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Professional Certificate in Clinic Operation

<table>
<thead>
<tr>
<th>Module Title</th>
<th>Module Hours</th>
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<tbody>
<tr>
<td>1. Clinic Dispensing Practice</td>
<td>50</td>
</tr>
<tr>
<td>2. Patient Care and Customer Services</td>
<td>25</td>
</tr>
<tr>
<td>3. Clinic Management and Informatics</td>
<td>25</td>
</tr>
<tr>
<td><strong>Total for the course</strong></td>
<td><strong>100</strong></td>
</tr>
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</table>

*6 hours will be exempted for participants who have successfully completed the course “Certificate in Introduction to Drug Dispensing in Office Clinic”*

Date: 14 March 2007 to 14 July 2007
Time: Wednesday 7:30 p.m. – 10:00 p.m., Saturday 2:30 p.m. – 5:30 p.m.
Venue: Hong Kong Institute of Vocational Education (Sha Tin campus)
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Speakers: Lecturers from Department of Applied Science, HKIVE(ST)
Course Fee: HK$3,988
Level of Award: Professional Certificate
Entry Requirement: Completion of F.5
Mode of Attendance: Part Time
Language: Cantonese (Supplemented with English)
Contact Person(s): Mr Yau Yiu Shu or Ms Joyce Chan
Telephone Number: 2256-7114 or 2256-7109
Email: joychan@vtc.edu.hk

Deadline of application: 14 February 2007
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Asthma Management in 2006: What’s New?

Dr. Christopher Lai
Private Respiratory Physician, Hong Kong
Editor

Prior to the era of inhaled corticosteroids (ICS), asthma patients in Hong Kong were commonly treated with a combination of oral bronchodilators, with the addition of systemic steroids at the times of exacerbations. Not surprisingly, recurrent hospital admissions were common and indeed, deaths from this disease were rising from the mid ’70s to the mid ’80s. With the implementation of local and international asthma management guidelines and the increasing use of ICS, asthma mortality rates in the territory have reduced significantly in the past 2 decades, from a peak of 1/100,000 to 0.2-0.3/100,000 in the past few years. However, similar to what is seen worldwide, asthma morbidity is still substantial in Hong Kong. Thus, a significant proportion of patients are having troublesome day-time and night-time symptoms, activity limitations, frequent use of unscheduled health care facilities including visits to clinic doctors, accident and emergency departments and hospitalisation. It is estimated that the direct health cost for asthma in Hong Kong amounted to ~$US1,000 per patient annually. These statistics serve as a painful reminder that current treatment strategies are far from adequate, and an urgent revamp in our thinking is necessary.

Paradigm shift

Past guidelines on asthma management have adopted a step-wise approach in treating patients according to their disease severity, with the goals of rendering them symptom-free, unrestricted in daily activities including sports and having normal lung function. These should be achieved with the minimal use of medications that have a high safety profile and without any unscheduled health care use. However, the treatment endpoints were not quantitatively defined and therefore no clear target (such as the HbA1c in diabetes mellitus or serum levels of cholesterol and triglycerides in reducing cardiovascular risks) is available to the clinicians. Thus most patients are left under-treated with preventive medications and therefore suffer unnecessarily from asthma. Using a combination of ICS and a long-acting β2 agonist (LABA), good asthma control (assessed by symptom frequency, rescue bronchodilator usage and lung function) could be achieved and attained in almost 70% of patients in the GOAL study. By aiming for a defined level of good control, even in patients who failed to do so, their level of control as well as quality of life were considerably better than at the entry of the study. In response to this, revised guidelines have been published in France and USA emphasising that treatment decisions should be based on achieving and maintaining asthma control and that control should be assessed by a combination of symptoms, degree of activity limitation, use of health care resources including rescue bronchodilators and systemic steroids, and if possible, lung function. Similar revisions are currently undertaken by GINA and a new set of guidelines is expected to be published in late 2006 or early 2007.
A simple and convenient way to assess asthma control has recently been developed and validated. The Asthma Control Test (ACT) comprises a 5-item questionnaire for self-completion by patients aged 12 years or above. These questions focus on the frequency of activity limitation due to asthma, daytime and nocturnal symptoms, use of rescue bronchodilator and self rating of control in the preceding 4 weeks. Researchers in the US have shown that this test correlates well with specialists’ rating of control, both in cross-sectional and longitudinal studies. A score of 19 is the cut-off point between well (>19) and not-well-controlled asthma (<19). A similar test has also been introduced for use in children <12 years. It consists of 4 questions for self-reporting by children and 3 questions for completion by their carers.

Safety of LABAs

Despite the overwhelming evidence supporting the clinical efficacy of combination therapy, concern has continued to be expressed on the safety of LABAs. The US Food and Drug Administration has issued a boxed warning on this class of medications that they could increase the risk of severe asthma-related adverse events including deaths since November 2005. This warning label was prompted by the findings of the Salmeterol Multi-center Asthma Research Trial (SMART) that salmeterol usage was associated with a >4-fold increased risk in the incidence of asthma-related deaths when compared with a matched-placebo over a 28-week unsupervised treatment period. However, this increased risk was only seen in those who were not taking ICS at entry to the study. Other studies, including some with a greater power in detecting the association of LABAs and asthma deaths, have failed to demonstrate a similar finding. It is likely that while unsupervised use of LABAs in patients who are not treated with ICS, especially when their disease is not well controlled, may potentially be detrimental and therefore should not be recommended, its combined use with ICS is safe and effective (reviewed in 13).

New drugs

Two new medications have been introduced in Hong Kong in the past year. Ciclesonide, a once-daily inhaled steroid, is concisely reviewed by Prof. Gary Wong in the Drug Review section of this current issue of the Medical Diary. As it is only converted into an active metabolite by the lungs, ciclesonide is much less likely to cause topical side effects, such as oral candidiasis or hoarseness, than the other currently available ICS. Omalizumab, a humanised monoclonal anti-IgE antibody, has been shown to exert its therapeutic effect on asthma by binding to free IgE and thereby inhibiting mast cell degranulation. Published data have demonstrated this agent, when given once every 2 to 4 weeks subcutaneously, is effective as an add-on therapy in patients with severe persistent allergic asthma whose symptoms persist despite combination treatment with high-dose ICS and LABAs (reviewed in 14). A trial of 16 to 24 weeks is recommended to assess its efficacy. With its anti-IgE properties, this drug may have the potential in treating associated allergic disorders such as rhinoconjunctivitis, urticaria, food and drug allergy. Its prohibitive high cost, however, limits its use to only a small proportion of patients with severe persistent asthma as an add-on treatment and not as a substitute for ICS.

References

11. FDA website - www.fda.gov/cder/drug/advisory/LABA.htm
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1. van der Veer W et al. Pulm Pharmacol Ther 2004; 17(2):89-95

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XOLAIR
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Antituberculosis Drugs and Hepatotoxicity

Dr. Wing-wai Yew
MBBS, FRCP(Edin)
Tuberculosis and Chest Unit, Grantham Hospital, Hong Kong, China

Dr. Chi-chiu Leung
MBBS, FHKAM(Medicine), FHKAM(Community Medicine)
Tuberculosis and Chest Service, Centre for Health Protection, Department of Health, Hong Kong, China

General Aspects

The three key anti-tuberculosis drugs, viz isoniazid, pyrazinamide and rifampicin, are potentially hepatotoxic.1 Deaths due to fulminant liver necrosis have been reported, albeit rare in occurrence. With the changing demographics and clinical characteristics of tuberculosis patients in many parts of the world, hepatotoxicity is of increasing concern in the treatment of this disease.

A meta-analysis has shown an incidence rate of liver toxicity of 2.6% with isoniazid and rifampicin co-administration, but only 1.1% with rifampicin alone, and 1.6% with isoniazid alone.2 Despite earlier controversies, more recent studies suggest an important hepatotoxic potential of pyrazinamide among various components of the short-course antituberculosis drug regimen. As the hepatotoxicity incurred by pyrazinamide is likely to be dose-related, several authorities now recommend the use of lower daily or thrice-weekly dosages of the drug.1,3 With its possibly lower potential for hepatotoxicity, the American Thoracic Society / Centers for Disease Control and Prevention / Infectious Disease Society of America (ATS/CDC/IDSA) currently recommend rifampicin to be restarted first, after recovery from antituberculosis chemotherapy-induced hepatitis.3

In contrast to the treatment of active disease, single drugs or simple 2-drug combinations are generally employed in the treatment of latent tuberculosis infection (LTBI). However, hepatotoxicity remains an important concern, especially for the use of 2 months of rifampicin plus pyrazinamide in the treatment of LTBI among individuals not infected with HIV.4 For unknown reasons, the reported hepatotoxicity rates were often higher than those reported in the historical short-course treatment trials involving the concomitant use of isoniazid, rifampicin and pyrazinamide. Such rates of major side-effects are unacceptable for a prophylactic therapy. The revised ATS/CDC recommendations now state that rifampicin plus pyrazinamide should generally not be offered to persons with LTBI.3

Mechanisms and Immunogenetics

The pathogenesis of drug-induced hepatotoxicity is still not entirely clear for most offending agents. While dose-related toxicity may exist, a direct correlation between serum drug levels and hepatotoxicity has not been well reported. Thus, the clinical relevance of therapeutic monitoring of serum rifampicin and isoniazid concentrations in managing antituberculosis drug-associated toxicity is still being explored. Hypersensitivity to antituberculosis drugs may be a possibility in some cases of drug-induced hepatitis, especially when patients present with concomitant skin rash, fever, arthralgia and eosinophilia. An altered profile of anti-oxidants with increased lipid peroxidation may suggest that isoniazid- and rifampicin-induced hepatotoxicity are mediated through oxidation damage. One possible mechanism for the additive or synergistic hepatotoxicity of isoniazid and rifampicin is through liver enzyme induction in the hydrolase system enhancing the toxicity of some of the isoniazid metabolites. Antituberculosis drug-induced hepatitis has also been found to be associated with acetylator phenotypes and other genetic polymorphisms, including cytochrome P450 2E1 and glutathione S-transferase M1, and certain Major Histocompatibility Complex Class II associated HLA-DQ alleles.

