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Asia Pacific Aesthetic Medicine

Certificate Course 2008
Macau Fisherman's Wharf
24-26 June

Jointly Organised by: American Academy of Aesthetic Medicine | mesotherapy | SEMAL | EZYHEALTH CONFERENCES & EVENTS

Supported by:

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MICHEL DELUNE, M.D. (USA)

Touted as the foremost authority in aesthetic dermatology, Dr. Delune is a Founding Member and President of the American Academy of Aesthetic Medicine (AAAM). He is also one of the founding and Honorary members of the European Academy of Dermatology and Venereology (EADV) and has been the first treasurer for many years before he became its President elected. As part of his experience and accomplishments, Dr. Delune is noted for his contributions in the private fellowship with the famed Dr. Obagi at the Obagi Dermatology Medical Clinic in Beverly Hills, California. He is also recognized for his educational contributions as invited professor of aesthetic medicine at international universities in Belgium, Italy, Spain and Mexico.

MELVIN L. ELSON, M.D. (USA)

Dr. Elson has researched in aging, photoaging and disorders, especially soft tissue augmentation and topical vitamins. He has authored numerous scientific papers and has written two books on the aging face and appearance. Dr. Elson holds the U.S. Patent #5,510,391 for the use of topical vitamin K. He also developed the MD Formulations glycolic acid skin care line and was the first to discover the treatment of stretch marks with Retin A. He has many firsts in his research armamentarium.

***Profile of Faculty Member from Hong Kong is not available at time of print.**

Level 1 - Certificate Course in Aesthetic Medicine (3-day course)

Day 1

0830 - 0900hrs
INTRODUCTION TO THE WORLD OF AESTHETIC MEDICINE
(Dr Michel Delune)

AESTHETIC DERMATOLOGY (PART 1)
(Dr Melvin Elson)

0900 - 1030hrs
- **Facial Wrinkles Classification**
- **Botulinum Toxin Type A (BTA)**
  - Introduction
  - Indications and consent
  - Selection of patients
  - Complications
  - Advice pearls

1100 - 1230hrs
Live Demonstration & Hands-on on Botulinum Toxin A

1330 - 1430hrs
Skin Fillers
1. Introduction and types
2. Indications and consent
3. Selection of patients
4. Complications
5. Advice pearls

1430 - 1600hrs
Live Demonstration & Hands-on on Skin Fillers

1630 - 1715hrs
Management of Complications of Botulinum Toxin A & Filler Injections

1715 - 1745hrs
Marketing - The Ethical Business of Aesthetic Medicine

Day 2

Faculty Member: Dr Michel Delune

0830 - 1000hrs
Skin Conditioning
- Indications and contraindications
- Side effects
- Results
- Skin regimen

1030 - 1200hrs
Chemical Peelings
1. Chemical peelings
   - Indications and patients selection
   - Contraindications
2. Peeling chemistry
   - Glycolic acid
   - Salicylic acid
   - Resorcin
   - Pyruvic
   - TCA
     - Easy Peel
     - Krystal Peel
     - Blue Peel
3. Apothepeel
4. Other peelings

1300 - 1500hrs
Live Demonstration & Hands-on on Chemical Peels
- Glycolic Acid Peel
- Easy Peel
- Salicylic Acid Peel
- Apothepeel

1530 - 1700hrs
Management of Complications of Chemical Peels

Day 3

Faculty Member: Dr Michel Delune

0830 - 1230hrs
LASERS, PHYSICAL PEELINGS AND TECHNOLOGIES IN AESTHETIC MEDICINE
1. Introduction to and the physics of lasers
2. Lasers safety
3. Types of lasers
4. Photorejuvenation techniques
   - Intense Pulsed Light (IPL)
   - Light Emitting Diode (LED)
   - Photodynamic Therapy (PDT)
   - Fraxel
5. Physical peelings
   - Cryopeeling
   - Microdermabrasion
   - Sandbrasion
   - Dermabrasion
6. Live Demonstration and Hands-on on Laser machines (1600 - 1700hrs)
7. **Management of Complications of Laser Treatment (1700 - 1730hrs)**

1730 - 1745hrs
Presentation of Certificates

> "Who should attend: Medical doctors, regardless of specialties"

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Editorial

Dr. Edmond CH Chan

Editor

Dr. Edmond CH Chan

Family doctors deal with all sorts of problems ranging from physical to mental illnesses. In the past decade, advances in treatment techniques and pharmacotherapeutics have revolutionized the management of diseases in mankind. It is therefore important for the generalists to acquaint themselves with the new knowledge so as to provide the most up to date and effective treatment to patients.

In this issue of the Medical Diary, I have asked several authoritative specialists to give brief but thorough reviews on a number of commonly encountered disease entities.

Therapeutic endoscopy has progressed enormously in recent years. Minimally invasive surgery is gradually becoming a commonly used tool in treating various gastrointestinal diseases aiming to avoid open surgery. There is also a section dedicated to discussing the current treatment in Chronic Hepatitis B, one of the most commonly found diseases in Hong Kong. We have also been able to provide you with updates on breast cancers and abdominal obesity.

Doctors lead stressful lives. I am sure you will find the article titled "Doctor and Stress" most relevant in your daily lives. Striving to achieve work life balance helps you become a better doctor as well as a healthier and happier person! Thus I have asked a gourmet and wine connoisseur to share his tips on food and wine. Enjoy! Bon appetit!

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* Myocardial infarction (MI), stroke, or cardiovascular (CV) death.
1. CAPRIE Steering Committee. Lancet 1996;348:1329-1339
2. Antithrombotic Trialists' Collaboration. BMJ 2002;324:71-86
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CAPRIE = Randomised, double-blinded trial to assess the relative efficacy of clopidogrel (75 mg qd) and aspirin (325 mg) in reducing the risk of a composite endpoint of myocardial infarction, ischaemic stroke and vascular deaths in 19,185 patients with symptomatic atherosclerotic disease (peripheral, cerebral or ischaemic heart disease)

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Doctors and Stress

Dr. Josephine GWS Wong

MBBS, MA, MRCPsych, FHKCPsych, FHKAM (Psychiatry)

Specialist in Psychiatry

Dr. Josephine GWS Wong

Introduction

It is well-known that being a doctor is stressful. Previous studies have shown a higher level of stress amongst doctors when compared to the general population. Firth-Cozens[1] noted that the proportion of doctors showing above threshold levels of stress is around 28%, in cross-sectional and longitudinal studies, compared to around 18% in the general working population. There is also evidence to show an increased rate of psychological morbidity, for example, depression, anxiety and substance abuse amongst doctors. Local data are still limited, but there is preliminary evidence to suggest elevated anxiety, depression and stress in Hong Kong medical students[2] and interns (unpublished data). Rates of stress are elevated in all doctors, regardless of the setting in which they work, but junior doctors and female doctors are particularly at risk. As doctors, we are accustomed to identifying stress in our patients. We inform them about health consequences of excess stress and advise them on lifestyle changes and relaxation. The pathology is usually in others, in patients we look after. Are we then able to identify stress in ourselves, manage our stress in an adaptive manner and seek help when such stress becomes too much to handle?

Transactional Model of Stress

Before we go further, it is important to understand what stress is. The transactional model of stress by Lazarus & Folkman[3] conceptualises stress as resulting from an imbalance between demands and resources, or as occurring when pressure exceeds one's perceived ability to cope. Therefore, what appears stressful to one person may be a welcome challenge or all-in-a-day's-work for someone else. More importantly, the transactional model introduces room for intervention. Stress can be reduced by enhancing the individual's resources, for example by helping people change their perception of stressors and by enabling them to cope and improve their confidence in their ability to do so. In addition, the demand can also be modified, for example by increasing its predictability and controllability through contingency planning, training and risk management. Primary and secondary prevention strategies are valuable interventions that modify the stress itself and response to stress. These will be discussed in detail later in the paper.

Sources of Stress

The sources of stress in medical practitioners vary with the type of medical practice (private vs. public, hospital-based vs. community-based) and specialty. There are many potential sources of stress that relate to the job, the organisation, the doctor himself/herself, work-life balance and relationships with other people (see Box 1). Usually, a number of these factors are present in an individual doctor, and therefore the difficulties faced by the doctor are compounded and complicated.

In addition, there is an apparent mismatch between what doctors are trained for and what they are required to do. For example, in the medical curriculum, there is much focus on patho-physiology, diagnosis and treatment. There is now increasing emphasis on communication skills, law and ethics in medical education. However, other key aspects of a doctor's job like administrative and financial management are poorly addressed, and these often cause stress amongst doctors.

Box 1 Sources of Stress for medical practitioners

The job
Workload
Time pressure
Administrative duties
Sleep deprivation
No regular meals
Threat of malpractice suits

The organisation
Career structure
Career uncertainties
Inadequacy of resources and staff
Lack of senior support
Culture and climate of the organisation

The doctor
Personality (e.g. perfectionistic, Type A)
High demands on self and others
Dealing with death and dying
Confrontation with emotional and physical suffering

Relationships with other people
Staff conflicts
Bullying
Professional isolation
Patient's expectations and demands
Level of support from friends and family

Work-life balance
Stress over-spill from work to home and vice versa
Lack of exercise and other leisure activities
Lack of free time
Home demands
Disruptions to social life

Consequences of Stress in Doctors

Physical complications of increased stress are well-known. These include: insomnia, gastrointestinal disturbance, tension headaches, hypertension, fatigue, lowered immunity, menstrual irregularities and sexual

dysfunction. Adverse effects of stress may affect not only the individual doctor, but also his/her family life, marriage and social life. Furthermore, stress is associated with burnout[4,5] (Box 2) in which 'what started out as important, meaningful and challenging work becomes unpleasant, unfulfilling and meaningless. Energy turns into exhaustion, involvement turns into cynicism and efficacy turns into ineffectiveness'. Burnout has been shown to be associated with increased depression and physical illness, notably musculoskeletal disorders in women and cardiovascular disorders in men. Burnout is also associated with an increase in malpractice suits to the extent that American insurance carriers are sponsoring stress reduction seminars as a liability prevention strategy[6]. Emotional exhaustion and detachment can fundamentally change a doctor's perception of the doctor-patient relationship, and can also affect interactions with family members. Stress also leads to increased rates of minor and major psychiatric illness, including mood disorders, anxiety disorders, substance abuse. As a result of stress, quality of patient care may be compromised and medical errors may increase[7].

Box 2 Burnout

Components of burnout (Maslach et al, 2001):

(1) Emotional exhaustion: feeling emotionally drained by one's contact with other people, lack of replenishment, unable to face another day or another person in need (individual stress dimension of burnout)
(2) Depersonalisation/ cynicism: negative feelings and cynical attitudes towards the recipients of one's service of care, can turn to dehumanisation (interpersonal dimension of burnout)
(3) Reduced personal accomplishment: a decline in feelings of competence and productivity at work, growing sense of inadequacy about ability to help others, may result in self-imposed verdict of failure (self-evaluation dimension of burnout)

Warning signs of burnout

- Chronic fatigue - exhaustion, tiredness, a sense of being physically run down
- Anger at those making demands
- Self-criticism for putting up with the demands
- Cynicism, negativity, and irritability
- A sense of being besieged
- Exploding easily at seemingly inconsequential things
- Frequent headaches and gastrointestinal disturbances
- Weight loss or gain
- Sleeplessness and depression
- Shortness of breath
- Suspiciousness
- Feelings of helplessness
- Increased degree of risk taking

Barriers to Care

Despite the high prevalence of stress in doctors, and a myriad of physical and mental health consequences, doctors are notoriously reluctant to seek help for themselves[8]. The subjective experience of being ill is not taught or much discussed at medical school. Doctors are often perfectionistic, self-sacrificing people with high levels of personal drive and altruism. This predisposes them to put others' needs before their own, thus increasing stress but their personality also makes it hard for doctors to self-reflect or to seek help. For most doctors, stress or illness is what happens to other people, and doctors are there to help them get better. It is sometimes very difficult for doctors to acknowledge their own stress and distress, and even more difficult to acknowledge that their work performance is affected as a result. Some doctors deal with stress by engaging in wishful thinking and emotional distancing, but these do not work long term. Doctors are also 'poor' patients due to maladaptive health behaviours[9,10] like self-medication, not seeking a formal medical consultation when ill and continuing to work when unwell. Most doctors do not have their own general practitioner. Some doctors regard falling ill as shameful, especially when the illness is psychological in nature. Some think that they should always be able to master and control their emotions and it is a sign of weakness when they experience emotional distress. There are also concerns about being stigmatised by fellow doctors or being discriminated against in their career development if they are in the mental health system.

These attitudes reflect widespread stigma towards mental illness in the general population and within the medical profession[11].

What Can We Do About This?

Prevention is Better than Cure

Stress is inevitable, but it is mismanaged stress that is damaging in its consequences. There is now much attention on measures that promote mental health and wellbeing in medical students and doctors, and prevention of stress-related morbidity. In considering preventative measures, it is important to address both primary and secondary prevention. Primary prevention aims to enhance mental health literacy and psychological wellbeing generally, in the population in question (in this case, doctors and medical students). This might include workshops on time management, stress management, mindfulness-based stress reduction, coping skills training, relaxation training, etc. Secondary prevention measures target the 'at risk' group such that help and support can be provided in a timely and proactive manner, to prevent further deterioration and impairment. Doctors themselves also have a role to play in looking after their own mental health and managing stress. Self help strategies are often adequate without having to seek outside assistance (Box 3).

Examples of Services Available

Below are examples (not an exhaustive list) that illustrate primary and secondary prevention resources currently available to medical students and practising doctors.

Medical Students

There are good reasons for starting prevention work in medical school. Medical students are our future doctors. Medical education is in itself a stressful process. A previous study found elevated depression, anxiety and stress in local medical students[2]. Students' mental health (or rather the lack of it) affects their academic attainment, social life, and the quality of service they provide to the community as future doctors. Moreover, their own mental distress may influence the way they perceive mental health and help-seeking in the care of their future patients. In a 2003 Royal College of Psychiatrists Report[12], it outlined a key responsibility of medical schools to ensure that their graduates are (1) aware of their personal and professional limitations; (2) willing to seek help when necessary; and (3) aware of the importance of their own health, and mental health and its impact on their ability to practise as a doctor.

One example of resources within medical school that address psychological wellbeing of the student body is the Programme for Effective Transition and Student Support (PETSS) at the medical faculty of the University of Hong Kong[13]. PETSS aims to promote mental health literacy, with student support services and activities to develop leadership within the student body. There are primary prevention activities that aim to enhance mental health awareness and resilience in medical students e.g. an educational website on mental health issues designed by medical students in a Mental Health Support Group[14], workshops on time management, study skills, mindfulness-based stress reduction, emotional and social competence, etc. In addition, there is a buddy scheme in which Year 1 students are mentored by more senior medical students to help them adapt to life in university.

Secondary prevention strategies that aim at helping 'at risk' medical students include the establishment of a Wellbeing Committee that consists of a group of volunteer teachers who provide support and counselling to students in need. The issues that students bring to the Wellbeing Committee include emotional problems, relationship issues, study difficulties, doubts about commitment to the course, etc. In addition, the Mental Health Support Group[14], a pioneering student-initiated peer support network for fellow medical students runs a discussion forum and offers email counselling for individuals. Mental Health Support Group members are trained in Mental Health First Aid and basic counselling such that they can respond appropriately if they come across students in distress. Preliminary evaluation suggests that MSG services are welcomed by medical students. These are specific services for medical students. Students can also access generic support services provided by the university itself through its health service or counselling centre.

Practising Doctors

For practising doctors, organisational and occupational changes such as increasing support for staff, reducing non-medical workload, and reducing working hours are all likely to reduce mental stress in doctors. The establishment of Oasis[15] at the Hospital Authority in 2002 was one example of how primary prevention can be initiated by an employer. Oasis, Centre for Personal Growth and Crisis Intervention, aims to promote a culture of care within the Hospital Authority. It organises primary prevention activities to enhance staff members' ability to develop and mobilise their own inner resources to overcome life's difficulties. There are educational talks, workshops (for example on resilience training, life education) and quiet rooms which provide an environment in which to meditate and have time to oneself. There is also training of critical incident management teams in each hospital in order to facilitate and coordinate timely staff support in case of a crisis, for example suicide of a colleague or a serious medical error. In addition, Oasis also provides treatment by clinical psychologists for health care workers (including doctors) who are at risk or already impaired, in a safe and confidential setting away from their usual workplace.

It is heartening to see that seeds appear to be sowed for a culture change within the medical profession such that high stress is acknowledged and taking steps to enhance one's own mental health is no longer embarrassing or burdensome. There is an increasing recognition that we need to 'care for the carers'. However, there is still room for improvement since services for doctors working outside the Hospital Authority is still lacking. For doctors under stress and in distress, it is important that they feel able to seek help and advice from a service that is confidential, accepting and accessible.

Ethical Issues in Treating Doctors as Patients

While primary and secondary prevention strategies are important, there will always be doctors whose psychological distress becomes so severe that clinical intervention becomes necessary. Although the ethical duties owed to a doctor-patient is the same as those to a member of the general public, there are unique challenges in treating doctors as patients and in establishing a therapeutic alliance[8]. As outlined earlier, there are barriers to a doctor seeking help for psychological distress. Sometimes, a doctor-patient may be unaware of or unwilling to accept the severity of his/her mental difficulties. In some situations, issues arise regarding the fitness of a doctor-patient to practise medicine. These present a difficult dilemma for the treating doctor as there is a conflict between his/her loyalties to a doctor-patient and his/her duty to report a doctor who may pose a risk to patient safety. Any disclosure of concerns about patient safety would affect the livelihood of the doctor-patient, and may result in suspiciousness and anger within the therapeutic relationship, with minimisation of symptoms, distress and functional impairment. The relationship between the treating doctor and the doctor-patient can turn from what should be supportive to adversarial. Whilst this dilemma is similar to other situations in which patient confidentiality conflicts with public safety, the treating doctor may find this particularly difficult because the doctor-patient is a colleague. The best approach would be one of frankness and open discussion about the treating doctor's concerns. It is likely that the doctor-patient would opt for voluntary sick leave or a temporary withdrawal from frontline clinical service, rather than making it necessary for the treating doctor to report him/her to the licensing authority.

Reflections and Conclusions

Being a doctor is physically and emotionally demanding. There is good evidence to show that doctors are at higher risk of stress than the general population. There needs to be a culture change within the profession for doctors and their employers to pay closer attention to how doctors deal with the demands of the job, how they look after their own mental health and attain wellbeing and a sense of balance between their working and personal lives. Doctors are expected to be conscientious, compassionate and self-sacrificing. However, we must remember that doctors need to nurture themselves, address their own spiritual needs and engage in self-care practices, in order to be able to give their best to patients.

Peer support and a sense of community are important. Sometimes, doctors feel that their problems cannot be understood by people outside of the profession, therefore developing and maintaining a professional network is valuable. Some private doctors work in a single-handed

practice, thus adding to a sense of professional isolation. Hong Kong may need to follow in the footsteps of other countries e.g. Australia[16] and Britain[17] in developing multi-faceted support services for doctors under stress. We quote a wise and insightful comment from Firth-Cozens 'Getting things right for patients means first getting things as good we can for those who deliver their care.' We look forward to further discussions about how psychological wellbeing of doctors in Hong Kong can be promoted.

Box 3 Self help

Doctors can help themselves to reduce the impact of stress and avoid burnout or other psychological morbidity.

(1) Identify the most important sources of stress in your life
(2) Time management: enhances doctor's sense of control, increased productivity, reduces overload strain therefore reduces anxiety.
(3) Managing political and people problems: make sure you give enough time to the people that matter, keep a distance from people who drain you of emotional energy, seek social support
(4) Avoid exhaustion: make sure you get enough rest, take a break from time to time, engage in a leisure activity, exercise regularly, have a healthy diet
(5) Protect the meaning of your job: manage your workload, focus on aspects of your job that gives you satisfaction, delegate when you can, learn to say no
(6) Maintain a good work-life balance
(7) Do not expect perfection
(8) Learn relaxation techniques
(9) Don't sweat the small stuff!

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What is the Role of Carotid Intimal Media Thickness (CIMT) in the Management of Atherosclerosis?

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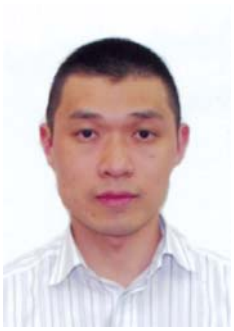

Dr. Chun-ho Cheng Dr. Yik-hon Cheng

This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded one CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 30 June 2008.

It appeared in the recent newspaper, a 53 year old gentleman developed sudden cardiac arrest in a gymnasium during his routine work-out on a treadmill. According to the information provided, he was engaged in regular exercise programme and underwent annual check-up. Even though the cause of his sudden death was not published, it was likely due to either cerebral or cardiac causes.

Routine screening can pick up significant stenotic lesion but it cannot prevent myocardial infarction. Increase plasma LDL cholesterol (LDL-C) may injure endothelial cells. Endothelial cell injury would subsequently lead to plaque formation which reduces lumen size and limit blood flow. Rupture of atherosclerotic plaque can be triggered by stress or exercising. The pre-ruptured plaque itself may not cause significant stenosis (lumen size 40%-60%) prior to the acute episode.

I would like to discuss several cases to illustrate our clinical decision.

Case No.1: Case No.1: A 57 years old gentleman suffers from hyperlipidaemia. He is also a hepatitis B carrier. During his annual checkup, his LDL-C was found to be 4.5 mmol/l. Routine exercise showed 1.5mm ST depression on his lateral chest leads. Myocardial perfusion scan performed which showed no evidence of reversible perfusion abnormality. His carotid intimal thickness study by ultrasound showed significant patchy thickening on both sides (1.3mm to 1.4mm). Based on these finding, he was advised to receive statin and aspirin treatment.

He turned down my offer and promised to come back for assessment six months later. He came back after two months and revealed that he has suffered from a heart attack during his trip to Toronto and required urgent angioplasty and stenting. Currently, he is maintained on high dose of statin, aspirin and plavix. The case illustrates that there is a strong correlation between CIMT and coronary atherosclerosis.

