Prim Care Respir J 2012; **21**(2): 233-237

Primary Care RESPIRATORY JOURNAL
www.thepcrj.org

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Asthma

Treatment for asymptomatic gastro-oesophageal reflux (GOR) does not improve asthma control in children

Writing Committee for the American Lung Association Asthma Clinical Research Centers. Lansoprazole for children with poorly controlled asthma: a randomised controlled trial.
JAMA 2012;**307**(4):373-80.
http://dx.doi.org/10.1001/jama.2011.2035

Given that asymptomatic GOR has been postulated to be a cause of poor asthma control in children, this is an important negative study. It was a 24-week randomised placebo-controlled trial of lansoprazole (n = 149) versus placebo (n = 157) in 306 children with poorly controlled asthma (mean age 11 years [SD 3 yrs]) receiving inhaled steroid treatment. The primary outcome measure was change in Asthma Control Questionnaire (ACQ); secondary measures were lung function, quality of life, and episodes of poor control. Mean difference in change in the ACQ score (lansoprazole minus placebo) was 0.2 units [95% CI; 0.0 - 0.3 units] (a 0.5-unit change is the minimal clinically important difference) and there were no statistically significant changes in the secondary outcome measures. In fact, the intervention group had more respiratory infections than controls (relative risk 1.3: 95% CI; 1.1-1.6). Therefore, addition of lansoprazole in children with asymptomatic GOR improved neither symptoms nor lung function but was associated with increased adverse events…

Mometasone furoate and formoterol in a combination inhaler

Meltzer *et al*. Mometasone furoate/formoterol reduces asthma deteriorations and improves lung function.
Eur Respir J 2012;**39**:279-89.
http://dx.doi.org/10.1183/09031936.00020310

This Phase III, 26-week, multicentre, double-blind, placebo-controlled study assessed the effect of the mometasone furoate (MF)/formoterol (F) combination inhaler on asthma deteriorations, lung function and asthma control versus its individually administered components. 746 poorly-controlled asthma patients were randomised equally to receive twice-daily placebo, MF/F 100/10 mcg, F 10mcg, or MF 100mcg. Primary endpoints were time to first asthma deterioration (to assess effect of MF) and change in FEV_1 area under the curve (AUC) over 12 hours post morning dose (to assess effect of F). Secondary endpoints included quality of life measured by ACQ. Discontinuation rate was 28%, mostly in the placebo and F groups. There was a delay in time to first asthma deterioration with MF/F versus F ($P<0.001$) and also with MF/F versus MF ($P=0.006$). FEV_1 AUC measurements were significantly better with MF/F versus MF ($P=0.001$). MF/F treatment produced statistically and clinically significant (0.5-unit change) improvements in ACQ score compared with placebo. Therefore, the MF/F combination inhaler has greater efficacy than its individual components, and both MF and F contribute to its efficacy.

Using nitric oxide or sputum eosinophils to tailor asthma treatment: is it better than traditional methods?

Petsky *et al*. A systematic review and meta-analysis: tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils).
Thorax 2012;**67**:199-208.
http://dx.doi.org/10.1136/thx.2010.135574

This systematic review evaluated the efficacy of tailoring asthma treatment based on inflammatory markers (sputum analysis or fractional exhaled nitric oxide [FeNO]) versus treatment tailored according to symptoms +/- peak flow or spirometry. Cochrane reviews, Cochrane-registered trials, MEDLINE, EMBASE, and reference lists of articles were searched. RCTs comparing asthma treatment based on FeNO or sputum analysis versus treatment based on symptoms/lung function measurement were assessed. Six studies on FeNO and three on sputum eosinophils met the inclusion criteria. Definitions of asthma exacerbations, length of study, and treatment change cut-off levels for both FeNO and sputum eosinophils varied between studies. Adults who had treatment adjusted according to sputum eosinophils had fewer exacerbations than controls ($P = 0.0006$), but there was no between-group difference for FeNO versus controls. The authors conclude that tailoring treatment based on sputum eosinophil counts is effective in reducing exacerbations but tailoring treatment according to FeNO is not – but also state that currently there is insufficient justification to use either…So we stick to traditional management for now.

