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Hepatitis B Prevention and Care Pathway in Kuwait: Assessing the Current Situation, Identifying Gaps and Recommending Actions

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Abstract

Introduction: Hepatitis B virus (HBV) infection remains a worldwide public health problem. The last major review of the epidemiology and management of HBV in the Middle East was published in 2011. This paper aims to assess the current situation of the HBV care pathway in Kuwait, identify gaps and barriers therein and recommend initiatives to improve patient management.

Materials and Methods: A literature search was conducted in PubMed as well as free internet searches. To provide context to the results and to collect information on areas for which limited evidence was found, interviews and group discussions were held with HBV experts.

Results: There is limited evidence on the national prevalence of HBV; however, prevalence is expected to be higher in those >30 years of age born before the introduction of the HBV vaccination program. There is also limited data on the burden of HBV-related hepatocellular carcinoma in the country. Public and health-care provider awareness of various aspects of the disease is perceived to be low. There are several mandated national screening structures; however, there are no country-specific HBV guidelines regarding diagnosis, linkage-to-care, treatment and follow-up.

Conclusion: Although significant improvements have been made in the past 30 years in Kuwait in terms of a decline in prevalence, both the burden due to HBV complications and the coverage of screening and treatment remain unclear. Efforts must be made in all areas of the HBV care pathway to improve morbidity and reduce mortality in Kuwait, and the interventions should be supported by research evidence.

Keywords: Hepatitis B; Epidemiology; Awareness; Diagnosis; Treatment

Introduction

Hepatitis B virus (HBV) infection remains a worldwide public health problem with an estimated prevalence of 468 million cases in 2016 according to the Global Burden of Disease [1]. The same study estimates prevalence of liver cancer due to HBV of 599,000 in 2016 and prevalence of cirrhosis and other chronic liver diseases due to HBV of 12 million [1]. Furthermore, globally 350,000 people died of liver cancer due to HBV in 2016, and 366,000 of cirrhosis and other chronic liver diseases due to HBV [2]. Unfortunately, only 22% of people living with HBV infection know their diagnosis, and of those diagnosed, only 8% received treatment [3].

The last major review of the epidemiology and management of HBV in the Middle East was published in 2011 [4]. The authors observed a trend from "high-to-intermediate" to "low-to-intermediate" endemicity. Medical experts considered it important to assess whether this trend continued, as well as to assess the current situation in the "HBV care pathway". In the WHO Eastern Mediterranean Region, an estimated 3.3% of the general population is infected with HBV [5].

At a population level, the "HBV prevention and care pathway" encompasses services that the community and patients must receive in order to optimise prevention and management of the disease.

The key stages to consider on the pathway are:

Stage 0 - Epidemiology of the disease and the awareness of different stakeholders about various aspects of the disease.

Stage 1 - Screening for disease, as well as diagnosing patients presenting with symptoms, reporting of positives and linking them to care.

Stage 2 - Appropriate evaluation of the disease and treatment initiation if needed.

Stage 3 - Compliance/adherence to treatment and periodic patient follow-up.

This paper aims to assess the current situation of the HBV care pathway in Kuwait, identify gaps/barriers therein and recommend potential initiatives to improve the management and prevention of the disease.

Materials and Methods

A pragmatic literature search was conducted in PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) to identify evidence on HBV in Kuwait using the key words "Kuwait", "hepatitis B or HBV or CHB", "hepatocellular carcinoma or HCC", "cirrhosis", "prevalence", "awareness", "epidemiology", "vaccination", "diagnosis", "screening", "treatment", "care pathway" and "adherence".

In addition, the reference lists of those articles were scanned for any additional articles. Also, free internet searches were conducted to supplement the literature search; these used similar key words to identify relevant reports, guidelines, conference abstracts, posters and presentations.

To provide context to the results from the literature review as well as to collect diverse stakeholder perspectives on those areas for which no or limited evidence was found in the literature, interviews were held with various HBV professionals.

