HONG KONG MEDICAL FORUM

HONG KONG MEDICAL FORUM,1996

13th-14th July 1996
Hotel Furama Kempinski Hong Kong

PROGRAMME BOOK

UNIVERSITY DEPARTMENT OF MEDICINE
QUEEN MARY HOSPITAL

THE UNIVERSITY OF HONG KONG

WELCOME MESSAGE

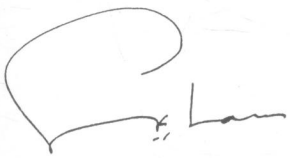
Dear Friends and Colleagues,

Recent advances of medicine have been so swift, and many of the subspecialities of internal medicine have been so differentiated that it is not easy for a present-day physician to determine what medicine is core and central to his or her office and hospital practice. It is with this practising physician in mind that the Department of Medicine, The University of Hong Kong at Queen Mary Hospital runs this theme-oriented, course-designed Medical Forum. It is also a response to the CME programme of the Hong Kong Academy of Medicine.

The Medical Forum this summer focuses on osteoporosis, viral infections, respiratory problems, and heart disorders.

On behalf of the Organizing Committee, I would like to express our heartfelt thanks for your participation. Please do not hesitate to give us your comments and feedback to help us plan your future Medical Forum.

Yours sincerely,



Shiu-kum Lam
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ORGANIZING COMMITTEE

Chairperson :	Dr. Mary IP
Members :	Prof. Shiu-kum LAM
	Prof. Wah-kit LAM
	Prof. Karen LAM
	Prof. Chu-pak LAU
	Dr. Ignatius CHENG
	Dr. Kenneth TSANG
Co-ordinator :	Miss Denise YU
Secretary :	Ms Joan LEE

TIME	ACTIVITY	SPEAKER/LOCATION
13:00-14:00	**Registration**	Coral Room Foyer, 3/F
13:30-14:00	**Welcome Cocktail Reception** Hosted by Astra Pharmaceuticals (HK) Ltd.	Coral Room, 3/F
14:00-14:10	**Opening Ceremony**	Coral Room, 3/F
14:10-15:10	**Plenary: *Prevention and Screening in Osteoporosis*** Chairperson: Prof. Rosie Young (HK)	Prof. Ego Seeman (Aust)
15:10-16:25	**Symposium: Osteoporosis** Chairpersons: Prof. Ego Seeman (Aust) & Prof. Karen Lam (HK)	Coral Room, 3/F
15:10-15:30	*The Epidemiology of Osteoporotic Fracture of Proximal Femur and Its Outcome in Hong Kong*	Dr. Peter KY Chiu (HK)
15:30-15:50	*The Role of Calcium and Vitamin D in Osteoporosis*	Dr. Annie Kung (HK)
15:50-16:10	*Inhibitors of Bone Resorption and Stimulators of Bone Formation*	Prof. Ego Seeman (Aust)
16:10-16:25	Discussion/Question Time	
16:25-16:45	**Coffee Break**	Coral Room, 3/F
16:45-18:00	**Symposium: Update Issues in Infections** Chairpersons: Prof. Shiu-kum Lam (HK) & Prof. Cyrus Kumana (HK)	Coral Room, 3/F
16:45-17:05	*Update on Methods of Diagnosis for Tuberculosis*	Dr. Kwok-yung Yuen (HK)
17:05-17:25	*HIV/AIDS: Learning from New Findings*	Dr. Shui-shan Lee (HK)
17:25-17:45	*Rapid Diagnosis of Cytomegalovirus and Other Viral Infections*	Dr. Joseph SM Peiris (HK)
17:45-18:00	Discussion/Question Time	

TIME	ACTIVITY	SPEAKER/LOCATION
09:30-10:30	**Registration**	Jade Ballroom Foyer, 3/F
10:30-11:30	**Plenary: *Gene Therapy for Respiratory Disease*** Chairperson: Prof. Wah-kit Lam (HK)	Dr. Duncan Geddes (UK)
11:30-12:45	**Symposium: Respiratory Medicine** Chairpersons: Dr. Loretta Yam (HK) & Dr. Kenneth Tsang (HK)	Jade Ballroom, 3/F
11:30-11:50	*Advances & Controversies in Sleep Related Breathing Disorders*	Dr. Mary Ip (HK)
11:50-12:10	*The Genetics of Asthma*	Dr. Duncan Geddes (UK)
12:10-12:30	*Current Treatment of Non-Small Cell Carcinoma of Lung (NSCLC) Based on Staging*	Prof. Wah-kit Lam (HK)
12:30-12:45	Discussion/Question Time	
12:45-14:00	**Luncheon** Hosted by Rhône-Poulenc Rorer Ltd.	Jade Ballroom, 3/F
14:00-15:00	**Plenary: *Strategies for the Treatment of Heart Failure*** Chairperson: Prof. Chu-pak Lau (HK)	Dr. Hamid Ikram (NZ)
15:00-16:15	**Symposium: Cardiovascular Medicine** Chairpersons: Dr. Stephen Lee (HK) & Dr. Cheuk-kit Wong (HK)	Jade Ballroom, 3/F
15:00-15:20	*Management of Acute Myocardial Infarction*	Prof. Chu-pak Lau (HK)
15:20-15:40	*Management of Coronary Artery Disease: Drugs, PTCA or Surgery?*	Dr. David Ho (HK)
15:40-16:00	*Diastolic Heart Failure*	Dr. Hamid Ikram (NZ)
16:00-16:15	Discussion/Question Time	
16:15-16:30	**Closing Speech**	Prof. Shiu-kum Lam (HK)

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Prevention and Screening in Osteoporosis
by
Prof. Ego Seeman

The presence of symptoms gives the physician and the patient a clear endpoint to treat. The management of the asymptomatic postmenopausal women is a dilemma because neither the doctor nor patient have a measure of what is being treated. A decision is made based in the belief that the treatment will reduce risk of an event that may never happen at the price of exposing this patient to side effects.

In preventative care in osteoporosis, the ultimate aim is not to prevent bone loss, nor is the aim to prevent fractures. The aim is to reduce over all morbidity and mortality. A small increase in side effects or adverse events can shift the balance from net benefit to net loss. The important principle of treatment in preventative health is that treatment must be safe because many will be treated with no certainty of benefit.

Hormone Replacement Therapy

Hormone replacement therapy (HRT) given at menopause will prevent bone loss for as long as it is given. Bone already lost may be restored if HRT is started within about 3 years of menopause. There is evidence that HRT in the elderly reduces bone turnover, increases bone density by 5 to 8 %, even in women in their mid seventies, and may reduce fracture rates. If HRT is stopped, bone loss will resume. There are several reasons for considering initiating treatment later: (i) long term compliance with HRT is poor, (ii) HRT probably must be given permanently (iii) HRT can increase BMD in the elderly (iv) bone loss does not diminish in older persons but accelerates.

Unopposed oestrogen therapy increases the risk for endometrial cancer. When a progestin is given the risk is less than that observed in the population. A major concern regarding oestrogen treatment is that there may be an increased risk for breast cancer. The increase in risk is reported to be about 20 % in some studies. Many studies do not support the view that HRT increases the risk for breast cancer.

Menopause may be an independent risk factor contributing to morbidity and mortality in women and HRT may be protective. The view that cardiovascular mortality is increased by menopause is derived largely from uncontrolled observational studies. The greatest risk reported for heart disease are found in oophorectomised women. HRT may be protective. The beneficial effects of oestrogens involve a reduction in LDL cholesterol and an increase in HDL cholesterol. This effect may be nullified by concomitant administration of some progestins. However, vessel wall compliance, plaque formation and blood flow, reduced oxidative change, reduce foam cell formation and lipid accumulation may contribute and studies in primates suggest that these effects are not reversed by progestins.

The natural oestrogens, conjugated equine oestrogen (premarin 0.625-1.25 mg/day), oestradiol valerate or progynova 1-2 mg/day and piperazine oestrone sulphate (ogen) 0.625-1.25 mg/day are commonly used. Medroxyprogesterone has the smallest effect on plasma lipids and is given in a dose of 5-10 mg/day for 12-14 days. Oestrogen is given daily without stopping treatment. A progestin is added from days 1 to 13 each month to prevent endometrial hyperplasia. Cyclical bleeding may occur on day 10 lasting for several days. A progestin is not needed in a women who has had a hysterectomy.

A combined continuous approach may be used in older women. Both the oestrogen and progestogen are given daily without a break. Younger women should use the cyclic hormone treatment. Transdermal oestrogens have been shown to prevent bone loss but may have less beneficial effects on lipid subfractions. LDL cholesterol is reduced but HDL cholesterol may not be increased as reported with oral oestrogens.

