Management of Chronic Hepatitis B: Knowledge and Practices of Physicians in Pakistan

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Background: In Pakistan, approximately 4.5 million people are afflicted with chronic hepatitis B (CHB). The compliance with hepatitis B virus (HBV) management guidelines is still unknown. This was the first study from Pakistan in which the knowledge and practices of treating physicians were compared with three standardized guidelines (Asia Pacific Association for the Study of the Liver (APASL) 2012/European Association for the Study of the Liver (EASL) 2012/American Association for the Study of Liver Diseases (AASLD) 2009). **Methods:** A cross-sectional study was conducted during 2014–2015 at four tertiary care teaching hospitals of Karachi, Pakistan. The study participants were internists, gastroenterologist, senior residents who were involved in the management of CHB patients. All participants were offered to fill the study questionnaire. **Results:** A total of 179 physicians (103 residents, 76 consultants) participated. Mean age of participant was 35 ± 9.3 years. Approximately one-third of them followed AASLD (27.3%) and EASL (24.0%) guidelines. Entecavir, tenofovir or Peg IFN ∞ 2a were considered as first line therapy by 43%, 38.5% and 30.2% respectively. However, 17.9% preferred entecavir with tenofovir for rescue therapy, 25.7% and 23.5% preferred tenofovir or entecavir as both first line and rescue therapy respectively. Serum HBV DNA, alanine transaminase levels were used to monitor during oral antivirals therapy by 45.3%. hepatocellular carcinoma screening was considered for all HBV cases by 51.4% using ultrasound (55.3%) and alfa fetoprotein (52.5%) every 6 months. Overall 40.2% participants had poor knowledge about indication of liver biopsy, treatment initiation and antiviral prophylaxis. Significant association was found between grades of knowledge and gender, age group, designation and specialty ($P < 0.05$). Younger physicians, consultants (age 25–40 years) and those who were practicing gastroenterology/hepatology were more likely to have higher knowledge scores in compliance with the guidelines as compared to others. **Conclusion:** Our study highlighted the gaps in knowledge and practices in managing CHB patients according to guidelines. Efforts to improve knowledge, refresher courses and appropriate coordination between gastroenterologists and internal medicine physicians could enable management and follow-up of patients with CHB effectively. (J CLIN EXP HEPATOL 2018;8:342–351)

Over the period of time chronic hepatitis B (CHB) infection has become a major global health problem. It affects 240 million people worldwide

and attributing to approximately 780,000 deaths per year which is quite high as compared to hepatitis C (affecting approximately 130–150 million people) and HIV (affecting more than 34.0 million people).^{1–3} The overall estimated prevalence of Hepatitis B in Asia ranged between 2% and 4%.⁴ In Pakistan, despite the availability of hepatitis B vaccine, approximately 2.5% of population is afflicted with CHB,^{5,6} hence leading to significant morbidity and mortality associated with end stage liver disease and hepatocellular carcinoma (HCC).⁷ The treatment of CHB is complex due to various phases in natural course of hepatitis B virus (HBV) infection. To guide treating physicians in decision making while managing patients with CHB, evidence based consensus guidelines have been developed by various societies including Asia Pacific Association for the Study of the Liver (APASL),⁸ European Association for the Study of the Liver (EASL)⁹ and American Association for the Study of Liver Diseases (AASLD).¹⁰ The treatment for HBV infection depends upon certain parameters including severity of fibrosis, serum HBV DNA and alanine transaminase (ALT) levels and HBeAg status. Significant variability in treatment of CHB among physicians

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Abbreviations: AASLD: American Association for the Study of Liver Diseases; ADV: adefovir; APASL: Asia Pacific Association for the Study of the Liver; CHB: chronic hepatitis B; EASL: European Association for the Study of the Liver; ESLD: end stage liver disease; ETV: entecavir; HBIG: hepatitis B immunoglobulin; HCC: hepatocellular carcinoma; LAM: lamivudine; NAs: nucleoside/nucleotide analogs; Peg IFN: pegylated interferon; PMDC: Pakistan Medical and Dental Council; TDF: tenofovir <https://doi.org/10.1016/j.jceh.2017.12.009>

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have been reported in various studies from Singapore,¹¹ Hong Kong,¹² China,¹³ Spain,¹⁴ US^{15,16} and Canada.¹⁷ Additionally lower compliance rates with APASL recommendations regarding HBV treatment have been reported in two studies from Asia.^{11,12} Moreover, 50% compliance with APASL recommendations for HBV treatment has been reported in one of these two studies.¹¹ However, no data is available from Pakistan regarding physician's practices in HBV management according to the guidelines.

