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# THE HONG KONG MEDICAL DIARY

# 香港醫訊

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## Hepatology

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# Contents



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# The Cover Shot


On this significant landmark in the history of the Federation of Medical Societies of Hong Kong, I have chosen the red colour to celebrate this festive occasion of her golden anniversary.

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Red, being a warm and positive colour, signifies our health care providers' utmost passion, pioneering spirits and leadership qualities in promoting health care services to our community.

**Mrs Carrie Wong**
BSc, MMedSc, MSSc, PCEd

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# Editorial

**Dr Nancy Wai-yee LEUNG**

BSc, MBBS, MSc, MD, FRCP(Edin), FRCP(Lon), FHKCP, FHKAM(Medicine)
*Specialist in Gastroenterology and Hepatology*
*Founding Chairperson Asiahep Hong Kong Ltd*

***Editor***

Dr Nancy Wai-yee LEUNG

I joined the Faculty of Medicine of The Chinese University of Hong Kong in 1985 and was tasked to establish Hepatology. At that time, Hong Kong was endemic for hepatitis B infections with a 10-15% prevalence for the hepatitis B surface antigen, viral hepatitis C was known as post-transfusional non-A non-B viral hepatitis, liver cancers were huge on presentation, cadaveric liver transplantation was just taking off with successful cyclosporine immunosuppression, and fatty liver was little known. Three decades on, the epidemiology of liver diseases in Hong Kong and globally has changed dramatically. In this issue, which is entirely dedicated to HEPATOLOGY, five outstanding hepatologists will update us with exciting advances on viral hepatitis B and C, fatty liver disease, liver cancer and liver transplantation.

Viral hepatitis B is still the most important cause of liver diseases in Hong Kong. It accounts for the majority of serious liver problems in the form of complications of cirrhosis and hepatocellular carcinoma. A universal vaccination programme for all newborns in Hong Kong since 1988 greatly reduced the incidence of mother-to-child transmission. Its impact on the incidence of cirrhosis complications and hepatocellular carcinoma will be realised in 20 years' time. Clinical benefits from antiviral therapy with a high genetic barrier for drug resistance have been substantiated. To leverage on these advances, a lot more effort has to be placed on public awareness, proper assessment of patients for therapy and management and surveillance to prevent complications.

This year is particularly exciting for viral hepatitis C. The cure for chronic hepatitis C can be achieved with eight to twelve weeks of a combination of oral agents. However, the cost is prohibiting. While transmission can be prevented by avoidance of risk activities and improvement in health care settings in the developing world, hepatitis C vaccine development is still crucial. The overall prevalence of chronic hepatitis C is around 0.5% in Hong Kong, mostly the result of having received blood transfusions years ago.

The Hospital Authority of Hong Kong recently published the Cancer Registry Data of 2011. The incidence of liver cancer has increased to 1,858 and accounted for 13.5% of all cancers in that year, male to female ratio being 3:1. The mortality rate of liver cancer is 1,536, ranked second for men. This reflects late presentation and therefore poor prognosis at the time of diagnosis. Liver cancer surveillance in the high risk population is the only way to reduce mortality. Although Hong Kong does not have published data on the incidence of advanced liver diseases, the waiting list for liver transplantation probably reflects the health burden and unmet needs. Living-related liver transplantation has transformed the transplantation landscape in Hong Kong, but advocacy for cadaveric organ donation is the mainstay .

Finally, attention must be drawn to the emerging liver disease of lifestyle that is entirely avoidable. With affluence, society tends to encourage over consumption of unhealthy food, increase intake of alcohol, and lack of exercise. Fatty liver is becoming so common that the alarm bell has to be sounded. The detrimental impact on the liver and related metabolic syndrome on overall health is surfacing. Doctors must be aware that fatty liver is not a benign insignificant finding but associated with advanced liver diseases, diabetes mellitus, hypercholesterolaemia, coronary heart disease, cerebrovascular accidents and colorectal cancer. Proper counselling and a management plan must be implemented.


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# New horizon for the management of chronic hepatitis B

**Prof Grace LH WONG**

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Prof Grace LH WONG

*This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 March 2015.*

Chronic hepatitis B virus (HBV) infections remain an important health problem in Hong Kong, affecting 10% of the adult population. Despite the implementation of universal vaccination to all newborns since 1988 and subsequent catch up vaccinations to children and adolescents, chronic hepatitis B (CHB) remains the leading cause of hepatocellular carcinoma (HCC) in this city.[1] An effective antiviral therapy for CHB is now available, which prevents disease progression from CHB to serious complications namely decompensated cirrhosis, liver failure and HCC.[2]

## Indications of antiviral therapy

Key treatment indications are defined according to the severity of disease such as presence of cirrhosis, serum alanine aminotransferase (ALT) (e.g. > 1-2 times the upper limit of normal [ULN]) and HBV DNA levels (>2,000 IU/ml). All international guidelines also recommend commencing antiviral therapy in cirrhotic patients as they are the high-risk group for HCC and decompensation.[3-5]

## Antiviral agents for CHB

Antiviral agents for CHB are classified into oral nucleos(t)ide analogues (NAs) and interferon. The former work by suppressing HBV replication by targeting at its polymerase (a reverse transcriptase).[6] Interferon has a dual mode of actions of inhibiting HBV DNA replication and modulating the host immune response against HBV.[7]

### *Interferon*

The first available antiviral therapy was conventional interferon-alfa (IFN-α), which was the only drug for CHB between 1985 and 1996. Pegylated formation of IFN-α (peginterferon), which is linked to polyethylene glycol (PEG) chains, was approved in 2005 for HBV treatment. Pegylated-interferon has a longer period of action and hence can be administered once weekly. Interferon has the advantage of a finite treatment course (24 to 48 weeks) and immunomodulatory effects. However, the side effects during treatment are common, ranging from flu-like symptoms, thyroid dysfunction, mood symptoms, to more serious thrombocytopenia and neutropenia requiring dose adjustment.[8] Although peginterferon has a high durability in HBeAg-positive patients, a proportion of patients require subsequent oral NAs due to virologic relapse after treatment.[9,10]

### *Oral nucleos(t)ide analogues (NAs)*

Oral NAs had shifted the paradigm of HBV treatment to daily oral dosing with fewer side effects since lamivudine was first approved in 1998.[11] There are currently five NAs approved for CHB treatment in Hong Kong: lamivudine, telbivudine and entecavir (nucleoside analogues), adefovir dipivoxil and tenofovir disoproxil fumarate (nucleotide analogues).[6]

NAs of earlier generations (e.g. lamivudine, adefovir) are susceptible to the emergence of drug resistance with time because of their relatively lower genetic barrier to resistance. The preferred first-line NAs by the latest international guidelines, (approved in 2005) and tenofovir disoproxil fumarate (approved in 2008) have high antiviral potency as well as a high barrier to resistance. These properties make drug resistance less of a problem nowadays.

## New horizon – from diagnostic, therapeutic to prognostic

There have been many new developments in different domains of the management of CHB. While new antiviral agents via different new pathways are currently in the pipeline, different useful diagnostic and prognostic tools are available to predict treatment response as well as future cancer risk.

## Diagnostic - quantitative HBsAg (qHBsAg)

Studies have shown that the serum HBsAg level or quantitative HBsAg (qHBsAg) correlates with that of covalently closed circular DNA (cccDNA) in the nucleus of hepatocytes.[12] True inactive carrier has been recently defined with a low HBV DNA (<2,000 IU/ml) plus a low HBsAg level (<1,000 IU/ml), as such patients had the lowest risk of HCC.[13]

qHBsAg is also well studied as a predictor of treatment response to peginterferon.[10] In HBeAg-positive patients, qHBsAg >20,000 IU/ml at week 12 or 24 can predict non-response; whereas <1,500 IU/ml at week 12 or 24 predicts HBeAg seroconversion.[14,15] In HBeAg-negative patients, HBsAg decline (either by 10% or by l log) at week 12, week 24 or the end of peginterferon therapy was also found predictive of sustained response (HBV DNA < 2,000

IU/ml or HBsAg loss) in HBeAg-negative patients.[16,17] The most discriminatory and best validated stopping rule is an absence of HBsAg decline together with a <2 log reduction in HBV DNA at week 12 in genotype D HBV infected patients.[18] These data lead to a concept of response-guided therapy for peginterferon-treated patients – early stop in non-responder, standard 48-week therapy for good responders, and extended duration of therapy (96 weeks) to partial responders.[19]

## Therapeutic – new combinations, new agents, new treatment targets

### *New combintations - new use of old agents*

Combining a potential NA (e.g. tenofovir disoproxil fumarate) with peginterferon is currently under investigation in a global large-scale randomised controlled trial (RCT) to see if this regime increases the seroclearance of HBsAg and sustained off-treatment virologic response (Clinicaltrials.gov Identifier NCT01277601). This approach is seeking its own success by synergising the potent viral suppression from NA and the immunomodulatory effect of peginterferon. The interim report of results by 72 weeks, the rate of HBsAg loss rose to 9.0% in the 48-week tenofovir plus pegylated interferon group, significantly higher than that in the 16-week tenofovir combination arm and interferon monotherapy arm (both 2.8%), and the tenofovir monotherapy arm (0%).[20]

On the other hand, whether a course of peginterferon therapy after NA-induced HBeAg-seroconversion allows early cessation of NA therapy and reduces the risk of virologic relapse is also being tested (Clinicaltrials.gov Identifier NCT02068365).

### *New oral nucleos(t)ide analogues*

Tenofovir alafenamide (formerly GS-7340) is another prodrug of tenofovir besides tenofovir disoproxil fumarate. With its better lymphoid distribution, a much lower dose of only 25mg daily is required. It is believed that a lower systemic exposure will help to avoid some the renal and bone toxicities associated with tenofovir. Two phase III RCTs are currently in progress to evaluate the safety and efficacy of tenofovir alafenamide 25mg daily versus tenofovir disoproxil fumarate 300mg daily for treatment of CHB patients (ClinicalTrials.gov Identifier NCT01940471 & NCT01940341).

Besifovir (LB80280) is an acyclic nucleotide phosphonate with similar chemical structure to adefovir and tenofovir. Recently, a phase IIb RCT compared the safety and antiviral activity of besifovir and entecavir in CHB patients.[21] At 48 weeks, 90mg and 150mg daily of besifovir were non-inferior to entecavir 0.5mg daily in treatment-naïve CHB patients. Asymptomatic L-carnitine (a transporter of fatty acid during breakdown of lipids in metabolism) depletion was observed in the majority of patients treated with besifovir. No significant changes in renal function were noted, and a minority (2.7%) experienced hypophosphataemia.

### *New treatment targets*

Now much attention has been switched back from the field of HCV to HBV therapeutics. There are many on-going clinical trials in their early phases.[22] Direct acting antiviral therapies for HBV include entry inhibitors (e.g. Myrcludex-B), small molecules that target the epigenetic control of nuclear cccDNA minichromosome, and assembly inhibitors. Indirect acting agents include immunomodulations via Toll-like receptor (TLR) and Programmed Death-1 (PD-1), therapeutic vaccines, small interfering RNA (siRNA), and other nucleic acid-based technologies. It is still too early to say which of these HBV therapies are going to succeed. But it is quite certain that some of these agents are going to provide us new insights into the novel therapeutic strategies for CHB.

## Prognostic - HCC risk scores

There are several HCC risk scores developed based on the well-established risk factors of HCC, namely advanced age, male gender, high viral load, cirrhosis etc. One of the few widely-adopted and user-friendly risk scores, the CU-HCC score, was confirmed to be accurate in both treatment-naïve and NA-treated patients.[23,24] A decrease in risk score after antiviral therapy is translated to a lower risk of HCC.[24] The CU-HCC score was recently optimised by replacing clinical cirrhosis with liver stiffness measurement (LSM), a more objective tool to detect early cirrhosis with transient elastography.[25] This new LSM-HCC score was found even more sensitive to predict HCC risk in 3 and 5 years.[25] Hence the LSM-HCC score is particularly good to identify low-risk patients.

## Future

The need of a long-term, if not indefinite, treatment duration remains a major downside of NA therapy. With the results of all these exciting clinical trials as well as the studies of new NAs, the era of achieving sustained off-treatment virologic response and even seroclearance of HBsAg with a course of antiviral therapy of a finite duration is getting close. Together with proper HCC risk stratification with risk scores, the prognosis of CHB patients will be much improved in the near future.