Case No.2: A 72 years old gentleman who sustained an inferior myocardial infarction 15 years ago. Since then, he has changed to a total vegetarian diet. His current LDL-C is 1.5mmol/l. He has decreased his body weight from 150lbs to 130lbs. In addition, he is maintained on a regular exercise programme. Recent myocardial perfusion abnormality showed no evidence of reversible ischaemia in the remaining territory. This case illustrates that dietary changes can reduce the LDL-C dramatically.

Nevertheless, one has to bear in mind that these changes can only be observed in certain subset of individuals.

The POSCH (Program on the Surgical Control of Hyperlipidaemia) study demonstrated that ileal bypass surgery can reduce the LDL-C by 38% and the CHD-Mortality by 39%.

Case No.3: A 65 years old gentleman who is a chronic smoker. He sustained a minor cerebellar infarct two years ago. Investigation showed his LDL-C was 3.8 mmol/l and HDL-C was 1.2 mmol/l. With statin therapy, his LDL-C has reduced to 1.8 mmol/l, but he continues to smoke. The CIMT showed definite progression despite a relative low LDL-C level. This case has high-lighted the importance of total risk management.

Cigar or cigarette smoking is one of the most important risks factors which can dilute or nullify the effect of lipid lowering drugs. The manufacturer or cigar shop has lured the middle or rich segment of our society that they are not inhaling the cigar smoke. The cigar smoke "only stays" in the upper airway. This "hypothesis" is well accepted by the rich and even the learned professionals. They continue to smoke cigar at regular intervals with the belief that it causes no risk to their cardiovascular system.

Apart from low fat diet, we should pay attention to unsaturated fats (both polyunsaturated and monounsaturated fats will lower the total cholesterol and LDL-C. Olive oil and peanut oils contain mainly monounsaturated fats. Excessive polyunsaturated fats may be associated with decrease in good cholesterol (HDL-C). Trans-fats are found in the food manufacturing process during which the product is hydrogenated to change oil from liquid to solid. This process can lengthen the shelf life and enhance the taste. Trans-fats are however detrimental to cardiac health

because they increase bad cholesterol, decrease good cholesterol and affect the essential fatty acids metabolism. Consumers are reminded of reading the labels when choosing packaged foods, and be aware of the names like hydrogenated oil, partially hydrogenated oil, shortening, etc. There is also a small amount of trans fat naturally found in animal meats as well as dairy products.

Despite the wide spread prescription of lipid lowering drug, only 51% of the patients on lipid lowering therapy achieved goal as in the Eurospire II study. In the NCEP ATP III, they have set different targets for different individuals with risk factors. The LDL-C target is 4.1mmol/l for individuals with less than 2 risk factors and this level is lowered to 1.8mmol/l for high risk individuals. I personally think that these guidelines will be changed as the CIMT provides a visual image of atherosclerosis. It may become the future tool for diagnosis and treatment of cardiovascular risk.

CIMT is able to help the clinician to make the following decision:-

(i) When to start treatment.
(ii) The need for further adjustment.
(iii) The need to look for other risk factors. (e.g. Homocystein, Lp(a))

The visual image recorded also enhances patient's compliance.

Why are patients on statin still at risk? The following are some of the causes:-
(1) Started too late.
(2) Additional (unknown) inadequately treated risk factors.
(3) Non compliance.
(4) Non responders.
(5) Insufficient treatment.

In real life, one can start the treatment earlier as primary prevention. Once again, we need to stress global risk and treat all modifiable risk factors. We may need to set new lower targets (the LDL-C level for 6 month old baby is 1.56mmol/l).

High dose statin may have additional pleotrophic effect. It can decrease inflammatory markers e.g. CRP level. Statin trials can reduce the cardiovascular event by 19% to 35%. In the HDL Atherosclerosis Treatment study (HATS), the combination therapy with simvastatin + niacin, alone or in association with autioxidants and vitamins, produces a statistically significant reduction in the composite end point between 90% to 60%, respectively, compared to placebo.

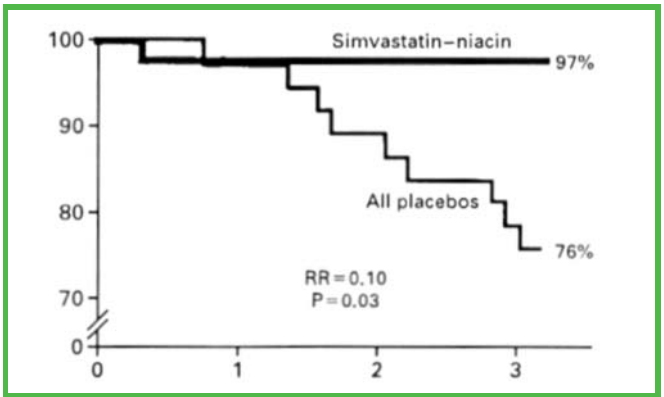

Figure 1. Kaplan-Meier Curves for the time of the first components of the composite primary clinical end point (death from coronary causes, nonfatal MI, confirmed stroke, or revascularization for worsening ischaemia. X-axis (Years); Y-axis (patients free of events %)

In the ARBITER - III trial, among 57 participants treated with extended - release niacin (ERN) for 24 months, there was additional significant regression of CIMT.

Metabolic syndrome is a potential major risk factor for coronary artery disease. The following are the criteria for metabolic syndrome:-

Defining Metabolic Syndrome

Individuals with any of the following:

Waist circumference	Men Women	>102 cm (>40 in) >88 cm (>35 in)
Triglycerides		≥1.7mmol/l (150 mg/dl)
HDL-C	Men Women	<1.03mmol/l (40 mg/dl) <1.29mmol/l (50 mg/dl)
Blood pressure		≥ 130/85 mm Hg
Fasting glucose		≥ 6.1mmol/l (110 mg/dl)

According to Framingham heart study, high level of HDL-C has a protective role (HDL-C > 1.68mmol/l). Apart from LDL-C lowering, efforts should be considered to raise HDL-C. Regular exercise is effective in raising HDL-C in certain subset of patients.

In a study which assesses the benefit of exercise, among the 59% of the activity-related reduction in CVD. Inflammatory/haemostatic biomarkers (high-sensitivity CRP, fibrinogen, and soluble intracellular adhesion molecule-1) provided the largest contribution to lowered risk (33%), followed by blood pressure (27%), lipids (19%), body mass index (10%), and glucose abnormalities (9%), with minimal contribution observed from measures of renal function or homocysteine (<1%). The inverse association between physical activity and CVD risk is mediated in substantial part by known risk factors particularly inflammatory, haemostatic factor and blood pressure.

Modern imaging techniques such as CT coronary angrogram can visualise the coronary anatomy. It enables us to pick up early atherosclerosis. In the presence of calcification, the accuracy of this technique has dramatically decreased. At present, I do not use this as a screening procedure because of the high dose of X-ray exposure.

Carotid artery intimal thickness study is useful in the assessment of atherosclerosis. It can provide a visual image to your patients.

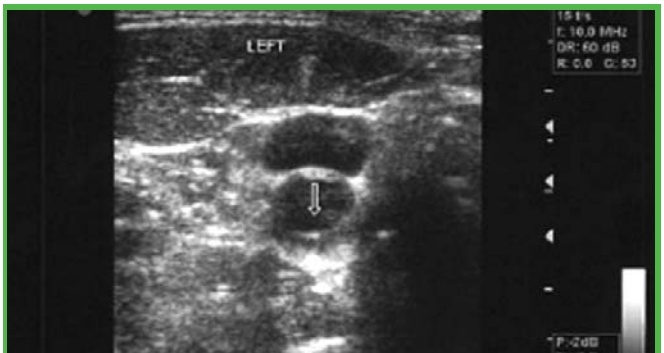

Figure 2. Cross-section of carotid artery showing soft atherosclerotic plaque in a male 40 years old patient

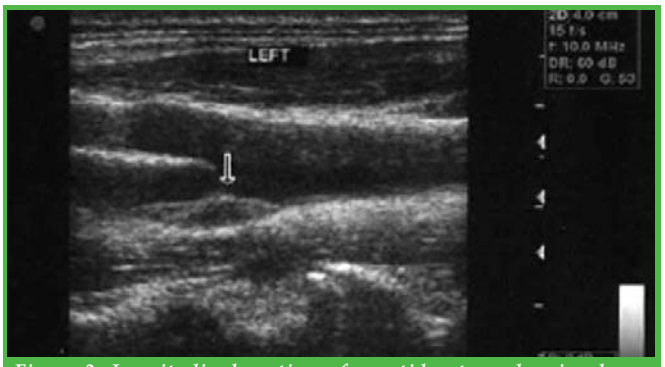

Figure 3. Longitudinal section of carotid artery showing large atherosclerotic plaque in 39 year old male patient

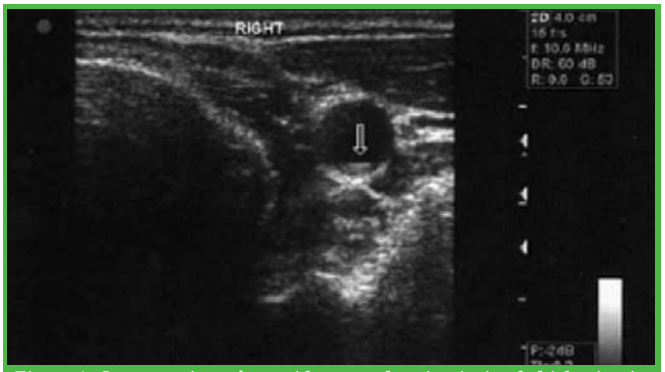

Figure 4. Cross-section of carotid artery showing intimal thickening in a male 45 years old patient

It can help us to make clinical decisions and is affordable in our daily practice. It can be repeated as frequently as necessary. In future, half-hearted approach is not useful in the prevention of atherosclerosis. Total risk management is essential.

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "What is the role of carotid intimal media thickness (CIMT) in the management of atherosclerosis?" by Dr.Chun-ho Cheng and Dr. Yik-hon Cheng, 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 30 June 2008. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

1. Smoking cigar has no effect on atherosclerosis.

2. Trans fats are detrimental to heart health.

3. High blood homocystein level is associated with low incidence of coronary atherosclerosis.

4. Increase level of lipo-protein (a) is associated with increase incidence of coronary atherosclerosis.

5. The low-density cholesterol level in 6 months old baby is 1.56 mmol/litre.

6. Regular exercise is effective in raising high density cholesterol level in every body.

7. There is an inverse association between physical activity and cardiovascular disease risk.

8. In the presence of coronary calcification, CT coronary angiogram enable us to assess coronary stenosis accurately.

9. Carotid artery intimal thickness study is useful in the assessment of atherosclerosis.

10. Total risk management is essential in the management of atherosclerosis.

ANSWER SHEET FOR JUNE 2008

Please return the completed answer sheet to the Federation Secretariat on or before 30 June 2008 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

What is the Role of Carotid Intimal Media Thickness (CIMT) in the Management of Atherosclerosis?

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Answers to May 2008 issue

Practical Hints in the Management of Urinary Tract Infections

1. **Fales** 2. **b** 3. **False** 4. **c** 5. **d**

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Abbreviated Prescribing Information

Product Name: Zeffix™

Active Ingredient: Lamivudine

Indications: treatment of patients with chronic hepatitis B (CHB) and evidence of hepatitis B virus (HBV) replication.

Dosage & Administration: *Adults:* 100mg once daily. Children (*2-17 years old*): 3mg/kg once daily up to max. 100mg/day. Children (*<2 years old*): insufficient data to propose specific dosage recommendation in this age group. Renal impairment: serum lamivudine concentrations (AUC) are increased in patients with moderate to severe renal impairment due to decreased renal clearance. The dosage should be reduced for patients with a creatinine clearance of <50ml/min (see Table).

Table: Adjustment of Adult Dosage in Accordance with Creatinine Clearance

Creatinine clearance (ml/min)	First dose of Zeffix	Maintenance Dose Once Daily
30 to <50	100 mg	50 mg
15 to <30	100 mg	25 mg
5 to <15	35 mg	15 mg
<5	35 mg	10 mg

Contra-indication: Zeffix tablets are contraindicated in patients with known hypersensitivity to Zeffix or to any ingredients of the preparations.

Warnings and Precautions: During treatment patients should be monitored regularly during treatment by a physician experienced in the management of chronic hepatitis B. If Zeffix is discontinued or there is a loss of efficacy, some patients may experience clinical or laboratory evidence of recurrent hepatitis. Exacerbation of hepatitis has primarily been detected by serum ALT elevations, in addition to the re-emergence of HBV DNA. Most events appear to have been self-limited. Fatalities are very rare and the causal relationship to discontinuation of Zeffix treatment is unknown. If Zeffix is discontinued, patients should be periodically monitored both clinically and by assessment of serum liver function tests (ALT and bilirubin levels), for at least four months for evidence of recurrent hepatitis; patients should then be followed as clinically indicated. For patients who develop evidence of recurrent hepatitis post-treatment, there are insufficient data on the benefits of re-initiation of Zeffix treatment. In patients with moderate to severe renal impairment, serum lamivudine concentrations (AUC) is increased due to decreased renal clearance, therefore the dose should be reduced for patients with a creatinine clearance of <50 ml/min. Transplantation recipients and patients with advanced liver disease are at greater risk from active viral replication. Due to marginal liver function in these patients, hepatitis reactivation at discontinuation of Zeffix or loss of efficacy during treatment may induce severe and even fatal decompensation. It is recommended that these patients are monitored for parameters associated with hepatitis B, for liver and renal function, and for antiviral response during treatment. If treatment is discontinued for any reason, it is recommended that these patients are monitored for at least 6 months post cessation of treatment. Patients experiencing signs of hepatic insufficiency during or post-treatment should be monitored frequently, as appropriate.

HBV viral subpopulations (YMDD and HBV) with reduced susceptibility to Zeffix have been identified during extended therapy. In a minority of cases this variant can lead to recurrent hepatitis. For the treatment of patients who are coinfected with HIV and are currently receiving or are planning to receive an antiretroviral treatment regimen including lamivudine, the dose of lamivudine usually prescribed for HIV infection should be maintained. There is no information available on maternal-foetal transmission of hepatitis B virus in pregnant women receiving treatment with Zeffix. The standard recommended procedures for hepatitis B virus immunization in infants should be followed. Patients should be advised that therapy with Zeffix has not been proven to reduce the risk of transmission of hepatitis B virus to others and therefore, appropriate precautions should still be taken.

Interaction: Zeffix is predominantly eliminated by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system e.g. trimethoprim.

Administration of trimethoprim/sulphamethoxazole 160 mg/800 mg increased Zeffix exposure by about 40%. Zeffix had no effect on the pharmacokinetics of trimethoprim or sulphamethoxazole. However, unless the patient has renal impairment, no dosage adjustment of Zeffix is necessary. A modest increase in Cmax (28%) was osbserved for zidovudine when administered with Zeffix, however overall exposure (AUC) was not significantly altered. Zeffix may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. Zeffix is therefore not recommended to be used in combination with zalcitabine.

Pregnancy and Lactation: Use in pregnancy should be considered only if the benefit outweighs the risk. Although the results of animal studies are not always predictive of human response, the findings in the rabbit suggest a potential risk of early embryonic loss. Consequently, Zeffix administration is not recommended during the first three months of pregnancy. For patients who are being treatment with Zeffix and subsequently become pregnant consideration should be given to the possibility of recurrence of hepatitis on discontinuation of Zeffix. Following oral administration of lamivudine was excreted in human breast milk at similar concentrations to those found in serum (range 1 – 8 micrograms/ml).

Undesirable effects: In clinical studies of patients with chronic hepatitis B, Zeffix was well tolerated. The incidence of adverse events and laboratory abnormalities (with the exception of elevations of ALT and CPK, see below) was similar between placebo and Zeffix treated patients.

The most common adverse events reported were malaise and fatigue, respiratory tract infections, headache, abdominal discomfort and pain, nausea, vomiting and diarrhea.

Elevations of ALT; Elevation in ALT were more common post-treatment in patients treated with Zeffix than placebo. In controlled trials in patients with compensated liver disease, however, there was no appreciable difference post treatment in clinically severe ALT elevations associated with bilirubin elevations and / or signs of hepatic insufficiency, between Zeffix and placebo treated patients. The relationship of these recurrent hepatitis events to Zeffix treatment or to the previous underlying disease is uncertain.

Elevation of CPK; In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of Zeffix.

Thrombocytopenia; muscle disorders (including myalgia, cramps and rhabdomyolysis).

In patients with HIV infection, cases of pancreatitis and peripheral neuropathy (or parasthesia) have been reported, although no relationship to treatment with lamivudine (3TC™) has been clearly established. In patients with chronic hepatitis B there was no observed difference in incidence of these events between placebo and Zeffix treatment patients.

Cases of lactic acidosis, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of combination nucleoside analogue therapy in patients with HIV. There have been occasional reports of these adverse events in hepatitis B patients with decompensated liver disease, however, there is no evidence that these events were related to treatment with Zeffix.

Overdose: If overdose occurs the patient should be monitored, and standard supportive treatment applied as required.

Storage condition: Store below 30°C.

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Full prescribing information is available on request

Abbreviated Prescribing Information version 2.0 prepared in May 2007.

1. Liaw YF, Sung JJ, Chow WC et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med 2004; 351: 1521-1531.

* Disease progression is defined as a ≥ 2 points increase in Child-Pugh score, spontaneous bacterial peritonitis, renal insufficiency, bleeding varices, the development of hepatocellular carcinoma, or liver-related death.

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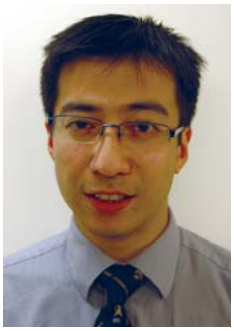
N07ZX311/10-2007 Expiry Date Nov 2008

Updates in the Treatment of Chronic Hepatitis B

Prof. Ching-lung Lai, MD
Dr. James Fung, MBChB, FRACP
Dr. Man-fung Yuen, MD, PhD


Prof. Ching-lung Lai Dr. James Fung Dr. Man-fung Yuen

Background

Approximately 400 million people worldwide are infected with chronic hepatitis B (CHB), with approximately 1 million deaths annually from hepatitis B virus (HBV)-related cirrhosis and hepatocellular carcinoma (HCC)[1]. The majority of Asian patients acquires HBV either at birth, or within the first few years after birth, and is characterised by a prolonged immunotolerant phase followed by a prolonged phase of immunoclearance. Patients will undergo hepatitis B e-antigen (HBeAg) seroconversion with development of antibodies to HBeAg (anti-HBe) during the natural evolution of the disease, median age of HBeAg seroconversion being around 35 years. However there may be ongoing disease progression to cirrhosis and HCC after HBeAg seroconversion in a proportion of patients.

Goals of Therapy

The ideal goal of CHB therapy is the complete eradication of HBV, which is not possible with the current available treatment. Even loss of the hepatitis B surface antigen (HBsAg) does not denote complete viral clearance. Hence, short-term goals include normalisation of serum alanine aminotransferase (ALT) levels, HBV DNA suppression, HBeAg seroconversion, and improvement in liver histology, with the aim of achieving the long-term goals of preventing liver cirrhosis, liver failure, and HCC.

Treatment Choices

There are six antiviral agents currently available for the treatment of CHB: lamivudine, adefovir, entecavir, telbivudine, interferon (IFN)- α, and pegylated IFN (peg-IFN). Treatment choice should take into account several important factors of the agent in question, namely antiviral efficacy, drug resistance profile, long-term safety profile, methods of administration, and cost-effectiveness[2].

IFN-α and pegylated IFN

Standard IFN-α has been shown to be effective in the treatment of CHB[3]. However, peg-IFN has largely surpassed standard IFN in CHB treatment. In one report using suboptimal dose of standard IFN-α, peg-IFN is superior to standard IFN in HBeAg clearance, HBV DNA suppression and normalisation of ALT[4]. Recent studies have focused on combination or sequential therapy with lamivudine[5]. Most studies have not shown any additional benefit of combining one year lamivudine treatment to IFN therapy when assessed at 6 months after stopping of therapies[6-11]. Although no additional antiviral efficacy is observed, there is evidence that the combination of IFN and lamivudine therapy decreases the development of lamivudine-resistant mutations[9,10]. (The limiting of lamivudine treatment to only one year in these studies is contrary to most current clinical practice with nucleoside analogues).

In addition, the long-term effectiveness of standard IFN has not been consistently shown. Long term benefits including preventing cirrhosis and HCC were not observed in earlier studies of Japanese and Chinese patients[12,13]. In a more recent retrospective study of Taiwanese patients with high ALT levels at baseline, IFN was shown to reduce HCC and cirrhosis in HBeAg-positive patients compared to untreated controls. Further results regarding peg-IFN with long off-treatment follow-up is needed to determine its long-term efficacy.

Lamivudine

Lamivudine is the first oral antiviral drug approved for the treatment of CHB, and is effective in reducing the complications of cirrhosis, including decompensation and HCC, in both cirrhotic and pre-cirrotic patients. [14,15]. However, lamivudine is associated with high rates of viral resistance, with a resistance rate of 76% after 8 years of treatment[15]. The initial benefits conferred by lamivudine are reduced in patients who develop lamivudine-resistant mutations during long-term follow-up[16]. However, even among those with drug resistance, the outcome remains better than for untreated patients[14,15]. Both adefovir and entecavir are effective against lamivudine-resistant CHB, and either can be used.

Adefovir

Adefovir dipivoxil has been shown to be effective in both HBeAg-positive and HBeAg-negative CHB, as well as lamivudine-resistant HBV[17-19], with proven long-term efficacy[20]. However, with newer and more potent antiviral agents now available, the main role of adefovir is in patients who have developed resistance to lamivudine or telbivudine. Some studies have shown that adefovir monotherapy in lamivudine-resistant patients is as effective for suppressing HBV DNA as combination therapy with lamivudine[21-23], while other studies have shown substantially lower rate of resistance to adefovir when treatment is continued in

combination with lamivudine[24-27]. We recommend the addition of adefovir for lamivudine-resistant patients as soon as genotypic resistance is detected. Adefovir-resistant HBV is sensitive to both entecavir and lamivudine [28].

