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Management of liver diseases: Current perspectives

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Abstract

There is increasing incidence and prevalence of acute and chronic liver diseases all over the world which influence the quality of life and can give rise to life threatening complications. The burden of advanced liver disease due to hepatitis B has been controlled by antivirals but its eradication is difficult soon. Highly effective directly acting antiviral therapy has reduced the burden of hepatitis C but is partially offset by increasing IV drug abuse. Non alcoholic fatty liver disease pandemic is on and there is recent alarming increase in alcohol related liver disease, both of which have no drug cure apart from control of the risk factors. Genetic factors have been identified in progression of all forms of chronic liver disease (CLD). Due to better management of complications of CLD, the life span of patients have increased spiking the number of hepatocellular carcinoma (HCC) and patients needing liver transplantation (LT). The present SARS-CoV pandemic has affected the outcome CLD including LT in addition to causing acute hepatitis. Better diagnostics and therapeutics are available for liver fibrosis, portal hypertension, HCC and post LT management and many drugs are under trial. The present review summarises the current scenario of the epidemiology and the advances in diagnosis and treatment of liver diseases including their complications like portal hypertension, HCC and LT.

Key Words: Chronic liver disease, genes, biomarkers, therapy, hepatocellular carcinoma, liver transplantation, recent advances

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Core Tip: The incidence and prevalence of liver disease is rising all over the world. Hepatitis B is difficult to eradicate and the benefit of DAA for hepatitis C is partially offset by increasing IV drug abuse. NAFLD pandemic is on and ALD is rising alarmingly, both having no drug cure. COVID 19 has affected the outcome of liver diseases. Due to better management of complications, patients of CLD are living longer spiking the number of HCC and patients needing LT. Better diagnostics and therapeutics are available for fibrosis, portal hypertension, HCC and post LT management which are discussed.

INTRODUCTION

CLD and cirrhosis pose substantial health burden worldwide. In the period 2007 – 2017, the age standardised prevalence increased 10.4% with 1.5 billion cases in 2017^[1]. Of the four chief etiology, HBV and HCV burden still remains high (though decreased due to availability of vaccination for HBV and DAA for HCV) although with the NAFLD pandemic and increasing global alcohol consumption, they are fast catching up. NAFLD is the leading cause in developed nations, it is also gradually becoming important in newly developed nations like India, China^[2,3]. The age standardised prevalence of HBV/HCV related CLD rose by 9%/10.2% in the last decade whereas for NAFLD it was 23.5%^[1]. The high HBV and HCV burden is mostly due to poor diagnostic coverage and linkage to treatment and care of the susceptible population.

HBV

The HBV pool is chiefly contributed to by the Western Pacific and Sub-Saharan Africa region (mostly tribals) and some Southeast Asian countries (China, Vietnam, Thailand, Laos) where the load remains high despite the success of HBV vaccination programme at birth. It is the leading cause of HCC in these countries^[4]. Among some developed and

newly developing nations where prevalence is intermediate to low, its burden is contributed by the indigenous tribal population like India, Australia^[5,6] maintained through intracaste marriages, close living, tribal customs, illiteracy and poor access to health care resources. With the present attrition rate (present burden of 296 million from 350 million 3 decades back and present annual mortality of 8 Lakh and addition of 1.5 million cases in 2019^[7]), it is still a long way for natural elimination of the pool. In future some redistribution is also likely due to population migration from high to low endemicity regions. WHO's ambitious programme for eradication of HBV by 2030 therefore incorporate the best preventive measures i.e. (i) increase vaccination at birth (ii) prevent vertical and horizontal transmission among toddlers by treating at risk mothers, (iii) scale up screening, care and treatment services. Curative treatment is difficult and < 20% who receive the currently approved drugs (interferon, NA or combination as sequential/add on/switch therapy) achieve loss of HBsAg (functional cure). Combination strategies are less cost effective than first line NA monotherapy although this may lead to more HBsAg loss in some subgroup of HBV patients^[8]. Even with long term NA monotherapy (Tenofovir disoproxil for 5 years) half fail to achieve fibrosis regression^[9] and there is high relapse rate in e negative patients (RETRACT B study showing relapse rate of 47.8% at 6 mo, 68.9% at 12 mo, 83.4% at 48 mo)^[10]. The other problem is the risk of relapse in previously exposed person or inactive HBsAg carriers (who constitute a sizable majority of the present pool not requiring drug therapy) needing immunosuppression or cancer chemotherapy. Fortunately, highly active antivirals are capable of controlling the virus and reducing the burden of advanced liver disease from HBV. The chief impediments to HBV functional cure are (i) intrahepatic viral reservoir cccDNA with integrated sequencing, (ii) high HBsAg levels, (iii) defective host innate and adaptive immune responses. Newer strategies target these e.g. (1) targeting HBV life cycle without damaging hepatocyte by inhibiting ccc DNA replenishment pathways or degrading them by (a) entry inhibitors like Bulevirtide (used for HBV/HDV coinfection including post LT), nucleic acid polymer assembly inhibitors (Lonafarnib) , CRISPR/Cas9 protein base editors (DNA endonucleases), si

