ABSTRACTS

DAY 1 - THURSDAY, 13TH NOVEMBER
DAY 2 - FRIDAY, 14TH NOVEMBER
DAY 3 - SATURDAY, 15TH NOVEMBER
DAY 4 - SUNDAY, 16TH NOVEMBER
Sleep-related breathing disorders (SRBD) data in Indonesia is still limited. Obstructive sleep apnea is the most SRBD that studied in Indonesia. From several study showed that OSA will be important health problems in Indonesia population for the future. OSA prevalence from several study were varied from 19.8% until 25% using Berlin questionnaire and 7.35% until 55.1% using polysomnography test. Sihombing (2008) reported that 55.1% taxi drivers with snoring proven OSA using portable polysomnography test. Wiadnyana and Susanto (2010) study in taxi drivers at Jakarta using Berlin questionnaire found 25% taxi drivers had high risk for OSA. Study in Children by Supriyatno (2010) found OSAS prevalence in children 10-12 y.o with obesity was 38.2%. Susanto et.al (2013) found 52.5% taxi drivers with overweight and obesity proven OSA base on clinical symptoms and polysomnography test. Susanto et.al (2014) found 21.7% police officers at Tangerang and East Jakarta have suspected OSA. Study in Department of Pulmonology and Respiratory Medicine Faculty of Medicine University of Indonesia by Astuti et.al in asthma patients found OSA prevalence was 19.8% using Berlin questionnaire and 9.8% with polysomnography test. Another study in COPD patients by Ratih et.al found 25% had high risk for OSA and 7.35% proven OSA by polysomnography test. From that all studies, the most OSA risk factors in Indonesia population were increased of body mass index, neck circumference and snoring history in the family.
The obstructive sleep apnea syndrome (OSAS) is common, affecting 2-4% of otherwise healthy children, and a much higher percentage of children with risk factors such as prematurity, Down syndrome, craniofacial anomalies or neuromuscular disease. OSAS result from a combination of anatomic and neuromotor factors. The American Academy of Pediatrics issued revised clinical practice guidelines for the diagnosis and management of childhood OSAS in 2012. These evidence-based guidelines were based on analysis of more than 3,000 articles. The following recommendations were made: (1) All children/adolescents should be screened for snoring; (2) Polysomnography should be performed in children/adolescents with snoring and symptoms or signs of OSAS; if polysomnography is not available, then alternative diagnostic tests or referral to a specialist for more extensive evaluation may be considered; (3) Adenotonsillectomy is recommended as the first-line treatment for patients with adenotonsillar hypertrophy; (4) High-risk patients should be monitored as inpatients postoperatively; (5) Patients should be reevaluated postoperatively to determine whether further treatment is required. Objective testing should be performed in patients who are high risk or have persistent symptoms/signs of OSAS following therapy; (6) Continuous positive airway pressure (CPAP) is recommended as treatment if adenotonsillectomy is not performed or if OSAS persists postoperatively; (7) Weight loss is recommended in addition to other therapy in patients who are overweight or obese; (8) Intranasal corticosteroids are an option for children with mild OSAS in whom adenotonsillectomy is contraindicated or for mild postoperative OSAS. Areas for further research will also be discussed.
Second Line Anti-TB Drugs: Mechanism of Action and Rational Use

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Based on findings of an individual patient data meta-analysis of 9153 multidrug-resistant tuberculosis (MDR-TB) patients, World Health Organization recommends that in the treatment of patients with MDR-TB, four second-line anti-tuberculosis drugs likely to be effective, as well as pyrazinamide, should be included in the intensive phase; regimens should include at least pyrazinamide, a fluoroquinolone (FQ), a parenteral agent, ethionamide (or prothionamide), and either cycloserine or PAS (p-aminosalicylic acid) if cycloserine cannot be used. The core drug in the treatment of MDR-TB is FQ. The newer FQs, sparfloxacin, gatifloxacin, and moxifloxacin, have lower minimum inhibitory concentrations (MICs) against *M. tuberculosis* than levofloxacin, ciprofloxacin, and ofloxacin, and their activity is concentration dependent. An animal study showed that moxifloxacin 400mg and levofloxacin 1000mg have comparable activities during the initial 2 months of treatment, and that moxifloxacin had greater activity during the continuation phase of treatment. The binding target of FQs in *M. tuberculosis* is DNA gyrase, consisting of two A and two B subunits encoded by the gyrA and gyrB genes, respectively. Missense mutations within the quinolone resistance-determining region (QRDR) have been identified as the primary mechanism conferring fluoroquinolone resistance. Studies reported that high dose (800mg) moxifloxacin achieved excellent *M. tuberculosis* microbial kill and suppressed drug resistance. An observational study using high dose gatifloxacin, clofazimine, ethambutol pyrazinamide, prothionamide, kanamycin and high-dose isoniazid for at least 4 months till sputum conversion followed by high dose gatifloxacin, clofazimine, ethambutol and pyrazinamide for 5 months achieved >85% relapse-free cure rate in Bangladesh.
World Health Organization estimated that globally, 3.6% (95% CI: 2.1–5.1%) of new TB cases and 20.2% (95% CI: 13.3–27.2%) of previously treated cases have multidrug-resistant tuberculosis (MDR-TB). On average, an estimated 9.6% (95% CI: 8.1%–11%) of MDR-TB cases have extensively drug-resistant tuberculosis (XDR-TB). The estimated number of incident MDR-TB cases globally in 2012 was 450 000 (range: 300 000–600 000), and that among patients with pulmonary TB notified in 2012 was 300 000 (range: 220 000–380 000). The burden of MDR-TB is high in South East Asia and Western Pacific Regions, especially in India, China, the Philippines, Indonesia, Myanmar, and Bangladesh. The proportion of TB cases with drug susceptibility testing (DST) for first line anti-tuberculosis drugs was low in South East Asia and Western Pacific Regions. In 2012, the proportion of retreatment TB cases with DST result was 7% in Bangladesh, 12% in China, 10% in Indonesia, 9% in the Philippines. Globally, 83 715 cases of MDR-TB were notified to WHO in 2012, represented 28% of the 300 000 pulmonary TB patients estimated to have MDR-TB in 2012. Outcome of MDR-TB was disappointedly low in both South East Asia and Western Pacific Regions. In both regions, the proportion of MDR-TB patients in the 2010 cohort who successfully completed treatment was <50%, while about 30% of cases were reported as lost to follow-up or had no outcome information. Intensified regional and national efforts to detect cases of MDR-TB and to improve treatment outcomes are urgently required.
Neuroendocrine tumours (NETs) of the lung include a spectrum from low-grade typical carcinoid (TC) and intermediate-grade atypical carcinoid (AC) to high-grade large cell neuroendocrine carcinoma (LCNEC) and small cell lung carcinoma (SCLC). LCNEC and SCLC are found in heavy-smoking, older patients, whereas smoking is not strongly associated with carcinoid tumours. It is difficult to diagnose AC and LCNEC in small biopsies or cytology and a definitive diagnosis usually requires a surgical specimen. SCLC, characterised by a rapid progression of symptoms and a bulky central and/or mediastinal tumour, can usually be reliably diagnosed by limited biopsy.

Surgery is the primary treatment for TC and AC. Up to 64% of patients with AC present with lymph node metastases, and 5-year survival ranges from 61% to 88%. In contrast, lymph node metastases are present in fewer than 15% of cases of TC, and 5-year survival exceeds 90%. The role of targeted therapy for TC and AT remains incompletely defined, with data from relatively few clinical trials to help guide clinical decision making. In patients with LCNEC, locally advanced or metastatic stages are usual at presentation and surgery is possible in less than a third of patients. Because of the rarity of LCNEC, treatment recommendations are not based on clinical trials, but are extrapolated from the approach to patients with NSCLC and SCLC as well as literature for LCNEC which is primarily retrospective in nature. Treatment of SCLC is usually chemotherapy.

Lung NETs have been underrepresented in clinical trials of NET treatments. In recent years, results specific to lung NETs have been reported only in a phase 2 retrospective study of the dacarbazine derivative temozolomide and the phase 3 RAD001 in Advanced Neuroendocrine Tumors Trial 2 (RADIANT-2) which evaluated the impact of combination therapy with the oral mammalian target of rapamycin (mTOR) inhibitor everolimus and the somatostatin analogue octreotide LAR in patients with advanced NET and carcinoid symptoms. The first large phase 2 prospective, randomised 3-arm trial to evaluate the efficacy and safety of pasireotide LAR alone or everolimus alone or in combination in patients with lung or thymus neuroendocrine carcinoma (LUNA Trial) is ongoing.
Community Acquired Pneumonia (CAP) in TB Endemic Countries
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India

Community acquired pneumonias (CAP) are common infectious diseases occurring worldwide with considerable morbidity and mortality. Last century witnessed considerable improvements in public health infrastructure, introduction of novel diagnostic methods, discovery of antibiotics and development of vaccines against influenza and Streptococcus pneumonia and all these developments had contributed to better diagnosis and treatment of community acquired pneumonias especially in industrially advanced countries. However, the emergence of human immunodeficiency virus and other immunodeficiency states have complicated the diagnosis and management of community acquired pneumonias. The diagnosis and treatment are further complicated in countries where tuberculosis is endemic. The increasing incidence of fungal pneumonias which are difficult to diagnose and treat is another challenge. The common causative agents of pneumonia in the community are Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, Legionella spp., Chlamydia pneumoniae and respiratory viruses (influenza A and B, adenovirus, respiratory syncytial virus and parainfluenza). The bacteriological profile of CAP is not the same across various countries and within the same country. This is due to differences in the frequency of use of antibiotics, environmental pollution, awareness of the disease and life expectancy. The most common causative pathogen reported from Europe, the United States and the United Kingdom is S. pneumoniae. However in Singapore, it is K. pneumonia. In a prospective study from Mumbai, S. pneumoniae was the leading cause of CAP in 22% and atypical organisms were identified in 19% of patients. Importantly, Mycobacterium tuberculosis was isolated in 7% of patients emphasizing the need for including diagnostic tests for tuberculosis in suspected cases of CAP from countries with high prevalence of tuberculosis. Blood cultures, sputum Gram-stain and culture are the most common tests used to identify the etiology of CAP. In addition to this, serological tests are also performed. Resistance to β-lactams and to macrolides is low in India. Chest radiograph is required to confirm the diagnosis of pneumonia, to detect associated lung disease, to assess severity and associated complications and to obtain baseline to assess the response to treatment. Pneumonia mortality risk can be predicted using either Pneumonia Severity Index or CURB 65 [confusion (C), blood urea (U), respiratory rate (R), blood pressure (B) and age ≥65 years (A)]. Fluoroquinolones are recommended as initial empirical therapy in CAP in some countries, as these drugs are resistant to streptococci in only about less than 3% of cases and have excellent activity against atypical organisms. Fluoroquinolones have also action against M. tuberculosis and are recommended for the treatment of multidrug-resistant tuberculosis and for shortening the duration of anti-TB treatment. Initiation of empirical therapy of CAP with fluoroquinolones is therefore, not recommended in countries with high prevalence of tuberculosis as this may have serious consequences of delayed initiation of anti-TB treatment and development of resistance to fluoroquinolone in case the CAP happens to be due to M. tuberculosis. In countries
with high TB prevalence, amoxicillin is the preferred drug for treatment of a patient with CAP with low severity and a β-lactam plus a macrolide for inpatients with CAP and with moderate severity. Intravenous β-lactam and a macrolide are required for patients with high severity. Pneumococcal infections can be prevented with pneumococcal pneumonia vaccines and influenza-related respiratory illnesses can be prevented with influenza vaccinations. Consumption of tobacco is an important risk factor for CAP and smoking cessation is important to reduce the burden of CAP.
Obstructive sleep apnea (OSA) is characterized by recurrent upper airway obstruction during sleep. The primary mechanisms linking OSA with poor cardiovascular outcome occur during sleep and are: 1. Mechanical: Generation of negative intrathoracic pressure swings during the futile efforts to breath against an occluded airway. The negative intrathoracic pressure in conjunction with acute (and frequently also sustained) high blood pressure are responsible for increased after load and heart remodeling. The vibration caused by snoring transmitted to the neck may also cause accelerated atherosclerosis at the level of the carotid arteries. 2. Neural: Arousals from sleep, that occur at the end of each obstructive events triggers sympathetic activity. Obstructive events also typically deprives patients from slow wave sleep. Deprivation of slow wave sleep caused by acoustic stimuli triggers metabolic dysfunction in normal subjects; 3. Chemical: Intermittent asphyxia, as characterized by episodes of hypoxia and hypercapnia. These primary mechanisms that occur during sleep triggers a cascade of intermediate pathways that are potentially deleterious to the cardiovascular system. The best studied and probably the most important intermediate mechanism is sympathetic activation that occurs during each episode of airway obstruction. Sympathetic over activation occurs not only during sleep but carry overs during the 24 hour period. In addition OSA may trigger several other mechanisms that are harmful to the cardiovascular system and includes oxidative stress, inflammation, insulin resistance, lipid dysfunction, endothelial dysfunction and accelerated atherosclerosis. There is evidence from animal models that intermittent hypoxia is a key mechanism linking OSA with poor cardiovascular outcome. All these mechanisms help to explain why OSA is associated with increased risk of cardiovascular death due to stroke and myocardial infarction.
The current GOLD strategy documents builds on the original contents dating back to 2001 and the 2011 revision. A clinical diagnosis of COPD requires a relevant exposure, symptoms and airflow limitation. The 2015 update has slightly expanded the GOLD “square” denoting a symptoms dimension and a risk dimension.

Symptoms are preferably assessed using a comprehensive and systematic assessment, although a simple assessment of breathlessness using the mMRC questionnaire is also possible. Risk is still best assessed using both history of exacerbations (including hospital admissions) and level of FEV1. Recent studies of population samples and patient cohorts have documented that in addition to being a guide to patient management, The A-D categorisation also has predictive value regarding both exacerbations and mortality.

GOLD still emphasises the need for proper assessment of comorbidities, not least cardiovascular comorbidities, and recent studies have shown that in particular Group B patients are at high risk of experiencing comorbidities, leading to a higher than expected mortality in this group.

Preventive measures are underlined, including smoking cessation and reduction of exposure to in- and outdoor pollution.

