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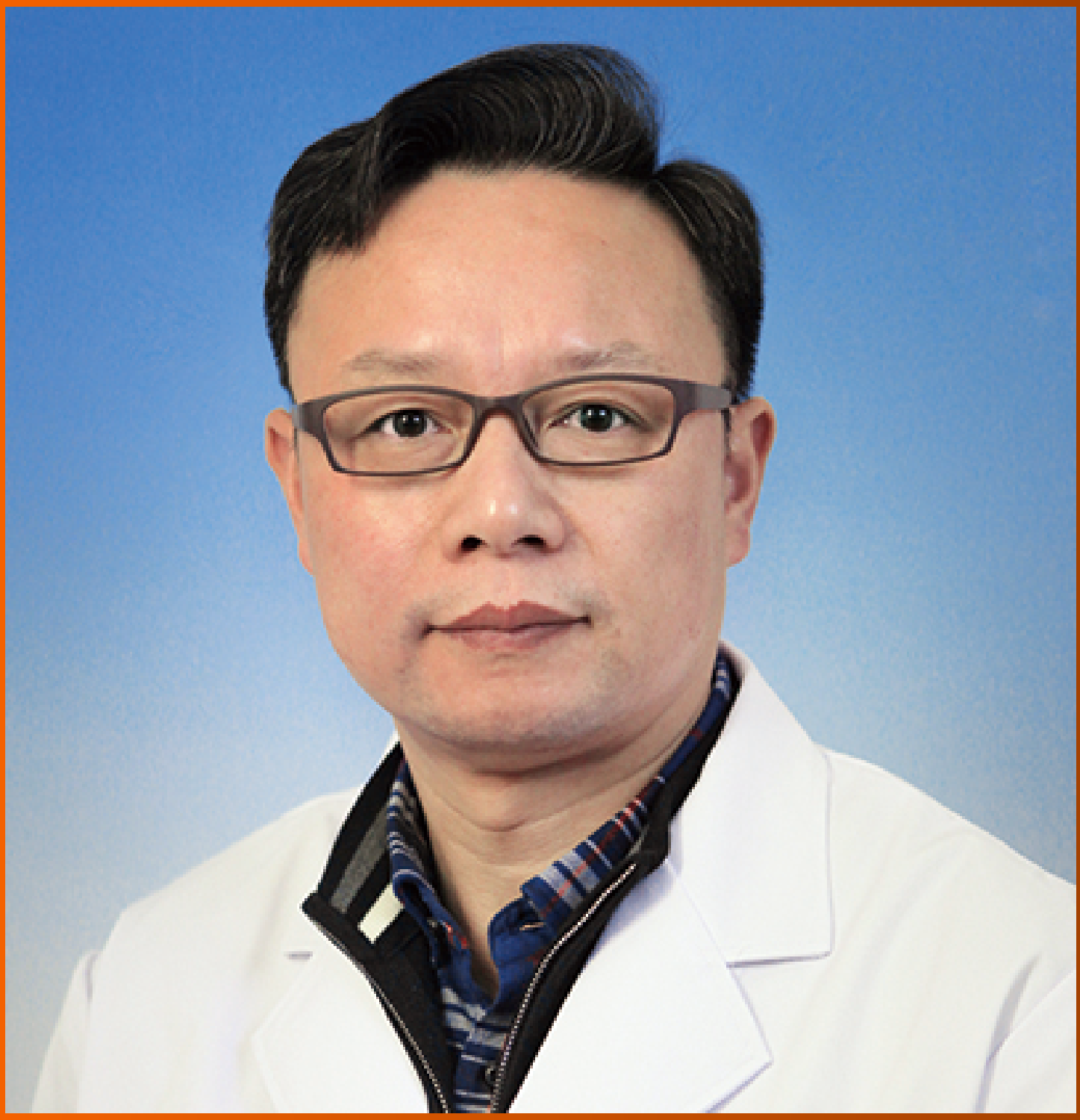

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Contents

Monthly Volume 13 Number 3 March 27, 2021

REVIEW

270 Molecular pathways of liver regeneration: A comprehensive review

Kiseleva YV, Antonyan SZ, Zharikova TS, Tupikin KA, Kalinin DV, Zharikov YO

MINIREVIEWS

291 Hepatitis D virus and liver transplantation: Indications and outcomes

Muhammad H, Tehreem A, Hammami MB, Ting PS, Idilman R, Gurakar A

300 Lymphatic dysfunction in advanced cirrhosis: Contextual perspective and clinical implications

Kumar R, Anand U, Priyadarshi RN

ORIGINAL ARTICLE

Basic Study

315 Papaya improves non-alcoholic fatty liver disease in obese rats by attenuating oxidative stress, inflammation and lipogenic gene expression

Deenin W, Malakul W, Boonsong T, Phoungpetchara I, Tunsophon S

328 Promotive action of 2-acetylaminofluorene on hepatic precancerous lesions initiated by diethylnitrosamine in rats: Molecular study

Hasanin AH, Habib EK, El Gayar N, Matboli M

343 Baculovirus repeat-containing ubiquitin conjugating enzyme regulation of β-catenin signaling in the progression of drug-induced hepatic fibrosis and carcinogenesis

Vilfranc CL, Che LX, Patra KC, Niu L, Olowokure O, Wang J, Shah SA, Du CY

Retrospective Study

362 Early tacrolimus exposure does not impact long-term outcomes after liver transplantation

Gastaca M, Ruiz P, Bustamante J, Martinez-Indart L, Ventoso A, Fernandez JR, Palomares I, Prieto M, Testillano M, Salvador P, Senosiain M, Suárez MJ, Valdivieso A

META-ANALYSIS

375 Efficacy and safety of once daily tacrolimus compared to twice daily tacrolimus after liver transplantation

Bzeizi KI, Albenmousa A, Shawkat AM, Ahmed Z, Alabbad S, Alhamoudi W, Troisi R, Broering D

CASE REPORT

384 Conversion hepatectomy for hepatocellular carcinoma with main portal vein tumour thrombus after lenvatinib treatment: A case report

