

APSR Respiratory Research Review

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Welcome to the 7th edition of APSR Respiratory Research Review.

This month, we profile a number of COPD studies. There is evidence for a greater benefit of ICS in ex-smokers with COPD compared with current smokers. A new study raises important issues around the administration of short acting bronchodilators prior to bronchoscopy in COPD patients. Plus a 'must read' study of the potential harm of administering high flow oxygen therapy in patients with exacerbations of COPD. We need to ensure that evidence/protocols for use of oxygen in COPD are implemented.

We also have further evidence that bystander cardiac only resuscitation is preferable to conventional CPR for out of hospital cardiac arrest. Likewise evidence guidelines may need to be revised based on findings. I hope you enjoy the latest edition and welcome your comments and feedback.

Kind regards,

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Asbestos-related diseases and historical consumption

Authors: Lin R et al

Summary: This international study sought to assess the ecological association between death rates from asbestos related diseases (pleural, peritoneal, and all mesothelioma, and asbestosis) and historical consumption of asbestos (kg per person per year, from 1960 to 69). Asbestos consumption was a significant predictor of mortality from mesothelioma in both sexes (adjusted R² = 0.74; p < 0.0001). Related deaths were generally higher for men with a 2.4-fold (95% CI 2.0–2.9) mortality increase per unit consumption for males (0.58; p < 0.0001) compared with a 1.6-fold (1.4–1.9) increase for women. For peritoneal mesothelioma in both sexes (0.54, p < 0.0001, 2.2-fold [1.6–2.9] for men, 0.35, p = 0.0008, and 1.4-fold for women [1.2–1.6]); pleural mesothelioma in men was (0.29, p = 0.0015, 1.8-fold [1.3–2.5]); and for asbestosis in men (0.79, p < 0.0001, 2.7-fold [2.2–3.4]). Since a clear association/correlation was demonstrated between these diseases and historical asbestos consumption, the authors recommend "that all countries should move towards eliminating use of asbestos".

Comment: This study is highly relevant to Australia with its major production and high per-capita consumption of asbestos. The recommendation that all countries should move towards eliminating the use of asbestos (and by implication its production) has major implications.

<http://www.thelancet.com/journals/lancet/article/PIIS0140673607604127/abstract>

Reference: *Lancet*. 2007; 369:844-9



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The effects of oxygen therapy in COPD patients

Authors: Joosten SA et al

Summary: A retrospective audit which examines oxygen administration practices in patients with acute exacerbations of COPD (AECOPD) and compares them with recommendations in international guidelines. Of 65 patients admitted with AECOPD, 95% defined as retaining carbon dioxide received oxygen at a flow rate greater than 2 L/min (a level outside of internationally accepted guidelines). This was initiated in the ambulance and continued in the ED, frequently without monitoring of ABG levels. Those patients who received high flow oxygen therapy, $\text{PaO}_2 \geq 74.5$ mmHg, had significantly longer length of stay ($p = 0.029$); greater need for NIV on admission ($p = 0.0124$); and higher rate of admission to the HDU ($p = 0.0124$) than those with a $\text{PaO}_2 < 74.5$ mmHg. In conclusion, the majority of patients presenting at this hospital received oxygen therapy outside of internationally accepted guidelines. This may have contributed to less favourable outcomes including increased length of stay, admissions to HDU and use of NIV.

Comment: A 'must read' study of the potential harm of administering high flow oxygen therapy in patients with exacerbations of COPD. The medical practice observed in this study is likely to be widespread throughout the region. We need to ensure that evidence-based protocols for the use of oxygen in patients with COPD are implemented.

http://www.mja.com.au/public/issues/186_05_050307/joo10890_fm.html

Reference: MJA. 2007; 186:235-8

Bronchodilators for bronchoscopy in patients with COPD

Authors: Stolz D et al

Summary: This randomised, double-blind, placebo-controlled trial analysed the effect of using short-acting bronchodilators prior to bronchoscopy, in patients with COPD. The 122 patients were randomised to receive either 200 µg of salbutamol, placebo or no inhaled medication. There were no significant differences in haemodynamic parameters before, during, and after bronchoscopy for the salbutamol and placebo groups. Following bronchoscopy the FEV_1 decreased significantly ($p = 0.432$) and to a similar extent in all three patient groups, with the median percentage of predicted FEV_1 being -4.7% , -4.8% and -10.0% for the salbutamol (interquartile range [IQR], -13.3 to 6.6), placebo (IQR, -19.9 to 8.4) and control subjects (IQR, -20.2 to -3.3) respectively ($p = 0.023$). The severity of COPD was inversely correlated to the relative change in FEV_1 ($p = 0.01$). In conclusion the authors do not recommend use of short-acting bronchodilators prior to bronchoscopy, on patients with COPD.

Comment: The crucial issue is the clinical uncertainty that may exist in the classification of patients with features of both COPD and asthma. A practical recommendation would be that all asthma patients and those COPD patients with a 'reversible component' should receive pre-medication with inhaled beta-agonist prior to bronchoscopy.

