CONTENTS

29 Primary Prevention of Sudden Cardiac Death

Dr Kathy Lee (李麗芬醫生);
Professor Lau Chu Pak (劉柱柏教授)

30 Hypertension and Atrial Fibrillation

Dr Siu Chung Wah, David (蕭頌華醫生)

33 The Role of Combination Therapy in the Management of Hypertension

Dr Miao Hu, Teresa (胡淼博士);
Professor Brian Tomlinson (湯寧信教授)

37 Non-alcoholic Fatty Liver Disease

Dr Ng Fook Hong (吳福康醫生)

41 Management of Chronic Hepatitis B Infection – Diagnosis

Dr Lui Yan Ni (呂恩妮醫生)
Tumor Radioresistance and p53: Focusing on Cancer Stem Cells

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The loss of p53 functions, either through mutations on the p53 gene itself or other factors, has long been associated with decreased radiosensitivity of human tumor cells. For example, patients with recurrent non-small cell lung carcinoma (NSCLC) whose tumors were found with mutations in exons 5-8 of the p53 gene were up to four times less likely to respond to radiotherapy than those patients whose tumors had wild-type p53. Similarly, analysis of glioblastoma multiforme brain tumor (GM) clonogenic cell lines has indicated that the lack of functional p53 was associated with resistance to fractionated irradiation. A closer look at the phenomenon suggests that tumor cells that retain radiation-induced G1 arrest and radiation-induced accumulation of p53 levels are those that show the highest sensitivity to ionizing radiation. Simultaneous detection of bcl-2 over-expression and p53 gene mutations in primary squamous-cell carcinoma of the head and neck (HNSCC) treated with conventional radiotherapy is associated with higher risk of locoregional failure and worse survival within 5 years.

Many such examples have pointed to a mechanism whereby tumor cells have become ionizing radiation-resistant because mutations in their p53 fail to induce cell death by apoptosis, or tumor cells have acquired other anti-apoptosis mechanisms such as when bcl-2 is expressed at high levels. As in normal cells, irradiated tumor cells seem to have the choice between dying by apoptosis and undergoing growth arrest, a process that seems to be dictated by the severity of DNA damage, and type of tissue (see review). When tumor cells lose p53 functions, they revert to growth arrest that give the cells a chance to repair DNA damage, and perhaps die by mitotic catastrophe if the damage cannot be repaired.

The idea that supplementing tumor cells with exogenous p53 by viral vector transduction would increase radiosensitivity, or equivalently, reverse radioresistance, has been tested in both pre-clinical and clinical settings by various groups. Indeed, human prostate cancer cell lines have been shown to become highly sensitive to ionizing radiation upon infection with an adenoviral vector containing the wild-type p53 in a viral dose-dependent manner, which also resulted in induction of G1 cell cycle arrest. Growth of human cervical cancer cells have also been shown to be inhibited by a combination of ionizing radiation and p53 added by viral transduction at a rate that was significantly higher than when the cells were treated by either method alone.

In a clinical study involving patients with advanced nasopharyngeal carcinoma (NPC), 42 subjects who were treated with a combination of adenalivir p53 gene therapy by intratumoral injection and local treatment with radiotherapy showed remarkable complete tumor response rate of 2.73 times higher than those 40 control patients who received radiotherapy alone. In addition, locoregional recurrence observed in follow-ups over a period of 6 years in the combination treatment group was only 2.7% compared to 28% for the group that received radiotherapy alone. Thus, at least for this study treatment of tumors in patients who received both gene therapy and radiation showed not only rapid complete tumor response but also long-term inhibition of local recurrence.

Solid tumors are complex structures involving heterogeneous types of tumor cells, stromal cells that support structure, endothelial cells that are involved in its vasculature, infiltrating immune cells of various kinds that are likely is suppressed state, and a subpopulation of cancer stem cells (CSCs). In particular, the CSCs have caught the attention of many investigators for they seem to be involved in resistance to genotoxic treatments, in the repopulation of the tumor mass, and in distant metastases (see review). Certain studies show that p53 is highly involved in the suppression of CSCs and that perhaps loss of p53 could lead to genetic instability, which in turn results in plasticity, a hallmark of CSCs, of certain phenotypes in the tumor population due to random mutations and clonal evolution. Loss of p53 and deregulation of growth factor signalling pathways are thought to be involved in the transformation of adult neural stem cells, and it is suggested treatments involving reactivation of p53 in brain tumor stem cell populations should be explored. In breast cancers, studies show that tumor cells can acquire stem cell properties when p53 functions are lost. As the focus in cancer treatment is turning towards the control of CSCs in which p53 seems to be central in its regulation, it is perhaps time to reconsider the role of p53 gene therapy in combination with conventional treatments in the development of highly effective regimens for various types of solid tumors.