Use of Bone Densitometry

Bone density should be measured if the result of the test will influence the decision. Women presenting at the time of menopause with bone mass above - 1 SD of the young normal mean do not require HRT to maintain bone mass. Women with BMD between -1 and -2 SD should consider HRT. Women with BMD below -2 to -2.5 SD should be encouraged to use HRT or other treatments.

Other Methods for Prevention of Bone Loss at Menopause

There is little evidence that calcium prevents bone loss at menopause. Initial studies using bisphosphonate therapy are promising. Calcitonin must be given by injection. There is no evidence that exercise during the menopause will prevent bone loss. Exercise plus calcium may reduce the rate of bone loss but it appears to be less effective than HRT.

Risk Factors

Smoking for 25 to 30 pack-years (i.e. about 20 cigarettes daily for 25 to 30 years) is associated with a reduction in bone mass of about 8 to 10 % and is associated with a doubling in risk for fracture. Other risk factors include low body weight (BMI < 18), excessive alcohol intake, a high salt diet, excessive phosphate, low calcium intake, high protein diets, lack of exercise.

Risk factors such as tobacco use, excessive alcohol intake, low body weight, use of medications that may increase the frequency or severity of falls should be identified and corrected. However, historical risk factors do not predict whether a person has a low bone mass. Nor have these risk factors proven useful in discriminating persons with fractures from those without fractures. This does not negate the relevance of correcting a risk factor which may contribute to reducing bone loss in an individual. The point is that the presence or absence of the risk factor cannot be used as a predictor of fracture risk. The best measure of fracture risk is a measure of bone density.

Falls and Trauma

Falls are a necessary condition for hip and forearm fracture. Risk factors for falls include advanced age, female gender, being ambulatory, disorientation, benzodiazepimes, barbiturates, impaired vision, lower limb dysfunction, neurological conditions. Hip protectors reduce the incidence of hip fractures but are poorly tolerated. Removal of environmental hazards (loose rugs, cords, grandchildren's toys), good lighting may reduce falls. Exercise to maintain mobility and quadriceps strength may reduce the chance of falls.

Diet and Exercise

Dietary calcium is safe. It is reasonable to recommend an intake of about 1200 mg/day after menopause. Although evidence is not strong, a high intake of salt, phosphate, and caffeine may contribute to bone loss and should be moderated.

Immobilisation causes bone loss. This does not prove that exercise causes bone gain. The available evidence suggests that bone mass can be preserved or increased slightly with supervised exercise in postmenopausal women, but the increase is small. It is unlikely that exercise can restore bone mass. Exercise associated with spine flexion may increase fracture rates and should be avoided. Weight bearing exercise should be recommended to maintain components of fitness such as muscle strength, mobility, flexibility and agility which may reduce the frequency and severity of falls.

Practical Assessment

The investigations outlined are guidelines only. Tests should be done if the information obtained will influence management.

Gynaecological History

- Late menarche : consider anorexia nervosa
- Primary amenorrhea : consider anorexia nervosa or Turners syndrome
- Secondary amenorrhea : consider anorexia nervosa, stress, hyperprolactinaemia or oligomenoerrhea (suggesting anovulatory cycles or prolongation of the luteal phase which may be associated with lower bone mass)
- Early menopause : tobacco use or pituitary disease
- Oophorectomy : may be associated with low bone mass
- History of hysterectomy : the most common reason women stop HRT is the recurrence of menstrual bleeding
- Oestrogen contraception : there is some evidence that this is associated with higher bone mass
- Nulliparity : may be associated with lower bone density
- Prolonged lactation : may be associated with lower bone mass

Previous or current Illnesses

- Anorexia nervosa, competitive athletics with amenorrhea, amenorrhea, galactorrhea (hyperprolactinaemia)
- Diarrhea (malabsorption, celiac disease), gastrectomy
- Polyuria, renal stones, abdominal pains (primary hyperparathyroidism)
- Weight gain, bruising, stretch marks (Cushing's syndrome)
- Weight loss, tremor, family history of thyroid disease (thyrotoxicosis)
- Alcohol intake (liver disease)

Family and past history, nutrition and drug history

- A family history of fractures. Daughters of women with hip or spine fractures may have lower bone density than expected for their age. A family history of breast cancer is a contraindication to HRT. Previous fracture, even in childhood is a risk factor for fractures. Nontraumatic fractures or loss of height (suggests previous vertebral fractures). The risk of fracture is increased in women with fractures in the past.
- Assess dietary calcium intake, protein, salt, phosphate, caffeine consumption.
- Glucocorticosteroids, dilantin, heparin, thyroxine, antacids, tobacco, excessive ethanol use

Examination : Caucasian or Asian origin

- Measure Height (fall in height from youth or from previous measurement suggests fractures)
- Low body weight (usually no cause, consider anorexia nervosa, thyrotoxicosis or malignancy)
- Thin skin, bruising, central obesity, striae or hypertension (corticosteroid excess)
- Hepatomegaly, splenomegaly (lymphoma, alcoholic liver disease, hemochromatosis, biliary cirrhosis)

Investigations

- Serum calcium (normal in osteoporosis, high (hyperparathyroidism, myeloma, metastatic cancer of breast, kidney other sites), low (osteomalacia, metastatic cancer prostate)
- Phosphate (normal in osteoporosis)
- Alkaline phosphatase
- Protein electrophoresis (myeloma, may be normal in nonsecretory myeloma)
- FBE suspect any mild anemia (myeloma, malabsorption)
- Liver function tests (liver disease, hemochromatosis), cortisols (am,pm), 24 hour urine free cortisols, thyroid function tests, 25 hydroxy vitamin D, urinary calcium excretion, serum and urine markers of bone turnover, parathyroid hormone

Radiologic and Bone Density Measurement

- Radiolucency may be due to technical factors. Presence of asymptomatic fractures may be due to early clinical disease or due to epiphysitis (Scheurmann's disease) which is not associated with low BMD
- Bone density should be measured if it will influence management

The Epidemiology of Osteoporotic Fracture of Proximal Femur and Its Outcome in Hong Kong

by

Dr. Peter Kwong-yuen Chiu

Osteoporotic fracture of the proximal femur is probably the most important orthopaedic problem that affects the elderly population. There has been very little information on its incidence in the Oriental populations. Chalmers and Ho (1970) reported that the annual fracture rate for Hong Kong Chinese who were 75 year-old or above was around 0.4% for both sexes from 1965 to 1967. These were significantly lower than the Caucasian fracture rates at that time. To find out the recent local fracture rates, we audited the patients admitted into Queen Mary Hospital, and examined the census statistics of Hong Kong Island published by the Hong Kong Government in 1981, 1986 and 1991. Compared with what were reported by Chalmers and Ho, the fracture rates for 50 year-old and above as a whole group from 1981 to 1991 were doubled for male and tripled for female. For the sex and age specific fracture incidences from 1981 to 1991, there was an obvious increase for women who were 65 year-old or above, and for men who were 75 year-old and above. For those who were 75 year-old or above, 1.3% of female population and 0.7% of male population sustained osteoporotic fracture of the proximal femur in 1991. The dramatic increase could be explained by the industrialization and urbanization process in Hong Kong over the past 20 years. The decrease in the proportion of the population who undertook heavy manual work eliminated the protective effect of physical activity on bone mass, and resulted in more osteoporotic fractures of the proximal femur.

We also looked at the factors that might predict the outcome after surgery for such fractures. A prospective study on 1,500 consecutive elderly patients admitted from 1986 to 1990 was analyzed. Using multivariate analysis, three independent pre-operative factors were found to be significant. They were the age of patient, the walking ability before the fracture and the presence of concomitant medical disease. One or more concomitant medical diseases were present in 802 (53.5%) patients. If the patients suffered from concomitant medical disease, the risk of having post-operative medical complications such as pneumonia, cardiac problem, pressure sore or venous thrombosis was significantly higher ($p<0.00001$). The hospital stay was longer ($p<0.01$) than if there was no medical disease. Fewer patients regained the pre-fracture walking ability ($p<0.00001$). The cumulative mortality rates at three months, one year and two years after surgery were two to four times higher ($p<0.0001$) if the patients had medical diseases. At the time of the final follow-up, they were more likely ($p<0.0001$) to be wheelchair-bound or bed-bound. Concomitant medical disease was thus an important prognostic factor. Patients who suffer from osteoporotic fracture of the proximal femur must be assessed carefully and any concomitant medical disease must be tackled aggressively.