Takahashi K, Kim J, Takahashi A, Hashimoto S, Doi M, Furuya K, Hashimoto R, Owada Y, Ogawa K, Ohara Y, Akashi Y, Hisakura K, Enomoto T, Shimomura O, Noguchi M, Oda T

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Contents

ABOUT COVER

Editorial Board Member of *World Journal of Hepatology*, Dr. Guang-Hua Luo is Director of the Clinical Medical Research Center in the Third Affiliated Hospital of Soochow University (China). He graduated from the Laboratory Medicine Department of Zhenjiang Medical College in 1996, obtained a PhD in 2013 at Soochow University, and was nominated to professorship in 2014. Currently, he is an editorial board member of Endocrine, Metabolic & Immune Disorders-Drug Targets. He has published more than 240 papers, 86 of which are included in SCI. Since 2009, four of his inventions have obtained patent authorization. His research activities mainly focus on molecular diagnostics in personalized medicine and on the regulatory role and mechanism of apolipoprotein M in liver diseases and chronic inflammatory diseases. (L-Editor: Filipodia)

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WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

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MINIREVIEWS

Hepatitis D virus and liver transplantation: Indications and outcomes

Haris Muhammad, Aniqa Tehreem, Muhammad Baraa Hammami, Peng-Sheng Ting, Ramzan Idilman, Ahmet Gurakar

ORCID number: Haris Muhammad 0000-0002-3472-6219; Aniqa Tehreem 0000-0002-1007-9395; Muhammad Baraa Hammami 0000-0002-6182-0227; Peng-Sheng Ting 0000-0003-1581-2354; Ramzan Idilman 0000-0001-8840-5472; Ahmet Gurakar 0000-0002-2221-9148.

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Haris Muhammad, Department ofInternal Medicine, Greater Baltimore Medical Center, Towson, MD 21204, United States

Aniqa Tehreem, Department of Internal Medicine, Sinai Hospital Baltimore, MD 21204, United States

Muhammad Baraa Hammami, Peng-Sheng Ting, Ahmet Gurakar, Division of Gastroenterology and Hepatology, Johns Hopkins University School of Medicine, Baltimore, MA 21205, United States

Ramzan Idilman, Department of Gastroenterology, Ankara University School of Medicine, Ankara 06690, Turkey

Corresponding author: Ahmet Gurakar, MD, Associate Professor, Director, Doctor, Division of Gastroenterology and Hepatology, Johns Hopkins University School of Medicine, 720 Rutland Avenue, Ross Research Building, Suite 918, Baltimore, MA 21205, United States.
aguraka1@jhmi.edu

Abstract

Hepatitis D virus (HDV) is a dependent virus that relies on hepatitis B virus for its replication and transmission. Chronic hepatitis D is a severe form of viral hepatitis that can result in end stage liver disease. Currently, pegylated interferon alpha is the only approved therapy for chronic HDV infection and is associated with significant side effects. Liver transplantation (LT) is the only treatment option for patients with end-stage liver disease, hepatocellular carcinoma, or fulminant hepatitis due to coinfection with HDV. As LT for HDV and hepatitis B virus coinfection is uncommon in the United States, most data on the long-term impact of LT on HDV are from international centers. In this review, we discuss the indications and results of LT with treatment options in HDV patients.

Key Words: Hepatitis delta virus; Liver transplant; Hepatitis B immunoglobins; Hepatocellular carcinoma

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Core Tip: Hepatitis D virus (HDV) is a dependent virus and relies on hepatitis B virus

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(HBV) to synthesize the pathogenic genomes. Therefore, it can only survive as a coinfection with HBV or as a superinfection. Chronic HDV infection results in rapid liver damage and can result in end stage liver disease. Currently, pegylated interferon alpha is the only approved therapy for chronic HDV infection and is associated with significant side effects. Thus, liver transplant remains the only option for patients with end-stage liver disease, hepatocellular carcinoma due to coinfection or superinfection with HDV and HBV, fulminant liver failure and those who cannot be treated with interferon-based therapies. Post transplantation reinfection with HDV/HBV is an undesirable outcome. Though, there is a consensus that hepatitis B immune globulin in combination with a potent nucleoside/nucleotide analogue have shown promising results. In addition, there is ongoing research for newer treatment drugs. This review article focuses on liver transplant in patients as a result of hepatitis D virus. We have discussed the epidemiology, pathogenesis, clinical presentation, indication of liver transplantation, treatment options and the outcomes. New therapy trials have been also discussed in the treatment section. We believe that this topic is an area of knowledge gap and this article will cover the basics.

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INTRODUCTION

Hepatitis D virus (HDV) was discovered in 1970s by Rizzetto *et al*[1]. It is formed by 1678 nucleotide single stranded ribonucleic acid (RNA) virus which is circular in shape and contains two viral proteins that are p24 and p27[2,3]. There is a total of 8 genotypes of HDV in the world[4]. HDV is not able to make its own proteins and relies on hepatitis B virus (HBV) to synthesize the pathogenic genomes. Therefore, it can only survive as a coinfection with HBV or as a superinfection. Around 5% of HBV carriers worldwide have been exposed to HDV and the prevalence of HDV coinfection in United States is reported to be 12%[5,6]. Chronic HDV infection results in rapid liver damage compared to patients infected with HBV alone. In addition, incidence of cirrhosis is almost three times with HBV/HDV chronic coinfection and associated with increased rate of early decompensation leading to hepatocellular carcinoma (HCC)[7]. As HDV uses host polymerase for replication, HBV polymerase inhibitors are not effective against it[8]. Therefore, the only widely accepted treatment is interferon at high doses which has a success rate of 25% to 30%, which is defined as virological response after one year of conventional or PEG-INFa treatment with most studies measuring virological response after 6 mo of treatment[9]. Thus, liver transplant (LT) remains the only option for patients with end-stage liver disease, HCC due to coinfection or superinfection with HDV and HBV, fulminant liver failure and those who cannot be treated with interferon-based therapies. In this review we discuss the indications of liver transplantation and its outcome in patients with HDV.

