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CONSENSUS STATEMENT

Utilization of hepatitis C virus–infected organ donors in cardiothoracic transplantation: An ISHLT expert consensus statement

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The advent of therapies for successful treatment of hepatitis C virus has allowed the heart and lung transplant community to re-explore the use of hepatitis C virus–positive donors for organ transplantation, with a benefit for many terminally ill patients. The consensus statements provided herein represent the current state of knowledge and expertise in this area, which we expect will continue to rapidly evolve over the next few years.
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Epidemiology of hepatitis C virus infection and implications for solid organ transplantation

Hepatitis C virus (HCV) is an RNA virus, consisting of at least 6 distinct genotypes and several subtypes. HCV infection lasting for many years is a leading cause of end-stage liver disease, hepatocellular carcinoma, and liver-related death globally.[1] Extrahepatic manifestations occur in up to 40% of patients with chronic (≥6 months) infection and include mixed cryoglobulinemia and porphyria cutanea tarda, B-cell non-Hodgkin and primary hepatic lymphoma, insulin resistance and diabetes mellitus, increased propensity for cardiovascular events, and membranoproliferative or membranous glomerulonephritis.[2–4] These manifestations may improve with successful HCV treatment.[2] Infection is associated with the production of proinflammatory cytokines and activation of transcription factors.[5] T cell–mediated immune response against the virus may lead to spontaneous recovery in 18% to 34% of immunocompetent individuals.[6]

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HCV epidemiology

Globally, the prevalence of HCV infection based on positive antibody (Ab) testing (i.e., seropositivity) was estimated to be approximately 110 million people in 2013, nearly 75% of whom exhibited HCV viremia.[7] Published prevalence rates of HCV infection based on positive Ab testing in deceased organ donors is variable based on geographic region and time period tested: 3.9% in Spain, 4.8% in Switzerland (1994), 7.3% in the USA (2017), and 11.8% in Taiwan (1985–1991).[8–10] Injection drug use is the most common risk factor for HCV acquisition; since 2002, there has been a

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significant increase in the incidence of acute HCV infection that is closely tied to the opioid epidemic in the United States and primarily affecting persons aged under 30 years.[11] Donors that die from drug overdose have increased rates of hepatitis B virus (HBV) infection as well as HCV.[12]

Solid organ transplantation before the direct-acting antiviral (DAA) era

Before the advent of DAA, several large registry-based analyses noted increased mortality following heart and lung transplantation in patients with pre-existing HCV infection relative to HCV seronegative patients undergoing transplant. Similarly, transplantation of thoracic organs from HCV seropositive donors was associated with inferior survival.[13–16] Recipients of HCV seropositive hearts were more likely to die of liver disease and cardiac allograft vasculopathy.[15] Analysis of HCV seropositive lung transplant recipients showed that although mortality was unaffected up to 2 years, it worsened by 3 years post-transplant, and differences persisted at the 10-year mark.[17] Only 0.2% of adult lung transplants in the US from 1994 to 2001 utilized HCV seropositive lungs for HCV seronegative recipients, with significantly shorter survival compared with transplantation of HCV seronegative allografts.[18]

Solid organ transplantation in the DAA era

The availability of DAA and resultant cure rates in excess of 95% with short course, well-tolerated, oral therapy has markedly altered the natural history of this infection and, consequently, the recovery rates for HCV-positive organs offered for transplantation.[19–22] Early data on patients who received kidney and liver transplants from HCV-viremic donors demonstrated that treatment of HCV infection post-transplantation was feasible and successful.[23–25] Data from single-center trials using HCV-viremic organs for cardiothoracic transplantation show excellent short-term outcomes.[26–31]

DAA therapy for HCV infection

The availability of DAA therapy for HCV infection has led to a paradigm shift in the clinical course and management of this disease. Previous interferon-based regimens have fallen out of favor because of lower efficacy, longer duration of therapy, higher pill burden, and unfavorable tolerability and toxicity.[32,33] A variety of oral regimens combining DAAs from different drug families (NS5B nucleoside inhibitors, NS5B non−nucleoside inhibitors, NS5A replication complex inhibitors, and NS3/4A protease inhibitors) are available, as noted in Table 1. Cure of HCV infection, denoted as sustained virological response at 12 weeks (SVR12), is defined as an absence of HCV viremia upon testing done at 12 weeks from the end of DAA therapy and is generally >95% with a relatively short course of oral regimens.[33] Early DAAs targeted specific HCV genotypes, although newer drugs are pan-genotypic.