The Role of Calcium and Vitamin D in Osteoporosis
by
Dr. Annie WC Kung

A number of observational and interventional studies confirm the role of calcium and vitamin D in the development and maintenance of bone integrity. An inadequate intake or malabsorption of calcium results in secondary hyperparathyroidism and increased bone turnover. Age-related increases in PTH level can be reversed by raising calcium intake. Increasing daily calcium intake to 1000 to 1500 mg reduces bone loss in postmenopausal women. The bioavailability of calcium depends on the nature of the calcium salts and other factors affecting calcium absorption. Calcium-fortified food may be a solution to diet with low calcium content, including Chinese diet. Calcium supplementation is also a key adjunctive therapy with estrogen and bisphosphonates as most women do not receive adequate calcium intake. With aging, calcium absorption declines as a result of decreased skin synthesis of vitamin D, decreased renal activation of vitamin D and a reduction of intestinal vitamin D receptors. Institutionalized subjects and others with little sun exposure are dependent upon dietary sources for vitamin D. Vitamin D is limited in the food chain and intake is often inadequate without supplementation. In those elderly with vitamin D deficiency, vitamin D supplementation is capable of reducing bone loss and the incidence of nonvertebral fractures. Active metabolites of vitamin D are being used to treat osteoporosis. These compounds are safe in patients with low calcium intake but require monitoring for hypercalciuria.

Inhibitors of Bone Resorption and Stimulators of Bone Formation
by
Prof. Ego Seeman

Bone loss occurs when there is an imbalance at the level of the basic multicellular unit (BMU) between the amount of bone resorbed and the amount replaced. In the setting of this imbalance, the higher the rate of bone turnover, the greater the bone loss because more of these sites in negative balance are actively 'turning over'. Although the negative balance may be due to deeper resorption, the evidence for this is weak. In general, 'increased' resorption refers to more actively turning over sites rather than deeper resorption sites, even after menopause. Indeed, the evidence suggests that resorption depth decreases with age.

The negative balance appears to be due to failure of bone formation resulting in a fall in mean wall thickness. Inhibitors of bone resorption reduce the rate of bone turnover so that initially, the increase in bone mineral density (BMD) is the result of bone formation going to completion and filling of resorption spaces created in the cycle before treatment was started. This is a transient remodeling. BMD usually increases by 3 to 5 percent due to this mechanism. If the drug has no effect on bone balance at the BMU, bone loss will proceed from the higher level achieved by the filling of the remodelling space. The new rate of loss is determined by the effect on turnover. If bone loss was 1%/year and turnover was halved, then bone loss proceeds at 0.5%/year. If the resorption inhibitor also improves bone balance by reducing cavity size or increasing bone formation, then bone loss will be slowed further. If the drug produces a positive balance at the BMU then it is theoretically advantageous to now increase bone turnover as each cycle should deposit more bone.

The higher the pretreatment bone turnover, the greater the increase in BMD in response to antiresorption agents such as calcitonin (CT) and oestrogen (E). E reduces bone turnover and increases BMD, even in the elderly, at the spine with less effect at appendicular sites. The increase in BMD with the bisphosphonate, alendronate, appears to be similar, irrespective of the rate of turnover. 'Turnover' is a surface phenomenon; the lesser effect of drugs on cortical sites is probably the result of cortical bone having less surface than trabecular bone per unit bone mass. (The lower turnover of cortical bone is a function of the lower surface to bone volume ratio.)

Whether these agents increase bone formation at the level of the BMU is uncertain. There is evidence for a continued increase in BMD in the second year and a positive effect on bone balance at the BMU using alendronate. Animal experiments suggest oestrogen (E) increases bone formation.

The large increases in BMD using norethisterone are unverified and comparative studies with other progestins should be undertaken. Medroxyprogesterone has not been shown to increase BMD. Raloxifene, a new oestrogen agonist free of some side effects that reduce compliance with oestrogen is being studied. Vitamin D analogs are classified as resorption inhibitors but the effects may be dose specific, with bone loss occurring at higher doses. Several studies suggest a reduction in bone loss or modest increases of 1 to 3 % using these agents.

The seemingly small increase in BMD obtained using resorption inhibitors is likely to be biologically 'worthwhile' as there is an exponential increase in fragility as bone density falls. Preventing further bone loss, which is eminently achievable, is likely to reduce the increased fracture risk that would otherwise occur had treatment not been given. Bone loss continues in the elderly and does not decelerate. It probably accelerates because endocortical resorption 'trabecularizes' cortical bone increasing the effective surface of cortical bone available for resorption to take place.

The stimulators of bone formation result in large increases in BMD but whether these changes translate to increased bone strength is uncertain. Fluoride (F) therapy has been widely studied with consistent increase in bone density of 4-6 % annually but the evidence for reduced fracture rates despite the increase in BMD is weak or negative. Animal experiments consistently demonstrate reduced bone strength. The drug should remain a research tool. The anabolic effects of F warrant further study, in particular with E, provided that the study design directly addresses the issue of the narrow toxic-therapeutic window. The use of parathyroid hormone (PTH) in low dose intermittent regimens as an anabolic agent has produced consistent increases in BMD at the spine similar to that of F, with variable changes in the appendicular skeleton. PTH increases bone strength, and with E, may increase connectivity. Initial studies in humans are encouraging but antifracture efficacy studies are not available. Studies in animals have shown increases in the breaking strength of bone. Anabolic steroids may increase BMD but are associated with unacceptable side effects.

Combined therapy using E and bisphosphonates is under study. Initial comparative studies suggest that clodronate and oestrogen both prevent bone loss with equal efficacy. One study comparing oestrogen, etidronate and both with placebo suggests that the effect on BMD is better with the combination. Combining a bisphosphonate with PTH has been attempted in animals and has not been proven to be advantageous in terms of changes in BMD or bone strength. Combining growth hormone plus IGF-1 with APD has resulted in increased bone strength over either agent alone.

The clinical test of a drug is its anti-fracture efficacy. Anti-vertebral fracture efficacy has been shown with etidronate, E patch, CT, and 1,25 dihydroxyvitamin D. Two studies using F were positive, 2 were negative. Hip fractures have been neglected. One study showed anti- hip fracture efficacy using vitamin D and calcium in nursing home dwellers, another showed no effect in community dwellers. There have been no anti-fracture studies in men or in corticosteroid related osteoporosis. Lack of independently repeated demonstration of efficacy, small fracture numbers, unplanned data pooling to attain significance leave uncertainty.

Alendronate, a new bisphosphonate was recently rigorously evaluated in a multicentre double blind randomized trial involving 994 postmenopausal women (mean age 64 years) at centres in the USA and internationally. Patients were included if BMD was 2.5 SD or more below the young normal mean. Patients received placebo or alendronate (ALN, 5 or 10 mg/day for 3 years, or 20 mg/day for 2 years then 5 mg/day for 1 year). All received 1 g elemental calcium as the carbonate. Analysis of anti-vertebral fracture efficacy was based on preplanned pooling of all treatments. Analysis of non-vertebral fractures was based on preplanned pooling of this protocol and 3 other studies. At 3 years, BMD was higher by 8.8 ± 0.4% (lumbar spine), 5.9 ± 0.5% (femoral neck) and 7.8 ± 0.6 (trochanter) in patients receiving 10 mg/day relative to the placebo group. One or more new vertebral fractures occurred in 17 of 526 patients receiving ALN (3.2%) and 22 of 355 patients receiving placebo (6.2%) (a 48% reduction, $p = 0.034$). Among women having fractures, 3 of 17 (18%) ALN treated patients and 15 of 22 (68%) receiving placebo had two or more vertebral fractures. That is, 0.6% of 526 given ALN vs 4.2% of 355 given placebo had multiple vertebral fractures (a risk reduction of 85%, $p < 0.001$). Among women sustaining vertebral fractures, height loss was 23.3 mm (~ 0.5 standard deviations) in the placebo and 5.9 mm in patients receiving ALN. The numbers needed to prevent one vertebral fracture when BMD < 2.5 SD, plus (i) age 48-80 is 33, (ii) over 65 years of age is 18, (iii) over 65 years plus fracture at baseline is 7-8. Non-vertebral fractures occurred in 73 of 1012 ALN treated women and 60 of 590 placebo group. After 3 years, the respective cumulative incidences were 9% (ALN) and 12.6% (placebo) or, 3.3 (ALN) vs 4.5 (placebo) women with fractures per 100 pt-years. There was a 29% reduction in absolute risk among women treated with ALN from non-vertebral fractures compared to placebo ($p = 0.048$).

In conclusion, there is an imperative to treat as bone loss accelerates in old age increasing fracture risk. Antiresorptive agents such as bisphosphonates and oestrogens, singly and in combination, hold promise as agents which reduce the risk of fracture. Further studies are needed focusing on surface specific therapy aimed at increasing trabecular thickness number and connectivity, and cortical thickness by influencing bone turnover on periosteal and endosteal surfaces.

