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UPLIFT® – Global landmark COPD Trial proves

Spiriva® impacts the clinical course of COPD over 4 Years[1]

Sustained greater improvements in **lung function**[1*]

Sustained greater improvements in **quality of life**[1]

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Impact on **mortality**[1,3**]

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Earlier treatment refers to the initiation of maintenance therapy with a long-acting bronchodilator like SPIRIVA® starting from Stage II, in accordance with GOLD guidelines, while approximately 1 in 2 trial patients were in GOLD Stage II[1,2]

* While Spiriva did not alter the rate of decline in lung function (the primary study endpoint), it did achieve significant results on important parameters, such as lung function, quality of life, exacerbations and mortality.[1]

A landmark 4-year, randomized, double-blind, placebo-controlled trial (UPLIFT®: Understanding Potential Long-term Impacts on Function with Tiotropium), involving 5993 COPD patients in 37 countries was initated to compare the long-term effects of tiotropium with placebo (control group) on the rate of decline in lung function and health status as well as the frequency of exacerbations. All patients were allowed to use all prescribed respiratory medications throughout the trial, except inhaled anticholinergics.

** A statistically significant 16% reduction in risk of mortality with Spiriva while patients received study medication. (p=0.016, on treatment analysis).
Effect extended to end of treatment period (day 1440), as defined by protocol (13% risk reduction. P=0.034, intention-to-treat analysis).
For the 30 days following the conclusion of treatment period (Day 1470) when, according to protocol, patients were discontinued from their study medication, the study revealed an 11% reduced risk reduction (p=0.086, intention-to-treat analysis).

References: 1. Tashkin DP, Celli B, Senn S, et al, on behalf of UPLIFT® study investigators. A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease. N Engl J Med. Vol 359;15: 1543-1554. 2. Global Initiative for COPD. Global strategy for the diagnosis, management, and prevention of COPD: executive summary. Updated 2007. http://www.goldcopd.com. Accessed September 5, 2008. 3. Data on file. Boehringer Ingelheim International GmbH; 2008.

Please consult full prescribing information before prescribing. COPD: Chronic Obstructive Pulmonary Disease

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SPIRIVA® (tiotropium)

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Asthma in 2008: What have We Learned from Epidemiology and Clinical Studies?

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Dr. Christopher Lai

Derived from the Greek word meaning "panting", asthma has been known and treated by various physical and chemical means in the past thousands of years. Although the recognition of asthma as a chronic airway inflammatory disease with the increasing use of inhaled steroids has led to significant reductions in its morbidity and mortality, it still affects 300 million people worldwide and no therapeutic cure is likely to emerge in the foreseeable future. Nevertheless, research in the past decade has provided some optimism in developing strategies that may eventually lead to successful primary prevention of asthma and improve its care so that patients can live a normal life with a minimal risk of suffering from treatment side effects. This article is to review recent advances in the understanding of asthma aetiology and its management strategies.

Asthma Aetiologic Factors

The increasing trends of asthma prevalence in the past several decades suggest that environmental factors are likely to play a significant role in enhancing the susceptibility of an individual to develop this airway disorder. While there are studies that suggest the importance of these putative factors, none of them can account for the wide geographic variations in asthma prevalence even amongst populations of similar ethnic origins, or the increasing time trends of asthma and allergies. Thus, despite having a high tobacco consumption and poor outdoor air quality, China has one of the lowest asthma prevalence rates in the world, whereas English speaking countries with its much "cleaner" air, have the highest. Atopy, a physiologic abnormality that is frequently seen in asthma subjects, only has a population attribution risk for asthma for up to 40% in affluent countries. Its importance as a risk factor in non-affluent countries is at best, minimal. Allergen exposure in infancy undoubtedly increases the risk of future sensitisation but there is no evidence this will lead to the development of asthma. Interestingly, several recent studies have shown that exposure to pets early in life may decrease the risk of asthma but consistency in the findings is lacking.

The hygiene hypothesis originated from the observation that children with hayfever in the United Kingdom were more likely to have -a fewer number of siblings¡Kthis is correct... A plausible explanation for this is that these children were likely to have less exposure to infective agents during early childhood and this may divert the T-helper cell differentiation to the Th2 pathway leading to the development of allergy. In support of this hypothesis, children who were brought up in day-care centres were less likely to develop asthma symptoms later in life. Recent studies in Europe have shown that children born and raised in livestock farms where the environments are rich in microbial organisms, have the lowest prevalence of asthma and atopy. In contrast, their urban counterparts have the highest and children who were born in the city but had frequent visits to the farms have intermediate prevalence. Exposure to microbial organisms may also increase the risk of developing asthma as shown by a recent study that neonatal colonisation of the hypopharynx with S. pneumoniae, M. catarrhalis and H. influenza, but not S. aureus, is associated with an

increase in the risk of asthma at age 5 years. While one cannot exclude -these findings may be a direct effect by these microbes this is correct, it may also be just a marker of innate immune system dysfunction that predisposes the individual to develop asthma. Further studies to explore the underlying mechanisms will provide clues to the aetiology of asthma.

One novel risk factor that has received increasing attention in recent years is the use of paracetamol. Globally, the increasing use of paracetamol over the past 50 years has occurred contemporaneously with the rising trends in asthma prevalence in different parts of the world. Paracetamol was lauched in the 1950s as an analgesic replacement for phenacetin, which was highly nephrotoxic. Its sales to children rocketed to the same level as aspirin by 1980 in the United States. In subsequent years, paracetamol has largely replaced aspirin as the analgesic and antipyretic of choice in infants and children due to concerns about the risk of Reye's syndrome with aspirin use. By 1990, this drug had become the most commonly dispensed medication in the United States, representing 5% of all treatments dispensed. Phase III of the International Study of Asthma and Allergies in Childhood (ISAAC) - the largest epidemiology study of childhood asthma ever undertaken - identified that the reported use of paracetamol for fever in the first year of life was associated with symptoms of asthma in the 6 to 7 years old children. The association was present in all major regions of the world, with a 50% increased risk following adjustment for other risk factors. A dose-dependent association was also observed between the current use of paracetamol and symptoms of asthma, with a 3-fold increased risk associated with usage of at least once per month compared with no use. An increased risk of rhinitis and eczema symptoms was also seen with the consumption of paracetamol. One of the possible mechanisms underlying this observed association is that paracetamol use results in a reduced ability to withstand oxidant stress as it depletes glutathione and glutathione dependent enzymes, thereby leaving the free oxygen radicals generated by allergic inflammation unchecked. Further, the reduced anti-oxidant ability can influence antigen recognition and lead to an enhanced Th-2 response. It is, however, premature to conclude that paracetamol is a causative factor for asthma and allergies, given the retrospective design of the study, albeit it involved over 200,000 6-7 years old children. A prospective randomised placebo-controlled longitudinal study during the first few years of life is warranted to testify this hypothesis. If the causation is confirmed, this observation will have major public and clinical implications. It must be emphasised that there is hithero no evidence that paracetamol use would trigger exacerbations in patients with asthma. Paracetamol should still be the preferred treatment for fever in childhood, but not be routinely and reserved for children with a high fever of >38.5, as recommended by the World Health Organization.

Asthma Management

Current guidelines advocate treatment should be based on the level of control rather than on severity (Table 1). This is because the former is responsive to treatment but the latter is an intrinsic feature of the disease in an individual and therefore is not modifiable. Each of the symptom criteria listed in Table 1 is a valid measure of control as each is associated with a significant increase in the risk of urgent health care utilisation if the threshold is exceeded. Thus, even the use of a rescue bronchodilator such as inhaled salbutamol for >2 times a week is associated with a 2.8-fold increase in the risk of hospitalisation when compared with no usage. The likelihood of future exacerbation is lowest in those whose disease is controlled, intermediate in partly controlled, and highest in the uncontrolled. Thus the target of treatment should be to achieve the control status, provided this can be done without undue adverse effects from the medications used.

Table 1: Putative risk factors for asthma

Tobacco smoke
Air pollution
Allergens/atopy
Obesity and diet
Microbial organisms (hygiene hypothesis)
? Paracetamol consumption

While lung function is a useful tool in assessing asthma control, it is not widely used by most general practitioners. The Asthma Control Test (ACT), a 5-item symptom-based questionnaire that includes frequencies of daytime and night-time symptoms, use of rescue bronchodilator, exercise limitations and patient's self-rating of control, may be a useful tool in busy clinical settings as it correlates well with asthma specialists' rating of control and their treatment decisions.

Inhaled corticosteroids (ICS) have been recommended as first-line treatment for asthma in the past 2 decades, given their efficacy and long-term safety data. However, once the dose of ICS reaches 400-500 g/day of beclomethasone dipropionate (BDP) or its equivalent, any further increase in the dose will only result in a modest improvement in response but the associated increase in systemic side effects may be considerable, especially when the dose reaches 1500 g/day (beclomethasone or equivalent). Current guidelines thus recommend the use of combination therapy [ICS and a long-acting agonist (LABA) such as Seretide and Symbicort] when asthma control is not attained at a dose of 400-500 g/day of BDP (or it equivalent). While combination therapy is not superior to mono-therapy with ICS in patients who are naive to ICS in reducing exacerbations, it is better in achieving a higher level of symptom control and lung function.

Combination therapy has been used as a fixed-dose regime for maintenance treatment for more than a decade. In recent years, there is evidence that a variable-dose regime using Symbicort as both a maintenance and reliever medication can be an effective alternative therapeutic strategy. It should be emphasised that the variable-dose regime still requires the continuous use of Symbicort at least 1 puff twice daily for background control and does not imply that the drug can be used as an as-need basis alone.

While it is logical to add drugs such as leukotriene receptor antagonists (LTRAs such as montelukast and

Zafirlukast) or theophylline to patients whose asthma cannot be controlled satisfactorily with combination therapy, there are little data to support such additional therapies will lead to improved control. A recent systematic review on 62 cases of Churg-Strauss syndrome (CSS) developed after the introduction of LTRAs suggests that the association may be causal. Thus, one should be mindful of the risk of CSS when using LTRAs in patients with moderate to severe asthma or in cases where oral steroid therapy is gradually withdrawn.

Omalizumad, a humanised monoclonal anti-IgE antibody, has been shown to be effective as an add-on therapy in patients with moderate to severe persistent allergic asthma who are not adequately controlled by a combination of high-dose ICS and LABA. This drug is administered by a subcutaneous injection every 2 to 4 weeks, depending on body weight and pre-treatment serum IgE level. A trial period of 16-24 weeks is recommended to assess its efficacy. Its high cost and the risk of anaphylaxis limits its use to only a small proportion of severe asthmatics who require either frequent or long-term use of oral steroids.

Newer treatment modalities such as tumour necrosis factor antibody, clarithromycin and thermoplasty have been shown to have some potential in the treatment of severe asthma in a few small-scale clinical studies. Their roles in asthma treatment have to be determined by further randomised placebo-controlled long-term trials.

While the primary prevention and cure of asthma remains elusive, advances in the understanding and treatment of this disease over the past 3 decades have contributed to significant reductions in morbidity and mortality to the majority of patients. Table 2 summarises the key points in current management strategy.

Table 2: Tips on current asthma management

- **The goal for asthma treatment is to achieve satisfactory control**
- **Asthma control is assessed by the following:**
  - Symptoms in the day and at night, including sleep disturbance
  - Need for rescue medications including short-acting bronchodilators and oral steroids
  - Limitations of activities
  - Exacerbations
- **Inhaled steroids are safe and effective in achieving and maintaining asthma control**
- **Combination therapy with inhaled steroids and a long-acting -agonist should be considered if asthma control is not achieved by inhaled steroids alone**
- **Leukotriene receptor antagonists may be considered in the following situations:**
  - as an alternative to low-dose inhaled steroids in patients with mild disease,
  - aspirin-sensitive asthma, and
  - exercise-induced asthma
- **Anti-IgE therapy as an add-on therapy in patients with severe persistent allergic asthma, especially if they require oral steroids.**
- **Re-consider the diagnosis of asthma if symptoms persist despite taking seemingly appropriate treatment for a fortnight.**

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Presentation: Budesonide/Formoterol Turbuhaler. **Indications:** Regular treatment of asthma where combination therapy w/ inhaled corticosteroid & long-acting β-agonist is appropriate. ***160/4.5 mcg & 320/9 mcg/dose Turbuhaler*** Symptomatic treatment of severe COPD. **Dosage: Asthma 1) Symbicort maintenance therapy *80/4.5 mcg & 160/4.5 mcg Turbuhaler*** *Adult≥ 18yr*: 1-2 inhalations bd. Max 4 inhalations bd. *Adolescent 12-17 yr*: 1-2 inhalations bd. *Childn ≥ 6yr:* 80/4.5 mcg Turbuhaler 2 inhalations bd. ***320/9 mcg Turbuhaler*** *Adult≥ 18yr*: 1 inhalation bd. Max: 2 inhalations bd. *Adolescent 12-17 yr*: 1 inhalation bd. **2) Symbicort maintenance and reliever therapy** Taken as regular maintenance treatment and as needed in response to symptoms is appropriate. ***80/4.5 mcg & 160/4.5 mcg Turbuhaler*** Adult≥ 18yr: Recommend maintenance dose is 1 inhalation bd and some may need 2 inhalations bd. Patient should take 1 additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken. No more than 6 inhalations should be taken on any single occasion. No more than 8 inhalations per day should be taken, however, total daily dose up to 12 inhalations could be used for a limited period. Symbicort maintenance and reliever therapy is not recommended for children and adolescents. **COPD *160/4.5 mcg Turbuhaler*** *Adult:* 2 inhalations bd ***320/9 mcg/dose Turbuhaler*** *Adult:* 1 inhalation bd. **Contraindications:** Hypersensitivity (allergy) to budesonside, formoterol inhaled lactose. **Precautions:** Acute or initial management of asthma; Taper dose when discontinuing treatment; Thyrotoxsis; phaeochromocytoma; diabetes mellitus; untreated hypokalaemia; hypertropic obstructive cardiomyopathy; idiopathic subvalvular arotic stenosis; severe hypertension; aneurysm or other severe cardiovascular disorders; quiescent pulmonary TB; fungal & viral infections in the airways; Patients should take Symbicort maintenance dose as prescribed even when asymptomatic. Symbicort as needed is not intended for regular prophylactic use, e.g. before exercise; If oropharyngeal thrush occurs, patients should rinse their mouth with water after inhalations; Pregnancy & lactation. **Interactions:** CYP P450 3A4 inhibitors (e.g. itraconazole, ritonavir), CYP3A4 inhibitors, beta-blockers, quinidine, disopyramide, procainamide, phenothiazines, terfenadine, MAOIs, tricylic antidepressants, levodopa, L-thyroxine, oxytocin, alcohol. **Undesirable effects:** Palpitations, Candida infections in the oropharynx, headache, tremor, mild irritation in the throat, coughing, hoarseness. **Full local prescribing information is available upon request. API.HK.SYM.1106**

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Clinical Management of COPD

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This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded one CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 December 2008.

Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease with significant extra-pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases[1] COPD is a common disease worldwide[2,3] with similar trends in the East and the West.[4] It is a disease with significant morbidity and incurs heavy utilisation of health care resources. The prevalence of COPD varied from 11.4 to 26.1% according a recent multi-city study that surveyed the population with spirometry.[2] The economic burden of COPD to the society is enormous. In 2005, COPD ranked second as a respiratory cause for hospitalisation and in-patient bed days in HK. In those >75 years of age, the hospitalisation rate for COPD was as high as 2,225/100,000.[5] The prevalence of moderate COPD, using the spirometric reference of FEV_1/FVC ratio of <70%, among 1,008 elderly HK Chinese (age≥60 years) in the community, were 19.6% and 11.9% in the male and female subjects respectively.[6] In this article, we will review the clinical management of COPD.

Management of Stable COPD Patients

The Global Initiative for Obstructive Lung Disease (GOLD) guideline has classified COPD into 4 different stages of severity according to the lung function of the patients, with recommendations on treatment for each stage of the disease (Figure 1).[1]

	I	II	III	IV
Stage	Mild	Moderate	Severe	Very severe
	FEV_1/FVC <0.7 FEV_1 ≥80% predicted	FEV_1/FVC <0.7 50%≤FEV_1<80% predicted	FEV_1/FVC <0.7 30%≤FEV_1<50% predicted	FEV_1/FVC <0.7 FEV_1<30% predicted, or FEV_1<50% predicted plus chronic respiratory failure
Therapy	Active reduction of risk factor(s); influenza vaccination Add short-acting bronchodilator (when needed)			
		Add regular treatment with one or more long-acting bronchodilators (when needed); Add rehabilitation		
			Add inhaled glucocorticosteroids if repeated exacerbations	
				Add long term oxygen if chronic respiratory failure. Consider surgical treatments

Figure 1. Staging of chronic obstructive pulmonary disease and the recommended therapy at each stage.[1]

1. Avoidance of Risk Factor

It has been projected by the WHO that the total mortality of COPD would increase by 30% over the next 10 years unless successful strategies are implemented to reduce the risk factors of COPD, particularly tobacco use. By 2030, COPD is estimated to become the fourth leading cause of death worldwide.[7] Smoking cessation is by far the single most effective and cost effective way to reduce exposure to COPD risk factors.[1] Smoking cessation can reduce the rate of accelerated FEV_1 decline that exists in smokers with COPD.[8] Clinician's advice and intervention, coupled with the use of appropriate drugs such as nicotine replacement therapy, bupropion and varenicline can improve the quit rate of the patients.[9]

2. Influenza and Pneumococcal Vaccinations

Infection of the respiratory tract is a common cause10-12 of acute exacerbation of COPD (AECOPD) and repeated exacerbations can lead to more rapid deterioration in the lung function and quality of life of these patients. The GOLD 2007 guideline has recommended routine prophylaxis with pneumococcal and influenza vaccines for the COPD patients.[1]

3. Bronchodilators

Bronchodilators are the therapeutic mainstay for patients with COPD. Short-acting bronchodilators alone or in combination may be sufficient to control symptoms in patients with Stage I disease (Figure 1). The principal bronchodilator treatments are 2-agonists, anticholinergics, and methylxanthines. For patients with stage 2 disease and above, regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators.[1]

Anti-cholinergic Agent

Tiotropium is a long-acting once daily inhaled anti-cholinergic agent for treatment of more severe COPD patients. Tiotropium can improve lung function, dynamic hyperinflation and symptoms in COPD patients.[13,14] In addition, it can reduce exacerbations[15] and improve the quality of life of the patients.16 A large scale clinical trial evaluating the impact of tiotropium

on the rate of long term lung function decline and mortality is underway.[17]

Long Acting Beta-agonist

Salmeterol and formoterol are long acting beta-agonists that can offer more sustained improvements in pulmonary function, chronic dyspnoea and quality of life than short-acting bronchodilators in patients with moderate to severe COPD.18 In the Towards a Revolution in COPD Health (TORCH) trial, salmeterol therapy was associated with reduced frequency and severity of exacerbation when compared to placebo.[19]

4. Inhaled Corticosteroid

Regular treatment with inhaled corticosteroid (ICS) alone does not modify the long term rate of decline of FEV1 in patients with COPD. However, for the symptomatic COPD patients with FEV_1 <50% predicted (Stage III and IV COPD patients, Figure 1) and repeated exacerbations (e.g. 3 times in the last 3 years), regular use of ICS is associated with a reduction in frequency of AECOPD.1 Furthermore, withdrawal of ICS may lead to exacerbations in some patients.[20] There is some concern over the use of ICS as the likelihood of pneumonia appears increased in the COPD patients.[19]

5. Combination Inhaled Steroid and LBAB

Several studies that have explored the role of combination therapy have shown significant improvements over single agents alone, but addition of ICS was associated with an increased risk of pneumonia.[21,22] In the TORCH trial, salmeterol in combination of fluticasone could improve lung function, health status and decrease the frequency of exacerbations when compared to placebo, salmeterol alone, or fluticasone alone.[19] Salmeterol plus fluticasone however, failed to achieve a statistically significant decrease in mortality when compared to placebo over a study period of 3 years.[19]

6. Theophyllines

Theophylline has some bronchodilatation and anti-inflammatory effects on the airway. Due to its potential systemic toxicity and narrow therapeutic index, inhaled bronchodilators are preferred when available. Theophyllline may be considered as an add-on therapy when symptoms persist in patients with more severe disease despite the use of other treatments.

7. Mucokinetic Agents

These drugs aim to decrease sputum viscosity and adhesiveness in order to facilitate expectoration.[9] In clinical trials of COPD patients, there are conflicting data whether the mucokinetic agents are useful. A large trial on oral acetylcysteine failed to document any substantial benefit.[23] However, a recent trial on carbocisteine found that the numbers of exacerbations per patient per year declined significantly in the carbocisteine group when compared against the placebo group.[24] In fact, both the above mentioned mucokinetic agents also have some anti-oxidant effects.

8. Non-pharmacological Therapy

Pulmonary Rehabilitation

The American Thoracic Society (ATS)/ European Respiratory Society (ERS) have defined pulmonary rehabilitation as "an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities. Integrated into the individualised treatment of the patient, pulmonary rehabilitation is designed to reduce symptoms, optimise functional status, increase participation, and reduce health care costs through stabilising or reversing systemic manifestations of the disease."[25] Patients with COPD often have decreased physical activity as exertion can worsen dyspnoea. This relative inactivity will lead to progressive deconditioning and may further initiate a vicious cycle, with dyspnoea becoming problematic at ever lower physical demands. Pulmonary rehabilitation aims to break the cycle.

Pulmonary rehabilitation consists of physical conditioning (e.g. training of the upper and lower limb muscles), breathing retraining, education, and psychological support. Pulmonary rehabilitation has been carefully evaluated in a large number of clinical trials and their benefits include improvement in exercise capacity and health-related quality of life. In addition, pulmonary rehabilitation can reduce the perceived intensity of breathlessness, number of hospitalisations and days in the hospital, and anxiety and depression associated with COPD.[1,26]

Oxygen Therapy

In patients with cor pulmonale, long-term oxygen therapy (LTOT) may improve secondary polycythaemia, right heart failure, neuropsychiatric function, and exercise performance, in addition to prolonging survival if usage is at least 15 hours each day.[27] LTOT should be considered for patients with COPD who have chronic respiratory failure when assessed at least twice during a stable period of 3 to 4 weeks apart, and who have an arterial oxygen tension (PaO_2) of ≥ 7.3kPa (54.8mmHg) or an arterial oxygen saturation (SaO_2) of 88%, with or without hypercapnia while breathing air. In patients with a PaO_2 of >7.3 kPa, treatment with oxygen confers no survival advantage. LTOT should be prescribed if 7.3 kPa<PaO_2<8kPa (60mmHg) or SaO_2 is 89%, in the presence of one of the following complications: secondary polycythaemia (haematocrit >55%), right heart failure, or pulmonary hypertension. However, this treatment is generally not recommended for patients who continue to smoke. The dose of oxygen should be adjusted to achieve a PaO_2 of ≥ 8kPa at sea level, or SaO_2 of ≥ 90% during rest, exercise, and sleep.

Surgical Treatments

In carefully selected cases, bullectomy is effective in reducing dyspnoea and improving lung function in patients with COPD who have large bullae (e.g. occupying 30% or more of the hemithorax) that cause significant compression of surrounding pulmonary parenchyma.

Lung volume reduction surgery (LVRS) is a form of palliative surgery in which parts of the lung are resected to reduce hyperinflation. This allows the respiratory muscles to be more effective pressure generators by improving their mechanical efficiency (as measured by length/tension relationship, curvature of the diaphragm, and area of apposition). In addition, LVRS increases the elastic recoil pressure of the lungs and thus improves expiratory flow rates. LVRS can potentially benefit

carefully selected patients with COPD who have an FEV_1 of 20-25% of the predicted value, hyperinflated lungs with a high residual volume (RV)/ total lung capacity (TLC) ratio, and a heterogeneous distribution of emphysema on high-resolution CT showing as upper lobe predominance. LVRS may improve symptoms and pulmonary function for several years in carefully selected patients with severe emphysema. The procedure involves excision of 20% to 30% of the volume of each lung by thoracotomy or video assisted thoracoscopy.[28,29]

Newer techniques with the use of endobronchial valve (a one-way valve that prevents air from entering into the isolated emphysematous segment while allowing the venting of expired gas and drainage of bronchial secretions distal to it) may be performed via bronchoscopy to achieve lung volume reduction.[30] Lung transplantation (double or single) may improve the quality of life, functional capacity, and may be considered in relatively young patients who have very limited exercise tolerance, poor lung function (eg FEV_1 <35% predicted, PaO_2 <7.3 to 8 kPa, arterial carbon dioxide tension [$PaCO_2$] >6.7 kPa), and secondary pulmonary hypertension.

Management of Acute Exacerbations

AECOPD is characterised by a sustained worsening of symptoms from stable condition that is acute in onset and this worsening of symptoms is beyond the day to day variation of symptoms as experienced by the patients. The symptoms usually include increased breathlessness, sputum purulence or increased sputum volume and in some patients, these are accompanied by other problems such as increasing cough, wheeze, chest tightness or fatigue. Infectious agents are recognised as a major pathogenic factor in AECOPD.[10-12] Other contributing factors for exacerbations include air pollution[31], low temperature, and interruption of regular treatment.

Patients with mild acute exacerbations can be managed as out-patients, whereas more severe cases require hospitalisation. The major components in managing AECOPD include the use of short acting inhaled beta-2 adrenergic agonist, anti-cholinergic bronchodilator, systemic corticosteroid, and antibiotic.[1] In some patients, controlled oxygen therapy and/or non-invasive positive pressure ventilation (NPPV) may be beneficial. More severe exacerbations may require invasive mechanical ventilation.

Bronchodilator provides symptomatic relief of lung hyperinflation, with improvement of shortness of breath, chest tightness and wheeze. The advantage of using inhaled short acting beta-2 adrenergic agonists for AECOPD is its fast onset of bronchodilatation. Anticholinergic bronchodilator is often used in combination with beta adrenergic agonists to produce bronchodilatation in excess of that achieved by either agent alone. Meta-analyses have shown no difference in the efficacy of delivering the bronchodilator therapy via a nebuliser over inhalation via a spacer device for patients with AECOPD.[32] There is currently no strong evidence to support the use of long acting bronchodilators in the treatment of exacerbations. The role of aminophylline in the treatment of AECOPD remains controversial. Recent studies have suggested that low dose theophylline (at plasma concentrations below 10 mg/l) has some anti-inflammatory effect on the COPD airway.[33,34] The proposed mechanism of its inflammatory effect includes reversal of steroid resistance of the airway by restoring the activity of histone deacetylase to normal levels.[35] However, the meta-analyses have failed to confirm the clinical benefits in terms of improvement of lung function and symptoms of patients with AECOPD treated with aminophylline.[36] In addition, there is a significant increase in adverse events such as nausea and vomiting in the aminophylline-treated patients.[36]

Systemic (oral or intravenous) glucocorticosteroid therapy is recommended for treating AECOPD as it significantly reduces treatment failure and the need for additional medical treatment.[37,38] Use of systemic corticosteroid for patients hospitalised for AECOPD accelerates the rate of lung function improvement and improves the sensation of dyspnoea over the first 72 hours of treatment although its use is associated with an increased rate of drug related adverse reactions.[38] The GOLD guideline recommends a 10-14 day course of 30-40 mg/day of oral prednisolone for treatment of AECOPD.[1]

Patients experiencing AECOPD with clinical signs suggestive of airway bacterial infection (e.g., increased sputum volume and change of colour of sputum, and/or fever) may benefit from antibiotic treatment.[1] In Hong Kong, beta-lactamase activity was noted in 10.1% and 54.5% of the admissions with positive sputum culture for *Haemophilus influenzae* and *Moraxella catarrhalis* respectively. At least intermediate resistance to penicillin was noted in 69.0% of hospital admissions with sputum that grew *Streptococcus pneumoniae*.[10] The Hong Kong Interhospital Multi-discipiniary Programme on Antimicrobial ChemoTherapy (IMPACT) guideline in 2005 has recommended oral/intravenous amoxicillin-clavulanate or ampicillin/sulbactam as the anti-microbial therapy for patients with AECOPD.[39] Alternative antibiotics include cefotaxime or a new anti-Gram positive fluroquinolone. A recent Cochrane review has also supported the use of antibiotic therapy for patients who are moderately or severely ill with AECOPD with increased cough and sputum purulence, as antibiotic treatment is associated with reduction in mortality, treatment failure and sputum purulence.[40]

Controlled oxygen therapy is needed for hypoxic patients. In patients with decompensated hypercapnic respiratory failure, the use of NPPV can decrease mortality and need for intubation. In addition, NPPV has led to a reduction in treatment failure, and a more rapid improvement within the first hour in both respiratory rate and pH in blood gas measurement. Furthermore, the hospital length of stay and complications associated with treatment for AECOPD are both reduced in the NPPV treatment group when compared to medical treatment alone.[41]

Conclusion

In summary, COPD is an important disease which imposes a heavy burden on the society. Proper management of the patients may improve their quality of

life, dyspnoea, and exercise capacity and prevent disease progression. Prompt treatment of acute exacerbations is important whereas preventive strategies (such as the use of long-acting bronchodilators, inhaled corticosteroid, pulmonary rehabilitation, seasonal influenza vaccination) to reduce recurrent exacerbations of COPD are needed to improve the health status of these patients.

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Clinical Management of COPD" by Dr. Fanny WS Ko and Dr. David SC Hui and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded 1 CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 December 2008. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please choose the best answer.

1. Which of the following statements about chronic obstructive pulmonary disease (COPD) is incorrect?
a. COPD is a preventable and treatable disease with some significant extra-pulmonary effects that may contribute to the severity in individual patients.
b. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.
c. According to the GOLD guideline (Global Obstructive Lung Disease guideline), COPD is defined by the spirometric criterion of FEV1/FVC ratio of <70%
d. The major factor leading to COPD is active smoking.
e. CXR and high resolution CT thorax are needed for making a definitive diagnosis of COPD

2. Which of the following statements about the classification of COPD in accordance with the Global obstructive Lung Disease 2007 guideline is correct?
a. Apart from Stage I to IV disease, there is an additional "At Risk" group with subjects who have normal spirometry despite having the symptoms of chronic cough and sputum production. This group of subjects will progress of COPD if they continue to smoke.
b. Patients with low FEV1 (i.e. FEV1 <80% predicted) with history of heavy smoking is considered having spirometric evidence of COPD though their FEV1/FVC ratio is >70%.
c. All Stage IV COPD patients should have FEV1 value less than 30% predicted normal.
d. Stage III COPD corresponds to COPD patients with "moderate severity".
e. None of the above

3. Which of the following medications is not useful for smoking cessation?
a. Nicotine replacement therapy
b. Bupropion
c. Counselling and behavioural therapy
d. Haloperidol
e. Varenicline

4. Which of the following statements concerning the use of inhaled corticosteroid (ICS) for treatment of COPD is incorrect?
a. ICS has been shown to reduce the frequency of exacerbations and thus improve health status in patients with mild to moderate COPD.
b. Regular treatment with ICS does not modify the long term decline of FEV1 in patients with COPD.
c. An ICS combined with a long acting beta-agonist is more effective than the individual components in reducing exacerbations and improving lung function and health status
d. Regular treatment with ICS is appropriate for symptomatic COPD patients with an FEV1 < 50% predicted and repeated exacerbations
e. Withdrawal of ICS can lead to exacerbations in some patients.

