

APSR Respiratory Research Review

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Welcome to the latest edition of APSR Respiratory Research Review.

The focus of this month's review is tuberculosis, in particular the emerging problem of extensively drug-resistant TB. The studies highlighted stress the importance of optimal initial management of TB and of infection control measures to reduce nosocomial transmission of drug-resistant TB. As proposed in the accompanying Lancet editorial "multidrug and extensive drug resistance are monsters of our own creation. They might be with us longer than we think and might need us to spend more than governments or institutions are willing or able to pay." (pp 1464-5)

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

H5N1 infection of the respiratory tract and beyond: a molecular pathology study

Authors: Gu J et al

Summary: The authors conducted a molecular pathology investigation of the tissues of two adults (a male and a pregnant female) who had been infected with avian influenza H5N1, and also of the foetus which the woman had been carrying. Investigations used to identify H5N1 viral genomic sequences and antigens included reverse-transcriptase, real-time and strand-specific PCR, nucleic acid sequence-based amplification, in-situ hybridisation and immunohistochemistry. In the adults, viral genomic sequences but not antigens were found in the intestinal mucosa. Both antigens and viral sequences were found in type II epithelial cells of the lungs and in tracheal epithelial cells. They were also present in lymph node T cells, brain neurons and the Hofbauer cells and cytotrophoblasts of the placenta. In the foetus, viral sequences and antigens were present in the lungs, circulating mononuclear cells, and liver macrophages. In conclusion, the H5N1 virus infects organs other than just the lungs and may be transmitted across the placenta from mother to foetus.

Comment: Evidence that avian influenza H5N1 virus can disseminate beyond the lungs and infect multiple organs. The observation that the virus infects and actively replicates in the small intestine may have important implications for infection control. Although most cases are due to animal-to-human spread, a few cases of probable human-to-human transmission have now been reported. (Also see editorial, pp 1106-8).

<http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed&uid=17905166&cmd=showdetailview&indexed=google>

Reference: *Lancet* 2007; 370:1137-45

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Effect of ICU organisational structure on outcomes in acute lung injury

Authors: Treggiari MM et al

Summary: This cohort study examined the effect of ICU organisational structure on outcomes for patients with acute lung injury (ALI). A mailed questionnaire was used to gather data on the organisational structure of 24 ICUs. They were classified as either closed (those in which patients were either transferred to or co-managed by an intensivist) or open where other models of care were employed. Outcome data for ALI were obtained from the King County Lung Injury Project. 13 of the 24 ICUs studied were classed as closed. In closed ICUs, the availability of physicians and nurses was greater. In the adjusted analysis, hospital mortality was reduced when patients with ALI were cared for in closed ICUs (OR 0.68, 95% CI 0.53 to 0.89; $p = 0.004$). There was no improvement in mortality for patients in open ICUs where a pulmonologist consulted (OR 0.94, 95% CI 0.74 to 1.20; $p = 0.62$).

Comment: A worthwhile checklist of the structural and organisational factors that have been associated with improved patient outcomes in ICU. In addition to the requirement for a co-attending intensivist, as shown in this study, a critical care team, fulltime director, 24 hour intensivist coverage, stable nurse/patient ratios around the clock, high volumes and pharmacist involvement all contribute to improved outcomes.

<http://ajrcm.atsjournals.org/cgi/content/abstract/176/7/685>

Reference: *Am J Respir Crit Care Med* 2007; 176:685-90

Use of tunnelled catheters for malignant pleural effusions in patients fit for pleurodesis

Authors: Tremblay A et al

Summary: The authors assessed the effectiveness of tunnelled pleural catheters (TPC) in patients with malignant pleural effusions who would otherwise be candidates for pleurodesis. Subjects were 97 patients (109 procedures) from a database of 250 who had previously received TPC. Inclusion criteria were eligibility for pleurodesis as defined by survival of ≥ 90 days and lung re-expansion $\geq 80\%$ post-drainage on a standard chest radiograph 2 weeks post TPC placement. 70% of procedures resulted in spontaneous pleurodesis after a mean of 90 days. For 92% of patients with spontaneous pleurodesis (87% of procedures) a single procedure was sufficient. There were no deaths resulting from TPC and complication rates were low. In conclusion malignant pleural effusions can be effectively controlled with TPC in patients who would otherwise be candidates for pleurodesis procedures.

Comment: An attractive alternative to talc pleurodesis for the treatment of malignant pleural effusions – the use of a tunnelled pleural catheter. This approach has comparable efficacy to talc pleurodesis in terms of both symptom control and successful pleurodesis rates, while having minimal complications and need for hospitalisation. From the patient's perspective, it allows them to remain in the comfort of their own home with family and friends without compromising comfort and symptom control.