OBJECTIVES

The main objective of the study was to evaluate the current CHB management practices of physicians in Karachi, Pakistan. The study also aimed to assess the degree to which our physician practices are in compliance with the recommendations of various HBV consensus guidelines (APASL 2012/EASL 2012/AASLD 2009).

METHODOLOGY

Study Design and Setting

This was a cross sectional study, conducted during July 2014 to July 2015 at four large tertiary care, teaching hospitals of Karachi, Pakistan.

Study Participants

According to Pakistan Medical and Dental Council's statistics, there are about 59,257 general physicians and 10,187 specialists registered in the province of Sindh.¹⁸ As the numbers of gastroenterologists are limited, patients with HBV infection are not only being treated by gastroenterologists but by general physicians as well. Karachi is the largest metropolitan city of Pakistan, located in the province of Sindh. Hence, we had selected four major (i.e. one government, one partially funded by government and two private tertiary care) hospitals of Karachi. All physicians/internists, gastroenterologists, senior residents (year III–IV resident) of gastroenterology and Internal Medicine who had experienced to manage hepatitis B patients and were working in these tertiary care hospitals were approached. Those who were unwilling to participate were excluded from the study. The study purpose and questionnaire were explained to eligible study participants. Those who agreed to participate were requested to fill the questionnaire after informed consent. Measures were taken to maintain confidentiality.

Questionnaire

The questionnaire (Supplementary File 1) comprised of following six sections: (A) demographic characteristics of participants and preference for guidelines to follow; (B) preferences for liver fibrosis assessment, treatment

initiation, treatment selection and antiviral prophylaxis; (C) monitoring of patients during and after stopping antiviral therapy; (D) scenarios for continuing and stopping antiviral therapy; (E) preference for HCC and HDV screening; (F) management of viral resistance.

Total 14 questions were used to assess the knowledge regarding management of CHB according to the guidelines. Out these 13 questions were scenario based assessing consideration for liver biopsy, treatment decision and consideration for antiviral prophylaxis. One question was regarding treatment choice in HBV-HDV co-infected patients while rests of the questions were related to evaluation of practices.

Data Analysis

Data was entered and analyzed by using Statistical Package for Social Science SPSS[®] (SPSS, Inc. Version 22.0). Frequencies and proportions were calculated for categorical variables. Mean $\pm$ standard deviation were calculated for quantitative variables. Knowledge scores were calculated ranging from 0 to 14 and a cut off value ≤ 7 was considered as poor, 8–9 as fair and ≥ 10 was considered as good. Comparative analysis between demographic and knowledge score, resistant management practices among gastroenterologists and internists were done by using Chi-square/Fisher exact test (where appropriate). A *P* value of <0.05 was taken as significant.

RESULTS

Overall 250 participants were approached out of which 50 participants were excluded from the study. The questionnaire was distributed among 200 eligible physicians. A total of 179 (103 residents, 76 consultants) filled the questionnaire completely; hence the response rate was 88.0% (Figure 1). Mean age of participants was 35 ± 9.3 years and most of them were males (69.3%). A total of 32.4% participants were affiliated with subspecialty of gastroenterology/hepatology and 67.6% were from internal medicine specialty. Almost half of the study participants had professional experience of ≤ 5 years and 60.3% had managed 11–100 CHB patients during last year. Overall 27.3% participants claimed to follow AASLD and 24.0% claimed to follow EASL guidelines (Table 1).

