

APSR Respiratory Research Review

Making Education Easy

Issue 11 - 2007

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Welcome to APSR Respiratory Research Review

In this edition of the APSR Respiratory Research Review, we promote the forthcoming Educational Seminar "AVIAN INFLUENZA: from basic biology to pandemic planning" to be held on Friday 30 November at the APSR Congress on the Gold Coast in Australia. Bringing together experts from the World Health Organisation, Centres for Disease Control and Prevention, American College of Chest Physicians and Asian Pacific Society of Respiriology, this educational seminar seeks to review the ecology and evolution of avian influenza H5N1 viruses from the perspective of pandemic risk; to address various aspects of human H5N1 disease in relation to its epidemiology, clinical presentation, pathogenesis, diagnosis, medical management; and finally to discuss issues relating to pandemic planning and preventive public health measures. Register now at www.apsr2007.org to make sure you can attend this important event.

We hope you enjoy the latest edition and welcome your feedback.

A multicentre, randomised, controlled trial of dexamethasone for bronchiolitis

Authors: Corneli HM et al

Summary: 600 infants aged 2 to 12 months who presented at the emergency department with a first episode of wheeze and diagnosed with moderate-to-severe bronchiolitis participated in this double-blind trial. Subjects were randomised to receive either a single dose of oral dexamethasone (1 mg/kg) or placebo. The primary outcome measure was hospital admission. In infants who received dexamethasone admission rates were 39.7% compared to 41.0% for those who received placebo (absolute difference, -1.3%; 95% CI, -9.2 to 6.5). Improvements in respiratory status were observed in both groups, 4-hour Respiratory Assessment Change Score (RACS) was -5.3 and -4.8 for dexamethasone and placebo respectively (absolute difference, -0.5; 95% CI, -1.3 to 0.3). No differences in results were observed with multivariate analysis. Later outcomes were not different between treatment groups. A single dose of oral dexamethasone did not significantly alter outcomes for infants with bronchiolitis compared to placebo.

Comment: The clinical implications of this large RCT are clear - oral dexamethasone cannot be recommended for the treatment of moderate to severe bronchiolitis in a single oral dose of 1mg/kg in infants under 12 months of age. These findings strengthen the recommendation from the American Academic of Pediatrics that corticosteroids not be routinely used for bronchiolitis.

<http://content.nejm.org/cgi/content/abstract/357/4/331>

Reference: *N Engl J Med* 2007; 357:331-9

Coming Educational Seminar of the APSR - ESAP

Avian/emerging flu - Basic biology to public health and disaster management
30 November 2007 - Gold Coast, Australia - Just prior to the 12th APSR Congress
For more information see: <http://www.apsresp.org/education/esap.html#esap004>

Healthcare-associated pneumonia (HCAP) requiring hospital admission

Authors: Carratala J et al

Summary: The authors of this paper aimed to examine the epidemiology, causative organisms, antibiotic susceptibilities and treatment outcomes for HCAP requiring hospitalisation. Data were collected from a prospective observational analysis of 727 cases of pneumonia in non-immunosuppressed, hospitalised adults. The majority of cases (82.7%) were community acquired pneumonia, with 17.3% considered to be HCAP. Patients with HCAP were older, had more comorbidity and were more likely to have high-risk pneumonia. 30-day mortality was greater in HCAP patients (10.3% vs 4.3%; $p = 0.007$). Streptococcus pneumoniae was the most common cause of infection in both groups. In patients with HCAP, drug-resistant pneumococci were more common as was aspiration pneumonia, Haemophilus influenzae, Staphylococcus aureus and gram-negative bacilli. Legionella pneumophila was less common in patients with HCAP. Patients with HCAP were more likely to receive inappropriate first-line antibiotic therapy (5.6 vs 2.0%, $p = 0.03$).

