Welcome to the latest edition of APSR Respiratory Research Review.

In this edition: idiopathic pulmonary fibrosis is a disease for which there are no really effective treatments, we profile a new placebo-controlled trial of the endothelial antagonist bosentan. We also feature studies which assess the benefits of auto-CPAP vs fixed-CPAP in OSA and review the survival benefits of ICU treatment for patients with lung cancer.

We welcome your comments and feedback.

Kind regards

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Young people, money, and access to tobacco

Authors: Wong G et al

Summary: This study utilised focus groups to determine how students accessed cigarettes. Particular attention was paid to their disposable income including sources of money, parental monitoring of the use of money as well as student access to cigarettes. Young people were easily able to buy cigarettes from tobacco retailers, friends or social suppliers. Family members or adults on the street were also reported as sources of cigarettes. “Roll your own” cigarettes were noted to be a particularly cheap way of purchasing tobacco. Money for purchasing cigarettes came from a number of sources including family, earnings and money borrowed or “scabbed” from friends. Parents were reported as paying little attention to the relatively small amounts of money used in the purchase of cigarettes and students felt they should have the final say on the way their money was spent.

Comment: New Zealanders under the age of 18 years of age spend an estimated $35 million/year on tobacco despite the legislative strategies in place to reduce access to cigarettes. This New Zealand study reports on the findings of twelve focus groups for Māori, Pacific Islander, New Zealand European, and Asian students by trained ethnically-matched student facilitators and researchers. The authors suggest that parental guidance is necessary when providing teenagers with pocket money. In addition, they suggest that legislation should be strengthened to reduce access to free or cheap cigarettes. Bottom line: 15% of New Zealand 11-15 year olds are current smokers.


Reference: NZMJ 2007; 120:1267
Outcome and prognostic factors for lung cancer patients

Authors: Adam K et al
Summary: This retrospective study (n = 139) was designed to identify measurable predictors of outcome for lung cancer patients admitted to a medical intensive care unit. The majority (69%) of patients had non-small cell lung cancer, 13% had small cell lung cancer, and one patient had mesothelioma. Mortality of patients was 22% in the MICU and 40% in-hospital. In the 49% of patients who required mechanical ventilation (MV), MICU mortality was 38% whilst in-hospital mortality was 53%. Factors identified as being independent predictors of poor outcome were: the need for MV; Acute Physiology And Chronic Health Evaluation III and Simplified Acute Physiology Score III scores; the use of vasopressors; positive blood cultures; high serum lactate; two or more organ system failures; and the need for adult cardiac life support. The need for vasopressors and the presence of two or more organ system failures were the only predictors confirmed by multivariate analysis.

Comment: The authors addressed the belief that patients with lung cancer should not be admitted to intensive care because of their poor survival outcome. They reviewed the cases of 139 patients with mostly stage III and IV lung cancer who were admitted to ICU with pneumonia, cardiac disorders, seizure disorder and other medical emergencies. Survival in lung cancer patients was similar to non-cancer patients, with survival determined by the severity of the acute illness. The authors and the related editorial suggest that aggressive therapy should be considered for patients with lung cancer.

http://dx.doi.org/10.1183/09031936.0031607
Reference: Eur Respir J 2008; 31:47-53

Deviation from guidelines in the management of primary spontaneous pneumothorax

Authors: Kelly A-M et al
Summary: This multicentre retrospective observational study which assessed the treatment of adult patients with primary spontaneous pneumothorax (PSP) was conducted at 19 emergency departments across Australia. The investigators found considerable deviation from published guidelines for the management of PSP and recommend a randomised, controlled trial to further assess management strategies.

