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Asthma

Maternal asthma severity, exacerbations and oral corticosteroid use associated with pre-term and low birth weight delivery

Namazy *et al*. Effects of asthma severity, exacerbations and oral corticosteroids on perinatal outcomes. *Eur Respir J* 2013;**41**:1082-90. http://dx.doi.org/10.1183/09031936.00195111

The 2012 BTS/SIGN asthma guideline (http://www.sign.ac.uk/pdf/sign101.pdf) contains a short section on asthma in pregnancy (pages 85-86) which highlights the fact that uncontrolled asthma is associated with many maternal complications including pre-eclampsia, hypertension, hyperemesis, complicated labour, and pre-term delivery. Effects on fetal outcomes have been less clear, but a number of studies have shown an increased risk of intra-uterine growth retardation (IUGR) and perinatal mortality. This paper is a systematic review and meta-analysis of cohort studies published between 1975 and 2012. 138 studies were identified and 9 met the inclusion criteria – i.e. they contained data on perinatal outcomes including low birth weight (< 2.5kg), pre-term birth (less than 37 weeks gestation), and small for gestational age (<10th centile) in women with asthma stratified by exacerbation rate, oral corticosteroid use and asthma severity. Asthma exacerbations increased the risk of low birth weight [relative risk (RR) 3.02; 95% CI 1.87 to 4.89] and pre-term delivery [RR 1.54; 95% CI 0.89 to 2.69]. Oral corticosteroid use also increased the risk of low birth weight [RR 1.41; 95% CI 1.94 to 1.93] and pre-term delivery [RR 1.51; 95% CI 1.15 to 1.98]. Maternal moderate-to-severe asthma was associated with an increased risk of small for gestational age [RR 1.24; 95% CI 1.15 to 1.35] and low birth weight [RR 1.15; 95% CI 1.05 to 1.26]. This data confirms the impact of maternal asthma on fetal outcomes, and highlights the importance of careful monitoring of women with asthma during pregnancy.

Dupilumab reduces exacerbations in eosinophilic moderate-to-severe asthma

Wenzel *et al*. Dupilumab in persistent asthma with elevated eosinophil levels. *New Engl J Med* 2013;**368**:245566 http://www.nejm.org/doi/full/10.1056/NEJMoa1304048

There is considerable international interest in the potential of stratified or personalised medicine. This randomised placebo-controlled trial is an efficacy and safety study of dupilumab, a new human monoclonal antibody which binds to the alpha subunit of the interleukin-4 receptor. Patients with moderate-to-severe asthma and an eosinophil count $\geq$ 0.3 x 10^9/litre, who were on treatment with an inhaled corticosteroid (ICS) and long-acting β_2-agonist (LABA), were randomised to receive weekly subcutaneous injections of dupilumab 300mg [n=52] or placebo [n=52] for 12 weeks. The LABA treatment was discontinued at week 4, and the ICS dose was reduced from week 6 until it was discontinued at week 9. The primary endpoint was the number of asthma exacerbations in each group, and the secondary endpoints included lung function, measures of asthma control, and a number of type 2 helper T-cell (Th2)-associated biomarkers. Three patients (6%) in the dupilumab group and 23 patients (44%) in the placebo group had an asthma exacerbation, corresponding to an 87% reduction in the dupilumab group [odds ratio (OR) 0.08; 95% CI 0.02 to 0.28]. Patients in the dupilumab group also had significant improvements in most of the secondary outcome measures including the Th2-related inflammatory biomarkers. It will be interesting to see whether these impressive results are maintained when patients continue their ICS and LABA treatment as per standard clinical practice, but nevertheless we probably won't need to wait too long before this new monoclonal antibody is licensed for clinical use…

Magnesium sulphate in adult severe acute asthma: no effect via nebuliser but may have a very limited role intravenously

Goodacre *et al*. Intravenous or nebulised magnesium sulphate versus standard therapy for severe acute asthma (3Mg trial): a double-blind, randomised controlled trial. *Lancet Respir Med* 2013;**1**:293-300. http://dx.doi.org/10.1016/S2213-2600(13)70070-5

This is the first of two studies in *Lancet Respiratory Medicine* this month on the role of magnesium sulphate in the management of acute severe asthma. This 4-year double-blind randomised controlled trial (RCT) recruited 1109 adults with acute severe asthma who were seen in the emergency departments of 34 hospitals in the UK. Patients were randomised to receive intravenous (i.v.) magnesium sulphate (2g over 20 minutes; n = 394), nebulised magnesium sulphate (three 500mg doses in one hour; n = 332), or placebo (n = 358), in addition to standard therapy. Patients with life-threatening asthma were excluded. There were two primary outcome measures: the proportion of patients in each group admitted to hospital within 7 days; and breathlessness measured on a 10cm visual analogue scale (VAS) 2 hours post-treatment. There was no significant difference in hospital admission rates between the three groups: 285/394 (72%) patients were admitted in the i.v. group, 261/332 (79%) in the nebulisation group, and 281/358 (78%) in the placebo group [odds ratio (OR) for hospital admission i.v. treatment versus placebo = 0.73 (95% CI 0.51 to 1.04); OR for hospital admission nebulised treatment vs. placebo = 0.96 (95% CI 0.65 to 1.40)]. There was no significant difference in the change in the VAS breathlessness score between the three groups, though the change in VAS score was slightly greater in the i.v. group than the nebulisation group. The authors conclude that nebulised magnesium sulphate has no role in the management of adult acute severe asthma, and that the role of i.v. magnesium is at best minimal.