5. Which of the following statements about long-acting bronchodilator for treatment of COPD is incorrect?
a. Treatment with tiotropium can reduce the rate of COPD exacerbation and related hospitalizations compared to treatment with placebo or ipratropium.
b. Long-acting beta-agonist (LABA) must be used in combination with inhaled corticosteroid for treatment COPD patients as the use of LABA alone is associated with increase COPD mortality.
c. Side effects of tiotropium include urinary retention and dry mouth.
d. Long-acting inhaled bronchodilators are more effective and convenient than short-acting inhaled bronchodilators .
e. None of the above

6. Which of the following statements about management of stable state COPD is correct?
a. Long-acting bronchodilator therapy is recommended for Stage II-IV COPD patients
b. Combination of fluticasone and salmeterol therapy for patients with moderate to severe COPD can reduce mortality.
c. Oral theophylline is the preferred therapy to inhaled long-acting bronchodilator as it has minimal side effect and oral therapy is considered more convenient to the patient than inhaler therapy.
d. Low dose long term oral steroid is helpful to prevent exacerbation of COPD
e. Leukotriene receptor anatagonist is a useful therapy for COPD.

7. Which of the following statements about long-term oxygen therapy (LTOT) for COPD patients is incorrect?
a. In patients with cor pulmonale, LTOT may improve secondary polycythemia, right heart failure, neuropsychiatric function, and exercise performance.
b. LTOT can only confer survival benefit if it is used for at least 15 hours each day
c. In patients with a PaO2 of >7.3 kPa, treatment with oxygen confers no survival advantage.
d. LTOT should be prescribed if 7.3 kPa<PaO2<8kPa (60mmHg) or SaO2 is 89%, and if one of the following complications is present: secondary polycythemia (hematocrit >55%), right heart failure, or pulmonary hypertension.
e. None of the above

8. Which of the following statements is not considered as a potential surgical intervention that can improve the well-being of COPD patients?
a. Lung volume reduction surgery by open thoracotomy
b. Lung volume reduction surgery by video assisted thoracoscopy
c. Lung volume reduction surgery by endobronchial valve insertion via bronchoscopy
d. Thoracoplasty
e. Bullectomy

9. Which of the following statements about acute exacerbation of COPD is incorrect?
a. It is an event in the natural course of the disease characterized by a change in the patient's baseline dyspnoea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD
b. Infection is an important cause of acute exacerbation of COPD
c. Increased ambient air pollution is associated with acute exacerbation of COPD
d. Influenza vaccination and pulmonary rehabilitation are both useful in reducing the rate of acute exacerbation of COPD
e. None of the above

10. Which of the following treatment modalities cannot prevent acute exacerbations of COPD?
a. Influenza vaccination
b. Pulmonary rehabilitation
c. Oral acetylcysteine
d. Combination inhaled steroid and long acting beta-agonist for patients with severe and very severe COPD
e. Long acting anticholinergic therapy for patients with at least moderate COPD

ANSWER SHEET FOR DECEMBER 2008

Please return the completed answer sheet to the Federation Secretariat on or before 31 December 2008 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Clinical Management of COPD

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Answers to November 2008 issue

Computed Tomography in Dentistry

1. T 2. T 3. F 4. F 5. T 6. F 7. F 8. T 9. F 10. T

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The State-of-the-Art Treatment of Non-small Cell Lung Cancer

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Introduction

Lung cancer has been a major health problem worldwide, accounting for a global incidence of 1.2 million new cases yearly and a staggering mortality of 1.1 million deaths in 2001.[1] In Hong Kong, lung cancer has remained the commonest malignancy in men and the third commonest in women, with a total of 4,135 new cases in 2005. Being the commonest cancer killer in both sexes, there were 3,686 deaths in the same year (Hong Kong Cancer Registry). The majority (>80%) of the lung cancers is non-small cell carcinoma (NSCLC), which is predominantly in advanced or metastatic stages upon presentation. The high mortality is mainly ascribed to disease recurrence after curative lung resection and the lack of effective treatment for advanced disease. The overall treatment plan for NSCLC largely depends on clinical staging: curative lung resection for early stages (mainly stage I and II), combined with chemoradiotherapy for locally advanced stages (mainly stage III), and systemic platinum-based chemotherapy for advanced metastatic stages (mainly stage IIIB and IV). Building on this framework of treatment strategies, there have been significant advances in the overall treatment for NSCLC over the past 5 years, especially with the emergence of targeted therapy. This review serves to highlight the important advances on the latest pharmacological treatment for NSCLC.

Adjuvant Chemotherapy for Resectable NSCLC

The staging system of NSCLC is based on the extent of involvement of primary tumour (T), regional lymph nodes (N) and distant metastases (M).[2] Early resectable stages often refer to stage I or II and selected stage IIIA with either ipsilateral microscopic mediastinal lymph node involvement or chest wall invasion. The current standard treatment for early disease is still complete surgical resection, unless medically contraindicated. However, the 5-year survival rate of resected early-stage disease is still suboptimal, mainly due to presence of micrometastases leading to subsequent recurrence in distant sites.[3] Therefore the use of adjuvant chemotherapy after lung resection appears to be the logical step to improve outcome. As early as in 1995, a meta-analysis from the Non-small Cell Lung Cancer Collaborative Group already suggested a slight survival benefit, though statistically insignificant, with the use of post-operative cisplatin-based chemotherapy.[4] More recently, there have been several large-scale randomised controlled trials reporting on adjuvant chemotherapy in over 4,000 patients with early-stage NSCLC.[5-8] In the largest randomised controlled trial reported so far on adjuvant chemotherapy, the International Adjuvant Lung Cancer Trial (IALT)[6], there were 1,867 patients with stages I to III NSCLC recruited into either postoperative chemotherapy (cisplatin combined with etoposide, vinorelbine, vinblastine, or vindesine) or no adjuvant chemotherapy. After a median follow-up of 56 months, the overall survival was significantly prolonged in the chemotherapy arm, with a 4.1% absolute survival benefit at 5 years and 14% relative reduction in risk of death (HR 0.86, 95% CI 0.76-0.98, $p<0.03$). This was also accompanied by an improved disease-free survival with postoperative chemotherapy (HR 0.83, 95% CI 0.74-0.94, $p<0.003$). The reported toxicity profile was generally well tolerated. Furthermore, a pooled analysis of the recent major randomised trials (the aforementioned 4 trials[5-8] and the Big Lung Trial[9]) suggested significant survival benefit with adjuvant chemotherapy compared to surgery alone, with a 5-year absolute benefit of 5.4%.[10] The survival benefit was largely limited to resectable stage II and III disease only. Therefore, especially in younger patients with good performance status after curative resection for early-stage II or IIIA NSCLC, adjuvant cisplatin-based chemotherapy can be considered as part of the current standard practice, though there is still controversy about the optimal regimen and schedule.

Newer Agents for Treatment of Advanced or Metastatic NSCLC

Although surgery can offer the best chance of cure for lung cancer, it is unfortunately only feasible for a minority of patients, in which there is no regional involvement of mediastinal lymph nodes, pleural or pericardial malignant effusion, or distant metastases. In the presence of extensive mediastinal lymphadenopathy and locally advanced disease, the current standard treatment is combined systemic chemotherapy and radiotherapy, either given in concurrent (preferred) or sequential manner.[11, 12] Over the years, systemic chemotherapy has become the standard first-line treatment for those with malignant effusion or distant metastases.[13] In such patients with good performance status, a combination of platinum (cisplatin or carboplatin) and a newer generation chemotherapeutic agent (e.g. paclitaxel, docetaxel or gemcitabine) has been demonstrated to improve overall

survival, disease-free survival and quality of life compared to best supportive care alone or older generation chemotherapy combinations in the first-line setting.[14] The overall international experience, however, showed that the improvement in survival is modest (around 2 months prolongation of median survival compared to best supportive care alone) and the time to disease progression is usually within a few months since commencement of chemotherapy.[15] Upon disease progression after first-line treatment, docetaxel as second-line monotherapy has been shown to have survival advantage over best supportive care alone or alternative chemotherapy[16,17], although the improvement is fairly modest at the expense of significant toxicity. Therefore there have been continued efforts looking for novel agents in the treatment of advanced or metastatic NSCLC.

Anti-angiogenesis agents in combination with chemotherapy as first-line

It has long been recognised that angiogenesis, regulated by proangiogenic and antiangiogenic factors, plays a crucial role in tumour growth and development of distant metastatases. One of the most important proangiogenic factors involved in tumour angiogenesis is vascular endothelial growth factor (VEGF), which serves as the main target for antiangiogenic therapy in NSCLC. Bevacizumab (Avastin™) is an anti-VEGF recombinant humanised monoclonal antibody, which blocks the binding of VEGF to its receptors and subsequent downstream biologic activities. A randomised phase II study of bevacizumab in combination with carboplatin and paclitaxel or same chemotherapy alone as first-line treatment in patients with stage IIIB or IV NSCLC has demonstrated superior response rate, time to progression and survival in the bevacizumab combination arm, but with increased risk of life-threatening haemoptysis in squamous cell carcinoma (a sub-type of NSCLC). [18]

As a result, a recent randomised phase III study (E4599) was conducted comparing the combination of bevacizumab with chemotherapy (carboplatin and paclitaxel) versus chemotherapy alone in the treatment of advanced chemonaive non-squamous NSCLC.[19] For the first time in phase III setting, this study has demonstrated a statistically significant survival benefit favouring the bevacizumab combination arm compared to the standard chemotherapy alone (median survival 12.3 months vs 10.3 months in bevacizumab combination vs chemotherapy alone arms, hazard ratio 0.79, p=0.003). The major toxicity appeared to be related to bleeding complications, in which the 5 deaths due to haemoptysis were exclusively from bevacizumab arm. A similarly designed phase III clinical trial on the combination of bevacizumab (at 2 doses) with chemotherapy (gemcitabine and cisplatin) has been conducted with demonstrable improvement in progression-free survival with the bevacizumab combination arm in preliminary analysis. However, this study was not designed to look into overall survival as the primary outcome. Overall, the approach in combining bevacizumab with standard platinum-based doublet chemotherapy is feasible and beneficial, at the expense of greater degree of toxicities (e.g. hypertension, proteinuria, bleeding) and cost. Ongoing studies will hopefully address the remaining controversies related to this approach, like treatment for selected squamous cell carcinoma and brain metastases.

Pemetrexed as Second-line Chemotherapy

With the current standard first-line chemotherapy treatment for advanced NSCLC, tumour response is expected to be transient with disease progression mostly occurring within a few months after cessation of chemotherapy.

Pemetrexed (Alimta™) is a novel multitargeted antifolate chemotherapy that has been shown to be active against NSCLC, which acts by inhibiting the three key enzymes in pyrimidine and purine synthesis. A recent randomised phase III trial comparing pemetrexed (with vitamin B12 and folate supplementation) versus docetaxel as monotherapy second-line treatment in advanced NSCLC has demonstrated similar median progression-free survival (2.9 months for each arm) and median survival (8.3 vs 7.9 months for pemetrexed vs docetaxel).[20] Importantly, pemetrexed treatment was associated with significantly less severe neutropenia, febrile neutropenia, neutropenia with infections, and hospitalisations for neutropenic fever compared with docetaxel. Based on this study, pemetrexed has been widely approved as second-line treatment for advanced NSCLC, equally effective as docetaxel but with more favourable toxicity profile.

Pemetrexed and Cisplatin as First-line Chemotherapy for Adenocarcinoma

Pathologically, non-small cell carcinoma comprises of squamous cell carcinoma, adenocarcinoma and large cell carcinoma. Traditionally, the pharmacological treatment for different subtypes of NSCLC is similar, i.e. no particular predilection for certain chemotherapy based on cell type. A recent phase III study was conducted to compare the clinical efficacy of pemetrexed/cisplatin with gemcitabine/cisplatin as first-line treatment for advanced NSCLC.[21] Apart from demonstrating non-inferior overall survival for the two chemotherapy regimens (median survival 10.3 months for both), pemetrexed/cisplatin entailed statistically superior survival vs gemcitabine/cisplatin among patients with adenocarcinoma (12.6 vs 10.9 months respectively) and large cell carcinoma (10.4 vs 6.7 months respectively).[21] In contrast, the opposite finding of survival superiority with gemcitabine/cisplatin compared to pemetrexed/cisplatin in squamous cell carcinoma (10.8 vs 9.4 months respectively) was observed.[21] This finding could be biologically plausible in light of the higher gene and protein expression of thymidylate synthase in squamous cell carcinoma compared with adenocarcinoma, thus making adenocarcinoma more prone to the anti-folate action (with thymidylate synthase as one of the key targets) of pemetrexed.[22]

Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR TKI)

In recent years, the concept of molecularly targeted therapy has evolved rapidly in the management of advanced NSCLC, which is best exemplified by the inhibition of EGFR pathway. Unlike conventional cytotoxic agents leading to non-specific cell damage or death, this class of novel agent targets specifically at the critical and unique pathway involved in tumourigenesis. The EGFR forms part of the signalling pathway that regulates tumour cell proliferation, invasion,

angiogenesis, metastasis, and apoptosis. Since overexpression of EGFR is commonly found in NSCLC, various novel agents that inhibit EGFR pathway have been developed for the treatment of this neoplasm. Apart from the use of monoclonal antibody that targets the EGFR extracellular binding site, small molecules that target the intracellular adenosine triphosphate (ATP) binding site of EGFR tyrosine kinase have been studied extensively. There are two clinically available EGFR TKIs, namely gefitinib (Iressa™) and erlotinib (Tarceva™), in which the readers are recommended to refer to a recent review for more details in The Hong Kong Medical Diary in August 2008. Overall, there are phase III data to support the clinical efficacy of either gefitinib (INTEREST trial) or erlotinib[23] as a single agent in the treatment of advanced NSCLC in the second- or third-line settings. The toxicity profile of EGFR TKI is rather different from that of systemic chemotherapy, in which the adverse effects of EGFR TKI are mostly skin reaction (dryness, pustular rash, paronychia), diarrhoea, and rarely interstitial pneumonitis. There have been several clinical (female, Asian descent, never smokers, adenocarcinoma) and molecular (EGFR gene mutations, EGFR gene copy number) predicting factors for response to treatment by EGFR TKI, though the relative importance of each of the factors is not completely elucidated.[24] Future research will also help to define better the role of EGFR TKI in other clinical settings especially as first-line treatment in an enriched population with anticipated favourable response to this class of medications.