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## MCHK CME Programme Self-assessment Questions

**Please read the article entitled "New horizon for the management of chronic hepatitis B" by Prof Grace LH WONG and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 March 2015. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.**

**Questions 1-10: Please choose the best answer.**

**1. Since when the implementation of universal vaccination to all newborns in Hong Kong was started?**
**A. 1980**
**B. 1984**
**C. 1988**
**D. 1997**

**2. The catch up vaccinations for hepatitis B virus were for:**
**A. Infants**
**B. Children and adolescents**
**C. Adults**
**D. Elderly**

**3. The leading cause of hepatocellular carcinoma (HCC) in Hong Kong is:**
**A. Chronic hepatitis B**
**B. Chronic hepatitis C**
**C. Autoimmune hepatitis**
**D. Nonalcoholic fatty liver disease**

**4. The key treatment indications for chronic hepatitis B include:**
**A. Absence of cirrhosis**
**B. Normal serum alanine aminotransferase level**
**C. High serum HBV DNA levels (>2,000 IU/ml)**
**D. Presence of fatty liver**

**5. The side effects of interferon include:**
**A. Flu-like symptoms**
**B. Thyroid dysfunction**
**C. Mood symptoms**
**D. All of the above**

**6. The approved oral nucleos(t)ide analogues as the treatment for chroinic hepatitis B include the following EXCEPT:**
**A. Entecavir**
**B. Tenofovir disoproxil fumarate**
**C. Oseltamivir**
**D. Lamivudine**

**7. The roles of quantitative hepatitis B surface antigen (HBsAg) include:**
**A. To identify true inactive carrier**
**B. To decide the need of antiviral treatment**
**C. To decide the need of liver cancer screening**
**D. None of the above**

**8. Combing oral nucleos(t)ide analogues with peginterferon is:**
**A. associated with fewer side effects**
**B. currently recommended to all patients with chronic hepatitis B**
**C. currently under investigation and may be associated with more HBsAg seroclearance**
**D. is only recommended to Asian patients**

**9. New oral nucleos(t)ide analogues for chronic hepatitis B currently under investigation in a Phase III clinical trial include:**
**A. Boceprevir**
**B. Tenofovir alafenamide**
**C. Sofosbuvir**
**D. Telbivudine**

**10. Liver stiffness measurement (LSM) replaces which of the following component in the CU-HCC score?**
**A. Serum albumin**
**B. HBV DNA**
**C. Age**
**D. Clinical cirrhosis**

## ANSWER SHEET FOR MARCH 2015

**Please return the completed answer sheet to the Federation Secretariat on or before 31 March 2015 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.**

# New horizon for the management of chronic hepatitis B

**Prof Grace LH WONG**
*Institute of Digestive Disease and Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong*

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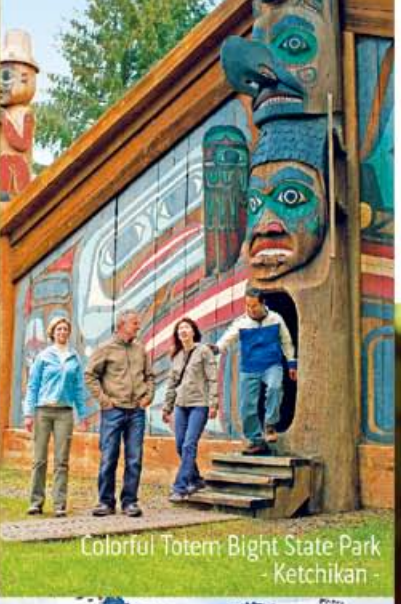
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# The road to eradication of hepatitis C virus

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Dr Wai-kay SETO

## The changing paradigm of chronic hepatitis C virus infection

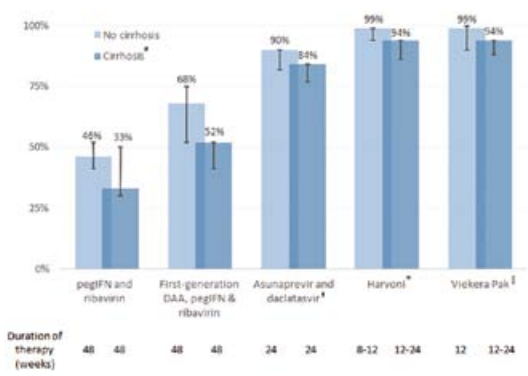
Although an estimated 180 million individuals are infected with hepatitis C virus (HCV) worldwide[1], the impact of chronic HCV infection in Hong Kong has been traditionally perceived to be low. Indeed, the seroprevalence of anti-HCV in various population groups in Hong Kong varies between 0.14-0.4% only[2], with HCV being an uncommon cause of hepatocellular carcinoma[3]. One would assume, with the universal screening of anti-HCV for all blood products implemented for more than 20 years, the impact of HCV in Hong Kong would only further decline with time. Nonetheless, we are now seeing a changing paradigm in the demographics of chronic HCV infection. Half of anti-HCV positive blood donors in Hong Kong are aged below 21 years, with no history of traditional high-risk behaviours including blood transfusion, intravenous drug use, dialysis and tattooing[4]. A possible contributing source of infection could be from the China Mainland, where the anti-HCV seroprevalence is estimated to be between 2.2 to 3.5%, with approximately 30 million infected individuals[5,6]. Non-traditional risk factors of HCV infections have been identified in the Mainland, including dental surgery, cosmetic surgery, acupuncture and intravenous or intramuscular drug injections[7] – all possibly related to contaminated medical equipment[8]. With the continued influx of migrants from the Mainland to Hong Kong, the clinical impact of HCV in Hong Kong could actually increase in the future.

One unique characteristic of HCV is an increased rate of disease progression and cirrhosis risk when acquiring the infection at an older age. For patients infected at age ≥40 years, the risk of cirrhosis after 16 years of infection is 50%[9]. HCV can be divided into 6 genotypes, with HCV genotype 1 being the most common in Hong Kong (63%), followed by genotype 6 (30%)[10]. The proportion of genotype 1 infection especially subtype 1b would probably further increase in the future, since genotype 1b contributes to the majority of HCV infections in China[6].

## Progress of HCV therapeutics

Until recently, standard-of-care HCV treatment consisted of pegylated interferon injections and oral ribavirin for 24 to 48 weeks, with durations depending on the genotype. Treatment is hampered by the poor tolerability of pegylated interferon (e.g. flu-like symptoms, neutropenia, thrombocytopenia, thyroid dysfunction, depression) and ribavirin (anaemia). The sustained virological response (SVR, defined as serum HCV RNA negativity 12-24 weeks post-treatment) for 48 weeks treatment in genotype 1 infections is also only 30-56%[11, 12] (Figure 1), the lowest of all 6 HCV genotypes. The suboptimal response rates, side-effect profile, need for injections and multiple pill burden of ribavirin meant drug non-adherence is a commonly-faced issue. In addition, no other therapeutic options existed for patients contraindicated or intolerant to interferon-based therapy.

**Figure 1.** The sustained virological response rates of different therapeutic regimes for chronic HCV genotype 1 infection




Bar charts shows sustained virological response rates for treatment-naïve genotype 1b infection, while error bars show variation in results found in different population subgroups, including treatment-experienced patients and patients with genotype 1a
*Only inclusive of Child's A cirrhosis
†Only including data on genotype 1b infection
‡Consist of sofosbuvir and ledipasvir
§Consist of ombitasvir, paritaprevir, dasabuvir and ritonavir. For cirrhosis, addition of ribavirin is required
HCV, hepatitis C virus; pegIFN, pegylated interferon; DAA, direct-acting antiviral agents

The molecular characterisation of the HCV viral genome has led to the development of oral direct-acting antiviral agents (DAAs) targeting the nonstructural viral genomes essential for viral replication, including NS3, NS5A and NS5B. The first-generation DAAs were NS3/4A protease inhibitors including boceprevir (Merck Sharp and Dohme) and telaprevir (Johnson & Johnson). Both were approved for use by the United States Food and Drug Administration (FDA) in 2011. When either were used with pegylated interferon and ribavirin for 48 weeks, the SVR rates for genotype 1 increased to 68-75% in treatment-naïve patients[13,14], and 51-59% in patients with previous treatment[15,16] (Figure 1). Despite the considerable improvements in SVR, both drugs had significant side-effects (boceprevir – anemia, telaprevir

– rash). In addition, in order to avoid the development of antiviral resistance, concomitant treatment with pegylated interferon and ribavirin is necessary, meaning the clinical issues associated with interferon-based therapy remained unresolved.

Nonetheless, SVR has also been demonstrated to be extremely durable. SVR-achieving patients had negligible rates of relapse and also histological improvement, with reversal of liver fibrosis and cirrhosis[17]. All available evidence suggest SVR is tantamount to cure of HCV infection.

## Interferon-free regimens – spectacular rates of HCV eradication

HCV therapeutics is undergoing a dramatic transformation with the introduction of interferon-free regimens based on next-generation DAAs, bringing forth shorter durations of treatment, good drug tolerability and very high SVR rates. All DAAs are prescribed in combination to improve efficacy and reduce antiviral resistance. This article will concentrate on the DAA combinations that would likely be available in Hong Kong (Figure 1).

### *Asunaprevir and daclatasvir (Bristol-Myers Squibb) – 24 weeks*

The dual regimen of asunaprevir, a NS3/4A protease inhibitor and daclatasvir, a NS5A inhibitor was approved for use in Japan in July 2014. In a phase 3 study performed across 18 different countries involving 645 patients with genotype 1b infection, asunaprevir and daclatasvir for 24 weeks, without the addition of pegylated interferon or ribavirin, achieved an SVR rate of 90% in treatment-naïve patients and 82% among non-responders or patients intolerant or contraindicated for interferon (Figure 1). Patients with compensated cirrhosis were also included; overall the SVR rate for cirrhotic patients was 84%. The two DAAs were also well-tolerated, with only 2% of patients having adverse events (elevation of liver enzymes) requiring treatment discontinuation[18].

While the combination of asunaprevir and daclatasvir can be recommended for HCV genotype 1b which is the predominant genotype in Chinese HCV patients, the SVR rate for genotype 1a had been suboptimal[19]. This subgenotypic difference in response implies HCV subgenotypic testing would be required in determining suitability for treatment.

### *Sofosbuvir and ledipasvir (Gilead Sciences) – 8, 12 or 24 weeks*

Other interferon-free regimens of shorter durations achieved even higher SVR rates (>90%). Previously, the combination of sofosbuvir, a NS5B inhibitor, with pegylated interferon and ribavirin for only 12 weeks achieved a SVR rate of 90%[20]. This was followed by studies showing the interferon-free combination of sofosbuvir with ledipasvir, a NS5A inhibitor, for 12 weeks in genotype 1 infections achieved SVR rates between 94-99%[21,22]. Addition of ribavirin did not achieve additional benefit, and there was no significant difference in SVR rates when comparing genotype 1a versus 1b. For patients with compensated cirrhosis, SVR rates were between 86-94%, although lengthening the treatment duration to 24 weeks improved SVR rates to almost 100%. Safety profile was excellent; among all 539 patients receiving sofosbuvir and ledipasvir for 12 weeks, only 2 (0.4%) discontinued therapy due to fatigue and headache.

More impressive is the possible shortening of sofosbuvir-ledipasvir treatment duration to only 8 weeks. In treatment-naïve noncirrhotic genotype 1 patients, the SVR rate was maintained at 94%[23]. The combination of sofosbuvir and ledipasvir was approved by the US FDA in October 2014 for HCV genotype 1 infection and is now marketed as a once-daily combined tablet (trade name: Harvoni), which would likely further improve drug compliance. Currently, sofosbuvir and ledipasvir are recommended for 12 weeks in treatment-naïve patients with or without cirrhosis and treatment-experienced patients without cirrhosis, and for 24 weeks in treatment-experienced patients with cirrhosis. For treatment-naïve noncirrhotic patients with a baseline HCV RNA below 6 million IU/mL, 8 weeks of treatment could also be considered.

### *Ombitasvir, paritaprevir, dasabuvir and ritonavir (AbbVie) – 12 or 24 weeks*

A third interferon-free multidrug regimen (trade name: Viekira Pak) for HCV genotype 1 infections consists of the following DAAs: ombitasvir, a NS5A inhibitor; dasabuvir, a NS5B inhibitor; paritaprevir, a NS3/4A protease inhibitor, and ritonavir, a pharmacoenhancer used to increase paritaprevir drug levels to allowing once-daily dosing. Ombitasvir, paritaprevir and ritonavir are formulated into 1 tablet to be taken as 2 tablets once daily, while dasabuvir is formulated separately, to be taken as 1 tablet twice daily.

In noncirrhotic HCV genotype 1b infections, Viekira Pak for 12 weeks achieved a SVR rate 99-100%[24,25]. For cirrhotic HCV genotype 1b, Viekira Pak together with ribavirin for 12 weeks achieved a SVR rate of 94.2%[26]. Genotype 1a SVR rates were slightly lower; 90.2% for noncirrhotics, 88.6% for cirrhotics when including ribavirin. Nonetheless, the addition of ribavirin increased the SVR rate for noncirrhotics to 97.0%, while extending the treatment duration to 24 weeks for cirrhotics increased the SVR rate to 94.2%[24,26]. Similar to previous regimens, Viekira Pak was well-tolerated, with treatment discontinuation only required in 0.3% due to headache and fatigue. Viekira Pak has also achieved a high SVR rate in liver transplant recipients with recurrent infection, a historically difficult-to-treat population[27].

Viekira Pak was approved by the US FDA for treatment HCV genotype 1 infections in December 2014. Pill count could become an issue especially when ribavirin is needed, although improved packaging and description could help in maintaining drug compliance.

## The end is nigh for HCV?

The answer is unfortunately no.

Despite the remarkable SVR rates achieved by the above DAA combinations, many difficulties still exist in genuinely eradicating HCV.The first hurdle is drug

cost. Harvoni, the combined tablet of sofosbuvir and ledipasvir, is priced at $63,000 US dollars for 8 weeks and $94,500 US dollars for 12 weeks. Viekira Pak for 12 weeks is priced at $ 83,319 US dollars. Asunaprevir and daclatasvir for 24 weeks in Japan is priced at 2.65 million Japanese Yen. The high cost of DAAs will preclude its wide usage in many low- or middle-income countries, or in regions which rely heavily on public health services, e.g. Hong Kong. Even in high-income countries, payers of medical resources might only selectively approve DAAs for certain patient subgroups and not for all patients[28].