Update on Methods of Diagnosis for Tuberculosis
by
Dr. Kwok-yung Yuen

Global and local significance of tuberculosis

The World Health Organization estimated that 4 to 5 million new highly infectious smear-positve case of pulmonary tuberculosis occur world-wide every year. With a rise in annual notification of tuberculosis in Hong Kong from 6283 in 1991 to 6537 cases in 1993, the incidence greatly exceeds the figure of 7 or less per 100,000 reported from other developed countries. This worrying situation will be sustained because of the increasing incidence of infection by the human immunodeficiency virus in our population and the influx of migrants from mainland China with the approach of 1997. Successful control of tuberculosis depends on 1) rapid detectionof *Mycobacterium tuberculosis* in patients' specimen, 2) early treatment with drugs to which *M. tuberculosis* is susceptible, and 3) efficient isolation of infectious cases and contact tracing. Unfortunately the presently available techniques are either insensitive, non-specific, slow in turnaround time (TAT), expensive†, labour-intensive or radiohazardous*(Table).

Table - The conventional laboratory tests for the control of tuberculosis

A. Available Diagnostic Techniques		
	Sensitivity Limit/Specificity	TAT
OAO/ZN smear	100 AFB/poor	2 hrs
LJ culture	10 to 100 AFB/poor	4 wks
BACTEC culture*	1 to 10 AFB/good	14 days
GUINEA PIGt	1 to 10 AFB/good	3-4 wks
ANTIGEN (ELISA)	poor/good	6 hrs
TBSA/(GLC-MS)	good/poor	4 hrs
Antibody (ELISA)	variable/variable	6 hrs
Immunospot test	variable/unknown	48 hrs
Mantoux test	variable/variable	72 hrs
B. Available Susceptibility Test		
	Labour intensity	TAT
MIC ratio	high	14 days
Proportional method	moderate	14 days
BACTEC (radiometric)*	low	4-5 days
C. Available Typing Methods		
	Typeability	Feasibility
Biotyping	poor	good
Antibiogram	poor	good
Phage typing	poor	good

The achievement and limitation of PCR in the diagnosis of tuberculosis

The gold standard for diagnosis depends on a positive culture but many specimens such as expectorated sputum have to undergo harsh decontamination procedures which effectively kill up to 90% of the mycobacteria present. The Mantoux test, serology by ELISA and immunospot assay enumerating B cells secreting anti-BCG antibody depend on the competence of the host to mount a T or B cell response. These tests are also confounded by non-specific responses mounted by hosts due to previous exposure to environmental mycobacteria or BCG vaccination. Since the introduction of polymerase chain reaction into the arena of diagnostic mycobacteriology, we have established the usefulness of this technique for the rapid detection of *M. tuberculosis* from respiratory secretion, rapid typing of isolates by amplityping and rapid detection of gene mutation encoding resistance to anti-tuberculous agents. However, the presently available nested PCR assay is found to be less sensitive for the detection of paucibacillary disease in extrapulmonary tuberculosis, subclinical disease of household contacts, some smear-negative pulmonary tuberculosis and in formalin fixed and paraffinished tissue specimens. The lower sensitivity of the assay for extrapulmonary clinical specimens is related to the presence of inhibitors and the paucibacillary nature of specimens such as cerebrospinal fluid, pleural fluid, urine, bone marrow and other tissues.

HIV/AIDS: Learning from New Findings
by
Dr. Shui-shan Lee

It has been 15 years since the first cases of AIDS were described in the United States. Medical advances have unfolded many of the mysteries surrounding AIDS and HIV, its causative virus. New ideas are emerging, amid the old verdict that the infection is still incurable.

Natural History of HIV Infection

About 50% of the infected people progress to AIDS in the course of 10 years. One-tenth deteriorated rapidly in the first 2-3 years. At the other end of the spectrum, some 5-10% are non-progressors after 7-10 years or longer. New evidence has emerged supporting the observation that a minority are not infected following exposure. Viral clearance is possible, and the subject is receiving wide attention.

Preventing HIV Infection

Vaccine research has continued to generate promising results, but its role in practice remains doubtful. Two other studies are, however, bringing hope to preventing HIV infection in clinical settings. The ACTG076 concluded that zidovudine could lead to a substantial reduction of the risk of perinatal HIV transmission. On the other hand, a retrospective study published in MMWR reported protective effects of the same drug in the management of needlestick injuries.

Treatment

Combination therapy is producing promising results in the treatment of HIV/AIDS. Protease inhibitor, a new class of antiretroviral drugs, has recently been taken from the bench to bedside. The options which can be offered to patients have increased substantially. The question now is not so much "why", but "who" and "when" to initiate treatment. Finally, some groups are measuring viral load as a means of monitoring disease activity and treatment response. It is hopeful that the quality of life of HIV/AIDS patients would improve further in years to come.

Rapid Diagnosis of Cytomegalovirus and Other Viral Infections

by

Dr. Joseph Sriyal Malik Peiris

Diagnosis based on virus culture and serology on paired sera usually take many weeks. However, rapid virus diagnosis based on virus antigen or nucleic acid detection and rapid shell vial culture methods have resulted in results being available within a few hours or days.

Cytomegalovirus is of particular importance as a pathogen in the immunocompromised patient where antiviral therapy or prophylaxis may be life saving. It can cause congenital or peri-natal infection in the neonate. Primary infection in the immuno-competent older child or adult may cause a "mononucleosis like" illness, hepatitis and the Guillain-Barre syndrome. Conventional culture for CMV takes 2-4 weeks. However, using shell vial centrifugation cultures (DEAFF test), CMV may be cultured rapidly (i.e. 1-4 days). CMV viraemia can be detected by looking for CMV pp65 antigen in buffy coat cells by immunofluorescence (CMV antigenaemia) or CMV DNA by PCR. CMV PCR on CSF is also useful in diagnosing CMV encephalitis in the immunocompromised patients, detection of CMV viraemia (CMV pp65 antigen or PCR in buffy coat cells) together with demonstration of virus by the shell vial assay in the relevant biopsy (if available) are the most useful. Many studies have shown that culture of CMV from urine or saliva is poorly correlated with CMV disease because asymptomatic reactivation with virus shedding from these sites is common. CMV pp65 antigenaemia has the added advantage that it is semi-quantitative, the level of viraemia being correlated with the risk of clinical disease (in contrast to asymptomatic reactivation). Response to therapy can be monitored by a decrease in the number of antigen positive cells. In severely neutropenic patients however (e.g. bone marrow transplant recipients) the added sensitivity of PCR is needed to guide diagnosis and management.

On the other hand, in the investigation of congenital infection, shell vial culture of the urine is often all that is required. There is a high level of virus shedding in the urine, and detection of virus within 21 days of birth is proof of congenital infection. Diagnosis of CMV in the immuno-competent adult or child may be accomplished by a combination of IgM serology, rapid culture of urine or saliva, and may occasionally require supporting evidence from CMV pp65 antigenaemia.

Similar strategies for rapid diagnosis are now applicable to other viruses as well. Some examples include respiratory virus or herpes simplex antigen detection in bronchial washings or tracheal aspirates; varicella-zoster or herpes simplex antigen detection and rapid culture from skin vesicle scrapings; and herpes simplex DNA detection by PCR for the diagnosis of encephalitis.

Gene Therapy for Respiratory Disease
by
Dr. Duncan M Geddes

The respiratory tract is ideally suited to the development of genetic based therapies. This is partly because the organ is accessible via the nebulised route and partly because there are a number of relatively common well defined inherited lung diseases as a first clinical target. These include cystic fibrosis and alpha-1 antitrypsin deficiency emphysema. There are also active research programmes into the gene therapy of lung cancer including mesothelioma and as the genetic basis of asthma and pulmonary fibrosis becomes better understood it is possible that these multifactorial diseases will also be amenable to gene therapy approaches.

There are two main approaches to transferring therapeutic genes. The first is to use a viral vector and the adenovirus has attracted the most attention, the second is to use liposomes and research is proceeding very fast in this area. Adenoviruses have been shown to transfer genes efficiently to pulmonary epithelium in a number of animal models with expression of a marker protein such as ß-galactosidase or a possible therapeutic protein such as CFTR or alpha-1 antitrypsin. In vivo gene delivery has proved more difficult than in vitro and a number of problems have been defined which are now being overcome. These include the immune response to the adenovirus and its associated proteins and the problem of down regulation of gene transfer with subsequent dosing. New viral vectors are being developed which perform better than the first generation but there are still many problems to be overcome.

