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AIM AND SCOPE

World Journal of Hepatology (*World J Hepatol*, *WJH*, online ISSN 1948-5182, DOI: 10.4254), is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJH covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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REVIEW

Global elimination of hepatitis C virus infection: Progresses and the remaining challenges

Reza Taherkhani, Fatemeh Farshadpour

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Abstract

Today, with the introduction of interferon-free direct-acting antivirals and outstanding progresses in the prevention, diagnosis and treatment of hepatitis C virus (HCV) infection, the elimination of HCV infection seems more achievable. A further challenge is continued transmission of HCV infection in high-risk population specially injecting drug users (IDUs) as the major reservoir of HCV infection. Considering the fact that most of these infections remain undiagnosed, unidentified HCV-infected IDUs are potential sources for the rapid spread of HCV in the community. The continuous increase in the number of IDUs along with the rising prevalence of HCV infection among young IDUs is harbinger of a forthcoming public health dilemma, presenting a serious challenge to control transmission of HCV infection. Even the changes in HCV genotype distribution attributed to injecting drug use confirm this issue. These circumstances create a strong demand for timely diagnosis and proper treatment of HCV-infected patients through risk-based screening to mitigate the risk of HCV transmission in the IDUs community and, consequently, in the society. Meanwhile, raising general awareness of HCV infection, diagnosis and treatment through public education should be the core activity of any harm reduction intervention, as the root cause of failure in control of HCV infection has been lack of awareness among young drug takers. In addition, effective prevention, comprehensive screening programs with a specific focus on high-risk population, accessibility to the new anti-HCV treatment regimens and public education should be considered as the top priorities of any health policy decision to eliminate HCV infection.

Key words: Hepatitis C virus; Epidemiology; Elimination; Injecting drug user; Prevention; Vaccine; Diagnosis; Treatment

Core tip: Despite the outstanding progresses in the management of hepatitis C virus (HCV) infection, the elimination of HCV would be difficult due to the emergence of injection drug use as the main source of HCV transmission. Asymptomatic nature of HCV infection,

restricted accessibility to diagnostic approaches and appropriate antiviral treatments in the injecting drug users (IDUs) community are the root cause of failure in control of HCV infection among IDUs. These circumstances create a strong demand for timely diagnosis and proper treatment of HCV-infected patients as well as raising general awareness of HCV infection through public education to mitigate the risk of HCV transmission.

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INTRODUCTION

With a global prevalence rate of 2.8%, equating to over 185 million infections, and more than 350000 deaths annually, hepatitis C virus (HCV) infection is undoubtedly considered a major public health problem[1]. Globally, an estimated 3 million to 4 million new cases of HCV infection emerge every year[1]. Furthermore, the HCV-related mortality is increasing and HCV infection is projected to be the most important leading cause of viral hepatitis-related mortality in the near future[1,2]. Apparently, the management of HCV infection faces several challenges. These challenges merit further attention if elimination of HCV infection is aimed to be achieved.

HCV

HCV is a member of the family *Flaviviridae* and the genus *Hepacivirus*. The HCV genome is a positive-stranded RNA, which encodes a core protein (C), two envelope glycoproteins (E1 and E2), and several non-structural proteins (NS1, NS2, NS3, NS4A, NS4B, NS5A and NS5B)[3,4]. This enveloped positive-stranded RNA virus is usually acquired through exposure to infected blood. This might happen through transfusion of blood and blood products, surgery, organ transplantation, intravenous drug use, tattooing, hemodialysis, unsafe injection practices, mother to fetus, and sexual intercourse[5-8]. However, sexual transmission of HCV is less common and most often observed among men who have sex with men and HIV-infected patients[9,10].

HCV is the causative agents of hepatitis C infection. This infection is characterized by an acute or chronic course in the host. The complications are preliminary asymptomatic, mild or severe, which spontaneously clear or slowly progress to chronic liver disease, cirrhosis and finally hepatocellular carcinoma (HCC) within about 20 years[11,12]. The clinical symptoms of acute HCV infection might include fever, fatigue, malaise, and gastrointestinal symptoms such as anorexia, nausea, vomiting, right upper quadrant pain, dark urine, grey-colored stool, and yellow skin and sclera of the eyes, the well-characterized symptoms of jaundice. These symptoms might appear from 3 to 12 wk after being infected. The clinical symptoms of chronic HCV infection might take decades to develop, and they are usually indicative of an advanced liver disease[13-15].

The long-term chronic HCV infection is capable of causing some extra hepatic manifestations with serious consequences, such as glomerulonephritis, diabetes mellitus, thyroid disorders, porphyria cutaneous tarda, mixed cryoglobulinemia, lichen planus, and B cell lymphoproliferative disorders[16-21]. These extrahepatic complications might outshine the hepatic manifestations of HCV infection, and the presence of HCV infection might be overlooked, paving the way for the silent development of advanced liver disease. Therefore, the possible role of HCV in the development of extrahepatic manifestations merits further attention.

Due to genomic heterogeneity, there are 7 major genotypes and over 67 subtypes of HCV[1,22,23]. HCV genotype distribution varies by the route of transmission and geographical location[24,25]. In addition, pathogenicity, response to antiviral therapy and the duration of treatment can be influenced by different HCV genotypes[5,24,26]. The genotypes 1, 2 and 3 show a widespread distribution in almost all parts of the world. HCV genotype 4 has been traditionally restricted to a few countries in the Middle East and Africa and is more prevalent in Saudi Arabia, Bahrain, Jordan, Egypt and Ethiopia[1,27,28]. HCV genotype 5, 6 and 7 have been reported in South Africa, South East Asia and Central Africa, respectively[11,29,30] (Figure 1).

Genotype 1 is more prevalent among patients with history of blood and blood products transfusion, surgery, and dental procedure[24,25,27]. Infection with HCV genotype 2 is mainly associated with nosocomial transmission and prior dental treatment[1,22]. Genotype 3 is frequently found in the intravenous drug user communities and in those with history of tattooing and piercing[24,31,32]. Genotype 4 is mainly transmitted through high-risk sexual practices, especially among homosexual males, and intravenous drug use[1,22].

Infection with HCV genotype 3 is associated with a more rapid progression of fibrosis, a higher degree of steatosis, and a higher incidence of cirrhosis and hepatocellular carcinoma[1,22,31,33]. Spontaneous clearance is more often observed in infection with HCV genotype 1, while if patients remain HCV RNA positive, the disease progresses in a more aggressive manner than the other genotypes[11]. Genotypes 1 and 4 are associated with lower response rates and higher treatment duration in response to interferon (IFN) and ribavirin (RBV) combination therapy as compared to genotypes 2 and 3[6,24,34].

PROGRESSES IN THE MANAGEMENT OF HCV INFECTION

In addition to IFN-based therapies, the direct-acting antivirals (DAAs) have been developed, which specifically

