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Asthma

Seasonal variations in asthma attacks: effect of sensitisation to pollens and moulds

Cabova *et al*. The influence of sensitisation to pollens and moulds on seasonal variations in asthma attacks. *Eur Respir J* 2013;**42**:935-45. http://dx.doi.org/10.1183/09031936.00097412

This is the largest study so far to report the seasonal variation in asthma attacks in a population of asthma patients who have had their allergen sensitivities assessed by skin-prick testing. The authors used data from the European Community Respiratory Health Survey (ECRHS), which randomly recruited a sample of over 3000 young adults aged 20-44 years old who completed a postal questionnaire, clinical interview, skin prick testing and blood tests between 1991-1993. 2637 adults living in 15 countries were recruited; they reported the months in which they usually had attacks of asthma, and all had complete skin-prick test data. Seasonal variation in asthma was not modified by sensitisation to house dust mite or allergens. However, patients sensitised to grass, birch and Alternaria had different seasonal patterns compared to those who were not sensitised. There was some geographical variation: in southern Europe, patients sensitised to grass were more likely to report attacks in spring or summer rather than winter (odds ratio (OR) March/April 2.60 [95% CI 1.70 to 3.97], OR May/June 4.43 [95% CI 2.34 to 8.39]), whereas in northern Europe the attacks were later and less clear-cut (OR May/June 1.25 [95% CI 0.60 to 2.64], OR July/August 1.66 [95% CI 0.89 to 3.10]). Young adults with hay fever but no sensitisation to grass showed no seasonal variation. Therefore, the seasonal variation in asthma attacks in young adults is because of different sensitivities to outdoor aeroallergens and not indoor allergens.

Fluticasone furoate/vilanterol has similar efficacy to fluticasone propionate/salmeterol in adults and adolescents

Woodcock *et al*. Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: a randomized trial. *Chest* 2013;**144**:1222-9. http://journal.publications.chestnet.org/article.aspx?articleid=1710127

806 patients aged ≥ 12 years with persistent asthma uncontrolled on a medium-dose of inhaled corticosteroid (ICS) were recruited to this phase 3, multicentre, randomised, double-blind, parallel group study. After screening, patients entered a 4-week run-in period during which they received fluticasone propionate (FP) 250 mcg twice-daily with salbutamol as their short-acting bronchodilator. They were then randomised to the new fluticasone furoate 100mcg/vilanterol 25mcg (FF/VI) fixed dose ICS/long-acting beta2-agonist (LABA) combination inhaler given once-daily (n = 403) or the pre-existing fluticasone propionate 250mcg/salmeterol 50mcg (FP/SAL) ICS/LABA inhaler (n = 403) administered twice-daily. The primary end point was change from baseline in the serial weighted mean FEV_1 over 24 hours after 24 weeks of t1reatment. Improvements in 0 to 24 hour weighted mean FEV_1 were observed with both inhalers (341 ml for FF/VI, 377 ml for FP/SAL), and the adjusted mean treatment difference between the two inhalers was not statistically significant (-37 ml, 95% CI -88 to 15). There was no difference in exacerbation rates between the two patient groups, and both treatments were well tolerated. The authors conclude that the efficacy of the two inhalers is similar, and that no safety issues were identified. No doubt the FF/VI fixed dose combination inhaler will be licensed soon…

What phenotypic characteristics predict response to oral steroid treatment in severe asthma?

Kupczyk *et al*. Phenotypic predictors of response to oral glucocorticosteroids in severe asthma. *Resp Med* 2013;**107**:1521-30. http://dx.doi.org/10.1016/j.rmed.2013.07.014

In this interesting double-blind, randomised, placebo-controlled study, 84 patients with severe asthma and 62 patients with moderate asthma were randomised to receive either oral prednisolone at a dose of 0.5mg/kg/day or placebo for two weeks, after a 4-week period of treatment optimisation. The aim was to assess how patient characteristics could predict the degree of response to oral corticosteroid. Responders to the oral prednisolone had a lower FEV_1 (73.7% versus 88.0%), lower FEV_1/FVC ratio (0.65 vs. 0.73), lower quality of life (St Georges Respiratory Questionnaire (SGRQ) score 39.1 vs. 31.4) and a higher number of sputum eosinophils (16.8% vs 6.3%) [$P < 0.05$] compared to non-responders. In those patients with severe asthma, sputum eosinophils > 3% [odds ratio (OR) 9.91], FEV_1 < 60% [OR 3.7], and SCRQ > 42.2 [OR 3.25] were associated with a good response to oral prednisolone. The sputum eosinophil count (> 3%) and the fraction of expired nitric oxide (FeNO, >45 ppb) gave the highest sensitivity and specificity for a > 12% increase in FEV_1 in patients with severe asthma. Therefore, sputum eosinophils and FeNO were the best predictors of a favourable response to oral prednisolone in patients with severe asthma.