Finally, inputs were taken from the Kuwait HBV working group (including leading hepatologists and gastroenterologists) via a working group meeting [6]. The results of the review of the literature, combined with the information from the individual interviews and focus groups are described below.

Results and Discussion

Prevalence of HBV infection

Kuwait, in the past, was considered to be an area of intermediate endemicity [7] with respect to the epidemiology/burden of HBV but there is negligible published literature to prove that. There are three studies (Table 1) on HBV prevalence among specific sub-populations. It is difficult to extrapolate the data points from these studies to the general population as they do not truly represent the prevalence in the whole population. A systematic review pooling data of 12,642 people from 2 studies from Kuwait published between 1965 and 2013 found a prevalence of 0.80% [8]. Note that it is not clear which studies were included in the review by Schweitzer A et al. and hence the estimate is, most probably, not representative of the epidemiology in the general population.

It is expected that the prevalence in the older population (>30 years) is higher because they were born in the pre-vaccination era, but surprisingly a study among Kuwaiti blood donors found that the prevalence was highest among those aged <20 years (2.5%) [9]. In the same study, the prevalence among non-Kuwaitis was high in the same age group (7.2%), but highest among those aged 50+ years (8.2%). Since this study was only conducted about 12 years after the start of the vaccination program in 1990, it is suggested that the high prevalence may be due to perinatal transmission among those adolescents/young adults who were not vaccinated. Data from the pre-marital screening over the period 2010-2015 shows an HBV prevalence of 0.74% (personal communication); 90.2% of all those tested were Kuwaiti [6].

In 1990, Kuwait was among the first countries in the Gulf Cooperation Council (GCC) region to introduce the HBV vaccine in its national immunization program. In 2013, HBV (HepB3) vaccine coverage among 1-year-olds was 99.0% [10]. In 2013 there was a campaign urging every person to get vaccinated with the HBV vaccine [11]. Together with the vaccination of new-borns, this campaign might have contributed to the decline in the number of HBV cases reported to MoH health centers over time (Figure 1) [12].

Year study	Population	Prevalence of HBV (HBsAg)	Reference
2002	First-time blood donors (n=12 798; 67% Kuwaiti)	1.1% Kuwaiti, 3.5% non-Kuwaiti	Ameen, 2005
2012-2013	Pregnant women 17-49 years (n=4 060; 64% non-Kuwaiti)	0.3% (0.3% Kuwaiti, 0.2% non-Kuwaiti)	Madi, 2014
2012	STD patients 19-58 years (n=1 298)	0%	Al-Mutairi, 2013

Table 1: Prevalence of HBV in Kuwait.

When assessing high risk groups, a study found that among 249 health care professionals that experienced incidents of occupational exposure to blood in 2010, 52.2% had been fully vaccinated against HBV [13]. Another study conducted in 2011 found that among primary health care workers, 74.7% had ever been vaccinated, of which 84.0% received the complete dosage [14].

No information was found with respect to awareness about HBV in the community, although this was rated low by the medical experts for all aspects (general awareness, prevalence of disease, origin, transmission and high-risk groups, symptoms) [6]. This might be because few government-funded HBV public awareness campaigns have been conducted in the past years besides the indicated vaccination campaign.

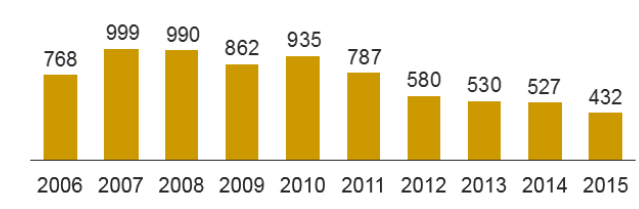

Figure 1: Cases of HBV reported at Government health centers.