EPIDEMIOLOGY

There are about 240 million people worldwide who have positive hepatitis B surface antigen (HBsAg). Amongst them 2% to 8% are co-infected with HDV resulting in approximately 20 to 40 million suffering from HDV[10,11]. However, recent studies have estimated the coinfection number to be higher as up to 72 million[12]. HDV is endemic in the Middle East, Mediterranean Area, Amazon Region, and African countries[13]. In Europe, HDV is mainly a problem in Eastern European immigrant populations and amongst intravenous drug users (IVDU)[14,15]. There are 8 different HDV genotypes and genotype 1 is the most common in North America[16]. Testing for HDV has not been widespread in the United States and the prevalence has been underestimated. There has been a 3.4% HDV seropositive rate reported in the veteran population positive

with HBsAg[17]. In comparison, National Health and Nutrition Examination Survey data (1999-2012) showed a significantly lower rate of HDV prevalence (0.02%) in the civilian population[18]. It increased to 0.11% in a repeat National Health and Nutrition Examination Survey (2011-2016) study[19]. Both these studies are limited as they excluded homeless, incarcerated, and other high-risk individuals. However, a study done among patients with IVDU in Baltimore by Kucirka *et al*[20] reported 11% prevalence of HDV in 2005-2006. Similarly, Gish *et al*[21] conducted a study in California on chronic HBV patients reporting a coinfection rate of 8%. This variability warrants routine testing of HDV in HBV carriers with specific recommendations for screening, treatment and follow-up. This will aid risk stratification of patients and allow for early discovery of complications, which in turn may improve outcomes.

PATHOGENESIS, CLINICAL FEATURES AND DIAGNOSIS

HDV is parenterally transmitted and has variable clinical manifestations. There are two major patterns of infection that are described in literature. Notably, coinfection of HBV with HDV and superinfection of HDV in chronic HBV-infected patients. HDV develops innate and adaptive immunity and there are specific markers such as HDV RNA, hepatitis D antigen and anti-HDV antibodies, such as IgM and IgG, which help to detect and differentiate the chronicity of the disease[22].

As HDV's virulence is dependent on HBV, coinfection results from simultaneous acute HBV and HDV. It is usually transient and cannot be clinically distinguished from HBV infection[23]. HDV has incubation period of approximately 1 mo resulting in clinical symptoms of fatigue, loss of appetite and nausea. It is accompanied with a rise in liver enzymes, including serum alanine aminotransferase and aspartate aminotransferase. Then comes the jaundice phase with increase in bilirubin levels. As it is usually self-limiting and most patients recover completely with only 2% leading to chronic infection[7,24].

Superinfection with HDV can also result in acute hepatitis which is more severe than seen with co-infection. This is because HBV has already set the ground for more aggressive disease progression. It can lead to acute liver failure with clinical symptoms starting as nausea and progressing to coagulopathy, encephalopathy and coma[25]. About 80% to 90% of patients progress to chronic hepatitis. Amongst them, some dated studies have reported up to 70% to 80% progress to cirrhosis within 5 to 10 years[26]. However, newer studies suggested a 4% annual progression to cirrhosis[27]. This variability might be due to the different genotypes of HDV. Although there is controversy in the literature over whether HDV has oncogenic properties, cirrhosis from HDV does increase the risk of HCC, which is the second most common cause of cancer deaths in men worldwide[28].

HBsAg is necessary before other markers for HDV are investigated to establish the diagnosis. One important distinguishing test is IgM anti-HBc, which is only present in acute HDV/HBV coinfection and not in acute HDV superinfection. Likewise, HDV RNA is a sensitive marker for acute infection and reaches a very high quantitative value in chronic patients. Similarly, the presence of anti-HDV IgM or high anti-HDV IgG titer can differentiate between current and past infections. Therefore, knowing these markers helps to differentiate the disease pattern (Table 1)[23].

INDICATIONS FOR LIVER TRANSPLANTATION

The global disease burden of HBV/HDV coinfection is increasing with 10.6% of HBsAg carriers without high risk sexual behavior or IVDU are HDV[12]. HDV can lead to a more severe form of viral hepatitis than in HBV mono-infection[29]. Irrespective of whether being coinfected with HBV or as superinfection, HDV can cause fulminant hepatitis[30]. The clinical course of fulminant hepatitis D is 4 to 30 d and transplant free survival is as low as 20%[7,31].

Chronic HDV results in rapid liver fibrosis, earlier decompensation, higher risk of HCC development and annual mortality rate between 7% to 9%[32]. Mortality rates of greater than 50% at 15 years follow up have been reported in Taiwan[33]. Though direct oncogenic properties of HDV is not clearly described, higher rates of cirrhosis in HDV patients can lead to increased rates of HCC[34]. Rates of HCC are variable across the globe with studies showing anti-HDV antibodies ranging from 4% to 23% in HBsAg positive HCC patients[35,36]. Treatment option for HDV has limited success. Therefore, the only definitive therapy for patients with end-stage liver disease, HCC, or

Table 1 Summarizes markers specific for coinfection and superinfection

	Coinfection	Superinfection
HDV infection	Acute	Acute or chronic
IgM anti-HBc	Positive	Negative
Serum HDV RNA	Transient	Persistent and high
IgM anti-HDV	Transient	Persistent
IgG anti-HDV	Late appearance and low	Persistent and high

HDV: Hepatitis D virus; RNA: Ribonucleic acid; HBc: Hepatitis B core.

fulminant hepatitis due to HDV is liver transplant[13].

