

## INVITED REVIEW

**Respirology year-in-review 2006: Clinical science**Y.C. GARY LEE<sup>1,2</sup> AND RICHARD BEASLEY<sup>3,4</sup>

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**INTRODUCTION**

Thanks to the support of researchers and clinicians worldwide, *Respirology* has flourished further in 2006. The number of submissions has increased significantly, and the journal now publishes six issues each year. More importantly, the quality and diversity of the publications also improved progressively. While *Respirology* remains firmly the regional respiratory journal for Asian and Pacific countries, the last 12 months have seen publication of articles from many countries beyond this region. The published papers not only covered issues of local interest, but also addressed worldwide respiratory problems through large clinical trials, authoritative reviews, as well as small pilot studies establishing proof of principles of exciting novel concepts.

In the Year-in-Review article of 2005, we found that articles on airways disease accounted for about half of the clinical studies published in *Respirology*. This year has seen an impressive increase in articles of other areas of chest medicine, further expanding the breadth of topics covered regularly in *Respirology*. In the following review, we highlight the key messages from articles published in *Respirology* in 2006.

**LUNG CANCER**

Lung cancer is the leading cancer cause of death. Based on 2002 estimates, over one million people

died of lung cancer worldwide. Although most cases are related to tobacco smoking, increasing concerns have been raised on development of adenocarcinoma in Asian women, many of whom never smoked.<sup>1</sup> Of interest to the clinicians in Asia-Pacific countries is the finding of high incidence of epidermal growth factor receptor (EGFR) mutations in lung cancers in Asian countries (e.g. Hong Kong and Japan). Many of these patients have no or modest smoking history.<sup>1</sup> Ho *et al.* also highlighted the importance of identifying lymphoepithelioma-like carcinoma of the lung—an uncommon but distinct form of non-small cell lung carcinoma that affects predominantly Asians.<sup>2</sup>

Increasing evidence suggests that Asian patients with lung adenocarcinomas show a higher response rate to gefitinib, a small-molecule EGFR tyrosine kinase inhibitor. *Respirology* provided a series of state-of-the-art reviews as well as original articles on the use of EGFR tyrosine kinase inhibitors in lung cancer. Ahmed and Salgia reviewed recent research efforts to identify genomic determinants of drug susceptibility to EGFR tyrosine kinase inhibitors,<sup>3</sup> revealing various EGFR kinase domain mutations that may influence response to drug treatment or differential susceptibility to various EGFR tyrosine kinase inhibitors.<sup>3</sup> Kato and Nishio presented a detailed review on the benefits as well as risks of these inhibitors in clinical practice.<sup>4</sup> A retrospective analyses of 23 Singaporean patients provided supportive data that EGFR tyrosine kinase inhibitors have anti-tumour activities.<sup>5</sup> Gefitinib can induce acute lung injury or interstitial pneumonitis as shown in two separate case reports published in *Respirology*. Both cases were successfully treated with cessation of the

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drug, with or without additional high-dose methylprednisolone treatment.<sup>6,7</sup>

Small cell lung cancer accounts for up to 25% of primary lung cancers. Cooper and Spiro reviewed the literature and emphasized that elderly patients with small cell lung cancer should not be discriminated for their age, as their response to chemotherapy is generally comparable to that of younger patients.<sup>8</sup>

Researchers are actively searching for a sensitive and specific method for early detection of lung cancer: CT screening, autofluorescence bronchoscopy, etc. are under study. A study of 137 patients with lung cancer showed that those ( $n = 19$ ) with early disease detected only on CT, but not on CXR, had significantly better prognosis (5-year survival 80% vs. 39%, respectively) than those with lung cancer visible on both CT and chest radiographs.<sup>9</sup> However, Shaipanich *et al.* believed that no single modality will achieve sufficient accuracy as a sole screening tool, and combination with additional biomarkers may be more likely to succeed.<sup>10</sup>

PET-CT is increasingly employed in the work-up of patients with lung cancer. Low *et al.* reviewed their experience of 54 patients who underwent PET-CT and reminded readers that false positives do occur, including in patients with tuberculosis lymphadenitis.<sup>11</sup> This is especially important for clinicians practising in regions where tuberculosis is endemic.

