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Asthma

The role of mepolizumab in the treatment of severe eosinophilic asthma

Pavord *et al*. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;**380**:651-9.
http://dx.doi.org/10.1016/S0140-6736(12)60988-X

Mepolizumab is a monoclonal antibody against interleukin 5 which inhibits eosinophilic airway inflammation. In patients with severe asthma who have exacerbations associated with eosinophilic inflammation, previous studies have suggested that it can reduce exacerbation rates. This was a multicentre, double-blind, 4-arm RCT in patients aged 12-74 years with a history of severe asthma exacerbations and documented eosinophilic inflammation. Patients were randomised to three different doses of intravenous mepolizumab given as 13 infusions at 4-weekly intervals [75mg (n = 154), 250mg (n = 152), or 750mg (n = 156)] or placebo (n = 159). Exacerbations were defined as acute asthma requiring treatment with oral steroids, hospital admission, or a visit to the emergency department. The exacerbation rate was 2.40 per patient per year in the placebo group, 1.24 in the 75mg mepolizumab group [48% reduction; 95% CI 31 – 61%], 1.46 in the 250mg group [39% reduction; 95% CI 19 – 54%], and 1.15 in the 750mg group [52% reduction; 95% CI 36 – 64%]. All three doses of mepolizumab were effective at reducing the risk of asthma exacerbation in patients with severe eosinophilic asthma. This is a good example of a personalised treatment option specifically tailored to one particular disease phenotype.

Fluctuating sputum inflammatory phenotypes in children with asthma

Fleming *et al*. Sputum inflammatory phenotypes are not stable in children with asthma.
Thorax 2012;**67**:675-81.
http://dx.doi.org/10.1136/thoraxjnl-2011-201064

In adults, two distinct asthma inflammatory phenotypes have been identified – eosinophilic and non-eosinophilic. These authors evaluated sputum cytology in 51 children with severe asthma and 28 with mild-to-moderate asthma. After sputum induction, samples were classified as eosinophilic (>2.5% eosinophils), neutrophilic (>54% neutrophils), mixed granulocytic (>2.5% eosinophils, >54% neutrophils), or paucigranulocytic (≤2.5% eosinophils, ≤54% neutrophils). In 59 children, further samples were taken at 3-monthly intervals over 1 year (severe asthma, n = 42) or over 3-6 months (mild-to-moderate asthma, n = 17) to assess stability of sputum phenotypes over time. 62 children (78%) had raised levels of inflammatory cells in at least one sputum sample, and 37/59 children demonstrated two or more phenotypes over time. There was variability in sputum phenotype in both the severe and mild-to-moderate asthma groups. Change in phenotype was not related to change in inhaled corticosteroid dose or asthma control, and 24 children (41%) exhibited eosinophilic asthma and non-eosinophilic asthma on different occasions. In conclusion, raised levels of inflammatory cells were frequently found in children with asthma of all severities, and sputum inflammatory phenotype changed over time – implying that the adult separation into two distinct stable inflammatory phenotypes is not yet established in childhood.

The characteristics of menstrual-linked asthma

Thornton *et al*. Clinical characteristics of women with menstrual-linked asthma.
Resp Med 2012;**106**:1236-43.
http://dx.doi.org/10.1016/j.rmed.2012.05.003

These authors set out to define the clinical characteristics of menstrual-linked asthma (MLA), which describes deterioration of asthma control peri-menstrually in pre-menopausal women. A comprehensive health questionnaire which included questions about MLA was used to perform a cross-sectional population survey in 1260 women with asthma aged 12-55 years. The response rate was 43% (540/1260). The prevalence of self-reported MLA was 11% (60/540). Compared to women without MLA, women with MLA had more emergency healthcare attendances per year [6.18 vs. 4.71; P = 0.033], more emergency department visits [1.50 vs. 0.88; P = 0.035], higher asthma-related work absenteeism [33/60 (57%) vs. 170/471 (37%); P = 0.003], and used almost twice the number of short-acting beta2-agonist (SABA) rescue doses/day [1.13 vs. 0.68; P = 0.015]. Using multivariate analysis, the differences in absenteeism and SABA use remained statistically significant. The low response rate here makes it difficult to estimate the true prevalence of menstrual-linked asthma, but nonetheless this study does suggest that MLA may be more common than previously thought. We therefore need to consider menstrual-linked asthma when discussing asthma management plans with pre-menopausal women.

Does treatment with inhaled steroids in childhood affect adult height?