Risk Factors

Clinical risk factors for drug-induced hepatotoxicity during treatment of tuberculosis include old age, extensive tuberculosis disease, malnutrition, alcoholism, chronic viral hepatitis B and C infections, and HIV infection. One recently published prospective cohort study from Spain6 has shown the incidence of antituberculosis drug-induced hepatotoxicity (serum transaminase >3 times the upper limit of normal) to be significantly higher in the group with risk factors (18.2%) than in the group without (5.8%). Severe hepatotoxicity (serum transaminase >10 times the upper limit of normal) occurred in 6.9% of the risk factor group and in 0.4% of the group without risk factors. Patients with chronic viral hepatitis B or C are at particular risk. Patients with chronic viral hepatitis B or C infections or HIV infection are subject to 3 to 5 times the risk of drug-associated hepatic dysfunction or toxicity. Chronic hepatitis B and C are of particular relevance in many parts of Asia, and HIV infection is also soaring in some Asian countries. A few studies have shown that the female gender is at an increased risk, but the underlying mechanism has yet to be unravelled. Organ transplant recipients are also at risk, and one possibility seems to be the additive toxic effects of immunosuppressive drugs administered concomitantly. Other examples of interactive toxicity with antituberculosis drugs include acetaminophen and anticonvulsants, particularly in those regimens including isoniazid.
Management Issues

Before commencement of antituberculosis chemotherapy, a detailed history should be obtained to identify possible risk factors for hepatotoxicity. Liver function tests should be performed to provide baseline values for comparison in due course. The patient should be advised to refrain from alcohol use, and both physicians and patients must be prudent in the co-administration of other medications.

To minimise the risk of hepatotoxicity, all patients should be thoroughly educated about the symptoms of hepatitis and the need for early evaluation. Close clinical monitoring is essential. Although there is some controversy regarding whether routine liver chemistry assessment should be carried out, those patients with risk factors for hepatotoxicity should have regular monitoring biochemically. Patients with underlying hepatic abnormality pose a significant problem. Fluctuations in biochemical indicators of liver function can confound monitoring for drug-induced hepatitis, and compromised liver reserve would also increase the risk for hepatotoxicity. Drug regimens with fewer potentially hepatotoxic agents might be beneficial for these patients. However, tuberculosis involvement of liver, usually in the form of microgranulomata, can occasionally cause abnormal baseline liver function tests, and these would in fact improve with effective antituberculosis treatment. Most drug-induced hepatitis occur within the initial 2 months of therapy. Closer monitoring, at weekly/biweekly intervals for example, is therefore recommended during the initial 2 months, followed usually by more widely spaced assessments all through the rest of treatment, for patients with significant underlying liver disease or otherwise at risk of major hepatotoxicity.

Transient changes in bilirubin and transaminase levels are relatively common during antituberculosis chemotherapy, and may not signify true organ toxicity. Table 1 depicts the cut-off levels of serum bilirubin and transaminases for withholding therapy among asymptomatic patients, as suggested by various professional authorities. Caution should also be exercised in the presence of a stepwise escalation of transaminase levels and/or a persistent elevation of bilirubin levels. It appears that for patients who are going to develop hepatitis eventually, an elevated enzyme level 3 times the upper limit of normal may easily become 5 times the upper limit of normal in due course. The American Thoracic Society indeed recommends stopping antituberculosis drugs when the serum transaminase level reaches 3 times the upper limit of normal for patients with symptoms suggestive of hepatitis. Symptoms like anorexia, nausea, vomiting, epigastric distension, right upper abdominal discomfort, malaise and weakness are important, and more so are relevant signs such as jaundice and hepatomegaly. Indeed, regardless of the concurrent severity of biochemical dysfunction, presence of definite and relevant symptoms would generally prompt the cessation of all antituberculosis drugs. On the other hand, there are possible limitations in symptom monitoring. Aside from concern over the specificity, symptoms can evolve very quickly in association with rapid deterioration of liver status, symptomatic thresholds may be affected by old age and other socio-epidemiologic factors such as drug addiction, alcoholism or psychiatric illnesses, and prolonged duration of symptoms may also be associated with a poorer overall prognosis.

Diagnosis of drug-induced hepatotoxicity is often based on circumstantial evidences, including the temporal relationship between the introduction of a drug and the onset of liver injury, as well as the resolution of manifestations of such injury following drug withdrawal. Endemic viral hepatitis can fortuitously occur during antituberculosis therapy, and they should be excluded wherever appropriate. Rechallenge with the suspected drug may not be safe or always necessary, unless alternatives do not exist. While some authorities found it possible to reinstitute the “full” antituberculosis regimen after recovery from the drug-induced hepatitis, it appears that most often dosage modification is necessary, especially for isoniazid and/or pyrazinamide, unless a predominant co-insulting factor such as alcohol could be totally withdrawn in the presence of very good liver function reserve/recovery.

If the tuberculosis disease is of lesser severity in terms of radiographic extent, bacillary load and infectiousness, it may be possible to withhold therapy until full recovery of liver chemistry. The desirable waiting time also depends on whether hepatotoxicity sets in during the initial, or the continuation phase of therapy, and the amount of therapy received prior to the onset of such toxicity. The patient can then be retreated with a regimen containing fewer potentially hepatotoxic drugs. The ATS / CDC / IDSA have made some suggestions regarding such regimens.

Table 2 shows some important examples of drugs with low or little hepatotoxic potential. One possible choice of such regimen embraces the use of streptomycin, ethambutol and isoniazid. Whenever possible, it seems advisable to resume the use of both isoniazid and rifampicin (by slow sequential introduction) so that the total duration of treatment will not be unduly long. Some fluoroquinolones such as ofloxacin / levofloxacin, and perhaps ciprofloxacin, were found to have low hepatotoxic potential in the majority of recipients who developed hepatic intolerance to the first-line antituberculosis drugs. Fluoroquinolone-containing interim regimens are often preferred if hepatotoxicity occurs during the initial intensive phase of chemotherapy, and the anticipated interruption of chemotherapy extends beyond 2 weeks, especially in the presence of severe tuberculosis. As the victim of hepatotoxicity has usually received pyrazinamide for sometime earlier on, this drug, with its significant hepatotoxic potential and putative activity mainly in the initial phase, is generally not suggested to be resumed after the successful reintroduction of both isoniazid and rifampicin for treating drug-susceptible disease. In uncommon occasions, when co-administration of rifampicin and isoniazid proves impossible, then the fluoroquinolone can be incorporated as a component of the final definitive antituberculosis drug regimen.
Table 1 Suggestions on Managing Drug-Induced Hepatitis in Tuberculosis

<table>
<thead>
<tr>
<th>Authority</th>
<th>Monitoring in presence of risk factors (especially liver diseases)</th>
<th>Stopping drugs if clinical or symptomatic hepatitis</th>
<th>Cut-off levels for stopping drugs (even when asymptomatic)</th>
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<tbody>
<tr>
<td>ATS</td>
<td>Yes</td>
<td>Yes</td>
<td>5X^A</td>
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<tr>
<td>BTS</td>
<td>Yes</td>
<td>Yes</td>
<td>5X</td>
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<tr>
<td>ERS</td>
<td>-</td>
<td>Yes</td>
<td>5X</td>
</tr>
<tr>
<td>HKTBS</td>
<td>Yes</td>
<td>Yes</td>
<td>3X*</td>
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# Kindly see text for details

ATS = American Thoracic Society

BTS = British Thoracic Society

ERS = European Respiratory Society

HKTBS = Hong Kong Tuberculosis Service

ALT = alanine transaminase

Bilirubin

Table 2 Antituberculosis Drugs and Their Comparative Potentials for Hepatotoxicity

<table>
<thead>
<tr>
<th>Greater Potential</th>
<th>Lower (or Little) Potential</th>
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<tbody>
<tr>
<td>Isoniazid</td>
<td>Streptomycin, Kanamycin, Amikacin, Capreomycin</td>
</tr>
<tr>
<td>Rifampicin, Rifabutin</td>
<td>Ethambutol</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Ofloxacin, Levofloxacin, Ciprofloxacin</td>
</tr>
<tr>
<td>Ethionamide, Prothionamide</td>
<td>Cycloserine</td>
</tr>
<tr>
<td>Para-aminosalicylic acid</td>
<td></td>
</tr>
</tbody>
</table>

References

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Management of Spontaneous Pneumothorax

Dr. Johnny WM Chan
MBBS (HK), MSc (Lond), MHA(NSW), MRCP(UK), FRCP (Edin & Glasg), FHKCP, FHKAM (Med)
Consultant Physician, Department of Medicine, Queen Elizabeth Hospital

Introduction

Pneumothorax is defined as the presence of air in the pleural space. Primary and secondary spontaneous pneumothoraces affect more than 20,000 patients per year in the United States, while mortality rates for combined primary and secondary pneumothoraces of 0.62/million per year for females and 1.26/million per year for males had been reported in UK between 1991 and 1995. Although published data from Hong Kong about its incidence are lacking, it is a common clinical condition that can potentially lead to significant morbidity and mortality if not timely or correctly managed.

Types of Pneumothorax

Spontaneous pneumothorax (SP), which occurs without an obvious precipitating event, can be divided into Primary spontaneous pneumothorax (PSP) and Secondary spontaneous pneumothorax (SSP). PSP occurs in patients without pre-existing clinically apparent lung disease, while SSP is found in those with underlying lung disease such as chronic obstructive pulmonary disease. Non-spontaneous pneumothorax can be subdivided iatrogenic and non-iatrogenic traumatic cases. While non-iatrogenic pneumothoraces usually result from trauma, iatrogenic pneumothoraces result from medical interventions. Tension pneumothorax is a medical emergency when intrapleural pressure exceeds atmospheric pressure throughout expiration, and can be developed from any aforementioned types of pneumothorax. The subsequent discussion would be focused on the general management of spontaneous pneumothorax.

General management options for spontaneous pneumothorax

Treatment of pneumothorax can be broadly divided into the evacuation of air from the pleural cavity and if necessary, the subsequent procedure to prevent its recurrence. While simple aspiration and chest tube drainage have both been employed in the evacuation of air inside pleural cavity, conservative management by simple observation can also be justified in certain cases. The decision is usually being based on the type and the size of the pneumothorax, together with the clinical symptoms and condition of the patient.