There is a wide disparity between the current DAAs prices and their estimated minimal manufacturing cost: the predicted minimum cost for a 12 week regimen of sofosbuvir and daclatasvir is estimated at $136 and $30 US dollars respectively[29]. Hence drug-access programmes are urgently needed to improve the affordability of DAAs, which would require the mutual cooperation of drug manufacturers, governments, health care funders and non-government organisations. One example is the Gilead Access Programme aimed at developing countries, including Cambodia, India, Indonesia and Vietnam. DAA combinations should not be limited by their manufacturer; the cross-pharmaceutical combination of sofosbuvir and daclatasvir can also achieve a very high SVR rate of 98%[30]. The relative success of providing expensive antiretroviral treatment to individuals with HIV in the developing world illustrates that such enormous challenges could be overcome[31].

Other hurdles exist. Pangenotypic coverage of DAAs is needed. Current DAA combinations lack evidence for usage in decompensated liver cirrhosis, meaning measures to improve the screening, diagnosis and monitoring of HCV need to be in place. Besides decompensated cirrhosis, studies involving special population groups (e.g. HIV co-infection, end-stage renal disease, post-renal transplantation) are needed. Reinfection is always a possibility, implying education and health promotion targeting high-risk behaviours are also essential. Only through the collaboration of the global health community then we can truly be on the road to the eradication of HCV.

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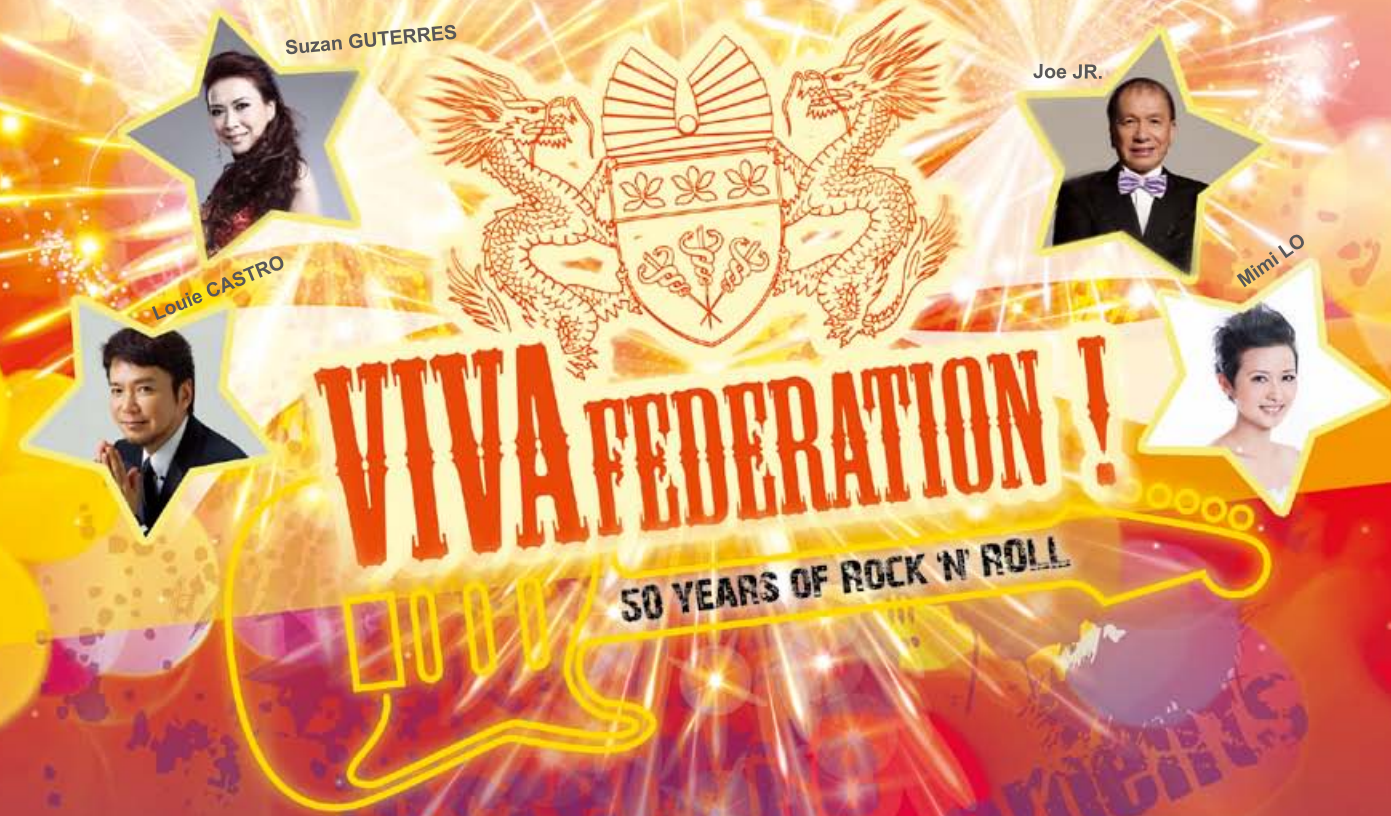


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# The emerging health burden – fatty liver diseases

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Prof Vincent WONG

Fatty liver is common. In Hong Kong, 25-30% of the general adult population have fatty liver.[1] Non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease are the main aetiologies of fatty liver, with the former being more common in Hong Kong. Secondary causes of fatty liver are much less common but should be suspected if the clinical presentation is atypical, e.g. fatty liver in the absence of the metabolic syndrome and excessive alcohol intake (Table 1). This article focuses on the assessment and management of NAFLD and alcoholic liver disease.

*Table 1. Causes of fatty liver*

| |
|---|
| Non-alcoholic fatty liver disease |
| Alcoholic liver disease |
| Endocrine disorders, e.g. hypothyroidism, polycystic ovarian syndrome, hypopituitarism, growth hormone deficiency, Cushing's syndrome, hypogonadism |
| Drug-induced steatosis, e.g. amiodarone, tamoxifen, methotrexate, steroids |
| Hepatitis C virus infection |
| Wilson's disease |
| Total parenteral nutrition |
| Total parenteral nutrition |
| Disorders of lipid metabolism, e.g. abetalipoproteinaemia, hypobetalipoproteinaemia, familial combined hyperlipidaemia, glycogen storage disease, Weber-Christian syndrome, lipodystrophy |

## NON-ALCOHOLIC FATTY LIVER DISEASE

Based on disease activity, NAFLD can be further divided into simple steatosis (or non-alcoholic fatty liver) and non-alcoholic steatohepatitis (NASH). NASH is the active form of NAFLD with hepatic necroinflammation and tissue injury. As a result, there is faster fibrosis progression. NASH patients are at a higher risk of developing cirrhosis, hepatocellular carcinoma (HCC) and liver failure. Once a patient reaches the stage of cirrhosis, the annual incidence of HCC is around 1-2%, which is not much different from that in patients with cirrhosis from other liver diseases.

That said, only around 20% of NAFLD patients have NASH. Patients with simple steatosis run a benign clinical course and should not be subject to unnecessary intervention and treatment. Therefore, one of the important jobs of doctors is to evaluate the severity of NAFLD.

### *Diagnosis and assessment*

The diagnosis of NAFLD is usually straightforward. Most patients are asymptomatic and have NAFLD detected incidentally during health check or investigations for unrelated disorders. Some patients may have fatigue or abdominal discomfort, but those symptoms are non-specific. Hepatomegaly may be detected on careful examination. Otherwise, stigmata of chronic liver diseases are rarely found. Signs of portal hypertension like ascites and splenomegaly occur when the liver begins to decompensate.

Abdominal ultrasonography is the most commonly performed investigation to confirm the diagnosis of fatty liver. Fatty liver has a bright echotexture. Because ultrasound energy dissipates faster in fatty liver, the deeper tissue also appears more blurred. After detecting fatty liver, the diagnosis of NAFLD requires the exclusion of other liver diseases. In Hong Kong, we at least have to carefully exclude the history of excessive alcohol consumption and perform blood tests to exclude hepatitis B virus and hepatitis C virus infection.

Liver function tests are often performed. Nevertheless, over half of the patients with NAFLD may have normal alanine aminotransferase (ALT) levels. The levels of liver enzymes also correlate poorly with disease severity.

Traditionally, a liver biopsy was the only investigation to determine the severity of NAFLD. However, it is an invasive procedure and is often not accepted by patients. Besides, it is unrealistic to recommend liver biopsy for a disease that affects a quarter of the general population.

In recent years, Fibroscan (Echosens, Paris, France) has emerged as a popular non-invasive test of liver fibrosis. It uses shear wave technology to measure the stiffness of the liver. The measurement is fast and reproducible and has been validated in NAFLD with an overall accuracy of 80-90% in diagnosing advanced liver fibrosis and cirrhosis.[2] The main drawback of Fibroscan is that measurements may fail in obese patients. To cater for this problem, the manufacturer has produced an XL probe that can also successfully measure liver stiffness in around 90% of obese patients. Moreover, the latest models of Fibroscan can also measure the controlled attenuation parameter, which reflects the amount of hepatic fat. It is therefore a convenient assessment of both hepatic steatosis and fibrosis in NAFLD patients.

Other radiological techniques like acoustic radiation forced impulse, real-time ultrasound elastography and

magnetic resonance elastography can also be used to assess NAFLD patients, though these modalities are less widely available and require interpretation by specially trained radiologists.

Another way to assess disease severity is to use prediction scores based on clinical parameters. The current American guidelines support the use of the NAFLD fibrosis score for screening.[3] The NAFLD fibrosis score is calculated as:

-1.675 + 0.037 × age (years) + 0.094 × body mass index (kg/m$^2$) + 1.13 × impaired fasting glucose/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio – 0.013 × platelet (×10$^9$/l) – 0.66 × albumin (g/dl)
(ALT = alanine aminotransferase; AST = aspartate aminotransferase; http://nafldscore.com/index.php)

A score below -1.455 has over 90% negative predictive value in excluding advanced fibrosis and cirrhosis.

In addition, since NAFLD is closely associated with the metabolic syndrome, doctors should not just focus on liver assessment. The suggested diagnostic workup for NAFLD patients is listed in Table 2. Table 3 illustrates the interpretation of the Fibroscan and NAFLD fibrosis score.

*Table 2. Diagnostic workup for NAFLD*

| | |
|---|---|
| **Diagnosis** | Abdominal ultrasonography<br>Alcohol history<br>Hepatitis B surface antigen and anti-hepatitis C virus antibody<br>Workup for other liver diseases as clinically indicated |
| **Liver assessment** | Liver function test<br>Fibrosis assessment, e.g. Fibroscan, NAFLD fibrosis score |
| **Associated disorders** | Body mass index<br>Blood pressure<br>Fasting plasma glucose ± oral glucose tolerance test<br>Lipids<br>Workup for cardiovascular disease and obstructive sleep apnoea as appropriate |

*Table 3. Interpretation of Fibroscan and NAFLD fibrosis score in NAFLD patients*

| Examination | Values | Interpretation |
|---|---|---|
| **Fibroscan** | | |
| **Controlled attenuation parameter (dB/m)** | <222 | S0 |
| | 222-232 | S1 |
| | 233-289 | S2 |
| | ≥290 | S3 |
| **Liver stiffness (kPa)** | <7.9 | F0-F2 |
| | 7.9-9.5 | Indeterminate |
| | ≥9.6 | F3-F4 |
| | ≥11.5 | F4 |
| **NAFLD fibrosis score** | < -1.455 | F0-F2 |
| | -1.455 to 0.675 | Indeterminate |
| | ≥0.675 | F3-F4 |

*S0 = steatosis with <10% hepatocytes; S1 = 11-33%; S2 = 34-66%; S3 = >66%*
*F3 = advanced fibrosis; F4 = cirrhosis*

### *Treatment*

Lifestyle modification remains as the most important management of NAFLD. A healthy diet and regular exercises are recommended. Patients should reduce carbohydrate and fat intake. In particular, they should avoid refined sugars and saturated fat. In addition, a high fructose intake is strongly associated with NAFLD. NAFLD patients should thus avoid beverages with high fructose corn syrup such as soft drinks.

Pharmaceutical treatment is only recommended for patients with confirmed NASH. Current guidelines support the use of vitamin E or pioglitazone in selected patients based on randomised controlled trials showing histological improvements with treatment. Vitamin E is an anti-oxidant, and the recommended dose is 800 IU per day. Although it effectively lowers liver enzymes and reduces hepatic steatosis and necroinflammation, its long-term safety is unclear. Some studies suggest that vitamin E use may increase the long-term mortality, though the magnitude is small. Pioglitazone is a thiazolidinedione that is used for the treatment of type 2 diabetes. It increases insulin sensitivity and similarly improves liver enzymes and liver histology. The main side effect of pioglitazone is weight gain.

One common misconception concerns the use of lipid lowering drugs in NAFLD patients. Because increased liver enzymes is a known side effect of statins, some doctors hesitate to use them in patients with liver diseases. Nevertheless, significant hepatotoxicity has not been detected in randomised controlled trials and cohort studies with serial liver biochemistry and liver biopsies. If anything, NAFLD patients taking statins are more likely to have normal liver enzymes. In patients with significant dyslipidaemia and/or associated metabolic diseases, the benefits of statins outweigh the risks.

In patients with morbid obesity, bariatric surgery is the most effective method for weight reduction. Bariatric surgery can also improve liver histology in patients with concomitant NAFLD.