TREATMENT OPTIONS

Currently there is no United States Food and Drug Administration approved treatment for HDV[37]. However, PEG-IFNa is commonly used and is also recommended by major liver societies such as American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver[38,39]. Pegylated form requires only weekly dosing and metanalysis has shown increased suppression (29%) of HDV RNA at 6 mo compared to standard IFN alpha (19%)[40]. In addition, PEG-IFNa is also associated with lower rates of side effects such as anorexia, nausea, weight loss, alopecia, leukopenia and thrombocytopenia[41,42]. Although there is no definite treatment duration, negative HDV RNA at 24 wk is being considered a reference for virological response and treatment for 48 wk is recommended[38,43]. Pegylated IFN has been studied in combination with nucleosides. The Hep-Net/International Delta Hepatitis Intervention Trial randomized 90 patients to adefovir, peginterferon, or the combination arm. Approximately 25% achieved virological response at 24 wk in the peginterferon and combination group and none in the adefovir group[44]. Similarly, the HIDIT-2 trial (which replaced adefovir with tenofovir) yielded similar results to the trial[21] and did not show a response in the nucleoside alone[45]. Thus, combination of interferon with nucleosides or increasing the duration of treatment has shown no additional benefits.

In addition, newer experimental treatments are currently underway. One such example is the use of oral prenylation inhibitor lonafarnib (LNF). Prenylation inhibitors have been shown to abolish HDV-like particle production *in vitro* and *in vivo* [46]. LNF interferes with the HDV cycle and targets the virion assembly step in the hepatocyte cytoplasm, where the nascent HDV nucleoprotein complex is enveloped by HBsAg[47]. To explore this, the LOWR HDV-1 [Lonafarnib with and without Ritonavir (RTV) in HDV-1] phase two clinical trial was conducted by Yurdaydin *et al*[47] with the intention to study optimal LNF dosing while assessing tolerability and viral response when combined with P450 3A4 inhibitor RTV or PEG-IFNa. Results showed that LNF, whether as monotherapy or as combination with PEG-IFNa, led to HDV-RNA viral load decline in all patients. All treated patients in different treatment regimens reported GI adverse effects consisting of anorexia and weight loss. Higher dose of LNF, 300 mg peroral BID, was associated with increased adverse effects. RTV helped to lower LNF dose (100 mg per oral BID dosing) while still achieving better antiviral results. Similarly, LNF 100 mg BID with PEG-IFNa helped in more substantial and rapid HDV-RNA reduction, compared to PEG-IFNa alone[47]. Such trials have opened the door to further explore newer treatment options for HDV.

PEG-IFNa is only used amongst patients with compensated liver disease. For those who undergo LT, long-term survival depends on the prevention of allograft reinfection. LT for HDV is not common in United States and studies in literature are mostly from other countries[48,49]. Due to antivirals and with hepatitis B immune globulin (HBIG), rates of HBV/HDV reinfection after LT has decreased[50]. Currently there is no specific prophylaxis for HDV. However, as its growth is dependent on HBV, the focus should be on preventing HBV infection.

Levels of HBV DNA (> 105 copies/mL) strongly predict HBV reinfection in HBsAg positive LT recipients[51]. As per AASLD recommendations, all HBsAg-positive recipients should receive prophylactic nucleoside/nucleotide analogs with or without

HBIG post-LT. In addition, pretransplant hepatitis B e-antigen/HBV-DNA levels should not be taken into consideration and HBIG monotherapy should not be used. They further suggest that entecavir, tenofovir disoproxil fumarate, and tenofovir alafenamide should be the preferred antivirals and continued indefinitely post-LT[38]. The use of HBIG depends on the recipient and virologic factors. In medically adherent HBV mono-infected recipients with undetectable or low-level viremia at the time of LT and no evidence of concurrent infection, no HBIG or a very short course (5 d) of HBIG post-LT combined with long-term antiviral therapy is highly effective in preventing HBV recurrence[38]. On the other hand, in HBV/HDV co-infected recipients, the combination of long-term HBIG and antiviral therapy may be the best approach in preventing HBV and HDV recurrence[38].

Data regarding the dosage of HBIG therapy varies across transplant centers. In previous studies HBIG has been given as either high (≥ 10000 IU/mL) or low (< 10000 IU/mL) dose for either a fixed duration (median of 6 mo) or indefinitely post-LT[50]. It is administered either intravenous or intramuscularly during an hepatic phase, followed by daily doses during the first week, with subsequent doses given monthly or by following anti-HBs titers based on the transplant center protocol[50]. A trough anti-HBs titer of at least 100 IU/L is thought to be protective and reinfection rate can be further reduced by maintaining anti-HBs titers consistently above 500 IU/L[52] (Figure 1)[48].

LIVER TRANSPLANT OUTCOMES

Long-term survival following LT for viral hepatitis depends on prevention of allograft reinfection[53]. This is a well-known concept for HBV as well as HCV and can be applied for HDV related LT as well. LT for HDV started in the late 1980s from Europe. One of the earliest reporting was from Rizzetto *et al*[54] from Italy, on 7 patients who underwent LT due to HDV cirrhosis. It resulted in reinfection rate of 70% with HDV and milder forms of hepatitis were reported in 40% of the cases. This encouraged others to believe that LT was a feasible option for ESLD from HDV. Ottobrelli *et al*[55] reported a larger series of 22 patients, which showed 80% reinfection rate and 73% survival rate at one year. Although the reinfection rate was high, the clinical course was mild, therefore giving hope to the patients that LT was the possible cure for HDV. At that time, it was unclear whether administration of HBIG will be beneficial in preventing reinfection. Therefore, a multicenter study was done in Europe and amongst 110 patients who underwent LT due to HDV cirrhosis, the three-year actuarial risk of HBV recurrence after transplantation was reported as 70% ± 14% in the group who received no HBIG and 17% ± 6% in patients who received HBIG for > 6 mo[56]. The actuarial three-year survival was reported as 83%. In that study, long-term administration of HBIG (RR: 2.22; 95% confidence interval: 1.13-4.33; $P < 0.001$) and HDV superinfection (RR: 6.25; 95% confidence interval: 3.13-12.42; $P < 0.001$) were reported as independent predictors of better survival[56]. With the passage of time and development of new antivirals which when used in combination with HBIG, post-LT HBV/HDV reinfection has significantly decreased. In a retrospective study Adil *et al*[57] reported HBV recurrence rate of 5.1% and no HDV recurrence among 255 patients, after a mean follow-up of 30 mo. Similarly, study by Idilman *et al*[58] endorsed this, showing that amongst 90 patients with delta co-infection-related cirrhosis who underwent LT, only one recipient (who received lamivudine and HBIG combination), had HBV recurrence upon follow up. Moreover, in an another study with 104 HDV patients, with a longer follow up of 82 mo, the survival and HBV recurrence rates were 97% and 13.4% respectively[59]. Thus, it was confirmed that it is very important for survival and viability of the graft that the patients remain HBsAg-negative after transplantation.