Dosing recommendations, including the ability to crush medication for enteral administration via nasogastric tube and renal dosing considerations, are noted in Table 1. DAAs, and risk of drug interactions pertinent to solid organ transplant recipients are detailed in Table 2. A careful review of all patient medications and potential interactions should take place before starting any DAA regimen. The following principal considerations should be included:

1. Sofosbuvir-containing DAA regimens may be associated with symptomatic bradycardia in patients taking amiodarone (because this drug has a prolonged clearance, and therapeutic effect may persist in the early weeks to months following transplantation even if discontinued), particularly in patients also receiving beta blockers or those with underlying cardiac comorbidities and/or advanced liver disease. Thus, if these drugs are used, close clinical monitoring for at least the first 2 weeks from when amiodarone was last used should be undertaken.[33,34] Amiodarone is often discontinued in heart transplant patients following transplant, although it may be initiated in the lung transplant setting because of post-operative atrial fibrillation.
2. Close monitoring of immunosuppressants, in particular calcineurin inhibitors and mammalian target of rapamycin inhibitors, is recommended while on DAA because of a variable effect on drug levels.
3. 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors should be used with caution as the concentration of these drugs is expected to increase with concomitant use of certain DAAs, as discussed in Table 2.

Resistance testing for HCV NS5A mutations is recommended for genotype 1a before treatment with elbasvir/grazoprevir, with the addition of ribavirin and prolongation of DAA therapy in the setting of drug resistance mutations.[33] Ribavirin may interfere with azathioprine metabolism and potentially lead to myelotoxicity.[35]

None of the DAAs are currently available in a parenteral or oral liquid formulation. Although there is limited published data on the safety or efficacy of crushing tablets for administration, most of the currently available DAAs are not enteric-coated or sustained release. In a recent clinical trial that demonstrated the effectiveness of a short course of sofosbuvir/velpatasvir in heart or lung transplant recipients, the drug was crushed and administered via nasogastric tube for a few days following surgery, which did not adversely affect DAA efficacy.[27] Published cases include the use of crushed ledipasvir/sofosbuvir and elbasvir/grazoprevir administered via a percutaneous endoscopic gastrostomy tube or gastrostomy button with successful outcome.[36–38] A Phase 1 study formally investigated the pharmacokinetics of crushing, cutting, and grinding glecaprevir/pibrentasvir in healthy subjects has suggested favorable drug levels.[39]

Responses to medical information requests to the drug manufacturers confirmed that sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, and ledipasvir/sofosbuvir are not enteric-coated and do not possess a sustained-release mechanism. Sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/

Table 1 DAA Regimens for Treatment of HCV Infection

Drug name	Approval year	**HCV** genotype	Duration of therapy[a]	Standard dose for adults	Administration	Renal dose adjustment	Common adverse events (>10%)
Ledipasvir/ sofosbuvir	2014	1a, 1b, 4, 5, and 6	12 weeks	One tablet (90 mg ledipasvir and 400 mg sofosbuvir) taken orally once daily	Give with/without food. Oral pellets can be mixed with food.	No adjustment for renal disease including dialysis	Headache, fatigue, asthenia
Daclatasvir	2015	1, 2, and 3	12 weeks in combination with sofosbuvir	One tablet 60 mg taken orally once daily	Give with/without food	No adjustment for renal disease including dialysis	Headache, fatigue, nausea, anemia
Elbasvir/ grazoprevir	2016	1a, 1b, and 4	12 weeks	One tablet (50 mg elbasvir and 100 mg grazoprevir) taken orally once daily	Give with/without food. May be able to cut/ crush, not recommended by manufacturer	No adjustment for renal disease including dialysis	Headache, fatigue, nausea
Velpatasvir/ sofosbuvir	2016	1—6	12 weeks	One tablet (400 mg of sofosbuvir and 100 mg of velpatasvir) taken orally once daily	Give with/without food. May be able to cut/ crush, not recommended by manufacturer	No adjustment for renal disease including dialysis	Headache, fatigue
Sofosbuvir/ velpatasvir/ voxilaprevir[b]	2017	1—6	8-12 weeks	One tablet (400 mg of sofosbuvir, 100 mg of velpatasvir, and 100 mg of voxilaprevir) taken orally once daily	Give with food	None needed for mild to moderate renal disease. No dosing recommendation for severe or dialysis	Headache, fatigue, diarrhea, nausea
Glecaprevir/ pibrentasvir	2017	1—6	8 weeks	Three tablets (each containing 100 mg of glecaprevir and 40 mg of pibrentasvir) taken orally once daily	Give with food. Can cut in half. May be able to crush/grind, not recommended by manufacturer	No adjustment for renal disease including dialysis	Headache, fatigue, nausea

Abbreviations: DAA, direct-acting antiviral; HCV, hepatitis C virus.