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RNAs, core protein modulators (Morphothiadin, Vebicorvir, Bersacapavir) and antisense oligonucleotide (Bepirovirsen), [2] immunomodulation to safely eliminate infected cells. Potential targets in innate immune response pathway include pathogen recognition receptors [Toll-like receptors 7/8, retinoic acid-inducible gene (RIG)-1-like receptors and nucleotide-binding oligomerization domain (NOD)-like receptors], natural killer cells and antigen presenting cells (dendritic cells and Kupffer cells) whereas in adaptive immune response pathway, it includes modulation of HBV-specific CD4+ and CD8+ T cell (especially the relative functional and numerical deficiency of CD8+ T-cells by PD-1 checkpoint inhibitors), regulatory T cell, HBV-specific T and B cell (autologous, engineered or by vaccine).

HCV

Gratifying results have been obtained with the introduction of affordable short term (3-6 mo) DAA therapy for HCV (with sustained viral response rates of >95%, decreased fibrosis and HCC) with increasing treatment coverage in newly developed and developing nations which have decreased the HCV burden to 58 million as of 2019[7]. HCV still remains the leading cause of HCC in the developed world (Western countries, Japan) though ALD/NAFLD are fast taking the lead due to treatment with DAA. But challenges still remain like limited drug availability, interaction with other drugs used to treat comorbidities (HIV, coronary artery disease and hyperlipidemia), inability to afford even the low drug cost by patients who pay from their own pocket and increasingly recognized metabolic dysfunctions associated with hepatitis C. Even in Denmark, 50% HCV patients are yet to attend specialist care especially IV drug users[11]. HIV coinfection is also a deterrent for good treatment outcome for both HBV and HCV. In future the HCV pool is likely to be maintained by intravenous drug users and the increasing population with drug/alcohol abuse and other psychiatric disorders, those needing repeated blood transfusion (for haematological disorders, hemodialysis) and reinfection in those who continue to have risk factors even after cure by DAA. WHO recommends increased access to treatment [i] by onsite diagnosis by dried blood spot

and initiating treatment at point of care and [ii] by trained non specialist doctors and nurses at harm reduction centres.

NAFLD

NAFLD is the most common liver disease worldwide affecting about a quarter population with regional differences^[12]. It is fast becoming the leading cause of cirrhosis in developed nations. Genetic inheritance (25–34%), ancestry (Hispanic American/ Asian/ Indian > European > African American), advancing age and male sex are non modifiable whereas obesity (especially central), diabetes mellitus, hyperlipidemia and insulin resistance are modifiable risk factors. There is currently no approved pharmacological therapy for NAFLD apart from those treating the risk factors. Weight loss through dietary alteration, physical exercises and bariatric surgery leads to improved liver histology but only small percentage of ¹patients can achieve and maintain the degree of weight loss needed for sustaining the benefit and 50% fail to improve histology^[13]. UDCA/OCA, Vitamin E have no proven benefit. Therefore it is the hottest area of newer drug research which modulate key metabolic, inflammatory, and fibrogenic pathway. Pan PPAR agonists [Lanifibranor], GLP 1 agonists [Semaglutide], CCR 5 inhibitors [Leronlimab], thyroid hormone receptor agonist [Resmetirom] and hepatic SCD1 inhibitor [Aramchol] are in phase 2 and 3 clinical trial [Table]. Other antifibrotic and disease modifying agents as well as genetic factors are discussed below. But considering the multiple risk factors and complex pathophysiology, it is unlikely that a panacea will be discovered soon.

