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Contents

Brief Update on Glitazone Therapy

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Thiazolidinedione (TZD) therapy has been widely established in the management of diabetes for many years[1]. Through binding to the gamma isoform of the peroxisome proliferators-activated receptors, this class of drugs (including rosiglitazone & pioglitazone) enhances insulin sensitivity, a key early feature of type 2 diabetes. The use of this class of drugs should be in the early stage of type 2 diabetes. Unfortunately, in certain settings, due to cost constraints TZD has been used as the last line of therapy in poorly controlled type 2 diabetes prior to the introduction of insulin therapy. Do we really expect TZDs to work in end-stage diabetes when there is insulin deficiency?

It is now well-established through numerous clinical studies that TZD has pleiotrophic effects beyond glucose-lowering. These include a reduction in inflammatory markers, microalbuminuria and a beneficial effect in lipid profile. For instance, in the PROACTIVE (PROspective pioglitAzone Clinical Trial) study[2], patients randomised to the pioglitazone arm has a significant increase in high-density lipoprotein cholesterol (HDL-c) compared to the placebo arm (+8.9%). This certainly contributed to a large extent to the reduction in myocardial infarction observed in the treatment arm. More recent studies showed that TZDs may even have a role in the management of pulmonary hypertension.

Another important effect of TZD therapy is the reduction of fatty liver, a frequently observed condition in the metabolic syndrome. Studies using the technique of magnetic resonance spectroscopy, several groups have demonstrated that both pioglitazone and rosiglitazone may reduce liver fat, partially through an increase in circulating adiponectin level. Furthermore, rosiglitazone has recently been shown to decrease the incidence of type 2 diabetes in subjects with impaired glucose tolerance in the DREAM (Diabetes REduction Assessment with rampril and rosiglitazone Medication) study[3]. When compared with metformin and sulphonylurea monotherapy, rosiglitazone may prevent the progression of type 2 diabetes in recently diagnosed patients[4].

One important limiting factor in the use of TZD therapy is the development of fluid retention or oedema, which may precipitate cardiac failure[5]. The aetiology of TZD-induced oedema is multifactorial including an increase in capillary permeability and an increase in vascular permeability growth factor. The use of diuretics in such situation is often disappointing. Recently, there is some clinical evidence that the combine use of TZD and fibrate therapy may prevent fluid retention[6]. The mechanism remains unclear and warrants further research. There has also been some concern about potential adverse effect of TZDs on bone mineral density[7]. The evidence so far is inconclusive and more research is required.

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Current Issues in the Management of Dyslipidaemia in Primary Care - a Perspective from the UK.

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It is remarkable how the treatment of lipid disorders has moved in just over a decade from the domain of a few interested secondary-care specialists to become a mainstream activity for all primary-care professionals. Clearly this represents an appreciation of the burden of atherosclerotic disease in society, the realisation of the central, causative role of abnormal lipid levels and the emergence of incontrovertible evidence of benefit from lipid-modifying trials.

The extent of dyslipidaemia in industrialized societies means that the burden of management logistically falls to primary care. Primary care must accept the challenge of identifying and treating patients at high global cardiovascular risk, help these individuals achieve target lipid goals and maximise long-term benefit by developing systems of care which ensure continuing target delivery and long-term compliance.

Identifying individuals for lipid-lowering treatment

There is broad consensus between modern international guidelines about who should be treated. The updated Joint British Societies' guidelines for the prevention of cardiovascular disease (JBS2) provide typical advice.[1] Treatment priority is given to a spectrum of high-risk individuals - people with established manifestations of cardiovascular disease (CVD), people with diabetes mellitus (whose current or future risk of CVD is high) and people whose 10-year risk of a CVD event exceeds 20%. The switch in focus from the estimation of risk of coronary heart disease to the risk of cardiovascular disease reflects recognition of the unifying pathology of atherosclerosis in the aetiology of ischaemic cardiovascular disease and emerging evidence of the especially high risk and potential for benefit in patients with existing cerebrovascular and peripheral arterial disease.[2, 3, 4] The choice of the 10-year 20% CV risk threshold for people without established CVD or diabetes is challenging as many people exceed this threshold. In the UK, 23% of men and 8% of women aged 40-74 years - some 3.3 million people are candidates for treatment. The workload and cost implications are significant.

Despite favouring a 20% 10-year CVD threshold for lipid-lowering intervention, the evidence from clinical trials suggests benefit at even lower thresholds of CVD risk. Evidence from primary prevention trials such as AFCAPS/TEXCAPS and ASCOT confirmed the benefits of lipid-lowering at levels of risk considerably below the

20% 10-year CVD threshold endorsed by current guidelines.[5,6] The recent MEGA study from Japan further expanded this evidence to the Asian population.[7] To widen the scope of lipid management further, however, would strain the twin constraints of affordability and practicality and currently a lifestyle approach is recommended. In the UK some individuals choose to buy simvastatin 'over the counter' in pharmacies although the uptake has not been significant.

What are the targets to aim for?

Lowering cholesterol and more specifically, low density lipoprotein cholesterol (LDL-C), lowers CV risk. Although it is clear that lipid-lowering agents have multiple actions (so called 'pleiotropic' effects), the message of the trials is that it is lowering of LDL-C that is the dominant effect.[8] LDL-C is a closer pathophysiological measure of the cholesterol fractions which are oxidised and deposited in arterial walls than total cholesterol and is accordingly, a better target than total cholesterol. In the USA, health professionals ignore total cholesterol levels and concentrate almost wholly on LDL-C, with a new lower target of <1.8mmol/L for those at very high risk.[9]

Figure 1 (taken from JBS2) shows the before and after values of LDL-C in a number of clinical trials and their attributed CHD risk. All the lines point downwards showing that events are consistently reduced with lower levels of LDL-C.
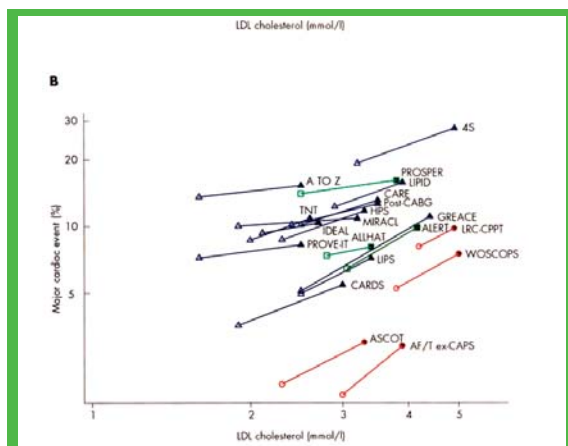
Figure 1. Absolute reduction in LDL cholesterol levels and CHD events in clinical trials. (Ignore 'B' and top LDL cholesterol- all lines can be same colour)

The Cholesterol Trialists' Collaboration estimated from clinical trials that every 1mmol/L lowering of LDL-C resulted in 12% fewer deaths, 19% fewer CHD events and 17% fewer strokes.[10] These benefits are seen irrespective of age or starting cholesterol, LDL-C and HDL-C, thereby supporting the approach to treat according to CV risk and not absolute cholesterol values. The benefits are seen within one year but increase subsequently. With the availability of cholesterol-lowering medication that can effect more than 1mmol/L LDL-C reduction clinical trials have been able to explore whether 'lower is better'.

Four well-conducted clinical trials have attempted to explore the value of driving LDL-C down to very low levels in high-risk people with CHD. A meta-analysis of their results confirms a significant 16% reduction in CHD death or non-fatal myocardial infarction in the more aggressively treated patients and it is this that has prompted the new lower target recommendations.[11] At the moment, there appears to be no lower threshold at which LDL-C reduction ceases to confer benefit. Speculation suggests a level of 1.3mmol/L (the level we are born with) might be the lowest point and trials are already designed to test this.

The recommendations of JBS2 suggest that for individuals in the priority, high-risk group total cholesterol should now be < 4.0mmol/L **and** LDL-C should be < 2.0mmol/L (or 25% reduction in total cholesterol **and** 30% reduction in LDL-C, whichever gets to the lowest cholesterol level). The addition of the percentage calculations is designed to ensure that individuals at risk achieve sufficient cholesterol lowering to derive benefit, even if their baseline cholesterol levels are low. In practice, few of us make these calculations and most concentrate on the target figures alone.

How to achieve and maintain target lipid values

Cholesterol-lowering trials are invariably conducted in individuals who have already received some lifestyle input. The power of drugs sometimes makes us diminish the impact of lifestyle change and in particular, healthy eating. Compliance with a pattern of diet and lifestyle that optimises weight, reduces fat (particularly saturated and trans fats) and incorporates soluble fibre, plant sterols and soya protein will have the greatest impact on cholesterol levels.

Once a drug is prescribed, one of the key issues is continuing compliance over the longer term with both lifestyle and pharmacological interventions. Central to success is the sort of educational and supportive relationship that is possible in primary care between healthcare professionals and the patient. New evidence from Scotland shows that treating to target in such a 'therapeutic alliance' is 2.5 times more likely to achieve target values than a 'fire and forget' approach.[12]

Statins are the mainstay of treatment, are remarkably well tolerated and with emerging patent expiries (in the UK, already on simvastatin and pravastatin), generic price reductions are significant. Simvastatin, by virtue of its moderate potency, its good tolerability and

extensive evidence base is a natural first choice and favoured by those that control the purse strings but may not always result in target values. Different statin strategies are used to achieve target values including up-titration at 4-6 week intervals, switching to more potent statins or using high doses of powerful statins to 'get it right first time'. The relative LDL-C lowering efficacy of the dose ranges of four statins is shown in Figure 2.
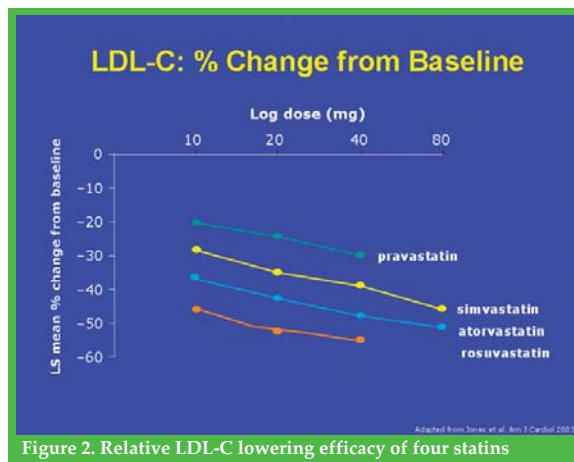
Figure 2. Relative LDL-C lowering efficacy of four statins

Mean cholesterol levels in older adults in the UK are just under 6mmol/L and LDL-C levels typically around 4mmol/L. Getting to TC<4.0mmol/L and LDL-C <2.0mmol/L is therefore quite a step and the new targets will favour the use of higher dose and more efficacious statin therapy and increasingly (as in blood pressure control) **combination** therapy.

Ezetimibe is a specific cholesterol absorption blocker which acts in the small intestine to stem the absorption of dietary and biliary cholesterol. In monotherapy it reduces LDL-C by about 18% but because its action is complementary to statins, really large reductions in LDL-C (up to 60%) can be seen when they are used together. New evidence shows its incremental action even in triple therapy, in combination with a statin and fenofibrate.[13] Other lipid-lowering drugs used in combination with statins are nicotinic acid, fibrates and specifically for lowering triglycerides, fish oil capsules.

What about HDL-C and triglycerides?

The data supporting HDL-C and triglycerides are largely epidemiological and, unlike the situation with LDL-C, it is difficult to know from current trial evidence whether specific modification of either results in preventing CV events. JBS2 approaches this dilemma by not setting specific target values for HDL-C and triglycerides but by recommending 'desirable values' - HDL >1.0mmol/L for men and > 1.2mmol/L for women and triglycerides < 1.7mmol/L.

Levels of HDL-C and triglceridess are dynamically linked and often track each other inversely. Raised triglycerides are associated with low levels of HDL-C in many individuals, typically in those with diabetes and those with abdominal obesity, glucose intolerance and other features of the metabolic syndrome. Raised triglycerides alter both LDL-C and HDL-C, producing

smaller, denser varieties which are in turn more atherogenics.

Although many statins have a moderate triglyceride-lowering effect (equivalent to their LDL-C lowering effect) they do little to raise HDL-C. Fibrates and particularly nicotinic acid preparations both lower triglycerides and raise HDL-C. Some patients may benefit from combination therapy if HDL-C is low and triglycerides raised, even if a statin has reduced their total and LDL-C to target.

The HDL-C story will expand with the development of several new specific HDL-C elevating drugs currently in the pipeline. Cholesteryl ester transfer protein (CETP) inhibitors have shown early promise but safety remains a concern.

Developing structured care

Many surveys show that implementation of the evidence base for lipid modification is suboptimal. The existence of the 'implementation gap' between expectation and reality underlines the failure, in many practices, to develop systematic care pathways for patients needing CVD prevention interventions. The computer is central to the efforts of most successful practices, and appropriate coding, database construction, and the use of templates and call and recall systems all enhance the delivery of care. Much research has focused on the role of the primary-care nurse, and data from the Grampian region in Scotland show significant improvements in the level of interventions and even the death rate at 4.7 years in CHD patients attending nurse-led clinics.[14]

Nurses already have established roles in chronic disease management in asthma and diabetes in primary care. As the aims are similar, a logical step would be to expand practice diabetes clinics to become CVD prevention clinics. In the UK, restructuring of the remuneration contract for GPs (the Quality and Outcomes scheme - QOF) has led to levels of achievement in lipid-lowering that have been internationally applauded.[15] In 2005-6, 78% of patients with CHD, 72% with stroke or TIA and 79% with diabetes achieved total cholesterol levels of <5mmol/L, the QOF target.

Much of the success of this primary care exercise in implementation has been ascribed to the development of structured care pathways and appropriate IT and audit support systems. Primary healthcare professionals however feel that the most important factor is that by utilising the characteristics of primary care practice they are able to establish an ongoing and special therapeutic relationship between themselves and their patients, to mutual advantage.

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[†] Results are based on subsets of 2 US, random surveys of 597 and 598 physicians representative of the AMA master file, conducted by Harris Interactive Inc from November 17, 2003, through January 9, 2004, and from April 25, 2005, through June 17, 2005.

[#] Those with diabetes, hypertension or CHD.