For non-pharmacological management, the value of both pulmonary rehabilitation and physical activity outside rehabilitation programs are highlighted. For pharmacological management, bronchodilators are central according to GOLD and focus is increasingly on long-acting inhaled bronchodilators. In patients at high risk of exacerbations, these can be combined with anti-inflammatory drugs. GOLD does not recommend use of macrolides for exacerbation prevention. The importance of proper follow-up of all treatments is underlined.
Thoracic CT Pattern in Lung Cancer: Correlation of CT and Pathological Diagnosis

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Japan

High-resolution CT (HRCT) is the main diagnostic tool for the diagnosis of lung cancer. HRCT images are correlated well with pathological findings. In 2011, the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society proposed a new classification system for lung adenocarcinoma. The new classification system is based on HRCT-pathologic correlation studies, and useful for predicting adenocarcinoma histologic subtype, patient prognosis and management. For example, ground-glass opacity extent within a pulmonary nodule on HRCT can be correlated with the extent of lepidic tumor growth on pathology. On the contrary, the size of the solid component on HRCT is frequently related with invasive component on pathology in lung adenocarcinomas manifesting as ground-glass nodules. In this presentation, I would like to show various HRCT findings of lung cancer by histologic subtypes, especially focus on ground-glass opacity neoplastic lung nodules.
The widespread use of multi-detector row CT in daily clinical practice detects a lot of incidental pulmonary nodules. The differential diagnosis is broad, ranging benign granuloma to malignancy. What is the appropriate management of these indeterminate nodules? The goal of nodule evaluation is to expedite resection of potentially curable lung cancer and to minimize resection of benign nodules. To achieve this goal, not only detailed analyses of morphologic characteristics on high-resolution CT but also the identification of clinical risk factors are important. In addition, it is helpful to use recently published guidelines for the management of pulmonary nodules. In this presentation, I would like to talk about a practical approach to the diagnosis and management of pulmonary nodules with reference to nodule guidelines by the Fleischner Society and American College of Chest Physicians.
Almost 60 sleep disorders are described in the International Classification of Sleep Disorders (ICSD-3, 2014). Included in ICSD 3 are 17 sleep-related breathing disorders (SRBDs) and 2 isolated symptoms and normal variants (snoring and catathrenia). SRBDs are divided into 4 groups: 1) obstructive sleep disorders, 2) central sleep apnea syndromes, 3) sleep-related hypoventilation syndromes, and 4) sleep-related hypoxemia disorders. Obstructive sleep disorders include adult and pediatric obstructive sleep apnea. Central sleep apnea syndromes include Cheyne-Stokes breathing (CSB), central apnea due to a medical disorder without CSB, central sleep apnea due to high altitude periodic breathing, central sleep apnea due to a medication or substance, primary central sleep apnea, primary central sleep apnea of infancy, primary central sleep apnea of prematurity, and treatment-emergent central sleep apnea. Sleep-related hypoventilation disorders include obesity hypoventilation syndrome, congenital central alveolar hypoventilation syndrome, late-onset central hypoventilation with hypothalamic dysfunction, idiopathic central alveolar hypoventilation, sleep-related hypoventilation due to a medication or substance, and sleep-related hypoventilation due to a medical disorder. There are several treatments for SRBDs such as body weight reduction, CPAP, NPPV, adaptive servo ventilation (ASV), oxygen, surgical therapies, tracheostomy with a ventilator, upper airway stimulation, etc. Patients with SRBDs very often have several comorbidities. Therefore, to administer appropriate therapy for SRBDs, it is important to know the pathophysiology, clinical characteristics, and available treatments and management strategies for SRBDs in adults and children and how to diagnose specific sleep disorders. The participants in this P-G course should know about SRBDs overall and management strategies presently available.
Based on the ATS/ERS Interpretation Algorithm of PFTs, each step will be explained and illustrated by the result of the correlative tests.

Measurement of ventilatory function with spirometry, body plethysmograph and measurement of gas exchange by diffusing capacity are used.

Identifying the presence or absence of obstruction, confirming the restriction with lung volumes will help to differentiate the obstruction, restriction or mixed patterns.

Some ways of classification of severity of airflow limitation and lung volumes impairment are presented.

DLCO interpretation and severity classification of diffusing capacity are explained.

The combination of the lung volumes, airflows and diffusing capacity results permits the differentiating 6 groups of lung functions:

1. Normal.
2. Pulmonary vascular disorders.
3. Chest wall and neuromuscular disorders.
4. Interstitial lung diseases and pneumonitis.
5. Asthma and chronic bronchitis and
6. Emphysema

Other factors such as performance, central airways disorders... must be considered.

Some issues of the ATS/ERS interpretation algorithm will be pointed out.

The conclusion will emphasize the fact that PFTs indicate only the syndrome or the assumption of one disease. The combination of careful patient history, clinical examination, imaging and bronchoscopy are often required to make an exact diagnosis.
Methods of Sleep Testing: Polysomnography and Portable Monitoring
Michelle Cheong
Hong Kong

Polysomnography is a sleep study, a diagnostic tool in sleep medicine used to identify sleep related breathing disorder, narcolepsy, periodic limb movement, hypersomnia, parasomnias and REM behavior disorder. A polysomnogram recorded a number of channels wire attachments to patients and wires for each channel of record data lead from the patient and converge to a headbox which is connected to a sleep monitoring recording system. During sleep, the computer monitoring can display all attached channels and recording all attached channels the whole night. After completing the whole night sleep recording, the recorded data will analyzes any breathing irregularities or abnormal cardiac rhythm, leg movement and arousals, sleep stages and sleep efficiency including oxygen saturation during sleep. Polysomnography is one method of sleep testing used in most hospital and sleep laboratory. Besides polysomnography, portable monitoring sleep systems currently popular because of their recording machine is smaller, convenient, patient can used this machine to sleep at home and they can hook sensors by themselves. Portable monitoring sleep test in the current market include sleep monitoring with brain activity signals, sensors like effort bands to test chest movement during sleep, airflow to monitor breathing and also saturation during sleep. The data can be wired or wirelessly transferred for remote monitoring. Sleep monitoring based on movement is current popular in the market such as fitbit, sleep cycle alarm, sleep tracker, jawbone and wakemate etc. Watch-pat is also portable device monitors changes in peripheral arterial tone and activity, as well as in blood oxygen saturation levels to detect sleep apnea events.

This presentation will detail sleep technology in sleep lab setting and why portable monitoring system is popular in current market.
Respiratory mechanics (lung/chest wall compliance, resistance, and time constants) has always been the mainstay of mechanical ventilation monitoring. This 30-minute lecture will discuss key definitions using airway graphics to explain airway pressures, volumes, compliance (dynamic and static) and time constants in patient-ventilator interactions. The interconnectedness between the “measured parameters” (Flow, Pressure, Time) and “calculated parameters” (Volume, Compliance and Resistance); and its clinical significance as it relates to patient-ventilator interaction will be discussed. Lastly, the pressure-volume (PV) curves will be used to explain the concept of lower and upper inflection points as it relates to optimal PEEP, over-distention and decrease lung compliance.
Patient-Oriented PFTs to Assist Clinical Decision-Making
Paul Enright
USA

This workshop is for pulmonary specialist clinicians who want to learn how to more effectively utilize pulmonary function tests to help with the differential diagnosis or to provide objective evidence of improvement or worsening during follow-up exams of patients who have been previously diagnosed. Everyone will have a clicker to respond to questions about which test to order, how you would interpret the results, and how you would change the treatment based on the PFT results. After each 30 minute presentation of cases, everyone will move to one of five tables filled with PFT instruments for a 30 minute demonstration of testing. You can test yourself. Then back to another 30 minute presentation of more cases, alternating throughout the day.

1a. Case presentations: adult smokers (COPD screening) one case with normal PEF (smoking cessation but no need for spirometry), and one case with low PEF, followed by pre- and post-BD spirometry showing severe CAO (FEV1 of 40% pred) with a follow-up exam after one month of tiotropium therapy.

1b. Hands-on pocket spirometry and diagnostic spirometry

2a. Case presentations: patients with episodic wheezing; a 6 year old child with normal spirometry but high eNO; a young adult with obstruction and a large BD response, follow-up after 1 month of moderate dose ICS+LABA; an older adult former smoker with obstruction but small BD response, 1 month follow-up after high dose ICS+LABA; a professional adult patient closet smoker with difficult-to-control asthma, using home monitoring during follow-up).

2b. Hands-on spirometry, PEF meter, and eNO testing

3a. Case presentations of differential diagnosis of patients with slow onset dyspnea and a relatively normal chest x-ray: a patient with normal PFTs (but severe anemia), a patient with previously undiagnosed asthma, a former smoker with emphysema phenotype COPD, a patient with obesity and poor conditioning, a patient with heart failure.

3b. DLCO demonstration

4a. Case presentations: Evaluation of patients with abnormal chest x-ray; initial and 3 month follow-up exams; a young adult with cystic fibrosis, a middle aged adult with IPF or sarcoidosis, a patient with severe kyphoscoliosis (chest wall restriction), an elderly smoker with heart failure and mild COPD, a patient with infiltrates but normal PFTs

4b. Demonstration of 6MWT with pulse oximetry; hands-on DLCO
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5a. Case presentations of patients with a chronic cough: a teenager with exercise-induced asthma, a patient with allergic rhinosinusitis, a patient with gastro-esophageal reflux, a smoker with chronic bronchitis, a patient with eosinophilic bronchitis.

5b. Demonstration of inhalation challenge testing, and perhaps a demonstration of allergen skin testing

6a. Case presentations of unusual patients: a patient with stridor following prolonged intubation (UAO); a patient with a neuromuscular disease; a patient with asbestosis referred for a disability exam; a patient with lung cancer and severe COPD for a pneumonectomy evaluation

6b. Hands-on maximal respiratory pressure tests (MIP and MEP) and flow-volume loops
Assessment of Exacerbations
Paul Jones
UK

Exacerbations in COPD drive lung function decline, cause poor health, trigger hospital admissions, cause deaths and increase health-care costs. Reducing the impact of exacerbations is a key outcome in COPD guidelines. Definitions of exacerbation differ widely across clinical studies and subjective assessment of symptoms lacks precision. The most widely used definitions have the following components: acute worsening, beyond normal day-to-day variation for 2-3 consecutive days, necessitating a change in treatment. Using this approach, the severity of the exacerbation is determined by the amount of health care utilization, but that will depend on systems of health care delivery. Development of standardised patient reported outcomes such as the EXACT daily diary now provide a more precise measurement of the frequency, severity and duration of exacerbations in clinical studies.

One of the new developments in the understanding of exacerbations is that, on average, patients have twice as many unreported exacerbations as those that are reported. Unreported exacerbations occur in less severe patients, although the reporting rate varies greatly by country. Unreported exacerbations show the same degree of worsening and medium term impact on health status as those that are reported (and therefore treated), but appear to recover more slowly than those that are reported.

Clinicians need to be alert to the possibility that their patients are having exacerbations that they don’t report and for which they don’t seek treatment. Patients need to be educated to understand that a ‘chest infection’ is an exacerbation that requires treatment.
Asthma and COPD are 2 common airway diseases that and co-exist and give rise to the asthma-COPD overlap syndrome (ACOS). This is recognised to arise in several different situations. The spectrum of ACOS includes long standing asthma that leads to incompletely reversible airflow obstruction, asthma and smoking leading to ACOS, COPD with late onset asthma, and COPD with eosinophilic bronchitis. Patients with ACOS experience greater morbidity than either disease alone. Biomarkers to recognise ACOS are under evaluation. Guideline approaches to asthma and COPD vary considerably and are based on evidence from randomised controlled trials. Since patients with ACOS are excluded from clinical trials, the evidence base for treatment recommendations in ACOS is limited. A clinically useful approach is to consider the specific disease components and direct treatment accordingly. This includes assessment and treatment in 4 domains, such as the airway component (which includes obstruction and inflammation), comorbidity, risk factors (such as smoking, nutrition, obesity), and behavioural issues. Preliminary evidence supports better outcomes when ACOS is managed in this way. Future developments will need to include clinical treatment trials in ACOS and studies of relevant mechanisms.
Thoracoscopy, medical thoracoscopy, pleuroscopy and video-assisted thoracic surgery (VATS) are terms used interchangeably to describe a minimally invasive procedure that provides the physician a window to the pleural space. Historically rigid endoscopic instruments such as stainless steel trocars and telescopes are used. Following the advent of the flex-rigid pleuroscope similar in design and handling to the flexible bronchoscope and compatible with standard light source and video processor available in most bronchoscopy suites, flex-rigid thoracoscopy has made significant inroads as a diagnostic and therapeutic tool. The current debate should not focus on “who and where” to perform thoracoscopy but rather “when and how” to use rigid and flex-rigid instruments in different clinical scenarios.
Thoracoscopy provides the physician a window to the pleural space, biopsy of the parietal pleura under direct visual guidance, chest tube placement and pleurodesis for recurrent pleural effusions or pneumothoraces in selected patients. Since its inception thoracoscopy was used to lyse adhesions to achieve therapeutic pneumothorax in pulmonary tuberculosis. Following effective anti-tuberculous drugs, it fell into oblivion except for few centers in Europe. The procedure enjoyed resurgence when thoracic surgeons introduced the technique for minimally invasive surgery known as video-assisted thoracic surgery (VATS). VATS is performed under general anaesthesia with single lung ventilation while pleuroscopy is performed by the pulmologist in an endoscopy suite using non-disposable rigid or flex-rigid instruments, local anaesthesia and conscious sedation. Pleuroscopy is useful for the diagnostic work up of pleural effusions while talc poudrage is an effective therapeutic option for patients with recurrent pneumothoraces and pleural effusions. Pleuroscopy has a place in interventional pulmonology and diagnostic and therapeutic indications will be discussed.
Pleural Disease: What Should We Know?
Richard W. Light, M.D.
USA

The most common etiology for a pleural effusion worldwide is congestive heart failure. The effusions due to heart failure are usually bilateral, symmetrical and are not associated with chest pain or fever. They disappear when the heart failure is treated. If the patient is on diuretics, the pleural fluid may meet Light’s criteria for an exudative effusion and the transudative nature can be verified by demonstrating a serum-pleural fluid gradient >3.1.

The presence of a malignant pleural effusion indicates that the patient cannot be cured by surgery. The diagnosis is most easily made with cytology. If the cytology is non diagnostic, image guided biopsy of the pleura or thoracoscopy are effective in making a diagnosis. If the patient is dyspneic and if the dyspnea is relieved with a therapeutic thoracentesis, efforts should be made to control the pleural fluid. The two most popular means of controlling the pleural fluid are the insertion of an indwelling pleural catheter or the injection of an agent into the pleural space to create a pleurodesis.

Parapneumonic effusions are those associated with a pneumonia. When a patient with a parapneumonic effusion is first evaluated, the pleural fluid should be sampled to ascertain whether therapy in addition to antibiotics is indicated. If the gram stain or culture is positive, if the pH is less than 7.20, if the effusion occupies more than 50% of the hemithorax, or if the glucose is less than 60 mg/dl, a chest tube should be inserted. If the pleural fluid is loculated, consideration should be given to the intrapleural administration of the combination of 5 mg DNase and 10 mg tPA.
Sleep apnea is often observed in patients with heart failure (HF). Sleep apnea consists of two types: obstructive and central sleep apnea (OSA and CSA, respectively). OSA results from upper airway collapse, whereas CSA arises from attenuations in central respiratory drive. In patients with OSA, blood pressure is frequently elevated as a result of sympathetic nervous system overactivation. The generation of exaggerated negative intrathoracic pressure during obstructive apneas further increases left ventricular (LV) afterload, reduces cardiac output, and may cause the progression of HF. Intermittent hypoxia and post-apneic reoxygenation cause vascular endothelial damage and possibly atherosclerosis and consequently coronary artery disease and ischemic cardiomyopathy. CSA is also characterized by apnea, hypoxia, and increased sympathetic nervous activity and, when present in HF, is associated with increased risk of death. In patients with HF, abolition of coexisting OSA by continuous positive airway pressure (CPAP) improves LV function and may contribute to the improvement of long-term outcomes. Although treatment options of CSA vary compared with OSA treatment, CPAP and other forms of positive airway pressure therapy improve LV function and may be a promising adjunctive therapy for HF patients with CSA. In this session, pathophysiology and treatment option of sleep apnea including both OSA and CSA will be summarized.
Inoperable central airway stenosis due to a malignant tumor is a relatively common condition and may be life threatening. Because of the poor prognosis, palliative methods are needed to maintain airway patency. In patients with severe malignant airway stenosis, interventional bronchoscopy is considered as a method of maintaining airway patency.

Flow limitation during forced expiration is affected by the relationship between transmural pressure and the cross-sectional area of the airway. The wave-speed is dependent on the stiffness of the airway wall, and on the cross-sectional area itself. The flow-limiting segment (FLS) occurs originally when the cross-sectional area of the airway is narrowest. On the basis of wave-speed concepts of maximal expiratory flow limitation, stenting at the FLS improved expiratory flow limitation by increasing the cross-sectional area supporting the weakened airway wall, and reliving dyspnea.
Chronic inflammation and oxidative stress is a prominent feature of smokers’ lungs and COPD. Cells lining terminal bronchioles are important source of antioxidants as well as inflammatory chemokines. Aging and cigarette smoke (CS) exposure are thus major risk factors for pathogenesis of COPD. Smoking cessation is regarded as an important strategy for prevention and treatment of COPD. However, little is known what makes the CS-induced injury chronic even after quitting smoking.