Observation alone

This can be considered in patients with small PSPs (<2 cm) without significant breathlessness. They can be discharged after observation in emergency department for 3-6 hours and discharged home if a repeated chest radiograph excludes further progression. Early outpatient follow-up, e.g. within 12 hours to 2 days, should be provided with clear written instructions. However, breathless PSP patients should not be left without intervention regardless of the size of the pneumothorax. On the contrary, caution must be exercised for those SSP cases when observation alone is adopted and hospital admission should be advised in these cases. High flow oxygen should be given, though with caution and in a controlled manner in patients with chronic obstructive pulmonary disease (COPD), to hasten the re-expansion process.

Simple aspiration or chest tube drainage?

Simple aspiration has been advocated as the first-line intervention for all symptomatic (and/or > 2 cm) PSP. Though regarded less likely to be successful, it can also be considered in selected cases of SSP (age<50) and with a rim smaller than 2 cm in the British guidelines. Similar degree of enthusiasm for the relatively conservative approach has not been equally found on the American side. Although the use of small-bore catheters (14F) has also been recommended to treat clinically stable patients with large (≥3 cm apex-to-cupola distance) PSP, chest tube drainage was recommended for SSP. Randomised controlled studies revealed similar efficacies, shorter hospital stays and less pain experienced in patients treated with simple aspiration, as compared to chest tube drainage. There has also been some data from Hong Kong, mainly from the Emergency Departments, on the use of simple aspiration in treating spontaneous pneumothoraces, and it was also noted that the procedure, while being safe, was found to be more successful only in relatively small pneumothoraces. Apart from the usual method of using manual aspiration with 50-ml syringe and 3-way valve with a catheter, connection to a negative pressure system via a one-bottle water seal vacuum system has also been described. The availability of relatively new pneumothorax kits like CASP (Catheter Aspiration of Simple Pneumothorax) catheter system using guidewires, with or without the subsequent attachment to a one-way valve (e.g. Heimlich valve) might improve the popularity of the technique in the future. However, chest tube drainage should be considered when such aspiration is
unsuccessful or in cases of SSP, especially if the patient is symptomatic or pneumothorax is of a considerable size (>1 cm or not just an “apical” one). Size of chest tubes for pneumothorax

Variation of opinions is again witnessed in the choice of the size of chest tubes for those indicated patients. The initial use of large chest tubes (20-24F), being not supported by evidence, has not been recommended by the British Guidelines, except where is a persistent air leak with the use of a smaller tube. However, larger tubes (24-28F) are favoured on the American side in managing SSP patients who are unstable or on mechanical ventilation because of the risk for larger air leaks.

Application of suction to a drainage system

Suction can be applied in cases where there is persistent lung collapse and/or persistent air leakage (e.g. beyond 48 hours), or for the removal of co-existing fluid (e.g. blood or pus) in the pleural cavity. However, immediate suction after drainage is usually not necessary and might produce reperfusion pulmonary oedema, especially in younger patients with larger pneumothoraces. A pressure range of -10 to -20 cmH₂O is usually sufficient.

Clamping or not?

Although clamping of chest drains is not absolutely forbidden in international guidelines, it remains a controversial issue with little evidence to support or refute its application. However, a “bubbling” chest drain, indicating continuous air leakage, should never be clamped. Even if there is no bubbling, a chest tube should not usually be clamped, especially during patient transport. If a chest tube is clamped, the patient should be under close respiratory medical and nursing attention. In case there is clinical deterioration with development of increasing dyspnoea, oxygen desaturation or with the development of/increasing subcutaneous emphysema, the clamp should be released immediately.

Prevention of recurrence: pleurodesis

The average recurrence rate after a first episode of PSP is 30%, varying from 16-52%. The corresponding rate of SSP is higher, varying from 40-80%, depending on the underlying cause. Procedures to prevent recurrence of PSP have usually been recommended for 2nd occurrence, although patients’ preferences and professions should also be taken into consideration. The occurrence of the first contralateral or bilateral spontaneous pneumothorax should also merit the consideration of pleurodesis. On the other hand, such procedures are preferred for the 1st occurrence of SSP, taking into the potentially serious consequences of such pneumothorax. Surgical methods (e.g. via video-assisted thoracoscopic surgery) are usually preferred with a recurrence rate less than 1%. Referral to surgeons has also been recommended when there is persistent air-leak or failure to re-expansion of more than 5-7 days. Medical pleurodesis, e.g. via the instillation of chemical, is only recommended if the patient is either unwilling or unable to undergo surgery. Tetracycline group such as doxycycline or minocycline is the commonest agents used with an overall efficacy of about 70% and is recommended by the British Guidelines as the first-line agents of choice. Talc has a higher reported efficacy (about 90%) and is cheaper. Both are associated with pain and fever upon administration, but more severe complications such as respiratory failure and ARDS have been reported with the use of talc. While there have been controversies over whether talc should be used for pleurodesis in light of such potential serious side effects, some recent evidence suggested that those might be related to the particle size of the talc preparation used.

Concluding remarks

Despite the presence of international guidelines, knowledge about the optimal management of spontaneous pneumothorax has not been supported with sufficient amount of high level evidence. As a result, some of these are based on consensus only and it is hardly surprising that variations in practice are still observed.

References

Recent Advances in the Management of Non-Small Cell Lung Cancer

Dr. James CM Ho
MBBS MRCP FHKCP FHKAM (Medicine)
Division of Respiratory Medicine, University Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong SAR, China

Prof. Wah-kit Lam
MD FRCP FRACP FHKCP FHKAM (Medicine)
Division of Respiratory Medicine, University Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong SAR, China

Introduction

Lung cancer has become the leading cause of cancer mortality in both men and women over the past few decades, with high incidence of 1.2 million new cases yearly and a staggering annual mortality of 1.1 million deaths worldwide in 2001.1 In Hong Kong, lung cancer has remained the commonest malignancy in men and second commonest in women, (and the commonest cancer killer in both sexes), accounting for a total of 3,972 new cases and 3,403 deaths in 2003.2 The majority (>80%) of lung cancer 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. In the past decade, there has been encouraging progress in various aspects of lung cancer treatment (e.g. chemotherapy, molecularly-targeted therapy, radiotherapy, surgery) and staging procedures. This review serves as an update for general physicians and practitioners on the latest advances and will mainly focus on the drug treatment for NSCLC both in the early and late stages of disease, together with highlights on other treatment modalities and diagnostic procedures.

Beyond Lung Resection for Resectable NSCLC: Adjuvant Chemotherapy

The staging system of NSCLC is based on the extent of involvement of primary tumour (T), regional lymph nodes (N) and distant metastases (M).3 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.4 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.5 More recently, there have been several large-scale randomized controlled trials reporting on adjuvant chemotherapy in over 3,400 patients with early-stage NSCLC.6,7,8 In the largest randomised controlled trial reported so far on adjuvant chemotherapy, the International Adjuvant Lung Cancer Trial (IALT),9 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). A more recent study also consistently demonstrated survival benefit of adjuvant chemotherapy in patients after resection for stage IB and II NSCLC, with improved overall survival by 15%.6 The reported toxicity profile was generally well tolerated. Furthermore, a recent meta-analysis of randomised trials reported since 1995 suggested significant survival benefit with adjuvant chemotherapy compared to surgery alone.10 Therefore, especially in younger patients with good performance status after curative resection for early-stage II NSCLC, adjuvant cisplatin-based chemotherapy can be considered as part of current standard practice, though there is still controversy about the optimal regimen and schedule.

Novel 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 diseases, the current standard treatment is combined systemic chemotherapy and radiotherapy, either given in concurrent or sequential manner.10,11 Over the years, systemic chemotherapy has become the standard first-line treatment for those with malignant effusion or distant metastases.12 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. An Asian multicentre phase II study of the efficacy and safety of docetaxel plus cisplatin in patients with metastatic or locally advanced NSCLC has been performed in 12 centres in seven Asian countries/regions, and showed an overall response rate of 46.9% and 14 months median survival. 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 median survival compared to best supportive care alone.

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. 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 chemotherapies, although the improvement is fairly modest at the expense of significant toxicity. Therefore there have been continued efforts looking for novel agents in treatment of advanced or metastatic NSCLC.

Anti-angiogenesis agent 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 metastases. 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 randomized 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).

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. Although the final analysis is still awaited, the planned interim analysis has demonstrated a statistically significant survival benefit favouring the bevacizumab combination arm (median survival 12.5 months vs 10.2 months in bevacizumab vs chemotherapy alone arms, p=0.0075). The major toxicity appeared to be related to bleeding complications, in which the 5 deaths due to haemoptysis were exclusively from bevacizumab arm.

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).

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.

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 signaling 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 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.

Gefitinib (Iressa®) was the first EGFR TKI used in the treatment of advanced NSCLC. Large-scale phase III trials (INTACT 1 and 2) failed to show clinical benefit by combining gefitinib with modern platinum-based first-line chemotherapy in advanced NSCLC. It was based on two large phase II trials (IDEAL 1 and 2) of gefitinib monotherapy in previously treated patients with advanced NSCLC, with objective response rate up to 18% and median survival of 7-8 months, that it was approved as second-line treatment. Similarly, a later developed EGFR TKI, erlotinib (Tarceva®), has been studied in a randomised, placebo-controlled phase III study (ISEL) of gefitinib in patients with advanced NSCLC refractory or intolerant to chemotherapy failed to demonstrate significant survival benefit compared to placebo, despite some benefit among never smokers and patients of Asian descent.
was found to be superior in response rate (8.9% vs 1%), progression-free survival (2.2 vs 1.8 months) and overall survival (6.7 vs 4.7 months) compared to placebo arm, which led to subsequent regulatory approval as second- or third-line treatment of advanced NSCLC.

Based on the recent studies of gefitinib and erlotinib in treatment of advanced NSCLC, there were several clinical and molecular predicting factors for response to treatment being identified (Table 1). Specific mutations in the EGFR tyrosine kinase domain (exons 18-21) have been shown to be associated with treatment response, while other mutations might predict drug resistance. The exact clinical application of the mutation study is currently still under investigation.

Modern Treatment Algorithm

With the aforementioned new armamentaria in the treatment of NSCLC, a suggested treatment algorithm is shown in Table 2.