Reference: 1. Data on file. Pfizer Inc., New York, NY.   **Detailed information available upon request.**

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Surgical Management of Thyroid Nodules

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Introduction

Referrals to specialists for thyroid nodules have become increasingly common. Controversies still exist over the clinical management, even with the published treatment protocols or recommendations[1-3]. Surgery is generally indicated if the thyroid nodule is proven or suspected to be malignancy, is causing thyrotoxicosis or is large enough to be accompanied by substantial local symptoms or unacceptable cosmesis, but associated with a unique set of complications. Over the last decade, there have been many advances in the diagnosis and therapy of thyroid nodules. Optimal outcomes in patients with thyroid nodules can only be achieved not until the plaudits and pitfalls of the various diagnostic methods, and the potential complications of surgery is well understood by both the clinicians and the patients. The objective of this article is to give an update in the surgical management of this commonly encountered condition.

Prevalence

The prevalence of palpable thyroid nodules was about 3-4%[4,5]. A 1955 study, however, showed that the true prevalence of thyroid nodules, based on the autopsy data, was greater than 50% in patients with clinically normal thyroid glands[6]. As technology improved, high-resolution ultrasonography (USG) has emerged as the commonly used imaging modality for the thyroid gland, the haunting prospect that thyroid nodules could be imaged in over half the population is becoming a clinical reality[7,8].

Unless a thyroid nodule is symptomatic, its significance is limited to the possibility that it represents a thyroid malignancy. Thyroid cancer, however, is an uncommon malignancy. In Hong Kong, there were 449 new cases (336 in women and 113 in men) in 2004, representing only 2% of all new cancers. Death from thyroid cancer is even less common, with an incidence of 28 deaths in 2004 representing only 0.24% of all cancer deaths[9].

Although clinically apparent thyroid cancer is relatively uncommon, clinically inapparent or occult thyroid cancer is quite common. Most define an occult thyroid cancer as a lesion less than 10 mm that is an unexpected and incidental finding during surgery or autopsy. The prevalence of occult thyroid cancer at autopsy has varied from 0.45% - 22% depending on the methods of detection[10,11]. Because of the discrepancy between the prevalence of clinically apparent and occult thyroid cancer, it is believed that most occult cancers have little biologic or clinical significance. Nonetheless, various reports have demonstrated nonnegligible prevalence of extrathyroidal invasion, nodal involvement, distant metastasis, and even mortality from occult thyroid cancers[12-17]. These findings suggested, but did not prove, that at least some of these occult cancers demonstrated aggressive behaviour and should, therefore, be considered biologically important, and it is impossible to fix an effective dimensional cut-off for the risk of thyroid cancers.

Hence, the main aim of management of patients with thyroid nodules is to identify the small proportion of patients with thyroid cancer who require treatment and avoid unnecessary testing and treatment for the majority.

Clinical assessment

With the discovery of thyroid nodules, a complete history and physical examination focusing on the functional status, the thyroid gland and adjacent cervical lymph nodes should be performed. Pertinent historical factors predicting malignancy include a history of head and neck irradiation, family history of thyroid cancer, and rapid growth and hoarseness. Pertinent physical findings suggesting possible malignancy include vocal cord paralysis, ipsilateral cervical lymphadenopathy and fixation of the nodule to surrounding tissues. The incidence of cancer in those with clinical features strongly suggestive of malignancy is high, but most patients do not have these features.

Laboratory test

Serum thyrotropin (TSH) level is the only test routinely performed. If the serum TSH is subnormal, a radionuclide thyroid scan should be obtained to document whether the nodule is functioning, isofunctioning, or hypofunctioning. Because functioning nodules rarely harbour malignancy, if one is found that corresponds to the clinical nodule, no additional cytological evaluation is necessary.

Measurement of serum thyroglobulin is useful in the detection of residual or recurrent disease after total thyroidectomy for differentiated thyroid cancer, but is of no value in the initial detection of the primary malignancy as serum thyroglobulin levels can be

elevated in most thyroid diseases[18]. Calcitonin is measured in screening families for medullary thyroid carcinoma. Prospective studies showed that routine measurement of serum calcitonin in patients with thyroid nodules may detect C-cell hyperplasia and medullary thyroid cancer at an earlier stage[19-21]. Further studies, however, are needed to evaluate the validity, cost-effectiveness and the effect on survival before routine serum calcitonin measurement is accepted in the evaluation of thyroid nodules.

Radiological assessment

Increasing numbers of physician in America would order an ultrasound to evaluate patients with thyroid nodules, both for diagnosis and to perform USG-guided needle aspirates, USG is becoming an extension of the thyroid physical examination[22]. A diagnostic USG should be performed to delineate the nodules unless the serum TSH is suppressed. Clinical criteria (solitary vs. multiple nodules, nodules greater vs. smaller than 10mm, cystic vs. solid nodules) were of no use in determining the risk of malignancy. Patients with multiple nodules on USG have the same risk of malignancy as those with solitary nodule. The diagnosis of thyroid cancer may be missed if only the dominant or largest nodule is aspirated[23]. Sonographic characteristics, including the presence of microcalcification, hypoechogenicity of a solid nodule, irregular or blurred margins and intranodular hypervascularity, have been shown to be closely linked to malignant lesions[24].

The systematic USG guided fine needle aspiration evaluation of thyroid nodules allows careful selection of the lesion, using sonographic criteria, to submit to fine needle aspiration (FNA), and may account for the higher prevalence of cancer in nonpalpable thyroid lesions (5.4 to 12%)[16,24,25], than that reported in palpable lesions (5.0 - 6.4%)[26].

Isotopes scans classify nodule function on their ability to trap iodine. A malignant nodule should appear as a "cold" non-functioning area, a benign nodule as "warm" or "hot". Since, however, most nodules are cold and generally benign, and warm or hot nodules can be malignant, many centres have abandoned isotope scan.

Cytological assessment

Fine needle aspiration cytology (FNAC) is the most accurate and cost effective method for the evaluation of thyroid nodules. Traditionally FNAC results are divided into four categories: nondiagnostic, benign, indeterminate or suspicious for neoplasm, and malignant. Up to 20% of the FNAC of thyroid nodules are initially nondiagnostic, particularly those with cystic component [16, 27-29]. Because of the 5% risk of malignancy for solitary nodule, such biopsy should be repeated using US guidance[30]. Cystic nodules that repeatedly yield nondiagnostic aspirates need close observation or surgical excision. Surgery should be considered if the cytologically nondiagnostic nodule is solid [29,31].

Indeterminate cytology, often reported as 'suspicious', 'follicular lesion/neoplasm' or 'Hurthle cell lesion/neoplasm', can often be found in 15%-30% of FNA specimens and the management is controversial. Some centres suggest a radioiodine thyroid scan, and if a concordant autonomously functioning nodule is not seen, lobectomy should be considered, whilst others would recommend lobectomy to make a definite histological diagnosis as the risk of malignancy is approximately 20% [32-34]. Molecular markers have been evaluated to improve diagnostic accuracy for indeterminate nodule but data are still insufficient [35,36].

Thyroid nodules diagnosed as benign on cytology require follow-up because of low, but not negligible, false negative rate of up to 5% with FNA. Easily palpable nodules should be followed clinically at 6-12 month interval. It is suggested that all other nodules be followed with serial USG 6-12 months after initial FNA. Nodule growth is an indication for repeat biopsy, preferably with US guidance (Fig 1.).

Potential complications of thyroid surgery

When surgery is recommended, informed consent should be obtained and patients should be fully informed of the potential benefits and risks of the procedures and of any suitable alternative management. In general, the essential objectives for thyroidectomy are conservation of the parathyroid glands, avoidance of injury to the recurrent laryngeal nerve, an accurate haemostasis and an excellent cosmesis. The complications of recurrent and superior laryngeal nerve injury as well as long-term hypoparathyroidism, although not life-threatening, can result in chronic functional disability that can be more problematic than the underlying disease. Therefore, complete disclosure, entailing explicit explanation using technical and lay terminology about known risks (including serious but low probability risks), relevant implications for the patient's life and occupation, and incidence in the general population and surgeon's practice, is important to most patients, in order to be aware, and psychologically prepared for potential outcomes.

Various risk factors have been identified to influence the likelihood of these complications, including the underlying disease (recurrent goitre, malignancy, hyperthyroidism, substernal goitre), the extent of resection, and the surgical technique (subcapsular dissection and routine identification of the recurrent laryngeal nerve)[37-42]. A clear association between the experience of the surgeon and a decrement in complication rates was also well demonstrated in numerous studies. The incidence of permanent complications following thyroidectomy, performed by surgeons with experience in endocrine surgery, should be less than 1%[38,42,43]. Any figure greater than this is generally considered unacceptable.

Laryngeal Nerve Injury

The symptoms of recurrent laryngeal nerve palsy

depend on the completeness of the nerve injury and the presence of associated injury to the superior laryngeal nerve (SLN) and the contralateral RLN. With isolated unilateral nerve injury, if the position of the paralysed cord is midline and compensated by the contralateral cord is effective, the damage may not be recognised. When the cord remains in the paramedian position, the voice may be hoarse and breathy. The patient's cough is weak, and aspiration may occur. Damage to the SLN affects voice pitch. Since the cord is unable to lengthen and tense, the voice is low in pitch and breathy in quality.

Bilateral RLN injury is a severe life-threatening complication that results in airway obstruction and requires immediate attention. In this condition, both vocal cords remain in a median or paramedian position. As a result, the patient exhibits inspiratory stridor, dyspnoea, tachypnoea, and nasal flaring, although the voice is near normal.

In addition to the functional disturbance, recurrent laryngeal nerve injury also accounted for majority of the medicolegal claims in thyroid surgery[44]. Surgical adjunct such as intraoperative neuromonitoring has recently been advocated to facilitate the identification of the recurrent laryngeal nerve, to predict postoperative outcome and to reduce the incidence of RLN injury. However, benefit of routine application of this new technique, in specialised centres, was not demonstrated [45,46].

Hypoparathyroidism
Hypoparathyroidism is another complication that may occur following thyroid surgery. Injury to the parathyroid glands may result from excision of the gland(s) during surgery, devascularisation of the glands, or destruction from capsular haematoma. Postoperative hypoparathyroidism results in hypocalcaemia and is manifested by numbness and tingling of the hands, feet, and lips. If calcium levels are not restored, muscle spasm, seizures and laryngeal stridor are imminent. It often extends the duration of the hospital stay and the need for biochemical tests, and it significantly increases the overall cost of a thyroidectomy. Although hypocalcaemia reverses spontaneously in most cases, it can remain permanent, and lifelong therapy and follow-up are then mandatory to avoid the subtle but severe and potentially lethal complications of chronic hypocalcaemia.

Postoperative Bleeding
Postoperative haemorrhage is an uncommon complication, reported in 0.3% to 1% of patients in most large series. However, it is a well recognised and potentially lethal complication. It usually results from a loosened tie around a ligated vessel. If not controlled, bleeding in the neck space may result in tension haematoma leading to tracheal compression and subsequent airway obstruction. Swelling of the neck and bulging of the wound can be followed shortly thereafter by respiration impairment. The urgency of treating this condition when it occurs cannot be overemphasised. Placing a drain is not adequate for decompression if bleeding is from a major vessel. Several studies have documented no benefit of using drains after thyroid surgery [47-49].

Thyroid surgery

Thyroidectomy is indicated for proven or suspected malignancy, for thyrotoxicosis in selected patients or for sizable lesion accompanied by substantial local symptoms or unacceptable cosmesis. The time-honoured procedure of unilateral subtotal lobectomy is rarely appropriate, the minimum satisfactory procedure being a total lobectomy on the side of the lesion with inclusion of the isthmus. This permits a full histological examination with virtually no risk of tumour seeding and further surgery, often difficult and hazardous, to remove the remnant left in situ after subtotal lobectomy is not needed.

A frozen section taken immediately is helpful if preoperative FNA is not done or nondiagnostic. A skilled pathologist is able to make a correct diagnosis in the majority of cases, permitting a correct operative strategy which may involve total thyroidectomy in many cases of cancer. The follicular lesion with minimal capsular invasion is not readily diagnosed on frozen section, but a simple lobectomy is invariably sufficient. If the definite histology should later reveal an invasive follicular carcinoma after only a lobectomy has been performed, removal of the remaining lobe and completion of the total thyroidectomy can easily be carried out in a few days.

Conclusion

Thyroid nodules are common and frequently benign. The author recommended that low risk, asymptomatic nodules should be followed up with clinical palpation or USG in 6-12 months. Fine needle aspiration, either US guided or palpation-directed, is reserved for nodules in the high risk group of patients in whom either the imaging features or the clinical history is worrisome for malignancy, irrespective of the size. Thyroid surgery, either for diagnostic or therapeutic purpose, is associated with minimal long-term morbidity when performed by experienced surgeons. Although the optimal management of thyroid nodules has not been clearly established, strategies such as these, which sensibly limit interventions, obtain reasonable yields, will only work with the collaboration of endocrinologists, radiologists, cytopathologists and surgeons, to establish the "standard of care".
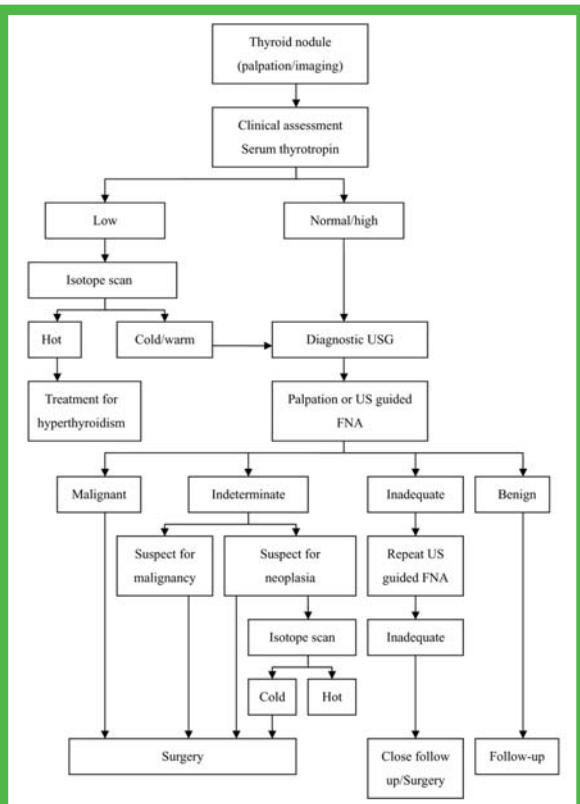
Figure 1. Algorithm for the management of patients with thyroid nodules.