Statins associated with reduced risk of asthma exacerbations

Sze Man Tse *et al*. Statin exposure is associated with decreased asthma-related emergency department visits and oral corticosteroid use. *Am J Resp Crit Care Med* 2013;**188**:1076-82. http://dx.doi.org/10.1164/rccm.201306-1017OC

Statins (HMG-CoA reductase inhibitors) have an anti-inflammatory action, and have already been shown to be associated with reduced mortality rates in patients with COPD (see http://dx.doi.org/10.4104/pcrj.2011.00095). In this prospective population-based cohort study, data from the Population-Based Effectiveness in Asthma and Lung study population were used to construct a cohort of 14,566 asthma patients who were on treatment with a statin; 8,340 were eventually matched to non-statin users according to age, baseline asthma therapy, site of enrolment, season at baseline, and propensity score based on patient demographics and their Deyo-Charlson scores (a co-morbidity index described by Charlson and Deyo in 1992, based on reported ICD-9-CM secondary

diagnosis codes). Asthma exacerbations (> 2 oral corticosteroid prescriptions, emergency department (ED) attendance, or hospitalisation) were assessed over a 2-year period. Statin treatment was associated with reduced asthma-related ED attendance [odds ratio (OR) 0.64; 95% CI 0.53 to 0.77] and 2 or more oral corticosteroid prescriptions [OR 0.90; 95% CI 0.81 to 0.99]. Asthma-related hospitalisation rates were similar between the two groups [OR 0.91; 95% CI 0.66 to 1.24]. The authors conclude that statin treatment is associated with a reduced risk of asthma-related ED visits and prescriptions for oral corticosteroids. No doubt this will be an area for future research…

A 1-year real life survey of omalizumab in children

Deschildre *et al*. Add-on omalizumab in children with severe allergic asthma: a 1-year real life survey. *Eur Respir J* 2013;**42**:1224-33. http://dx.doi.org/10.1183/09031936.00149812

This is a 'real-life' 1-year observational study on the efficacy and safety of omalizumab in 104 children aged 6-18 years treated in tertiary centres throughout France. Interestingly, the overall conclusion is that the observed benefit from omalizumab was greater than that reported in clinical trials to date… The 104 children all had severe asthma; there was an average of 4.4 exacerbations/year in the year before omalizumab treatment, with 44% requiring hospitalisation, 20 children requiring more than one admission, and eight requiring admission to an intensive care unit. Six (5.8%) were on regular oral corticosteroids. 66% had sensitisation to at least three allergens, they had high IgE levels (mean IgE level 1125 kU/L), and high ICS use (mean daily ICS dose was 703 mcg fluticasone equivalent). After one year's treatment with omalizumab, asthma control levels defined as good, partial, or poor increased from the baseline levels of 0%, 18% and 82%, respectively, to 53%, 30% and 17%, respectively [P < 0.0001]. Exacerbation and hospitalisation rates dropped by 72% and 88.5%, respectively, and mean ICS dose decreased by 30%. These data therefore suggest that omalizumab is an effective add-on therapy for children with uncontrolled severe allergic asthma.

COPD

Indacaterol versus tiotropium for severe COPD

Decramer *et al*. Once-daily indacaterol versus tiotropium for patients with severe chronic obstructive pulmonary disease (INVIGORATE): a randomised, blinded, parallel-group study. *Lancet Respir Med* 2013;**1**:524-33. http://dx.doi.org/10.1016/S2213-2600(13)70158-9

The aim of this large multicentre, randomised, double-dummy, parallel group study was to assess whether indacaterol was non-inferior to tiotropium using two quite specific endpoints: trough FEV_1 at 12 weeks (the primary endpoint), and rate of COPD exacerbations over the 52 weeks of follow-up. Adverse event monitoring was also used to assess safety. Patients with severe COPD (aged > 40 years) with at least one moderate to severe exacerbation in the previous year were randomly allocated to either indacaterol 150mcg [n=1723] or tiotropium 18mcg [n=1721] once-daily. Analysis was per protocol. At week 12, difference in mean trough FEV_1 between the groups using a least squares mean calculation was not significant [least squares mean with indacaterol 1.134L versus tiotropium 1.145L, one-sided 97.5% CI -0.026L (which was above the pre-specified non-inferiority margin of -0.055L)]. However, the annual exacerbation rates were in favour of tiotropium, with rates of 0.79 for indacaterol (n=1529) vs. 0.61 for tiotropium (n=1543) [ratio 1.29]. Adverse event rates were similar between the two groups. The authors conclude that both indacaterol and tiotropium resulted in clinically relevant improvements in 12-week lung function values, that they have similar safety profiles, and that tiotropium provided slightly greater reductions in exacerbation rates...