To address this question, we have investigated the cellular and molecular changes that occur in cells lining terminal bronchioles in response to CS. We have successfully utilized laser capture microdissection in combination with quantitative RT-PCR in order to quantify the cell-type specific mRNAs in animals in vivo. Our results showed that a variety of bronchiolar genes are affected by smoking and that the profile is dramatically changed by chronic exposure. We then tested whether the duration of CS exposure affects recovery from CS-induced inflammation after cessation of smoking. Our data help in dissecting the mechanisms by which the CS-induced injury become chronic even after smoking cessation, also suggests bronchiolar epithelium could be a target site to prevent them to be chronic.
The functional interplay between cancer cells and marrow stromal cells (MSCs) is of great interest because of the MSC tropism for tumors. In this study, we investigated human MSC-secreted paracrine factors that potentially contribute to regulation of cancer stem cell subpopulations. Treatment with MSC-conditioned media led to decreased proportion of the cancer stem cell-enriched compartment, which is detected as the side population and the quiescent (G0) cell cycle fraction, in human lung cancer cells, but not in non-lung cancer cells. Of note, the lung cancer-specific suppression of the cancer stem cell-enriched compartment is ensured by fibroblast growth factor (FGF) 10 secreted from MSCs; the MSC-mediated suppression of the compartment was attenuated by neutralization of FGF10 and was substituted by recombinant FGF10 protein. Moreover, the supplementary FGF10 alleviated mRNA expression of stemness marker genes encoding OCT3/4 and SOX2. Consistently, addition of FGF10 to the lung cancer cell culture impaired formation of floating spheres in serum-free condition, suggesting that self-renewal capacity of lung cancer cells was diminished by FGF10. The clinical relevance of these findings was confirmed by in vivo tumor growth as well as in vitro proliferation, in which the FGF10 treatment rendered the lung cancer cells to be more responsive to an anticancer agent probably due to the reduction of chemoresistant cancer stem cells. Collectively, these results suggest that the pharmacological strategy using FGF10 in conjunction with chemotherapeutic agents may exhibit a therapeutic potency in lung cancer treatment.
Clinical Application of Pulmonary Function Testing
Yasutaka Nakano, MD., Ph.D.
Japan

Structural changes of the lung may occur in the subsequence of pulmonary diseases. These lung structural changes influence the patients to show the abnormal results of the pulmonary function testing. Thus, physicians usually use pulmonary function testing as a tool to detect the structural changes of the lung and to estimate and diagnose the underlying diseases. We use pulmonary function testing to diagnose chronic obstructive pulmonary disease (COPD), asthma, interstitial lung diseases, and so on. We use pulmonary function testing to evaluate the treatment. We use pulmonary function testing to follow the disease progression. We use pulmonary function testing to know that the subject does not have any lung diseases. In this lecture, clinical application of pulmonary function testing which is seen at the daily respiratory clinic will be discussed. Representative pulmonary diseases, such as COPD, asthma and interstitial lung diseases will also be discussed.
This lecture will briefly review the pathology of asbestos-related disease, and more specifically comment on controversial areas. The differences between chrysotile and commercial amphibole (amosite, crocidolite) asbestos in terms of producing disease will be emphasized. Asbestos induces a variety of benign pleural diseases including pleural effusions, visceral pleural fibrosis, pleural plaques, and rounded atelectasis. Fiber burdens studies show that a vastly greater dose of chrysotile compared to amosite or crocidolite asbestos is required to cause a pleural plaque. The presence of pleural plaques may indicate individuals at risk of developing mesothelioma but not lung cancer. The pathologic criteria for the diagnosis of asbestosis have been recently refined; in particular actual interstitial fibrosis and not just fibrosis of airway walls is now required, along with 2 or more asbestos bodies/cm² of tissue. Fiber burden studies show that asbestosis is a dose-response disease and high doses are required for its development. Asbestosis clearly predisposes to the development of lung cancer, but the possible association of asbestos exposure and lung cancer in the absence of asbestosis remains extremely controversial. The development of mesothelioma is strongly dependent on fiber type. Fiber burden studies complement epidemiologic studies in showing that chrysotile asbestos (with its contaminant tremolite) can cause pleural mesothelioma, but only at very high fiber burdens, whereas amosite (and crocidolite) can induce pleural mesothelioma at several hundred fold lower concentrations. High (asbestosis level) exposure to amosite or crocidolite can produce peritoneal mesothelioma, but there is no convincing evidence that chrysotile can produce peritoneal mesothelioma.
Obstructive sleep apnea (OSA) is a common disorder with major neurocognitive and cardiovascular sequelae. Nasal continuous positive airway pressure (CPAP) is the treatment of choice for OSA based on randomized trials as it can have transformative benefits for some patients. However, other patients have trouble tolerating CPAP and thus alternative therapies are being sought by studying underlying mechanisms. The pathogenesis of the condition is complex but involves an interaction of anatomical factors, upper airway dilator muscle dysfunction, instability in ventilatory control, and other factors. Recent studies suggest that different OSA patients develop the disease for varying reasons. While some OSA patients have primarily anatomical problems, others have primarily dysfunction in upper airway dilator muscles while others have instability in ventilatory control driving apnea occurrence. Some patients likely have combinations of abnormalities driving OSA. Individualized therapy is being considered whereby uvulopalatopharyngoplasty may be highly effective in patients with velopharyngeal compromise. Hypoglossal nerve stimulation may be particularly effective for patients with dysfunction in upper airway dilator muscles. Agents such as oxygen and acetazolamide may help to improve or eliminate OSA in patients with unstable ventilatory control. Combination therapy may be helpful for patients with multiple underlying mechanisms. The arousal threshold is also receiving increasing attention such that patients with a low arousal threshold may be amenable to sedative/hypnotic agents. The raising of arousal threshold may allow the accumulation of respiratory stimuli during stable sleep which can activate pharyngeal dilator muscles and maintain stable breathing. Research is ongoing in this area to define the pathophysiological mechanism underlying OSA using strategies that are readily accessible in the clinic. Such approaches will be critical for the concept of personalized medicine to be widely applied to OSA patients.
The obstructive sleep apnea syndrome (OSAS) is common, affecting 2-4% of otherwise healthy children, and a much higher percentage of children with risk factors such as prematurity, Down syndrome, craniofacial anomalies or neuromuscular disease. OSAS result from a combination of anatomic and neuromotor factors. The primary treatment in children is adenotonsillectomy, but approximately 20% may not improve due to ongoing structural abnormalities or neuromotor deficits. This talk will discuss risk factors for those who are less likely to improve after surgery. Continuous positive airway pressure (CPAP) is usually the second line of therapy, but adherence remains a major barrier to its use. Factors predicting CPAP adherence include age, race and maternal education; family interactions are important for CPAP adherence in adolescents. Mode of ventilation is unlikely to affect adherence. Alternative therapeutic methodologies for children with OSAS include weight loss (whether medical or surgical), anti-inflammatory medications, orthodontic treatment and craniofacial surgery. In addition, the role of newer modalities such as nasal expiratory positive airway pressure are being studied. The pros and cons of each therapy, and criteria for patient selection and management, will be presented.
Day 2  Friday, 14th November

Community Based Management of Chronic Obstructive Pulmonary Disease
Chau Ngo Quy, MD, PhD
Vietnam

Introduction: COPD is one of the chronic diseases, causing a serious public health problem in over the world. Community based management (CBM) of chronic obstructive pulmonary disease is a model, which focus on patient. Getting optimal care requires an individualized, patient-centered approach, not only COPD management but also the systemic effects and comorbidities.

Model of CBM: Based on the Bodenheimer T’s model to improve chronic illness care, they suggest the model of care for COPD patient and believe that patient–provider interactions result in care that improves outcomes.

Objectives of CBM:

COPD Prevention: increasing knowledge of community about risk factors of COPD, especially smoking and improving access to community-based smoking cessation.

Early diagnosis of COPD: Provider spirometry and filters for community, increasing programs for screening focus on individuals with chronic respiratory symptoms and or history of exposure smoking and biomass fuel.

Management of COPD and co-morbidities: Providing pharmacological and non-pharmacological managements for patients at primary care level. In addition, never forget to screen comorbidities. Patient’s education about self-management, using drug delivery devices, exercise training and action plans. To achieve these goals, it is necessary to reduce the gap between GP and specialists and expand the range of community-based ambulatory services for COPD and develop integrated referral pathways and protocols.

Conclusions: COPD is a chronic, progressive and complex disease that requires an individualized, patient-centered approach. Community based management may help to its management.
Real-life studies – A Poor Relation or Important Partner to the Respiratory RCT?

David Price
Singapore

RCTs are recognised as the gold standard for assessing efficacy, but real-life studies play a complimentary role in evaluating effectiveness. While RCTs are designed to study narrow populations in highly controlled conditions, real-life observational studies and pragmatic trials examine broader populations in less controlled settings. Due to their different designs, conflicting results sometimes arise. These might best be resolved by assessing how rigorous the methods and analyses of each study are.

The different study designs and patient populations of RCTs and real-life studies enable them to answer different important clinical questions. RCTs are suitable for obtaining drug licenses. On the other hand, real-life studies can evaluate questions about practical issues unanswerable by RCTs, such as patient and physician behaviours and preferences, adherence to therapy, inhaler technique, and ethical questions. For example, in the MASCOT trial examining paediatric asthma therapy step-up, recruited patients were already on optimised therapy. Randomisation to alternative therapies, as required for examining step-up, would have been unethical, so the trial was cancelled and a similar real-life study was done instead. Real-life studies have also been used to evaluate treatment effects beyond indications established in RCTs, such as statin use in COPD.

In support of the complementarity of RCTs and real-life studies, the 2014 Global Initiative for Asthma recommendations have recently been updated to suggest that both efficacy (e.g. RCTs) and effectiveness studies (e.g. real-life studies) should be considered when making choices about controller therapy. Real-life studies are increasingly becoming established as important partners to respiratory RCTs.
Basic premises of tuberculosis are: 1. progress toward elimination is too slow; 2. active tuberculosis comes from latent tuberculosis; 3. tuberculosis spreads before the diagnosis is made; and 4. treating latent disease is effective.

Past successes of treating latent disease have largely been with isoniazid, but this drug is not effective against dormant bacilli. Since latent tuberculosis mainly involves dormant organisms, why not use drugs that kill dormant organisms? In fact, the rifamycins are active against dormant bacilli and do shorten regimens. Pyrazinamide, metronidazole, moxifloxacin, aminoglycosides, capreomycin, linezolid, clofazimine, bedaquiline, delamanid, and PA-824 all have activity against nonreplicating bacilli (depending on the assay).

The decision whether or not to treat latent tuberculosis is based on risk-benefit considerations that are over 40 years old and developed to balance the risk of developing tuberculosis occurring in an individual against the toxicity of taking isoniazid for 12 months. They did not consider the long-term protection against tuberculosis versus the risk of side-effects occurring only during the treatment period. Nor did they take into account public health. Shorter courses and more effective medicine change these considerations. The rifapentine once-weekly course was as effective as the standard isoniazid course and had less toxicity (0.5%) and a higher completion rate (82%). With shorter and safer therapy, the risk-benefit balance has swung toward treating all persons with latent tuberculosis.
Current Situation in Asia Pacific: What We Have Learned
Dr Chi Chiu Leung
Hong Kong

The Asia-pacific region is on track to meet all the three 2015 targets in the reduction of tuberculosis (TB) incidence, prevalence and mortality. However, the burdens of TB, drug-resistant TB and latent TB infection (LTBI) remain huge in this most populous region of the world. Many TB cases are still being missed in South-east Asia. Detection and treatment of multidrug-resistant (MDR) / extensively drug-resistant (XDR)-TB remain formidable challenges in the region as a whole.

Achieving the new 2025 and 2035 milestones of 50% and 90% reduction in TB incidence would require accelerated annual rates of decline of 6.7% and 14.9% respectively (c.f. just 2% now). Timely and efficient scaling-up of integrated, patient-centred care and prevention on a population scale is therefore crucial. Furthermore, innovative ways in implementation of both old and new diagnostic and treatment tools are urgently required to curb the further emergence and transmission of drug-resistant TB.

Controlling ongoing transmission alone will not curb endogenous reactivation from LTBI within the human life-span. Revolutionizing improvements in existing LTBI screening and treatment tools are necessary for the daunting task of screening the entire population and treating 1/3 of them. The existing BCG vaccine offers only partial and unreliable protection against pulmonary TB, the crucial transmission link for this airborne infection. With the absence of long-lasting immunity after natural infection, novel ways of augmenting the immune response would be required to realize a major breakthrough in this critical area.
In life science field, high throughput genomic and proteomic analysis so-called ‘omics analysis’ using next-generation sequencing and mass-spectrometry has spawned a variety of global analysis methods to assess abnormalities in the genome, epigenome, transcriptome, and proteome which are useful to detect new biomarkers for development, inflammation, and carcinogenesis. The markers revealed by these analyses is important both to identify potential therapeutic targets and/or to suggest molecular markers that might predict patient outcome. To identify these markers in the patients with cancer, the cancer liquid diagnosis using plasma free DNA and CTCs (circulating tumor cells) are now developed as minimum invasive method. Moreover, to distinguish the difference among cells and to detect intracellular changes, we developed imaging mass-spectrometry and single cell analysis so called ‘cellomics’. Single-cell analysis has attracted attention in many fields of biological studies as a tool to survey the precise mechanisms of cellular and molecular behavior. The development of sensitive mass spectrometry allows the study of molecules in single cell or small regions. In this technology, nanospray-mediated sampling and ionization named Live Single-cell Mass Spectrometry can be used for real-time analysis. And imaging mass-spectrometry is also available for detecting the molecules and drugs in the cells and tissues mounted on slide. This session focuses into the recent advances of molecular diagnostic technologies applicable to pulmonary diseases including lung cancer.
Molecular Diagnosis of Lung Cancer
Eiso Hiyama, MD, PhD.
Japan

Identification of sensitive biomarkers predictive of diagnosis, prognosis and drug sensitivity could have a clinically significant impact on cancer treatment strategies. Recently, molecular-targeted therapies have been developed for cancer treatment, especially for lung cancer treatment. Non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (EGFR) gene mutations have shown a dramatic response to EGFR tyrosine kinase inhibitors (EGFR-TKI) such as gefitinib and erlotinib. In addition, echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) fusion protein is present in approximately 5% of the patients with adenocarcinomas and Crizotinib is an oral tyrosine kinase inhibitor (TKI), which silences the protein product of the ALK fusion gene and has recently been approved for the treatment of NSCLC aberrantly expressing ALK. In neuroblastoma, one of the major childhood cancers, ALK activated mutations in tyrosine kinase domain are also present in approximately 5% of the patients and reported as responsible genes for familiar or multifocal neuroblastomas. Crizotinib is currently under development for lung cancer and neuroblastoma patients as clinical trials. In this paper, I reviewed the current development of molecular diagnosis of cancers, especially in the aspect for target therapies against lung cancer.
Obstructive sleep apnea (OSA) is an underdiagnosed condition characterized by recurrent episodes of obstruction of the upper airway leading to sleep fragmentation and intermittent hypoxia during sleep. Obesity predisposes to OSA, and the prevalence of OSA is increasing worldwide because of the ongoing epidemic of obesity. Recent evidence has shown that surrogate markers of cardiovascular risk, including sympathetic activation, systemic inflammation, and endothelial dysfunction, are significantly increased in obese patients with OSA versus those without OSA, suggesting that OSA is not simply an epiphenomenon of obesity. Moreover, findings from animal models and patients with OSA show that intermittent hypoxia exacerbates the metabolic dysfunction of obesity, augmenting insulin resistance and nonalcoholic fatty liver disease. In patients with the metabolic syndrome, the prevalence of moderate to severe OSA is very high (~60%). In this population, OSA is independently associated with increased glucose and triglyceride levels as well as markers of inflammation, arterial stiffness, and atherosclerosis. Several cohort studies have consistently shown that OSA is associated with increased cardiovascular mortality, independent of obesity. Taken together, these results support the concept that OSA exacerbates the cardiometabolic risk attributed to obesity and the metabolic syndrome. Recognition and treatment of OSA may decrease the cardiovascular risk in obese patients. However, most evidence comes from small trials. There is a urgent need for large randomized multi-center trials to investigate the impact of the treatment of OSA with CPAP in hard end points such as mortality.
In May 2014, the World Health Assembly passed a resolution approving a new global tuberculosis strategy with ambitious targets aiming at a major reduction of TB incidence and mortality by 2035.