Kelly *et al*. Effect of inhaled glucocorticoids in childhood on adult height.
New Engl J Med 2012;**367**:904-912.
http://www.nejm.org/doi/full/10.1056/NEJMoa1203229

Currently accepted wisdom is that the use of regular inhaled corticosteroids (ICS) in prepubertal children causes a slight reduction in growth velocity 1-4 years after starting treatment but no absolute reduction in the child's final adult height. However, these authors measured the height of 943 out of 1041 adults

(90.6%; mean age 24.9 [+/- SD 2.7] years) who had been enrolled aged 5-13 into the US Childhood Asthma Management Programme; this involved randomisation to either 400mcg/day budesonide, 16mg/day nedocromil, or placebo, for 4-6 years. Differences in adult height between the three treatment groups were calculated using multiple linear regression, with adjustment for demographic factors, asthma features, and height at trial entry. Mean adult height was 1.2cm lower [95% CI -1.9 to -0.5] in the budesonide group compared to the placebo group, particularly in children who were prepubertal at study entry, and a larger daily dose of ICS was associated with a greater reduction in adult height (-0.1cm for each mcg per kg body weight) [P = 0.007]. The reduction in final height in the budesonide group was the same as that seen after 2 years' treatment (-1.3cm; 95% CI -1.7 to -0.9). So this study conflicts with the current consensus; it may well be that long-term ICS treatment does indeed fractionally alter final attained adult height. It certainly adds to the debate on the safety of long-term ICS in children.

The benefits of tiotropium in asthma poorly controlled with standard combination treatment

Kerstjens *et al*. Tiotropium in asthma poorly controlled with standard combination therapy.
New Engl J Med 2012;**367**:published online 3rd September 2012.
http://www.nejm.org/doi/full/10.1056/NEJMoa1208606

Ipratropium has been used to treat asthma for decades, and the long-acting muscarinic antagonist tiotropium is now well-established in the management of COPD. It's therefore not surprising that a study on the use of tiotropium in asthma has now been published. This paper reports two identical randomised controlled trials (RCTs) involving 912 patients (mean age 53 years) whose asthma was not controlled with combination ICS and long-acting beta2-agonist (LABA) treatment. All had an FEV_1 ≤80% predicted (mean 62% predicted) and had had at least one severe exacerbation in the previous year. Patients received either additional tiotropium 5mcg or placebo once daily via soft-mist inhaler for 48 weeks. By 24 weeks, the mean change from baseline in both peak and trough FEV_1 values was greater with tiotropium than with placebo: differences (+/- standard error) were 86 +/- 34ml [P=0.01] and 154 +/- 32ml [P<0.001] for peak values, and 88 +/- 31ml [P=0.01] and 111 +/- 30ml [P<0.001] for trough values, in trials 1 and 2, respectively. Addition of tiotropium also increased the time to first severe exacerbation (282 days vs. 226 days), an overall risk reduction of 21% [hazard ratio 0.79; P=0.03]. There were similar numbers of adverse events in both groups. Therefore, for asthma patients with at least moderately severe disease, it very much looks as though tiotropium will have a role…

Vitamin D deficiency is associated with poorer lung function in children with asthma on inhaled steroids

Chen Wu *et al*. Effect of vitamin D and inhaled corticosteroid treatment on lung function in children.
Am J Resp Crit Care Med 2012;**186**:508-513.
http://dx.doi.org/10.1164/rccm.201202-0351OC

Low vitamin D levels are associated with asthma and decreased airway responsiveness, but what impact does this have on asthma when it's being treated? These authors set out to assess the effect of vitamin D levels on FEV_1 bronchodilator response and responsiveness to methacholine in children with asthma treated with ICS. Serum 25-hydroxyvitamin D levels were measured in 1,024 children at the time of enrolment into the US Childhood Asthma Management Programme. 663 (65%) children were vitamin D sufficient (>30ng/ml), 260 (25%) had vitamin D insufficiency (20-30ng/ml), and 101 (10%) had vitamin D deficiency (<20ng/ml). Covariates included age, treatment, sex, BMI, race, history of emergency room visits and hospitalisation, and the season that the vitamin D assay was measured. Those with vitamin D deficiency were more likely to be older, African American, and obese. Over 12 months, pre-bronchodilator FEV_1 increased by 290ml in the vitamin D sufficient group, by 330ml in the vitamin D insufficient group, but by only 140ml in the vitamin D deficient group [P = 0.007]. Therefore, in children with asthma treated by ICS, vitamin D deficiency is associated with poorer lung function than in children with vitamin D sufficiency or insufficiency.