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Management of Common Pubertal Problems

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This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded one CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 May 2007.

Puberty is the period when sexual maturity is completed, resulting in the capacity for reproduction. It consists of maturation of the primary and secondary sexual characteristics.

Physiology of normal puberty

Puberty starts when there is pulsatile secretion of gonadotrophin-releasing hormone (GnRH) from hypothalamus. GnRHs then stimulates the pituitary gland to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In boys, LH stimulates the Leydig cells to produce testosterone which induces the secondary sexual characteristics. FSH binds to the Sertoli cells and enhances spermatogenesis. In girls, LH stimulates proliferation of follicular and thecal cells while FSH stimulates the follicles to secrete estradiol. Ovulation results from interaction of LH, FSH and estradiol. The hypothalamus-pituitary-gonads axis is regulated by negative feedback mechanism since foetal life.[1] To cope with changes in foetal, neonatal, childhood and pubertal period, there is a change in the sensitivity of this feedback system as reflected by the pronounced LH response to exogenous GnRH stimulation in puberty.[2]

Normal female development

Most of the girls start puberty with thelarche (onset of breast enlargement), also known as breast budding (Table 1). The mean age for the onset of puberty in Hong Kong girls is about 9.8 years, with a range from 7.1 to 12.3 years.[3] They start to develop pubic hair at the age of 9.5 to 13 years.[3] (Table 2 for pubic hair staging) Growth acceleration usually occurs at Tanner breast stage 2 to 3 with peak growth velocity up to 10cm/year. Girls menstruate at breast stage 4 to 5, which is around 12.4 years in Hong Kong.[3] After that they grow much slower to gain another 4-5 cm reaching their final height.

Normal male development

The first sign of male puberty is the enlargement of testis. A pubertal sized testis (Genital stage 2) has its longest axis of 2.5cm or volume of 4ml by orchidometer.(Table 3) It occurs between 9-14 years with a mean of 11.4 years in Hong Kong boys.[4] The mean age of having stage 2 pubic hair is 12.7 years.[4] In contrast to their female counterparts, boys have their peak growth spurt at genital stage 3 to 5 with growth velocity up to 11.7cm/year.[5,6] That would explain why boys are generally shorter than girls in late primary or early secondary school years.

Precocious puberty

By definition, girls enter puberty before 8 years old and boys before 9 years old are precocious puberty. But nowadays, we consider girls having breast development between 7-8 years old as early puberty rather than precocious puberty because of the downward secular trend in sexual maturation.

Precocious puberty may be due to central or peripheral causes. (Table 4) Central precocious puberty (CPP) is diagnosed if the development of physical pubertal changes and biochemical testings are consistent with normal puberty but just occur earlier than it should be. It is driven by the GnRH. The majority of girls and nearly half of boys with precocious puberty have the central form.[7] Peripheral precocious puberty means that the puberty is not driven by GnRH, it is caused by either endogenous or exogenous estrogen or androgen.

The commonest differential diagnosis in girls are: idiopathic central precocious puberty, congenital adrenal hyperplasia (CAH), ovarian cyst and premature thelarche. In boys, idiopathic central precocious puberty is less common. CNS anomalies should be screened for.

Three cases are shown here for better illustration of pubertal disorders and their management.

Case 1

A 3-year-old girl presents with two episodes of vaginal bleeding each lasted 2 days. Her parents noticed that she grew faster in the past 4 months and now became the tallest one in the nursery. On physical examination, her height was 5cm above the 97th percentile line while mid-parental height was 50th percentile. She had bilateral stage 3 breast development and stage 1 pubic hair. There was no relevant past medical history. Her mother's menarche was at 12 years old. There were no oral contraceptive pills at home.

What is the diagnosis and what further investigations should be carried out?

This young girl has breast development, rapid height gain and cyclic vaginal bleeding (menstruation). She is having puberty at a much earlier age, i.e. precocious puberty. Her bone age was 6 years old which was 3 years advanced. She also had an exaggerated LH and FSH response to GnRH stimulation. (GnRH stimulation test) Therefore she has central precocious puberty(CPP). Although the majority of girls with CPP have an idiopathic aetiology, it is now regarded as good practice to carry out pituitary imaging with MRI. Her MRI turned out to be normal. The final diagnosis is idiopathic CPP. Given the age of the girl, the intensity of pubertal tempo and the advanced bone age which means short final height, suppressive therapy with GnRH analog is recommended.

A number of studies have been done to investigate the effect of GnRH analog on final height. Several studies have demonstrated that patients with CPP were shorter than their mean target height by 4-8cm.[8,9,10,11] With the use of GnRH agonists, the genetic adult height is preserved in most girls and boys.[11,12,13,14] However treatment with GnRH analog improves final height only in those with true precocious puberty and it is more clear-cut in children less than 5-6 years old.[15,16] No apparent effect on final height was seen in girls with 'early puberty' who starts at 7.5-8.5 years or older then 8 years.[17,18,19] For those children with 'early puberty', combination of growth hormone and GnRH may remarkably improve predicted adult height and/or final height.[20,21]

Case 2

A one and a half years old girl presented to you because of URTI symptoms. On chest examination, you noticed that she had bilateral stage 2 breast. Her length had been on 25th percentile line in the past one year, and mid-parental height between 25th to 50th. There was no vaginal discharge or bleeding.

What is the most likely diagnosis?

This young girl has only breast development without any other signs of puberty. The most likely cause would be premature thelarche, which means isolated premature breast development. It commonly occurs before 24 months or after 5-6 years old. For the former, it is due to a persistence of infant gonadotrophin making ovarian hormone production greater than later childhood period. In this case, it will almost always regress after 2 years of age. For the latter, it may be due to oversensitivity of breast tissue to low levels of estrogen. In uncertain cases, GnRH stimulation test can be performed and there would be dominant FSH rather than LH response.[22] No treatment is indicated since it is benign and will regress in most of the cases.

Occasionally, we might see young girls presented with mild breast enlargement and vaginal bleeding for once or twice only and yet GnRH response is prepubertal. It might be due to the presence of ovarian cyst, which is self-limiting. It has autonomous estrogen production causing the breast enlargement (peripheral precocious puberty). When the cyst regresses spontaneously, estrogen level falls and induces withdrawal bleeding.

Ultrasound will pick up the ovarian cyst before it regresses. No treatment is needed but follow up is recommended because there might be a few more similar episodes.

Delayed Puberty

Using the similar definition of precocious puberty, delayed puberty occurs when girls and boys do not develop signs of puberty by the age of 13 and 14 respectively. It may be due to the problems in the hypothalamus and pituitary (central causes) or in the gonads (peripheral causes). For the central one, it includes delay but intact hypothalamo-pituitary axis and impaired axis. Differential diagnosis is shown in table 5. The commonest cause of delayed puberty is constitutional delay of growth of puberty, especially in boys.[23,24,25] Other potential causes include chronic systemic illness, CNS pathologies and primary gonadal failure. Klinefelter's syndrome in boys and Turner's syndrome in girls are relatively common examples of gonadal failure in otherwise healthy children.

Case 3

A 14-year-old boy was referred because of short stature and lack of signs of puberty. His past medical history was unremarkable. His mother's menarche was at 12 years and his dad vaguely remembered that he was almost the shortest one in the class when he was a Form 2 student. But later on he grew very fast and now his height is on 75th percentile. On examination, the boy's height is on 3rd percentile. There were no signs of puberty. Investigations showed a bone age of 12 years. Biochemistry confirmed hypogonadotrophic hypogonadism (low FSH/LH and low testosterone).

What is the likely cause of delayed puberty and does he need any treatment?

This boy most likely suffered from constitutional delay in growth and puberty because his father has similar history. Sometimes it is the mother who has significant delayed puberty shown by having menarche at an older age. For this boy, his predicted final height based on his bone age would be around 175cm which coincides with his mid-parental height. No treatment but regular follow up is needed to monitor the progress. Should this boy show significant psychological stress for his delay in puberty, a small dose of testosterone (50mg of testosterone esters once every month) for a short period of time (3-6months) should be given to stimulate the hypothalamo-pituitary axis.[26,27] In most cases, spontaneous pubertal development will "kick in" and normal growth velocity is maintained.[28] Most specialists would not consider this treatment unless the patient is 14 years old or his bone age is at least 12 years old since below these ages, the risk of reducing final height is increased.[28,29,30]

If this boy has no family history of delayed puberty and he showed no pubertal response after 2-3 cycles of testosterone induction, he might have hypogonadotrophic hypogonadism. In this case, investigations should be done to make sure that other pituitary hormones are normal. In terms of management, testosterone replacement can induce secondary sexual characteristics but it won't increase

the testicular volume. Therapy with gonadotrophins or GnRH are alternative options.[31,32,33] Human chorionic gonadotrophins (hCG) may be used, which has effects similar to those of LH, at a dose of 500-1500IU on alternative days for 6-12 months or until the testicular volume is satisfactory. FSH can then be added to induce spermatogenesis.[34] After that, testosterone is used as maintenance therapy. Apart from injectable testosterone, orally active testosterone undecanoate is also available. It is absorbed via the lymphatic system and therefore escaping first-pass metabolism. But because of its short half-life and wide fluctuation of serum testosterone level, it is not an ideal method of androgen replacement.[35] Transdermal testosterone patch is another choice. With daily patch applied to the skin, it can provide physiological testosterone in over 90% of adults. But skin reaction occurs in up to 50% of patients, which greatly limited its use.[35]

Primary gonadal failure is diagnosed when FSH and LH are high in the presence of low testosterone or estrogen. Unless there is obvious reason to account for the primary failure, further investigation is needed. For example, chromosomal analysis is needed in boys or girls with gonadal failure to look for Klinefelter's syndrome or Turner's syndrome respectively. These conditions are treated with sex steroid replacement. Small dose of testosterone for boys and estrogens for girls should be started at the beginning and gradually increase to full maintenance dose, mimicking physiological pubertal change and prevent early closure of growth plates. For girls, progesterone should be added in the cycle once there is withdrawal bleed.

Puberty is a transitional period between infancy and adulthood when important physical and psychological changes take place. Problems occur with puberty may affect the child's physical and/or psychological health. Early diagnosis and adequate management by early referral to paediatrician (table 6) who is familiar with puberty problems is of great importance to ensure normal sexual development in affected children.

Table 1 Tanner Breast Staging

B1	Prepubertal
B2	Breast budding
B3	Enlargement of breast and areola
B4	Secondary mound of areola
B5	Adult size and shape

Table 2 Tanner Pubic hair staging for boys and girls

P1	No pubic hair
P2	Fine hair over mons pubis and / or scrotum/labia
P3	Adult type hair (coarse, curly) but distribution confined to pubis
P4	Extension to near adult distribution
P5	Adult distribution

Table 3 Tanner Genital Staging

G1	Prepubertal (testis volume less than 4ml)
G2	Testicular enlargement with no penile enlargement (volume 4-8ml)
G3	Increase penile length and width with further testicular enlargement (volume 10-15ml)
G4	Increased penile size with pigmentation of scrotum (volume 12-20ml)
G5	Adult size and shape (volume 15-25ml)

Table 4 Common Differential Diagnosis of Precocious Puberty

Central (GnRH driven)
    Idiopathic
    Central nervous system abnormalities (e.g. tumours, radiation, surgery, congenital anomalies)
Peripheral (GnRH independent)
    Genetic disorders (e.g. CAH, McCune-Albright syndrome, male testotoxicosis)
    Tumours (e.g.ovarian, adrenal or testicular tumour and other gonadotrophin producing tumours)
    Chronic primary hypothyroidism
    Ovarian cysts in girls
    Exogenous sex steroid or gonadotrophins
Variants of normal puberty
    Premature thelarche
    Premature pubarche

Table 5 Common Differential Diagnosis of Delayed Puberty

Hypogonadotrophic status (hypothalamic-pituitary defect or lag)
    Intact hypothalamic-pituitary axis
        Constitutional delay of growth and puberty
        Chronic illness
        Excessive exercise
        Hypothyroidism
    Impaired hypothalamic-pituitary axis
        Hypopituitarism
        Gonadotrophin deficiency (e.g. Prader-willi syndrome, Kallmann syndrome, Septo-optic dysplasia)
Hypergonadotrophic status (primary gonadal failure)
    Chromosomal/genetic disorders
        Klinefelter syndrome
        Androgen insensitivity syndrome
        Turner syndrome
    Acquired
        Post chemotherapy, irradiation, surgery, torsion, infection

Table 6 Conditions for referral to specialists

Boys	Girls
Testicular enlargement before age of 9	Breast development before age of 8
No signs of puberty at age of 13-14	No signs of puberty at age of 12-13
	vaginal bleeding with only minimal or without other signs of pubery

Children at higher risk of developing pubertal problems:
 -history of intracranial tumor/ CNS infection
 -history of intracranial/gonadal radiation
 -history of chemotherapy
 -strong family history of early or delayed puberty

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Management of Common Pubertal Problems" by Dr. Pik-shun 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 31 May 2007. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please choose the best answer.

1. Which is the first sign of puberty in most of the boys on physical examination?
a. Change in voice
b. Penile enlargement
c. Testicular enlargement
d. Pubic hair development
e. Acne

2. Concerning peak growth velocity during puberty, which of the following is correct?
a. It always starts together with the first sign of puberty.
b. It starts in earlier pubertal stage in girls than it does in boys.
c. It starts in earlier pubertal stage in boys than it does in girls.
d. It starts at the same pubertal stage in both boys and girls.
e. It has no relationship with the pubertal stage.

3. Precocious puberty means
a. Start of breast development before age of 8 in girls
b. Start of menstruation before age of 8 in girls.
c. Voice changed before age of 9 in boys.
d. Have peak growth velocity before age of 9 in boys.
e. None of the above

4. Which is the most common cause/category of precocious puberty in girls?
a. Idiopathic central precocious puberty
b. Peripheral precocious puberty
c. Congenital adrenal hyperplasia
d. Ovarian cyst
e. Central precocious puberty due to CNS abnormalities

5. A 4-year-old girl with growth acceleration, breast development and vaginal bleeding is most likely to have
a. Congenital adrenal hyperplasia
b. Ovarian cyst
c. Central precocious puberty
d. Premature thelarche
e. Normal puberty

6. For the above mentioned girl, what is the most appropriate treatment?
a. Observe
b. Growth hormone since she is going to be short
c. GnRH analog
d. Replacement therapy for congenital adrenal hyperplasia
e. None of the above

7. Concerning delayed puberty, which of the following statement is incorrect?
a. The most common cause is constitutional delay of growth and puberty.
b. The problem is always in hypothalamus and pituitary.
c. Klinefelter's syndrome is a cause of delayed puberty in boys.
d. Turner's syndrome is a cause of delayed puberty in girls.
e. History of mumps may be a cause of delayed puberty in boys.