Entecavir

Entecavir is the third oral antiviral agent approved for CHB treatment, and is superior to lamivudine[29-31]. Furthermore, no virological breakthrough from entecavir resistance has been observed after 2 years of treatment in treatment-naive HBeAg-positive patients[32]. The resistance rate in treatment-naive patients is only 1.2% in 5 years. Entecavir has been shown to be effective against lamivudine-resistant HBV at the higher daily dose of 1 mg instead of the recommended 0.5 mg daily dose for treatment-naive patients [33,34]. However, in patients with pre-existing lamivudine-resistant mutations, there is a lower viral response rate, and higher rate of developing entecavir resistance[35]. The reason for the higher rate of resistance is because the mutations that characterise lamivudine resistance predispose patients to develop subsequent resistance to entecavir. Therefore, entecavir switching therapy may be less optimal than adefovir add-on therapy for CHB associated with lamivudine resistance.

Telbivudine

Telbivudine has been shown to be more potent than lamivudine and adefovir against HBV[36,37]. However, telbivudine is still associated with higher resistance rates than adefovir or entecavir[38]. Resistance to telbivudine occurs at the same mutation site responsible for resistance to lamivudine; therefore neither is essentially effective for one another once resistance develops. The rate of genotypic resistance after 2 years of telbivudine treatment is 22% and 8.6% among HBeAg-positive and HBeAg-negative patients, respectively [38].

Viral Resistance

The resistance rates of different antiviral agents are shown in figure 1. Development of drug resistance remains a major issue as the majority of CHB patients will require long-term therapy. Flares of hepatitis, liver decompensation and death have been reported to occur in patients who develop viral resistance [39].

The development of drug resistance also affects further treatment options. Patients who developed lamivudine resistant mutations will have a higher rate of developing subsequent adefovir resistant mutations compared to those patients without lamivudine resistant mutations[40]. Likewise, as described previously, patients who have lamivudine-resistant HBV will also have a higher rate of developing subsequent entecavir resistance [33].

Given the adverse impact of drug-resistant HBV on the clinical outcome and on subsequent antiviral therapy, the risk of developing resistance should be considered prior to starting antiviral therapy. With the availability of newer and more potent antiviral drugs, the high resistance rate associated with lamivudine limits its use as a first-line agent. However, lamivudine remains the least expensive oral antiviral agent with the longest and largest profile of safety data. Use of the roadmap concept, as outlined later, may identify those patients who will respond more favourably in the long term.

Treatment Endpoints:

As complete eradication of HBV is currently not possible with available therapy, various endpoints have been adopted as surrogate markers of successful treatment. These include HBeAg seroconversion, normalisation of ALT, and HBV DNA suppression.

HBeAg seroconversion

Traditionally, HBeAg seroconversion has been used as a marker of treatment success, and is included in various treatment guidelines [2,41-43]. Those patients who have undergone HBeAg seroconversion are termed "healthy carriers", with low HBV DNA levels, normal ALT, and resolution of necro-inflammatory activity within the liver [44,45]. However, recent studies have shown that over 70% of CHB patients are HBeAg-negative at the time of developing HCC [46,47].

As disease progression still occurs after HBeAg seroconversion in patients who acquire the disease at birth or during early childhood, HBeAg seroconversion should therefore be considered as part of the natural history/progression of CHB infection, and should be taken as a treatment endpoint only in conjunction with other criteria, specifically the HBV DNA and ALT levels [48, 49].

HBV DNA levels

Serum HBV DNA levels have been shown to be important in both the development of liver cirrhosis and for development of HCC. Higher levels of HBV DNA are associated with the development of HCC independent of the HBeAg status and ALT levels [46, 50]. There is no current level of HBV DNA which is considered 'safe' from disease progression or from development of HCC [46]. A cut-off level of >2000 IU/mL was shown to be a strong risk predictor of HCC independent of HBeAg status, serum ALT and underlying cirrhosis [50]. However, even lower HBV DNA levels have been associated with the development of HCC [46]. Given the absence of a 'safe' lower limit for disease non-progression, the optimal treatment goal should therefore be to suppress HBV DNA to the lowest possible level, that is, non-detectability by PCR assays.

ALT levels

In Asian CHB patients, it has been shown that patients with ALT levels below half the upper limit of normal (ULN) have the lowest risk of complications compared to those with 0.5 x ULN to 2 x ULN [47].

Patients who have undergone HBeAg seroconversion with subsequent normal ALT have been traditionally regarded as "healthy carriers" with no or minimal disease progression. However, even in patients with normal ALT after HBeAg seroconversion, the cumulative probability of developing cirrhosis after 17 years was 13%[51]. A recent study of CHB patients showed that 37% of those with persistently normal ALT had significant fibrosis or inflammation on liver

histology, and the majority of cases with fibrosis occurred in those with high-normal ALT [52].

In the light of these recent studies, the cut-off for the upper limit of normal for ALT is most likely to be lower than the values that are currently used. Even patients with ALT in the upper range of the currently accepted normal range are at risk of developing cirrhosis. Ongoing disease monitoring with consideration of antiviral therapy should be given for patients with significant degree of liver fibrosis. Furthermore, treating only those patients with ALT >2 x ULN, as indicated by most current guidelines, would exclude a significant proportion of patients (patients with ALT 0.5 - 2 x ULN) who would benefit most from antiviral therapy because of the higher risk of having or developing significant liver disease in these patients[43].

Candidates for Therapy

In HBeAg-positive patients, the ideal candidates for treatment would be those with a prolonged phase of immune-clearance. Immunotolerant patients, that is, young patients with normal ALT levels, can be monitored and treatment may not be required until active hepatitis occurs during the onset of loss of immunotolerance. Unfortunately, there are as yet no specific criteria to define or identify the time at which immunotolerance ends and immune clearance starts. An elevated ALT level is used as a surrogate marker of inflammation and histological activity, and as a marker for loss of immunotolerance. Whether this is an adequate marker remains to be determined. Nonetheless, it seems reasonable that patients with ALT levels between 1 - 2 X ULN should probably be treated. In patients with evidence of cirrhosis and HBV DNA >2000 IU/mL, they should receive antiviral treatment regardless of the ALT levels.

A significant proportion of patients who become HBeAg-negative with positive anti-HBe will have elevated HBV DNA levels[53]. Although the median HBV DNA levels are lower than for HBeAg-positive patients, these patients tend to be older and have more advanced underlying liver disease[47]. In the current AASLD guidelines, indications for treatment include patients with ALT≥2 x ULN and HBV DNA levels ≥20,000 IU/mL, and no treatment for those with ALT <1 x ULN irrespective of HBV DNA levels[43]. This would exclude a substantial amount of patients who would be at high risk of disease progression, including patients who already have cirrhosis. In an alternative treatment algorithm, indications for treatment included ALT >1 x ULN and HBV DNA >2,000 IU/mL, whereas those with HBV DNA <2000 IU/mL and normal ALT would not be treated[2]. Both guidelines suggest liver biopsy to determine disease activity and stage of fibrosis in patients who have ALT and HBV DNA levels in the range outside the definite treatment or within the non-treatment levels [2, 43]. The summary of the AASLD guidelines and the alternative treatment algorithm is shown in figure 2 and 3 respectively. The arguments against the current AASLD treatment guidelines have been summarised in a recent review article [48].

Duration of Therapy

Given the lack of a clearly defined endpoint in the treatment of CHB, the duration of therapy is likewise not clearly defined. The long-term goals of preventing cirrhosis and the development of HCC are likely to be achieved by prolonged suppression of HBV replication. In HBeAg-positive patients, the current AASLD guidelines suggest stopping treatment 6 months after HBeAg seroconversion (regardless of HBV DNA or the ALT levels), and re-treat if relapse should occur [43]. An alternative treatment algorithm suggests that treatment can be stopped 6-12 months after HBeAg seroconversion, providing HBV DNA is undetectable by PCR. The latter approach would seem more appropriate given the inadequacy of HBeAg seroconversion alone as a treatment endpoint, and also the high rate of relapse after discontinuation of therapy. Close monitoring of patients after stopping therapy is mandatory. We would recommend checking the HBV DNA levels 1 month after stopping therapy, and 3 monthly thereafter. Antiviral therapy should be restarted in those with evidence of reactivation. For HBeAg-negative patients, both guidelines suggest that long-term therapy is required.

Long-term antiviral therapy raises the concern about the development of drug-resistant mutations. Despite this, patients will still benefit from antiviral therapy even with the occurrence of drug-resistant mutations. In patients treated with prolonged lamivudine therapy, patients with drug-resistant HBV still benefit from treatment when compared to patients with no treatment[14, 54]. With newer and more potent antiviral drugs with higher genetic barrier, such as entecavir, resistance is likely to become a lesser problem.

Prolonged antiviral therapy also raises the concern about drug toxicity. Older agents, such as lamivudine and adefovir, have established long-term safety data, whereas newer agents are currently lacking in long-term data both for efficacy and safety. Despite this, long-term drug toxicity with long-term therapy is an unlikely problem given the preclinical safety results of the currently licensed nucleotide/nucleotide analogues. In general, all the available oral nucleoside analogs are well tolerated. The documented nephrotoxic effect of adefovir occurs rarely at the dose used for HBV treatment, although renal function should be monitored regularly whilst patients remain on treatment [55].

The advantage of interferon-based therapy over oral antiviral therapy is that the duration of therapy is more clearly defined. However, the optimal length of interferon therapy remains to be determined. The advantage of a defined treatment length is offset by its side effects and the high proportion of patients who will not respond to IFN therapy and will require further therapy with oral nucleoside analogs [56]. Even in patients with IFN-associated HBeAg seroconversion, long-term monitoring of HBV DNA levels should be performed.

Monitoring Therapy

None of the published guidelines provide specific

criteria for on-treatment monitoring of patients. During antiviral therapy, the degree of viral suppression has been shown to be the most important determinant of therapeutic outcomes[57]. More specifically, the importance of effective early viral suppression in determining long term treatment outcome has been shown in several studies using lamivudine, adefovir, peg-IFN-α-2a, and telbivudine[58,59,60,61]. A more recent study of lamivudine treatment has shown that HBV DNA levels of less than 2,000 IU/mL as early as week 4 can be used to predict accurately HBeAg seroconversion with ALT normalisation and HBV DNA levels <2000 IU/mL without emergence of lamivudine-resistant mutations, at year 5 [62].

The use of early monitoring of viral suppression is the mainstay of the recently published roadmap concept, as shown in figure 4 [63]. Assessment at week 12 and 24 for primary non-response and early predictors of efficacy respectively should be used to guide subsequent treatment choices[63]. The roadmap concept is useful when initiating therapy with a drug with higher rates of resistance or lower antiviral potency, and maybe potentially useful in patients with pre-existing drug-resistant mutations. Recent evidence showed that early viral suppression with adefovir in treating lamivudine-resistant HBV was associated with more favourable outcomes[64, 65]. Future trials will determine whether the roadmap concept can be applied to those patients with pre-existing drug-resistant mutations.

Conclusions

The treatment paradigm is continuing to evolve with better understanding of the natural history of HBV infection. Currently, long-term suppression of HBV replication should be the primary aim. Although peg-IFN therapy offers a finite duration of therapy, the long-term outcomes remain to be fully determined. In addition, only patients with high ALT levels are suitable, and a high proportion of patients have a suboptimal response in terms of HBV DNA suppression. Although long-term benefits are established for oral nucleoside/nucleotide analogues, the benefits of treatment are reduced with the development of drug-resistant mutations.

The optimal choice of the antiviral agent in treatment-naive patients should be a drug with high antiviral potency coupled with a high genetic barrier to reduce the risk of resistance. Entecavir is a significant improvement in the current antiviral strategy, achieving both sustained viral suppression with minimal risk of drug resistance. If a drug with lower genetic barrier is used, identifying early factors such as viral load to predict long-term outcome is important. This would select out patients most likely to achieve successful long-term viral suppression with their current regimens, and an alternative agent can be offered to those with suboptimal early viral response.

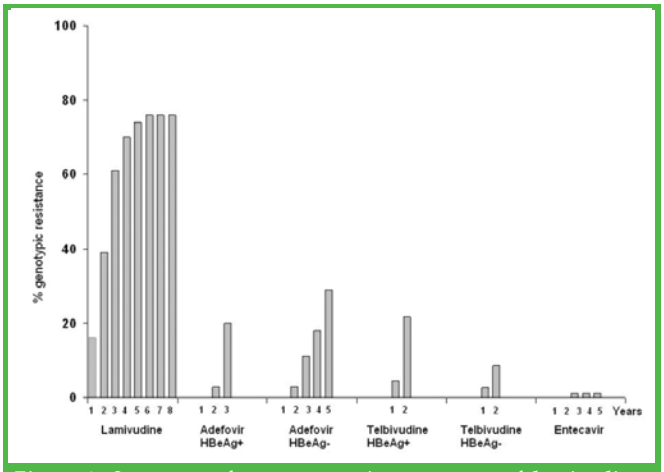


Figure 1. Summary of genotype resistance rates of lamivudine, adefovir, telbivudine and entecavir in treatment-naive patients from different studies.

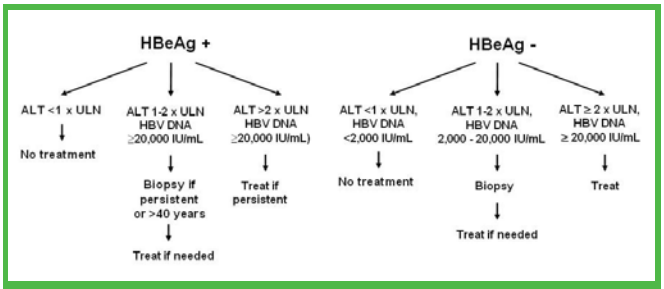


Figure 2. The American Association for the Study of Liver Diseases Guidelines

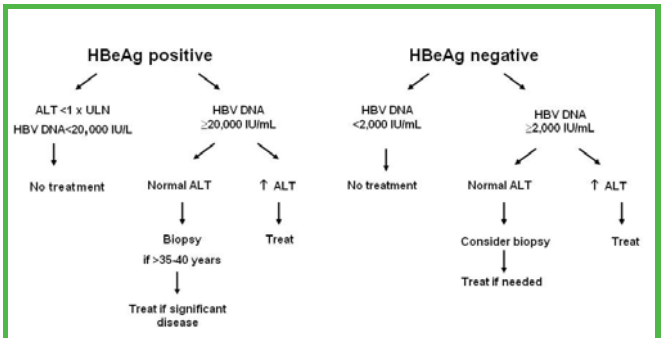


Figure 3. The alternative treatment algorithm for treatment of hepatitis B

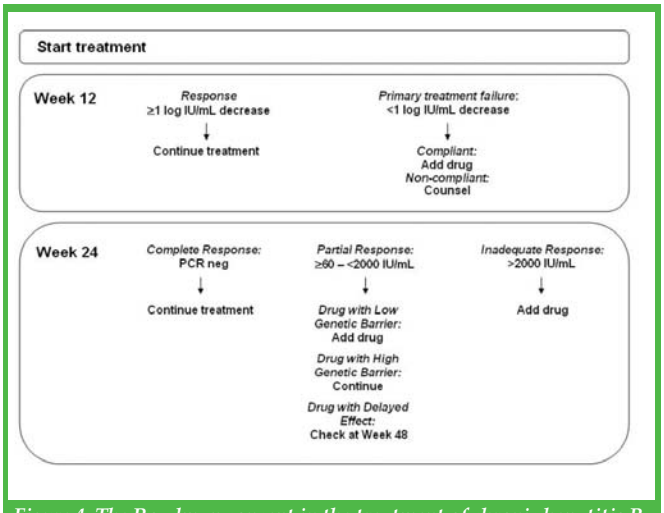


Figure 4. The Roadmap concept in the treatment of chronic hepatitis B

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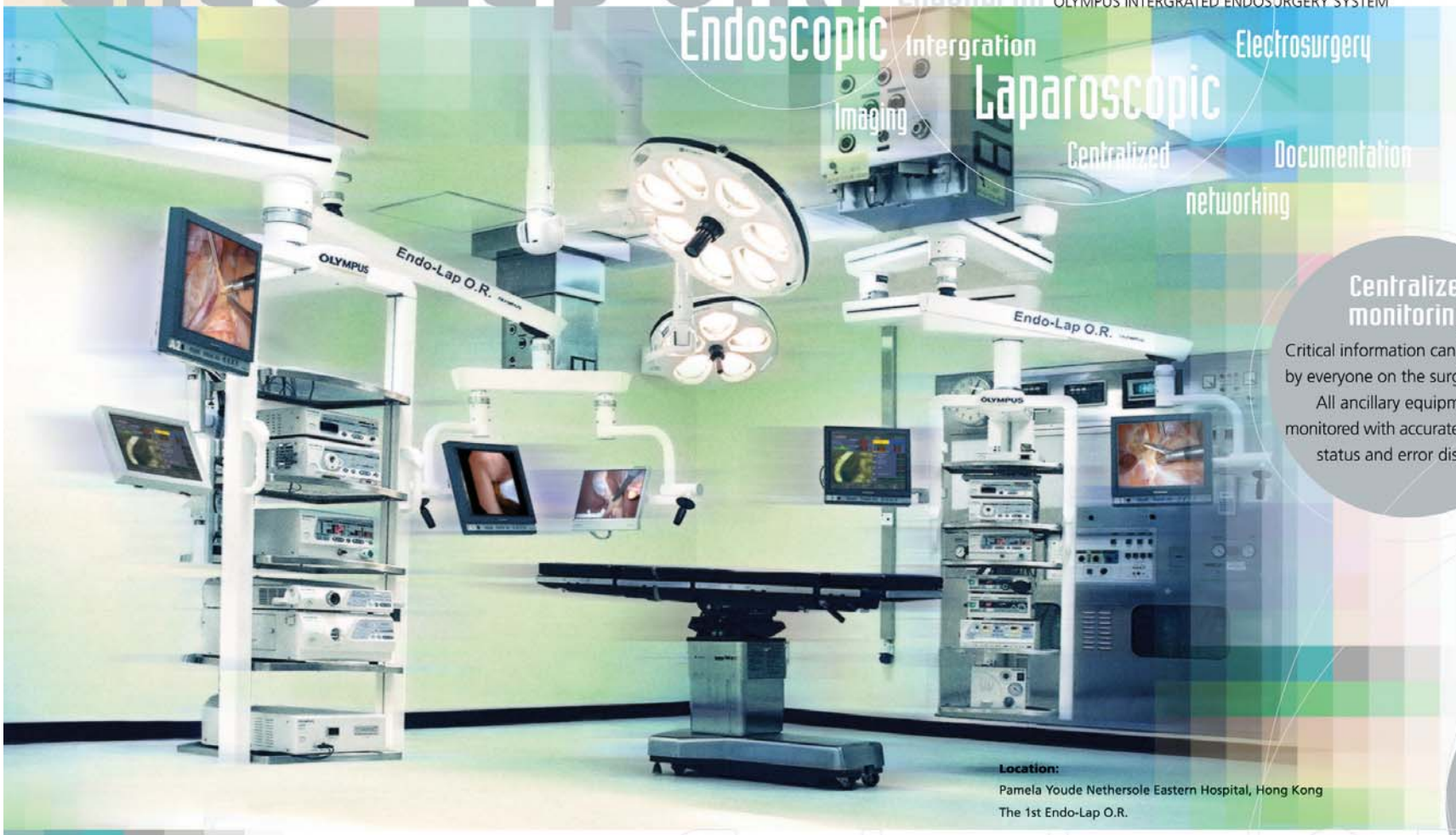

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Therapeutic Endoscopy for Gastrointestinal Disease

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The use of flexible endoscopy in the management of gastrointestinal diseases has proliferated in the last three decades. With the technology advancement and development of innovative endoscopic accessories, flexible endoscopy not only plays a significant diagnostic role in most gastrointestinal diseases and offers an effective therapeutic option at the same time. In particular, therapeutic endoscopy now plays an important role in the management of a variety of gastrointestinal diseases such as acute upper gastrointestinal bleeding (variceal and non-variceal), foreign body ingestion, acute cholangitis, acute biliary pancreatitis and distal colonic obstruction. This article aims to highlight the indications and recent advances in therapeutic endoscopy.

Gastrointestinal Bleeding

Peptic Ulcer Bleeding

Eighty percent of ulcer bleeding patients stop spontaneously without intervention. A subgroup of patients who have uncontrolled bleeding or clinical rebleeding requires aggressive intervention. Prior to the development of endoscopic haemostasis, surgery was the only effective means to control bleeding. With the bleeding point being well visualised during the endoscopy, endoscopic haemostasis is feasible and thus avoids laparotomy. Three endoscopic techniques can be used to control acute gastrointestinal bleeding: injection, thermal / laser coagulation, and application of mechanical haemostatic or ligation devices.

1. Endoscopic Injection

Injection is the most simple and safe means to control bleeding. No specialised instrument or endoscope is necessary. Success rates of 80-100% have been reported in uncontrolled and also controlled trials. Agents that have been used included adrenaline[1-3] hypertonic saline[4], sclerosants such as absolute alcohol[5] or pilidocanol[6]. These substances are injected directly into the bleeding ulcer area by a flexible injection needle inserted through the biopsy channel of the endoscope. Adrenaline and saline injections control bleeding by local tissue oedema to tamponade the bleeding vessel and the effect is immediate. Vasoconstriction induced by adrenaline is a later effect. Sclerosants induce tissue inflammation and thrombosis. The tissue damage induced may cause perforation and injection of sclerosants requires more attention and post-treatment monitoring.