Highlights Of Other Advances

As in other solid malignancies, the prognosis of lung cancer depends heavily on staging, which is crucial in the decision of treatment modalities. Among other imaging modalities, positron emission tomography (PET) has been extremely useful in the evaluation of solitary pulmonary nodule, clinical staging of lung cancer, and perhaps subsequent monitoring of treatment response. With the evaluation of metabolic activity based on Standardised Uptake Value (SUV), preferably with the incorporation of computed tomography for accurate anatomical delineation, PET-CT allows a whole-body search of potentially occult distant metastases which can affect the overall plan of management of lung cancer. Endobronchial ultrasound (EBUS) is a recently emerging technique to permit access to mediastinal lymph nodes with real-time ultrasound-guided needle aspiration via bronchoscopy, which can potentially spare some of the invasive staging procedures by mediastinoscopy. Video-assisted thoracoscopic surgery (VATS) is now performed in both staging and major pulmonary resections (either lobectomy or pneumonectomy) for lung cancer, which entails early postoperative recovery. New modes of radiotherapy, including Intensity Modulated Radiotherapy (IMRT) and tomotherapy, have also been introduced in Hong Kong, aiming at delivery of high radiation dose to the planning treatment volume (maximise efficacy) while preserving the adjacent normal tissues (minimise toxicity).

Conclusion

Over the past few years, there has been encouraging progress in both clinical and basic research on non-small cell lung cancer, which still remains the most devastating malignancy worldwide. The future directions in treatment will undoubtedly be the development of various types of novel molecularly-targeted therapy and their combination with existing chemotherapy (concurrent or maintenance treatment) at different stages of disease. With all the advances in diagnosis, staging and treatment modalities, the overall prognosis of lung cancer may hopefully be improved in the near future.

### Table 1. Predictors for response to EGFR TKI in patients with advanced NSCLC*

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Molecular</th>
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<tbody>
<tr>
<td>East Asian descent</td>
<td>EGFR TK domain-sensitising mutations</td>
</tr>
<tr>
<td>Female gender</td>
<td>EGFR polymorphisms</td>
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<tr>
<td>Nonsmokers</td>
<td>EGFR amplification</td>
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<tr>
<td>Adenocarcinoma histology</td>
<td>EBB3 expression</td>
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* Adapted from reference no. 25

### Table 2. Treatment algorithm for non-small cell lung cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>First-line treatment</th>
<th>Second-line treatment</th>
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<tbody>
<tr>
<td>IA</td>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>IB-H</td>
<td>Surgery + adjuvant (cisplatin-based chemotherapy (especially in younger patients with good performance status)</td>
<td></td>
</tr>
<tr>
<td>IIA-III (non-effusion)</td>
<td>Surgery for selected inoperable stage IIA cancer (single-drug or combination chemotherapy and thoracic RT for non-resectable stages (concurrent or sequential)</td>
<td></td>
</tr>
<tr>
<td>III (effusion-IV)</td>
<td>Options: Cisplatin-based chemotherapy (doublet) Bevacizumab combined with cisplatin-based doublet chemotherapy (non-squamous NSCLC)</td>
<td></td>
</tr>
<tr>
<td>Options: Docetaxel or Pemetrexed (non-squamous NSCLC)</td>
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</tr>
</tbody>
</table>

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

### References

Please read the article entitled “Recent Advances in the Management of Non-Small Cell Lung Cancer” by Dr. James CM Ho and Prof. Wah-kit Lam, 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 January 2007. 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 about lung cancer in Hong Kong over the past few years is/are true?
   a. >80% due to non-small cell carcinoma
   b. Around 4,000 new cases per year
   c. Top cancer killer in both men and women
   d. Majority presented with advanced or metastatic diseases

2. Based on recent randomised controlled studies on adjuvant chemotherapy post-resection for early stage non-small cell lung cancer, adjuvant cisplatin-based chemotherapy can improve 5-year survival up to:
   a. 15%
   b. 25%
   c. 35%
   d. 45%
   e. 55%

3. The current optimal treatment for medically fit patients with locally advanced (extension mediastinal lymphadenopathy) non-small cell lung cancer is:
   a. Surgery
   b. Radiotherapy alone
   c. Chemotherapy alone
   d. Combined chemotherapy and radiotherapy
   e. Epidermal growth factor receptor tyrosine kinase inhibitor

4. The following are current standard first-line chemotherapy options for young and medically fit patients with metastatic non-small cell lung cancer except:
   a. Docetaxel and cisplatin
   b. Paclitaxel and carboplatin
   c. Pemetrexed monotherapy
   d. Gemcitabine and cisplatin
   e. Gemcitabine and carboplatin
5. The following are true about bevacizumab (Avastin™) except:
   a. A recombinant humanised monoclonal antibody
   b. An anti-angiogenesis agent
   c. Combination with platinum-based chemotherapy has shown promising improvement in survival for stage IIIIB or IV non-small cell lung cancer
   d. Can be used in treatment of squamous cell lung cancer
   e. Severe life-threatening haemoptysis can occur in treatment of lung cancer

6. The following are true about pemetrexed (Alimta™) except:
   a. A multi-targeted tyrosine kinase inhibitor
   b. Currently approved in Hong Kong as second-line treatment for advanced non-small cell lung cancer
   c. Needs vitamin B12 and folate supplementation to reduce myelosuppression
   d. Similar efficacy as docetaxel in second-line treatment for advanced non-small cell lung cancer
   e. More favourable toxicity profile compared to docetaxel

7. Which of the following is/are regulated by the epidermal growth factor receptor signaling pathway in non-small cell lung cancer?
   a. Tumour cell proliferation
   b. Invasion
   c. Angiogenesis
   d. Metastasis
   e. All of the above

8. The following are true about erlotinib (Tarceva™) except:
   a. An epidermal growth factor receptor tyrosine kinase inhibitor
   b. Combination with platinum-based chemotherapy can improve survival compared to chemotherapy alone in advanced non-small cell lung cancer
   c. Approved as second-line treatment for advanced non-small cell lung cancer
   d. Common side effects include skin rash and diarrhoea
   e. Available as oral preparation

9. Which of the following are favourable factors for good response to gefitinib (Iressa™) or erlotinib (Tarceva™) in treatment of advanced non-small cell lung cancer?
   a. Asian descent
   b. Female gender
   c. Never smoker
   d. Adenocarcinoma
   e. All of the above

10. Which of the following staging investigations is based on increased “metabolic activity” of tumour cells?
    a. Computed tomography scan
    b. Positron emission tomography
    c. Endobronchial ultrasound
    d. Video-assisted thoracoscopic surgery
    e. Magnetic resonance Imaging

Please return the completed answer sheet to the Federation Secretariat on or before 31 January 2007 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Recent Advances in the Management of Non-Small Cell Lung Cancer

Dr. James CM Ho MBBS MRCP FHKCP FHKAM (Medicine)  
Prof. Wah-kit Lam MD FRCP FRACP FHKCP FHKAM (Medicine)  
Division of Respiratory Medicine, University Department of Medicine,  
The University of Hong Kong, Queen Mary Hospital, Hong Kong SAR, China

Name (block letters):____________________________________ HKMA No.: ____________________________
HKID No.:______-______-______-______ X X (x)  Others Membership No.
(please indicate): ____________________________
Contact Tel No.:_________________________________________________

Answers to December 2006 issue

Influenza is primarily a disease of shore birds and aquatic birds, with sea mammals, horses, pigs, poultry and humans as incidental hosts. Human influenza is a disease with two faces. Seasonal influenza is endemic with annual winter peaks. Attack rate could be 25-30% but case-fatality rate is relatively low and mostly affects the very young, the very old, and those with chronic sickness. Pandemic influenza occurs once every few decades and may be associated with a high case-fatality rate. Deaths typically involve all age groups and previously healthy people are not exempt.

The influenza virus

Influenza virus belongs to the family orthomyxoviridae and is classified into types A, B, and C. Influenza A is the most important one as it causes frequent epidemics and occasional pandemics. Influenza B causes epidemics but not pandemics, and influenza C only causes mild disease in humans.

The influenza A virion consists of a protein coat enveloping 8 single stranded, negative-sense RNA genes coding 11 proteins. Matrix protein 1 (M1) forms the main structure of the protein coat. Matrix protein 2 (M2) is located within the protein coat and is a channel enabling exchange of ions between the virion and the environment. Protruding from the protein coat are two surface proteins: the spike-like haemagglutinin (HA1, HA2) and the mushroom-like neuraminidase (NA). Haemagglutinin attaches to sialic acid receptors on host mucosal cells to initiate an infection. It is divided into 16 antigenic subtypes. Neuraminidase frees progeny viruses from attachment to the original host cell so that they can go forth to infect other host cells. It is divided into 9 antigenic subtypes. Inside the virion is a nucleoprotein (NP) which together with the RNAs forms the structure of the genes. The NP gene is also involved in many viral functions including interaction with host proteins thereby playing a role in host specificity. The RNA-polymerases (PA, PB1, PB2) are responsible for replication of the viral RNAs, while the non-structural proteins (NS1, NS2) are believed to interfere with host defences such as interferon production.

Influenza viruses do not have proofing enzymes for RNA replication so that “mistakes” are very common. It was estimated that a nucleotide change happens as often as one in ten thousand. Since there are approximately ten thousand nucleotides in the influenza genome, every newly formed influenza virion has a good chances of having at least one mutation. While most mutations are either meaningless or deleterious, some do confer survival advantage via a number of possible mechanisms. This constant change (antigenic drift) explains why humans do not have lasting immunity against the influenza virus. Another mechanism for emergence of new influenza strains is for two different strains to infect the same host cells with exchange of genes during assembly of new virus particles. Such genetic reassortment results in more dramatic changes and is associated with “antigenic shift”.

Aquatic and shore birds strike a much better balance with influenza viruses, with the birds not getting sick and the viruses hardly changing over a century. This “evolutionary stasis” led biologist to believe that these birds have been infected with influenza viruses for a very long time, and is the “primordial host” of it.

Seasonal influenza

Seasonal influenza is endemic and often reaches epidemic proportions in winter months. In Hong Kong and other sub-tropical and tropical regions there may be an additional summer peak, or the seasonal pattern may be totally irregular. In 1968 an H3N2 subtype replaced the previously circulating H2N2 as the dominant influenza A subtype for seasonal influenza. In 1977 H1N1 returned and instead of replacing H3N2 co-circulated with it up to the present day. Along with influenza B there are thus 3 subtypes of influenza regularly infecting humans.