8. A 14-year-old boy showed no signs of puberty, both parents couldn't remember when they went into puberty. What is the most appropriate first line management?
a. Reassure, it must be constitutional delay.
b. Blood for FSH, LH and testosterone, bone age
c. Chormosomal analysis
d. Start testosterone treatment
e. Start hCG

9. A 13-year-old girl was short and had no signs of puberty, her FSH and LH were high and her estrogen level was low. Which of the following statement is correct?
a. She has hypogonadotrophic hypogonadism.
b. She most likely has constitutional delay in growth and puberty.
c. It is a good practice to have pituitary imaging in this case.
d. Blood for chromosomal analysis is necessary.
e. Start estrogen replacement right now since she has primary gonadal failure.

10. Concerning final height in precocious puberty, which statement is correct?
a. Final height will be improved it someone has precocious puberty.
b. GnRH analog alone improves final height significantly in girls who start puberty between 7-8 years old.
c. GnRH analog and Growth Hormone are standard treatment option now for all cases of precocious puberty.
d. GnRH analog is a recommended treatment in cases of central precocious puberty for the benefit of final height especially in those younger than 6 years old.
e. Non of the above

ANSWER SHEET FOR MAY 2007

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

Management of Common Pubertal Problems

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| 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | 7 | | 8 | | 9 | | 10 | |

Name (block letters):_____ HKMA No.: _____

HKID No.:___ ___ - ___ ___ ___ ___ X X (x)

Other Membership No.
(please indicate): _____

Contact Tel No.:_____

Answers to April 2007 issue

Chronic myeloid leukemia

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

Diabetic Neuropathy

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Diabetic neuropathy (DN) refers to the signs and symptoms of peripheral neuropathy in a person with diabetes mellitus in whom other causes of nerve dysfunction have been excluded. It can affect both Type 1 and Type 2 diabetics[1,2]. The exact mechanism has not been fully elucidated but most research has focused on the consequences of chronic hyperglycaemia which can result in depletion of nerve myoinositol and accumulation of sorbitol and fructose; the potential effects of deranged lipid, amino acid and electrolyte metabolism is less well studied. In addition endoneural hypoxia, oxidative stress, impaired axonal transport and reduced Na-K ATPase activity have been reported.

The incidence depends on the criteria used to determine DN, the sample population and the rigour with which it is sought; it is higher in the elderly, in hospital series and with longer duration of disease. In general around 50% of patients with diabetes have DN of which 15% are symptomatic. At presentation the incidence is 7.5% and rises to 50% after 25 years. Careful examination shows that overt and sub-clinical neuropathy can be elicited in two third of patients. With aging of the population in Hong Kong and with more people becoming overweight, the prevalence is expected to rise.

DN can be classified into two broad categories:
1) Focal and multifocal neuropathies. Mononeuropathy and entrapment neuropathy are more common in people with diabetes; the most commonly involved nerves are the median, ulnar, radial, peroneal, medial and lateral plantar nerves. Cranial neuropathy typically occurs in an abrupt manner, affecting the occulomotor followed by the trochlear nerves in order of frequency. Pain is present in half the cases, which can mimic a "surgical third nerve". Multiple neuropathies are thought to be due to occlusion of vasa nervosum and are less commonly seen. In diabetic proximal neuropathy the roots or proximal nerves are affected, examples include thoracic radiculopathy or weakness of the thighs, pain and subsequent wasting, what was previously termed diabetic amyotrophy[3]. In mild to moderate cases, improvement may take many months.

2) Symmetrical polyneuropathies. Diabetic symmetrical peripheral neuropathy (DSPN) is the most widely recognised type and accounts for the majority of cases of DN. The usual picture is a patient with long standing DM who complains of numbness in a glove and stocking distribution[4,5]. In addition to this scenario there are patients who have primarily autonomic neuropathy, presenting with gastrointestinal, cardiovascular and urinary disturbances. This disorder can result in silent myocardial ischaemia and reduced life expectancy[5,6]. Also DN can occur before diabetes is clinically diagnosed, a condition that is called impaired glucose tolerance neuropathy. This early involvement of the nerves increases the risk of progression to actual DM. It has been estimated that for every case with DN, there is one patient with impaired glucose tolerance and painful neuropathy[7,8]. This review focuses on DSPN, which comprises 75% of patients with clinical neuropathy. Around a tenth of those with DSPN have persistent neuropathic pain which is regarded as chronic if it lasts over six months. Most patients will not have positive symptoms but suffer from sensory loss while others will complain of pain. Allodynia refers to pain from stimuli that would normally be innocuous (reduced pain threshold) while hyperalgesia describes exaggerated response to noxious stimuli. Pain in these cases can lead to impaired mobility, poor sleep, feelings of helplessness and interference with employment and other social activities. Besides these quality-of-life issues, a major concern is the risk of foot ulcers and amputations - over 50% of non-traumatic lower limb amputations in the US is related to diabetes. Patients with diabetes should be routinely asked about the presence of neuropathic signs and symptoms. Simple bedside examination can detect early sensory loss[9]. Vibration can be assessed using a 128 Hz tuning fork, light touch with cotton wool and pain can be tested using disposable pins (of course reusable sharp objects, needle syringes should not be used and breaking off wooden sticks and tongue depressors is unreliable). One example of a reproducible severity score that looks at the degree of neuropathic deficits is shown in Table 1. Nerve conduction study is recommended particularly in cases with prominent weakness or autonomic symptoms. In one study that followed up patients with newly diagnosed DM, serial assessment of nerve conduction parameters showed progressive deterioration over the years. In addition to correlation with clinical severity, sensory nerve action potential amplitude is also linked with myelinated fibre density. Admittedly routine electrophysiology, which measures large nerve fibre function, can be insensitive in detecting neuropathy secondary to small fibre disorder but it is important to exclude other treatable conditions and alternative causes of peripheral nervous disease. More refined tests include 10-g monofilaments, that apply a specific pressure on the skin to see whether the patient has intact sensation. In selected cases, skin biopsy to assess small nerve fibre density and sural nerve biopsy can be performed.

Management is directed at preventing progression and providing symptomatic relief[10]. It is important to remember that in 10% of patients thought to have DN, the neuropathy may be due to causes other than diabetes. Alternative causes such as autoimmune or neoplastic disease should be considered while entrapment neuropathies eg carpal tunnel syndrome or conditions like plantar fasciitis or vitamin B12 deficiency are easily amenable to effective treatment. Patients should be advised about the consequence of neuropathy and advised on self-care. These simple preventative measures are critical in reducing foot complications (Table 2). Drugs that aim to reverse the metabolic derangement and improve nerve condition - such as aldolase reductase inhibitors, C-peptide, lipoic acid, carinitne, recombinant nerve growth factor - have not been shown to produce consistently beneficial results.

Patients with poor glycaemic control have a higher prevalence of DN[11]. Intensive insulin therapy slows down the progression of neuropathy but the effect on autonomic neuropathy is more disappointing[12]. In those with established polyneuropathy, both sensory perception and neurophyisological values are improved with tight control of diabetes - conduction velocities increases by 1.3 m/s for every 1% improvement in HbA1c. Table 3 shows drugs used for the symptomatic control of painful neuropathy[13]. The numbers need to treat (NNT) refers to the numbers of cases to be treated in order to obtain 50% pain relief in one patient. For the tricyclics the NNT ranges from 1.4 to 3; for anti-epileptic drugs the NNT varies from 3.3 to 4 while that for Mexiletine is 10. Fluoxetine is ineffective and phenytoin is not recommended due to uncertainty in efficacy and the risk of precipitating hyperosmolar coma. Some authors recommend specific drugs for different qualities of pain, so anti-depressants are used for burning pain and anticonvulsant for lancinating or shooting pain but the evidence for this strategy is uncertain.

Drug treatment for chronic painful DN can be challenging. Patients with significant pain or weakness, asymmetric distribution of disease, autonomic involvement or systemic complaints such as fever, history of malignancy should be referred for specialist work up.

Table 1. Neuropathy disability score (adapted from ref 2)

Ankle reflexes
Vibration perception threshold
Pin-prick sensation
Temperature sensation
Reflexes:
        Normal = 0
        Present with reinforcement = 1
        Absent = 2 at each side
Sensory modalities:
        Present = 0
        Reduced or absent = 1 at each side
NDS score: 3-5 = mild; 6-8 = moderate; 9-10 = severe

Table 2. Foot Care in Diabetic Neuropathy

- Daily feet cleansing with warm water and mild soap; carefully dry between toes.
- Avoid soaking feet
- Inspect feet and toes daily for cuts, blisters, redness.
- Moisturise feet with lotion.
- Cut toenails regularly and file edges.
- Do not walk barefoot
- Before wearing shoes, check inside.
- Wear well-fitted shoes.
- Inform health care provider if changes in the appearance of or unusual sensations in feet.

Table 3. Symptomatic treatment of painful diabetic neuropathy

- Tricyclic agents
  - Amitriptyline
  - Nortriptyline
  - Imipramine
- Selective serotonin reuptake inhibitors
  - Paroxetine
  - Citalopram
  - Paroxetine
- Other anti-depressants
  - Venlafaxine
- Anti-epileptic drugs
  - Carbamazepine
  - Gabapentin
  - Lamotrigine
  - Pregabalin
  - Topiramte
- Other medications
  - Lidocaine
  - Mexiletine
  - Tramadol

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Management of Hyperthyroidism in Primary Care Setting

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Dr. Wing-bun Chan

Hyperthyroidism is one the commonest endocrine diseases encountered in our daily practice. The classical features of hyperthyroidism include palpitation, tremor, heat intolerance, anxiety and weight loss despite increase in appetite. Although the clinical features are easy to recognise in most of the patients, it is important to recognise a large variety of atypical presentations. Some patients may present to gastroenterologists with symptoms such as diarrhoea and vomiting[1], or to cardiologists with cardiac problems such as atrial fibrillation and congestive heart failure[2]. Raised alkaline phosphatase with weight loss may mislead the physicians to the suspicion of underlying malignancy or liver problem[3]. Thyrotoxic patients may also present with generalised weakness due to either myopathy or hypokalaemia, which leads to the suspicion of underlying neurological problem[4]. Hyperthyroidism may present with apathy and decreased appetite in elderly instead of common presentation of increased appetite[5].

The diagnosis of hyperthyroidism can be established by demonstrating a raised free T4, free T3 and a fully suppressed TSH. Total T4 and total T3 are of limited value due to confounding conditions that may affect their interpretations. Disconcordant findings between free T4, free T3 and TSH point to either rare causes of hyperthyroidism or an alternative diagnosis, which require endocrinologists input. The management of hyperthyroidism requires not only the establishment of biochemical diagnosis, but also the underlying aetiology since hyperthyroidism due to different aetiologies is treated quite differently. Causes of hyperthyroidism can be classified according to radioactive iodine uptake, details of which are listed in table 1. The most common cause of hyperthyroidism is Graves' disease. Extensive investigations are not required in a typical patient with Graves' disease after the biochemical diagnosis is established. Thyroid ultrasonography is important if patient is clinically found to have thyroid nodules to rule out underlying malignancy and to establish the diagnosis of multinodular goitre. Radioactive iodine uptake scan is helpful to establish the diagnosis of toxic solitary nodule if a solitary nodule is found. Thyroglobulin autoantibody (TGAb) and thyroid aeroxidase autoantibody (TPOAb) although not specific for Graves' disease, give supporting evidence to the diagnosis. It is especially important to recognise the low radioactive iodine uptake ones since they need quite different management compared with those suffering from Graves' disease. Thionamides are often not effective or even contra-indicated in these patients. Take subacute

thyroiditis as an example, patients often present with neck pain, pyrexia of unknown origin and a biochemical picture of hyperthyroidism. However, they do not respond to thionamides since the disease is destructive in nature and thionamides are in fact contraindicated in this condition[6].

The most common cause for hyperthyroidism is Graves' disease, which is an autoimmune disease characterised by antibodies against the thyrotropin receptor[7]. The clinical features of Graves' disease not only include those of hyperthyroidism, but also autoimmune features such as Graves' ophthalmopathy and pretibial myxoedema, which are specific features of Graves' disease. As an autoimmune disease, it runs a remission relapsing course. It has a chance of going into permanent remission with medical treatment, which makes its treatment modality different from other causes.[8] The possible modalities of treatment include thionamides, surgery and radioactive iodine(RAI) treatment. Despite being the most common cause of hyperthyroidism, there are few comparative study looking at the long term outcome of these modalities of treatment. The most long term study which compared these three modalities at a time interval of 48 months found that all three treatments are equally effective in normalising thyroid function[9]. Since all the 3 modalities have their own advantage and drawback, the choice of treatment will highly depend on patient and physician's preferences. This is well demonstrated by the fact that radioactive iodine treatment is the preferred treatment in USA in 69% of patients, while it is only chosen as preferred treatment in 22% of European doctors and 11% in Japanese[10]. The pros and cons of all these modalities are listed in table 2. In Hong Kong, thionamides are often used as the first line treatment for Graves' disease. Patients are usually treated with thionamides for one to two years. High starting dose lead to a quicker fall in free T4, but a higher chance of transient hypothyroidism[11]. It is still not sure whether thionamides induce remission of the disease or buy time for the disease to go into spontaneous remission. Nevertheless, thionamidse can only induce permanent remission in less than half of the patients and short duration of treatment less than 6 months is associated with higher chance of relapse[12]. Furthermore, there are certain hyperthyroidism related complications or coexisting diseases that make hyperthyroidism a more high-risk condition than usual. These conditions include thyrotoxic periodic paralysis, atrial fibrillation, congestive heart failure, ischaemic heart disease, etc. In the presence of these conditions, the aim of treatment is to render the patient euthyroid and minimise the

relapse rate as much as possible. We therefore recommend using RAI or surgical treatment to avoid possibility of disease relapse under these conditions. Furthermore, although thionamides are considered drugs with good safety, rare but potentially life threatening side effects including agranulocytosis did happen occasionally[12]. In the presence of such side effects, thionamides should no longer be introduced and changing to another thionamide is not a safe measure. Should the patient show multiple relapse on thionamide treatment, he should be advised on either long term thionamide treatment or alternatively definitive treatment including RAI and thyroidectomy. RAI may also be considered as the first line treatment in Graves' disease. It is in fact a safe and effective treatment for Graves' disease. It can render the patients enthyroid or hypothyroid in 6-18 weeks time. High dose of RAI will lead to higher chance of cure, but at the expense of higher rate of hypothyroidism.[13] The incidence of hypothyroidism is approximately 2-3 % per year after the first year.[14] Approximately 10-20% of patients need second dose of RAI. Although some observational study showed an increase in incidence of thyroid cancer, especially in those with nodular goitre, however, the overall cancer incidence is decreased and the thyroid cancer is also well known to be increased in toxic nodular goitre[15]. Therefore, the possible carcinogenic effect of RAI is still considered small. Recent clinical trials demonstrated an increase in new onset or worsening of ophthalmopathy with RAI treatment, although most of which were mild[16]. The worsening of ophthalmopathy can be prevented by concurrent steroid treatment and RAI treatment is usually delayed if the patient has moderate to severe ophthalmopathy. Surgical treatment is becoming less popular nowadays. In USA, less than 1% of thyroid specialst will choose surgery as their first line treatment[10]. Surgery is best considered for patients who had strong fear of RAI, large goitre with airway obstruction, suspicion of concomitant thyroid malignancy and unacceptable side effect with thoinamides. The success rate of surgical treatement is similar to RAI. More aggressive surgery is associated with high rate of cure, again at the expense of high rate of hypothyroidism[17]. Complications of thyroid surgery include wound infection, keloid formation at the site of the incision, transient and permanent hypoparathyroidism and recurrent laryngeal nerve palsy.