Characteristics and outcomes of COPD in never-smokers

Thomsen *et al.* Characteristics and outcomes of chronic obstructive pulmonary disease in never smokers in Denmark; a prospective population study. *Lancet Respir Med* 2013;**1**:543-50. http://dx.doi.org/10.1016/S2213-2600(13)70137-1

The major risk factor for COPD in industrialised countries is tobacco smoking, but this interesting study assessed the characteristics and outcomes of patients with COPD who have never smoked. Lung function measurements were performed on 68,501 participants with complete data on smoking history recruited into the Copenhagen General Population Study. 6623 were identified with a spirometric diagnosis of COPD (FEV_1/FVC ratio < lower limit of normal (LLN)) without any self-reported diagnosis of asthma. Of these, 1476 (22%) were never-smokers, 2696 (41%) were former smokers, and 2451 (37%) were current smokers. In order to assess general characteristics including symptoms, disease severity, co-morbidities, lung-related hospital admissions and mortality, 24,529 never-smokers without COPD from the same dataset were included in the analysis. Never-smokers with COPD had fewer symptoms and milder disease than former and current smokers with COPD. Hazard ratios (HRs) for hospital admission due to COPD were 8.6 [95% CI 5.3 to 14] in never-smokers, 30 [95% CI 22 to 41] in former smokers, and 43 [95% CI 32 to 59] in current smokers compared to never-smokers without COPD. Risk of cardiovascular co-morbidities and all-cause mortality was increased in former and current smokers, but not in never-smokers with COPD. So the never-smokers with COPD had milder disease with less hospital admissions, but they did have significant morbidity compared to never-smokers without COPD. Of course, we must remember that in some middle- and low-income countries, the major risk factor for COPD especially in women is not tobacco smoking but cooking with biomass fuels (see a recent paper from sub-Saharan Africa http://dx.doi.org/10.4104/pcrj.2013.00064 together with its accompanying editorial http://dx.doi.org/10.4104/pcrj.2013.00079).

Which lung function indices are best at predicting mortality in COPD?

Boutou *et al.* Lung function indices for predicting mortality in COPD. *Eur Respir J* 2013;**42**:616-25. http://dx.doi.org/10.1183/09031936.00146012

The rationale for this study is that the relative usefulness of a range of pulmonary function tests – such as spirometry, gas transfer measurements, lung volumes obtained by body plethysmography, and arterial blood gas analysis – in determining the severity of COPD is unclear. Given that the prognostic impact of many other pulmonary and non-pulmonary factors has been investigated, do any of these lung function-specific factors provide added value in determining mortality risk and informing future management decisions? Data on 604 patients attending a hospital outpatient clinic were prospectively entered onto a clinical audit database and a multivariate Cox proportional hazard model was used to assess association with survival. The patients (62.9% males) had a mean +/- SD age of 61.9 +/-9.7 years and an FEV_1 of 37 +/- 18.1% predicted, and 229 (37.9%) died during the median follow-up of 83 months. The only lung function parameters independently associated with mortality were the carbon monoxide transfer factor [hazard ratio (HR) for best % predicted quartile versus lowest quartile = 0.33; 95% CI 0.172 to 0.639] and arterial oxygen partial pressure [HR 0.85; 95% CI 0.77 to 0.94]. Age [HR 1.04; 95% CI 1.02 to 1.06] was also independently associated with mortality. The authors conclude that gas transfer measurement provides additional prognostic information compared to spirometry in these patients under hospital follow-up, and therefore ought to be performed routinely.

The mMRC grade correlates closely with health status scores in COPD

Jones *et al*. Comparisons of health status scores with MRC grades in COPD: implications for the GOLD 2011 classification. *Eur Respir J* 2013;**42**:647-54. http://dx.doi.org/10.1183/09031936.00125612

Both the COPD Assessment Test (CAT) and the modified Medical Research Council (mMRC) scale are now incorporated into the GOLD guideline COPD severity and future risk assessment, with an mMRC scale of > 2 and a CAT score > 10 signifying more severe disease. The aim of this study was to test the equivalence between these two symptom cut-off points by examining their relationship with a number of other health status scores including the St George's Respiratory Questionnaire (SGRQ), the 12-item Short-form Health Survey (SF-12), and the Functional Assessment of Chronic Illness Therapy (FACIT) fatigue scale. The authors performed a retrospective analysis of the Health-Related Quality of Life in COPD in Europe Study (HEED) database, a large primary care dataset of COPD patients aged 40-80 years with a smoking history > 10 pack-years. Mean health status scores were reported in each of the mMRC grades, and analysis of variance (ANOVA) between groups was used to test the association between mMRC grade and each health status score. Data from 1,817 patients (mean +/- SD FEV_1 = 1.6 +/- 0.6 L) were available. Patients in all four GOLD groups, as categorised by mMRC grade > 2, had worse health status scores and more fatigue compared with the equivalent group categorised by a CAT score > 10. There was a significant association between mMRC and all four health status scores (SGRQ, SF-12, CAT and FACIT) [p<0.0001]. Interestingly, the mMRC classified 57.2% patients as having low symptoms (GOLD Groups A and C) compared with 17.2% with the CAT. Even an mMRC grade of

0 gave modestly elevated health status scores [mean SGRQ +/- SD = 28.5 +/- 15.1; CAT 11.7 +/- 6.8]. The authors conclude that the mMRC shows a clear relationship with health status scores, but that the criteria used to differentiate between the four different GOLD groups may need further clarification.