Assessment of Knowledge Regarding CHB Management

The knowledge of participants regarding management of hepatitis B was assessed using 14 questions (Table 2). Each response was scored as 'yes', 'No' or 'May Be'. Each correct answer was given a score of 1. To calculate the "knowledge score", cumulative score of correct answers for each participant was calculated separately. Moreover, quartiles of knowledge score were estimated and knowledge score was

Figure 1 Study flow diagram for participants selection.

Table 1 Baseline Characteristics of the Study Participants (n = 176).

Characteristics	N	%
Gender		
Male	124	69.3
Female	55	30.7
Age (mean = 35 years $\pm$ 9.35)		
25–40 years	137	76.5
41–61 years	42	23.5
Designation		
Consultant	76	42.5
Resident	103	57.5
Specialty		
Gastroenterology/Hepatology	58	32.4
Internal Medicine	121	67.6
Years of professional experience		
≤ 5 years	101	56.4
6–10 years	36	20.1
More than 10 years	42	23.5
No. of patients managed during last year		
1–10	41	22.9
11–100	108	60.3
101–1000	30	16.8
Guidelines followed		
AASLD ^a	49	27.3
EASL ^b	43	24.0
APASL ^c	21	11.7
Followed more than one guideline	38	21.2
Do not follow any guideline	28	15.6

^aAmerican Association for the Study of Liver Diseases.

^bEuropean Association for the Study of the Liver.

^cAsia Pacific Association for the Study of the Liver.

Table 2 Consideration for Liver Biopsy, Treatment and Antiviral Prophylaxis in HBeAg +ve and HBeAg –ve Patient.

Case scenarios	Yes (%)	No (%)	May be (%)
Do you consider liver biopsy for following cases?			
(a) HBeAg –ve, ALT > 2 × ULN, age > 40 years, HBV DNA > 2000 IU/ml	26.3	54.7	18.4
(b) HBeAg +ve, ALT > 2 × ULN, age > 40 years, HBV DNA > 20,000 IU/ml	24.6	64.8	9.5
(c) HBeAg –ve, normal ALT, age > 40 years, HBV DNA > 20,000 IU/ml	50.3	29.1	19.6
Would you start treatment for CHB in following cases?			
(a) HBeAg –ve, normal ALT, age > 40 years, HBV DNA > 2000 IU/ml	24.0	51.4	23.5
(b) HBeAg –ve, normal ALT, age < 40 years, HBV DNA > 2000 IU/ml	22.9	54.7	20.1
(c) HBeAg –ve, ALT > 2 × ULN, age < 40 years, HBV DNA > 2000 IU/ml	69.8	11.7	17.9
(d) HBeAg +ve, normal ALT, age > 40 years, no cirrhosis, DNA > 20,000 IU/ml	59.2	21.8	19.0
(e) HBeAg +ve, ALT > 2 × ULN, age < 40 years, HBV DNA > 20,000 IU/ml	92.2	2.2	5.0
(f) HBeAg +ve, normal ALT, age > 40 years, moderate to severe cirrhosis, DNA > 20,000 IU/ml	66.5	18.4	14.0
Do you consider antiviral prophylaxis for following patients undergoing immunosuppression or chemotherapy?			
(a) HBsAg +ve, HBV DNA < 4 log	43.6	39.7	15.1
(b) HBsAg +ve, HBV DNA > 4 log	73.2	15.1	10.6
(c) HBsAg –ve, antiHBc +ve, HBV DNA undetectable	24.0	60.3	14.5
(d) HBsAg –ve, antiHBc +ve, HBV DNA detectable	54.2	27.4	16.8

divided in to three categories; (1) Poor knowledge (knowledge score ≤ 7), (2) Fair knowledge (knowledge score 8–9) and (3) Good knowledge (knowledge score ≥ 10). Overall the mean knowledge score was 8.2 ± 2.3 (range = 3–13). A total of 53 (29.6%), 54 (30.2%) and 72 (40.2%) participants had good, fair and poor knowledge respectively.