Reducing stress using 'mindfulness training' improves asthma quality of life and lung function

Pbert *et al*. Effect of mindfulness training on asthma quality of life and lung function: a randomised controlled trial.
Thorax 2012;**67**:769-776.
http://dx.doi.org/10.1136/thoraxjnl-2011-200253

Mindfulness training involves recognising and discriminating between various thoughts, feelings and sensations, and developing an increased awareness of them. Mindfulness-based stress reduction (MSBR) is a group-based training programme that reduces perceived stress, disease-related distress and reported medical symptoms in a range of chronic diseases. This RCT is the first to investigate the effectiveness of this approach in asthma. Patients with persistent asthma of varying severity were randomised to an 8-week MSBR programme [n=42] or an educational control programme [n=41]. Follow-up was at 10 weeks, 6 and 12 months. The primary outcomes were quality of life (measured by the Asthma Quality of Life Questionnaire, AQLQ) and lung function (change from baseline in 2-week average morning PEF values). Secondary outcomes were asthma control (NIH guidelines) and stress (measured by the Perceived Stress Scale, PSS). At 12 months, MBSR resulted in clinically significant improvements from baseline in quality of life [differential change in AQLQ for MBSR vs. control = 0.66; 95% CI 0.30 – 1.03] and in perceived stress [differential change in PSS score for MBSR vs. control = -4.5; 95% CI -7.1 to -1.9]. There were no changes in lung function or asthma control. MBSR therefore improved quality of life and reduced stress in patients with persistent asthma despite there being no improvement in lung function.

No difference between symptom-based, nitric oxide-based or physician-based adjustment of inhaled steroid dose in mild to moderate asthma

Calhoun *et al*. Comparison of physician-, biomarker-, and symptom-based strategies for adjustment of inhaled corticosteroid therapy in adults with asthma. The BASALT Randomised Controlled Trial.
JAMA 2012;**308**:987-997.
http://dx.doi.org/10.1001/2012.jama.10893

Debate has raged for years on the best way of constructing management plans for asthma, and in particular what information should be used to adjust the dose of inhaled corticosteroids (ICS). Should self-management plans be based on symptoms or PEF measurements? Should the ICS dose be supervised by a clinician at regular clinic appointments? Or (more recently) should we use exhaled nitric oxide levels to adjust the ICS dose? This randomised, parallel group, 3-arm RCT assessed physician-based adjustment (n=114; 101 completed), nitric oxide-based adjustment (n=115; 92 completed), and self-managed symptom-based adjustment (n=113; 97 completed) in adults with mild to moderate asthma controlled by low-dose ICS. Follow-up was for 9 months. In the physician-based and nitric oxide-based groups, ICS dose was adjusted every 6 weeks. The primary outcome was time to treatment failure – i.e. loss of asthma control. There were no significant differences in time to treatment failure: 9-month Kaplan-Meier failure rates were 22% [97.5% CI 14 – 33%] for physician-based adjustment, 20% [97.5% CI 13 – 30%] for nitric oxide-based adjustment, and 15% [97.5% CI 9 – 25%] for symptom-based adjustment. Therefore, for adults with mild to moderate asthma controlled on ICS, there were no significant differences between the three mechanisms of adjusting the ICS dose.

Primary care at-risk asthma registers: effect on exacerbations and hospitalisation

Smith *et al*. The at-risk registers in severe asthma (ARRISA) study: a cluster-randomised controlled trial examining effectiveness and costs in primary care.
Thorax 2012;**67**:1052-60.
http://dx.doi.org/10.1136/thoraxjnl-2012-202093

There has been much discussion on the rationale for at-risk asthma registers in primary care (see http://dx.doi.org/10.4104/pcrj.2012.00033 for recent correspondence from the authors of this study) and this is the first published

RCT, with cluster-randomisation at the practice level. 29 GP practices in Norfolk and Suffolk were recruited, and 911 at-risk asthma patients were identified using BTS/SIGN guideline criteria. Intervention practices used computer alerts to identify at-risk patients, and received practice-based training on improving patient access and management. Control practices continued routine care. The primary outcome was total numbers of moderate to severe exacerbations. There was no significant effect of at-risk registers on exacerbation frequency: intervention group 53.6%, control group 46.5% [odds ratio (OR) 1.30; 95% CI 0.93 – 1.80]. However, the composite outcome of 'total exacerbations' masks a possible shift of exacerbations in a milder direction: exacerbations requiring hospitalisation in the intervention group were significantly reduced [OR 0.50; 95% CI 0.26 – 0.94], and there was a trend to lower A+E admissions [OR 0.74; 95% CI 0.42 – 1.31] and out-of hours contacts [OR 0.79; 95% CI 0.45 – 1.37], and an increase in oral prednisolone prescribing [OR1.31; 95% CI 0.92 – 1.85]. If the different severities of exacerbation (causing death, near-fatal attack, hospitalisation, A+E attendance, or primary care-managed) had been considered as joint primary outcomes, this might well have demonstrated a shift in the exacerbation curve to the milder end of the spectrum in the intervention group… But as it stands, this is a negative study.