Interestingly, studies have shown that presence of HDV infection appears to provide a protective effect against HBV reinfection in LT patients, possibly *via* suppression of HBV replication resulting in longer survival rates[49]. Recently a study published on LT patients in Brazil showed significantly higher 4-year survival rate of 95% in HDV group ($n = 29$), compared to 75% in HBV group ($n = 40$)[60]. One of the largest series involving hepatic transplantation in patients with HDV ($n = 76$), identified 88% survival after 5 years[61]. This is likely because of low HBV recurrence rate in these series.

HDV leading to HCC has also been treated with LT. Romeo *et al*[27] performed a retrospective study where 29 of 299 patients diagnosed with HBV/HDV had liver transplant; amongst these 29 patients, 10 patients (34%) had HCC. After transplant, 5

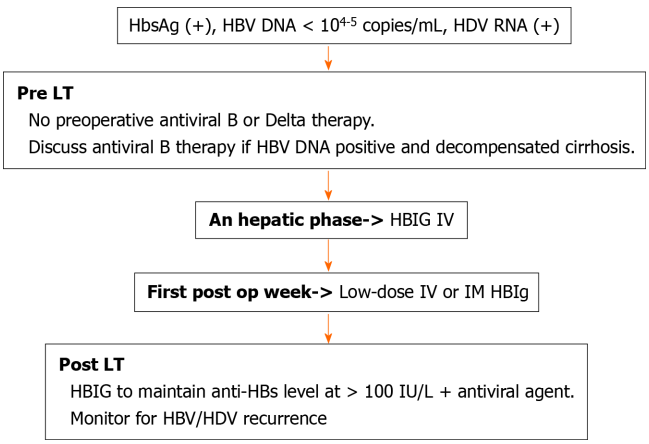

Figure 1 Possible treatment flowchart in hepatitis D virus liver transplant patients. HbsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; DNA: Deoxyribonucleic acid; RNA: Ribonucleic acid; HBIG: Hepatitis B immune globulin; LT: Liver transplantation.

patients died (3 with primary graft failure, 1 with tumor recurrence, and 1 with non-liver–cancer-related reasons). Similarly, a retrospective study was conducted in Turkey amongst 25 live donor LT recipients with chronic HBV/HDV, 11 of which had HCC. The cumulative 5-year survival was 74%. In the HCC group, 7 of 11 tumors matched the Milan criteria and 4 patients did not (in whom 2 patients had HCC recurrence after 2 years which was treated by ablation techniques)[32]. Thus, results from our review supports the AASLD guideline, that using HBIG in conjunction with oral antivirals post-transplantation, changes the natural history of the liver disease even among recipients with HCC.

CONCLUSION

HDV presents a severe health burden with liver transplantation as the only treatment for patients with End-stage Liver Disease, hepatocellular carcinoma, or fulminant hepatitis. Post transplantation reinfection with HDV/hepatitis B virus is an undesirable outcome as it affects survival. While transplant centers across the world have their own protocols, there is a consensus that hepatitis B immune globulin in combination with a potent nucleoside/nucleotide analogue have shown promising results. In the future, with the potential approval of the pipeline drugs for HDV treatment, their role in the post-transplant setting also needs to be explored. Currently, the data on liver transplant due to HDV is limited and more randomized controlled trials investigating the duration and frequency of hepatitis B immune globulin as well as the specific anti-HBs titer level are needed to optimize the pre- and post-transplant treatment plans.

REFERENCES

1 **Rizzetto M**, Canese MG, Aricò S, Crivelli O, Trepo C, Bonino F, Verme G. Immunofluorescence detection of new antigen-antibody system (delta/anti-delta) associated to hepatitis B virus in liver and in serum of HBsAg carriers. *Gut* 1977; **18**: 997-1003 [PMID: 75123 DOI: 10.1136/gut.18.12.997]

2 **Wang KS**, Choo QL, Weiner AJ, Ou JH, Najarian RC, Thayer RM, Mullenbach GT, Denniston KJ, Gerin JL, Houghton M. Structure, sequence and expression of the hepatitis delta (delta) viral genome. *Nature* 1986; **323**: 508-514 [PMID: 3762705 DOI: 10.1038/323508a0]

3 **Chang FL**, Chen PJ, Tu SJ, Wang CJ, Chen DS. The large form of hepatitis delta antigen is crucial for assembly of hepatitis delta virus. *Proc Natl Acad Sci USA* 1991; **88**: 8490-8494 [PMID: 1924308 DOI: 10.1073/pnas.88.19.8490]

4 **Wranke A**, Wedemeyer H. Antiviral therapy of hepatitis delta virus infection - progress and challenges towards cure. *Curr Opin Virol* 2016; **20**: 112-118 [PMID: 27792905 DOI: 10.1016/j.coviro.2016.10.002]

5 **Te H**, Doucette K. Viral hepatitis: Guidelines by the American Society of Transplantation Infectious Disease Community of Practice. *Clin Transplant* 2019; **33**: e13514 [PMID: 30817047 DOI: 10.1111/ctr.13514]

6 **Martins EB**, Glenn J. Prevalence of Hepatitis Delta Virus (HDV) Infection in the United States:

Results from an ICD-10 Review. *AASLD abstracts* 2017; **152**: S1085 [DOI: 10.1016/S0016-5085(17)33657-0]
7 **Farci P**, Niro GA. Clinical features of hepatitis D. *Semin Liver Dis* 2012; **32**: 228-236 [PMID: 22932971 DOI: 10.1055/s-0032-1323628]
8 **Wranke A**, Serrano BC, Heidrich B, Kirschner J, Bremer B, Lehmann P, Hardtke S, Deterding K, Port K, Westphal M, Manns MP, Cornberg M, Wedemeyer H. Antiviral treatment and liver-related complications in hepatitis delta. *Hepatology* 2017; **65**: 414-425 [PMID: 27770553 DOI: 10.1002/hep.28876]
9 **Yurdaydin C**. Treatment of chronic delta hepatitis. *Semin Liver Dis* 2012; **32**: 237-244 [PMID: 22932972 DOI: 10.1055/s-0032-1323629]
10 **Schweitzer A**, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. *Lancet* 2015; **386**: 1546-1555 [PMID: 26231459 DOI: 10.1016/S0140-6736(15)61412-X]
11 **Hughes SA**, Wedemeyer H, Harrison PM. Hepatitis delta virus. *Lancet* 2011; **378**: 73-85 [PMID: 21511329 DOI: 10.1016/S0140-6736(10)61931-9]
12 **Chen HY**, Shen DT, Ji DZ, Han PC, Zhang WM, Ma JF, Chen WS, Goyal H, Pan S, Xu HG. Prevalence and burden of hepatitis D virus infection in the global population: a systematic review and meta-analysis. *Gut* 2019; **68**: 512-521 [PMID: 30228220 DOI: 10.1136/gutjnl-2018-316601]
13 **Wedemeyer H**, Manns MP. Epidemiology, pathogenesis and management of hepatitis D: update and challenges ahead. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 31-40 [PMID: 20051970 DOI: 10.1038/nrgastro.2009.205]
14 **Wedemeyer H**, Heidrich B, Manns MP. Hepatitis D virus infection--not a vanishing disease in Europe! *Hepatology* 2007; **45**: 1331-1332; author reply 1332 [PMID: 17464980 DOI: 10.1002/hep.21590]
15 **Cross TJ**, Rizzi P, Horner M, Jolly A, Hussain MJ, Smith HM, Vergani D, Harrison PM. The increasing prevalence of hepatitis delta virus (HDV) infection in South London. *J Med Virol* 2008; **80**: 277-282 [PMID: 18098143 DOI: 10.1002/jmv.21078]
16 **Radjef N**, Gordien E, Ivaniushina V, Gault E, Anaïs P, Drugan T, Trinchet JC, Roulot D, Tamby M, Milinkovitch MC, Dény P. Molecular phylogenetic analyses indicate a wide and ancient radiation of African hepatitis delta virus, suggesting a deltavirus genus of at least seven major clades. *J Virol* 2004; **78**: 2537-2544 [PMID: 14963156 DOI: 10.1128/jvi.78.5.2537-2544.2004]
17 **Kushner T**, Serper M, Kaplan DE. Delta hepatitis within the Veterans Affairs medical system in the United States: Prevalence, risk factors, and outcomes. *J Hepatol* 2015; **63**: 586-592 [PMID: 25962883 DOI: 10.1016/j.jhep.2015.04.025]
18 **Njei B**, Do A, Lim JK. Prevalence of hepatitis delta infection in the United States: National Health and Nutrition Examination Survey, 1999-2012. *Hepatology* 2016; **64**: 681-682 [PMID: 26453027 DOI: 10.1002/hep.28279]
19 **Patel EU**, Thio CL, Boon D, Thomas DL, Tobian AAR. Prevalence of Hepatitis B and Hepatitis D Virus Infections in the United States, 2011-2016. *Clin Infect Dis* 2019; **69**: 709-712 [PMID: 30605508 DOI: 10.1093/cid/ciz001]
20 **Kucirka LM**, Farzadegan H, Feld JJ, Mehta SH, Winters M, Glenn JS, Kirk GD, Segev DL, Nelson KE, Marks M, Heller T, Golub ET. Prevalence, correlates, and viral dynamics of hepatitis delta among injection drug users. *J Infect Dis* 2010; **202**: 845-852 [PMID: 20701536 DOI: 10.1086/655808]
21 **Gish RG**, Yi DH, Kane S, Clark M, Mangahas M, Baqai S, Winters MA, Proudfoot J, Glenn JS. Coinfection with hepatitis B and D: epidemiology, prevalence and disease in patients in Northern California. *J Gastroenterol Hepatol* 2013; **28**: 1521-1525 [PMID: 23574043 DOI: 10.1111/jgh.12217]
22 **Abbas Z**, Afzal R. Life cycle and pathogenesis of hepatitis D virus: A review. *World J Hepatol* 2013; **5**: 666-675 [PMID: 24409335 DOI: 10.4254/wjh.v5.i12.666]
23 **Negro F**. Hepatitis D virus coinfection and superinfection. *Cold Spring Harb Perspect Med* 2014; **4**: a021550 [PMID: 25368018 DOI: 10.1101/cshperspect.a021550]
24 **Caredda F**, Rossi E, d'Arminio Monforte A, Zampini L, Re T, Meroni B, Moroni M. Hepatitis B virus-associated coinfection and superinfection with delta agent: indistinguishable disease with different outcome. *J Infect Dis* 1985; **151**: 925-928 [PMID: 3989325 DOI: 10.1093/infdis/151.5.925]
25 **Rajaram P**, Subramanian R. Acute Liver Failure. *Semin Respir Crit Care Med* 2018; **39**: 513-522 [PMID: 30485882 DOI: 10.1055/s-0038-1673372]
26 **Rizzetto M**, Verme G, Recchia S, Bonino F, Farci P, Aricò S, Calzia R, Picciotto A, Colombo M, Popper H. Chronic hepatitis in carriers of hepatitis B surface antigen, with intrahepatic expression of the delta antigen. An active and progressive disease unresponsive to immunosuppressive treatment. *Ann Intern Med* 1983; **98**: 437-441 [PMID: 6340574 DOI: 10.7326/0003-4819-98-4-437]
27 **Romeo R**, Del Ninno E, Rumi M, Russo A, Sangiovanni A, de Franchis R, Ronchi G, Colombo M. A 28-year study of the course of hepatitis Delta infection: a risk factor for cirrhosis and hepatocellular carcinoma. *Gastroenterology* 2009; **136**: 1629-1638 [PMID: 19208358 DOI: 10.1053/j.gastro.2009.01.052]
28 **Jemal A**, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69-90 [PMID: 21296855 DOI: 10.3322/caac.20107]
29 **Fattovich G**, Giustina G, Christensen E, Pantalena M, Zagni I, Realdi G, Schalm SW. Influence of hepatitis delta virus infection on morbidity and mortality in compensated cirrhosis type B. The European Concerted Action on Viral Hepatitis (Eurohep). *Gut* 2000; **46**: 420-426 [PMID: 10673308