2. Thermal Methods

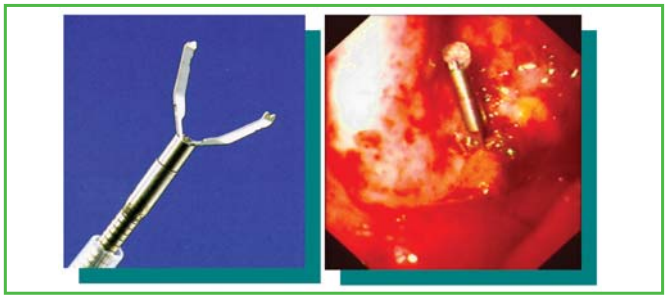
Thermal method to coagulate bleeding vessel is by contact probes which compress the bleeding vessel and apply heat energy simultaneously. The most popular contact thermal probes are heater probe system[7-8] and the bipolar electrocoagulation (BICAP)[9-10]. Both have a portable generator with the probe pass through the biopsy channel of the endoscope. They both have a wash channel which allows the lesion to be washed clean prior to coagulation.

Laser light energy is absorbed by the target tissue and changed into heat which coagulates the bleeding vessel. Nd-YAG and Argon lasers[11-12] have been used. However the laser unit is bulky, inconvenient, expensive and may cause transmural injury.

3. Mechanical Methods

Arterial clips[13] can be applied endoscopically by a spring-loaded system. Since the initial description of endoscopic metallic clips application in 1975, various authors reported the use of endoscopic clips in hemostasis, marking lesions, closure of perforations, fistulas and anastomotic leaks. Hemoclip placement is also effective in offering primary hemostasis and prevent rebleeding in cases with severe bleeding in GI tract. The technique of clip placement could be cumbersome and difficult in some anatomical positions. An endoscopic sewing machine and banding device has been described but has not been used clinically.

There is no doubt that endoscopic haemostasis is the treatment of choice for most patients with bleeding ulcers. Indeed, the value of endoscopic haemostasis has been validated in 2 meta-analysis studies of published control trials[14-15]. Compared to standard therapy for bleeding peptic ulcers, patients who underwent endoscopic therapy had 69%, 62% and 30% reduction rate in rebleeding, emergency surgery and mortality respectively. In addition, comparison studies on injection therapy, electrocoagulation and heater probe suggested that they are equally effective and safe to control ulcer bleeding.



However it must be remembered that 80% of ulcers stop bleeding spontaneously. A selective policy should be adopted for endoscopic haemostasis. Active bleeding ulcers (Forrest's Type I) are no doubt to be treated at the time of endoscopy. In patients with visible vessel (Type IIA) or adherent clots (Type IIB) and associated with haemodynamic instability on admission, we prefer to treat them prophylactically in an attempt to prevent rebleeding. Ulcers with flat pigment spot (Type IIC) or clean ulcers (Type III) should not be treated in view of negligible chance of rebleeding.

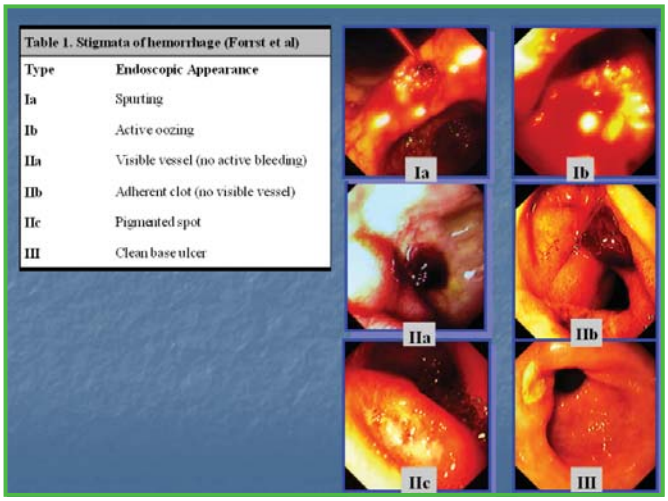
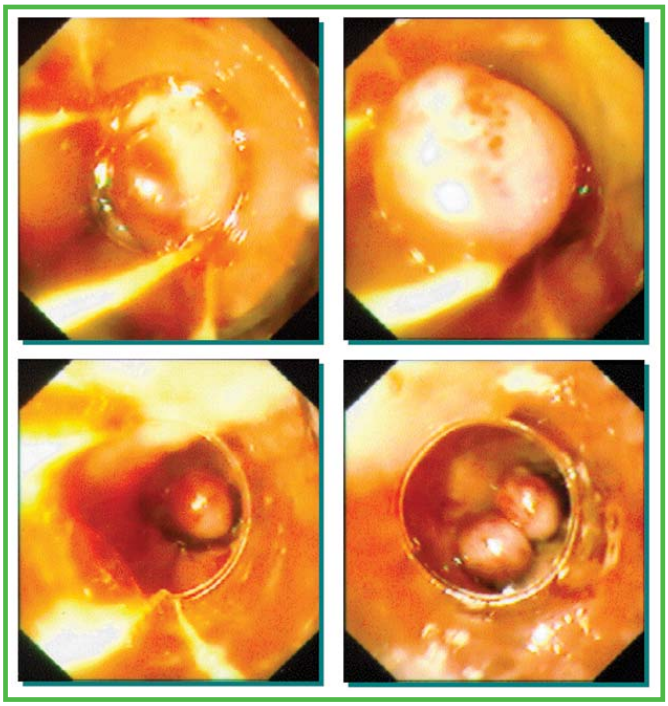


Table 1. Stigmata of hemorrhage (Forrst et al)

Type	Endoscopic Appearance
Ia	Spurting
Ib	Active oozing
IIa	Visible vessel (no active bleeding)
IIb	Adherent clot (no visible vessel)
IIc	Pigmented spot
III	Clean base ulcer

Variceal Haemorrhage

In the past, injection sclerotherapy is the standard treatment for bleeding oesophageal varices in most institutions. The overall success rate of controlling acute bleeding is over 90% and the chance of re-bleeding is reduced by repeated injections until obliteration of varices. In our institution, we used 3% sodium tetradecylsulphate (STD) as the sclerosant and the varices are injected intravariceally by free hand technique[16]. The injection is started at the cardia and working upwards.



The variceal columns at the inferior half of oesophageal wall are first injected so as to prevent blood obscuring the superior wall columns. 2 ml of STD are injected at each puncture site but not exceeding a maximum of 20 ml. Brisk bleeding sometimes results when the needle is withdrawn from the varice. Tamponade of the area by inserting the scope into the stomach can usually control the bleeding. Fever and retrosternal pain are almost universal after sclerotherapy. Oesophageal ulceration is common at the site of injection and results in later stricture formation in some cases. Delayed perforation from excessive injection of sclerosant is rare but frequently fatal.

Band ligation of the oesophageal varices has almost replaced injection sclerotherapy as the treatment of choice for bleeding varices. It has fewer treatment complications, particularly stricture formation. The ligation device comprises an outer "friction-fit" adaptor which fits on the end of the endoscope, an inner cylinder preloaded with an elastic "O" ring and a trip wire for pulling the inner cylinder into the adaptor to release the ring. In the earliest model, an overtube is first inserted to the oesophagus and the device is loaded onto the endoscope. To reduce the complications related to overtube insertion and problem with reloading, multiple bands have been preloaded in a single shooter (4-shooter, 6-shooter, 8-shooter) and is more convenient to the endoscopist to perform the banding. Similar to injection sclerotherapy, banding usually starts at the cardia and working upwards. When a variceal column is chosen, strong suction is activated to draw the varix into the inner cylinder and the band is released by pulling the trip wire. Then the suction is released to allow inspection. The ligation procedure is repeated until all columns are banded. An average of 4 sessions per patient is required for variceal obliteration.

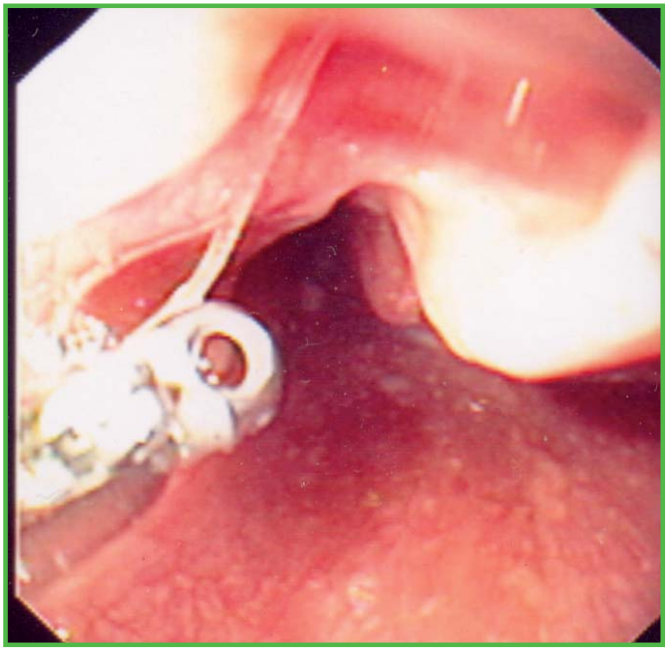
Foreign Body Ingestion

Lodgment of foreign bodies in the upper digestive oesophagus is one of the common complaints for emergency room attendance. In Hong Kong, most of the foreign bodies are fish bones. Young children often swallow a wide variety of objects such as coins and batteries. With the availability of expertise and various endoscopic accessories, great majority of foreign bodies nowadays can be removed with the aid of flexible oesophagoscope without general anaesthesia.

For patients with history of fish bone ingestion, the oropharynx and hypopharynx should be examined before proceeding to oesophagoscopy. Most of these fish bones reside in the vallecula and the piriform fossa. These areas can be viewed with direct laryngoscope (rigid or flexible) and fish bones can be removed accordingly. Patients who complain of retrosternal pain on swallowing are indicated for oesophagoscopy.

The pharynx, hypopharynx and oesophagus are carefully examined for laceration, haematoma and foreign bodies. When a foreign body is found, the accessories should be chosen according to the size and shape of the object. Small fish bones can be grasped with biopsy forceps. Crocodile forceps have a firmer grip and are suitable for larger fish bones or pork bones. Coins are best grasped

at the edge by the rat tooth forceps. Food boluses are better pushed into the stomach rather than removed. For larger objects such as false dentures that cannot be passed into the over-tube, they are pushed down to the stomach and fragmented into small pieces before removal. Laser is particularly useful in this situation to fragment the hard object[17]. Once the object has passed to the stomach, most of them will be gradually propelled through the rest of the bowel uneventfully and passed out. However, sharp objects such as needle, long sharp fish bone which can perforate the bowel wall and disc batteries which can erode the bowel wall, should be removed from the stomach.



Before attempting to remove large sharp foreign body from the oesophagus, an over-tube should be inserted over the endoscope to protect the oesophagus and pharynx from laceration by sharp pointed objects and prevent dropping the object into the trachea on pulling out the scope. Attempts to remove a sharp object from the oesophagus without protection will result in full thickness perforation in a long segment of oesophagus. The over-tube is pre-loaded onto the endoscope and slide into place after the endoscope is passed into oesophagus. Foreign body lodged at the upper oesophagus may need to be pushed down to the distal oesophagus to allow the passage of the over-tube. After the foreign body is securely grasped into the over-tube, the endoscope and the foreign body together with the over-tube are removed.

Close co-operation between the endoscopist and the assistant is essential during the procedure. A video-monitoring system that allows the assistant to see what he is to catch will be particularly helpful. After the removal of foreign body, a full examination of the oesophagus is essential to exclude malignant stricture at the site of impaction or other mucosal lesion.

Treatment of Biliary Tract Diseases

Therapeutic endoscopy is also used in the treatment of numerous pathological conditions of the biliary tree and pancreas.

Acute Cholangitis

Patients with bile duct stones often present with acute cholangitis with the classic Charcot's triad i.e. acute abdominal pain, fever and jaundice. The cholangitis can be due to an isolated obstructed segment within the liver (intrahepatic stones) or more commonly due to the presence of common duct stones. The initial management on admission includes nil by mouth, fluid resuscitation and intravenous antibiotics. The preferred antibiotic regimen consists of a second or third generation cephalosporins and metronidazole to cover the anaerobes. More than 80% of patients respond to the initial treatment and definitive treatment can be scheduled.

The endoscopic management for patients with acute cholangitis should be adjusted according to the clinical condition of the patients. Clinically stable patients with mild attack of cholangitis can be managed successfully with papillotomy and stone extraction at the first session of ERCP. However, urgent intervention is mandatory for patients with confusion and septicaemia shock (Reynold's pentad). These patients have high intrabiliary pressure and require urgent drainage decompression.

In acute phase the aim is to decompress the infected biliary system as soon as possible. The role of endoscopic drainage by naso-biliary drain is now firmly established in various studies[18-19]. The mortality rate was much reduced compared to emergency exploration. In patients with common ductal stones, a 7-holes naso-biliary catheter is inserted to the intrahepatic duct to provide drainage of the common duct and intrahepatic duct. Turbid bile or pus will drain out once the duct is deep cannulated. In patients with obstructed intrahepatic segment, a 4-holes naso-biliary catheter is preferred which facilitates subsequent check cholangiogram to delineate the obstructed segment. In this situation, the difficulty lies in the localisation of the obstructed segment during ERCP, particularly in those cases with associated biliary stricture that may not appear on the initial cholangiogram. When the bile duct is deep-cannulated, the bile should be aspirated out for examination. Purulent bile may suggest a non-drained obstructed intrahepatic segment. Balloon cholangiogram at the hilar level may be required to show up the segment in some of the cases. Once the segment is identified, the guide-wire is directed to the segment and bile is aspirated for confirmation. Purulent bile indicates the correct segment and a 4-holes naso-biliary catheter is inserted for temporary drainage.

However, it was not uncommon to have the naso-biliary catheter dislodged spontaneously or being pulled out by the confused septic patients. In addition, patients often complained of nasal discomfort and sore throat due to the irritation of the catheter. These problems could be avoidable if an in-dwelling plastic biliary stent is used to provide temporary biliary drainage.

Occasionally, patients with failed cannulation or failure to negotiate the guide-wire into the correct segment due to the angulation or stricture, emergency percutaneous transhepatic drainage (PTBD) under ultrasound

guidance can be offered. Subsequent stone clearance can be done with the combined endoscopic techniques. With these approaches, emergency surgical exploration is now a rarity.

For patients with malignant obstruction or blocked biliary stents, emergency biliary decompression can be similarly achieved with the change of stent or naso-biliary drain insertion.

Acute Biliary Pancreatitis

Prospective randomised trials have demonstrated the safety and benefit of early ERCP in biliary pancreatitis[20-21]. Emergency ERCP reduces the morbidity in patients with severe pancreatitis and CBD stones compared to conservative group. The procedure is safe and biliary decompression can be performed with nasobiliary drain or stone extraction after endoscopic papillotomy if the patient's condition allows.

Post-operative Bile Leaks

Temporary decompression of the bile duct with drainage of bile collection is indicated for treatment of persistent bile leakage from slippage of cystic duct stump clip or ligatures, damaged bile ducts and Duct of Luschka after cholecystectomy and hepatectomy. Endoscopic decompression of bile duct by endoscopic papillotomy, naso-biliary catheter or plastic biliary stent can be performed with low morbidity. In general, biliary stenting with plastic endoprosthesis is the preferred method of choice. Stent will be removed after 4-6 weeks when there is no leakage on repeat cholangiogram. However, surgical repair should be offered to patients with major duct injuries that carry a long term morbidity and mortality.

Benign Biliary Stricture

Endoscopic balloon dilatation and stenting can be a safe alternative treatment option for patients with benign biliary strictures as a result of recurrent cholangitis, sclerosing cholangitis, iatrogenic bile duct injury and chronic pancreatitis. Medium and long term success rates of maintaining bile duct patency have been reported in 80% of selected patients although there was no randomised trial to compare surgical bypass.

Malignant Biliary Stricture

Malignant biliary obstruction as a result of inoperable hepato-biliary-pancreatic cancers can be palliated by surgical bypass or endoscopic biliary stenting. Conventional plastic biliary stenting has the advantages of easy insertion, less morbidity and mortality rates compared to surgical bypass operation. However, these patients often require stent replacement at 2-3 month intervals due to stent clogging. Controlled studies have shown stents with larger luminal diameter had longer time of patency and a minimum of 10F size plastic stent should always be used in stenting. Non-covered self-expandable metal stents with larger inner diameter (8 - 10mm) have been developed to improve patency rate and several different types of metal stents are now commercially available. Randomised studies have demonstrated that metal stents had significantly less stent blockage in mid and distal bile duct obstruction. The probability of stent patency was 78% at 7 months. Stent clogging was still due to tumour ingrowth into the metal mesh and tumour overgrowth below & distal to the stent, which can be re-treated with insertion of second plastic stenting. Newer model of covered metal stent is also being made to reduce tumour ingrowth and its benefit needs to be confirmed on further randomised studies.

Treatment of Polyps and Neoplasia

Polypectomy

Polypectomy can be applied to any part of the alimentary tract, and is commonly performed for colonic polyps.[22-24] It decreases the development of neoplastic changes in colon from adenoma to adenocarcinoma. Majority of the small polyps can be resected by ordinary or hot biopsy forceps, while stalked polyps are removed by snare with a blended cutting and coagulation current. Bleeding or perforations are potential complications of the procedure.

Mucosectomy and Endoscopic Submucosal Dissection

Endoscopic mucosal resection is an established method for treating intramucosal gastric and oesophageal neoplasms. Conventional endoscopic mucosal resection has predominantly been performed using strip biopsy, or cap method. En bloc resection is often difficult when dealing with lesions > 10 mm using conventional methods. Moreover, specimens resected piecemeal often cannot be used to judge curability.

Endoscopic submucosal dissection has recently been introduced by Japanese endoscopists using new devices such as an insulation-tip diathermic knife. [25] The target lesion is marked by needle knife. Glycerin containing a small amount of indigocarmine dye is injected into the submucosal layer around the lesion to lift and detach the mucosal lesion. After cutting mucosa around the marking spots, the submucosal layer was dissected using the IT-knife, flex knife or hook knife and lesions were able to be completely resected in one piece.

Percutaneous Endoscopic Gastrostomy (PEG) / Jejunostomy

Under gastroscopy guidance, percutaneous endoscopic gastrostomy tube can be placed into the stomach through the abdominal wall. PEG tubes may also be extended into the small bowel. The procedure is primarily indicated as a long-term means of providing nutrition to patients who cannot productively take food orally. PEGs may also be inserted to decompress the stomach in cases of gastric volvulus.

Self-expanding Metallic Stent Placement for Palliation of Upper and Lower Digestive Tracts Malignancies

Oesophageal Stenting

Self-expandable metal stents provide effective palliation of malignant dysphagia and tracheo-oesophageal fistulation. The procedures are associated with few complications and highly preferable for patients with limited life-span. Successful use of self-expandable stents depends on knowledge of the properties of these stents and tumour configurations. Controlled trials are required to compare different stents in difficult tumour configurations to improve the choice of stents in malignant dysphagia.

Gastric Outlet Obstruction

In the past, patients with malignant gastric outlet obstruction due to pancreatic cancer compression or gastric cancer were only amenable to surgical bypass (gastrojejunostomy) in case the tumour was not resectable. This bypass operation required general anaesthesia and often carried a significant morbidity due to poor nutrition reserve of the patients. Metallic stenting across the obstructive antral-duodenal region provides an alternative treatment option that can be done under sedation and thus laparotomy is avoided.

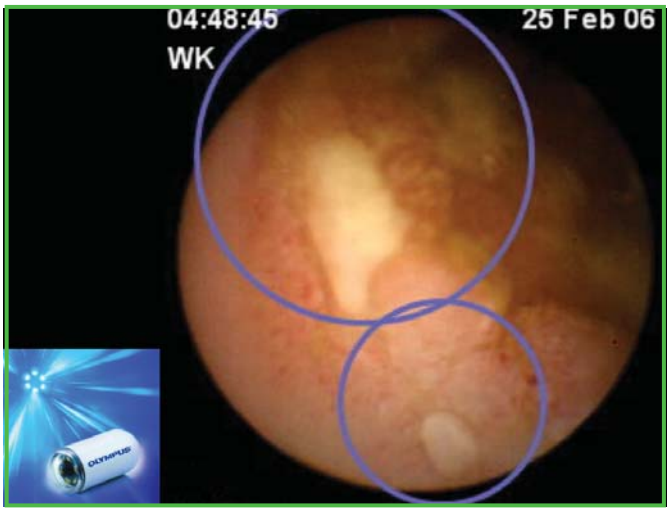
Acute Distal Colonic Obstruction

Recently, expandable metal enteral stent has been used to relieve obstruction caused by recto-sigmoid tumours with success[26-29]. It offers a palliative option for patients with obstructive rectosigmoid cancers and metastatic diseases. Besides, stent placement can also relieve acute large bowel obstruction and thus avoid emergency surgery. It allows better patient preparation for elective definitive surgery at one setting. Primary anastomosis is thus safer in this situation and defunctioning colostomy can be avoided with better bowel preparation.

This enteral stent has the advantage of being able to be inserted via the operating channel of the endoscope (3.7mm diameter) and is deployed under direct visualisation and with the aid of fluoroscopy. It thus can be passed safely inside the sigmoid colon despite of the looping.

Small Bowel Enteroscopy

Small bowel examination can be performed with conventional contrast study but the quality is usually not much helpful in the diagnosis of small bowel pathology except the luminal stricture. Capsule endoscopy allows direct visualisation of the small bowel mucosa. The procedure is painless and can be done in ambulatory setting. However, capsule endoscopy has its own limitation and obviously, no therapeutic procedure can be offered by the capsule. Small bowel enteroscopy allows for extensive antegrade or retrograde evaluation of the small bowel by passage of a specialised small bowel endoscopy.[30-31] The procedure is performed after bowel preparation and consists of a series of insertion and withdrawal manoeuvres, accompanied by serial inflation and deflation of the endoscope and overtube balloon to reduce small bowel loops, resulting in relative straightening of the small bowel and scope advancement. The primary indication for small bowel enteroscopy is for evaluation of unexplained acute, recurrent, or obscure gastrointestinal bleeding for patients who have previously undergone both oesophagogastroduodenoscopy and colonoscopy. Other indications include evaluation and treatment of patients with polyposis syndromes, Crohn's disease.



