Welcome to this edition of the APSR Respiratory Research Review and thank you for the feedback.

This edition of the APSR Respiratory Research Review may help you to negotiate the seven sins of COPD care: Sloth, as in therapeutic minimalism in the light of airway therapy and smoking cessation therapy; Gluttony, in the form of wasteful overprescribing of antibiotics; Pride, as expressed by the unmet hope to have found the magic bullet of inhaler therapy; Lust, as in wanting to ‘cure’ all aspects of COPD – both systemically and pulmonary, before clinical data are available and Envy, when seeing the 25% reduction in COPD exacerbation rate in China at a cost of $US90 per year.

Kind regards,
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Varenicline versus transdermal nicotine patch for smoking cessation

Authors: Aubin H-J et al

Summary: The efficacy of varenicline for smoking cessation was compared with nicotine replacement therapy (NRT) in this study. Participants were randomised to receive 12 weeks’ treatment with varenicline uptitrated to 1mg twice daily (n = 376) or 10 weeks’ treatment with transdermal NRT 21 mg/day decreased to 7 mg/day (370), and followed for 52 weeks after treatment. The self-reported continued abstinence rate for the last 4 weeks of treatment (primary outcome measure) was significantly greater for varenicline recipients than it was for NRT recipients (55.9% vs. 43.2%; OR 1.70; 95% CI 1.26, 2.28, p<0.001), although the difference at 52 weeks’ follow up was not significant (26.1% vs. 20.3%; 1.30; 0.99, 1.79; p = 0.056). Cravings, withdrawal symptoms and smoking satisfaction were all significantly reduced with varenicline compared with NRT (p<0.001 for all three comparisons)

Comment: This trial was conducted in 24 centres throughout Europe and USA. Participants were offered 10-minute counselling, telephone follow-up and randomised to treatment groups receiving either NRT or varenicline. At three months, 53.6% of the varenicline and 43.1% of the NRT group were smoke free. Even with therapy and in centres of excellence, only 26% of the varenicline and 20% of the NRT group remained smoke-free at 1 year. The accompanying editorial reminds us that around two thirds of patients will resume smoking again within 2 years, as smoking is a behaviour largely explained by addiction. We have a long way to go with smoking cessation therapies, but we can now add varenicline to our pharmacological weaponry of bupropion, nortriptyline and NRT.

http://thorax.bmj.com/cgi/content/abstract/63/8/717
Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of COPD

Authors: Aaron SD et al

Summary: The addition of salmeterol (SAL) and salmeterol plus fluticasone propionate (SFC) to tiotropium bromide (TIO) to improve outcomes in COPD was explored in this RCT. Participants (n = 449) received 1 year of treatment with TIO + placebo, TIO + SAL or TIO + SFC. There was no significant difference between the proportion of TIO + placebo recipients and TIO + SAL or TIO + SFC recipients who experienced an exacerbation of COPD requiring systemic corticosteroid or antibiotic therapy, although sensitivity analyses revealed a shift in the confidence intervals favouring TIO + SAL and TIO + SFC. However, compared with TIO + placebo, TIO + SFC was associated with significant improvements in lung function (p = 0.049), disease-specific quality of life (p = 0.01) and number of hospitalisations for both COPD exacerbation and all causes (incidence rate ratios 0.53; 95% CI 0.33, 0.86 and 0.67; 0.45, 0.99, respectively); lung function and hospitalisation rates did not differ significantly between the TIO + SAL and TIO + placebo groups.

Comment: This Canadian study investigates the clinical outcomes of triple therapy in COPD. Just like the TORCH study, which did not reach its primary endpoint of mortality reduction, this study also failed to reach its primary endpoint of reducing COPD exacerbation rates. However, the study does find improvements in lung function, quality of life and hospitalisation rates. The accompanying editorial calls it ‘the search for the magic combination’. It reminds us of the possibility of increased cardiac morbidity and pneumonias, but hopes that we are at the brink of identifying therapy that decreases morbidity and mortality in COPD. We need cardiology type studies with more patients, international scope and endpoints that reflect disease modification.

http://www.annals.org/cgi/content/abstract/146/8/545

Superiority of salmeterol/fluticasone propionate plus tiotropium bromide versus individual components in moderate to severe COPD