ALCOHOL

Approximately 2 billion people worldwide consume alcohol of whom 283 million suffer from AUD^[14]. ALD is most prevalent in the western world and in some affluent Asian countries (South Korea, Japan) though there is increasing global trend especially in newly industrialised southeast Asian nations (China, India, Vietnam, Thailand) where it was low due to traditional “dry” culture. ALD has become the leading cause of CLD/cirrhosis in India ^[5]. The recent COVID-19 pandemic has significantly increased the incidence of ALD in young adults. ²DALYs per 1,000 people due to ALD was highest

in India (2356.4), followed by the US (467.9), China (466.3), Nigeria (424.5) and Indonesia (365.1). For alcohol related liver cancer, DALYs were highest for China followed by Vietnam, Russia, Thailand, India^[15]. Consumption depends on age, sex, religion, culture, health status and national income distribution. Globally it is a tussle between national income from alcohol retail *vs* health expenditure for AUD, the latter being dismal even in developed nations. Being a fully preventable disease, WHO's "best buys" are the most cost effective ways for prevention. i.e. increasing taxation⁴ on alcoholic beverages, enforcing bans or comprehensive restrictions on exposure to alcohol advertising and restricting physical availability of retailed alcohol. A recent global study shows no safe dose for alcohol^[16]. Abstinence can reverse fatty liver and halt the progression of CLD. It is responsible for 50% of deaths due to CLD because no specific drug therapy is available apart from some short term benefit of steroids in pure acute hepatitis. Tumour necrosis factor alpha, growth hormone, pentoxifylline and antioxidants at best show mixed results from highly variable to weak, efficacy depending on the stage of disease. The unclear molecular mechanism of disease deter identifying treatment target and disincetivize drug development. Naltrexone, disulfiram and acamprosate helps to decrease addiction. Obesity and cigarette smoking are known risk factors so weight control and quitting smoking are routinely encouraged². A poor overall nutritional status (protein calorie malnutrition, micronutrient deficiencies) often accompanies ALD and correlates positively with the development of serious complications hence a well-conceived nutrition support by oral, enteral, and parenteral routes is an essential part of standard care. Recent evidence also strongly implicates intestinal dysbiosis in ALD progression. These targets are being addressed by trials of probiotics, fecal microbiota transplantation, growth factors (granulocyte colony stimulating factor, bovine colostrum), antioxidants (w5 and synthetic fatty acids, S-adenosyl methionine + choline, N-Acetyl cysteine, vitamin C), in addition to liver regenerative biologics and device assisted behavioural alteration^[17]. The other hindrances are disease stratification for early identification when it is most reversible, monitoring abstinence (as recidivism is high) and identifying risky drinking

behaviour like binges. Various biomarkers under study for this purpose include ² circulating small noncoding RNAs (miRNAs), long noncoding RNAs (lncRNAs), selective cytokines profiles, phosphatidyl ethanol and urine ethyl glucuronide and ethyl sulphate^[18-21].

AUTOIMMUNE LIVER DISEASE

Autoimmune hepatitis appears to be increasing in incidence as a part of the general increase in immune mediated and allergic diseases resulting from decreasing infectious disease with mounting antibiotics use globally. Some antibiotics like nitrofurantoin, minocycline and coamoxyclav can induce autoimmune hepatitis by themselves and some antibiotic associated DILI may resemble autoimmune hepatitis. The standard treatment of autoimmune hepatitis is with steroids with/without azathioprine. Mycophenolate mofetil is a second line drug. Substantial advances in treatment of autoimmune cholangiopathies has been achieved with PPAR α agonist bezafibrate, FXR agonist OCA and recombinant FGF 19 (which alter bile acid synthesis along with antifibrogenic effect^[22], see below) and drugs inhibiting intestinal apical sodium-dependent bile acid transporter (lincicibat, maralixibat, odevixibat)^[23]. in addition to bile acid resins and UDCA. Combinations of such enterohepatic with cholehepatic and/or anti-fibrotic drugs could result in synergistic/additive effects in decreasing the fibrosis along with the pruritus.

ADVANCES IN DIAGNOSIS

Non invasive biomarkers of CLD (patented ones like fibrotest, fibrometer, Hepascore, ELF model and non patented ones like FIB 4 index, APRI, BARD, NFS) and elastography (fibroscan, MRE, point SWE, 2D-SWE, 3D Velacur™) or their combination (MEFIB, MAST FAST) have been investigated across the whole spectrum of NAFLD to delineate the stage as well as correlating genes with liver fat, enzymes and fibrosis^[24]. Novel ones like CT scan with objective measures of liver nodularity and shunts, multiparametric MRI [iron corrected T1, cT1], extracellular vesicles, microbiome (stool microbial profiles), biomarker for extracellular matrix remodelling (TGF- β , MMP,

TIMP)^[25-27] are being investigated. Graph convolution networks (a deep learning technique) is being tested for quantitative assessment of fibrosis^[28].