Natural Orifice Transluminal Endoscopic Surgery (NOTES)

This technique uses the flexible endoscope to create a controlled transvisceral incision, usually in the stomach, rectum or vagina, to enter the peritoneal cavity as an alternative to conventional surgery. [32]Reports describing various NOTES procedures have primarily been studied in animal models and the techniques are still experimental at the current stage.

Conclusion

Therapeutic endoscopy has progressed enormously in recent years. Endoscopic procedures are minimally invasive in nature and able to offer new treatment options for patients with various digestive tract pathologies, conventional open surgical procedures are thus avoided.

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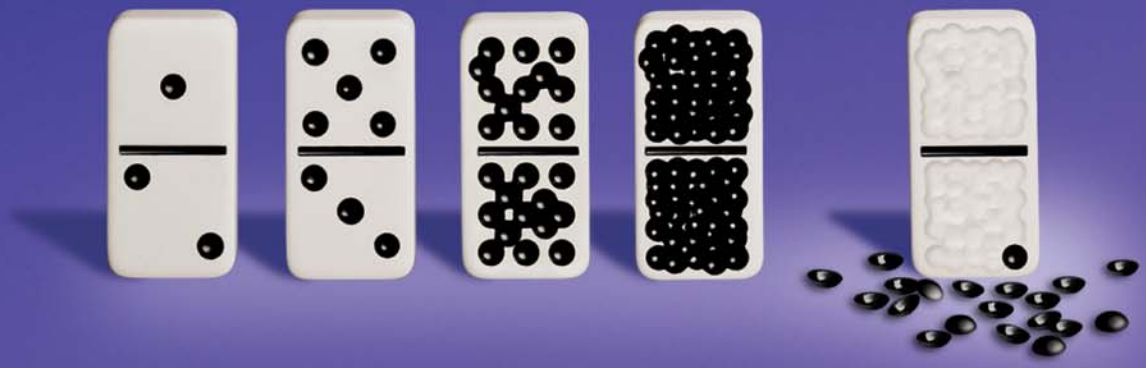
A new treatment option for patients with chronic hepatitis B infection

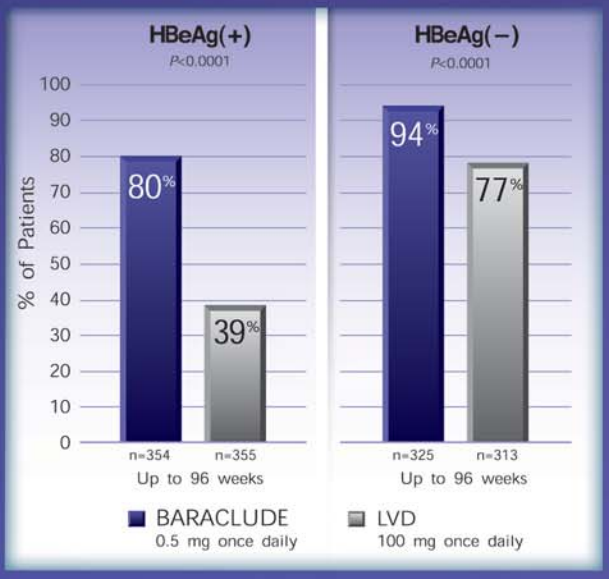
From a virus that's uncontrollable



to a virus that's undetectable
(<300 copies/mL)

Undetectable viral load with <1% viral rebound due to resistance† in nucleoside-naïve patients.[1,2,3]

Patients with undetectable viral load up to 96 weeks[‡§2,3]



Results of two randomized, double-blind, multinational studies comparing BARACLUDE 0.5 mg once daily and lamivudine 100 mg once daily for a minimum of 52 weeks in 709 HBeAg-positive and 638 HBeAg-negative nucleoside-naïve patients with chronic hepatitis B.

† Viral rebound defined as ≥ 1 log increase from nadir by PCR.

‡ HBV DNA measured using Roche COBAS Amplicor® PCR assay (LLOQ=300 copies/mL). Results reported are from an Intent-to-Treat (ITT) analysis.

§ Cumulative proportion of treated subjects who ever achieved a confirmed endpoint during the 96-week period. Confirmed=2

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Presentation: CoAprovel®: Irbesartan and hydrochlorothiazide tablet **Indication:** Essential hypertension. The fixed dose combination is indicated in patients whose blood pressure is not adequately controlled on irbesartan or hydrochlorothiazide alone. **Dosage:** CoAprovel 150mg/12.5mg once daily may be administered in patients whose BP is not adequately controlled with hydrochlorothiazide or irbesartan 150mg alone. CoAprovel 300 mg/12.5mg once daily may be administered in patients whose BP is not adequately controlled with hydrochlorothiazide or irbesartan 300mg alone. Maximum daily dose: 300mg irbesartan /25mg hydrochlorothiazide. **Contra-indications:** Pregnancy and lactation, hypersensitivity to the active substance. Hydrochlorothiazide is contraindicated with severe renal dysfunction (creatinine clearance <30ml/min), refractory hypokalemia, hypercalcaemia, severe hepatic impairment, biliary cirrhosis and cholestasis. **Precautions:** Intravascular volume depletion, renovascular hypertension, renal impairment, kidney transplantation, hepatic impairment, primary aldosteronism, patients at risk of aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy, electrolyte imbalance. **Drug interaction:** other antihypertensives, lithium, potassium supplements and K-sparing diuretics, NSAIDs. Hydrochlorothiazide may interact with the following drugs: alcohol, barbiturates, narcotics, antidiabetics, cholestyramine, corticosteroids, NSAIDs, pressor amines, skeletal muscle relaxants, antigout medication & calcium salt. **Undesirable Effects:** Dizziness, nausea/ vomiting, abnormal urination, fatigue, increases in BUN, creatinine & creatinine kinase. **Preparations:** 150mg/12.5mg x 28 s, 300mg/ 12.5 x 28 s. ***Full prescribing information is available upon request.***

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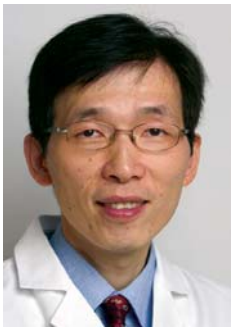

Dr. Kwok-wing Lo

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Introduction

For decades 'classical' risk factors such as elevated LDL-cholesterol, hypertension and elevated blood glucose have played important roles in the pathogenesis of cardiovascular disease. Though various treatments have been used to reduce individual risk factors, cardiovascular disease remains the leading cause of death worldwide. The MRC/BHF Heart Protection Study showed a majority of cardiovascular risk remains unaffected after effective statin treatment.[1] Almost 20% of patients in the statin group had a major cardiovascular event during the 5-year follow-up period.[1] Therefore, in spite of therapeutic advances, cardiovascular disease has more impact on mortality rates than other major sources of mortality, such as cancer, respiratory disease, accidents or diabetes.

Intra-abdominal Adiposity and Cardiometabolic Risk

The cluster of risk factors, including hypertension, high LDL-cholesterol, low HDL-cholesterol, smoking, and intra-abdominal adiposity (IAA) are known as the cardiometabolic risk and are the underlying cause of type 2 diabetes and cardiovascular disease (Figure 1a).[2-3] In particular, IAA, as measured by waist circumference, is associated with insulin resistance, hyperglycaemia, dyslipidaemia, hypertension, and prothrombotic/proinflammatory states (Figure 1b).[4-6] Excess IAA typically is accompanied by elevated levels of C-reactive protein (CRP) and free fatty acids (FFAs), as well as decreased levels of adiponectin. Elevated levels of CRP are considered to be predictive of cardiovascular disease and insulin resistance.[4-6] Elevated FFA levels are believed to play a significant role in the cause of insulin resistance.[4-6] It has been suggested that elevated FFAs and intracellular lipids inhibit the insulin signalling mechanism, leading to decreased glucose transport to muscle. FFAs also play a mediating role between insulin resistance and β-cell dysfunction, indicating that a reduction in FFA level could be a desirable therapeutic target. Adiponectin is an adipose tissue-specific circulating protein which is involved in the regulation of lipid and glucose metabolism.[4-6] Adiponectin has been shown to be reduced in adults with obesity and type 2 diabetes.[4-6] In non-diabetics, hypertriglyceridaemia and low HDL-cholesterol have been shown to be associated with low plasma adiponectin concentrations.[4-6] All of these components help to explain why excess abdominal adiposity is considered to be a great threat to cardiovascular and metabolic health.

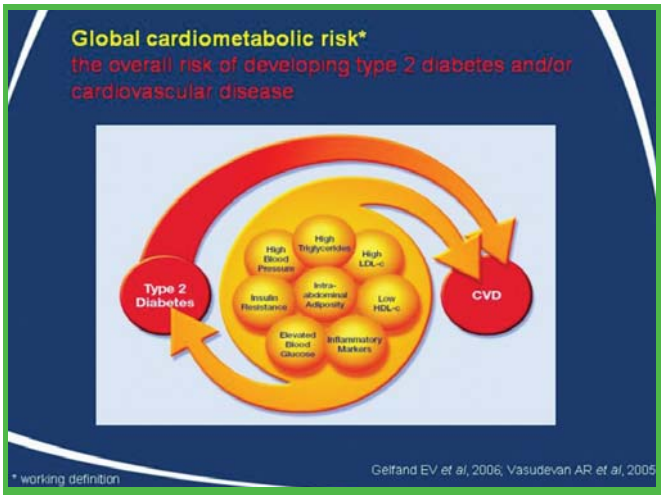

Figure 1a. Cardiometabolic risk factors.[2-3]

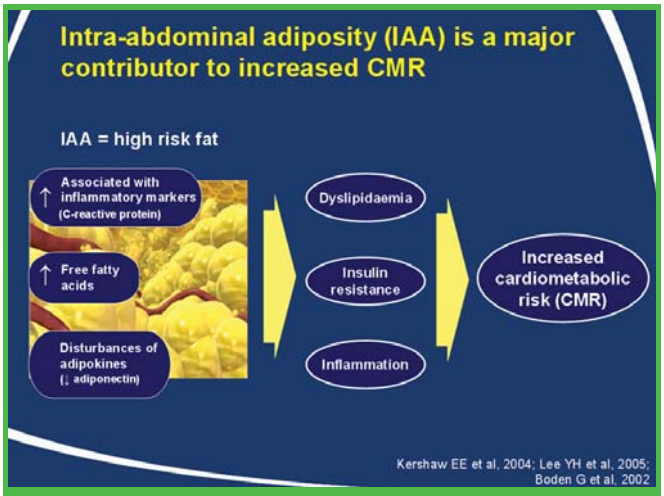

Figure 1b. IAA is associated with numerous cardiometabolic risk factors.[4-6]

Given this association of metabolic and cardiovascular diseases with IAA, it is logical to presume that improvement in abdominal obesity would diminish risk factors and alleviate complicating disease. Several landmark trials have shown that treatments targeting individual risk factors such as hyperlipidaemia significantly reduce the risk of cardiovascular events.[7] Yet cardiovascular disease remains the leading cause of death worldwide. A more comprehensive pharmacotherapy focusing on improving the metabolic risk profile of abdominally obese patients might therefore be required.

The Endocannabinoid System

The newly discovered endocannabinoid system (ECS) contributes to the physiological regulation of energy balance, food intake, and lipid and glucose metabolism through both central and peripheral effects.[8-10] This system consists of endogenous ligands and two types of G-protein coupled cannabinoid receptors: CB1 and CB2. CB1 receptors are located in several brain areas8,[10-13] and in a variety of peripheral tissues including adipose tissue8,[10-13] the gastrointestinal tract[14], skeletal muscle[15] and liver[16]; whereas CB2 receptors can be found in the immune system.[17] Overactivation of the ECS is associated with multiple cardiometabolic risk factors, such as intra-abdominal adiposity, dyslipidaemia, and insulin resistance (Figure 2).[12, 15-16, 18-19]

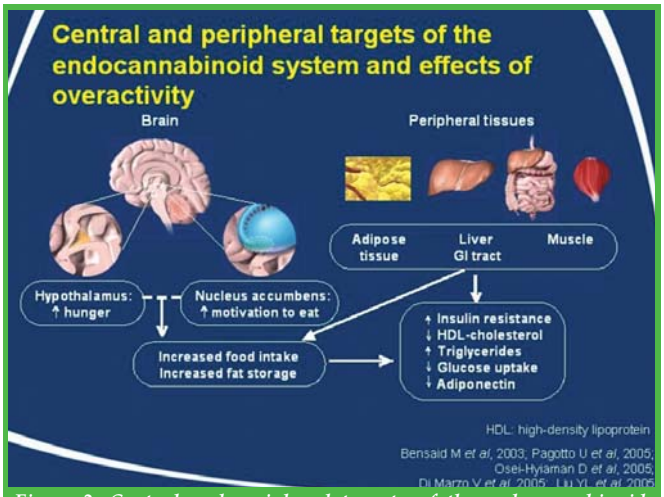

Figure 2. Central and peripheral targets of the endocannabinoid system and effects of overactivity. [12,15-16,18-19]

Three lines of pre-clinical evidence support the modulation of the ECS for the treatment of obesity. Firstly, feeding lowered, and fasting raised, hypothalamic, but not cerebellar, levels of endocannabinoids.[20] Secondly, CB1-receptor deletion or pharmacological blockade blunted re-feeding activity in fasted animals (with no added effect of CB1 blockade in CB1 knock-out mice).[10] Thirdly, local injection of endocannabinoids into the hypothalamus stimulated feeding activity in satiated animals, and this was blocked by CB1-receptor antagonist.[21] These observations implicate the ECS as a homeostatic feedback system regulating acute feeding activity, i.e. increased ECS activity stimulates feeding behaviour and feeding behaviour inhibits ECS activity. The ECS might therefore provide a possible treatment target for high-risk overweight or obese patients.

Rimonabant - The First Selective CB1 Blocker

Rimonabant is the first selective CB1 receptor antagonist and was first described in 1994 by Rinaldi-carmona et al.[22] The drug displays only a very low affinity for CB2 receptors.[22] It is rapidly absorbed. Plasma concentrations of the drug reach a maximum approximately 1-2 hours after oral administration.[23] Age, gender, body weight/BMI have no effect on exposure.[23]

Rimonabant is also highly bound to proteins (>99%), and is extensively metabolised by CYP3A and amidohydrolase(s) (predominantly hepatic) pathways.[23] It is mainly eliminated via metabolic/biliary pathways.[23] The terminal half-life of rimonabant is about 9 days in non-obese subjects and 16 days in obese subjects.[23]

The RIO Programme

The Rimonabant in Obesity (RIO) was a phase 3 programme of 4 randomised, double blind, placebo controlled clinical trials (Figure 3).[13,24,25,27] Results from all 4 studies consistently showed that rimonabant improved weight, waist circumference, HbA1c, HDL-cholesterol and triglycerides ($p<0.001$) in over 6,600 overweight/obese patients.[13, 24-25]

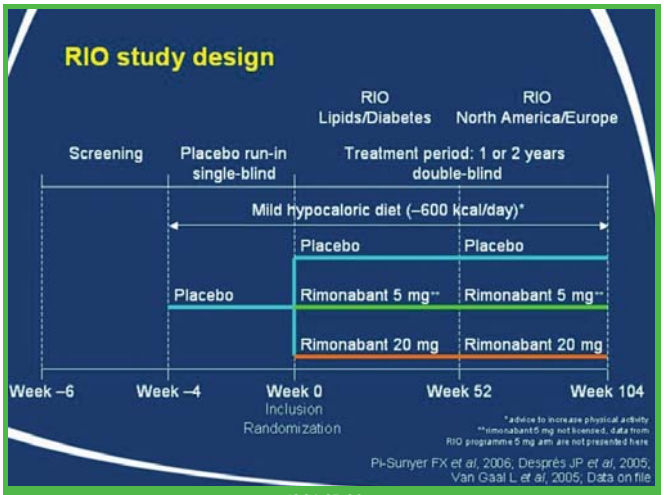

Figure 3. The RIO programme.[13,24, 25, 26]

Weight loss

After 1 year of rimonabant 20 mg treatment, there was a significant weight reduction of 8.6 kg (vs 3.6 kg in placebo). [13] This was accompanied by a 8.5 cm reduction in waist circumference (vs 4.5 cm in placebo).[13] In addition, a weight loss of 7.2 kg was maintained at 2 years (Figure 4).[26] As maintaining weight loss for a long period of time is a difficult task, these results are encouraging for patients and is of great clinical significance.

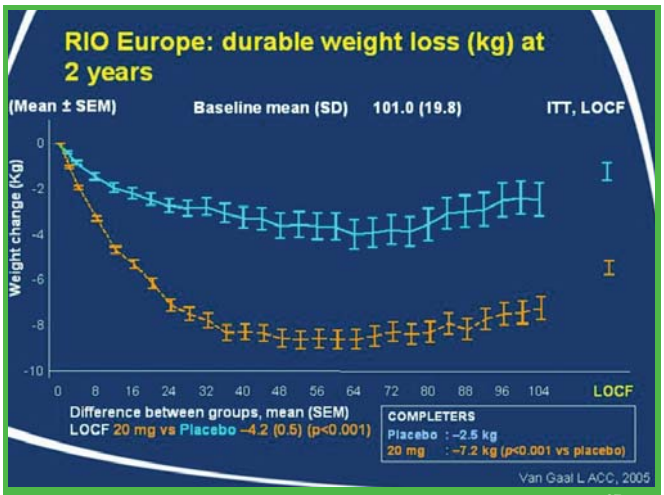

Figure 4. Rimonabant resulted in sustained weight loss at 2 years.[27]

Glycaemic control

In abdominally obese patients with type 2 diabetes, rimonabant 20 mg treatment for 1 year led to a 0.7% decrease in HbA1c.[27] In addition, 42.9% patients, achieved the target HbA1c of < 6.5% as recommended by

the International Diabetes Federation (IDF) (Figure 5).[27] The 0.7% reduction in HbA1c levels is clinically relevant, since every 1% reduction in HbA1c is associated with a 21% risk reduction in any endpoint related to diabetes.[28]

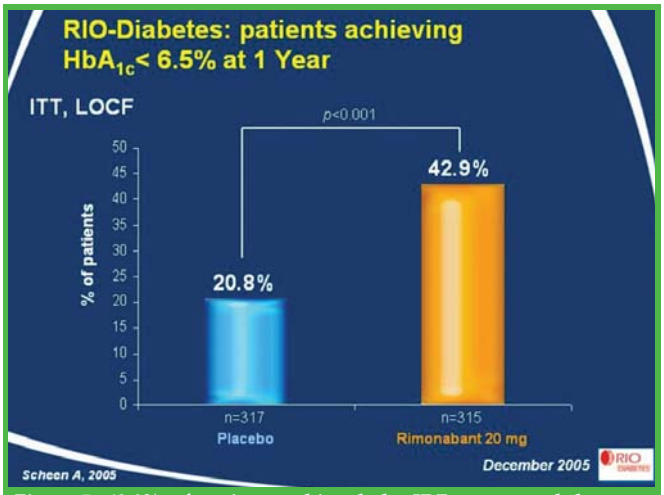

Figure 5. 42.9% of patients achieved the IDF recommended target HbA_{1c} of < 6.5% after 1 year of rimonabant 20 mg treatment.[27]

SERANADE

Similar to data of the RIO programmes, findings from the Study Evaluating Rimonabant Efficacy in Drug-Naive Diabetic Patients (SERENADE) showed that rimonabant was effective in the treatment of type 2 diabetes.[29] SERENADE was the first trial of rimonabant in diabetics with HbA1c as a primary endpoint.[29] It was a multi-centre, randomised, placebo controlled study evaluating the effects of rimonabant 20 mg once daily on blood glucose control in treating naive type 2 diabetics not adequately controlled by diet alone.[29]

At baseline, both the placebo and rimonabant groups had a HbA1c levels of 7.9%. By the end of the 6-month treatment, patients treated with rimonabant showed a significant 0.8% lowering of HbA1c from baseline, compared to 0.3% in placebo (p=0.002).[29] In addition, those with levels of HbA1c of 8.5% or greater at baseline demonstrated a dramatic decline of 1.9% in HbA1c with rimonabant, compared to 0.7% with placebo (p<0.0009).[29] Along with these improvements, rimonabant improved a range of other cardiometabolic risk factors as well, with the exception of blood pressure (Table I).[29]

Table I - Primary and secondary endpoints of SERENADE[29]

Change in parameter	Rimonabant 20 mg once daily (n=131)	Placebo (n=131)	P-value
HbA1c (%)	-0.8	-0.3	0.002
Body weight	-6.7	-2.7	<0.0001
Waist circumference (cm)	-6.1	-2.4	<0.0001
HDL-cholesterol (%)	+10.1	+3.2	<0.0001
Triglycerides (%)	-16.3	-4.4	0.0031
Systolic blood pressure (mmHg)	-5.0	-2.2	NS

Approximately 57% of the improvements in HbA1c were independent of the weight loss achieved, suggesting a direct pharmacologic effect of rimonabant on blood sugar and further support the use of rimonabant as an add-on therapy in abdominally obese patients with type 2 diabetes.[29]

Lipid metabolism

In abdominally obese patients with dyslipidaemia, rimonabant 20 mg treatment for 1 year significantly increased HDL-cholesterol by 23.4% and decreased triglycerides by 15.8%, but has no significant effect on LDL (Figure 6).[25]

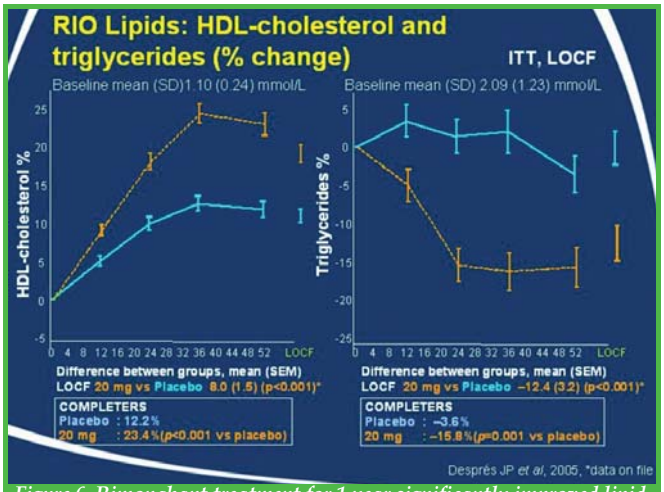

Figure 6. Rimonabant treatment for 1 year significantly improved lipid metabolism in abdominally obese patients with dyslipidaemia.[25]

In addition to lipids and glycaemic control, rimonabant also increased adiponectin levels, an important adipocytokine involved in the regulation of insulin sensitivity and lipid metabolism, especially HDL-cholesterol.[25]

C-reactive protein

Rimonabant 20 mg treatment also had a positive impact on C-reactive protein (CRP), an inflammatory biomarker considered to be a moderate predictor of cardiovascular disease.[30] Compared to placebo, rimonabant 20 mg treatment for 1 year significantly reduced CRP level by 29%.[25] This adds to all the above data that rimonabant is effective in lowering cardiometabolic risk.

