – is a key extra-pulmonary and bothersome manifestation of COPD. A distinction can be made between cachexia as such (defined by the European Respiratory Society (ERS) Task Force on nutritional assessment in COPD as unintentional weight-loss >5% in the past 6 months and low fat-free mass index (FFMI) <17/15 kg/m^2 for males/females) and precachexia. This is defined as unintentional weight loss >5% in past 6 months with normal FFMI. The prevalence of cachexia and precachexia in outpatients with COPD were assessed by Kwan et al. as well as comparing the clinical characteristics of patients with and without cachexia [11]. Also, the longitudinal validity of the ERS definitions of cachexia and precachexia against mortality were evaluated. A total of 1,755 outpatients with stable COPD, of which 57% was male with a mean age of 70 years, a FEV_1 % predicted of 48.6 and a body mass index (BMI) of 27.8 kg/m^2 were recruited between January 2012 and May 2017. These patients were stratified by the ERS definitions of cachexia and precachexia (non-cachexia was defined as no recent unintentional weight loss with low or preserved FFMI). It emerged that the prevalence of cachexia and precachexia was 4.6% (95% CI: 3.6-5.6) and 1.6% (95% CI: 1.0-2.2) respectively. Patients with cachexia had lower FEV_1 % predicted (MD 11.6% predicted; 95% CI: 7.3-15.9), exercise capacity (incremental shuttle walk; MD 59 meters; 95% CI: 30-87), and muscle strength (quadriceps maximum voluntary contraction normalised to height squared; MD 2.2 kg/m^2; 95% CI: 0.9-3.5) as compared with non-cachectic patients. Both cachexia and precachexia were associated with increased mortality, whilst low FFMI alone without recent weight-loss did not confer increased mortality. In a multivariate analysis, recent weight-loss, older age, male sex, lower FEV_1 % predicted, and reduced exercise capacity remained independent predictors of mortality. In fact, the presence of recent weight-loss was the strongest predictive factor in the model (HR 2.23). Although these results reveal a low prevalence of cachexia and precachexia in outpatients with stable COPD, cachexia is associated with reduced exercise capacity, decreased muscle strength, and increased mortality. The researchers stated that the findings suggest recent unintentional weight-loss, rather than low FFMI, provides the most useful prognostic information in this patient group [11].

References

1. Nair P, et al. Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. N Engl J Med. 2017;376:2448-58.
2. Lugogo N, et al. Benralizumab Improves Morning Peak Expiratory Flow While Reducing Oral Corticosteroid Dosages for Patients with Severe, Uncontrolled Asthma in the ZONDA Phase III Trial. A2488/410. ATS 2018.
3. Wang F, et al. Macrolides for the Treatment of Asthma - An Updated Systematic Review and Meta-Analysis. A1086/414. ATS 2018.
4. Sharma S, et al. Lung Function and Patient-Reported Outcomes Response to Indacaterol/Glycopyrrolate (UTIBRON™ Neohaler®) in Chronic Obstructive Pulmonary Disease (COPD) Patients by Reversibility: Pooled Analysis of the FLIGHT1 and FLIGHT2 Studies. A2386/P457. ATS 2018.
5. Wenzel S, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. Lancet 2016;388:31-44.

6. Rabe KF, et al. Dupilimumab in Patients with Corticosteroid-Dependent Severe Asthma: Efficacy and Safety Results from the Randomized, Double-Blind, Placebo-Controlled Phase 3 LIBERTY ASTHMA VENTURE Study. A7712. ATS 2018.
7. Bafadhel M, et al. Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease (COPD): A Meta-Analysis of METREX and METREO Exacerbation Endpoints. A5912. ATS 2018.
8. Lipson DA, et al. Single Inhaler Triple-Therapy (ICS/LAMA/LABA) Versus Dual-Therapy (ICS/LABA or LAMA/LABA) in Patients with COPD at Risk of Exacerbations: Efficacy and Safety Results of the Phase III IMPACT Trial. A1014. ATS 2018.
9. Panigrahi MK, et al. Relationship Between Sleep Quality, Asthma Control and Quality of Life in Adults with Asthma. A1089/417. ATS 2018.
10. Chapman KR, et al. Withdrawal of Inhaled Corticosteroids from COPD Patients Inhaling Long-Term Triple Therapy: The SUNSET Study. A1009. ATS 2018.
11. Kwan H, et al. Cachexia, Precachexia and Mortality in Chronic Obstructive Pulmonary Disease (COPD). A2451. ATS 2018.

Oncology

Treatment options in lung cancer are increasingly expanding and provide better outcomes for patients. Data on long-term effects are accumulating. The occurrence of sometimes serious AEs is being more easily recognised. Simultaneously, screening remains an important early stage diagnostic tool. It should be considered in a large number of individuals who may be at high risk of developing cancer.

Clinicians need to be aware of immune-related AEs when PD-1 inhibitors are used

The use of immunotherapy in non-small cell lung cancer (NSCLC) has seen a significant uprise and is expected to increase further over the coming years. Immunotherapy has dramatically changed patients' outcomes and has been hailed as a real game-changer in treating a difficult disease which has been characterised by a poor prognosis for decades. However, immunotherapy has been known to be associated with AEs, more specifically immune-related AEs. In a retrospective observational study, Chang et al. aimed to determine the characteristics of immune-related AEs, specifically pneumonitis in the use of programmed death-1 (PD-1) inhibitors [1]. A total of 100 NSCLC patients (adenocarcinoma: n=74 and squamous cell carcinoma: n=26) who had been treated with PD-1 inhibitors between January 2014 and June 2017 were included. Of those, 90 received nivolumab, 9 pembrolizumab, and 1 patient was treated with avelumab. Of these patients, 15% developed immune-related AEs and 8% of these developed signs and symptoms suggestive of pneumonitis. Other immune-related AEs (such as diarrhoea, colitis, rash, rheumatoid arthritis flare, polymyalgia rheumatica, and bullous pemphigoid) were less frequent. The onset of pneumonitis ranged from 28 days to 294 days (mean 123 days). Of the 8 patients who developed signs and symptoms suggestive of pneumonitis, 5 developed grade 3 pneumonitis which required hospital admission. The most common radiographic findings were ground-glass opacities (63%). Only 2 patients underwent bronchoscopy and bronchoalveolar lavage. Cultures and cytology were negative. None of the patients underwent lung biopsy. All patients with immune-related AEs were treated with corticosteroids. Out of 8 patients with pneumonitis, 2 showed improved symptoms and radiographic changes after stopping treatment with the PD-1 inhibitor and starting corticosteroids. One of them was treated for 4 weeks, the other patient for 12 weeks.A total of 6 patients developed respiratory failure and were transitioned to a hospital. The researchers concluded that – especially as the use of PD-1 inhibitors is expected to further increase – it is important for clinicians to be aware of immune-related AEs . Another important finding was that although this was a single-centre study, a higher incidence of pneumonitis than described in the literature was observed. Finally, as the diagnosis of pneumonitis can be challenging and findings could be attributable to infectious process or cancer progression, early diagnosis is essential. This can be done by imaging, possible bronchoscopy with bronchoalveolar lavage, and transbronchial biopsy [1].