[a]Duration of therapy refers to FDA-approved duration in patients without underlying cirrhosis.

[b]Sofosbuvir/velpatasvir/voxilaprevir is not a first-line agent for HCV infection but indicated in the case of failure of a previous DAA regimen.

Table 2 Common Drug Interactions Associated with DAAs as Pertinent to Cardiothoracic Transplantation

Drug class	Ledipasvir/sofosbuvir	Daclatasvir	Elbasvir/grazoprevir	Sofosbuvir/Velpatasvir	Sofosbuvir/velpatasvir/ voxilaprevir	Glecaprevir/pibrentasvir
Amiodarone	↑ Bradycardia—CAUTION	↑ Bradycardia—CAUTION	↑ Bradycardia—CAUTION	↑ Bradycardia—CAUTION	↑ Bradycardia—CAUTION	Potential interaction (P-gp) use with caution
Anti-coagulants	Not studied, close monitoring for increased anticoagulant side effects is recommended	Potential interaction—monitor closely	Not studied, close monitoring for increased anticoagulant side effects is recommended	Potential interaction—monitor closely	Do NOT coadminister dabigatran, monitor closely for other anti-coagulants	Do NOT give with dabigatran, potential interaction with warfarin, rivaroxaban, and apixaban
Anti-convulsants	Carbamazepine, phenytoin, phenobarbital, or oxcarbazepine ↓ ledipasvir, and ↓ sofosbuvir CONTRAINDICATED	Phenytoin, carbamazepine ↓ daclatasvir concentration—CONTRAINDICATED	Phenytoin, carbamazepine ↓ elbasvir/ grazoprevir concentration—CONTRAINDICATED	Carbamazepine, phenytoin, phenobarbital and oxcarbazepine ↓ sofosbuvir and velpatasvir—CONTRAINDICATED	Phenytoin, phenobarbital and carbamazepine ↓ sofosbuvir/ velpatasvir, +/- voxilaprevir CONTRAINDICATED	Carbamazepine ↓ glecaprevir/ ↓ pibrentasvir. Not recommended
Azole antifungals	Not reported	↑ Daclatasvir concentration —reduce to 30 mg when used in combination, EXCEPT with fluconazole	Coadministration with ketoconazole is not recommended as ↑ grazoprevir potentially causing hepatotoxicity	No significant interactions	No significant interactions	May have a potential interaction with posaconazole and ketoconazole
Calcineurin inhibitors	No significant interaction with tacrolimus, cyclosporine	—No significant interaction with tacrolimus, cyclosporine	Grazoprevir ↑ tacrolimus concentrations—monitor levels. ciclosporin ↑ grazoprevir concentration —CAUTION	No significant interactions	Ciclosporin ↑ voxilaprevir - NOT recommended No interaction with tacrolimus	cyclosporine ↑ glecaprevir/ ↑ pibrentasvir. Doses of cyclosporine >100 mg/day are not recommended. No interaction with tacrolimus
mTOR inhibitors	Not reported	Not reported	↑ mTOR concentration—CAUTION	Not reported	Not reported	May ↑ mTOR—CAUTION
Calcium channel blockers	No significant interaction with verapamil	↑ Daclatasvir concentration —CAUTION	Not studied	Not reported	Not reported	No significant interactions with amlodipine, felodapine
CYP 3A4 inducers [a]	↓ Ledipasvir/ ↓ sofosbuvir concentration—CONTRAINDICATED	↓ Daclatsavir concentration —CONTRAINDICATED	↓ Elbasvir/ grazoprevir concentration—CONTRAINDICATED	↓ Sofosbuvir/ velpatasvir concentration-CONTRAINDICATED	↓ Sofosbuvir/ velpatasvir, +/- voxilaprevir—CONTRAINDICATED	↓ Glecaprevir/ ↓ pibrentasvir concentration—CONTRAINDICATED
CYP 3A4 inhibitors[b]	↑ Ledipasvir/ ↑ sofosbuvir/	↑ Daclatasvir concentration —reduce daclatasvir to 30mg	Strong CYP3A inhibitors may ↑ elbasvir/ ↑ grazoprevir concentrations. Not recommended	↑ Sofosbuvir/ velpatasvir	↑Sofosbuvir/ velpatasvir, +/- voxilaprevir —	Potential interaction with diltiazem—monitor heart rate/ blood pressure
Digoxin	↑ Digoxin concentration (monitor levels)	↑ Digoxin concentration (monitor levels)	No significant interaction	↑ Digoxin concentration (monitor levels)	↑ Digoxin concentration (monitor levels)	Reduce digoxin dose by ~50% (monitor levels)