The incubation period of influenza is 18 to 72 hours. Virus shedding can precede symptom onset by up to 24 hours, and lasts up to 5 days after symptom onset. Virus transmission is mainly through large droplets and fomites but there is increasing evidence for aerosol transmission which raises the advocate that N95 masks and not surgical masks should be used for infection control involving influenza. With the above features, it is easy to appreciate that influenza can spread very quickly in dense human populations, and is the ideal pathogen for severe epidemics.

The onset of symptoms is typically rapid, with fever, chills, cough, and prominent systemic symptoms such as malaise, headache, and myalgia. Although influenza can often be distinguished from common cold, infections by some other viruses like respiratory syncytial virus and parainfluenza viruses may give very
similar clinical features. Utilising data from multinational drug trials, Zambon et al found that using a clinical diagnostic criterion of fever (≥37.8°C for <65 year old and ≥37.2°C for ≥65 year old) plus any two of headache, myalgia, sore throat, and cough, 77% of laboratory-confirmed influenza correctly identified during influenza seasons. Sore throat however was found to be negatively correlated, and the same finding was reported by similar studies. So sore throat is a negative predictor of influenza and should be dropped from the diagnostic criteria. Outside influenza seasons, the low influenza prevalence would render such diagnostic criteria much less useful. Furthermore, it has been shown that for elderly people, infection by different respiratory viruses were clinically indistinguishable.

With the non-specific clinical features, laboratory confirmation of influenza is highly desirable for decisions on treatment and isolation as well as for epidemiological surveillance. Serology testing using paired serum for haemagglutination-inhibition study as well as viral culture are gold standards, but both require weeks for results to become available so they are more suitable for epidemiology and research. Reverse-transcription polymerase chain reaction (RT-PCR) can provide results within a few hours and a number of studies have found that it identified more true-positive samples than either serology or virus culture. These findings led some investigators to consider that RT-PCR should be the gold standard for the diagnosis of influenza. However, RT-PCR can only be done in the hospital setting. Other rapid tests such as Directigen FluA+B employ an enzyme immunoassay technology and can be used in the clinic setting. A local study on nasopharyngeal aspirates mainly from children <6 years old found that the sensitivity, specificity, and positive and negative predictive values of the Directigen FluA+B test for influenza virus type A were 96%, 99.6%, 96%, and 99.6%, respectively, and for influenza virus type B they were 87.5%, 96.8%, 80%, and 98%, respectively. Others have reported variable results and one study reported a sensitivity of only 43.83%, although specificity was excellent. Decreased sensitivity is seen in adult patients as well as use of specimens other than nasopharyngeal aspirate. Other rapid tests for influenza A and B such as Binax NOW and QuickVue have similar sensitivity and specificity to Directigen.

Beside bed-rest, adequate fluid intake, and symptomatic relief, antivirals have recently been the focus for influenza treatment. Amantadine was introduced soon after the Hong Kong flu of 1968. It is active against influenza A but ineffective for influenza B. Its main antiviral mechanism is believed to be interference of M2-protein mediated ion transport and resistance involving M2 mutations develop easily.

DANA (2-deoxy-2,3-dehydro-N-acetyl neuraminic acid) was a molecule designed to form a complex with the active 'pocket' of the influenza neuraminidase in the early 1990s. Improved visualisation of the 3-dimensional structure of neuraminidase led to modifications of DANA resulting in the introduction of zanamivir followed by oseltamivir in 1999. The former is in the form of capsules for inhalation while the latter are capsule for oral intake. Both formulations, if taken within 48 hours of symptom onset, can reduce duration of fever and duration of symptoms, and reduce the rate of complications and need for antibiotics. Both formulations have also been shown to prevent influenza in household contacts. Oseltamivir is more popular since oral intake is more preferred by patients, but there is recent concern on development of drug resistance. However, since the mechanism for oseltamivir resistance does not affect the action of zanamivir, resistance to the latter has so far not been reported. With the marginal benefit of neuraminidase inhibitors on seasonal influenza and the increasing risk of drug resistance, it has been proposed that the neuraminidase inhibitors should be reserved for pandemic influenza.

The tri-valent influenza vaccine has an efficacy of 70-90% in adults aged <65 years in influenza seasons in which the circulating strains are well matched to the vaccine strains, and is 38-52% when the circulating strains are significantly different from the vaccine strains. Elderlies have a poorer antigenic response and the vaccine efficacy has been estimated to be only 17-53% depending on circulating viruses. For the winter of 2006-07, the Advisory Committee on Immunisation Practices has recommended the following vaccine composition: A/New Caledonia/20/1999 (H1N1)-like, A/Wisconsin/67/2005 (H3N2)-like, and B/Malaysia/2506/2004-like antigens. Target groups for vaccination include:

- Persons at high risk for influenza-related complications and severe disease, including:
  - children aged 6-59 months,
  - pregnant women,
  - persons aged ≥50 years,
  - persons of any age with certain chronic medical conditions; and
- Persons who live with or care for persons at high risk, including:
  - household contacts who have frequent contact with persons at high risk and who can transmit influenza to those persons at high risk,
  - health care personnel on all health care settings.

The importance of administering 2 doses of influenza vaccine for children aged 6 months to <9 years who were previously unvaccinated was highlighted.

Pandemic Influenza

There were about three influenza pandemics each century for the last 3 centuries. The "Spanish flu" of 1918-19 was probably the worse pandemic the human race has ever seen, and killed some 40-50 million people worldwide. The 1997 outbreak of avian influenza in Hong Kong caused tremendous concern not only because it was the first time that a totally avian influenza virus was clinically indistinguishable.
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At present no specific treatment for human H5N1 disease has been shown to be effective. Based on in-vitro sensitivity, the WHO is recommending oseltamivir 75mg twice daily orally for 5 days, although higher doses and longer treatment duration may be required. Oseltamiravir resistance has however been reported for H5N1, and other antivirals which has shown in-vitro susceptibility such as amantadine and ribavirin are being considered as add-on therapy to oseltamivir. Steroids and other immunomodulating agents are not considered useful at this juncture. General medical, nursing, and respiratory related support would likely be the mainstay of treatment.

In order to control pandemic influenza at source, we need first of all to know how pandemic influenza strains come about. Previously it was believed that pandemic strains resulted from genetic reassembly between an avian influenza strain and a human influenza strain, with the pig being the "missing vessel"35. While the 1957 and 1968 pandemic influenza strains were in reassembly, evidence for the pig being the mixing vessel was lacking. Furthermore, the 1918 pandemic strain is found to result from adaptive mutation of an avian virus without reassembly with human viruses36. Added to recent reports of direct infection of humans by various avian influenza viruses it is now believed that such infections have been occurring regularly and frequently for a long time37. The pool of avian influenza viruses undergo continuous reassembly within their natural hosts, and is a potent source for pandemic virus candidates38,39. It is thus very important for surveillance systems to pick up highly pathogenic avian influenza viruses in both birds and humans quickly and to control their onward passage by culling of infected flocks and isolation of infected humans. Should a pandemic start to result from adaptive mutation of an avian virus without reassembly with human viruses40, it will be of utmost importance for countries to elaborate preparedness plans to combat a major pandemic, but the effectiveness of such plans has been subject to much scepticism41.

virus infected and killed humans, but also that it was roughly 30 years after the previous influenza pandemic in 1968, and another one was thought to be imminent. Having been eradicated in Hong Kong by poultry depopulation H5N1 continued its evolution elsewhere and caused a true poultry pandemic in late 2003, with isolated human cases carrying a high mortality rate but causing a true poultry pandemic in late 2003, with isolated human outbreaks with human cases are still seen today. H5N1 continues to be the top candidate for the next influenza pandemic because the only hurdle it has to overcome is the ability to transmit efficiently among humans.

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20
Management of Acute Exacerbation of COPD

Dr. Fanny WS Ko
MBChB, MRCP, FHKCP, FHKAM, FCCP
Associate Consultant, Department of Medicine and Therapeutics, The Chinese University of Hong Kong

Dr. David SC Hui
MD(UNSW), FRACP, FRCP(Lond, Edin, Glasg), FHKCP, FHKAM(Med)
Department of Medicine and Therapeutics, The Chinese University of Hong Kong

Chronic obstructive pulmonary disease (COPD) is a disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. It is a common disease worldwide with a significant morbidity and incurs heavy utilisation of health care resources. In Hong Kong, COPD was the 5th leading cause of death, and accounted for at least 4% of all public hospital acute admissions in 2003. The prevalence of COPD among elderly Chinese (age ≥ 70 years) living in Hong Kong is estimated to be 9%.5

Acute exacerbation of COPD (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.3 AECOPD is defined by some authorities using strict criteria with at least two of the following major symptoms (including increased dyspnoea, increased sputum purulence, increased sputum volume), or one major and one minor symptom (nasal discharge/congestion, wheeze, sore throat, cough) for at least two consecutive days.4,5 However, the severity of exacerbations can be extremely heterogeneous, ranging from mild increase in symptoms to serious and severe respiratory failure.

Infectious agents are recognised as a major pathogenic factor in AECOPD. Other contributing factors for exacerbations include air pollution6, low temperature, and interruption of regular treatment. A 1-year prospective study from 2004 to 2005 in Hong Kong has shown a positive sputum culture rate of 32.3% in patients admitted to hospital with AECOPD.7 Haemophilus influenzae was the commonest organism identified in sputum culture (13.0%), followed by Pseudomonas aeruginosa (6.0%) and Streptococcus pneumoniae (5.5%). A positive viral culture from nasopharyngeal aspirate specimen was noted in 9.7% of our patients, with influenza A, respiratory syncytial virus and influenza B being the commonest viral pathogens.7 In contrast, previous studies using polymerase chain reaction technique in examining respiratory specimens have found rhinovirus as the commonest viral pathogen.4 The role of bacteria in causing AECOPD has been controversial as the same organisms may be isolated in some patients at clinical stability.3 Evidence to support the causative role of bacteria in AECOPD includes the identification of a new strain of bacteria using the technique of cell lysate polyacrylamide-gel electrophoresis.8 The benefits to patients seen in trials of antibiotics for AECOPD also support bacteria as an important trigger for the exacerbations.9

Patients with mild acute exacerbations can be managed as out-patients, but 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.