## ALCOHOLIC LIVER DISEASE

Although alcoholic liver disease has not been a major health issue in Hong Kong, the worldwide consumption of alcohol is increasing. In USA, alcoholic liver cirrhosis is the second leading indication for liver transplantation. Excessive alcohol consumption leads to hepatic steatosis, oxidative stress, lipid peroxidation and endoplasmic reticulum stress.

Though significant liver injury mostly occurs when the daily alcohol consumption exceeds 80 g, the risk of developing alcoholic liver disease begins at 30 g per day. Women are at a higher risk of alcoholic liver disease. The current recommended alcohol intake is less than 30 g per day in men and 20 g per day in women, which roughly corresponds to 3 and 2 drinks, respectively.

### *Diagnosis and assessment*

Patients with alcoholic liver disease are asymptomatic until a later stage. Nevertheless, since excessive alcohol consumption is a prerequisite for the development of alcoholic liver disease, the patients may have other concomitant problems. Some patients may have features of alcohol dependence such as tolerance and withdrawal symptoms. At the clinic setting, the CAGE questionnaire may be quickly performed to detect alcoholism (Table 4). Moreover, patients with alcoholism may also suffer from chronic pancreatitis and have chronic abdominal pain, steatorrhoea and malabsorption. Furthermore,

excessive alcohol has effects on the nervous system. The Wernicke-Korsakoff syndrome and peripheral neuropathy may be present. On physical examination, patients with alcoholic liver disease often have hepatomegaly because of fatty liver. Stigmata of chronic liver disease such as spider naevi are more common in alcoholic liver disease. Alcoholics may also have parotid swelling.

*Table 4. CAGE questionnaire for alcoholism*

| |
|---|
| Have you ever felt you needed to Cut down on your drinking? |
| Have people Annoyed you by criticising your drinking? |
| Have you ever felt Guilty about drinking? |
| Have you ever felt you needed a drink first thing in the morning (Eye-opener) to steady your nerves or to get rid of a hangover? |

Because of alcohol-induced mitochondrial toxicity, the AST level is often higher than the ALT level; both enzymes however seldom exceed 300 IU/l. Gamma-glutamyl transpeptidase is induced by alcohol and may be used to detect and monitor alcohol abuse. Macrocytosis is also common.

Abdominal ultrasonography can detect fatty liver, cirrhosis and portal hypertension. Nevertheless, it is not sensitive to mild fatty liver and early cirrhosis. Liver biopsy and Fibroscan may be performed to assess disease severity as described in the last section.

### *Severe alcoholic hepatitis*

Severe acute alcoholic hepatitis is a unique presentation of alcoholic liver disease. The patient may present with fever, anorexia and jaundice. The condition should be suspected in a patient with recent liver decompensation. It can progress to liver failure rapidly and carries a high mortality rate. Some centres routinely perform liver biopsy to confirm the diagnosis, though the practice is debatable.

### *Treatment*

The most important treatment for alcoholic liver disease is to avoid harmful drinking. A multidisciplinary approach with the involvement of primary care physicians, hepatologists, psychiatrists and allied health workers is often required. The contribution of patient support groups such as Alcoholics Anonymous (http://aa-hk.org/Chinese.htm) cannot be overemphasised.

When a patient with alcoholic liver disease is admitted to the hospital, apart from treating the acute medical problem, alcohol withdrawal and delirium tremens should be treated aggressively. Benzodiazepines such as chlordiazepoxide may be used for this purpose. Thiamine supplements should also be given.

The Maddrey discriminant function predicts the mortality of patients with acute alcoholic hepatitis. It is calculated as (4.6 × [patient's prothrombin time – control prothrombin time (seconds)]) + total bilirubin (mg/dl). When the score is 32 or above, the administration of systemic steroids or pentoxifylline may improve the short-term mortality. Recent data suggest that systemic steroids are superior to pentoxifylline.[4] Nevertheless, steroids are associated with high rates of infections, and the mortality in the long run remains high.

Liver transplantation in patients with alcoholic liver disease is highly controversial. The main concerns include alcohol reinstatement and poor adherence to immunosuppressants and follow-up. However, liver transplantation for patients with alcoholic hepatitis has been successfully performed in France with excellent long-term outcomes.[5] In many countries, a period of alcohol abstinence for at least 6 months is often required before a patient can be listed for transplantation.

## CONCLUSIONS

NAFLD and alcoholic liver disease are the most common causes of fatty liver worldwide. Doctors have important roles in assessing disease severity, providing patient education and offering prompt and effective treatments.

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# Dermatological Quiz

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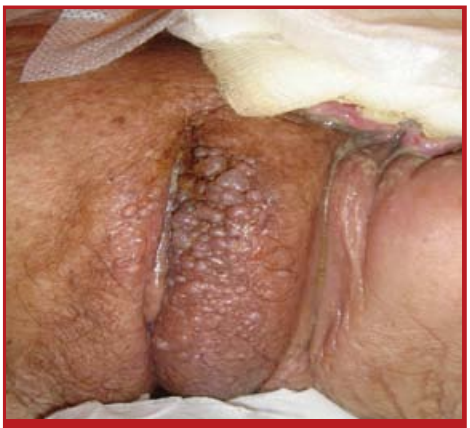

*Fig. 1: Multiple vesicular lesions over mainly left vulva*

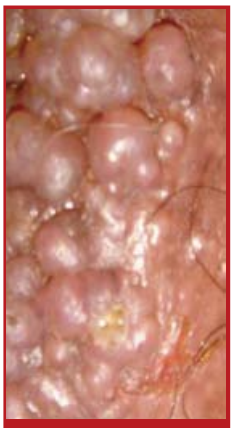

*Fig. 2: Closer view of the vesicular lesions*

This 80-year-old woman had history of carcinoma of rectum and carcinoma of uterus with operation and radiation therapy done three years ago. She was bed bound and on Ryle's tube feeding. She was noticed to have clusters of vesicular lesions over both vulva (Fig.1 & Fig.2). Each vesicle was around three mm in diameter. The vesicles were mainly on the left vulva without causing any symptom.

## Questions:

1. What is the diagnosis of her skin lesion?
2. What is the precipitating factor and why the left side is more severe than the right side?
3. How do you treat this patient?

*(See P.36 for answers)*

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**Presentation:** Film-coated tablet containing 300 mg of tenofovir disoproxil fumarate (TDF). **Indications:** 1. Treatment of chronic hepatitis B (CHB) in adults. 2. In combination with other antiretroviral medicinal products for treatment of HIV-1 infected adults and pediatric patients 12 years of age and older. **Dosage:** Adults: One tablet once daily taken orally, without regard to food. Pediatric patients: CHB: Not recommended; HIV-1: One tablet once daily taken orally, without regard to food for patients ≥12 years of age and ≥35 kg. Elderly: Insufficient data to make dose recommendations for patients >65 years. The dosing interval of VIREAD should be adjusted in patients with baseline creatinine clearance <50 mL/min. **Contraindications:** None. **Warnings and Precautions:** Lactic acidosis/severe hepatomegaly with steatosis; severe exacerbation of hepatitis after discontinuation of anti-HBV treatment; new onset or worsening renal impairment; coadministration with products containing TDF or adefovir dipivoxil; patients coinfected with HIV-1 and HBV; decreases in bone mineral density; fat redistribution; immune reconstitution syndrome; early virologic failure. **Interactions & Side effects:** refer to Package Insert.
**Before prescribing, please consult full prescribing information which is available upon request.**



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# Update on management of hepatocellular carcinoma

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## INTRODUCTION

Hepatocellular carcinoma (HCC), the most common primary liver cancer, is the number three cancer killer in Hong Kong. There are about 1,700 new cases per year, and about 1,500 patients died of the disease. The incidence of HCC in Hong Kong is much higher than that in Western countries, and is related to the high incidence of hepatitis B virus (HBV) infection in Southeast Asia. More than 80% of all HCC in Hong Kong are associated with chronic HBV infection. Other aetiologies include hepatitis C infection, alcohol abuse, metabolic diseases and unknown causes. Hepatic resection remains the treatment of choice that can offer a meaningful chance of long-term survival for patients with HCC. Liver transplantation is the preferred treatment for the selected group of patients with chronic liver disease and early HCC. Other treatment modalities include local ablative therapy, regional chemotherapy, systemic chemotherapy, target therapy and radiotherapy.

## EVALUATION AND SELECTION CRITERIA FOR RESECTION

Careful preoperative evaluations of the tumour status and the patients' condition are essential for the successful surgical management of patients with HCC. These include liver function, chest X-ray, ultrasonography, and helical contrast computed tomography (CT) scan or magnetic resonance imaging (MRI) of the upper abdomen. CT scan and MRI are considered suitable for assessment of the relationship of the tumour to the major hepatic vasculatures, detection of satellite nodules or intrahepatic metastases, tumour invasion to the major vessels including the inferior vena cava and the portal vein.[1] PET scan especially with $^{11}$C-acetate has recently been proved to be useful in the differentiation of HCC from other benign hepatic lesions and in the detection of distant metastases.[2]

The usual selection criteria of patients for hepatic resection in terms of the tumour status include the absence of extrahepatic metastasis and absence of tumour thrombi in the inferior vena cava or main portal vein, although hepatic resection with removal of tumour thrombi in these major vessels has been advocated. The role of hepatic resection for bilobar HCC is more controversial. A major hepatic resection in one lobe combined with a wedge resection for a smaller lesion in the other lobe is possible in some patients. Alternatively, a hepatic resection in one lobe can be combined with local ablation of a smaller lesion in the contralateral lobe using radiofrequency ablation. A previous study showed that hepatic resection for patients with bilobar HCC resulted in a better survival outcome than non-resectional therapies.[3] Since the majority of the patients with HCC have underlying chronic liver diseases including cirrhosis, careful assessment of the liver function reserve is important in patient selection for hepatic resection to avoid postoperative liver failure and mortality. The Indocyanine green (ICG) clearance test is a useful investigation in predicting postoperative mortality in patients undergoing major hepatic resections.[4]

Measurement of the volume of the liver remnant by CT volumetry has been shown to be helpful in selecting patients for a major hepatic resection.[5] For patients who require a major hepatic resection for HCC, but have inadequate liver remnant volume, preoperative portal vein embolisation can be used in selected patients to induce atrophy of the right lobe of the liver that harbours the HCC, and hypertrophy of the left lobe of the liver.[6] It allows a safer hepatic resection in patients who have a small liver remnant, and helps to minimise the postoperative morbidity and mortality.

## OPERATIVE TECHNIQUES

A right subcostal or a bilateral subcostal incision with an upward midline extension is sufficient in most circumstances for hepatic resection for HCC. With a self-retaining retractor, the costal arch is pulled up cranially and the entire anterior surface of the liver can be exposed. The use of an ultrasonic dissector is recommended for accurate and safe parenchymal transection of the liver with less operative blood loss and a wider tumour-free resection margin compared with the modified finger-fracture technique.[7]

A right or extended right hepatic resection for large HCC represents one of the major challenges to surgeons. Complete mobilisation of the right lobe of the liver with the right hepatic vein controlled outside the liver before parenchymal transection has been a standard for the conventional approach during a major right hepatic resection for HCC. However, injudicious mobilisation of the liver in the conventional approach may have the theoretical risks of excessive bleeding caused by avulsion of the hepatic vein and caval branches, prolonged ischaemia of the liver remnant from rotation of the hepatoduodenal ligament, iatrogenic tumour rupture, and spillage of cancer cells into the systemic circulation. Alternatively, the anterior approach can be

adopted for patients with major right hepatic resections for HCC. The technique involves initial vascular inflow control, completion of parenchymal transection, and complete venous outflow control, before the right lobe is mobilised.[8] It was considered to have beneficial effects in preserving the liver function of the liver remnant by avoiding warm ischaemia of the latter related to pedicle torsion during mobilisation of a huge tumour. A prospective randomised study on 120 patients with large right lobe HCCs has shown that the anterior approach technique was associated with significantly better operative and survival outcomes.[9]

Traditionally, an abdominal drain is routinely inserted into the subphrenic or subhepatic space close to the resection surface in patients who have undergone hepatic resections. This serves to release the intraabdominal tension due to ascitic fluid accumulation, and allows the monitoring of the occurrence of postoperative intraabdominal bleeding, as well as the detection and drainage of any bile leakage. In a prospective randomised study, 104 patients who had underlying chronic liver diseases were randomised to have either closed suction abdominal drainage or no drainage after elective hepatic resection. A significantly higher overall operative morbidity in the drainage group was observed. This was related to a higher incidence of wound complications and septic complications in the drainage group compared with the non-drainage group. The postoperative hospital stay of the drainage group was also significantly longer than that of the non-drainage group.[10] As a result, routine abdominal drainage after hepatic resection for HCC is not recommended.

Laparoscopic liver resection has been advocated recently and is considered feasible in a selected group of patients with hepatocellular carcinoma. Lesions located in the posterior or superior part of the liver are generally considered unsuitable for laparoscopic approach, because of the limited visualisation and the difficulty in controlling bleeding. Therefore laparoscopic resection is usually performed in selected patients with small peripherally and anteriorly located tumours.[11] The technique is safe in the hands of trained surgeons with expertise in hepatobiliary and laparoscopic surgery, with acceptable postoperative and oncologic outcomes. However, whether it is comparable to conventional open resections in terms of operative and long term survival outcomes requires evaluation in a prospective randomised controlled trial setting.