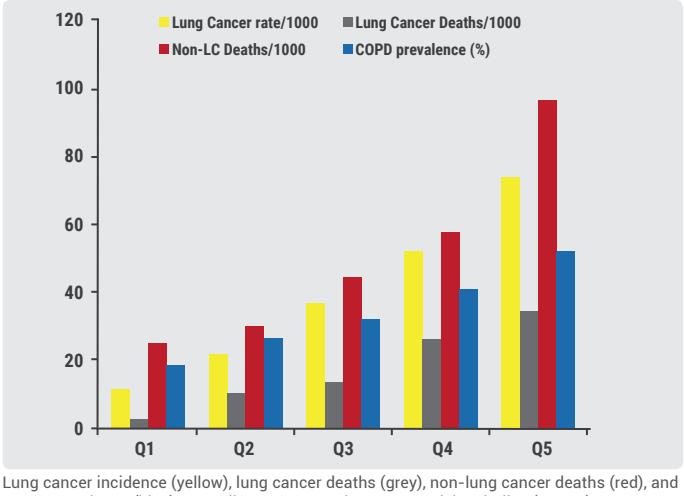
The $PLCO_{2012}$ model for lung cancer risk predicts increasing likelihood of having COPD

It has previously been reported in a retrospective analysis of the National Lung Screening Trial (NLST)-ACRIN sub-study of more than 10,000 participants that increasing airflow limitation is independently associated with increasing risk of lung cancer. Recently, it has become clear that increasing

airflow limitation is also associated with an increasing risk of dying of a non-lung cancer cause. This creates a competing cause of death effect as several of the lung cancer risk variables in the widely used Brock $PLCO_{2012}$ model are also risk factors for developing COPD. Young et al. investigated whether the $PLCO_{2012}$ model for lung cancer risk also predicts an increasing likelihood of having COPD [2]. This was done by using 10,054 subjects from the NLST-ACRIN cohort (a sub-study of the NLST which recruited high-risk smokers and followed them for an average of 6.4 years). The AUC for developing lung cancer was assessed and compared to the AUC for having airflow limitation (COPD) based on baseline spirometry. Also, smokers were stratified into quintiles of risk according to the $PLCO_{2012}$ model and the prevalence of COPD was assessed. It was found that the AUC for developing lung cancer according to the $PLCO_{2012}$ model was 0.67 (95% CI: 0.65-0.70) compared to the AUC for the presence of COPD (AUC 0.65; 95% CI: 0.64-0.67). After stratifying high-risk smokers from the NLST-ACRIN subgroup according to $PLCO_{2012}$ lung cancer risk quintiles, a linear relationship was found; an increasing risk quintile was associated with an increased risk of having COPD and increased risk of dying of a non-lung cancer related death. However, this linear relationship between $PLCO_{2012}$ risk and outcomes diverges when compared to the rates of dying of lung cancer (Figure 1).

Thus, the $PLCO_{2012}$ model for lung cancer risk also predicts an increasing likelihood of having COPD. In these circumstances, screened participants with the greatest risk of lung cancer (Q5) have the highest prevalence of COPD (52%) and greatest risk of dying of a non-lung cancer death [2].

Figure 1 Lung cancer incidence, deaths and non-lung cancer deaths, and COPD prevalence [2]



Lung cancer incidence (yellow), lung cancer deaths (grey), non-lung cancer deaths (red), and COPD prevalence (blue), according to $PLCO_{2012}$ lung cancer risk quintiles (Q1-Q5).

CRP to albumin ratio as prognostic factor in lung cancer

It has been shown by Jin et al. that C-reactive protein (CRP) to albumin ratio is an independent prognostic marker in lung cancer after adjusting for other confounding factors [3]. This was done by a retrospective analysis of 210 patients with lung cancer between 2008 and 2014. For 197 of these patients, the CRP to albumin ratio was calculated and both univariate and multivariate Cox regression analysis was performed to determine the associations of CRP to albumin ratio with overall survival. It was found that when compared with low CRP to albumin ratio (<0.43), high CRP to albumin ratio (≥0.43) at diagnosis was associated with unfavourable tumour characteristics, including late tumour stage (3+4 in low vs high, 76.9% vs 89.2%, respectively, P=0.029), elevated low density lipoprotein (P<0.001), platelet-to-lymphocyte ratio (P=0.001), neutrophil-to-lymphocyte ratio (P=0.001) and other tumour markers, such as neuron-specific enolase (P<0.001) and carcinoembryonic antigen (P=0.004). Furthermore, overall survival was also worse in high CRP to albumin ratio group at diagnosis (<0.43 vs ≥0.43, median overall survival 27 vs 13 months, P<0.001). In multivariate cox analysis, CRP to albumin ratio (adjusted HR: 2.42, 95% CI: 1.35-3.7, P=0.002) and carcinoembryonic antigen at diagnosis (adjusted HR: 1.002, 95% CI: 1.000-1.004, P=0.040) were identified as independent prognostic factors for poor overall survival. As a result of these findings, it was hypothesised that CRP to albumin ratio could be a readily available biomarker in a clinical setting [3].

Pulmonary Large Cell Neuro-Endocrine Cancer: rare and difficult to diagnose

Gour et al. presented a rare case of a large cell neuroendocrine carcinoma (LCNEC). This is a rare pulmonary tumour which is diagnosed based on high-grade features (>10 mitotic figures in 2 mm^2 of viable tumour), and the presence of both neuroendocrine morphology as well as immunohistochemical evidence of neuroendocrine markers. In the 2015 WHO classification, it is grouped with the pulmonary neuroendocrine tumours. In this case, a 72 year old male with a strong smoking history of 45 packs per year and construction dust exposure presented with abnormal imaging findings. PET/CT of the chest was significant for a PET avid left lower lobe speculated nodule measuring 1.4x1.2cm along with small PET avid right sided paratracheal (4R) and subcarinal (7) lymphadenopathy. An endobronchial ultrasound guided fine needle aspiration was performed on the 4R and 7 lymph nodes but its cytology was inconclusive. A

robotic assisted thoracoscopy was subsequently performed and left lower lobectomy. Although the dissected lymph nodes were negative again for malignant cells, the left lower lobe nodule was found to be positive for LCNEC [4]. It needs to be noted that the clinical presentation, natural history, and molecular profiling of LCNEC appear similar to SCLC but there are two major exceptions: LCNECs tend to present early (stage 1-2) and located peripherally rather than centrally, both of which apply to this case. Since immunohistochemical evidence of neuroendocrine markers is difficult on cytology and small biopsies, diagnosis is made post-resection. At the same time, the rarity of the disease and lack of clinical trials makes optimal management difficult. Treatment is based on extrapolation from established literature but this is primarily retrospective in nature. Since prognosis is poor as compared to other forms of NSCLC, adjuvant chemotherapy may offer best chance for survival for these patients [4].