Bronchodilators provide 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.11 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.12,13 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. However, meta-analysis has failed to confirm the benefits in terms of improvement of lung function and symptoms of patients with AECOPD treated with aminophylline.14 In addition, there was a significant increase in adverse events such as nausea and vomiting in the aminophylline-treated patients.14

Systemic (oral or intravenous) glucocorticosteroid therapy is recommended for treating AECOPD as it significantly reduces treatment failure and need for additional medical treatment.15,16 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.16 The Global Initiative for Chronic Obstructive Lung disease (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 of airway infection (e.g., increased sputum volume and change of colour of sputum, and/or fever) may benefit from antibiotic treatment.1 The choice of antibiotic should reflect the local patterns of antibiotic sensitivity to Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis. 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.7 The Hong Kong Interhospital Multi-disciplinary Programme on Antimicrobial ChemoTherapy (IMPACT) guideline in 2003 has recommended oral/intravenous amoxicillin-clavulanate or ampicillin/sulbactam as the anti-microbial therapy for patients with AECOPD.17 Alternative antibiotics include cefotaxime or a new anti-Gram positive fluoroquinolone. 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.10

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 use 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 compared to medical treatment alone.18 The use of central respiratory stimulants such as doxapram for treatment of respiratory failure has gone out of favour since the introduction of NPPV. The use of doxapram is commonly associated with side effects, particularly agitation. NPPV is much more effective in correcting respiratory failure than doxapram.19 In addition, NPPV use is associated with much less side effects when compared with doxapram use.19

Recurrent AECOPD is associated with harmful health effects and poor outcome. Local data have shown that COPD patients have on average 2.2±1.8 episodes of re-admissions to hospital for AECOPD within one year.20 For those patients whose COPD exacerbations were severe enough to warrant application of NPPV respiratory support, the 1 year mortality rate was 49.1%.21 Previous studies have shown that pulmonary function and quality of life are adversely affected by frequent exacerbations, particularly in active smokers.1,22

As recurrent episodes of AECOPD have such harmful health effects, it is important to prevent exacerbations and the possible strategies include smoking cessation, pulmonary rehabilitation, use of long acting bronchodilators, use of inhaled corticosteroid and influenza vaccination. There is some evidence that the use of long acting bronchodilator such as tiotropium may lengthen the time from first COPD exacerbation and reduce health care utilisation for exacerbations.23 In the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) trial, the use of the inhaled corticosteroid fluticasone propionate in patients with moderate to severe COPD was associated with fewer exacerbations and a slower decline in health status when compared to patients on placebo.24 Withdrawal of inhaled steroid from stable COPD patients was associated with increased rates of exacerbations and hospital admissions.25,26 In a major randomized placebo-controlled study in 50 centers, N-acetylcysteine was shown to be ineffective in preventing deterioration in lung function and a reduction of exacerbations in patients with COPD.27 There is currently some evidence to support the role of pulmonary rehabilitation post acute exacerbations in reducing the risk of readmissions to hospital and mortality,28 but more data from randomized controlled trials are needed. In addition, there is suggestion that integrated care programme may help decreasing exacerbations of COPD in certain European countries.29 The integrated intervention consists of an individually tailored care plan upon discharge shared with the primary care team, and accessibility to a specialized nurse case manager through a web-based call centre. Whether a similar type of integrated care model is suitable for COPD patients in Hong Kong needs further investigation. Influenza vaccination has been shown to be effective in the prevention of influenza-related acute respiratory illness in COPD patients30 and the GOLD guideline recommends annual influenza vaccination for all COPD patients.1

In summary, AECOPD causes harmful health effects on the patients and imposes a considerable burden on the health care system. Prompt treatment of acute exacerbations and prevention strategies to avoid recurrent exacerbations among COPD patients are needed to improve their health status and reduce utilisation of health care resources.

References


THE HONG KONG MEDICAL DIARY
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- **targeting** cholinergic constriction for 24 hours,\(^1\)^\(^2\)\(^3\)  
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- **reducing** air trapping,\(^5\)  
- **reducing** the number of exacerbations,\(^6\)  
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Fax: (852) 2827 0162

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Ciclesonide: A New Inhaled Corticosteroid

Dr. Gary WK Wong

Introduction

Asthma is one of the most common chronic respiratory conditions. The exact etiology of asthma is still unknown but the main state of treatment is to control the underlying airway inflammation. Currently there is no cure for the disease, many adults and children with asthma require prolong treatment of many years to decades. Therefore, it is very important to balance the safety and efficacy in prescribing treatment for asthmatic patients. As described clearly in many asthma treatment guidelines, the goal of asthma treatment is to achieve long term control of asthma symptoms with no significant side effects from their treatment. Inhaled corticosteroids (ICSs) are the cornerstone of asthma therapy and are recommended as daily therapy for persistent asthma. The use of ICSs may be limited by the possible local or systemic side-effects such as adrenal suppression, osteoporosis, and growth retardation in children. Ciclesonide is a new preparation of ICS with unique pharmacology to minimise the possible side-effects of ICS. In this article, we will review the pharmacology, efficacy, and safety profile of this drug for the treatment of asthma.

Pharmacology

Ciclesonide is a new inhaled corticosteroid (ICS) with unique pharmacokinetic and pharmacodynamic properties which differentiate it from other ICSs. Ciclesonide is an inactive pro-drug and it has to be converted to the active metabolites, desisobutyryl-ciclesonide (des-CIC). The conversion process occurs primarily in the lung. Both ciclesonide and its active metabolite have shown to be highly protein bound thereby reducing the potential for systemic side effects. Ciclesonide is extensively metabolised by the liver to inactive metabolites. Because of this fast pass-metabolism, the systemic bioavailability of ciclesonide after oral ingestion is less than 1%. Furthermore, it has been demonstrated in trials of healthy individuals that conversion of ciclesonide to its active metabolite in the upper oropharynx was extremely low. This property most likely contributes to the low incidence of local side-effect of this drug.

Clinical studies

There have been many clinical studies involving both adults and children with comparison of ciclesonide against placebo and other ICSs. The recommended dose for the maintenance treatment of persistent asthma in adults is 160-320 μg per day. Langdon et al conducted a 12-week placebo-controlled study comparing ciclesonide (80 or 320 μg ex-actuator) given to 360 patients with bronchial asthma and these patients have been previously treated with a constant dose of beclomethasone dipropionate. The results showed that both dosages significantly improve in lung function including peak expiratory flow (PEF) and forced expiratory volume in 1 second (FEV1). These results were confirmed with a similar 12-week trial of 329 patients with persistent asthma treated with ciclesonide 160 or 640 μg ex-actuator HFA pMDI.

Buhl et al. conducted a study comparing ciclesonide 160 μg once daily in the evening with fluticasone 88 μg twice daily (ex-actuator HFA-MDI for both drugs) in 529 patients with asthma. The results showed that subjects taking ciclesonide had morning PEF that were similar to those taking fluticasone. There was similar reduction of symptom score and need for rescue medication.

In a recent randomised, double blind, parallel-group comparative study between ciclesonide and fluticasone in 556 children aged 6-15 yrs, both treatments were shown to be effective in improving lung function. There was also significant improvement of asthma symptom score, reduction of use of rescue medication in both treatment groups. Interestingly, the 24hr urine cortisol levels increased significantly from baseline levels by 10% only in the ciclesonide group. Furthermore, there were also recent studies of ciclesonide taken once daily and it was found to be as effective as budesonide taken twice daily. Putting the data of these studies together, it appears that ciclesonide taken once daily is as effective as the other currently available ICSs taken twice daily.

Safety profile of ciclesonide

Long term safety is particularly important for the drugs that patients have to take for long periods of time. For inhaled corticosteroid, one should be considering both local and systemic side-effects. In a study comparing high dose ciclesonide and fluticasone in adult asthmatics with mild-to-moderate persistent asthma, 2.4% of the patients taking ciclesonide (320-640μg/day) were diagnosed as having oral candidiasis (confirmed by culture) vs 22.0% of the patients taking fluticasone propionate (880 μg/day). The low deposition of ciclesonide in the oropharynx and the low conversion of
ciclesonide to desisobutyryl-ciclesonide in the oropharynx most likely contribute to such difference.

The important systemic side-effects are adrenal suppression and growth retardation especially when high dose of ICSs are used. Measurement of short-term lower-leg growth rate in children by knemometry is a sensitive measure of systemic activity of topical steroids in children. In a recent study using knemometry to assess lower leg growth in children, it has been demonstrated that both short term lower-leg growth rate and HPA axis function were not affected by treatment with ciclesonide. The effect of ciclesonide on HPA axis function in treatment of mild-to-moderate persistent asthma has been extensively investigated in asthmatics with different degrees of severity. Lipworth et al conducted a study of adults with mild-to-moderate persistent asthma to evaluate the effects of ciclesonide and fluticasone on the hypothalamic-pituitary-adrenal (HPA) axis. Patients were randomised to receive 320 mcg of ciclesonide once daily, 320μg ciclesonide twice daily, or 440μg fluticasone twice daily for 12 weeks. Assessment of HPA axis included ACTH test and 24 hour urine collection for free cortisol measurement. Only the two groups randomised to receive ciclesonide did not show any significant suppression of ACTH response and urinary free cortisol excretion. Szeffler et al conducted a similar study to assess patients with moderate-to-severe persistent asthma and showed that oral inhalation of ciclesonide up to 1280μg per day did not suppress the HPA axis as reflected by serum cortisol measurement.

Summary

Inhaled corticosteroids are the mainstay of treatment for persistent asthma in children and adults. Ciclesonide is a new preparation of ICS which can be used in a once-daily routine. It is a pro-drug requiring conversion to the active metabolite, desisobutyryl-ciclesonide (des-CIC), in the lungs. Because of its unique pharmacology and bioavailability, it has been shown to have a very low incidence of local side effects. Multiple studies have also demonstrated that the HPA axis is not significantly suppressed with ciclesonide. Longer term studies are needed to evaluate the possible effects of ciclesonide on bone density of asthmatic patients.

References


Classified Advertisement

- **Vacancies**
- **Rental**
- **Office Vacancies**
- **For Sale**

Please contact the Federation Secretariat at 2527 8898 for placement of classified advertisement.