Comment: One of the key findings of the randomised controlled trial on the management of primary spontaneous pneumothorax published by John Harvey and colleagues in the BMJ (Harvey J, Prescott RJ. Simple aspiration versus intercostal tube drainage for spontaneous pneumothorax in patients with normal lungs. BMJ 1994; 309:1338–1339) was that the success of aspiration was independent of the size of the pneumothorax. These findings have been repeated in another trial and are reflected in international guidelines. It is disappointing to see that in the above audit 62% of patients with a pneumothorax with a rim of > 2cm were treated with an intercostal drain. The authors reflect on possible causes for the non-adherence to international guidelines such as lack of awareness and lack of confidence in the evidence or habit.


Impact of a spirometry expert system on general practitioners’ decision making

Authors: Poels PJ et al
Summary: This cluster-randomised controlled trial (n = 78) studied GP spirometry interpretation following support by either expert system (expert support group) or by sham information (control group). GP standardised paper case descriptions were compared to expert panel judgement. The expert support had no impact on GP diagnosis of chronic obstructive pulmonary disease (OR 1.08, 95% CI 0.70 to 1.66), asthma (1.13, 0.70 to 1.80), and absence of respiratory disease (1.32, 0.61 to 2.86). GPs in the expert support group did however order more diagnostic tests. The authors conclude that expert support for computerised spirometry adds no detectable benefit to GPs ability to diagnose chronic respiratory disease.

Comment: This group assessed the impact of a computerised interpretation support system on the spirometric diagnosis of General Practitioners. This is a negative study for all the right reasons: a) The GP’s clinical diagnosis prior to spirometry was correct in 60% of cases b) the interpretative achievements of GP’s in this study exceeded the researchers assumptions c) GP using more spirometry were noted to have a trend for more diagnostic agreement with the expert panel. The main concern highlighted by this study was that incorrectly performed tests were only noticed by about a quarter of the GPs. This is an encouraging study allowing us to trust GP spirometry during the work-up of our breathless patients.

http://dx.doi.org/10.1183/09031936.00012007
Reference: Eur Respir J 2008; 31:84-92

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Nasal surgery for fixed nasal obstruction in obstructive sleep apnoea

Authors: Koutsourelakis I et al
Summary: Patients (n = 49) with obstructive sleep apnoea (mean apnoea/hypopnoea index [AHI] 30.1±16.3 events·h–1) with symptomatic fixed nasal obstruction due to deviated septum were randomly assigned to either septoplasty or sham surgery (placebo). Whilst no patients in the placebo group responded, 14.8% of patients in the surgery group were responders and exhibited considerable increase in nasal breathing epochs (epochs containing more than three consecutive phasic nasal signals). The change in nasal breathing epochs was inversely related to the change in AHI, and baseline nasal breathing epochs were positively related to the percent change in AHI. Responders had among the lowest baseline nasal breathing epochs; a cut-off value of 62.4% of total sleep epochs best separated (100% sensitivity, 82.6% specificity) responders/nonresponders. The authors conclude that nasal surgery rarely treats OSA effectively and that nasal breathing epochs can be a predictor of surgery outcome.

Comment: A group of ENT surgeons is using a RCT including a sham operation to investigate the role of nasal surgery (septoplasty) in the management of obstructive sleep apnoea. Even in patients with a deviated nasal septum, only 15% improved after surgery. Septoplasty was very helpful for patients who were not breathing through their nose at night (less than 62% nasal epochs) if the surgery restored nasal breathing. This study confirms that ENT surgery should not be the first step in the management of OSA and also highlights the important role of an ENT surgeon as part of a multi-disciplinary approach to obstructive sleep apnoea.