References:
In medicine, prevention is better than cure, and in no field is this adage more important than cardiovascular (CV) disease. Hypertension is a major CV risk factor, and in this issue, Professor Tomlinson and Professor Siu explore its implications for patient management and atrial fibrillation (AF). Early use of antihypertensive combination therapy can significantly enhance efficacy and reduce side effects. The role of optimal hypertension treatment to prevent AF is controversial, and is of great importance as AF leads to stroke and heart failure. Dr Kathy Lee summarizes the latest guidelines for preventing sudden cardiac death, particularly in patients with prior myocardial infarction and left ventricular dysfunction. Also in this issue, Dr Ng and Dr Lui review the early diagnosis and prevention of fatty liver disease and hepatitis B. Both are common problems encountered by practising physicians.
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Primary Prevention of Sudden Cardiac Death

Primary prevention of sudden cardiac death involves prophylactic intervention in individuals with no history of spontaneous life-threatening arrhythmias. The mechanism of sudden death is most likely acute myocardial infarction (MI) with plaque rupture, which results in ventricular fibrillation or other fatal complications. The main strategies to prevent sudden death should be prevention, early diagnosis and timely treatment of coronary artery disease. Pharmacological agents, such as antiplatelet agents and statins for plaque stabilization, decrease coronary death and sudden deaths. Large-scale randomized clinical trials have shown that implantable cardioverter-defibrillator devices (ICDs) also decrease mortality, particularly sudden cardiac deaths.

The American College of Cardiology, the American Heart Association and the Heart Rhythm Society published the latest guidelines on using ICDs in 2008. Primary prevention is indicated in patients with prior MI, New York Heart Association (NYHA) Class I and left ventricular (LV) ejection fraction 0.30 or less. Prophylactic ICDs are indicated for:

- Patients with prior MI, NYHA Class II or III, and LV ejection fraction of 0.35 or less.
- Patients with non-ischaemic heart failure with NYHA Class II or III symptoms, and LV ejection fraction of 0.35 or less.
- Certain conditions known to be associated with high risk of sudden death, when symptoms or risk markers are present; for example, long-QT syndrome, Brugada syndrome, hypertrophic cardiomyopathy, and arrhythmogenic right-ventricular cardiomyopathy.

Patients with structural heart disease, notably previous MI or LV dysfunction, are at risk of sudden death. A major problem in preventing sudden death is the lack of accurate and reliable ways to identify most at-risk individuals in whom an ICD would be of greatest benefit. So far, only LV ejection fraction and inducibility during programmed electrical stimulation have demonstrated predictive value in risk stratification. Other non-invasive strategies, including signal-averaged electrocardiography, microvolt T wave alternans and heart rate turbulence, have not proven discriminatory in patient selection. Primary prevention is both costly and demanding in technical complexity, with a number-needed-to-treat in primary prevention clinical trials that ranges from 8 to 20. Ongoing ICD trials are evaluating various risk assessment strategies designed to make prophylactic ICD more cost-effective. Future clinical trials may also identify other high risk populations that may benefit from prophylactic ICD.

Although patients with mild coronary disease and normal systolic function have only modestly increased mortality, they account for a major proportion of sudden deaths, because many individuals have this condition and so constitute a much bigger denominator. However, the overall population risk should be low and prophylactic device implantation is not practical.

The availability of public-access automated external defibrillators and personnel trained in cardiopulmonary resuscitation are both important to improving outcomes in out-of-hospital cardiac arrest. Heart-health education and increased awareness of heart diseases are also essential to combat sudden death in the community.
Introduction

Elevated blood pressure (BP), termed hypertension, is the principal and most prevalent risk factor for atrial fibrillation (AF), and is the most common co-morbidity in AF patients. The increasing prevalence of hypertension and AF worldwide due to population aging, contributes to stroke, heart failure and overall mortality. However, it remains unclear whether or not treating hypertension prevents AF or reduces the risk of AF related complications. This article reviews the epidemiology and therapeutic implications of AF in hypertensive patients.

Epidemiology

Approximately 1% of the overall population has AF. With increasing population ageing, the total number of AF patients is expected to increase by two to three times over the next 20–30 years. Recently, the Atherosclerosis Risk in Communities (ARIC) study confirmed that common cardiovascular risk factors, including tobacco smoking, diabetes mellitus, hypertension, overweight/obesity and prior cardiac disease, contribute to 57% of incident AF. Among these risk factors, elevated or borderline BP was the most important contributor, accounting for 20–25% of AF.

Pathophysiology

Despite the association between hypertension and AF, the pathophysiological link remains unclear. To date, two major mechanisms have been proposed: 1) Haemodynamic changes in the atria due to hypertension; and 2) Activation of the renin-angiotensin-aldosterone system (RAAS).