Up to 50% of patients with mild asthma have non-eosinophilic disease…

McGrath *et al*. A large subgroup of mild-to-moderate asthma is persistently noneosinophilic.
Am J Resp Crit Care Med 2012;**185**:612-19
http://dx.doi.org/10.1164/rccm.201109-1640OC

Even though airway eosinophilia is typical of asthma, it is absent in a subgroup of patients; the size of this subgroup is uncertain because previous studies have been unable to differentiate between intermittent and persistent airway eosinophilia (or no eosinophilia) because of infrequent/irregular sputum analyses. These authors analysed sputum cytology data from 995 subjects enrolled in US Asthma Clinical Research Network trials who had undergone repeated sputum cytology analysis together with assessment of response to standard asthma treatments. In cross-sectional analyses, sputum eosinophilia

(≥2% eosinophils) was found in 36% of asthma patients not on treatment with inhaled corticosteroid (ICS) and in 17% of ICS-treated patients. In those not taking ICS, 22% had sputum eosinophilia on every occasion ('persistent eosinophilia'), 31% had eosinophilia on at least one occasion ('intermittent eosinophilia'), and 47% had no eosinophilia on every occasion ('persistent non-eosinophilia'). So up to a half of patients with mild asthma (not on ICS treatment) have persistent non-eosinophilic disease – a subgroup that typically responds poorly to anti-inflammatory treatment…

New European guidelines for managing work-related asthma

Baur *et al*. Guidelines for the management of work-related asthma.
Eur Respir J 2012;**39**:529-45.
http://dx.doi.org/10.1183/09031936.00096111

Work-related asthma includes both occupational asthma and work-aggravated asthma. Occupational asthma is caused by specific workplace agents producing either IgE-mediated asthma, irritant asthma (including reactive airways dysfunction syndrome [RADS]), or asthma by (as yet) unknown pathophysiological mechanisms. Work-aggravated asthma is exacerbation of pre-existing asthma. These new European Respiratory Society (ERS) Guidelines involved a systematic literature review of 1,329 papers graded according to SIGN criteria, and formulation of statements according to the Royal College of GPs (RCGP) 3-star system. They highlight the need for a comprehensive diagnostic approach, early recognition and diagnosis, and a medical screening and surveillance programme for at-risk workers. They emphasise that the main form of treatment is eliminating exposure to the causative agent since this leads to the best health outcomes – but if this is not possible then reduction of exposure is the next best option. Respirators are of limited value in reducing allergen or irritant load. Eliminating exposure in the first place is the best primary prevention approach.

Has mannitol a role in the management of severe asthma in primary care?

Lipworth *et al*. A randomised primary care trial of steroid titration against mannitol in persistent asthma. STAMINA trial.
Chest 2012;**141**:599-606.
http://dx.doi.org/10.1378/chest.11-1748

This RCT in patients with persistent asthma compared titration of ICS dose according to airway hyperresponsiveness (AHR – measured by the provocative dose of mannitol causing a 10% fall in FEV_1 [PD10]) (AHR group, n=61), versus titration according to symptoms, reliever use and lung function (controls, n=58). Time to first mild exacerbation was not significantly different between the two groups (hazard ratio 1.29, 95% CI 0.72 - 2.31, P=0.40). Though there were 27% fewer mild exacerbations in the AHR group (84 vs 115, P=0.03), the number of severe exacerbations was the same. There were no other significant differences between the two groups, except that titration against mannitol PD10 led to a higher ICS dose: the final mean daily ciclesonide dose was higher in the AHR group (514mcg vs 208mcg, P=0.0001) with no increased suppression of overnight urinary cortisol. The authors conclude that mannitol challenge was well tolerated in a primary care setting, and that use of mannitol to measure AHR resulted in a higher ICS dose with equivocal effects on exacerbations and no adrenal suppression. However, the benefits of a mannitol/AHR strategy seem small given the extra work involved…

Mobile phone monitoring of asthma is not cost-effective

Ryan *et al*. Clinical and cost effectiveness of mobile phone supported self-monitoring of asthma: multicentre randomised controlled trial.
BMJ 2012;**344**:e1756.
http://dx.doi.org/10.1136/bmj.e1756

