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Reviews on the Epidemiology, Quality of Life, and Management of Chronic Hepatitis B (CHB)

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1. Introduction

Chronic hepatitis B (CHB) remains a major global health problem. About 400 million people are chronic hepatitis B carriers. CHB can affect health-related quality of life (HRQOL). Several anti-viral drugs are available for CHB patients.

2. Reviews on the epidemiology, Quality of Life, and management of Chronic Hepatitis B (CHB)

This chapter first reviews the epidemiology of hepatitis B virus (HBV) and recommended management for CHB to identify the health problems and service needs of these patients. The findings from studies on health-related quality of life (HRQOL) and CHB is highlighted to identify any knowledge gaps. Finally, available HRQOL measures are reviewed to determine which one is the most suitable for applications for the evaluation of Chinese CHB patients in Hong Kong.

2.1 Epidemiology and management for Chronic Hepatitis B (CHB)

2.1.1 Epidemiology and natural history of CHB

Hepatitis B is one of the most common infectious diseases and a leading cause of death in the world (Lai, Ratziu, Yuen, & Roynard, 2003; Lavanchy, 2004, 2005; Maynard, 1990; Wright, 2006). Approximately 2 billion are infected and more than 400 million people of those are chronically infected with hepatitis B virus (HBV) (Fattovich, Bortolotti, & Donato, 2008; Lai et al., 2003). Chronically infected individuals defined as those who have diagnosed with hepatitis B surface antigen (HBsAg) for more than six months (A S Lok & McMahon, 2009; Maddrey, 2000). It was estimated that 75% of chronic hepatitis B (CHB) carriers were found in Asia and the Western Pacific regions (Gust, 1996; Maddrey, 2000; Maynard, 1990; Merican et al., 2000). HBV results in 500,000 to 1.2 million deaths per year caused by cirrhosis, liver failure or hepatocellular carcinoma (HCC) (Lavanchy, 2004, 2005). The incidence of HCC is increasing and is the fifth most common cancer worldwide killing 300,000-500,000 people per year (Lavanchy, 2004). Worldwide, approximately 30% of cirrhosis was attributable to HBV and over half (53%) of HCC was due to HBV (Perz, Armstrong, Farrington, Hutin, & Bell, 2006). HBV infection accounted for more than 50% of HCC (65%) and cirrhosis (57%) in Western Pacific regions (Perz et al., 2006).

In Hong Kong, HCC is the fourth common cancer and the third leading cause of cancer deaths (H. A. Hong Kong Cancer Registry, 2008). In 2006, there were 1745 (1462) new cases (deaths) of liver cancer registered in Hong Kong, representing 7.3% (12.1%) of all cancers in total (H. A. Hong Kong Cancer Registry, 2008). There was a male predominance with a male-to-female ratio of 3:1 (Hong Kong Cancer Registry, 2006), and the age of onset is earlier in males (Department of Health HKSAR, 1998). The age-standardized incidence (mortality) rates for males and females were 29.3 (23.3) and 8.0 (6.7) per 100,000 population, respectively (Hong Kong Cancer Registry, 2006). HBV was significantly contributed to HCC, with 80% of HCC patients found to be hepatitis B carriers (Department of Health HKSAR, 1998). Therefore, HBV infection accounts for the majority of both cirrhosis and HCC worldwide (Perz et al., 2006).

The prevalence of HBV varies notably between and within countries (Custer et al., 2004; Gust, 1996; Lavanchy, 2004, 2005; Maddrey, 2000; Maynard, 1990). It could be categorized as high, intermediate and low HBV endemicity (Custer et al., 2004; Lavanchy, 2004; Maddrey, 2000). In areas of high endemicity, ≥8% are CHB carriers and account for a total of 45% of the global population (Lavanchy, 2004). They include South East Asia, China including Hong Kong, sub-Saharan Africa and the Amazon Basin (Custer et al., 2004; Lavanchy, 2004; Maddrey, 2000). In areas of intermediate endemicity, such as eastern and southern Europe, the Middle East, Japan and part of South America, 2-7% of the population are chronic carriers (Custer et al., 2004; Lavanchy, 2004; Maddrey, 2000). The endemicity of HBV is low in most developed countries, such as North America, Northern and Western Europe and Australia, where less than 2% of the population are chronic carriers (Custer et al., 2004; Maddrey, 2000).

Hepatitis B virus (HBV) is present in the blood, saliva, semen, vaginal secretions, menstrual blood, and to a lesser degree sweat, breast milk, tears and urine of infected individuals (Lavanchy, 2004; Wright, 2006). Since HBV is resistant to breakdown outside the body, it is easily transmitted through contact with infected body fluids (Lavanchy, 2004; Wright, 2006). Three modes of HBV transmission have been categorized as: perinatal (from an infected mother to her child), horizontal transmission through mucosal contact with infected blood or bodily fluid secretions and parenteral or percutaneous transmission (such as injection drug use and needlestick injury) (C. J. Chen, Wang, & Yu, 2000; Gust, 1996; Lavanchy, 2004; Maddrey, 2000; Wright, 2006).

Routes of HBV transmission vary depending on the prevalence of HBV infection (Lavanchy, 2004; Maddrey, 2000). In areas of high endemicity, perinatal transmission is the most common route and the majority of HBV infection is acquired during the preschool years (Lavanchy, 2004; Maddrey, 2000). The lifetime risk of HBV infection is greater than 60% (Lavanchy, 2004; Maddrey, 2000). In areas of intermediate endemicity, most HBV infection occurs in infant or childhood, with lifetime risk of 20-60% (Lavanchy, 2004; Maddrey, 2000). In areas of low endemicity, HBV infection is acquired primarily by horizontal transmission (between individuals) in adolescents or early adulthood, for instance, through intravenous drug use or unprotected sexual transmission (Lavanchy, 2004; Maddrey, 2000). The lifetime risk of acquiring HBV is <20% (Lavanchy, 2004; Maddrey, 2000).

The natural history of HBV infection has three phases including immune tolerance, immune clearance and a residual phase (Lai et al., 2003; McMahon, 2008; Wright, 2006). The first phase of HBV is immune tolerance (Lai et al., 2003; McMahon, 2008; Merican et al., 2000;

Wright, 2006). During this phase, patients are hepatitis B e-antigen (HBeAg) positive and have high levels of serum HBV DNA (ranges between 10^7-10^{11} copies/mL) (Lai et al., 2003; McMahon, 2008; Merican et al., 2000; Wright, 2006). However, liver inflammatory disease is minimal or absent, with normal or minimally elevated alanine aminotransferase (ALT) level and minimal histological activity in the liver (Lai et al., 2003; McMahon, 2008; Merican et al., 2000; Wright, 2006). It usually occurs in children and young adults and may last for 10-30 years in Asian patients who acquired HBV infection during the perinatal period (Lai et al., 2003; Merican et al., 2000; Yuen, 2007). Patients in this phase are highly contagious and can transmit the disease easily (Yuen, 2007).

The second phase is immune clearance and it usually occurs when patients are aged between 15-35 years old (Lai et al., 2003; McMahon, 2008; Merican et al., 2000). It is characterized by HBeAg positive, lower level of viral replication (presented by low serum HBV DNA level), evaluated or fluctuating levels of ALT, moderate or severe liver necroinflammation and more rapid progression of fibrosis compared to the previous phase (Lai et al., 2003; McMahon, 2008; Merican et al., 2000). This phase may last for several weeks to several years (Merican et al., 2000). Liver damage has been established and the progression of the disease to a more advanced stage of illness such as cirrhosis depends on the duration of this stage (McMahon, 2008; Wright, 2006; Yuen, 2007).

In the third phase, patients undergo HBeAg seroconversion, with loss of HBeAg and appearance of an antibody to HBeAg, namely anti-HBe (European Association For the study of the liver, 2008; Keeffe et al., 2008; Lai et al., 2003; McMahon, 2008; Merican et al., 2000; Wright, 2006; Yuen, 2007). This phase is usually characterized by very low or undetectable serum HBV DNA levels (usually 10^3-10^5 copies/mL), persistent normal ALT level and inactive liver histology with minimal fibrosis (European Association For the study of the liver, 2008; Keeffe et al., 2008; McMahon, 2008; Wright, 2006; Yuen, 2007).

Some patients may progress to the immune phase (phase 4), with clearance of HBsAg and appearance of an antibody to HBsAg (anti-HBs) (Merican et al., 2000). It indicates the development of full immunity to HBV (Merican et al., 2000). Serum HBV DNA tends to become undetectable and risk of re-infection or reactivation is low (Merican et al., 2000). However, this phase is rare in Asian patients, but it may occur in Caucasians at the rate of 1-2% annually which increase with time (Merican et al., 2000).

Understanding the epidemiology and natural history of CHB infection helps us to prevent HBV infection and to use anti-viral treatment more effectively. There is little benefit to treat patients in phase 1 or phase 3 (Merican et al., 2000). Based on current clinical guidelines, the goal of treatment for CHB is to reduce the risk of disease progression in phase 2, aiming to eliminate the viral replication of HBV (Merican et al., 2000).