Hemodynamic Changes in Atria

In long-standing hypertension, the excessive after-load imposed on the left ventricle leads to progressive thickening of the left-ventricular wall and left-ventricular hypertrophy (LVH). The increased left-ventricular stiffness and diastolic and systolic dysfunction accompanying LVH inevitably raise left-atrial pressure. This chronic atrial stretch results in progressive left-atrial enlargement, with decreased atrial contractility and increased atrial compliance. Left-atrial enlargement and mechanical dysfunction are all important predictors of AF.

Renin-angiotensin-aldosterone System Activation

Emerging evidence suggests that RAAS activation contributes to AF. Experimental studies have demonstrated that angiotensin II induces atrial fibrosis and hypertrophy, causes changes in expression of ion channels, gap junction and calcium handling, as well as increasing oxidative stress and inflammation.

Therapeutic Implications

The pathophysiological links between hypertension and AF offer opportunities for therapeutic intervention to prevent AF in hypertensive patients. Effective BP control per se may be one of the most important ways to prevent AF, by reducing left-atrial enlargement and LVH. Furthermore, it is well known that despite comparable BP lowering effects, anti-hypertensive agents that block RAAS appear to be more effective than those that do not in reversing LVH, and thus preventing AF.

Primary Prevention of AF by RAAS Inhibition

A retrospective analysis by the USA drug administration, which suggested that angiotensin conversion enzyme inhibition (ACEI) decreased the risk of AF by 15%
over 4.5 years compared with a calcium channel blocker (CCB), provided the earliest evidence supporting therapeutic RAAS inhibition to prevent new AF.17 Recent clinical trials on angiotensin receptor blockers (ARBs) showed more consistently beneficial effects in preventing AF. In the secondary analysis of the Losartan Intervention For End Point Reduction in Hypertension (LIFE) study,18 losartan reduced new AF by 33% compared with atenolol (3.5% vs. 5.3%, p < 0.001). In the Valsartan Antihypertensive Long-Term Use Evaluation Trial (VALUE), a valsartan-based regimen reduced new AF by 16% compared with an amiodipine-based regimen. In both studies, the prevention of AF appears to exceed that expected from BP control alone. Furthermore, a nested case-control study in UK also demonstrated that treatment with ACEI-based and ARB-based regimens was associated with a 25–29% reduction in AF compared with CCB-based regimens.20 In meta-analyses, ACEIs and ARBs had similar overall benefit for AF prevention, but there are no head-to-head data.21 Comparing LIFE versus VALUE suggests that ARB is more beneficial than a CCB for preventing AF in hypertensive patients with LVH. Indeed, recent European Society of Cardiology guidelines recommend that ACEIs and ARBs should be considered for preventing new AF in patients with hypertension, particularly those with LVH (Class IIa, level B).22 In patients with uncomplicated hypertension, optimal BP control with any effective anti-hypertensive drugs, rather than a specific class, to prevent LVH and left-atrial enlargement appears to be more important to prevent AF.

Up to 85% of patients in GISSI-AF had hypertension, and there was no significant reduction in AF recurrence between patients randomized to valsartan versus placebo. Likewise, the Japanese Rhythm Management Trial for Atrial Fibrillation (J-RHYTHM) II study24 showed no reduction in AF recurrence with candesartan versus amiodipine, as monitored by daily transtelephonic electrocardiogram recording in 318 hypertensive patients with paroxysmal AF. Moreover, in the Atrial fibrillation Clopidogrel Trials with Irbesartan for prevention of Vascular Events-Irbesartan (ACTIVE II) trial, irbesartan did not reduce the risk of AF recurrence in paroxysmal AF patients (n = 1730) who were in sinus rhythm on enrollment.26 Overall, these studies suggest that neither ACEIs nor ARBs alone prevent arrhythmic recurrence in hypertensive patients with paroxysmal AF or those with persistent AF after cardioversion. It is therefore possible that ACEIs and ARBs cannot prevent progression of AF in individuals who have significant atrial remodeling.

**Conclusions**

Hypertension is the most common attributable risk factor for the increasing population burden of AF. Both clinical and experimental studies have demonstrated a close pathophysiological link between AF and hypertension. While optimal BP control with antihypertensive agents in hypertensive patients may potentially reduce the risk of AF, the promise of RAAS blockade with ACEIs and ARBs for primary and secondary prevention of AF remains unproven. Further randomized studies are needed to define the optimal antihypertensive agents for preventing AF recurrence and progression.