This UK multicentre randomised controlled trial (RCT) of mobile phone monitoring versus standard monitoring in poorly-controlled adolescent and adult asthma patients is an important negative study. The mobile phone group (n = 139) intervention was twice-daily recording and mobile phone-based transmission of symptoms, drug use and peak flow with immediate feedback and action according to an agreed plan. The control group (n = 139) had standard paper-based monitoring. Importantly, both groups had BTS/SIGN guideline-standard care. The main outcomes were changes in Asthma Control Questionnaire (ACQ) scores and self-efficacy scores (using the KASE-AQ questionnaire) at six months, together with a cost-effectiveness analysis. There was an improvement in ACQ scores in both groups with no significant difference between the two [mobile phone group mean change 0.75 versus 0.73 in the paper-based group; mean difference in change –0.02 (95% CI –0.23 – 0.19)]. Similarly, there was no difference in change in KASE-AQ scores [mean change –4.4 versus –2.4; mean difference 2.0 (95% CI –0.3 – 4.2)]. Numbers of acute exacerbations, steroid courses, and unscheduled consultations were similar in both groups, with similar healthcare costs. Therefore, guideline-driven care led to improvements in both groups, and mobile phone monitoring did not have any appreciable benefits over standard care and was thus not cost-effective.

Allergy

Atopy and fever in infancy are risk factors for persistent asthma and wheeze

Kusel *et al*. Febrile respiratory illnesses in infancy and atopy are risk factors for persistent asthma and wheeze.
Eur Respir J 2012;**39**:876-82.
http://dx.doi.org/10.1183/09031936.00193310

The aim of this prospective cohort study was to investigate associations between severe respiratory infections and atopy in early childhood with wheeze and asthma persisting into later childhood. In 147 children at high risk of atopy, data were collected on respiratory infections in infancy and their viral aetiology, history of wheeze, and doctor-diagnosed eczema or asthma until age 10. Skin-prick testing was performed at age 6 months, and then at age 2 and 5 years. At age 10, 60% were atopic, 25.9% had current eczema, 18.4% current asthma, and 20.4% had persistent wheeze. 35.8% had experienced at least one lower respiratory tract infection (LRTI) associated with fever and/or wheeze in their first year of life. Children who had LRTI complicated by wheeze and (particularly) fever and who were atopic by the age of 2, were significantly more likely to have persistent wheeze [relative risk (RR) 3.51; 95% CI 1.83 – 6.70; P<0.001] and current asthma [RR 4.92; 95% CI 2.59 – 9.36; P<0.001] at age 10. The authors conclude that severe viral LRTIs in infancy and early atopy are risk factors for persistent wheeze and asthma, and that fever is the strongest marker of the potential for asthma following early LRTIs.

COPD

Do Vitamin D levels affect COPD exacerbation rates?

Kinisaki *et al*. Vitamin D levels and risk of acute exacerbations of chromic obstructive pulmonary disease. A prospective cohort study
Am J Resp Crit Care Med 2012;**185**:286-90.
http://dx.doi.org/10.1164/rccm.201109-1644OC

Since low levels of 25-hydroxyvitamin D [25(OH)D] are associated with an increased risk of respiratory infections, might low levels also predispose to an increased risk of COPD exacerbation? The answer is no, according to this 1-year US study of azithromycin and its effect on acute exacerbations of COPD (AECOPD). 973 patients with severe COPD (mean FEV_1 1.12L; 40% predicted) had plasma 25(OH)D levels measured at baseline and subsequently throughout the study period. The primary outcome was time to first AECOPD; secondary outcome was COPD exacerbation rate. A third (33.1%) of the patients had Vitamin D insufficiency (between 20 and 30 ng/ml), a third (32%) had Vitamin D deficiency (< 20 ng/ml), and 8.4% had severe Vitamin D deficiency (<10ng/ml). Baseline 25(OH)D levels were not related to time to first AECOPD or COPD exacerbation rates. An interesting idea – but a negative study.