Most patients with hepatitis B have no symptoms until they have developed cirrhosis or HCC, both of which are very debilitating conditions that can markedly decrease HRQOL. Patients in the advanced stages of illness often have fatigue, pain, poor appetite, jaundice, ascites, variceal bleeding, and impaired cognitive function(L. M. Martin, Dan, & Younossi, 2006; L. M. Martin & Younossi, 2005), all of which may affect the patient's physical functioning, work, activities of daily living, social functioning and emotions. These domains should be included in the evaluation of the HRQOL of CHB patients. Anti-viral treatments for phase 2 CHB to prevent or delay disease progression not only reduce mortality but can preserve HRQOL through the prevention of morbidity.

2.2 Health service needs of CHB patients and HRQOL

Chronic hepatitis B (CHB) is a chronic disease that can lead to very disabling and even lethal complications, which require different health care services at different stages of the illness.

2.2.1 Monitoring

Individuals who are chronically infected with HBV require lifetime monitoring of the status of infection and follow-up for the development of liver complications, for instance active chronic hepatitis, cirrhosis and HCC (Keeffe et al., 2008; Y F Liaw et al., 2008; A S Lok & McMahon, 2009). International guidelines recommend the initial evaluation of patients with CHB infection should include a thorough history, physical examination and laboratory tests to identify the current stage and the phases of HBV infection (Keeffe et al., 2008; Y F Liaw et al., 2008; A S Lok & McMahon, 2009). We also need to take into consideration family history of HBV and liver cancer, risk factors for co-infection and alcohol consumption (Keeffe et al., 2008; Y F Liaw et al., 2008; A S Lok & McMahon, 2009). Laboratory investigations should comprise HBsAg, HBeAg and anti-HBe, quantification of viral replication by levels of HBV DNA, tests for co-infection with other types of hepatitis (hepatitis C virus and hepatitis D virus), and HIV in high-risk group (Keeffe et al., 2008; Y F Liaw et al., 2008; A S Lok & McMahon, 2009). Liver biopsy should be considered in those infected individuals with elevated ALT or HBV DNA levels (Keeffe et al., 2008; Y F Liaw et al., 2008; A S Lok & McMahon, 2009). Patients should be counseled on preventive measures against transmission of HBV infection through household or sexual contacts (Keeffe et al., 2008; Y F Liaw et al., 2008). Abstinence from alcohol is highly recommended (Keeffe et al., 2008). Negative impacts on psychological, physical and social well being should be considered (Y F Liaw et al., 2008). Previous studies showed that patients with CHB had lower HRQOL scores even in the absence of cirrhosis or cancer (Y F Liaw et al., 2008; S C Ong, Mak, Aung, Li, & Lim, 2008). All infected individuals with HBV infection who are not immuned to hepatitis A should be vaccinated according to Centers for Disease Control and Prevention (CDC) recommendations (Keeffe et al., 2008; A S Lok & McMahon, 2009). After initial evaluation, the frequency and tests of monitoring depends on the stage of illness.

Patients with persistently normal ALT levels often have minimal histological changes and poor response to currently available anti-viral drugs (Y F Liaw et al., 2008). Therefore, no anti-viral drug therapy is recommended for this patient group (Y F Liaw et al., 2008). However, they should be monitored regularly and HCC surveillance may be needed. There is currently no consensus on frequency or type of test for monitoring. The updated Asia-Pacific consensus statements recommends patients with active viral replication should have HBV DNA level, ALT and HBeAg testing every 3 months for the first year and then every 3-6 months, but this is rarely feasible because of limitation in resources (Y F Liaw et al., 2008). The American Association for the Study of Liver Disease (AASLD) guidelines recommend individuals in the immune tolerant phase (stage 2) who are HBeAg-positive but with normal ALT should have ALT and AST tests every 3 months for the first year and then every 6 months (A S Lok & McMahon, 2009). Screening for HCC is particularly important for high-risk group, such as Asian men aged >40 years old or Asian women aged >50 years old, with cirrhosis and family history of severe liver disease (Keeffe et al., 2008; A S Lok & McMahon, 2009).

2.2.2 Anti-viral drug treatment

If patients have higher serum HBV DNA levels and increased ALT levels, drug treatment is recommended (Keeffe et al., 2008; Y F Liaw et al., 2008; A S Lok & McMahon, 2009). A liver biopsy is suggested before receiving drug therapy in order to evaluate the necroinflammatory grade and stage of fibrosis and exclude other reasons of elevated ALT levels (Y F Liaw et al., 2008). The ideal goal of CHB therapy is the complete eradication of HBV but this is still impossible. The short-term goals of CHB treatment include suppression of serum HBV DNA, normalization of ALT, HBeAg seroconversion and improvement in liver histology (European Association For the study of the liver, 2008; Keeffe et al., 2008; Y F Liaw et al., 2008; A S Lok & McMahon, 2009). The ultimate goal of long term treatment is to prevent or delay the onset of liver complications including cirrhosis and HCC, and to prolong survival (European Association For the study of the liver, 2008; Keeffe et al., 2008; Y F Liaw et al., 2008; A S Lok & McMahon, 2009). Current clinical guidelines and treatment algorithms focus on the suppression of viral replication to maintain serum HBV DNA at the lowest possible levels (European Association For the study of the liver, 2008; Keeffe et al., 2008; Y F Liaw et al., 2008; A S Lok & McMahon, 2009). This has been shown to prevent and slow the progression to cirrhosis, liver failure or HCC (European Association For the study of the liver, 2008; Keeffe et al., 2008; Y F Liaw et al., 2008; A S Lok & McMahon, 2009).

Currently, seven drugs are available for management of CHB infection including lamivudine (LVD), adefovir (ADV), entecavir (ETV), telbivudine (LdT), and tenofovir (TDF) and interferon (IFN-α), and pegylated IFN (peg-IFN) (European Association For the study of the liver, 2008; Keeffe et al., 2008; Y F Liaw et al., 2008; A S Lok & McMahon, 2009). The choice of treatment should take into account treatment efficacy, risk of developing drug resistance, long term safety profile, side effects, mode of administration and cost of drug (Fung, Lai, & Yuen, 2008).

Interferon (IFN-α) is the first drug used for the treatment of CHB (Lai & Yuen, 2008; Yuen & Lai, 2001). It has to be given by injection which limits its acceptability (Jacobson, 2006). Standard IFN-α has been used for treatment of CHB for more than two decades (Y F Liaw et al., 2008; Marcellin, Asselah, & Boyer, 2005). This treatment stimulates the immune system to eradicate HBV (Ayoub & Keeffe, 2008; Jacobson, 2006; Y F Liaw et al., 2008; A S Lok & McMahon, 2009; Marcellin et al., 2005). The efficacy of standard IFN-α has been demonstrated to be effective in suppression of HBV replication and in inducing remission of liver disease in Western populations (Fung et al., 2008; Jacobson, 2006; Y F Liaw et al., 2008; A S Lok & McMahon, 2009; A. S. Lok et al., 1992; Yuen & Lai, 2001). Peg-IFN, in a newer generation of IFN, has been shown to be superior in terms of HBeAg clearance, normalization of ALT and HBV DNA suppression (Ayoub & Keeffe, 2008; Cooksley et al., 2003; Fung et al., 2008; Keeffe et al., 2008; Y F Liaw et al., 2008; A S Lok & McMahon, 2009; Zoulim & Perrillo, 2008). The advantage of standard IFN-α or peg-IFN is a definite duration of treatment (Ayoub & Keeffe, 2008; Fung et al., 2008; Jacobson, 2006; Lai & Yuen, 2008; Y F Liaw et al., 2008). Long-term effectiveness of standard IFN has shown to be inconclusive (Fung et al., 2008; Y F Liaw et al., 2008; A S Lok & McMahon, 2009; Marcellin et al., 2005; Yuen & Lai, 2001). The efficacy of IFN is limited to CHB patients with high pretreatment ALT levels (Jacobson, 2006; A S Lok & McMahon, 2009), which is uncommon for Asian CHB patients (Fung et al., 2008). Some studies in Japanese and Chinese patients failed to demonstrate a long-term benefit of standard IFN therapy. However, a recent study of Taiwanese patients with a high ALT

pretreatment level has shown a beneficial effect on reduction of liver-related complications, for instance, cirrhosis and HCC (Fung et al., 2008). The occurrence of adverse event is the main concern. Standard IFN and peg-IFN have similar side effect profiles but is less common in peg-IFN (A S Lok & McMahon, 2009). The most common side effect is influenza-like symptoms consisting of fever, chills, headache, malaise and myalgia (Jacobson, 2006; Y F Liaw et al., 2008; A S Lok & McMahon, 2009). Other side effects comprise fatigue, anorexia, weight loss and hair loss (Y F Liaw et al., 2008). Patients receiving IFN should have regular follow-up for mood deterioration (Jacobson, 2006). Recently, studies have focused on combination or sequential therapy with LVD (Y F Liaw et al., 2008). No superior effects have been found with combination therapy of IFN and lamivudine (LVD) (Jacobson, 2006; Y F Liaw et al., 2008). It reduced the risk of developing resistance.