**Secondary Prevention with RAAS Inhibition**

Currently, there are very limited data to support using ACEIs or ARBs for secondary prevention of AF in patients with hypertension. The Gruppo Italiano per lo Studio della Sopravvivenza nell’Insufficienza cardiaca Atrial Fibrillation (GISSI-AF)23 was the largest secondary prevention study, involving 1,442 patients with either paroxysmal or recently cardioverted persistent AF.
The prevalence of hypertension continues to rise in most regions of the world, despite better understanding of the predisposing factors, largely fueled by increasing rates of obesity. Hypertension is often considered the most important cardiovascular risk factor, because it is not only prevalent, but also contributes to large population-attributable fractions of mortality from coronary heart disease and both haemorrhagic and ischaemic stroke. Furthermore, although there are several generally-available international guidelines and effective medications for appropriate management of hypertension, the proportion of patients reaching the recommended blood pressure targets is disappointingly small. In the United States, the control of hypertension increased from 27.3% in 1988–1994 to 50.1% in 2007–2008; however, this situation clearly remains suboptimal and is worse in many other countries.

Appropriate lifestyle advice for all hypertensive patients is essential. Nevertheless, drug therapy should not be delayed unduly in high-risk patients while waiting for lifestyle changes to take effect. Hypertension guidelines emphasize that most patients will require more than one drug to achieve adequate blood pressure control; if pre-treatment blood pressure is more than 20/10 mmHg above target or there is a high overall level of cardiovascular risk, it is desirable to start treatment with a two-drug combination. In patients with mild hypertension and low/moderate cardiovascular risk, treatment can commence at a low dose of a single drug, but in other cases using a low-dose dual combination is advisable. Moreover, if the starting dose of a single drug does not control blood pressure adequately, it is more effective to add a low dose of a second drug with a complementary mechanism of action, than to double the dose of the initial drug. In a meta-analysis of 354 trials of common antihypertensive drug classes, all five categories produced similar effects, with average blood pressure reductions of 7.1/4.4 mmHg at half-standard doses and 9.1/5.5 mmHg at the standard doses. Doubling the standard dose had little additional affect, whereas adding a second complementary drug reduced blood pressure by an average 14.6/8.6 mmHg, which was close to an additive effect. Figure 1 shows appropriate combinations of different classes of antihypertensive drugs. The 2009 reappraisal of the European guidelines on hypertension management additionally advised that an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) combined with a diuretic or a calcium channel blocker (CCB) were either supported by recent large-scale trials or appeared to be rational and effective, and are therefore favoured first-line options. The use of fixed-dose or single pill combinations may be preferable, because simplifying treatment improves compliance with therapy.

Dihydropyridine CCBs have become very popular antihypertensives, because they are effective in most patients and have few contraindications. A recent large meta-analysis found that CCBs prevented stroke to a greater extent than the other main antihypertensive drug classes. Amlodipine is one of the most popular CCBs; its very long plasma elimination half-life yields prolonged duration of action and persisting antihypertensive effects even with missed doses. Outcomes in trials of amlodipine have been favourable compared to alternative antihypertensive regimens; for example, the overall outcome with amlodipine-based therapy in ALLHAT (The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial), was similar to that with lisinopril-based therapy and was better for some endpoints, notably stroke.

It is logical to combine a CCB with a renin-angiotensin-aldosterone system

Key words:
Hypertension (高血壓), combination therapy (合併療法), angiotensin receptor blockers (血管緊張素受體拮抗劑).
ACE inhibitors have many clinical advantages, including reducing cardiovascular events in high-risk patients, as shown with ramipril in the HOPE (Heart Outcomes Prevention Evaluation) study.\(^1\) CCBs have not been shown to reduce mortality and morbidity associated with heart failure or renal disease, whereas some ACEIs and ARBs appear to have these benefits. Few clinical trials have compared different combination therapy regimens; however, in the ACCOMPLISH (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension) trial, combining the ACEI benazepril with amlopridine was superior to its combination with hydrochlorothiazide in reducing cardiovascular events in high-risk hypertensive patients, despite having a similar effect on blood pressure.\(^1\) This may suggest that a RAAS inhibitor and CCB combination is better than CCB combined with a diuretic.

ACEIs have many clinical advantages, including reducing cardiovascular events in high-risk patients, as shown with ramipril in the HOPE (Heart Outcomes Prevention Evaluation) study.\(^1\) Although generally well-tolerated, ACEIs do have the side effect of irritating dry cough, which probably occurs more commonly than has been reported and is certainly frequent in some Asian populations. ACEI-induced cough may lead 5% or more of patients to discontinue therapy.\(^1\) In a study of patients who received initial angiotensin monotherapy, those prescribed ACEIs had the lowest discontinuation rate, except for those started on ARBs.\(^1\) Adherence to long-term treatment is obviously important in managing hypertension and is influenced by several factors in addition to the tolerability of individual drugs. A systematic review reported that simplifying dosing regimens increased relative adherence by 8% to 19.6%.\(^1\) In a large Italian study of newly diagnosed hypertensive patients, antihypertensive combination therapy was one of the factors associated with high adherence, and highly-adherent patients had significantly fewer cardiovascular events than those with poorer adherence.\(^1\)