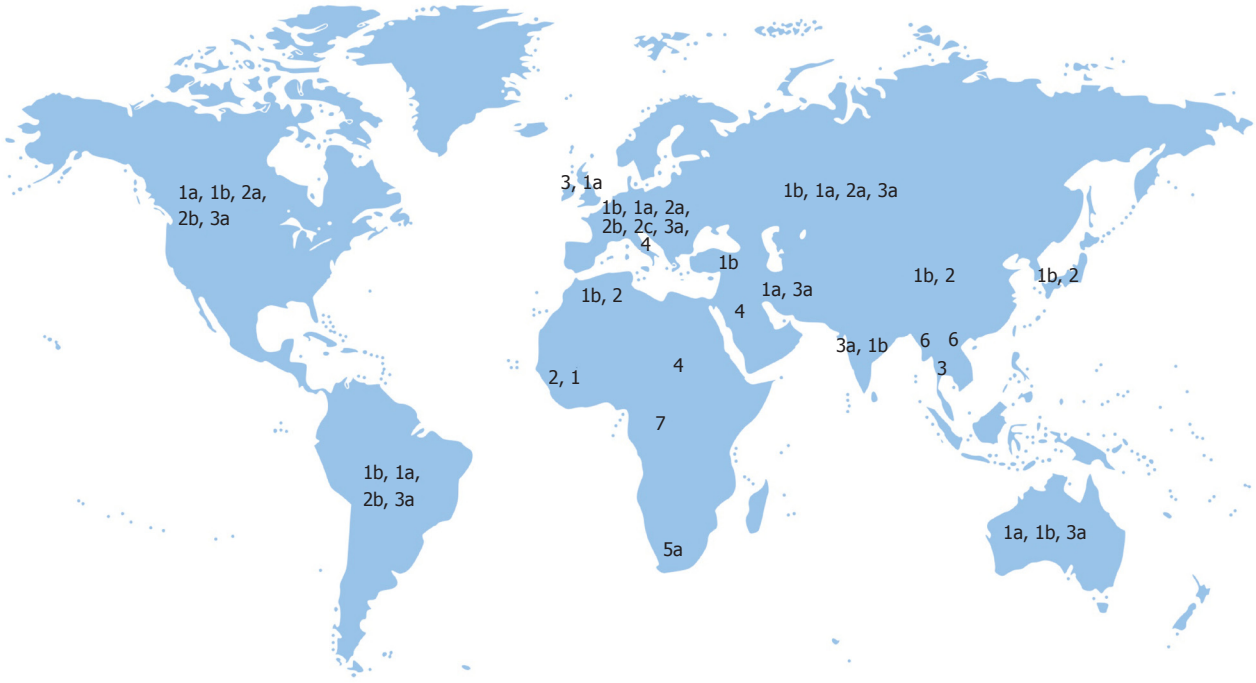

Figure 1 Geographical distribution of hepatitis C virus genotypes. Hepatitis C virus (HCV) genotypes 1, 2 and 3 show a widespread distribution in almost all parts of the world. HCV genotype 4 has been restricted to a few countries in the Middle East and Africa. HCV genotype 5, 6 and 7 have been reported in South Africa, South East Asia and Central Africa, respectively[1,11,30,35,36].

inhibit the function of viral proteins that are essential for viral replication[4,37,38]. These DAAs include NS3/4A protease inhibitors, NS5A replication complex inhibitors, nucleoside NS5B polymerase inhibitors, and non-nucleoside NS5B polymerase inhibitors (Table 1)[39-43]. These novel antiviral drugs, despite having considerable advantages over conventional IFN-based therapy, suffer from the resistance-associated mutations, which occur naturally during the replication of the virus and select under the pressure of DAAs. The emergence of HCV resistance-associated variants (RAVs) decreases the susceptibility to DAAs and finally results in treatment failure[38,44-46]. Assessment of resistance substitutions at pretreatment baseline in patients candidate for DAA therapy seems to be the best option to optimize first-line therapeutic strategies, to avoid the fitness of resistant variants as the predominant viral population and to prevent DAA failure due to baseline resistant variants. In addition, failing DAA-based therapy should be discontinued as soon as possible to avoid an increase in the frequency of RAVs, to preserve HCV re-treatment options. Finally, development of next-generation DAAs with higher resistance barrier is strongly recommended[45,47].

Telaprevir and boceprevir are not recommended by WHO due to the frequent adverse effects and low cure rates[79].

Prior to the treatment, the infected individuals need to be identified. HCV infection is described by the presence of anti-HCV antibodies and HCV-RNA in plasma or serum with either elevated or normal levels of liver enzymes[29]. Anti-HCV antibodies are detected by using serological screening tests, including enzyme linked immunosorbent assay and recombinant immunoblot assay. Detection of anti-HCV antibodies indicates current or past HCV infection. An additional test called HCV RNA test or reverse transcriptase polymerase chain reaction assay (RT-PCR) is needed to determine if a person is currently infected with HCV[17,80-82].

However, those infected individuals with undetectable levels of HCV-RNA in serum or plasma might remain undiagnosed. In this condition, HCV-RNA can be detected in peripheral blood mononuclear cells (PBMCs) specimens, liver biopsies, and ultracentrifugated serum samples[81,83]. Serological screening tests might be negative or positive in these patients. This kind of infection is defined as occult HCV infection, which is a serious threat to blood safety[84,85]. Since, despite having undetectable level of HCV RNA, blood and blood products are potentially infectious[84,86]. In fact, the presence of blood donors with occult HCV infection can increase the risk of HCV transmission through blood transfusion and therefore is a potential source of HCV transmission in the society[87].

Despite having appropriate antiviral treatments and diagnostic approaches, diagnosis rate and access to treatment is considerably low especially in resource-limited settings. Perhaps the most promising strategy to control HCV infection is the development of a prophylactic vaccine[88,89]. Several vaccine candidates against HCV have been developed so far, including recombinant protein vaccine, peptide-based vaccine,

Table 1 Profile of direct-acting antiviral agents[4,37,40,42,44,48-78]

Direct-acting antiviral agent	Generic name (abbreviation)	Code name	Trade name	Active against HCV genotype (based on clinical trial outcomes)	Combination therapy
NS3/4A protease inhibitors (-previr)	Telaprevir (TVR)	VX-950	Incivek/ Incivo	1	TVR + IFN ± RBV
	Boceprevir (BOC)	SCH-503034 EBP-520	Victrelis	1	BOC + IFN ± RBV
	Faldaprevir (FDV)	BI-201335	-	1	FDV + Peg-IFN + RBV
	Simeprevir (SIM)	TMC-435	Olysio	1 and 4	SIM + SOF ± RBV
	Vaniprevir (VNV)	MK-7009	Vanihep	1	VNV + IFN ± RBV
	Asunaprevir (ASV)	BMS-650032	Sunvepra	1 and 4	ASV + DCV
	Paritaprevir (PTV)	ABT-450	Veruprevir	1 and 4	PTV+R+OBV+DAV ± RBV
	Voxilaprevir (VOX)	GS-9857	-	Pan-genotypic antiviral activity	VOX + SOF + VPR
	Sovaprevir	ACH-1625	-	1	Sovaprevir + ODV + RBV
	Grazoprevir (GZP)	MK-5172	-	1a, 1b, 4 and 6	Zepatier (GZP + EBV)
	Danoprevir (DNV)	RG-7227 ITMN-191 ASC08	-	1 and 4	DNV + PEG-IFN + RBV DNV + R + PEG-IFN + RBV
	Deldeprevir (DDV)	ACH-2684	-	1	DDV + ODV
	Neceprevir	ACH-0142684			
	Narlaprevir (NVR)	SCH-900518	Arlansa	1	NVR + R + PEG-IFN ± RBV
	Vedroprevir (VDV)	GS-9451	-	1	VDV + LDV + SOF VDV + LDV + TGV + RBV
	Glecaprevir (GLE)	ABT-493	-	Pan-genotypic antiviral activity	GLE + PIB ± RBV
	-	GS-9256	-	1	GS-9256 + PEG-IFN + RBV GS-9256 + TGV + Peg-IFN ± RBV
NS5A replication complex inhibitors (-Asvir)	Daclatasvir (DCV)	BMS-790052	Daklinza	1, 2 and 3	Sovodak (DCV + SOF) ± RBV DCV + VX-135
	Ledipasvir (LDV)	GS-5885	-	1, 3, 4, 5 and 6	Harvoni (LDV + SOF) ± RBV LDV + SOF ± (VDV or Radalbuvir)
	Ombitasvir (OBV)	ABT-267	-	1 and 4	Viekira Pak (OBV + PTV + R + DSV) ± RBV Technivie (OBV + PTV + R)
	Elbasvir (EBV)	MK-8742	-	1a, 1b, 4 and 6	Zepatier (EBV + GZP) ± RBV
	Velpatasvir (VPR)	GS-5816	-	Pan-genotypic antiviral activity	Epclusa (VPR + SOF) ± RBV
	Odalasvir (ODV)	ACH-3102	-	1	ODV + Sovaprevir + RBV
	Ravidasvir (RVD)	PPI-668 ASC16	-	4	RVD + SOF ± RBV
	-	PPI-461	-	1	-
	-	JNJ-56914845 GSK2336805	-	1	GSK2336805 + PEG-IFN + RBV GSK2336805 + VX-135 + SIM
	Samatasvir	IDX-18719 IDX-719 MK-1894	-	1, 2, 3 and 4	Samatasvir + SIM + RBV
	-	BMS-824393	-	1	BMS-824393 + PEG-IFN + RBV
	Pibrentasvir (PIB)	ABT-530	-	Pan-genotypic antiviral activity	PIB + GLE ± RBV
	Ruzasvir (RZR)	MK-8408	-	Pan-genotypic antiviral activity	RZR + UPR + GZP
Nucleoside NS5B polymerase inhibitors (-Buvir)	Sofosbuvir (SOF)	PSI-7977; GS-7977	Sovaldi; Soforal	Pan-genotypic antiviral activity	SOF + IFN ± RBV Sovodak (DCV + SOF) ± RBV
	Mericitabine (MCB)	RG-7128 RO5024048	-	1 and 4	MCB + PEG-IFN + RBV MCB + DNV MCB + R + DNV ± RBV
	-	VX-135 ALS-2200	-	1	VX-135 + GSK2336805 + SIM VX-135 + TVR + RBV VX-135 + DCV VX-135 + RBV VX-135 + SIM
	Valopicitabine	NM283	-	1	Valopicitabine + Peg-IFN
Non-nucleoside NS5B polymerase inhibitors (-Buvir)	Beclabuvir (BCV)	BMS-791325	-	1	BCV+ ASV+ DCV