Novel Treatments on the Horizon

Besides the various advances in drug treatment as highlighted above, there have been concerted efforts worldwide in the development of novel targeted agents in the battle against NSCLC. In the years to come, we will be hearing more and more about alternative anti-angiogenesis agents with small molecules (VEGFR TKI), newer targets (like specific inhibitors of EGFR downstream signalling pathway), multi-targeted kinase inhibitors (like combined VEGFR and EGFR inhibitors), and monoclonal antibody targeting EGFR (like combination of cetuximab (an anti-EGFR) with chemotherapy).

The State-of-the-Art Treatment Algorithm

With the aforementioned new armamentaria in the treatment of NSCLC, a suggested treatment algorithm is shown in Table 1.

Table 1 Treatment algorithm for non-small cell lung cancer

Stage	First-line treatment	Second-line treatment
I	Surgery	
II	Surgery + adjuvant cisplatin-based chemotherapy (especially in younger patients with good performance status)	
IIIA-IIIB (non-effusion)	Surgery for selected resectable stage IIIA ± chemotherapy ± RT Combination of cisplatin-based chemotherapy and thoracic RT for non-resectable stages (concurrent more effective than sequential)	
IIIB (effusion)-IV	Options: Cisplatin-based chemotherapy (doublets) Bevacizumab combined with cisplatin-based doublet chemotherapy (non-squamous NSCLC) EGFR TKI	Options: Docetaxel Pemetrexed EGFR TKI

RT, radiotherapy; EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor

Conclusion

Over the past few years, there have been substantial and promising advances in both clinical and basic research on non-small cell lung cancer, leading to an era of targeted approach to lung cancer treatment. With the emergence of newer, more effective, and safer drug therapies, the overall prognosis of lung cancer may hopefully be improved in the near future.

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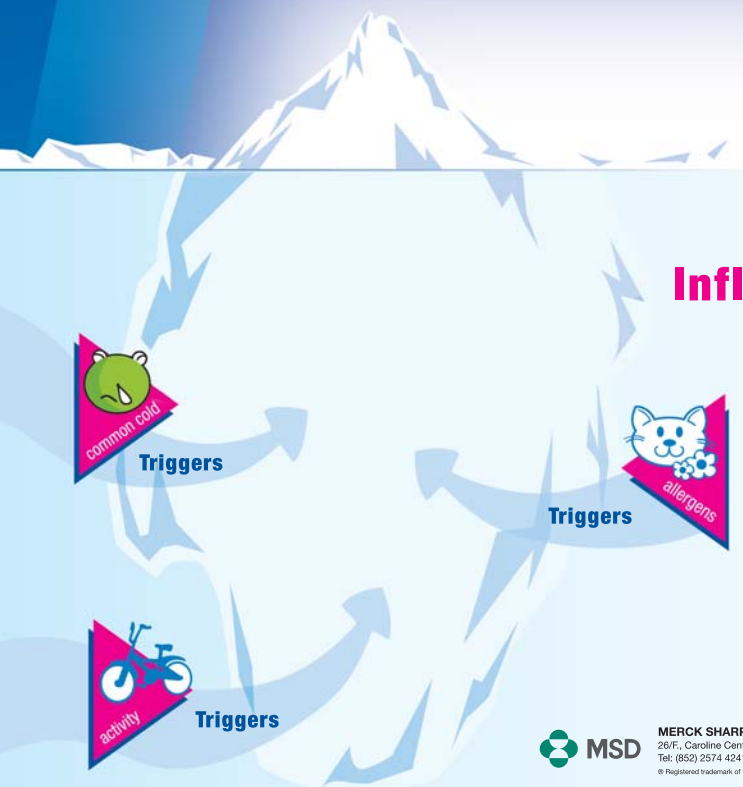

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Management of Community Acquired Pneumonia

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Introduction

Pneumonia is the 3rd leading cause of death in Hong Kong, and it accounts for more than 4000 deaths per year locally.[1] It can be categorised into community-acquired or hospital-acquired, and it can affect immuno-competent or immuno-compromised hosts. In this review, we will focus on the management of community-acquired pneumonia (CAP) in an immuno-competent host.

Definition

Pneumonia is an acute lower respiratory tract infection associated with fever, symptoms and signs in the chest, and abnormalities on the chest x-ray. Community-acquired pneumonia is defined as the presence of symptoms and signs which are consistent with an acute lower respiratory tract illness associate with new radiographic shadow for which there is no other explanation in a patient who has not recently been hospitalised.[2]

Aetiologies

Common bacterial pathogens causing CAP include *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Mycoplasma pneumoniae, Chlamydophila pneumoniae* and *Legionella pneumophila*. In Hong Kong, tuberculosis may masquerade as CAP in about 12% of patients.[3] Influenza and other respiratory viruses (e.g. respiratory syncytial virus, adenovirus) can be complicated by viral pneumonia or secondary bacterial pneumonia. In patients with chronic medical illness and/or alcoholism, *Klebsiella pneumoniae* may cause a fulminant pneumonia. Fulminant bacteraemic *Acinetobacter baumannii* CAP is a newly described entity which may occasionally cause rapidly fatal pneumonia in Hone Kong and other tropical countries.[4]

Patient with travel history or unusual exposure might contract unusual organisms. A thorough history taking is most important to provide clues to these unusual agents (Table 1).

Clinical and Radiological Features

Common clinical features of CAP include cough, fever, sputum production, dyspnoea and pleuritic chest pain. Other features include gastrointestinal symptoms and mental state changes. General examination reveals febrile, tachyponea or tachycardia. Examination of the chest detects localised crackles or bronchial breath sound. Chest radiograph (CXR) is helpful in confirming the diagnosis of pneumonia.

Radiographic changes include lobar consolidation, either unilobar or multilobar; interstitial infiltrates, cavitation, with or without pleural effusion. However, the pattern of radiological involvement is seldom predictive of the likely aetiology in CAP.

Table 1. Epidemiological clues to community-acquired pneumonia

Epidemiological links	Organisms
Air conditioning, cooling towers, travel and hotel, mist machine, hospital	*Legionella pneumophila*
Cattle, sheep, goats	*Coxiella burnetii*
Windstorm in endemic area (e.g. California)	*Coccidioides immitis*
Homeless, prison	Tuberculosis
Military camp	*Streptococcus pneumoniae, Chlamydophila pneumoniae,* adenovirus, *Mycoplasma penumoniae*
Nursing home	Influenza A or B, *Chlamydophila pneumoniae,* Respiratory Syncytial Virus, *Streptococcus pneumoniae*
Bat caves	*Histoplasma capsulatum*
Turkeys, chickens, ducks, birds	Influenza A, *Chlamydophila psittaci*
Rabbits	*Francisella tularensis*
Health care worker	Tuberculosis, HIV, Influenza A or B, SARS
Thailand/SE Asia	*Burkholderia pseudomallei*
Alcoholism	*Streptococcus pneumoniae, Klebsiella pneumoniae, Staphylococcus aureus,* anaerobes

Assessment of Severity

CAP presents to physicians both in primary and secondary care settings as a wide spectrum of illness, from mild and self-limiting to life-threatening or even fatal disease. The decision regarding out-patient treatment or in-patient care is the first and single most important decision for general practitioners.

Different criteria and models have been developed to give an objective assessment of the severity of pneumonia and to predict the mortality of pneumonia. They can assist in identifying patients with CAP who may be candidates for out-patient treatment. The two most commonly used prediction rules are the Pneumonia Severity Index (PSI) and CURB-65.

PSI is a prognostic model which uses demographics, co-morbidities, findings on physical examination and laboratory findings to stratify patients into 5 mortality risk classes. Class I and II patients should be treated as out-patient, risk class III patients should be treated in an observation unit or with a short hospitalisation, and risk class IV and V patients should be treated as in-patients.[5]

CURB-65 is a severity assessment score which stratifies patients into different mortality groups suitable for different management pathways. One point is given for each of following factors: **C**onfusion (based on a specific mental test or disorientation to person, place, or time), *U*rea >7mmol/L (20mg/dL), **R**espiratory rate ≥ 30 breaths/min, low **B**lood pressure (systolic < 90mmHg or diastolic ≤ 60mmHg), and age ≥ **65** years.[6] The higher the score, the higher the mortality risk (Score 0, 0.7%; Score 1, 5.3%; Score 2, 13%; Score 3, 17%, Score 4, 41.5%; Score 5, 57%). This score is adopted by the updated BTS guideline as a severity assessment model (Table 2). Patients with CURB-65 score of 0-1 can be treated as out-patients, those of score 2 should be considered for a short stay in-patient treatment or hospital supervised out-patient treatment, and patients with the score ≥ 3 should be managed in hospital and may need ICU care.[7]

Table 2. Severity assessment of CAP using CURB-65 score, adopted from BTS guideline for management of community acquired pneumonia in adults - 2004 update

Confusion*
Urea > 7mmol/l
Respiratory rate ≥ 30/min
Blood pressure (SBP < 90mmHg or DBP ≤ 60mmHg)
Age ≥ 65 years

Score 1 point for each feature present

CURB-65 Score	0 or 1	2	3 or more
	Likely suitable for home treatment	Consider hospital supervised treatment	Manage in hospital as severe pneumonia Assess for ICU admission especially if CURB-65 score = 4 or 5

*Defined as a Mental Test Score of 8 or less, or new disorientation in person, place or time.

The Abbreviated Mental Test (each question scores 1 mark, total 10 marks): Age, date of birth, time (to nearest hour), year, hospital name, recognition of two persons, recall address, date of First World War, name of monarch, count backwards 20→1

Complications

Pleural effusion occurs in 40% of bacterial pneumonia.[8] Usually the parapneumonic effusion is small and resolves with appropriate antibiotics. However, it can become complicated if there is persistent bacterial invasion of the pleural space (which is indicated by a pH of <7.2 and/ or LDH >1000 IU/l). Empyema thoracis develops if the bacteria are not cleared, which is characterised by bacterial organisms seen on Gram stain or positive culture, or aspiration of pus from thoracentesis.

Lung abscess formation is another complication of pneumonia. It is commonly caused by aspiration pneumonia (e.g. in alcoholic or debilitated patients), or less commonly, due to bacteraemia or tricuspid valve endocarditis with septic emboli to the lung. This can be diagnosed by chest radiograph or more sensitively, by CT scan.

Treatment

In Hong Kong, *Streptococcus pneumoniae* is the single most common pathogen in CAP. Therefore, the choices of empirical therapy need to take into account of the local data of drug-resistant *S. pneumoniae* (DRSP). Also, the role of atypical pathogens in CAP (e.g. *Chlamydia pneumoniae, Mycoplasma pneumoniae* and *Legionella species*) is increasingly recognised, patients should be covered for the possibility of these infections. Lastly, the place of starting the antibiotic (out-patient or in-patient) and the presence of modifying factors, including risk factors for DRSP, enteric Gram negatives and *Pseudomonas aeruginosa* are also important factors to consider for the choice of antibiotic.

The following recommendations are based on the local guideline IMPACT.[9] For out-patient treatment of CAP, empirical therapy should cover the usual organisms, which includes an oral amoxicillin-clavulanate or ampicillin-sulbactam ± macrolide or amoxicillin + a newer macrolide. For in-patient treatment, the preferred regimen includes intravenous or oral amoxicillin-clavulanate or ampicillin-sulbactam ± macrolide. The alternative treatment includes cefotaxime or ceftriaxone ± macrolide. In serious CAP which requires ICU admission, the treatment options should also cover *Enterobacteriacea*; choices include intravenous piperacillin-tazobactam or cefotaxime or ceftriaxone + macrolide; another alternative is cefepime + macrolide (Table 3). If a patient is at risk of Pseudomonas infection, an anti-Pseudomonal antibiotic should be prescribed.

Table 3. Recommendation for the empirical therapy of community-acquired pneumonia according to IMPACT (3rd edition)

CAP	*Usual organisms*	*Preferred regimens*	*Alternatives*
CAP, not hospitalised	*S. pneumoniae* *H. influenzae* *C. pneumoniae* *C. psittaci* (influenza A, *M. tuberculosis)*	PO Amoxicillin-clavulanate or ampicillin-sulbactam ± a macrolide *or* PO amoxicillin + a newer macrolide	
CAP, hospitalized in general ward	As above	IV/ PO Amoxicillin-clavulanate or ampicillin-sulbactam ± a macrolides	Cefotaxime or ceftriaxone ± a macrolides
CAP, hospitalized in ICU for serious pneumonia	As above + *Enterobacteriaceae*	IV Piperacillin-tazobactam or cefotaxime or ceftriaxone + a macrolide	Cefepime + a macrolide

Fluoroquinolone is not recommended as the first line therapy for CAP in Hong Kong. The resistance of this class of drug is rapidly emerging among the *S. pneumonia* in this locality.[10] Moreover, tuberculosis is prevalent in Hong Kong. Excessive use of fluoroquinolone may lead to delay in diagnosis of tuberculosis and increased fluoroquinolone resistance among *Mycobacterium tuberculosis*.[11,12]

Besides antibiotics, supportive treatment should be given as appropriate. Oxygen therapy should be given if the patient is hypoxic, those with volume depletion may require intravenous fluid. In those with prolonged illness, nutritional support is important.

The presence of empyema thoracis requires early and effective drainage with chest tubes. In a local study, *Streptococcus milleri, Bacteroides* and *Klebsiella pneumoniae* were the most common cultured organisms.[13] The choice of antibiotic in these cases should cover Gram negative and anaerobic organisms as well. If the above treatments fail, surgical drainage is required. Lung abscesses usually respond to a prolonged course of antibiotics. Lobectomy is seldom required.

Approach to Unresolved Pneumonia

When the pneumonia is not responding to treatment, careful analysis of the history, physical examination, radiology and laboratory features is required. There are many possibilities of unresolved pneumonia. It can be due to inadequate dosage or coverage of antibiotics, resistant or unusual organisms, underlying immunodeficiencies, persistent predisposition of pneumonia (e.g. foreign body, obstructing tumour, aspiration), development of complications (empyema thoracis, lung abscess, metastatic infection), or concomitant processes (e.g. line sepsis, drug fever, Lemierre's syndrome, transfusion reaction, pulmonary embolism, pseudomembranous colitis) causing fever. Finally, some diseases can also cause similar symptoms, signs and radiographic changes, mimicking pneumonia e.g. drug reaction, eosinophilic pneumonia, extrinsic allergic alveolitis, bronchiolitis obliterans organising pneumonia (BOOP), diffuse alveolar damage (DAD), vasculitides, lipoid pneumonia, connective tissue disease and neoplasm. CT thorax, bronchoscopy and/or open lung biopsy may be required to differentiate the causes.

Prognosis

With treatment, most CAPs resolve within days to weeks. However, in older patients, presence of co-existing disease, high CURB-65 score, hypoxaemia, multilobar involvement, bacteraemia, fulminant organisms and development of complications are associated with adverse outcomes.

Conclusion

With the correct choice of antibiotic, a general practitioner can safely manage patients with low risk CAP in the out-patient setting. A follow up CXR is necessary to confirm resolution of pneumonia. However, in high risk patients (Table 2) and in non-responding cases, early referral for specialist care is advised.

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Any Better Guns For Nosocomial MRSA Pneumonia

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Methicillin Resistant *Staphylococcus aureus* (MRSA) is still an important nosocomial pathogen. It accounts for about 10% of all pathogens isolated from the Respiratory Tract in the Adult Intensive Care Unit (ICU) of Queen Mary Hospital in year 2006.