Weight-independent effect

Furthermore, rimonabant improved multiple cardiometabolic parameters to a greater degree than could be attributed to body weight loss. After adjustment to body weight loss, regression analyses of the RIO data suggest that 50% of the overall treatment difference was accounted for by the direct CB1 inhibition of peripheral tissues by rimonabant (Figure 7).[31] In other words, the antagonist property of rimonabant directly increased HDL-cholesterol and adiponectin levels, reduced triglycerides and improved HbA1c (diabetic patients) as well as fasting insulin (non-diabetic patients).[31]

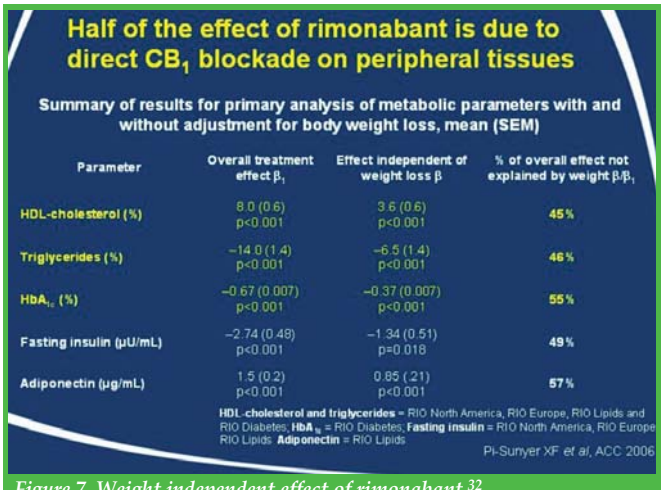

Figure 7. Weight independent effect of rimonabant.[32]

Clinical Safety

Safety assessment based on an extensive exposure of > 13,000 patients showed that rimonabant was safe and well-tolerated for up to 2 years.[24] Most frequent reported adverse events were gastrointestinal, nervous system and psychiatric in nature (Figure 8).[24] Adverse events usually occurred during the first months and were generally of mild to moderate intensity.

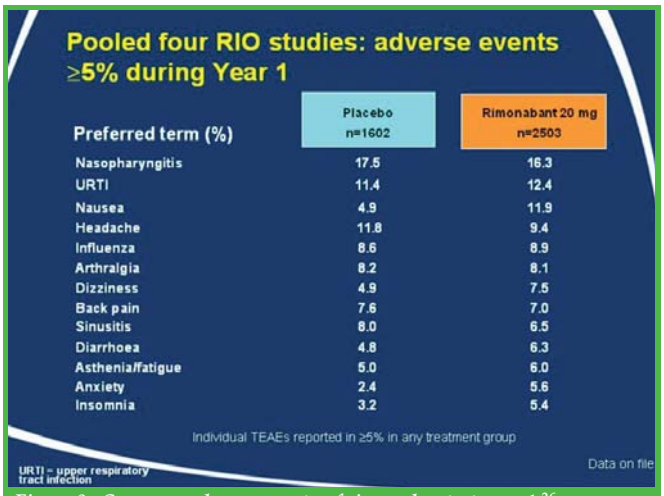

Figure 8. Common adverse events of rimonabant at year 1.[26]

Though the use of rimonabant was associated with an increase in the incidence of depression-related events and anxiety, the overall incidence remained relatively low. Most adverse events were mild to moderate intensity and non-serious, and there was no evidence of increased suicidality. Long-term exposure did not identify new or increased risks. No adverse changes in laboratory variables, electrocardiogram variables or vital signs.

Right Patient Profile

Rimonabant is indicated as an adjunct to diet and exercise for the treatment of obese patients (BMI > 30 kg/m2), or overweight (BMI > 27 kg/m2) patients with associated risk factors, such as type 2 diabetes or dyslipidaemia

The drug is best used in patients who are willing to embrace long-term treatment and concomitant lifestyle changes with BMI > 27 kg/m2, abdominal obesity and type 2 diabetes or dyslipidaemia (low HDL-cholesterol and/or high triglycerides).

Rimonabant is contraindicated/not recommended in
- Pregnant or breast-feeding women
- Children below age 18
- Patients with uncontrolled serious psychiatric illness such as major depression
- Patients receiving antidepressant medication, or have past history of depressive disorder.
- Patients with severe renal/hepatic impairment

Rimonabant should be used with caution in
- Patients receiving potent CYP3A4 inhibitors
- Patients treated for epilepsy

Summary

In summary, obesity profoundly and severely increases our risk of developing cardiovascular disease and type 2 diabetes. Pre-clinical data in animal models showed that overactivation of the ECS is associated with abdominal obesity and provides the foundation for the use of CB1 antagonist to target obesity and reduce associated complications. The RIO programmes, which evaluated over 6,600 obese/overweight patients showed that the selective inhibition of the CB1 receptor by rimonabant significantly reduced weight and waist circumference as well as improved lipid and glucose metabolism in a weight-independent manner. Data from SERANADE further support the use of rimonabant as an add-on therapy in abdominally obese patients with type 2 diabetes. In addition, rimonabant was well tolerated and had a favourable safety profile for up to 2 years. All these data suggest that rimonabant is a promising agent for long-term management of obese or overweight patients with elevated cardiometabolic risk.

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Medical & Dental Directory of Hong Kong, 8th Edition

On behalf of the Editorial Board, it is our great pleasure to announce that the Medical & Dental Directory of Hong Kong (8th Edition) has been published. In this edition, we have prepared an electronic version of the Directory in form of a CD ROM. The CD has incorporated various search functions so that one can easily locate the information of the doctor, the dentist, the hospital, medical and dental websites and etc with great ease. The Editorial Board has made every effort to ensure accuracy. Notwithstanding that, we apologize for the errors made in the Directory. We will publish any corrigendum/updates in the next few issues of Medical Diary for your update.

Corrigendum/Updates to Medical & Dental Directory of Hong Kong (8th Edition)

Page No.	Particulars
442	Qualification attained by HO Hung Kwan, Michael should read as "MB BS (**Syd**) 1994"
455	"KONG Hot Tai" should read as "KONG **Hoi** Tai"
478	"LAU The Shan" should read as "LAU **Teh** Shan" and the Chinese name should read as **劉德譫**
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Practical Approach to the Management of Breast Cancer

Dr. Polly SY Cheung

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MBBS(HK) FRCS(Glasg) FRACS FACS FHKAM (Surgery) FCSHK
Specialist in General Surgery
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Introduction

Breast cancer has become the commonest cancer affecting women in Hong Kong since 1994. The number of new cases rises by an average of 6.4% every year in the last decade, a trend faster than the growth of all other cancers in women including colorectal and lung cancer. Almost 60% of cases are seen in the age group between 40 to 60 years. However, age-adjusted incidence rises with increasing age which does not drop after the age of 70. Patients under the age of 40 constitutes about 10% of all breast cancers.

First Presentation of Breast Cancer

According to the multidisciplinary breast conference database at the Hong Kong Sanatorium and Hospital, almost 80% of patients noticed a painless lump in their breast accidentally, either during bath, massage or felt by their partner. The first medical visit they pay is usually to their family doctor, or gynaecologist.

To differentiate a benign from malignant breast lump, the usual criteria of hard consistency and irregular edge apply. However, the picture is often confused when a painless mobile lump occurs in a relatively young patient, or a plague of thickening in a lumpy breast in women in their thirties and forties. Slow growing cancer such as tubular or mucinous carcinoma can mimick a fibroadenoma on physical examination. Fibrocystic breast change with sclerosing adenosis or excessive fibrous stroma, or deep seated cyst beneath hyperplastic breast tissue can produce irregular hard thickening mimicking a malignant growth.

What to Choose for Imaging of a Palpable Breast Lump

Most doubtful lumps on physical examination could easily be clarified on *breast ultrasound*, with high resolution probe of 10 -13 MHz. Benign solid lumps are usually seen as flattened homogeneous hypoechoeic mass with well defined echogenic rim around it. Cysts are usually anechoeic with posterior wall enhancement. Any tall shaped hypoechoeic lesion with heterogeneity, highly irregular outline, microlobulated or serrated edge, or posterior wall shadowing calls for suspicion and warrants further investigation. Breast ultrasound is superior to mammogram in diagnosing breast cancer in palpable lump, as shown in the multidisciplinary breast conference data (91% vs 77%).

Our young patients usually have dense breasts with little intraparenchymal fat, therefore forming a distinct layer of subcutaneous and retromammary fat, sandwiching a compact layer of breast parenchymal tissue. On ultrasound, the normal breast parenchyma appears as a layer of light coloured echoes, while the normal fat layer appears as a darker layer. Abnormal growth, be it solid or cystic, benign or malignant, stands out as a darker shadow inside the lighter background of breast parenchyma. On mammogram, glandular tissue is lighter ('whiter") in colour and fatty tissue is dark. Abnormal lesions all appear as whiter opacity on mammogram. Therefore it would be easily masked in a background of "white" glandular layer. This explains the non-visualisation of some benign or malignant lumps in dense breasts, even if they are palpable.

However, when intramammary fat content increases in obese patients, or postmenopausal women, these appear as patchy dark shadows inside the breast parenchyma. Abnormal tumour growth may then become masked by such shadows on ultrasound but become better visualised on mammogram. The accuracy of mammogram increases with more fatty content of the breasts, therefore its diagnostic accuracy increases with age. It is also supported by evidence from our Multidisciplinary Breast Conference database.

Place of Mammogram in Breast Cancer Diagnosis and Management

Early breast cancer that is too small to cast a shadow on ultrasound, may appear as microcalcifications or architectural distortion on *mammogram*. Microcalcifications are seen in about 40% of all breast cancers, according to Canadian experience. These represent cancer cell necrosis especially in high grade cancers, and become the earliest sign of cancer even before they form a mass. Microcalcifications can be visualised even in dense mammograms and form the basis of early detection that brings about impact on mortality reduction in many screening programmes.

In our experience, screening mammogram detects 12% obviously benign macro or microcalcifications that do not need further intervention. For indeterminate lesions that require biopsy, 1 out of 4 is confirmed cancer. For a palpable lump that already shows a malignant picture on ultrasound, mammogram is essential before contemplating breast conserving surgery, to exclude any nonpalpable multicentric growth that produces early mammographic signs such as suspicious microcalcifications or architectural distortion.

When to Use MRI Breasts

With improved technology in magnetic resonance imaging, *MRI* breasts provides additional information on the breasts when findings are equivocal on ultrasound or mammogram. This often occurs in patients with severe fibrocystic breast change that casts multiple ill-defined shadows in ultrasound, and mammogram often shows dense breast tissue only. We have experience in detecting extensive DCIS that do not form microcacifications and multicentric tumours that are difficult to be differentiated from benign breast change by ultrasound or mammogram. Indeed recent study conducted at Yale University showed that 28% of planned lumpectomy breast cancer cases changed their plan of management to mastectomy because of additional findings in MRI. Unfortunately, the false positive rate of MRI is between 35 to 40% in reported series in literature and therefore is yet to be evaluated as a necessary investigation for all breast cancer undergoing surgery.

At the present time, imaging of breast by MR is recommended for equivocal lesions by other imaging methods, and as a routine screening procedure in addition to mammogram and ultrasound in BRCA1&2 gene mutation carriers but not replacing them. In fact, cancer detected with malignant microcalcifications are not all seen on MRI.

Importance of Triple Assessment

Apart from clinical diagnosis based on physical examination and imaging diagnosis based on ultrasound and/or mammogram, cytohistological assessment is an important part in the trio.

Fine needle (FNA) or core needle biopsy (CNB) should always be considered in the triple assessment of palpable breast lumps. Mucinous carcinoma, which notoriously gives a benign appearing picture simulating fibroadenoma on physical and ultrasound examination, would easily be missed without a cytology arm of assessment. It is therefore a routine to biopsy using at least a fine needle (FNA) for young women with presumably palpable fibroadenoma, if the lump is to be observed.

For nonpalpable breast lesions which are seen on ultrasound, radiology opinion should be sought as to the degree of suspicion whether needle biopsy is needed. One should avoid excessive biopsy of all ill defined hypoechoeic lesions which are often seen in fibrocystic breast change. In short, the need for such biopsy should be guided by radiology recommendation.

The choice between fine or core needle biopsy lies with the clinician. Both carry a high accuracy of over 90% as seen in our Multidisciplinary breast conference data. FNA is simple, carries no subsequent scar, and has few complications apart from occasional bruising. CNB needs local anaesthetic, has a small nick wound, and has a small rate of intraparechymal bleeding that may mask the original tumour. However, it provides information on the presence of invasion and grading of tumour that help preoperative planning of surgery. As there is a small false positive rate in FNA, we will perform mastectomy based on core needle biopsy result but not FNA.

For nonpalpable lesions that are indeterminate in picture, higher tissue yield and increased accuracy can be achieved with the use of ultrasound or mammogram guided (stereotactic) vacuum assisted biopsy (VAB). Its use in removing benign tumours by piecemeal is faced with a recurrence rate of around 12-16% which should be explained to the patient before the procedure and that a FNA diagnosis to confirm its benign nature should be done before the attempted mammotomy removal (guidelines from American Society of Breast Surgeons).

Staging of Breast Cancer

When a lump or nonpalpable lesion is diagnosed as breast cancer, staging procedure could be simple chest x-ray, abdominal ultrasound and blood test, to look for distant metastasis. Breast ultrasound and mammogram may have already provided information on gross nodal status in the axilla and local region. If there is obvious nodal involvement proven on cytohistology, more detailed staging procedure such as PET-CT fusion scan, whole body MRI, or CT thorax and abdomen and bone scan could be performed.

Principles of Breast Cancer Treatment

Surgery is still the main treatment that brings about cure of breast cancer. This applies to early stage disease in stage 0,1 and 2. However, for stage 3 disease, neoadjuvant drug therapy should be considered before definitive surgery for upfront control of micrometastasis which becomes highly probable. It can also render locally advanced disease more operable, and in selected cases, may be able to downsize tumour to avoid mastectomy. For stage 4 disease, cure is unlikely and the main treatment is systemic drug therapy for control of disease. In this situation, surgery and radiotherapy are palliative measures to prevent complications.

Surgical Treatment of Breast Cancer

Surgery of breast cancer can be divided into two parts: breast and ipsilateral axilla.

Randomised studies have proven that breast conserving surgery coupled with irradiation has equivalent outcome as mastectomy in terms of local recurrence and survival. It should be reminded that the purpose of breast conserving surgery is to avoid long term psychosocial sequelae of mastectomy. Local mammoplasty procedures are often employed to restore an aesthetically intact breast and to facilitate subsequent mammogram surveillance. It should be offered as an option to suitable patients. According to our Multidisciplinary Breast Conference database, about half of breast cancer patients can be treated with breast conserving surgery. From medical viewpoint,

case selection is based on relative tumour size to breast volume, tumour location (medial especially medial-lower quadrant tumours may create more difficulties in local mammoplasty), safety of breast irradiation in patients with autoimmune skin disorders and cardiac disease. Age of patient, presence of axillary lymph nodes or histological type of cancer are not contraindications to breast conserving surgery.

For those that require mastectomy, the option of immediate or delayed breast reconstruction should be offered. From our experience, immediate reconstruction is preferred as the cosmetic outcome is much better, allowing for skin sparing, or even areolar or nipple sparing techniques in mastectomy, and the patient will not suffer from a period of physical loss of breast. There is ample evidence in the medical literature that reconstruction will not mask local recurrence or cause undue delay in subsequent systemic treatment.

For the treatment of regional lymph nodes, level I and II dissection has been the conventional approach as a staging and treatment procedure. For those with palpable axillary nodes and confirmed involvement by FNA, this is still the standard procedure. With detection of earlier stage disease through population based screening, sentinel node biopsy is invented in the early nineties as an axillary staging procedure for early stage cancer. The aim is to avoid unnecessary axillary dissection that carries long term morbidity such as upper limb lymphedema. It has been shown to carry the advantage of enhanced pathology in diagnosing micrometastatic spread in axilla and has a high accuracy rate of over 95% in large medical centres in staging of the axilla. Ongoing randomised trials have shown no deleterious effect or excessive local axillary recurrence over conventional axillary dissection.

Adjuvant Systemic Therapy for Early Breast Cancer

Randomised trials have shown improved survival with the use of adjuvant drug therapy after breast cancer surgery for stage 2 and selected stage 1 cancers. Age of patient, tumour size, tumour grade and nodal status are important determinants on the need for adjuvant drug therapy. Factors such as oestogen and progesterone receptors, c-erbB2 receptors are predictive factors for the effectiveness of certain targeted therapy and chemotherapy.

As adjuvant therapy, patient treatment should be individualised. Decisions will also take into account the patient's past medical health, balancing the benefits and risk of individual drug therapy against the documented evidence of gain in survival.

The use of drug therapy after breast cancer surgery is to eliminate any possible micrometastasis which may be harbouring in the body and disseminated at the time of presentation of disease. Unfortunately, there is no known test which can predict the presence of these micrometastasis. Hopefully, development in gene signature can solve this problem in future. Until such time, our recommendations for such treatment is based on current available medical evidence.

The Trend in Breast Cancer Management

Launch of regular breast cancer screening programmes worldwide leads to detection of breast cancer at an earlier stage. This allows for more breast conserving surgery to be performed and the physical stigma of cancer surgery to women can be reduced.

Breast cancer is a heterogeneous disease. With more understanding of breast cancer biology and research into targeted therapy, treatment can be more individualised and treatment sufferings can be reduced.

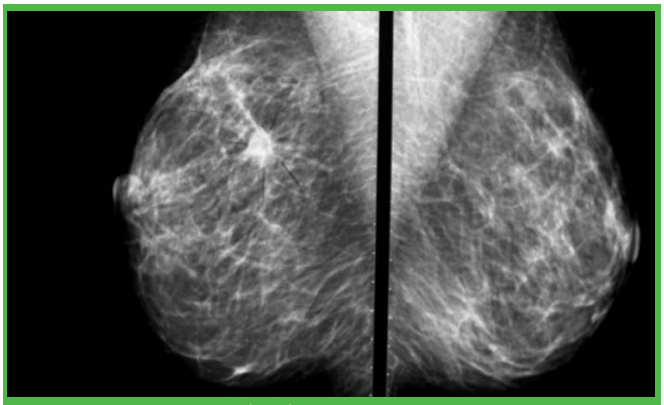

Fig 1. Breast cancer: spiculated opacity on mammogram

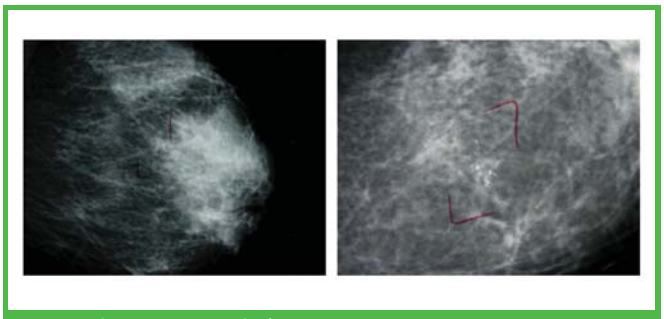

Fig 2. Malignant microcalcifications on mammogram

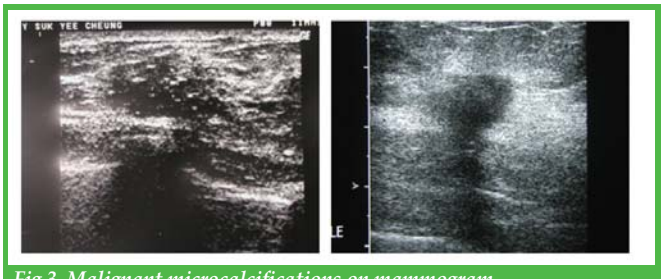

Fig 3. Malignant microcalcifications on mammogram

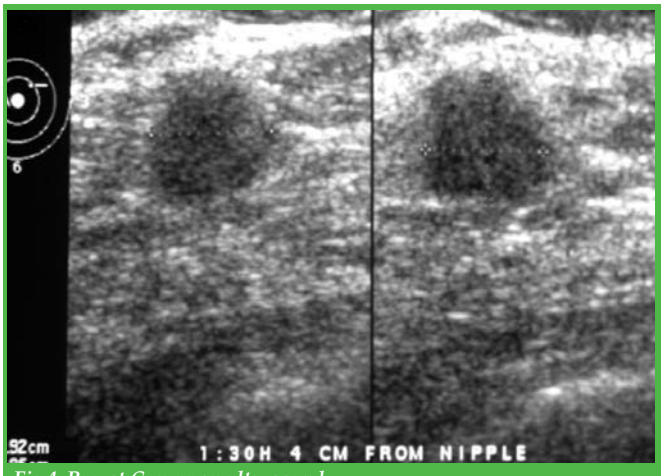

Fig 4. Breast Cancer on ultrasound

Table 1. Triple Assessment of breast lump

- Clinical diagnosis
- Imaging diagnosis
- Cytopathological diagnosis

If concordant, >95% accuracy in diagnosis of the underlying nature

Table 2. Multimodality treatment of breast cancer

Surgery: main treatment for curable cancer

Systemic drug therapy : adjuvant or neoadjuvant, to treat micrometastasis; main treatment for metastatic cancer

Radiation therapy: reduce local recurrence and translate into survival gain

Table 3. Systemic drug therapy for breast cancer

- **Chemotherapy**
  - Anthracycline, taxane
  - Navelbine, gemzar
  - Xeloda oral
- **Hormonal therapy**
  - Tamoxifen
  - Aromatase inhibitor: arimidex, femara, aromasin
- **Biological therapy (targeted at receptors)**
  - HER-2 receptor: Herceptin, Lapatinib
  - Angiogenesis Inhibition: Avastin

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† Phase III open-label trial in 324 women with ErbB2+ locally advanced/metastatic breast cancer who progressed after treatment with regimens that included an anthracycline, a taxane and trastuzumab. Women were randomized to receive either: 1250 mg OD PO every day plus capecitabine 2000 mg/m^2/day PO in 2 divided doses days 1-14 every 21 days, until disease progressed or unacceptable toxic events occurred (n=163), or capecitabine 2500 mg/m^2/day PO in 2 divided doses days 1-14 every 21 days until disease progressed or unacceptable toxic events occurred (n=161).