Nebulised magnesium sulphate in paediatric acute severe asthma

Powell *et al*. Magnesium sulphate in acute severe asthma in children (MAGNETIC): a randomised, placebo-controlled trial. *Lancet Respir Med* 2013;**1**:301-08. http://dx.doi.org/10.1016/S2213-2600(13)70037-7

In this second RCT on the role of magnesium sulphate in acute severe asthma, 508 children aged 2-16 years with severe acute asthma were recruited from 30 hospitals in the UK over a 26-month period. They were randomised to receive three doses of 150mg nebulised magnesium sulphate (n = 252) or nebulised isotonic saline (n = 256) over 1 hour together with nebulised salbutamol and ipratropium. The primary outcome was

the Yung Asthma Severity Score (ASS) at 60 min post nebulisation, a score derived from the extent of wheeze, heart rate and accessory muscle use in children with severe asthma (see Jung *et al., J. Paed and Child Heath* 1996;**32**:261-4). A between-group difference in the ASS of 0.5 was considered *a priori* as the minimal clinically significant difference. The mean ASS at 60 min was lower in the magnesium sulphate group (4.72; SD 1.37) than in the placebo group (4.95; SD 1.40) [adjusted difference -0.25; 95% CI -0.48 to -0.02], but this was not clinically significant. The difference was more noticeable in children with more severe asthma attacks (SaO_2 < 92%) and those with symptoms for less than 6 hours. The authors conclude that nebulised magnesium sulphate, given as an adjunct to standard treatment, does not result in a clinically significant improvement in mean ASS scores, though there appears to be a larger response to treatment in more severe and more sudden attacks.

Relationship between ageing and airway neutrophilia

Brooks *et al*. Relationship between airway neutrophilia and ageing in asthmatics and non-asthmatics. *Respirology* 2013;**18**: 857-65. http://dx.doi.org/10.1111/resp.12079

Though increased sputum neutrophilia has been observed in asthma, it is also a feature of ageing. These authors obtained sputum samples from 194 asthma patients and 243 non-asthma controls. Regression analysis was used to assess the relationship between age and airway neutrophilia, adjusting for confounders including asthma status, atopy, gender, smoking, and current ICS use. Increasing age led to an increase in sputum neutrophilia in adults both with and without asthma, with a 0.46% increase [95% CI 0.18 to 0.73%] and 0.44% increase [95% CI 0.25 to 0.64%] in neutrophil count per year, respectively. Individuals with high sputum neutrophilia were significantly more likely to have asthma [OR 2.5; 95% CI 1.3 to 5.0], and this effect was most marked in older people. Atopy, male gender and current use of ICS were also independently associated with increased sputum neutrophil levels. The authors conclude that airway neutrophilia is related to older age in adults, and that a neutrophilic asthma phenotype is indeed present in older adults.

Body mass index or the metabolic syndrome: which is the strongest predictor of asthma?

Assad *et al*. Body mass index is a stronger predictor than the metabolic syndrome for future asthma in women: the longitudinal CARDIA study. *Am J Resp Crit Care Med* 2013;**188**: 319-26. http://dx.doi.org/10.1164/rccm.201303-0457OC

We already know that obesity is a risk factor for asthma, especially in women (see for example http://dx.doi.org/10.1183/09031936.00012112 and http://journal.publications.chestnet.org/article.aspx?articleid=1377967 which we reviewed in the March Journalwatch http://dx.doi.org/10.4104/pcrj.2013.00057). In order to compare the relative strengths of the association between both body mass index (BMI) and the metabolic syndrome with incident asthma in adults, these authors studied 4,619 adults from the Coronary Artery Risk Development in Young Adults (CARDIA) cohort. Incident asthma was defined as a new self-reported doctor diagnosis and/or the use of asthma treatment. Over the 25-year follow-up, 602 subjects (417 women, 185 men) developed incident asthma. The hazard ratios in patients with the metabolic syndrome were 1.50 in women and 0.98 in men [P = 0.01 and 0.93, respectively]. The hazard ratios in patients with a raised BMI were 1.19 in women and 1.04 in men [P = < 0.001 and 0.60, respectively]. The association between metabolic syndrome and incident asthma in women was no longer significant after adjusting for BMI [P = 0.44], whereas the association between BMI and asthma was still significant after adjustment for the metabolic syndrome [P = 0.01]. Therefore, BMI is a stronger predictor than the metabolic syndrome of incident asthma in women. Neither BMI nor the metabolic syndrome are predictors of asthma in men. Yet further evidence that obesity increases asthma risk in women and that obesity-associated asthma in women may indeed be a distinct clinical phenotype…

Maternal use of asthma controller therapy: impact on perinatal outcomes

Cossette *et al*. Impact of maternal use of asthma-controller therapy on perinatal outcomes. *Thorax* 2013;**68**:724-30. http://dx.doi.org/10.1136/thoraxjnl-2012-203122