Authors: Singh D et al

Summary: In this randomised cross-over study, the combination of salmeterol and fluticasone propionate (SFC) combined with tiotropium bromide (TIO) was compared with SFC alone and TIO alone in 41 patients with COPD. The postdose specific airways conductance area under the curve on day 14 (primary endpoint) was significantly better with SFC + TIO than with SFC or TIO alone (p<0.001 for both comparisons). SFC + TIO was also associated with significant improvements in trough FEV1, and inspiration measurements on day 14, compared with SFC and TIO alone. Furthermore, clinically relevant improvements were seen in Transition Dyspnoea Index scores among SFC plus TIO recipients compared with TIO alone (but not SFC alone). Also, SFC plus TIO recipients required rescue medication on 1.0 less occasion than those who received TIO alone (p<0.001) and 0.06 less occasions than those who received SFC alone (p = 0.01). The investigators concluded that triple therapy with SFC plus TIO improves bronchodilation compared with TIO or SFC alone, and that the advantages of such therapy can be seen across a variety of physiologically important parameters.

Comment: Researchers from Britain and Belgium recruited 41 patients with COPD in five centres. In addition to traditional respiratory measurements, the authors measured the area under the curve of airway conductance. Patients receiving ‘triple therapy’ with tiotropium, salmeterol/fluticasone reported a reduction in their dyspnoea index, less rescue medication use and higher airway conductance when compared with the single components after 2 weeks of therapy. Interestingly, no improvement in the FEV1 was noted. This short trial in a small number of patients provides a rationale to a widely employed clinical practice and calls for adequately powered long-term studies.

Reference: Thorax 2008; 63(7): 592-8
http://thorax.bmj.com/cgi/content/abstract/63/7/592
Comparison of a combination of tiotropium plus formoterol to salmeterol plus fluticasone in moderate COPD

Authors: Rabe KF et al

Summary: The combinations of two bronchodilators (tiotropium bromide 18μg once daily plus formoterol 12μg twice daily; TBF) and a bronchodilator plus inhaled corticosteroid (salmeterol 50μg twice daily plus fluticasone dipropionate 500μg twice daily; SFC) were compared in 592 evaluable participants in this study. After 6 weeks’ treatment, TBF recipients had significantly better FEV1, AUC1–12h, and FVC AUC, 12h than SFC recipients (mean differences 78mL; p = 0.0006 and 173mL; p < 0.0001, respectively). Peak FEV1, and FVC responses at individual time points after each dose were also significantly superior with TBF. Predose FEV1, and rescue medication use did not differ significantly between the treatment groups, but TBF was associated with a significantly higher predose FVC.

Comment: This Dutch RCT of about 600 COPD patients compared the use of two separate bronchodilators with a combined product of a bronchodilator and inhaled corticosteroid (ICS). The primary outcome of this 6-week study was an improvement in lung function, measured by AUC of FEV1, and peak FEV1. This study showed that there was a greater improvement in lung function when using two bronchodilators than an ICS/LABA combination product. Despite some limitations of the study, which the authors acknowledge, there is reason to believe that the improved lung function could translate to reduced exacerbations and better quality of life.

http://www.annals.org/cgi/content/abstract/146/8/545

Serum magnesium is an independent predictor of frequent readmissions due to acute exacerbation of COPD

Authors: Bhatt SP et al

Summary: Predictors of readmission for acute exacerbations of COPD were investigated in 100 patients (mean age 71.9 years) admitted with this condition over a 2-year period and retrospectively followed until readmission or death. Among the study population, 87 patients were readmitted once or more during the first follow-up year, 23% had frequent readmission (>3 per year) and 5% died. Low serum magnesium level at the time of admission was a predictor of frequent readmission (adjusted OR 0.903; 95% CI <0.001, 0.55; p = 0.03). Vaccination against influenza or pneumococcal disease, and corticosteroid (inhaled or oral) or diuretic administration at discharge were not predictors of frequent readmission.

Comment: This group of American researchers used markers such as age, FEV1, disease duration, performance status or hypercapnia at discharge to predict readmissions for COPD exacerbations. They performed a detailed retrospective multivariate analysis of 20 characteristics of 100 COPD patients. They found that none of these markers, nor corticosteroid use, or pneumococcal or influenza vaccination predicted readmission. However, the authors did discover that a low magnesium level on admission was an independent predictor of frequent admissions. The authors are aware of the limitations of their study, but given a similar observation in asthma exacerbations, find their results plausible and worthy of further investigation.

http://dx.doi.org/10.1016/j.rmed.2008.02.010

Short-course antibiotic treatment in acute exacerbations of chronic bronchitis and COPD

Authors: El Moussaoui R et al

Summary: This meta-analysis compared the efficacy of a short antibiotic course (<5 days) with conventional longer courses in acute exacerbations of COPD and chronic bronchitis. The analysis included 21 eligible studies (mean Jadad score 3.9) involving 10,688 patients. The summary ORs for clinical cure with short courses at early (<25 days) and late follow-up were 0.99 (95% CI 0.90, 1.08) and 1.0 (0.91, 1.10), respectively, while the summary OR for bacteriological cure at late follow-up was 1.05 (95% CI 0.87, 1.26). The summary ORs observed for early cure were similar in subanalyses of trials with the same antibiotic agent in short- and long-course arms, and of trials grouped by antibiotic class used in the short-course arm.