## OPERATIVE OUTCOMES

About a decade ago, hepatic resection was considered a risky operation with a high operative blood loss and operative mortality. More than 95% of the patients received blood transfusion and hospital mortality rate was as high as 10%, especially in patients with liver cirrhosis. With careful operative and perioperative management, hepatic resection has become a relatively safe operation, and operative mortality has rarely occurred. Operative blood loss has significantly decreased in recent years, and blood transfusion is only required in about 2% of the patients. The 3-year and 5-year survival rates of patients who underwent hepatic resections for HCC are >60% and >50%, respectively.[12]

## OTHER SURGICAL TREATMENT MODALITIES

If partial hepatectomy is contraindicated, local ablation can be offered for cure. Depending on various factors including the tumour size and location, ablation therapy can be performed with a percutaneous, laparoscopic or an open laparotomy approach. There are several ablative methods including percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), microwave ablation, cryotherapy and high-intensity focused ultrasound. RFA has currently become the most frequently employed ablative treatment modality for HCC. RFA could achieve a complete tumour ablation rate of up to 95% in solitary HCC of less than 3 cm in diameter. For small HCC, it has also been shown in randomised studies that the 3-year survival rates between ablation and partial hepatectomy were comparable, although RFA appeared to have an inferior disease-free survival outcome.

Liver transplantation appears to be the preferred treatment option in patients with early HCC with underlying chronic liver diseases. HCC patients who meet the "Milan criteria" (solitary tumour smaller than 5 cm in size, or 2 to 3 tumour nodules, each smaller than 3 cm without vascular invasion or extra-hepatic disease) are considered eligible for liver transplantation.[13] In patients with HCC and within the Milan criteria, the tumour recurrence rate after liver transplantation is low (<15% at 5 year) with a 5-year survival rate about 70%. The University of California San Francisco (UCSF) criteria are also commonly employed for selecting patients with HCC for liver transplantation.[14] They include patients with a single lesion smaller than 6.5 cm, or 2 to 3 lesions, each smaller than 4.5 cm with a maximum tumour burden of 8.0 cm. The reported results of liver transplantation using the UCSF criteria are comparable to those based on the Milan criteria. Due to the scarce availability of deceased donors, partial liver grafts from live donors are frequently used for liver transplantation in patients with HCC especially in Asian countries.

## PALLIATIVE TREATMENT

If curative options are not feasible, palliative treatment including loco-regional therapy can be considered. Since HCC tumour nodules rely mostly on arterial blood supply, selective delivery of intra-arterial chemotherapeutic agents, embolic agents or radioactive substances into the tumours can effectively induce tumour necrosis. Chemoembolisation (TACE) and radioembolisation (TARE) are transarterial locoregional therapies that have gained widespread recognition. TACE is shown to result in a significantly prolonged overall survival when compared to best supportive treatment. For TARE, yttrium-90 microspheres are injected through the hepatic artery, become trapped at the pre-capillary level and emit internal radiation to kill the tumour cells. The reported outcome of TARE is similar to that of TACE in published studies. In patients who are considered not suitable for loco-regional therapy, including those with extrahepatic disease, systemic chemotherapy or targeted therapy with sorafenib has been shown to prolong survival.

## SUMMARY

With recent advances including more accurate preoperative evaluation, improved perioperative care and improved operative techniques, satisfactory results of hepatic resection for HCC with low operative mortality and good long-term survival outcomes have been achieved. Liver transplantation provides an ideal treatment option for patients with early HCC associated with chronic liver diseases especially cirrhosis. Local ablative treatment can result in excellent survival outcomes in selected groups of patients. Effective palliation and prolonged survival in patients not suitable for surgical treatment can also be achieved with loco-regional therapy and systemic treatment.


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# Evolving Status of Liver Transplantation

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## Introduction

Liver transplantation (LT) is currently a well-established therapeutic modality for the treatment of decompensated cirrhosis and for those with unresectable hepatocellular carcinoma (HCC). There have been major milestones accomplished since the first attempt at, and subsequently the first successful human orthotopic LT, performed in 1963 and 1967 respectively by Dr Thomas Starlz at the University of Colorado.[1, 2] Despite the initial surgical success, the 1-year survival rate was consistently low, presumably due to the use of suboptimal immunosuppressive therapy such as azathioprine and anti-lymphocyte antibodies. The next major breakthrough after the initial pioneering surgical development arrived with the discovery of an effective immunosuppressive agent in the form of cyclosporine in the 1970s, which improved long-term survival significantly.[3] Presently, calcineurin inhibitors remain the cornerstone of immunosuppressive therapy after LT, with tacrolimus being more widely used. Other major developments have occurred in anaesthesia during LT, organ preservation, intensive care management, management of LT patients in the peri-operative period, and in the medical management in the post-operative period. All of these factors are interdependent in ensuring the excellent long-term outcome after LT that is currently observed.

In Hong Kong, the first LT was performed at the Queen Mary Hospital in October 1991. In a space of a decade, the results compared favourably with other well-established LT centres worldwide.[4] The Liver Transplant Centre at the Queen Mary Hospital currently serves the entire population of Hong Kong. To date, it has performed over 1,200 liver transplants. In November 2008, the Hong Kong Government established the Centralised Organ Donation Register for people to register their wish to donate organs after death. As of September 2014, over 152,000 registrations have been recorded, which is approximately 2% of the population. Currently, around 100 patients remain on the LT waiting list at any one time.

## Increasing the donor pool

The major hurdle for most transplant centres worldwide is the shortage of organ donors. In Hong Kong, this is no exception. The reluctance to donate may further be compounded by religious, cultural, or ethnical beliefs. Several strategies have been adopted in order to increase the chance of organ availability.

### *Living donor liver transplantation*

The first successful living donor liver transplantation (LDLT) was performed in Australia in 1989.[5] LDLT was first introduced in the paediatric population, ensuring donor safety by the removal of only a small portion of the liver. With ongoing shortage of organs from deceased donors along with an increasing number on the waiting list, LDLT using the left lobe was subsequently introduced in adults. However, donation of the left lobe of the liver, although sufficient for the paediatric population, is frequently insufficient to meet the metabolic demands for adult recipients.

The adequacy of the graft size to meet the metabolic demand of the recipient is considered one of the most important aspects in achieving an optimal outcome. However, donor safety may be compromised by the removal of a larger portion of the liver parenchyma. Either the graft-to-recipient weight ratio (GRWR) or the graft volume as a percentage of the standard liver volume (GV/SLV) of the recipient is used to calculate the required size of the allograft. A GRWR between 0.6 and 0.8, or the GV/SLV of 30-40% is widely used to determine the required size of the allograft. An insufficient graft size may lead to the development of the small for size syndrome (SFSS), with prolonged cholestasis and the production of ascites, and may be irreversible. To overcome the inadequate graft volume posed by using left lobe grafts, right lobe LDLT in an adult was first reported in Japan for adult LDLT in 1996.[6] In 1997, Hong Kong became the first group to report the use of the right lobe liver graft including the middle hepatic vein (MHV) in adult LDLT to overcome the problem of graft-to-body size mismatch.[7]

There are certain advantages with LDLT, including a short ischaemic time, the ability to determine the exact time of LT, and the guarantee of good quality graft. This is balanced against the disadvantages of a more complicated procedure, and the risk of donor morbidity and mortality. Presently, LDLT continues to be an important component of the LT programme in Hong Kong, contributing up to two-thirds of the total LT performed each year.

### *Split Liver Transplantation*

Two separate groups first reported split LT in the late 1980s.[8, 9] Liver splitting and transplantation of partial liver grafts is complex and demands high technical expertise and meticulous coordination by the transplant team. To date, split LT contributes approximately 2% of the total LT performed at the Queen Mary Hospital. Common scenarios include splitting the left lateral

segment for a child and extended right lobe for an adult recipient, or full right and left grafts for two adult recipients. Split LT should only be considered for optimal donors who meet stringent criteria including younger age, haemodynamic stability with minimal vasopressor support, evidence of adequate liver function on blood tests, and the absence of significant steatosis. Even if the graft appears optimal in quality, the quantity, or graft volume, must be sufficient to achieve good outcomes for both recipients. Potential complications with split LT include transection surface bleeding, small for size syndrome, increased risk of vascular and biliary complications, and the risk of segment IV hypoperfusion.

### *Domino Liver Transplantation*

Domino LT has been used to increase the donor pool by using livers from donors with metabolic diseases, which can be used for highly selected recipients. Familial amyloidotic polyneuropathy (FAP), an autosomal dominant disease, is the most common indication for domino LT. Patients with FAP harbour a mutation of the transthyretin (TTR) gene, with abnormal deposition of TTR amyloid fibrils in various organs, including the peripheral and autonomic nervous system. The liver is the main production site accounting for over 95% of circulating TTR, and LT can be curative if performed in a timely manner prior to the establishment of advanced disease from amyloid deposition. Apart from the production of TTR amyloid, the FAP liver is otherwise functionally and structurally normal, and can then be transplanted into a recipient. There is however a risk of de novo FAP developing in the recipient. Therefore, recipients who may otherwise not receive a graft with advanced age, or those who are likely to be delisted with progressive disease may be the most suitable. In Hong Kong, a series of 5 FAP liver recipients was reported, with the first recipient developing de novo FAP at six years after domino LT.[10]

### *ABO-Incompatible Donor*

The lack of a suitable graft is not uncommon, and can be due to various reasons, including advanced age, existing medical comorbidities, insufficient liver volume, and also blood group incompatibility. The latter can be overcome by using donor-interchange grafts, and this has been performed successfully in Hong Kong. However, this is only feasible when a pair of donors is available, suitable, and agreeable for interchange. Furthermore, the procedure is extremely labour intensive, as two LDLTs are performed simultaneously.

In Hong Kong, ABO-incompatible (ABOi) LT remains an alternative option. The use of ABOi grafts can be complicated by severe antibody-mediated rejection (AMR) secondary to preformed antibodies, and higher rates of vascular and biliary complications. Therefore it is important to target B cells with immunosuppressive therapy commenced before LT to prevent AMR, which usually occurs very early in the post-operative period. A major milestone was the use of rituximab, a monoclonal anti-CD20 antibody, in depleting B cells prior to LT. Since its introduction in 2002 as prophylaxis in ABOi LT, the use of rituximab has resulted in significant improvements in outcome.[11] Typically there is an induction period with commencement of immunosuppressive therapy including rituximab, steroid, and mycophenolate several weeks before LT, along with sessions of plasma exchange in the perioperative period. Prophylactic splenectomy remains controversial, but is likely unnecessary with adequate desensitisation protocols. Despite the significant improvement in outcome observed with ABOi LT, the intensive desensitisation regimen administered prior to LT precludes those patients who are severely ill, and unlikely to tolerate high doses of immunosuppression. There is also the potential risk for an increase in HCC recurrence after LT. Therefore, stringent donor and recipient selection is of paramount importance to ensure good long-term outcome with ABOi LT.

### *HBsAg-positive grafts*

In Asia-Pacific where chronic hepatitis B (CHB) continues to be endemic, potential grafts may be declined because of the donor hepatitis B status. Currently those with potential occult hepatitis B infection as evident by positive anti-HBc antibody are acceptable. The recipient of anti-HBc positive grafts will require long-term antiviral prophylaxis to prevent reactivation. In the near future, grafts positive for HBsAg from deceased donors may also be used, and protocols are currently being drawn up. A stringent assessment must be employed to ensure that the quality of the graft is not compromised. It is anticipated that these grafts will be for recipients who are already hepatitis B carriers. Recently, in Hong Kong, a graft from a CHB patient who underwent a LT eleven years ago was successfully re-transplanted into another recipient with acute flare of CHB.

## Chronic Hepatitis B

CHB remains the leading underlying liver disease for LT in Hong Kong. This is seemingly unfortunate as the complications of CHB can be preventable with proper screening and the use of antiviral therapy. Presently, LT for CHB-related complications have been associated with one of the best long-term outcomes after transplantation. However, less than two decades ago, CHB was a relative contraindication to LT due to high rates of recurrence of hepatitis after transplantation leading to graft loss. The major milestone was the discovery of effective antiviral prophylaxis, including hepatitis B immune globulin (HBIG) and lamivudine, which was able to reduce the recurrence rate to below 5% when used in combination.[12, 13] As HBIG remains expensive, inconvenient, and at times hard to source, Hong Kong has adopted an HBIG-free regimen successfully with the use of lamivudine alone, and add-on adefovir in the event of lamivudine resistance.[14, 15] Further recent studies from our centre have demonstrated that the use of newer nucleoside analogues such as entecavir alone with HBIG provides highly effective protection against recurrent graft hepatitis, and that excellent long-term outcomes can be achieved with an HBIG-free regimen.[16,17] With time, it is likely that an increasing number of LT centres will eventually adopt a regimen similar to Hong Kong that does not require HBIG administration.