This study from Quebec, Canada, provides valuable reassurance for all clinicians who manage pregnant women with asthma. Using two large databases, the authors constructed a cohort of women aged 45 or less with current asthma who had 7376 singleton pregnancies between 2002 and 2008. The aim was to investigate the safety of long-acting beta2-agonists (LABAs) together with various doses of inhaled corticosteroids (ICS) in terms of their impact on low birth weight (< 2.5kg), preterm birth (delivery before 37 weeks gestation), and small for gestational age (birth weight below the 10th centile). Exclusion criteria included use of theophylline, cromoglycate, nedocromil or ketotifen, and the authors also excluded 20 pregnancies in women on LABA without ICS. 8.8% of pregnancies were exposed to LABA and 56.9% exposed to ICS. The prevalence of low birth weight, preterm birth and small for gestational age was 7.7%, 9.5% and 13.5%, respectively. Analysis involved consideration of potential confounding variables (e.g. 20 potential other risk factors for abnormal perinatal outcomes), assessment of asthma control, and estimation of smoking status. LABA use was not associated with an increased prevalence of low birth weight [OR 0.81; 95% CI 0.58 to 1.12], preterm birth [OR 0.84; 95% CI 0.61 to 1.15], or small for gestational age [OR 0.92; 95% CI 0.70 to 1.20]. There was a non-significant increasing trend in the prevalence of the three abnormal perinatal outcomes with increasing doses of ICS > 125mcg/day fluticasone equivalent, but no increase with doses < 125mcg/day. So LABA use and low dose ICS use are not associated with any increase in abnormal perinatal outcomes. However, the impact of higher doses of ICS requires further study.

COPD

QVA149 (indacaterol/glycopyrronium) versus glycopyrronium and tiotropium: effect on COPD exacerbations

Wedzicha *et al.* Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK); a randomised, double-blind, parallel-group study. *Lancet Respir Med* 2013;**1**:199-209. http://dx.doi.org/10.1016/S2213-2600(13)70052-3

This large, randomised, double-blind, parallel-group efficacy and safety study shows that combination treatment with a long-acting β_2-agonist (LABA) bronchodilator (indacaterol) and a long-acting muscarinic antagonist (LAMA) bronchodilator (glycopyrromium) reduces the rate of moderate-to-severe COPD exacerbations compared to the LAMA alone. COPD patients aged ≥ 40 years (GOLD stage 3 or 4 disease and one or more moderate exacerbations in the last year) were randomised to receive once-daily QVA149 (indacaterol 110mcg/glycopyrronium 50mcg) [n=729], glycopyrronium 50mcg [n=739], or tiotropium 18mcg [n=737] for 64 weeks, with stratification for smoking status. The LABA/LAMA combination inhaler reduced the rate of moderate-to-severe exacerbations versus glycopyrronium alone by 12% (annualised exacerbation rate 0.84 [95% CI 0.75 to 0.94] vs. 0.95 [95% CI 0.85 to 1.06]; rate ratio 0.88 [95% CI 0.77 to 0.99]). Adverse event rates, including exacerbations, were similar in all three groups, at around 93%; serious adverse event rates (COPD worsening being the most common) were also similar between groups, at about 23%. So, dual bronchodilation with indacaterol/glycopyrronium significantly reduced moderate-to-severe exacerbation rates compared to the glycopyrronium alone. Dual LABA/LAMA bronchodilation therefore appears to have more of a role in the treatment of moderate-to-severe COPD than it has hitherto.

Once-daily fluticasone furoate/vilanterol versus vilanterol only: effect on COPD exacerbations

Dransfield *et al*. Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. *Lancet Respir Med* 2013;**1**:210-23. http://dx.doi.org/10.1016/S2213-2600(13)70040-7

Another large double-blind parallel-group 1-year study with the primary outcome being the yearly rate of moderate and severe COPD exacerbations, this time comparing treatment with a combination inhaler containing fluticasone furoate (a once-daily inhaled corticosteroid, ICS) and vilanterol (a once-daily LABA), versus vilanterol alone. In fact, this is a report of two identical studies which were analysed separately and then had their results pooled; Study 1 enrolled 1622 patients, and Study 2 1633 patients. Patients were aged ≥ 40 years, had a smoking history of ≥ 10 pack-years, an FEV_1/FVC ratio < 0.7, an FEV_1 ≤ 70% predicted, and > 1 moderate or severe exacerbation in the preceding year. They were randomised in a 1:1:1:1 ratio to combination treatment with vilanterol 25mcg and either 50mcg, 100mcg or 200mcg fluticasone furoate, or to vilanterol 25mcg only. In Study 1, there was no significant difference in exacerbation rate between the fluticasone furoate 200mcg/vilanterol 25mcg combination and the vilanterol alone [mean 0.90 event/year versus 1.05 events/year; ratio 0.9; 95% CI 0.7 to 1.0]. In Study 2, there were significantly fewer moderate-to-severe exacerbations in all three ICS/LABA groups compared to the vilanterol alone. In the pooled analysis, P values for the reduction in 1-year exacerbation rate for the ICS/LABA groups versus the LABA alone were 0.014 for the 50mcg fluticasone group, <0.0001 for the 100mcg group, and

0.0003 for the 200mcg group. Interestingly, there was an increased risk of pneumonia in COPD patients receiving combination ICS/LABA treatment (in accordance with other recent work), with eight deaths from pneumonia in the fluticasone/vilanterol groups and none in the vilanterol-only group…

COPD patients on fluticasone/salmeterol likely to have higher risk of pneumonia than patients on budesonide/formoterol

Janson *et al*. Pneumonia and pneumonia related mortality in patients with COPD treated with fixed combinations of inhaled corticosteroid and long-acting β_2-agonist: observational matched cohort study (PATHOS). *BMJ* 2013;**346**:f3306. Published online 22nd March 2013. http://dx.doi.org/10.1136/bmj.f3306

