

APSR Respiratory Research Review

Making Education Easy

Issue 4 - 2007

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Welcome to the 4th edition of APSR's Respiratory Research Review.

This edition features some highly relevant, topical and concerning data for the Asia Pacific region. The latest WHO data has confirmed the substantial burden from multi-drug resistant tuberculosis in a number of Asia Pacific countries. In regard to potential mortality from a global influenza pandemic, an analysis published in the Lancet (see this page) shows the projected impact also predominantly affecting the Asia Pacific region. We need to ensure that programmes are in place for both these major public health problems.

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

Kind regards,

Richard Beasley

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Global pandemic influenza mortality based on vital registry data from the 1918-20 pandemic

Authors: Murray CJ et al.

Summary: The authors identified all countries with high-quality vital registration data for the 1918-20 influenza pandemic. The data were used to calculate excess mortality, which was then related to per-head income and absolute latitude. This model was then applied to 2004 population data in order to estimate mortality had a pandemic occurred in that year. During the 1918-20 influenza pandemic, population mortality varied over 30-fold across countries, primarily due to differences in per-capita income. Analysis of a potential 2004 pandemic predicted approximately 62 million deaths (range 51-81 million). Global mortality would be increased by 114% if this occurred during a single year. Around 96% (95% CI 95-98) of the total mortality was predicted to occur in the developing world.

Comment: The dire predictions of mortality from pandemic influenza in the Asia Pacific region – about half the deaths globally are predicted to occur in Asia Pacific, and about two-thirds are expected to occur in those aged ≤ 30 years. The impact is likely to be particularly great in low income countries, in which public health resources are already scarce.

<http://www.thelancet.com/journals/lancet/article/PIIS0140673606698954/abstract>

Reference: *Lancet* 2006 Dec 23;368(9554): 2211-8



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Epidemiology of anti-tuberculosis drug resistance: an updated analysis

Authors: Aziz MA et al.

Summary: The authors present combined data collected from the first, second and third (1999-2002) round of surveillance by the WHO and International Union Against Tuberculosis and Lung Disease Global Project on Anti-tuberculosis Drug Resistance Surveillance. Drug susceptibility testing data were gathered for isoniazid, rifampicin, ethambutol, and streptomycin. Standardised guidelines were used to ensure comparability between and within countries. 76 countries or geographical regions participated. Median prevalence of resistance to a single anti-tuberculosis drug was 10.2% (range 0.0-57.1). There was a 1% (range 0.0-14.2) median prevalence of multi-drug resistance in new cases of tuberculosis. Multi-drug resistance above 6.5% was reported in Kazakhstan, Tomsk Oblast (Russia), Karakalpakstan (Uzbekistan), Estonia, Israel, the Chinese provinces Liaoning and Henan, Lithuania, and Latvia. An increasing prevalence of multi-drug resistance was reported from Tomsk Oblast ($p < 0.0001$). Decreasing prevalence was reported from Hong Kong ($p = 0.01$) and the USA ($p = 0.0002$).

Comment: Contrasting statistics for multi-drug resistant tuberculosis in the Asia-Pacific region. Alarming high rates in certain provinces in China, India and Russia, yet decreasing rates in Hong Kong. Programmes are urgently required throughout the Asia-Pacific region that can offer effective diagnosis and treatment for MDR tuberculosis, particularly in China, India and Russia, which account for around two thirds of the estimated global burden.

<http://www.thelancet.com/journals/lancet/article/PIIS0140673606698632/abstract>

Reference: Lancet 2006 Dec 16; 638(9553): 2142-54

5-year survival rates in women and men with non-small cell lung cancer

Authors: Cerfolio RJ et al.

Summary: In this prospective cohort of consecutive patients with non-small cell lung cancer, 671 men and 414 women were clinically and pathologically staged with stage I, II, or III disease. Treatment was in accordance with the same treatment algorithm and follow-up was over 7 years. Baseline characteristics were similar in men and women, however women were younger ($p = 0.014$), were more likely to have adenocarcinoma ($p = 0.01$), and presented at an earlier pathologic stage ($p = 0.01$) than men. Overall age and stage-adjusted 5-year survival rates were significantly improved in women (60% vs 50%, respectively; $p < 0.001$). Stage-specific 5-year survival rates were also greater in women at stage I (69% vs 64%; $p = 0.034$), stage II (60% vs 50%; $p = 0.042$) and stage III (46% vs 37%; $p = 0.024$). Higher rates of complete and partial response occurred with neoadjuvant chemotherapy alone in women vs men ($n = 142$; $p = 0.025$).

Comment: A timely reminder of the increasing burden of lung cancer in women, and the need to define with more certainty their clinico-pathological features and response to treatment regimes. There is now evidence to suggest that there may be important clinical differences in lung cancer between females and males, including a better response in women to neoadjuvant chemotherapy.

<http://www.chestjournal.org/cgi/content/abstract/130/6/1796>

Reference: Chest 2006; 130: 1796-1802

Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer

Authors: Sandler A et al.