Comment: A new category of patients with community-acquired pneumonia to consider – healthcare associated pneumonia – representing patients who have had recent contact with the healthcare system through nursing homes, home healthcare programmes, haemodialysis clinics or prior hospitalisation. This category makes up a substantial number of patients with community-acquired pneumonia and may require a targeted approach when selecting empiric antibiotic therapy.

<http://archinte.ama-assn.org/cgi/content/abstract/167/13/1393>

Reference: Arch Int Med 2007; 167:1393-9

Staffing level: a determinant of late-onset ventilator-associated pneumonia

Authors: Hugonnet S et al

Summary: A cohort of 2,470 patients at risk for ICU-acquired infection was followed during an ICU stay in order to determine the effect of staffing levels on ventilator-associated pneumonia (VAP). 936 subjects required mechanical ventilation, and of these 209 (23%) developed VAP, with a total of 262 episodes recorded. 61% of all episodes were late-onset VAP. Subjects with VAP spent longer ventilated compared to those without, mean 11 days vs 3 days. The rate of VAP was 37.6 episodes per 1000 days at risk. There was a median daily nurse/patient ratio of 1.9. Early-onset VAP was not correlated with staffing levels, however late onset VAP was less likely to occur when the nurse/patient ratio was high (HR 0.42, 95% CI 0.18 to 2.2).

Comment: If the nursing levels in your ICU are low, show this study to “management”. Ventilator-associated pneumonia is a common cause of premature morbidity and mortality, generating substantial costs. The importance of maintaining adequate nursing levels is well illustrated in this study.

<http://ccforum.com/content/pdf/cc5974.pdf>

Reference: Crit Care Med 2007; 11:R80 (doi:10.1186/cc5947)

The epidemiology of lymphangioliomyomatosis (LAM) in Japan

Authors: Hayashida M et al

Summary: The authors collected data with regard to the characteristics and prognostic factors associated with lymphangioliomyomatosis (LAM) using a nationwide survey. 173 patients with pulmonary LAM were identified. 37% of subjects presented with exertional dyspnoea (group A) and 43% with pneumothorax (group B). Survival rates were 85 and 95% at 5 years, 60 and 89% and 10 years, and 47 and 89% at 15 years in groups A and B respectively. Group A presented at an older age, however prognosis was related to initial presentation even when age was controlled for. (Group A/B hazard ratio 5.732, $p < 0.01$). In patients presenting with poorer respiratory status, (FEV1 >1000 mL, FEV1/FVC >40% or %DLCO > 40%) deterioration was significantly more rapid in subjects from group A. Two subgroups of patients with LAM appear to exist. Those who present with pneumothorax develop symptoms at a younger age and have a more favourable prognosis than those presenting with exertional dyspnoea.

Comment: This nationwide survey of LAM in Japan provides evidence that there are at least two subgroups of LAM patients with different clinical and physiological characteristics and prognosis. These findings contrast and complement those from the United States and Europe and reinforce the importance of studying respiratory disorders in different populations in the Asia Pacific region.

<http://www.blackwell-synergy.com/doi/abs/10.1111/j.1440-1843.2007.01101.x>

Reference: Respirol 2007; 12:523-30



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- Nan Shan Zhong, China

Cabin pressure during Boeing 747-400 commercial aircraft flights

Authors: Kelly PT et al

Summary: Low air pressure during commercial airline flights may accentuate hypoxaemia in patients with heart or lung disease. Regulations suggest a minimum cabin pressure of 750 hPa. The authors investigated cabin pressure during 45 commercial flights (average duration 10 hours) in Boeing 747-400 aircraft belonging to three airlines. During flight the average cabin pressure was 846 hPa, and mean cabin pressure fell below 800 hPa for only 2% of the total flight time. The lowest recorded pressure was 792 hPa which occurred at 40,000 ft in altitude. There was a linear relationship between increasing altitude and falling cabin pressure (8 hPa for every 1,000 ft, $r^2 = 0.993$; $p < 0.001$). The authors concluded that "current fitness-to-fly evaluations simulate cabin conditions that passengers will not experience on these aircraft. There may be increased risks to patients should new or older aircraft operate nearer to the present minimum standard."