## Chronic Hepatitis C

The field of hepatitis C has been rapidly evolving over

the last several years, with the approval of various combinations of direct acting antiviral (DAA) agents by the Food and Drug Administration (FDA). Prior to the advent of DAAs, combination therapy with pegylated interferon and ribavirin had been the standard of care therapy with modest sustained virological response (SVR) rates. Interferon-based therapies are largely contra-indicated prior to LT, especially for those with evidence of decompensated cirrhosis. After LT, treatment with pegylated interferon and ribavirin is notoriously difficult, and has been associated with suboptimal SVR rates of approximately 20%.[18] Furthermore, disease progression is accelerated after LT, with a predicted median duration to cirrhosis of 10 years.[19] The development of fibrosing cholestatic hepatitis has also been associated with high rates of graft loss with poor response to interferon-based therapy. Indeed, the introduction of DAAs will be a game changer in the management of hepatitis C patients after LT. The initial first generation DAAs including telaprevir and boceprevir was still interferon dependent, and was associated with significant drug interaction with the immunosuppression agents used, thereby requiring significant dose adjustments, with modest increase in SVR rates.[20, 21] A recent study has demonstrated a high SVR response of 97% with an all-oral regimen consisting of ombitasvir coformulated with ritonavir-boosted ABT-450, dasabuvir, and ribavirin.[22] The major barrier to the use of DAAs is its high cost, and will likely restrict its use presently for those who do not respond or tolerate interferon-based therapy, and with evidence of disease progression.

## Hepatocellular Carcinoma

LT remains the best curative option for those with unresectable hepatocellular carcinoma (HCC) that meet the criteria for transplantation. However, as recent as 1989, the US Department of Health deemed HCC was a relative contra-indication to LT. It was not until 1996 with the pivotal study outlining the Milan Criteria that demonstrated good outcome that HCC became an accepted indication for LT.[23] The Milan Criteria, as defined by a single tumour not greater than 5cm or multiple tumours not over 3 in number, of which none are greater than 3cm, without evidence of macrovascular invasion, has become the benchmark for selecting eligible patients for LT. Although the good outcome associated with the Milan Criteria has been tried and tested and has been shown to be highly reproducible, there is an argument that it may be too restrictive. On the other hand, by expanding the criteria to include those with a higher number of tumours and/or with larger tumour sizes, the risk of recurrence after LT is increased. Similar outcomes have been reported from the University of California San Francisco (UCSF) criteria using single tumours not larger than 6.5cm, or multiple tumours not over 3 in number, none of which is over 4.5cm, with a total tumour volume not over 8cm.[24] The 'up-to-seven' criteria include those having the sum of tumours not exceeding 7 and diameter of the largest tumours not exceeding 7cm, without macrovascular invasion.[25] Currently in Hong Kong, the UCSF criteria are adopted for patient selection for deceased donor LT. For LDLT, a recent study from our centre demonstrated good outcome in LDLT for solitary HCC up to 8cm.[26]

The use of bridging therapies can control tumour growth and reduce the chance of dropout from the waiting list. The use of downstaging therapy is more controversial, as it entails conversion of the tumour burden that exceeds the accepted criteria to one that is within the criteria. Different treatment modalities can be used, including radiofrequency ablation (RFA), transarterial chemoembolisation (TACE), transarterial radio-embolisation (TARE), and percutaneous ethanol injection (PEI), and the choice of therapy will depend on the availability of therapy, tumour size and location. In Hong Kong, high-intensity focused ultrasound (HIFU) is also available, and has been shown to be safe and effective as a bridging therapy prior to LT.[27, 28]

## Summary

Within the period of three decades, LT has emerged from an experimental procedure to a well-established therapeutic option associated with excellent long-term survival. Many diseases previously deemed contraindications to LT, including CHB infection, HCC, and alcohol-related liver diseases have now become the most common indications for transplantation. The widening indications for LT will highlight the major challenge for all centres, including Hong Kong, which is that of organ shortage. In the future, advances in regenerative medicine, stem cell technology, and 3-dimensional printing may contribute to a potentially expansive source of liver tissue. Until then, public awareness and education will continue to have a significant role in promoting organ donation.

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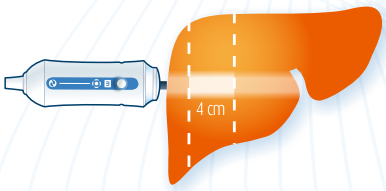


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AASLD Recommendations for Testing, Managing, and Treating Hepatitis C (2014)
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# Nature, Culture and the Divine: In Search of the Sacred Path

**Dr Nancy Wai-yee LEUNG**

BSc, MBBS, MSc, MD, FRCP(Edin), FRCP(Lon), FHKCP, FHKAM(Medicine)

*Specialist in Gastroenterology and Hepatology*
*Founding Chairperson Asiahep Hong Kong Ltd*

Dr Nancy Wai-yee LEUNG

I am sure many of you share my passion for travelling, from which I derive much joy and inspiration. Travelling bridges cultural diversities, reminds us of the long history of mankind and civilisation. Trips organised by museum societies with special guides give extra dimensions, an example is my recent trip to Japan, entiltled - "Nature, Culture and the Divine: In Search of the Sacred Path", organised by the Hong Kong University Museum Society, led by Professor Puay-peng Ho, professor of Architecture at CUHK and a renounced expert in Buddhism. To quote him - "The land of divine is usually magical, mythical, and stunningly beautiful." Our journey is a pilgrimage starting with amazing contemporary arts and architecture and followed by history and art of Buddhism introduced from China to Japan.

Our first night was spent in an authentic Japanese ryokan in Yunogo Onsen. This is a hot spring town in Mimasaka city (birthplace of the samurai Miyamoto Musashi) in Okayama Prefecture, western Japan. Cleansing in mineral-rich water was perfect after a tiring long flight and coach ride!

The next day, we visited Benesse Art Site Naoshima, a collective name for art-related activities conducted by the Benesse Holdings Inc. and Fukutake Foundation on the islands of Naoshima, Inujima, and Teshima.

The Inujima Seirensho Art Museum preserves and reuses the remains of a copper refinery, bringing together architecture by Hiroshi Sambuichi (using existing smokestacks and karami bricks from the refinery, solar, geothermal, and other natural energies to reduce the burden on the environment) and art by Yukinori Yanagi (sounding warnings over aspects of Japan's modernisation). The project embraces the concept of a recycling-based society, regional revitalisation through industrial heritage, architecture, art, and the environment. The Inujima 犬島 Art House Project was developed by art director Yuko Hasegawa and architect Kazuyo Sejima for the village on Inujima in 2010. It brings arts and vitality to a village with an ageing population.

To me, the most impressive work was at the Teshima Museum 豊島美術館, shaped like a drop of water, surrounded by once-fallow rice terraces that have been restored with help from local residents. Artist Rei Naito and architect Ryue Nishizawa, created ever-flowing fountains and an ambiance that changes from hour to hour and season to season, revealing countless appearances as time passes. In absolute quietness and tranquility, I gazed intensely at beads of pearly water, swelling from the cement ground, till they took off and flew on the surface in unexpected directions, coalesced to form a bigger puddle, and eventually ran into a tiny hole, making a clear ringing sound!!

Our nature and art exploration continued at the Benesse Park, Naoshima 直島 (which offered views of a verdant green lawn and the sparkling inland sea with the mountains of Shikoku rising up in the horizon) and the Chichu Art Museum 地中美術館 with artworks by Claude Monet, James Turrell, and Walter De Maria on permanent display in a building designed by Tadao Ando, one of Japan's most famous architects.

Our visual senses were further stimulated at the Lee

Ufan Museum, a collaboration between internationally acclaimed artist Lee Ufan, and architect Tadao Ando. The Ando-designed semi-underground structure houses paintings and sculptures by Lee spanning a period from the 1970s to the present day. Positioned in isolation in a valley surrounded by mountains and sea, the museum offers a harmony between nature, architecture, and art, where visitors will be offered an opportunity to return to their original natures and to find time for quiet reflection in a society overflowing with material goods.

Next, Professor Ho led us to explore the mystery of the sacred land of Shinto legends, the gods in Kumano (one of the three sites in Japan designated as UNESCO World Heritage), and Grand Shrones of the Isle. We also visited temples, monasteries in Nara and Kyoto for Buddhist interpretation of nature and the divine, expressed in garden art and Pure Land monasteries. The journey allowed the participants to search for spirituality, rethink one's relationship with nature and the divine, and to understand oneself.

A number of sites need special mention. Firstly, the Daihoonji Temple (also called Senbon Shakado Temple), a famous temple of Shingon Sect. Kukai (774-835), also known posthumously as Kobo-Daishi, the Grand Master who Propagated the Buddhist Teaching, was a Japanese monk, civil servant, scholar, poet, artist and founder of the Shingon or "True Word" school of Buddhism. Designated as a National Treasure, the main Shaka Hall is an original wooden structure built in 1222 in the Kamakura period and it is the oldest Buddhist Hall in Kyoto. The rarely-shown statue of Shaka Nyorari or Buddha is housed here while other cultural assets are placed in the treasure house.

Secondly, the Kozanji 高山寺, a buddhist temple of the Kegon sect of Shingon Buddhism dedicated to Shaka Nyorai Buddha, said to be founded in 774 by the order of Emperor Konin. In 1206, the scholar and monk Myoe (1173-1232) served as abbot of Kozanji. The temple is renowned for its numerous national treasures and important properties, registered as one of the UNESCO World Heritage Sites in Kyoto in 1994.

Thirdly, in Nara, Mujroji a temple of Omoto School of Shangon Buddhism, which unlike other temples of the time, was opened to females; Nara National Museum 奈良國立博物館 for special exhibition; Toshdaiji 唐招提寺, one of Unesco World Heritage Sites founded in 759 by Ganjin, a Chinese monk who was invited by the Japanese emperor to train monks and improve Buddhism in Japan.

Fourthly, Ise Jingu, the Ise Shrine 伊勢神宮, sacred due to the forests of sacred Japanese cypress trees. In the earliest time, cypress trees were worshipped in nature without any buildings. Around 680, Emperor Temmu established Ise as the primary Shinto shrine of imperial Japan and built the first temple on the site. It consists of two major Shinto sanctuaries – Naiku (the Inner Shrine where ancestral kami of the Imperial Family is worshipped) and Geku (the outer shrine, where kami of agriculture and industry is worshipped). Access to both sites is strictly denied to the public. However, our group was given special permission to enter the inner sacred shrines of Geku and Naiku to pay respect, guided by a Jingu Shinto priest.

Finally. We arrived at the ancient Kumano region, nested in the verdant mountains of Wakayama prefecture – the spiritual heartland of Japan. The lush and rugged area has been considered the abode of the gods and worshipped for centuries. The Kumano Kodo in Japan and the Way of St. James in Spain are the only two pilgrimage routes designated as UNESCO World Heritage sites. The three deities of the Kumano Sanzan became a unique mixture of Shinto and Buddhism. We walked along the Kumano Kodo 熊野古道 pilgrimage path, passed by the Kumano Nachi Taisha and Nachi Water Falls and Seiganto-ji Temple. This is the first stop on the Saigoku Kannon pilgrimage path of 33 Buddhist temples throughout the Kansai region of Japan.