Indication for liver biopsy was assessed via three scenarios and correct answers were given by 54.7%, 64.8% and 50.3% participants. For considering the treatment, six different clinical scenarios were given and correct answers were reported by 51.4%, 54.7%, 69.8%, 21.8%, 92.2% and 66.5% respondents. Indication of HBV anti-viral prophylaxis in patients receiving immunosuppressive or chemotherapeutic agents was assessed via four scenarios and correct answers were conferred by 43.6%, 73.2%, 60.3% and 54.2% participants (Table 2). The 14th question was regarding screening of CHB patients for hepatitis D and treatment of choice in case of HBV-HDV co-infection. Approximately 79.3% of participants reported screening of CHB patients for HDV in routine and only 62.6% were compliant with guidelines and were using Peg IFN or conventional interferon as a treatment choice for HBV-HDV co-infected patients.

Comparative analysis was done to assess the factors associated with knowledge scores (Table 3). In general greater proportion of males had fair (63.0% vs. 37.0%) and good knowledge (83.0% vs. 17.0%) as compared to females (P -value 0.03). Moreover, physicians aged 25–40 years, consultants and those who were practicing gastroenterology/hepatology in routine had significantly higher knowledge scores in compliance with the guidelines as compared to others ($P < 0.05$). However, no significant

difference was found as per years of professional experience or number of cases managed last year.

Assessment of the Practices Toward Management of CHB

Non-Invasive Assessment of Liver Fibrosis

Overall 55 (30.7%) and 57 (31.8%) participants preferred ultrasound and fibroscan respectively as non-invasive method to assess the liver fibrosis. In addition, 19%, 7.8%, 3.4% preferred Fibro test, CT scan and HEPA score respectively. Approximately 2.8% used other method and 4.5% did not use any other test to assess fibrosis.

Factors Affecting the Choice of Drug

For choosing the drug to treat patients with CHB, majority of the participants considered drug efficacy (93.3%), cost of treatment (82.1%), safety (79.9%) and low resistance (57.7%) as a top four key elements while rest of the participants choose patient preference (27.9%), finite duration of therapy (24.6%), history of flare and hepatic function (12.8%), and promotion by drug company (3.4%) as other factors.

Drug Preferences for CHB Therapy

Approximately 25.7% and 23.5% participants preferred tenofovir (TDF) and entecavir (ETV) as first line and rescue therapy. ETV (43.0%), TDF (38.5%) and Peg IFN ∞ 2a (30.2%) were considered as the preferred first line therapy by most of the participants. While, 17.9% participants selected combination of ETV with TDF as a rescue therapy followed by adefovir (ADV) monotherapy (16.2%),

Table 3 Assessment of Factors Associated With Knowledge Score Variables.

Variables		Knowledge score N (%)			P-value ^a
		Poor ≤7	Fair 8–9	Good ≥10	
Gender	Male	46 (63.9)	34 (63.0)	44 (83.0)	0.035
		26 (36.1)	20 (37.0)	09 (17.0)	
Age group	25–40 years	62 (86.1)	40 (74.1)	35 (66.0)	0.029
	41–60 years	10 (13.9)	14 (25.9)	18 (34.0)	
Designation	Consultant	22 (30.6)	25 (46.3)	29 (54.7)	0.021
	Resident	50 (69.4)	29 (53.7)	24 (45.3)	
Specialty	Gastroenterology/Hepatology	11 (15.3)	16 (29.6)	31 (58.5)	<0.001
	Internal Medicine	61 (84.7)	38 (70.4)	22 (41.5)	
Year of professional experience	≤5 years	47 (65.3)	32 (59.3)	22 (41.5)	0.100
	6–10 years	13 (18.1)	09 (16.7)	14 (26.4)	
	>10 years	12 (16.7)	13 (24.1)	17 (32.1)	
No. of patients managed last year	1–10	22 (30.6)	11 (20.4)	08 (15.1)	0.179
	11–100	42 (58.3)	31 (57.4)	35 (66.0)	
	101–1000	08 (11.1)	12 (22.2)	10 (18.9)	

^aChi-square test was applied to calculate P-value.