Settings where TB elimination could be pursued are low-TB incidence countries with <100 cases per million people.

WHO and ERS established an expert group and, in consultation with more than 30 country representatives, developed a framework of measures to accelerate TB control towards elimination.

This adaptation addresses the fundamental challenges in low-incidence settings with the objective to reach a “pre-elimination phase” defined as <10 cases per million people by 2035 to achieve elimination before 2050.

Low-incidence countries have essentially four major challenges: (1) TB concentrated in vulnerable and high-risk groups; (2) re-activation of latent infection is more important than recent transmission; (3) cross-border migration; (4) dwindling visibility, clinical expertise and political commitment.

FACING these challenges requires interventions in 8 priority areas: from ensuring government commitment to focusing interventions on vulnerable people and migrants, and investing in surveillance, research, and global aid.

Consensus on new targets followed intensive dialogue among country representatives with some concerned that targets are too ambitious: major reduction in incidence and mortality would be possible only with the availability of new tools allowing rapid diagnosis in vulnerable populations, large-scale screening and treatment of latent infection in high-risk groups, until a vaccine is available.

Indeed, the possibility of providing chemoprophylaxis to a vast number of people at risk is one of the controversial issues to be addressed in future efforts.
Targeted strategies have become the mainstream of the lung cancer treatment. Most of the molecular targeting drugs are tyrosine kinase inhibitors. Because of the tyrosine kinases have stemmed from a common ancestral gene, the molecular structure is similar, and therefore a single drug inhibits multiple tyrosine kinases. Therefore, using drugs that have already on the market, we may be able to target several driver oncogenes. Such drug and target pair include gefitinib, erlotinib, and afatinib against EGFR mutated lung cancer, crizotinib and alecxinib against lung cancer with ALK fusion gene, crizotinib against lung cancer with ROS1 fusion gene, vandetanib against lung cancer with RET fusion gene, and sorafenib and vemurafinib against BRAF mutated lung cancer. These indicate that we need to test multiple genes that are “druggable” before determining the treatment regimen of lung cancer. The framework that enables multiple genetic tests may be constructed by utilizing a high-speed DNA sequencer. Clinical samples are limited in amount, and the turn-around time should be short for the genetic information is readily utilized before initiation of the treatment. I would like to consider how such system may be constructed and how it is applied to the clinical oncology.
Lung cancer is one of the most difficult cancers to cure. More than half of the patients are found their disease in an advanced, inoperable stage. Up until ten years ago, they had been treated chemotherapy and/or radiotherapy: the overall survival was less than one year, and nobody survived more than 2 years. The discovery of the mutation of the epidermal growth factor receptor (EGFR) changed the entire picture of the treatment. When mutation-positive patients are treated with the regimen containing EGFR tyrosine kinase inhibitor (EGFR-TKI), the overall survival extends to 2 to 3 years. Concurrent administration of chemotherapy and EGFR-TKI is expected to further extend overall survival. The discovery of oncogenic fusion genes, EML4-ALK, has made ALK-TKI as a therapeutic option for the lung cancer positive for the gene. For adenocarcinoma without EGFR mutation, a new chemotherapy agent, pemetrexed, and anti-angiogenic monoclonal antibody, bevacizumab, have demonstrated an apparent efficacy. The discovery of molecular mechanism that causes cancer, and the results of the clinical trials investigating the effect of molecular targeting agents, advances the science of lung cancer. I would like to review the progression of this field.
Airway diseases are a growing burden around the world. However, the pace of new drug and biomarker discovery has lagged behind those of other common disorders such as cardiovascular diseases and diabetes. One major barrier in airways research has been the inability to accurately visualize large and small airway remodeling using non or minimally invasive instruments. Optical coherence tomography is a new bronchoscopic imaging technique that has generated considerable interest because the spatial resolution approaches that of histology. While relatively more invasive than computed tomography, it has the advantage of not exposing the patient to ionizing radiation. Thus, with the aid of OCT, we may be able to accurately determine and quantify the extent of airway remodeling in asthma and chronic obstructive pulmonary disease. Therefore, these new imaging techniques are very likely to play a front-line role in the study of airways disease and will, hopefully, allow clinicians to phenotype individuals, thereby personalizing their treatment.
Omalizumab Improves Quality of Life and Asthma Control in Chinese Patients with Moderate-to-Severe Asthma: A Randomised Phase III Study

Jing Li, Jian Kang, Janice Canvin, Changzheng Wang, Jing Yang, Michael Humphries, Nanshan Zhong

China

Introduction: Omalizumab, an anti-IgE monoclonal antibody, has been found to be effective and safe in the treatment of patients of different ethnicities with moderate-to-severe allergic asthma. We report here the effect of omalizumab on the quality of life, asthma control and safety in Chinese patients with moderate to severe allergic asthma.

Methods: This was a randomised, double blind, parallel group, placebo controlled, phase III study to assess the quality of life, asthma control and safety of 24 weeks of omalizumab therapy in Chinese patients, aged 18-75 years, with moderate-to-severe persistent allergic asthma. Asthma Quality of Life Questionnaire (AQLQ) and Asthma Control Questionnaire (ACQ) scores were assessed at baseline and at week 24. Asthma exacerbation rates were also analysed.

Results: Among the 608 patients included in the full analysis set, at week 24 a higher proportion of patients treated with omalizumab (n=306), vs. placebo (n=302), achieved clinically relevant improvements in AQLQ (58.2% vs. 39.3% [analysed n=182 vs. 178]; p<0.001; change from baseline [ΔBL]=0.51 vs. 0.10) and ACQ (49.5% vs. 35.5% [analysed n=210 vs. 211]; p=0.003; ΔBL=−0.51 vs. -0.34) scores. Although not powered to study differences in exacerbation rates (p=0.097), exacerbations in winter months were less frequent in the omalizumab group vs. placebo (2 vs. 21). Adverse event and serious adverse event rates were comparable in both groups. One death from asthma exacerbation occurred in the omalizumab group.

Conclusions: Omalizumab improves quality of life and asthma control in Chinese patients with moderate-to-severe persistent allergic asthma with a good safety profile.
Airway mucus hypersecretion is one of the characteristic features of COPD, and a large amount of secretions stagnated in the respiratory lumen may cause airflow limitation, impairment of mucociliary transport, and recurrent respiratory infection. Although there are several mucoactive agents, these symptoms are generally difficult to treat. A recent GOLD guideline recommends PDE4 inhibitors for patients with severe COPD, but the role of PDE4 in mucus hypersecretion remains uncertain. We studied the effects of ibudilast, a PDE4 inhibitor, on MUC5AC expression in NCI-H292 cells in vitro, and found that exposure of cells to TGFα increased MUC5AC protein and mRNA expression, and this effect was inhibited by pretreatment with ibudilast in a concentration dependent manner. We then conducted an open, non-controlled trial, and examined the effect of ibudilast on sputum production and its impact in patients with COPD whose symptoms were resistant to conventional bronchodilators, mucoactive agents, macrolides or inhaled corticosteroids. Treatment of patients with ibudilast for 8 weeks caused favorable influences on sputum hypersecretion, judging from CASA-Q, a cough and sputum assessment questionnaire. Additionally, ibudilast significantly shortened nasal clearance time measured by saccharine test and decreased solid composition of the sputum (dry/wet weight ratio), indicating a reduction of mucus glycoprotein synthesis and an improvement of airway mucociliary clearance. These results suggest that PDE4 plays a role in airway mucus hypersecretion and that the inhibition of this enzyme may be one of the important strategies for the treatment of COPD patients especially with bronchitic phenotype.
Lung cancer is the leading cause of cancer death worldwide. However, the prognosis of patients with advanced non-small cell lung cancer (NSCLC) is gradually improving. This phenomenon may be due to several reasons. One is the development of molecular targeting drugs, including epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKI) and anaplastic lymphoma kinase (ALK) inhibitors. The second reason is the introduction of second and later line(s) chemotherapy into clinical practice, such as regimens using docetaxel, pemetrexed and erlotinib. The third reason is the introduction of maintenance therapy. In fact, the PARAMOUNT study, a randomized phase III study comparing the continuation of pemetrexed with a placebo as maintenance therapy following induction treatment consisting of cisplatin plus pemetrexed in patients with non-squamous NSCLC, revealed that continuation maintenance with pemetrexed prolongs overall survival. In this symposium, I would like to provide an overview of the current status and future perspectives of second-line treatment in patients with NSCLC. I will also touch on the efficacy of continuation of EGFR-TKI beyond progress disease.
Prevalence of obstructive sleep apnea (OSA) has been increasing in parallel with the obesity epidemic, and intermittent hypoxemia, frequent arousals and sleep fragmentation by OSA cause systemic inflammation, sympathetic activation and oxidative stress. These responses lead to hypertension and cardiovascular consequences, insulin resistance and diabetes mellitus, dyslipidemia, and metabolic syndrome. On the other hand, short sleep and sleep restriction also alter sympathetic nervous system activity and increase inflammatory markers such as C-reactive protein, tumor necrosis factor -α and interleukin -6, and now there is a growing body of evidence to suggest that short sleep duration is a risk factor for mortality, hypertension and cardiovascular consequences, insulin resistance and diabetes mellitus, and metabolic syndrome. Thus, each of OSA or/and short sleep can induce inflammatory responses, sympathetic activation and subsequent metabolic dysregulations. Thus, it is important to consider the associations among several factors such as OSA, sleep duration, sleep fragmentation and sex differences and how combined effects of OSA, short sleep duration and sleep fragmentation affect overall morbidities.

In this symposium, we discussed 1) the relationships among body mass index (BMI), respiratory disturbance index (RDI) and sleep duration, 2) hypertension, sleepiness, sleep duration and OSA, 3) glucose metabolism, diabetes mellitus, sleepiness and OSA, 4) dyslipidemia, serum lipid profile, sleep duration and OSA, and 5) metabolic syndrome, OSA and sleep duration. In conclusion, OSA, sleep duration and metabolic dysregulations are interrelated each other. However, because of complexity of these interactions, all of the associations or mechanisms have been not elucidated.
There has been no evidence-based recommendation for the treatment of asthma COPD overlap syndrome (ACOS) because of the exclusion of smoking asthmatics and COPD patients with reversible airflow obstruction from almost all clinical trials. Patients with ACOS experience acute exacerbations with higher frequency and greater severity than lone COPD. Pharmacotherapeutic considerations for ACOS require an integrated approach, first to identify the relevant clinical phenotypes, then determine the best available classes of drugs that provide the beneficial effects on important outcomes including lung function, acute exacerbations, quality of life and mortality. In addition, it is also important to target treatments to disrupt pathobiologic processes particularly small airway inflammation and smooth muscle dysfunction that give rise to pathophysiologic pattern in ACOS. Current drug treatments that can effectively prevent acute exacerbations of asthma and COPD and control symptoms may be applied to ACOS for the time being until the presence of clinical trials to demonstrate their effectiveness in controlling both symptoms and reducing exacerbations in ACOS either in a single or combination manner. Revised GINA guideline 2014 has recommended to start the initial therapy for ACOS by commencing treatment as for asthma until further investigation and adding long-acting beta2 agonist (LABA) as necessary. If the further assessment suggests COPD, symptomatic treatment with bronchodilator or combination therapy should be started, but not ICS alone as monotherapy. Other therapeutic strategies for ACOS should be included, including smoking cessation, pulmonary rehabilitation, vaccination and treatment of comorbidities.
Role of Spirometric Full Flow-Volume Curve in Searching Causes of Dyspnea

Le Thi Tuyet Lan
Vietnam

Dyspnea is the common chief complaint of the patients with respiratory diseases. Besides clinical examination and imaging, pulmonary function tests are crucial for making diagnosis the cause of dyspnea.

Spirometry is the basic test and is used widely. But up to now, some doctors use only the expiratory (upper) part of the flow-volume curve.

We use the full flow-volume curve of spirometry to differentiate many causes of dyspnea. The abnormalities of flow-volume curve could be divided into 2 groups: restriction and obstruction. The later one has three subgroups:

1. Only in the expiratory part (variable, intrathoracic obstruction).
2. Only in the inspiratory part (variable, extrathoracic obstruction).
3. In both parts (fixed obstruction in upper airway).

The flow-volume curve of the diseases in each subgroup are illustrated and additional test are included where needed to have a final diagnosis.

Besides the common diseases such as asthma and COPD, the expiratory part of the flow volume curve can help to orient the physician to less frequent disease such as vascular ring, mediastinal mass, tracheomalacia, endobronchial tuberculosis and even achalasia.

The emphasized point is the need of using the inspiratory (lower) part of the flow-volume curve: many vocal cord disorders, tumor of thyroid gland are detected based on the lower part of the curve.

The fixed obstruction, presented as plateaus in both inspiratory and expiratory parts could orient the diagnosis toward stricture or tumor of the trachea. The stricture sequelae of tracheo-bronchial tuberculosis is common and often was misdiagnosed as asthma.

Other abnormalities such as sleep apnea, foreign body can also be shown on flow volume curve of the spirometry.

Conclusion: The dyspneic patients may have disorders in the inspiratory, expiratory part or both.

The flow-volume curve must be used routinely in full form in order to help doctors in orientation toward an accurate diagnosis.
Asthma is an inflammatory airway disease from the central to small airways. Especially, small airways are important because the mucosal area is wide and difficult to reach inhalation agents. Recently, it has been reported that the concentration of nitric oxide originating in the small airways is elevated in asthmatic patients with frequent exacerbations, suggesting that prolonged inflammation in small airways could be a key target for assessing the future risk of asthma. Airway remodeling in small airways via fibrotic changes in the airway wall causes persistent airflow limitation. These fibrotic changes are due to oxidative stress and inflammatory transcriptional up-regulation. In this talk, I will cover the importance of small airway diseases in asthma and discuss how to treat it.
Clinical Importance of Digital Imaging of Terminal Airspace Enlargement in COPD
Michiaki Mishima
Japan

The clinical importance of the digital imaging of terminal airspace enlargement in COPD mainly from our data will be presented. Haruna A et al. reported that emphysematous change had strong association with mortality and may predict respiratory mortality in COPD (Chest, 2010). Tanabe N et al. demonstrated that exacerbations are involved in emphysema progression in patients with chronic obstructive pulmonary disease (AJRCCM, 2011). Mishima M et al. reported that the cumulative size distribution of the LAA clusters followed a power law characterized by an exponent D (fractal dimension), and showed that D value is a sensitive and powerful parameter for the detection of the terminal airspace enlargement (PNAS, 1999). Recently, Gotoh S et al. developed a novel method to efficiently isolate alveolar type two (AT2) cells from induced pluripotent stem (iPS) cells in the by way of endodermal lineage. This method may be useful to address the pathogenesis of COPD and regenerative medicine to repair the destroyed lung (Stem Cell Reports, 2014).
Clinical Application of iPS Cell in the Respiratory Field Including COPD and Asthma
Michiaki Mishima
Japan

Induced pluripotent stem (iPS) cells, developed by Shinya Yamanaka in Kyoto University who won the Nobel Prize in 2012, theoretically have a potential to differentiate into any cells in the body.

In this paper, the updated our outcome of iPS research in the respiratory field collaborated with Prof. Yamanaka will be demonstrated. Since alveolar type I cells differentiated from alveolar type II (AT2) cells, the key cells for lung regeneration is AT2 cells. We have been developing a strategy to induce AT2 cells from iPS cells by way of endodermal lineage. Recently, Gotoh S et al. developed a novel method to efficiently isolate alveolar type AT2 cells from induced iPS cells by way of endodermal lineage. This method may be useful to address the pathogenesis of COPD or asthma and regenerative medicine to repair the destroyed lung (Stem Cell Reports, 2014; 3(3): 394-403). We expect that this investigation must convey the new paradigm in the respiratory medicine.
The Implications of Real-Life (Comorbid Conditions, Inhaler Technique And Lifestyle Factors) on Asthma Management: Is There Any Evidence Available?