<http://www.chestjournal.org/cgi/content/abstract/131/3/765>

Reference: Chest. 2007; 131:765-72

Analysis of FEV1 decline in COPD patients taking inhaled corticosteroids

Authors: Soriano JB et al

Summary: The ISSEC study (Inhaled Steroids Effect Evaluation in COPD) combined data from seven long-term (≥ 12 months), randomised placebo controlled trials of inhaled corticosteroids (ICS) in 3,911 patients with moderate-to-severe COPD. Over the first 6 months ICS use was associated with a significant increase in FEV_1 of $2.42 \pm 0.19\%$ vs placebo ($p < 0.01$); 42 mL in men and 29 mL in women. However there was no significant difference between placebo and ICS therapy from 6 to 36 months (FEV_1 of $-0.01 \pm 0.09\%$; $p = 0.86$). During the initial 6 months ex-smokers showed a larger increase in FEV_1 , than those who continued to smoke, with female ex-smokers having a larger increase than their male counterparts. The authors conclude that the initial 6 months of ICS therapy, is more effective at improving lung function in ex-smokers than in current smokers and that women may have a more favourable response to ICS than men. However after 6 months, the decline in FEV_1 is not modified with continued ICS therapy.

Comment: One of the intriguing findings of this study is the greater benefit of ICS in ex-smokers with COPD compared with current smokers. Similar findings have been reported in both short-term and long-term treatment with ICS in asthma. These observations have major implications in clinical practice and raise the issue as to whether smokers with asthma or COPD should receive higher doses of ICS than non-smokers.

<http://www.chestjournal.org/cgi/content/abstract/131/3/682>

Reference: Chest. 2007; 131:682-9

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Accuracy and reliability of physical signs in the diagnosis of pleural effusion

Authors: Kalantri S et al

Summary: This blind and independent evaluation of 278 patients admitted for respiratory symptoms, compared physical signs with the reference standard (chest radiograph). Physical signs assessed included asymmetric chest expansion, vocal fremitus, percussion note, breath sounds, crackles, vocal resonance and auscultatory percussion. Investigators were blind to history and chest radiograph findings, and to each other's results. The prevalence of pleural effusion was 21%. Likelihood ratios for both positive and negative signs (excluding pleural rub) ranged from 1.48 to 8.14 (95% CI) and 0.13 and 0.71 respectively. Interobserver reliability ranged from excellent (chest expansion, vocal fremitus, percussion and breath sounds (κ 0.84–0.89) to good (vocal resonance, crackles and auscultatory percussion (κ 0.68–0.78). Asymmetric chest expansion and dull percussion note were found to be independent predictors of pleural effusion (OR 5.22, 95% CI 2.06–13.23; OR 12.80, 95% CI 4.23–38.70). Whilst physical signs may be useful in ruling out a diagnosis of pleural effusion they do not always provide a certain indicator of this condition.

Comment: It is good to see the sensitivity, specificity and inter-observer reliability determined for physical signs in the same way as for investigative tests.

<http://www.sciencedirect.com>

Reference: *Resp Med.* 2007; 101:431-8

Efficacy of bystander CPR by chest compressions only

Authors: SOS-KANTO Study Group

Summary: This prospective, multicentre, observational study compared neurological outcomes of patients receiving cardiac-only resuscitation (chest compressions without mouth-to-mouth ventilation) with those receiving conventional CPR. Of the 4,068 adult patients who had out-of-hospital cardiac arrest witnessed and/or treated by bystanders; 439 (11%) received cardiac-only resuscitation, 712 (18%) received conventional CPR, and 2917 (72%) received no CPR. Any resuscitation attempt was associated with a more favourable neurological outcome (5.0 vs 2.2%, $p < 0.0001$). A higher proportion of those receiving cardiac-only resuscitation had a favourable outcome compared with those receiving CPR, in patients with apnoea (6.2 vs 3.1%; $p = 0.0195$), with shockable rhythm (19.4 vs 11.2%; $p = 0.041$), and with resuscitation that started within 4 min of arrest (10.1 vs 5.1%; $p = 0.0221$). The authors concluded "there was no evidence for any benefit from the addition of mouth-to-mouth ventilation in any subgroup" with the adjusted odds ratio for a favourable neurological outcome after cardiac-only resuscitation being 2.2 (95% CI 1.2–4.2).

Comment: We need to be better aware of the evidence that bystander cardiac only resuscitation is preferable to conventional CPR in witnessed out of hospital cardiac arrest. The accompanying editorial recommending that guidelines are urgently needed is worth reading (*Lancet.* 2007; 369:882-4).