(Charge: HK$ 600 per 30 word unit, HK$50 per additional 10 word unit)
Clinical Quiz

Dr. KS Tai
Department of Radiology, Queen Mary Hospital, Hong Kong

Diagnosis: Cervical spinal schwannoma

Clinical history:
A thirty-six years old lady presented with sudden onset of left side weakness and numbness when she bended forward. Acute stroke was suspected but her brain CT scan on admission was normal. MRI scan of the cervical spine was performed followed by emergency operation.

MRI findings (Figure 1 & 2):
1. T1W/T2W isointense lesion enlarging the left C3-4 and C4-5 neuroforamina (arrows).
2. Intraspinal component noted compressing the cervical cord which was displaced to the right.
3. Intense contrast enhancement was seen at the lesion.
4. Cystic change was also present within the tumour.

Operative findings:
Urgent surgery was done with total removal of tumour. The neurological symptoms resolved after the operation. Pathological examination revealed schwannoma.

(See P. 32 for answers)

The Medical and Dental Directory of Hong Kong - new 8th Edition

Call for submission of individual data from all medical and dental practitioners

To all medical and dental practitioners,
We would like to take this opportunity to invite you to send us your most up-to-date information. You can complete the form and return to us by facsimile, through mail or via our Federation’s Home Page: www.fmshk.org/directory . All respondents will be entitled to a free copy of the Medical & Dental Directory of Hong Kong 2007 upon submission of data. A voluntary contribution of HK$100 or above is welcome and upon submission, a data CD and Directory will be sent to your office (includes postage and package), otherwise you may have to pick up the Directory from the Federation office yourself if no contribution is made. In case we do not hear from you, basic information will be extracted from the available records of the Medical Council of Hong Kong and the Dental Council of Hong Kong. Thank you for your co-operation.
Master of Public Health Programme (full time / part time)

The MPH provides broad public health perspectives and skills necessary to assume effective leadership in public health practice, reflecting the three domains of health improvement, health protection and health service quality. All students will complete courses in the core disciplines, selected courses in their areas of concentration, as well as elective courses relevant to their specialized area.

<table>
<thead>
<tr>
<th>Core Areas:</th>
<th>Epidemiology and Biostatistics</th>
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<tr>
<td>Foundations of Public Health</td>
<td>Infectious Diseases</td>
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<td>Epidemiology I</td>
<td>Occupational Health</td>
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<tr>
<td>Biostatistics I</td>
<td>Gerontontology and Geriatrics</td>
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<td>Health Policy and Management</td>
<td>Health Services Management</td>
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<td>Sociomedical (Behavioural) Sciences</td>
<td>Women’s Health</td>
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<tr>
<td>Sciences</td>
<td>Public Health in Practice</td>
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</table>

Postgraduate Diploma Programme in Health Services Management and Public Health (part time)

This programme provides training in Foundations of Public Health, Epidemiology, Biostatistics, Health Policy and Management, Environmental Health Sciences, and Sociomedical (Behavioural) Sciences for practitioners in public health and hospital administration in Hong Kong.

Open Day and 1st Information Session: January 20, 2007

MBA Programme in Health Care (full time / part time)

The programme is jointly offered by the Faculties of Business Administration and Medicine. The MBA Programme in Health Care aims to provide health care professionals with relevant and innovative management education and evidence-based health care skills. Students will complete 36 units (full time) or 33 units (part-time) from the MBA Programme and 16 units from the Master of Public Health Programme.

1st Information Session: January 19, 2007

* All degrees are quotable

Admission Requirements:
Bachelor’s Honours Degree (not lower than Second Class Lower Division Honours or B Grade); or a Bachelor’s degree in Medicine or an approved public health related field.

Application Deadline: April 30, 2007

Enquiries:
Please contact Ms. Queenie Chan, 4/F, School of Public Health, PWH, Shatin, N.T., Hong Kong
Tel: (852) 2252 8886  Fax: (852) 2606 3791 Email: mph_cuhk@cuhk.edu.hk
MBA: www.cuhk.edu.hk/mphmph
MBA (Health Care): www.baf.cuhk.edu.hk/mbahealth
Pg Dip HSMPh: www.cuhk.edu.hk/mad/cmd/dip_hsm.html
News from FMSHK Secretariat

Ms. Sue S.Y. Cheng has been promoted to Executive Manager effective from 6 December 2006.

Ms. Kitty Y.L Leung, Administrative Manager left FMSHK on 1 December 2006 after 16 years of service. We wish her all the best in her future developments.

Central Western Health Festival 2006

The Central Western Health Festival was held on 25 and 26 November 2006 at Sheung Wan Sports Centre with over 2000 participants attending. Dr Raymond Lo was the Chairman of the Organizing Committee, and members included Mr Samuel Chan, Mr Peter To and Ms Tina Yap. HKFMS Foundation Ltd contributed 2 booths, focusing on Elderly Health - Balance, Nutrition and Home & Environmental Safety. There were interactive games with bone density and balance diagnosis. The HKFMS Foundation booths were very popular with participants fully enjoying the infotainment, games and gifts. Dr Raymond Lo would like to express his sincere gratitude to all organizations which supported HKFMS Foundation Ltd in this event:

AVC Medical Technology Limited
Hong Kong Occupational Therapy Association
Hong Kong Physiotherapy Association
Hong Kong Practising Dietitians Union
Quality Healthcare Elderly Services
The International Medical Company
The Pharmaceutical Society of Hong Kong
The Hong Kong Nutrition Association Ltd

News from Member Societies

St. Paul’s Doctors’ Association
New office-bearers for the year are as follows: Chairman: Dr. Paul YUNG, Hon. Secretary: Dr. Robert LI, Council Representative: Dr. Ka-leung CHUNG.

The College of Dental Surgeons of Hong Kong
New office-bearers for the year are as follows: President: Dr. John Yu-kong LING, 1st Vice-President: Dr. Joseph Choyee CHAN, 2nd Vice-President: Dr. Roch Kwing-hong LEE, Hon. Secretary: Dr. Anthony Siu-kwong TSE, Hon. Treasurer: Dr. Michael Ngai-ying CHAU.

The FMSHK would like to send its congratulations to the new office-bearers and look forward to working together with their societies.
**Certificate Course on Medical Genetics**
- Monday, 1st
- Wednesday, 3rd

**Certificate Course on Drug Dispensing in Office Clinics**
- Thursday, 4th

**Certificate Course on Drug Dispensing in Office Clinics**
- Thursday, 4th
  - (1) Therapeutic Drug Monitoring and Tuberculosis
  - (2) What Lies Beneath

**Certificate Course on Medical Genetics**
- Monday, 15th
- Wednesday, 17th

**Certificate Course on Medical Genetics**
- Monday, 22nd
- Wednesday, 24th

**Certificate Course on Medical Genetics**
- Monday, 28th
- Wednesday, 31st
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<tr>
<td>3</td>
<td>7:00 pm - 8:00 pm (10, 17, 24, 31)</td>
<td>Certificate Course on Medical Genetics</td>
<td>Ms. Karen CHU  Tel: 2865 3515  Fax: 2865 0345  Sugar Tel: 2527 9255  Fax: 2838 6280</td>
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<tr>
<td>3</td>
<td>8:30 am - 12:30 noon (5, 10, 12, 17, 19, 24, 26, 31)</td>
<td>Certificate Course on Drug Dispensing in Office Clinics</td>
<td>Ms. Karen CHU  Tel: 2865 3515  Fax: 2865 0345  Miss Christine WONG  Tel: 2527 8285</td>
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<td>4</td>
<td>7:00 pm - 8:30 pm (16)</td>
<td>Certificate Course on Drugs Safety in Old Aged Home</td>
<td>Ms. Karen CHU  Tel: 2865 3515  Fax: 2865 0345  Miss Tammy TAM  Tel: 2527 8941</td>
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<tr>
<td>4</td>
<td>8:00 pm</td>
<td>HKMA Council Meeting</td>
<td>Miss Nina HUNG  Tel: 2861 1979  (Registration fee is required)  1 CME Point</td>
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<tr>
<td>5</td>
<td>2:00 pm</td>
<td>HKMA Structured CME Programme with Hong Kong Sanatorium &amp; Hospital Year 2007 (I)</td>
<td>Miss Nina HUNG  Tel: 2861 1979  (Registration fee is required)  2 CME Points</td>
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<td>6</td>
<td>2:30 pm</td>
<td>HKMA Refresher Course for Health Care Providers 2006/2007 (V) - Cardiac Topics - ECGs, Lab Investigations and Others</td>
<td>Ms. Clara TSANG  Tel: 2527 8285  2 CME Points</td>
</tr>
<tr>
<td>6</td>
<td>7:00 pm</td>
<td>2nd HKMA Sports Night</td>
<td>Ms. Dora HO  Tel: 2527 8285  2.5 CME Points</td>
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<td>7</td>
<td>7:00 pm</td>
<td>Seminar on Infectious Diseases - Community Acquired Infection with Outbreak Potential</td>
<td>Miss Nina HUNG  Tel: 2861 1979  (Registration fee is required)  2.5 CME Points</td>
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<td>8</td>
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<td>HKMA Structured CME Programme Year 06/07 (X)-Ophthalmology</td>
<td>Miss Nina HUNG  Tel: 2861 1979  (Registration fee is required)  6 CME Points</td>
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<tr>
<td>10</td>
<td>6:30 pm - 8:00 pm</td>
<td>(1) Therapeutic Drug Monitoring And Tuberculosis (2) What Lies Beneath</td>
<td>Dr. W.M. CHAN / Dr. C.M. CHU  Tel: 2853 5824  Fax: 2853 9667</td>
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<tr>
<td>11</td>
<td>1:30 pm</td>
<td>3rd HKMA Exercise Prescription Certificate Course (Module 1-4)</td>
<td>Miss Gloria CHEUNG  Tel: 2527 8285  (Registration fee is required)  1.5 CME Points</td>
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<tr>
<td>11</td>
<td>6:30 pm - 8:00 pm</td>
<td>2nd Certificate Course in Recent Medical Advances for General Practitioners</td>
<td>Hospital Administration Department  Tel: 2835 9000  Fax: 2835 8082  E-mail:<a href="mailto:hospadm@hksh.com">hospadm@hksh.com</a>,  <a href="mailto:bobso@hksh.com">bobso@hksh.com</a>/CME/pdf  (Registration fee is required)  2 CME Points</td>
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<td>12</td>
<td>6:30 pm - 8:30 pm</td>
<td>Inside the Medical Council: The Mechanics of Medical Council Disciplinary Proceedings</td>
<td>Ms. Masen KAY  Tel: 3420 9663  E-mail:<a href="mailto:masen.kay@hksh.com">masen.kay@hksh.com</a>, Registration fee is required  CME &amp; CPD approved</td>
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<tr>
<td>14</td>
<td>3:00 pm</td>
<td>International Colorectal Disease Symposium (ICDS) 2007</td>
<td>Ms. Olivia HO  Tel: 2955 6362  Fax: 2515 3195</td>
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<td>21</td>
<td>1:30 pm</td>
<td>3rd HKMA Exercise Prescription Certificate Course (Module 5-7)</td>
<td>Miss Gloria CHEUNG  Tel: 2527 8285  (Registration fee is required)  2 CME Points</td>
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<td>21</td>
<td>6:30 pm - 8:00 pm</td>
<td>HKMA Structured CME Programme at Kwong Wah Hospital Year 06/07 (X) - Rehabilitation</td>
<td>Miss Nina HUNG  Tel: 2861 1979  (Registration fee is required)  3 CME Points</td>
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<tr>
<td>22</td>
<td>6:30 pm - 8:30 pm</td>
<td>Drowning Under Work: Take Control and Manage Your Time Effectively</td>
<td>Ms. Masen KAY  Tel: 3420 9663  E-mail:<a href="mailto:masen.kay@hksh.com">masen.kay@hksh.com</a>, Registration fee is required  CME &amp; CPD approved</td>
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Meetings