	Dasabuvir (DAV)	ABT-333	Exviera	1	DAV + OBV+ PTV + R ± RBV
	Lomibuvir	VX-222 VCH-222	-	1	VX-222 + TVR + RBV VX-222 + Filibuvir
	Filibuvir	PF-00868554, PF-868554	-	1	Filibuvir + Peg-IFN + RBV Filibuvir + VX-222
	Setrobuvir (STV)	ANA-598 RO-5466731 RG-7790	-	1	STV + IFN + RBV STV + R + DNV + RBV ± MCB
	Nesbuvir (NBV)	HCV-796 VB-19796	-	1	NBV +Peg-IFN + RBV
	Tegobuvir (TGV)	GS-9190	-	1	TGV + GS-9256 +Peg-IFN ± RBV TGV + LDV + VDV + RBV
	Deleobuvir (DBV)	BI-207127	-	1	DBV + PEG-IFN + RBV DBV + FDV DBV + FDV + RBV
	Uprifosbuvir (UPR)	MK-3682	-	Pan-genotypic antiviral activity	UPR + RZR UPR + RZR + GZP
	Radalbuvir	GS-9669	-	1	Radalbuvir + LDV + SOF
	AL-335	ALS-335	-	1	AL-335 + ODV + SIM

IFN: Interferon; RBV: Ribavirin; R: Ritonavir; PEG-IFN: Pegylated interferon.

virus-like particles, bacterial-vectored vaccine, viral-vectored vaccine, and DNA vaccine (Table 2)[29,88,90-96]. The currently developed vaccines against HCV, despite inducing strong humoral and cellular immune responses in preclinical animal models or clinical trials in humans, have not been approved for use in human beings[89,90,97]. The reason is high genomic diversity of HCV and viral escape from immune responses[88,90,93,98,99]. Targeting the conserved regions within HCV proteins might help to overcome this genetic variability[100].

In the absence of an approved prophylactic vaccine for hepatitis C, reducing exposure to HCV through prevention seems to be the best option. This can be achieved through routine screening of donated blood for HCV markers, providing safe medical procedures, promoting risk-reduction counseling and services for at risk population, increasing public awareness and offering regular HCV testing to high-risk populations with the goal of breaking the cycle of HCV transmission in the society[7,9,82,133]. Despite the so-called improvements in the management of HCV infection, still a long way is ahead to achieve a world free of HCV infection. Here, the remaining challenges to eliminating HCV infection will be discussed.

REMAINING CHALLENGES TO ELIMINATING HCV INFECTION

For many years, IFN-based therapy, despite having frequent side effects, poor tolerability, suboptimal efficacy and prolonged treatment course, was recommended as the standard treatment for HCV infection[134,135]. Introduction of IFN-free DAAs has solved most of these problems in the treatment course of HCV infection. Switch the HCV treatment regimens from IFN-based therapy to DAA therapy is a desirable approach, yet encounter practical barriers such as high price and the restricted accessibility of DAAs[135-138]. Most of the time, the cost of antivirals rather than their effectiveness is the main driver in the treatment decisions. The use of these DAAs is far beyond the financial means of the most-in-need patients especially those who are IFN-intolerant or non-responder. While, equity in health demands that all patients with every socioeconomic status have equitable access to these treatment regimens. Currently, reducing treatment costs and providing DAAs with a relatively high health insurance coverage seem to be best options to improve access to DAA therapy[139].

Accessibility to DAAs, though, by itself is a superb health achievement, still alone might not be sufficient to mitigate the burden of HCV infection. A further challenge is continued transmission of HCV infection in high-risk population specially injecting drug users (IDUs) as the major reservoir of HCV infection[133,137,139]. Considering the fact that most of these infections remain undiagnosed, unidentified HCV-infected IDUs are potential sources for the spread of HCV infection in the society[133,139-141]. While, silent introduction of HCV infection into the community is a serious threat to the national effort to eliminate HCV infection, a threat that will increase with time. Therefore, timely diagnosis of HCV-infected patients through risk-based screening is of the greatest importance[126,133,137]. Screening of blood donations for hepatitis C initiated in the early 1990s has remarkably reduced the risk of HCV transmission through blood transfusion since then. Blood transfusion before the early 1990s was a major contributor to the HCV transmission, but today this risk has become minute[142]. However, it is far, far more difficult to screen IDUs, those who most need risk assessment. Despite the remarkable advantages, the cultural objections hinder screening progress, resulting in low diagnosis rate and, consequently, persistent silent spread of infection. On the other hand, the stigma of injecting drug use makes recognition of all HCV-infected IDUs impossible or logistically difficult at best[133]. In addition, establishment of HCV screening system with a specific

Table 2 Vaccine candidates against hepatitis C virus in preclinical and clinical trials