GENETIC FACTORS IN CLD

Genetic factors are important in progression of all forms of CLD (ALD, NAFLD, metabolic associated fatty liver disease, chronic hepatitis) including HCC with interplay of genes involved in glucose, lipid and iron metabolism, insulin signalling, oxidative stress, inflammatory pathways and fibrogenesis. Most reliable fatty liver genes include PNPLA3, TM6SF2, HSD17B13, GCKR and MBOAT7 (associated with increased liver fat, NASH, cirrhosis, HCC). The evidence for others like MARC1, GPAM, APOE, ALDH1B, PCKS7, SERPINA1, HNF1A etc are less robust. Rare variants like APOB and MTTP are associated with an increased risk of fat accumulation leading to HCC while protecting at the same time against dyslipidemia and cardiovascular risk^[24]. Polygenetic risk score [with/without clinical risk markers] are being investigated to stratify disease risk *e.g.* PNPLA3 and TM6SF2 can become a reason for HCC surveillance whilst giving protection from cardiovascular complications^[29] It can also help in proper drug selection. Genetic therapies in CLD include gene silencing approaches (PNPLA3, HSD17B13), CRISPR/Cas9-based approaches^[30] (which alter responsible genes) and modulating genes involved in liver regeneration.

ACUTE HEPATITIS

The etiology of acute liver failure (in those with normal liver) varies in different countries at different times. Most commonly these include viruses (Hepatitis A, B and E), DILI (CAM, anti tuberculous drugs, paracetamol, anticonvulsants, antibiotics), toxins (herbs, alcohol) and autoimmune flares; else these may precipitate acute liver failure in those with CLD (ACLF). HEV may be associated with fulminant course in pregnancy. In tropical areas, malaria, dengue, enteric fever, leptospirosis and scrub typhus may also cause acute hepatitis. Traditionally Wilson disease and autoimmune hepatitis has been considered to cause acute liver failure but in adults majority of such acute flares occur on background CLD. Most acute hepatitis of viral etiology recover by themselves and of drug/toxin on their discontinuation, some DILI may need

corticosteroid (especially those resembling autoimmune hepatitis). Bacterial infections respond to antibiotics. But the course of ACLF depends on the stage of the background CLD and the precipitating cause, alcohol having the worst outcome^[31,32]. Undefined number of acute hepatitis are occurring recently due to COVID 19 infection, recreational drugs and alcohol.

PORTAL HYPERTENSION AND LIVER FIBROSIS

With the increasing prevalence of CLD, portal hypertension and its complications are also increasing. Refractory ascites/HRS/hydrothorax are now being better managed with terlipressin, noradrenaline, midodrine, octreotide and long-term albumin supplementation (with its newly discovered wider pleiotropic non-oncotic properties positively impacting decompensated CLD). SGLT 2 inhibitors and Alfa pump are under trial. Endohepatology (the application of endoscopic ultrasound in liver disease treatment)^[33] has brought about dramatic improvement in the treatment of variceal bleed by better delineation of collaterals and guided treatment (coiling, balloon retrograde transvenous occlusion of collaterals, glue injection in gastric varix), directed liver biopsy, portal pressure gradient measurement and deployment of dedicated esophageal stents. Pre emptive transjugular intrahepatic portasystemic shunt has been used for uncontrollable ascites or variceal bleed.

Fibrosis in the liver is caused by activated HSC whose biology connects damage, regeneration and cancer. Severe hepatic fibrosis represses regeneration and accumulation of senescent HSCs creates a pro-inflammatory, pro-fibrotic environment. Fibrogenesis inhibitor drugs resolve inflammation, cause loss of activated myofibroblasts, and ECM degradation Those under investigation (Table) include [FXR agonist OCA/cilofexor, acetyl-coenzyme A carboxylase inhibitor Firsocostat, ASK-1 inhibitor Selonsertib, CCR 2/5 inhibitor Cenicriviroc, FGF 19 analog Aldafermin/21 analogue Pegbelfermin, PPAR α/δ agonist Elafibranor, PPAR γ agonist pioglitazone, PPAR α/γ agonist Saroglitazar, galectin 3 inhibitor Belapectin, CB1 antagonist Rimonabant, ECM production inhibitors like TIMP and MMP, Lysyl oxidase 2 inhibitor Simtuzumab, HSP 47 inhibitor Pirfenidone, pan caspase inhibitor Emricasan and anti

inflammatory lipids derivatives of PUFA (lipoxins, resolvins, protectins, and maresins)]^[34-36]. Statins have been found to have beneficial effect in halting the progress of CLD^[37].