The ARBs are all well-tolerated, but differ in certain pharmacological respects (Table 1). Comparing pharma-

![Figure 1. Recommended dual-drug combinations for treating hypertension.](image1)

The drugs outlined by frames have proven beneficial in controlled intervention trials. Drug classes joined by continuous lines are recommended in combination therapy. The drug classes joined by red lines were recommended for priority use in the 2009 reappraisal. The bold dashed line joining beta-blockers and diuretics is used because these combinations can improve clinical outcomes, but in some cases will increase the risk of developing diabetes and so have not been recommended.

Adapted from reference 5 and 7.

![Figure 2. Complementary benefits of combined calcium channel blocker plus angiotensin receptor blocker.](image2)

A) Calcium channel blockers (CCBs) produce peripheral oedema and counter-regulatory effects with activation of the renin-angiotensin-aldosterone system (RAAS). B) RAAS activation and peripheral oedema can be reduced by combining CCBs with ARBs and such combinations provide additional clinical benefits.

BP, blood pressure; ARB, angiotensin receptor blocker; CHF, chronic heart failure.
cokinetics, telmisartan has the longest plasma elimination half-life, which results in very effective 24-hour blood pressure control, and is highly lipiod-soluble with the largest volume of distribution, indicating high tissue penetration. In addition, telmisartan is the only ARB shown to activate peroxisome proliferator-activated receptor-gamma at clinically relevant doses; this effect inhibits vascular tension in resistance arteries by increasing nitric oxide. All ARBs are approved for treating hypertension and some for the additional indications of renal disease, heart failure, or left ventricular dysfunction. However, based on the ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) study, which showed that telmisartan had similar benefits to ramipril on vascular events and major renal outcomes, telmisartan is the only ARB approved for patients with high cardiovascular risk, including those with type 2 diabetes and target-organ damage.

Fixed-dose ARB plus diuretic combinations have been available for several years and recently combinations of losartan with some ARBs, including olmesartan, telmisartan and valsartan have been introduced. These provide very effective and well-tolerated treatment that can be initiated as a first-line option in newly diagnosed patients with moderate to severe hypertension, or those with high overall cardiovascular risk, and do not have adverse effects on the additional risk factors. The contraindications are similar to those of ARBs alone and include pregnancy, hyperkaemia and severe renal or hepatic impairment. These ARB/CCB combinations are likely to be effective in most patients, irrespective of whether the high blood pressure results from high salt intake or high plasma renin activity. Combining amlopidine with an ARB has also been found to reduce the side effect of ankle swelling; for instance, combined amlopidine and telmisartan reduced the incidence of peripheral oedema significantly, to 5.2% compared with 17.8% of patients on 10 mg amlopidine monotherapy.

**The recent introduction of fixed-dose amlopidine plus ARB combination tablets provides a new option for initiating antihypertensive treatment**

In conclusion, the recent introduction of fixed-dose amlopidine plus ARB combination tablets provides a new option for initiating antihypertensive treatment or for switching from other combination regimens to reduce the number of tablets taken per day, which should improve adherence to long-term drug therapy. These combinations have synergistic mechanisms of action and complementary clinical indications, and are extremely well-tolerated with few contraindications. Consequently, their use should help more patients to achieve the blood pressure targets that current guidelines recommend and eventually reduce the overall mortality and morbidity related to coronary heart disease and stroke.
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Introduction

Non-alcoholic fatty liver disease (NAFLD) is a clinico-histopathological diagnosis. Although the histological features resemble alcohol-induced liver injury, patients have little or no history of alcohol consumption. The histological spectrum ranges from fat accumulation in hepatocytes without concomitant inflammation or fibrosis (simple hepatic steatosis), to hepatic steatosis with a necroinflammatory component (steatohepatitis) that may or may not have associated fibrosis. Non-alcoholic steatohepatitis (NASH) is a more severe form of NAFLD, with hepatocellular injury that may progress to fibrosis, cirrhosis and hepatocellular carcinoma in 50%, 15% and 4% of patients, respectively.2 NASH is now recognized as a leading cause of cryptogenic cirrhosis.3

The pathogenesis of NAFLD is likely to result from obesity-related insulin resistance and additional oxidative injury. Hepatic steatosis is a manifestation of excessive triglyceride accumulation in the liver; this can be due to excessive importation of free fatty acids (FFA) from adipose tissue, diminished hepatic export of FFA (secondary to reduced synthesis or secretion of very-low-density lipoprotein), or from impaired beta-oxidation of FFA. Both elevated peripheral fatty acids stored in adipose tissue and fatty acids newly made within the liver contribute to the accumulation of hepatic and lipoprotein fat in NAFLD.4 Insulin resistance is the key mechanism leading to hepatic steatosis and, potentially, steatohepatitis.5-7