COPD

Using beta$_2$-agonists for the first time may increase the risk of cardiac arrhythmia in COPD

Wilchesky *et al*. Bronchodilator use and the risk of arrhythmia in COPD: Part 2: reassessment in the larger Quebec cohort.
Chest 2012;**142**:305-11. http://dx.doi.org/10.1378/chest.11-1597

This is the second of two papers which report that new use of short- and long-acting beta$_2$-agonists may increase the risk of cardiac arrhythmia in patients with COPD. The first paper was limited by its small cohort size. This paper uses a larger cohort of 76,661 COPD patients aged ≥ 67 years formed from the Quebec Healthcare Database, of whom 5,307 developed an arrhythmia (621 were fatal). Using a nested case-control study design, each arrhythmia patient was matched with 20 age- and sex-matched controls. The rate ratio (RR) of arrhythmia associated with new use of bronchodilators was estimated using logistic regression, adjusting for COPD disease severity, cardiovascular disease, and other co-morbidities. The risk of cardiac arrhythmia was elevated with new use of short-acting [RR 1.27; 95% CI 1.03 – 1.57] and long-acting [RR 1.47; 95% CI 1.01 – 2.15] beta$_2$-agonists. It was also slightly elevated with new use of ipratropium [RR 1.23; 95% CI 0.95 – 1.57] and methylxanthines [RR 1.28; 95% CI 0.93 – 1.77], though in both cases this was not statistically significant (i.e. the 95% CI values cross 1.0). Therefore, new use of beta$_2$-agonists may slightly increase the risk of cardiac arrhythmia in patients with COPD.

Worldwide patterns of bronchodilator responsiveness

Tan *et al*. Worldwide patterns of bronchodilator responsiveness: results from the Burden of Obstructive Lung Disease study.
Thorax 2012;**67**:718-26.
http://dx.doi.org/10.1136/thoraxjnl-2011-201445

The Burden of Obstructive Lung Disease (BOLD) study was formed in 2002 to set quality standards for defining COPD in epidemiological studies – see http://dx.doi.org/10.4104/pcrj.2012.00082 for a recent editorial on the challenges involved in studying COPD prevalence. Here, the BOLD Collaborative Research Group have investigated bronchodilator responsiveness in 10,360 adults aged 40 or over from 14 countries in North America, Europe, Africa and Asia, all of whom participated in the BOLD study. Pre-and post-bronchodilator spirometry was used to determine bronchodilator responsiveness in population-based samples of healthy non-smokers and patients with airflow obstruction. In 3922 healthy never-smokers, bronchodilator response in terms of change in FEV_1 from baseline was 284 ml [95% CI 263 – 305], a 12.0% change [95% CI 11.2 – 12.8%] relative to the initial value. The mean change from baseline in FVC was 322 ml [95% CI 271 – 373], a 10.5% [95% CI 8.9 – 12.0%] change relative to the initial value. In those patients with COPD at GOLD stage 2 or above, the proportion who exceeded these threshold values for bronchodilator responsiveness was 11.1% (stage 2), 30.8% (stage 3) and 12.9% (stage 4) for FEV_1, and was 22.6% (stage 2), 28.6% (stage 3) and 22.1% (stage 4) for FVC. These results provide reference values for bronchodilator responsiveness worldwide.

Patients at risk of late recovery from acute exacerbations of COPD

Anzueto *et al*. Identifying patients at risk of late recovery (≥8 days) from acute exacerbation of chronic bronchitis and COPD.
Resp Med 2012;**106**:1258-67.
http://dx.doi.org/10.1016/j.rmed.2012.06.002

This is a further analysis of data from a large international RCT of moxifloxacin treatment for acute exacerbations of chronic bronchitis or COPD. Here, the authors report an observational, non-intervention cohort study in those patients who received moxifloxacin (n = 40,435, aged ≥35 years, 63.1% male, mean age 60.4 years, 60.6% current or ex-smokers), in order to identify factors associated with late recovery (≥8 days) from an exacerbation. All patients had had >2 exacerbations in the previous year. 6,408 patients (19.7%) underwent spirometry, and mean FEV_1 was 1.7 litres. The clinical factors significantly associated with late recovery were age ≥65 years, duration of chronic bronchitis >10 years, cardiac co-morbidity, >3 exacerbations in the previous year, more severe exacerbation, and hospitalisation in the previous year. This is just what one would expect – but it serves to remind us of the importance of COPD exacerbations and cardiac co-morbidities…