Cationic lipids are less efficient than viruses at transferring genes in vitro but have the advantages that they are not toxic and they are not immunogenic. In vivo gene transfer into CF mice has shown expression of the gene and correction of the electrophysiological defect of CF as a basis to human trials. Liposome mediated gene transfer has been demonstrated following instillation into the nose in CF volunteers with partial correction of the CF ion transport defect and lung trials are now beginning. The main challenges are to improve both liposomal and adenoviral gene transfer efficiency and to develop efficient non-toxic agents which can be given by nebulisation. Progress is rapid but it will still be some years before the initial optimism for gene based therapies can be fully realised.

Advances and Controversies in Sleep Related Breathing Disorders
by
Dr. Mary Ip

Advancement in medical science often evoke controversies, especially in the early phases of the new knowledge or technology. Some of the recent issues regarding obstructive sleep apnoea are presented and discussed.

Long Term Cardiovascular Morbidity of OSA

These include hypertension, ischaemic heart disease, arrhythmias and strokes. It has long been observed that OSA and hypertension are associated, and investigators have attempted for years to assess the relationship between these two illnesses. They share many confounding variables, including the high prevalence of both conditions, increased incidence of both with ageing, obesity and male sex. Moreover, antihypertensive medications may also adversely affect OSA. Earlier works have sided on a comorbid association, while more recent studies tend to support an independent effect of OSA on hypertension, and there are still many questions regarding the relationship between these two conditions. Other aspects of cardiovascular morbidity are also undergoing investigations, including OSA and atherogenesis.

Threshold of Active Treatment

This relates to our knowledge of the long term morbidity and mortality risks of OSA. Most of these data come from analysis of patients who have not received active treatment in the past. Current recommendations for indication of treatment are therefore based on a combination of epidemiological data and individual clinician's assessment of the individual patient. For those with severe symptoms and high apnoea scoring, the indication is clear, while the grey zone for borderline cases is high, especially when the patients have few symptoms.

"Intelligent" CPAP -

Since there is variation in the degree and duration from event to event throughout one night, and from night to night, the development of a CPAP device that would adjusts the pressure for each hypopneic/apnoeic event would have two advantages: it can be used for auto-titration of the overall CPAP pressure requirement, and if used on long term basis, may yield lowest requirement of pressure for best abolition of events. So far, there is reasonable evidence to suggest its utility for auto-titration while its benefits in long term use remains to be determined.

Implications of Diagnosis of OSA on "High-Risk" Jobs

A cardinal feature of OSA is excessive daytime sleepiness. It has been shown that the condition predisposes to traffic accidents. By similar analogy, there may also be an accident-prone risk for other job-related or domestic activities. The diagnosis of OSA will thus have profound implications on those whose jobs involve public safety. Fortunately, symptoms are highly amenable to therapy although non-compliance or unintentional omission may be disastrous to oneself and other individuals.

The Genetics of Asthma
by
Dr. Duncan M Geddes

It has long been known that atopy and asthma runs in families and there has been a recent research effort to define the genes responsible. The basic approach is to define the asthma or allergy phenotype and then to do genetic linkage studies in affected families. The first approach was to examine the inheritance of high IgE levels using IgE as a marker of allergy. A number of models of inheritance were proposed during the 1970's and 80's but renewed interest in the field developed in 1989 when atopy was linked with markers on chromosome 11. This work has been confirmed by many but not all interested research groups and attention has focused on the high affinity IgE receptor. One study has shown linkage between atopy and a mutation in the beta chain of this receptor and further studies are ongoing.

Other groups have explored linkage on chromosome 5 where the gene for the T cell receptor is found and chromosome 7 which accommodates the interleukin gene cluster. Evidence for linkage with asthma on both sites has been presented and the picture is built of a number of different genetic markers all associated with immune mechanisms involved in allergic inflammation.

A recent independent line of investigations have looked at polymorphisms of the ß2 receptor. There are four mutations of this receptor which have been explored and two of them have shown linkage to the severity of asthma as well as to the ability of the receptor to down regulate after repeated stimulation. While this approach is not directly related to the immunopathogenesis of asthma it nevertheless represents a highly important aspect of asthma genetics which may be susceptible to new treatment approaches.

In conclusion, the genetics of asthma is being rapidly unravelled and this has two advantages: first to give further information about the pathogenesis of the condition, and secondly to suggest new approaches to treatment. Nevertheless, the over-riding importance of the environment must not be forgotten.

Current Treatment of Non-Small Cell Carcinoma of Lung (NSCLC) Based on Staging by Prof. Wah-kit Lam

In Hong Kong, NSCLC (squamous cell, adenocarcinoma, and large cell carcinoma) accounts for about 85% of all lung cancers. Basing on the International T (tumour) N (nodal) M (metastasis) Staging System (1986), the four stages (I-IV) account for about 10%, 15%, 40% and 35% of all cases respectively.

Stages I & II These are early staged tumours potentially curable with surgery alone. For stage I, the overall 5-year survival rate is about 55%, which rises to 70% in the small subgroup with T1 disease. Once hilar lymph node is involved (N1, Stage II), 5-year survival rate decreases to 25-40% after surgery alone. Post-operative thoracic radiotherapy may decrease the rate of local recurrence, but not the overall survival. Likewise, a recent meta-analysis showed that adjuvant cisplatin-based chemotherapy gave an absolute benefit of 5% at 5-years, but this was not statistically significant (p=0.08).

Stage III Stage III is subdivided into Stage IIIA (T1-3 NO-2) and Stage IIIB (T1-4 NO-3), and even Stage IIIA itself is a heterogeneous group consisting of T3 and N2 patients with different prognosis and treatment approach.

Stage IIIA T3 disease These tumours are potentially operable. Pre-op or post-op radiotherapy (RT) is given for T3 superior sulcus tumour. Addition of post-op cisplatin-based chemotherapy (CT) did not improve survival significantly by meta-analysis of studies. Likewise, RT as primary therapy did not improve survival. Overall, 5-year survival is about 30%.

Stage IIIA N2 disease These are localised but unresectable tumors. Treatment needs to address local control and prevention of distant relapse (>50%). Meta-analysis showed that cisplatin-based CT+RT gave a 4% absolute improvement in survival in 2 years over RT alone (p=0.01). Recent trials have employed multimodality treatment with neoadjuvant CT±RT to downstage tumour followed by surgery. Early results have been encouraging. Overall, 5-year survival for clinically occult N2 disease is 15-25%, and for clinically evident N2 disease is < 10%.

Stage IIIB disease These are locally advanced and unresectable tumours. Clinical trials have favoured the combined use of cisplatin-based CT+RT over RT alone.

Stage IV disease These are metastatic and incurable tumours, and the primary goals of therapy are palliation of symptoms and improvement in median survival. Recent meta-analysis showed that compared to supportive treatment alone, cisplatin-based CT increased survival by about two to three months and disease symptoms were probably improved. CT can be offered to fully ambulatory patients with evaluable tumour lesions who are motivated and fully understand the limitations of CT. Over the past several years, a number of new agents (e.g. taxanes, topoisomerase I inhibitors, gemcitabine, vinorelbine) with activities of 15-38% as single agents have reached the level of phase II and III testing.

Current research would focus on refining multimodality therapy (including schedules, sequences, dose) for Stages II & III disease, and new drugs in combination, high-dose chemotherapy with marrow support and new innovative therapy (e.g. antigrowth factors) for Stage IV disease.

Strategies for the Treatment of Heart Failure
by
Dr. Hamid Ikram

Heart failure is a clinical syndrome characterised by effort intolerance, oedema, dyspnoea and arrhythmias. It has a very high mortality and morbidity. Both the incidence and prevalence of heart failure is rapidly increasing in developed and probably in developing countries.

The major aetiological factors for heart failure are:-

1. Coronary Heart Disease
2. Hypertension
3. Diabetes Mellitus

Once heart failure develops, further progression depends on the generic response of the cardiovascular system irrespective of aetiology.

Treatment strategies for heart failure are, similarly, generic and independent of the cause, but where possible, the cause should be corrected e.g. valvular or congenital heart disease.Treatment strategies for heart failure are aimed at 2 different goals, improvement of **symptoms** and increasing **survival.**

Symptomatic Treatment of Heart Failure

1. Relief of congestion

The primary symptoms of heart failure are pulmonary and peripheral congestion. These are usually due to fluid retention and are managed by salt reduction in the diet and diuretics. These drugs have been shown to improve patients' quality of life considerably. Patients will ultimately become resistant to diuretic therapy but this is delayed enormously by the concomitant use of ACE inhibitors. Diuretic combinations and combination with aldosterone antagonists is another strategy.