Tiotropium improves walking capacity

Bedard *et al*. Tiotropium improves walking endurance in COPD.
Eur Respir J 2012;**39**:265-71.
http://dx.doi.org/10.1183/09031936.00059511

Well-conducted randomised controlled trials (RCTs) using constant-load cycling endurance tests have shown that long-acting bronchodilators like tiotropium improve exercise tolerance in COPD. These authors argue that the endurance shuttle walk test (ESWT) is better at assessing functional status than cycling tests and the 6-minute walking test. [See http://dx.doi.org/10.4104/pcrj.2011.00031 for a recent review of methods for measuring functional status in COPD]. In this double-blind, placebo-controlled parallel-group 3-week study, they randomised 36 COPD patients to receive either tiotropium 18 mcg once daily or placebo. Pre-dose (trough) and 2-hour post-dose pulmonary function was measured and the ESWT completed, at baseline and three weeks later. At 3 weeks, walking endurance time for the tiotropium group was significantly improved, with a mean [SD] between-group difference of 128 [141] secs (P = 0.017). Lung parameters such as trough and post-dose FEV_1 and FVC values, ventilation and tidal volume, were also significantly improved. As expected, tiotropium significantly improves walking capacity in COPD patients after three weeks…

What stops primary care providers following COPD guidelines?

Perez *et al*. Barriers to adherence to COPD guidelines among primary care providers.
Resp Med 2012;**106**:374-81.
http://dx.doi.org/10.1016/j.rmed.2011.09.010

How to implement guideline recommendations successfully is the $64,000 question in clinical medicine. If we can understand the barriers to adoption, perhaps we can circumvent them? These authors surveyed 154 clinicians in two general medical practices in New York City to assess barriers to GOLD guideline implementation. They were particularly interested in issues such as familiarity with the guidelines, disagreement, perceptions of poor benefit and efficacy, and time constraints. Adherence to guideline recommendations was best as regards influenza vaccination and smoking cessation, intermediate as regards prescribing of inhaled steroids and long-acting bronchodilators, and poor as regards referral for pulmonary rehabilitation and using FEV_1 to guide management. Low familiarity, low perceptions of efficacy, and time constraints were significantly associated with non-adherence to > 2 recommendations. No real surprises then…

COPD self-management is generally ineffective, but may have a role in younger patients who have social support

Bucknall *et al*. Glasgow supported self-management trial (GSuST) for patients with moderate to severe COPD: a randomised controlled trial
BMJ 2012;**344**:e1060. http://dx.doi.org/10.1136/bmj.e1060

This RCT compared supported COPD self-management (patients trained in recognising and treating increased symptoms with prednisolone, antibiotics or both, with ongoing nurse support for 12 months; n=232) versus usual care (n=232) in 464 patients admitted to hospital with a COPD exacerbation. Randomisation was stratified by age, sex, FEV_1 % predicted, recent pulmonary rehabilitation, smoking status, deprivation and previous COPD admissions. The primary outcome was hospital readmission or death due to COPD. There was no difference between the two groups: 111 readmissions or deaths in the supported self-management group (48%) versus 108 in the usual care group (47%); hazard ratio 1.05; 95% CI 0.80 – 1.38. However, at the study end, half the remaining self-management group (75/150) had self-managed appropriately. Using exploratory subgroup analysis, on stepwise regression the factors predicting successful self-management were younger age (P=0.012) and living with others (P=0.010). Successful self-managers exhibited reduced COPD readmissions/deaths compared with unsuccessful self-managers: 20/75 (27%) versus 51/105 (49%); hazard ratio 0.44; 95% CI 0.25 – 0.76; P=0.0003. So COPD self-management was ineffective in reducing hospital admissions and mortality – except perhaps in a select group of younger patients who have social support.