Omar S Usmani
United Kingdom

Randomized controlled trials (RCTs) in asthma include tightly-controlled, well-characterised populations that represent only a subgroup of the broadly heterogeneous patient population treated in everyday clinical practice.

Patients with asthma, including those with comorbid conditions (e.g. rhinitis, obesity), those who smoke, or those with poor inhaler technique are not included in RCTs due to highly selective inclusion/exclusion criteria. Hence, concerns exist about the extent to which RCT data can be accurately extrapolated to reflect treatment effectiveness and long-term safety in real-life asthmatic patient populations. RCTs should be complemented by a diversity of approaches that involve analysing the totality of the evidence base.

Guidelines focus on therapeutic drug in the management of patients with asthma, but often do not evaluate the differences between inhaler devices or take into account inhalation technique that can modulate the effectiveness of the drug in day-to-day real-life practice. Adherence to inhaler therapy is near optimal in RCTs, but in clinical practice we struggle as practitioners to engage our patients to take their medications as prescribed. Smokers are typically excluded from asthma RCTs, but their inclusion in observational asthma studies and pragmatic trials provides a way of assessing the relative effectiveness of different treatment options to manage this important clinical subgroup constituting approximately 20% of patients with asthma.

Is there any available evidence? This presentation will highlight how real-life effectiveness research can use observational or clinical trial designs with emphasis on high external validity to complement classical efficacy RCTs with their high internal validity.
Does the Treatment of the Small Airways Matter?

Omar S. Usmani

UK

There is increasing academic interest and clinical awareness in the understanding of the contribution of the small airways to the clinical expression of disease in patients with asthma. Pathological evidence shows small airways disease is present throughout the airway tree in patients with all severities of asthma. Physiological data clearly reveal that the main site of airflow limitation in asthma and chronic obstructive pulmonary disease (COPD) is that of the small airways. There is reinvigoration in physiological tests to identify distinct airways responses in this region from those of large airways. New imaging modalities are also allowing investigators to understand structure function relationships within the airway tree. These techniques are now being utilised to investigate whether targeting inhaled therapies to the small airways is of benefit to patients. In order to achieve this, it is recognised that aerosol drug particle size and patient inspiratory flow are the major determinants influencing the extent, distribution and site of inhaled drug deposition within the airways and regional targeting of the small airways. With the technology to direct inhaled therapy to the small airways coupled with the ability to assess small airway responses the challenge now is to understand whether small airways therapy translates to better patient centred outcomes such as asthma control.
Lung Function in Various Diseases. How to Use Pulmonary Function Tests Most Effectively to Guide Correct Diagnosis and Treatment

Paul Enright
USA

PFT results only increase or decrease the pre-test probability of disease. You should be uncertain that the results are normal or abnormal when they are near the lower limits of the normal range. Use as few parameters as possible when interpreting the results.

The most common reasons for ordering PFTs when managing patients are for 1) dyspnea evaluations (order spirometry, DLCO, and BNP), 2) infiltrates on chest x-ray (order spirometry and DLCO), 3) chronic cough (if spirometry is normal, consider an inhalation challenge test), and 4) to verify treatment response during follow-up visits (measure change in FEV1, FVC, or DLCO).

Lack of a bronchodilator response does not rule out asthma nor confirm COPD. More than half of patients with severe COPD are Bd “responders.” Hyperinflation and air trapping are proportional to obstruction severity, so lung volume tests are not helpful for patients with airway obstruction and a chest x-ray. About 20% of patients with severe COPD also have heart failure, so order a BNP to screen for heart failure. DLCO is the second most valuable PFT for clinicians, and is now available as a small instrument. A low DLCO predicts oxygen desaturation during exercise. The six-minute walk test provides an objective measure of exercise limitation and is easy to perform in outpatient settings.
Inhaled corticosteroids (ICS) and long-acting β2-agonists (LABA) will continue to be the mainstay of asthma therapy in the future, including patients with ACOS - who require maximal bronchodilatation for the COPD component and corticosteroids to deal with the asthmatic component. In addition, these patients are likely to benefit from a long-acting muscarinic antagonist (LAMA), several of which are now becoming available. ACOS patients may therefore be suitable for triple therapy (ICS+LABA+LAMA), although developing such combinations may be challenging. Twice daily (ciclesonide/formoterol/tiotropium and budesonide/formoterol/glycopyrrolate) and once daily triples (fluticasone furoate/vilanterol/umeclidinium and mometasone/indacaterol/glycopyrrolate) are already in development. The main challenge in future asthma therapies is in treatment of patients with severe disease who are relatively resistant to the anti-inflammatory effects of corticosteroids. This has led to a search for alternative anti-inflammatory treatments, such as phosphodiesterase-4 and p38 MAP kinase inhibitors, although these drugs are limited by side effects. More specific therapies include cytokine blockers, such as anti-IL-5 and anti-IL-13, which may be suitable for specific phenotypes of asthma with eosinophilia or ACOS patients with eosinophilia. ACOS patients may have predominantly neutrophilic inflammation and this may be targeted by antagonists of the chemokine receptor CXCR2, non-antibiotic macrolides and by blockers of IL-17. An alternative approach is to target the corticosteroid resistance mechanisms, which involve a reduction in histone deacetylase-2 through the activation of phosphoinositide-3- kinase-δ. This pathway may be targeted by existing treatments, including theophylline, nortriptyline and macrolides, or by newly developed inhaled PI3Kδ inhibitors. Since this pathway is driven by oxidative stress novel antioxidants, such as Nrf2 activators are also in development.
What Happens to a Child with Untreated Obstructive Sleep Apnoea?
Rosemary SC Horne
Australia

During childhood sleep is at a lifetime maximum. Sleep disordered breathing (SDB) is common in childhood and affects up to 35% of children. SDB forms a spectrum of severity from primary snoring, where there are no associated gas abnormalities or sleep disruption to obstructive sleep apnoea (OSA) which is associated with repetitive hypoxic events and frequent arousals from sleep. Primary snoring is most common form of SDB, with OSA occurring in 1-5% of children. SDB of all severities is associated with significant adverse daytime consequences including behaviour, attention and learning. SDB is also associated with adverse effects on the cardiovascular system including elevated heart rate and blood pressure and impaired autonomic cardiovascular control. In children, SDB is primarily due to enlarged tonsils and adenoids and the primary treatment is surgical removal of these tissues. Surgery is however usually only carried out in children with more severe disease, with the majority of children with primary snoring not having surgical intervention. Despite the frequency of adenotonsillectomy there have been limited studies of the effectiveness of this treatment is ameliorating the behavioural, neurocognitive and cardiovascular effects and most of these studies have only followed children up in the short term (i.e. < 1 year). There are even fewer studies of what happens to children who are not treated. Data from longer term follow up studies (3-4 years) will be presented. These studies highlight the need to consider the age of the child and suggest that the threshold for treatment in children should be revised.
Clinicians have been long aware that neither the traditional distinctions of “emphysema” versus “chronic bronchitis” nor the traditional clinical phenotypes of “blue bloater” and “pink puffer” are sufficient to categorize patents that suffer from chronic obstructive pulmonary disease (CoPD). With an increased understanding of pathophysiologic variation, COPD now clearly represents a spectrum of overlapping diseases with important extrapulmonary consequences.

A “phenotype” describes the outward physical manifestations of a particular disease, and comprises anything that is part of the observable structure, function or behavior of an individual. Such phenotypic distinctions in COPD include: frequent exacerbator, pulmonary cachectic, rapid decliner, airways hyperresponsiveness, impaired exercise tolerance, and emphysema versus airways disease. These variable manifestations, each with unique prognostic, clinical and physiologic implications, represent distinct phenotypes within COPD. While all of these phenotypes have smoking as a common risk factor, the other risk factors that determine these phenotypes remain poorly understood. An individual smoker has variable expression of each phenotype and there is mounting evidence that COPD phenotypes have different clinical outcomes. These phenotypes can be broadly classified into one of three groups: clinical, physiologic and radiographic.

To understand the heterogeneity of COPD in Asian countries we organized Asian Network for Obstructive Lung Diseases (ANOLD) in 2008. Through this network we found that characteristics of COPD patients in Asian countries vary and the history of exposure to biomass fuels or dusty jobs was related to frequency of symptoms, severe airflow limitation, and poor quality of life. We also evaluated whether there are subgroups of COPD patients with distinct phenotypes and found subgroups of COPD patients with distinct phenotypes. The fractions of the COPD subgroups among four Asian regions were different and might suggest that there are substantial differences in the severity and a potential subtype in Asian regions.
Compensation for Asbestos-Related Diseases in Korea: Current Situation
Soon-Hee Jung, M.D., Ph.D
Republic of Korea

In Korea, the asbestos-related diseases (ARDs) patients and the bereaved can be compensated through Asbestos Damage Relief Law enacted by the Ministry of Environment in 2011 to provide fair, prompt relief to victims and to the bereaved of ARDs and to address the health damage caused by asbestos exposure. The ARDs include malignant mesothelioma, lung cancer, and asbestosis. The damaged patients can be compensated by medical expense, medical treatment allowance, relief benefit adjustment money, and funeral service expense. The special bereaved families can be compensated by special condolatory expense for the bereaved and special funeral service expense. The applicants can be certified by three steps through Judgment Committee, Review Committee, and Re-review Committee.

During the last three years after enforcement of asbestos damage relief act in 2011, 1,740 asbestos-related diseases (ARDs) patients and the bereaved applied for the compensation of asbestos damage and 1,261 (72.5%) applicants were certified. The percent of applicants among certified applicants was 50.9% in MM, 40.6% in asbestosis, and 8.5% in lung cancer. The certified percent of patients was 91.2% in MM, 66.2% in asbestosis, and 8.0% in lung cancer. The certified bereaved was 77.5% in MM, 1% in asbestosis, and 9.3% in lung cancer.

For the certification of MM, the patient and the bereaved have to apply with pathologic report and an application letter. They can be compensated through the pathologically confirmation after the review of pathologists among the committee members. However, we have experienced many MM cases with diagnostic pitfalls, diagnosed at the several hospitals because of absence of diagnostic guidelines of MM. Asbestosis and lung cancer were same situation.

So we have studied the project of diagnostic guideline of ARDs to provide a fair, prompt relief to victims of ARDs in Korea through the financial support of Korea Environment Industry & Technology Institute (KEITI).
Mesothelioma is an uncommon neoplasm arising from the mesothelial cells of the pleura, peritoneum, pericardium and tunica vaginalis. A total of 80% of all mesothelioma are pleural in origin. The increasing incidence of mesothelioma in almost all industrialized countries is characterized by its association with commercially used asbestos, and its long latency period of 40 years. High iron content of amphiboles fibers contributes to their higher carcinogenic potential with generating reactive oxygen and nitrogen species. Paradoxically, oxidoreductase enzyme thioredoxin acts as one of antioxidants, and its overexpression has been demonstrated in mesothelioma cells, and serum level is significantly increased in patients with malignant pleural mesothelioma (MPM). Early stage MPM frequently present with asymptomatic pleural effusion as the first clinical sign. Therefore fluid cytology is the first step for diagnosis and thoracoscopy is the key investigation to obtain sufficient material allowing immunohistochemical characterization and adequate visual examination in the pleural cavity. Cisplatin+pemetrexed is the standard first line chemotherapy, which has remained unchanged for 10 years since the randomized trial in 2003. Radical surgery extrapleural pneumonectomy is associated with 4-9.5% mortality and >25% serious complications. Pleurectomy/Decortication (P/D) is well tolerated and produces low mortality and morbidity, but does not offer a macroscopic complete resection in most cases. However, retrospective analyses demonstrated better outcomes among those who underwent P/D. The role of surgery has been the subject of debate, however, surgical MCR and control of micrometastasis and invasion are pivotal role in the multimodality therapy for MPM.
Fluid Shift in Patients with the Sleep Disordered Breathing
Takatoshi Kasai
Japan

The high prevalence of sleep disordered breathing (SDB) in patients with fluid retention such as heart failure (HF), renal failure (RF) and drug resistant hypertension (DRH) led us to hypothesize that fluid retention and, more specifically, nocturnal shift of dependent fluid rostrally while recumbent during sleep, is involved in the pathogenesis of SDB. Recently, our group demonstrated that in response to an application of lower body positive pressure, neck circumference increased, the pharyngeal cross-sectional area decreased, and pharyngeal resistance and collapsibility increased simultaneously with a reduction in leg fluid volume. We also demonstrated that in patients with HF, RF, and DRH, there were direct relationships between the volume of fluid displacedgravitationally from the legs overnight and both the overnight increase in the neck circumference and the severity of SDB. These data suggest that rostral fluid shift in patients with SDB behaves in a way that would predispose to upper airway obstruction during sleep. In this session, I would review these data and discuss possibilities to utilize this concept for the treatment of SDB.
Recent studies suggest that bronchiolar progenitors that exist within bronchioles are capable of long-term self-renewal to maintain the normal airway epithelium. In this study, for development of novel therapeutic strategies to modulate the stem cell-like capacity, we characterized the gene expression profile of mouse bronchiolar progenitors by using the Agilent microarray system. Bronchiolar progenitor and club cell (formerly known as Clara cell) subsets were isolated according to the surface phenotype of CD31neg CD45neg CD34neg Sca-1pos with low and high autofluorescence, respectively. Among genes that represented significant differences of expression in bronchiolar progenitors compared to club cells, we picked an up-regulated gene, and referred to the gene product as bronchiolar progenitor factor 1 (BPF1) on an assumption that BPF1 may be requisite for the bronchiolar progenitor behavior. Contrary to the assumption, the genetic deficiency of BPF1 increased the number of bronchiolar progenitors, and decreased lung inflammation following naphthalene-induced lung injury. In further gene expression microarray experiments, we found a gene with the most remarkable up-regulation in bronchiolar progenitors of BPF1-deficient mice compared to those of wild-type mice, and referred to the gene product as bronchiolar progenitor factor 2 (BPF2). Upon treatment with intravenous administration of recombinant protein BPF2, wild-type mice displayed the similar phenotype to BPF1-deficient mice; the BPF2 treatment dampened the naphthalene-induced inflammation with the increased number of bronchiolar progenitors. These results suggest that BPF2 may provide novel therapeutic approaches to inflammatory lung disorders.
Tissue fibrosis has been suggested to be associated with an abnormal wound healing process derived from sustained chronic injury and consequent excessive healing. Persistent injury from various stimuli activates the epithelial cells, which produce abundant several cytokines, chemokines, and growth factors. These mediators promote chronic airway inflammation, which induce excessive repair process and provide fibrotic change in tissue. The cells related with fibrosis have been reported to originate at residual fibroblasts, bone marrow-derived progenitors of fibroblasts, or mesenchymal cells that underwent epithelial-mesenchymal transition (EMT) from epithelial cells. Transforming growth factor (TGF)-β is one of the key mediators involved in the pathogenesis of fibrosis, since TGF-β regulates production of extracellular matrix proteins, proliferation, and differentiation of fibrosis and myofibroblasts. Also, TGF-β is a potent inducer of EMT and would play important roles on the fibrosis through induction of EMT process. Since chronic inflammation induces abundant TGF-β and associates with the formation of fibrosis, several inflammatory mediators in the airway, such as tumor necrosis factor (TNF)-α, interleukin-1β, and TNF superfamily 14 which is called as LIGHT, would affect EMT process in association with TGF-β. The mechanisms of EMT in airway epithelial cells under chronic airway inflammation would be summarized.
Phenotyping Lung Disease Using Computed Tomography
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Japan

Structural changes of the lung may occur in the subsequence of pulmonary diseases. These lung structural changes influence the function of the lung. Structural and functional changes of the lung work together and lead to symptoms. Part of the structural changes of the lung could be assessed using computed tomography (CT).