Continuing the theme of an increased risk of pneumonia with ICS/LABA treatment for COPD, this large retrospective pairwise cohort study from Sweden compared the rates of pneumonia and pneumonia-related mortality in COPD patients treated with fluticasone/salmeterol versus budesonide/formoterol. Medical records from 76 primary healthcare centres (covering 8% of the population) were searched for COPD patients who were on ICS/LABA combination treatment. These patients' records were then linked to national registry morbidity and mortality data, data on inpatient and outpatient hospital care, and drug prescription data from the Swedish Prescribed Drug Register. Data were collected for the 10-year period 1999-2009. 9893 patients were eligible for inclusion, and two propensity-matched cohorts were constructed with 2734 patients on fluticasone/salmeterol and 2734 on budesonide/formoterol. The yearly pneumonia rate was higher in the fluticasone/salmeterol group than the budesonide/formoterol group [rate ratio (RR) 1.73; 95% CI 1.57 to 1.90], as was the hospital admission rate for pneumonia [RR 1.74; 95% CI 1.56 to 1.94]. Mortality related to pneumonia was also higher in the fluticasone/salmeterol group than the budesonide/formoterol group [97 deaths versus 52 deaths; hazard ratio 1.76; 95% CI 1.22 to 2.53]. There was no difference in all-cause mortality between the two groups. This is an important study, which shows an intra-class difference between the two different ICS/LABA combination inhalers in terms of pneumonia risk and pneumonia-related mortality…

Roflumilast reduces the frequency of exacerbations in the frequent exacerbator COPD phenotype

Wedzicha *et al.* Efficacy of roflumilast in the COPD frequent exacerbator phenotype. *Chest* 2013;**143**:1302-11. http://journal.publications.chestnet.org/article.aspx?articleid=1388068

This is a *post hoc* pooled analysis of two 1-year placebo-controlled studies of roflumilast 500 mcg once-daily in symptomatic COPD patients with severe airflow obstruction. Data on 3,091 patients were available, 92% of whom had GOLD stage 3 (62.5%) or 4 (29.2%) disease. At study entry they were divided into 'frequent' (≥ 2 exacerbations in the previous year) or 'infrequent' (<2 exacerbations in the previous year) exacerbators. Exacerbation frequency was assessed one year later. After one year, the frequent exacerbators on treatment with roflumilast had a significant reduction in number of exacerbations compared to those on placebo [32.0% versus 40.8%; P=0.148]. Furthermore, fewer of the infrequent exacerbators went on to become frequent exacerbators when treated with roflumilast compared to those on placebo [17.5% vs. 22.9%; P=0.002]. This reduction in exacerbations was independent of other treatment with LABAs or ICS. Of the GOLD 3 patients, 26.4% of those on roflumilast continued to be frequent exacerbators compared to 38.9% on placebo [P=0.004]. This is an interesting analysis, albeit post hoc, showing a significant switch from the 'frequent' exacerbator to the 'infrequent' exacerbator phenotype in patients with severe symptomatic COPD treated with roflumilast.

Systemic steroid treatment for acute exacerbations of COPD: 5 days versus 14 days

Leuppi *et al*. Short-term conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. *JAMA* 2013;**309**:2223-31. http://dx.doi.org/10.1001/jama.2013.5023

The aim of this multicentre RCT was to investigate whether a 5-day course of oral corticosteroids was non-inferior to a 14-day course for treatment of an acute exacerbation of COPD. Current international guidelines are quite vague and recommend a 7- to 14-day course. 314 patients with mostly severe COPD (mean FEV_1 = 31% predicted) who presented to the emergency department of five Swiss teaching hospitals with a COPD exacerbation were recruited. They received 40mg i.v. methylprednisolone, and were then randomised to receive 40mg prednisolone for 14 days ('conventional' group) or 40mg prednisolone for 5 days plus 9 days placebo ('short-term' group). They also received standard treatment including antibiotics, nebulised bronchodilators, and triple inhaler therapy (ICS/LABA and tiotropium). The primary endpoint was time to next exacerbation over the 6-month follow-up period. The predefined non-inferiority criterion was an absolute increase in exacerbations of up to 15% in the short-term group, corresponding to a hazard ratio of 1.52 or less. 311/314 patients were included in the intention-to-treat analysis and 296 patients in the per-protocol analysis. The hazard ratios for re-exacerbation for the short-term versus conventional group were 0.95 [90% CI 0.70 to 1.29] in the intention-to-treat analysis and 0.93 [90% CI 0.68 to 1.26] in the per-protocol analysis; re-exacerbation rates were 37.2% [95% CI 29.5 to 44.9%] in the short-term group and 38.4% [95% CI 30.6 to 46.3%] in the conventional group, a difference of -1.2% [95% CI -12.2 to 9.8%]. Median time to next exacerbation was 43.5 days [interquartile range (IQR) 13 to 118] in the short-term group and 29 days [IQR 16 to 85] in the conventional group, and was not significantly different. There was no difference between the two groups in the various secondary outcome measures. The results therefore met the a priori definition of non-inferiority. However, the definition of non-inferiority here – an increase in exacerbation rate in the short-term group of up to 15%, equating to one extra exacerbation for every 7 patients – is probably too large and is a limitation of this study. Nevertheless, the almost identical re-exacerbation rates and suggestion of a longer time to next exacerbation in the short-term group are very reassuring indeed.