Cardiovascular safety of roflumilast

White *et al*. Cardiovascular safety in patients receiving roflumilast for the treatment of COPD. *Chest* 2013;**144**:758-65. http://journal.publications.chestnet.org/article.aspx?articleid=1573738

Cardiovascular co-morbidity is a common finding in patients with COPD, and so the cardiovascular safety of treatments for COPD is of paramount importance. This is a very reassuring study for prescribers of, and patients on, roflumilast, a selective, long-acting PDE-4 inhibitor used to treat and prevent COPD exacerbations in patients with severe COPD who have the chronic bronchitis phenotype. The authors pooled the data from 14 intermediate and long-term placebo-controlled trials to analyse the effect of roflumilast on major adverse cardiovascular events as judged by an independent adjudication committee who were blinded to study details and treatment. Major cardiovascular events were cardiovascular death, non-fatal myocardial infarction and stroke. Analysis was according to treatment group. The 14 trials were in patients with moderate to very severe COPD, and ranged in length from 12 to 52 weeks. There were 52 major cardiac events among the 6,563 patients who received roflumilast (14.3 events per 1,000 patient-years) and 76 major cardiac events in the 5,491 patients receiving placebo (22.3 events per 1,000 patient-years), giving a hazard ratio for roflumilast versus placebo of 0.65 [95% CI 0.45 to 0.93]. So, roflumilast looks to have a very safe cardiovascular profile when used in COPD, and the data indicate that it may even be beneficial. Could this be due to its anti-inflammatory activity perhaps? No doubt this will be evaluated in future controlled clinical trials…

A meta-analysis of macrolide antibiotic prophylaxis for COPD

Donath *et al*. A meta-analysis on the prophylactic use of macrolide antibiotics for the prevention of disease exacerbations in patients with chronic obstructive pulmonary disease. *Resp Med* 2013; **107**:1385-92. http://dx.doi.org/10.1016/j.rmed.2013.05.004

This is a very topical subject… Two months ago we reviewed a large retrospective cohort study by James *et al.* on the current use of prophylactic antibiotics in COPD which showed that 0.61% of patients in the UK had received at least one long-term antibiotic course over a 10-year period (see http://dx.doi.org/10.4104/pcrj.2013.00061). These authors report a meta-analysis of 6 RCTs after performing a literature search for all relevant RCTs on the use of macrolides for prevention of COPD exacerbations with the incidence of COPD exacerbations as the primary endpoint. Secondary endpoints were mortality, hospitalisation rates, adverse events, and likelihood of at least one exacerbation. The authors comment that their analysis is limited by a lack of consistency in adverse event reporting and some clinical and statistical heterogeneity between the 6 studies. Nevertheless, use of macrolides led to a 37% reduction in COPD exacerbations compared to placebo [relative risk (RR) 0.63; 95% CI 0.45 to 0.87]. There was also a 21% reduced risk of hospitalisation [RR 0.79; 95% CI 0.69 to 0.90] and a 68% reduced risk of having at least one exacerbation [RR 0.34; 95% CI 0.21 to 0.54]. As Miravitlles writes in his linked editorial (http://dx.doi.org/10.4104/pcrj.2013.00074) to the James *et al.* paper: various questions need to be addressed before a broader recommendation on the use of long-term antibiotics in COPD can be made – for example, it is not clear which is the best antibiotic, whether it is better to use the same drug or to rotate different antibiotics, which is the best dose for macrolides and, once started, what the duration of treatment should be. No doubt there will be more studies to come on this subject…

GOLD spirometry grades predict mortality better than the new ABCD groups

Leivseth *et al*. GOLF classifications and mortality in chronic obstructive pulmonary disease: the HUNT Study, Norway. *Thorax* 2013;**68**:914-21. http://dx.doi.org/10.1136/thoraxjnl-2013-203270

The initial Norwegian Nord-Trondelag Health (HUNT) study recruited patients in 1995–1997, and in this prospective cohort study the authors have followed-up 1540 COPD patients through to May 2012 and collected data on all-cause mortality. The aim was to compare the old GOLD stages (stages 1-4, based on spirometrically-defined lung function) with the new ABCD GOLD groups and to determine which classification best predicts mortality in patients with COPD. The 1540 patients were distributed as follows: 28% in GOLD stage 1, 57% in stage 2, 13% in stage 3, and 2% in stage 4, versus 61% in group A, 18% in group B, 12% in group C, and 10% in group D. Over a median follow-up of 14.6 years, 837 people (54%) died. Using GOLD stage 1 as the baseline, mortality increased with higher spirometric GOLD grade: adjusted hazard ratio (HR) for mortality for GOLD 2 was 2.29 [95% CI 1.66 to 3.16] for women and 1.44 [95% CI 1.15 to 1.80] for men; for GOLD 3 it was 6.23 [95% CI 4.15 to 9.36] for women and 2.04 [95% CI 1.56 to 2.68] for men; and for GOLD 4 it was 6.97 [95% CI 3.95 to 15.91] for women and 4.28 [95% CI 2.57 to 7.00] for men. Mortality rates were less clear-cut with the ABCD groups: they were similar in groups A and B, especially in women – HR for mortality for group B compared to group A was 1.12 [95% CI 0.78 to 1.62] – and fairly similar in groups C and D. The authors conclude that the old spirometric GOLD grades predict mortality better than the new ABCD groups in this cohort of patients with COPD.