Swimming pool-based exercise is good for COPD

De Souto Araujo *et al*. Effectiveness of low-intensity aquatic exercise on COPD: a randomised clinical trial.
Resp Med 2012;**106**:1535-1543.
http://dx.doi.org/10.1016/j.rmed.2012.06.022

The benefits of aquatic exercise have been reported in a number of studies, though little work has been done in COPD. In 2009, a qualitative study of 16 COPD patients reported on the feasibility and acceptability of swimming pool-based exercise as pulmonary rehabilitation (see http://dx.doi.org/10.3132/pcrj.2008.00052): significant improvements were observed in dyspnoea score and walking distance, and most patients enjoyed being in the water, overcame their fears, and valued learning about COPD and socialising with fellow COPD sufferers. This RCT evaluated the impact of low-intensity water exercises ('Aquatic group') and floor exercises ('Floor group') versus controls in 42 patients with moderate to very severe COPD. Outcome measures included spirometry, 6-minute walk test (6MWT), MRC Dyspnoea score, BODE index, and St George's Respiratory Questionnaire. The aquatic group showed significantly improved 6MWT times [P=0.02] and had significantly improved MRC dyspnoea scores [P=0.00] compared to controls. The BODE index decreased in both the floor group and the aquatic group. Therefore, both forms of low-intensity exercise produced clinically significant benefit for patients with moderate to very severe COPD.

Vitamin D deficiency is associated with poorer lung function in adult smokers

Lange *et al*. Vitamin D deficiency, smoking, and lung function decline in the Normative Aging Study.
Am J Resp Crit Care Med 2012;**186**:616-21.
http://dx.doi.org/10.1164/rccm.201110-1868OC

Given that Vitamin D has immune-modulatory and anti-inflammatory effects, this study examined the effect of Vitamin D deficiency on lung function and lung function decline in 626 men recruited to the Normative Aging Study who had 25-hydroxyvitamin D levels measured on three occasions between 1984 and 2003 together with concurrent spirometry. Using cross-sectional modelling, Vitamin D status did impact on the association between lung function and smoking: lung function (as shown by FEV_1, FVC, and FEV_1/FVC ratio) was lower in current smokers with vitamin D deficiency (serum levels < 20 ng/ml) than in smokers who were Vitamin D sufficient [P≤0.001]. In

addition, on longitudinal analysis, there were more rapid rates of decline in FEV_1 [P=0.023] per pack-year of smoking in Vitamin D-deficient smokers compared to smokers with Vitamin D sufficiency. Therefore, having sufficient levels of Vitamin D may have a protective effect against the damaging effects of smoking on lung function. Of course, these results need to be confirmed in further studies which assess smoking and other factors that might affect lung function.

Efficacy of antibiotic therapy for mild to moderate COPD exacerbations

Llor *et al*. Efficacy of antibiotic therapy for acute exacerbations of mild to moderate chronic obstructive pulmonary disease.
Am J Resp Crit Care Med 2012;**186**:716-23.
http://dx.doi.org/10.1164/rccm.201206-0996OC

Should we treat milder exacerbations of COPD with antibiotics? This was a multicentre, parallel group, double-blind, placebo-controlled, randomised controlled trial (RCT) in smokers or ex-smokers (10 pack-years or more) aged over 40 with spirometrically-defined mild to moderate COPD (FEV_1 > 50% predicted, FEV_1/FVC < 0.7) who presented with an exacerbation. They received either co-amoxiclav 500/125 (n=158) or placebo (n=152) three times daily for 8 days. The primary outcome was clinical cure at the end-of-treatment visit (day 9-11). 117/158 patients (74.1%) in the co-amoxiclav group and 91/152 (59.9%) in the placebo group were considered cured [difference = 14.2%; 95% CI 3.7 – 24.3]. Additionally, the median time to the next exacerbation was significantly longer with co-amoxiclav compared to placebo [233 days (interquartile range (IQR) 110 – 365) versus 160 days (IQR 66 – 365); P<0.05]. Therefore, in these patients with mild to moderate COPD who had mild 'ambulatory' exacerbations, co-amoxiclav was more effective than placebo and significantly prolonged the time to the next exacerbation.