Transbronchial needle aspiration of lymph nodes is widely used nowadays for sampling enlarged nodes to aid diagnosis and staging of lung cancer patients. A large study of 153 patients explored the value of routine sampling of subcarinal lymph nodes in patients with lung cancer, with or without enlarged lymph nodes on CT scanning.<sup>12</sup> This sampling procedure contributed to the staging and/or diagnosis of 16% (25/153) of the patients. In particular, seven patients had no CT evidence of subcarinal node involvement were positive for tumour metastases on needle aspiration.<sup>12</sup> The role of routine transbronchial aspiration deserves further exploration.

Sputum cytology may still hold a role in the diagnostic algorithm for lung cancer. In a large series of 601 patients who had atypical cells identified in the sputa, more than 90% were eventually diagnosed to have lung cancer.<sup>13</sup> Imaging-guided transthoracic needle aspiration is another commonly used diagnostic method for lung cancers. In 35 resected surgical specimens, Unver *et al.* showed that the diagnostic sensitivity of needle aspiration was similar using 18-, 22- and 25-gauge needles.<sup>14</sup>

Readers are reminded that not all pulmonary nodules turned out to be malignant. Various case reports published in *Respirology* attested to the variety of other pathologies that may mimic lung cancers, including endobronchial mucosal lesions from Churg–Strauss syndrome,<sup>15</sup> atypical mycobacterium infection,<sup>16</sup> dirofilariasis (infection of the dog heartworm) and chest wall involvement from multifocal mesenchymal hamartoma.<sup>17</sup> Coexistence of blastoma

within bronchoalveolar cell carcinoma was also reported.<sup>18</sup> Readers were also reminded of rare neoplasms, such as pulmonary epithelioid hemangioendothelioma<sup>19</sup> and pulmonary sarcoma,<sup>20</sup> emphasizing the need of histological confirmation of the lesions.

Pulmonary endometriosis, giving rise to recurrent haemoptysis, can raise concern for lung cancer. Successful treatment of endobronchial endometriosis by argon plasma<sup>21</sup> or by video-assisted thoracoscopic surgery<sup>22</sup> has been described in separate reports in *Respirology*.

## INTERSTITIAL LUNG DISEASES

Diffuse interstitial lung diseases encompass a wide range of heterogeneous conditions with varying prognosis. Within the Asia–Pacific region, the incidences of different interstitial lung diseases vary. For example, a retrospective series suggested that the incidence of idiopathic pulmonary fibrosis may be lower in Maori and Pacific Islanders than the Caucasians in New Zealand.<sup>23</sup> In northern Israel, the incidence of sarcoidosis was found to be similar between Arabic and Jewish subjects, though the former presented usually with earlier-stage disease.<sup>24</sup>

This year, *Respirology* has published overviews on extrinsic allergic alveolitis (a topic seldom reviewed)<sup>25</sup> and also on diffuse panbronchiolitis, a condition most common in East Asia.<sup>26</sup> The exact aetiological mechanisms remain unclear for both diseases. Steroid is useful in some cases of extrinsic allergic alveolitis.<sup>25</sup> On the other hand, macrolides remain the choice of treatment for diffuse panbronchiolitis.<sup>26</sup>

Diagnosis of interstitial lung diseases is now largely dependent on CT scanning, but gravity-dependent changes are known to occur with supine scanning, and may be mistaken as early interstitial changes. A multivariate analysis of 1098 patients suggested that subjects who were over 70 years of age, obese (BMI >25) and current smokers (>20 pack year) were more likely to have dependent changes on helical CT screening, mimicking interstitial lung diseases.<sup>27</sup>

The spectrum of drugs and environmental agents that can induce interstitial lung diseases continue to expand. *Respirology* included several case reports on acute lung injury from new cancer drugs, such as trastuzumab (herceptin)<sup>28</sup> and gefitinib. Early recognition of this complication and withdrawal of medication result in good outcome. An interesting case of pulmonary alveolar proteinosis associated with initiation of leflunomide was described and was successfully treated with drug withdrawal and whole lung lavage.<sup>29</sup> Acute interstitial pneumonia from inhalation of fumes of nickel and chrome, successfully treated with corticosteroids, was also reported.<sup>30</sup> Demirkok *et al.* observed that Lofgren's syndrome was more common in May and least so in January in 87 Turkish patients, suggesting a possible environmental aetiology.<sup>31</sup>