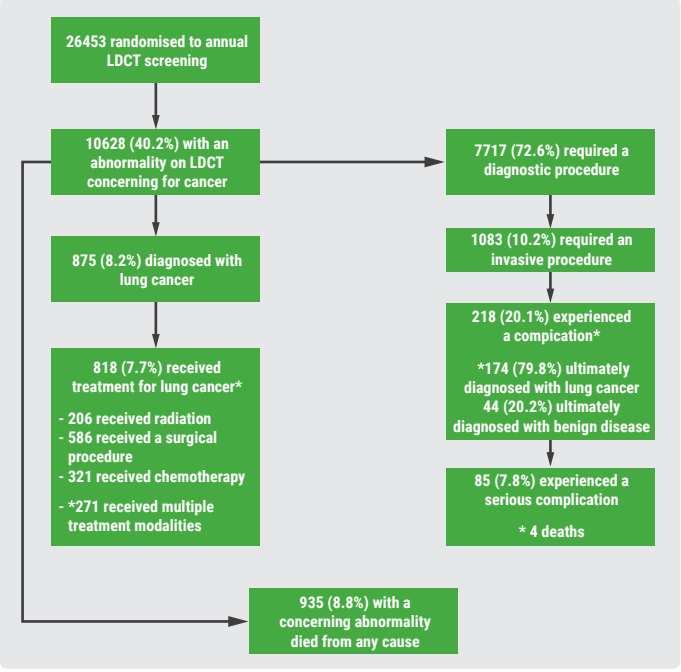
Some elderly patients with stage 4 NSCLC may benefit from chemotherapy

Until recently, it was not clear whether elderly patients (>70 years) with stage 4 NSCLC may benefit from chemotherapy. A Dutch study compared unselected elderly stage 4 NSCLC patients receiving chemotherapy vs supportive care regarding patient characteristics, living condition, comorbidities, and overall survival. Furthermore, in the chemotherapy group, patient characteristics associated with treatment tolerance were identified. This was done by a retrospective cohort study which included all patients aged ≥70 years diagnosed with stage 4 NSCLC in 2009-2013. The follow-up lasted until January 2016. Treatment tolerance was defined as patients completing therapy without unplanned hospitalisations. A total of 102 patients were included of which 32% received chemotherapy and 68% received supportive care. Patients receiving chemotherapy were significantly younger (P=0.003), had less severe comorbidities (P=0.073) and had a significantly better survival compared to those receiving supportive care (median survival of 182 vs 53 days, respectively; P=0.029). Of patients treated with chemotherapy, only 24% tolerated treatment. There were no clear differences between patients who tolerated treatment and those who did not. It was concluded that the majority of elderly patients with stage 4 NSCLC in this particular centre received supportive care rather than chemotherapy. Patients receiving chemotherapy were younger, had less severe comorbidities and better survival. Treatment tolerance was poor but seemed unrelated to age or comorbidities. This retrospective data suggest that a subgroup of elderly patients with stage 4 NSCLC may benefit from chemotherapy. Prospective studies are needed to identify predictors of treatment outcomes and to learn whether, in view of the poorly tolerated chemotherapy, longer survival adds to patients quality of life [5].

Large number of patients had suspicious CT finding during low-dose CT screening in NLST

Iaccarino et al. performed a post-hoc analysis of patients randomised to yearly low-dose CT screening during the NLST [6]. By doing so, patients who had an abnormal finding "concerning for cancer" (non-calcified pulmonary nodule >4mm or lymphadenopathy >1cm) on any of the 3 annual CT screens were identified. The outcomes of these patients were followed throughout the data collection period. Patients were evaluated for whether they underwent a diagnostic procedure (including invasive testing or imaging other than next annual low-dose CT) related to the screening study and whether they experienced any complications from a procedure. Patients were also evaluated for whether they received a final diagnosis of lung cancer, whether they underwent treatment for lung cancer, or if they died during the data collection period. A total of 26,453 patients was randomised to the low-dose CT screening arm, of which 40.2% had a finding concerning for lung cancer. Of these, 72.6% required further diagnostic workup related to the screening CT and 10.2% required an invasive procedure. A procedure-related

Figure 2 Trajectory and outcomes of patients randomised to the low-dose CT arm of the NLST [6]



complication occurred in 20.1% of patients who required an invasive procedure for diagnostic workup; in 7.8%, this was a major complication. Finally, in 8.2% of patients with a suspicious finding, a lung cancer diagnosis was made. This concerned 875 patients and 818 of these had treatment. During the data collection period, 8.8% of patients with a suspicious finding on CT imaging died from any cause [6].

It was concluded that a large number of patients were found to have a CT finding suspicious for lung cancer during low-dose CT screening in the NLST. Complications related to invasive diagnostic procedures were not uncommon. These findings provide important patient-level outcomes data that can be utilised by clinicians during shared decision-making discussions about lung cancer screening [6].

References

1. Chang WJ, et al. Immune-Related Adverse Events, Specifically Pneumonitis, with the Use of Programmed Death-1 Inhibitors. A4530/210. ATS 2018.
2. Young RP, et al. The Relationship Between Lung Cancer Risk According to the Brock $PLCO_{2012}$ Model and Prevalence or Presence of COPD in the NLST-ACRIN Sub-Study (N=10,054). A4411/105. ATS 2018.
3. Jin J, et al. C-Reactive Protein to Albumin Ratio as a Prognostic Factors in Lung Cancer. A7333/P333. ATS 2018.
4. Gour AC, et al. Pulmonary Large Cell Neuro-Endocrine Cancer: A Diagnostic Difficulty and Therapeutic Dilemma. A4021/P286. ATS 2018.
5. Helfrich G, et al. Treatment Initiation, Tolerance and Survival in Elderly Patients with Stage IV Non-Small Cell Lung Cancer (NSCLC). A7337/P337. ATS 2018.
6. Iaccarino J, et al. Patient-Level Trajectories and Outcomes After Low-Dose CT Screening in the National Lung Screening Trial. A4407/101. ATS 2018

Infection

Respiratory infections remain a burden worldwide, and new therapeutic strategies continue to be investigated. Also, underlying causes and risk factors have been subjected to extensive research, elucidating some of these processes.

Continuation of bedaquiline-containing regimens for M/XDR-tuberculosis safe

Although bedaquiline, a new drug effective against multi- and extremely drug resistant (M/XDR) tuberculosis, was granted accelerated approval by the FDA in 2012, it is not recommended by the WHO beyond the first 6 months of treatment. This decision was based on the lack of safety data. Therefore, Skrahina et al. assessed the safety of treatment with bedaquiline plus the WHO-recommended optimised background regimen for M/XDR-tuberculosis [1]. This was done by comparing the occurrence of AEs during the first 6 months of treatment with that during the continuation of bedaquiline treatment after 6 months. A total of 178 patients were included between August 2015 and June 2016. The mean number of drugs incorporated into the treatment regimen was 5.75 together with bedaquiline. The mean duration of treatment with bedaquiline was 268 days. In total, 3,120 AEs were observed. Amongst these, 3 deaths, 21 hospitalisations, 12 life-threatening events, and 3,113 non-serious AEs were observed. The treatment beyond 180 days was associated with significantly less overall AEs than that during the first 6 months (OR: 0.364; 95% CI: 0.331-0.402; P<0.001; Table 3).