Insulin resistance results in important changes in lipid metabolism, such as enhanced peripheral lipolysis, increased triglyceride synthesis and increased hepatic uptake of fatty acids.8 Obesity and type 2 diabetes mellitus (T2DM) are frequently associated with NAFLD. Additional oxidative injury is required to manifest the necroinflammatory component of steatohepatitis. FFAs induce several cytochrome P-450 microsomal lipoxygenases that produce hepatotoxic oxygen free-radical species. Increased FFA beta-oxidation and hepatic oxidative stress are present in both NAFLD and NASH, but only NASH is associated with mitochondrial structural defects.5

Epidemiology

NAFLD is the most common liver disorder in Western developed countries, and affects 20–40% of the general population. In Asia, large population-based surveys in China, Japan and Korea indicate that the current prevalence of NAFLD is 12–24%.9 In 2011, a population study in Hong Kong reported the population prevalence of NAFLD to be 27%; the estimated prevalence of advanced fibrosis in patients with fatty liver in the community was 4%.10 Body mass index and alanine aminotransferase (ALT) level were independent factors associated with liver stiffness.

The major risk factors for NAFLD are central obesity, T2DM, hyperlipidaemia and metabolic syndrome. Patients with NASH have prevalences of obesity, T2DM and hyperlipidaemia (hypertriglyceridaemia and/or hypercholesterolaemia) of approximately 69–100%, 34–75% and 20–80%, respectively.11,12

Clinical Manifestations

NAFLD or NASH most commonly present as asymptomatic elevation of liver aminotransferases detected on routine laboratory testing. Some patients present with fatigue, malaise and vague right-upper abdominal discomfort.13 Serum aspartate transaminase (AST) and ALT are elevated in 90% of patients, with an AST/ALT ratio usually lower than 1. In contrast, the ratio in alcoholic hepatitis is usually above 2.14,15 Alkaline phosphatase elevation and hyperbilirubinaemia are uncommon. However, amongst patients with NAFLD, normal serum AST or ALT do not exclude the presence of advanced histologic features. Of 51 patients with NAFLD and normal ALT levels, 12 (24%) had bridging fibrosis, whereas 6 (12%) had cirrhosis.16 Diabetes was the only factor independently associated with an increased risk of advanced fibrosis (bridging fibrosis or cirrhosis).

Diagnosis

Ultrasonography is the most common modality used to discose NAFLD, which appears as a hyperechoic texture or bright liver, because of diffuse fatty infiltration.17 Computed tomography (CT) and magnetic resonance imaging (MRI) can identify steatosis.18 However, ultrasonography is not specific, and ultrasonography, CT and MRI are unable to differentiate the histological subtypes of relatively benign non-alcoholic hepatic steatosis or more aggressive NASH.

Transient elastography can accurately diagnose advanced liver fibrosis in
most NAFLD patients.\textsuperscript{19} At a cut-off value of 7.9 kPa, the sensitivity, specificity, and positive and negative predictive values for advanced fibrosis (F3 or above) were 91\%, 75\%, 52\%, and 97\%, respectively. With high negative predictive value and modest positive predictive value, transient elastography is a useful screening test to exclude advanced fibrosis.

Liver biopsy is not only the sole means of diagnosing NASH definitively, but also enables determination of disease severity and may provide insight into prognosis. However, serious complications occur in approximately 1\% of patients biopsied,\textsuperscript{20} with an overall mortality risk of 0.2\%.\textsuperscript{21}

**Natural History**

In a population-based study in the United States, patients with NAFLD had slightly lower overall survival than expected for the general population (standardized mortality ratio of 1.34; 95\% confidence interval [CI] 1.00–1.76).\textsuperscript{22} Higher mortality was associated with increasing age (hazard ratio per decade, 2.2; 95\% CI, 1.7–2.7), impaired fasting glucose (hazard ratio, 2.6; 95\% CI, 1.3–5.2), and cirrhosis (hazard ratio, 3.1; 95\% CI, 1.2–7.8). Most mortality was due to cardiovascular disease, although liver disease accounted for a sizeable minority (14\%).\textsuperscript{23}

Recently, a longitudinal study followed up 52 patients (age 44±9 years) with biopsy-proven NAFLD. Liver biopsies were repeated at month 36.\textsuperscript{24} Overall, 14 (27\%) patients had fibrosis progression, 25 (48\%) had static disease, and 13 (25\%) had fibrosis regression. Reduction in body mass index and waist circumference was independently associated with nonprogressive disease activity and fibrosis.