Lamivudine (LVD) is a nucleoside analog and the first oral anti-viral drug licensed since 1998 for the treatment of CHB infection (Ayoub & Keeffe, 2008; Lai & Yuen, 2008). It has an excellent safety profile (Ayoub & Keeffe, 2008; Fung et al., 2008; Jacobson, 2006; Leung, 2008; Y F Liaw et al., 2008) and is the least expensive of all nucleoside analogs approved for the treatment of CHB (Dan, Aung, & Lim, 2008; Zoulim & Perrillo, 2008). It is effective in suppressing HBV DNA, normalizing ALT and HBeAg seroconversion (Dienstag et al., 1999; Fung et al., 2008; Lai et al., 1998; Y F Liaw et al., 2008; A S Lok & McMahon, 2009). Previous studies showed that LVD led to significant histological improvement and reduction in the progression of liver fibrosis (Ayoub & Keeffe, 2008; Dienstag et al., 1999; Lai et al., 1998; Leung, 2008). Long-term LVD therapy reduces the risk of developing cirrhosis and HCC in precirrhotic/cirrhotic and non-cirrohotic patients (Y. F. Liaw et al., 2004; Yuen et al., 2007). Duration of LVD therapy remains controversial in HBeAg negative CHB patients (A S Lok & McMahon, 2009). For patients who are HBeAg positive, LVD can be stopped 6-9 months after HBeAg seroconversion (A S Lok & McMahon, 2009). Hepatic flares, defined as increased serum ALT levels to ≥ 5 times upper normal limit, may develop on stopping LVD and result in hepatic decompensation (Fung et al., 2008; Y F Liaw et al., 2008). Earlier studies demonstrated about 50% of the patients achieved a sustained response after stopping LVD treatment (Y F Liaw et al., 2008). In one of the studies by Chan et al, 89 Chinese CHB patients with HBeAg negative received two years of LVD treatment resulted in 56% complete response (defined as normalization of ALT and HBV DNA level of $< 10^4$ copies/mL) (Y F Liaw et al., 2008). The response was sustained in 26% of patients 6 months after stopping LVD treatment (Y F Liaw et al., 2008). The main drawback of LVD is development of drug resistance (Jacobson, 2006; Y F Liaw et al., 2008; Nguyen & Keeffe, 2009; Yuen & Lai, 2001; Zoulim & Perrillo, 2008). According to a recent review, LVD drug resistance rates are approximately 50% after 3 years and 76% after 8 years (Ayoub & Keeffe, 2008; Fung et al., 2008; Leung, 2008; Nguyen & Keeffe, 2009; Yuen et al., 2007). The incidence of drug resistance increased with the duration of therapy (Ayoub & Keeffe, 2008; Fung et al., 2008; Jacobson, 2006; Leung, 2008). Benefits induced by LVD therapy are reduced once drug resistance occurs (Fung et al., 2008; Jacobson, 2006). However, even those who develop LVD-resistance, their treatment outcome is still better than untreated patients.

Adedovir (ADV) is the second oral nucleoside analog approved for CHB and has been shown to be effective, irrespective of HBeAg status or LVD-resistance (Hadziyannis et al., 2006; Hadziyannis et al., 2003; Lampertico et al., 2005; Leung, 2008; Marcellin et al., 2003). Although ADV has fairly slow action compared with other oral anti-viral treatments (in terms of HBAg seroconversion, normalization of ALT and suppression of HBV DNA),

treatment with ADV up to 5 years results in significant histologic, virologic and biochemical improvement (Hadziyannis et al., 2005). Currently, ADV is primarily used in patients who have developed resistance to LVD (Fung et al., 2008; Zoulim & Perrillo, 2008). Some studies have shown the addition of ADV to LVD rather than switchover to ADV monotherapy produced a lower rate of resistance to ADV (Lampertico et al., 2007; Manolakopoulos et al., 2008; Rapti, Dimou, Mitsoula, & Hadziyannis, 2007; van der Poorten et al., 2007; Zoulim & Perrillo, 2008). Other studies have shown that ADV monotherapy in patients with LVD-resistant was as effective for HBV DNA suppression as combination therapy (Fung et al., 2007; Fung et al., 2008; Y F Liaw et al., 2008; Peters et al., 2004). Most guidelines recommended to add on ADV in LVD-resistant patients in order to minimize the development of ADV-resistance and maintain HBV DNA suppression in the long term (European Association For the study of the liver, 2008; Keeffe et al., 2008; Y F Liaw et al., 2008; A S Lok & McMahon, 2009). ADV has a higher genetic barrier than LVD resulting in lower rates of resistance (Fung et al., 2008). The cumulative incidence of ADV-resistance is 29% after 5 years of treatment in patients with HBeAg negative and about 20% in HBeAg positive patients (Hadziyannis et al., 2006; A S Lok & McMahon, 2009). According to a large trial, ADV in 10-mg doses was well tolerated and had similar safety profile as placebo (Hadziyannis et al., 2006). However, renal abnormalities were reported with 30 mg of ADV (Marcellin et al., 2003). Continued treatment of ADV up to 5 years induces a reversible increase in serum creatinine of more than 0.5 mg/dL (Hadziyannis et al., 2006). Therefore, renal function should be monitored regularly and closely (A S Lok & McMahon, 2009).

Entecavir (ETV) is the third oral nucleoside analog licensed for CHB (Lai & Yuen, 2008). It was superior to LVD and ADV in rates of histologic, biochemical and virologic responses, irrespective of HBeAg status (T. T. Chang et al., 2006; Lai et al., 2002; Lai et al., 2006; Leung, 2008). In a viral kinetic study ETV showed a more dramatic decline in HBV DNA levels than ADV (Y F Liaw et al., 2008). After 2 years of ETV treatment, no virological breakthrough from ETV resistance has been found (Fung et al., 2008; Lai & Yuen, 2008; Y F Liaw et al., 2008). The rate of resistance to ETV was very low at 1.2% in treatment-naïve patients after 5 years (Ayoub & Keeffe, 2008; European Association For the study of the liver, 2008; Lai & Yuen, 2008; Y F Liaw et al., 2008; A S Lok & McMahon, 2009; Nguyen & Keeffe, 2009). ETV has demonstrated to be effective in LVD-resistant patients, but was associated with a lower response rate and a higher resistance rate of 39.5% after 4 years (Ayoub & Keeffe, 2008; Keeffe et al., 2008; Y F Liaw et al., 2008; A S Lok & McMahon, 2009; Nguyen & Keeffe, 2009). Therefore, LVD should be discontinued when patients are switched to ETV in order to reduce the risk of ETV resistance (Fung et al., 2008; A S Lok & McMahon, 2009). ADV add-on therapy may be better than ETV switching therapy for patients with LVD-resistance (Fung et al., 2008; Keeffe et al., 2008; A S Lok & McMahon, 2009). ETV therapy is best given to treatment naïve patients (Leung, 2008).

Telbivudine (LdT) is more potent than LVD and ADV in HBV DNA suppression (H. L. Chan et al., 2007; Keeffe et al., 2008; Lai et al., 2005; A S Lok & McMahon, 2009). A phase III controlled trial showed that 60% of patients who received LdT had an undetectable HBV DNA level compared to those who received LVD (40%) after 2 years of treatment (Keeffe et al., 2008; Y. F. Liaw et al., 2009). Resistance rate increases dramatically after one year of LdT to 25.1% in HBeAg positive and 10.8% in HBeAg negative patients after 2 years of treatment (Y F Liaw et al., 2008; A S Lok & McMahon, 2009). LdT was well tolerated when used as a monotherapy and has a similar safety profile to LVD (Keeffe et al., 2008; Leung, 2008; A S Lok & McMahon,

2009). Increase in creatine kinase levels (a level of >7 times upper limit of normal (ULN)) was more commonly found in patients receiving LdT than LVD (7.5% vs. 3.1%) (Leung, 2008; Y F Liaw et al., 2008). However, it improved spontaneously with continued drug therapy. Cases of reversible myopathy and peripheral neuropathy have been reported (Leung, 2008; Y F Liaw et al., 2008; A S Lok & McMahon, 2009). Although LdT is more potent than LVD, its high resistance rate and cost limit its use as the first line treatment for CHB (Keeffe et al., 2008; Leung, 2008; Y F Liaw et al., 2008; Zoulim & Perrillo, 2008).