Benefits of a primary care-based structured education pulmonary rehabilitation programme

Casey *et al.* The effectiveness of a structured education pulmonary rehabilitation programme for improving the health status of people with moderate and severe chronic obstructive pulmonary disease in primary care: the PRINCE cluster randomised trial. *Thorax* 2013;**68**:922-8. http://dx.doi.org/10.1136/thoraxjnl-2012-203103

The aim of this single-blind, 2-arm, cluster randomised controlled trial from Ireland was to assess the effectiveness of a structured education pulmonary rehabilitation (PR) programme delivered by the practice nurse and a physiotherapist. The primary outcome was the effect on health status as measured by the total disease-specific Chronic Respiratory Questionnaire (CRQ) score; the CRQ consists of 20 items across 4 domains – dyspnoea (5 items), fatigue (4 items), emotional function (7 items) and mastery (4 items) – and the higher the score the better the quality of life. The pre-specified minimal clinically important difference (MCID) in the CRQ was 0.5. Secondary outcomes included the incremental shuttle walk test. Randomisation was at the general practice level. 259 practices were assessed for eligibility, and 32 practices were randomised either to the structured PR programme [16 practices, 178 patients] or usual care [16 practices, 172 patients]. Primary and secondary outcome data collection occurred 12-14 weeks after the PR programme. Patients in the intervention group had statistically significant higher mean CRQ scores compared to controls [adjusted mean difference 1.11; 95% CI 0.35 to 1.87], albeit the smaller 95% CI was within the MCID. There were no statistically significant differences in the secondary outcome measures. Therefore, a structured education PR programme is feasible in primary care, and that this can increase the accessibility of PR programmes to patients with moderate-to-severe COPD.

Relationship between Vitamin D and emphysema

Berg *et al.* Vitamin D, vitamin D binding protein, lung function and structure in COPD. *Resp Med* 2013;**107**:1578-88. http://dx.doi.org/10.1016/j.rmed.2013.05.010

This aim of this pilot study was to examine the relationship between vitamin D status, vitamin D binding protein (DBP), FEV_1, and CT scan-defined emphysema, in patients with COPD. 498 patients were recruited from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study. All had their serum vitamin D and DBP measured. Patients were recruited equally from the smoker/non-smoker control groups, as well as from GOLD stages 2, 3 and 4. Vitamin D levels correlated closely with FEV_1 [$P = 0.01$], severity of emphysema [$P < 0.01$], 6-minute walk test [$P = 0.02$] and bronchodilator response [$P = 0.04$]. DBP was associated with bone attenuation in subjects with CT-defined emphysema, but was not associated with FEV_1 or emphysema per se. Vitamin D and DBP were inversely associated [$P = 0.01$]. This is, therefore, the first study to demonstrate a relationship between CT scan-defined emphysema, FEV_1, and vitamin D. No doubt further studies will follow…

Risk of death with tiotropium delivered by Respimat versus Handihaler

Wise *et al*. Tiotropium Respimat inhaler and the risk of death in COPD. *New Engl J Med* 2013;**369**:1491-501 http://www.nejm.org/doi/full/10.1056/NEJMoa1303342 http://dx.doi.org/10.1056/NEJMoa1303342

This randomised, double-blind, parallel-group non-inferiority study between the two formulations of tiotropium adds to the current debate on death rates attributable to the Respimat Soft-mist inhaler [see our review earlier this year

(http://dx.doi.org/10.4104/pcrj.2013.00029) of the systematic review published in Thorax (http://dx.doi.org/10.1136/thoraxjnl-2012-201926)]. 17,135 patients were randomised to receive either the tiotropium Respimat inhaler at a dose of 2.5 mcg or 5 mcg once-daily, or to receive the tiotropium Handihaler 18mcg once-daily. The primary endpoints were risk of death and risk of first exacerbation. Safety analysis focussed on cardiovascular safety in patients with stable cardiovascular disease, and mean follow-up was 2.3 years. The Respimat inhaler was non-inferior to the Handihaler as regards death rates [hazard ratio (HR) Respimat 5 mcg versus Handihaler = 0.96 (95% CI 0.84 to 1.09); HR Respimat 2.5 mcg vs. Handihaler = 1.00 (95% CI 0.87 to 1.14)]. The risk of first exacerbation was similar for both formulations [HR Respimat 5mcg vs. Handihaler = 0.98; 95% CI 0.93 to 1.03]. Major cardiovascular adverse events were similar in the three groups. The authors conclude that the two different tiotropium formulations have similar efficacy and safety profiles.