Two reports in *Respirology* this year reminded us the potential connection between autoimmunity and seemingly unrelated pulmonary diseases. Kudou *et al.* reported that rheumatoid factor correlated well with eosinophil counts in a patient with chronic eosinophilic pneumonia. In particular, the titre of rheumatoid factor may even rise prior to clinical exacerbation—an observation that may deserve verification in larger series.<sup>32</sup> Coexistence of antiphospholipid syndrome in a patient with biopsy-proven sarcoidosis was also discussed.<sup>33</sup>

## PLEURAL DISEASES

The incidence and patterns of pleural diseases vary significantly within the Asia-Pacific region.<sup>34</sup> This is to some extent reflected in the range of pleural research papers published in *Respirology* in 2006.

A single-centre, randomized study from Japan compared the efficacy of cisplatin, OK-432, or combination of both, as pleurodesing agents. Given intrapleurally, the combination of cisplatin and OK-432 provided a significantly higher success rate of 86% than intrapleural administration of either agent alone (35% and 47%, respectively) in patients with malignant effusions from lung cancer.<sup>35</sup> From India, Agarwal *et al.* showed that intrapleural instillation of iodopovidone was safe and could induce successful pleurodesis in more than 80% of patients with malignant effusion or pneumothorax.<sup>36</sup> Side-effects (mainly pain and fever) were compatible with commonly used pleurodesing agents.

Several papers describe less common causes of pleural effusions. Rice *et al.* reported that more than half of the patients with superior vena cava obstruction had a pleural effusion, the majority (60%) turned out to be from malignant aetiology.<sup>37</sup> Subarachnoid-pleural fistula was reported in a patient with mesothelioma. The diagnosis was confirmed by the demonstration of beta-trace protein (usually only found in cerebrospinal fluid) in the pleural fluid.<sup>38</sup>

Adenosine deaminase is now considered part of the standard work-up for tuberculous pleuritis in many endemic countries. A study of 27 samples confirmed that adenosine deaminase measurements were stable at room temperature up to 10 days after thoracentesis.<sup>39</sup>

## INTERVENTIONAL PULMONOLOGY

Murgu and Colt provided a comprehensive review on tracheobronchomalacia and excessive dynamic airway collapse, including the latest treatment options and experimental approaches.<sup>40</sup> Increasing interests are shown in the use of argon plasma coagulation, for example in the management of post-intubation tracheal stenosis,<sup>41</sup> endobronchial endometriosis<sup>21</sup> and devitalizing tissue in the presence of airway stents.<sup>42</sup>

Stenting is another option of managing stenotic airways. In a retrospective review of 100 stents placed for post-tuberculous or post-intubation tracheal stenosis, the effectiveness and safety of a new silicone airway stent (Natural stent) was found to be comparable to that of more commonly used Dumon stents.<sup>43</sup>

Bronchial artery embolization is an important management option for patients with haemoptysis. In a large series of 118 patients with significant haemoptysis (96% had >100 mL/day) from tuberculosis or lung cancer, no significant re-bleeding was found in 73% of cases after bronchial artery embolization.<sup>44</sup> Repeat embolization controlled the bleeding in 12 of 32 patients who failed the first procedure. Patients with aspergillosis were particularly at risks of re-bleeding after embolization.<sup>44</sup> Incidentally, chronic necrotizing pulmonary aspergillosis can develop as a complication in patients with *Mycobacterium avium* complex infection,<sup>45</sup> as shown in a case series from Japan.

## OSA

The public health importance of OSA has been increasingly recognized over the last decade. In their extensive review, McNicholas and Ryan discuss the basic mechanisms that contribute to the development of OSA and its cardiovascular consequences and how an understanding of these mechanisms can be translated into clinical practice.<sup>46</sup> An important example raised is the development of auto-adjusting CPAP in response to the understanding that the pressure required to prevent upper airway collapse fluctuates throughout the night and results in a lower mean pressure that may be more comfortable for some patients.

It is well recognized that OSA is associated with increased cardiovascular morbidity and mortality due to the frequent apnoeic events associated with oxygen desaturation during sleep. The study of Hayashi *et al.* has investigated potential mechanisms to explain this association, and provided evidence that atherosclerosis-associated molecules in the peripheral blood may be upregulated by repetitive hypoxaemia in OSA and suggest that they may have a pathogenic role in the development of atherosclerosis in OSA.<sup>47</sup>

In a fascinating study based on previous research in Nepal, Burgess *et al.* showed that moderately severe OSA at sea level was completely replaced by severe central sleep apnoea at a simulated altitude of 2750 m.<sup>48</sup> It was proposed that OSA resolved because of an increased respiratory rate and an increase in upper airway tone, whereas central sleep apnoea developed because of hypocapnia during non-rapid eye movement sleep.