Figure 2 What are your choices for CHB therapy?

lamivudine (LAM) in combination with ADV (15.6%) and TDF monotherapy (15.1%) as shown in Figure 2.

Monitoring Parameters During and After CHB Therapy

In our study, for patients receiving nucleoside/nucleotide analogs (NAs) 45.3% participants reported serum ALT and HBV DNA monitoring every 3 months, 37.4% reported HBeAg/anti-HBeAg testing every 6 months, while 36.9% participants stated quarterly monitoring of renal

functions. In case of IFN based therapy majority of participants reported monitoring of blood cell counts (66.5%) and serum ALT (53.1%) every month while quarterly monitoring of serum HBV DNA and thyroid stimulating hormone (TSH) were reported by 47.5% and 30.7% participants respectively. However, only 3.1.3% participants reported testing of HBeAg/anti-HBeAg at 6 months interval. After completion of therapy 55.3% participants stated biannually monitoring of quantitative HBV DNA and 41.9% reported quarterly monitoring of ALT.

Continuing and Stopping Criteria

Almost half of the participants followed APASL guideline to continue treatment in the absence of HBeAg seroconversion (Figure 3); almost 64.8% and 67% participants followed stopping rule recommended by APASL in case of undetectable HBV DNA for two or three years after HBeAg seroconversion respectively. Only 34.6% participants choose to stop the treatment in case of primary treatment failure (HBV DNA <1 log₁₀ reduction at 3 months therapy) whereas 73.7% choose to stop the therapy when resistance occur which was not in compliance with guidelines.

Preference for Antiviral Prophylaxis

In present study the drug preference for prophylaxis in immunocompromised cases was as follows: ETV (46.9%), TDF (45.3%), LAM 54 (30.2%), ADV 17(9.5%), LAM + hepatitis B immunoglobulin (HBIG) 16(8.9%) and IFN 8 (4.5%). All three guidelines has recommended antiviral prophylaxis in immunocompromised patients with reactive HBSAg (LAM for short duration, ETV or TDF for longer duration >12 months of immunosuppression) regardless of HBV DNA levels. While in HBSAg negative patients (LAM or NA) depends on HBV DNA levels in preventing HBV recurrence.

HCC Surveillance

Overall 92.2% reported screening for HCC in routine and this practice was significantly common among gastroenterologists as compared to internists (96.3% vs. 89.3%, $P = 0.02$). Overall 51.4%, 31.3%, 11.7%, 6.7%, 5.6%, 0.6% of participants were screening all HBV cases, only

cirrhotic, patients ≥ 40 years of age, HBV-HDV co-infected patients, patients with active disease and only male patients respectively. However, 4.5% did not screen patients at all due to high cost of screening and 3.3% considered it unnecessary. Majority of the participants used ultrasound (55.3%), alfa fetoprotein (AFP) (52.5%) every 6 months for HCC screening.

Viral Resistance Monitoring and Management

About 76 (42.5%) participants used combination of serum HBV DNA and ALT to identify suspected cases with drug resistance. A total of 59 (33.0%) used only HBV DNA and 11 (6.1%) monitored ALT only for this purpose. However, 33 (18.4%) did not monitor viral resistance at all. Resistance specific tests were not included in survey due to their unavailability in Pakistan.

Participants were questioned regarding modification of treatment in case of suspected antiviral resistance (Table 4). In patients with LAM resistance 56.9% participants from gastroenterology and 36.4% participants from internal medicine specialty preferred to switch the treatment as compared to 19.0% (gastroenterology) and 16.5% (internal medicine) who preferred to add on other antiviral drug and adopted both switch and add on strategies depending upon clinical scenario. In LAM resistance, about 31.8% and 15.1% participants preferred to switch and add-on to ETV which is inconsistent with all three guidelines which did not recommend ETV. APASL and EASL recommend switch to TDF or add-on ADV therapy while AASLD preferred add-on ADV or TDF. In case of ADV resistance 63.8% participants from gastroenterology and 30.6% participants from internal medicine specialty

Figure 3 Scenarios for continuing and stopping antiviral therapy for the patients who are currently on CHB therapy.