Aclidinium bromide – a new long-acting muscarinic antagonist

Fuhr *et al*. Efficacy of aclidinium bromide 400mcg twice daily compared with placebo and tiotropium in patients with moderate to severe COPD.
Chest 2012;**141**:745-52. http://dx.doi.org/10.1378/chest.11-0406

This phase IIa randomised double-blind, double-dummy, crossover trial assessed the efficacy and safety of Almirall's new long-acting muscarinic antagonist (LAMA) aclidinium bromide. 27 patients with moderate to severe COPD received aclidinium 400mcg twice-daily (bd), tiotropium 8mcg once-daily, and placebo, each for 15 days, with a 9- to 15-day washout period in between. The primary endpoint was mean change from baseline in FEV_1 area under the curve (AUC) for various time periods on day 15. Secondary endpoints included other AUC values as well as morning pre-dose FEV_1, peak FEV_1, and COPD symptom scores. Mean change from baseline in FEV_1 $AU_{C0\text{-}12/12h}$ at day 15 was significantly greater for aclidinium and tiotropium over placebo (P<0.0001). Mean changes from baseline in secondary endpoints were significantly greater for aclidinium and tiotropium versus placebo (P values all < 0.001). COPD symptoms were significantly improved from baseline with aclidinium versus placebo (P<0.05) but not with tiotropium. The authors conclude that aclidinium 400mcg bd provided clinically meaningful improvements in 24-hour bronchodilation comparable to tiotropium but with a significant difference in favour of aclidinium overnight. Further phase IIb and III studies will no doubt follow…

Outcomes for COPD patients hospitalised with community-acquired pneumonia

Liapikou *et al*. Severity and outcomes of hospitalised community-acquired pneumonia in COPD patients.
Eur Respir J 2012;**39**:855-61.
http://dx.doi.org/10.1183/09031936.00067111

This was a prospective case-control study of 1,379 patients (212 with spirometrically-confirmed COPD and 1,167 without COPD) who were hospitalised with community-acquired pneumonia (CAP) over a 4-year period. The aim was to assess the impact of COPD on CAP outcomes. COPD patients (mean FEV_1 47.7 +/- 16.3% predicted) were older and more likely to have received antibiotics prior to admission [37.1% versus 28.3%; P<0.01] than non-COPD patients, and had more severe respiratory failure and more severe pneumonia [pneumonia severity index 118.3 vs. 108.5; P<0.001]. However, COPD patients had less multi-lobar infiltration [44 (21%) vs. 241 (24%); P<0.01] and fewer pulmonary complications [24 (14%) vs. 241 (24%); P<0.01] than non-COPD patients. There was no significant difference in 30-day mortality between the two groups [9 COPD deaths (4.3%) vs. 81 (7.0%) non-COPD deaths; P = 0.14], but this may have been due to the study being under-powered for mortality outcomes. The authors conclude that COPD patients with CAP had similar mortality rates to non-COPD CAP patients, and that this may be due to increased use of pre-hospital antibiotics and a reduced incidence of pulmonary complications…

Ischaemic heart disease and its impact on COPD

Patel *et al*. The impact of ischemic heart disease on symptoms, health status, and exacerbations in patients with COPD.
Chest 2012;**141**:851-7. http://dx.doi.org/10.1378/chest.11-0853

Given that both conditions have cigarette smoking as their major aetiology, it's not surprising that COPD patients often have co-morbid ischaemic heart disease (IHD). But the impact of IHD on COPD needs to be elucidated further. The authors collected stable-state data on health status (St George's Respiratory Questionnaire, SGRQ) and symptoms (MRC dyspnoea score) in 386 patients from the London COPD Cohort between 1995 and 2009, and then prospectively collected exacerbation data. Patients with IHD (n = 64, 16.6%) had significantly worse health status [SGRQ score 56.9+/-18.5 versus 49.1+/-10.0; P = 0.003] and more severe breathlessness [MRC score 4-5 in 50.9% vs. 35.1%; P = 0.029] than COPD patients without IHD. COPD patients with IHD also had lower exercise capacity [6-minute walking distance 225+/-89 m vs. 317+/-85 m; P = 0.002]. There was no difference in the rate of COPD exacerbations between the two groups [median 1.95 (IQR 1.20-

3.12) vs. 1.86 (IQR 0.75-3.96) per year; P = 0.294], but exacerbations were longer in those patients with co-morbid IHD [symptom recovery time 17.0 days (IQR 9.8-24.2) vs. 12.0 days (IQR 8.0-18.0; P = 0.009]. Therefore, in COPD patients, co-morbid IHD is associated with worse health status, lower exercise capacity, more breathlessness and longer exacerbations – albeit that the rate of exacerbations remains the same.