<http://www.erj.ersjournals.com/cgi/content/abstract/30/4/759>

Reference: *Eur Respir J* 2007; 30:759-62

Trends in hospitalisation rates for acute allergic reactions in Australia

Authors: Poulos LM et al

Summary: The authors describe Australian trends in the age-standardised rates of hospital admission for anaphylaxis, angioedema, and urticaria between 1993-1994, and 2004-2005. The annual rate of increase in admissions for each condition over the study period was 3% for angioedema, 5.7% for urticaria and 8.8% for anaphylaxis. In children aged under 5 years there was a sharp increase in hospitalisation rates for food-related anaphylaxis. Non-food-related anaphylaxis occurred primarily in adults. Male children had higher admission rates than females, but amongst adults, hospitalisation rates were highest in women. 106 deaths relating to anaphylaxis or angioedema occurred over 8 years. The authors noted that the nature and aetiology of hospital admissions for acute allergic reactions was different between adults and children but that rates were increasing in both groups. Further investigations in relation to allergen sensitisation rates in the community are required.

Comment: The increase in life-threatening angioedema and anaphylaxis in Australia parallels trends observed in the United Kingdom and the United States. The time trends are likely to be due to an increase in the incidence of these allergic conditions, or an increase in their severity, or both. The possible role of ACE inhibitors and aspirin in the increase in the rates of anaphylaxis and angioedema in older adults is worthy of consideration.

http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=Retrieve&db=PubMed&list_uids=17931562&dopt=AbstractPlus

Reference: *J Allergy Clin Immunol* 2007; 120:878-84



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Is it time to change the approach to oxygen therapy in the breathless patient?

Authors: Beasley R et al

Summary: The authors discuss the potential risks of the routine use of high flow oxygen therapy in breathless patients who do not necessarily have arterial hypoxia. They propose that the least recognised risk is that its use may lead to a delay in the ability to recognise and treat a progressive deterioration in pulmonary function. This risk is quantified through modelling of the effects of different oxygen regimes in the situation of a progressively increasing intrapulmonary shunt. In contrast, if low flow oxygen therapy is initially used to achieve oxygen saturations around 95%, a subsequent clinical deterioration is likely to be recognised sooner through pulse oximetry, and there is then the option of increasing the oxygen therapy while medical review and the required intervention is undertaken.

Comment: This editorial argues that there needs to be a better appreciation of the potential risks of the inappropriate use of high flow oxygen therapy. This risk includes both adverse physiological effects and the potential for a delay in the recognition of the deteriorating clinical condition. This is contrary to a commonly held belief that administering high flow oxygen to a breathless patient will somehow be beneficial and have a protective effect in the event that pulmonary function worsens. The take home message is that oxygen is a drug that should be prescribed for defined indications, in which the benefits outweigh the risks and that prescription should specify the dose, method and duration of delivery and the patient's response to oxygen therapy should be monitored.

<http://thorax.bmj.com/cgi/content/extract/62/10/840>

Reference: *Thorax* 2007; 62:840-1

Biomass fuels are the probable risk factor for COPD in rural South China

Authors: Liu S et al

Summary: The prevalence of COPD (post-bronchodilator FEV₁/FVC < 70%) in subjects aged 40 years and older was assessed in 1 rural and 1 urban community in Guangdong province in China. Overall prevalence was 9.4%. Rates were significantly greater in the rural (12.0%) compared to the urban (7.4%) community, and in non-smoking women living in the rural vs the urban community (7.2% vs 2.5%, respectively). Biomass fuel use was 88.1% in the rural area compared to 0.7% in the urban area and resulted in significantly greater kitchen concentrations of particulate matter (aerodynamic diameter ≤ 10 µm), sulphur dioxide and nitrogen dioxide. Exposure to biomass fuel used for cooking was positively associated with COPD risk.

Comment: Further evidence that indoor pollutants from biomass fuels are an important risk factor for COPD in developing countries. These exposures are likely to contribute to the unexpectedly high prevalence of COPD in non-smoking women in rural communities in the Asia Pacific region. In these communities the total population exposed to indoor pollution from the use of biofuels for cooking and heating is large. Initiatives to improve the cooking and ventilation conditions in rural communities in the Asia Pacific region are a high priority.

<http://thorax.bmj.com/cgi/content/full/62/10/889>

Reference: *Thorax* 2007; 62:889-97

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The prevalence of chronic obstructive pulmonary disease in China

Authors: Zhong N et al

Summary: 20,245 Chinese subjects aged 40 or older had their lung function assessed via questionnaire and spirometric testing. Overall prevalence of COPD (post-bronchodilator FEV₁/FVC < 70%) was 8.2%. Factors associated with COPD were rural location, older age, smoking, lower BMI, less education, poor kitchen ventilation, occupational exposure to dusts or biomass fuels, and pulmonary problems in childhood or a family history of pulmonary disease. Individuals with COPD were often asymptomatic (35.3%). Only 35% reported a previous diagnosis of bronchitis, emphysema, or other COPD, and only 6.5% had received previous spirometric testing.

Comment: Alarming statistics from China. China is the world's leading producer and consumer of tobacco products, accounts for one-third of all smokers in the world, and not surprisingly has a high rate of COPD. Tobacco control measures will be essential if the high rates of smoking-related diseases in China are to be reduced.