Comment: Reassuring data that cabin pressures in Boeing 747 aircraft are higher than that required by regulation. The main clinical implication is that current fitness to fly evaluations simulate cabin pressure and associated hypoxic conditions that are lower than passengers will experience on the aircraft. This may explain why some patients are able to travel without adverse events, even though severe hypoxia is seen in an 8000 feet simulation.

<http://www.blackwell-synergy.com/doi/abs/10.1111/j.1440-1843.2007.01104.x>

Reference: *Respirol* 2007; 12:511-5

Selecting patients with acute pulmonary embolism for initial outpatient therapy

Authors: Jiménez D et al

Summary: This study compared the performance of two models in predicting 30-day outcomes for patients with pulmonary embolism (PE). 599 patients with PE were classified using the 5-class PE severity index (PESI) or the Geneva low and high-risk strata. Significantly fewer patients were classified as low risk with the PESI (36%) compared to the Geneva model (84%, $p < 0.0001$). Both models predicted relevant 30-day differences in mortality for the low risk groups (PESI, 0.9%; 95% CI, 0.3 to 2.2; vs Geneva, 5.6%; 95% CI, 3.6 to 7.6, $p < 0.0001$). Rates of nonfatal recurrent venous thromboembolism and major bleeding were statistically similar for both models, however the area under the receiver operating characteristic curve was higher for the PESI (0.76; 95% CI, 0.69 to 0.83) than for the Geneva (0.61; 95% CI, 0.51 to 0.71, $p = 0.002$). In conclusion, the PESI was a more effective model for quantifying prognosis for patients with PE, and the authors suggest it may be used to identify patients with a very low risk for adverse events who may be suitable for treatment in the outpatient setting.

Comment: With pressure on hospital beds it has become important to be able to identify patients with PE who may be able to be managed as outpatients. This requires a prognostic model that can predict short term mortality. This study shows that the PE severity index has good discriminatory power in identifying patients with very low risk of 30 day mortality (<1%), thereby assisting in selecting patients with PE who might be safely treated as an outpatient. This index can now be incorporated in PE protocols used in the ED.

<http://www.chestjournal.org/cgi/content/abstract/132/1/24>

Reference: *Chest* 2007; 132:24-30

Safety of inferior vena cava filter retrieval in anti-coagulated patients

Authors: Hoppe H et al

Summary: This retrospective study of 115 consecutively attempted inferior vena cava filter retrievals assessed safety in therapeutically anticoagulated patients (group 1) in comparison to prophylactically (group 2) or not therapeutically anticoagulated (group 3) patients. Filter retrievals were successful in 61 of 65 attempts in 61 patients in group 1, 23 attempts in 22 patients in group 2, and 21 of 27 attempts in 27 patients in group 3. Haemorrhagic complications were unrelated to the retrieval procedures regardless of the group. The authors conclude that "retrieval of vena cava filters in anticoagulated patients is safe. Interruption or reversal of anticoagulation for the retrieval of vena cava filters is not indicated."

Comment: The recommendation from this case series is clear – anticoagulation does not need to be stopped or reversed for the retrieval of inferior vena cava filters.

<http://www.chestjournal.org/cgi/content/abstract/132/1/31>

Reference: *Chest* 2007; 132:31-6

*Independent commentary
by Professor Richard Beasley*

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Respiratory Research Review**

<http://www.apsresp.org/pdf/review-sponsorship.pdf>

Reference ranges for exhaled nitric oxide

Authors: Travers J et al

Summary: A random sample of adults aged 25 to 75 years was used to derive reference ranges for the fraction of nitric oxide in exhaled breath (FENO). Subjects were from Wellington, New Zealand and were predominantly white. They were assessed using a detailed respiratory questionnaire and pulmonary function tests. An online nitric oxide monitor was used to measure FENO. Mean FENO was 17.9 parts per billion (ppb) with a 90% confidence interval for an individual prediction (reference range) for normal subjects of 7.8 to 41.1 ppb. Factors affecting FENO levels included sex, atopy and smoking status. Subjects with asthma and allergic rhinitis had higher FENO levels, however FENO measurement was not an effective means of identifying steroid-naïve subjects with asthma.