The genetics of COPD: reduced small airway expression of pentraxin-3

Van Pottelburge *et al*. COPD is associated with reduced pulmonary interstitial expression of pentraxin-3.
Eur Respir J 2012;**39**:830-8.
http://dx.doi.org/10.1183/09031936.00138110

Pentraxin-3 (PTX3) is a protein involved in antimicrobial defence, apoptic cell clearance and extracellular matrix stability. Given that these processes are altered in COPD, these authors aimed to investigate the genetic expression of PTX3 in COPD versus non-COPD patients. PTX3 expression was quantified using immunohistochemical staining of lung biopsy samples from never-smokers, smokers without COPD, and COPD patients. mRNA expression in total lung tissue was assayed by polymerase chain reaction (PCR) techniques, and PTX3 concentration was measured in induced sputum and plasma by ELISA. PTX3 was mainly localised in the interstitium of small airways and alveolar walls, and its expression in small airways correlated significantly with FEV_1 [r = 0.35; P=0.004]. In the alveolar walls, PTX3 expression correlated significantly with carbon monoxide (CO) transfer coefficient [r = 0.28; P = 0.04]. Systemic levels of PTX3 tended to be lower in severe COPD versus mild COPD. Therefore, in COPD, more severe airflow obstruction (lower FEV_1) and reduced CO transfer coefficient are associated with lower pulmonary interstitial expression of PTX3.

Infections

Management of paediatric pneumonia by community health workers in Pakistan

Soofi *et al*. Effectiveness of community case management of severe pneumonia with oral amoxicillin in children aged 2-59 months in Matiari district, rural Pakistan: a cluster-randomised controlled.
Lancet 2012;**379**:729-37.
http://dx.doi.org/10.1016/S0140-6736(11)61714-5

This was a cluster-randomised controlled trial of management of severe pneumonia in children aged < 5 yrs by community health workers (CHWs) in the Matiari rural district of Pakistan. Rural areas usually have higher morbidity and mortality from childhood pneumonia due to problems with hospital referral. Children in 18 matched and randomly allocated clusters (cluster unit was 'union councils', the smallest district unit) were randomised to either oral amoxicillin 90mg/kg/day for 5 days at home (intervention arm, n = 2341) or a single dose of co-trimoxazole plus hospital referral and i.v. antibiotics according to government policy (controls, n = 2069) following screening and diagnosis of severe pneumonia by CHWs. The primary outcome was treatment failure (lack of clinical improvement) at day 6. There were 187 treatment failures (8.0%) in the intervention group and 273 failures (13.0%) in the control group. After adjustment for clustering, the risk difference for treatment failure was -5.2% [95% CI; -13.7% - 3.3%]. Therefore, non-medical CHWs could be a key component of community detection and management strategies for childhood pneumonia in countries where hospital referral is difficult.

Quarterly Vitamin D supplementation does not reduce pneumonia incidence in high-risk infants

Manaseki-Holland *et al*. Effect on the incidence of pneumonia of vitamin D supplementation by quarterly bolus dose to infants in Kabul: a randomised controlled superiority trial.
Lancet 2012;**379**:1419-27
http://dx.doi.org/10.1016/S0140-6736(11)61650-4

This is another important negative study. Given its role in regulating immune function, Vitamin D deficiency has been suggested as a risk factor for childhood pneumonia. This large RCT compared 100,000 IU (2.5mg) oral vitamin D3 (n = 1524) versus placebo (n = 1522) given every three months for 18 months in children aged 1-11 months in Kabul, Afghanistan. The primary outcome was the first or only episode of radiologically-confirmed pneumonia. Analysis was by intention-to-treat. There was no significant difference in pneumonia incidence between the vitamin D3 group [0.15 per child per year; 95% CI 0.13 – 0.16] and the placebo group [0.14; 95% CI 0.12 – 0.16]. The incidence rate ratio was 1.06 [95% CI 0.89 – 1.27]. Therefore, quarterly oral vitamin D3 supplementation in infants does not reduce the incidence of pneumonia – at least in this setting…

An increased risk of TB in pregnancy?