Multinodular goitre and autonomous nodule are less common compared with Graves' disease. It is important to recognise these two conditions since the treatment plan is different from Graves' disease. Physical examination, thyroid ultrasonography and radioactaive iodine uptake scan are helpful to differentiate these two conditions from Graves' disease. Unlike Graves' disease, treatment with thionamides for these two conditions will not induce permanent remission. The disease is bound to come back once medical treatment is stopped. Therefore, these 2 diseases are usually treated either surgically or with RAI. The success rate for RAI treatment with these two conditions is very high. Although RAI is known to induce hypothyroidism in Graves' disease, hypothyroidism is less likely with RAI treatment in these two conditions[18]. Surgery is also often used to treat toxic multinodular goitre and toxic thyroid adenoma and is safe and effective treatment[19]. Thionamides are usually used only to control the thyrotoxic symptom while waiting for the more definitive treatment, or as an alternative long term treatment only when patient cannot receive RAI or surgery due to other reasons.

Irrespective of choice of treatment, all thyrotoxic patients need life long monitoring of thyroid function.

In summary, hyperthyroidism is a common endocrine condition. However it should be remembered that some patients present atypically. Hyperthyroidism should be managed according to the underlying aetiology. Although Graves' disease is the most common cause and is often treated with thionamides, it should be realised that aetiologies other than Graves' disease need different treatment and some patients may need different treatment modalities such as RAI and surgery due to comorbidities, complications, side effects or patient's preference.

Table 1. Classification of hyperthyroidism according to radioactive iodine uptake

Normal / High RAIU	Low RAIU
Graves' disease	Subacute thyroiditis
Toxic multinodular goitre	Postpartum thyroiditis
Solitary toxic nodule	Painless(silent)thyroiditis
Choriocarcinoma or hydatiform mole	Exogenous thyroxine
Hyperemesis gravidarum	Iodine-induced hyperthyroidism
TSH - secreting pituitary adenoma	Metastatic functioning thyroid carcinoma
Pituitary selective thyroid hormone resistance syndrome	

Table 2 Summary of Advantages and Disadvantages of Different Treatment Modalities

Therapy	Advantages	Disadvantage
Thionamides	Avoid permanent Hypothyroidism Chance of permanent remission Low cost	High chance of relapse Small risk of life threatening side effects
RAI	High chance of permanent remission of hyperthyroidism	Possibility of permanent of hypothyroidism Possibility of worsening of ophthalmopathy Radiation precaution during RAI treatment
Surgery	Rapid and high chance of permanent remission of hyperthyroidism	Possibility of permanent hypothyroidism Possibility of surgery related complications including laryngeal nerve palsy hyporarathyroidism, mostly irreversible High cost

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Diploma in Child Health Examination (DCH) 2007

The Hong Kong College of Paediatricians (HKCPaed) and the Royal College of Paediatrics and Child Health (RCPCH) will hold a Joint Diploma in Child Health Examination in Hong Kong this year, awarding DCH (HK) and DCH (International) to successful candidates.

The Examination is divided into two parts, Written (MRCPCH Pt IA) and Clinical. The MRCPCH Part 1A Examination is held three times a year in Hong Kong. The next MRCPCH Part 1A Examination will be held on **Tuesday, 4 September 2007**. The examination fee is **HK$3,200** for Part IA. Candidates who wish to enter the examination must hold a recognized medical qualification in Hong Kong.

Application: Candidates who wish to sit the examination in Hong Kong **MUST** apply through the Hong Kong College of Paediatricians (HKCPaed). For application details, please visit the HKCPaed website at www.paediatrician.org.hk or call the College Secretariat at 28718871.

Deadline for Application: Friday, 8 June 2007

Important Notice
**New Clinical Examination for DCH from March 2006**

A new format of the DCH clinical examination has been adopted since March 2006. Details of the new format and other relevant information can be viewed on the RCPCH website at: www.rcpch.ac.uk

Clinical Evaluation of a Patient with Familial Periodic Fever Syndrome

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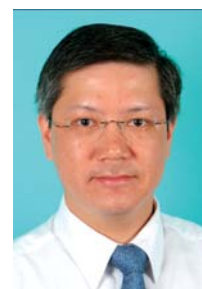
Dr. Tsz-leung Lee

I. Introduction

"Familial periodic fever syndromes" or "hereditary autoinflammatory syndromes" are a group of syndromes with a central clinical phenotype of recurrent febrile episodes with other symptoms of systemic inflammation. They are characterised by unprovoked inflammatory episodes without high-titre autoantibodies. The fever attacks often start during childhood but late onset in adolescence (like familial Mediterranean fever syndrome [FMF]) or even early adulthood (like tumour necrosis factor receptor-associated periodic syndrome [TRAPS]). The duration of attacks vary from hours (in familial cold autoinflammatory syndrome [FCAS]) to weeks (like TRAPS). The frequency of attacks could range from once every few days to once or twice a year. Symptoms of systemic inflammation include serositis (presenting as peritonitis, pleuritis and pericarditis), myalgia, arthropathy and cutaneous lesions. These symptoms resolve spontaneously with asymptomatic periods between attacks except neonatal onset multisystem inflammatory disease (NOMID) / chronic infantile neurologic cutaneous and arthropathy (CINCA) syndrome.

There are at least eight major clinical syndromes and genetic mutations identified in recent years. However, the percentage of patients that present with a clinical autoinflammatory phenotype but in whom no genetic mutation can be found is still very high. In this brief review, the clinical features and genetic mutation of these syndromes and a clinical algorithm for diagnosing a child with recurrent febrile attacks will be discussed[1-4].

II. Characteristics of Different Syndromes

A. Familial Mediterranean fever syndrome

Inheritance	Autosomal recessive
Gene	MEFV
Chromosome	16p13
Protein	Pyrin / marenostrin
Ethnicity / geographic	Jewish, Armenian, Arab, Turkish, Italian
Clinical features	
Fever duration	1-3 days
Periodicity of attacks	Irregular : from weekly to 3-4 monthly
Distinguishing clinical features	• Polyserositis (sterile peritonitis presenting as abdominal pain, pleuritis and pericardial effsuion) • Erysipelas-like rash • Scrotal pain and swelling • Episodic monoarthritis; sacroiliitis
Laboratory	Elevated acute phase reactants
Amyloidosis	Common[5]
Treatment	Colchicine

B. Familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), neonatal onset multisystem inflammatory disease (NOMID) / chronic infantile neurologic cutaneous and arthropathy syndrome (CINCA) syndrome

These three syndromes are all autosomal dominant diseases. They have all been linked to mutations in the CIAS1 gene (also known as NALP3 or PYPAF1) on chromosome 1q44. The gene protein product is cryopyrin. They are classified as cryopyrin-associated periodic syndromes. They represent a clinical spectrum of disease severity, with FCAS as the mildest and NOMID/CINCA the most severe. They present since infancy with non-pruritic urticarial rash and fever. Overlapping clinical features between FCAS and MWS are conjunctivitis whilst between MWS and NOMID are sensorineural hearing loss and aymloidosis. Feature more unique to FCAS is the precipitation of attacks by generalized cold exposure and feature unique to NOMID/CINCA is more severe central nervous system involvement including papilledoema, chronic aseptic meningitis and mental retardation. For articular involvement, the severity increases from arthralgia in FCAS to synovitis in MWS to deforming arthropathy with premature ossification and bony overgrowth in NOMID/CINCA. Thalidomide, etanercept and anakinra have been shown to be effective in case reports in controlling the inflammation. Long term studies are not available.

C. Hyperimmunoglobulinaemia D with periodic fever syndrome (HIDS)

Inheritance	Autosomal recessive
Gene	MVK
Chromosome	12q24
Protein	Mevalonate kinase
Ethnicity / geographic	Dutch, French, others
Clinical features	
Fever duration	3-7 days
Periodicity of attacks	• every 4 to 8 weeks or Irregular • decreasing frequency with age in some patients
Distinguishing clinical features during attacks	• prominent cervical lymphadenopathy and splenomegaly • polyarthralgia • abdominal pain with diarrhoea • maculopapular rash
Laboratory	Elevated Ig A and Ig D level (>100 IU/ml) Elevated urinary mevalonate during attacks Reduced mevalonate kinase activity
Treatment	Simvastatin (preliminary) anti-TNF-α (etanercept) (preliminary)

D. Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome

Inheritance	Autosomal dominant
Gene	CD2BP1/PSTPIP1
Chromosome	15q24
Protein	CD2BP1/PSTPIP1
Ethnicity / geographic	No ethnic predilection
Clinical features	
Fever duration	~ 4 days
Periodicity of attacks	Every 3 to 6 weeks
Distinguishing clinical features during attacks	• Early destruction of joints by recurrent, sterile neutrophil-laden effusions • Myalgia • Numerous cutaneous manifestations including severe acne, expanding purulent ulcerating lesions (pyoderma gangrenosum) and sterile abscess at injection sites
Treatment	Corticosteroid; anecdotal anakinra (anti-IL-1) and etanercept (anti-TNF-α)

E. Tumour necrosis factor receptor-associated periodic syndrome (TRAPS)

|	
Inheritance	Autosomal dominant
Gene	TNFRSF1A
Chromosome	12p13
Protein	TNFRSF1A
Ethnicity / geographic	Any ethnic group
Clinical features	
Fever duration	Often >1 week
Periodicity of attacks	Irregular intervals; varying from weeks to years

Distinguishing clinical features during attacks	migratory myalgia
	• skin rash
	• peri-orbital edema
	  abdominal pain
	  arthritis

Amyloidosis	~10 % of cases
Treatment	corticosteroid anecdotal etanercept (anti-TNF-α)

F. Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenopathy (PFAPA) syndrome[6]

Inheritance	unknown
Gene	Not identified
Ethnicity / geographic	Any ethnic group
Clinical features	
Fever duration	3-6 days
Periodicity of attacks	Every 3 to 6 weeks
Distinguishing clinical features during attacks	• pharyngitis • aphthous stomatitis • cervical lymphadenopathy • normal growth
Amyloidosis	none
Treatment	• 1-2 doses of corticosteroid may help shortening or aborting the attacks

III. Evaluation of patient with recurrent attacks of fever

In patients presenting with recurrent fever, we have to exclude other differential diagnoses like infections, malignancies, as well as atypical presentations of more common autoimmune diseases such as systemic juvenile idiopathic arthritis, systemic lupus erythematosus and other vasculitis syndromes. On evaluating the possibility of hereditary autoinflammatory syndromes, we should gather information like ethnicity, family pedigrees, other clinical features like age of onset and frequency and duration of attacks, physical examination findings and relevant non-genetic laboratory tests[1,7]. Genetic testing should be reserved for more ambiguous cases or there are issues of genetic counselling[8]. (Figure 1)

Figure 1 Algorithm for evaluating a child with recurrent febrile attacks
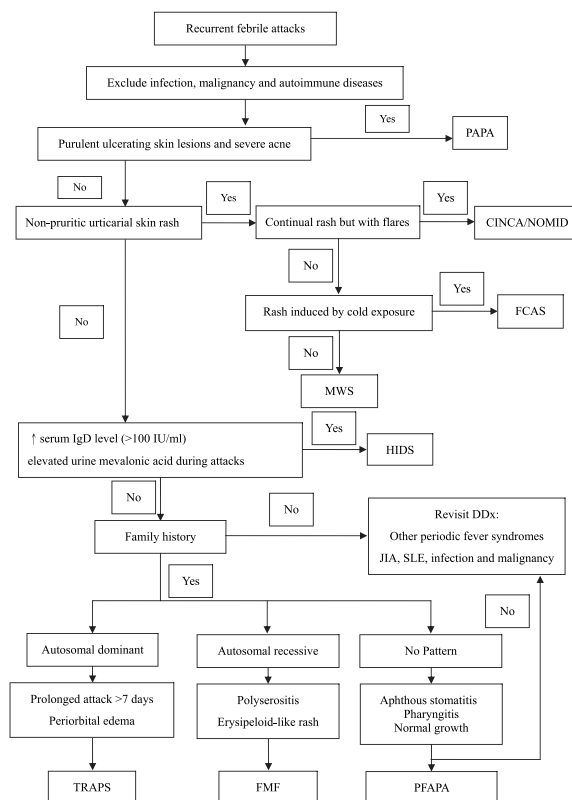
IV. Conclusion

A child with prolonged fever of unknown origin or clinical course compatible with non-infectious periodic fever syndrome should be referred to a tertiary hospital with multi-disciplinary care where specific diagnostic tests and interventions may be available. Moreover, genetic counselling and follow up for evolution of disease or its complications are also crucial.