HCC

The chief cause of HCC in the West is hepatitis C followed by NAFLD and alcohol whereas it is hepatitis B in Asia and Africa. 80% occur in low and middle resource countries. Screening programme for HCC in cirrhotics is cost effective and better cancer surveillance can be achieved by the recently developed GALAD (incorporating AFP, AFP-L3, PIVKA, age and sex) screening tool^[38] along with radiologic strategies (contrast enhanced ultrasonogram using LI-RADS, Multiphasic CT/aMRI scan) every 6 mo in high risk patients. 90% HCC occur on background CLD which pose additional health risk to HCC itself. Liver biopsy carries risk hence liquid biopsy using detection of circulating tumor cells specific to HCC, mutation or methylation of circulating tumor DNA, and transcriptomic profiling of extracellular vesicles are promising. The widely followed BCLC staging system have been upgraded (to be more inclusive for surgery with/without downgrading of tumor) and provide better platform for optimal use of different treatment modalities like ablation, resection, LT, stereotactic body radiation, locoregional and systemic therapy. LT has been extended outside Milan criteria to include more patients by various expanded selection criteria with reduced but excellent long term results^[39]. Cancer in non cirrhotic liver is treated by LT with better understanding of transplant oncology. Newer drugs like multikinase inhibitors (Lenvatinib, Regorafenib, Cabozantinib, Ramucirumab), checkpoint inhibitors (atezolizumab, bevacizumab, durvalumab, pembrolizumab, nivolumab, ipilimumab and tremelimumab) are now available over sorafenib for systemic therapy with better outcome ^[40]. Limitations are their unclear safety profile in Child Pugh stage B, best response not more than 50%, unclear treatment sequence and use in early stage of tumor.

LT

ALD is now the predominant cause for LT followed by HCV and NAFLD in the West^[41] whereas it is still HBV/HCV in the East with ALD at its heels^[42]. With good patient selection, the present 1 year survival is 90% and 5 year of 70%. Good outcome has been substantially influenced by betterment of surgical techniques, perioperative management, organ preservation (normothermic machine perfusion), recipient selection (through organ sharing network), post transplant immunosuppressive management and of viral etiology (DAA for HCV. Bulevirtide/NA for HBV/HDV). The challenge of limited organ availability has been addressed by accepting marginal and extended criteria donors (donors of cardiac death, 30% - 60% steatotic explant liver without inflammation, HBsAg and HCV positive donors), split liver grafts and live donor transplant especially in Asia^[41]. Liver regeneration based approaches like stem cell therapy and organ bioengineering can also help. Most post transplant morbidity arise from prolonged use of immunosuppressive with resultant infections, hypertension, dyslipidemia, cardiovascular events, renal failure, malignancy and chronic organ rejection. Long term outcome can be improved by minimising/Late introduction of standard IS or withdrawing it completely (20% become operationally tolerant) and using less toxic IS drugs (mToR inhibitors, interleukin 2 receptor blockers). With increased understanding of transplant immunology, research is on whether IS can be completely withdrawn after finite treatment by modulating recipient immunity (by CD4 Treg cells, regulatory dendritic cells or hematopoietic stem cell transplantation)^[43]. The problem of HCV relapse leading to cirrhosis in 30% has been addressed by DAA. Present challenges for liver transplant are (i) high alcohol recidivism, (ii) ACLF grade 3 and severe acute alcohol related hepatitis (iii) NAFLD/non-alcoholic steatohepatitis with high comorbidities, (iv) frailty in advance CLD, (v) recipient and caregiver challenges (vi) genetic variants and (vii) COVID-19. SARS-CoV vaccine fails to decrease mortality as the patient's immunity is already weakened.

Artificial intelligence and digital transformation of various diagnostic modalities, decision making tool and management will further advance the treatment of liver diseases.

CONCLUSION

The current scenario of the epidemiology and the advances in diagnosis and treatment of liver diseases including their complications are summarised in this review.

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