Table 4 Modification of Treatment for Suspected Antiviral Resistance.

	All participants <i>n</i> = 179 <i>N</i> (%)	Gastroenterology Specialty (<i>n</i> = 58) <i>N</i> (%)	Internal Medicine Specialty (<i>n</i> = 121) <i>N</i> (%)	<i>P</i> -value ^a
On LAM				
Switch to	77 (43.0)	33 (56.9)	44 (36.4)	<0.001
Switch to ADV	12 (6.7)	2 (3.4)	10 (8.3)	
Switch to ETV	57 (31.8)	16 (27.6)	41 (33.9)	
Switch to TDF	40 (22.3)	26 (44.8)	14 (11.6)	
Add on	31 (17.3)	11 (19.0)	20 (16.5)	0.094
Add on ADV	26 (14.5)	8 (13.8)	18 (14.9)	
Add on ETV	27 (15.1)	8 (13.8)	19 (15.7)	
Add on TDF	8 (4.5)	6 (10.3)	2 (1.7)	
Switch to & Add on both	31 (17.3)	11 (19.0)	20 (16.5)	
Not sure what to do	40 (22.3)	3 (5.2)	37 (30.6)	
On ADV				
Switch to	74 (41.3)	37 (63.8)	37 (30.6)	<0.001
Switch to ETV	55 (30.7)	21 (36.2)	34 (28.1)	
Switch to LAM	8 (4.5)	–	8 (6.6)	
Switch to Interferon	9 (5.0)	2 (3.4)	7 (5.8)	
Switch to TDF	27 (15.1)	21 (36.2)	6 (5.0)	0.658
Add on	21 (11.7)	9 (15.5)	12 (9.9)	
Add on LAM	15 (8.4)	4 (6.9)	11 (9.1)	
Add on ETV	31 (17.3)	12 (20.7)	19 (15.7)	
Switch to and Add on both	25 (14.0)	7 (12.1)	18 (14.9)	
Not sure what to do	59 (33.0)	5 (8.6)	54 (44.6)	
On ETV				
Switch to	74 (41.3)	34 (58.6)	40 (33.1)	<0.001
Switch to ADV	7 (3.9)	2 (3.4)	5 (4.1)	
Switch to LAM	11 (6.1)	1 (1.7)	10 (8.3)	
Switch to Interferon	25 (14.0)	2 (3.4)	23 (19.0)	
Switch to TDF	56 (31.3)	35 (60.3)	21 (17.4)	0.411
Add on	21 (11.7)	12 (20.7)	9 (7.4)	
Add on ADV	11 (23.9)	3 (16.7)	8 (28.6)	
Add on TDF	30 (65.2)	14 (77.8)	16 (57.1)	
Add on LAM	5 (10.9)	1 (5.6)	4 (14.3)	
Switch to and Add on both	25 (14.0)	6 (10.3)	19 (15.7)	
Not sure what to do	58 (32.4)	5 (8.6)	53 (43.8)	
Multidrug resistant (LAM + ADV OR ADV + ETV)				
Switch to	84 (46.9)	44 (75.9)	40 (33.1)	<0.001
Switch to TDF	31 (17.3)	23 (39.7)	8 (6.6)	
Switch to TDF + ETV combination	53 (29.6)	21 (36.2)	32 (26.4)	
Not sure what to do	94 (52.5)	13 (22.4)	81 (66.9)	

LAM: lamivudine; ADV: adefovir; ETV: entecavir; TDF: tenofovir.

Telbivudine and truvada not available in Pakistan so not included in the survey.

^aChi-square/Fisher's exact test (when a cell had an expected frequency <5) was applied to calculate *P*-value.

preferred to switch the treatment as compared to 15.5% (gastroenterology) and 9.9% (internal medicine) who preferred to add on other treatment. Whereas 12.1% gastroenterology and 14.9% internal medicine participants adopted both switch and add on strategies depends on

the cases. In ADV resistance, about 30.7% and 17.3% participants preferred switch and add-on to ETV which was consistent with AASLD. However APASL recommended switch to TDF and add-on LAM or ETV and EASL recommended only switch to either TDF or ETV.