Tenofovir (TDF) is an oral anti-viral drug and has been approved for the treatment of CHB in 2008 (Ayoub & Keeffe, 2008; A S Lok & McMahon, 2009). It belongs to the same family of nucleotide analogs as ADV (Ayoub & Keeffe, 2008; Keeffe et al., 2008; A S Lok & McMahon, 2009; Zoulim & Perrillo, 2008). It has been shown to be more potent than ADV particularly in early suppression of HBV (Ayoub & Keeffe, 2008; Keeffe et al., 2008; Lai & Yuen, 2008; Leung, 2008; Marcellin et al., 2008). In a phase III clinical trial in HBeAg positive patients, TDF resulted in a significantly higher percentage of patients with undetectable HBV DNA levels compared with ADV (76% vs. 13%) after 48 weeks (Ayoub & Keeffe, 2008; Y F Liaw et al., 2008; Marcellin et al., 2008). No resistance mutations associated with TDF were found at week 48 and 72 (Ayoub & Keeffe, 2008; Keeffe et al., 2008; Lai & Yuen, 2008; Leung, 2008). The incidence of adverse events was similar in TDF and ADV (Ayoub & Keeffe, 2008; Keeffe et al., 2008). The incidence of ALT flares (>2 times baseline values) was higher in patients receiving TDF than those with ADV (11% vs. 4%) (Keeffe et al., 2008). Studies are still ongoing for long-term efficacy and safety.

2.2.3 Screening for HCC

As defined in the published guideline (Bruix, Sherman, & Practice Guidelines Committee, 2005), "screening refers to an application of diagnostic tests in patients at risk for HCC, but in whom there is no prior reason to suspect that HCC is present". It states clearly that screening is to detect the presence of HCC among the asymptomatic hepatitis B carriers. The ultimate goal of screening for HCC is to reduce morbidity and mortality (Bruix et al., 2005; Ying, 2009; Yuen & Lai, 2003). That means to detect early preclinical and early HCC that can be cured (resection).

Screening for disease should fulfill certain criteria to be medically and economically acceptable. Wilson's criteria are widely used to judge whether a disease should be screened for and they are shown as follows (Wilson & Jungner, 1968):-

i. The condition sought should be an important health problem;
ii. There should be an accepted treatment for patients with the recognized disease;
iii. Facilities for diagnosis and treatment should be available;
iv. There should be a latent or early symptomatic stage;
v. There should be a suitable test or examination;
vi. The test should be acceptable to the population;
vii. The natural history of the condition should be adequately understood;
viii. There should be an agreed policy on whom to treat as patients;
ix. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole;
x. Case-finding should be a continuing process and not a once and for all project.

Although there are several published guidelines for HCC screening, there is no consensus regarding screening for HCC (Bruix et al., 2005; Keeffe et al., 2008; Y F Liaw et al., 2008; A S Lok & McMahon, 2009; Omata et al., 2010). A recent AASLD practice guideline has been published and recommended that HBV carriers at high risk should be screened with ultrasound (US) every 6-12 months and alpha-fetoprotein (AFP) alone if US is not available (A S Lok & McMahon, 2009). Ultrasound and AFP are currently two commonly used screening tests for HCC (A S Lok & McMahon, 2009). High risk group is defined as Asian men aged >40 years old, Asian women aged >50 years old, those with cirrhosis or family history of severe liver disease, with persistent or intermittent ALT elevation and/or high HBV DNA level >2000 IU/mL (A S Lok & McMahon, 2009). On the other hand, the latest Asia-Pacific consensus suggested that only male HBV carriers aged 40 or above with cirrhosis or family history of serious liver disease should be screened with US and AFP every 3-6 months (Y F Liaw et al., 2008). In general, HCC screening should be considered for patients with cirrhosis. However, it remains unclear whether screening for HCC in an asymptomatic population has beneficial outcomes, what is the best screening strategy and whether screening is cost-effective.

2.2.4 Health services for CHB in Hong Kong

The Hong Kong Government provides healthcare service to patients with HBV infection, but resources are limited and management has to be prioritized according to the severity of the illness. For patients found to be CHB carriers, the frequency of monitoring and types of laboratory tests differed by the severity of their diseases.

In Hong Kong, lamivudine (LVD), adefovir (ADV) and entecavir (ETV) are the standard antiviral drugs used for the treatment of CHB (Fung et al., 2008). Interferons are of doubtful use for Chinese patients (Fung et al., 2008). Telbivudine (LdT) is seldom used because of its cost and high resistance rate (Fung et al., 2008; Zoulim & Perrillo, 2008). The long-term effect of tenofovir (TDF) is unknown (Keeffe et al., 2008; Lai & Yuen, 2008; Y F Liaw et al., 2008).

Anti-viral drugs are expensive and the government provides subsidy for patients with cirrhosis and HCC only in public service. Most CHB patients with impaired liver function (ILF) need to pay for their full drug cost and HBV DNA assay. The costs of anti-viral treatment range from HKD 1,000 to HKD 3,000 per month depending on the drug choice (Yeo B, 2008). Patients' willingness to pay may influence treatment options which also affects the duration of treatment, effectiveness, drug resistance and side effects. Many patients cannot afford or are not willing to pay for treatment even though it is recommended by physicians. There is no policy on hepatitis B screening (Hong Kong (China). Dept. of Health., 1998), which is not routinely provided by the public service.

Free printed information on hepatitis is available from the Department of Health to educate the public about the prevention of spread of the disease, indication for treatment and treatment options (Department of Health). Primary care doctors or specialists can easily distribute these printed information to their patients during the consultation but this not often done because time is limited and the evaluation of disease pathology and its complication take top priority.

a. Management of Asymptomatic Hepatitis B (AHB) carriers

Most infected individuals are asymptomatic and CHB is usually diagnosed incidentally during blood donation, health assessment or when they develop liver complications such as cirrhosis or HCC. Asymptomatic hepatitis B (AHB) carriers may be followed-up yearly at General Outpatient Clinic (GOPC) or private primary care doctors with liver function test (LFT) and alpha fetoprotein (AFP) but many are not. According to a local study in a primary care setting, most of HBV carriers did not attend GOPC for following up of their disease (Kung, Lam, & Li, 2004). Furthermore, there were large variations in follow-up period and test intervals (Kung et al., 2004). It ranges from 1 to 14 months for follow-up, 2 to 36 for blood tests, and 6 to 60 months for ultrasound (Kung et al., 2004). One month follow-up may be given to those who were very anxious about their condition (Kung et al., 2004). Since they are asymptomatic population, they do not need to take anti-viral treatment unless liver-related complications developed (European Association For the study of the liver, 2008; Keeffe et al., 2008; Y F Liaw et al., 2008; A S Lok & McMahon, 2009). Both HCC screening and HBV DNA assay are not available for AHB carriers. AHB carriers are at risk of developing cirrhosis or HCC but screening is rarely done for these patients (Yuen et al., 2005).

b. Management of patients with Impaired Liver Function (ILF)

Patients with ILF usually have close monitoring and follow-up at Specialist Outpatient Clinics (SOPC) with LFT and AFP tests regularly. The frequency of follow-up contact may vary. It is determined by a combination of variables: results of LFT, degree of viral replication, and need of anti-viral drug. Patients with ILF who receive drug treatment often need to pay for their drug costs and HBV DNA assay. Screening for HCC is not available for patients with ILF.

c. Management of patients with cirrhosis or HCC

Patients with cirrhosis or HCC have close monitoring and follow-up at Specialist Outpatient Clinics (SOPC) with LFT and AFP tests regularly. Patients may receive anti-viral drug free of charge. Screening for HCC and HBV DNA assay are available for patients with cirrhosis.

Clinical guidelines have been established to provide guidance to healthcare providers and physicians for diagnosis and management of CHB infection to reduce the development of complications (Keeffe et al., 2008; Y F Liaw et al., 2008; A S Lok & McMahon, 2009). However, the following issues remain unresolved. Firstly, not the majority of infected individuals are identified. Secondly, many CHB patients do not receive adequate management and follow-up, in particular, for those who initially do not consider anti-viral drug treatment. Despite numerous studies on the epidemiology, natural history and management of CHB, little has been done on the gap in healthcare services and patients' willingness to pay for their CHB treatment. Understanding patients' perceived needs can help to make service more patient-centered and improve the quality of life to CHB patients.

2.2.5 HRQOL and service utilization

Studies have shown a significant inverse relationship between HRQOL and service utilization in Western population (Dominick & Ahern, 2004; Ethgen & Kahler, 2002; Nelson & McHorney, 1998; Parkerson & Gutman, 2000; Singh & Nelson, 2005). Nelson et al found

that physical functioning and mental health were important indicators of both outpatient visits and hospitalization for patients with chronic disease after controlling for confounding variables (Nelson 1998). Another study by Mulunpalo et al showed that a significant linear relationship between HRQOL and outpatient physician visits for working-age population in Finland (Mulunpalo 1997). Furthermore, Dominick et al pointed out that HRQOL can be valuable tools for predicting future health care for older patients with osteoarthritis (Dominick 2004). Poorer general health was correlated with increased likelihood of analgesic or anti-inflammatory use (Dominick 2004). Poor mental health was associated with increased likelihood of analgesic or anti-inflammatory use (Dominick 2004).