10-11/02/2007
Cancer Imaging 2007 - Joint Meeting of the International Cancer Imaging Society & Hong Kong College of Radiologists
Organised by: International Cancer Imaging Society & Hong Kong College of Radiologists
Chairman: Ms. Lilian LEONG
Speaker: Various
Enquiries: corres@hkr.org

13-17/06/2007
The 21st Congress of International Association of Paediatric Dentistry IAPD
Organised by: Hong Kong Society of Paediatric Dentistry
Enquiries: Mr. Daniel CHOK
Website: http://www.iapd2007.com

7-8/07/2007
Head and Neck Course 2007 - Surgery for Nasopharyngeal Cancer
Organised by: Department of Surgery, Li Ka Shing Faculty of Medicine, University of Hong Kong Medical Centre, Queen Mary Hospital, Pokfulam, Hong Kong
Enquiries: Course Secretariat
Website: http://www.hku.hk/surgery

12-14/07/2007
The 50th Hong Kong Surgical Forum
Organised by: Department of Surgery, Li Ka Shing Faculty of Medicine, The University of Hong Kong, and American College of Surgeons, Hong Kong Chapter
Enquiries: Forum Secretary
Website: http://www.hku.hk/surgery

12/07/2007
The 1st Nursing Forum
Organised by: Department of Surgery; Department of Nursing Studies, Li Ka Shing Faculty of Medicine, The University of Hong Kong & American College of Surgeons, Hong Kong Chapter
Enquiries: Forum Secretary
Website: http://www.hku.hk/surgery

Courses

2,7,9,14,16,24/02/2007
The Role of the Medical Expert in Personal Injury Litigation
Organised by: British Medical Association & The New Medico-Legal Society of Hong Kong
Speakers: Various
Enquiries: Ms. Maseedis KAY
Website: http://www.hks.hk/CME.pdf

11/2/2007
2nd Certificate Course in Recent Medical Advances for General Practitioners
Organised by: College of Nursing, Hong Kong
Enquiries: Sugar
Website: http://www.hku.hk/CME.pdf

14/07/2007
Professional Certificate in Clinic Operation
Organised by: Hong Kong Institute of Vocational Education (Shatin)
Enquiries: Mr. YAU Yiu Shu & Ms. Joyce CHAN
Website: http://stas.vtc.edu.hk or http://www.fmshk.org

Answer to Clinical Quiz

Spinal schwannomas are slow growing tumours comprising 30% of spinal neoplasms. They usually occur as solitary lesion unless present as part of the inherited syndromes. Male and female are equally affected with peak incidence at 4th-6th decades. Multiple schwannomas are seen in patients with neurofibromatosis type II (NF-2). Malignant transformation is rare. Usual presentation includes pain mimicking sciatica or disc herniation. Histologically schwannomas are composed of Schwann cells that develop into neoplastic compact interlacing groups associated with fibrous strands. Treatment is by total microsurgical resection.

The best imaging clue for diagnosis is the well delineated enhancing nerve root mass. About 70-75% are found as intradural extramedullary lesions. Plain film findings include posterior scalloping of vertebral bodies and widening of the neural foramina. On MRI most tumours are isointense on T1W images and 75% of the lesions are T2W hyperintense with cystic changes occurring in 40% (Figure 1). They almost always show intense contrast enhancement which can be of uniform or heterogeneous pattern (Figure 2). Differential diagnosis includes neurofibroma which may not be distinguishable from schwannoma on imaging alone. The absence of “dural tail” sign also helps to differentiate it from spinal meningioma.

References:

Dr. KS Tai
Department of Radiology, Queen Mary Hospital, Hong Kong
Certificate Course on Medical Genetics

Objective: The field of medical genetics has seen rapid advances in the last ten to twenty years, especially so with the knowledge brought about by the Human Genome Project. This course aims to provide the participants an overview and update in this field, so that they can appreciate how the practice of medicine is changing with the genetic advances.

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<tr>
<th>Date</th>
<th>Topic</th>
<th>Lecturer</th>
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<tr>
<td>3 January 2007</td>
<td>Medical Genetics in Hong Kong - An Overview</td>
<td>Dr. Stephen Lam</td>
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<tr>
<td>10 January 2007</td>
<td>Genetic Counseling</td>
<td>Dr. Ivan Lo</td>
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<td>17 January 2007</td>
<td>Chromosomal Disorders in Hong Kong</td>
<td>Mr. Chan Wing-kwong</td>
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<td>24 January 2007</td>
<td>Application of Molecular Genetics in Patient Care</td>
<td>Dr. Brian Chung</td>
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<tr>
<td>31 January 2007</td>
<td>Prenatal Diagnosis &amp; Therapy</td>
<td>Dr. Leung Kwok-yin</td>
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<td>7 February 2007</td>
<td>Treatment Strategies in Genetic Diseases</td>
<td>Dr. Larry Baum</td>
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<td>Dr. Richard Choy</td>
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Date: 3 January 2007 to 7 February 2007 (Every Wednesday)
Time: 7:00 p.m. - 8:30 p.m.
Venue: Lecture Hall, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong
Course Fee: HK$960 (6 Sessions)
Language: English
Certificate: Awarded to participants with a minimum attendance of 70%
Enquiry: The Secretariat of the Federation of Medical Societies of Hong Kong
Tel.: 2527 8898 Fax: 2865 0345 Email: info@fmshk.org

CME/CPE Accreditation applied for
For downloading the application form, please refer to our website:
http://www.fmshk.org
Certificate Course on Drugs Safety in Old Aged Home
(Course No. C112)

Objective: To enhance safety of drugs handling in old aged home

<table>
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<th>Date</th>
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<tr>
<td>9 January</td>
<td>7:00 p.m. - 8:30 p.m.</td>
<td>Lecture Hall, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong</td>
<td>HK$350 (2 Sessions)</td>
<td>Cantonese (Supplemented with English)</td>
<td>Awarded to participants with a minimum attendance of 70%</td>
<td>The Secretariat of the Federation of Medical Societies of Hong Kong</td>
<td>2527 8898</td>
<td><a href="mailto:info@fmshk.org">info@fmshk.org</a></td>
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<td>16 January</td>
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THE FEDERATION OF MEDICAL SOCIETIES OF HONG KONG

CERTIFICATE COURSE FOR MEDICAL AND HEALTHCARE PROFESSIONALS

Certificate Course on Drug Dispensing in Office Clinics

(Objective: To enhance safety and efficacy of clinic assistants in drug dispensing in office clinics.)

Drug Classification in Hong Kong – A Simple Approach
Mr Wilson Wong

Drugs Stock Keeping and Recording
Mr Wilson Wong

Good Dispensing Guidelines
Dr Ben Feng

Clinic Dispensing Management
Mr Wilson Wong

Date: 2007年1月4日至2007年1月25日
Time: 下午2时至3时30分
Place: 馬鞍山亞公角道33號，沙田醫院一樓會議室(I)
Fee: 每位港幣$500元(4堂)
Language: 粵語
Note: 如出席率達70%，可獲發證書

For inquiries and registration, please contact the Medical Society Secretariat.

香港醫學組織聯繫

電話: 2527 8898 傳真: 2865 0345 電郵: info@fmshk.org

或瀏覽網址: www.fmshk.org 下載報名表格
Application Form for Certificate Course

Name of Applicant:(Prof/Dr./Mr./Ms./Mrs.)* ________________________ (English) ____________________ (Chinese)
*Please delete as appropriate (in block letters)

Correspondence Address: ____________________________________________________________

Tel. No.: ___________________ Fax No.: ___________________ Age: _________ Sex: __________

Email Address: ____________________________ Occupation: ____________________________

Course Title:  □ Certificate Course on Drugs Dispensing in Office Clinic (C114)
              □ Certificate Course on Medical Genetics (C111)
              □ Certificate Course on Drugs Safety in Old Age Home (C112)

Education :  □ Secondary □ Undergraduate □ Postgraduate □ Others________________________
(please tick)

Fee enclosed (please tick):

□ Cheque No: ______________________ made payable to The Federation of Medical Societies of Hong Kong

□ Cash HK$ ______________________

_________________________________________  ______________________________________
Signature                                      Date

Note:
1. The application form together with the appropriate fee should be sent to the Secretariat of the Federation of Medical Societies of Hong Kong, 4/F Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong.
2. Fees are not refundable, except in the event of a course being oversubscribed or cancelled.
3. The Federation of Medical Societies of Hong Kong reserves the right to cancel the course should too few participants enroll for the course.
4. No classes will be held when typhoon signal No. 8 or above or black rainstorm warning is still hoisted after 12:00 noon. Please contact the Secretariat at 2527 8898 to enquire matters regarding cancellation of class due to typhoon or black rainstorm.

For office use:

Registration confirmed on: ______________________  Registration Number: ______________________
Cheque Issuing Bank: ______________________  Cheque Number: ______________________
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