Zenner *et al*. Risk of tuberculosis in pregnancy: a national primary care-based cohort and self-controlled case series study.
Am J Resp Crit Care Med 2012;**185**:779-84.
http://dx.doi.org/10.1164/rccm.201106-1083OC

This UK cohort study had two aims: to analyse the epidemiology of TB in pregnancy, and to assess whether pregnancy is an independent risk factor for TB. All women who became pregnant between 1996 and 2008 were enrolled using the General Practice Research Database. Incidence rates and incidence rate ratios (IRRs) of TB diagnoses during three time periods – pregnancy, 6-month postpartum, and outside pregnancy – were calculated and compared using a Poisson regression analysis. A nested self-controlled case series compared TB risk in the time periods, adjusting for individual and time-bound confounders. The crude TB rate for the combined pregnancy/postpartum period (15.4 per 100,000 person-years) was significantly higher than outside of pregnancy (9.1 per 100,000 person-years; P = 0.02). The adjusted TB risk was higher postpartum than outside pregnancy [IRR 1.95; 95% CI 1.24 – 3.07], whereas risk during pregnancy was not significantly increased [IRR 1.29; 95% CI 0.82 – 2.03]. Therefore, the incidence of TB diagnosis is significantly increased postpartum. The authors postulate that this might still reflect an increased risk of TB in pregnancy which only manifests as a diagnosis postpartum due to diagnostic delay. They call for targeted TB screening of high-risk women during and after pregnancy.

Sleep disorders

The impact of CPAP on cardiovascular remodelling in patients with obstructive sleep apnoea

Colish *et al*. Obstructive Sleep Apnoea. Effects of continuous positive airway pressure on cardiac remodelling as assessed by cardiac biomarkers, echocardiography, and cardiac MRI.
Chest 2012;**141**:674-81. http://dx.doi.org/10.1378/chest.11-0615

Obstructive sleep apnoea (OSA) is associated with increased cardiovascular morbidity and mortality. Previous echocardiography studies have shown short-term improvements in cardiac remodelling in patients with OSA receiving continuous positive airway pressure (CPAP) therapy. This is a prospective case series of 47 patients with OSA who received CPAP for one year. Cardiac biomarkers including C-reactive protein (CRP), N-terminal pro-B-type natriuretic peptide (NT-proBNP) and troponin T (TNT) were measured at baseline and serially over the year. Baseline and serial echocardiography and cardiac MRI were performed. After three months, echocardiography showed improvements in right ventricular end-diastolic diameter, left and right atrial volume indices, and pulmonary hypertension, and these improvements continued throughout the year. CRP, NT-proBNP and TNT levels did not change significantly from normal baseline values. Left ventricular mass as shown by cardiac MRI scanning decreased from 159 +/- 12 g/m^2 to 141 +/- 8 g/m^2. This study suggests that systolic and diastolic abnormalities in OSA patients can be reversed as early as three months into CPAP therapy, and that there is progressive cardiovascular remodelling. Therefore, we should continue to make every effort to diagnose OSA and treat with CPAP appropriately.

Fibrotic lung disease

Pulmonary rehabilitation for interstitial lung disease

Holland *et al*. Predictors of benefit following pulmonary rehabilitation for interstitial lung disease.
Resp Med 2012;**106**:429-35.
http://dx.doi.org/10.1016/j.rmed.2011.11.014

Pulmonary rehabilitation (PR) has been shown to improve functional capacity and symptoms in interstitial lung diseases (ILDs), but response varies. Here, 54 patients (25 with idiopathic pulmonary fibrosis, IPF) had eight weeks of PR, and the relationship between aetiology, markers of disease severity, and response to PR were assessed immediately after PR and at 6 months. In IPF, greatest improvement as shown by improvement in 6-minute walking distance (6MWD) was associated with milder disease (larger FVC, less exercise-induced oxyhaemoglobin desaturation and lower right ventricular systolic pressure). With other ILDs there was no relationship between 6MWD and any of the baseline variables. More severe baseline dyspnoea and non-IPF diagnosis predicted greater improvement in dyspnoea at 6-month follow-up. The authors conclude that patients with IPF attain greatest benefit from PR when they have mild disease, whereas patients with other ILDs achieve benefits regardless of severity. In IPF, early referral to PR should be considered.