These outcomes suggest that continuation of bedaquiline-containing regimens for M/XDR-TB after the initial 6 months may be considered as safe. This provides possibilities for longer treatment which may be beneficial to patient outcomes [1].

A1AT may be an important anti-nontuberculous mycobacteria factor

Alpha 1 antitrypsin (A1AT) – a glycoprotein which is a major circulating inhibitor of serine proteases limiting host tissue injury at sites of inflammation – modulates macrophage function by limiting monocyte activation. It enhances the release of IL-10 and suppresses nontuberculous mycobacteria (NTM) macrophage infection. The frequency of abnormal A1AT alleles in subjects with documented NTM

Table 3 Outcomes at various treatment durations [1]

Endpoints	Bedaquiline treatment up to 180 days	Bedaquiline treatment beyond 180 days
Number of deaths	2	1
Number of hospitalisations	11	10
Life-threatening events	6	6
Non-serious AEs	1,840	1,273

disease has been reported to be 1.6 times higher than in the general United States population. This finding suggests that A1AT may be an anti-NTM host-defence factor. As abnormal A1AT phenotypes may constitute a risk factor for NTM pulmonary disease, the prevalence of NTM infection was evaluated in a population of 1,000 veterans with abnormal A1AT genotypes [2]. This population was defined as having a pre-bronchodilator airflow obstruction and they were screened between July 2012 and December 2016. The design of the study was a retrospective 1:3 case-control analysis of subjects with abnormal A1AT genotypes randomly matched by age and gender to subjects with a normal genotype *(MM).* It emerged that 9.6% of subjects had abnormal genotypes; 1% had cultures positive for NTM. The abnormal A1AT alleles found were *MS, MZ, MF, MI, SS, SZ,* and *FS*, but no *ZZ* subjects were detected. There were no differences in age, gender, smoking history, diagnosis of COPD, asthma, or pulmonary function test results between subjects with normal vs abnormal A1AT genotypes. Although no statistically significant differences were noted, the prevalence of positive NTM cultures among subjects with abnormal A1AT alleles (4.2%) was higher than in the 297 controls (2%). The extrapolated point prevalence for these groups were 4,167 per 100,000 and 2,020 per 100,000 respectively. When distribution of NTM species between groups was analysed, *M. fortuitum* was found to have the highest prevalence in the abnormal A1AT genotype group. The observation that the prevalence of NTM infection is doubled among subjects with abnormal A1AT genotypes is consistent with the hypothesis that A1AT may be an important anti-NTM factor. This finding suggests that NTM infection should be considered in the evaluation of symptomatic subjects with abnormal A1AT alleles [2].

Atrial fibrillation significant risk factor for pneumonia

The relationship between atrial fibrillation (AF) and pneumonia in general (PNA) has been widely evaluated by Gul et al. [3] as until now, only relatively small studies have identified AF as a risk factor for hospital-acquired pneumonia. A total of 54,981,595 hospital admissions and 1,619,380 PNA admissions which projected to 7,991,916 PNA admissions were analysed for AF and dysrhythmia as secondary diagnosis and as a comorbidity. AF was listed as comorbidity in 14.3% of cases of PNA admissions vs 7.7% of cases in general admissions. Dysrhythmias other than AF were listed as comorbidity in 3.8% of the cases vs 3.4% of cases in general admissions (OR 3.7; 95% CI: 3.69-3.76; P<0.0001). AF was listed as a second diagnosis in 1.6% of cases of PNA admissions vs 1.1% of cases in general admissions. Dysrhythmias other than AF were listed as a second diagnosis in 0.65% of PNA vs 0.8% of cases in general admissions. PNA cases increased by 4.5 for every case of AF listed as second diagnosis (P=0.04). Pearson Correlation coefficient of PNA with AF as second diagnosis was 0.774 (P=0.041). Mean in-hospital mortality for PNA admissions was recorded at 3.77% (95% CI: 3.7-3.84) vs PNA with AF as comorbidity at 7.04% (95%: CI 6.9-7.18) and PNA with cardiac dysrhythmia other than AF as a comorbidity at 5.77 (95% CI: 5.59-5.94). Mean length of stay for PNA admissions was 5.41 days (95% CI: 5.37-5.44) vs PNA admissions with AF as comorbidity which was 6.55 (95% CI: 6.5-6.6).

Interestingly, AF is almost twice as prevalent in PNA admissions than AF in general admissions and at least thrice as prevalent in PNA admissions compared to other cardiac dysrhythmias in PNA. The mortality almost doubled for PNA admissions with AF as comorbidity and also resulted in increased morbidity. According to researchers, this means that the role of better management of AF in cases of PNA needs to be elucidated to improve outcomes for patients [3].

Gut microbiota are critical regulator of intravascular immunity during sepsis

It is widely known that the gut microbiota are essential for maintaining general health. In patients who are admitted to the intensive care unit (ICU), significant alterations in the gut microbiota have been identified in critically ill septic patients, but the impact of this "dysbiosis" on host immune defences during sepsis are poorly understood. Understanding the nature and mechanisms by which the microbiota impacts host immune function (or dysfunction) during sepsis represents an important unanswered question in the field of critical care research, and may uncover new therapeutic avenues to combat the scourge of sepsis-related morbidity and mortality. It is hypothesised that the normal gut microbiota protects against the spread of infection during sepsis through the regulation of intravascular innate immune defences. This was evaluated by McDonald et al. [4] by using a mouse model of bacterial sepsis induced by *Staphylococcus aureus* (MRSA, USA300) bacteraemia in mice with normal gut microbiota compared to animals with disrupted microbiota using antibiotic-mediated microbiota ablation. It was found that in septic controls, neutrophils and macrophages within the microvasculature efficiently captured and cleared MRSA from the bloodstream through the release of intravascular neutrophil extracellular traps (NETs) as well as macrophage-

mediated phagocytosis of bacteria. In contrast, animals with depleted gut microbiota displayed severe abnormalities of intravascular anti-bacterial defences, leading to increased levels of bacteraemia as well as dissemination of infection. *In vivo* characterisation of neutrophil and macrophage effector functions revealed profound impairment of NET production in microbiota-depleted mice, resulting in an inability to capture and clear bacteria from the bloodstream. In addition to defects in host defence, microbiota-depleted animals displayed further immunopathology including augmented systemic inflammation with increased serum levels of pro-inflammatory cytokines as well as increased inflammatory lung injury. This leads to the conclusion that the disruption of normal gut microbiota results in impaired host defence during sepsis as a result of defective intravascular NET production, which results in the spread of bacterial infections as well as augmented systemic inflammation and end-organ damage. These findings reinforce the theory that gut microbiota are a critical regulator of intravascular immunity during sepsis [4].