**Treatment**

In patients with NAFLD, the management of comorbidities such as obesity, hyperlipidaemia and diabetes, is generally recommended. Weight loss and increased physical activity can lead to sustained improvement in liver enzymes, histology, serum insulin levels and quality of life in patients with NASH. Liver-protective and anti-inflammatory drugs to prevent and treat steatohepatitis and advanced fibrosis may be beneficial.\textsuperscript{27} Essential phospholipids (EPL) comprise the highly purified fraction of phosphatidylcholine with polysaturated fatty acids in positions C1 and C2, of which 1,2-dilinoleoyphosphatidylcholine is the main active ingredient.\textsuperscript{25} Phosphatidylcholine is an important structural component of cellular membranes and helps to break down fats.\textsuperscript{29} Incorporation of EPL into damaged hepatocyte cell membranes can restore normal membrane structure. EPL has antioxidant activity and protects against lipid peroxidation, is antifibrogenic and reduces transforming growth factor-β1-mediated collagen accumulation in hepatic stellate cells.\textsuperscript{30} EPL also reduces the interaction between immune effector cells and hepatocytes.\textsuperscript{31} In a prospective study, EPL significantly improved liver biochemistry after 8 weeks and reduced the degree of steatosis, necroinflammation and fibrosis after 6 months.\textsuperscript{32} No known toxicity or serious side effects have been reported.\textsuperscript{29} Vitamin E decreases oxidative stress and has therefore been evaluated in patients with NASH. In a randomized controlled study, vitamin E (800 IU daily) was associated with significantly improved global histology scores compared with placebo.\textsuperscript{33} However, mortality was increased in patients who received high-dose vitamin E supplementation (>400 units/day),\textsuperscript{34} with an apparent dose-response relationship.

**Conclusions**

NAFLD is common in Hong Kong. NAFLD is associated with central obesity, T2DM, hyperlipidaemia and hypertension. The management of these comorbidities is generally recommended. Weight loss and increased physical activity can lead to sustained improvement in liver enzymes, histology, serum insulin levels and quality of life in patients with NASH. Liver-protective and anti-inflammatory drugs to prevent and treat steatohepatitis and advanced fibrosis may be considered. EPL, which have no known toxicity or serious side effects, may be used. High-dose vitamin E supplementation (800 units/day) reduced necroinflammation and steatosis, but is not recommended because it is associated with higher mortality.

**References**

6. Chitturi S, Abegunazeraka S, Farrel GC, et al. NASH and insulin resistance: Liver biopsy is not only the sole means of diagnosing NASH definitively, but also enables determination of disease severity and may provide insight into prognosis. However, serious complications occur in approximately 1% of patients biopsied,\textsuperscript{20} with an overall mortality risk of 0.2%.\textsuperscript{21}

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¹ K.U. Gundemann. The ‘Essential’ Phospholipids as a Membrane Therapeutic. 1993, p.34, 121-125, 185-186, 213

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**References:**


Management of Chronic Hepatitis B Infection – Diagnosis

Chronic hepatitis B virus (HBV) infection is a widely prevalent global health problem. Approximately 350–400 million people worldwide are chronic HBV carriers.1,2 In high prevalent areas such as China, Southeast Asia and Sub-Saharan Africa, as many as 10–15% of the population are chronically infected with HBV. Chronic HBV carriers are at risk of liver cirrhosis, liver failure and hepatocellular carcinoma (HCC),3 and HBV-related diseases are estimated to account for 500,000–700,000 deaths annually.4

Chronic HBV infection usually follows a characteristic disease course. During the immune tolerance phase, patients are HBV e antigen (HBeAg)-positive and have high serum levels of HBV DNA. However, serum alanine aminotransferase (ALT) levels remain normal with patients having negligible liver damage. The immune clearance phase is characterized by elevation of ALT levels, before transiting to the low replication phase, better known as the ‘inactive carrier state’. In some patients, the immune clearance phase may be protracted. Protracted immune clearance is associated with recurrent hepatitis flares which can result in severe hepatitis, and may be followed by fibrosis and cirrhosis. During the low replication phase, spontaneous HBeAg seroconversion may occur; patients have normal ALT levels and low or normal serum HBV DNA levels.

In approximately 10–20% of inactive carriers, reactivation of HBV replication and exacerbations of hepatitis may occur after years of quiescence (Table).5,6 Therefore, lifelong follow-up with serial testing is necessary to determine the maintenance of a patient’s ‘inactive carrier’ state.