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Please refer to the TYKERB Prescribing information for contraindications, warnings, precautions, adverse events, dosing information and patient selection criteria.

REFERENCES: 1. Product Monograph for TYKERB™. GlaxoSmithKline Inc. 2007. 2. Geyer CE, Forster J, Lindquist D, *et al.* Lapatinib plus Capecitabine for HER2-Positive Advanced Breast Cancer. *NEJM* 2006;355:2733-43.

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CONTRAINDICATIONS None.

WARNINGS AND PRECAUTIONS TYKERB has been reported to decrease LVEF. Caution should be taken if TYKERB is to be administered to patients with conditions that could impair left ventricular function. LVEF should be evaluated in all patients prior to initiation of treatment and during treatment. TYKERB has been associated with reports of interstitial lung disease and pneumonitis. Patients should be monitored for pulmonary symptoms indicative of interstitial lung disease/pneumonitis. Caution is warranted if prescribed to patients with moderate or severe hepatic impairment. Diarrhoea, including severe diarrhoea, has been reported. Proactive management of diarrhoea with anti-diarrhoeal agents is important. Severe cases of diarrhoea may require administration of oral or intravenous electrolytes and fluids, and interruption or discontinuation of TYKERB. Concomitant treatment with inhibitors or inducers of CYP3A4 should proceed with caution due to risk of increased or decreased exposure to TYKERB, respectively. Coadministration of TYKERB with medications with narrow therapeutic windows that are substrates of CYP3A4 or CYP2C8 should be avoided.

INTERACTIONS TYKERB is predominantly metabolised by CYP3A. Therefore, inhibitors or inducers of these enzymes may alter the pharmacokinetics of TYKERB. Coadministration of TYKERB with known inhibitors or inducers of CYP3A4 should proceed with caution and clinical response and adverse events should be carefully monitored. If patients must be coadministered a strong CYP3A4 inhibitor, a dose reduction to 500 mg/day of TYKERB is predicted to adjust the TYKERB AUC to the range observed without inhibitors and should be considered. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors. If the strong inhibitor is discontinued, a washout period of approximately 1 week should be allowed before the TYKERB dose is adjusted upward to the indicated dose. If patients must be coadministered a strong CYP3A4 inducer, the dose of TYKERB should be titrated gradually from 1,250 mg/day up to 4,500 mg/day based on tolerability. This dose of TYKERB is predicted to adjust the TYKERB AUC to the range observed without inducers and should be considered. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued the TYKERB dose should be reduced over approximately 2 weeks to the indicated dose. TYKERB inhibits CYP3A4 and CYP2C8 in vitro at clinically relevant concentrations. Caution should be exercised when dosing TYKERB concurrently with medications with narrow therapeutic windows that are substrates of CYP3A4 or CYP2C8. TYKERB is a substrate for the transport proteins Pgp and BCRP. Inhibitors and inducers of these proteins may alter the exposure and/or distribution of TYKERB. TYKERB inhibits the transport proteins Pgp, BCRP and OATP1B1 in vitro. The clinical relevance of this effect has not been evaluated. It cannot be excluded that TYKERB will affect the pharmacokinetics of substrates of Pgp (e.g. digoxin), BCRP (e.g. topotecan) and OATP1B1 (e.g. rosuvastatin). Concomitant administration of TYKERB with capecitabine or trastuzumab did not meaningfully alter the pharmacokinetics of these agents (or the metabolites of capecitabine) or TYKERB. The bioavailability of TYKERB is affected by food.

PREGNANCY AND LACTATION TYKERB can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. Women should be advised not to become pregnant when taking TYKERB. TYKERB was not teratogenic when studied in pregnant rats and rabbits but caused minor abnormalities at doses which were maternally toxic. It is not known whether TYKERB is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breast-feeding infants from TYKERB, a decision should be made whether to discontinue nursing or to discontinue the drug. it is recommended that breast-feeding be discontinued in women who are receiving therapy with TYKERB.

ADVERSE REACTIONS Decreased LVEF. Diarrhoea. Anorexia. Interstitial lung disease/pneumonitis. Nausea. Vomiting. Hyperbilirubinaemia. Rash. Fatigue. Dyspepsia. Dry skin. Stomatitis, constipation, abdominal pain. Palmar-plantar erythrodysaesthesia. Mucosal inflammation. Pain in extremity, back pain. Headache. Insomnia.

OVERDOSE There is no known antidote for overdoses of TYKERB. The maximum oral dose of TYKERB that has been administered in clinical trials is 1800 mg once daily. More frequent ingestion of TYKERB could result in serum concentrations exceeding those observed in clinical trials, therefore missed doses should not be replaced, and dosing should resume with the next scheduled daily dose. There has been a report of one patient who took an overdose of 3000 mg of TYKERB for 10 days and suffered grade 3 diarrhoea and vomiting on day 10. The symptoms resolved following IV hydration and interruption of treatment with TYKERB and letrozole. TYKERB is not significantly renally excreted and is highly bound to plasma proteins, therefore haemodialysis would not be expected to be an effective method to enhance the elimination of TYKERB.

Abridged PI (GDS 02)

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Eat, Drink and Be Merry

Dr. George MH Ng

MBBS(Syd), DFM(CUHK), Dip P Derm(CARDIFF)
Family Physician

As doctors we all get a hefty dose of stress daily. I wash away mine by drinking and eating, or more accurately, sniffing a good glass of wine and gorging myself with flavorful dishes. OK, I go to gym regularly, but that's not for stress relief (it helps a bit); I sweat on the treadmill because that gets rid of the excessive calories.

So here I am going to talk about some of my favourite restaurants in Hong Kong, and the memorable wines I drank to go with their signature dishes. But a word of warning, you might not find the same experience as I do. As regular customers to the following establishments, they know my family well (my 2 boys, aged 6 and 9 make us very recognisable). They serve me the daily fresh, the best cut, and try that just bit harder. As our doctors' tasting group would point out, the food and service was better when they dined with me in these restaurants, than when they went by themselves. I guess you do the same to your most faithful patients.

1) Toscana in the Ritz-Carlton Hotel, Central

By the time this article is published, this joint is gone- the Ritz-Carlton would have been pulled down. They will reopen on the Kowloon side, but don't know when. And Chef Umberto Bombana has gone to Beijing (his wife is a local Chinese lady and his boys go to a local school). It was rumoured to get one Michelin star (along with Ah Yat Abalone).

My 2 boys putting on the gloves, getting ready to shave the white truffles, with the restaurant manager Attilio looking on; chef Umberto had his day-off. The occasion was my elder son's 8th birthday.

This is all very sad-it is our family restaurant; my boys were welcome to the kitchen, watch the cooking and eat freshly prepared gelato. I can't say enough of the white Truffles season here, served with the raviolo (a ravioli with a sunny-side up egg inside), the homemade fettuccine, and the risotto. Umberto would shave us heaps of the fungus on top of the dishes and even let my boys do it. And he would cook us items not on the menu-a semi-raw scallop salad with shredded fresh black truffles and celeriac, stewed octopus in white wine (one of the tricks in this dish is that they also put in the wine cork in the stewing process, to render the octopus tender and not chewy), sliced Challand duck breast with a slice of foie gras on the side etc.

Ms Eliza Scavino, daughter of Enrico Scavino with my wife outside their estate (Paolo Scavino) in Castiglione Falleto, in Langhe, Piedmonte. Generally, the vignerons in Italy are very friendly and they really appreciate having people visiting, and they open their best wines for you to taste. Two producers actually had us to stay for dinner.

Naturally, the best wines to drink with the food here are Italian (the food style is Northern Italian), and particularly Piedmontese-a well-aged Barolo does have a white truffle smell. I opened numerous Barolos and Barbarescos here, when they were still relatively cheap; these days a Barolo from a good recent vintage and famous producer would cost > $1500 a bottle. The three that really stood out were the 1990 Scavino Barolo Bric del Fiasc, the 1990 Giacosa Barbaresco Santo Stefano, and the 1989 Aldo Conterno Barolo Colonnello. They all carried aged nebbiolo characters: bright ruby red colour (which is very pretty, compared with inky, over-extracted deep purple modern wines), nose of truffles, rose petals, red fruits and almond, and palate of cherries, tobacco and tar with that touch of sweet herbs.

Truffle hunting with Signore Ezio, a trifolao (truffle hunter) and one of his champion dogs. My wife just picked up a small one. We stayed in his 19th century refurbished farmhouse in Monchiero for a few days and his wife, Clelia, is a great cook and serves up the truffles. Look up: www.traarteequerce.com

A magnum of 98 Giacosa Barbaresco Asili, 90 Scavino Barolo Bric Del Fiasc, and 98 Sandrone Le Vigne; and a bottle of 98 Conterno Monfortino, the Petrus equivalent in Barolo. Boy, do I love these nebbiolos.

2) Lao Shanghai (formerly Lao Ching Hing), Novotel Century, Wan Chai

Needless to say, they serve Shanghaiese-style food here. Try the braised turtle in Xiao Xing wine and superior soup -the exotic taste of the "skirt" and the meat of the animal demands full-bodied fruit bombs. For my 10th year wedding anniversary dinner, I drank a 1994 Guigal Cote Rotie La Mouline with abundant mint, flowers, herb, blueberries and prune. Australian shiraz is also great, and the 96 Brokenwood Graveyard is a real gem-I purchased a case some years back for Aus$60 each. Now a recent vintage in Watson's would set you back HK$1000+. This has blossomed into a soft, earthy, leathery, juicy and pruny elixir, with that enchanting bouquet of concentrated blackberries-a classic Hunter Valley shiraz indeed.

I only have the 94 Landonne and Turque left. I finished the Mouline last year as it is the earliest maturing.

During the hairy crab season, they serve the crab roe to accompany different dishes. My favourite is fried crab roe mixed with plain noodles. And champagne has the right acidity to cut into the oiliness of the crab roe. I have fond memories of the 82, 85, 88, 90 Krug and Dom. Perignon, and the 90 Bollinger RD. Aged champagne is considerably less bubbly and gaseous, and I find this less filling and less likely to make me burp (and the reflux thing-alright, no medical talk here, but needless to say PPI saves the day).

96 Krug clos du Mesnil

For younger champagnes, I find the decanting process render them rounder and mellower. The Baccarat people do make a beautiful flute-shaped champagne decanter (the flute shape allows the decanter to stay in the ice bucket). Try doing this with the Billecart-Salmon NV Rose; I consider this to be the best value amongst all Rose champagne. The wonderful strawberry finish to this wine is captivating.

3) The Derby, Jockey Club, Happy Valley

I think they label this as a French Restaurant, but the food is like classic French with elements of Italian and Asian, and just that touch of modern Australian-no wonder as Chef Donovan Cooke used to own restaurants in Melbourne and he apprenticed under Marco Pierre White.

The dish here to pre-order is the steamed Bresse pigeon breast, wrapped in Savoy Cabbage together with a thick slice of foie gras, and served with Albufera sauce (this is made from pureed foie gras and thick chicken stock). This has to be the richest tasting dish you could ever put in your mouth, and aged red Burgundies, with their exquisite finesse, provides a refreshing touch. I am very fond of 1991 red Burgundies; this is an under-rated vintage because of initial harsh tannins, and their prices were quite reasonable as a result in the 1990s. But the ones from reputable producers had enough fruit in them to survive the tannin, which has by now completely melted away. Good examples are the 91 DRC La Tache, DRC Grands Echezeaux, Jean Gros Richebourg, Mongeard-Mugneret Richebourg, and the Rousseau Ruchottes Chambertin-their bouquet is that of black truffles, forest floor, red fruits and the taste is that of creamy raspberries and red cherries caressing the palate to an enveloping and smooth finish.

Back in the mid-90s, I paid only 2500 for the La Tache and around 600 for the Mongeard-Mugneret Richeburg.

In April, Chef Donovan serves the Pauillac lamb; these are milk-fed baby lambs from the Acquitaine region of France. Their pinkish meat is very flavourful (but not strongly lamb-ish) and tender, and I adore their sweet bread, which is the thymus gland-this is probably a cholesterol bomb but I just couldn't keep my fork away. Naturally Bordeaux reds are the perfect accompaniment to this meat. I am not going to exalt the virtues of First Growths or great Pomerols here, but I have to tell you we blind tasted three cabernet-based wines in 2006, namely 90 Penfold 707, 90 Mondavi Cab Reserve, and 90 Pichon Baron. The winner? Well, the 3 couples present each had their own favourite and each wine did have its own pleasing characters, but the finesse of the cab fruit of the Mondavi, with the inherent flowing blackcurrant and violets, carrying a long and convincing finish, blew me away (I purchased it for around HK$500 from Remy fine wines years ago).

4) Carriana (Chiu Chow) Restaurant, Gloucester Road, Wan Chai

This place purveys the best cold crabs of all Chiu Chow restaurants. These are huge beasts, filled with succulent chunky meat and eating the claws is not unlike eating a chicken drumstick. I always ask the lady manageress to reserve me a good one before I go; she never fails to deliver, as her boss is a patient of mine. The perfect match is an Alsacien Riseling, the citrusy apple and peach fruitiness of which simply takes the salty crabmeat taste to a higher level. A particular wine that sticks in my mind is the 89 Trimbach Clos St Hune Riseling VT (Vendage Tardive, meaning late picked). This is a VT that they fermented it totally dry, and the result is a mixture of stone minerality, flowers, honey, peach and lime that exploded from the glass. It smelled and tasted sweet, but not sugary so. I paid around ¢G 50 for this wine some years back in Heathrow.

Their Chiu-Chow style braised goose is also first-rated, and their shark fin (make sure it is in clear ham broth, not Chiu-Chow style sticky soup, which is too filling) excellent. Last year I drank a 97 Tignanello with these; this sangiovese-based wine (with 10% cabernet) was fully mature, supple and fragrantly filled with red and black cherries, the tannin and acidity of which had all but vanished. The 96 IL carbonaione (100% sangiovese) is in a similar vein, but with a touch of acidity, and hence more structure, which is welcome in sweet sauce based Chinese cuisine.

5) Restaurant O-La-La, Wan Chai

This French style bistro serves what I call soul food, i.e. excellent ingredients prepared simply, but expertly. The cold seafood platter, piled with clams, oysters, prawns, boulots (sea whelks) and a crab, is a must. The Belon oysters are good, chunky and meaty, but a notch above is the Perle Blanche (white pearl). This is a sweet tasting and crunchy oyster with mild seawater saltiness. With oysters, I am partial to Graves Blanc, and luckily, my milestone years, 94 (I got married), 98 and 2001 (the birth years of my boys) were all great years for Bordeaux whites-for the reds these are so-so years-hence the price of white are not as steep. For collections sake, I bought a lot of Laville Haut Brion and Haut Brion Blanc for these vintages. But for everyday personal consumption purpose, the 2001 De Fieuzal Blanc is superb. It has a lovely lime and grapefruit taste, which merges well with the briny oyster; the 01 Chevalier Blanc is on a higher level with additional smoky oak and vanilla. With some age, the 94 Domaine de Chevalier Blanc and the 94 de Fieuzal Blanc had all but extra orange peel, honey and melon. And for the greats like 92, 94, 98 Haut Brion Blanc and 89, 94, 98 Laville Haut Brion, they are a myriad of caramel, Kumquats, grapefruit, lanolin, wet stones and Chinese incense.

The 2001 Haut Brion Blanc and Domaine de Chevalier blanc.

Other flavorful dishes here are the spit-roasted chicken (stuffed full of garlic) and the roast pigeon. Chateauneuf-du-Pape is the answer to these poultry dishes: recently I had a 98 Domaine du Pegau Cuvee Laurence; it smelled of lavender and raisin, and on the palate it was grapes and prunes, entirely mesmerising. I gave a glass to the proprietor of the restaurant, who is affectionately known to customers as "Brother Fat Boy", and he was completely bowled over.

The 98 Pegau Cuvee Laurence

Some of my beloved CDPs: 88, 89 Rayas, 98 Pegau Cuvee da Capo and Cuvee Reserve

6) Kumatei Japanese Restaurant, Jaffe Road, Wan Chai

I always drink Rhone white with Japanese food, as I consider the Marssanne and/Roussanne varietals has the right combination of acidity, sweetness and oiliness

to balance out the fishy, wasabi taste of sashimi and sushi. In fact, these white wines also make great accompaniments to Robatayaki (Japanese style grill), as the full-bodiness of them can handle even red meat. The Roussanne VV (veille-vignes, meaning old vines) by Chateau de Beaucastel is a winner year-in year-out: I have yet to find a disappointing bottle since I started purchasing it in the mid-1990s, from vintage 1992 to 2005-this wine even performed well in vintage 2002 when the whole Chateauneuf du Pape was flooded: which says so much about the merits of fruits from old vines. Round and fat, this is a compelling mixture of marmalade, yeast, white peaches, white flowers, honey and sweet passion fruit. These wines predictably shut down 5-6 years after the vintage, coiling up to become an alcoholic shell, and wake up some 10 to 15 years later. My few bottles left from vintage 1993 were dead from 1998 til 2006, and then I opened my last 2 in 2007 and boom!! They had all but additional white truffles, earthiness and caramel to them.

In Kumatei, you would have the usual freshest Shimachi, Hamachi, Toro etc, but the special items to try are the Japanese "three knives" fish sashimi and horse meat sashimi-they both have a ethereal flavor that one must try to know. The grilled Canadian rib, ox tongue and Hamachi head are also sensational, as is the fish soup. Last but not least, you should finish your meal with one of the many choices of sorbet; my personal favorites are the mandarin, grapefruit and pumpkin.

7) Manor Restaurant, Austin Road, TST

As the name suggests, this is not a cheap eat place; we come here especially for celebratory occasions such as Mother's day or Birthdays. My wife's most preferred place for refined Cantonese cooking, this place offers magnificently prepared abalone, fish blubber, shark-fin soup with chunky red-crab meat, bird's nest (in a sweet freshly ground almond paste rendered smooth with just-cooked egg white), scampi in clear broth (I don't know why people eat this deep-fried in chilli salt and pepper, which kills the delicate taste of the scampi meat), and salt-baked Chicken (their version is that they fried the salt with star-anise, scallions, shallots and ginger and the mixture is then stuffed into and pasted onto the chicken, which is thence baked to slightly brown). Even simple things like vegetables in clay pot seasoned with shrimp paste, fried egg noodle with soy-sauce (there is not a drop of oil to be found dripping from the hair thin noodles or on the plate, yet the noodle retains a fantastic chewy texture and doesn't feel dry), the clay pot rice with Chinese cured meat and sausages and salted-duck, and the congees are done to perfection. As for the fish blubber, we were fortunate that we had our fair share before; we used to order a whole piece (2-3 pieces to a catty, or "2 heads", which measures 3-4 palm areas and 2-2.5 cm thick once cooked) and it would cost around $2000. Because of the economic boom in China and the consequent insatiable demand for luxury items, a piece of "2 head" blubber would now cost $10000 (look at also what happened to the price of First Growth Bordeaux in the last 2 years). Of the 4 treasures of Cantonese cuisine, i.e. abalone, sea cucumber, shark fin, and fish blubber, my wife and I appreciate the blubber most-it is very sad that we can't afford this anymore.

Majestic food demands majestic wine, and there is none more appropriate than a white Burgundy. Lamentably, the days of a Leflaive Puligny-Montrachet premier cru or a Comte Lafon Mersault premier cru costing less than $1000 are gone, and I am surviving on my remaining stock purchased years ago-ahhh, the memories of 92 and 95 Leflaive Chevalier Montrachet. Nevertheless, a 2001 Henri Boillot Mersault Charmes, which I opened recently, gave me tremendous pleasure. Supple, full-bodied and smooth as a dream, it was like drinking pureed peaches and melon, with a gentle dose of toasted oak. Other relatively inexpensive ones I had were the 2001 Louis Latour Corton Charlemagne and the 2002 Bonneau du Matray Corton Charlemagne.

The 2001 Boillot Chevalier Montrachet and 01 Comte Lafon Meursault Charmes

8) Kam Shan Seafood Restaurant, Woo Sung Street, Jordan

My wife and I wandered into this restaurant because we saw a lot of people waiting outside for a table, and what a discovery! This place scores zero for ambience (noisy and the decor is old-fashioned), but full marks for the food. The live seafood displayed on the front of the restaurant, can be cooked in whatever way you desire, but the captain, "Brother Wai" can recommend some nouveau approaches, eg. Mexican butterfly clams (I think they call it pipys in Australia) cooked in a Thai-styled broth with red chilli, galangal, tumeric and lemon grass. The razor clams are good either steamed with garlic or stirred fried with black-bean paste. My wife's favorite is the steamed small crab "Yim Chai", filled with so much crab roe. And the huge deep-sea garoupa, once stirred-fried, is like eating steak. But I preferred it cooked up in a smooth egg paste, on top of fried rice noodles. Similarly, I love the lobster cooked in congee with Dalian abalone and bits of the garoupa head and bones.

For such delicious seafood with complex flavours, you need a fresh, fruity, simple yet succulent white wine. New Zealand sauvignon blancs are good, so are those Australian unoaked Chardonnays. But lately I drank a 2006 Giacosa RoeroArneis (Piedmonte) and a 2006 Schiopetto Pinot Bianco (Friuli) and they were marvellously juicy and refreshing.