RV521 possible agent to treat RSV in adults and children

Although respiratory syncytial virus (RSV) is a key cause of lower respiratory tract infections, no effective antiviral treatment exists. Currently, RV521 (an oral small molecule RSV fusion inhibitor) is in development for the treatment of RSV infection in infants and adults. It was evaluated in a phase 2a, randomised, double-blind clinical trial in healthy adult volunteers inoculated with the RSV-A isolate Memphis-37 [5]. Participants received RV521 or placebo (2:1), twice-daily for 5 days, either 12 hours after confirmation of active RSV infection or on the fifth day after inoculation if RSV was not detected. Viral load, disease severity, pharmacokinetics, and safety were measured throughout the 12-day study quarantine period. The primary efficacy endpoint was the AUC of RSV viral load determined by RT-qPCR from nasal wash samples collected immediately prior to administration of the first dose of RV521 and twice-daily through the 12th day following inoculation in subjects with confirmed RSV infection. It was tested in a total of 66 participants; they were randomised to receive RV521 at doses of 200 mg or 350 mg orally twice-daily, with no loading dose or placebo (2:1). Of these, 80% were confirmed to be infected with RSV by RT-qPCR. The AUCs for RT-qPCR viral load were significantly lower for 350 mg RV521 (n=16) and 200 mg RV521 (n=18) compared to placebo (n=19) with reductions in group mean log10 RT-qPCR viral AUCs of 63% and 55% respectively. The AUC for viral load by quantitative culture, AUC of total symptom score, and the total mucus weight produced were also significantly reduced in participants receiving RV521 compared with the placebo group. There were no changes in laboratory determined safety parameters, and a balanced AE profile between and within both dose groups and placebo and no treatment-related serious AEs occurred. Thus, therapeutic administration of RV521 safely and effectively reduces viral load and disease severity in a phase 2a challenge model. This prompts further evaluation in RSV-infected adults and children [5].

References

1. Skrahina A, et al. Is M/XDR-TB Treatment with Bedaquiline Beyond Six Months Safe? A1142/803. ATS 2018.
2. Luna LV, et al. Prevalence of NTM Infection in Subjects with and Without Normal Alpha-1 Antitrypsin Genotypes. A2600. ATS 2018.
3. Gul MH, et al. Association of Atrial Fibrillation in Pneumonia and Their Outcomes A2624. ATS 2018.
4. McDonald B, et al. The Gut Microbiota Promotes Intravascular Immunity Against Bacterial Dissemination During Sepsis. A2775. ATS 2018.
5. DeVincenzo J, et al. Safety and Efficacy of Oral RV521 in a Human Respiratory Syncytial Virus (RSV) Phase 2a Challenge Study. A7715. ATS 2018.

Pulmonary Vascular Disease and Interstitial Lung Disease

In recent years, significant advances have been achieved in treating idiopathic pulmonary fibrosis and pulmonary arterial hypertension. Subsequent challenges in the clinic include optimal treatment of elderly patients and possible association between various treatments and conditions.

Nintedanib and pirfenidone safe in patients eligible for a lung transplant

Li et al. assessed the impact of treatment with antifibrotic medications nintedanib and pirfenidone on waiting list survival and peri-operative and post-surgical outcomes after lung transplant in idiopathic pulmonary fibrosis (IPF) patients [1]. The underlying reason to do so was the concern that these recently approved drugs to delay IPF progression may impair wound healing or contribute to bleeding during transplantation. In this retrospective cohort analysis, all IPF patients placed on anti-fibrotic drugs prior to transplantation at the Vanderbilt University from 2012 to 2017 were identified; of those, peri-operative and post-transplant outcomes were analysed. A total of 14 patients who received anti-fibrotic medications prior to transplant were identified; 12 of these received pirfenidone (median lung allocation score 39.4; range 34.3-47.4) and two patients received nintedanib (median lung allocation score 48.9; range 46.7-51.2) prior to transplantation. No patients placed on pirfenidone or nintedanib died while on the transplantation waiting list. One patient required a post-surgical revision secondary to bleeding. Another patient developed a peri-incisional haematoma that required subsequent drainage. The remainder of patients tolerated transplantation well. Post-transplantation survival was 92% at 3 months and 85% at 1 year. It was thus concluded that antifibrotic medications are likely to be safe for IPF patients awaiting lung transplant; however, further investigation is required [1].

Possible relationship between IFN-β treatment, MS, and PAH development

There may be a relation between pulmonary arterial hypertension (PAH) and treatment with interferon beta (IFN-β) in patients with multiple sclerosis (MS). Safdar et al. presented a case series of 4 patients who developed PAH after undergoing treatment with IFN-β for MS [2]. The mean age was 51 years, all were females, 3 were Caucasians, and 1 was Hispanic. The age at the time of MS diagnosis was 35 years and the age at the time of PAH diagnosis was 47 years. All patients received IFN-β prior to developing PAH. There was a lag of 12 years between developing PAH after IFN-β treatment. Two patients were on intravenous prostacyclin therapy plus oral agents (epoprostenol+tadalafil and treprostinil+macitentan), whereas 2 patients were on oral PAH medications (ambrissentan+tadalafil and macitentan+tadalafil). Haemodynamics from right heart catheterisation done at the time of diagnosis showed a mean pulmonary artery pressure of 53 mmHg, right atrial pressure of 7 mmHg, mixed venous saturation was 71%, pulmonary capillary wedge pressure was 12 mmHg, thermodilution cardiac output was 4.66 ml/min, and cardiac index was 2.55 ml/min/m^2. Haemodynamics from recent echo showed a right ventricular systolic pressure of 70 mmHg, right atrial pressure of 6 mmHg, cardiac output of 6.2 L/min, and cardiac index of 3.5 L/min/m^2. The recent 6 minute walk distance (6MWD) was 435 meters and the Borg dyspnea score ranged from 0.5 to 4. All patients were alive at the time of last follow-up which was 16 years from MS diagnosis. These cases provide further evidence of the possible relationship between IFN-β treatment, MS, and PAH development. In contrast to other reports, none of these PAH patients had a reversibility of PAH with cessation of IFN-β treatment suggesting early screening of MS patients for PAH may be useful [2].

Associations of anti-hypertensive treatments and outcomes in IPF

A post-hoc analysis evaluated associations of anti-hypertensive treatments, including angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), calcium channel blockers (CCB), and β-blockers (BB), with the course of IPF [3]. Patients that had been randomly assigned to receive placebo in the ASCEND (NCT01366209) and CAPACITY (NCT00287716 and NCT00287729) phase

3 trials were now grouped by ACEi, ARB, no ACEi/ARB, and CCB and/or BB (CCB/BB) treatment (CCB/BB group did not receive concomitant ACEi or ARB). Groups were based on self-reported concomitant use at study entry. Primary outcome was a composite endpoint defined as the first occurrence of death, absolute decline in percent predicted forced vital capacity (% FVC) ≥10%, or decline in 6MWD ≥50 m. Secondary outcomes included mortality, change in % FVC, and hospitalisations. Of 624 patients who received placebo in the ASCEND and CAPACITY trials, 17.8% received ACEi, 19.4% received ARB, 62.8% received neither ACEi nor ARB, and 14.6% received CCB/BB without concomitant ARB or ACEi. Groups were similar with regard to age, sex, and pulmonary function at baseline, but more patients in the ACEi and CCB/BB groups (52.3% and 41.8%, respectively) had a history of cardiovascular disease compared with the ARB and non-ACEi/ARB groups (27.3% and 19.4%, respectively). Mean follow-up ranged from 333 to 355 days across groups. Fewer patients met the primary outcome in the ACEi group (32.4%) compared with the ARB and non-ACEi groups (40.5% and 43.4%, respectively). A trend toward lower risk of % FVC decline ≥5% was associated with ACEi use but not ARB (P=0.047), and a trend toward elevated mortality risk was associated with ARB use but not ACEi (P=0.013). All-cause hospitalisations occurred in similar proportions across groups. Trends were similar when ACEi and ARB use was compared with CCB/BB use (Table 4) [3].