Efficacy and safety of aclidinium bromide

Jones *et al*. Efficacy and safety of twice-daily aclidinium bromide in COPD patients: the ATTAIN study.
Eur Respir J 2012;**40**:830-6.
http://dx.doi.org/10.1183/09031936.00225511

This was a 24-week, double-blind, RCT comparing aclidinium (Almirall's new long-acting muscarinic antagonist), 200 or 400 mcg twice-daily versus placebo in patients with moderate to severe COPD. 828 patients were randomised. The primary endpoint was change in trough FEV_1 at week 24. Other endpoints included peak FEV_1, St George's Respiratory Questionnaire (SGRQ), and dyspnoea (Transitional Dyspnoea index, TDI). Both aclidinium groups (200mcg and 400mcg) showed significantly improved trough FEV_1 values [an increase of 99 and 128ml, respectively; both P< 0.001] and peak FEV_1 values [increases of 185 and 209ml, respectively; both P<0.001] versus placebo. Aclidinium 200mcg and 400mcg produced significant improvements in the SGRQ score [-3.8 and -4.6, respectively; both P<0.001] and TDI score [0.6 and 1.0 units, respectively; P<0.05 and P< 0.001]. The incidence of anticholinergic side-effects was low and comparable to placebo. The authors conclude that twice-daily aclidinium significantly improved bronchodilation, health status and dyspnoea in patients with moderate to severe COPD. We await the comparative trials…

COPD patients with airway hyper-responsiveness to mannitol respond well to inhaled steroids

Scherr *et al*. Response to add-on inhaled corticosteroids in COPD based on airway hyperresponsiveness to mannitol.
Chest 2012;**142**:919-26. http://dx.doi.org/10.1378/chest.11-2535

There is increasing interest in different COPD phenotypes and how patients may differ in their response to various treatments. The aim of this double-blind RCT was to determine whether or not airway hyper-responsiveness to mannitol might identify COPD patients who are more likely to respond to add-on inhaled corticosteroids (ICS). 68 patients, all of whom were on regular tiotropium, were randomised to inhaled budesonide 1,600 mcg/day (n=31) or placebo (n=37) in addition to tiotropium, for 3 months. 38 patients had airway hyper-responsiveness to mannitol (17 in the ICS group, 21 in the placebo group). Budesonide was associated with improved quality of life in those patients showing airway hyper-responsiveness to mannitol [difference in SGRQ score over 3 months -9.1; 95% CI -15.8 to -2.3]. In addition, ICS treatment led to a reduction in airway hyper-responsiveness to mannitol [difference in $\log_{10}$ response-dose ratio -0.3; 95% CI -0.6 to -.0.04]. Therefore, in patients with mild to moderate COPD and airway hyper-responsiveness to mannitol, quality of life and airway hyper-responsiveness improved after ICS treatment added to tiotropium. Perhaps not all that surprising, but this study demonstrates yet again the need to tailor treatments to the individual…

Infections

Azithromycin for preventing exacerbations of bronchiectasis

Wong *et al*. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial.
Lancet 2012;**380**:660-7.
http://dx.doi.org/10.1016/S0140-6736(12)60953-2

Once the diagnosis of non-cystic fibrosis bronchiectasis is made by high-resolution CT (HRCT) scan, a key treatment option is antibiotic prophylaxis to reduce the frequency of exacerbations. The macrolide azithromycin has anti-inflammatory and immunomodulatory properties. This randomised controlled trial (RCT) from New Zealand compared azithromycin 500mg three times a week (n = 71) versus placebo (n = 70) in adults who had had at least one exacerbation of HRCT-diagnosed bronchiectasis in the previous year. Treatment allocation was double-blind, and analysis of exacerbation rate was by intention-to-treat. The exacerbation rate was 0.59 per patient in the azithromycin group versus 1.57 per patient in the placebo group over the 6-month trial period [rate ratio 0.38; 95% CI 0.26 – 0.54]. Neither group showed any significant change in pre-bronchodilator FEV_1 or St George's Respiratory Questionnaire scores by the end of the study. Azithromycin is therefore an option for prevention of exacerbations in non-cystic fibrosis bronchiectasis.