CT is a precise tool to measure the specific gravity. Using this function, CT has been used to evaluate and quantify the structure of the lung. This type of approach is now called as ‘Quantitative Computed Tomography (QCT)’ analysis. In chronic obstructive pulmonary disease (COPD), emphysematous lesions and airway lesions are evaluated using QCT analysis. CT extent of emphysematous lesions are calculated as the percentage of low attenuation volume at the threshold of -950 Hounsfield units (%LAV-950) and airway lesions are quantified as the square root of wall area of a hypothetical airway with an internal perimeter of 10 mm (SRWA-Pi10). Using these two parameters patients with COPD could be divided into phenotypes: airway dominant, emphysema dominant, and mixed (airway plus emphysema). The difference of these phenotypes will also be discussed in this lecture.
When magnetic resonance (MR) imaging was first implemented, many investigators were interested in this new technique for not only brain, but also other areas including chest. As a result, from the 1980s to the early 1990s, MR imaging was tested to evaluate different lung diseases as well as mediastinal, pleural and cardiac diseases by many physicists and radiologists. However, the MR systems, sequences and other applications at that time were very primitive and limited, adequate image quality within an appropriate examination time could not be realized. Therefore, it could not be demonstrated that MR could be substituted for computed tomography (CT), pulmonary angiography and/ or nuclear medicine studies. Until 2000, MR imaging was therefore used only for some minor clinical indication.

In the 2000s, however, technical advances were reported by many basic and clinical researchers, in particular for lung MR imaging, which has been one of the more challenging fields for MR imaging. State of the art pulmonary MR imaging can provide not only functional and metabolic information, but also morphological information with relatively high spatial resolution within appropriate examination time, and may therefore be able to perform as a substitute and/or in a complimentary role in management of patients with pulmonary and/ or cardiopulmonary diseases.

This lecture covers 1) state-of-the-art pulmonary MR techniques applied for phenotyping of lung diseases, and 2) future direction of pulmonary MR imaging.
Therapeutic Effects of Histone Deacetylase Enzyme 6 Inhibitors (HDAC6i) in a Murine Asthma Model

Yuan Ren
China

Background and purpose: Airway inflammation, airway remodeling and airway hyperresponsiveness are major aspects of asthma pathology. Histone deacetylase inhibitors have a wide range of effects that demonstrate therapeutic effects in animal models of chronic inflammatory diseases. In this study, we investigated the effect of Tubastatin A HCl, a selective HDAC6 inhibitor, on the development of chronic allergic airway disease mice with airway inflammation, airway remodeling and airway hyperresponsiveness.

Methods: Wild-type BALB/C mice were immunized intraperitoneally three times with ovalbumin (OVA) + aluminum hydroxide gel (on weeks 0, 1, 2) and nebulized 1 week (early phase) or 8 weeks (prolonged phase). Ovalbumin-exposed mice were treated with Tubastatin A HCl or vehicle control. Airway inflammation was assessed by bronchoalveolar lavage fluid cell counts and HE staining of lung tissue sections. Airway remodeling was assessed by Alcian blue-Periodic acid Schiff staining and Masson trichrome staining. Airway hyperresponsiveness was assessed by plethysmography measurement of airway resistance.

Results: Tubastatin A HCl treatment relieved airway inflammation compared with vehicle treated mice (P < 0.05), but its effect was worse than dexamethasone treatment. However, Tubastatin A HCl treatment reduced the quantity of goblet cell (P < 0.05), subepithelial collagen deposition (P < 0.05) and attenuated airway resistance (P < 0.05).

Conclusion: These results demonstrate that treatment with HDAC6 inhibitors can reduce airway inflammation, airway remodeling and airway hyperresponsiveness, suggesting that blockade of HDAC6 may be a useful treatment for bronchial asthma.
HRCT surveys have found evidence of interstitial lung disease (ILD) in 8 to 15% of smokers. The recent pathology literature has described a new form of ILD in smokers under the names “smoking-related interstitial fibrosis,” “airspace enlargement with fibrosis,” and “RBILD with fibrosis.” To avoid confusion with other forms of smoking-related ILD, we suggested that this lesion be called “respiratory bronchiolitis with fibrosis” (RBF). RBF is characterized pathologically by localized patches of quite marked subpleural paucicellular interstitial fibrosis mixed with emphysema and smoker’s macrophages. We have shown that this lesion is often visible on HRCT as distinctive subpleural upper or mid-zonal circumscribed patches of reticulation surrounding emphysematous spaces. Some cases also demonstrate patchy ground glass opacities. Pulmonary function tests typically show mild airflow obstruction, sometimes with a disproportionately decreased diffusing capacity. In a survey of 200 heavy smokers, we observed this lesion on HRCT in 7% of patients. The lesion was radiologically stable in 86% and showed mild progression in 14%. However, in no case did the patient develop a diffuse fibrosing lung disease. RBF is often mistaken pathologically and radiologically for a functionally impairing ILD. We propose that, like smoker’s respiratory bronchiolitis (RB), most cases of RBF have no functional consequences; but, analogous to RBILD, some patients with RBF have evidence (reticulation, decreased diffusing capacity) of a ILD; ie, RBFILD. RBFILD may account for a substantial proportion of the ILD seen in HRCT surveys of cigarette smokers. The relationship of RBILD and RBFILD to DIP will be discussed.
Tuberculosis, Tobacco and Smoking Cessation
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Bangladesh

Tuberculosis and Tobacco are a deadly pair

Smokers are roughly twice as likely to become infected and develop active TB compared to nonsmokers. They are usually diagnosed at a more severe stage of the disease, since cough is often neglected as smoker’s cough. Passive smoking increases the risk of TB, especially in children.

Smokers with TB, have a poorer prognosis, a greater risk of relapse, and are less likely to comply with TB treatment. In addition, tobacco increases the risk of dying from TB. There is a “dose response” relationship between smoking and TB – that is, the more cigarettes smoked daily, or the longer duration someone has smoked, increases the vulnerability to TB.

Smoking Cessation Reduces the Risk of TB

Tobacco control has been neglected as a means of reducing TB. The strong links between TB and smoking make smoking cessation imperative for TB patients as well as people at risk for TB. Proven tobacco control initiatives should be integrated within TB control strategies, especially in low-income and middle-income countries, where the tobacco industry is aggressively expanding its markets. Smokers who quit reduce both their risk of becoming infected with TB and dying from it.

The message for health care providers, particularly clinicians and policymakers, is clear: Aggressive and sustained tobacco control is important in achieving effective TB control. This should be a priority for governments in high burden countries who are fighting relentlessly to achieve the Millennium Development Goals.
The Asia–Pacific region is home to a large heterogeneous population whose respiratory health is influenced by diverse social, economic and environmental factors. The most prevalent causes of respiratory morbidity and mortality are tobacco smoking, infection, and air pollution. Tobacco smoking is a significant contributor to respiratory ill-health and death in the Asia–Pacific region as it is worldwide. Tobacco use is one of the biggest contributors to the epidemic of non-communicable disease in the Western Pacific Region.

This review aims to summarize current respiratory health issues in the Asia–Pacific region including smoking-related diseases especially COPD, lung cancer, cardiovascular disease. Among the Asia Pacific Region’s developing countries, tobacco use adversely impacts five of the top 10 diseases and injuries: Cerebrovascular disease, lower respiratory infections, chronic obstructive pulmonary disease, ischemic heart disease... Among the developed countries tobacco ranks as the leading health risk factor of over 50% of the population attributable fraction for COPD and lung cancer. Tobacco use also plays a role in the causation of ischemic heart disease and cerebrovascular disease, which are two leading diseases that make up over 15% DALYs.
Respiratory infections are common in the ICU setting. There are a number of different aspects of the care of these patients that are important to consider and review. Many patients with community-acquired pneumonia require ICU hospitalization, particularly for the management of acute respiratory failure and/or septic shock. Pneumonia is the most common infectious cause of septic shock. There are important features of septic shock management, including antimicrobial therapy, shock assessment and treatment, and supportive care that will be discussed. Key aspects of mechanical ventilation of patients with severe pneumonia, including pneumonia-related ARDS are evolving and will be reviewed. Further, critically ill patients who are receiving mechanical ventilation can develop nosocomial infection – ventilator-associated pneumonia (VAP), which is associated with worse patient outcomes. There are important strategies designed to reduce the chances of developing VAP, which will be reviewed. The important role of multi-drug resistant microorganisms in VAP will be emphasized and the impact on antimicrobial management discussed. In summary, the speaker will address key concepts in the epidemiology, prevention, and management of respiratory infections in the ICU.
One of the most important health challenges of today is the non-communicable diseases, which kill more than 36 million people annually and cause untold suffering that stress the health care systems of all countries. Attenuating risks today from tobacco, excess alcohol, physical inactivity, and unhealthy diets will mean a healthier tomorrow. The United Nations deemed them so important that it held a high-level meeting on their prevention and control in 2011.

Of these risks, tobacco use is the most harmful and modifiable. Important gains have been made in tobacco control using strategies such as “denormalizing” its use, but a new challenge has arisen, electronic nicotine delivery systems. Heavily marketed worldwide as fashionable, their popularity has spread exponentially. E-cigarettes are unregulated, readily available to all ages, and produced in flavors that appeal to young people. These products have not been adequately studied for safety, their effects on the health of populations, or as smoking cessation devices.

The Asian Pacific Society of Respirology and its partner organizations in Forum for International Respiratory Societies presented a joint statement in association with a follow-up high-level meeting of the United Nations on non-communicable diseases in July 2014. The statement advised that “The potential benefits of electronic cigarettes to an individual smoker should be weighed against harm to the population of increased social acceptability of smoking and use of nicotine...” It recommended that “Electronic nicotine delivery devices should be restricted or banned until more information about their safety is available. If they are allowed, they should be regulated as medicine or tobacco products.”
TB Control and MDR-XDR Prevention in India

Dr. V. K. Vijayan

India

The estimated incidence of new tuberculosis cases in India is 2.2 million and the prevalence is 2.8 million cases. Approximately 5% of TB patients have an estimated HIV positivity. Drug resistant TB has been reported in 2.2% of new cases and 15% of previously treated cases. India accounts for about 23.3% of the global prevalence and is the highest TB burden country in the world. Considering the magnitude of the problem and to achieve a control, the Revised National TB Control Programme (RNTCP) was launched in 1997 in India and RNTCP has expanded across the country in a phased manner. The objectives of the programme are to achieve and maintain cure rate of at least 85% among New Sputum Positive (NSP) patients and to achieve and maintain case detection of at least 70% of the estimated NSP cases in the community. The current focus of the programme is on ensuring “universal access” to good quality early diagnosis and treatment for all TB patients. The program is covering the entire nation since March 2006 reaching over a billion population (1164 million). Annually more than 1.5 million TB patients are placed on DOTS treatment under RNTCP. In 2011, RNTCP has achieved the new sputum positive case detection rate of 71% and treatment success rate of 88% which is in line with the global targets for TB control. Throughout the country a network of more than 600,000 trained directly observed treatment (DOT) providers provide directly observed treatment (DOT) to more than a 1.5 million patients diagnosed as TB each year. The success of the RNTCP is the result of a comprehensive and appropriate strategy, systematic and timely planning, robust systems of quality assurance for diagnosis and treatment, methodological logistics management, well defined human resource development strategy including trainings, clear defined technical and operational guidelines and a built in supervision and monitoring mechanism. All states in India are implementing the “Supervision and Monitoring strategy”, detailing guidelines, tools and indicators for monitoring the performance from the peripheral health institution (PHI) level to the national level. Regular internal and external evaluations ensure quality program implementation. The program is focusing on the reduction in the default rates among all new and retreatment cases and is undertaking steps for the same. quality assured anti-TB drugs for the full course of treatment to the patients through patient wise boxes. Decentralized treatment is provided to the patients as near to their home as possible. The programme is in the process of establishing a network of accredited culture and drug susceptibility testing (DST) Intermediate Reference Laboratories (IRLs) across the country in a phased manner for diagnosis and follow up of MDR TB patients. Multi Drug resistant TB (MDR TB) services have been initiated in all states in the country. RNTCP has involved NGOs and private practitioners. corporate hospitals and medical collages as part of Public Private Mix (PPM) for successful implementation of the programme.
The positive impact of the programme can be seen from the fact that TB mortality in the country has reduced from over 39 per hundred thousand population in 1990 to 29 hundred thousand population in 2010. The prevalence of TB in the country has reduced from 459 per hundred thousand population in 1990 to 256 per hundred thousand population by the year 2010 (WHO Global TB Report, 2011). As per the National Strategic Plan of Government of India to be implemented during 2012-2017, the vision is to have a “TB-free India” with the goal of Universal Access to quality TB diagnosis and treatment for all pulmonary and extra pulmonary TB patients including drug resistant and HIV associated TB.
Moving COPD Beyond FEV1: Role of Pulmonary Imaging
Harvey O Coxson
Canada

Forced expiratory volume in 1 second (FEV1), measured using spirometry, provides a straightforward, widely-available and inexpensive global measurement of airflow limitation and lung function. For decades, FEV1 has remained the main intermediate endpoint used in research studies and for the development of new COPD therapies. Not surprisingly, therapies that acutely improve FEV1, dominate as COPD therapies. However, in COPD patients, the relationship of FEV1 with symptoms and outcomes such as exacerbations and mortality is weak, and importantly, FEV1 does not take into account the heterogeneity of COPD nor its different phenotypes. Thoracic imaging provides a way to quantify airway remodeling, emphysematous destruction, regional ventilation abnormalities (ventilation defects) and gas trapping in ex-smokers in whom FEV1 may be normal and in COPD patients with very modest lung function deterioration. In individual patients and in COPD cohort studies, thoracic imaging using x-ray computed tomography (CT), and magnetic resonance imaging (MRI) (conventional 1H as well as hyperpolarized noble gases such as 129Xe, 3He) and optical coherence tomography can be used to directly visualize the structural and functional consequences of COPD and thus provide a clearer picture of COPD mechanisms, disease progression and response to therapy. We briefly describe pulmonary imaging methods that provide a way to visualize and quantify with high spatial and temporal resolution, regional ventilation abnormalities, gas trapping, emphysema and airway remodeling in COPD. Finally we discuss the implications of recent imaging findings and their impact on future biomarker and therapy research aimed at improving COPD outcomes.
In 2013 the most recent world conference on pulmonary hypertension (PH) was performed in Nice. The classification of PH was updated and it remained to minor revision. The concept of classification would be basically considered that the same group has the common pathologic and hemodynamic characteristics and also common therapeutic approaches. Aspire Registry, however, shows that outcomes and characteristics differed not only between PH groups but within PH groups. Three-year survival for PAH (Group 1), PH with left heart disease (PH-LHD; Group 2), PH with chronic lung disease (PH-CLD; Group 3), and chronic thromboembolic PH (CTEPH; Group 4) was 68%, 73%, 44%, 71%, respectively. Even within groups, PAH is a heterogeneous condition; 3-yr survival for PAH with systemic sclerosis (PAH-SSc), idiopathic PAH (iPAH), and Eisenmenger’s PH was 52%, 63% and 85%, respectively. It is conceivable that the different forms of PH present with either a predominance of pulmonary arterial remodeling such as iPAH or vein remodeling such as pure pulmonary veno-occlusive disease (PVOD) or a contribution of both such as SSc-PAH. PVOD/PCH (pulmonary capillary hemangiosis) remain difficult disorders to classify since they share the same characteristics as iPAH but exhibit many differences, so PVOD/PCH were classified to Group 1’ in the world conference in Dana Point in 2008. Survival in PH-CLD was most poor among all groups. Moreover, Group 3 was inferior and Group 4 was superior compared with Group 1. In order to discuss therapeutic strategies for PH-CLD, one severe PH case will be presented in the session.
Redefining COPD

Jørgen Vestbo
Denmark

The well-known heterogeneity of COPD has led to the concept of phenotypes as a way of understanding and treating separate components of the disease separately – a way of introducing precision medicine into COPD.

A phenotype of COPD was defined by Han et al as “a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, rate of disease progression, or death).”