High-dose N-acetylcysteine for the treatment of stable COPD

Tse *et al*. High-dose N-acetylcysteine in stable COPD. *Chest* 2013;**144**:106-18. http://journal.publications.chestnet.org/article.aspx?articleid=1559995

Previous studies on N-acetylcysteine (NAC) use in COPD patients have been inconclusive, possibly due to the insufficient dose of NAC used. This 1-year double-blind RCT from the Kwong Wah Hospital in Hong Kong recruited 120 Chinese patients aged 50 to 80 years with stable COPD. 93.2% were men, mean age was 70.8 +/- 0.74 years, and mean FEV_1 53.9+/-2.0% predicted. After a 4-week run-in, patients were randomised to receive high-dose NAC 600mg twice-daily or placebo. Outcome measures were assessed at baseline and then every 16 weeks throughout the 1-year study period; they included lung function parameters, symptom scores, modified Medical Research Council (mMRC) and St George's Respiratory Questionnaire (SGRQ) scores, 6-minute walking distance (6MWD), and exacerbation and admission rates. After 1 year, patients in the NAC group showed significant improvements in forced expiratory flow 25% to 75% [P=0.037], a significant reduction in exacerbation rate [0.96 episodes/year versus 1.71 episodes/year; P=0.019], and a non-significant tendency towards reduced hospitalisation admission rate [0.5 times/year vs. 0.8 times/year; P=0.196]. There were no significant differences in mMRC and SGRQ scores, and 6MWD, between both groups. There were no major adverse events. The authors conclude that one year's high-dose NAC treatment resulted in significantly improved small airway function and a reduced exacerbation rate. No doubt further trials of high-dose NAC in the management of COPD will follow…

Resting heart rate is a predictor of all-cause mortality in COPD

Jensen *et al*. Resting heart rate is a predictor of mortality in COPD. *Eur Respir J* 2013;**42**:341-9. http://dx.doi.org/10.1183/09031936.00072212

The Copenhagen City Heart Study is a prospective study of a random population sample of people aged ≥ 20 years living in Copenhagen, Denmark. Initiated in 1976, there have been four major surveys conducted so far. In this study, only subjects aged ?40 years were included [n = 16,696]. The aims were: 1. to see if COPD severity was associated with an increase in resting heart rate; 2. to examine whether resting heart rate was associated with cardiovascular and all-cause mortality in COPD; 3. to examine whether resting heart rate could improve prediction of median life expectancy beyond that predicted by GOLD stage; and 4. to examine whether adding resting heart rate to prediction models with GOLD stage alone or FEV_1 % predicted alone could reclassify subjects into clinically meaningful risk categories. During the 35.3 years of follow-up (mean 20.1 years), 5,394 cardiovascular deaths and 10,986 all-cause deaths occurred. Resting heart rate increased with severity of COPD [P < 0.001], and was also associated with both cardiovascular and all-cause mortality across all stages of COPD [P < 0.001]. Resting heart rate improved prediction of median life expectancy: a heart rate of < 65/min compared to > 85/min improved life expectancy by 5.5 years in patients without COPD, by 9.8 years in patients with GOLD stage I disease, by 6.7 years in those with GOLD stage II disease, and by 5.9 years in GOLD stage III or IV disease [P < 0.001]. The authors conclude that resting heart rate does indeed increase with increasing severity of COPD, can be used to improve risk prediction in COPD patients, and consequently may be a target for therapeutic intervention.

Simvastatin inhibits tobacco smoke-induced airway epithelial injury

Davis *et al*. Simvastatin inhibits smoke-induced airway epithelial injury: implications for COPD therapy. *Eur Respir J* 2013;**42**:350-61. http://dx.doi.org/10.1183/09031936.00042512

It's unusual for us to review a basic science paper, but this *ERJ* paper provides a fascinating insight into the possible reasons for the benefit of statins in patients with COPD (for example, see the national cohort study from New Zealand which we published in March 2012 http://dx.doi.org/10.4104/pcrj.2011.00095 and the accompanying editorial http://dx.doi.org/10.4104/pcrj.2012.00020). No previous studies have evaluated whether systemic treatment with statins inhibits smoke-induced large airway or bronchial epithelial damage. Groups of six 12-week old spontaneously hypertensive rats were given either: daily injections of simvastatin for a week followed by 3 days of tobacco smoke exposure with simvastatin injection 30 minutes before each smoke exposure; or simvastatin treatment 30 minutes before each smoke exposure over the 3 days only; or no simvastatin treatment at all. After the 3 days of smoke exposure, pulmonary function testing was performed under deep sedation. The rats were then killed and bronchoalveolar lavage was performed followed by histological analysis. Pre-treatment with simvastatin for the week prior to tobacco smoke exposure reduced tobacco smoke-induced leukocyte, neutrophil and macrophage recruitment to the lung, whereas treatment only on the smoke exposure days had no effect. Rats exposed to tobacco smoke with no simvastatin treatment had extensive damage to the airways, with numerous neutrophils and macrophages present. Those rats treated with just 3 days' simvastatin during tobacco smoke exposure had similar damage. However, rats pre-treated with simvastatin for the week prior to smoke exposure had virtually no tobacco-smoke-induced large airway epithelial injury [P = 0.02]. The authors conclude that a critical 'preconditioning' phase may be required for statins to have an anti-inflammatory effect, and that they could well become adjunctive therapy for smoke-induced lung diseases such as COPD…