Interventions – particularly use of CRP testing – may help reduce antibiotic prescribing for lower respiratory tract infections

Llor *et al*. Interventions to reduce antibiotic prescription for lower respiratory tract infections: Happy Audit study.
Eur Respir J 2012;**40**:436-41.
http://dx.doi.org/10.1183/09031936.00093211

This study shows the effects of an educational intervention and use of C-reactive protein (CRP) testing on Spanish GPs' prescribing of antibiotics for lower respiratory tract infections (LRTIs). The GPs registered all LRTIs (n = 5,385) over two 3-week periods before and after the intervention. GPs in the full-intervention group (n = 210) received educational courses, discussion sessions after the first 3-week period, guidelines, patient information leaflets, and workshops on use of rapid testing including CRP. The partial intervention group (n = 70) received all the interventions except the workshops on rapid testing, and they didn't have access to CRP tests. The control group (n = 58) who were recruited later didn't receive any intervention. Analysis was by multilevel logistic regression. Compared with the control group, the odds ratio for antibiotic prescription after the intervention was 0.42 [95% CI 0.22 – 0.82] for the partial intervention group, and 0.22 [95% CI 0.12 – 0.38] for the full intervention group. Although the authors used a fairly weak study design, these results suggest that an educational intervention may be effective in reducing antibiotic prescribing for LRTIs, particularly when CRP rapid testing is available.

No reduction in the incidence or severity of upper respiratory tract infections (URTIs) following Vitamin D supplementation

Murdoch *et al*. Effect of Vitamin D_3 supplementation on upper

respiratory tract infections in healthy adults. The VIDARIS randomised controlled trial.
JAMA 2012;**308**:1333-9.
http://dx.doi.org/10.1001/jama.2012.12505

Epidemiological studies have shown an association between low serum Vitamin D levels and a variety of respiratory tract infections. However, previous trials of vitamin D supplementation have been inconclusive. In this double-blind placebo-controlled RCT, 322 healthy adults were randomised to vitamin D supplementation (200,000 IU oral Vitamin D_3 initially, 200,000 IU one month later, then 100,000 IU monthly; n=161) or placebo (n=161) for 18 months. The primary endpoint was the number of upper respiratory tract infection (URTI) episodes, and the secondary endpoints were the duration and severity of URTIs and number of days missed from work. The mean [SD] baseline Vitamin D level was 29 [+/-9] ng/ml, and in the Vitamin D supplementation group this increased to >48 ng/ml. There were 593 URTIs in the Vitamin D group [mean 3.7 per person] and 611 in the placebo group [mean 3.7 per person], with no statistically significant difference between the two groups [risk ratio (RR) 0.97; 95% CI 0.85 – 1.11]. Similarly, there was no significant difference for any of the secondary endpoints: in both groups, mean duration of URTI symptoms was 12 days per episode [RR 0.96; 95% CI 0.73 – 1.25], and mean number of days missed from work was 0.76 [RR 1.03; 95% CI 0.81 – 1.30]. These findings were unchanged even when analysed according to season or baseline Vitamin D levels. Therefore, Vitamin D supplementation does not reduce the incidence or severity of URTIs in healthy adults.

Miscellaneous

Resection rates for non-small cell lung cancer in England have increased

Riaz *et al*. Recent trends in resection rates among non-small cell lung cancer patients in England.
Thorax 2012;**67**:811-814.
http://dx.doi.org/10.1136/thoraxjnl-2012-201768

This study reports data from the English Cancer Repository Dataset on 286,217 patients with non-small cell lung cancer diagnosed between 1998 and 2008. Data on surgical resection was extracted from linked hospital Episode Statistics records. The odds ratio [OR] of undergoing surgery was calculated for each 1-year increment by age, sex, socioeconomic deprivation and type of surgery. The proportion of patients undergoing surgery increased from 8.8% in 1998 to 10.6% in 2008. The increase was slightly more pronounced among women [OR 1.02; 95% CI 1.012 – 1.03] than men [OR 1.01; 95% CI 1.01 – 1.02], and as most pronounced with increasing age [75-79 age group: OR 1.05; 95% CI 1.04 – 1.06, versus 85+ age group: OR 1.13; 95% CI 1.07 – 1.19]. Increasing age was also associated with a decreased likelihood of undergoing pneumonectomy [OR 0.88; 95% CI 0.87 – 0.89 per 5-year age increment] or sleeve resection [OR 0.75; 95% CI 0.71 – 0.79] compared with lobectomy. Therefore, resection rates for non-small cell lung cancer have increased in England in recent years, most markedly in older patients.