There were several studies on the association between HRQOL and service utilization for Asian population (T. Chen & Li, 2009; C. L. K. Lam & Fong, 2002; Matsumura, 2000). A study by Matsumura in Japan found that subjects with Short Form-36 (SF-36) physical component summary (PCS) score below 40 were more likely to use outpatient services and to be hospitalized than those who had scores greater than 50 (Matsumura 2000). Subjects with both SF-36 physical and mental component summary scores below 40 were more likely to have taken sick leave than those who had scores greater than 50 (Matsumura, 2000). A large study in Hong Kong showed that a linear relationship between HRQOL and service utilization in the local Chinese population (C. L. K. Lam & Fong, 2002). Five out of eight SF-36 scores were independent determinants of consultation rates (C. L. K. Lam & Fong, 2002). Role limitation due to physical problem and bodily pain were associated with hospitalization (C. L. K. Lam & Fong, 2002).

A recent study assessing the effect of HRQOL on service utilization was conducted in 737 primary care patients in Mainland China (Chen 20009). Lower HRQOL scores were correlated with higher service utilization rates (Chen 20009). Three out of eight SF-36 scales were associated with both inpatient and outpatient consultation (Chen 20009).

Numerous studies reported on the relationship between HRQOL and service utilization for Western and Asian populations (T. Chen & Li, 2009; Dominick & Ahern, 2004; Ethgen & Kahler, 2002; C. L. K. Lam & Fong, 2002; Matsumura, 2000; Nelson & McHorney, 1998; Parkerson & Gutman, 2000; Singh & Nelson, 2005), but no data were available for CHB patients. More studies are needed to explore the effect of HRQOL on service utilization in patients with CHB.

2.3 Health-related Quality of Life (HRQOL) as a health outcome measure for Chronic Hepatitis B (CHB) patients

The goal of healthcare is to maintain, restore and improve health of patients. Traditionally, clinicians have focused primarily on 'hard' clinical outcomes, for instance, patient's mortality and morbidity (Eisen, Locke, & Provenzale, 1999). Clinicians are more likely to judge the effectiveness or efficacy of a therapy in terms of survival rate, biochemical parameters such as liver function, viral markers, and symptoms (Eisen et al., 1999). Traditional clinical outcomes (i.e. morbidity and mortality) are important but they do not adequately reflect patients' perceived health, feelings and the impact of illness on life. Health-related quality of life (HRQOL) can provide additional information on the effectiveness and quality of care.

Chronic hepatitis B (CHB) is a chronic debilitating condition that can lead to progressive impairment of physical and mental health as the disease progresses. Improvements in medical and surgical therapies in liver diseases have led to more people living with CHB. HRQOL should be considered an important outcome measures for assessing the impact of CHB and the effectiveness of treatment. The expansion from traditional clinical outcomes to include HRQOL outcomes will enable us to measure modern health care more sensitively (Younossi, 2001). HRQOL is more sensitive in capturing the effect of illness and interventions for those with uncomplicated disease (Bondini et al., 2007; Levy et al., 2008; Nokhodian, Ataei, Kassaian, Adibi, & Farajzadegan, 2009; S C Ong et al., 2008; Tan, Cheah, Teo, & Yang, 2008; Yi, 2006). Furthermore, HRQOL provides additional information for the prioritization of needs among patients with similar clinical severity defined by traditional clinical outcomes. The effect of an intervention on HRQOL has become a very important topic for both consumers and providers of health services (R. C. Martin, Eid, Scoggins, & McMasters, 2007; Poon et al., 2001; Yi, 2006).

The applications of HRQOL measures can be categorized as evaluative, discriminative and predictive (Preedy, Watson, & Lam, 2010; Yacavone, Locke, Provenzale, & Eisen, 2001). Evaluative measures are the most widely used in different populations or patients groups (Preedy et al., 2010). It is used to assess the impact of an illness, effectiveness or side effect of treatment, and quality of healthcare delivery (Preedy et al., 2010; Yacavone et al., 2001). Discriminative measures can be used to differentiate between groups in terms of HRQOL (Preedy et al., 2010; Yacavone et al., 2001). Predictive measures are used to identify people who are at risk or predict service needs for different populations or patient groups (Preedy et al., 2010). HRQOL measures can apply in economic evaluation in relation to treatment (Kanwal et al., 2005; Sun, Qin, Li, & Jiang, 2007; Takeda, Jones, Shepherd, Davidson, & Price, 2007; Veenstra, Spackman, Bisceglie, Kowdley, & Gish, 2008; Yuan, Iloeje, Li, Hay, & Yao, 2008).

The World Health Organization (WHO) states that 'health is a state of complete physical, mental and social well-being' (WHO, 1947). Well-being is the subjective perception of an individual's state of living, which has a similar concept as quality of life. It is noted that health is only one of many determinants of a person's quality of life, others include social environment, economy, religion etc. In the context of health services, the focus is on health-related quality of life (HRQOL) in an attempt to quantify the net consequence of a disease and its treatment on the patient's perception of his/her ability to live a useful and fulfilling life (Schipper, Clinch, & Olweny, 1996).

In the last few decades, there has been an increasing interest in the evaluation of HRQOL in patient groups, including those with chronic liver disease (Foster, Goldin, & Thomas, 1998; J. J. Gutteling, de Man, Busschbach, & Darlington, 2007; Younossi, 2001). The number of articles in gastroenterology on quality of life (QOL) or HRQOL has increased significantly in recent decades (Foster et al., 1998; L. M. Martin et al., 2006; L. M. Martin, Sheridan, & Younossi, 2002; L. M. Martin & Younossi, 2005; Younossi et al., 2001; Younossi, Kiwi, Boparai, Price, & Guyatt, 2000). HRQOL has become standard outcome measure in patients with chronic liver diseases in western countries especially in patients with chronic hepatitis C (CHC) (Chong et al., 2003; Foster, 1999; Foster et al., 1998; Kwan et al., 2008; Spiegel et al., 2005). It should also become an important outcome measure in CHB patients.

2.3.1 Impact of CHB on HRQOL

Although numerous studies have shown significant lower health-related quality of life (HRQOL) scores in patients with chronic liver diseases (CLD), there is relatively little attention on the impact of HRQOL in patients with hepatitis B virus (HBV) because most data come from western populations where CHB is uncommon (J. J. Gutteling et al., 2007; L. M. Martin et al., 2002). In general, studies showed a significant decline in HRQOL in patients with hepatitis C virus (HCV) (Foster et al., 1998; Heitkemper, Jarrett, Kurashige, & Carithers, 2001; Koff, 1999; Kwan et al., 2008; Miller, Hiller, & Shaw, 2001; Spiegel et al., 2005; Strauss & Dias Teixeira, 2006). Only a few papers explored the effect of CHB on HRQOL (Bondini et al., 2007; Levy et al., 2008; Nokhodian et al., 2009; S C Ong et al., 2008; Tan et al., 2008). The first paper on HRQOL of CHB was published by Foster et al in 1998, which evaluated the impact of chronic hepatitis C (CHC) and CHB by a generic measure of HRQOL, the Medical Outcomes Study Short Form-36 (SF-36) Health Survey (Foster et al., 1998). Patients with CHB had significant lower HRQOL scores in mental health and general health perception aspects, but their physical related HRQOL scores were comparable to the healthy control (Foster et al., 1998). The results indicated patients with CHB infection did not have significant lower scores in physical functions but the results were limited by a very small sample of CHB patients (Foster et al., 1998).

Studies with a larger sample size and patients with different stages of CHB are needed in order to provide more precise measures of HRQOL. One study found that CHB patients had similar HRQOL scores to the healthy control group, as measured by both generic (Short Form-36 Health Survey, SF-36) and disease-specific (Chronic Liver Disease Questionnaire, CLDQ) questionnaires (Bondini et al., 2007). CHB patients had lower HRQOL scores in only two (fatigue and worry) out of six CLDQ scales and two (physical functioning and vitality) out of eight SF-36 scales compared to the norm (Bondini et al., 2007). However, health preference values (utility) of CHB patients were lower than the population norm (Bondini et al., 2007).

Recently, two large studies showed that CHB infection had a negative impact on HRQOL (Levy et al., 2008; S C Ong et al., 2008). Asymptomatic hepatitis B (AHB) carriers, CHB patients with impaired liver function (ILF), and compensated cirrhosis (CC) patients had a small to moderate but significant effect on HRQOL, and decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC) patients had the lowest HRQOL scores (S C Ong et al., 2008). Ong et al demonstrated that HRQOL measured by the generic HRQOL measures, the SF-36 Health Survey and EQ-5D, in Chinese AHB carriers was comparable to healthy controls, although those with ILF and CC patients showed a significant reduction in general health and mental health dimensions (S C Ong et al., 2008). Patients with more advanced stages of CHB (DC and HCC) had the lowest HRQOL scores in all dimensions (S C Ong et al., 2008). The results indicated deterioration in physical health while the disease progresses (S C Ong et al., 2008).