In the study of Windisch *et al.* it was shown that the connecting tube is the major determinant of the resistance originating from facial appliances used for non-invasive positive pressure ventilation.<sup>49</sup> The size of the nasal mask seems to play a minor role with respect to resistance.

## COPD

COPD is one of the leading causes of morbidity and mortality and according to the World Health Organization will become the third leading cause of mortality in 2020 worldwide. The review of Viegi and colleagues provided a timely reminder of the important role of air pollution as a contributing cause of this morbidity and mortality.<sup>50</sup> They challenge respiratory physicians as well as public health professionals to advocate for a cleaner environment and this would appear to be a particular priority in the Asia-Pacific region.

Infection with the intracellular bacterium *Chlamydia pneumoniae* has been associated with a number of chronic diseases including asthma and coronary heart disease. A pathogenic role has also been proposed for COPD with patients having a high prevalence of antibodies against *C. pneumoniae*. The study by Kurashima *et al.* provided further evidence for such a role, with the demonstration of high antibody titres against *C. pneumoniae* linked to severity of emphysema.<sup>51</sup> There is probably now sufficient evidence to warrant a clinical trial of long-term macrolide therapy in COPD.

One of the major advances in the management of COPD over the last decade has been the availability of long-acting bronchodilators including the anticholinergic agent tiotropium. The study by Perna *et al.* provided further evidence of the clinical benefit in lung function and quality of life with tiotropium in subjects with severe COPD.<sup>52</sup> One of the important findings from the study was that the bronchodilator response to ipratropium did not predict the improvement in lung function obtained with tiotropium. As a result, demonstration of bronchodilator responsiveness should not be a prerequisite for giving COPD patients a trial of tiotropium.

Further evidence for the efficacy of low-dose theophylline in the long-term treatment of stable COPD was provided by Zhou *et al.*<sup>53</sup> As in the treatment of asthma, oral theophylline represents an alternative to inhaled long-acting beta agonist therapy in COPD, particularly in developing countries where cost is an important determinant of the availability of medications.

With the clear demonstration of efficacy with the asthma self-management plan system of care, there have now been attempts to develop similar plans for COPD. There were two studies that investigated the efficacy of a similar self-management plan, both reporting no added health benefit to usual care in the general practice management of COPD.<sup>54,55</sup> This suggests that there may need to be significant changes in the format and components of the COPD self-management plans, which are currently based on their asthma counterparts. As a result further research is required before the widespread adoption of action plans in COPD can be recommended.

The study of Cao *et al.* provided concerning data about the major morbidity and poor quality of life of subjects with recurrent hospital admissions for

COPD.<sup>56</sup> It would be reasonable to target such individuals within the community as severe COPD appears to be an inadequately managed health problem.

One of the initiatives in COPD has been the objective measurement of airflow obstruction through the implementation of spirometry in general practice and Australia has led the way in this regard. However, the study of Johns *et al.* showed that it is inadequate to simply introduce spirometers into general practice and that an implementation and training programme is required to ensure benefits are obtained.<sup>57</sup> In terms of types of spirometers, Walters *et al.* have confirmed that the EasyOne spirometer maintains its calibration during routine clinical use in general practice and thus passes the required quality-control tests.<sup>58</sup>

One of the challenges in pulmonary rehabilitation is to determine the components of the programme that lead to benefit and how the programme can be practically implemented within a community. The study by Cockram *et al.* provides a simple prototype pulmonary rehabilitation programme, supervised by a physiotherapist but combined with a home exercise programme and shown that it is an effective intervention for achieving and maintaining improvements in function.<sup>59</sup>

Eastwood *et al.* reported that a high-intensity inspiratory muscle training programme combined with general whole body exercise training was capable of improving respiratory muscle function to a point where these muscles that were unable to work anaerobically before training, were subsequently able to do so.<sup>60</sup> This study is the first to have shown that COPD patients can increase inspiratory muscle work rate to a level requiring a major energy contribution from anaerobic glycolytic metabolism. Previously this function had only been shown in healthy individuals. Consistent with these observations, Vella *et al.* provided evidence that the oxygen cost of ventilation may be a limiting factor in exercise capacity, a finding that has clinical significance to respiratory disorders.<sup>61</sup>