Researchers concluded that these findings suggest that there may be complex relationships between anti-hypertensive treatments and clinical outcomes in IPF which clearly highlights the need for further study [3].

Table 4 Outcomes by treatment subgroup at 52 weeks [3]

Outcome*	Unadjusted Outcomes, %				Hazard ratio, (95% CI)	
	ACEi (n=111)	ARB (n=121)	Non-ACEi/ ARB (n=392)	CBB/BB (n=91)	ACEi vs Non-ACEi/ ARB	ARB vs Non-ACEi/ ARB
Composite endpoint	32.4	40.5	43.4	41.8	0.6 (0.4, 0.9) P=0.026	0.9 (0.6, 1.2) P= 0.413
Death	5.4	9.1	3.8	5.5	-	-
Absolute %FVC decline ≥10%	10.8	9.9	15.3	14.3	-	-
6MWD decline ≥50 m	18.9	24.0	26.5	24.2	-	-
Mortality						
All-cause	8.1	11.6	4.8	7.7	1.1 (0.5, 2.9) P=0.782	2.5 (1.2, 5.2) P=0.013
IPF-related	3.6	8.3	3.6	5.5	0.7 (0.2, 2.5) P=0.540	2.5 (1.0, 5.9) P=0.042
Change in %FVC from baseline to 52 weeks						
Absolute decline ≥10%	12.6	16.5	20.2	17.6	0.7 (0.4, 1.3)‡ P=0.264	0.9 (0.5, 1.5)‡ P=0.603
Absolute decline ≥5%	33.3	36.4	44.6	48.4	0.7 (0.5, 1.0)‡ P=0.047	0.8 (0.6, 1.1)‡ P=0.182
All-cause hospitalisation	22.5	17.4	18.6	18.7	0.9 (0.5, 1.4)‡ P=0.547	0.8 (0.5, 1.4)‡ P=0.473

*Only confirmed cases were included, defined as those for which follow-up assessment was repeated ≥6 weeks following initial assessment and criteria for the outcome were met.
‡Death was treated as a competing risk.

Low tolerability IPF medication in elderly patients

Tolerability and therapeutic effect of antifibrotic agents for IPF patients ≥75 years were retrospectively evaluated by Sawata et al. [4]. A total of 69 IPF patients ≥75 years who received antifibrotic agents for IPF were included. Pirfenidone was administered to 52 patients (male: n=40, female: n=12, mean age: 81.6 years). Nintedanib was administered to 17 patients (male: n=14, female: n=3, mean age: 81.4 years). The median duration of treatment was 183 days for pirfenidone and 91 days for nintedanib. AEs occurred in 88.4% of patients being treated with pirfenidone and 94.1% in those treated with nintedanib. Treatment was discontinued in 69.6% of patients using pirfenidone (anorexia: n=23, disease progression: n=9) and in 93.8% of patients using nintedanib (anorexia/diarrhoea: n=9, disease progression n=4). Patients who continued treatment for 52 weeks or more amounted to 15.4% with pirfenidone (average ΔFVC=-125 mL; 1 patient with nintedanib, average ΔFVC=24.4 mL); compared with patients discontinuing treatment within 52 weeks, patients with pirfenidone had significantly lower cardiac disease prevalence (12.5% vs 70.5%; P=0.04), and tended to have higher BMI (23.4 vs 17.4; P=0.098), while there were no significant differences in patients with nintedanib. These results clearly show that antifibrotic agents have a low tolerability in elderly patients which makes carefully selecting target patients a key strategy [4].

Switching from pirfenidone to nintedanib is feasible

The indications for switching from pirfenidone to nintedanib and the subsequent effect on healthcare utilisation were assessed in a British retrospective analysis [5]. To do so, IPF patients who had switched from pirfenidone to nintedanib were identified. Healthcare utilisation was defined as telephone or email communication initiated by patients seeking clinical advice on drug side-effect management. During the study period, 53 patients switched from pirfenidone to nintedanib (M:F ratio 43:10, mean age at initiation 72 years, FVC 69%, diffusing capacity of carbon monoxide 39%,

Figure 3 Healthcare utilisation per month on treatment [5]

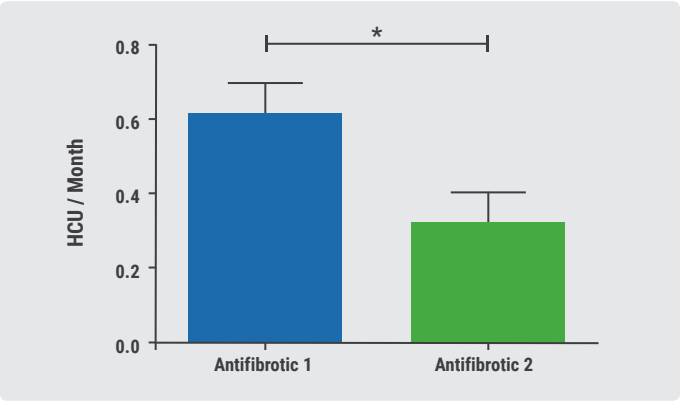
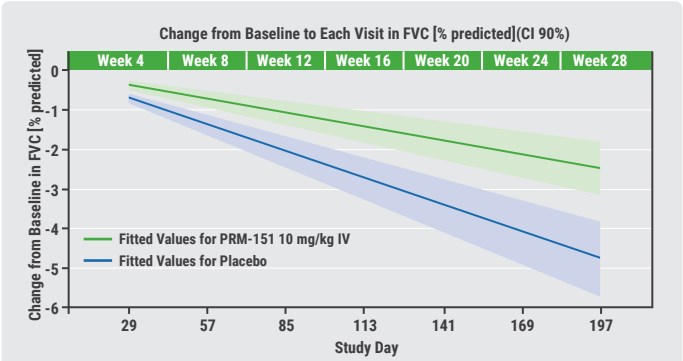


Figure 4 Primary efficacy analysis; FVC % predicted least squares mean for change at each visit [6]



and BMI 28.3). The most common indication for switching therapy was gastrointestinal side-effects including nausea (43%). Others included rash (19%), fatigue (17%), and weight loss (13%). In total, 28% of patients switched due to IPF disease progression. One patient switched due to derangement of liver function. After switching antifibrotic agent, 70% continued on treatment while 17% discontinued the second agent due to side-effects. Eight patients died and 1 received a lung transplant. Mean duration on pirfenidone was 11.0 months and on nintedanib at the time of censoring was 7.2 months. Given treatment was ongoing for patients taking nintedanib, healthcare utilisation was adjusted for duration on treatment. Mean number of healthcare utilisation episodes per month on the first antifibrotic was 0.62 which was significantly greater than that for the second antifibrotic (0.32; P=0.007; Figure 3) [5].