Mortality of MRSA vs MSSA Pneumonia

In spite of being a well described infection, at least for MRSA pneumonia, it was still controversial as to whether Methicillin resistance confers higher mortality. A recent Meta-analysis by Athanassa[1] suggested that in patients with ventilators associated pneumonia, Methicillin resistance is associated with a higher crude mortality, but the relationship could be largely accounted for by confounding factors such as the appropriateness of the initial antibiotics. So if an appropriate antibiotic was started for MRSA pneumonia, the overall outcome could be similar to that of infections due to strains of Methicillin Sensitive *Staphylococcus aureus* (MSSA)[2].

However, knowing the very limited choice of antibiotics for MRSA, that makes the initial choice of an appropriate antibiotic for patients having nosocomial pneumonia and at risk of MRSA infection being difficult.

Vancomycin in Treatment of Nosocomial MRSA Pneumonia

Vancomycin is still the standard antibiotics for the treatment of Nosocomial Pneumonia, as recommended in the most recent guideline endorsed by the American Thoracic Society and the Infectious Disease Society of America[3].

There are still many controversies surrounding the use of Vancomycin in the treatment of MRSA Pneumonia. In particular, because of the poor pulmonary penetration, there had been debates about the optimal dosing of Vancomycin, either by a continuous infusion or by targeting a higher trough level. Continuous infusion of vancomycin was not associated with an improved outcome in the treatment of MRSA infection. The trough level was more of a concern, and a trough concentration of 15mg/L has been suggested as the target. A recent retrospective review of 102 patients with Health Care Associated Pneumonia by Jeffres[4], however, noted that the mean (±SD) vancomycin trough concentrations (13.6 ± 5.9 vs 13.9 ± 6.7 μ/mL, respectively; p = 0.866) were not different between the survivors and non-survivors. He also analysed by stratifying patients into groups with steady state trough level of Vancomycin < 15 μ/mL (n = 68) and ≥ 15 μ/mL (n = 34). Again there was no difference in the Hospital mortality or duration of mechanical Ventilation.

However, another review by Hidayat[5] suggested that Minimal Inhibitory Concentration (MIC) of the strain to Vancomycin could be the determinating factor, rather than the trough level. He conducted a prospective cohort study of using high dose vancomycin to target the trough vancomycin level be at least 4 times the MIC of the strain. Even with this strategy, the group infected with MRSA for which the MIC to Vancomycin was above 2 μ/mL, the treatment failure rate was still higher than the group with lower MIC (24% vs 10%) at the end of treatment. There was also a trend towards more nephrotoxicity in the group with trough level >15 μ/mL. So it seems that a higher trough level is not generally accepted, the confounding factor could be the MIC of the strain of MRSA with respect to Vancomycin, instead of the dosing algorithm.

So it would seem that the conventional treatment strategy with Vancomycin still works on MRSA pneumonia. There are situations where alternatives need to be considered for the treatment of this infection. These situations include:

- Hypersensitivity reactions to glycopeptides, excluding the Red Man Syndrome
- Problem with dosing frequency in adjustment for Creatinine Clearance
- Strains with higher MIC to Vancomycin (>2mg/L)
- Situations where intravenous therapy are becoming difficult or undesirable, such as unnecessary prolongation of hospital stay or problematic intravenous access.

New Agents

Linezolid

Linezolid belongs to a class of its own known as oxazolidinones. Linezolid might also work for strains of MRSA that have a high MIC to vancomycin.

Two randomised trials compared the efficacy of Linezolid against Vancomycin, both combined with Aztreonem, in the treatment of nosocomial Pneumonia[6,7]. Wunderink summarised the findings in a meta-analysis by extracting all patients in these two

trials who had Staphylococcal Pneumonia, including 160 with MRSA pneumonia[8]. The subgroup analysis claimed that linezolid treatment was associated with a significantly higher survival rate of 59.0% against 35.5% of Vancomycin. The finding, however, cannot be taken as conclusive as this is not a pre-planned analysis. Also, the reported survival rate of the group receiving vancomycin, of only 35.5%, was much lower than that usually reported. Another recent paper by Wunderink[9] also suggested a trend towards earlier MRSA eradication in patients with VAP due to MRSA, when compared to Vancomycin.

The side effect profile of Linezolid also raised concerns. Thrombocytopenia, in particular, has been reported to be a known side effect. Gerson[10] reported a significant shift towards thrombocytopenia in 4.1% of subjects compared to only 1% in the comparator arm. Most of these occurred in patients who have received 14 days or more of Linezolid. These tend to be mild and reversible. However, the two previously reported clinical trials by Wunderink and Rubinstein did not identify a difference in the adverse event profile between the Linezolid and the vancomycin arm.

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In spite of all these, there are distinct advantages of Linezolid over Vancomycin, including its availability of an oral form with excellent bioavailability, having no need for dosage adjustment in renal failure and no need for therapeutic drug level monitoring, make it an attractive choice in some patient population. Thus, linezolid has been recommended in the joint guideline published in 2005 by the American Thoracic Society and the Infectious Disease Society of America[3] as an alternative to Vancomycin for treatment of hospital acquired MRSA pneumonia.

There are still Phase III clinical trials on going with Linezolid for MRSA pneumonia and thus all these efficacy concerns and side effect profile will be addressed and hopefully resolved.

Tigecycline

Tigecycline (Tygacil) has not been compared with standard treatment in multicentre randomised Trials. Tigecycline is a broad glycylcycline antibacterial with a very broad spectrum bacteriostatic activities across Gram negative and Gram positive organisms, which included MRSA. Tigecycline has not been tested in clinical trials focusing on nosocomial pneumonia. However, recently, it is approved by the FDA for the treatment of Community Acquired Pneumonia. Study of wild strains of nosocomial MRSA isolates in Belgium also suggests that they have low MIC to Tigecycline[11]. Similar findings of activities of Tigecycline against community and nosocomial respiratory isolates were also reported by Fritsche[12]. There were also suggestions that Tigecycline was able to achieve clinical cures when used in treatment of skin and soft tissue infection due to MRSA[13]. All these suggest that Tigecycline might be hopeful as a treatment for nosocomial MRSA pneumonia, pending confirmation by clinical trials.

Daptomycin

Daptomycin (Cubicin) is going to be available locally. It belongs to a new class of antibiotics,cyclic lipopeptides, with activities against Gram Positive organisms, including MRSA and strains of Vancomycin Resistant *Enterococcus*. It has been approved by the Food and Drug Administration (FDA) of the United States to treat skin and soft tissue infections due to Gram Positive organisms and also right side endocarditis due to *Staphyloccocus aureus*. There are great concerns about the inactivation of Daptomycin by pulmonary surfactants[14] and thus it is not recommended for treatment of MRSA Pneumonia.

Infection Control Measures

MRSA infection is a rather preventable infection. The experience in the Adult ICU was that if evidence based methods were implemented, the incidence of MRSA infection could be reduced. The policy that we have adopted included strict cohort isolation of MRSA carriers or infected patients, practice of contact isolations, observance of antibiotics policy and hand hygiene practice. With these, the rate of MRSA isolation in Adult ICU fell for 5 consecutive years comparing to the baseline at year 2002, to a level of about one sixth of that at baseline.

Conclusion

The optimal strategy to treat MRSA pneumonia still needs to be decided. While Vancomycin is still considered the standard treatment now, promising data are coming with some new antibiotics. In particular, linezolid is getting close to challenge this golden standard, but just more data from randomised trials are needed to clarify this issue.

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An Overview on the Management of Influenza in Adult Patients

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Global & Local Epidemiology

Influenza is a respiratory illness of birds and mammals caused by RNA viruses of the Orthomyxoviridae family. Influenza A and B are the two types of viruses in this family that commonly cause human disease.[1] Seasonal influenza epidemics are reported to cause 250,000 to 500,000 deaths worldwide and it is also estimated to be responsible for 226,000 hospitalisations per year in the United States alone.[2]

In Hong Kong, influenza A is more commonly seen infecting humans, especially those of subtypes H1N1 and H3N2. Due to the new variant formation of the influenza virus from frequent antigenic changes, vigilant monitoring and reformulation of the influenza vaccine are in progress in order to prevent and minimise widespread outbreaks in the community. Locally, seasonal peaks are generally recorded from February to March and from June to July. Individuals at the extremities of age are at particular risk of complications or death once they have contracted the influenza virus. It has been estimated that 13-58 per 10,000 elderly individuals are hospitalised each year due to these associated complications of pneumonia, exacerbation of chronic obstructive pulmonary disease, coronary heart disease and congestive heart failure. [3]

Clinical Features and Diagnosis

Influenza viruses are spread primarily through *droplet* transmission, usually due to close contact between the source and the recipient although it is also possible to acquire the infection through contact and airborne transmission. The incubation of influenza is 1 to 4 days, though infected individuals can be infectious one day before symptom onset. Symptoms usually appear quite suddenly within a day. Commonly in uncomplicated influenza, individuals develop a mild headache, fever, chills, rhinitis, sore throat and myalgia and the bulk of these usually subside after 3 to 7 days. In complicated influenza, however, individuals can develop viral pneumonia, exacerbating underlying pulmonary or cardiovascular diseases, and leading to secondary bacterial pneumonia, sinusitis or otitis.[4] Though sometimes it can be difficult to distinguish between "common cold" and influenza due to the similarity of their presentations, symptoms of influenza tend to manifest more severely than their common cold equivalents.[5] Sometimes diagnosis of influenza solely by clinical means may be difficult, particularly in individuals with atypical presentation of the disease. A study of non-hospitalised adult patients showed that fever, cough and acute onset only had a positive predictive value of 30% for influenza.[6] Similarly, the absence of typical symptoms is unable to exclude the diagnosis of influenza, as only 51% of hospitalised patients with laboratory confirmed influenza infections have displayed typical symptoms.[7] A recent study of elderly persons living in residential care homes in HK has shown that clinical presentation of influenza-like illness is non-specific and is mainly due to bacterial and other viral infections than influenza.[8]

Laboratory Diagnosis

Influenza can be diagnosed by various laboratory tests. Viral cultures on nasopharyngeal specimens are both sensitive and specific, but may take up to 3 to 10 days, which severely limits clinical usefulness. However, this method is particularly useful in determining the exact subtype of the infecting virus and hence is able to aid in the surveillance, chemoprophylaxis and development of the appropriate vaccine for the following year. Rapid antigen testing, immunofluoresence assays, and reverse transcriptase-polymerase chain reaction are also used in the diagnosis of influenza.

Commercial rapid diagnostic tests on nasopharyngeal aspirates and nasal/throat swabs are available and can detect the influenza virus within 30 minutes.[9] However, different tests may detect either influenza A or B, or some while detecting both, may or may not be able to differentiate between the two. These tests are particularly useful in the hospital setting, where early confirmation helps the implementation of appropriate infection control measures, though they are unable to provide information as to the exact subtype of the infecting influenza virus. Specimen samples taken nasally and within the first few days of illness can lead to the high sensitivity about 70% and over 90% specificity of rapid diagnostic testing.

Treatment

The treatment of influenza comprises of symptomatic relief and the possible administration of antivirals. Anti-pyretics can be given to lower high temperatures and adequate hydration should be provided in anticipation to large amounts of fluid losses due to fever.

Antiviral agents with neuraminidase inhibition such as oseltamivir and zanamivir are effective against both influenza A and B. They have been demonstrated to be

effective in shortening both the duration of influenza and the total length of hospital stay when initiated within 48 hours of symptom onset[10-12] Both drugs are recommended to be taken for 5 days in the form of either oral oseltamivir 75mg twice daily or inhaled zanamivir 10mg twice daily. However, care must be taken to reduce to a once daily dosing of oseltamivir in patients with renal impairment. Before the initiation of antiviral treatment, consideration of their side effects, particularly nausea, vomiting associated with the use of oseltamivir, whereas bronchospasm in individuals using zanamivir, ought to be taken into account of.

Previously, adamantanes such as amantadine and rimantadine were used for the treatment of influenza. However, due to recent reports of increasing resistance of the virus to these drugs, their usefulness has become somewhat limited.[13]

Prevention

The prevention of influenza is primarily divided into two general principles: Infection control and vaccination.

The adoption of vigilant hand hygiene, especially after handling of respiratory secretions and the covering of the nose and mouth while coughing and sneezing help to decrease the spread of the virus, as does the appropriate use of surgical masks in individuals who display symptoms of upper respiratory tract infection.[14]

Antiviral prophylaxis with oral oseltamivir 75mg daily or 2 puffs of inhaled zanamivir daily to patients and contacts where there is a clustering of influenza cases is effective in preventing the development of a florid outbreak.[15]

In the United States, there are two vaccines available for the prevention of influenza: The injected trivalent inactivated vaccine (TIV), and the live attenuated influenza vaccine (LAIV), which is an intra-nasal spray. Both vaccines contain three strains of influenza: 1) influenza A subtype H3N2, 2) influenza A subtype H1N1 and 3) an influenza B virus.

The influenza vaccine is effective in preventing the development of influenza, its complications, hospitalisations and even death. However, it is not 100% effective in preventing a person from developing influenza altogether. Hence, a vaccinated person may well develop influenza of an ever slightly different strain to that with which he/she was vaccinated.

In Hong Kong, yearly influenza vaccination campaigns consisting of vaccines targeting the latest influenza strains have been offered to the community as recommended by the World Health Organization. For the 2008-2009 year, the Scientific Committee on Vaccine Preventable Diseases recommends the following target groups for influenza vaccination in Hong Kong[16]:

- Elderly persons living in residential care homes
- Long-stay residents of institutions for the disabled
- Elderly persons aged 65 years or above
- Persons with chronic illnesses*
- Children aged between 6 months and 6 years
- All pregnant women
- Health care workers
- Poultry workers

Saying thus, vaccination is offered to anyone who wishes to receive it, so long as he/she is not contraindicated to taking it.

Individuals with known allergies to egg, previous influenza vaccines, specific vaccine components such as neomycin and polymyxin should not receive the vaccine, as should patients who are pyrexic on the day of vaccination be advised to defer the vaccination until they completely recover.

The vaccine is generally well-tolerated. However, soreness over the injection site, fever, myalgia and arthralgia are not uncommon.

Rarely, the vaccine has been reported to cause serious adverse events such as Guillain-Barre syndrome (1 to 2 cases per million vaccinated), meningitis or encephalopathy (1 in 3 million vacinnated) and anaphylaxis (9 in 10 million vaccinated).

Despite these reported adverse effects, the annual influenza vaccination remains the most effective strategy for reducing the effect of the illness.[17] Both locally and internationally highly publicised government endorsements to both the mass public and to the high risk groups such as health care personnel are currently under progress in the hope to ensure that the transmission and thus the destructive impact of the virus is maximally reduced during the upcoming seasonal influenza epidemic.

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Current Management of Pulmonary Tuberculosis

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Introduction

Tuberculosis (TB) has been a fatal infectious disease of humans for centuries, though potentially treatable in recent decades. Worldwide, the TB-infected population is huge. It was estimated that one third of the world's population were infected with Mycobacterium tuberculosis (MTB). Every year, the disease develops in over 8 million and claims the lives of about 3 million people. The problem of TB is further complicated by an upsurge of cases with multidrug-resistant (MDR-)* and extensively drug-resistant (XDR-)# bacilli in recent years. TB affects the respiratory system mainly with pulmonary tuberculosis (PTB), either on its own or together with TB of other sites, accounting for more than 85% of all TB cases notified in Hong Kong.