Type of vaccine	Vaccine structure/ adjuvant	Stage of development	Outcome	Application	Developer	Year	Current status	Ref.
Recombinant protein vaccine	Recombinant E1 or E2/MF59	7 chimpanzees	Induce strong humoral immune response; complete protection in 5 chimpanzees	Prophylactic vaccine	Chiron/ Novartis	1994	Completed	[101]
	Recombinant E1 or E2/Alum	4 Chimpanzees	Induce antigen-specific T-helper cytokines in either E1 or	Therapeutic vaccine	BPRC	2011	Published	[102]
	Recombinant E1/Alum	Phase Ⅰ 20 healthy volunteers	E2-vaccinated animals; clear HCV infection in only E1-vaccinated animals (neutralizing antibodies) Induce strong cellular and humoral anti-E1 responses	Therapeutic vaccine	Fujirebio Europe	2004	Published	[103]
	Recombinant E1 and E2/MF59	Phase Ⅰ 60 healthy volunteers	Induce humoral and cellular immune responses	Prophylactic vaccine	Novartis	2010	Completed	[104]
	Recombinant E1/Alum	Phase Ⅰ/Ⅱ 20 healthy volunteers and 35 patients with chronic HCV infection/122 HCV-infected patients	Induce HCV specific humoral and cellular immune responses (Th1 type); no change in HCV viral load	Therapeutic vaccine	Innogenetics/ GenImmune	2003/2008	Published	[103,105,106]
	HCV core protein/ ISCOMATRIX	Phase Ⅰ/Ⅱa 30 healthy volunteers	Induce strong humoral immune responses in all except one patients; induce CD8+ T cell responses in 2 of 8 patients receiving the highest dose	Prophylactic vaccine	CSL Ltd	2009	Published	[107]
	GI5005: Inactivated recombinant Saccharomyces cerevisiae expressing NS3-core fusion protein/ GI-5005 plus SOC	Phase Ⅰ/Ⅱ 66 patients with chronic HCV infection/	Improve SVR	Therapeutic vaccine	GlobeImmune	2009/2010	Completed	[108,109]
Peptide-based vaccine	Peptide from core protein (C35-C44)/ ISA51	Phase Ⅰ 26 patients with chronic HCV infection	Induce peptide-specific cellular and humoral immune responses in 15 of 25 patients; decline HCV viral load in 2 of 25 patients	Therapeutic vaccine	Karume University	2009	Published	[110]
	Four peptides from E1, E2, NS3 and NS5A/Freund's adjuvant	Phase Ⅰ 12 nonresponder patients with chronic HCV infection	Induce peptide-specific cellular and humoral immune responses; decline HCV viral load in 3 patients	Therapeutic vaccine	Karume University	2007	Published	[111]
	Autologous dendritic cell delivered six CD8+ T cell epitope peptides from core, NS3 and NS4B	Phase Ⅰ 6 nonresponder patients with chronic HCV infection	Induce transient T-cell response	Therapeutic vaccine	Burnet Institute + others	2010	Completed	[112]

	IC41: Five peptides from core, NS3, and NS4/Poly-L-arginine	Phase Ⅰ / Ⅱ 128 volunteers/60 non-responders with chronic HCV infection	Induce HCV-specific T-cell responses	Therapeutic vaccine	Intercell AG	2006/2008	Published	[113,114]
	IC41/Poly-L-arginine + imiquimod	Phase Ⅰ 54 healthy volunteers	Induce significant T cell responses; low immunogenicity of topical imiquimod	Therapeutic vaccine	Intercell AG	2010	Published	[115]
	IC41 + imiquimod	Phase Ⅱ 50 HCV-infected patients	Decline viral load; induce T cell responses	Therapeutic vaccine	Intercell AG	2012	Completed	[116]
Virus-like particles	Recombinant HCV-like particles (HCV-LPs) containing core, E1, and E2/AS01B	4 chimpanzees	Induce HCV-specific cellular immune responses; viral clearance	Prophylactic vaccine	NIH	2007	Published	[117]
	Recombinant baculovirus containing core, E1 and E2	Mice	Induce high titers of anti-E2 antibodies and strong HCV-specific cellular immune responses (CD8+ T and Th1 cells)	Prophylactic vaccine	NIH	2001	Published	[118]
Bacterial-vectored vaccine	Attenuated Salmonella typhimurium containing *NS3* gene	Mice	Induce long-lasting T-cell responses	Therapeutic vaccine	NIH	2001	Published	[119]
Viral-vectored vaccine	Recombinant adenoviral vectors and plasmid DNA expressing NS3-NS5B	5 chimpanzees	Induce memory HCV-specific T cells; control of viremia	Prophylactic vaccine	NIH/Okairos	2012	Completed	[120]
	Multiple adenoviral vectors (Ad5, Ad6, Ad24, ChAd32 and ChAd33) expressing NS3-NS5B proteins	Mice and rhesus macaque	Induce strong cellular immune responses; long-term maintenance of memory cells	Prophylactic vaccine	Okairos	2006	Published	[121]
	Recombinant vaccinia viruses (rVV) expressing core, E1, E2, P7, NS2 and NS3	4 chimpanzees	Induce cellular immune responses; reduce viral load; resolve HCV infection	Prophylactic vaccine	NYC Blood Center	2008	Published	[122]
	Recombinant adenoviral vectors (Ad6 and ChAd3) expressing NS3-NS5B proteins	Phase Ⅰ 40 healthy volunteers	Induce sustained HCV-specific T cell responses	Prophylactic vaccine	Okairos	2012	Completed	[123]
	Adenovirus vector (Ad6 and ChAd3) expressing NS3-NS5B proteins	Phase Ⅰ 36 healthy volunteers	Highly immunogenic; induce HCV specific T cell responses	Prophylactic vaccine	Okairos and Oxford University	2009	Published	[124]
	TG4040: MVA vector expressing NS3, NS4 and NS5B proteins	Phase Ⅰ 15 patients with chronic HCV infection	Decline HCV viral load in 7 of 15 patients associated with T-cell response	Therapeutic vaccine	Transgene	2009	Withdrawn	[125]
	MVA and ChAd3 vectors expressing NS3, NS4, NS5A and NS5B proteins	Phase Ⅰ / Ⅱ Healthy at risk population (68/472 IDU)	July 28, 2018: Final data collection date	Prophylactic vaccine	NIAID	2017	Ongoing	[126]
	TG4040 + SOC	Phase Ⅱ 153 patients with chronic HCV infection	Induce HCV- and MVA-specific T-cell responses; develop anti-MVA antibodies; increase rate of early virologic response	Therapeutic vaccine	-	2014	Published	[127]
DNA vaccine	Recombinant DNA plasmid encoding E2	2 chimpanzees	Induce humoral and cellular immune responses; resolve the infection; prevent progression to chronicity	Prophylactic vaccine	NIAID/NIH	2000	Published	[128]

Recombinant DNA plasmid and adenovirus vector expressing core, E1, E2 and NS3-5	8 chimpanzees	Induce HCV-specific T-cell and long-lasting E2-specific antibody responses; reduce viral load	Prophylactic vaccine	NIH	2005	Published	[129]
Recombinant DNA plasmids and MVA vector expressing core, E1, E2 and NS3	6 chimpanzees	Induce HCV-specific immune responses; reduce viral load; early control of acute HCV infection; fail to impact on chronicity	Prophylactic vaccine	Transgene	2007	Published	[130]
CIGB-230: Plasmid expressing core/E1/E2 plus recombinant core protein	Phase Ⅰ 15 non-responder patients with chronic HCV infection	Induce humoral and cellular immune responses; no viral clearance	Therapeutic vaccine	University of Montreal + others	2009	Published	[131]
ChronVac-C: Plasmid expressing NS3 and NS4A delivered by in vivo electroporation	Phase Ⅰ / Ⅱa 12 HCV-infected patients	Decline HCV viral load in 4 of 6 patients receiving the highest dose with corresponding HCV-specific T-cell response in 3 patients	Therapeutic vaccine	Tripep AB	2009	Recruiting	[132]

HCV: Hepatitis C virus; SOC: Standard-of-care (PEGylated-IFNalpha and ribavirin); Imiquimod: An activator of the toll-like receptor (TLR) 7; Ad: Human Adenovirus; ChAd: Chimpanzee Adenovirus; MVA: Modified vaccinia Ankara virus; IDU: Injecting drug user.

focus on IDUs imposes high financial burden on the health system. Given the treatment expenses and dependence of these expenses on the stage of liver disease, screening of all at-risk populations seems much more affordable in a long run. Overall, in addition to interrupting unrecognized transmission of HCV, a part of costs expended in the treatment sector will also be saved with the prompt diagnosis and timely treatment of infected but asymptomatic patients[133,143]. While this process would demand allocation of adequate budgets and resources to integrate routine screening of high-risk population into national health programs.