In a study conducted among 534 primary health care workers, 76.2% were aware that HBV could be transmitted from patients to health workers; 57.7% knew that HBV could be transmitted from

health workers to patients; 81.5% were aware of vaccination; 65.0% knew the complete vaccination schedule; 44.4% knew the intervals between doses; and 73.8% declared that they need more information regarding HBV [14]. While their general awareness about the disease is appraised as medium to high by the HBV Working Group, primary health practitioners' awareness with respect to other aspects is considered low-medium (prevalence of disease, origin and transmission, high-risk population; primary and secondary prevention) and low for diagnosis and reading/interpreting serology.

Chronic HBV burden

People with chronic HBV (CHB) have a lifetime risk of 15% to 40% of developing end-stage liver disease including cirrhosis, liver failure and hepatocellular carcinoma (HCC), a primary malignancy of the liver [15]. Furthermore, it was found that the health-related quality of life in patients with CHB tends to be impaired in the later stages of liver disease [16-19]. In the Arab world, an estimated 6,447 deaths occurred from HBV-associated HCC in 2010 and from 1990 to 2010, the burden of HBV-associated HCC deaths increased at a much faster rate (137% increase), compared to the rest of the world (62% increase) [20].

In Kuwait liver cancer cases are registered nationally: in 2007, 3.7% of cases among Kuwaiti men were diagnosed with liver cancer, with an age-standardised incidence rate (ASIR) of 4.3/100,000 [21]. In the period 2000-2009 liver cancer was in the top 10 most commonly diagnosed cancers for Kuwaiti men: 151 liver cancer cases (4.8% of all cancer cases), with an ASIR of 7.4 per 100,000 [22]. In total there were 170 deaths due to liver cancer in that period (117 among males – 9.9% of all cancer deaths; 53 among females – 5% of all cancer deaths) [23]. However, it is not known if these cases or deaths are related to HBV [24].

Although vaccines have been proven very effective in HBV prevention in adolescents and led to a decrease in prevalence, it takes decades to observe their effect in HCC reduction in adults [25]. Therefore, the burden of end-stage liver disease secondary to CHB might not reduce yet, due to the ageing of previously infected children. No research studies were found on the awareness of the patients or key populations on the chronicity of HBV, although the medical experts rated the awareness of the community about clinical sequelae of disease to be low and that of GPs to be medium [6]. Genotype D HBV was found to be significantly associated with more advanced stages of liver disease [25]. One study (n=80) was conducted in Kuwait which found that 79% of chronic HBV patients had genotype D [26].

Screening and diagnosis

There are a number of mandated screening structures (Figure 2) present in the country identifying patients through blood tests (HBsAg test, antibodies for blood donors) [24,27,28]. HBV tests are free of charge for all Kuwaitis [24].

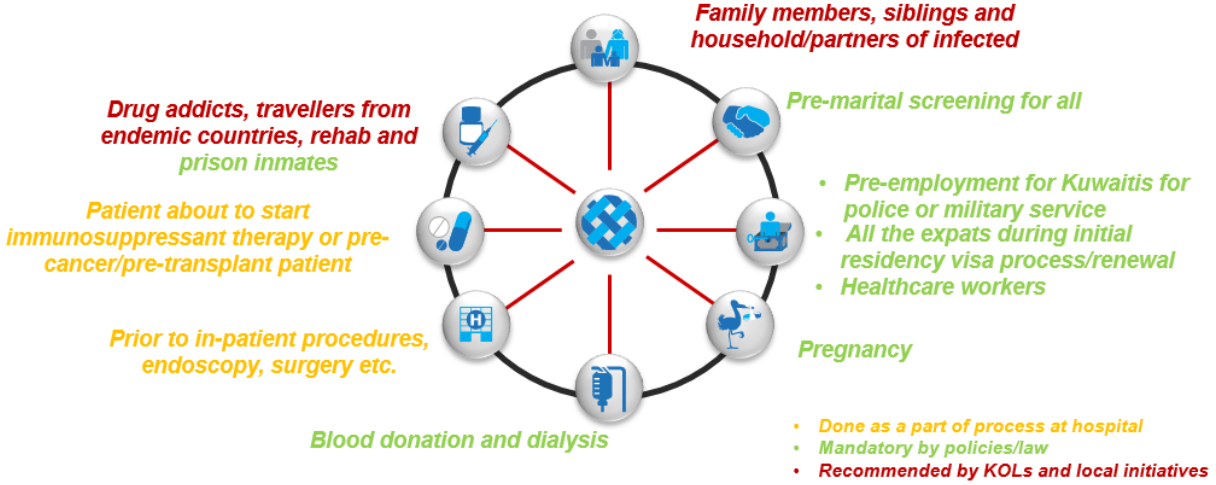

Figure 2: Potential HBV screening points in Kuwait.