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HK-SH-DEX-12/06-2013

| Date / Time | Function | Enquiry / Remarks |
|---|---|---|
| **3 TUE** 1:00 pm | **HKMA Kowloon West Community Network – Optimizing Glycemic Control to Improve Renal Outcomes: Findings from ADVANCE-ON**<br>Organiser: HKMA Kowloon West Community Network; Chairman: Dr. LAM Ngam, Raymond; Speaker: Dr. TSANG Man Wo; Venue: Crystal Room I-III, 30/F, Panda Hotel, 3 Tsuen Wah Street, Tsuen Wan, NT | Miss Hana YEUNG<br>Tel: 2527 8285<br>1 CME Point |
| 8:00 pm | **HKMA Council Meeting**<br>Organiser: The Hong Kong Medical Association; Chairman: Dr. SHIH Tai Cho, Louis; Venue: HKMA Head Office, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong | Ms. Christine WONG<br>Tel: 2527 8285 |
| 8:00 pm | **FMSHK Officers' Meeting**<br>Organiser: The Federation of Medical Societies of Hong Kong; Venue: Gallop, 2/F, Hong Kong Jockey Club Club House, Shan Kwong Road, Happy Valley, Hong Kong | Ms. Nancy CHAN<br>Tel: 2527 8898 |
| **5 THU** 1:00 pm | **HKMA Hong Kong East Community Network – Update on Post-herpetic Neuralgia and its Prevention**<br>Organiser: HKMA Hong Kong East Community Network; Chairman: Dr. NGAN Sze Yuen, Silas; Speaker: Dr. TONG Ka Fai, Henry; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong | Ms. Candice TONG<br>Tel: 2527 8285<br>1 CME Point |
| **6 FRI** 1:00 pm | **HKMA Yau Tsim Mong Community Network – Mood & Pain; What is Patent and Why Should Doctors be Concerned about it**<br>Organiser: HKMA Yau Tsim Mong Community Network; Speakers: Dr. LEE Wing King & Ms. Antia LEUNG; Venue: Jade Ballroom, Level 2, Eaton, Hong Kong, 380 Nathan Road, Kowloon | Ms. Candice TONG<br>Tel: 2527 8285 |
| **10 TUE** 7:30 pm | **41st C Elaine Field Lecture 2015 – "Improving Outcomes in Early Onset Family"**<br>Organiser: The Hong Kong Paediatric Society; Chairman: Dr. WONG Hiu Lei, Lilian; Speaker: Prof. Helen Cross; Venue: Sheraton Hong Kong Hotel – Ching and Sung Room, 20 Nathan Road, Kowloon | Ms. Kit TANG<br>Tel: 2578 3833<br>1 CME Point |
| **11 WED** 1:00 pm | **HKMA Central, Western & Southern Community Network – Recommendation on Herpes Zoster Vaccination for Adults**<br>Organiser: HKMA Central, Western & Southern Community Network; Chairman: Dr. POON Man Kay; Speaker: Dr. YIP Wai Man; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong | Miss Hana YEUNG<br>Tel: 2527 8285<br>1 CME Point |
| **12 THU** 1:00 pm | **HKMA Hong Kong East Community Network – Mood & Pain; What is Patent and Why Should Doctors be Concerned about it**<br>Organiser: HKMA Hong Kong East Community Network; Chairman: Dr. TUET On Sang; Speakers: Dr. MAK Ki Yan & Ms. Antia LEUNG; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong | Ms. Candice TONG<br>Tel: 2527 8285 |
| 1:00 pm | **HKMA Kowloon East Community Network – Annual Meeting cum CME lecture on "Emerging Role of DPP4i and TZD Combination in the Management of T2DM"**<br>Organiser: HKMA Kowloon East Community Network; Chairman: Dr. AU Ka Kui, Gary; Speaker: Dr. TSUI Hon Yee, Tinny; Venue: V Cuisine, 6/F, Holiday Inn Express Hong Kong Kowloon East, 3 Tong Tak Street, Tseung Kwan O | Miss Hana YEUNG<br>Tel: 2527 8285<br>1 CME Point |
| 2:00 pm | **HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2015 – PET Scan – Current Applications**<br>Organisers: Hong Kong Medical Association & Hong Kong Sanatorium & Hospital; Speaker: Dr. HO Chi Lai, Garrett; Venue: Function Room A, HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong | HKMA CME Dept.<br>Tel: 2527 8452<br>1 CME Point |
| 6:30 pm | **MPS Workshop – Mastering Difficult Interactions with Patients**<br>Organisers: Hong Kong Medical Association & Medical Protection Society; Speaker: Dr. CHENG Ngai Shing, Justin; Venue: Holiday Inn Golden Mile Hong Kong | HKMA CME Dept.<br>Tel: 2527 8452<br>2.5 CME Points |
| **13 FRI** 7:30 pm | **HKMA Gourmet Dinner**<br>Organiser: The Hong Kong Medical Association; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong | Mr. Benjamin CHAN<br>Tel: 2527 8285 |
| **14 SAT** 1:30 pm | **19th Annual Scientific Meeting 2015 – "Managing Antimicrobial Resistance"**<br>Organiser: The Hong Kong Society for Infectious Diseases; Chairman: Dr. Thomas SO; Speakers: Prof. Bin Cao (Beijing), Dr. Tin-ya WONG, Dr. Graeme Moyle (UK), Prof. Young-kyung YOON (Korea); Venue: Eaton Hotel, Hong Kong | Dr. Ada LIN<br>Tel: 2116 2903 |
| 2:15 pm | **Refresher Course for Health Care Providers 2014/2015- Emergencies in primary care**<br>Organisers: Hong Kong Medical Association & HK College of Family Physicians & HA – Our Lady of Maryknoll Hospital; Speaker: Dr. LAM Wing Wo; Venue: Training Room II, 1/F, OPD Block, Our Lady of Maryknoll Hospital, 118 Shatin Pass Road, Wong Tai Sin, Kowloon | Ms. Clara TSANG<br>Tel: 2354 2440<br>2 CME Points |
| 2:30 pm | **MPS Workshop – Mastering Your Risk**<br>Organisers: Hong Kong Medical Association & Medical Protection Society; Speaker: Dr. CHENG Ngai Shing, Justin; Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong | HKMA CME Dept.<br>Tel: 2527 8452<br>2.5 CME Points |
| **15 SUN** 9:30 am | **HKMA Lantau Hiking Team – Fellowship Program F1**<br>Organiser: The Hong Kong Medical Association; Chairperons: Dr. HO Chung Ping & Dr. SIN Pui Yee, Helena; Venue: Lantau Island | Mr. Benjamin CHAN<br>Tel: 2527 8285 |
| 2:00 pm | **Chinese Medicine Hospital in Hong Kong: Building Up Directions**<br>Organiser: Hong Kong Association for Integration of Chinese-Western Medicine; Chairmen: Dr. Yu Chau Leung and Dr. Yip Wai Chun; Speakers: Dr. Cheung Wai Lun, Prof. Lao Lixing and Prof. Wu Chi Yuen, Justin; Venue: Lecture Theatre, M/F, HA Building, 147B Argyle Street, Kowloon | Miss YC Yeung<br>Tel: 3119 1858<br>2 CME Points (CMP) (Pending) |
| 6:30 pm | **FMSHK 50th Anniversary Gala Dinner**<br>Organiser: The Federation of Medical Societies of Hong Kong; President: Dr Raymond SK LO; Venue:InterContinental Ballroom, 18 Salisbury Road, Kwoloon | Ms Nancy CHAN<br>Tel: 2527 8898 |
| **17 TUE** 1:00 pm | **HKMA Kowloon West Community Network – 1. Understanding on Acid Pocket 2. Update on Pharyngitis Management**<br>Organiser: HKMA Kowloon West Community Network; Chairman: Dr. CHAN Siu Man, Bernard; Speakers: Dr. SZE Wan Chee & Dr. NG Kit Chung; Venue: Crystal Room I-III, 30/F, Panda Hotel, 3 Tsuen Wah Street, Tsuen Wan, NT | Miss Hana YEUNG<br>Tel: 2527 8285<br>1 CME Point |
| **19 THU** 1:00 pm | **HKMA Hong Kong East Community Network – Practical Tips for GERD Management**<br>Organiser: HKMA Hong Kong East Community Network; Chairman: Dr. CHAN Hoi Chung, Samuel; Speaker: Dr. LI Tat Wing, Francis; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong | Ms. Candice TONG<br>Tel: 2527 8285<br>1 CME Point |
| 1:00 pm | **HKMA New Territories West Community Network - Emerging Role of DPP4i and TZD Combination in the Management of T2DM**<br>Organiser: HKMA New Territories West Community Network; Speaker: Dr. YEUNG Chun Yip; Venue: Plentiful Delight Banquet (元朗喜尚嘉喜酒家), 1/F., Ho Shun Tai Building, 10 Sai Ching Street, Yuen Long | Miss Hana YEUNG<br>Tel: 2527 8285<br>1 CME Point |

# Calendar of Events in March

| Date / Time | Function | Enquiry / Remarks |
|---|---|---|
| **19 THU** 6:30 pm | **MPS Workshop – Mastering Shared Decision Making**<br>Organisers: Hong Kong Medical Association & Medical Protection Society; Speaker: Dr. FUNG Shu Yan, Anthony; Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong | HKMA CME Dept.<br>Tel: 2527 8452<br>2.5 CME Points |
| 6:30 pm | **Dinner Symposium on Authma Management**<br>Organisers: Hong Kong Society of Dermatology and Venereology and The Hong Kong Society for Paediatric Dermatology; Speaker: Prof. Johannes Wohlrab; Venue: Langham Place Hotel | Meeting Secretariat.<br>Tel: 2116 4348 |
| 8:00 pm | **FMSHK Executive Committee Meeting**<br>Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong | Ms. Nancy CHAN<br>Tel: 2527 8898 |
| **21 SAT** 2:30 pm | **MPS Workshop – Mastering Professional Interactions**<br>Organisers: Hong Kong Medical Association & Medical Protection Society; Speaker: Dr. LEE Wai Hung, Danny; Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong | HKMA CME Dept.<br>Tel: 2527 8452<br>2.5 CME Points |
| **22 SUN** 9:00 am | **Annual Scientific Meeting 2015**<br>Organisers: Hong Kong Thoracic Society and Amberican College of Chest Physicians; Venue: Hong Kong Convention and Exhibition Centre | Meeting Secretariat<br>Tel: 2116 4348 |
| **24 TUE** 7:30 pm | **25th James Hutchison Memorial Lecture – "The Perinatal Microbiome: Implications for Future Health"**<br>Organiser: The Hong Kong Paediatric Society; Chairman: Dr. WONG Hiu Lei, Lilian; Speaker: Prof. Josef Neu; Venue: Jade Ballroom, 2/F, Eaton Hong Kong, 380 Nathan Road, Hong Kong | Ms Kit TANG<br>Tel: 2578 3833<br>1 CME Point |
| **25 WED** 1:00 pm | **HKMA Central, Western & Southern Community Network – The Current Management of Herpes Zoster and Herpes Simplex Infection**<br>Organiser: HKMA Central, Western & Southern Community Network; Chairman: Dr. TSANG Chun Au; Speaker: Dr. CHAN Hau Ngai, Kingsley; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong | Miss Hana YEUNG<br>Tel: 2527 8285<br>1 CME Point |
| 1:30 pm | **MPS Workshop – Mastering Adverse Outcomes – 2 hours**<br>Organisers: Hong Kong Medical Association & Medical Protection Society; Speaker: Dr. LEUNG Kwok Ling, Ares; Venue: Eaton, Hong Kong, 380 Nathan Road, Kowloon | HKMA CME Dept.<br>Tel: 2527 8452<br>2 CME Points |
| **28 SAT** 9:00 am *(29)* | **Hong Kong Pharmacy Conference 2015**<br>Organiser: The Pharmaceutical Society of Hong Kong; Venue: Hong Kong Convention and Exhibition Centre | Meeting Secretariat.<br>Tel: 2116 4348 |
| **31 TUE** 1:00 pm | **HKMA Kowloon West Community Network – Management of Post Herpetic Neuralgia in an Era of Aging Population**<br>Organiser: HKMA Kowloon West Community Network; Speaker: Dr. TONG Ka Fai, Henry; Venue: Crystal Room I-III, 30/F, Panda Hotel, 3 Tsuen Wah Street, Tsuen Wan, NT | Miss Hana YEUNG<br>Tel: 2527 8285<br>1 CME Point |

## Public Talk for Pre-Delivery Check-up and Preparation

The Public Talk for Pre-Delivery Check-up and Preparation was held at the Federation Lecture Hall on 4 Jan 2015. It was our pleasure and privilege to invite Dr Felix Ying-fung IU, Specialist in Obstetrics & Gynaecology, who delivered a talk on "為何需要產前檢查，產前不適及孕媽媽分娩過程，準爸爸陪產須知 and 孕媽媽產前準備" and Dr Enders NG, Deputy Laboratory Director of DiagCor Bioscience Ltd. and Honourary Assistant Professor at the University of HK, who delivered a talk on "非入侵性產前測試知多D". The participants' active questioning in the Q&A section helped to complete a very successful & interactive seminar. The event concluded with Dr Mario CHAK, Hon. Secretary of the Federation, thanking the two speakers with souvenirs presentation.

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## Answers to Dermatological Quiz

**1. Lymphangioma circumscriptum**

The diagnosis is lymphangioma circumscriptum. It is due to underlying abnormally dilated lymphatic vessels. It often presents as multiple, saccularly, clustered translucent lymphatic vesicles on the skin. The appearance resembles frog spawn. The differential diagnoses are mainly other vesicular forming or bullous dermatoses such as herpes simplex, herpes zoster and bullous pemphigoid.

**2. Radiation therapy and internal malignancy**

Lymphangioma circumscriptum commonly describes the congenital condition at birth and appears in childhood. The common areas are the shoulder girdle and proximal limbs. However, this is a morphologically identical acquired variant due to the lymphatic obstruction after radiation therapy and operation of her carcinoma of uterus and carcinoma of rectum. As the sites involved were mainly the pelvic region and left lower abdomen, this is why the left vulva was more severely affected than the right side.

**3. Conservative Treatment**

There are different treatment modalities for lymphangioma circumscriptum in which surgical removal is the common option. However, adequate and extensive excision is difficult to achieve and the local recurrence rate is high. MRI is sometimes required before operation to clearly delineate the deep lymphatic involvement. Other methods including vapourisation by $CO_2$ laser, cryotherapy, cauterisation and sclerosing therapy are reported but not very effective. In this lady, conservative approach is the treatment option. It is because the lesion is asymptomatic and she had a poor pre-morbid state. In case of any complication with secondary bacterial infection, a course of antibiotic can help.

**Dr Chi-keung KWAN**
MBBS(HK), MRCP(UK), FHKCP, FHKAM(Medicine)
*Specialist in Dermatology and Venereology*

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**INTEGRATED SAFETY INFORMATION**

**CONTRAINDICATIONS:** Hypersensitivity to entecavir or any component of the product. **WARNINGS AND PRECAUTIONS:** Hepatic function should be monitored closely with both clinical follow-up and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy. Initiation of anti-hepatitis B therapy may be warranted if appropriate. Particular caution should be exercised when administering nucleoside analogues to any patient with known risk factors for liver disease. Treatment with entecavir should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations). Not recommended for HIV/HBV co-infected patients who are not receiving highly active antiretroviral therapy (HAART). Before initiating entecavir therapy, HIV antibody testing should be offered to all patients. Not recommended for use as a treatment for HIV infection. Dosage adjustment of entecavir is recommended for patients with a creatinine clearance<50ml/min, including patients on hemodialysis or CAPD. Renal function must be carefully monitored both before and during treatment with entecavir for a liver transplant recipient who has received or is receiving an immunosuppressant that may affect renal function, such as cyclosporine or tacrolimus. **INTERACTIONS:** Drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of either entecavir or the coadministered drug. Patients should be monitored closely for adverse events when coadministered with other drugs that are renally eliminated or are known to affect renal function. **PREGNANCY AND LACTATION:** No adequate studies in pregnant women of entecavir. Use only after careful consideration of the risk and benefits during pregnancy. Mothers should be instructed not to breast-feed if they are taking this product. The following most common adverse events have been reported: ALT elevation, headache, fatigue, dizziness, nausea, bellyache, abdominal discomfort, epigastric pain, hepatic discomfort, myalgia, insomnia and urticaria.