The 5-repetition sit-to-stand test: a functional measure in COPD

Jones *et al*. The five-repetition sit-to-stand test as a functional outcome measure in COPD. *Thorax* 2013;**68**:1015-20. http://dx.doi.org/10.1136/thoraxjnl-2013-203576

Current COPD guidelines emphasise the multisystem nature of COPD. The time taken to move from sitting to standing five times in succession – the five-repetition sit-to-stand test (5STS) – is dependent on lower limb muscle function and balance, and has been validated as a functional performance measure in healthy older community-living populations as well as patients with stroke, Parkinson's disease and vestibular disorders. There is little data on its use in COPD populations. The aim of this study from Harefield Hospital was to determine the reliability, validity and responsiveness of the 5STS in COPD patients. To assess test-retest and observer reliability, 50 patients had a 5STS measurement on two separate occasions 24-48 hours apart, observed by the same person. To assess construct validity, 475 patients performed both the 5STS and the incremental shuttle walk test, and data were collected on their lower limb strength, health status (St George's Respiratory Questionnaire, SGRQ), MRC scores, and the ADO and BODE indices. Responsiveness was assessed before and after a course of pulmonary rehabilitation (PR) in 239 patients. Test-retest and interobserver intraclass correlation were excellent, at 0.97 and 0.99, respectively. The 5STS correlated significantly with all of the comparative validity measures. The median (25th; 75th centiles) 5STS time following PR decreased from 14.1 seconds (11.5; 21.3) to 12.4 seconds (10.2; 16.4) [$P < 0.001$]. The estimate for the minimum clinically important difference was 1.7 seconds. The 5STS has considerable advantages: it is quick, cheap, requires minimal space, and is straightforward to assess. Its major limitation is a 'floor' effect, with up to 15% of the patients being unable to complete the test. Therefore, the 5STS may be of particular use in patients with better physical function…

Inhaled corticosteroids in COPD is associated with an increased risk of serious pneumonia

Suissa *et al.* Inhaled steroids in COPD and the risk of serious pneumonia. *Thorax* 2013;**68**:1029-36. http://dx.doi.org/10.1136/thoraxjnl-2012-202872

Previous research has shown that inhaled corticosteroids (ICS) slightly increase the risk of pneumonia in patients with COPD. However, questions remain as to whether this is a class effect or whether it's worse with one (or more) particular ICS, and whether or not the increased risk is related to dose and duration of treatment. This is a large cohort study of 163,514 COPD patients aged ≥ 55 years who were new users of ICS between 1990 and 2005, identified from Quebec health insurance databases. They were followed up until 2007, or until they had an episode of serious pneumonia (the 'index date', defined as first hospitalisation for, or death from, pneumonia). Mean duration of follow-up was 5.4 years, during which 20,344 patients had serious pneumonia; 19,667 were hospitalised, and 677 died. For each case, 10 controls were identified on the index date, matched for age and time of cohort entry. A nested case-control analysis was then used to estimate the rate ratio (RR) of serious pneumonia associated with current ICS use, adjusted for age, sex, COPD disease severity and co-morbidity. Current ICS use was associated with a 69% increase in the rate of serious pneumonia [RR 1.69; 95% CI 1.63 to 1.75]. This risk continued with long-term use, but disappeared after ICS had been stopped for at least 6 months [RR1.08; 95% CI 0.99 to 1.17]. The rate of serious pneumonia was higher with fluticasone [RR 2.01; 95% CI 1.93 to 2.10] and lower with budesonide [RR 1.17; 955 CI 1.09 to 1.26]. This is a reminder that we need to consider carefully the risk/benefit equation when prescribing ICS in COPD patients.

Increase in sputum purulence and CRP testing predict likely need for antibiotics for COPD exacerbations

Miravitlles *et al*. Is it possible to identify exacerbations of mild to moderate COPD that do not require antibiotic treatment? *Chest* 2013;**144**:1571-7. http://dx.doi.org/10.1378/chest.13-0518

The aim of this study was to evaluate those factors which best predict outcomes following a mild to moderate exacerbation of COPD in patients not treated with antibiotics. The authors used data from 152 patients recruited into the placebo arm of a previous RCT on co-amoxiclav treatment for COPD exacerbations. Using multivariate logistic regression analysis, they then assessed clinical response according to point-of-care C-reactive protein (CRP) testing and the Anthonisen criteria for COPD exacerbations (Type I = most severe, with all three symptoms of increased sputum volume, increased purulence, and increased dyspnoea; Type II = any two of the three symptoms; Type III = one symptom plus an upper respiratory tract infection (URTI)/fever/increased cough or wheeze). Increased sputum purulence was significantly associated with an increased risk of clinical failure without antibiotics (i.e. eventual need for antibiotic treatment) [odds ratio (OR) 6.1; 95% CI 1.5 to 25.0]. A CRP value > 40mg/L was also associated with increased risk of treatment failure [OR 13.4; 95% CI 4.6 to 38.8]. There was good correlation between Anthonisen type and clinical outcome. Therefore, lack of sputum purulence, a low CRP value, and a milder Type III Anthonisen category, indicate those mild to moderate COPD exacerbations which are not likely to require antibiotics.