Comment: Reference ranges are provided to assist in the interpretation of FENO measurements in clinical practice. The disappointing finding from this study was that measurement of FENO had poor discriminatory ability to identify steroid naïve subjects with asthma in the community. Robin Taylor provides a helpful update on the clinical use of FENO measurements in the accompanying editorial [pp 221-3].

<http://ajrccm.atsjournals.org/cgi/content/abstract/176/3/238>

Reference: *Am J Respir Crit Care Med* 2007; 176:238-42

The use of exhaled nitric oxide to guide asthma management

Authors: Shaw DE et al

Summary: This randomised controlled trial examined the rates of severe exacerbations in subjects with asthma, whose corticosteroid dose was based on either the concentration of exhaled nitric oxide in exhaled breath (FENO) or the British Thoracic Society guidelines. Participants were 118 patients with a diagnosis of asthma, randomised to 12 months single-blind treatment with corticosteroids. Frequency of exacerbation was similar in both treatment groups, 0.33 vs 0.42 for the FENO group and controls respectively (mean difference, -21%; 95% CI, -57 to 43%; $p = 0.43$). The final corticosteroid dose was lower in the FENO group (557 vs. 895 µg; mean difference, 338 µg; 95% CI, -640 to -37; $p = 0.028$), however there was an 11% greater use of inhaled corticosteroids overall in the FENO group (95% CI, -17 to 42%; $p = 0.40$). An asthma treatment strategy based on FENO measurements did not have benefits compared to standard asthma management.

Comment: The other disappointing findings on FENO published in the Blue journal this month – FENO driven asthma management did not result in better outcomes or less ICS treatment than traditional management. It seems premature to recommend the routine use of FENO in the diagnosis or management of asthma at this stage – further studies are required before this test finds its role in clinical practice.

<http://ajrccm.atsjournals.org/cgi/content/abstract/176/3/231>

Reference: *Am J Respir Crit Care Med* 2007; 176:231-7

Once-daily inhaled ciclesonide in adults with mild to moderate asthma

Authors: Adachi M et al

Summary: The safety and efficacy of ciclesonide, a novel pro-drug inhaled corticosteroid was assessed in this placebo-controlled, randomised, double-blind trial. Adults with mild-to-moderate asthma received beclomethasone dipropionate (400 µg/day) during a 4 week baseline period, and were then randomised to once-daily ciclesonide (100, 200 or 400 µg) or placebo for 8 weeks. Morning PEF was the primary outcome measure. At endpoint, morning PEF remained similar to that observed during the baseline period for subjects receiving ciclesonide. Change in morning PEF was 4.23, 3.75 and -0.40 L/min in the 100, 200 and 400 µg ciclesonide groups respectively, compared to -24.95 L/min with placebo ($p < 0.001$ for all comparisons). Rates of adverse events were similar in both ciclesonide and placebo-treated patients. The authors concluded that once daily administration of ciclesonide 100, 200 and 400 µg was effective and well tolerated in adults with mild-to-moderate asthma.

Comment: Confirmation of the efficacy of once-daily ciclesonide in the treatment of adult patients with mild to moderate asthma. The most interesting observation in this study was the lack of a dose-response relationship with 100µg per day of ciclesonide having similar efficacy to the 200 and 400µg daily dose regimes. This finding is consistent with the known dose-response relationship of other inhaled corticosteroids in which the dose-response curve becomes flat at what is generally considered to be low to moderate doses (Holt et al. *BMJ* 2001; 323: 253-6).

<http://www.blackwell-synergy.com/doi/abs/10.1111/j.1440-1843.2007.01111.x>

Reference: *Respirol* 2007; 12:566-72

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