**ABBREVIATED PRESCRIBING INFORMATION**

**ENTIKAV™ (ENTECAVIR) DISPERSIBLE TABLETS 0.5MG**

**INDICATIONS** For treatment of the chronic hepatitis B virus infection in adults with evidence of active viral replication and either the evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease. **DOSAGE AND ADMINISTRATION** Adults and adolescents of 16 years old or older: 0.5mg once daily (1 tablet). Patients with a history of hepatitis B viremia while receiving lamivudine or with known lamivudine resistance mutations: 1 mg once daily (two tablets). Dosage adjustment for patients with creatinine clearance<50mL/min [including patients of hemodialysis or continuous ambulatory peritoneal dialysis (CAPD)]. Administered on an empty stomach (at least 2 hours after a meal and 2 hours before the next meal). May be swallowed or taken orally after dispersed with water. **CONTRAINDICATIONS** Hypersensitivity to entecavir or to any components of the product. **WARNINGS AND PRECAUTIONS** Exacerbations of hepatitis after discontinuation of treatment. Hepatic function should be monitored closely. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported on using nucleoside analogues alone or in combination with other antiretroviral drugs.Caution should be exercised when administering nucleoside analogues to any patient with known risk factors for liver disease. Treatment with entecavir should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations). Not recommended for HIV/HBV co-infected patients who are not receiving highly active antiretroviral therapy (HAART). HIV antibody testing should be offered to all patients before initiation of treatment. Entecavir has not been studied as a treatment for HIV infection and is not recommended for this use. Dosage adjustment is recommended for patients with a creatinine clearance<50ml/min, including patients on hemodialysis or CAPD. If Entikav treatment is necessary for a liver transplant recipient who has received or is receiving an immunosuppressant that may affect renal function, such as cyclosporine or tacrolimus, renal function must be carefully monitored both before and during treatment. **INTERACTIONS** Since entecavir is primarily eliminated by the kidney, coadministration of entecavir with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of either entecavir or the coadministered drug. Patients should be monitored closely for adverse events when coadministered with other drugs that are renally eliminated or are known to affect renal function. **PREGNANCY AND LACTATION** No adequate studies in pregnant women of entecavir. It can be used during pregnancy only after careful consideration of the risk and benefits. Mothers should be instructed not to breast-feed if they are taking this product. **ADVERSE REACTIONS** ALT elevation, headache, fatigue, dizziness, nausea, bellyache, abdominal discomfort, epigastric pain, hepatic discomfort, myalgia, insomnia and urticaria. **OVERDOSE** No experience of entecavir overdosage reported in patients. If overdose occurs, the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary. Abbreviated Prescribing Information based on PI version CN31Aug10/USOct2012/HK (v3)

**REFERENCES: 1.** Human Bioequivalence Study of the Entecavir Dispersible Tablets, Data on file, 2009.

**The material is for the reference and use by healthcare professionals only.** For adverse event reporting, please call GlaxoSmithKline Limited at (852) 9046 2498.
Please read the full prescribing information prior to administration. Full prescribing information is available on request from GlaxoSmithKline Ltd, 23/F, Tower 6, The Gateway, 9 Canton Road, Tsimshatsui, Kowloon, Hong Kong.
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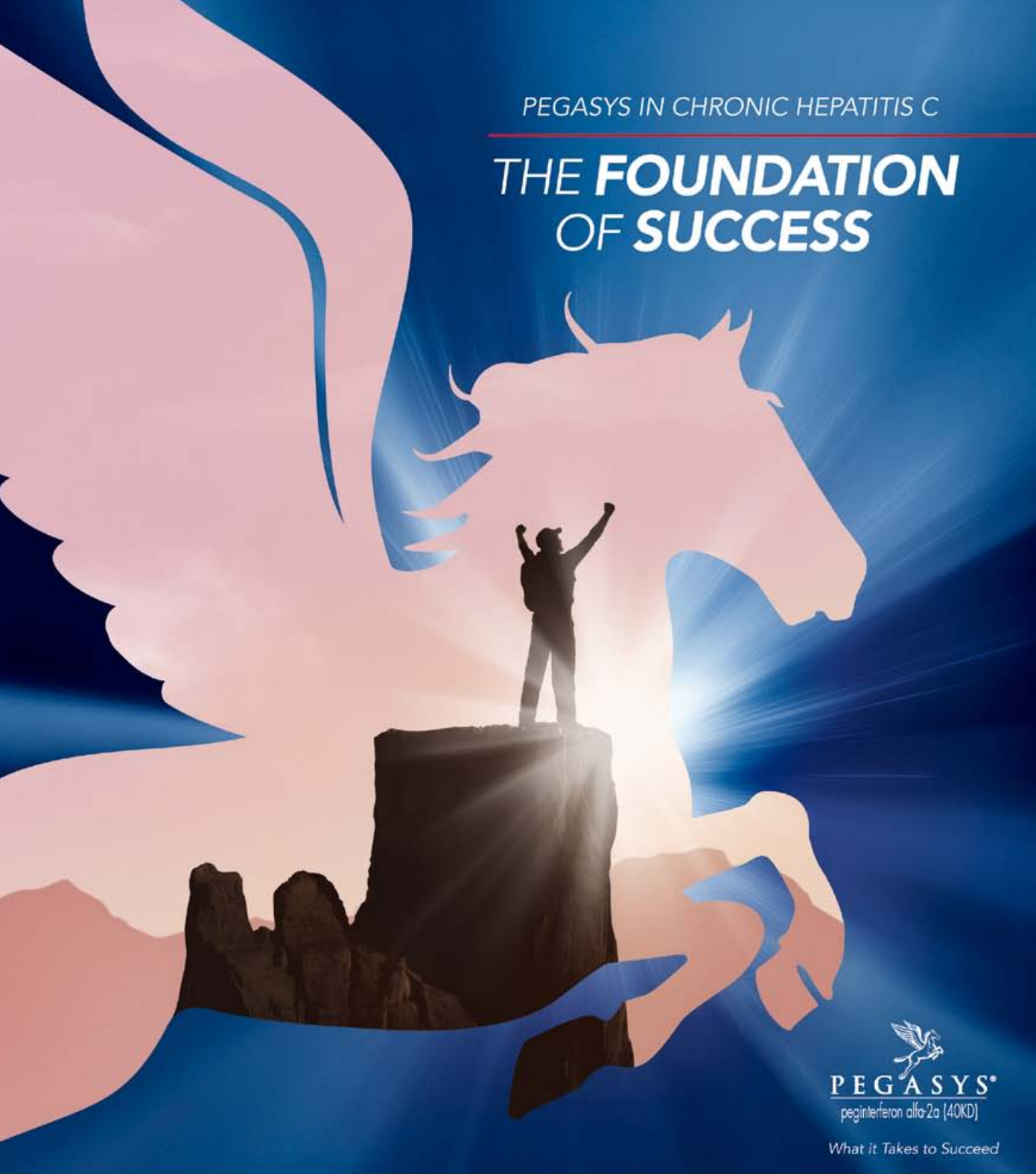


**Abbreviated Prescribing Information - Pegasys (peginterferon alfa 2a) pre-filled syringes** 180mcg/0.5ml and 135mcg/0.5ml. **Indications:** Treatment of chronic hepatitis B, including HBeAg positive or HBeAg negative disease in adult patients with compensated liver disease and evidence of viral replication, increased ALT and histologically verified liver inflammation and/or fibrosis. Treatment of chronic hepatitis C in adult patients who are positive for serum HCV-RNA, including patients with compensated cirrhosis and/or co-infected with clinically stable HIV. Optimal use of Pegasys in chronic hepatitis C is in combination with ribavirin. Monotherapy is indicated mainly in cases of intolerance or contraindication to ribavirin. **Dosage & administration:** By s.c. administration in the abdomen or thigh. Chronic hepatitis B: 180 µg once weekly for 48 weeks. Chronic hepatitis C: 180 µg once weekly as monotherapy or in combination with oral ribavirin or as monotherapy. Duration of combination therapy depends on viral genotype. Patients infected with HCV genotype 1 who have detectable HCV RNA at week 4 regardless of pre-treatment viral load should receive 48 weeks of therapy. Treatment for 24 weeks may be considered in patients with genotype 1 with LVL (≤ 600,000 IU/ml) at baseline or genotype 4, who become HCV RNA negative at week 4 and remain HCV RNA negative at week 24. 24 weeks of treatment may be associated with higher risk of relapse than 48 week duration. Tolerability and other prognostic factors should be taken into account when deciding on treatment duration. Limited data suggest a negative impact on SVR by shortening the treatment duration in patients with genotype 1 and high viral load (>600,000 IU/ml) at baseline who become HCV RNA negative at week 4 and remain HCV RNA negative at week 24 and more caution is recommended. 24 weeks of treatment for patients with genotype 2 or 3 who have detectable HCV RNA at week 4. Treatment for 16 weeks may be considered in easier to treat genotype 2 or 3 with LVL at baseline who become HCV negative by week 4 of treatment and remains HCV negative by week 16. Overall 16 weeks of treatment may be associated with a lower chance of response and is associated with a higher risk of relapse than a 24 week treatment duration. Tolerability and other prognostic factors should be taken into account when deciding on treatment duration. Shortening the treatment duration in patients with genotype 2 or 3 with HVL (>600,000 IU/ml) at baseline who become HCV RNA negative at week 4 should be considered with more caution. The recommended duration of Pegasys monotherapy is 48 weeks. HIV-HCV co-infection: Pegasys 180mcg s.c weekly for 48 weeks, alone or in combination with ribavirin 800mg/day. Please refer to the full prescribing information on ribavirin dose and Pegasys dose adjustments. **Contraindications:** Hypersensitivity to alpha interferons, E. coli derived products, polyethyleneglycol or any excipients; autoimmune hepatitis; decompensated cirrhotic HIV-HCV co-infection with cirrhosis & Child-Pugh score >6, except if only due to indirect hyperbilirubinemia caused by drugs such as atazanavir and indinavir; neonates & infants up to 3 years old. Pregnancy/abortive contraception therapy in women who are pregnant. For contraindications of ribavirin please refer to the Copegus package insert. **Warnings & Precautions:** Please refer to the Copegus package insert when it is used in combination with Pegasys. Recommend to obtain complete blood counts pre-treatment and monitor routinely during therapy. Use with caution in patients with baseline neutrophil counts < 1500 cells/mcL with baseline platelet count <90,000/mmCr or baseline hemoglobin <12 g/dL. Associate with decreases in WBC count, ANC, platelet count and anemia. Serious infections have been reported during treatment with alpha interferons including Pegasys. Exacerbation of autoimmune disease and aggravate hypothyroidism & hyperthyroidism has been reported in patients receiving alpha interferon therapy. Use with caution in patients who report a history of depression, and to monitor patients for evidence of depression. Retinopathy which may result in loss of vision have been reported with interferons including Pegasys. HCV patients with history of significant of unstable cardiac disease in previous 6 months should not use ribavirin. Recommend patients with pre-existing cardiac abnormalities to have electrocardiogram prior to initiation of therapy. Discontinue or suspend therapy if deterioration of cardiovascular status. Pulmonary disorders e.g. dyspnea, pneumonia including fatality have been reported. Discontinue if patient develop evidence of hepatic decompensation during treatment. During treatment, HIV-HCV co-infected patients should be closely monitored for sign's and symptoms for hepatic decompensation, and to discontinue treatment immediately in patients with hepatic decompensation. Do not use in children ≤ 18 years during pregnancy or lactation. Pediatric subjects treated with Pegasys plus ribavirin combination therapy showed a delay in weight and height increases after 48 weeks of therapy compared with baseline. **Drug Interactions:** Theophylline, methadone, zidovudine antiretroviral. **Use in Pregnancy & Lactation:** Pegasys should not be used in pregnant women. Women of childbearing potential receiving Pegasys should be advised to use effective contraception during therapy. Ribavirin therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant. It is not known whether Pegasys and/or ribavirin are excreted in human milk. A decision should be made either to discontinue nursing or treatment, based on the importance of the therapy to the mother. **Undesirable effects:** The adverse reactions observed with other alpha interferons, alone or in combination with ribavirin, may be expected with Pegasys or Pegasys/ribavirin combination therapy, respectively. Most commonly reported adverse reactions include anorexia, weight decreased, insomnia, depression, irritability, concentration impaired, anxiety, headache, dizziness, dyspnea, cough, nausea, diarrhea, abdominal pain, alopecia, pruritus, dermatitis, dry skin, myalgia, arthralgia, fatigue, pyrexia, rigors, injection site reaction, pain & asthenia. Post-marketing: Erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis, pure red-cell aplasia (PRCA) and homicidal ideation reported very rarely. **Date of preparation:** December 2012. Full prescribing information should be viewed prior to prescribing. Refer to HKPI Current at May 2012.

Further information is available upon request :
Roche Hong Kong Limited
24/F, Caroline Centre, 2-28 Yun Ping Road, Causeway Bay, Hong Kong
Tel. (852) 2723 2832 Fax.(852) 2369 0503

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