Thus, switching antifibrotic therapy because of side-effects or IPF disease progression is feasible and tolerable, allowing over two thirds of such patients to remain on treatment. Furthermore, after switching agents, there is evidence for a reduction in healthcare utilisation. When sufficient follow-up data is available, it will be important to assess whether the lung function of those patients switching due to disease progression stabilises on the second agent. Future studies will also be required to establish whether similar results are obtained for patients who switch from nintedanib to pirfenidone [5].

Significant positive treatment effect of PRM-151 in IPF patients

Efficacy and safety of PRM-151 – a recombinant human pentraxin-2 for the treatment of fibrotic disorders – was assessed in a multinational phase 2 trial in patients with IPF [6]. The study was randomised (2:1), double-blind, and placebo-controlled. PRM-151 was administered 10 mg/kg intravenous every 4 weeks for 24 weeks in subjects with IPF, stratified based on background IPF therapy. Eligible patients had a FVC ≥50% and ≤90% of predicted, diffusing capacity for carbon monoxide ≥25% and ≤90% of predicted, and ≥150 meters 6MWD. The primary endpoint was change from baseline to week 28 in mean FVC % predicted. Secondary endpoints included 6MWD and safety assessment. The majority of patients was male (81%, mean age 68.6 years, 97.4% Caucasian, mean disease duration 3.8 years). Baseline demographics, including pulmonary function were similar for the two groups. At the time of enrolment, 78.4% were receiving therapy with pirfenidone or nintedanib: 116 patients (placebo: n=39; PRM-151: n=77) received ≥1 dose of study drug. PRM-151 had a significant positive effect on FVC decline over time. The least squares mean change in FVC % predicted from baseline to week 28 was 4.8 (95% CI: 5.9 to -3.6) for placebo vs -2.5 (95% CI: -3.3 to -1.7; P=0.0014) for PRM-151 (Figure 4) [6].

For the 6MWD, the least squares mean change from baseline to week 28 was -31.8 meters (95% CI: 45.2 to 18.3) in the placebo group vs -0.5 meters (95% CI: -10.1 to 9.2) in the PRM-151 group which was a significant (P=0.0002) and clinically meaningful treatment effect of 31.3 meters. Treatment-emergent AEs occurred in a similar percentage of subjects in both groups; 85% were mild and unrelated to PRM-151. Serious treatment-emergent AEs occurred in 10.3% of placebo subjects and 7.8% of subjects on PRM-151; none were considered possibly or probably related to the study drug. It was concluded that PRM-151 had a significant positive treatment effect in patients with IPF as measured by changes in FVC % predicted and 6MWD during the 28-week period. PRM-151 was well-tolerated at a dose of 10 mg/kg intravenous every 4 weeks, without any safety

concerns. These data warrant a phase 3 clinical trial of PRM-151 in patients with IPF [6].

References

1. Li D, et al. Nintedanib and Pirfenidone as a Bridge to Lung Transplant in Idiopathic Pulmonary Fibrosis A1630. ATS 2018.
2. Safdar Z, et al. Relationship of Interferon Beta Use in Multiple Sclerosis and Development of Pulmonary Arterial Hypertension. A2122. ATS 2018.
3. Kreuter M, et al. Association of Angiotensin Modulators with the Course of Idiopathic Pulmonary Fibrosis A1634. ATS 2018.
4. Sawata T, et al. A Study of Tolerability and Therapeutic Effect of Antifibrotic Agents for Elderly Patients with Idiopathic Pulmonary Fibrosis. A1632. ATS 2018.
5. Hogben C, et al. Indication for and Impact of Switching from Pirfenidone to Nintedanib in Idiopathic Pulmonary Fibrosis. A1635. ATS 2018.
6. Raghu G, et al. Efficacy and Safety of Recombinant Human Pentraxin-2 in Patients with Idiopathic Pulmonary Fibrosis. A2440. ATS 2018.

Critical Care and Sleep Problems

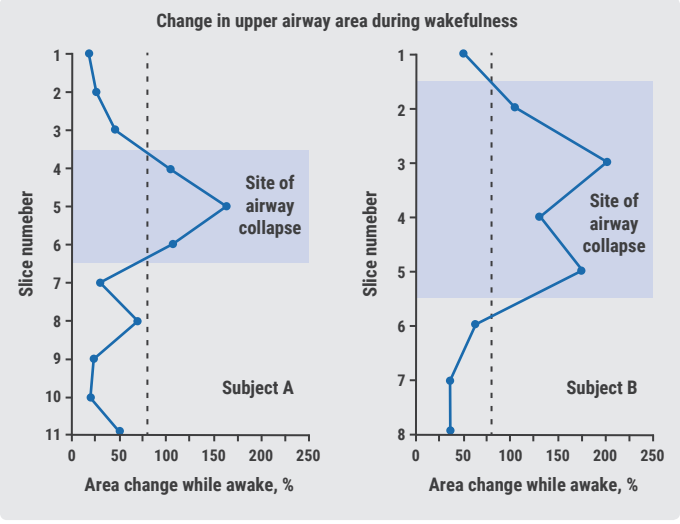
Issues surrounding sleep and critical care generally affect the more fragile patient, which calls for careful assessment and subsequent treatment or intervention. New insights into these complex situations may contribute to improved outcomes.

Potential role for dynamic OSA imaging during wakefulness

Darquenne et al. aimed to determine if upper airway dynamics measured during awake tidal breathing in subjects with obstructive sleep apnoea (OSA) can predict the site of upper airway collapse during sleep [1]. Therefore, dynamic MR images of the upper airway were obtained on a 1.5T MR scanner in contiguous 7.5 mm-thick axial slices from the hard palate to the epiglottis. Data were acquired in 7 OSA subjects (6 men, 1 woman, mean age 59, and BMI 28.5 kg/m^2, Apnoea-Hypopnoea Index 56/hr). During the scan, nasal and oral airflow, and electroencephalogram were simultaneously recorded. It was found that the narrowest area of the upper airway in awake OSA subjects was located in the low retropalatal region with a mean area over a tidal breath of 22.1 mm^2 (n=7). All 7 OSA subjects fell asleep in the scanner with 4 of them experiencing obstructive apnoeas during MR imaging. There was variability among subjects in the site and length over which the airway collapsed during an obstructive apnoea event with the obstruction extending over 2 (~15 mm), 3 (~22 mm; this is subject A in Figure 5), 4 (~30 mm, this is subject B in Figure 5); or 5 slices (~37 mm).

In 3 of the subjects, the airway collapsed in the retropalatal region while in the fourth subject the collapse extended over both the retropalatal and retroglossal regions. In all cases, the site of collapse occurred in slices that exhibited the largest dynamic change during awake tidal breathing (see Figure 5 where the shaded area indicates the site of upper airway collapse during obstructive apnoeas, area changes are shown from the hard palate (Slice 1) down to the tip of the epiglottis). Thus, it was shown that in a small group of OSA subjects, the site of airway collapse during sleep corresponds to the region of the upper airway where changes in upper airway calibre during awake tidal breathing are the greatest. These preliminary observations support a potential role for dynamic OSA imaging during wakefulness [1].