Great progress has been made in the comprehension of the familial periodic fever syndromes from identifying the genetic mutations in many of these syndromes. It does not only shed light on elucidation of their molecular aetiopathogenesis but also provides rationales of targeted therapeutic interventions within the immune cascade with different biologics like inhibitors of tumour necrosis factor(TNF) and interleukin-1β [9].

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Attention Deficit Hyperactivity Disorder

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He is the three-year old with a never-stopping engine; his throttle opens wide every waking moment of the day (and a good deal of the night). He twists, jumps, climbs, opens, closes, probes, shoves, and bull dozes over playmates.

He is the five-year old whose preschool check up is a headache of his doctor's afternoon. Even if the appointment is delayed for only a few minutes, he will rapidly turn over every surface and pieces of equipment within reach. Permanent alternations of the room's contents could result, uncontrolled by the mother or nurses.

He is the fourth grader who squirms, fiddles with shoelaces, looks out the window, drops his pencil, and talks out. "Hey Jude!" he yells over the top of several desks, "wanna play soccer after school?" Nobody likes to play with him; he is a poor listener; he does not follow rules; he is impatient to wait for his turn; he cannot cooperate; and he has unpredictable moods. His list of friends is as short as his attention span.

He is the young man who has dropped out of school, lost his job and can not maintain a relationship. He can not finish any assignments, is easily distracted by sights and sounds. His room is always in a chaotic mess; he often loses pens, books, and other materials. He has even been hurt in road accidents twice in two months.

Variations on the Theme :

These vignettes illustrate variations on the theme called Attention Deficit Hyperactivity Disorder (ADHD), which is affecting 5 to 10% of children in most studies[1,2] including Hong Kong, i.e. 2 to 4 students in a class of 40.

ADHD comprises marked inattentiveness (attention-deficit) and a lack of inhibition (impulsivity), often accompanied by restlessness (hyperactivity) present in two or more settings, of at least six months' duration, with onset before age seven years, and no indications for any major psychosis or other mental disorders, such as a mood disorder, anxiety, dissociate disorder, or personality disorder[3], that might account for the behaviours. The behaviour should be atypical for the age and IQ of the child, often being described as maladaptive and inconsistent with the developmental level (National Institutes of Health, 2000).

ADHD, with or without hyperactivity, is a syndrome of various aetiologies that interfere with the child's coping with the environment. The aetiologies may impair attention, resulting in an uninhibited, often overly active reaction to the distorted input (National Institutes of Health, 2000). Common associated problems include mood lability, stubbornness, bullying, poor response to discipline, and temper. The children often demonstrate low frustration tolerance and low self-esteem.

Boys with ADHD outnumber girls by at least 4 to 1. However, many girls with ADHD may be overlooked because their symptoms are usually not as flagrant. Despite a common belief that this problem would disappear during adolescence; it usually does not.[4] However with help (by medication when appropriate), adolescents and adults can learn to cope and live successfully with this condition.

Overall, the intelligence of children with ADHD is normal, and they show no signs of serious emotional disturbance. According to Barkley[5], a common theme unifies ADHD symptoms: impairment in inhibition, which makes it hard to delay action in favour of thought. Consequently such children do poorly on tasks requiring sustained attention, find it hard to ignore irrelevant information, and have difficulty with memory, planning, reasoning and problem solving.

While inattention and distractibility are the common elements of "ADHD", hyperactivity is prominent only in 30% of children who have the disorder. So the diagnosis is more likely to be missed in the subtype without hyperactivity, especially for girls. In contrast to those with attention-deficit disorder with hyperactivity disorder, children with attention-deficit disorder without hyperactivity exhibit poorer school performance with higher rates of retention; are socially withdrawn, less popular with peers, more likely to have depressed moods, anxious, and appear sluggish, even though they are less impulsive and less likely to have evidence of oppositional or conduct disorder.[5, 6]

Origins of ADHD:

Heredity plays the major role in ADHD. The disorder runs in families, and identical twins share it more often than fraternal twins.[7] The frontal lobe and basal ganglia are reported as being nearly 10% smaller in children with ADHD. Polymorphism in the dopamine

D4 receptor and transporter genes has been suggested.[8] In a SPECT study, 65% of patients with ADHD showed decreased perfusion in the frontal areas[9], the same areas that tend toward abnormal slow activities on quantitative EEG studies of ADHD.[10] This has been referred to as a "lazy frontal lobe". [11]

Reduced dopaminergic activity in the prefrontal-striatal circuitry pertaining to sensory input relates to attention, activity, and inhibition, with executive function deficits. Reduced norepinephrine activity in the prefrontal cortex and cingulated pertaining to executive function may produce deficits in inhibition. Brainstem norepinephrine activity may be diminished, possibly affecting alertness. Presynaptic dopamine activity appears to be impaired. Stimulants work by countering these deficits. Treatment data suggest a catecholamine hypothesis of ADHD, since nearly all medications effective in ADHD affect catecholamine transmissions of norepinephrine and dopamine.[12]

ADHD is often associated with environmental factors, but a stressful home life rarely causes ADHD. Instead the behaviour of these children can contribute to family problems, which intensify the child's pre-existing difficulties. Furthermore, prenatal teratogens like illegal drug abuse, alcoholism and cigarette smoking of the pregnant mother are linked to inattention and hyperactivity, and so is the use of phenobarbitone in the children.[13, 14]

In fact, children with epilepsy are at risk for symptoms of ADHD. Children with epilepsy have poorer concentration and mental processing and are less alert than age-matched non-epileptic children[15]. Alertness may be depressed in children with epilepsy[16].

ADHD is frequently present in children and adults with partial seizure disorders, but it may also occur in primary generalized epilepsy. ADHD is seen in up to 48% of children with epilepsy, especially in boys[17]. Epileptic students show reduced alertness.[18]

Examples of Comorbidity with ADHD

ADHD~11% learning disabled in either reading or arithmetic
  ~35% to 65% oppositional or conduct disorders
  ~20% to 25% affective or anxiety disorders

33% of children with learning disabilities satisfy criteria for attention-deficit hyperactivity disorder.[19] Forty % of children with Tourette Syndrome also exhibit ADHD.

Treating ADHD:

It is evident that as long as dosage is carefully regulated, the drugs in the Table are able to reduce activity level and improve attention, academic performance and peer relations for above 70% of children who take them.[20] Stimulant medications seem to increase activity in the frontal lobes, thereby improving the child's capacity to sustain attention and to inhibit off-task and self-stimulating behaviour.

Medication	Dose	Comments	
Stimulants Methylphenidate (Ritalin)	0.3-0.8 mg/kg Usual initial dose: 5-10 mg Increment by 5 mg every 3 days Usually given 8am and noon	Dose-related side effects of growth suppression, tics Usually transient side effects of insomnia, decreased appetite, stomach aches, and headaches	Shafritz and Shaywitz, 2004[21]
Ritalin (LA)	5mg at 8am with gradual increments of 5-10mg weekly in adults	Swallow whole	Fitzpatrick et al., 1992[22]; Pelham et al., 2002[23]
Methylphenidate HCl (Concerta)	18mg once daily morning dose Dosage adjustments weekly intervals maximum 54mg once daily	Swallow whole better compliance Contraindicated in patients with marked anxiety, glaucoma, Tourette's Syndrome, concomitant or within 14 days of MAOI therapy	Swanson et al 1991 & 2003[24, 25], Pelham et al 2002[23],
Mood Modifiers Atomoxetine (Strattera)	Single daily morning dose Initiate at 0.5mg/kg maintained for a minimum of 7 days, increased to maximum of 1.2mg/kg/day	Swallowed whole better compliance less insomnia better for tics Contraindicated with concomitant use of MAOIs, narrow angle glaucoma	Kelsey et al 2004 [26], Buitelaar et al 2006[27]

Although medications currently used are relatively safe, their impact is short-term, and should not be abused or overused. Diagnosis, reassessment and treatment by team work (well-trained and experienced doctors, child neurologists, psychiatrists, psychologists, social workers and teaching staff) would prevent misdiagnosis. No drugs can teach children how to compensate for inattentions and impulsivity. Combining medications with interventions that model and reinforce appropriate academic and social behaviour, as well as family intervention, is the most effective treatment approach.[28]

It is important to have good rapport and communication with the parents to yield favourable results with better compliance, which can be better achieved by the use of long-acting medications.

Because ADHD can be a lifelong disorder, it often requires a long-term therapy. Adults with ADHD need help structuring their environment, regulating negative emotions, selecting appropriate career, and understanding their condition as a biological deficit rather than a character flaw.

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Why Should We Convince Expectant Mothers to Breastfeed?

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As doctors, we are often called upon to advise expectant mothers on the issue of infant feeding. Myriad of reasons are given for not breast-feeding; lack of milk, lack of time, lack of sleep, and even cosmetic considerations are the most frequent excuses. Our duty is to convince our patients to do what is best for themselves and their offspring. In order to do that, we need to give convincing reasons why breast-feeding is the best option under most circumstances.

When an infant is born, its immune system is incomplete. This immature immune system is incapable of producing antibodies, which is needed to protect the baby from various infections. There are five different kinds of antibodies, and fortunately, the most important kind, IgG, is transmitted to the infant from the mother during gestation. However, the level of IgG declines after birth until around 6 months of age when the baby's immune system starts to make its own antibodies. Breast milk is rich in another form of antibody called IgA. IgA is normally present in secretions such as tear and saliva, and is an important part of our mucosal immunity against bacteria and viruses. It has been shown that breast milk IgA can protect the baby's respiratory system and gut.

The newborn infant's digestive system is also immature. Incompletely digested foreign proteins can pass through the bowel wall, and these proteins can often cause allergies. Infants born to allergic parents are particularly at risk. It is not uncommon for bottle-fed babies to develop allergy to cow's milk proteins. Quite often, the baby is then changed to a soy-based formula, only to develop allergies to that as well. Symptoms of cow's milk allergy may include abdominal colic, reflux or vomiting after feeding, excessive gas, eczema and other more serious symptoms such as failure to thrive, bloody diarrhoea and anaemia.

There have been many studies looking at the effects of breast-feeding on childhood infections. Studies have shown that exclusive breast-feeding for at least four months can protect against otitis media. Another study looking at 170 healthy newborns showed that the incidence of acute respiratory infections was significantly lower in fully breast-fed infants than formula-fed infants. Other studies have looked at the effect of breast-feeding on gastrointestinal illnesses, and concluded that breast-feeding is protective. More significantly, breast milk has been found to contain IgA antibodies against several intestinal pathogens that can cause diarrhoea. This is of particular importance in the third world, where infant diarrhoea is responsible for a significant proportion of infant deaths, and clean water for mixing formula is often scarce.

Results from studies looking at allergies have been even more interesting. A five-year study showed that high-risk infants who were breast-fed showed a significantly lowered incidence of allergic diseases such as eczema and asthma, when compared to cow's milk-fed infants. Another study carried out in Sweden followed 150 healthy infants for 17 years. Subjects who had prolonged (> 6 months) breast-feeding have a substantially lower incidence of severe allergy at the age of 17.

In conclusion, it appears that breast milk is part of an infant's immune system during the first six months of life. We can easily understand how breast milk may protect the infants from infectious diseases. How breast milk protects infants from allergic diseases is less well understood. Nevertheless, it has been clearly shown that prolonged breast-feeding can protect infants from food allergies during the first year of life, and can also prevent the development of asthma and eczema throughout childhood. One must remember that prolonged breast-feeding refers to six months of exclusive breast-feeding. Mixing breast-feeding with cow's milk formula will probably lessen this protective effect. Mothers should therefore be strongly encouraged to breast-feed their infants, since one would still be enjoying the benefits long after the inconvenience is forgotten.

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Type 2 diabetes is a progressive, metabolic disorder characterised by two fundamental defects: insulin resistance at peripheral target tissues and pancreatic beta-cell dysfunction. Insulin sensitivity declines as an individual moves from normal to impaired glucose tolerance state. Pancreatic beta cells compensate by hyper-secretion of insulin in order to maintain normoglycaemia. When pancreatic beta cells exhaust and the function of pancreatic beta cells deteriorates progressively, an individual progresses from the state of impaired fasting glucose or impaired glucose tolerance to frank diabetes[1, 2].

Despite good compliance to treatment, the glycaemic control of type 2 diabetes deteriorates progressively. Analysis from the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that after 3 years of longitudinal follow up, only 50% of the initial cohort could achieve the target haemoglobin A1c (HbA1c) control of <7% while the remaining 50% required the addition of a second drug for diabetes control. By the time of nine years, 75% of patients required multiple therapies to achieve the target HbA1c control[3]. Hence, new therapeutic agents are continuously being developed to help our diabetes population. Recent studies have shown that early intervention at pre-diabetes state[4, 5] and beta cell protection with insulin sensitisers[6] may improve the prognosis of diabetes.

Dipeptidyl peptidase (DPP)-IV inhibitors, which act via enhancing the incretins, represent another new therapeutic approach to the treatment of type 2 diabetes. Glucagon-like peptide 1 (GLP-1) and glucose dependent insulinotropic peptide (GIP) account for the majority of incretin action[7]. GLP-1 is a gut hormone that plays a key role in glucose homeostasis via its incretin effect. GLP-1 is produced from the enteroendocrine L-cell of small intestine and is secreted in response to meal and nutrients (Table 1). It stimulates insulin release from the pancreatic islets in a glucose dependent manner. It restores the defective first and second phases of insulin response to glucose in type 2 diabetes patients[8,9]. Moreover, GLP-1 suppresses post-prandial glucagon release, delay gastric emptying and increase satiety[10-12]. In animal models, GLP-1 and its analogs are shown to stimulate beta-cell proliferation and differentiation. These may help in preserving the pancreatic beta cell mass and function, and thus have beneficial effect in the prognosis of type 2 diabetes[13,14]. However, GLP-1 has a very short half-life. It is rapidly degraded inside our body by the enzyme dipeptidyl peptidase (DPP)-IV. Therapeutic agents, that can block the DPP-IV enzyme (DPP-IV inhibitor), can increase the endogenous GLP-1 level and thus enhances the incretin action.

