

## Journalwatch@pcrj

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### Asthma

#### Inhaled steroids for asthma associated with increased risk of pneumonia

McKeever *et al.* Inhaled corticosteroids and the risk of pneumonia in people with asthma: a case-control study. *Chest* 2013;**144**:1788-94. <http://dx.doi.org/10.1378/chest.13-0871>

This case-control study is yet another reminder that we should balance the benefits and risks when prescribing high dose ICS. Previous studies have shown an association between ICS use and increased risk of pneumonia in patients with COPD. This is the first study to show a similar relationship between ICS use and risk of pneumonia in patients with asthma. Data from The Health Improvement Network (THIN) database were used to identify 6,857 patients with asthma and pneumonia or lower respiratory tract infection (LRTI), and then to identify 36,312 age- and sex-matched controls from a total cohort of 359,172 people with asthma. Mean age of the population was 54 years (range 18-80 years). Using conditional logistic regression, the authors determined the association between the dose and type of ICS and the risk of pneumonia or LRTI. After adjusting for confounders, there was a small increased risk of pneumonia or LRTI for patients prescribed budesonide [odds ratio (OR) 1.20; 95% CI 1.06 to 1.35]. There was also a higher risk of pneumonia or LRTI in patients receiving fluticasone propionate [OR 1.64; 95% CI 1.50 to 1.79]. None of the other ICS (beclometasone, ciclesonide, mometasone) were associated with an increased risk of pneumonia or LRTI. There was a dose-response relationship between strength of ICS and infection risk [ $P < 0.001$  for trend]; after adjusting for confounders, patients receiving the highest doses of ICS (> 1000mcg beclometasone equivalent) were 2.04 [95% CI 1.59 to 2.64] times more likely to have pneumonia or LRTI. The authors conclude that pneumonia should be considered as a possible side effect of ICS, and therefore we should always strive to use the lowest possible dose of ICS to manage asthma.

#### Metabolic syndrome associated with increased risk of incident asthma

Brumpton *et al.* Metabolic syndrome and incidence of asthma in adults: the HUNT study. *Eur Respir J* 2013;**42**:1495-1502. <http://dx.doi.org/10.1183/09031936.00046013>

The Norwegian Nord-Trøndelag Health (HUNT) study recruited patients in three phases. 65,237 participants completed the second survey (HUNT 2) during 1995–1997, and of these, 37,071 also participated in HUNT 3 ten years later (2006–2008); these participants constituted the initial study cohort for this analysis. After excluding people with asthma or metabolic syndrome and those aged > 65 years, the authors constructed a final analysis cohort of

23,191. The aim was to explore the association between metabolic syndrome and the cumulative incidence of self-reported asthma. Length of follow-up was 11 years. Metabolic syndrome was categorised according to international criteria which include waist circumference, lipid profile, blood pressure, use of antihypertensive medication, serum glucose level, and self-reported diabetes. Extensive data were available on covariates such as age, sex, family history of asthma, smoking status, physical activity level, educational level, receipt of social benefits, and history of allergic rhinitis and/or acid reflux. After adjustment for all covariates, metabolic syndrome was associated with incident asthma [odds ratio (OR) 1.57; 95% CI 1.31 to 1.87]. Two components of the metabolic syndrome continued to show an association with incident asthma after adjustment for all the other metabolic syndrome components: high waist circumference [OR 1.62; 95% CI 1.36 to 1.94], and elevated glucose level or presence of diabetes [OR 1.43; 95% CI 1.01 to 2.04]. Therefore, metabolic syndrome and two of its components were associated with an increased risk of incident asthma in adults.

#### An update on formoterol safety: no increased risk of asthma-related deaths

Sears *et al.* Safety of formoterol in asthma clinical trials: an update. *Eur Respir J* 2014;**43**:103-14. <http://dx.doi.org/10.1183/09031936.00004713>

In 2009, these authors reported the safety outcomes for formoterol from all of the 117 AstraZeneca clinical trials that had been completed up to the end of 2006. This paper provides updated information from a further 32 trials completed by December 2011, giving a complete dataset of 149 trials involving 104,463 patients. However, in this study the authors restricted their main statistical analysis to parallel-group trials of 3-12 months duration, thus excluding 70 trials involving 9779 patients, and they also excluded patients who had been randomised to salmeterol or 'current best practice' ( $n = 4170$  and  $n = 4394$ , respectively). Therefore, the primary dataset consisted of 79 trials involving 67,380 formoterol patients and 18,740 patients randomised to non-LABA treatment. Primary outcomes were all-cause mortality, asthma-related deaths, and non-fatal asthma-related serious adverse events (SAEs). Secondary outcomes were overall SAEs, non-fatal cardiac-related SAEs, and discontinuations due to adverse events. There were no new asthma-related deaths in this expanded primary dataset, leaving a total of 8 asthma-related deaths in the formoterol group and 2 in the non-LABA group [relative risk (RR) 1.13; 95% CI 0.23 to 10.9]. There were 15 cardiac-related deaths in the formoterol group versus 9 in the non-LABA group [RR 0.47; 95% CI 0.19 to 1.22]. Non-fatal asthma-related SAEs were significantly reduced in the formoterol group [RR 0.63; 95% CI 0.53 to -0.75]. The authors conclude that there is no increased risk of asthma-related deaths with formoterol versus

non-LABA treatment – though they do highlight the very wide 95% confidence intervals which preclude certainty...

### As-needed combination budesonide/formoterol improves exercise-induced bronchoconstriction

Lazarinis *et al.* Combination of budesonide/formoterol on demand improves asthma control by reducing exercise-induced bronchoconstriction. *Thorax* 2014;**69**:130-36.