There is increasing interest in the use of CT scanning in the characterization of subjects with COPD. Ohara and colleagues provide further evidence that measurement of airway dimensions and lung attenuation still does not yet have an established role in the clinical investigation of patients with COPD.<sup>62</sup> Omori *et al.* report that a considerable percentage of subjects with emphysema detected by CT screening have mild COPD, with Global Initiative for Chronic Obstructive Lung Disease stage 0. A better understanding of the progression of emphysema in these subjects will be required before CT screening can be recommended to detect early-stage emphysema.<sup>63</sup>

## PREDICTION EQUATIONS

A number of studies highlighted the importance of using reference equations for lung function tests derived and/or validated in the population in whom they are used. On behalf of the Australian and New

Zealand Society of Respiratory Science, Hall and Gain expressed concern that only a small proportion of lung function laboratories had validated their reference data with appropriate controls representative of local healthy subjects.<sup>64</sup> They recommended that validation of reference data and/or derivation of normative reference values is a high priority for all respiratory departments in the region. In support of this recommendation, Poh *et al.* reported that published equations derived from Caucasian subjects overestimate 6-min walk distance in Singaporean Chinese and provided relevant predicted values.<sup>65</sup> Likewise, Amra *et al.* provided normative reference values for lung transfer factor in Iran.<sup>66</sup> Williams *et al.* provide preliminary data of the ability of the 15-count breathlessness score to quantify breathlessness and recommended further research in this field.<sup>67</sup> Similar to the situation with lung function testing, Aggarwal *et al.* reported that standard severity scoring systems developed in western countries are poor at predicting patient outcome in critically ill patients admitted to respiratory intensive care units in Northern India.<sup>68</sup>

## ASTHMA

The Asthma Insights and Reality in Asia-Pacific study has shown that the burden of asthma in the Asia-Pacific region is substantial. In the most recent publication from this study, which was undertaken in eight centres of the Asia-Pacific region, data were provided that management of asthma fell far short of that recommended by international consensus guidelines.<sup>69</sup> While there was significant variation between countries, overall the considerable morbidity that was experienced could be attributed to inadequate assessment and management. These findings indicate that measures to improve the management of asthma in accordance with international guidelines within the Asia-Pacific region are a high priority.

In asthma one of the research priorities is to characterize different phenotypes of asthma in an attempt to not only better understand the pathogenesis of the different forms of this disease, but also to guide therapeutic interventions. Simpson *et al.* have demonstrated that assessment of inflammatory cellular subtypes obtained from induced sputum can identify distinct phenotypic groups and proposed that this method may be important in clinical studies of asthma.<sup>70</sup>

With the increasing recognition of a pathogenic role of the intracellular bacteria including *Chlamydia* and *Mycoplasma* species, there has been interest in the potential role of other intracellular bacteria such as *Simkania negevensis*. Reassuringly, Korppi *et al.* report that although *S. negevensis* appears to cause respiratory infections in Finnish infants, there is no apparent association with asthma.<sup>71</sup>

Among the diseases that may mimic asthma and COPD are tracheobronchomalacia and excessive dynamic airway collapse, two forms of dynamic central airway obstruction that may coexist. Murgu and

Colt review these entities and make recommendations regarding their diagnosis and treatment in their comprehensive review.<sup>40</sup> George and colleagues illustrated the utility of virtual bronchoscopy by 3D reconstruction of the tracheobronchial tree from thin-slice CT scanning in the diagnosis of Williams–Campbell syndrome, which can give rise to expiratory collapse of bronchi.<sup>72</sup>

Hassan *et al.* reported that significant bronchospasm occurs in a sizeable proportion of patients presenting with painful sickle cell crises.<sup>73</sup> Importantly they provide evidence to suggest a pathogenic role for the pulmonary sequestration of eosinophils in the bronchoconstriction, which occurs in sickle cell disease. Their findings support the recommendation that bronchodilator therapy should represent part of the treatment of patients with sickle cell disease who have respiratory symptoms.