In patients with ETV resistance 58.6% participants from gastroenterology and 33.1% participants from internal medicine specialty preferred to switch the treatment as compared to 20.7% vs. 7.4% preferred to add on other treatment whereas 10.3% gastroenterology and 15.7% internal medicine specialty participants adopted both switch& add on strategies depends on the cases. In case of ETV resistance, about 31.3% and 65.2% participants preferred switch and add-on to TDF. However APASL recommend only add-on TDF or ADV therapy, AASLD recommended only switch to TDF and EASL recommended switch to TDF or add-on TDF/ADV.

In our study, over 52.5% participants were not sure about how to manage the multidrug resistant cases. However, only 29.6% participants knew that TDF in combination with ETV is a drug of choice in multidrug resistant case as per guidelines.

DISCUSSION

This is the first study evaluating the knowledge and practices regarding HBV among health care physician in Karachi, Pakistan. In our study 72 (40.2%) participants had poor knowledge in 4 principal areas of CHB management, i.e. liver biopsy, treatment initiation, antiviral prophylaxis consideration in immunocompromised patients and drug of choice in HBV-HDV co-infected patients. However, only 29.6% participants scored for good knowledge in compliance with guidelines.

Almost >50% of the participants knew criteria for liver biopsy according to existing guidelines. Regarding initiation of treatment most of them were able to make a correct decision in HBeAg positive patients with elevated ALT (92.2%) and cirrhotics (66.5%). However, only 21.8% participants decided correctly for not to start treatment in HBeAg positive and for immune tolerant patients (Table 2).

In our study 51–69.8% questions related to decision of treatment in HBeAg negative patients were answered correctly. In a survey from Singapore,¹¹ 25.4–42.5% participants choose to initiate the treatment outside the APASL recommendation which was comparable to our study (22.9–59.2%). In another study,¹² about 89.5% respondents recommend treatment in patients with high ALT level which was consistent with our results. It should also be noted that almost up to 20% of participants answered “may be” when asked about the all four aspects of knowledge. About 43.6–73.2% participants recommended antiviral prophylaxis in HBsAg positive patients regardless of DNA level because of high risk of HBV reactivation which was consistent with EASL recommendations.⁹ In HBsAg negative patients, reactivation of HBV at immunosuppression depends on the level of HBV DNA⁹ and almost half of participants recommended antiviral prophylaxis rightly. Only difference found among the guidelines was about

duration of antiprophylaxis for instance APASL and AASLD recommends continuing antivirals for 6 months and EASL recommends for 12 months after stopping immunosuppressive therapy. None of the guideline recommends IFN as prophylaxis because of its bone marrow suppression effect.

Due to high diagnostic accuracy, EASL guideline recommends transient elastography (fibroscan) as a noninvasive tool for the detection of liver cirrhosis.⁹ However only few (31.8%) participants preferred using fibroscan. All guidelines recommended antiviral with high potency and high resistant barrier as first line therapy.^{8–10} In HBeAg positive compensated and decompensated cirrhosis ETV and TDF are considered most potent antiviral while in HBeAg negative patients TDF is considered as best option.^{19,20} However the same has not been recommended in the guidelines. In HBeAg negative patients HBVDNA suppression, ALT normalization and HBsAg loss at 1 year occur in 90–91%, 78–88% and 0–1% with ETV and 93%, 76% and 0% with TDF respectively.²¹ In the present study most of the physician preferred oral NAs (ETV or TDF) as first line therapy by choosing the efficacy, cost, safety and low resistance profiles as the most common reason of considering this treatment which were consistent with the other studies.^{11,12} In a cross sectional survey from San Francisco, participants monitored ALT levels (79%) and HBV DNA levels (44%) every 6–12 months during CHB therapy.¹⁶ Similar practices were reported in our study and our participants were using ALT and HBV DNA for monitoring but at the interval of 3 months. However, all guidelines recommend monitoring of ALT and CBC every 1–3 months and renal function monitoring during oral antiviral therapy every 3–6 months. However, APASL recommends monitoring of HBV DNA, HBeAg/anti-HBeAg every 3 months while EASL recommends HBV DNA and HBeAg/anti-HBeAg every 6 months and TSH every 3 months. However in contrary to APASL and EASL, AASLD recommends 3 monthly monitoring of HBV DNA and TSH, rechecking HBeAg/anti-HBeAg every 6 months.