Summary: Subjects were 878 patients with recurrent or advanced non-small-cell lung cancer (stage IIIB or IV), excluding those with squamous-cell tumours, brain metastases, clinically significant hemoptysis, inadequate organ function or performance status (ECOG performance status, > 1). Patients were randomised to chemotherapy with paclitaxel and carboplatin alone (6 cycles per 3 weeks) ($n = 444$) or paclitaxel and carboplatin alone (6 cycles per 3 weeks) plus bevacizumab (3 weekly) ($n = 434$). Treatment was continued until toxicity became intolerable or until disease progression. Median survival was significantly improved in the bevacizumab group (12.3 vs 10.3 months; HR for death 0.79; $p = 0.003$). Disease free survival (6.2 vs 4.5 months; HR for progression 0.66; $p < 0.001$) and response rates (35 vs 15%; $p = 0.001$) were also significantly improved with bevacizumab. Bevacizumab treated-patients had significantly higher rates of clinically significant bleeding (4.4 vs 0.7%; $p < 0.001$), and 15 treatment-related deaths (including 5 from pulmonary haemorrhage) occurred in this group.

Comment: Important proof of concept study. Although the survival benefit with bevacizumab was statistically significant, the differences were small in a highly selected group of patients.

<http://content.nejm.org/cgi/content/abstract/355/24/2542>

Reference: N Engl J Med 2006; 355: 2542-50

Independent commentary by Professor Richard Beasley

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Clinical syndromes and outcomes in patients with pulmonary embolism

Authors: Lobo JL et al.

Summary: The authors present findings from the Registro Informatizado de la Enfermedad TromboEmbólica (RIETE), an ongoing database of consecutive patients with acute venous thromboembolism. Clinical characteristics, laboratory findings, and 3-month outcomes of enrolled patients with symptomatic, objectively confirmed pulmonary embolism (PE) (n = 3,391) and no pre-existing cardiac or pulmonary disease were compared. In patients with pulmonary infarction (50%), the mortality rate during days 1-15 was 4.4%. For patients with isolated dyspnea (32%) and circulatory collapse (18%), mortality rates were 6.2 and 6.5% respectively. Recurrent PE occurred in 31 patients during days 16-90. Mortality from recurrent PE was 36, 50 and 100% in patients with pulmonary infarction, isolated dyspnea and circulatory collapse.

Comment: Expanding the risk profile of patients presenting with PE – isolated breathlessness and hypoxaemia indicates an increased risk of death, similar in magnitude to circulatory collapse. Other useful markers of risk include ECG or echo-cardiographic evidence of RV strain, a raised troponin-T, hypotension (systolic <100mmHg) and pulse >110/min.

<http://www.chestjournal.org/cgi/content/abstract/130/6/1817>

Reference: *Chest* 2006; 130: 1817-1822

Is methamphetamine use associated with idiopathic pulmonary arterial hypertension?

Authors: Chin KM et al.

Summary: The aim of this retrospective study was to determine if rates of stimulant use were increased in patients presenting with idiopathic pulmonary arterial hypertension (PAH). Use of stimulants (amphetamine, methamphetamine or cocaine) was retrospectively determined for 340 patients presenting with idiopathic PAH, PAH and known risk factors, and chronic thromboembolic pulmonary hypertension (CTEPH). Rates of stimulant use were 28.9, 3.8 and 4.3% for patients presenting with idiopathic PAH, PAH and known risk factors, and CTEPH respectively. Patients presenting with idiopathic PAH were significantly more likely to have used stimulants (age-adjusted rates) compared to those presenting with PAH and known risk factors (OR 10.14; 95% CI 3.39 to 30.3; p < 0.0001) or CTEPH (OR 7.63; 95% CI 2.99 to 19.5; p < 0.0001). The authors concluded that patients with idiopathic PAH were significantly more likely to have used stimulants than patients with other forms of pulmonary hypertension.

Comment: Strong evidence that methamphetamine use is an important and common risk factor for idiopathic PAH. Enquiry of illicit drug use in patients presenting with PAH now represents an essential component of the history.

<http://www.chestjournal.org/cgi/content/abstract/130/6/1657>

Reference: *Chest* 2006; 130: 1647-1663

Outcomes in children treated for persistent bacterial bronchitis

Authors: Donnelley D et al.

Summary: Persistent bacterial bronchitis (PBB) may be under-recognised and misdiagnosed as asthma. Treatment may prevent progression to bronchiectasis. This retrospective chart review assessed the outcomes of patients with PBB attending a paediatric respiratory clinic. Data were available from 81 patients with PBB, based on the standard diagnostic criterion of a persistent, wet cough for >1 month that resolves with appropriate antibiotic treatment. A persistent cough or difficult asthma were the most common reasons for referral. Symptoms had started prior to the age of 2 in most patients, and in 59% of cases had persisted for >1 year. 11% of patients were receiving antibiotics at referral, and 59% asthma treatment. The most commonly isolated organisms were *Haemophilus influenzae* and *Streptococcus pneumoniae*. Two courses of antibiotics were sufficient for over 50% of patients. 13% of patients required > 6 courses of antibiotics.