All diagnosed cases should be reported to the MoH. Experts comment that the current screening initiatives mainly target younger vaccinated people and miss the older population (aged >40 years) [6]. This could contribute to the decreasing number of cases reported to the MoH (Figure 1) as the appropriate population is not targeted.

The typical HBV patient journey in Kuwait is illustrated in Figure 3 [6]. If screened positive, patients are either referred to a specialist in the public sector or a private or public GP. If diagnosed positive by a GP or in a PHC/out-patient clinic of a general hospital, patients will be referred to a specialist for further diagnosis and treatment. Genotyping is not routinely conducted, and fibroscan is not widely available in the country [6].

Medical experts believe that 65-70% of people that attend a specialist are received from classical screening programs such as pre-marital, 5-15% from GPs/PHCs/out-patient clinics; and the rest of the cases are referred from other specialties such as nephrologists, gynaecologists, fertility clinics [6]. Note that medical experts often question the ability of health care practitioners (HCPs) in primary care to test and interpret test results (low to medium awareness). Stigma has

been raised as an obstacle to continued screening by medical experts [6] although no scientific evidence could be found on this for Kuwait.

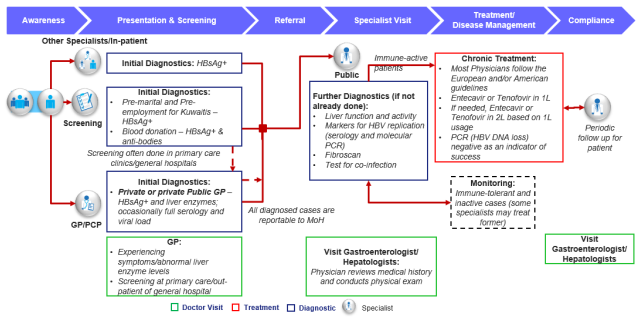

Figure 3: HBV patient journey in Kuwait.

Treatment/disease management

Treatment is delivered to patients only in the public sector. The majority of the referrals are received by specialists - hepatologists and gastroenterologists - in their outpatient clinics in one of the six major MoH general hospitals followed by those at Kuwait oil medical centres and military hospitals providing this service. Expats in Kuwait may not always face loss of employment, but do not have optimum access to treatment and may be limited to less expensive/older therapy such as lamivudine (LAM). Furthermore, they have limited coverage for HBV treatment and often depend on government patient funds, NGOs and out-of-pocket [6].

Figure 4 displays the CHB care pathway cascade for Kuwaitis. Of the about 13,600 prevalent cases in the country (assuming a prevalence of 1.1%) [29], 5,900 (57%) are estimated to be diagnosed [Based on medical experts' assumption that 80% of all cases reported in the past 10 years, about 7,400 in Figure 1, are Kuwaitis as screening for expats is strict.] Of those diagnosed, about 20% are eligible for long-term treatment [30,31]. In reality; however, of those eligible for treatment, only 34% are currently on treatment [32].

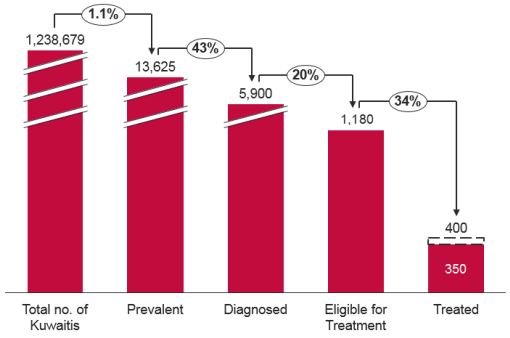

Figure 4: CHB care pathway cascade for Kuwaitis.