When responding to the clinical scenarios regarding stopping and continuing antiviral therapy, responses were found more consistent with the guidelines as compared to these studies.^{11,12} APASL guidelines recommended the discontinuation of treatment if HBeAg negative patient treated for at least 2 years with HBV DNA loss on 3 separate occasions 6 months apart.⁸ However, EASL and AASLD have strict criteria of stopping antiviral therapy in HBeAg negative patients which is until HBsAg clearance.^{9,10}

All guidelines recommended HCC screening with liver ultrasound with/without AFP for individuals at risk after every 6 month. However there is some difference in criteria for high-risk group in between these guidelines.^{8,10,22} These recommendations were followed by almost half of the participants in our study, however the compliance

was lower as compared to another survey of Asian Americans (79%).¹⁵ Hence, most of the participants used ALT in combination with HBV DNA to identify the resistance while in the study from Singapore study, HBV DNA was used most commonly for this purpose.²³ In a drug resistance management survey among physicians in China, South Korea, Taiwan and Thailand²³ add-on ADV therapy approach was commonly used in case of LAM resistance while in present study maximum participant switched the patient to ETV therapy (31.8%) followed by TDF therapy (22.3%). In a study from Taiwan, 40% participants switched patients to ETV in case of ADV resistance²³ which is comparable to our study (30.7%). However majority of participants lack experience for managing ETV and multidrug resistant case and were unsure about that.

There are number of limitations in the study. Firstly, though the study was conducted at four major tertiary care hospitals of the largest city of Pakistan, cannot predict knowledge and practices in other areas of country especially smaller cities. Secondly, the study population was not homogenous but that actually reflects the real life scenario from a developing country where other than gastroenterologists, such patients are treated by internist and residents as well. Thirdly, due to the unavailability of resistance specific tests such as gene sequencing or line probe assay in Pakistan, physicians used HBV DNA and ALT levels for managing the suspected resistance.

Lack of awareness and familiarity has been reported as the most important barrier which could affect the knowledge of the physician related to the guidelines. Lack of agreement with specific guideline recommendation, poor self-efficacy, lack of outcome expectancy and the resistant behavior to previous practices were found the possible barriers which affect the practices of physician related to the guidelines²⁴ so in order to overcome these barriers several prospects for improvement should be offered.

CONCLUSION

Our study has highlighted the gaps in knowledge and practice deficit in managing CHB patients according to the guidelines. Variability has been found in knowledge and practices of specialties and individuals with different level of experiences. Efforts to improve knowledge, refresher courses and appropriate coordination between gastrointestinal and internal medicine physicians could enable evidence based management and follow-up of patients with CHB effectively.

ETHICAL APPROVAL AND INFORMED CONSENT

The study was conducted in compliance with the institutional ethical standards and with the declaration of Helsinki 1975. The study was approved by the institutional

ethical review committee (ERC) of each participating hospitals, i.e. Aga Khan University Hospital (No: 3056-Pha-ERC-14), Dow university of Health Sciences/Civil Hospital (No: IRB-523/DUHS/-14) and Jinnah Post Graduate Medical Centre (No: F.2-81/2015-GENL/12679/JPMC). Informed consent was obtained from all participants included in the study.

CONFLICTS OF INTEREST

The authors have none to declare.

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APPENDIX A SUPPLEMENTARY DATA

Supplementary material related to this article can be found, in the online version, at <https://doi.org/10.1016/j.jceh.2017.12.009>.

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