Comment: A greater awareness of the clinical significance and therapeutic approach to persistent bacterial bronchitis (PBB) is required. This study is worth reading, especially the discussion of the "vicious circle" hypothesis, the role of PBB in the development of bronchiectasis, and its overlap with clinical asthma.

<http://thorax.bmj.com/cgi/content/abstract/62/1/80>

Reference: *Thorax* 2007; 62: 80-84



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Early switch from oral antibiotics in severe community acquired pneumonia

Authors: Oosterheert JJ et al.

Summary: This Dutch multi-centre, randomised controlled study was designed to compare the effectiveness of an early switch to oral antibiotics with the standard 7-day course of intravenous antibiotics in severe, community-acquired pneumonia. 302 patients in non-intensive care wards with severe community acquired pneumonia were randomised to either 3 days of treatment with intravenous antibiotics, followed by oral antibiotics when clinically stable, or by 7 days of intravenous antibiotics. Mortality (day 28) was 4 and 6% in the intervention and control groups respectively. Clinical cure was 83 and 85%. Duration of intravenous treatment was 3.6 and 7.0 days for the intervention and control groups respectively, and length of hospital stay was 9.6 and 11.5 days. The authors concluded that: "Early switch from intravenous to oral antibiotics in patients with severe community acquired pneumonia is safe and decreases length of hospital stay by 2 days."

Comment: Early transition to oral antibiotics can be safely implemented in patients with severe community-acquired pneumonia not requiring ICU care who respond well to initial therapy. The criteria used to switch to oral antibiotics on day 3 are: respiratory rate <25/min, O₂ sats >90%, haemodynamically stable, >1°C decrease in temperature, no mental confusion and able to take oral antibiotics.

<http://www.bmj.com/cgi/content/abstract/333/7580/1193>

Reference: BMJ doi: 10.1136/bmj.38993.560984.BE (published 7 November 2006)

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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.

Early switch to oral antibiotics and early discharge guidelines for community-acquired pneumonia

Authors: Lee RWW, Lindstrom ST.

Summary: This study assessed the benefits and safety of early switch to oral antibiotics and early discharge guidelines in an Australian respiratory medicine unit. 125 patients with community acquired pneumonia were consecutively recruited over a 6-month period. Guidelines for early switch to oral antibiotics and early discharge were implemented 1 month before evaluation. Data were compared to a historical control group (n = 100) with similar baseline characteristics, who were treated prior to the introduction of the guidelines. Significant reductions in mean duration of IV antibiotic treatment (3.38 vs 3.99 days; p = 0.03) and length of hospital stay (3.38 vs 3.99 days; p = 0.03) were observed in the intervention group compared to controls. Only 6% of intervention group patients required readmission within 30 days. Patient satisfaction with treatment was 93.9%.

Comment: Extending the guidelines for an early switch to oral antibiotics, to those for early discharge. Note the ATS guidelines on which the criteria are based. (Am J Respir Crit Care Med 2001; 163:1730-54).

<http://www.blackwell-synergy.com/doi/abs/10.1111/j.1440-1843.2006.00931.x>

Reference: Respiriology 2007; 12: 111-116

Diagnostic techniques for ventilator-associated pneumonia

Authors: Lee RWW and Lindstrom ST.

Summary: Subjects in this multi-centre study were 740 immunocompetent adults who were receiving mechanical ventilation and who had suspected ventilator-associated pneumonia after 4 days in the intensive care unit. Patients were randomised to receive either bronchoalveolar lavage with quantitative culture of the bronchoalveolar-lavage fluid or endotracheal aspiration with nonquantitative culture of the aspirate. All patients received empirical antibiotic therapy followed by targeted therapy once culture results were available. 28-day mortality was not different in the bronchoalveolar-lavage and endotracheal aspiration groups (18.9 and 18.4%; p = 0.94). There were no significant differences in other outcomes including rates of targeted therapy (74.2% vs 74.6%; p = 0.90), days alive without antibiotics (10.4 vs 10.6; p = 0.86), and maximum organ-dysfunction scores (mean 8.3 vs 8.6; p = 0.26), length of hospital or ICU stay. Both bronchoalveolar-lavage and endotracheal aspiration with nonquantitative culture of the aspirate were associated with similar clinical outcomes and similar overall use of antibiotics.

Comment: A study to refer to for the next ICU consult for bronchoscopy to help diagnose the organisms in ventilator-induced pneumonia – endotracheal aspiration has similar utility. Regardless of the method used, the initial priority is to ensure the prompt empiric use of broad spectrum antibiotics, pending the microbiological results. As outlined in the accompanying editorial, the other priority is to minimise the development of resistance by vigorously using a de-escalation strategy, i.e. reducing the initial antimicrobial regimen once the microbiological data becomes available and use antimicrobial therapy for the shortest duration that is clinically effective.

<http://content.nejm.org/cgi/content/abstract/355/25/2619>

Reference: Am J Respir Crit Care Med 2001; 163: 1730-54

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