2. Improvement in tissue perfusion

The other major symptom of heart failure is fatigue, which is consequence of reduced forward flow. This is treated by vasodilators. The most effective agents are the ACE inhibitors which also relieve congestive symptoms. Other vasodilators have similar symptomatic benefits e.g. a mixture of hydrallazine and isosorbide dinitrate but their impact on survival is not as great. ACE inhibitors are indicated for heart failure whenever diuretic therapy is indicated.

3. Impaired contractile function

Digitalis is effective in relieving symptoms of heart failure even in individuals in sinus rhythm. The recent DIG trial showed a null effect on heart failure mortality, placing digitalis therapy in the symptomatic relief of heart failure. Other inotropic agents also relieve symptoms, but decrease survival, and so are generally avoided.

4. Concomitant Conditions

Arrhythmias - The most useful drug for the treatment of symptomatic arrhythmias in heart failure patients is low-dose amiodarone, which has very little tendency of proarrhythmia.

Intramural Clots and Pulmonary Embolisation - These require anticoagulant therapy.

Survival

The only drugs to regularly show improved survival in symptomatic and asymptomatic left ventricular dysfunction are the ACE inhibitors. They are first line therapy in the management of heart failure. A mixture of isosorbide dinitrate and hydrallazine and also low dose amiodarone also improve survival. The role of beta blockers particularly carvedilo is under review.

Surgery

Several surgical series show marked benefits from revascularisation procedures in selected patients with poor left ventricular function and heart failure. Aneurysmectomy is also valuable in selected patients. Novel surgical approaches such as cardiomyoplasty and artificial hearts are still highly experimental. The ultimate surgical answer is the total cardiac transplant.

Management of Acute Myocardial Infarction
by
Prof. Chu-pak Lau

Pathophysiology of AMI

Transmural AMI is usually secondary to thrombotic occlusion of an epicardial coronary artery. The pathophysiology of AMI is divided into two phases:

A. Evolving phase

This is the first 6 hours from the time of pain. Myocardial injury has occured although myocardial cells are still viable. Myocardial salvage can be achieved if blood supply is restored by pharmacological or mechanical revascularisation. Heart rate and blood pressure control can also help to prolong this phase by decreasing oxygen demand.

B. Convalescence phase

If blood supply is not resumed after the evolving period, infarcted muscle will not recover and changes in left ventricular size, shapes and thickness involving both the infarcted and non-infarcted segments of the ventricle often occur, a process referred to as "ventricular remodeling". Acute reperfusion, an open infarct artery per se, intravenous nitroglycerin and angiotension-converting enzyme inhibitor can attenuate infarct expansion and ventricular dilatation.

Management of AMI

The principal objectives of management of the patient with AMI are to prevent death from arrhythmia and to minimise the mass of infarcted tissue. Most deaths from AMI occur withint the first few hours after its onset and is usually due to ventricular fibrillation. The biggest delay of patient's coming under medical observation is between the symptom onset and the patientís decision to call for help. This can be best reduced by public education concerning the significance of chest pain and the importance of seeking early medical attention. Arrhythmias can usually be managed successfully when trained personnel and appropriate equipment are available. Coronary care units have resulted in improved patient care in AMI, reduction in mortality rates, and major increases in knowledge about myocardial infarction.

General measures should include a liquid diet for 24 hours followed by soft diet. Then a regular diet low in cholesterol and saturated fats is appropriate. Stool softener should be used to prevent constipation and straining. Patients need not be confied to bed for more than 24 to 36 hours in the absence of complications. Hypoxaemia is common in patients with AMI and the delivery of 2 to 4 litres/min of 100% oxygen is satifactory for most patients. Control of cardiac pain can be achieved by narcotic analgesics, nitrates and beta-adrenoceptor blockers.

Evolving phase

Thrombolysis has been clearly shown to reduce mortality and improve myocardial function. In the absence of contraindications, either one of the thrombolytic agents (streptokinase, anisoylated plasminogen streptokinase activator complex, tissue plasminogen activator) should be administered preferably within 6 hours of pain onset to AMI patients. Possible benefits of thrombolysis may extend to 12 hours. A recent trial demonstrated a small benefit with "front-loaded" tPA and adjunctive intravenous heparin over conventional streptokinase.

Primary percutaneous transluminal coronary angioplasty (PTCA), i.e. without preceding thrombolysis, has also been reported to be effective in restoring reperfusion in AMI. Morbidity and mortality reduction is even greater than thrombolytic agents, especially in patients with cardiogenic shock. However, this technique is very expensive in terms of personnel and facilities and generalized application of primary PTCA as the reperfusion strategy for AMI will be restricted.
Aspirin also reduces mortality especially in conjunction with thrombolysis. The rate of reinfarction is reduced on long term follow up.

In addition to thrombolytic agents and aspirin, intravenous beta-blocker and nitroglycerin are recommended within the first 6 hours for their effect on limiting infarct size.

Convalescence phase

Oral beta-blocker and angiotensin converting enzyme (ACE) inhibitor should be commenced after the evolving phase and both improve survival. Recent evidence suggests that aggressive reduction of cholesterol level with statins reduce the incidence of future cardiac events and overall mortality (Table 2). ACE inhibitors should be given at a small starting dose and forced titration to the maximum tolerated dose should be carried out before hospital discharge (Table 3).

Non-Q myocardial infarction

Diltiazem may reduce reinfarction in non-Q wave myocardial infarction in those patients without heart failure.

Table 1 - Benefits of short-term treatments for acute myocardial infarction.

Treatment	Problems prevented per 1,000 patients treated
Intravenous beta-blocker	7 deaths
Aspirin	23 deaths
Streptokinase	25 deaths
ACE inhibitors - all patients	5-8 deaths
ACE inhibitors - patients with heart failure	20-30 deaths

Table 2 - Benefits of long-term secondary prophylactic treatment after myocardial infarction

Treatment	Problems prevented per 1,000 patient years of treatment*
Oral beta-blockers	13 deaths/5 MI
Aspirin	16 deaths/MI/strokes
HMG-CoA reductase inhibitor	6 deaths/12 MI/4 CHF/11 revascularisation**
ACE inhibitor - low LVEF (SAVE)	12 deaths/9 MI/16 CHF/10 revascularisation**
ACE inhibitor - low WMI (TRACE)	6 deaths
ACE inhibitor- heart failure (AIRE)	45 deaths/26 CHF

Clinical trails: SAVE = Survival and Ventricular Enlargement
TRACE = Trandolapril Cardiac Evaluation
AIRE = Acute Infarction Ramipril Efficacy

MI = myocardial infarction
WMI = wall motion index
CHF = congestive heart failure
LVEF = left ventricular ejection fraction

* e.g. 200 patients treated for five years.
** revascularisation = coronary angioplasty or bypass surgery

Management of Coronary Artery Disease: Drugs, PTCA or Surgery?
by
Dr. David Ho

Increased experience and improvements in PTCA hardware over the last decade have allowed patients with multivessel disease and complex lesions to be treated. The complexity of cases treated by PTCA has broadened from single, discrete, concentric, noncalcified lesion in a patient with single vessel disease and good ventricular function to multiple, diffuse, eccentric, calcified lesions in a patient with multivessel disease and poor ventricular function. Over the last 10 years, number of PTCA performed has increased markedly and has exceeded CABG in most countries. Despite the improvements in hardware and operator experience, there remain 3 major limitations: 1. Failure to cross some lesions, particularly chronic total occlusion. 2. Acute closure. 3. Restenosis.

Increase in luminal diameter during PTCA is due to expansion of both the inner and outer diameters of the vessel. This "controlled injury" led to "cracking" of calcified or densely fibrotic plaque. This has several consequences: 1. Exposure of subintimal tissue (eg. collagen) will lead to adhesion of platelets and clotting proteins. 2. Release of potent mitogens (PDGF) may lead to excessive local smooth muscle cell proliferation, resulting in restenosis over the subsequent 3 to 6 months. 3. When a dissection is extensive, excessive platelet activation and thrombus formation may lead to acute vessel closure. Acute closure occurs in around 2-8% of patients undertoing PTCA and accounts for most of the major in-hospital complications (death, MI, CABG). Before the availability of the intracoronary stent, around 35% would require emergency CABG, 40% would sustain a MI and 4% would die in-hospital. The intracoronary stent has largely reduced the complications associated with acute vessel closure and the need for urgent CABG. The coronary stent has also been shown to be effective in reducing restenosis in several randomized studies. A major problem with the stent is stent-thrombosis within the first 2 weeks post stenting, resulting in dealth or MI. Aggressive anticoagulation in an attempt to prevent thrombosis has led to significant bleeding and puncture site complications. Attention to the technical details of stents placement, sizing and supplemental high pressure inflation to achieve a smooth lumen have reduced the incidence of stent thrombosis. These approaches have eliminated the need for anticoagulation, leading to a reduction in bleeding complications and hospital stay.