Changes in the CAT score following pulmonary rehabilitation in COPD and non-COPD patients

Kon *et al*. Response of the COPD Assessment Test to pulmonary rehabilitation in unselected chronic respiratory disease. *Respirology* 2013;**18**:974-7. http://dx.doi.org/10.1111/resp.12084

Use of the COPD Assessment Test (CAT) is now widespread, and it has been incorporated into the GOLD guidelines as one of the components for assessing COPD severity. A recently-published RCT showed that use of the CAT improved the quality of COPD consultations in primary care (see http://dx.doi.org/10.4104/pcrj.2013.00001), and pulmonary rehabilitation (PR) has been shown to improve the CAT score in patients with COPD. These authors have now assessed the CAT score in patients with non-COPD respiratory disease… 365 consecutive patients referred for PR (255 COPD patients, 110 non-COPD patients) completed the CAT before and after an 8-week PR programme. Changes in CAT scores were correlated with change in Chronic Respiratory Questionnaire (CRQ) scores. In both COPD and non-COPD patients, there was a similar significant improvement in CAT scores pre- and post- PR (change in COPD patients -3.0 [95% CI -2.2 to -3.8]; change in non-COPD patients -2.1 [95% CI -1.0 to -3.2]), and changes in CAT scores matched changes in all the domains of the CRQ in both COPD and non-COPD patients [all P values < 0.01]. The authors conclude that the CAT is immediately responsive to PR in both COPD and non-COPD patients, and is a practical alternative to other longer health status questionnaires.

Infections

RSV infection implicated as a mechanism of recurrent wheeze in healthy preterm infants

Blanken *et al*. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. *New Engl J Med* 2013;**368**:1417-27 http://www.nejm.org/doi/full/10.1056/NEJMoa1211917

This is the first report from the MAKI Trial – a multicentre, double-blind, placebo-controlled RCT from the Dutch RSV Neonatal Network – the aim of which was to assess the preventive effects of the monoclonal antibody palivizumab on recurrent wheeze following respiratory syncytial virus (RSV) infection in preterm infants. In so doing, the researchers hoped to shed some light on the question: is RSV infection the cause of recurrent wheeze, or is it the first indication of a pre-existing vulnerability to wheeze in preterm infants? Preterm infants born between 33 and 35 weeks gestation were randomised to monthly palivizumab injections [n=214] or placebo [n=215] during the RSV season. Nasopharyngeal swabs were taken for viral analysis. Palivizumab treatment caused a relative reduction of 61% [95% CI 56 to 65] in the total number of parent-reported wheezing days in the first year of life; 930 out of 53,075 days (1.8%) in the palivizumab group versus 2309 out of 51,726 days (4.5%) in the placebo group. The proportion of infants with recurrent wheeze was similarly reduced: 11% in the palivizumab group vs. 21% in the placebo group [P = 0.01]. The authors conclude that the prevention of RSV episodes and subsequent recurrent wheeze in the palivizumab group suggest that RSV infection is an important mechanism of recurrent wheeze in healthy preterm infants.

Risk factors for bronchiectasis in children with cystic fibrosis

Sly *et al*. Risk factors for bronchiectasis in children with cystic fibrosis. *New Engl J Med* 2013;**368**:1963-70 http://www.nejm.org/doi/full/10.1056/NEJMoa1301725

In previous studies on infants with cystic fibrosis (CF), bronchiectasis has been found to occur as early as 10 weeks of age. These authors used data from the Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST CF) programme to determine the risk factors for onset of bronchiectasis in children with CF aged 3 months to 3 years. They studied 127 infants with a new-born screening diagnosis of CF, and performed CT scans and bronchoscopy at age 3 months and 1, 2, and 3 years. Following each bronchoscopy, bronchoalveolar lavage (BAL) specimens were assayed for free neutrophil elastase activity. Neutrophil elastase has been implicated in a variety of inflammatory diseases, including idiopathic pulmonary fibrosis, rheumatoid arthritis, adult respiratory distress syndrome, and cystic fibrosis; it attacks a number of proteins including lung elastin and fibronectin. The point prevalence of bronchiectasis was 29.3% at age 3 months, and 61.5% at age 3 years. Using multivariate analysis, risk factors for bronchiectasis were meconium ileus [odds ratio (OR) 3.17; 95% CI 1.51 to 6.66], respiratory symptoms at the time of the CT scan and bronchoscopy [OR 2.27; 95% CI 1.24 to 4.14], free neutrophil elastase activity in the BAL fluid [OR 3.92; 95% CI 1.70 to 5.35], and gas trapping on the CT scan [OR 2.05; 955 CI 1.17 to 3.59]. Free neutrophil elastase activity in BAL fluid at age 3 months was also associated with persistent bronchiectasis. The authors conclude that neutrophil elastase activity in BAL fluid is associated with early bronchiectasis in children with CF.