Reference: Eur Respir J 2008; 31:110-117

Auto-CPAP versus fixed-CPAP in patients with obstructive sleep apnoea

Authors: Kin W et al
Summary: This study randomised 43 patients newly diagnosed with severe obstructive sleep apnoea to either auto-CPAP or fixed-CPAP for 2 months and then crossed over after a washout period of 1 week for another 2 months. Auto-CPAP was used significantly more in the first and second month than fixed-CPAP (mean 129.7 and 130.5 hours versus 115.2 and 113.2 hours; p = 0.04 and 0.01) whilst mean hourly use per night was 4.3 and 4.4 hours versus 3.8 and 3.7 hours, respectively. After one month the Epworth sleepiness scores improved for both treatments (13.4 to 8.5 and 8.2, p < 0.01 for both). Both treatments improved the sleep apnoea quality of life index over the first month; 4.6 (0.2) to 5.0 (0.2) for auto-CPAP and 4.9 (0.2) for fixed-CPAP (p = 0.01 and 0.04, respectively), with no difference between the two treatments. More patients however preferred fixed-CPAP (30) than auto-CPAP (9).

Comment: In this study researchers from Hong Kong compared the efficacy of auto versus fixed-CPAP in improving symptoms and health status in Chinese patients with severe obstructive sleep apnoea. The results show that auto-CPAP and fixed-CPAP were equally effective in improving health outcome. Patient compliance was a little better with auto-CPAP devices, however more patients preferred the fixed-CPAP as a long-term treatment option. Bottom line: In countries with limited health resources better with auto-CPAP devices, however more patients preferred the fixed-CPAP as a long-term treatment option. Bottom line: In countries with limited health resources fixed CPAP should be the first line of treatment.


Chronic sleep restriction and daytime sleepiness

Authors: Bartlett DJ et al
Summary: This study of randomly selected community-dwelling Australian adults (n = 3,300) examined typical sleep duration and the prevalence of chronic sleep restriction and chronic sleepiness. The mean duration of sleep was 7.25±1.48h/night during the week and 7.53±2.01h/night in the weekends. Chronic daytime sleepiness was present in 11.7% and in those individuals of working age, 18.4% reported sleeping less than 6.5h/night. Independent risk factors for excessive daytime sleepiness included, sleeping less than 6.5h/night during the week, being older, getting qualitatively insufficient sleep, having at least one symptom of insomnia and lacking enthusiasm (marker of depression). The authors suggest that if the experimentally observed health effects of sleep restriction also operate at a population level, this prevalence of chronic sleep restriction is likely to have a significant influence on public health in Australia.

Comment: This group of Australian researchers addresses another important cause of daytime sleepiness: chronic sleep restriction. This study was hampered by a low response rate, but found that almost a fifth of the study population are sleep restricted (< 6.5h/night) and about 10% report daytime sleepiness (ESS > 10). The authors quoted literature which indicates that sleep restriction may contribute to burnout, impaired immune function, decreased insulin sensitivity and associated weight gain, as well as an increased risk of diabetes and cardiovascular disease. Further studies will be needed to investigate sleep habits and the effects on daytime function and health.


Disclaimer: This publication is not intended as a replacement for regular medical education but to assist in the process. The reviews are a summarised interpretation of the published study and reflect the opinion of the writer rather than those of the research group or scientific journal. It is suggested readers review the full trial data before forming a final conclusion on its merits.
Salmeterol/fluticasone propionate versus tiotropium for prevention of COPD exacerbations

Authors: Wedzicha JA et al

Summary: This randomised, 2-year, double-blind, double-dummy, parallel group study (n = 1,323) compared the relative efficacy of the long-acting inhaled bronchodilator/anti-inflammatory combination (salmeterol/fluticasone propionate 50/500 µg twice daily) and the long-acting bronchodilator (tiotropium 18 µg once daily) for prevention of exacerbations in severe and very severe COPD. The probability of withdrawing from the study was 29% greater for patients in the tiotropium group than for those taking salmeterol/fluticasone propionate (p = 0.005) however there was no significant difference in the exacerbation rates between the groups (1.28 and 1.32 respectively, p = 0.656). At two years the salmeterol/fluticasone propionate group had a significantly lower SGRQ total score (difference of 2.1 units, 95% CI 0.1 to 4.0, p = 0.038) and mortality rate (3% versus 6%, p = 0.032) compared to patients taking tiotropium. Higher rates of pneumonia were reported in the salmeterol/fluticasone propionate group (p = 0.008).