Reference: *Lancet.* 2007; 369:920-6

PMID: 17368153

Analysis of pleural effusions in acute pulmonary embolism

Authors: Porcel JM et al

Summary: This 9 year retrospective observational study of 230 patients diagnosed with acute pulmonary embolism (PE) examined the frequency and characteristics of pleural effusions. Spiral CT pulmonary angiography (CT) and high-probability ventilation and perfusion scans revealed pleural effusions in 47% and 32% of patients respectively. These effusions were typically unilateral (85%) and small (90% occupied less than one third of the hemithorax) with 21% showing loculation. In those patients with loculated pleural fluid the diagnosis of PE was delayed, taking a mean of 12.2 days after the patient became symptomatic. The presence of pleural fluid was not related to infarction and all fluids met Light's criteria for exudate (58% contained erythrocyte counts $>10,000/\mu\text{L}$ and 46% showed neutrophilic predominance). Only 28% of patients with PE underwent thoracentesis.

Comment: A reminder of the common occurrence of pleural effusions in pulmonary embolism – always an exudate, not necessarily related to pulmonary infarction, occasionally a substantial size, and with the potential to become loculated.

Ref: *Respirology.* 2007; 12:234-9
PMID: 17298456

*Independent commentary
by Professor Richard Beasley*

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Recent asthma exacerbations as a predictor of future exacerbations

Authors: Miller MK et al

Summary: This 1.5-year prospective study analysed data from 2,780 patients from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens study. Severe exacerbations of asthma were defined as either an asthma-related ED visit or overnight hospitalisation in the 3 months prior. Patients with a recent severe exacerbation were at increased risk of future exacerbation (OR 6.33; 95% CI 4.57-8.76), even after adjustment for demographics and clinical factors (OR 3.77; 95% CI 2.62-5.43), asthma severity (OR 5.62; 95% CI 4.03-7.83), National Asthma Education and Prevention Program (OR 5.07; 95% CI 3.62-7.11), Global Initiative for Asthma (OR =5.32; 95% CI 3.80-7.47), and asthma control (OR 3.90; 95% CI 2.77-5.50). The authors recommend that since recent severe asthma exacerbations are a strong predictor of future exacerbations, they "should be considered as part of the clinical assessment of patients with severe or difficult-to-treat asthma".

Comment: The take-home message from this study is that a recent severe exacerbation (i.e. an ED visit or hospital admission) identifies a patient at risk of subsequent severe morbidity and mortality (see also Crane et al. *Int J Epidemiol.* 1992; 21:737-44). As a result, enquiry as to a recent severe exacerbation is an essential part of the history of a patient with asthma.

<http://www.sciencedirect.com>

Ref: *Resp Med* 2007; 101:481-9

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Use of short-acting β_2 -agonists during pregnancy

Authors: Martel MJ et al

Summary: This study of pregnant asthmatic women (n = 302) utilised a nested case-control design with each patient with pregnancy-induced hypertension (PIH [gestational hypertension, preeclampsia, or eclampsia]) being matched to up to 10 control subjects (total of 3,013 patients) for the year of conception and gestational age. The use of inhaled short-acting β_2 -agonists (SABAs) during pregnancy was significantly associated with a reduced risk of PIH (adjusted rate ratios: > 0-3 doses/week, 0.62 (95% CI, 0.44-0.87); > 3-10 doses/week, 0.51 (95% CI, 0.34-0.79); and > 10 doses/week, 0.48 (95% CI, 0.30-0.75). The investigators conclude that this further supports the safety of inhaled SABA use during pregnancy and suggest that pharmacologic and physiological effects or residual confounding may explain the association with reduced risk of PIH.

Comment: This study adds to the excellent summary of "Asthma in Pregnancy" in the British Guideline on the Management of Asthma (Thorax. 2003; 58 (Suppl 1):47-50).

<http://www.jacionline.org/article/PIIS009167490602327X/abstract>

Reference: *Journal of Allergy and Clinical Immunology.* 2007; 119:3:576-582

New tests for the diagnosis of latent tuberculosis infection

Authors: Menzies D et al

Summary: This meta-analysis sought to estimate sensitivity, specificity, and reproducibility of IGRAs (QuantIFERON [QFT] and Elispot) for diagnosing latent TB infection in healthy and immune-suppressed persons. The sensitivity of all assays was suboptimal when newly diagnosed active TB was used as a surrogate for latent TB infection and no test distinguishes active from latent TB. Pooled specificity was 97.7% (95% CI, 96-99) and 92.5% (95% CI, 86-99) for QFT and for Elispot, respectively. Both tests were more specific than the tuberculin skin test in samples vaccinated with BCG. In 3 studies of immune-compromised samples the Elispot was more sensitive than the tuberculin skin test. Frequent discordant tuberculin skin test and IGRA reactions were noted and these were largely unexplained. The latter may be related to varied definitions of positive test results. Although new IGRAs show considerable promise and excellent specificity, more research is still required.

Comment: The current state of knowledge of the performance of IGRA's to diagnose latent tuberculosis. IGRA's are at least as good as the tuberculin test and probably superior in BCG-vaccinated patients. A case can now be made for utilising IGRA's in the investigation of BCG-vaccinated adult patients.

<http://www.annals.org/cgi/content/abstract/146/5/340>

Reference: *Ann Int Med.* 2007; 146:340-54

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