<http://dx.doi.org/10.1136/thoraxjnl-2013-203557>

The normal treatment for exercise-induced bronchoconstriction (EIB) in patients with mild asthma is a short-acting beta<sub>2</sub>-agonist (SABA) inhaler used as-needed. In this randomised, double-blind, parallel-group, 6-week trial, the authors investigated three different treatment regimens for EIB: regular budesonide 400mcg daily with terbutaline 500mcg before exercise and as-needed [n = 21, group A]; regular placebo once daily with terbutaline 500mcg before exercise and as-needed [n = 22, group B]; and regular placebo once daily with combination budesonide 200mcg/formoterol 6mcg before exercise and as-needed [n = 23, group C]. The 66 patients (aged > 12 years, all with verified EIB) exercised three to four times a week during the 6-week study period. The primary outcome was the change from baseline in maximal post-exercise decrease in FEV<sub>1</sub> after a standard exercise test (i.e. EIB) after 6 weeks of treatment. Secondary outcome measures included patient-reported symptoms and use of as-needed medication. Compared with baseline, the maximum post-exercise FEV<sub>1</sub> fall after 6 weeks treatment was 5.4% smaller [95% CI -8.9 to -1.8] in the budesonide/formoterol as-needed group (group C), 6.6% smaller [95% CI -10.3 to -3.0] in the regular budesonide group (group A), and 1.5% greater [95% CI -2.1 to +5.1] in the terbutaline as-needed group (group B). The total budesonide dose was 2.5 times smaller in the as-needed budesonide/formoterol group compared to the regular budesonide group. The authors conclude that as-needed budesonide/formoterol reduced EIB by a similar amount as regular budesonide, with a 2.5 times smaller total dose of budesonide, and that other treatment options should therefore be available for EIB in addition to a SABA on an as-needed basis.

### Efficacy and safety of fluticasone furoate treatment for asthma

Lotvall *et al.* Efficacy and safety of fluticasone furoate 100 mcg once-daily in patients with persistent asthma: a 24-week placebo and active-controlled randomised trial. *Resp Med* 2014;**108**:41-9. <http://dx.doi.org/10.1016/j.rmed.2013.11.009>

Fluticasone furoate is a once-daily inhaled corticosteroid (ICS), and its once-daily dosage regimen may well have advantages in terms of patient compliance. This was a 24-week, double-blind, placebo-controlled efficacy and safety study of 343 asthma patients aged 12 years and over whose asthma was not controlled by their pre-existing ICS. They were randomised in a 1:1:1 ratio to receive fluticasone furoate 100mcg daily, placebo, or fluticasone propionate (FP) 250mcg twice daily. The primary endpoint was change from baseline in the pre-dose evening FEV<sub>1</sub> at week 24. The secondary endpoint was change from baseline in the percentage of rescue-free days. As might be expected, both of the fluticasone treatments improved pre-dose evening FEV<sub>1</sub> at week 24 compared to placebo (fluticasone furoate +146ml versus placebo [P = 0.009]; FP +145ml vs. placebo [P = 0.011]). The percentage of rescue-free days was also increased in both of the fluticasone groups (+14.8% for the fluticasone furoate group, +17.9% for the FP group [both P < 0.001]). The severe asthma exacerbation rate was also lower in both fluticasone groups (3% in the fluticasone furoate group, 2% in the FP group, 7% in the placebo group). Again, as might be expected, there was significant urinary cortisol suppression at week 24 in both fluticasone groups versus placebo. The authors conclude that fluticasone furoate 100mcg daily achieves similar improvements in lung function and rescue inhaler use to FP 250mcg twice-daily, with a similar safety profile. No doubt there are more studies to come...

## COPD

### Effect of telemonitoring on hospital admission for COPD exacerbations

Pinnock *et al.* Effectiveness of telemonitoring integrated into existing clinical services on hospital admission for exacerbation of chronic obstructive pulmonary disease: researcher blind, multicentre, randomised controlled trial. *BMJ* 2013;**347**:f6070. Published online 17th October 2013.

<http://dx.doi.org/10.1136/bmj.f6070>

So far there have been five systematic reviews on the effectiveness of telemonitoring in COPD and all have been inconclusive. The concern is that the positive effect of telemonitoring seen in previous trials could be due to enhancement of the clinical service provided to the telemonitoring group rather than the telemonitoring itself. These authors piloted a mixed methods study in order to clarify methodological design issues (see <http://dx.doi.org/10.4104/pcrj.2011.00065>). In this randomised controlled trial (RCT), COPD patients with at least one hospital admission in the previous year were randomised to telemonitoring [n = 128] or usual care [n = 128]. The telemonitoring consisted of a daily questionnaire about symptoms and treatment, and monitoring of oxygen saturation using linked instruments; alerts were generated if the readings or symptom scores breached agreed thresholds. Importantly, care for the telemonitoring group was integrated into existing clinical services so that, other than the intervention, both groups had access to the same clinical care. The primary outcome was time to hospital admission due to COPD exacerbation in the year after randomisation. Secondary outcomes included number and duration of admissions, health-related quality of life, anxiety and depression, self-efficacy, knowledge, and adherence to treatment. There was no increase in the time to hospital admission between the two groups [adjusted hazard ratio 0.98; 95% CI 0.66 to 1.44], and no reduction in the number of admissions [telemonitoring 1.2 admissions per person (SD 1.9) versus control 1.1 (SD 1.6); P=0.59] or the length of hospital stay [9.5 days per person (SD 19.1) vs. 8.8 days (SD 15.9); P=0.88]. There was no significant difference in any of the other secondary outcomes. Therefore, in patients with a previous admission for COPD exacerbation, telemonitoring does not postpone further admission or improve quality of life.