(* MDR: meaning resistant to the two most powerful anti-TB drugs, isoniazid and rifampicin, at least;
XDR: meaning MDR plus resistant to any fluoroquinolone and at least one of the three injectable second-line drugs, amikacin, kanamycin or capreomycin.)

Many factors contribute to the continuous prevalence of this infectious disease. They include:

1. the existence of a stage of latent TB infection that occurs in many asymptomatic subjects in high prevalence countries,
2. the breaking down of latent infection into progressive disease when immunity of host wanes,
3. the late presentation of many infectious, open PTB patients,
4. the long duration of treatment that is required for PTB,
5. the lack of good TB control programmes in many countries,
6. the increasing prevalence of other immunocompromising conditions like HIV infection, use of immunosuppressive drugs or even an ageing population itself and
7. the trend of globalisation and increased population movement between states and continents.

Successful control of TB relies on the existence of good TB control programme and initiative in all parts of the world especially the underprivileged and developing areas. Affordable and reasonably accurate laboratory testing, early detection and treatment of smear positive cases, effective and continuously available chemotherapy, experienced and dedicated healthcare team together with surveillance and monitoring mechanisms are mandatory to such programmes. The ultimate outcome of our battle against TB will depend on the concerted effort of all countries in running and maintaining a good TB control programme of their own. World Health Organization (WHO) and International Union Against Tuberculosis and Lung Diseases (IUATLD) are committed to this work of fighting TB through collaboration of countries with different socio-economic, cultural and religious background.

In the frontline, we, clinicians, should familiarise ourselves with updates in the diagnosis and treatment of the disease in order to assist in the "fighting TB" battle.

Diagnosis of PTB

Microbiology

Sputum microscopy and conventional solid medium culture are still the cornerstones in the diagnosis of PTB nowadays. They are cheap and widely available. Sputum direct smearing for acid fast bacilli, using the Ziehl-Neelsen or auramine staining, has the disadvantage of a low yield (positive in about 30% of all active PTB cases) but detects cases of open PTB to allow early treatment and reduces infectivity. Sputum culture for MTB on conventional solid medium (Lowenstein Jensen medium) can diagnose 50-60% of all active PTB cases. Its limitation is a long turn-around-time (TAT) of 3-8 weeks and an additional 4-6 weeks for drug susceptibility result. Rapid culture systems (in liquid media) by detecting CO2 production or O2 consumption (the BACTEC and MGIT systems) are more sensitive and has a slightly shorter TAT of about 2 weeks compared with conventional solid medium culture. The technology and cost needed to operate these broth-based culture systems, however, limit their availability in poor countries.

Nucleic Acid Amplification (NAA) methods for detection of segments of MTB-DNA or RNA, such as Polymerase chain reaction (PCR-MTB), were widely investigated and used for the diagnosis of TB in recent years. These tests have higher sensitivity than sputum smear and approach the sensitivity of culture. They are rapid (TAT: 1-2 day) but costly. Refinements to NAA tests allow detection of drug resistance by finding resistant mutations, like rpo-B gene, readily. With its inherent high specificity, NAA test is particularly helpful in diagnosing paucibacillary extrapulmonary TB, like TB meningitis, peritonitis and pericarditis By the same token, it also helps differentiating MTB from other atypical mycobacteria with the various commercially available DNA probes that are specific for the common species of Mycobacterium.

Another method investigated recently for rapid diagnosis and drug susceptibility testing of TB is called the microscopic observation drug susceptibility (MODS) assay. The technique is a relatively simple approach which uses little new technology. A sample is decontaminated and aliquotted into wells containing 7H9 broth with or without anti-TB drugs on a 96-well plate. The plate is examined under inverted microscope daily after inoculation for the characteristic cording appearance of growing MTB. A preliminary study showed encouraging results with MODS giving a sensitivity of 97.8% as compared with 89% for broth-based culture and 84% for culture on solid medium. The medium time to culture positivity was 7, 22 and 26 days for the three techniques respectively.

Radiology

Many patients with active PTB are still diagnosed on radiological grounds as a result of initial negative bacteriology. Patients with "typical TB changes" on chest radiographs (such as upper lobe predominant, patchy consolidations, fibrocavitory lesions, miliary lesions, granuloma or granulomata with calcification) and clinical picture highly suspicious of PTB (fever, night sweating, cough, haemoptysis, perhaps together with a strongly positive tuberculin skin test for patients in or coming from an area with high TB prevalence) are often diagnosed as suffering from active PTB and treated as such. They should be carefully monitored for response to treatment and side effects of drugs and subsequently revealed with culture results.

Computed Tomography (CT thorax) is occasionally useful in detecting subtle lesions not discernable on plain x-ray. It also can depict small airway disease pattern (tree-in-bud appearance), endobronchial or mediastinal involvement by TB. It is important to recognise that the proportion of PTB patients with underlying immunodeficiency state is increasing with time. The radiological presentations of such patients can be fairly atypical (like inconspicuous lesions or mottlings in patients with HIV co-infection or lymphopenia, lower lobe consolidations or tumour-like masses in diabetics). Under such circumstances, invasive investigations such as fibreoptic bronchoscopy, needle lung biopsy or even video-assisted thoracoscopic surgical (VATS) biopsy may be required to make a diagnosis of PTB.

Treatment of PTB

Directly observed therapy, short-course (DOTS) is the key to success for anti-tuberculosis chemotherapy nowadays. It involves the use of a multi-drug regimen with isoniazid (H), rifampicin (R) and pyrazinamide (Z) as essential drugs and a fourth drug, streptomycin (S) or ethambutol (E), was usually added in countries with high prevalence of drug resistance. These four drugs are administered together for 2 months (the intensive phase), followed by a continuation phase of 2 drugs, HR for 4 months (2HRZS or 2HRZE/ 4HR), in a fully supervised fashion. Medications should never be divided and taken at different times of the treatment day. Treatment success with DOTS was found to occur in over 95% of patients suffering from drug susceptible PTB. Alternative but less potent regimens for treatment of PTB include 2HRZE/ 6HE, 2HRZS/ 6S2H2Z2 and 2HRE/ 7HR. These alternative regimens should be considered as inferior to the standard regimen and are only employed in case of intolerance to pyrazinamide or because of financial problem from the high cost of rifampicin. Immunocompromised patients, those with coexisting silicosis or suffering from miliary, extrapulmonary or extensive pulmonary TB should receive prolonged therapy. They are preferably managed by pulmonologists with experience in treating TB.

Adverse effects of anti-TB drugs are many. Most of them are mild such as gastrointestinal and cutaneous reactions and may not require treatment cessation or modification. The most important adverse effect of anti-TB treatment is hepatotoxicity as all three key anti-TB drugs (H, R and Z) are potentially hepatotoxic. This may be further aggravated by underlying hepatitis-B virus infection, alcoholic liver disease, etc. It is recommended that liver function test should be checked at pre-treatment and be repeated any time after treatment when hepatotoxicity is suspected. Management of drug-induced hepatotoxicity could be complicated and specialists' (pulmonologist's and hepatologist's) consultations are recommended.

Some common or important-to-remember side effects of anti-TB drugs are: pyridoxine deficiency, peripheral neuropathy and lupus-like reaction for H, thrombocytopenia, "flu syndrome" and interstitial nephritis for R, pigmentation, hyperuricaemia, arthritis or arthralgia for Z, retrobulbar neuritis for E and nephrotoxicity and ototoxicity for S. Baseline testings for visual acuity and red-green colour discrimination are recommended for patients receiving ethambutol. Baseline platelet count and renal function/hearing function tests are preferred for patients receiving rifampicin and streptomycin respectively. Blood level of uric acid should be assayed for patients with a history of gout or chronic renal failure for whom pyrazinamide is to be prescribed. All tests should be repeated as indicated after commencement of therapy.

Drug interaction should also be watched out carefully as patients with PTB require a prolonged period of therapy with multiple anti-tuberculosis drugs that might interact with other co-administered agents. Common examples of drug interaction include warfarin, corticosteroids, oral contraceptives, anti-diabetic and anti-retroviral drugs with rifampicin and anti-convulsants with isoniazid and rifampicin.

Adjunctive corticosteroid or surgery is occasionally employed in the management of PTB patients. Systemic steroid can ablate severe inflammatory reaction, sometimes associated with immune reconstitution, occurring in some patients after the commencement of anti-TB treatment. The condition is commonly encountered in patients with TB lymphadenitis, TB pleuritis and in HIV-infected subjects after anti-retroviral therapy. Systemic steroid is also recommended for patients suffering from TB meningitis, tuberculoma of central nervous system or TB pericarditis.

Surgery is mainly a diagnostic tool for difficult or atypical cases of PTB. It may infrequently be required for treatment in PTB patients with severe and uncontrollable haemoptysis and in selected cases of

endobronchial, pleural, pericardial, lymph nodal or other extrapulmonary forms of TB.

MDR- and XDR-TB usually stemmed from inadequate or ineffective previous treatment thus reiterating the importance of DOTS and good TB control programme in a community. Although MDR-and XDR-TB together only account for about 1% of all TB cases in Hong Kong, the corresponding figures of our neighbouring countries or regions are relatively high. We should therefore be vigilant and watch out carefully for drug resistant TB in our daily clinical practice especially in high risk cases. Treatment for MDR- and XDR-TB is very challenging both for the patients and their physicians. It involves the use of less potent but more toxic second-line agents together with those first-line drugs that are still efficacious according to drug sensitivity result of individual patients. The reserve (second-line) drugs include the anti-TB fluoroquinlone: ofloxacin, levofloxacin or moxifloxacin, the injectable second-line drugs: amikacin, kanamycin or capreomycin, ethionamide or prothionamide, Para-amino Salicylic Acid (PAS) and cycloserine. By combining 5 to 6 of these drugs, given for an extended duration of 12-24 months, with meticulous monitoring of response to treatment and adverse effects of drug and with the help of surgeons in a few suitable cases, favourable outcome could be seen in about 70-80% of cases. Failure cases often progress to become reservoirs of transmission and pose great hazard to public health. Newer agents for treatment of drug resistant TB are slow in their development and their pre-market clinical evaluation pathway is also very long. In Hong Kong, MDR- and XDR-TB patients should always be referred to the Tuberculosis & Chest Service of the Department of Health for evaluation, management and follow up. Designated centres for management of drug resistant TB patients were also set up in certain hospitals under the Hospital Authority.

Conclusion

The impact of emerging infections like SARS and avian Influenza has received much attention from the public, the policymakers and the administration. Resources diverted toward research and measures taken for preparing possible outbreaks of these fancy infections have been tremendous. TB, a continuous and genuine threat to lives of millions all over the world, on the other hand, had only received a disproportionately small share of healthcare dollar in most countries. Calls for proper focusing and distribution of resources have been voiced out repeatedly by professionals and international organisations. Globally, development of new anti-tuberculosis drugs for treatment and investigational tools for diagnosis of TB is of low priority and improvement of TB control programme in poor countries is still being neglected, up to this moment.

As a result, it will still be a long way to go before we can see the fading away of tuberculosis just as what we saw with leprosy, syphilis and smallpox. So, keep updating on TB management, whether we like it or not.

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2. **Echinocandins** such as caspofungin (Cancidas), micafungin (Mycamine) and anidulafungin (Eraxis).

Azoles

Like amphotericin, azoles target ergosterol in fungal cell membrane. Unfortunately there is cross-inhibition of some cytochrome dependent enzymes in humans by azoles, which contribute to drug toxicity & drug interaction potentials. Voriconazole is fungistatic against Candida, but fungicidal against Aspergillus. Posaconazole is the only azole active against zygomycetes.

The azoles have the advantage of oral administration. Intravenous formulation of voriconazole is made possible by the addition of a chemical called SBECD, which may accumulate in those with severe renal impairment and is potentially nephrotoxic. There is no intravenous preparation for posaconazole.

Oral absorption of voriconazole is reduced when taken with food. Voriconazole is metabolised in the liver and its dose should be reduced with hepatic impairment. Its pharmacokinetics is also affected by CYP2C19 enzyme genetic variability. Nineteen percent of Asians & 2% of Caucasians have poor CYP2C19 activity, resulting in high drug blood levels.

Voriconazole is usually well tolerated. Common adverse events include

1. Transient & reversible visual changes (photopsia). Patients should be advised to use with caution when driving a motor vehicle.
2. Hepatotoxicity which, on occasion, can be serious.
3. Prolonged treatment leads to photosensitivity.
4. Visual hallucinations are more common with intravenous formulation.

Oral absorption of posaconazole is increased with food, especially with fatty meals and is not affected by antacids. Oral absorption is even better with multiple dosing e.g. qid. Posaconazole is metabolised in the liver through glucuronidation & is excreted in the bile. However, it inhibits liver CYP3A4 system, resulting in high blood levels of those drugs using the same system. Posaconazole also inhibits gastric P-glycoprotein, leading to unopposed GI absorption of those drugs using this pathway.

The safety profile of posaconazole seems to be better than voriconazole. Common adverse reactions include headaches & gastrointestinal complaints.

Echinocandins

Unlike amphotericin & azoles, they act specifically on fungal cell walls by inhibition of D-glucan synthase which is absent in mammalian cells.
Echinocandins are fungicidal against Candida & fungistatic against Aspergillus. Micafungin & anidulafungin have lower MIC90 for Candida than caspofungin.

They are only available as intravenous preparations due to their large molecular structures and poor bioavailability.

Infusion related reactions due to histamine release may occur with all echinocandins.

No dosage adjustment for caspofungin and micafungin is necessary for renal insufficiency. For patients with moderate hepatic impairment, a lower dose of caspofungin is advisable; but no adjustment is needed for micafungin.

Co-administration of cyclosporine with caspofungin may increase risk of hepatotoxicity (much less with micafungin and anidulafungin).

Enzyme inducers (e.g. phenytoin, rifampicin) may increase clearance of caspofungin; dose of caspofungin should then be increased.

Mycafungin may raise sirolimus or nifedipine level.

Anidulafungin seems to have the least adverse effects among echinocandins.

Indications (Table 1)

Oesophageal Candidiasis

Fluconazole (Diflucan) remains the first choice. New

azoles are indicated for fluconazole-resistant Candida. New echinocandins, though effective, are less preferred due to lack of oral formulation.

Candidemia

Fluconazole is indicated if there is no neutropenia and there is no prior exposure to azole. Otherwise new echinocandins are preferred.

New antifungals are also indicated for non-albicans Candida which are usually resistant to fluconazole, with the exception of posaconazole as it may take up to 1 week to achieve a steady drug level.

Prophylaxis Against Invasive Fungal Infection

In USA, posaconazole is approved for prophylaxis against fungal infections in severely immunocompromised patients such as haematopoietic stem cell transplant patients (HSCT) with graft versus host disease (GVHD) and neutropenic patients with haemic malignancy. It was demonstrated to be better than fluconazole. However, the probability of breakthrough infections with posaconazole increased with low posaconazole blood levels. Therefore, monitoring posaconazole plasma concentrations is warranted in high-risk populations.

Empirical Treatment of Invasive Fungal Infection in Patients with Febrile Neutropenia

Intravenous voriconazole, caspofungin or micafungin is preferred.

Salvage therapy with posaconazole may be considered for those refractory diseases.