Another study by Tan et al showed that hepatitis B carriers in Singapore had good physical and mental health measured by both generic (SF-36 Health Survey) and disease-specific (Hepatitis Quality of Life Questionnaire) HRQOL measures (Tan et al., 2008). There was no significant difference in HRQOL between the 108 hepatitis B carriers in the study and general population, except in social functioning (Tan et al., 2008).

A recent study assessing HRQOL in patients with CHB infection was conducted using a disease-specific HRQOL measure (Chronic Liver Disease Questionnaire) in Iran (Nokhodian et al., 2009). A sample of 61 patients with CHB infection and 60 age and sex-matched healthy control were recruited in this study (Nokhodian et al., 2009). Patients had lower (worse) scores in three out of six CLDQ scales, including fatigue, abdominal and systemic symptoms, as compared to controls (Nokhodian et al., 2009). Surprisingly, CHB patients had a higher score on the worry scale, i.e. less worry, than the control groups (Nokhodian et al., 2009).

Findings from a multi-country study on health preference values found that health states related to CHB infection had significant reduction in HRQOL (Levy et al., 2008). Health preference is a composite HRQOL value that ranges from 0 (death) to 1 (perfect health), with higher scores implying better HRQOL (Brazier, Roberts, & Deverill, 2002). Patients with ILF and CC had a moderate impact on HRQOL with health preference values ranging from 0.68 to 0.80 (Levy et al., 2008). On the other hand, patients with DC or HCC had a stronger impact with health preference values ranging from 0.35 to 0.41 (Levy et al., 2008). Variation in health preference values was found between countries with lower health preference values found in Hong Kong and Mainland China than countries (Levy et al., 2008).

These studies provided some evidence on the negative HRQOL impact of CHB but they are limited by small sample size, inconsistent results and a lack of differentiation between CHB patient types (Bondini et al., 2007; Foster et al., 1998; S C Ong et al., 2008; Tan et al., 2008). Although studies have reported that HCC or cirrhosis patients had poorer overall HRQOL scores compared with the general population (Chong et al., 2003; A. A. Dan et al., 2008; S C Ong et al., 2008), it is still unclear whether patients with asymptomatic, CHB infection with or without ILF have poorer HRQOL than the general population, and whether any significant difference in HRQOL was found among different CHB groups.

An analytic investigation on factors affecting HRQOL enables better targeting of management. Previous studies suggested that biochemical markers, socio-demographic and psychosocial factors did affect HRQOL in patients with CLD but it has not been fully examined in Chinese CHB patients (Afendy et al., 2009; Bianchi et al., 2003; J J Gutteling et al., 2006; Hauser, Schnur, Steder-Neukamm, Muthny, & Grandt, 2004; Hussain et al., 2001; Marchesini et al., 2001; Sobhonslidsuk et al., 2006; Sumskiene, Sumskas, Petrauskas, & Kupcinskas, 2006; Younossi et al., 2001; Younossi et al., 2000). Disease severity, as measured by Child-Pugh scores or stage of CHB illness (asymptomatic, impaired liver function, cirrhosis and HCC), was one of the commonest factors that had a negative relationship with HRQOL (Bianchi et al., 2003; J J Gutteling et al., 2006; Marchesini et al., 2001; Sobhonslidsuk et al., 2006; Sumskiene et al., 2006; Younossi et al., 2001; Younossi et al., 2000). However, some studies did not find any significant effect between HRQOL and disease severity (Hauser, Holtmann, & Grandt, 2004; Hauser, Zimmer, Schiedermaier, & Grandt, 2004). One large cross-sectional study in Singapore found that disease severity was an important determinant of HRQOL of Chinese patients with CHB, controlling for demographic characteristics (S C Ong et al., 2008). Unfortunately, this study did not include some important clinical and co-morbidity variables in regression model, for instance, duration of illness and chronic co-morbidity (S C Ong et al., 2008).

One study examining the impact of liver cirrhosis found that the presence of cirrhosis was associated with lower HRQOL scores (Bondini et al., 2007). But Dan et al did not find any significant relationship between presence of cirrhosis and HRQOL (A. A. Dan et al., 2008). These two studies only included a small number of patients with CHB infection (Bondini et al., 2007; A. A. Dan et al., 2008). More studies are needed to confirm the relationship between the severity of liver disease and HRQOL in patients with CHB infection.

Liver biomarkers, such as alanine transaminase (ALT), was not found to have any significant association with HRQOL (Bondini et al., 2007; Hussain et al., 2001; Miller et al., 2001), though it is an important clinical markers to assess the severity of liver and determine indication for treatment (Fung et al., 2008; Keeffe et al., 2008; Y F Liaw et al., 2008; A S Lok & McMahon, 2009; McMahon, 2006). However, Kondo et al found an association between HRQOL and serum albumin (Kondo et al., 2007), which is a marker of severity of liver disease.

Physical symptoms, for instance, joint pain, muscle cramps, itching and abdominal pain, were also correlated with HRQOL (J. J. Gutteling et al., 2007; Marchesini et al., 2001; Younossi, 2001). Fatigue was also a concern for patients with chronic liver disease (J. J. Gutteling et al., 2007; J J Gutteling et al., 2006).

Anti-viral treatment may improve patients' HRQOL (Bernstein, Kleinman, Barker, Revicki, & Green, 2002; S. C. Chang, Ko, Wu, Peng, & Yang, 2008; Kang, Hwang, Lee, Chang, & Lee, 2005; McHutchison et al., 2001; Perrillo et al., 2004; Ware, Bayliss, Mannocchia, & Davis, 1999), but side effects can be a problem (Fung et al., 2008; Keeffe et al., 2008; Y F Liaw et al., 2008; A S Lok & McMahon, 2009). Foster et al showed that patients with HCV receiving anti-viral treatment of 6-12 months had decreased HRQOL because of side effects (Foster, 1999). Other studies demonstrated a sustained response to treatment was associated with improved HRQOL in patients with HCV infection (Bernstein et al., 2002; S. C. Chang et al., 2008; Kang et al., 2005; McHutchison et al., 2001; Perrillo et al., 2004; Ware et al., 1999). Studies are needed to confirm the effect of anti-viral treatment on HRQOL.

Socio-demographic factors also play an important role in HRQOL, including age, gender, education levels, marital status and socio-economic status (J. J. Gutteling et al., 2007; L. M. Martin et al., 2002). Previous studies found a significant effect of age and gender on HRQOL in patients with chronic liver disease, including patients with CHC and CHB (J. J. Gutteling et al., 2007; L. M. Martin et al., 2002). Older age was associated with lower HRQOL in patients with chronic liver disease (Afendy et al., 2009; J J Gutteling et al., 2006; Kondo et al., 2007; Sobhonslidsuk et al., 2006; Younossi et al., 2001), but insignificant or positive effect on physical or mental HRQOL (Bianchi et al., 2003; Bondini et al., 2007; A. A. Dan et al., 2008; Hauser, Holtmann, et al., 2004; Hauser, Zimmer, et al., 2004; Hussain et al., 2001; Sumskiene et al., 2006). Consistently, females were more likely to have poorer HRQOL than males (Afendy et al., 2009; Bianchi et al., 2003; A. A. Dan et al., 2008; J J Gutteling et al., 2006; Hussain et al., 2001; Sobhonslidsuk et al., 2006). This pattern is found on the general population as well as patients with CLD (C. L. Lam, Lauder, Lam, & Gandek, 1999; E. T. Lam, Lam, Lo, & Grandek, 2008). Very few data have demonstrated the effect of other socio-demographic factors (Hauser, Holtmann, et al., 2004; Hussain et al., 2001; Sobhonslidsuk et al., 2006), such as education level, marital status and social class/ socio-economic status. Studies showed that level of education was positively correlated with HRQOL (Hussain et

al., 2001; Sobhonslidsuk et al., 2006). Data from Hussain et al found there was weak correlation between level of education and physical HRQOL (Hussain et al., 2001). On the other hand, another study proved that patients with lower education level had significant lower mental HRQOL scores (Sobhonslidsuk et al., 2006).

Chronic co-morbidity also affected HRQOL in patients with chronic liver disease (Hauser, Holtmann, et al., 2004; Hauser, Zimmer, et al., 2004; Hussain et al., 2001). Hauser et al examined 94 patients with CHC attending a liver clinic and showed that psychiatric co-morbidities was one of important determinant of mental component summary (MCS) score of SF-36 (Hauser, Zimmer, et al., 2004). The number of active co-morbidities was associated with the SF-36 physical component summary (PCS) score (Hauser, Zimmer, et al., 2004).