Infections

Internet-based training improves primary care antibiotic prescribing rates for acute respiratory infections

Little *et al*. Effects of internet-based training on antibiotic prescribing rates for acute respiratory-tract infection: a multinational, cluster, randomised, factorial, controlled trial. *Lancet* 2013;**382**:1175-82. http://dx.doi.org/10.1016/S0140-6736(13)60994-0

There are considerable challenges when attempting to prove the effectiveness of educational interventions, but this multinational cluster randomised trial appears to have done just that. There was an initial baseline assessment of antibiotic prescribing for upper and lower respiratory tract infections (URTIs and LRTIs, respectively) performed in 259 primary care practices from 6 European countries in 2010. Data were collected on 6771 patients, and 5355 (79.1%) were prescribed antibiotics. 246 practices were then cluster randomised to usual care, additional internet-based training in the use of point-of-care CRP testing, additional training in communication skills, or both interventions. Post-intervention data were collected on 4264 patient interactions. Antibiotic prescribing rates were lower following internet-based CRP training compared to usual care [33% vs. 48%, adjusted risk ratio (RR) 0.54, 95% CI 0.42 to 0.69]. Similarly, antibiotic prescribing rates were lower following the enhanced communication training [36% vs. 45%, RR 0.69, 95% CI 0.54 to 0.87]. Combining the two interventions caused the greatest reduction in antibiotic prescribing rate [RR 0.38, 95% CI 0.25 to 0.55]. The authors conclude that internet education on antibiotic prescribing and training achieved important reductions in unnecessary antibiotic prescribing for URTIs and LRTIs.

Diagnosing pneumonia: clinical judgement versus chest radiography

van Guyt *et al.* Diagnosing pneumonia in patients with acute cough: clinical judgement compared to chest radiography. *Eur Respir J* 2013;42:1076-82. http://dx.doi.org/10.1183/09031936.00111012

This is another report from the GRACE (Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe) study. The aim was to assess the diagnostic accuracy of a purely clinical diagnosis of pneumonia, versus an X-ray finding of pneumonia as the reference standard, in a large sample of patients presenting with acute cough in primary care. 294 GPs from 12 European countries recruited 3106 patients presenting with acute cough. 296 were excluded because chest X-ray was not performed (n = 258) or was of insufficient quality (n = 28), and 10 were excluded because results of the GP's clinical judgement were not available; the final study population was 2810. GPs recorded whether they thought pneumonia was present

immediately after history-taking and examination. Chest X-ray was performed within 1 week by the local radiology department (blinded to patient characteristics). 140 patients had an X-ray diagnosis of pneumonia; of these, 41 (29%) had been clinically diagnosed. A further 31 patients had a clinical diagnosis of pneumonia that was incorrect – i.e. not confirmed by X-ray. In those patients with suspected pneumonia, 57% were subsequently diagnosed by X-ray. The negative predictive value, sensitivity and specificity of GPs' clinical diagnoses were 96%, 29% and 99%, respectively. The authors conclude that the majority of pneumonia diagnoses were not suspected on clinical grounds, but the high negative predictive value of GPs' clinical judgement could be helpful in routine clinical care.

Paracetamol, ibuprofen and steam treatment for acute respiratory tract infections in primary care

Little *et al.* Ibuprofen, paracetamol, and steam for patients with respiratory tract infections in primary care: a pragmatic randomised factorial trial. *BMJ* 2013;**347**:f6041. Published online 25th October 2013. http://dx.doi.org/10.1136/bmj.f6041

Upper respiratory tract infections (URTIs) are the commonest acute condition seen in primary care, often managed with antipyretics such as paracetamol and/or ibuprofen, together with steam inhalations. However, recent systematic reviews have concluded that ibuprofen is more effective than paracetamol alone for treating fever in children, but there have also been recent concerns about the cardiovascular risk of NSAIDs in adults. Furthermore, there is little evidence for the efficacy of steam inhalations… Therefore, this pragmatic randomised factorial trial had three aims: 1. to assess the difference in effectiveness between three different antipyretic regimens – ibuprofen, paracetamol, and combined ibuprofen and paracetamol; 2. whether regular antipyretic dosing gives better control of symptoms and temperature than 'as required' dosing; and 3. whether regular inhalation with steam improves symptom control. The primary outcome was symptom severity on days 2-4 measured by a 0-7 score (7 = most severe), and secondary outcomes were temperature, antibiotic use and repeat consultations. 889 patients were randomised, and follow-up was for at least 1 month. There was no difference in outcomes between the two antipyretic dosing regimens (regular vs. 'as needed') and between the steam inhalation/no inhalation groups. Overall, symptom severity was little different with paracetamol vs. ibuprofen [adjusted difference 0.04; 95% CI –0.11 to 0.19) or the ibuprofen/paracetamol combination [0.11; 95% CI –0.04 to 0.26]. There was no selective benefit for ibuprofen overall, but there was some evidence that the ibuprofen/paracetamol combination was better in patients with chest infections. Repeat consultations occurred in 12% of those advised to take paracetamol, 20% of those advised to take ibuprofen [adjusted risk ratio (RR) 1.67; 95% CI 1.12 to 2.38], and 17% of those advised to take the combination (RR 1.49; 95% CI 0.98 to 2.18). The authors conclude that we should stop advising patients to use steam inhalations, that there is no difference between regular or 'as required' analgesia, and that for most patients paracetamol should be the first line analgesic – except in those with chest infections and in children, when ibuprofen might be of more benefit.