The risk of disease progression to liver cirrhosis and HCC in chronic HBV infection patients is strongly correlated with the viral load. The Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV) study conducted in Taiwan demonstrated that the multivariable-adjusted relative risk of HCC increased from 1.1 at HBV DNA levels of 300 to <10⁴ copies/mL to 2.3 at HBV DNA levels of 10⁴ copies/mL to <10⁵ copies/mL, and to 6.1 at HBV DNA levels of >10⁵ copies/mL.7 A further subanalysis of the REVEAL-HBV study revealed that patients with persistently low levels of HBV DNA (300 to <10⁴ copies/mL) were found to have increased risk of developing HCC as compared with those with undetectable levels of HBV DNA (<300 copies/mL).8 The correlation between HBV DNA levels and risk of HCC was independent of age, gender, HBeAg status, presence of liver cirrhosis and viral genotypes.7 Furthermore, a direct relationship between the cumulative incidence of cirrhosis and HBV DNA levels was also demonstrated.9 All these findings point to the critical role of viral replication in the progression of liver disease and the subsequent development of liver-related complications in chronic HBV infection patients. Thus, the primary goal of antiviral therapy is to achieve a durable suppression of viral replication, with the aim of preventing progression of liver diseases – liver cirrhosis, liver failure and/or HCC – in chronic hepatitis B patients. Current first-line antiviral agents, such as entecavir and tenofovir, have been shown to be effective in achieving and maintaining viral suppression.10–12

The simple to use “Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B” (REACH-B) scoring system

| Table 1. Definitions of chronic hepatitis B infection, chronic active hepatitis B infection and inactive chronic hepatitis B carrier status

<table>
<thead>
<tr>
<th>Diagnostic criteria</th>
<th>Chronic hepatitis B infection</th>
<th>Chronic active hepatitis B infection</th>
<th>Inactive chronic hepatitis B carrier</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• HBsAg-positive for more than 6 months</td>
<td>• HBsAg-positive for more than 6 months</td>
<td>• HBsAg-positive for more than 6 months</td>
</tr>
<tr>
<td></td>
<td>• Serum HBV DNA ≥20,000 IU/mL, but lower HBV DNA levels (2,000–20,000 IU/mL) are often seen in HBeAg-negative chronic active hepatitis B</td>
<td>• Persistent or intermittent elevation in ALT/AST levels</td>
<td>• HBsAg-positive for more than 6 months</td>
</tr>
<tr>
<td></td>
<td>• Liver histology suggestive of chronic hepatitis with moderate or severe necroinflammation</td>
<td>• Liver histology suggestive of chronic hepatitis with moderate or severe necroinflammation</td>
<td>• HBeAg negative and anti-HBeAb positive</td>
</tr>
</tbody>
</table>

HBsAg, hepatitis B surface antigen; HBV DNA, hepatitis B virus deoxyribonucleic acid; ALT/AST, aminotransferase/alanine aminotransferase ratio.
has been recently developed and validated. The score accurately estimated the risk of developing HCC at years 3, 5, and 10 in patients with chronic hepatitis B. The scoring system uses parameters including age (advanced age is associated with higher risk of HCC), gender (male patients had higher risk of HCC), HBeAg status (HBeAg positive is associated with higher risk of HCC), ALT level (higher ALT level is associated with higher risk of HCC), and viral load (higher viral load is associated with higher risk of HCC). Clinical decisions can be made based on the patient’s risk of developing HCC as assessed by the REACH-B scoring system.

Since the progression of liver diseases in chronic hepatitis B infection can lead to significant liver-related morbidity and mortality, identification of patients who require antiviral therapy through monitoring is critical to improving clinical outcomes. Table 2 summarizes the current American Association for the Study of Liver Diseases (AASLD) recommendations on the monitoring of chronic hepatitis B patients. Parameters, including the presence of fibrosis/cirrhosis, viral load, HBeAg status, and ALT level, should be considered prior to reaching any clinical decision. Although liver biopsy remains the gold standard for assessing liver fibrosis/cirrhosis, recent developments have focused on measuring liver stiffness using transient elastography (Fibroscan®, Echosens, Paris, France). Previous studies have demonstrated the diagnostic value of liver stiffness measurement in patients with significant liver fibrosis, with good correlation to liver biopsy established for patients with pericellular fibrosis. As such, liver stiffness measurement can potentially provide clinicians with a simple, noninvasive modality of liver fibrosis/cirrhosis monitoring in chronic hepatitis B infection, as well as a wide range of other liver diseases.

### Summary

Prevention of liver disease progression is the ultimate treatment goal for patients with chronic hepatitis B infection. Management of chronic hepatitis B infection patients should be guided by clinical parameters, including the presence of liver fibrosis/cirrhosis, HBV viral load, HBeAg status, ALT level, as well as host factors such as age and gender. Specialist referral should be considered for patients with active chronic hepatitis B infections to evaluation of the need for antiviral therapy.

### References

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**References:**