Miscellaneous

Smoking cessation in pregnancy: we've got a lot to do…

Coleman *et al*. A randomised trial of nicotine-replacement therapy patches in pregnancy.
NEJM 2012;**366**:808-18.
http://www.nejm.org/doi/full/10.1056/NEJMoa1109582

Nicotine-replacement therapy is now widely recommended for smoking cessation but there is little evidence regarding its use in pregnancy. This is a negative study, the interpretation of which is limited by poor compliance – an 8-week randomised controlled trial (RCT) of active nicotine patches (n=521) versus placebo patches (n=529) in 1050 women aged 16-50 who were 12-24 weeks gestation. Both groups received behavioural cessation support prior to randomisation. The primary outcome was abstinence from smoking until delivery as assessed by exhaled carbon monoxide or salivary cotinine. There was no significant difference in abstinence rate between the nicotine-replacement and placebo groups: 9.4% versus 7.6%, respectively (odds ratio (OR) 1.26; 95% CI 0.82 – 1.96). However, only 7.2% in the nicotine-replacement group and 2.8% in the control group used patches for more than one month. Rates of adverse pregnancy and birth outcomes were similar in both groups. Conclusion? We clearly have more work to do to try and engage with pregnant women who smoke…

CT screening for lung cancer increases pick-up of early disease

Saghir *et al*. CT screening for lung cancer brings forward early disease. The randomised Danish Lung Cancer Screening Trial: status after five annual screening rounds with low-dose CT.
Thorax 2012;**67**:296-301.
http://dx.doi.org/10.1136/thoraxjnl-2011-200736

This is the 5-year report on the Danish Lung Cancer Screening Trial. 4104 healthy heavy smokers or former smokers were randomised to five annual low-dose CT screenings versus no screening (usual care). Nodules 5-15mm diameter were rescanned after 3 months, and nodules increasing in size (>25% volume increase and/or volume doubling time < 400 days) or nodules > 15mm diameter were referred for diagnostic work-up. Participation rates were high in both groups (screening 95.5%, control 93.1%, P<0.001). More lung cancers were diagnosed in the screening group (69 vs 24, P<0.001) but most were low stage (48 vs 21 stage I – IIB non-small cell and limited stage small cell lung cancer, P=0.002). Pick-up rates of high-stage lung cancer were the same in both groups (21 vs 16 stage IIIA – IV non-small cell and extensive stage small cell lung cancer, P=0.509). 61 patients died in the screening group and 42 in the control group (P=0.059), with 15 and 11 dying of lung cancer, respectively (P=0.428). Therefore, CT screening increases the diagnostic pick-up of early lung cancer, but at this stage no reduction in mortality has been observed.

Rivaroxaban: an oral factor Xa inhibitor to treat pulmonary embolism

The EINSTEIN-PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism.
NEJM 2012;**366**:1287-97.
http://www.nejm.org/doi/full/10.1056/NEJMoa1113572

Anti-coagulant treatment with warfarin carries an increased risk of bleeding and can be a real inconvenience for patients particularly if they need frequent blood test monitoring. This was a randomised open-label non-inferiority trial comparing rivaroxaban (a factor Xa inhibitor without the need for laboratory monitoring; 15mg twice daily for 3 weeks followed by 20mg once daily) versus standard therapy (enoxaparin followed by a vitamin K antagonist) for 3, 6, or 12 months. 4832 patients with acute symptomatic pulmonary embolism with or without deep vein thrombosis were recruited. The primary outcome was symptomatic recurrent venous thromboembolism (VTE), and the principal safety outcome was major or clinically relevant bleeding. Rivaroxaban was non-inferior to standard therapy, with 50 VTE events in the rivaroxaban group (2.1%) versus 44 in the standard therapy group [hazard ratio 1.12; 95% CI 0.75 – 1.68]. Major bleeding was observed in 26 rivaroxaban patients (1.1%) versus 52 standard therapy patients (2.2%) [hazard ratio 0.49; 95% CI 0.31 – 0.79]. Rivaroxaban's non-inferior efficacy was confirmed, and its safety profile was shown to be better than standard therapy. Potentially a major advance for patients…

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