Comment: In light of the recent publicity of adverse effects from antibiotic treatment this meta-analysis has clinical relevance. The authors reviewed 21 studies, enrolling more than 10,000 patients with an acute exacerbation of COPD. In patients with mild-to-moderately severe COPD, a short course of treatment, usually five days, is equally effective as longer courses (7–10 days). As the accompanying editorial points out, advantages include better compliance, fewer adverse effects and perhaps a reduced risk of antibiotic resistance.

http://thorax.bmj.com/cgi/content/abstract/63/5/415

Dyspnea on exertion in obese women: association with an increased oxygen cost of breathing

Authors: Babb TG et al

Summary: Whether dyspnea on exertion in otherwise healthy obese females is due to an increase in the oxygen cost of breathing or cardiovascular deconditioning was explored in this study, which included two independent experiments (n = 16 and 14 for experiments 1 and 2, respectively). The oxygen cost of breathing in obese women who exhibited dyspnoea on exertion was 38–70% greater than in women who did not (p<0.01), and there was a significant correlation between the oxygen cost of breathing and perceived breathlessness during exercise tests (r2 = 0.57 and 0.72, for experiments 1 and 2, respectively; p<0.001). There were no between-group differences in fat distribution, cardiovascular exercise capacity and respiratory mechanics.

Comment: This is a further study investigating the relationship between obesity and shortness of breath. This well-conducted American study asked the question whether obese women who report shortness of breath on exertion have a reduced exercise capacity (deconditioning) or an increased oxygen cost of breathing. Through a number of elegantly conducted experiments, they concluded that: 1) 37% of obese women report shortness of breath on exercise, 2) obesity-related changes in pulmonary function or fat distribution did not seem to cause breathlessness, 3) peak cardiovascular capacity was not decreased and 4) shortness of breath during exertion is related to the oxygen cost of breathing.

http://ajrccm.atsjournals.org/cgi/content/abstract/178/2/116

Independent commentary by Dr Lutz Beckert, Respiratory Physician at Christchurch Hospital, New Zealand.
Effect of carbocisteine on acute exacerbation of chronic obstructive pulmonary disease (PEACE Study)

Authors: Zheng J-P et al

Summary: The effect of mucolytic treatment on the yearly exacerbation rate in patients with COPD was investigated in this RCT. Patients with COPD stable for 4 weeks and ≥2 exacerbations within the previous 2 years were randomised to receive carbocisteine 1500 mg/day (n = 354) or placebo (355) for 1 year. Carbocisteine recipients experienced 1.01 exacerbations per year, compared with 1.35 in the placebo group (risk ratio 0.75; 95% CI 0·62, 0·92; p = 0·004). There were nonsignificant interactions between the preventive effects and smoking, COPD severity and inhaled corticosteroid (ICS) use.

Comment: Mucolytic medications such as carbocisteine, bromhexine or N-acetylcysteine are used to aid sputum elimination. This Chinese study included 709 patients with COPD who were randomised to either a carbocisteine or placebo group. There was a 24.5% reduction in exacerbations in the carbocisteine group (439 in the placebo, 325 in the treatment group). This effect was noted after only 3 months of treatment, with only very few adverse events observed. An improvement in the quality of life with St George’s Respiratory Questionnaire was also noted. Only 16.7% of the participants were ICS or LABA recipients experienced 1.01 exacerbations per year. Compared with control subjects, alveolar macrophage expression of mannose receptors and mannos-β-binding lectin and surfactant protein levels were significantly reduced in participants who received azithromycin. Baseline phagocytic ability also improved from 9.9% to 15.1% after azithromycin treatment, while bronchial epithelial cell apoptosis decreased from 30.0% to 19.7%, peripheral blood mannose receptors increased and peripheral blood inflammatory markers decreased. The investigators commented that these findings show that mannose receptors are: a) implicated in defective alveolar macrophage phagocytic function in patients with COPD; and b) a target for improved phagocytic ability with azithromycin.