Source: Total no. of Kuwaitis from 2016 mid-year estimates of Kuwait Central Bureau of Statistics accessed on 22nd August 2017, Prevalent figure obtained by applying 1.1% on the population estimate, diagnosed is no. of Hep B reported cases of Kuwaitis at Government health centres over a 10-year period and Treated obtained from reference 32.

There is no recent local guideline for HBV – the last one dating from 2009 [33] - hence most specialists follow the European Association for the Study of the Liver (EASL) [34] or American Association for the Study of Liver Diseases (AASLD) [35] guidelines. However, experts indicate that there might be minor variations in specialists' interpretation of phasing (HBV DNA levels and serum alanine aminotransferase upper limit of normal (ALTULN)) and subsequent treatment initiation [31]. There are varying opinions with respect to the treatment of immune-tolerant patients; while some specialists may not treat them at all, others do treat them as they believe that these patients are at risk for the development of fibrosis/cirrhosis due to a high viral load and can be at risk of transmitting the disease [31].

The primary goal of HBV therapy is to improve survival and quality of life by preventing disease progression and death. For chronic treatment, the recommended antiviral therapies for CHB treatment in the country are entecavir (ETV) and tenofovir disoproxil fumarate (TDF). Although others Pegylated interferon (Peg-IFN-alfa-2a), lamivudine (LAM), telbivudine (TEL), adefovir (ADV) - have also been approved [34,35]. TDF, ETV, Peg-IFN-alfa-2a and LAM are available in the public hospital formularies and provided for free to Kuwaitis based on specialist prescription. Physicians prefer ETV above TDF: data [32] shows that ETV is prescribed in about 70% of the cases considering only nucleos(t)ide analogues (NAs) followed by LAM (12%), ADV (10%) and TDF (9%). Physicians' lower prescription of LAM emanates from their poor experience with these as patients developed resistance. A systematic review found that resistance to LAM emerges in approximately 20% of patients after one year and in 70% of patients after five years of treatment [36]. Resistance to ETV is rarely seen and in the unlikely scenario that a patient develops resistance to ETV, physicians will prescribe TDF in the second line. The other case that may prompt a physician to switch to TDF is when pregnancy is confirmed and the patient has previously been on ETV [6]. In a recent retrospective-prospective study on efficacy and safety of ETV in CHB West Asian Patients with Genotype D, 70 patients in two Kuwaiti hospitals were assessed over a period of 54 months [37]. 82.6% of HBeAg +ve patients had complete HBV-DNA suppression after a median period of 7 months, while all HBeAg –ve patients had complete HBV-DNA suppression after a median period of 5 months. None of the patients showed primary non-response to ETV in both groups.

The main limitation of current antiviral therapy is that the long-term toxicity and health effects are unknown as lifelong treatment might be needed. Further, disease progression is likely to occur when the suppressive effect of NAs is removed; especially in cases of treatment cessation due to drug-related adverse events (AEs) or drug resistance [17,34]. There is an unmet need for a treatment that can cure HBV. In the absence of such a curative therapy, there is a need for new effective treatment options with a higher barrier to resistance and with fewer treatment-related AEs than the currently available treatment options.

Compliance/adherence

It is recommended that all patients treated with NAs should be followed with periodical assessments [35]. Non-adherence with recommended follow-up visits is a major barrier for completing treatment and is consequently associated with unfavorable clinical

outcomes. No information could be found on chronic care and periodic patient follow-up among HBV patients in Kuwait. The HBV Working Group, however, rate the compliance/adherence to treatment among Kuwaiti to be high: about 80% of the patients who start treatment remain compliant. Possible factors related to non-adherence could be lifestyle among the youth, nature of treatment (lifelong) and lack of education [31].

Conclusion and Recommendations

Four broad categories of gaps exist on the patient care pathway (Figure 5), and the related recommendations (Figure 6) are discussed below.