### Benefits of beta-blockers after myocardial infarction in adults with COPD

Quint *et al.* Effects of beta-blockers on mortality after myocardial infarction in adults with COPD: population based cohort study of electronic healthcare records. *BMJ* 2013;**347**:f6650. Published online 22nd November 2013. <http://dx.doi.org/10.1136/bmj.f6650>

The aim of this population-based cohort study was to investigate whether beta-blocker use in patients with COPD having a first myocardial infarction (MI) is associated with survival. Using data from the UK national registry of myocardial infarction (Myocardial Ischaemia National Audit Project (MINAP) and the General Practice Research Database (GPRD), the authors constructed a cohort of 2209 COPD patients with a first myocardial infarction occurring between 2003 – 2008; of these, 1063 had yes/no coding for beta-blocker usage and were included in the final analysis. The primary outcome was all cause mortality after a first ST elevation MI (STEMI) or non-ST elevation MI. Data on cause of death were obtained from death certificates. Cox proportional hazard ratios (HR) were calculated, corrected for covariates including age, sex, smoking status, drugs, co-morbidities, type of myocardial infarction, and severity of infarct. Follow-up was for a median period of 2.9 years. After adjustment for sex and history of smoking, and stratification by age, patients with COPD prescribed a beta-blocker during the hospital admission for MI had better survival than those never prescribed a beta-blocker [HR 0.45; 95% CI 0.34 to 0.60]. Those patients prescribed a beta-blocker before the MI also had better survival [HR 0.72; 95% CI 0.57 to 0.90]. The authors conclude that beta-blocker use before and at the time of an MI is associated with improved survival – an important message which should prompt further RCTs on this subject.

**BOLD: the impact of COPD on health status**

Janson *et al.* The impact of COPD on health status: findings from the BOLD study. *Eur Respir J* 2013;**42**:1472-83.

<http://dx.doi.org/10.1183/09031936.00153712>

Another interesting paper from the BOLD study, which was set up to estimate the social and economic burden of COPD around the world using standardised spirometry and a structured face-to-face interview incorporating the Short-Form 12 (SF-12) questionnaire. The aims of this analysis were to describe the impact of COPD on health status in adults aged > 40 years and to identify determinants of low health status in these patients. The SF-12 incorporates the mental and physical scores from the longer SF-36, and higher scores indicate better health status. Data were also obtained on educational level, smoking history, co-morbidities, symptoms, medication, and COPD exacerbations. 11,985 subjects were included in the final analysis, 2,269 of whom had COPD. Those with COPD were older, more often male, had a lower BMI, lower educational level, and a higher prevalence of heart disease, hypertension and stroke. Subjects with COPD had lower SF-12 physical component scores [44 +/-10 versus 48 +/-10;  $P < 0.0001$ ] and lower mental health component scores [51 +/-10 vs. 52 +/-10;  $P = 0.005$ ] than people without COPD. The effect of co-morbidities such as heart disease, hypertension and diabetes on the physical scores (-3 to -4 units) was less than the effect of having severe (Grade 3, -8 units) or very severe (Grade 4, -11 units) COPD. Dyspnoea was the most important determinant of low SF-12 physical and mental component scores. Low FEV<sub>1</sub>, chronic cough, and chronic phlegm production were also associated with lower SF-12 physical component scores. Therefore, COPD is associated with poorer health status – particularly the physical aspects of health status, and the negative impact of COPD is greater than its co-morbidities such as heart disease and diabetes.

**Dual bronchodilatation with combination indacaterol/glycopyrronium versus its separate components, tiotropium and placebo**

Bateman *et al.* Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. *Eur Respir J* 2013;**42**:1484-94. <http://dx.doi.org/10.1183/09031936.00200212>

QVA149 is a fixed-dose LABA/LAMA combination inhaler containing indacaterol 110mcg and glycopyrronium 50mcg. In this multicentre, randomised, double-blind, parallel-group, placebo-controlled study, the authors have assessed the efficacy and safety of QVA149 compared to its separate components, tiotropium, and placebo, in patients with moderate-to-severe COPD. After a 1-week wash-out and 2-week run-in period, patients (mean FEV<sub>1</sub> 55.2% predicted) were randomised to QVA149 [ $n = 475$ ], indacaterol 150mcg [ $n = 477$ ], glycopyrronium 50mcg [ $n = 475$ ], tiotropium 18mcg [ $n = 483$ ] and placebo [ $n = 234$ ]. The primary endpoint was trough FEV<sub>1</sub> at week 26, and secondary endpoints included dyspnoea, health status, rescue medication use and safety. 99.6% of patients were included in the final analysis and 89.1% of randomised patients completed the study. Trough FEV<sub>1</sub> at 26 weeks was significantly improved with QVA149 compared to indacaterol and glycopyrronium [treatment differences of 0.07L and 0.09L, respectively; both  $P < 0.001$ ], and compared to tiotropium and placebo [treatment differences of 0.08L and 0.2L, respectively; both  $P < 0.001$ ]. Treatment differences were present from day 1 and continued throughout the 26 weeks. QVA149 also significantly improved dyspnoea and health status versus placebo [ $P < 0.001$  and  $P = 0.002$ , respectively] and versus tiotropium [ $P = 0.007$  and  $P = 0.009$ , respectively]. Dual LABA/LAMA bronchodilation with QVA149 therefore showed superior efficacy compared to placebo, its separate components, and tiotropium, in patients with moderate-to-severe COPD. This supports the GOLD 2013 alternative choice strategy of adding in a second bronchodilator early for COPD Groups B, C and D.