As another solution, the coverage of needle and syringe exchange program should be expanded to increase the daily access to fresh needles and syringes among IDUs[144]. However, this program has not been very successful to control HCV transmission thus far, as the prevalence of HCV infection among IDUs is on the rise[139]. In fact, the overall focus on syringe sharing as the main vehicle for HCV spread has taken focus away from the other risk behaviors of IDUs such as the shared use of drug ampoules or the other injecting paraphernalia, engagement in high-risk sexual practices and the other drug-related harms[145]. These circumstances create a strong demand for precise surveillance of IDUs to obtain a reliable insight into risk behaviors of IDUs community, and subsequently harm reduction interventions should be tailored to the common risk behaviors among IDUs to mitigate the risk of HCV transmission. In addition, raising general awareness of HCV infection, diagnosis and treatment through public education should be the core activity of any harm reduction intervention, as the root cause of failure in control of HCV infection has been lack of awareness among young drug takers[133,141,146]. The growing number of IDUs and the relatively young age distribution of HCV-infected IDUs have evoke huge attention and provided a good opportunity to drive down the increasing trend of HCV-related mortality in near future through timely interventions and appropriate treatment[139,147].

The changes in HCV genotype distribution attributed to injecting drug use is another challenge in eliminating HCV infection. The changes in genotype distribution are so slight as to be unnoticeable but can have a deep impact on the epidemiology of HCV infection in a long run. These changes merit further attention if we want to properly manage the future burden of HCV infection. Globally, the most prevalent genotype is 1 (46%), followed by 3 (22%), 2 (13%) and 4 (13%)[35,137]. Over the last decade, however, a gradual decrease in the prevalence of genotype 1 and an increase in genotype 3 have been reported due to some changes in the route of transmission, risk factors, source of infection, human migration flow, and age distribution[148,149].

Blood transfusion before 1990 was the most important contributor to the spread of HCV, which has been reflected in the predominance of genotype 1 among older individuals[149,150]. In fact, screening for hepatitis C made blood transfusion remarkably safe since 1990s, paving the way for a gradual increase in the prevalence of genotype 3, which is mostly transmitted by IDU[148-150]. In recent years, IDU has become the main source of HCV transmission[35,137,144,145]. Globally, the estimated number of HCV-infected IDUs is up to 10.0 million (6.0-15.2 million), most of whom are young[35,139,144,147,151]. Meanwhile, the most common risk behavior of IDUs, syringe sharing, is more frequent among young drug injectors than in experienced and long-term injectors[152], amplifying the transmission of HCV among young IDUs population and favoring the continuous increase of HCV genotype 3. In

addition to the change in the route of HCV transmission, the ongoing civil strife in the Middle East and the active migration flow from India, Afghanistan and Pakistan, where subtype 3a is endemic, have fuelled the increasing prevalence of genotype 3[148]. On the other hand, death of elderly HCV carriers is slowly driving down the prevalence of HCV genotype 1.

These changes in genotype distribution have profound effects on the prevalence of HCV infection, response to antiviral therapy, cost and duration of treatment, and future burden of HCV infection. Given the higher rates of sustained virological response (SVR) to IFN-based therapy, the first-line therapy in low- and middle-income countries, in patients with HCV genotype 3 as compared to genotype 1[149], an increase in the prevalence of genotype 3 beneficially affects the treatment course both in terms of duration and in terms of cost and brings high benefits on an individual level. However, this increase would impose a greater risk on a population level. In reality the rising prevalence of HCV infection along with the continuous increase in the number of IDUs outweigh this benefit. The disastrous interacting epidemics of HCV infection and IDU are harbinger of a forthcoming public health dilemma, presenting a serious challenge to control transmission of HCV infection. On the other hand, high prevalence of HCV infection among young IDUs is a cause for concern, paving the way for rapid spread of HCV in the community. The old story of hepatitis C has gotten a new scenario. The emergence of IDU as the main risk factor for transmission of HCV is a surrogate in this new scenario. If this scenario is to continue, the emergence of an uncontrollable epidemic of hepatitis C will be expected in the near future.

CONCLUSION

The global community has always been concerned about the future burden of HCV infection. Although action on this concern has started many years ago with great hopes to eliminate HCV infection, the success remains elusive and will become even more elusive if the current HCV management paradigm is to be continued. We believe that it is now time to reconsider the wisdom of the current management strategies, admit failure, and act with all the strength. If we want to succeed in eliminating HCV infection, a more integrated international effort will be required, involving health policy makers, healthcare practitioners, public health organizations, antiviral drug manufacturers, health insurance companies, and all major stakeholders. In addition, effective prevention, comprehensive screening programs with a specific focus on high-risk population, accessibility to the new anti-HCV treatment regimens and public education should be considered as the top priorities of any health policy decision to eliminate HCV infection. While waiting for a solution, prevalence of HCV infection continues to increase. If we do not want to encounter another uncontrollable public health dilemma, the time to act is now, tomorrow will be very late.

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CASE REPORT

Diagnostic and therapeutic challenge of heart failure after liver transplant: Case series

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Abstract

Heart failure (HF) following liver transplant (LT) surgery is a distinct clinical entity with high mortality. It is known to occur in absence of obvious risk factors. No preoperative workup including electrocardiogram, echocardiography at rest and on stress, reasonably prognosticates the risk. In patients of chronic liver disease, cirrhotic cardiomyopathy, alcoholic cardiomyopathy, and stress induced cardiomyopathy have each been implicated as a cause for HF after LT. However distinguishing one etiology from another not only is difficult, several etiologies may possibly coexist in a given patient. Diagnostic dilemma is further compounded by the fact that presentation and management of HF irrespective of the possible underlying cause, remains the same. In this case series, 6 cases are presented and in the light of existing literature modification in the preoperative workup are suggested.

Key words: Liver transplant; Heart failure; Cirrhotic cardiomyopathy; Stress cardiomyopathy; Alcohol cardiomyopathy

Core tip: Heart failure following liver transplant surgery occurs in absence of any obvious risk factors and is associated with high mortality. No preoperative workup including electrocardiogram, echocardiography at rest and on stress, reasonably prognosticates the risk. While cirrhotic cardiomyopathy, alcoholic cardiomyopathy, and stress induced cardiomyopathy each have been

implicated, distinguishing one from another is difficult and several etiologies may possibly coexist. In this case series, 6 cases are presented and in the light of existing literature modification in the preoperative workup are suggested.

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INTRODUCTION

Heart failure (HF) is defined as "Inability of the heart to keep up with the demands on it and, specifically, failure of the heart to pump blood with normal efficiency". HF following liver transplant (LT) surgery is recognized as a distinct clinical entity with a prevalence of 3%-7%[1,2].

On retrospective analysis of 360 recipients who underwent liver transplantation at our tertiary care institute from 2011 to 2016, we identified six patients who developed heart failure in the immediate post-operative period. We diagnosed heart failure by severely decreased left ventricle ejection fraction (LVEF) on echocardiography. Clinical presentation was similar in all six recipients, only two survived. The details of each case are presented with discussion of different etiologies and specific management (Table 1).

CASE REPORT

Case 1

A 38-year-old male with cryptogenic chronic liver disease with a "model for end stage disease" (MELD) score of 16 underwent uneventful live related liver transplantation. No abnormality was detected in preoperative electro-cardiogram (EKG) and resting echocardiography. The Dobutamine stress echocardiography (DSE) was inconclusive due to chronotropic incompetence (failure to achieve target heart rate). Patient was weaned from mechanical ventilation and trachea was extubated six hours after surgery.

Twelve hours after extubation, patient complained of dyspnoea with coarse crepitations suggestive of pulmonary edema unresponsive to diuretics necessitating reintubation with supportive mechanical ventilation. Soon, hemodynamic instability sets in with increasing inotropes requirement to maintain perfusion pressures. Transthoracic Echocardiography (TTE) diagnosed left ventricle (LV) systolic failure with LVEF of 25% and increased systemic vascular resistance (SVR) of 1400 dynes.sec.cm^{-5}. "Troponin T" test was negative but Creatine kinase-MB (CK-MB) was elevated (16.8% of CK).