Other devices like the laser catheter, rotablator and directional athrectomy device have each got its own advantage in certain lesion morphology. Except for stents, none of the new devices have been shown to reduce restenosis, while some are associated with an increased incidence of procedural complications.

Success rate for PTCA in reported series depends on definition and other factors (patients, vessel and lesional characteristics). A common definition is a residual stenosis of <50% (angiographically), without any major in-hospital complications (death, MI, CABG). In the NHLBI Registry I (1979-81) and Registry II (1985-86), success rates were 65% and 85% respectively. In most current series, success rate is around 90-95%. The most common cause of failure is due to inability to cross the target lesion with a guidewire or balloon catheter.

The incidence of restenosis depends on the definition used and the measurement technique employed. Most studies define restenosis as 50% narrowing of the diameter of the lumen at the site of previously successful PTCA. Around 20-25% of patients redevelop evidence of ischemia at 6 months following PTCA. If routine follow up angiogram is performed in 4-6 months, an additional 10-15% of patients will demonstrate restenosis. Most cases respond well to 1 or more repeat dilatations. Restenosis is partly due to elastic recoil, and partly due to smooth muscle cell proliferation. In recent stent series, the restenosis rate has fallen to 10-20%. To solve the restenosis problem, research are being performed using different stent coatings (heparin, hirulog), local drug delivery (C7E3, MK-383) and low-dose ionizing radiation.

For patients with coronary artery disease, the choice of therapy should take into account:

1) patient's overall condition (e.g. activity level, age, LV function, other medical problems, prior CABG etc),
2) lesion and vessel characteristics, and
3) capabilities of the operator and equipment.

Available data regarding results of PTCA and alternative management options (eg results of CABG of the local surgical center) must be considered.

PTCA vs Medical Treatment in patients with single-vessel disease and stable angina : PTCA

Relieves angina more effectively?	Yes
Reduces the need for antianginal medications?	Yes
Improves exercise performance?	Yes
Improves "quality of life" (in both physical and psychological measures)?	Yes
Was associated with a higher incidence of MI and emergency CABG?	Yes
Improves resting LV systolic performance?	No
Reduces incidence of MI?	No
Improves survival?	No

PTCA in Multivessel Disease

Despite the increased application of PTCA, its complication rate has remained reasonably low. For elective PTCA, the risk of death is ≤1%, MI 2-4%, emergency CABG 1-2%.

CABG vs Medical Therapy: CABG

Relieves angina more effectively?	Yes
Reduces the need for antianginal medications?	Yes
Improves survival?	Only for those with extensive disease
Reduces the incidence of MI?	No
Improves LV function?	No
Increase the likelihood of a return to gainful employment?	No

Operative mortality for CABG is around 1% in low risk patients when performed electively. Efficacy declines after 7 years, due to degeneration of saphenous vein grafts and progression of atherosclerosis in native vessels.

PTCA vs CABG in Multivessel Disease

{from published randomised trials: RITA (n-1011) f/u 2.5 yrs., EAST (n=392) f/u 3 yrs and GABI (n=359) f/u 1 yr.}

PTCA	CABG
Similar incidences of "death or MI" at follow up Similar improvements in exercise capacity In-hospital deaths: 0.8-1.1% for PTCA vs 1.0-2.5% for CABG	
• More likely to have persistent angina* • More likely to require antianginal medications • More likely to need another revascularisation procedure (38-44% vs 11-14%)	• More in-hospital Q-MI (8.1-10.3% vs 2.3-3%) • More stroke, pneumonia, wound infection, redo sternotomy for bleeding, pulmonary embolism • Longer hospital stay (median 12-19 days vs 4-5 days)

*GABI showed equivalent improvement in angina

Choice of Therapy	Medical	CABG	PTCA
• Patients with 1VD	√	-	√
• Patients with 2VD, 3VD (not involving the proximal LAD) and who has normal LV systolic function	√	√	√
• Patients with LMCA disease, or multivessel disease involving the proximal LAD, or 3VD with impaired LV function	-	√	√

Diastolic Heart Failure
by
Dr. Hamid Ikram

Cardiac *Systole* and *Diastole* are two independent, but inter-dependent aspects of cardiac mechanical function. They can be likened to the "Yin" and "Yang" of Chinese philosophy, Systole being "Yin" or the active part, whereas Diastole being entirely passive. This in large measure explains the disproportionate attention lavished on the systolic phase of the cardiac cycle.

It is now known that diastole is not a mere absence of systole, but a dynamic, energy-consuming process which has unique structural and biochemical mediators, while also sharing certain of these with systole.

The term "diastole" has an ancient lineage, being used by Galen 131-201 AD, Serveteus 1511-1533, Boerhave 1668-1738, Harvey 1628, Frank 1895 and almost every other great name in haemodynamics. Its meaning has however, changed, over the years and is now taken to mean the period between 2 systolic periods.

Physiologically, Systolic Heart Failure, can be regarded as failure to empty, while Diastolic Heart Failure can be defined as failure to fill. A formal definition of diastolic heart failure is the inability of either ventricle to fill adequately. Abnormalities of filling can be due to 2 fundamental abnormalities:

- Decrease in compliance due to structural changes in the wall
- Impairment of relaxation

These may occur globally or locally. There is a third mechanism which may impair ventricular diastolic function, **heart rate.** A tachycardia does not abbreviate the duration of systole, but all tachycardias shorten diastole. Hence, a certain amount of impaired compliance and relaxation may be accommodated at slow heart rates, but may lead to impaired filling i.e. diastolic dysfunction at faster rates.

A wide range of aetiological agents cause diastolic heart failure which include obstruction to filling e.g. valvular stenoses, alteration in left ventricular wall compliance e.g. amyloid disease, impaired relaxation due to ischaemic heart disease and dilated cardiomyopathy. Cardiac hypertrophy caused by hypertension or valvular disease, is a common cause of diastolic dysfunction. Perhaps manifestations of diastolic heart failure in their purest form are seen in constrictive pericarditis.

The clinical manifestations of diastolic heart failure are essentially those of raised venous pressure and congestion due to impaired capacity to fill the ventricle. A third heart sound, paradoxical venous and arterial pulses and gross oedema and ascites are the usual findings. The trans-mitral flow patterns on the doppler echo provide a ready assessment of diastolic dysfunction, although several problems remain. Catheter studies, MRI, CT scans and myocardial biopsy have their place in selected cases. Quantification of severity is more difficult than for systolic dysfunction and the prognostic value of various indices unknown.

Treatment depends largely on cause. Control of hypertension, valve surgery and pericardiectomy may be curative. In ischaemic disease, relief of ischaemia by interventional techniques may provide relief. Where there is widespread ischaemia or hypertrophy, treatment with beta blockers or calcium channel blockers will improve relaxation and relieve dyspnoea.

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Last but not least, we would like to thank all speakers, chairpersons and delegates for their participation and contribution.

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- Combine pronounced anti-inflammatory activity[1] with negligible systemic effect.[2]
- Suitable for prophylactic treatment for asthma of all severities.