Jenkins *et al.* reported the first study of the efficacy of the high-dose budesonide/formoterol combination inhaler in patients with severe asthma not controlled on high-dose inhaled corticosteroids.<sup>74</sup> Disappointingly the efficacy was not superior to budesonide and formoterol administered via separate inhalers, which one might have expected should the use of combination inhalers increase compliance. It is now crucial that the effectiveness of combination therapy is assessed in the ‘real world’, outside the strict environment of a randomized controlled trial and that there is direct assessment of compliance and its influence on clinical outcomes.

It has previously been demonstrated that the combination salmeterol/fluticasone inhaler may achieve bronchodilation that lasts for 24 h when administered in the evening in adults.<sup>75</sup> Aldington *et al.* have now demonstrated that the bronchodilation with this combination inhaler persists for at least 20 h when administered in the evening to children with asthma.<sup>76</sup> The authors recommend that clinical studies are now undertaken to determine whether the use of combination inhaler therapy in the evening may be suitable for children with nocturnal asthma.

Tobin *et al.* have shown that systemic salbutamol may impose ventilatory demands by increasing metabolic rate and serum lactate.<sup>77</sup> While a control group receiving inhaled salbutamol was not studied, this study provides further evidence that high-dose nebulized salbutamol is preferred to i.v. salbutamol in the treatment of life-threatening asthma.

The use of complementary and alternative medicine in the management of asthma is under-recognized, particularly in western countries. However, it was evident from the review by Slader *et al.* that complementary and alternative medicine is commonly used by both children and adults, although strong evidence for effectiveness for any of the modalities reviewed was lacking.<sup>78</sup> They propose that further work in this area is required in order to direct future research endeavours, as well as provide useful information for health-care practitioners regarding the use of complementary and alternative medicines by their patients with asthma.

## VENOUS THROMBOEMBOLISM AND PULMONARY HYPERTENSION

There were two studies that investigated the role of risk factors for venous thromboembolism (VTE). Hughes *et al.* reported that in a New Zealand population, long-distance air travel is an important risk factor for VTE requiring hospital admission.<sup>79</sup> There was documentation of recent long-distance air travel in around one in 10 people admitted to hospital with a deep vein thrombosis or pulmonary embolism. This figure is likely to represent an underestimate of the true prevalence due to the incomplete ascertainment of this aspect of the history from the medical records surveyed.

The study of Öner Erkekol *et al.* assessed the relevant importance of different genetic and acquired forms of thrombophilia in the development of VTE.<sup>80</sup> The authors provide evidence that elevated plasma factor VIII levels are a strong independent risk factor for VTE and suggest that this should be included in the battery of tests for thrombophilic states.

The requirement to consider the complex pathophysiological and genetic factors contributing to pulmonary arterial hypertension as a guide to treatment is discussed in the review by Martin *et al.*<sup>81</sup> They elegantly detail how recent research highlighting new pathways affecting pulmonary vasomotor tone and cellular proliferation has provided the basis for new therapeutic approaches to this devastating disease.

Relevant to the pathogenesis of idiopathic pulmonary arterial hypertension, Itoh *et al.* reported that plasma monocyte chemoattractant protein-1 was elevated in patients with this disorder, particularly in the early stages of disease.<sup>82</sup> When the chemoattractant activity of monocyte chemoattractant protein-1 is considered, these results imply that it may have a role in the development of pulmonary hypertension and that its measurement may be a useful tool in the diagnosis of this condition.

## SMOKING

The importance of smoking cessation programmes is underscored by the recent World Health Organization predictions that around 4.5 million people die prematurely each year because of cigarette smoking. Many different models for smoking cessation programmes have been developed and the study of Akkaya *et al.* from Turkey reports the effect of an intensive programme, as well as the factors that influence outcome.<sup>83</sup> Motivational training and telephone counselling were found to be key features of their cost-effective programme.

There is a widely held view that smoking tobacco by alternative methods to standard cigarettes is associated with less harm. The study by Al Mutair *et al.* investigated the effects of hubble-bubble (Sheesha or Hookah) smoking, a traditional method of smoking tobacco leaves in the Middle East and Indian Subcontinent.<sup>84</sup> They provide evidence that this alternative

method does not limit the risk of adverse health effects of tobacco smoking. Similar research into the risks of other forms of tobacco and marijuana smoking is urgently required in view of the increasing rates of smoking worldwide.