Pharmacologic intervention was aimed at decreasing pre- and after load using-injection Labetalol, and Nitroglycerine. Low perfusion pressure (mean blood pressure-50 mmHg) was accepted. SVR was maintained between 800-900 dynes.sec.cm^{-5}. Mechanical ventilation was continued for 4 d. LV ejection fraction improved over the period from 25% to 40%. Patient was weaned off mechanical ventilation on POD 5 (postoperative day). Labetalol infusion was continued and was replaced with oral doses from POD 8 onwards. Patient made complete recovery and was discharged from hospital with LVEF of 55% on POD 26.

Case 2

A 53-year-old male with ethanol related CLD, MELD score of 35, chronic smoker with 6 mo abstinence presented for LT. His preoperative TTE at rest showed normal ejection fraction of 65% with absence of in-ducible ischemia on DSE. His ECG was unremarkable but for a prolonged rate corrected QT (QTc) interval of 519 ms. Patient had acute kidney injury (AKI) for which Terlipressin infusion was started in the preoperative period and was continued perioperatively. His portal vein was thrombosed and required thrombectomy.

On POD 1, inotropes requirement increased with a high normal SVR and low stroke volume variation (< 10%). On TTE, LV systolic failure with LV EF of 25% was diagnosed. Hemodynamic parameters were supported using Dobutamine and Nor-adrenaline infusion. "Troponin T" test was inconclusive while Creatine kinase-MB (CK-MB) was elevated (15.1% of CK). Supportive care with mechanical ventilation was continued and LVEF improved over next 10 d. However, sepsis with gram negative infections led to multi-organ dysfunction resulting in patient mortality on the 14th POD.

Case 3

A 55-year-old female with cirrhosis due to extrahepatic portal vein obstruction with intraparenchymal extension with MELD of 9 presented for LT surgery. Her TTE at rest as well as DSE was normal. On her ECG, QTc interval was prolonged (532 ms). Packed red blood cells (15 units) were transfused during the surgery on account of blood loss during dissection of her native liver. In the immediate postoperative period, with progressive increase in inotropes and vasopressors requirement, it became difficult to maintain perfusion pressures. LV failure with EF of 20% was diagnosed on Transesophageal echocardiography (TEE). CK-MB was raised (14.68% of CK). In spite of maximal therapeutic management, hemodynamics deteriorated on second postoperative day leading to multiorgan dysfunction and death.

Case 4

A 26-year-old female with acute liver failure of unknown etiology with normal preoperative TTE, an unremarkable EKG but for a prolonged QTc interval (540 ms) underwent uneventful liver transplantation. She was weaned off respiratory support after overnight mechanical ventilation.

Table 1 Demography, Cardiology workup Pre-Transplant, Clinical course and outcome

(S No.) Demography, age, gender, etiology MELD score	Cardiology workup EKG, QTc, CI, echocardiography EF, DSE	Clinical course: Intraop, post op	CPKMB % of Ck on diagnosis of HF (normal 3%-5%)[25]	Possible underlying cause of heart failure in decreasing order of possibility	Outcome
(1) 38 yr, male, cryptogenic, MELD 16	QTc < 445 ms CI: Present EF: 65% DSE: Inconclusive	Uneventful LDLT; Extubated POD 1; Pul. Edema POD 2; EF: 25%	16.80%	CiCd ABS CAD ALC	EF recovered to 40% on POD 4; EF: 55% on discharge at POD 25; Survived to discharge;
(2) 53 yr, male, ethanol MELD 35	QTc: 519 ms CI: Absent EF: 65% DSE: Negative for inducible ischemia	Uneventful LDLT; Portal vein thrombectomy; Terlipressin infusion preop and intraop; POD 1: EF: 25%; Gram negative sepsis with MOD	15.10%	ALC CiCd CAD ABS	EF recovered to 55% at POD 10; Died
(3) 55 yr, female, EHPVO with intraparenchymal extension, MELD 15	QTc: 532 ms CI: Absent EF: 65% DSE: Negative for inducible ischemia	Turbulent LDLT; Increasing inotrope and vasopressor requirement; EF: 20%; Severe vasoplegia	14.68%	ABS CiCd CAD ALC	EF never recovered; Vasoplegia did not respond; Died
(4) 26 yr female, ALF	QTc: 540 ms CI: Absent EF: 70% DSE: Not done	Uneventful LDLT; Re-exploration POD2 for bleed; SVT; EF: 25%;	14.84%	ABS CiCd CAD ALC	EF recovered to 50% at POD 4; Died
(5) 40 yr, male, ethanol MELD 21	QTc: 550 ms CI: Absent EF: 65% DSE: Negative for inducible ischemia	Uneventful DDLT POD1: EF: 30%	Not done	ALC CiCd ABS CAD	EF recovered to 40% at POD 4; Survived
(6) 38 yr, male, ethanol MELD 32	QTc: 550 ms CI: Absent EF: 65% DSE: Negative for inducible ischemia	Uneventful; POD 1: EF: 20%; Recurrent SVT	39.40%	ALC CiCd ABS CAD	EF never recovered; Died

CI: Chronotopic incompetence; EF: Ejection fraction; DSE: Dobutamine stress echocardiography; CiCd: Cirrhotic cardiomyopathy; HF: Heart failure; ABS: Acute broken heart syndrome; ALC: Alcoholic cardiomyopathy; MOD: Multi-organ dysfunction; QTc: Rate corrected QT interval on ECG.

The postoperative course was complicated with hemoperitoneum on second day necessitating emergency laparotomy. Bleeder was identified and repaired. During this surgery, she had an episode of ventricular tachycardia which responded to lignocaine bolus. Subsequent to VT, LV EF was decreased (25%). The "Troponin T" test was inconclusive while CK-MB was increased (14.84% of CK). Over next four days, LV EF improved to 40%. Hemodyamics were supported during this period using dobutamine infusion which was then tapered and trachea was extubated after successful sponataneous breathing trial. However, on 7th POD, sepsis was diagnosed with positive microbiological cultures which led to multiorgan dysfunction and refractory vasoplegia. She succumbed to septic shock and died on POD 18.

Case 5

A 40-year-old male with ethanol related CLD with MELD score of 21 presented for LT. Preoperative EKG and TTE at rest were normal with LVEF of 60%. DSE was negative for inducible ischemia. After uneventful deceased donor liver transplantation (DDLT), patient was weaned off mechanical ventilation, 5 h after the surgery. On POD 1, patient developed respiratory distress with pulmonary edema, global hypokinesia with LVEF of 30% was diagnosed on TTE. Troponin T card test was negative. Systemic vascular resistance was 1250 dynes.sec.cm^{-5}. Noninvasive mechanical ventilation support was instituted along with preload and after-load reduction with Nitroglycerine infusion and Tablet Amlodepine. Tablet Prazocin was added subsequently. Patient improved symptomatically. LVEF improved to 40% by POD 4. Nitroglycerine infusion was tapered off while Tablet Prazocin and Tablet Amlodepine were continued. Patient was discharged to home with normal LVEF.

Case 6

A 38-year-old male with ethanol related CLD with MELD score of 32 underwent deceased donor liver transplant (DDLT). His preoperative Echocardiography was negative for inducible ischemia with minimal left to right intrapulmonary shunting with prolongation of QTc interval on EKG. Patient was weaned off mechanical ventilation on POD 2. On postoperative day 3, he developed low cardiac output with pulmonary edema with LVEF of 20% on TTE. CK-MB was elevated (39.4% of CK). Mechanical ventilation with tracheal intubation was initiated while

hemodynamic was supported using Nitroglycerine and Levosimendan infusion. Patient developed recurrent tachyarrhythmia in absence of any obvious electrolyte disorder for which Amiodarone was given. Patient was weaned off mechanical ventilation after 2 d but had to be re-intubated very next day on account of repeat episode of supra-ventricular tachycardia (SVT) with pulmonary edema. Subsequently several attempts to wean off mechanical ventilation were not successful. SVT continued to re-occur. Tracheostomy was done and patient was given increasing duration of spontaneous breath trials. However LVEF failed to improve and patient died on POD 29.