Sitagliptin is a potent and highly selective DPP-IV inhibitor. It is the first from this novel class of oral anti-hyperglycaemic agent that has been approved by the United States (US) FDA in October 2006 for the treatment of type 2 diabetes. It can be used as a monotherapy or in combination with metformin or thiazolidinedione. Sitagliptin is orally active and can be administrated once daily. A single oral dose of Sitagliptin ≥ 100mg can inhibit plasma DPP-IV activity 80% over 24 hours of time[15]. By slowing incretin degradation, Sitagliptin increases meal-stimulated active GLP-1 level to two to threefold, leading to increase in insulin and C-peptide levels, reduction in plasma glucagon levels, reduction in post-prandial glucose excursion and better glycaemic control in type 2 diabetes patients[16]. A 24-week randomised, double-blinded, placebo-controlled study in type 2 diabetes patients demonstrated that Sitagliptin 100mg daily monotherapy improved fasting and postprandial glycaemic control, reduced HbA1c by 0.79% (p<0.001), improved beta-cell function, with neutral effect on body weight, similar incidence of hypogycaemia, slightly higher overall gastrointestinal adverse experiences when compared with placebo. Patients with baseline HbA1c ≥ 9% had greater reductions in placebo-substracted HbA1c (-1.52%) than those with baseline HbA1c <9%[17]. DPP-IV inhibitor had been shown to improve beta cell function in patients and animal models with type 2 diabetes[18-21]. In animal models, DPP-IV inhibitor can lead to beta cell neogenesis and survival[22,23]. Nonetheless, long term clinical studies are required to see whether similar beta cell effects are found in patients with type 2 diabetes. Vildagliptin is another DPP-IV inhibitor which acts via similar mechanism as Sitagliptin but has not yet been approved by US FDA.

In summary, DPP-IV inhibitors is a novel class of oral hypoglycaemic agent with potentials in improving pancreatic beta cell function and the clinical course of type 2 diabetes. More clinical trials are needed to explore their long-term clinical effects and their potential beneficial effects in human beta cell neogenesis and survival.

Table 1. Action of Glucagon-like peptide (GLP-1).
Action of GLP-1:
1. Stimulate insulin secretion in glucose-dependent manner.
2. Decrease glucagon secretion in glucose-dependent manner.
3. Delay gastric emptying.
4. Decrease appetite.
5. Increase pancreatic beta cell mass.

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Clinical Quiz

Dr. Godwin TC Leung

FHKCP, FHKAM

Specialist in Cardiology, CardioMed Heart Centre

Dr. Godwin TC Leung

Fig 1

A 58-year-old lady presented with progressive decrease in exercise tolerance for 3 years and chest discomfort worse on carrying heavy objects. Her blood pressure was normal. Coronary angiogram was normal 2 years ago.
Her ECG showed giant negative T waves in anterior leads. (Fig 1)
Magnetic resonance imaging of the heart was performed. End-diastolic still images of wall motion scans of the 2- and 4-chamber views are shown. (Fig 2 and 3)
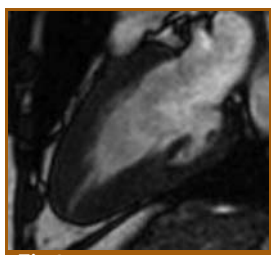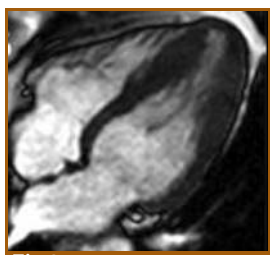

Fig 2

Fig 3

Questions:

- What is the diagnosis?
- How do you manage this patient?
- What is the prognosis?

News from Member Societies:

Hong Kong Paediatric Haematology & Oncology Study Group
New office-bearers for the year 2007-2008 are as follows: President: Dr. CHIANG, Kwok-shing, Alan, Hon. Secretary: Mr. LEE Vincent, Council Representative: Mr. LEE Vincent.

The Hong Kong Chinese Medical Association
New office-bearers for the year 2007-2008 are as follows: President: Mr. CHAO S.C. William, Hon. Secretary: Mr. CHAN C.W. Angus, Hon. Treasurer: Mr. SHUM Kwok-yan, Council Representative: Mr. SHUM Kwok-yan.

The Hong Kong Medical Association, founded in 1920, is the largest and most representative medical organization in Hong Kong. It aims to bring together public and private medical practitioners for an effective exchange of views and coordination of efforts. The Association elects its Council in a democratic manner and represents the profession in the medical sub-sector of the Election Committee and the Medical Council. The Association speaks out collectively for its members and keeps members abreast of medical ethics, professional issues and recent advances. The foremost objective of the Association is to safeguard the health of people of Hong Kong.

香港醫學會成立於一九二零年，是本港最大及最具代表性的醫學團體。旨在聯繫公私營醫生交流意見，團結一心。香港醫學會致力將最新的醫療資訊及發展傳遞與會員，提倡會員遵守專業操守，目的在於服務社會，維護民康。

Hong Kong Chinese Medical Association (HKCMA) is organizing a "Clinical Management Series" for family physicians. This structured initiative will take the form of monthly lunch symposia held on Sundays and cover specific topics with which family physicians frequently come across. Further to the first meeting held on 15 April 2007 at the Chariot Club in Central which dealt with depression and suicide risk assessment, subsequent symposia on Mental Health are scheduled for May 20, June 10 and July 15. For reservation and enquiries, please call Ms. Gigi Lui on 2901 6085.

Answer to Clinical Quiz

Answer :

1. Apical hypertrophic cardiomyopathy (HCM).

    Apical HCM is a variant form of HCM, in which left ventricular wall thickening is confined to the apex. The prevalence of apical HCM can vary depending on the population; it is highest in Japanese (up to 23%). It is less common in other populations worldwide. The typical ECG finding is giant negative T waves in anterior leads. The diagnosis is confirmed by echocardiography, left ventriculogram or computed tomography, but is most accurate with cardiac magnetic resonance imaging.

    When a patient is found to have hypertrophy, other causes for the hypertrophy should be excluded. Hypertension and aortic stenosis may cause severe secondary hypertrophy. Myocardial ischaemia may occur in HCM despite normal epicardial coronary arteries.

2. This patient was treated with diltiazem 200mg daily and perindopril 4mg daily with significant improvement in symptoms. Drugs with both negative inotropic and chronotropic properties (beta-blockers, non-dihydropyridine calcium channel blockers and disopyramide) are the main therapies in HCM. A decrease in heart rate and contractility result in reduction in myocardial oxygen demand, prolong the diastolic filling period and thereby enhance left ventricular filling. ACEI therapy has been shown to improve diastolic parameters in patients with non-obstructive hypertrophy. Family screening should be considered because around 15% of the family members may be affected (although familial cases are more common in HCM with asymmetric septal hypertrophy).

3. Patients with apical HCM have a benign clinical course compared to that of other forms of HCM. Heart failure, arrhythmia, sudden death and left ventricular aneurysm due to the destruction of hypertrophied muscle are relatively rare.

Dr. Godwin TC Leung
FHKCP, FHKAM
Specialist in Cardiology, CardioMed Heart Centre

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
		1 ★ HKMA Newsletter Editorial Meeting	**2** ★ Fetal Origins of Adult Diseases	**3** ★ HKMA Council Meeting ★ Advanced Wound Care Management (Code No. TC-AWCM-0107-CNSG)	**4** ★ Basic Wound Management (Code No. TC-BWC-0107-CNSG)	**5**
6 ★ 2007 Paediatrics Update No 1 Pharmacogenomics and Pharmacogenetics in Paediatric Therapies ★ HKMA Structured CME Programme 07/08 (II) - Paediatrics ★ Dragon Boat Practising Session	**7** ★ A Patient with Persistent Bladder Outlet Obstruction	**8**	**9**	**10** ★ Advanced Wound Care Management (Code No. TC-AWCM-0107-CNSG) ★ HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2007 (V) - Update on Pharmacotherapy in Diabetes ★ 176th WMA Council Session ★ (1) AOB? (2) "The Longest Day"	**11** ★ Basic Wound Management (Code No. TC-BWC-0107-CNSG) ★ 176th WMA Council Session	**12** ★ 176th WMA Council Session ★ HKMA Refresher Course for Health Care Providers 2006/2007 (IX) - Primary Care Paediatrics
13 ★ Dragon Boat Practising Session ★ 8th Regional Osteoporosis Conference	**14**	**15**	**16** ★ Guidelines for Hormone Treatment of Women in the Menopausal Transition & Beyond and the Most Advance Treatment for Menopause	**17** ★ Advanced Wound Care Management (Code No. TC-AWCM-0107-CNSG) ★ A Patient with Persistent Bladder Outlet Obstruction	**18** ★ Basic Wound Management (Code No. TC-BWC-0107-CNSG) ★ IOF Osteoporosis Diagnosis Course	**19** ★ IOF Osteoporosis Diagnosis Course ★ 8th Regional Osteoporosis Conference
20 ★ Dragon Boat Practising Session ★ 8th Regional Osteoporosis Conference	**21**	**22**	**23** ★ 健康服務助理員訓練課程 (Code no. TC-HCA-0207) ★ 醫療護理常用英語初階 (Code No. SUS MH 025 0 (C)) ★ FMSHK Executive Committee Council Meeting	**24**	**25** ★ Basic Wound Management (Code No. TC-BWC-0107-CNSG) ★ 健康服務助理員訓練課程 (Code no. TC-HCA-0207)	**26**
27 ★ Dragon Boat Practising Session ★ HKMA Squash Tournament ★ HKMA Structured CME Programme Year 07/08 (II)	**28** ★ 醫療護理常用英語初階 (Code No. SUS MH 025 0 (C))	**29**	**30** ★ 健康服務助理員訓練課程 (Code no. TC-HCA-0207) ★ 醫療護理常用英語初階 (Code No. SUS MH 025 0 (C)) ★ 病人安全及急救知識 (Code No. SUS MH 004 0 (A))	**31**		

Date / Time	Function	Enquiry / Remarks
2 WED 7:00 pm - 9:30 pm	**Fetal Origins of Adult Diseases** Organised by: The Obstetrical and Gynaecological Society of Hong Kong Chairman: Dr. S.K. LAM Speaker: Prof. John P NEWNHAM # Ballroom, Langham Hotel, Tsim Sha Tsui, Kowloon	Ms. Teresa CHAN Tel: 2510 6310 Fax: 2969 5511 1 CME Point
3 THU 8:00 pm 6:00 pm - 8:00 pm (10,17)	**HKMA Council Meeting** Organised by: The Hong Kong Medical Association # HKMA Head Office, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong **Advanced Wound Care Management (Code No. TC-AWCM-0107-CNSG)** Organised by: College of Nursing, Hong Kong	Ms. Christine WONG Tel: 2527 8285 Secretariat Tel: 2572 9255 Fax: 2838 6280 8 CME Points
4 FRI 6:00 pm - 8:00 pm (11,18,25)	**Basic Wound Management (Code No. TC-BWC-0107-CNSG)** Organised by: College of Nursing, Hong Kong	Secretariat Tel: 2572 9255 Fax: 2838 6280 21 CME Points
6 SUN 2:00 pm - 5:00 pm 2:00 pm 3:00 pm (13,20,27)	**2007 Paediatrics Update No 1 Pharmacogenomics and Pharmacogenetics in Paediatric Therapies** Organised by: Hong Kong College of Paediatricians Chairman: Prof. CHEUNG Pik Ho Speaker: Various # Lecture Theatre, Hospital Authority, Kowloon **HKMA Structured CME Programme 07/08 (II) - Paediatrics** Organised by: The Hong Kong Medical Association and Queen Elizabeth Hospital Chairman: Dr. T.C. SHIH Speaker: Various # Lecture Theatre, G/F., Block M, Queen Elizabeth Hospital, Kowloon **Dragon Boat Practising Session** Organised by: The Hong Kong Medical Association Chairman: Dr. H YEUNG & Dr. I CHAN # Sai Kung	Ms. Karen YU Tel: 2871 8871 Fax: 2785 1850 3 CME Points Miss Nina HUNG Tel: 2861 1979 (Registration fee is required) 3 CME Points Ms. Dora HO Tel: 2527 8285
7 MON 7:30 pm - 8:30 pm	**A Patient with Persistent Bladder Outlet Obstruction** Organised by: Hong Kong Urological Association Chairman: Dr. HO Kwan Lun Speaker: Dr. Ringo CHU # Seminar Room, G/F, Block A, Queen Elizabeth Hospital, Kowloon	Dr. CHAN Kwok Keung Sammy / Ms. Siddy MA Tel: 2958 6006 Fax: 2958 6076 1 CME Point
8 TUE 8:00 pm	**HKMA Newsletter Editorial Meeting** Organised by: The Hong Kong Medical Association Chairman: Dr. H.H. TSE # HKMA Head Office, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Tammy TAM Tel: 2527 8941
10 THU 2:00 pm (11,12) 6:30 pm - 8:00 pm	**HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2007 (V) - Update on Pharmacotherapy in Diabetes** Organised by: The Hong Kong Medical Association & Hong Kong Sanatorium & Hospital Chairman: Dr. T.C. SHIH Speaker: Dr. LO Kwok Wing # HKMA Dr. Li Shu Pui Professional Education Centre , 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong **176th WMA Council Session** # Divonne-les-Bains, France **(1) AOB? (2) "The Longest Day"** Organised by: Hong Kong Thoracic Society / ACCP (HK & Macau Chapter) Chairperson: Dr. SO Kit Ying Loletta & Dr. LIU Wai To Raymond Speaker: Dr. CHEUNG Chun Yu & Dr. Alwin YEUNG # LG1, Lecture Room, Ruttonjee Hospital, Wanchai	Miss Nina HUNG Tel: 2861 1979 (Registration Fee is required) 1 CME Point Dr. C.Y. TAM / Dr. Maurine M.L. WONG Tel: 2468 5407 Fax: 2468 6188 1 CME Point
12 SAT 2:30 pm	**HKMA Refresher Course for Health Care Providers 2006/2007 (IX) - Primary Care Paediatrics** Organised by: The Hong Kong Medical Association & Our Lady of Maryknoll Hospital Chairman: Dr. T.C. SHIH 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, Hong Kong	Ms. Clara TSANG Tel: 2354 2440 2 CME Points
16 WED 7:00 pm - 9:30 pm	**Guidelines for Hormone Treatment of Women in the Menopausal Transition & Beyond and the Most Advance Treatment for Menopause** Organised by: The Obstetrical and Gynaecological Society of Hong Kong Chairman: Dr. S.K. LAM Speaker: Prof. Wulf H. UTIAN # Ballroom, Sheraton Hotel, Tsim Sha Tsui, Kowloon	Ms. Karen PO Tel: 2599 8851 Fax: 2599 8890 1 CME Point
18 FRI (19)	**IOF Osteoporosis Diagnosis Course** Organised by: The Osteoporosis Society of Hong Kong, The University of Hong Kong (The Osteoporosis Centre & Research Centre of Heart, Brain, Hormone and Healthy Aging) Chairman: Dr. T.C. CHEONG # 6/F, Old Wing, The Hong Kong Convention & Exhibition Centre	Ms. Cissy SOONG Tel: 2855 4353 Fax: 2855 1701
19 SAT (20)	**8th Regional Osteoporosis Conference** Organised by: The Osteoporosis Society of Hong Kong & The University of Hong Kong (The Osteoporosis Centre & Research Centre of Heart, Brain, Hormone & Healthy Aging) Chairman: Dr. T.C. CHEONG # 6/F, Old Wing, The Hong Kong Convention & Exhibition Centre	Ms. Cissy SOONG Tel: 2855 4353 Fax: 2855 1701
23 WED 7:00 pm - 10:00 pm 8:30 am - 12:30 pm (25,30) 6:30 pm - 9:30 pm (28,30)	**FMSHK Executive Committee Council Meeting** Organised by: The Federation of Medical Societies of Hong Kong # 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong 健康服務助理員訓練課程 (Code no. TC-HCA-0207) Organised by: College of Nursing, Hong Kong 醫療護理常用英語初階 (Code No. SUS MH 025 0 (C)) Organised by: College of Nursing, Hong Kong	Ms. Carmen CHEUNG Tel: 2821 3512 Fax: 2865 0345 Secretariat Tel: 2572 9255 Fax: 2838 6280 Secretariat Tel: 2572 9255 Fax: 2838 6280
27 SUN 2:00 pm 2:00 pm	**HKMA Squash Tournament** Organised by: The Hong Kong Medical Association Chairman: Dr. H YEUNG # Kowloon Cricket Club, Kowloon **HKMA Structured CME Programme Year 07/08 (II)** Organised by: The Hong Kong Medical Association and Kwong Wah Hospital Chairman: Dr. T.C. SHIH Speaker: Various # Lecture Theatre, 10/F, Yu Chun Keung Memorial Medical Centre, Kwong Wah Hospital, Kowloon	Ms. Dora HO Tel: 2527 8285 Miss Nina HUNG Tel: 2861 1979 (Registration Fee is required) 3 CME Points
30 WED 6:00 pm - 10:00 pm	病人安全及急救知識 (Code No. SUS MH 004 0 (A)) Organised by: College of Nursing, Hong Kong	Secretariat Tel: 2572 9255 Fax: 2838 6280