2.3.2 HRQOL measures applicable to CHB

Health-related quality of life (HRQOL) can be measured by generic and disease specific measures (M.S. Bayliss, 1999; Brown, 1999; Eisen et al., 1999; J. J. Gutteling et al., 2007; Yacavone et al., 2001; Younossi, 2001; Younossi & Guyatt, 1998). Generic HRQOL measures can be applied to different patient populations (M.S. Bayliss, 1999; Eisen et al., 1999; J. J. Gutteling et al., 2007; Yacavone et al., 2001; Younossi, 2001; Younossi & Guyatt, 1998). The advantage of using this instrument is that it can compare with other types of diseases or healthy control population (M.S. Bayliss, 1999; Eisen et al., 1999; J. J. Gutteling et al., 2007; Yacavone et al., 2001; Younossi, 2001; Younossi & Guyatt, 1998). Therefore, it is widely used in health services and comparative studies. However, generic measures may not detect small but important clinical changes specific to a particular patient group. The Medical Outcomes Study Short Form-36 (SF-36) is the most commonly used (J. J. Gutteling et al., 2007; Yacavone et al., 2001; Younossi, 2001; Younossi & Guyatt, 1998). It showed in a study by Foster et al. that CHB patients had significant lower HRQOL scores in mental health and general health perception aspects, but their physical related HRQOL scores were comparable to the healthy control (Foster et al., 1998). Previous studies on the use of SF-36 on CHB patients have demonstrated that patients with less severe disease had lower HRQOL scores in general health compared to those with general population or healthy controls (Bondini et al., 2007; Foster et al., 1998; S C Ong et al., 2008; Tan et al., 2008). Once they developed complications, lower HRQOL scores was found in both physical and mental health (S C Ong et al., 2008). The effectiveness of anti-viral treatment was detected by the SF-36 in a longitudinal study on 150 Chinese CHB patients at different stages of illness receiving LVD treatment (Yi, 2006).

A disease-specific measure theoretically can detect small but clinically important changes on HRQOL that are unique to the particular condition although it does not allow for comparison with the general population or other disease groups (M.S. Bayliss, 1999; Eisen et al., 1999; Younossi, 2001; J. J. Gutteling et al., 2007; Yacavone et al., 2001). Several HRQOL measures specific for chronic liver disease patients, such as the Chronic Liver Disease Questionnaire (CLDQ) (Younossi, Guyatt, Kiwi, Boparai, & King, 1999), the Hepatitis Quality of Life Questionnaire (HQLQ) (M. S. Bayliss et al., 1998), the Liver Disease Quality of Life Questionnaire (LDQOL) (Gralnek et al., 2000), the Liver Disease Symptom Index (LDSI 1.0 and 2.0) (Unal et al., 2001; van der Plas et al., 2004), the Hepatitis B Quality of Life (HBQOL) (Spiegel et al., 2007) and Chronic Liver Disease-Specific Quality of Life (CLD-QOL) (Lee et al., 2007) are available. Each instrument has its

advantages and disadvantages. Table 1 presents the characteristics of these disease-specific HRQOL measures.

	HQLQ	CLDQ	LDQOL	HBQOL	CLD-QOL
Author	Bayliss et al	Younossi et al	Granlnek et al	Spiegel et al	Lee et al
Year	1998	1999	2000	2007	2007
Country	USA	USA	USA	USA	Korea
# of items	69	29	111	31	27
# of scales	13	6	20	6	5
Total score	No	Yes	Yes	Yes	No
Scales	8 scales from SF-36	Fatigue	8 scales from SF-36	Psychological well-being	Specific symptoms
	Positive well-being	Activity	Symptoms of LD	Anticipation anxiety	Social function
	Sleep somnolence	Emotional function	Effects of LD	Vitality	Emotional status
	Health distress	Abdominal	Concentration	Stigmatization	General
	Limitations	Systemic	Memory	Vulnerability	Uncertain
	Health distress	Worry	Quality of social	Transmission	
			Health distress		
			Sleep		
			Loneliness		
			Hopelessness		
			Stigma of LD		
			Sexual		

Table 1. Characteristics of Disease-specific HRQOL Measures

The Chronic Liver Disease Questionnaire (CLDQ) is the first disease-specific HRQOL measure for evaluating patients with chronic liver disease (CLD) developed by Younossi et al (Younossi et al., 1999). The CLDQ has 29 items generated by patients with chronic liver disease, hepatologists, and a review of literature (Younossi et al., 1999). The CLDQ has six scales measuring fatigue, activity, emotional function, abdominal symptoms, systemic symptoms and worry (Younossi et al., 1999), which captures the important problems associated with CHB infection and its complications. It is scored with six domain and one summary scores (Younossi et al., 1999). This short measure can be completed in less than 15 minutes, a criterion for assuring a good response rate (Cella & Tulsky, 1990; McColl,

Christiansen, & Konig-Zahn, 1997). Patients with different types and stages of liver disease were included in the development and validation process supporting its broad application in hepatology research (Younossi et al., 1999). It has been shown to have adequate internal reliability, validity and sensitivity (Younossi et al., 1999). The CLDQ has been shown to be suitable for cross-cultural adaptation to different cultures (Ferrer et al., 2006; Hauser, Schnur, et al., 2004; Rucci et al., 2005; Sobhonslidsuk, Silpakit, Kongsakon, Satitpornkul, & Sripetch, 2004; Wu, Deng, Ji, & Yan, 2003) including Italian, German, Chinese (Mainland) and Thai. Recently, it has also been translated into Portuguese and Bengali (Mucci, Citero Vde, Gonzalez, De Marco, & Nogueira-Martins, 2010; Ray, Dutta, Basu, & De, 2010). However, the responsiveness of the CLDQ has not been investigated widely. Further research is needed to demonstrate its ability to detect change over time or with intervention.

The other liver disease specific HRQOL measures are less widely used because they are either much longer or have relatively few data supporting their validity or sensitivity. The HQLQ developed by Bayliss has 69 items combining the generic SF-36 scales with three additional generic scales (positive well-being, sleep and health distress) and two hepatitis C specific scales (health distress and limitations because of hepatitis C) and was intended for patients with chronic hepatitis C (CHC) infection (M. S. Bayliss et al., 1998). It has been shown to be sensitive in patients with CHC but data on patients with CHB infection are few (M. S. Bayliss et al., 1998). The instrument was recently translated and validated in patients with CHB in Singapore (S. C. Ong, Lim, & Li, 2009, 2010). The main disadvantage of the HQLQ is many liver disease specific symptoms, such as abdominal pain, are not addressed despite its length (M. S. Bayliss et al., 1998). Furthermore, significant ceiling effects of three scales were observed (M. S. Bayliss et al., 1998), and the instrument's responsiveness remains unknown (S. C. Ong et al., 2009, 2010).

The Liver Disease Quality of Life instrument (LDQOL) was developed by Gralnek et al consisting of generic and disease-specific scales with a total of 101 items (Gralnek et al., 2000). It is not very widely used because its length limits its acceptability. It is applicable mainly to patients with advanced liver disease or waiting for liver transplantation (Casanovas et al., 2003; Dias Teixeira, de Fatima Gomes de Sa Ribeiro, & Strauss, 2005). In other words, it was not designed for patients with less severe liver disease. The LDQOL has been translated and adapted into Spanish and Catalan in transplant patients as well as Brazilian Portuguese in patients with chronic liver disease (Casanovas et al., 2003; Dias Teixeira et al., 2005). Pilot testing has supported the reliability and validity of the LDQOL but it has not been tested in longitudinal studies (Dias Teixeira et al., 2005; Gralnek et al., 2000). Recently, a short form (36 items) of the liver disease quality of life instrument (SF-LDQOL) was validated on patients with advanced liver disease (Kanwal et al., 2008). However, its validity may not be generalizable to patients with asymptomatic hepatitis B or an early stage of liver disease (Kanwal et al., 2008).

The Liver Disease Symptom Index (LDSI) is a short instrument that consists of 18 items that measure nine disease-specific symptoms and the hindrance that patients experience from these symptoms (Unal et al., 2001; van der Plas et al., 2004). It has been validated on 374 patients but the data on its validity and other psychometric properties on CHB patients are limited (Unal et al., 2001).

The Hepatitis B Quality of Life instrument (HBQOL) is the first HRQOL measures designed for specifically hepatitis B patients without cirrhosis (Spiegel et al., 2007). It is a 31 items

questionnaire including items assessing psychological well-being, anticipation anxiety, vitality, disease stigma, vulnerability, and transmissibility (Spiegel et al., 2007). It has shown to be valid and reliable in English-speaking patients in the United States (Spiegel et al., 2007). The validity and applicability of this instrument on CHB patients with complications and other cultures are not known.