Sleep disorders

Uvulopalatopharyngoplasty improves obstructive sleep apnoea

Browaldh *et al.* SKUP randomised controlled trial: polysomnographic results after uvulopalatopharyngoplasty in selected patients with obstructive sleep apnoea. *Thorax* 2013; **68**:846-53. http://dx.doi.org/10.1136/thoraxjnl-2012-202610

Obstructive sleep apnoea (OSA) is associated with considerable morbidity and increased mortality. Prior to the advent of widely-available continuous positive airway pressure (CPAP) treatment in the 1990s, uvulopalatopharyngoplasty (UPPP) was the predominant treatment worldwide for OSA. CPAP is successful when used properly by the patient, but studies have shown that the median compliance rate is 50-77% after 1-3 years. Part of the problem with the earlier UPPP treatment was that there was no real evidence base to assist in patient selection, and there was no randomised controlled trial (RCT) evidence of its efficacy. This singe-centre, prospective randomised two-arm trial is the first RCT of UPPP in patients with OSA. 65 consecutive patients with moderate-to-severe OSA (apnoea-hypopnoea index (AHI) $\geq$ 15 events per hour sleep, Epworth Sleepiness Scale $\geq$ 8, Friedman stage I or II [i.e. the position of the tongue and palate – in both, the uvula is still visible]) were randomised to UPPP within 1 month [n=32] or no treatment for 7 months followed by UPPP [n=33]. Randomisation was stratified according to body mass index (BMI; < 30 kg/m^2 or 30-35.9 kg/m^2) and Friedman stage (I or II). Polysomnography was carried out at baseline and then 6 months later. The mean AHI (SD) in the UPPP group decreased significantly from 53.3 (19.7) to 21.1 (16.7) events/hour, a reduction of 60% [p<0.001]. The control group also showed a slight improvement in AHI (a decrease from 52.6 (21.7) to 46.8 (22.8) events/hour). Importantly, there was a significant difference in AHI improvement between the two arms [p<0.001]. There were no severe surgery complications. Therefore, this trial provides powerful evidence for the efficacy of UPPP in the treatment of selected patients with OSA, and it is likely to change clinical practice especially for patients who fail with CPAP.

Miscellaneous

Screening for lung cancer with CT or chest X-ray

Aberle *et al*. Results of the Two Incidence Screenings in the National lung Screening Trial. *New Engl J Med* 2013;**369**:920-31 http://www.nejm.org/doi/full/10.1056/NEJMoa1208962

The US National Lung Screening Trial (NLST) was established to compare two ways of detecting lung cancer: low-dose helical computed tomography (CT) versus standard chest X-ray. Both chest radiography and low-dose CT scanning have previously been used to find lung cancer early, but the effects of these screening techniques on lung cancer mortality rates have not been determined. NLST enrolled 53,454 current or former heavy smokers from 33 sites. The first NLST report was published in the ***NEJM*** in August 2011 and revealed that participants who received low-dose helical CT scans had a 20.0% lower risk of dying from lung cancer than participants who received standard chest X-ray screening. This paper reports the results after two screening rounds, T1 and T2. CT scanning produced positive screening results in 27.9% and 16.8% of subjects in T1 and T2 respectively. Chest radiography produced positive results in 6.2% and 5.0% of subjects in T1 and T2, respectively. For low-dose CT scanning at T1, the sensitivity was 94.4%, specificity 72.6%, positive predictive value 2.4% (increasing to 5.2% at T2), and the negative predictive value was 99.9%. For chest radiography, sensitivity was 59.6%, specificity 94.1%, positive predictive value 4.4% and the negative predictive value was 99.8% at T1, with sensitivity and positive predictive value increasing slightly at T2. The conclusion: as compared with radiography, the two annual incidence screenings with low-dose CT resulted in an increase in the number of early-stage lung cancers diagnosed and an accompanying decrease in the number of advanced-stage cancers identified.

The value of lung function testing, lung volume, airway resistance and diffusing capacity testing for respiratory disease diagnosis

Decramer *et al*. Contribution of four common pulmonary function tests to diagnosis of patients with respiratory symptoms: a prospective cohort study. *Lancet Respir Med* 2013;**1**:705-13. http://dx.doi.org/10.1016/S2213-2600(13)70184-X

This secondary care-based prospective cohort study shows the value of four of the classic diagnostic tests used in pulmonary medicine. 1023 patients with respiratory symptoms but no clear diagnosis were enrolled in 33 hospitals; 979 were analysed. All patients had spirometry, lung volume, airway resistance, and diffusing capacity testing, followed by all the other tests required to make a diagnosis. Given the clinical history and the pulmonary function data, local focus groups of respiratory experts established the differential diagnosis, and a 'preferred diagnosis', after each of the four initial tests. The final diagnosis was established by the patient's attending physician and then validated by the local focus group. For each of the four initial diagnostic tests, the primary outcome was 1/number of differential diagnoses, corrected for the accuracy of the diagnosis. The primary outcome score was 0.226 after spirometry, 0.296 after lung volume measurement, 0.373 after airway resistance testing, and 0.540 after diffusing capacity measurement [P < 0.0001 for each step]. The number of differential diagnoses decreased after each step [4.2, 3.4, 4.0 then 2.4; P < 0.0001 for each step]. The authors conclude that each of these four classic pulmonary function tests contributes significantly and independently to the final diagnosis in new patients seen by pulmonologists, and they use this as a justification for the funding of these tests in this setting.