Meetings

9-10/6/2007	**Sports Medicine And Rehabilitation Therapy Convention 2007** Organised by: CUHK-WHO Collaborating Centre for Sports Medicine and Health Promotion & Asian Federation of Sports Medicine # Postgraduate Education Centre, Prince of Wales Hospital, Shatin Enquiry: Miss Po-yee TONG & Miss Bell CHUNG Tel: 2632 2798, 2646 1477 Fax: 2646 3020 Email: poyee@ort.cuhk.edu.hk, bellise@ort.cuhk.edu.hk Website: http://www.cuhk.edu.hk/whoctr/smart07/
13-17/06/2007	**The 21st Congress of International Association of Paediatric Dentistry IAPD** Organised by: Hong Kong Society of Paediatric Dentistry # Hong Kong Convention & Exhibition Centre Enquiry: Mr. Daniel CHOK Tel: 2871 8896 Fax: 2871 8898 Email: info@iapd2007.com Website: http://www.iapd2007.com
16-17/6/2007	**Skin Diseases: Integrating Chinese and Western Medicine** Organised by: Hong Kong Association for Integration of Chinese Western Medicine; Hospital Authority; Guangdong Provincial Association of Traditional Chinese Medicine & Guangdong Provincial Hospital of I.C.M. Chairman: Dr. KO Wing Man & Prof. CHEN Da Can # Hong Kong Academy of Medicine, 99 Wong Chuk Hang Road, Aberdeen, Hong Kong Enquiry: Mr. Daniel CHOK / Miss Y.C. YEUNG Tel: 2871 8896, 2871 8815 / 3119 1858 Fax: 2871 8898
12/7/2007	**The 1st Nursing Forum** Organised by: Department of Surgery, Li Ka Shing Faculty of Medicine, The University of Hong Kong; American College of Surgeons, Hong Kong Chapter & Department of Nursing Studies, Li Ka Shing Faculty of Medicine, The University of Hong Kong # Underground Lecture Theatre, New Clinical Building, Queen Mary Hospital, Pokfulam, Hong Kong Enquiry: Forum Secretary Tel: 2855 4885 / 2855 4886 Fax: 2819 3416 Email: hksf@hkucc.hku.hk Website: http://www.hku.hk/surgery
12-14/7/2007	**The 50th Hong Kong Surgical Forum** Organised by: Department of Surgery, Li Ka Shing Faculty of Medicine, The University of Hong Kong & American College of Surgeons, Hong Kong Chapter # Underground Lecture Theatre, New Clinical Building, Queen Mary Hospital, Pokfulam, Hong Kong Enquiry: Forum Secretary Tel: 2855 4885 / 2855 4886 Fax: 2819 3416 Email: hksf@hkucc.hku.hk Website: http://www.hku.hk/surgery
19-22/10/2007	**16th Asian Congress of Surgery & 3rd Chinese Surgical Week** Organised by: Asian Surgical Association & The Chinese Surgical Society of the Chinese Medical Association # Grand Epoch City, Beijing, China Enquiry: ASA Congress Secretariat Tel: 2855 4235 / 2855 4993 Fax: 2818 1186 Email: info@AsianSurgAssoc.org Website: www.AsianSurgAssoc.org
20/10/2007 1:00 pm - 5:30 pm	**The Federation's Annual Scientific Meeting 2007 - Targeted Therapy in Tumours** Organised by: The Federation of Medical Societies of Hong Kong # M/F, Lecture Theatre, Hospital Authority Building, Kowloon Enquiry: Ms. Karen CHU Tel: 2821 3515 Fax: 2865 0345 Website: www.fmshk.org
17-18/11/2007	**Annual Scientific Meeting in Anaesthesiology 2007 - Expanding the Boundaries** Organised by: The Hong Kong College of Anaesthesiology & The Society of Anaesthetists of Hong Kong # Hong Kong Convention and Exhibition Centre Enquiry: CMPMedica Pacific Limited Tel: 2559 5888 Fax: 2559 6910 Email: meeting.hk@asia.cmpmedica.com Website: www.hkca.edu.hk/asm2007.htm

Courses

1,8,15,22,29/6/2007, 6/7/2007	**Basic Wound Management (Code No. TC-BWC-0107-CNSG)** Organised by: College of Nursing, Hong Kong Enquiry: Secretariat Tel: 2572 9255 Fax: 2838 6280
4,6,11,13,18,20,25/6/2007	**醫療護理常用英語初階 (Code No. SUS MH 025 0 (C))** Organised by: College of Nursing, Hong Kong Enquiry: Secretariat Tel: 2572 9255 Fax: 2838 6280
4,6,11/6/2007	**病人安全及急救知識(Code No. SUS MH 004 0 (A))** Organised by: College of Nursing, Hong Kong Enquiry: Secretariat Tel: 2572 9255 Fax: 2838 6280
6,8,13,15,20,22,27,29/6/2007, 4,6,11,13,18,20,25,27/7/2007, 1,3,8,10,15,17,22,24,29,31/8/2007, 5,7,12,14,19,21,28/9/2007, 3,5,10,12,17,24,26,31/10/2007	**健康服務助理員訓練課程 (Code no. TC-HCA-0207)** Organised by: College of Nursing, Hong Kong Enquiry: Secretariat Tel: 2572 9255 Fax: 2838 6280
7,14,21,28/6/2007, 5,12,19,26/7/2007, 2,9/8/2007	**Certificate Course in Mentoring in Nursing (Code No. TC-MN-0107)** Organised by: College of Nursing, Hong Kong Enquiry: Secretariat Tel: 2572 9255 Fax: 2838 6280
9,16/6/2007	**醫院危機處理及職業安全的基本知識 (Code No. SUS MH 003 0 (B))** Organised by: College of Nursing, Hong Kong Enquiry: Secretariat Tel: 2572 9255 Fax: 2838 6280
11,13,18,20/6/2007	**協助病人處理日常生活功能(ADL)技巧(Code No. SUS MH 002 0 (A))** Organised by: College of Nursing, Hong Kong Enquiry: Secretariat Tel: 2572 9255 Fax: 2838 6280
11,13,18,20,25,27/7/2007, 1,3,8,10/8/2007	**醫療護理常用英語進階 (Code No. SUS MH 026 0 (C))** Organised by: College of Nursing, Hong Kong Enquiry: Secretariat Tel: 2572 9255 Fax: 2838 6280
20,27/6/2007, 4,11,18,25/7/2007, 1,8,15,22,29/8/2007, 5/9/2007	**Certificate Course on Quality Management (Code No. TC-CQM-0107)** Organised by: College of Nursing, Hong Kong Enquiry: Secretariat Tel: 2572 9255 Fax: 2838 6280
9,10,11/7/2007	**Definitive Surgical Trauma Care (DSTC) Course** 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 # Skills Development Centre, Department of Surgery, Li Ka Shing Faculty of Medicine, University of Hong Kong Medical Centre, Queen Mary Hospital, Pokfulam, Hong Kong Enquiry: Program Manager Tel: 2855 4885 Fax: 2819 3416 Email: hnsrg@hkucc.hku.hk Website: http://www.hku.hk/surgery
24,25,26/8/2007	**Advanced Trauma Life Support (ATLS) Student Course** 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 # Skills Development Centre, Department of Surgery, Li Ka Shing Faculty of Medicine, University of Hong Kong Medical Centre, Queen Mary Hospital, Pokfulam, Hong Kong Enquiry: Program Manager Tel: 2855 4885 Fax: 2819 3416 Email: hnsrg@hkucc.hku.hk Website: http://www.hku.hk/surgery

Certificate Course on Transplantation and Organ Donation

器 官 移 植 及 器 官 捐 贈 課 程

(Course No. C123)

Jointly organized by

FOR THE FAVOUR OF POSTING

The Federation of Medical Societies of Hong Kong

香 港 醫 學 組 織 聯 會

&

Hong Kong Society of Transplantation

香 港 移 植 學 會

Objective: For education of the public on organ transplant and organ donation.

Date	Title of Lecture	Speaker
Jun 5, 2007	**Renal Transplantation** 腎臟移植	Dr. Choy Bo Ying, Cindy 蔡寶英醫生
Jun 12, 2007	**Liver Transplantation** 肝臟移植	Dr. Chan See Ching 陳詩正醫生
Jun 26, 2007	**Heart Transplantation** 心臟移植 **Lung and Heart-lung Transplantation** 肺移植及心肺移植	Dr. Chau Mo Chee, Elaine 周慕慈醫生 Dr. Wong Chi Fong 王志方醫生
Jul 3, 2007	**Cornea Transplantation** 角膜移植的最新發展	Dr. Cheng Chak Kwan, Arthur 鄭澤鈞醫生
Jul 10, 2007	**Bone Marrow Transplant for Adults** 骨髓移植漫談 **Bone Marrow Transplant for Children** 兒童骨髓移植	Dr. Au Wing Yan 區永仁醫生 Dr. Li Chi Kong 李志光醫生
Jul 17, 2007	**Brain Death and Organ Donation Process** 腦死亡及器官捐贈流程	Ms. Wong Kar Wai, Angela 黃嘉慧女士

Date : June 5, 2007 to July 17, 2007 (Every Tuesday)
Time : 7:00 p.m. – 8:30 p.m.
Venue : Lecture Hall, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong
Course Fee: HK$750 (6 Sessions)
Language : Cantonese (Supplemented with English)
Certificate : Awarded to participants with a minimum attendance of 70%
Enquiry : The Secretariat of the Federation of Medical Societies of Hong Kong
Tel. : 2527 8898　　　Fax: 2865 0345　　　Email: info@fmshk.org

CME/CPE Accreditation applied for
For downloading the application form, please refer to our website: http://www.fmshk.org

THE FEDERATION OF MEDICAL SOCIETIES OF HONG KONG
香 港 醫 學 組 織 聯 會

Duke of Windsor Social Service Building, 4/F, 15 Hennessy Road, Hong Kong
Tel: (852) 2527 8898   Fax: (852) 2865 0345   Homepage: www.fmshk.org   E-mail: info@fmshk.org

Application Form for Certificate Course

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

Correspondence Address: _____

_____

Tel. No. : _____   Fax No.: _____   Age: _____   Sex: _____

Email Address: _____   Occupation: _____

Course Title: ☐ Certificate Course on Transplantation and Organ Donation (C123)
(please tick)

Education :   ☐Secondary   ☐Undergraduate   ☐Postgraduate   ☐Others _____
(please tick)

Fee enclosed (please tick):

☐Cheque No: _____ made payable to **The Federation of Medical Societies of Hong Kong**

☐Cash HK$ _____

_____   _____
            Signature   Date

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

For office use:

Registration confirmed on : _____   Registration Number : _____

Cheque Issuing Bank : _____   Cheque Number: _____

50th Hong Kong Surgical Forum

Thursday to Saturday, 12 - 14 July 2007

1st Hong Kong Nursing Forum

Thursday, 12 July 2007

1983

Overseas Speakers:

Jacques Belghiti, *France*
Kenneth D. Boffard, *South Africa*
Ara W. Darzi, *United Kingdom*
Richard J. Finley, *Canada*
Yuman Fong, *USA*
Ada S. Hinshaw, *USA*
John G. Hunter, *USA*
Jonas T. Johnson, *USA*
Masaki Kitajima, *Japan*
Anne Kolbe, *New Zealand*
Fabrizio Michelassi, *USA*
Carlos A. Pellegrini, *USA*
Anne M. Rafferty, *United Kingdom*
Nathaniel J. Soper, *USA*
Donald D. Trunkey, *USA*

Venue :

Underground Lecture Theatre
Queen Mary Hospital
Pokfulam, Hong Kong

Organisers:

Departments of Surgery and Nursing Studies
Li Ka Shing Faculty of Medicine
The University of Hong Kong
and
Hong Kong Chapter
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Tel: (852) 2855 4885 / 2855 4886
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