Treatment of Known Invasive Aspergillus Infection

Voriconazole has replaced amphotericin as the treatment of choice for invasive aspergillosis because of better tolerability & outcome. If Aspergillus is resistant to voriconazole, it is not certain whether change into another class of drugs (e.g. amphotericin or caspofungin) or combination therapy will work.

Conclusion

These new antifungals are promising. However they should be administered with prudence in view of their high cost and potential for emergency of resistant strains if abused.

Table: Use of antifungal agents in invasive fungal infections.

Infection	AmBisome	Diflucan	Vfend	Noxafil	Cancidas	Mycamine	Eraxis
Candidemia	+++	+++	+++	?	+++	+++	+++
Oesophageal candidiasis	+	+++	+++	+++	++	+++	++
Cryptococcal meningitis	+++	+++	?	?	---	---	---
Empiric therapy for febrile neutropenia	+++	+	++	+++	+++	?	?
Porphylaxis of invasive infections in high-risk patients	?	+	++	+++	?	+++	?
Aspergillus pneumonia	+++	?	+++	+	++	?	+
Zygomycosis	++	---	---	+	---	---	---

+++ = highly recommended ? = inadequate data ---- = strongly discouraged

Useful References

1. Treatment of Aspergillosis. Clinical practice guidelines of the Infectious Diseases Society of America. Clinical Infectious Diseases 2008; 46: 327-60.
2 Mohr J, Johnson M, Cooper T, Lewis JS, Ostrosky-Zeich L. Current options in antifungal pharmacotherapy. Pharmacotherapy 2008; 28(5): 614-645.

越南攝影之旅

黃健明醫生

MBBS (HK), DFM (CUHK), DOM (CUHK), DDME(CUHK)

黃健明醫生

越南是香港人冷門旅遊國家，一般旅行社舉辦之行程，主要到胡志明市及附近城鎮、湄公河、越戰地道等觀光。

近日流行的攝影旅行團，有別於觀光團，所到之處，多為窮鄉僻壤，住不好，食不好，旅途艱苦。但攝影發燒友只求拍得與別不同之照片，其他在所不計。

今次筆者參加之越南攝影旅行團，所到之城鎮，如平順市、藩切、勒山、大勒市高原山城、网罟鄉、寶木皇宮等，相信香港人甚少聽過或到過。城鎮市容面貌，還停留於五、六十年代，置身其中，感覺時光倒流。最特別之景點為鹽田、沙丘、海邊、漁港和街市，也是攝影發燒友必到之地。

鹽田

越南海岸線很長，利用海水造鹽是一門生意。大型鹽場收成時，有上千工人開工。一望無際的鹽田盛滿海水，空氣中充滿鹹味，一堆堆收集好的鹽，排列整齊，大群挑夫不停地將一籮籮雪白的鹽堆成小山。所有工序全部人手操作。

作者:黃健明醫生
私人執業醫生，沙龍畫意攝影愛好者。2007年黑白、彩色照片及幻燈片組三組同獲世界十傑名銜。

沙丘

未到過的越南，你絕不會相信有這麼多沙丘。有紅色、白色、金色。陽光下，越南少女、小童、光影全都是沙龍照片得獎的元素。沒有駱駝，但有山羊。走在軟綿綿的沙上，除了受太陽暴曬之苦外，也相當有趣。

小圓舟

小圓舟為越南獨有的海上交通工具，機動性很強，轉彎靈活。可載貨、捕魚，為漁船必備之工具。泊在岸邊的小圓舟，也構成很有趣的圖案。

Melamine Tainted Milk Product-related Renal Disorder - What Do We Know So Far?

Dr. Wai-ming Lai

Dr. Wai-ming Lai

MBBS, FHKAM(Paed), FHKCPaed, FRCP Edin

Deputy Consultant, Department of Paediatrics & Adolescent Medicine, Princess Margaret Hospital
President, Hong Kong Paediatric Nephrology Society

As the melamine milk tainted products (MTMP) crisis in Hong Kong has started to cool down, it is high time to review the experience gained on MTMP in the recent 1 1/2 months. Around 3 weeks after the Hospital Authority set up the screening and treatment programme for children with history of consuming MTMP, a melamine tainted milk product symposium was held on 18 October 2008 in the Princess Margaret Hospital (PMH). It was jointly organised by the Department of Paediatrics & Adolescent Medicine of PMH, the Hong Kong Paediatric Society and the Hong Kong Paediatric Nephrology Society.

The opening remarks were given by Professor Gabriel Leung (Under Secretary for Food & Health) and Dr. Lily Chiu (Cluster Chief Executive, Kowloon West Cluster, Hospital Authority).

While there are no previous human data on the toxicity of melamine, extrapolation from animal studies may be used to project the adverse effects on humans. Dr. SN Wong (*Consultant Paediatrician, TMH*) discussed on the outbreak of renal failure associated with ingestion of pet food containing melamine and cyanuric acid in cats and dogs in 2004 and 2007. Melamine alone is of low toxicity but studies have shown that combination of it with cyanuric acid leads to crystal formation and subsequent kidney toxicity. Renal histology in animals showed melamine-cyanuric acid crystals in distal tubules with tubulitis, necrosis and tubulointerstitial nephritis.

Human cases of toxicity of melamine were first reported on September 11, 2008 that infants and young children with kidneys stones and renal failure were admitted to hospitals in the China Mainland after consumption of infant formula contaminated with melamine. Dr. MC Chiu (*Chief of Service, Dept of Paediatrics & Adolescent Medicine, PMH*) presented on the outbreak in humans. By October 15, more than 54,000 cases had sought treatment for kidney stones with 14,000 infants hospitalised and 4 deaths reported. The visits to Hebei and Beijing by Hong Kong delegates were also presented. The vast majority of cases involved children below 3 years of age and were linked to the consumption of Sanlu powdered infant formula. From the experience of the Mainland, the stones were loose and sand-like which could be passed out spontaneously with hydration and alkalinsation of urine. Surgical intervention including cystoscopic retrograde catheterisation into ureters, percutaneous kidney drainage, and lithotripsy (second line treatment) were required in some children.

The situation in Hong Kong was discussed by Dr. KC Tse and Dr. WM Lai (*Department of Paediatrics & Adolescent Medicine,PMH*). Dr. Tse discussed on the screening programme for MTMP in Hong Kong. 18 Designated Clinics (DC) and 9 Special Assessment Centres (SAC) have been set up for the assessment of those eligible children under the age of 12 who have history of consumption of MTMP. At the DCs, children with consumption of MTMP from the Mainland or those listed in the Centre for Food Safety and/or with symptoms of kidney stone, renal disease and renal failure are referred to SACs for further assessment. Urinalysis and ultrasound (USG) of the kidneys are performed in the SAC and those with USG showing kidney stones of ≥ 4 mm are referred to the Designated Treatment Centre in the Paediatric Nephrology Centre in Princess Margaret Hospital for further evaluation and treatment. As of 17 October, 40,772 had attended the DCs and 12,022 had been assessed in the SACs. The incidence of kidney stones is very low with only 5 cases detected (0.04%). At the PMH SAC screening clinic, haematuria, proteinuria and abnormal USG were detected at 0.73%, 0.45%, and 2.9% respectively.

The cases of MTMP-related kidney stones in Hong Kong were presented by Dr. WM Lai. The MTMP-related kidney stones are radiolucent and are not shown in KUB. USG of the kidney remains the mainstay of investigation tool while non-contrast CT and MAG3 scan are required in those children to whom surgical intervention is contemplated. 10 cases of suspected MTMP-related kidney stones have been reported to the Centre for Health Protection (5 cases were detected in SAC). 6 cases were asymptomaic while 4 cases presented with either dysuria/ haematuria /or passing stone. The kidney stones were small and ranged from 4 to 7 mm. All cases were managed with conservative medical management including hydration therapy except one case which required lithotripsy in a private hospital. The patients were not treated with alkalinsation of urine as its effectiveness requires further evaluation. In Hong Kong, around 5-6 children are diagnosed to have kidney stones in the HA hospitals every year. It is difficult to be certain that the kidney stones in the 10 cases are due to MTMP and further evaluation is required.

Investigation with USG only detects kidney stones and cannot exclude other kidney adverse effects of melamine such as tubular crystals and tubulointerstitial nephritis which have been reported in animal studies. Dr. WL Mak (Consultant Chemical

Pathologist, Toxicology Reference Laboratory, PMH) successfully developed an urine test for melamine and he discussed the possible clinical application for MTMP-related kidney disorders. Further studies would be required.

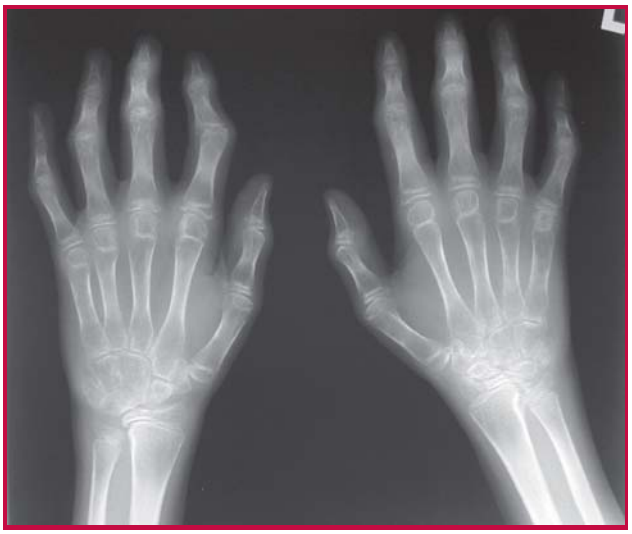
Dr. YY Ho (*Consultant, Centre for Food Safety (CFS)*) discussed on the surveillance, sampling and testing of milk and dairy products for melamine by the CFS. He also discussed on the amended Harmful Substances in Food Regulation standards for melamine which define a tolerable daily intake of 1mg/kg (1 ppm) for milk, any food intended to be consumed principally by children under the age of 36 months and those by pregnant or lactating women; and 2.5 mg/kg (2.5 ppm) for other food.

At the end of the symposium, there were fruitful discussion and conclusions by the expert discussants (Prof. Chan Yan Keung, Dr. Chow Chun Bong, Dr. Paul SF Lee, Dr. Leung Ting-Hung, Prof. Paul KH Tam, and Dr. Peggy SK Chiu) together with the speakers. The problem of MTMP-related renal disorder is much less severe than cases in the Mainland. All the suspected cases in Hong Kong suffered from small kidney stones ranging from 4 mm to 7 mm. This is probably related to the much lower level of melamine in our milk products (e.g. Yili melamine level of 9.9mg/kg in HK compared with Sanlu powdered infant formula melamine level of up to 2500 mg/kg in the Mainland). There are difficulties in confirming that the kidney stones are related to MTMP as there is no confirmatory test so far. Other causes of kidney stones have to be ruled out. The role of alkalinisation of urine still requires further evaluation and the constituents of the stones need to be well studied. In the Mainland, alkali therapy has been tried because uric acid has been found but if the stones contain melamine cyanuric complex then they will dissolve better in acid pH instead. It is not yet known what long-term complications such as tubulointerstitial nephritis melamine may cause. It definitely requires long term follow-up for those high risk cases.

Radiology Quiz

Dr. Wendy WM Lam

Consultant, Department of Radiology, Queen Mary Hospital



Clinical History:

Male/13

C/O joint pain
This is his XR hands.

Questions:

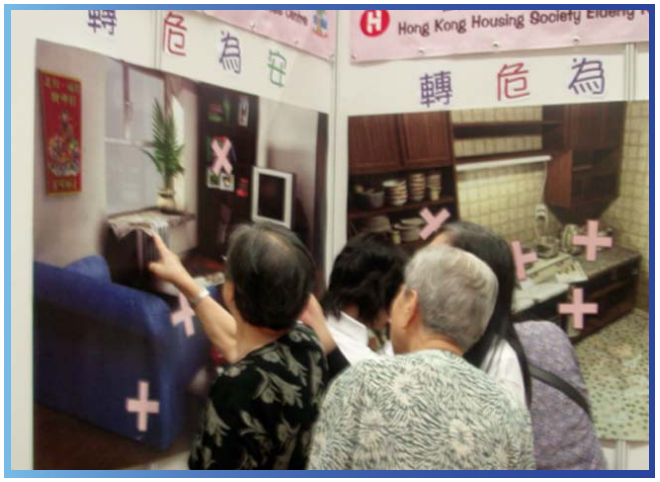
1. What are the radiological findings?
2. What is your diagnosis or DDX?

(See P.37 for answers)

Central & Western District Health Festival 2008/2009

HKFMS Foundation Limited has been actively involved in the Central & Western District Health Festival in the past years, and we continue to support this year. The festival was held at Sheung Wan Sports Centre on 1st and 2nd November with over 1,000 participants.

The Foundation organised two booths with the theme 'Health & Safety Promotion'. It has been a great success, largely contributed by our co-organising parties, including PolyVision, Hong Kong Housing Society, Hong Kong Occupational Therapy Association and Center for Health & Medical Research.



Special thanks should also go to Dr. BW Que, Mr. Ernest Yu and Ms. Judy Lee for delivering health talks that were highly welcomed by the general public in health promotion. Last but not least, we would like to express our heartiest thanks to our sponsors SureCare Medical and Health Network, Mekim Limited and The International Medical Co Ltd for their support, both financially and in gifts donation. The Organising Committee look forward to continue our contribution from Foundation towards public health and education in future health festivals.

(Organising Committee: Dr. Raymond Lo, Chairman; Mr. Nelson Lam, Mr. Samuel Chan, Ms. Tina Yap, Mr. Peter To and Mr. Stanley Lee).

Federation President Cup Soccer Five Tournament 2008

With the honorable presence of Mr. Lee Ming Kwai, Dr. Godfrey CF Chan (Assistant Dean, Li Ka Shing Faculty of Medicine of the University of Hong Kong), Prof. Wing Yun Kwok (Assistant Dean, Faculty of Medicine of the Chinese University of Hong Kong) and our President Dr. Dawson Fong, we kicked off the Federation President Cup Soccer Five Tournament at the opening ceremony held at Ying Wa College on 19 October 2008. You may share the highlights of the opening ceremony in these photos.