DISCUSSION

We observed heart failure after LT even with normal preoperative echocardiography, negative DSE for inducible ischemia and without any obvious cause. Literature suggests a "non-ischemic" cause for the systolic failure with after LT[3,4].

Cardiac risk factors in chronic liver disease

Cardiac risk factors have been identified in patients with chronic liver disease. These include coronary artery disease (CAD) (6%-26%), valvular heart disease (27.5%), asymptomatic foramen ovale (4%), cirrhotic cardiomyopathy (CiCd) (40%-90%), portopulmonary hypertension (2%-14%) and other diseases like amylodosis and hemochromatosis (45%). Cumulative risk of mortality in presence of these risk factors has been calculated to be 50%. Of these, presence of cirrhotic cardiomyopathy alone is associated with 3%-7% risk of severe HF in the post-operative period with 45% risk of mortality[5].

Risk factors associated with heart failure after liver transplantation

General: Presence of diabetes, hypertension, mean arterial pressure $\leqslant$ 65 mmHg, mean pulmonary artery pressure $\geqslant$ 30 mmHg, mean pulmonary capillary wedge pressure $\geqslant$ 15 mmHg, hemodialysis and brain natriuretic peptide (BNP) level (> 50 pg/mL) have been found to be predictive for the development of new-onset systolic heart failure after liver transplantation[1,5].

Etiology specific cirrhotic cardiomyopathy: Cirrhotic cardiomyopathy (CiCd) is defined as a "form of chronic cardiac dysfunction in patients with cirrhosis, characterized by blunted contractile responsiveness to stress, and/or altered diastolic relaxation with electrophysiological abnormalities in the absence of other known cardiac disease"[6].

QTc interval prolongation is a typical feature of CiCD. It is observed more frequently in patients who died after LT than in survivors and QTc interval > 450 ms have been found to be predictive for the development of new-onset systolic heart failure after liver transplantation[7]. We found increased preoperative QTc > 450 ms in 4 out of the 6 recipients with CLD who developed postoperative heart failure. Chronotropic incompetence, another feature of CiCd, was however observed only in one of these 6 recipients.

Alcoholic cardiomyopathy: Alcoholic cardiomyopathy shares pathophysoiology with CiCd. However, the co-existence of liver disease due to cirrhosis may give rise to diagnostic confusion and is therefore a diagnosis of exclusion[8]. Three out of these 6 recipients with postoperative heart failure had ethanol related liver disease and therefore could have had alcoholic cardiomyopathy. Association between Alcoholic cardiomyopathy and Supraventricular arrhythmias is known[9]. Alcoholics with simultaneous cardiomyopathy and cirrhosis are known to have a poor prognosis[10]. Case number 6 discussed in this report had supraventricular arrhythmias in the setting of HF after LT for ethanol related CLD and he did not survive.

Coronary artery disease: The prevalence of CAD in LT candidates over the age of 45-50 years ranges between 6% and 26%. Two of our patients were older than 50-year-old but had no symptoms suggestive of cardiac disease. Even preoperative DSE was negative for inducible ischemia.

Due to presence of ascites, poor nutritional status, cachexia, limited physical activity, it is difficult to diagnosis CAD in patients with CLD. In presence of limited physical activity, presenting signs and symptoms of angina and or angina equivalent are either not present or are not attributable to CAD. DSE has limited usefulness for diagnosing CAD in patients with CLD as it is often inconclusive in such patients due to chronotropic incompetence with resultant failure to achieve target heart rate. Similarly Dipyridamole or Adenosine nuclear myocardial perfusion scan also remain inconclusive as coronary vasculature is already maximally dilated in cirrhotics and therefore like DSE, are relied upon for their negative predictive value only.

Alternative tests like Single-photon emission computed tomography (SPECT) scanning, Cardiac magnetic resonance imaging, Carotid intima-media thickness, and Coronary artery calcification score (CACS) measured by computerized tomography have also been used to investigate presence of coronary artery disease though they have their own limitations[11].

Stress-related cardiomyopathy: Early-onset HF after surgery, directly reflects surgery related stress to the myocardium or hemodynamic changes. Stress related cardiomyopathy therefore cannot be missed as a cause of systolic heart failure in the perioperative period of non-cardiac surgery[12]. Similar conclusion was drawn by Mandell *et al*[1] who concluded that patients having HF after LT, either suffered from stress cardiomyopathy and therefore had no evidence of impaired contraction before the event or the echocardiographic predictors of HF were masked by circulatory changes in patients with cirrhosis.

Stress induced cardiomyopathy, or acute broken heart syndrome (ABS) also known as Takotsubo cardiomyopathy is understood to be caused by catecholamine surge which leads to diffuse microvascular spasm to cause myocardial stunning and HF. ABS and myocardial infarction (MI) share similar clinical and ECG presentation and blood biochemical tests.

To distinguish fromMI and for diagnosing ABS, Mayo clinic has therefore proposed following 4 point criteria[13]: (1) transient LV Systolic dysfunction (hypokinesis, akinesis, dyskinesis): The wall motion abnormalities are typically regional and extend beyond a single epicardial coronary distribution; (2) absence of obstructive coronary disease or angiographic evidence of acute plaque rupture. If coronary disease is found, the diagnosis of stress cardiomyopathy can still be made if the wall motion abnormalities are not in the distribution of the coronary disease; (3) new electrocardiographic abnormalities (either ST-segment elevation and/or T wave inversion) or modest elevation in cardiac troponin; and (4) absence of pheochromocytoma or myocarditis.

Patients in this case series satisfied 3 out of the 4 criteria except for the absence of obstructive coronary lesion or angiographic evidence of acute plaque rupture, which could not be ruled out in absence of coronary angiogram.

Serum cardiac troponin levels and brain natriuretic peptide (BNP) or N-terminal pro-BNP are elevated in most patients with stress cardiomyopathy in the International Takotsubo Registry study[14]. In the patients discussed, while Troponin card test was negative and BNP levels were not done, CPK MB was elevated. These patients therefore could have had ABS manifesting as HF.

In the present case series, only two patients, case No. 2 and 3, aged 53 and 55 years and possibly case No. 5 aged 40 in view of age and lifestyle were at risk of having CAD and these three patients were able to achieve target heart rates on DSE (Otherwise a limitation in patients with cirrhosis of Liver). DSE in these patients was negative for inducible ischemia. Considering this with ongoing hemodynamic instability and presence of global and not regional wall motion abnormality specific to any coronary artery supplied region and the younger age of rest of the patients, decision was taken to not to do coronary angiogram in these patients.

Most patients discussed in this case series had several possible etiologies responsible for the observed heart failure which could not have been definitely identified from one another. In absence of coronary angiogram, evidence against CAD is only circumstantial and therefore cannot be completely ruled out. Diagnosis of ALC and CiCd also cannot be certainly made except on the basis of history of ethanol abuse and presence underlying chronic liver disease. Similarly the diagnosis of ABS in absence of coronary angiogram does not entirely satisfy the Mayo's diagnostic criteria and is also possibly a diagnosis of convenience. It is also possible that several etiologies might be coexisting and therefore the high mortality in these patients.

New preoperative prognostic markers for heart failure after LT

In a prospective study of "myocardial injury after noncardiac surgery" (MINS), troponin elevations, any peak Troponin T (TnT) of 0.03 ng/mL or greater, without a non-ischemic explanation (*e.g.,* sepsis and pulmonary embolus) was diagnostic of MINS[15]. Patients with MINS were at higher risk of congestive heart failure (OR, 10.34; 95%CI: 7.99-13.37, $P < 0.001$) compared with patients who did not suffer MINS. In another study, mortality increased exponentially as a function of peak postoperative troponin concentration[16].