**Risk factors and co-morbidities in very early COPD**

van Remoortel *et al.* Risk factors and co-morbidities in the preclinical stages of chronic obstructive pulmonary disease. *Am J Resp Crit Care Med* 2014; **189**:30-38.

<http://dx.doi.org/10.1164/rccm.201307-1240OC>

This study on the prevalence of co-morbidities and risk factors in early preclinical COPD adds to the body of evidence in favour of early screening for COPD. 60 subjects with spirometrically-defined COPD but without any symptoms (mean age 63 +/- 6 years; 68% male) were compared with two different sets of age-matched controls – 60 smokers with no evidence of COPD (mean age 62 +/- 7 years; 70% male), and 60 never-smokers without COPD (mean age 62 +/- 6 years; 57% male). Data were collected on cardiovascular, metabolic and musculoskeletal co-morbidities, and daily physical activity was measured by a multisensor activity monitor. The prevalence of pre-morbid risk factors was similar in the preclinical COPD group and the smoking control group, but was significantly lower in the never-smoker control subjects. Cardiovascular disease and musculoskeletal disease were the most prevalent co-morbidities (15% and 12%, respectively), and using multivariate logistic regression analysis, physical inactivity and smoking were independent risk factors for having two or more co-morbidities. These results are intuitively correct, of course – smoking and physical inactivity are risk factors for COPD and numerous other diseases – but they emphasise the importance of early COPD diagnosis and subsequent lifestyle advice.

**Lower plasma vitamin D levels associated with faster decline in lung function and a higher risk of COPD**

Afzal *et al.* Plasma 25-hydroxyvitamin D, lung function and risk of chronic obstructive pulmonary disease. *Thorax* 2014;**69**:24-31. <http://dx.doi.org/10.1136/thoraxjnl-2013-203682>

Research into the role of Vitamin D in the lung is accelerating at a remarkable rate. The pathogenesis of COPD involves protease-antiprotease imbalance, inflammation, lung remodelling and oxidative stress, and lower vitamin D levels have been shown to regulate each of these processes. In this study, the authors used data from 10,116 patients recruited into the Copenhagen City Heart Study (a prospective cohort study started in 1976, with four follow-up assessments in 1981, 1991 and 2001) and data from 8,391 patients recruited into the Copenhagen General Population Study (a general population study started in 2003 which is ongoing). All patients had plasma 25-hydroxyvitamin D [25(OH)D] samples taken and full lung function data available; those in the Copenhagen City Heart Study also had three lung function measurements performed over 20 years which permitted analysis of lung function decline. Overall, FEV<sub>1</sub> and FVC percent predicted were 7% lower in patients with the lowest decile 25(OH)D concentration. Those patients with 25(OH)D in the lowest quintile also had a faster decline in FEV<sub>1</sub> and FVC percent predicted over 20 years. In cross-sectional analyses, for the patients in the Copenhagen City Heart Study, multivariable adjusted odds ratios (ORs) for developing COPD in the lowest versus the highest 25(OH)D quintile were 2.30 [95% CI 1.55 to 3.41] and 3.06 [95% CI 1.97 to 4.76] according to either GOLD or lower limit of normal (LLN) criteria, respectively. Similar ORs applied to patients in the General Population Study. This is the first study to show that low vitamin D level (as plasma 25-hydroxyvitamin D) is associated with faster lung function decline and future risk of COPD in the general population.

**No association between vitamin D levels and COPD exacerbations in primary care settings**

Pulhan *et al.* No association of 25-hydroxyvitamin D with exacerbations in primary care patients with COPD. *Chest* 2014;**145**:37-43. <http://dx.doi.org/10.1378/chest.13-1296>

To continue the vitamin D theme... The aim of this study was to identify any association between plasma 25-hydroxyvitamin D [25(OH)D] and exacerbations and mortality in primary care patients with COPD. Its strengths are the efforts to minimise misclassification of COPD exacerbations and the influence of confounders, and also its longitudinal 'real world' design. The authors used data from 356 patients with COPD (GOLD stages II to IV) who were originally recruited into a prospective cohort study in Switzerland and the Netherlands. All had 25(OH)D measurement performed at baseline. Baseline mean 25(OH)D concentration was 15.5 +/- 8.9 ng/dL. The majority of patients [ $n = 274$ , 77.0%] had vitamin D deficiency (i.e. 25(OH)D concentration < 20 ng/dL), and 106 (29.8%) had severe deficiency (< 10



ng/dL). There was no difference in exacerbation rate in patients with severe vitamin D deficiency versus those with moderate deficiency (10-19.99 ng/dL) or vitamin D 'insufficiency' (20-29.99 ng/dL): incidence rate ratios were 1.01 [95% CI 0.77 to 1.57] and 1.00 [95% CI 0.62 to 1.61], respectively. There was a lower risk of exacerbation in patients with 'desirable' vitamin D levels (> 30ng/dL), though this was imprecisely estimated (incidence rate ratio 0.72 [95% CI 0.37 to 1.42]). Therefore there was no association between vitamin D levels and COPD exacerbations or mortality rates.