Comment: The TORCH study (NEJM 2007;356:775-89) was designed to investigate the effects of salmeterol/fluticasone on mortality in the treatment of COPD. The study failed to reach statistical significance for the mortality outcome, but did show significant improvement in health status, FEV1 for the mortality outcome, but did show significant difference was found for the secondary endpoints of time to death or disease progression, a trend in favour of salmeterol was observed. The latter was more pronounced in a patient subgroup diagnosed using surgical lung biopsy (post hoc analysis; HR 0.315, 95% CI, 0.126 to 0.789, p = 0.009). Assessments of dyspnea and QOL at 12 months favoured treatment with salmeterol.

BUILD-1: Bosentan for idiopathic pulmonary fibrosis

Authors: King TE et al

Summary: This double-blind, multicentre trial randomised 158 patients with idiopathic pulmonary fibrosis to receive either oral bosentan (62.5 mg bd for 4 weeks, increased to 125 mg bd thereafter), or placebo for 12 months or longer. At month 12 there was no significant difference between bosentan and placebo in the primary endpoint, the six-minute-walk test. Whilst no significant difference was found for the secondary endpoints of time to death or disease progression, a trend in favour of bosentan was observed. The latter was more pronounced in a patient subgroup diagnosed using surgical lung biopsy (post hoc analysis; HR 0.315, 95% CI, 0.126 to 0.789, p = 0.009). Assessments of dyspnea and QOL at 12 months favoured treatment with bosentan.

Comment: After the lack of benefit of gamma interferon in the treatment of idiopathic pulmonary fibrosis, hopes were high to ascertain a benefit of the endothelial antagonist bosentan in the management of IPF. Bosentan led to increased LFT in 20% of patients and 12.2% of patients had to stop bosentan. The bosentan treatment group showed no significant improvement in the primary endpoint – the six minute walk test. It did however show promising trends in reduction of shortness of breath, improvement of quality of life and survival. Further studies are under way, with Build3 assessing the effect on mortality and morbidity in patients with IPF. At the present time we are left without an effective treatment for our patients with idiopathic pulmonary fibrosis.

http://dx.doi.org/10.1164/rcrm.200705-732OC

Reference: J Resp Crit Care Med 2008; 177:75-81

Broncho-alveolar lavage and response to cyclophosphamide in scleroderma interstitial lung disease

Authors: Strange C et al

Summary: This study (n = 201) evaluated whether the presence of inflammatory cells on broncho-alveolar lavage could be used to identify distinct subsets of disease and/or predict cyclophosphamide responsiveness. Patients with ≥3% polymorphonuclear and/or ≥2% eosinophilic leukocytes on lavage and/or ground-glass opacification on computed tomography, received either baseline lavage or high-resolution computed tomography as part of this randomised trial of cyclophosphamide versus placebo. Abnormal cellularity was observed in 71.6% of patients amongst which there was a higher proportion of men (p = 0.04); more severe lung function, including worse FVC (p = 0.003), worse total lung capacity (p = 0.005) and diffusing capacity of the lung for carbon monoxide (p = 0.004), more extensive ground-glass opacity (p = 0.005), and more extensive fibrosis in the right middle lobe (p = 0.005). However, abnormal cellularity was not an independent predictor of disease progression or response to cyclophosphamide in 1 year.

Comment: The evidence for cyclophosphamide in the management of scleroderma interstitial lung disease is limited but despite this it is one of the most often prescribed medications. The authors in this study used broncho-alveolar lavage to define subgroups who might respond better to therapy. Although lavage identified patterns of disease severity, it did not add value to the prediction of disease progression or treatment response. The related editorial suggests that the authors finding might be flawed by performing lavages always in the right middle lobe and not where most of the abnormalities were, thereby ignoring “Sutton’s Law”.

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