The Chronic Liver Disease-Quality of Life questionnaire (CLD-QOL) was designed to measure HRQOL of Asian patients with chronic liver disease, the first of its kind (Lee et al., 2007). There are 27 items which are organized into the domains of specific symptoms, social function, emotional status, general symptoms and uncertain future (Lee et al., 2007). Lee et al found a significant difference in HRQOL scores between patients with mild stage of cirrhosis and moderate to severe stage of cirrhosis, supporting construct validity of CLD-QOL (Lee et al., 2007). Further evaluation on its psychometric properties on patients without cirrhosis is needed before the instrument can be applied more widely.

2.3.3 Preference-based measure (utility) of HRQOL

Cost-effectiveness analysis (CEA) is an area of increasing interest among researchers, physicians and policy makers (Sun et al., 2007). CEA is a method of summarizing the health benefits and resources used by health programmes, therefore policy makers can select among them (Russell, Gold, Siegel, Daniels, & Weinstein, 1996; Weinstein, 1990; Weinstein, Siegel, Gold, Kamlet, & Russell, 1996). It summarizes all programme costs and benefits (effectiveness), and uses economic theory to aid choice between competing health programmes when resources are scarce (Russell et al., 1996; Weinstein, 1990; Weinstein et al., 1996). CEA can express health benefits in more generic terms, such as quality adjusted life years (QALYs) gained (Weinstein, 1990). It provides a common unit to allow comparisons between different disease groups or intervention programmes (Weinstein, Torrance, & McGuire, 2009). This method is particularly useful in the analysis of preventive health programmes, such as anti-viral treatment in CHB patients (Kanwal et al., 2005; Sullivan et al., 2007; Sun et al., 2007; Yuan et al., 2008).

Most HRQOL measures give a profile of domain scores that are not designed for economic evaluation. Treatment evaluation by profile scores may give inconsistent results and lead to a piecemeal understanding of the impact of an intervention because of variations in the effect on different domains. For example, one scale indicates a beneficial effect whereas other scales may give negative results. Therefore, there is a need for methods to combine multidimensional information in more systematic ways. Research has shown that multi-dimensional HRQOL states can be converted to a composite preference value expressed on a numerical scale ranging from 0 (death) to 1 (perfect health) (Brazier et al., 2002), based on preference valuation by subjects from the general population (Guide to the methods of technology appraisal). It is possible to have negative preference for states that are worse than being dead (Preedy et al., 2010).

An important application of preference based measures is a measure of effectiveness in health economic evaluation (Preedy et al., 2010). Quality adjusted life year (QALY) is increasingly used as a measure of health outcomes in the past 20 years (Neumann, Greenberg, Olchanski, Stone, & Rosen, 2005). QALYs give a single index combining morbidity and mortality and is easy to calculate if the preference of health status is known

(Weinstein et al., 2009). It provides a common metric to compare with different treatment options with the other, to compare treatment side-effects versus benefit, or to compare intervention programs with another one (Preedy et al., 2010; Weinstein et al., 2009). QALYs have been applied to different diseases or intervention programs, for instance, treatment of coronary heart disease and screening for breast cancer (Chan, Nallamothu, Gurm, Hayward, & Vijan, 2007; Wong, Kuntz, Cowling, Lam, & Leung, 2007). Information on the preference values of different CHB states can be combined with life years gain in the evaluation of the cost-effectiveness of different anti-viral treatment strategies for CHB (Kanwal et al., 2005; Sullivan et al., 2007; Veenstra et al., 2008; Yuan et al., 2008).

Three most commonly used preference based measures of health are the Short Form-6D (SF-6D), the Health Utilities Index (HUI) and the EuroQol EQ-5D (Brazier et al., 2002; Brooks, 1996; Feeny, Furlong, Boyle, & Torrance, 1995). They are most useful for the evaluation of the cost-effectiveness of anti-viral treatment for CHB. Table 2 summarizes the domains of the commonly used generic HRQOL measures including the SF-6D, HUI and EQ-5D. They may give different results and interpretations because of different dimensions and methods of preference valuation. Preference values are also population specific that scoring algorithms derived from America or Europe may not apply to the Chinese. The SF-6D is the only measure that has been translated for and validated in the Chinese population in Hong Kong (C. L. K. Lam, Brazier, & McGhee, 2008).

	SF-6D	HUI	EQ-5D
HRQOL	Utility	Utility	Utility
Author	Brazier et al	Feeney et al	EuroQol Group
Year	2002	1995	1990
Country	UK	USA	
# of items	10	31	5
# of scales	6	8	5
Total score	Yes	Yes	Yes
Scales	Physical functioning	Vision	Mobility
	Role limitations	Hearing	Self-care
	Social functioning	Speech	Usual activity
	Pain	Ambulation	Pain/discomfort
	Mental Health	Dexterity	Anxiety/depression
	Vitality	Emotion	
		Cognition	
		Pain	

Table 2. The Comparison of Content Domains among Different HRQOL Measures

Several studies have assessed health preference in chronic liver diseases, but the majority of them were on chronic hepatitis C (CHC) (Chong et al., 2003; McLernon, Dillon, & Donnan, 2008; Thein, Krahn, Kaldor, & Dore, 2005). Only two large studies evaluating health preference of CHB values were found in the literature (Levy et al., 2008; S C Ong et al., 2008). The first one was a multi-center study to elicit utilities for six hypothetical states from infected and uninfected individuals by Levy et al (Levy et al., 2008). The results found that health preference values declined with disease progressing from 0.68 in uncomplicated CHB to 0.35 in decompensated cirrhosis (DC) (Levy et al., 2008). Patients with DC and

hepatocellular carcinoma (HCC) had very low preference values (Levy et al., 2008), indicating a strong impact of CHB. The results of Levy's study had limitations because it rated preference values on disease-specific health states (Levy et al., 2008), which is in contrary from NICE's recommendation that health preference should be measured by generic measures based on valuations by the general public (Guide to the methods of technology appraisal). The other study was conducted in Singapore by Ong et al, which found significantly lower health preference values measured by EQ-5D in patients with DC and HCC compared with asymptomatic hepatitis B (AHB) carriers (S C Ong et al., 2008). A small study on 140 patients with chronic liver diseases, with 36% having CHB found that patients with CHB had better health preference values than patients with other liver diseases (A. A. Dan et al., 2008).

More studies on health preference values associated with each stage of CHB from AHB, to CHB with ILF, cirrhosis and HCC, using locally validated preference-based measures, are needed to provide more accurate estimates of the change in preference value with disease progression. Such information is useful for the evaluation the cost-effectiveness of anti-viral treatments.

3. Conclusion

Hepatitis B is a significant health problem in Southern China and Hong Kong. Chronic hepatitis B (CHB) is a chronic disease that puts significant demand on health services. Regular monitoring is needed for progression of disease and development of complications. Anti-viral treatments may be needed for the eradication of the virus and other interventions are required when complications develop. Understanding the impact of illness on quality of life can make health care more responsive to patients' needs. Studies have shown significant lower health-related quality of life (HRQOL) scores in CHB patients especially in the presence of complications. Data on HRQOL in patients with CHB are limited. Generic and disease specific measures can complement each other in the evaluation of the impact of CHB on HRQOL. The Chronic Liver Disease Questionnaire (CLDQ) is a liver disease-specific HRQOL measure applicable to patients with chronic liver disease at different stages of illness. It has the best face validity for adaptation to be used in Chinese patients with CHB in Hong Kong. There are lots of potential applications of HRQOL data of CHB patients. It can inform policy and practice to make health service more patient-centered. HRQOL may also be used as an outcome measure of effectiveness of treatment and quality of care. HRQOL can be converted into a preference value for the calculation of quality adjusted life year (QALYs) in cost-effectiveness analysis of medical intervention.

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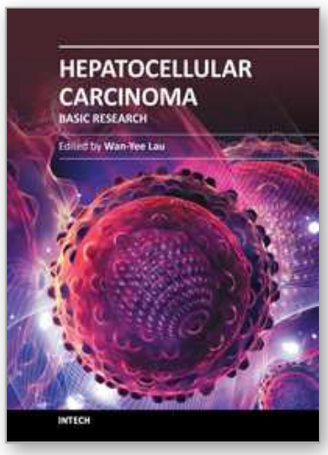

Hepatocellular Carcinoma - Basic Research

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Hepatocellular Carcinoma represents a leading cause of cancer death and a major health problem in developing countries where hepatitis B infection is prevalent. It has also become increasingly important with the increase in hepatitis C infection in developed countries. Knowledge of hepatocellular carcinoma has progressed rapidly. This book is a compendium of papers written by experts to present the most up-to-date knowledge on hepatocellular carcinoma. This book deals mainly with the basic research aspect of hepatocellular carcinoma. The book is divided into three sections: (I) Biomarkers / Therapeutic Target; (II) Carcinogenesis / Invasion / Metastasis; and (III) Detection / Prevention / Prevalence. There are 18 chapters in this book. This book is an important contribution to the basic research of hepatocellular carcinoma. The intended readers of this book are scientists and clinicians who are interested in research on hepatocellular carcinoma. Epidemiologists, pathologists, hospital administrators and drug manufacturers will also find this book useful.

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