Some of the most important phenotypes of COPD are the frequent exacerbator, chronic bronchitis, having systemic inflammation and being a rapid decliner. Exacerbations are frequent in COPD but there is ample evidence that some patients have frequent exacerbations and some rarely have any. Predictors are available and specific treatments aimed at reducing the burden of exacerbations. Future treatments are likely to be guided by biomarkers. Chronic bronchitis is strongly associated with smoking and in younger patients a predictor of poor prognosis; specific treatments are lacking. Systemic inflammation is still poorly understood but relates to both exacerbations and risk of patterns of comorbidities.

I propose that phenotypes should be evaluated according to underlying activity of COPD. Biomarkers for this are urgently needed but required for further progress in the understanding and management of COPD.
Despite advances in the treatment of asthma, exacerbations remain common. The National Heart Lung and Blood Institute’s National Asthma Education and Prevention Program Guidelines recommend early treatment of asthma exacerbation as “key in management”, but do not provide specific information or guidance about signs and symptoms that may present before lower respiratory symptoms. We aimed to describe early signs and symptoms of an impending asthma exacerbation in children, and to study how these symptoms vary during a well-period and illness periods.

To collect and study these signs and symptoms we performed focus groups followed by administration of surveys with a 57-symptom inventory (Asthmatic Child Early Signs and Symptoms (ACcESS) inventory) to 200 caregivers of children aged 1-12 years with physician diagnosed persistent asthma recruited from our pediatric asthma clinics. We then recruited caregivers (same inclusion criteria) to perform daily diary cards based on the symptom inventory during a 4-week well-period (ACQ<1.5) in the summer (n=19) and a 16-week winter period (n=27) where there was likelihood of loss of control (>2 consecutive days of increased LR symptoms).

A wide variety of symptoms were reported as preceding an asthma exacerbation. We categorized these into three main categories: non-respiratory (NR), upper respiratory (UR), and lower respiratory (LR). NR symptoms were further subdivided into changes in eating habits, appearance, activity, and behavior. The most common NR symptoms included decreased activity (31%), decreased appetite (25%), irritability (20%), difficulty falling asleep (19%), and paleness (11%). A total of 25% of caregivers reported runny nose as an early symptom and 68% reported cough. The very first symptom was NR in 25%, UR in 15%, and LR in 60%. Ninety-seven percent of caregivers were able to identify a first symptom, and 89% reported that this first symptom was present always or almost always. There was no difference in symptom reporting or symptom reporting category (NR, UR, LR) according to child’s age, gender, ethnicity, race, or use of asthma controller, or the caregiver’s age, gender, ethnicity, race, insurance type, income, and education.

During the 4-week well period, there was little symptom variability across all symptom categories. During the 16-week winter period, overall there was a trend for increased likelihood of reporting NR symptoms in the 3 days before loss of control episodes, including changes in behavior, mood, and appearance as compared to period were asthma was controlled. Some NR symptoms were consistently increased over the 3-4 days prior to an episode, with others increased only the day prior to an episode of loss of control. Overall, UR symptoms were not increased during the days prior to a loss of control episode.
In conclusion, caregivers identify a wide variety of signs and symptoms as occurring before an asthma exacerbation. These include non-respiratory symptoms and upper respiratory symptoms, in addition to the typical lower respiratory symptoms of asthma. These symptom patterns are not different by specific parental or child characteristics. The symptoms that were significantly increased before episodes of loss of control were mostly NR in nature. Furthermore, these symptoms do not significantly vary during a well period, and some children may exhibit symptom patterns with recurrent illnesses. A study is currently underway to assess whether augmentation of inhaled corticosteroids triggered by an ACcESS inventory-guided asthma management plan will change asthma morbidity by decreasing severity of asthma exacerbations.
Lung cancer is the leading cause of cancer death worldwide. Despite progress in the use of platinum-based chemotherapy, the median survival time of patients with inoperable non-small cell lung cancer (NSCLC) remains poor. One recent advancement in the treatment of inoperable lung cancer is the development of molecular targeting drugs, including gefitinib, erlotinib and afatinib, that target the epidermal growth factor receptor (EGFR). However, most patients with NSCLC harboring EGFR activating mutations who respond to EGFR-TKI become resistant to treatment nine to 14 months after the start of therapy via various molecular mechanisms, including gatekeeper mutations in EGFR, such as the T790M mutation, in which threonine (T), at the 790th amino acid, is converted to methionine (M), cMET amplification, hepatocyte growth factor (HGF), overexpression and PTEN downregulation. Several other molecular mechanisms of acquired resistance have been identified, including the epithelial-mesenchymal transition (EMT) and involvement of cancer stem cells (CSCs). We have intensively investigated precise EGFR-TKI resistance mechanisms that function independent of T790M and recently clarified several novel potential mechanisms. In this lecture, I would like to review the mechanisms underlying EGFR-TKI resistance and introduce our recent novel findings, which may identify potential novel molecular targets in patients with advanced NSCLC.
In the 1990’s, investigators first in Japan and then the United States began studying low-dose CT screening for lung cancer. These low-dose CT trials were designed as single-arm studies, which led to the detection of more early stage lung cancers. However, the single arm studies did not determine whether low-dose CT screening affected lung cancer mortality due to lead-time, length-time, and over-diagnosis biases. To answer the question whether screening with low-dose CT reduces lung cancer mortality, several randomized control trials have been conducted. Findings of the US National Lung Screening Trial showed a 20% reduction in lung cancer mortality and a 6.7% decrease in all-cause mortality. Recently, the US Preventive Service Task Force recommended that screening should be implemented. However, many questions remain, including whom to screen, how often, and for how long. Furthermore, costs and effects on the health care system remain unclear. In this presentation, I would like to briefly review the history of lung cancer screening, discuss the results of the National Lung Screening Trial, and address some of the unanswered questions.
The mean pulmonary arterial pressure (mPAP) in patients with COPD is an extent of more than 20 mmHg at rest, of which pulmonary hypertension is mild or even absence. COPD cases corresponding to severe pulmonary hypertension have been reported to be at most 1%; it is not a small number on estimation that the number of patients with COPD is approximately 200 million in the world. Comparing with the forced expiratory volume in 1 second and lung diffusion capacity, the severity of pulmonary hypertension is the crucial factor in determination of the prognosis. However, since the airflow obstruction does not correlate with the severity of pulmonary hypertension, when the respiratory functions could not explain the reduction of exercise tolerance, it is very important to examine the pulmonary circulation system. It is lack of evidences of treatment for pulmonary hypertension associated with COPD by the medicines those are approved for clinical management of pulmonary arterial hypertension (PAH). Because PAH therapeutic agents may contribute to mismatch of ventilation-perfusion, it is not recommended for the administration of pulmonary hypertension associated with COPD at present time. However, as the clinical course of a number of severe cases of pulmonary hypertension due to COPD is similar to that of PAH, PAH therapeutic agents might be considered reasonably in the treatment of severe pulmonary hypertension associated with COPD.
Bronchial Thermoplasty in the Management of Asthma
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USA

Asthma remains one of the most common diseases worldwide and results in significant societal healthcare costs and morbidity and mortality to those afflicted. In spite of currently available medications, many asthmatics have severe disease with debilitating symptoms and/or life threatening exacerbations. Bronchial thermoplasty (BT) is a bronchoscopic device-based therapy that utilizes thermal energy to disrupt airway smooth muscle. In addition to improving asthma related quality of life, BT has been shown to reduce exacerbations and improve important measures of asthma control with good safety and efficacy data, now demonstrated out to 5 years.
Recent Strategies for Chronic Thromboembolic Pulmonary Hypertension
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Japan

Chronic thromboembolic pulmonary hypertension (CTEPH) is a form of pulmonary hypertension caused by non-resolving thrombi in the pulmonary arteries. It was previously believed that recurrent pulmonary embolism might be a major cause of CTEPH. However, recent evidence suggests that venous thromboembolism might be a trigger, and in situ thrombosis in the pulmonary artery and small vessel vasculopathy similar to pulmonary arterial hypertension could be important for progression of CTEPH. In addition CTEPH is more prevalent in women in Japan, in contrast to Western countries. A Japanese multicenter study reported that a form of CTEPH related to deep vein thrombosis is associated with HLA-B*5201. Pulmonary ventilation-perfusion scans are necessary for screening of CTEPH. Furthermore, contrast CT scans can detect segmental emboli and are useful for the differential diagnosis of pulmonary vascular disease. However, pulmonary angiography is still the gold standard for assessment of surgical accessibility and small vessel disease. The prognosis of this disease was poor in the 1980’s (5-year survival ~40%). Pulmonary endarterectomy with median sternotomy under intermittent deep hypothermia has decreased operative mortality to <5% at Chiba University as well as other expert centers. Advances in balloon angioplasty techniques have resulted in marked improvement in pulmonary hemodynamics, quality of life and survival for inoperable patients in Japan. A soluble guanylate cyclase activator (riociguat) has just become available for patients with inoperable or persistent/recurrent pulmonary hypertension after surgery. It must be emphasized that this disease is treatable once patients with dyspnea on exercise have been accurately diagnosed with CTEPH.
Respiratory diseases make up four of the top ten causes of death globally (lower respiratory infections, COPD, tuberculosis and lung cancer). There is a worldwide shift from infectious to non-communicable disease and the World Health Organisation lists respiratory disease as one of the four major non-communicable diseases for the coming decade. In Asia Pacific chronic lung disease and lung cancer are fuelled by high smoking prevalence in many countries as well as high levels of air pollution, while tuberculosis and lower respiratory infections remain major problems. Air pollution is now recognised to be a major cause of cardiovascular disease, stroke and respiratory disease. The shift to less polluting nuclear power in the region has slowed as a result of the Fukushima nuclear power plant disaster. Childhood deaths in Asia Pacific lead the world although rapid progress in lowering childhood and maternal mortality is being made. There is mixed news about improvements in extending life expectancy with large variations across the region since 1990. With reduction in mortality and an ageing population there is an increase in the burden of disability with its resultant increased costs of healthcare. Respiratory disease is deserving of greater attention by governments and health care organisations.
COPD is a complex condition with multiple pathogenic pathways causing symptoms that are directly related to the lungs such as breathlessness and cough, and other symptoms unrelated to the chest, such as fatigue, sleep disturbance, muscle weakness and depression. Whilst breathlessness and exercise limitation are important determinants of impaired health and poor quality of life, they account for less than half of the poor health status that patients report. Comprehensive assessment of COPD requires health status measurement.

The older questionnaires such as the St George’s Respiratory Questionnaire (SGRQ) were too complex to use in routine practice, but the COPD Assessment Test (CAT) was designed for use in routine clinical care and only takes 2-3 minutes to complete. There is good evidence that the CAT performs the same way in Asia as in the rest of the world.

A CAT score of 10 appears to be a reasonable threshold for starting regular bronchodilator therapy and score >20 in patients with a history of exacerbations predicts a high probability of another exacerbation within a few weeks. That study was performed in Asia. A recent review provides a very comprehensive review of the performance of the CAT (Gupta et al Eur Respir J 2014; 44: 873).

An analysis of clinical trials using the SGRQ has shown that patients in low-medium socio-economic countries have very large improvements in health status just by entering a clinical trial, even if they receive placebo. However they also show a similar or slightly greater improvement with treatment compared to patients in high-income countries.

In summary, sophisticated health status measurement can be performed routinely in the clinic, more simply and quickly than spirometry.
Dynamic Change of House Dust Mites and Its Components-
sIgE&sIgG4 in Specific Immunotherapy
Pei-yan Zheng, Bao-qing Sun*, Ni-li Wei, Hui-min Huang, Guang-qiao Zeng
China

Objective: This project aimed to analyze the levels of specific IgE (sIgE) to Dermatophagoides pteronyssinus (Der p) and its main components including Der p1, Der p2 and Der p10 before specific immunotherapy (SIT), and observe the dynamic change of sIgE and sIgG4 to Der p, Der p1 and Der p2 after SIT, so as to evaluate the significance of applying of SIT of Der p in clinical diagnosis.

Methods: The dynamic change of the sIgE, sIgG4 and correlation between each antibody before and after SIT were analyzed.

Results: The positive rate of serum sIgE in vitro to Der p10 from patients with mild-moderate rhinitis or coexisting asthma was only 1.6%. Moreover, there was no significant difference on the levels of serum sIgE and sIgG4 to Der p10 before and after SIT (p<0.05). After 17 weeks of SIT the levels of serum sIgE to Der p, Der p1 and Der p2 increased continuously (t=4.78, 6.21, 4.21, p<0.01). However, along with SIT, sIgE decreased significantly again after 57 weeks of SIT, which resulted in no difference as pre-SIT. The levels of sIgG4 to Der p, Der p1 and Der p2 were dynamically observed and recorded in each of the three periods. The levels of sIgG4 increased significantly along with the process of SIT. After 57 weeks of SIT, the increasing range of Der p sIgG4 reached to the maximum, followed by Der p1 and then Der p2. In each of the three periods, there was a significant correlation between sIgE and sIgG4 to Der p, Der p1 and Der p2 representing on the change of increasing range (p<0.01). And the order of the correlative degree of the sIgE in each period was: Der p and Der p1 reached the highest, followed by Der p and Der p2, and the lowest were Der p1 and Der p2. There was also a correlation between sIgE and sIgG4 to Der p and Der p2 (p<0.05).

Conclusions: The results showed that SIT was a dynamic immune process and sIgE and sIgG4 to Der p and its components reflected the immune status of the immune process.
This presentation gives us an overview of the diagnosis and management of TB and HIV when they overlap in patients as well as MDR- TB and HIV. There were an estimated 194,000 TB patients with HIV in the Asia Pacific region in 2012. An estimated 11-13% of new cases of TB were HIV positive, and people living with HIV (PLWH) have a 20-fold risk of developing TB in their lifetimes.

Discussions will concentrate on the peculiarities attendant to dealing with both TB and HIV, including timing of treatments, diagnostic issues, drug interactions, updates on diagnosis and management as well as treatment recommendations when dealing with drug sensitive as well as drug resistant TB in the HIV patient. Approaches to optimize treatment outcomes will be highlighted.
Spontaneous pneumothorax (SP) refers to air in the pleural cavity which occurs without preceding trauma or obvious precipitating cause, and is sub-divided into primary and secondary. Secondary spontaneous pneumothorax (SSP) occurs as a complication of underlying pulmonary disorder most often chronic obstructive pulmonary disease (COPD) while primary spontaneous pneumothorax (PSP) affects an individual without clinically apparent lung disease. Annual incidence of SSP is 6.3/100,000 population in males and 2/100,000 in females while PSP affects 18-28 males/100,000 population and 1.2-6 females/100,000. Together they account for 130 million dollars in health care expenditures. The course of SP is variable with recurrence rate 25-54% and presence of lung disease is a major determinant. The American College of Chest Physicians and BTS guidelines recommend VATS staple bullectomy and parietal pleural abrasion for SSP since surgical options are more effective. Medical chemical pleurodesis with tetracycline and its derivatives or graded talc may be appropriate if the patient declines or is unfit for surgery. Management of persistent air leak due to COPD and PTB with autologous blood patch and potential role conferred by bronchoscopic valves will be discussed.
In recent years it has been shown that a pleural fluid N-terminal BNP level greater than 1500 is diagnostic of congestive heart failure. Serum N-terminal BNP levels are as efficient as pleural fluid N-terminal BNP levels in making the diagnosis.

The approach to patients with undiagnosed after a diagnostic thoracentesis had typically been to perform thoracoscopy. However, recently it has been shown that image guided pleural biopsy (CT scan or ultrasound) in patients with pleural thickening or pleural nodules is almost effective as thoracoscopy. The advantage of image guided pleural biopsy is that it is less invasive.

The management of patients with complicated parapneumonic effusions is difficult. It has now been shown that the intrapleural administration of 5 mg DNase and 10 mg tPA twice a day for three days increases the rate at which the pleural fluid disappears and also decreases the duration of hospitalization and the need for surgical intervention. The intrapleural injection of a fibrinolytic itself such as tPA is ineffective in treating complicated parapneumonic effusions.