(From left to right)
Mr. Carmond Chan, Mr. Stephen Leung (Country Manager of Pfizer Corporation Hong Kong Ltd), Mr. Samuel Chan (Chairperson of Hong Kong Occupational Therapy Association), Dr. Sigmund Leung (President of Hong Kong Dental Association), Dr. Dawson Fong (President of FMSHK), Mr. Lee Ming Kwai, Dr. Chan Hau Ngai (Executive Committee Member of Hong Kong Medical Association), Dr. Godfrey Chan (Assistant Dean, Li Ka Shing Faculty of Medicine of the University of Hong Kong), Prof. Wing Yun Kwok (Assistant Dean, Faculty of Medicine of the Chinese University of Hong Kong)

Match Result for 26 Oct 08

Final Round Robin

SECTION A

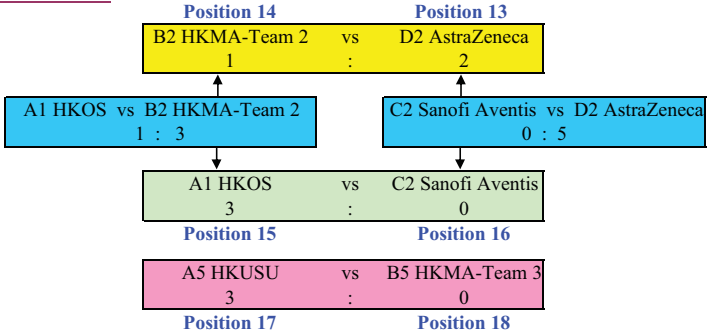
	A3 (HKOTA)	B3 (HKUSU-Team 2)	C3 (Janssen)	D1 (Pfizer-Team 2)	Points	Goal Scored	Goal Lost	Goal Diff.	Position
A3 (HKOTA)		3 vs 0	1 vs 2	4 vs 0	6	8	2	6	2
B3 (HKUSU-Team 2)	0 vs 3		1 vs 3	3 vs 0	3	4	6	-2	3
C3 (Janssen)	2 vs 1	3 vs 1		3 vs 0	9	8	2	6	1
D1 (Pfizer-Team 2)	0 vs 4	0 vs 3	0 vs 3		0	0	10	-10	4

SECTION B

	A2 (HKMA-Team1)	B1 (HKDA)	C1 (Pfizer-Team 1)	D4 (IDS)	Points	Goal Scored	Goal Lost	Goal Diff.	Position
A2 (HKMA-Team1)		1 vs 1	1 vs 2	2 vs 3	1	4	6	-2	4
B1 (HKDA)	1 vs 1		3 vs 1	1 vs 2	4	5	4	1	3
C1 (Pfizer-Team 1)	2 vs 1	1 vs 3		3 vs 0	6	6	4	2	1
D4 (IDS)	3 vs 2	2 vs 1	0 vs 3		6	5	6	-1	2

Match Result for 26 Oct 08

Knock-out Round



The competitions have been very exiting. We have 18 teams coming from medical societies, dental society, medical and dental students, and pharmaceutical companies. After rounds of keen competition held for three Sundays, the semi-final results are as tabled.

The top 12 teams will come together again on 30 November 2008 to compete for the President Cup.

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
	★ A Bladder Mass and a Retroperitoncal Mass **1**	★ HKMA TSWN/YL Community Network - Certificate Course in Vascular Diseases ★ Reducing the Burden of HPV-related Diseases with Vaccination ★ FMSHK Officers' Meeting **2**	**3**	★ HKMA Hong Kong East Community Network - Certificate Course in Common Psychiatric Problems in Our Community ★ HKMA Council Meeting **4**	★ HKMA Shatin Community Network - Certificate Course on Cardiovascular System **5**	**6**
★ HKMA Structured CME Programme at Queen Elizabeth Hospital Year 08/09 (IX) - A&E and Anaesthesia ★ HKMA Tennis Tournament **7**	**8**	**9**	★ Hong Kong Neurosurgical Society Monthly Academic Meeting - Salvage of Cranial Nerve Palsy **10**	★ HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2008 (XII) **11**	★ HKMA Shatin Community Network - Certificate Course on Cardiovascular System **12**	★ Refresher Course for Health Care Providers 2008/2009 - Approach to Patients with Visual Loss **13**
★ TSW/ YL Community Network Community: Health Awareness Program- Heart Disease and Stroke Prevention Day ★ Joint Professional Table-Tennis Tournament **14**	**15**	★ FMSHK Executive Committee Meeting **16**	**17**	**18**	★ New Insight from a 4-year COPD Landmark Trial - UPLIFT **19**	**20**
21	**22**	**23**	**24**	**25**	**26**	**27**
28	**29**	**30**	★ The Federation Annual Dinner 2008 - Light & Beauty ★ HKMA 88th Anniversary Ball **31**			

Medical Diary of December

Date / Time	Function	Enquiry / Remarks
1 MON 7:30 pm - 8:30 pm	**A Bladder Mass and a Retroperitoncal Mass** Organised by: Hong Kong Urological Association Chairman: Dr. Berry FUNG Speaker: Dr. Thomas LAM # Seminar Room, G/F., Block A, Queen Elizabeth Hospital, Kowloon	Dr. HUNG Hing Hoi / Ms. Siddy MA Tel: 2958 6006 Fax: 2958 6076 1 CME Point
2 TUE 1:00 pm	**HKMA TSWN/YL Community Network - Certificate Course in Vascular Diseases** Organised by: HKMA Tin Shui Wai North Community Network, HKMA Yuen Long Community Network & Pok Oi Hospital Speaker: Dr. WONG Wing Kwong Raymond & Dr. KO Tin Choi Gary # Harbour Plaza Resort City	Ms. Jo WONG / Ms. Alice TANG Tel: 2527 8285 1.5 CME Points
8:00 pm - 9:30 pm	**Reducing the Burden of HPV-related Diseases with Vaccination** Organised by: The Hong Kong Society for Colposcopy and Cervical Pathology Chairman: Prof. Annie CHEUNG Speaker: Prof. Margaret STANLEY & Prof. Hextan NGAN # Shek O Room, Lower Level 1, Kowloon Shangri-la Hotel	Secretariat Tel: 2836 0728 Fax: 2834 0756 1.5 CME Points
8:00 pm - 10:00pm	**FMSHK Officers' Meeting** Organised by: The Federation of Medical Societies of Hong Kong # Gallop, 2/F., Hong Kong Jockey Club Club House, Shan Kwong Road, Happy Valley, Hong Kong	Ms. Paulina TANG Tel: 2527 8898 Fax: 2865 0345
4 THU 1:00 pm	**HKMA Hong Kong East Community Network - Certificate Course in Common Psychiatric Problems in Our Community** Organised by: HKMA Hong Kong East Community Network Speaker: Prof. LAM Chiu Wa Linda #HKMA Dr. LI Shu Pui Professional Education Centre, 2/F., Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	Ms. Jo WONG / Ms. Alice TANG Tel: 2527 8285 1 CME Point
8:00 pm	**HKMA Council Meeting** Organised by: The Hong Kong Medical Association Chairman: Dr. H.H. TSE # HKMA Head Office, 5/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Christine WONG Tel: 2527 8285
5 FRI 1:00 pm *(12)*	**HKMA Shatin Community Network - Certificate Course on Cardiovascular System** Organised by: HKMA Shatin Community Network Speaker: Dr. KUM Chi Chiu # 3/F, Royal Park Hotel, Shatin	Miss Viviane LAM Tel: 2527 8452 1 CME Point
7 SUN 2:00 pm	**HKMA Structured CME Programme at Queen Elizabeth Hospital Year 08/09 (IX) - A&E and Anaesthesia** Organised by: The Hong Kong Medical Association & Queen Elizabeth Hospital Speaker: Dr. CHAN Chun Man; Dr. LEE Yeuk Ying Samantha # Lecture Theatre, G/F, Block M, Queen Elizabeth Hospital, Kowloon	Miss Viviane LAM Tel: 2527 8452 (Registration Fee is required) 3 CME Points
7:30 pm	**HKMA Tennis Tournament** Organised by: The Hong Kong Medical Association Chairman: Dr. C.W. CHIN # Kowloon Tong Club	Ms. Dora HO Tel: 2527 8285
10 WED 7:30 am	**Hong Kong Neurosurgical Society Monthly Academic Meeting - Salvage of Cranial Nerve Palsy** Organised by: Hong Kong Neurosurgical Society Chairman: Dr. LUI Wai Man Speaker: Dr. LAW Hing Yuen # Seminar Room, G/F., Block A, Queen Elizabeth Hospital, Kowloon	Dr. Y.C. PO Tel: 2990 3788 Fax: 2990 3789 2 CME Points
11 THU 2:00 pm	**HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2008 (XII)** Organised by: The Hong Kong Medical Association & Hong Kong Sanatorium & Hospital Speaker: Dr. CHAN Chi Wai Angus # HKMA Dr. LI Shu Pui Professional Education Centre, 2/F., Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	Miss Viviane LAM Tel: 2527 8452 (Registration Fee is required) 1 CME Point
13 SAT 2:30 pm	**Refresher Course for Health Care Providers 2008/2009 - Approach to Patients with Visual Loss** Organised by: The Hong Kong Medical Association & Our Lady of Maryknoll Hospital Speaker: Dr. HO Kai Kit # Training Room II, 1/F., OPD Block, Our Lady of Maryknoll Hospital, 118 Shatin Pass Road, Wong Tai Sin, Kowloon, Hong Kong	Ms. Clara TSANG Tel: 2354 2440 2 CME Points
14 SUN 1:00 pm	**TSW/ YL Community Network Community: Health Awareness Program- Heart Disease and Stroke Prevention Day** Organised by: HKMA Tin Shui Wai North Community Network, HKMA Yuen Long Community Network & Pok Oi Hospital # Harbour Plaza Resort City	Ms. Jo WONG / Ms. Alice TANG Tel: 2527 8285
2:00 pm	**Joint Professional Table-Tennis Tournament** Organised by: The Hong Kong Medical Association Chairman: Dr. Hilton KOO # Cornwall Street Park & Table Tennis Centre	Ms. Dora HO Tel: 2527 8285
16 TUE 8:00 pm - 10:00 pm	**FMSHK Executive Committee Meeting** Organised by: The Federation of Medical Societies of Hong Kong # Council Chambers, 4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Paulina TANG Tel: 2527 8898 Fax: 2865 0345
19 FRI 1:00 pm	**New Insight from a 4-year COPD Landmark Trial - UPLIFT** Organised by: The Hong Kong Medical Association Speaker: Dr. LEUNG Chung Chuen Roland # The HKMA Dr. Li Shu Pui Professional Education Centre, 2/F., Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	Miss Viviane LAM Tel: 2527 8452 1 CME Point
31 WED 7:30 pm	**The Federation Annual Dinner 2008 - Light & Beauty** Organised by: The Federation of Medical Societies of Hong Kong Chairman: Dr. S.K. CHAN # Run Run Shaw Hall, The Hong Kong Academy of Medicine Jockey Club Building, 99 Wong Chuk Hang Road, Aberdeen, Hong Kong	Ms. Paulina TANG Tel: 2527 8898 Fax: 2865 0345
7:30 pm	**HKMA 88th Anniversary Ball** Organised by: The Hong Kong Medical Association # Conrad Hong Kong, Pacific Place, 88 Queensway, Hong Kong	Ms. Candy YUEN Tel: 2527 8285

Meetings

8-10/1/2009	**Asian Australasian Society of Stereotactic and Functional Neurosurgery (AASSFN)/ The Chinese Society of Stereotactic and Functional Neurosurgery (CSSFN)/ Brain 2009. The Chinese University of Hong Kong Conjoint Meeting** Organised by: Neurosurgery, Neurology, Neuropathology, The Chinese University of Hong Kong & Asian Australasian Society of Stereotactic and Functional Neurosurgery (AASSFN) & The Chinese Society of Stereotactic and Functional Neurosurgery (CSSFN) Chairman: Prof. Wai-sang POON Speakers: Overseas (Benabid, Lozano, Rezai, Peter Burger) and local # Postgraduate Education Centre, Prince of Wales Hospital, Hong Kong Enquiry: Secretariat Tel: (852) 2632 2951 Fax: (852) 2637 3074 Email: aassfn2009@surgery.cuhk.edu.hk Website: http://www.surgery.cuhk.edu.hk/aassfn2009
11/1/2009	**A One Day Course - "Synopsis: Oral, Inhalation and Intravenous Sedation in Dentistry"** Organised by: Hong Kong Society of Paediatric Dentistry Chairman: Prof. Stephen WEI Speaker: Dr. Thomas LENHART, DMD # Lim Por Yen Lecture Theatre, HKAM Jockey Club Building, 99 Wang Chuk Hang Road, Aberdeen, Hong Kong Enquiry: Ms. Zinnia PANG Tel: 2859 0251 Fax: 2559 3803
19-21/2/2009	**International Colorectal Disease Symposium 2009** Organised by: Hong Kong Society for Coloproctology & Minimal Access Surgery Training Centre, PYNEH Chairman: Mr. Michael K.W. LI & Dr. Cliff C.C. CHUNG Speaker: Local and Overseas # Hong Kong East Cluster Training Centre, PYNEH, 3 Lok Man Road, Chai Wan, Hong Kong Enquiry: Ms. Christina LO Tel: 2595 6416 Fax: 2515 3195
20-22/2/2009	**CardioRhythm 2009** Organised by: Hong Kong College of Cardiology & Chinese Society of Pacing and Electrophysiology Co-Chairman: Prof. LAU Chu Pak Enquiry: Secretariat Tel: 2899 2035 Fax: 2899 2045 Email: info@cardiorhythm.com Website: http://www.cardiorhythm.com

Answer to Radiology Quiz

Radiological Findings:

1. Generalized decreased in bone density, particularly at peri-articular region.
2. Narrowing of bilateral DIP & PIP joint spaces.
3. Deformity, subluxation and bony erosion at Rt 2nd PIP joint.
4. Ankylosis at Rt carpal bones.
5. Bony erosion also seen at bilateral distal radio-ulnar joints.
6. Loss of joint spaces is seen at bilateral carpal joints.
7. Deformity seen at Lt carpal bones.
8. Peri-articular soft tissue swelling seen.
9. All the metacarpal epiphyses are square and enlarged in size.

Diagnosis:

Juvenile rheumatoid arthritis

Discussion:

There are 3 main subgroups account for 70% of cases.

1. Systemic onset:
   Most common at 1-5 yrs. M=F. Joint involvement is late, but eventually a polyarthritis affects especillay knees, wrists, carpi, ankles and tarsi.
2. Polyarticular onset:
   Onset at any age. More common in females. The cervical spine is involved frequently and early.
3. Pauciarticular or monoarticular onset:
   Most commonly presents at 1-5 yrs. Four or less joints involved at the onset, including knees, ankles and hips are most common.

Radiological Changes:

1. Periarticular soft tissue swelling.
2. Osteopenia- juxta-articular, diffuse or band-like in the metaphyses, the latter particularly in the distal femur, proximal tibia, distal radius and distal tibia.
3. Acclerated bone growth with large epiphyses and early fusion of growth-plates.
4. Over- or undergrowth of diaphyses.
5. Periostitis- will eventually result in enlarged rectangular tubular bones.
6. Erosions and joint space narrowing are late manifestation.
7. Epiphyseal compression fractures.
8. Subluxation and dislocation
9. Bony ankylosis- especially in the carpus and tarsus

Dr. Wendy WM Lam
Consultant, Department of Radiology, Queen Mary Hospital

The Federation Annual Dinner 2008

31st December, 2008 (Wednesday)

Run Run Shaw Hall

The Hong Kong Academy of Medicine Jockey Club Building
99 Wong Chuk Hang Road, Aberdeen, Hong Kong

Light & Beauty

We have the Grand Sensation LEXUS Hybrid Car Show for the car lovers...

We have Leica Digital Cameras to give the camera lovers the hands-on experience, or you can bring in your own Leica camera to try on the various M lenses. What's more, bring in your Leica products to redeem a LEICA SOUVENIR!

We have a photo corner set up by Hasselblad for the photogenics...

every venture tells a story

Come and explore the stories of the Federation officers...

We have star performance from Suzan who will lead us to countdown, dance performance to lead you to the dance floor, lucky draw to start your lucky charm into 2009, ... for sure everyone will bring home a happy memory!

Don't forget to bring your camera to capture the memory of this photogenic New Year Eve.

Tickets are now available. Please contact the Secretariat on 2527 8898

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