Figure 5 Changes in upper airway area during wakefulness [1]



Association between long-term use of PAP therapy and lower mortality and duration of hospital stays

A study by Woehrle et al. investigated long-term hospitalisation and mortality rates in matched sleep apnoea patients who did and did not receive positive airway pressure (PAP)

therapy [2]. It was performed as an exploratory, retrospective, longitudinal, two-cohort study using German health-claims data from the Health Risk Institute research database for the period 2008-2013. Eligible patients had complete medical records and ≥1 sleep apnoea-related diagnosis in 2009. To minimise selection bias, those prescribed PAP as part of their routine clinical care were propensity score matched with a control group not treated with PAP. A total of 2,176 PAP therapy recipients were matched with 2,176 controls. The PAP therapy group had a higher rate of hospitalisation in the year prior to sleep apnoea diagnosis (80.2% vs 26.6% in the control group; P=0.0016). After sleep apnoea diagnosis, average length of stay per hospitalisation was lower in the PAP group (P<0.05 vs control at years 1, 2, and 4). All-cause mortality in years 3 (3.4% vs 4.6%; P=0.0287) and 4 (4.8% vs 6.5%; P=0.0175) was significantly lower in sleep apnoea patients receiving PAP vs controls, corresponding to a 25.5% relative reduction in the risk of death at 4 years in users of PAP therapy compared with controls. The findings of this analysis of a large cohort of real-world sleep apnoea patients followed over 4 years showed an association between long-term use of PAP therapy and lower mortality and duration of hospital stays [2].

Factors predicting ICU mortality in patients on IMV treatment discovered

Ozlu et al. aimed to define clinical and laboratory criteria predicting the patients that will not benefit from invasive mechanical ventilation (IMV) treatment [3]. Correct selection of patients is of great importance due to limited bed capacity of most ICUs as well as optimal use of (scarce) healthcare resources. This was a prospective study, conducted between January and May 2017 in ICUs from different geographical areas of Turkey. The patients who were treated in coronary ICU and post-anaesthesia care unit, and were 18 years or older. A total of 1,463 adult patients (42.7% women/57.3% men) were included; the median age was 71 years. A total of 60.2% died, 25.2% were successfully weaned/extubated, 11.5% underwent persistent tracheostomy because of ventilator dependence, and 3.2% were transferred to another centre. Logistic regression analysis showed that ICU nurse care requirement, presence of interstitial lung diseases, pulmonary and central nervous system malignancies, other oncologic solid tumours, high Sequential Organ Failure Assessment Score (SOFA), Acute Physiology and Chronic Health Evaluation (APACHE-II) score, as well as age were found to be associated with mortality (Table 5) [3].

Thus, situations requiring ICU nursing care, presence of interstitial lung disease and solid organ tumours (mostly pulmonary), and cardiac arrest history were found to be strongly associated with ICU mortality. Situations expected to benefit from IMV and intensive care were neurodegenerative diseases, type 3 respiratory failure, pulmonary oedema, and COPD exacerbation. The researchers strongly emphasised the need for new algorithms to be developed in order to select the correct patients who will benefit from ICU and IMV [3].

Table 5 Factors which predict ICU mortality in patients who receive IMV treatment [3]

	Odds Ratio	95% CI for Odds	Sig.
Situations Requiring Nursing care in ICU	20.741	2.699 - 159.406	0.004
Interstitial Lung Disease	15.126	3.36 - 68.105	<0.001
Pulmonary Malignancy	6.366	2.794 - 14.505	<0.001
CNS Malignancy	4.679	1.241 - 17.641	0.023
Other Oncologic Solid Tumors	3.796	1.085 - 13.283	0.037
Cardiac Arrest	1.599	1.176 - 2.174	0.003
SOFA	1.09	1.053 - 1.128	<0.001
APACHE-II	1.047	1.03 - 1.065	<0.001
Age	1.018	1.01 - 1.025	<0.001
COPD Exacerbation	0.669	0.493 - 0.908	0.010
Pulmonary Edema	0.574	0.362 - 0.91	0.018
Type III Respiratory Failure	0.299	0.149 - 0.601	0.001
Neurodegenerative Disease	0.287	0.109 - 0.754	0.011

References

1. Darquenne CJ, et al. Linking Upper Airway Dynamics in Awake Tidal Breathing Obstructive Sleep Apnea (OSA) Subjects with Site of Upper Airway Collapse During Sleep: Preliminary Results. A1239. ATS 2018.
2. Woehrle H, et al. Long-Term Mortality in Sleep Apnea (SA) Patients Treated with Positive Airway Pressure (PAP) Therapy: Analysis of a Large German Healthcare Database. A1041. ATS 2018.
3. Ozlu T, et al. Factors Predicting Patients that Will Not Benefit from Invasive Mechanical Ventilation A5083. ATS 2018.

Medicom Conference Report Series in
Pulmonology/Allergy

Editor Vacancies: Call for Applications

We are looking to recruit handling Editors for our annual Medicom Conference Report Series in Pulmonology/Allergy.
Medicom publishes a series of high-quality peer-reviewed Medical Conference Reports for clinicians and medical professionals around the world, both in print and online. Our publications cover the latest clinical developments in medicine, presented at the annual recurring European and American conferences, and are published online within 6-8 weeks after the conference.

Within the specialty area Pulmonology/Allergy, we publish the annual EAACI, ATS and ERS Conference Reports.

Responsibilities of the editor
The Editor will nominate reviewers and suggest topics and sessions to be included in the conference reports. Medicom customers are also invited to suggest interesting topics and sessions for Editor consideration and approval. The Advisory Board, consisting 1 Editor and 2-3 reviewers, will review and advise on the report, particularly on its scientific accuracy. The Editor will have final Editorial decision responsibility.

We are looking for candidates who:
- are active researchers, who have gained recognition as an expert within Pulmonology/Allergy. You have a good understanding of related and interdisciplinary areas, a feel for how your field is developing and a view of the emerging topics
- have a network of international contacts and collaborators, and can attract key scientists as reviewers and/or editorial board members
- together with the Editorial Project Manager, would be interested in developing ideas about future directions for our conference series in Gastroenterology

The initial term of appointment is 1 year for all Medicom conferences covered in the specialty area Pulmonology/Allergy during 2018, currently projected to be EAACI, ATS and ERS. Alternatively an Editor role for a single conference report is open for discussion. Compensation for time, and Editor recognition in the conference report series.

Please submit a resume and cover letter explaining your suitability and interest for the role to Medicom Medical Publishers, to the attention of Lisa Colson, Editorial Project Manager.
e-mail: MCREditor@medicom.nl

- **Our Medicom Conference Reports fill the gap between live presentation at the conference and the publication in scientific journals. We publish the outcomes well before the information is available in journals.**
- **The Medicom Conference Reports facilitate a faster and broader dissemination of the breakthrough findings from a conference, while maintaining scientific quality standards.**
- **For recent publications please visit us at www.medicom.nl/mcr**