### Serum uric acid is associated with 30-day mortality and future exacerbations of COPD

**Bartziokas et al.** Serum uric acid as a predictor of mortality and future exacerbations of COPD. *Eur Respir J* 2014;**43**:43-53. <http://dx.doi.org/10.1183/09031936.00209212>

Uric acid is the final product of purine metabolism, and levels increase during hypoxia and systemic inflammation. One study from Japan has previously reported an association between uric acid levels and airflow obstruction in the general population. The aim of this prospective cohort study was to evaluate serum uric acid as a biomarker for predicting mortality and future exacerbations in 314 consecutive patients presenting with an acute exacerbation of COPD to a hospital respiratory department in Athens, Greece. All patients were current or ex-smokers with a physician diagnosis of COPD. All had their serum uric acid measured; values < 6.9 mg/dL were considered 'low', and values > 6.9 mg/dL were considered 'high'. Assessment took place on admission and at discharge, and follow-up was by monthly telephone review over the 1-year study period. Uric acid levels were higher in patients with more severe airflow obstruction; median FEV<sub>1</sub> percent predicted was 45.0 [interquartile range (IQR) 34.0 to 63.0] in patients with low uric acid levels, and was 32.0 [IQR 22.0 to 39.0] in patients with high uric acid levels. Using multivariate Cox regression, high uric acid levels were shown to be an independent predictor of 30-day mortality [hazard ratio (HR) 1.312; 95% CI 1.01 to 1.74] but not of 1-year mortality. Patients with high uric acid required longer in hospital and were more likely to need admission to the intensive care unit. In the 12 months post admission, high uric acid levels were associated with an increased risk of further COPD exacerbation [rate ratio 1.184; 95% CI 1.13 to 1.25]. Therefore, serum uric acid looks to be an effective low-cost biomarker for increased 30-day mortality and increased risk of subsequent exacerbation, and therefore could be very useful in identifying patients with an acute exacerbation of COPD who need more intensive management. But this finding now needs replicating in another population group...

### Long-term safety and efficacy of acclidinium bromide in COPD patients

**Gelb et al.** Long-term safety and efficacy of twice-daily acclidinium bromide in patients with COPD. *Resp Med* 2013;**107**:1957-65. <http://dx.doi.org/10.1016/j.rmed.2013.07.001>

This is a 52-week, parallel group, double-blind efficacy and safety study on acclidinium, a new long-acting muscarinic antagonist (LAMA). 605 patients with moderate-to-severe COPD were randomised to receive 200 mcg or 400 mcg acclidinium twice-daily. Data were collected on adverse events (AEs), and there was regular monitoring of haematological and biochemical indices, vital signs and ECGs. Efficacy was assessed by regular spirometry, rescue medication use, and the St George's Respiratory Questionnaire (SGRQ). The percentages of patients reporting any AEs were comparable between the two groups, and most were mild and infrequent. Anticholinergic AEs such as dry mouth or constipation were also infrequent (dry mouth – 1.3% in patients on 200mcg inhaler, 2.7% for the 400mcg inhaler; constipation – 2.9% for 200mcg inhaler, 1.7% for 400mcg inhaler). Cardiac AEs were infrequent (< 2% for any cardiac event in either group) and not dose dependent. There were improvements in FEV<sub>1</sub> from baseline to week 52, which were greater in the 400mcg group, and there were clinically significant improvements in SGRQ scores and reduction in rescue medication use in both groups. The authors conclude that long-term treatment with acclidinium was well tolerated and that there were significant benefits in lung

function and health status throughout the 1-year study period. No doubt there will be comparative studies to come...

### N-acetylcysteine reduces exacerbations in moderate-to-severe COPD

**Zheng et al.** Twice daily N-acetylcysteine 600mg for exacerbations of chronic obstructive pulmonary disease (PANTHEON): a randomised, double-blind placebo-controlled trial. *Lancet Respir Med* 2014, published online 30th January 2014.

[http://dx.doi.org/10.1016/S2213-2600\(13\)70286-8](http://dx.doi.org/10.1016/S2213-2600(13)70286-8)

The aim of this randomised, double-blind, placebo-controlled, parallel-group study was to see if N-acetylcysteine, given its antioxidant and anti-inflammatory properties, might have a therapeutic role in the management of COPD. After stratification according to inhaled corticosteroid (ICS) use – i.e. regular ICS use or not – 1006 patients with moderate-to-severe COPD (FEV<sub>1</sub> 30-70% predicted) recruited from 34 hospitals in China were randomised to receive N-acetylcysteine 600mg twice-daily [n = 504] or placebo [n = 502]. The primary outcome was the annual exacerbation rate in patients who had received at least one dose of study drug and who had attended at least one study visit post-randomisation. There were 497 exacerbations in 482 patients in the N-acetylcysteine group (1.16 exacerbations per patient per year) and 641 exacerbations in 482 patients in the placebo group (1.49 exacerbations per patient per year), giving a risk ratio of 0.78 [95% CI 0.67 to 0.90]. The adverse event (AE) rate was similar in both groups (29% of patients in the N-acetylcysteine group, 26% in the placebo group) with 48 versus 46 serious AEs, respectively. Therefore, in this group of patients, N-acetylcysteine reduced COPD exacerbation rate over a 1-year period and was well tolerated. Further studies will be required in different patient populations with differing degrees of COPD severity, but N-acetylcysteine looks to be a potential addition to the COPD therapeutic armamentarium...

### Safety of benzodiazepines and opioids in severe COPD

**Ekstrom et al.** Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. *BMJ* 2014; **348**:g445. Published online 30th January 2014.