In the setting of surgery for LT, Coss *et al*[17] in a multivariate analysis of 230 transplant recipients found that an abnormal pretransplant troponin I level (> 0.07 ng/mL) predicted postoperative cardiovascular complications in their patients. They concluded that raised Toponin I levels > 50 pg/mL indicate latent cardiac dysfunction that is not recognized by conventional screening methods[17].

While quantitative assay of troponin is not available at our institute, we observed negative test on qualitative analysis using Trop T sensitive test Card test (detects Troponin T $\geqslant$ 0.1 ng/mL in blood). Creatine kinase-MB (CK-MB) was done and was significantly elevated soon after the clinical and echocardiography diagnosis of HF in our patients in absence of any other identifiable cause for the same.

Another novel marker, BNP level and QTc interval > 450 ms were concluded to be predictive for the development of new-onset systolic heart failure after LT in a study by Qureshi *et al*[3].

Management

Therapeutic strategies for addressing this acute and possibly life-threatening complication of heart failure after LT are not well defined. Similarly there is no established treatment for patients suffering MINS. In light of findings of decreased 30 d mortality in POISE trial (PeriOperative Ischemic Evaluation), acetyl-salicylic acid and statin therapy may possibly benefit patients who suffer MINS[18-20].

CiCd, Alcoholic cardiomyopathy, and ABS, all are characterized by inotropic incompetence. After LT, blood pressure is known to rise significantly which may possibly precipitate inotropic incompetence and subsequent HF in such patients[21,22]. Management of heart failure in the post-LT period therefore does not differ from usual heart failure therapies. Diuretics, inotropes, inodilators and vasopressor support form the foundation pillars of treatment.

Heart failure guidelines, such as those adopted by the European Society of Cardiology or the American College of Cardiology/American Heart Association should be followed. Cardio-selective Beta-blockers, ACE inhibitors or angiotensin receptor blockers (ARBs), diuretics and digitalis may be used for management

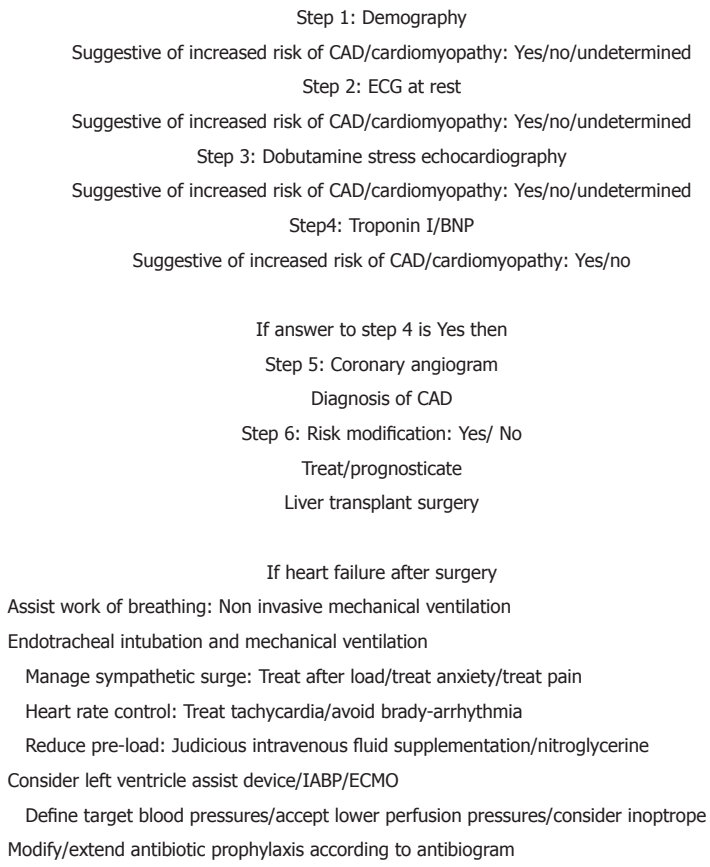

Figure 1 Suggested stepwise approach for diagnosis of patients at risk and for management of heart failure after liver transplant. CAD: Coronary artery disease; ECMO: Extracorporeal membrane oxygenator.

of HF after LT. It is important to treat the adrenergic surge causing raised systemic vascular resistance and also to manage the preload to avoid further worsening of cardiac function. In our case series, LVEF of 4 out of 6 patients recovered with use of therapy aimed at decreasing pre- and after load and adrenergic surge.

Several authors have reported successful outcome after aggressive management of HF following LT using extracorporeal membrane oxygenator (ECMO) and ventricular assist device (VAD), though cost may be a constraint[4,23,24]. Considering advances in clinically applied biomarkers and success of aggressive measures in managing such cases, a stepwise approach to identify patients at risk and for management should be adopted (Figure 1).

In our series, out of 6 patients, only 2 survived despite recovery of EF. Survival therefore is perhaps determined by factors other than myocardial performance like duration and severity of liver disease, presentation either acute or chronic, age of the patient, co-morbid conditions and presence of sepsis. Two patients who survived were relatively younger, aged 38 and 40 years and had chronic and not acute liver disease. Those who did not survive either had ALF or increased severity of CLD as reflected in their MELD scores or additional insult in form of sepsis in the setting of HF.

In conclusion, high MELD, Acute liver failure and sepsis in the setting of Heart failure after LT are probably associated with grave prognosis. While different etiologies may cause HF after LT, combination of several may possibly coexist. It may be prudent to routinely do quantitative Troponin I and/or BNP levels before LT surgery to identify and prognosticate recipients likely to be complicated by heart failure. While Heart Rate control, preload and after-load reduction are the pillars of management, ECMO and VAD may allow sufficient time for recovery of heart failure. In view of the limitations of the commonly used diagnostic modalities and poor outcome, better aides to identify patients at risk are needed which would require greater interdisciplinary interaction involving clinicians and laboratory scientists. Till such time, this entity, Heart failure after Liver transplant continues to remain an enigma.

ARTICLE HIGHLIGHTS

Case characteristics

Patients of acute liver failure and of chronic liver disease, presenting with systolic heart failure within 7 d after the liver transplant surgery in absence of any preoperatively identified and obvious predisposing risk factor.

Clinical diagnosis

Systolic heart failure was diagnosed on basis of clinical presentation and echocardiography with greatly reduced left ventricle ejection fraction.

Differential diagnosis

Liver graft dysfunction and severe sepsis may cause hemodynamic instability

and were ruled out. Underlying cause for the observed systolic heart failure could not be made.

Laboratory diagnosis

Creatine kinase-MB was elevated upon diagnosis of systolic heart failure after liver transplant. Troponin T sensitive card test was negative.

Imaging diagnosis

Severely reduced left ventricle ejection fraction was diagnosed on echo-cardiography.

Pathological diagnosis

Could not be made conclusively.

Treatment

Respiration was assisted. Hemodynamics supported using inotropes and inodilators and beta blockers, aimed at preload and after load reduction. Sedation and analgesia were taken care of to reduce sympathetic adrenergic activity.

Term explanation

Cirrhotic cardiomyopathy and alcohol cardiomyopathy have been described as specific clinical entities that describe cardiomyopathy in setting of underlying chronic liver disease and with history of alcohol indulgence respectively. Acute broken heart syndrome describes the cardiomyopathy typically seen under stressful conditions and not necessarily after surgery and is said to resemble acute myocardial infarction.

Experiences and lessons

In absence of established clinical features and limitations of existing prevalent diagnostic modalities, Bio-chemical makers like BNP and Troponin I may be routinely done as part of preoperative workup of patients posted for liver transplant surgery to help identify patients at greater risk of heart failure after the surgery.

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