Patients with malignant pleural effusions often have the quality of their lives decreased by dyspnea. Recently the insertion of an indwelling catheter by which the pleural fluid can be intermittently drained has become accepted as a treatment for malignant pleural effusions. The advantages of the indwelling catheter as compared with pleurodesis are that the patient does not need to be hospitalized and the total number of hospital days associated with management of the pleural effusion is reduced.
Improving Outcome of CAP
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Canada

Community-acquired pneumonia (CAP) is a common infection and is associated with potentially lethal consequences. The most important bacterial pathogen in CAP is Streptococcus pneumoniae, though a variety of other organisms, including Haemophilus influenzae and the atypical pathogens, M. pneumoniae and Legionella pneumophila, are also implicated. The majority of patients with mild-to-moderate CAP are treated in the community setting with empiric antimicrobial therapy. Patients with more serious disease or who are elderly or have co-morbidities may be hospitalized, though even in this setting, empiric antimicrobial therapy is usually started. A number of severity scoring systems have been developed to assist in “the admit to hospital” decision and “the transfer to ICU” decision. The CURB65 rule and the PORT score have been validated in a variety of clinical settings. Biomarkers such as procalcitonin have been demonstrated to shorten antibiotic duration. All admitted patients should receive their first dose of antibiotic therapy as soon as possible after arrival to the hospital. While 4 hours has been the recommended standard, it is not clear that every patient must be treated that quickly because the diagnosis of pneumonia often takes longer than 4 hours to establish and treatment should not be started until other diagnostic possibilities have been excluded. Guideline directed therapy improves outcomes especially mortality. Treatment failure rates even with guideline-driven empiric therapy have been reported as high as 15%. Resistant and unusual microorganisms and noninfectious causes are usually responsible. Knowledge of local resistance rates may allow better initial empiric therapy choices. Shortening the course of antibiotic therapy and rapidly switching from intravenous to oral therapy, and discharging patients from hospital when they have stabilized, have all been demonstrated to shorten hospital without compromising outcomes. Pneumococcal vaccination, particularly the new 7-valent conjugated vaccine offered only to children, reduces invasive pneumococcal disease in vaccinated children and in unvaccinated adults via herd immunity. The older 23 valent polysaccharide vaccine is not effective in preventing pneumonia but may reduce invasive pneumococcal disease. The new 13-valent protein conjugate vaccine is effective in reducing pneumonia in the elderly and may supplant the 23-valent polysaccharide vaccine for routine use in adults.
The convergence of emerging resistance, newly recognized pathogens, altering healthcare systems, and changing patient type yields a more complex situation for today’s prescriber. The need to treat more resistant pathogens in a rapid manner reduces the empiric options available. Treatment failures with first line antibiotics are common especially among patients with chronic respiratory exposed frequently to antibiotics. COPD patients are at risk of frequent exacerbations if they have more severe disease (FEV1 usually < 50% predicted), a history of frequent exacerbations (usually ≥ 2/year) and symptoms of chronic bronchitis. The strongest predictor of an AECOPD in a given year is the presence of an exacerbation in the previous year. Elevated systemic biomarkers also predict frequent exacerbations but treatment with a statin does not change this observation. Antibiotics reduce the likelihood of clinical failure and respiratory fluoroquinolones appear to be the most potent of treatment options. COPD patient exhibiting severe airflow obstruction, isolation of a potentially pathogenic microorganism, or at least one hospital admission due to COPD exacerbation in the previous year are very likely to have concomitant bronchiectasis. Preventive therapy with influenza or pneumococcal vaccines is not very effective. Chronic antibiotic administration may be necessary in some selected cases.

Non-cystic fibrosis bronchiectasis is the best example of pulmonary infection in chronic respiratory disease. Most cases are either idiopathic or post-infectious. H influenzae and Pseudomonas are the most common isolates but a broad variety of organisms are found in the bionome. Treatment of the underlying condition, promotion of bronchial hygiene, identification of acute exacerbations and administration of antibiotics, suppression of the microbial load, reduction of the excessive inflammatory response, and control of bronchial hemorrhage are the basic principles of management. Patients chronically colonized by Pseudomonas have a faster decline in annual FEV1 compared to those not colonized. Long term oral and/or inhaled antibiotics are gaining an increasing role in the management of these patients. Chronic suppressive therapy with inhaled antibiotics looks especially promising.
Lower respiratory tract infection is a leading cause of death worldwide in any age group. Older adults are at increased risk of invasive pneumococcal disease, due to contributing immunologic factors, such as changes in the aging immune system (immunosenescence). These changes include complex changes in the innate immunity and adaptive immunity. Older age, current smoking, diabetes mellitus, congestive heart failure, lung cancer, COPD, asthma, were independently associated with and increased risk for all causes of community acquired pneumonia. In Asia Pacific, the common comorbidities associated with CAP include bronchopulmonary diseases, smoking history, cardiovascular disorders, malignancy and neurologic disorders. Comorbidities and risk factors add mortality rate in elderly. In the current presentation, the impact of comorbidities and risk factors on the burden of pneumococcal disease in elderly are discussed.
Idiopathic Pulmonary Fibrosis is a disease characterized by progressive deterioration of lung function which leads to respiratory failure. IPF has median survival time of 3 years after diagnosis, —worse than survival of some cancer. IPF occurs among elderly, some with history of smoking. Environmental factor might induce IPF in susceptible individual. Respiratory infection has been sought to have role in disease pathogenesis and progression. Viruses might play in part in acute exacerbation, and increase in mortality. Infection in IPF showed related with increase morbidity and mortality. In this presentation, the role of infection in disease pathogenesis and progression in IPF were presented.
Comorbidities in COPD
Suzanne Hurd
USA

COPD patients have been shown to have a higher prevalence of osteoporosis, anxiety/panic attacks, heart trouble, heart attack, and heart failure; COPD patients with comorbid conditions have been shown to have poor clinical outcomes. In this presentation, the recommendations from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) for treatment of COPD of patients with comorbid conditions will be presented. The recommendations for diagnosis of Asthma COPD Overlap Syndrome will also be discussed.
Functional Bronchoscopy and Interventional Pulmonology, which includes laser ablation and stenting, bronchoscopic lung volume reduction (BLVR) with bronchial valve or coil for COPD, bronchial thermoplasty for bronchial asthma and targeted lung denervation for COPD. It is important to take into account the respiratory physiological characteristics of individual patients. For example, in the case of airway stenosis, an appropriate stent must be accurately placed at the flow-limiting segment to obtain optimal results. In this sense, pathological conditions can be evaluated in real-time by measuring the airway pressure gradient between the airway pressures at both sides of the stenosis using a bronchial catheter during bronchoscopy.

In addition, collateral ventilation positive is problematic for BLVR with bronchial valve placement for COPD. In this regard, interlobar collateral ventilation evaluation using the Chartis System is useful for the preoperative selection of patients. In cases of heterogeneous upper lobe emphysema without collateral ventilation, valve placement is most effective.

Ideal functional bronchoscopy is defined as bronchoscopy with an ultrathin catheter bronroscope equipped with sensors for measuring pH, temperature, O2, CO2, airflow, pressure, etc. Local lung function is examined by inserting the bronroscope into the segmental or sub-segmental bronchi, smaller airways, or peripheral bronchi. An O2 sensor can be used for evaluating segmental bronchial ventilation, and a CO2 sensor can be used for evaluating the perfusion pulmonary blood flow of segmental lobar bronchi based on CO2 output.
Cystic fibrosis (CF) is the most common, life-shortening inherited disease of Caucasians. An autosomal recessive defect, occurring in approximately 1 in 3500 live births in the United States based on data from neonatal screening, the life expectancy of a child born with CF has gradually improved and is now over 38 years. Cystic fibrosis is caused by defects in the cystic fibrosis transmembrane conductance regulator (CFTR), a cyclic adenosine monophosphate (cAMP)-regulated chloride channel expressed on the surface of airway epithelial cells and the serous cells of the submucosal glands. The CFTR is functionally linked to other apical chloride channels, and aberrant expression or function of the CFTR in the airway leads not only to reduced chloride conductance but dysregulation of epithelial sodium channel activity. Failure of chloride secretion and massive sodium hyperabsorption results in dehydration of the airway surface. The dessicated secretions obstruct the airways and reduce mucociliary clearance, thus permitting bacterial infection to become established and allowing the inflammatory response to be amplified. Other gaps in innate defenses, including impaired antibactericidal activity, contribute to bacterial persistence and chronic infection in the CF airway.

Cystic fibrosis patients acquire bacterial pathogens in an age dependent manner that over time will chronically infect their airways. Initially, Staphylococcus aureus is isolated from the lungs of infants and young children, and its prevalence, particularly methicillin-resistant strains, has greatly increased. Pseudomonas aeruginosa emerges as the predominant organism over time and most CF children have had lung infection with P. aeruginosa by 3 years of age. Approximately 80% of CF adults in the United States are persistently infected with P. aeruginosa. Acquisition of S. aureus and P. aeruginosa from the lungs of CF patients is associated with a poorer prognosis, but recent studies treating initial acquisition of P. aeruginosa have shown that it can be eradicated with aggressive antibiotic therapy. While patients reacquired the organism later, the realization that early P. aeruginosa infection can be effectively eradicated has changed treatment strategies for CF. No longer are antibiotics solely used to treat symptomatic disease; now they are used to treat early positive P. aeruginosa cultures, even in the absence of symptoms, though data showing that early eradication impacts later lung function are lacking at this time.
While the pathogenesis of idiopathic pulmonary fibrosis (IPF) is yet unclear, we have questioned and learned considerable basics on the clinical diagnosis and therapeutic responses. Let us think over what we have learned in these 15 years. The first step was to move to positive fibrosis histologic photos from X-ray negative films. VATS procedure enabled less invasive sampling. Development of HRCT also enabled the diagnosis of typical IPF without surgery. This accumulation of experiences led to the Consensus Statement of ATS/ERS in 2000. What was the second step? When Japanese doctors started the clinical trial of pirfenidone in patients with IPF, we were fumbling to write a protocol. What should be the primary endpoint? What kind of patients should be enrolled? Because we had a 10-year experience of using staging system in IPF, we planned to enroll patients with slowly progressive (i.e. stage II to III). We know that the difference between the pirfenidone and placebo arms should be significant in a period of 52 weeks, and if pirfenidone has a power to slow the fibrosing course, proper patients will be in stages II or III. This strategy was proved right and we succeeded in the phase III clinical trial. Pirfenidone was approved in 2008 in Japan, and is now on the market all over the world through CAPACITY and ASCEND studies. More recently, using nintedanib, a tri-kinase inhibitor, doctors succeeded in TOMORROW and IMPULSIS studies. FDA has just approved it. Now we have two drugs with different mechanism for patients with IPF. The next challenge will be the timing of drug administration and choice of combination. We are in the exciting time of novel intervention for IPF.
Acute Exacerbation of IPF
Yasuhiro Kondoh
Japan

The clinical course of idiopathic pulmonary fibrosis (IPF) is usually chronic, but some patients may experience episodes of acute respiratory worsening. Although these episodes may occur secondary to common conditions such as pneumonia, pulmonary embolism, pneumothorax or cardiac failure, the term acute exacerbation of IPF (AE-IPF) has been used when a cause cannot be identified for the acute respiratory worsening. Because AE-IPF is a crucial and lethal complication of IPF, its prevention and better management is an urgent need.

AE-IPF is a diagnosis of exclusion, so diagnostic approach includes physical examination, laboratory tests, biomarkers, HRCT, BAL, and echocardiogram. Possible pathophysiology for AE-IPF are accelerated primary disease process, and occult etiology. BAL and lung surgery are known as precipitating factors for AE-IPF. PaO2/FIO2, CRP, LDH, KL-6, % lymphocytes in BAL, CT patterns, and CT extent are reported to be prognostic factors.

Corticosteroids with or without immunosuppressant are commonly prescribed and are thought as mainstream therapy. Noninvasive positive pressure ventilation should be a first-line mechanical ventilation, and invasive mechanical ventilation may be a reasonable intervention in a minority. Because of poor prognosis, experimental therapies such as low molecular weight heparin, recombinant thrombomodulin, and PMX hemoperfusion therapy were reported to be possible candidate therapies. Extracorporeal membrane oxygenation has been used mainly as a bridge to transplantation.
Despite the greater understanding of refractory or difficult to treat asthma that has come with phenotyping, asthma remains a highly treatable condition. In the majority of people, currently available treatments prevent exacerbations, control daily symptoms and maintain lung function, reduce airway inflammation and airway hyperresponsiveness and prevent lung function decline over time. So, considerations of future therapies should address not only the proportion of people with currently untreatable disease, but also those whose disease is eminently treatable but for whom daily preventer therapy is too big a challenge. Currently available therapies may fail due to the requirement for long term daily adherence, the lack of perceived benefit, the belief that reliever therapy is a reliable rescue, and the burden of cost. New treatments, targeted at refractory asthma, such as anti-TNFα agents have been disappointing, although monoclonal antibody treatments targeted at severe eosinophilic asthma such as mepolizumab (anti-IL-5) have shown reduced asthma exacerbations, but surprisingly also a dissociation between preventing attacks and modifying daily symptoms and lung function. Other monoclonal antibody treatments such as dupilumab, lebrikizumab and reslizumab targeted at specific interleukins in the TH-2 pathways offer hope to a small proportion of patients but the cost of these treatments means they may only be affordable for a tiny minority initially. For the rest we must employ key management strategies that make current therapies more effective and safe. Refinement of current treatments such as once daily ICS-LABA, inhaled steroid sparing therapies, greater understanding of bronchial thermoplasty, and new oral medications also provide opportunities for better asthma outcomes.
Asthma in Asia Pacific: The Burden

Christopher Lai

Hong Kong

The International Study of Asthma and Allergies in Childhood (ISAAC) studies have provided valuable data on asthma prevalence in schoolchildren worldwide, including those in AP. In the Phase 3 study, conducted in the early millennium, the regional prevalence of “wheeze in the past 12 months”, was 8.8%, ranging from 0.8% in Tibet (China) to almost 30% in Ho Chi Minh City (Vietnam). Comparison between Phase I (1994-95) and Phase 3 data showed the annual change in current wheeze was 0.07%, ranging from -0.55% in Hong Kong and Manila (Philippines) to 0.52% in Bandung, (Indonesia). While there is no good comparative data on asthma prevalence in adults in AP, various studies using different definitions of asthma revealed the rates ranged from 1.7% in Japan to 10.3% in India.

Although asthma mortality has shown a decreasing trend in many developed countries worldwide, the disease is still causing significant morbidity, with about 1 in 3 patients suffering from uncontrolled asthma in AP. This poor control is likely the consequence of under-usage of inhaled steroid, and over-estimation of control (both on the part of patients and physicians). Uncontrolled asthma, as defined by GINA, is associated with a higher risk of exacerbation that requires urgent health care utilization, including emergency room attendance, unscheduled medical visits and hospitalization. Tackling these issues related to poor asthma control, as well as identifying the risk factors associated with the development of asthma, may help reduce the burden of disease.
Bronchial asthma is characterized by chronic inflammation, responsive to corticosteroids, a powerful anti-inflammatory agent. Current guidelines (GOLD 2014) recommended inhaled corticosteroid combined with long acting beta 2 agents is preferred, when dose of inhaled corticosteroids alone failed to control asthma (Bateman 2008 NAEDP 2007). At the receptor level addition of LABA facilitate steroid effect. Fixed-dose combination of LABA/ICS had given patients more palpable effect of symptoms improvement, increasing adherence to ICS intake lowered frequency of dosing and maintain disease control. Thus, the addition of LABA to ICS had become a preference to patients, improving compliance and overall better disease control. Quick acting LABA had further enhanced their role in being able to act as a reliever (GOLD 2014). The safety of LABA in Asthma had been questioned (Martinez 2005). The Cochrane systematic review however had shown evidence that when LABA is added to ICS beneficial effects are seen in asthma control.

The use of long acting anti-muscarinic agents (LAMA) in asthma is currently limited. In a recent study (Kert Jens 2012) when LAMA was added to poorly controlled asthmatics already on ICS and LABA, there was less worsening of exacerbation that required systemic corticosteroids with sustained bronchodilation.