<http://dx.doi.org/10.1136/bmj.g445>

This national population-based longitudinal cohort study included 2249 patients aged 45 or older (59% women) who started long-term oxygen (LTOT) between 2005 and 2009 and who were included in the national Swedevox Register (comprising about 85% of those patients starting LTOT in Sweden). They were follow-up prospectively until December 2009. No patient was lost to follow-up. The aim was to evaluate the safety of benzodiazepines and opioids – i.e. risk of hospital admission or death – in patients with very severe COPD. Data were obtained from the prescribed drug register (national register on drugs), and national hospital admission and mortality registers. Daily doses of benzodiazepines and opioids were estimated from the prescriptions provided in the three months before starting LTOT, expressed as 'defined daily doses'. There were 1625 dispensed prescriptions for benzodiazepines, which included oxazepam (74%), diazepam (17%), and alprazolam (8%). Opioids (1417 prescriptions) included tramadol (31%), oxycodone (15%), morphine (11%) and fentanyl (5%). During follow-up, 1681 patients (76%) were admitted to hospital, and 1129 (50%) died. Statistical analysis included consideration of numerous potential confounders, including age, sex, PaO<sub>2</sub>, FEV<sub>1</sub>, smoking status, BMI, number of admissions in the 4 years prior to study inclusion, and an extensive list of co-morbidities. Use of benzodiazepines or opioids was not associated with increased admission to hospital – adjusted hazard ratios (HR) were 0.98 [95% CI 0.87 to 1.10] and 0.98 [95% CI 0.86 to 1.10], respectively. However, benzodiazepine use was associated with increased mortality [HR 1.21; 95% CI 1.05 to 1.39]. Lower dose opioids (≤ 30mg oral morphine equivalents/day) were not associated with increased mortality [HR 1.03; 95% CI 0.84 to 1.26], whereas higher dose opioids were [HR 1.21; 95% CI 1.02 to 1.44]. Therefore, benzodiazepines and higher dose opioids were associated with increased mortality in patients with very severe COPD

on LTOT. This study has obvious relevance for any clinician looking after patients with very severe COPD. We await further confirmatory studies in this area.

### Positive expiratory pressure therapy for acute exacerbations of COPD: no effect on short-term or long-term outcomes

Osadnik *et al.* The effect of positive expiratory pressure (PEP) therapy on symptoms, quality of life and incidence of re-exacerbation in patients with acute exacerbations of chronic obstructive pulmonary disease: a multicentre, randomised controlled trial. *Thorax* 2014;**69**:137-43.

<http://dx.doi.org/10.1136/thoraxjnl-2013-203425>

This is an important negative study which will have implications for routine clinical care in the hospital setting. Positive expiratory pressure (PEP) has hitherto been used to enhance sputum clearance during acute exacerbations of COPD. In this multicentre, randomised controlled trial (RCT) from Melbourne Australia, 92 patients (58 men, mean age 68.6 yrs, mean FEV<sub>1</sub> 40.8% predicted) were randomised to receive usual care for their COPD exacerbation (which included bronchodilators, corticosteroids, antibiotics, oxygen, non-invasive ventilation if needed, and physiotherapy) or usual care plus PEP. Patients were assessed at admission, discharge, and at 8 weeks and 6 months post-discharge. The primary outcome was self-reported symptom severity as measured by the Breathlessness, Cough and Sputum scale (BCSS), a validated daily score ranging from 0 (no symptoms) to 12 (severely affected), which the patients completed on a daily basis for the whole 6-month period. Secondary outcomes included the St George's Respiratory Questionnaire (SGRQ) and the BODE index. 44 patients in each group were included in the primary analysis. There were no significant differences in any of the outcomes between the two groups at discharge, 8 weeks and 6 months, apart from dyspnoea which improved more rapidly in the PEP group over the first 8 weeks but was then not significantly improved at 6 months. Therefore, PEP did not improve short- or long-term outcomes for patients with acute exacerbations of COPD.

## Infections

### Montelukast is not an effective treatment for post-infectious cough

Wang *et al.* Montelukast for postinfectious cough in adults: a double-blind randomised placebo-controlled trial. *Lancet Respir Med* 2013. Published online 2nd December 2013.

[http://dx.doi.org/10.1016/S2213-2600\(13\)70245-5](http://dx.doi.org/10.1016/S2213-2600(13)70245-5)

Post-infectious cough is extremely common. Given that the pathogenesis of post-infectious cough (including whooping cough) involves the cysteinyl leukotrienes, the aim of this RCT was to assess the effectiveness of montelukast, a leukotriene receptor antagonist (LTRA), for the treatment of post-infectious cough. Over an 18-month period, non-smoking adults aged 16-49 years with a 2-8 week history of post-infectious cough were randomised to receive montelukast 10mg daily [n = 137] or placebo [n = 139] for 2 weeks. Patients could then choose to stay on treatment for a further 2 weeks. 25% of patients had laboratory-confirmed pertussis. The primary outcome measure was change in cough-specific quality of life using the Leicester Cough Questionnaire (LCQ) – a validated 19-item self-completed quality of life measure – completed at baseline and at 2 and 4 weeks. At 2 weeks, both groups showed an improvement in mean LCQ score [montelukast 2.7 (95% CI 2.2 to 3.3); placebo 3.6 (95% CI 2.9 to 4.3)], but the difference did not meet the minimum clinically important difference (MCID) of 1.3 [mean difference -0.9; 95% CI -1.7 to -0.04]. Of those patients with complete data, 99 of 129 patients on montelukast (77%) and 93 of 130 patients on placebo (72%) chose to stay on treatment until week 4. Again, at 4 weeks there were improvements in LCQ scores in both groups [montelukast 5.2 (95% CI 4.5 to 5.9); placebo 5.9 (95% CI 5.1 to 6.7)] but the mean difference of 0.5 [95% CI -1.5 to 0.6] was less than the MCID.

Therefore, this is an interesting negative study: montelukast is not an effective treatment for post-infectious cough.