Nicotine spray is effective in smoking cessation

Tonnesen *et al*. Efficacy of a nicotine mouth spray in smoking cessation: a randomised, double-blind trial.
Eur Respir J 2012;**40**:548-554.
http://dx.doi.org/10.1183/09031936.00155811

The theoretical advantage of a nicotine mouth spray is that it will have a faster uptake of nicotine compared to other forms of nicotine replacement therapy – and therefore faster relief of craving. This is a multicentre double-blind RCT of active nicotine spray (n=318) versus placebo (n=161) for 12 weeks in addition to low-intensity counselling. Self-reported, carbon monoxide-verified abstinence from smoking was assessed at weeks 2, 6, 24 and 52. The active nicotine spray group showed higher abstinence rates than placebo at week 6 [26.1% versus 16.1%; relative success rate (RR) 1.62; 95% CI 1.09 – 2.41], week 24 [15.7% vs. 6.8%; RR 2.30; 95% CI 1.23 – 4.30], and week 52 [13.8% vs. 5.6%; RR 2.48; 95% CI 1.24 – 4.94]. Adverse events (AEs) were mostly mild; 9.1% of the active group withdrew due to AEs compared to 7.5% on placebo. Therefore, nicotine mouth spray delivered significantly higher abstinence rates than placebo. No doubt we will hear more about this way of delivering nicotine replacement therapy…

Plasma fibulin-3 levels: a potential biomarker for pleural mesothelioma

Pass *et al*. Fibulin-3 as a blood and effusion biomarker for pleural mesothelioma.
New Engl J Med 2012;**367**:1417-27
http://www.nejm.org/doi/full/10.1056/NEJMoa1115050

Fibulin-3 is one of a group of extracellular proteins expressed in the basement membranes of blood vessels. In this potentially ground-breaking study, these authors have assessed its role as a possible biomarker for mesothelioma. Mesothelioma can occur decades after asbestos exposure and is often diagnosed late: the median survival is 12 months post-diagnosis. Therefore, any biomarker which can facilitate early diagnosis could be extremely valuable. Plasma fibulin-3 levels were measured in patients with mesothelioma (n=92), effusion not due to mesothelioma (n=93), asbestos-exposed subjects without cancer (n=136), and 43 healthy controls. Fibulin-3 levels were also measured in the effusion fluid of 74 mesothelioma patients, 39 patients with benign effusions, and 54 with malignant effusions not due to mesothelioma. In two different cohorts of patients (from Detroit and New York), plasma fibulin-3 levels were significantly higher in patients with mesothelioma than in asbestos-exposed subjects without mesothelioma [105+/-7 and 113+/-8 ng/ml, versus 14+/-1 and 24+/-1 ng/ml, respectively; P<0.001]. Effusion fibulin-3 levels were also significantly higher in mesothelioma vs. non-mesothelioma patients [694+/-37 and 636+/-92 ng/ml vs. 212+/-25 and 151+/-23 ng/ml, respectively; P<0.001]. In addition, fibulin-3 preferentially stained mesothelioma tumour cells in 26 out of 26 samples. More research is needed, but it looks as though plasma fibulin-3 levels can distinguish mesothelioma from previous benign asbestos exposure, and that effusion fibulin-3 levels can differentiate mesothelioma effusions from other malignant and benign effusions.

Using the Wells score plus D-dimer testing (almost) excludes pulmonary embolism in primary care

Geersing *et al*. Safe exclusion of pulmonary embolism using the Wells rule and qualitative D-dimer testing in primary care: prospective cohort study.
BMJ 2012;**345**:e6564. http://dx.doi.org/10.1136/bmj.e6564

This is a prospective cohort validation study to assess whether or not the Wells score for pulmonary embolism (PE) – a 7-point yes/no clinical scoring system used to assess the likelihood of PE, see http://www.mdcalc.com/wells-criteria-for-pulmonary-embolism-pe/ – combined with a point-of-care D-dimer test can safely exclude PE in primary care. In three different regions of the Netherlands, 598 adults with suspected PE were all referred to secondary care after having a D-dimer test and their Wells score calculated. PE was diagnosed by the usual reference standards including spiral CT scanning and 3-month follow-up. PE was confirmed in 73 patients (12.2%). Using a Wells score of ≤4 and a negative D-dimer test to define low risk, 272 patients (45.5%) were classified as low risk – but 4 of these were subsequently shown to have a PE [false negative rate 1.5%; 95% CI 0.4 – 3.7]. The sensitivity and specificity of this combined Wells score/D-dimer approach was 94.5% [95% CI 86.6 – 98.5] and 51.0% [95% CI 46.7 – 55.4], respectively. The authors conclude that a Wells score ≤4 and a negative D-dimer test safely and efficiently excludes PE in primary care – though if these patients are not to be admitted to hospital this seems a little optimistic given a false negative rate of 1.5% for a condition which can be fatal…