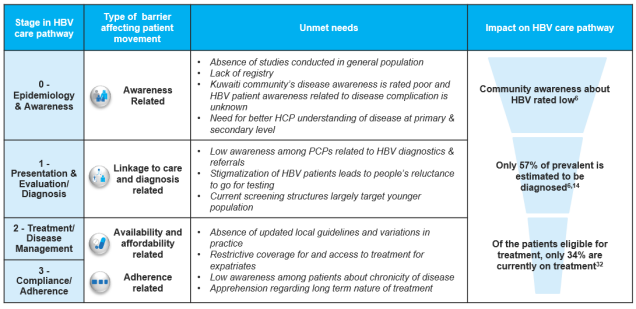

Figure 5: Barriers affecting the Kuwait HBV patient care pathway.

There is a need for a nationally representative cross-sectional population-based prevalence study (using HBsAg testing) of sufficient size. Only then an accurate overall prevalence can be estimated, by citizenship status, which stratifies the figure by age (especially the population aged 40+ years) and gender. It is recommended to repeat this survey periodically to observe changes. Medical experts advised to establish a national hepatitis/liver registry which collects socio-demographic characteristics, vaccination status, HBeAg status, genotype and mode of transmission data. Information from the registry will help inform prevention strategies.

Experts strongly advise that research should be conducted on the status of the awareness about HBV in the general population and high-risk groups (including medical staff and IV drug users). Absence of community-wide awareness campaigns in recent years necessitates the need for government-funded interventions to educate the populous about the nature of the disease, consequently encourage testing and help patients initiate treatment. Use of technology (e.g. social media) and public spaces (e.g. malls) are strongly suggested. As a part of the campaign, necessary guidance to travellers going to HBV endemic countries should be included.

The WHO advocacy brief "Combating hepatitis B and C to reach elimination by 2030" highlights that certain prevention and diagnosis targets should be achieved to reach HBV elimination [38]. Medical experts find it necessary to include the older population (40+) in the current screening structures. Furthermore, it is important that GPs/ primary health care workers conduct screening of at risk patients (including family members/close contacts/household contacts of infected Kuwaitis and the older (aged >40 years) population who were at high risk of exposure from the pre-vaccination era), as these engage with the broader community daily. Hence, with respect to HCPs at primary care level, it is anticipated that establishing training programs as well as tools/algorithms for GPs/public health physicians, to assess high risk patients visiting their clinics, will lead to improved diagnosis and referral rates as they would conduct a complete assessment and refer only those that need specialist treatment.

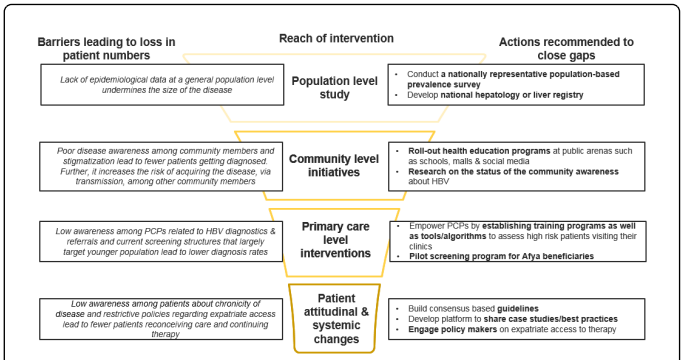

Figure 6: Action recommended to address gaps and optimize care pathway.

Medical experts propose that a national consensus-based guideline be developed that all specialists will benefit from. Furthermore, it is advised that the best way to increase access to testing and treatment for expatriate workers is by engaging the authorities to reconsiders their policies and to make coverage rules less restrictive.

In conclusion, significant improvements have been made in Kuwait over the past 30 years to reduce HBV prevalence. However, relevant challenges remain concerning CHB management. Efforts must be made by all key stakeholders, including policy makers, in all phases of the HBV care pathway to reduce both morbidity and mortality in the Kuwait population.

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