### Inhaled steroids associated with increased risk of TB in South Korea

Lee *et al.* Use of inhaled corticosteroids and the risk of tuberculosis. *Thorax* 2013;**68**:1105-13.

<http://dx.doi.org/10.1136/thoraxjnl-2012-203175>

TB is still one of the leading causes of infectious disease morbidity and mortality worldwide. Active TB can result from reactivated latent TB, and risk factors for reactivation include HIV infection, chronic renal failure, and poorly controlled diabetes. Inhaled corticosteroids (ICS) can decrease local immunity in the lung, and a number of studies and meta-analyses have shown an association between ICS use in patients with COPD and increased risk of pneumonia. Therefore, the aim of this nested case-control study from South Korea – which is categorised by WHO as an intermediate-TB-burden country – was to examine the association between ICS use and development of TB among patients with various respiratory diseases. Using data from the Health Insurance Review and Assessment Service database which covers the entire South Korean population, the authors constructed a cohort of 853,439 new users of any respiratory inhaler between January 2007 and December 2010 who were aged over 20 and did not have a previous TB diagnosis. During the study period, 4,146 individuals were newly diagnosed with TB. Each case was then randomly matched (for age, sex, diagnosis of asthma or COPD and respiratory inhaler initiation date) with up to five controls; 20,583 controls were ultimately identified. ICS use included inhaled beclomethasone, budesonide, ciclesonide and fluticasone. ICS use was associated with an increased rate of TB diagnosis [adjusted odds ratio (OR) 1.20; 95% CI 1.08 to 1.34]. Furthermore, this increased risk of TB was dose dependent [P < 0.001 for trend]. Therefore, clinicians need to be aware that long-term high dose ICS is associated with an increased risk of TB development.

### Serotypes 3, 19A and 19F are important risk factors for respiratory failure following pneumococcal pneumonia

Burgos *et al.* Risk factors for respiratory failure in pneumococcal pneumonia: the importance of pneumococcal serotypes. *Eur Respir J* 2014;**43**:545-53. <http://dx.doi.org/10.1183/09031936.00050413>

*Strep. pneumoniae* is the leading cause of pneumonia worldwide, and quoted mortality rates from pneumococcal pneumonia are 10-30% in adults and < 3% in children. Patient factors such as immunosuppressive status are important, but increasingly there is evidence that organism-related factors affect mortality too. There are more than 90 different pneumococcal serotypes, with varying characteristics. The aim of this large observational study was to analyse possible risk factors associated with the development of respiratory failure in adults with invasive pneumococcal pneumonia (IPP). All adults aged 18 or over admitted to two teaching hospitals in Catalonia, Spain since 1996 with invasive pneumococcal pneumonia were enrolled [n = 1258]. Data were collected on socio-demographics (including age, sex, tobacco smoking, vaccination status with the 23-valent polysaccharide vaccine PPV-23, and time of influenza epidemic), medical history (including comorbidities and immunosuppressive status), respiratory status (presence of respiratory failure, need for mechanical ventilation, and chest X-ray appearance), clinical presentation, antimicrobial therapy, and microbiological findings (including serotype and antibiotic sensitivities). 615 patients (48.9%) had respiratory failure on admission; they were older (mean age 62.1 years versus 55.4 years; P<0.001) and were more likely to have comorbid conditions. After extensive adjustment for confounding variables, independent risk factors for respiratory failure were: age > 50 years [odds ratio (OR) 1.63; 95% CI 1.15 to 2.3], chronic lung disease [OR 1.54; 95% CI 1.1 to 2.15], chronic heart disease [OR 1.49; 95% CI 1.01 to 2.22], and infection by serotypes 3 [OR 1.97; 95% CI 1.23 to 3.16], 19A [OR 2.34; 95% CI 1.14 to 4.42], and 19F [OR 3.55; 95% CI 1.22 to 10.28]. As pneumococcal vaccines continue to be developed, these important findings will need to be borne in mind...

## Sleep disorders

### Upper airway stimulation for moderate-to-severe obstructive sleep apnoea

Strollo *et al.* Upper-airway stimulation for obstructive sleep apnea. *New Engl J Med* 2014;**370**:139-49

<http://www.nejm.org/doi/full/10.1056/NEJMoa1308659>

This interesting uncontrolled prospective cohort study involved 126 patients (83% men; mean age 54.5 years; mean BMI 28.4) who had difficulty accepting or adhering to the standard treatment for obstructive sleep apnoea (OSA), i.e. continuous positive airway pressure (CPAP). They all underwent surgical implantation of an upper airway stimulation device. The primary outcome measures were the apnoea-hypopnoea index (AHI – i.e. the number of apnoea or hypopnoea events per hour; a score of  $\geq 15$  indicates moderate-to-severe OSA) and the oxygen desaturation index (ODI – i.e. the number of times per hour that blood oxygen levels fall by  $\geq 4$  percentage points from baseline). There were various secondary outcomes measures including the Epworth Sleepiness Scale. The main evaluation was at 12 months post-surgical implantation. Those patients who responded well were subsequently included in a randomised controlled extension to the study in which therapy was withdrawn from half the patients. At 12 months, the median AHI score decreased from 29.3 events/hour to 9.0 events/hour [ $P < 0.001$ ], and the ODI score decreased from 25.4 events/hour to 7.4 events/hour [ $P < 0.001$ ]. Secondary outcome measures were also improved. 46 patients entered the randomised controlled treatment withdrawal phase. For the 23 patients who continued with the stimulation device, the mean AHI score showed no significant change from their 12-month score. However, the 23 patients in the therapy withdrawal arm showed a significant increase in their mean AHI score following removal of the stimulation device, from 7.6 events/hour to 25.8 events/hour [ $P < 0.001$ ]. Procedure-related serious adverse events were rare ( $< 2\%$ ). Presumably there will be larger randomised controlled trials (RCTs) to come, but insertion of an upper airway stimulation device may well prove to be a therapeutic option for those patients with OSA who can't tolerate CPAP.