Different phenotypes of non-cystic fibrosis bronchiectasis

Anwar *et al.* Phenotyping adults with non-cystic fibrosis bronchiectasis: a prospective observational cohort study. *Resp Med* 2013;**107**:1001-07. http://dx.doi.org/10.1016/j.rmed.2013.04.013

Bronchiectasis is a chronic, debilitating condition characterised by persistent cough, excessive sputum production and recurrent chest infections; for a primary care summary of the British Thoracic Society (BTS) non-cystic fibrosis bronchiectasis management guideline see http://dx.doi.org/10.4104/pcrj.2011.00007. However, research on the different aetiologies and phenotypes of bronchiectasis is sparse. This is a prospective observational cohort study of 189 bronchiectasis patients from two hospitals in the north-east of England with a follow-up period of 2 years. Information was obtained using a dedicated screening proforma. The aetiology of bronchiectasis was identified in 107 patients (57%), and 'idiopathic' bronchiectasis constituted the other 43%. Within the 57% of patients with a known cause, post-infection bronchiectasis constituted the largest proportion (24%). Overall, there was a diagnostic delay of 17 years: mean age +/- SD of symptom onset was 37 +/- 24 years, whereas mean age at diagnosis was 54 +/- 20 years. In patients with post-infective bronchiectasis, age of symptom onset was significantly younger than in those patients with idiopathic disease [P<0.0001]. Screening for allergic bronchopulmonary aspergillosis (ABPA) and immunoglobulin deficiency was useful in that 9 patients (5%) were identified who then went on to have tailored treatment. The authors conclude that idiopathic and post-infective bronchiectasis accounts for two-thirds of the bronchiectasis patients seen in their clinics, and that routine screening for ABPA and immunoglobulin deficiency should be employed.

Improving primary care prescribing in acute respiratory infections

Gjelstad *et al*. Improving antibiotic prescribing in acute respiratory tract infections: cluster randomised trial from Norwegian general practice (prescription peer academic detailing (Rx-PAD) study. *BMJ* 2013;**347**:f4403. Published online 26th July 2013. http://dx.doi.org/10.1136/bmj.f4403

This cluster randomised controlled study from Norway confirms that educational interventions can work. The aim was to assess the effects of a GP educational intervention on antibiotic prescription rates for acute respiratory infections and use of broad spectrum antibiotics. The intervention was multifaceted, and in particular it

required GPs to share their own antibiotic prescribing data with their continuing medical education (CME) group as well as reflecting critically on the need for change with a peer academic detailer (acting as an 'active listener'). 250 CME groups in 11 counties in southern Norway (all GPs in Norway are required to be a member of a CME group) were invited to participate, and 79 groups completed the interventions and provided complete data. Randomisation was at the group level. The active intervention groups (n = 39, 183 GPs) had two visits by peer academic detailers, the first focussed on national clinical guidelines and recent research evidence on prescribing for acute respiratory tract infections, the second based on feedback reports on each GP's antibiotic prescribing profile from the preceding year. Regional one day educational seminars were also arranged. The control groups (n = 40, 199 GPs) received a different educational intervention targeting prescribing practice for older patients. The main outcome measures were prescription rates and the proportion of non-penicillin V antibiotics prescribed at the group level pre- and post-intervention. The 39 intervention groups showed a reduction in prescribing of antibiotics for acute respiratory tract infections compared with controls [odds ratio (OR) 0.72; 95% CI 0.61 to 0.84]. The OR for prescribing a non-penicillin V antibiotic was also reduced [OR 0.64; 95% CI 0.49 to 0.82]. Prescriptions per 1000 listed patients increased from 80.3 to 84.6 in the intervention arm and from 80.9 to 89.0 in the control arm, but this was due to a higher incidence of infections (particularly pneumonia) that needed treating in the intervention arm. The authors conclude that the educational intervention led to improved antibiotic prescribing for respiratory tract infections in a representative sample of Norwegian GPs.

Fibrotic lung disease

Ambulatory oxygen has no benefit in pulmonary fibrosis patients without resting hypoxaemia

Nishiyama *et al*. Effect of ambulatory oxygen on exertional dyspnoea in IPF patients without resting hypoxaemia. *Resp Med* 2013;**107**:1241-6. http://dx.doi.org/10.1016/j.rmed.2013.05.015

When patients with idiopathic pulmonary fibrosis (IPF) become increasingly dyspnoeic, it is perfectly understandable when they enquire about the possible benefit of oxygen treatment. This is an interesting negative study which provides some answers to guide treatment decisions. It was a double-blind, placebo-controlled, randomised crossover trial of ambulatory oxygen versus ambulatory air in patients with IPF without any resting hypoxaemia but with desaturation on exertion (i.e. PaO_2 between 60 and 80 mmHg at rest, and desaturation down to O_2 saturations of < 88% in air after a 6-minute walk test). 20 patients were recruited (16 men, mean age 73.5 +/- (SD) 4.1 years, FVC of 71.0 +/- 13.3 % predicted, diffusion capacity for carbon monoxide (DL_{CO}) 57.0 +/- 13.3 % predicted, PaO_2 72.5 +/- 5.4 mmHg at rest).They performed a 6-minute walk-test and a 6-minute 'free-walk' test on either oxygen or air delivered at 4 L/min. Dyspnoea was evaluated immediately and at 1 and 2 minutes post-test. There were no significant differences between the two groups in dyspnoea scores at any of the time points. The authors conclude that routine prescribing of ambulatory oxygen is unnecessary for IPF patients with no resting hypoxaemia. However, there was some variation between the patients, and so they advise that individual assessment is still necessary…

Miscellaneous

Comparing lung cancer survival rates in different countries

Walters *et al*. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004-2007. *Thorax* 2013;**68**:551-64. http://dx.doi.org/10.1136/thoraxjnl-2012-202297