FLIXOTIDE™ INHALER/FLIXOTIDE™ ROTADISKS™/DISKHALER™ ABRIDGED PRESCRIBING INFORMATION *(Please refer to the full data sheet before prescribing)* **Presentation:** Flixotide Inhaler is a pressurised metered-dose inhaler which delivers 25, 50, 125 or 250mcg of fluticasone propionate per actuation. Each Flixotide Rotadisks comprises of four, regularly spaced, double-foil blisters each containing a mixture of microfine fluticasone propionate (50mcg) and larger particle size lactose. **Indications:** Fluticasone propionate has a marked anti-inflammatory effect in the lungs. It reduces symptoms and exacerbations of asthma in patients previously treated with bronchodilator alone or with other prophylactic therapy. Prophylactic management in mild, moderate and severe asthma in adults and children. **Dosage and Administration:** Flixotide Inhaler is administered by the inhaled route only. For optimum benefit, use regularly, even when asymtomatic. The dosage of fluticasone propionate should be adjusted according to the individual response. If patients find that relief with short-acting bronchodilator treatment becomes less effective or they need more inhalations than usual, medical attention must be sought. Adults and children over 16 years of age: Mild asthma: 100 to 250mcg twice daily; Moderate asthma: 250 to 500mcg twice daily; Severe asthma: 500 to 1000mcg twice daily. Children over 4 years of age: 50 to 100mcg twice daily. **Contra-indications:** History of hypersensitivity to any component of the preparation. **Special warnings and special precautions for use:** Increasing use of short-acting inhaled beta-2 agonists to control symptoms indicates deterioration of asthma control. Sudden and progressive deterioration in asthma control is potentially life-threatening and consideration should be given to increasing corticosteroid dosage. Flixotide Inhaler is not for relief in acute attacks but for regular daily treatment. Patients will require fast- and short-acting inhaled bronchodilator to relieve acute asthmatic symptoms. Lack of response or severe exacerbations of asthma should be treated by increasing the dose of inhaled fluticasone propionate and, if necessary, by giving a systemic steroid and/or an antibiotic if there is an infection. For the transfer of patients being treated with oral corticosteroids: • Add fluticasone propionate to existing oral steroid therapy which is then gradually withdrawn. • Monitor patients with adrenocortical suppression regularly and reduce oral steroid cautiously. • Consider supplying oral steroids for use in times of stress e.g. worsening asthma attacks, chest infections, surgery. • Replacement of systemic steroid with inhaled therapy sometimes unmasks allergies outside the pulmonary tract previously controlled by the systemic drug. Adrenal function and adrenal reserve usually remain within the normal range on inhaled fluticasone propionate. However, some systemic effects may occur in a small proportion of adult patients after prolonged treatment at the maximum recommended daily dose. Patients transferred from other inhaled steroids or oral steroids remain at risk of impaired adrenal reserve for a considerable time after transferring to inhaled fluticasone propionate. Treatment should not be stopped abruptly. Active or quiescent pulmonary tuberculosis. **Pregnancy and Lactation:** Careful consideration necessary when used during pregnancy. **Side Effects:** Candidiasis of mouth and throat. Hoarseness. Paradoxical bronchospasm. Cutaneous hypersensitivity reactions. **Pharmaceutical Precautions:** Flixotide Inhaler: Store below 30°C. Protect from frost and direct sunlight. Flixotide Rotadisks: Store below 30°C. Blisters must only be pierced immediately prior to use.

REFERENCES: 1. Phillipps GH. Respiratory Medicine (1990) 84 (Supplement A) 19-23. **2.** Skidmore IF, Satellite Symposium of the European Respiratory Society Annual Congress, Vienna, 92:9-12.

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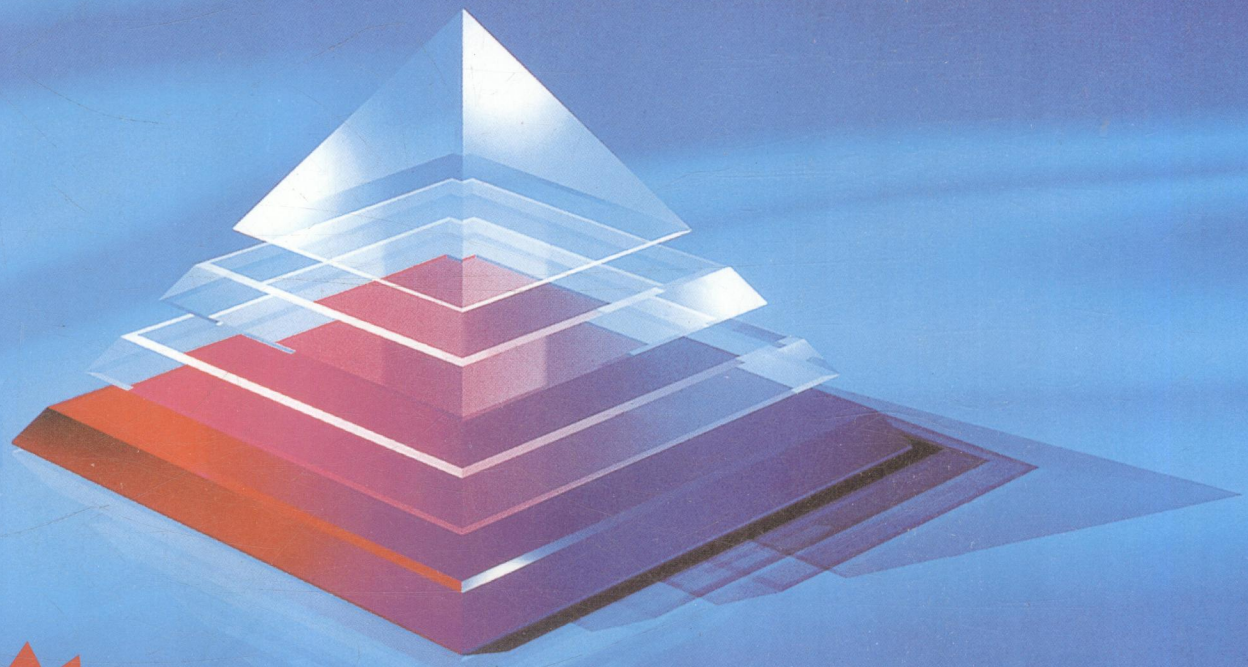

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ABBREVIATED INFORMATION

DESCRIPTION Maxipime® is a sterile mixture of cefepime hydrochloride and L-arginine. **INDICATIONS** Maxipime® is indicated in the treatment of the following infections, when caused by susceptible strains of bacteria: • lower respiratory tract infections (including pneumonia and bronchitis) • urinary tract infections (both complicated, including pyelonephritis, and uncomplicated) • skin and skin structure infections • intra-abdominal infections (including peritonitis and biliary tract infections) • gynecologic infections • septicemia • empiric treatment in febrile neutropenic patients **DOSAGE AND ADMINISTRATION** The usual dosage for adults (and children 13 years and older) is 1g administered intravenously or intramuscularly every 12 hours. However, the dosage, route and duration vary according to susceptibility of the causative organism, the severity of the infection and the condition and renal function of the patient. *Patients with impaired renal function* In patients with renal impairment (creatinine clearance < 30 ml/min.), the dose of Maxipime® should be adjusted. *Administration* Maxipime® may be given intravenously or by deep intramuscular injection into a large muscle mass (e.g. upper outer quadrant of gluteus maximus). **CONTRAINDICATIONS** Maxipime® is contraindicated in patients who have shown immediate hypersensitivity reactions to cefepime or L-arginine, to cephalosporins generally, to penicllins or to other betalactam antibiotics. **PRECAUTIONS / WARNINGS** Caution is required in any patients who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to Maxipime® occurs, treatment should be discontinued. Pseudomembranous colitis has been reported with most broad-spectrum antibiotics. It is important to consider this diagnosis in patients who develop diarrhea during the therapy with Maxipime®. *Pregnancy/Lactation* Reproduction studies in animals showed no evidence of impaired fertility or harm to the fetus; however, there are no adequate studies in pregnant women. The drug should therefore be used in pregnancy only if clearly needed. Maxipime® is excreted in human breast milk in very low concentrations. Caution should be used when Maxipime® is administered to nursing mothers. The efficacy of maxipime® in children below the age of 13 has not been established. **SIDE EFFECTS** Maxipime® is generally well tolerated. The incidence of adverse events associated with its administration was low in clinical trials. The most common adverse events were gastrointestinal symptoms and hypersensitivity reactions. See full prescribing information. **PACKAGING** Maxipime® is supplied in individual vials of 500 mg, 1 g and 2 g.

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1. Dictionnaire Vidal 1994 2. Le Chevalier B. Activities en reanimation at urgences. 1993: 227-241 3. Comite d' antibiogramme 1994. 4. Canton R. et al. In-vitro activity of Sparfloxacin compared with those of five other quinolones. Antimicrobial Agents and Chemotherapy. 36: 558-565, 1992. 5. Loza E., et al. Activity of Sparfloxacin against G + bacteria: Effect on organisms with PBP - mediated Beta-lactam resistance. European Journal of Clin. Microbio and infectious Diseases Special Issue: 550-553, 1991. 6. Habernat H., et al. Comparative in-vitro activity of sparfloxacin against H. Influenzae and B.Catarrhalis. European Jourrnal of Clin. Microbio. and Infectious Dsease special Issue: 544-545, 1991. 7. Copper MA., et al In-Vitro activity of sparfloxacin, a quinolone antimicrobial agent. Journal of Antimicrobial Chemotheraphy 26: 667 - 676, 1990. 8. Scorneaux B., et al Comparative in-vitro activity of sparfloxacin and erythromycin in a model of J774 Macrophages infected with chlamydia pneumoniae. Abstract no 511, 31st ICAAC. Chicago, 29 Sept-2 Oct, 1991. 9. Renaudin H, Brbear C, Activite in-vitrode la sparfloxacin sur les mycoplasmes. Pathologie Biologie. 40: 450-454, 1992. 10. Gaja M, et al. In-vitro and In-vivo antibacterial evaluation of sparfloxacin, a new oral pytridone carboxylic acid derivative against legionella intection. European Journat of Clin. Microbio and Infectious Diseases Special Issue: 557-558, 1991.

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