## Fibrotic lung disease

### Pulmonary rehabilitation associated with improved outcomes in patients with interstitial lung disease

Ryerson *et al.* Pulmonary rehabilitation improves long-term outcomes in interstitial lung disease: a prospective cohort study. *Resp Med* 2014;**108**:203-10.

<http://dx.doi.org/10.1016/j.rmed.2013.11.016>

Pulmonary rehabilitation (PR) has proven efficacy in the management of patients with COPD. There have also been some studies on its role in patients with interstitial lung disease (ILD). This prospective cohort study incorporated data from three different PR programmes. 54 patients with ILD were recruited, 22 of whom had idiopathic pulmonary fibrosis (IPF); 50 patients completed their PR programme, and 39 attended for 6-month follow-up. Data were collected on various functional assessments including 6-minute walking distance (6MWD) and 4-metre walk time, as well as various quality of life questionnaires, measured at baseline, on completion of PR, and at 6 months. 6MWD improved by 57.6 metres [95% CI 40.2 to 75.1] after PR, and was still significantly improved at 6 months (49.8 metres above baseline [95% CI 15.0 to 84.6]). 51% of patients achieved the minimum clinically important difference (MCID) for improvements in quality of life, 65% achieved the MCID for improvement in dyspnoea, and 52% achieved the MCID for improvement in depression. A low baseline 6MWD was the only independent predictor for improvement in 6MWD during PR. Therefore, PR can improve short- and long-term outcomes for patients with ILD, and patients with the worst baseline 6MWD show the most improvement...

## Miscellaneous

### Tobacco control reduces smoking-related premature deaths

Holford *et al.* Tobacco control and the reduction in smoking-related premature deaths in the United States, 1964 - 2012. *JAMA* 2014;**311**:164-71. <http://dx.doi.org/10.1001/jama.2013.285112>

It is 50 years exactly since the first US Surgeon General's report on smoking and health, and this study highlights the reduction in smoking-related mortality associated with tobacco control in the US since then. Data were obtained on smoking histories for the US adult population between 1964 and 2012 from National Health Interview Surveys. Death rates by smoking status were derived from mortality rate ratio estimates based on studies of the effect of smoking on mortality. An important part of the study design was an estimation of smoking histories for individual birth cohorts under different scenarios had tobacco control not been in force; the authors were therefore able to compare actual smoking-related mortality with estimated mortality (with upper and lower 'credible ranges' based on various different scenarios) as if there had been no tobacco control. The primary outcome measures were the number of premature deaths avoided and the years of life saved, and the secondary outcome was the change in life expectancy at age 40 associated with a change in smoking status. Between 1964 and 2012, there were an estimated 17.7 million smoking-related deaths, but this was 8.0 million [credible range (CR) 7.4 to 8.3 million] fewer deaths than would have occurred if tobacco control had not been in place. This resulted in 157 million life-years saved [CR 139 to 165 million]. Over this 50-year period, life expectancy at age 40 increased by 7.8 years for men and 5.4 years for women, of which tobacco control contributed 2.3 years [CR 1.8 to 2.5] for men and 1.6 years [CR 1.4 to 1.7] for women. Justifiably, the authors conclude that tobacco control represents a significant public health achievement, but they note that there is still more work to be done...

### Varenicline and bupropion versus varenicline alone: improved smoking abstinence after 12 and 26 weeks but not at 52 weeks.

Ebbert *et al.* Combination varenicline and bupropion SR for tobacco-dependence treatment in cigarette smokers: a randomised trial. *JAMA* 2014;**311**:155-63.

<http://dx.doi.org/10.1001/jama.2013.283185>

Both varenicline and bupropion have been shown to improve rates of smoking cessation when used to treat patients who are addicted to tobacco smoking. In this randomised, blinded, placebo-controlled, efficacy and safety study, 12 weeks combination treatment with varenicline and sustained release (SR) bupropion was compared to 12 weeks treatment with varenicline and placebo. 506 adults aged  $> 18$  years were randomised, and 315 (62%) completed the study. Follow-up was for 52 weeks. There were 2 primary outcomes: the abstinence rate at week 12 ('prolonged abstinence' – i.e. no smoking from 2 weeks after the quit date to week 12); and '7-day point-prevalence' – i.e. no smoking in the past 7 days. Secondary outcomes were the prolonged abstinence and point-prevalence rates at weeks 26 and 52, respectively. At week 12, the prolonged abstinence rates were 53.0% in the combination group and 43.2% in the varenicline-only group [odds ratio (OR) 1.49; 95% CI 1.05 to 2.12], whereas the 7-day point prevalence abstinence rates were not significantly different at 56.2% versus 48.6%, respectively [OR 1.36; 95% CI 0.95 to 1.93]. Similarly, at week 26, the prolonged abstinence rates were 36.6% in the combination group versus 27.6% in the varenicline-only group [OR 1.52; 95% CI 1.04 to 2.22], but the 7-day point-prevalence rates were not significantly different at 38.2% vs. 31.9% [OR 1.32; 95% CI 0.91 to 1.91]. At 52 weeks, neither prolonged abstinence nor 7-day point prevalence abstinence rates were significantly different between the two groups. Therefore, prolonged abstinence at 12 and 26 weeks (which is the more important measure clinically) was improved with the varenicline/bupropion combination.

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