Lung cancer is the leading cause of cancer death worldwide, with wide variations in lung cancer survival rates between countries. Differences in stage at diagnosis are thought to be one explanation, but could there be other factors as well? In order to assess international comparisons of the effectiveness of health systems, comparative population-based studies are required, and this is the first international population-based study of lung cancer survival according to stage at diagnosis. Out of 232,278 adults diagnosed between 1995 to 2007 and registered in regional and national cancer registries in Australia, Canada, Denmark, Norway, Sweden and the UK, data analysis was subsequently restricted to those diagnosed between 2004 and 2007 when stage data were more complete – leaving 57,532 patients in the final analysis. Flexible hazard models were used to estimate net survival at 1 year and the excess hazard up to 18 months post diagnosis. Survival rates varied widely. Age-standardised 1-year net survival for non-small cell lung cancer (NSCLC) ranged from 30% in the UK to 46% in Sweden, with Denmark near the bottom and Australia and Canada near the top. These differences were partly explained by stage at diagnosis (particularly for Denmark), but there were significant differences in stage-specific survival rates; for example, survival from TNM stage I NSCLC was 16% lower in the UK than in Sweden. The variations were similar for small cell lung cancer. The authors conclude that, despite international comparability issues and differences in stage at diagnosis, other factors such as differences in stage-specific treatment are likely to be involved…

Inhaled corticosteroids and the risk of adrenal insufficiency

Lapi *et al*. The use of inhaled corticosteroids and the risk of adrenal insufficiency. *Eur Respir J* 2013;**42**:79-86. http://dx.doi.org/10.1183/09031936.00080912

This was a nested case-control study examining the relationship between inhaled corticosteroid (ICS) use and risk of adrenal insufficiency. Fluticasone, which has higher lipophilicity and a more prolonged half-life, has previously been implicated in the majority of cases of ICS-induced adrenal insufficiency. However, these Canadian authors contend that previous studies have failed to allow for the pattern of fluticasone prescribing (particularly in the UK), which may have channelled its use towards patients with more severe disease. In Canada, fluticasone is the preferred inhaled corticosteroid (ICS) among all categories of prescribers, accounting for >75% of all ICS prescriptions, making this 'channelling' or confounding by indication less likely. Using data from the Régie de l'assurance médicale du Québec (RAMQ), with healthcare utilisation information on all 7 million residents of Quebec, they constructed a cohort of 368,238 people who were regular users of respiratory medication. Within this cohort, they then identified 392 cases of adrenal insufficiency (incidence rate 1.1 per 10,000 person-years), and up to 10 matched controls (for age and cohort entry) for each case. Cases had more severe respiratory disease, as shown by the higher frequency of asthma and COPD hospitalisations and the higher number of prescriptions for respiratory drugs, antibiotics and oral corticosteroids. The odds ratio (OR) for adrenal insufficiency was not significantly elevated for current ICS use [OR 1.22; 95% CI 0.85 to 1.70]. However, the risk was significantly greater among those exposed to the highest doses of ICS [OR 1.84; 95% CI 1.16 to 2.90], and this was confirmed by the increased risk for the highest tertile of ICS dose [OR 1.90; 95% CI 1.07 to 3.37]. The authors conclude that physicians should be sensitive to the signs and symptoms of adrenal insufficiency in patients with respiratory disease taking ICS especially at daily doses equivalent to fluticasone ≥1000 mcg per day.

A successful smoking cessation strategy for hospital inpatients

Murray *et al*. Systematic identification and treatment of smokers by hospital based cessation practitioners in a secondary care setting: cluster randomised controlled trial. *BMJ* 2013;**347**:f4004. Published online 8th July 2013. http://dx.doi.org/10.1136/bmj.f4004

This open parallel cluster randomised controlled trial conducted on the medical wards of the Nottingham City Hospital, a large teaching hospital in the UK, is a great example of an intensive smoking cessation programme aimed at a 'captive' audience of adult smokers and ex-smokers (who had quit in the four weeks before admission). For those patients admitted to any of the 18 medical wards between October 2010 and August 2011, the ward was the unit of randomisation, and wards were allocated randomly to the intervention [264 patients] or usual care [229 patients]. Staff and patients were aware of the randomisation. For patients on the usual care wards, smoking status was obtained and smoking cessation advice provided in accordance with standard practice. On the intervention wards, smoking cessation practitioners personally questioned patients regarding their smoking history, offered one-to-one counselling throughout the hospital stay, arranged post-discharge follow-up and referral to community smoking cessation services, and prescribed dual nicotine replacement therapy (or bupropion or varenicline treatment if preferred or if nicotine was contra-indicated). Only 46% of patients received at least brief advice to quit smoking in the usual care group, compared to 100% of the intervention group. 38% of the intervention group (n=98) and 17% of the usual care group (n=37) achieved smoking cessation at 4 weeks [odds ratio (OR) 2.10; 95% CI 0.96 to 4.61]. Uptake of inpatient behavioural support, use of pharmacotherapy, and referral to and uptake of community support after discharge were all statistically significantly higher in the intervention group than in the usual care group. Cessation at 6 months was achieved by 19% (n=47) of the intervention group and 9% (n=19) of the usual care group [adjusted OR 1.53; 95% CI 0.60 to 3.91]. The authors conclude that this sort of systematic secondary care smoking cessation programme with community follow-up can provide significantly increased quit rates. An example to us all…