<http://ajrccm.atsjournals.org/cgi/content/abstract/176/8/753>

Reference: *Am J Respir Crit Care Med* 2007; 176:753-60

Traffic exposure and lung function in adults

Authors: Kan H et al

Summary: Data from a community-based cohort of 15,792 middle-aged adults taking part in the Atherosclerosis Risk in Communities study were used to investigate associations between lung function and exposure to traffic (calculated using measures of traffic density and distance to major roads). In women but not men, higher traffic density was associated with reduced lung function (FEV₁ and FVC) after adjustment for demographic factors, personal and neighbourhood level socio-economic characteristics, cigarette smoking and background air pollution. Women, but not men, living within 150m of a major road also had had reductions in FEV₁ and FVC. There were no changes in FEV₁/FVC ratio which correlated with traffic exposure.

Comment: Although there was an association between reduced lung function and road traffic exposure, as measured by traffic density and distance to roadways, the magnitude of the effects was smaller than those due to environmental tobacco smoke exposure. However, these results add to the growing evidence that chronic exposure to traffic-related air pollution may adversely affect respiratory health.

<http://thorax.bmj.com/cgi/content/abstract/62/10/873>

Reference: *Thorax* 2007; 62:873-9

Independent commentary by Professor Richard Beasley

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Prevention of nosocomial transmission of extensively drug-resistant TB in rural South African hospitals

Authors: Basu S et al

Summary: This epidemiological modelling study examined the potential effects of various infection control strategies on the course of the extensively drug-resistant (XDR) TB epidemic in the Tugela Ferry area of rural South Africa. The authors used a mathematical model with more than 2 years worth of inpatient and community data which simulated TB transmission in the hospital and community settings and considered the effects of HIV and antiretroviral therapy. The model predicted 1,300 new cases of XDR-TB by the end of 2012 under existing conditions, with over 50% resulting from nosocomial transmission. Mask use would be effective in preventing many cases of XDR TB amongst hospital staff. Mask use plus reduced hospitalisation time would reduce the total number of cases by 30%. The addition of improved ventilation, rapid drug resistance testing, HIV treatment, and tuberculosis isolation facilities would prevent 48% of all cases.

Comment: These findings are crucial if effective strategies are to be developed to reduce the incidence of XDR-TB. Most cases of XDR-TB are due to nosocomial transmission and a combination of simple infection control measures together with community-based programmes has the potential to prevent around half of all XDR-TB cases – even in resource limiting settings.

[http://dx.doi.org/DOI:10.1016/S0140-6736\(07\)61636-5](http://dx.doi.org/DOI:10.1016/S0140-6736(07)61636-5)

Reference: *Lancet* 2007; 370:1500-7

Clinical and operational value of the extensively drug-resistant tuberculosis definition

Authors: Migliori GB et al

Summary: The authors investigated differences in outcomes between patients with extensively drug-resistant tuberculosis (XDR-TB) and multi-drug-resistant TB (MDR-TB). Of 4,583 cases of TB diagnosed in Estonia, Germany, Italy and the Russian Federation between 1999 and 2006, 7.9% were MDR and 1.4% were XDR. The relative risk (RR) of an unfavourable outcome was 1.58 for individuals with XDR compared to those with MDR resistant to all first-line drugs (isoniazid, rifampicin, ethambutol, streptomycin and, when tested, pyrazinamide). The risk increased to RR 2.61 for those with XDR compared to MDR susceptible to at least one first-line drug (ethambutol, pyrazinamide, streptomycin). Public health measures in order to prevent the development of further drug resistance in Europe are urgently required.

Comment: Evidence that XDR-TB has a worse clinical outcome than MDR-TB. The observation that 75% of XDR-TB cases and 50% of MDR-TB cases were previously treated for TB reinforces the crucial role of optimal initial TB management.

<http://erj.ersjournals.com/cgi/content/abstract/30/4/623>

Reference: *Eur Respir J* 2007; 30:623-6

Patient choice promotes adherence in preventive treatment for latent tuberculosis

Authors: Rennie TW et al

Summary: In this retrospective analysis, the records of 675 patients who received chemoprophylaxis for latent TB were used to compare differences between a 3-month course of treatment with rifampicin and isoniazid (3RH) or 6-months of isoniazid alone (6H). When a further 2,000 patients were given a choice of treatments, most opted for the 3-month regimen. Patients who were more likely to complete treatment were offered a choice of regimen and were compliant with pre-treatment clinic visits. Overall, 53.5% of subjects completed treatment successfully. Most treatment discontinuations occurred during the first 4 weeks of treatment in both groups. Rates of adverse reactions were similar in both groups. Discontinuation due to adverse events occurred in 5.1 and 5.8% of patients receiving the 3RH and the 6H regimens respectively. Treatment costs were higher with the 6H regimen.

Comment: The message of the study is clear – a 3 month regime is the patient's preferred choice of treatment for latent TB, and results in better outcomes than the 6 month regime.

<http://www.erj.ersjournals.com/cgi/content/abstract/30/4/728>

Reference: *Eur Respir J* 2007; 30:728-35

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.

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