Well, I have introduced to you some of my favorite haunts and hopefully will run into some of you one day.

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Reference: 1. The ONTARGET Investigators. Telmisartan, Ramipril or Both in Patients at High Risk for Vascular Events. *N Engl J Med.* 2008;358:1547-59

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Dermatological Quiz

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Yaumatei Dermatology Clinic, Social Hygiene Service

Dr. Ka-ho Lau

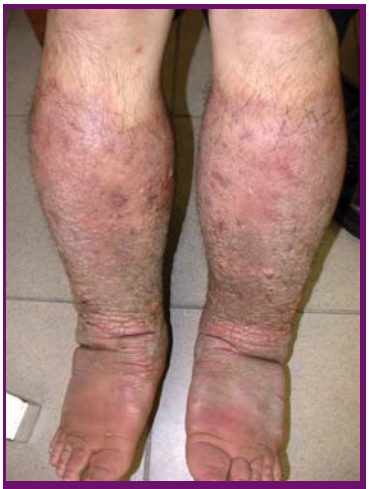

Fig 4: Lesions at both legs

This 50-year-old man developed these non-itchy lesions at his shins, calves and dorsa of his feet for more than five years. He had history of goiter and received treatment from physician for more than ten years.

Questions:

1. What is your diagnosis?
2. What other relevant physical signs will you elicit in order to support your clinical diagnosis?
3. How will you mange this man?

(See P. 49 for answers)

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The New FMSHK Team (Executive Assistant - Ms June Tsang)

Ms June Tsang has joined FMSHK in the position of Executive Assistant since 21 April 2008. June has over 10 years experience in project coordination, customer service and executive support. Having spent 4 years in Malaysia and the past 8 years in the United States, June possesses extensive overseas work and life experience as well. Prior to this engagement, she had actively involved in assisting with a variety of exchange activities among practitioners in healthcare, education and commerce from the East and West.

Society News

News from Member Societies:

The Hong Kong Association of Oral and Maxillofacial Surgeons (Ltd)
Updated office-bearers for the year 2008-2009 are as follows: President: Dr. Kiang-cheong CHOW; Honorary Secretary: Dr. Wai-kuen CHIU; Honorary Treasurer: Dr. Kin-man LEE

Hong Kong Association for Integration of Chinese-Western Medicine
Updated office-bearers for the year 2008-2010 are as follows: President: Dr. Vivian Chi-woon WONG-TAAM; Honorary Secretary: CMP Ping-shun CHAN; Honorary Treasurer: Mr. Hung-pun TAM

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Updated office-bearers for the year 2008-2009 are as follows: President: Prof. Stephen H. Y. WEI; Honorary Secretary: Dr. Michelle Yuen-man CHEUNG; Honorary Treasurer: Dr. Kitty Nei-yin HSE

Hong Kong Society of Transplantation
Updated office-bearers for the year 2008-2009 are as follows: President: Dr. Ka-foon CHAU; Honorary Secretary: Dr. Cindy Bo-ying CHOY; Honorary Treasurer: Dr. Chi-kong LI

St. Paul's Doctors' Association
Updated office-bearers for the year 2007-2008 are as follows: Chairman: Dr. Sau-ying TO; Honorary Secretary: Dr. Robert LI; Honorary Treasurer: Dr. Ka-leung CHUNG

The Hong Kong Association of the Pharmaceutical Industry
Updated office-bearers for the year 2008-2009 are as follows: President: Mr. Steven E. HARDACRE; Honorary Treasurer: Mr. Sunny CHEUNG

The Hong Kong Nutrition Association
Updated office-bearers for the year 2008-2009 are as follows: President: Mr. Terry TING; Honorary Secretary: Ms. Carmela LEE; Honorary Treasurer: Ms. Veronica CHAN

The Hong Kong Society of Gastroenterology
Updated office-bearers for the year 2008-2009 are as follows: President: Dr. Yat-wah YEUNG; Honorary Secretary: Dr. Judy Wai-chu HO; Honorary Treasurer: Mr. Wai-cheung LAO

Change of Member Society Name:

HONG KONG ASSOCIATION FOR INTEGRATION OF CHINESE-WESTERN MEDICINE LIMITED has been changed to **HONG KONG ASSOCIATION FOR INTEGRATION OF CHINESE-WESTERN MEDICINE**

The Hong Kong Association for the Study of Liver Diseases

Dr. Chan Lik Yuen, Henry
President

The Hong Kong Association for the Study of Liver Diseases (HKASLD) was established in 1987. The primary objective of our Association is to promote the advancement in the study of the liver. We aim to enhance the knowledge in the diagnosis, management and prevention of liver diseases in the medical profession through academic meetings and research. To achieve this goal, we are holding bi-monthly scientific meetings with journal updates and topic reviews. This year is the 18th year we are holding our annual International Symposium on Hepatology, in which overseas and local experts will share their experience with local attendees. We have also collaborated with various local societies in gastrointestinal diseases to hold an annual joint scientific meeting. We have started to extend our activities to mainland China and conducted our First Guangzhou-Hong Kong International Symposium on Hepatology this year in Guangzhou. To facilitate the training of young doctors with interest in Hepatology, our Association is granting a fellowship to support their overseas training every year.

We welcome all doctors who are interested in liver diseases to be our members. Our members include hepatologists, gastroenterologists, infectious disease specialists, hepatobiliary surgeons, microbiologist and pathologists. We hope our Association will serve as a bridge for doctors of different fields to come together and work towards a better future in the treatment of liver diseases.

The Hong Kong Society of Gastrointestinal Motility

The Hong Kong Society of Gastrointestinal Motility was established by a group of Gastroenterologists in 1998, and was incorporated with limited liability in 2006.

The main objectives of our Society are to promote the study, diagnosis and management of diseases of gastrointestinal motility. In furtherance of the objectives, the Society encourages research, public education, teaching and training of medical practitioners and paramedical personnel on gastrointestinal motility diseases.

In addition to annual general meeting and scientific meeting held in the last quarter of each year, scientific symposium and workshop on gastrointestinal motility are organized at different times of the year.

Answer to Dermatological Quiz

Answer :

1. The clinical diagnosis is pretibial myxedema. There are extensive erythematous, firm, non-pitting edematous brawny peau-d'orange-like waxy infiltrative patches and plaques symmetrically affecting this patient's shins, calves, ankles and dorsa of his feet. Most of the skin in the affected area is thickened by the infiltrative process. Small verrucous infiltrative nodules are formed which give rise to a "pseudo-elephantiasis like" appearance. Together with a history of goiter, the clinical diagnosis of pretibial myxedema as a cutaneous manifestation of Grave's disease can be made.

2. Graves' disease consists of a triad of hyperthyroidism, eye changes and skin lesions. Relevant signs of hyperthyroidism include goiter, hand tremors, sweaty palms, palmar erythema and diffuse alopecia with fine soft scalp hair. Eye changes include a "stare and frightened" appearance due to lid lag, lid retraction, proptosis and periorbital swelling. Skin lesions of pretibial myxedema and thyroid acropathy are characteristic. Pretibial myxedema is found in 1-5% of patients with Graves' disease, but in up to 25% of patients with exophthalmus. A serum factor (unrelated to long-acting thyroid stimulating hormone) could incite fibroblasts to produce mucin. Fibroblasts from the dermis of the lower extremities have been found to be more sensitive to this factor than fibroblast elsewhere in the body. An insulin-like growth factor, trauma, and lymphatic obstruction due to mucin may also play roles in the pathogenesis.

3. Corticosteroid applied under occlusive dressings or delivered by intralesional injection may help. Gradient pneumatic compression has been of some benefit. The thyroid status of the patient should be worked up and treated accordingly by endocrinologist. But in general, therapy for the associated hyperthyroidism does not improve the cutaneous lesion, and often, localized myxedema develops after treatment has been instituted.

Dr. Ka-ho Lau
MBBS(HK), FRCP(Glasg), FHKCP, FHKAM(Med)
Yaumatei Dermatology Clinic, Social Hygiene Service

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
* HKMA Structured CME Programme at Queen Elizabeth Hospital Year 08/09 (III) - Surgery * Dragon Boat Practice Session **1**	* Certificate Course in Update in Cardiac Care (Code No. TC-CC-0801) * Certificate Course in Mentoring in Nursing (Code No. TC-MN-0801) * HKMA Choir Rehearsal **2**	* FMSHK Officers' Meeting **3**	**4**	* Certificate Course on Wilderness Medicine * HKMA Council Meeting **5**	**6**	**7**
* Tuen Ng Dragon Boat Races **8**	* HKMA Choir Rehearsal **9**	* Certificate Course on Drug Dispensing in Office Clinics **10**	**11**	* Certificate Course on Wilderness Medicine * HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2008 (VI) **12**	**13**	* Hong Kong International Dragon Boat Races * Refresher Course for Health Care Providers 2007/2008 (X) - Management of Febrile Children with Rash **14**
* Hong Kong International Dragon Boat Races **15**	* Certificate Course in Update in Cardiac Care (Code No. TC-CC-0801) * Certificate Course in Mentoring in Nursing (Code No. TC-MN-0801) * HKMA Choir Rehearsal **16**	* Certificate Course on Drug Dispensing in Office Clinics * FMSHK Executive Committee Meeting **17**	**18**	* Certificate Course on Wilderness Medicine * Inauguration of the HKMA Hong Kong East Community Network cum Press Conference **19**	**20**	**21**
* HKMA Table Tennis Tournament **22**	* Certificate Course in Update in Cardiac Care (Code No. TC-CC-0801) * Certificate Course in Mentoring in Nursing (Code No. TC-MN-0801) * HKMA Choir Rehearsal **23**	* Certificate Course on Drug Dispensing in Office Clinics **24**	**25**	* Certificate Course on Wilderness Medicine **26**	**27**	* Fourth Annual Training Program **28**
* HKMA Table Tennis Tournament **29**	* Certificate Course in Update in Cardiac Care (Code No. TC-CC-0801) * Certificate Course in Mentoring in Nursing (Code No. TC-MN-0801) * HKMA Choir Rehearsal **30**					

Medical Diary of June

Date / Time	Function	Enquiry / Remarks
1 SUN 2:00 pm	**HKMA Structured CME Programme at Queen Elizabeth Hospital Year 08/09 (III) - Surgery** Organised by: The Hong Kong Medical Association & Queen Elizabeth Hospital Speaker: Various # Lecture Theatre, G/F., Block D, Queen Elizabeth Hospital, Kowloon	Miss Viviane LAM Tel: 2527 8452 (Registration Fee is required) 3 CME Points
3:00 pm	**Dragon Boat Practice Session** Organised by: The Hong Kong Medical Association # Sai Kung	Ms. Dora HO Tel: 2527 8285
2 MON 6:30 pm - 9:30 pm *(16,23,30)*	**Certificate Course in Update in Cardiac Care (Code No. TC-CC-0801)** Organised by: College of Nursing, Hong Kong	Secretariat Tel: 2572 9255 Fax: 2838 6280 24 CNE Points
6:30 pm - 9:30 pm *(16,23,30)*	**Certificate Course in Mentoring in Nursing (Code No. TC-MN-0801)** Organised by: College of Nursing, Hong Kong	Secretariat Tel: 2572 9255 Fax: 2838 6280 24 CNE Points
8:00 pm *(9,16,23,30)*	**HKMA Choir Rehearsal** Organised by: The Hong Kong Medical Association # Hong Kong Professional Teachers' Union Causeway Bay Service Centre	Ms. Candy YUEN Tel: 2527 8285
3 TUE 8:00 pm - 10:00pm	**FMSHK Officers' Meeting** Organised by: The Federation of Medical Societies of Hong Kong # Gallop, 2/F., Hong Kong Jockey Club Club House, Shan Kwong Road, Happy Valley, Hong Kong	Secretariat Tel: 2527 8898 Fax: 2865 0345
5 THU 7:00 pm - 8:30 pm *(12,19,26)*	**Certificate Course on Wilderness Medicine** Organised by: The Federation of Medical Societies of Hong Kong & Hong Kong Society for Emergency Medicine & Surgery Speaker: Various # 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. June TSANG Tel: 2527 8898
8:00 pm	**HKMA Council Meeting** Organised by: The Hong Kong Medical Association Chairman: Dr. K CHOI # HKMA Head Office, 5/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Christine WONG Tel: 2527 8285
8 SUN	**Tuen Ng Dragon Boat Races** Organised by: The Hong Kong Medical Association # Sai Kung	Ms. Dora HO Tel: 2527 8285
10 TUE 7:00 pm - 8:30 pm *(17,24)*	**Certificate Course on Drug Dispensing in Office Clinics** Organised by: The Federation of Medical Societies of Hong Kong Speaker: Various # 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. June TSANG Tel: 2527 8898
12 THU 2:00 pm	**HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2008 (VI)** Organised by: The Hong Kong Medical Association & Hong Kong Sanatorium & Hospital Speaker: Dr. LEUNG Tse Ngong Danny # HKMA Dr. LI Shu Pui Professional Education Centre, 2/F., Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	Miss Viviane LAM Tel: 2527 8452 (Registration Fee is required) 1 CME Point
14 SAT *(15)*	**Hong Kong International Dragon Boat Races** Organised by: The Hong Kong Medical Association # Shing Mun River, Shatin	Ms. Dora HO Tel: 2527 8285
2:30 pm	**Refresher Course for Health Care Providers 2007/2008 (X) - Management of Febrile Children with Rash** Organised by: The Hong Kong Medical Association & Our Lady of Maryknoll Hospital Speaker: Dr. KO Po Wan # Training Room II, 1/F., OPD Block, Our Lady of Maryknoll Hospital, 118 Shatin Pass Road, Wong Tai Sin, Kowloon	Ms. Clara TSANG Tel: 2354 2440 2 CME Points
17 TUE 7:00 pm - 10:00 pm	**FMSHK Executive Committee Meeting** Organised by: The Federation of Medical Societies of Hong Kong # Council Chambers, 4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Secretariat Tel: 2527 8898 Fax: 2865 0345
19 THU 1:00 pm	**Inauguration of the HKMA Hong Kong East Community Network cum Press Conference** Organised by: The Hong Kong Medical Association Speaker: Dr. CHOI Kin Gabriel & Dr. WONG Bun Lap Bernard # 3/F, Victoria Room, Regal Hongkong Hotel, 88 Yee Wo Street, Causeway Bay, Hong Kong	Miss Jo WONG Tel: 2527 8285 1 CME Point
22 SUN 2:00 pm *(29)*	**HKMA Table Tennis Tournament** Organised by: The Hong Kong Medical Association # Cornwall Street Squash & Table Tennis Centre	Ms. Dora HO Tel: 2527 8285
28 SAT 8:55 am - 5:30 pm	**Fourth Annual Training Program** Organised by: Hong Kong Society of Inborn Errors of Metabolism Chairman: Dr. T.S. LAM Speaker: Prof. HOFFMANN, Prof. TREFZ & Dr. M Van RIJN # 7/F, Block H, Princess Margaret Hospital, Lai Chi Kwok, Kowloon	Dr. WONG Kar Yin Tel: 2855 3485 Fax: 2818 4290

Meetings

11-12/7/2008	**Hong Kong Surgical Forum, Summer 2008** Organised by: Department of Surgery, Li Ka Shing Faculty of Medicine, University of Hong Kong Medical Centre; Queen Mary Hospital & Hong Kong Chapter of the American College of Surgeons # Underground Lecture Theatre, New Clinical Building, Queen Mary Hospital, Pokfulam, Hong Kong Enquiry: Forum Secretary Tel: 2855 4885 Fax: 2819 3416 Email: hksf@hkucc.hku.hk Website: http://www.hku.hk/surgery
26 - 28 /9/2008	**3rd Regional Conference in Dermatological Laser and Facial Cosmetic Surgery 2008** Organised by: The Hong Kong Association of Specialists in Dermatology, The Hong Kong Society of Dermatology and Venereology & Hong Kong Society of Plastic, Reconstructive and Aesthetic Surgeons # Hong Kong Convention and Exhibition Centre, Wanchai, Hong Kong Enquiry: Ms. Ruby LUI Tel: 3151 8813 Fax: 2590 0099 Website: www.dlfcs2008.com
22-25/11/2008	**2nd Asian Preventive Cardiology & Cardiac Rehabilitation Conference cum 7th Certificate Course in Cardiac Rehabilitation** Organised by: Hong Kong College of Cardiology Co-Chairman: Prof. LAU Chu Pak & Dr. LAU Suet Ting Speaker: Various # Hong Kong Convention & Exhibition Centre, 1 Expo Drive, Wanchai, Hong Kong Enquiry: Secretariat Tel: 2527 8285 Fax: 2865 0943 Email: dorahkma@hkma.org Website: http://www.apccrc.com
27-30/11/2008	**Human Dignity in Modern Medicine & 14th Congress of Asian Federation of Catholic Medical Associations** Organised by: The Guild of St. Luke, St. Cosmas and St. Damian Hong Kong Chairman: Dr. Peter AU YEUNG Speaker: Prof. Fr Louis Aldrich SJ & Prof. Luke Gormally # Catholic Disease Centre Enquiry: Congress Secretariat Tel: 2363 0598 Fax: 3764 0579
20-22/2/2009	**CardioRhythm 2009** Organised by: Hong Kong College of Cardiology & Chinese Society of Pacing and Electrophysiology Co-Chairman: Prof. LAU Chu Pak Enquiry: Secretariat Tel: 2899 2035 Fax: 2899 2045 Email: info@cardiorhythm.com Website: http://www.cardiorhythm.com

Upcoming Certificate Courses of the Federation of Medical Societies of Hong Kong

Date	Course No	Course Name	Co-organiser	Target Participants
5 Jun - 10 Jul 2008	C131	Certificate Course on Wilderness Medicine	Hong Kong Society for Emergency Medicine & Surgery	General Public
10 Jun - 8 Jul 2008	C129	Certificate Course on Drug Dispensing in Office Clinics	NIL	Medical and Health Care Professional
5 Aug - 16 Sep 2008	C132	Common Psychiatric Problems for GPs and Healthcare Professionals	The Hong Kong College of Psychiatrists	General Practitioners & Healthcare Professionals
4 Sep - 25 Sep 2008	C134	Clinical Management of Vertigo	NIL	General Practitioners & Paramedic

CALL FOR SUBMISSION OF ARTICLES FOR PUBLICATION IN THE HONG KONG MEDICAL DIARY

The Editorial Board of the Hong Kong Medical Diary invites you to send in your interesting articles for publication in the Hong Kong Medical Diary (500 -1,500 words per article). Abstracts from recent local or international meetings/symposia are also welcome. You can send in your manuscript by facsimile at 2865 0345, through mail or via email at karen.chu@fmshk.org. The Editorial Board of the Hong Kong Medical Diary will give you a prompt reply.

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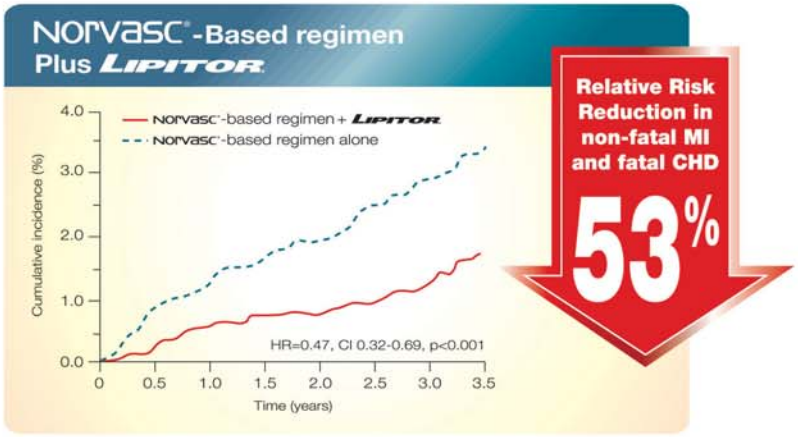

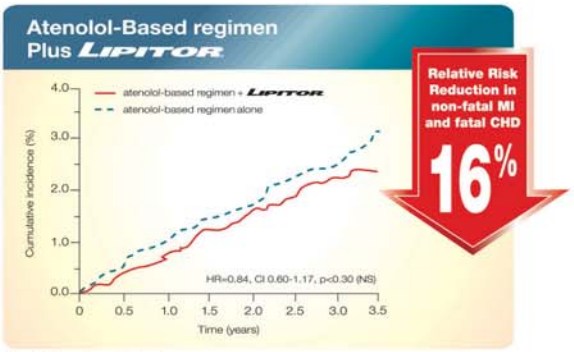

Adapted from Sever P, et al.[1]

Reference: 1. Dahlöf B, Sever PS, Poulter NR, et al for the ASCOT steering committee members. Potential synergy between lipid-lowering and blood-pressure-loweeing in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT 2x2): a multicentre randomised controlled trial. European Heart Journal (2006) 27, 2982-2988. **Detailed prescribing information is available upon request**

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Dear members and colleagues,

For the last 2 weeks, gruesome pictures of devastation and tragic stories of separation and death flooded our media. This worst earthquake that hit China in three decades has ripped the hearts of everyone in Hong Kong. In the worst of times, we also witness abound the best of humanity - selflessness, benevolence, courage and sacrificial love. Donation keeps pouring in as well as enthusiastic individuals and organizations racing to provide rescue operations. After the cataclysm and sorrow, it would be a long period for rehabilitation.

On behalf of the Federation of Medical Societies of Hong Kong, I appeal to you all to do your part in the relief operation for the hundreds of thousands of victims in Sichuan. We have, from the local provincial government and various sources, complied a list of much-needed items, medicine and equipments and regularly update it on our website www.fmshk.org. Donors are welcome to contact our secretariat at 2527 8898 and we will follow up making sure that these articles will be delivered to the region. If you find donating money is still the easiest, you can send a cheque payable to " The HKFMS Foundation Ltd " and send it to us at 4/F Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong.

Recovery and restoration of this scale take time and the Federation pledges to coordinate your efforts in this respect as development unfolds.

Yours sincerely,

Dawson Fong
President, FMSHK