## RESPIRATORY INFECTIONS

The different possible case scenarios and logistic issues relevant to an H5N1 pandemic are discussed in a guest editorial.<sup>85</sup> The worst case scenario is presented in which 10–20% of an entire population could become affected and become gravely ill requiring intensive care therapy and cross-infecting health-care workers and other patients, and thus rapidly paralysing health-care systems. It is suggested that no contingency plan could cater for such health-care requirements and prioritization would be needed to preserve key personnel for the aftermath. Another scenario proposed is an outbreak similar to SARS, a situation in which close contacts and health-care workers would be cross-infected. The health-care and public health measures similar to those adopted for SARS should be effective and a pandemic potentially preventable. The editorial provides clear guidelines for the systems that need to be established for diagnosis, management, prioritization according to risk, as well as the clinical research studies that should be pre-established for rapid deployment in the event of an outbreak. The guidelines presented form a good basis for public health strategies that can be adopted in different countries within the Asia-Pacific region.

While the international focus has moved from SARS to avian influenza, there is still considerable interest in the epidemiology of SARS, which was a life-threatening pandemic, affecting more than 8000 people worldwide with a case fatality rate as high as 10%. It is known that the rapidly progressive atypical pneumonia that characterizes SARS is caused by a novel coronavirus, against which almost all patients with SARS mount an antibody response. The Guangzhou group has now shown that the antibody response may persist for up to 2 years, suggesting that SARS patients may be protected from a recurrent SARS coronavirus infection during this period.<sup>86</sup>

Varicella pneumonia is associated with significant morbidity and mortality and the role of high-dose steroids has been uncertain. Adhami *et al.* report a case series providing evidence that corticosteroids accelerate the physiological recovery and shorten the duration of mechanical ventilation.<sup>87</sup> While this was not a randomized controlled trial, the greater severity of the patients receiving corticosteroids on admission would support the efficacy of high-dose steroids in this situation.

With the limitation of medical resources, one of the key issues is how to identify which patients should undertake diagnostic tests. Okimoto *et al.* have identified which clinical features predict the presence of pneumonia on CXR in subjects with community-acquired pneumonia.<sup>88</sup> The presence of

all four clinical signs: fever, cough, sputum and coarse crackles, had a high positive predictive value and can be recommended for use in general practice.

In a case-control study, serological evidence of acute, but not chronic, infection of *C. pneumoniae* was more commonly found (25% vs. 5%) in 37 patients with chronic cough compared with age-matched controls.<sup>89</sup> The journal also included two cases of recurrence of bronchiectasis after bilateral lung transplantation—a concern for future recipients.<sup>90</sup> Extending the use of Factor VIIa in haemophilia to a patient with diffuse alveolar haemorrhage from pulmonary-renal syndrome was demonstrated to be successful.<sup>91</sup>

## TUBERCULOSIS

Pulmonary tuberculosis continues to be a significant health problem in most Asia-Pacific countries. A Malaysian study showed that the diagnosis of 4.9% of 346 admissions for community-acquired pneumonia turned out to be tuberculosis.<sup>92</sup> A long duration of symptoms, presence of night sweats, upper lobe disease, cavitations, lymphocytopenia and lack of leucocytosis should raise suspicion of tuberculosis.<sup>92</sup> Hepatic toxicity is a well recognized complication of anti-tuberculous drugs. Yew and Leung reviewed the risk factors and management for drug-induced liver disease from common anti-tuberculous drugs.<sup>93</sup> An economic study suggested that treatment of multidrug-resistant tuberculosis cost 7–22 times more than drug-sensitive tuberculosis in Korea.<sup>94</sup>

Continuing the great tradition of tuberculosis research in Hong Kong, Chan-Yeung *et al.* report that between one-fifth and one quarter of new cases of active tuberculosis in Hong Kong are due to recent transmission.<sup>95</sup> The authors propose that in addition to the early diagnosis and successful treatment of all active disease, treatment of latent disease should receive more attention in the control of tuberculosis in Hong Kong.

## CONCLUSION

In conclusion, this 'year in review' once again highlights the considerable breadth and depth of clinical research published in *Respirology*. Importantly, it illustrates that *Respirology* has now come of age as an international respiratory medicine journal. The benefits to respiratory medicine in the Asia-Pacific region are self-evident.

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