DOI: 10.1136/gut.46.3.420]
30 **Botelho-Souza LF**, Vasconcelos MPA, Dos Santos AO, Salcedo JMV, Vieira DS. Hepatitis delta: virological and clinical aspects. *Virol J* 2017; **14**: 177 [PMID: 28903779 DOI: 10.1186/s12985-017-0845-y]
31 **Sánchez-Tapias JM**, Mas A, Costa J, Bruguera M, Mayor A, Ballesta AM, Compernolle C, Rodés J. Recombinant alpha 2c-interferon therapy in fulminant viral hepatitis. *J Hepatol* 1987; **5**: 205-210 [PMID: 3693864 DOI: 10.1016/s0168-8278(87)80574-3]
32 **Öcal S**, Korkmaz M, Harmancı Ö, Ensaroğlu F, Akdur A, Selçuk H, Moray G, Haberal M. Hepatitis B- and hepatitis D-virus-related liver transplant: single-center data. *Exp Clin Transplant* 2015; **13** Suppl 1: 133-138 [PMID: 25894142]
33 **Su CW**, Huang YH, Huo TI, Shih HH, Sheen IJ, Chen SW, Lee PC, Lee SD, Wu JC. Genotypes and viremia of hepatitis B and D viruses are associated with outcomes of chronic hepatitis D patients. *Gastroenterology* 2006; **130**: 1625-1635 [PMID: 16697726 DOI: 10.1053/j.gastro.2006.01.035]
34 **Romeo R**, Foglieni B, Casazza G, Spreafico M, Colombo M, Prati D. High serum levels of HDV RNA are predictors of cirrhosis and liver cancer in patients with chronic hepatitis delta. *PLoS One* 2014; **9**: e92062 [PMID: 24658127 DOI: 10.1371/journal.pone.0092062]
35 **Abbas Z**, Abbas M, Abbas S, Shazi L. Hepatitis D and hepatocellular carcinoma. *World J Hepatol* 2015; **7**: 777-786 [PMID: 25914778 DOI: 10.4254/wjh.v7.i5.777]
36 **Mahale P**, Aka P, Chen X, Pfeiffer RM, Liu P, Groover S, Mendy M, Njie R, Goedert JJ, Kirk GD, Glenn JS, O'Brien TR. Hepatitis D virus infection, cirrhosis and hepatocellular carcinoma in The Gambia. *J Viral Hepat* 2019; **26**: 738-749 [PMID: 30661282 DOI: 10.1111/jvh.13065]
37 **Food and Drug Administration**. Chronic Hepatitis D Virus Infection: Developing Drugs for Treatment Guidance for Industry 2019 [cited March 7, 2021]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/chronic-hepatitis-d-virus-infection-developing-drugs-treatment-guidance-industry.
38 **Terrault NA**, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RS Jr, Bzowej NH, Wong JB. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018; **67**: 1560-1599 [PMID: 29405329 DOI: 10.1002/hep.29800]
39 **European Association for the Study of the Liver**. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; **67**: 370-398 [PMID: 28427875 DOI: 10.1016/j.jhep.2017.03.021]
40 **Alavian SM**, Tabatabaei SV, Behnava B, Rizzetto M. Standard and pegylated interferon therapy of HDV infection: A systematic review and meta- analysis. *J Res Med Sci* 2012; **17**: 967-974 [PMID: 23825999]
41 **Abbas Z**, Khan MA, Salih M, Jafri W. Interferon alpha for chronic hepatitis D. *Cochrane Database Syst Rev*2011: CD006002 [PMID: 22161394 DOI: 10.1002/14651858.CD006002.pub2]
42 **Castelnau C**, Le Gal F, Ripault MP, Gordien E, Martinot-Peignoux M, Boyer N, Pham BN, Maylin S, Bedossa P, Dény P, Marcellin P, Gault E. Efficacy of peginterferon alpha-2b in chronic hepatitis delta: relevance of quantitative RT-PCR for follow-up. *Hepatology* 2006; **44**: 728-735 [PMID: 16941695 DOI: 10.1002/hep.21325]
43 **Mentha N**, Clément S, Negro F, Alfaiate D. A review on hepatitis D: From virology to new therapies. *J Adv Res* 2019; **17**: 3-15 [PMID: 31193285 DOI: 10.1016/j.jare.2019.03.009]
44 **Wedemeyer H**, Yurdaydin C, Dalekos GN, Erhardt A, Çakaloğlu Y, Değertekin H, Gürel S, Zeuzem S, Zachou K, Bozkaya H, Koch A, Bock T, Dienes HP, Manns MP; HIDIT Study Group. Peginterferon plus adefovir *vs* either drug alone for hepatitis delta. *N Engl J Med* 2011; **364**: 322-331 [PMID: 21268724 DOI: 10.1056/NEJMoa0912696]
45 **Wedemeyer H**, Yurdaydin C, Hardtke S, Caruntu FA, Curescu MG, Yalcin K, Akarca US, Gürel S, Zeuzem S, Erhardt A, Lüth S, Papatheodoridis GV, Keskin O, Port K, Radu M, Celen MK, Idilman R, Weber K, Stift J, Wittkop U, Heidrich B, Mederacke I, von der Leyen H, Dienes HP, Cornberg M, Koch A, Manns MP; HIDIT-II study team. Peginterferon alfa-2a plus tenofovir disoproxil fumarate for hepatitis D (HIDIT-II): a randomised, placebo controlled, phase 2 trial. *Lancet Infect Dis* 2019; **19**: 275-286 [PMID: 30833068 DOI: 10.1016/S1473-3099(18)30663-7]
46 **Glenn JS**, Watson JA, Havel CM, White JM. Identification of a prenylation site in delta virus large antigen. *Science* 1992; **256**: 1331-1333 [PMID: 1598578 DOI: 10.1126/science.1598578]
47 **Yurdaydin C**, Keskin O, Kalkan Ç, Karakaya F, Çalişkan A, Karatayli E, Karatayli S, Bozdayi AM, Koh C, Heller T, Idilman R, Glenn JS. Optimizing lonafarnib treatment for the management of chronic delta hepatitis: The LOWR HDV-1 study. *Hepatology* 2018; **67**: 1224-1236 [PMID: 29152762 DOI: 10.1002/hep.29658]
48 **Roche B**, Samuel D. Liver transplantation in delta virus infection. *Semin Liver Dis* 2012; **32**: 245-255 [PMID: 22932973 DOI: 10.1055/s-0032-1323630]
49 **Rifai K**, Wedemeyer H, Rosenau J, Klempnauer J, Strassburg CP, Manns MP, Tillmann HL. Longer survival of liver transplant recipients with hepatitis virus coinfections. *Clin Transplant* 2007; **21**: 258-264 [PMID: 17425755 DOI: 10.1111/j.1399-0012.2006.00636.x]
50 **Cholongitas E**, Papatheodoridis GV. High genetic barrier nucleos(t)ide analogue(s) for prophylaxis from hepatitis B virus recurrence after liver transplantation: a systematic review. *Am J Transplant* 2013; **13**: 353-362 [PMID: 23137006 DOI: 10.1111/j.1600-6143.2012.04315.x]
51 **Chun J**, Kim W, Kim BG, Lee KL, Suh KS, Yi NJ, Park KU, Kim YJ, Yoon JH, Lee HS. High viremia, prolonged Lamivudine therapy and recurrent hepatocellular carcinoma predict posttransplant hepatitis B recurrence. *Am J Transplant* 2010; **10**: 1649-1659 [PMID: 20642687 DOI:

10.1111/j.1600-6143.2010.03162.x]
52 **de Villa VH**, Chen YS, Chen CL. Hepatitis B core antibody-positive grafts: recipient's risk. *Transplantation* 2003; **75**: S49-S53 [PMID: 12589141 DOI: 10.1097/01.tp.0000047006.96782.64]
53 **Muhammad H**, Hammami MB, Ting PS, Simsek C, Saberi B, Gurakar. Can HCV Viremic Organs Be Used in Liver Transplantation to HCV Negative Recipients? *OBM Hepatol and Gastroenterol* 2020; **4** [DOI: 10.21926/obm.hg.2002046]
54 **Rizzetto M**, Macagno S, Chiaberge E, Verme G, Negro F, Marinucci G, di Giacomo C, Alfani D, Cortesini R, Milazzo F. Liver transplantation in hepatitis delta virus disease. *Lancet* 1987; **2**: 469-471 [PMID: 2887774 DOI: 10.1016/s0140-6736(87)91789-2]
55 **Ottobrelli A**, Marzano A, Smedile A, Recchia S, Salizzoni M, Cornu C, Lamy ME, Otte JB, De Hemptinne B, Geubel A. Patterns of hepatitis delta virus reinfection and disease in liver transplantation. *Gastroenterology* 1991; **101**: 1649-1655 [PMID: 1955130 DOI: 10.1016/0016-5085(91)90404-9]
56 **Samuel D**, Muller R, Alexander G, Fassati L, Ducot B, Benhamou JP, Bismuth H. Liver transplantation in European patients with the hepatitis B surface antigen. *N Engl J Med* 1993; **329**: 1842-1847 [PMID: 8247035 DOI: 10.1056/nejm199312163292503]
57 **Adil B**, Fatih O, Volkan I, Bora B, Veysel E, Koray K, Cemalettin K, Burak I, Sezai Y. Hepatitis B Virus and Hepatitis D Virus Recurrence in Patients Undergoing Liver Transplantation for Hepatitis B Virus and Hepatitis B Virus Plus Hepatitis D Virus. *Transplant Proc* 2016; **48**: 2119-2123 [PMID: 27569956 DOI: 10.1016/j.transproceed.2016.02.076]
58 **Idilman R**, Akyildiz M, Keskin O, Gungor G, Yilmaz TU, Kalkan C, Dayangac M, Cinar K, Balci D, Hazinedaroglu S, Tokat Y. The long-term efficacy of combining nucleos(t)ide analog and low-dose hepatitis B immunoglobulin on post-transplant hepatitis B virus recurrence. *Clin Transplant* 2016; **30**: 1216-1221 [PMID: 27409074 DOI: 10.1111/ctr.12804]
59 **Serin A**, Tokat Y. Recurrence of Hepatitis D Virus in Liver Transplant Recipients With Hepatitis B and D Virus-Related Chronic Liver Disease. *Transplant Proc* 2019; **51**: 2457-2460 [PMID: 31405744 DOI: 10.1016/j.transproceed.2019.01.163]
60 **Lima DS**, Murad Júnior AJ, Barreira MA, Fernandes GC, Coelho GR, Garcia JHP. LIVER TRANSPLANTATION IN HEPATITIS DELTA: SOUTH AMERICA EXPERIENCE. *Arq Gastroenterol* 2018; **55**: 14-17 [PMID: 29561969 DOI: 10.1590/S0004-2803.201800000-06]
61 **Samuel D**, Zignego AL, Reynes M, Feray C, Arulnaden JL, David MF, Gigou M, Bismuth A, Mathieu D, Gentilini P. Long-term clinical and virological outcome after liver transplantation for cirrhosis caused by chronic delta hepatitis. *Hepatology* 1995; **21**: 333-339 [PMID: 7843702 DOI: 10.1002/hep.1840210211]

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