(*continued on next page*)

Table 2 (*Continued*)

Drug class	Ledipasvir/sofosbuvir	Daclatasvir	Elbasvir/grazoprevir	Sofosbuvir/Velpatasvir	Sofosbuvir/velpatasvir/ voxilaprevir	Glecaprevir/pibrentasvir
HMG-CoA Reductase Inhibitors (statins)	↑ Concentration of rosuvastatin and atorvastatin—CAUTION No significant interaction with pravastatin	↑ Statin concentration—CAUTION	↑ Statin concentration; do not exceed atorvastatin/ fluvastatin/lovastatin/ simvastatin 20 mg dose; do not exceed rosuvastatin 10 mg dose	↑ Rosuvastatin max 10 mg daily	↑ Pravastatin—max 40 mg ↑ rosuvastatin - CONTRAINDICATED ↑ Other statins - NOT recommended	↑ Statin levels. Do not exceed pravastatin 20 mg, rosuvastatin 10mg, use the lowest dose for fluvastatin. Atorvastatin, lovastatin, and simvastatin are CONTRAINDICATED
H2 blockers	↓ Ledipasvir/ sofosbuvir concentration—H2-blockers may be administered simultaneously with or 12 hours apart from ledipasvir/ sofosbuvir at a dose that does not exceed doses comparable to famotidine 40 mg twice daily	No significant interaction with famotidine	No significant interactions	H2-blockers may be administered simultaneously with or staggered from at a dose that does not exceed doses comparable to famotidine 40 mg twice daily	↓ Velpatasvir. H2-blockers may be administered simultaneously with or staggered at a dose that does not exceed doses comparable to famotidine 40 mg twice daily	Potential weak interaction, but no suggested dose change
PPI	↓ Ledipasvir/ sofosbuvir concentration—PPI doses comparable to omeprazole 20 mg or lower can be administered simultaneously with ledipasvir/ sofosbuvir under fasted conditions	No significant interaction with omeprazole	No significant interactions	Coadministration with PPI is NOT RECOMMENDED. If it is considered necessary to coadminister, then sofosbuvir/ velpatasvir should be administered with food and taken 4 hours before PPI at max doses comparable to omeprazole 20 mg	PPIs may be coadministered at a dose that does not exceed doses comparable with omeprazole 20 mg	No interaction with omeprazole

Abbreviations: CYP3A, cytochrome P4503A; DAA, direct-acting antiviral; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-coenzyme A; mTOR, mammalian target of rapamycin; PPI, proton pump inhibitor; P-gp, P-glycoprotein.

This is not an all-inclusive list. Please see prescribing information for a full list of interactions.

[a]Protein CYP 3A4 inducers include carbamazepine, phenytoin, rifampin among others.

[b]Protein CYP 3A4 inhibitors include clarithromycin, diltiazem, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole.

voxilaprevir, and ledipasvir/sofosbuvir tablets can be disintegrated in water, juice, or milk with minor stirring and pressure with a spoon. However, the pharmacokinetic parameters of these drugs when disintegrated, crushed, or split have not been compared with the whole tablet.

Currently, there are no commercially available tests that can be used to assess for therapeutic DAA levels in the setting of crushing or cutting tablets. Stopping or interrupting HCV treatment could lead to the development of resistance or treatment failure, and thus, continuation of DAAs is paramount for their complete recommended course. Until further pharmacokinetic studies are available, the benefit of continuing DAA therapy in a crushed form appears to outweigh the risk of DAA interruption.

Donor profiles and recipient selection criteria when considering HCV-infected donors

Clarification and accurate interpretation of a donor's HCV testing profile is imperative to educate potential recipients and their providers about the likelihood of disease transmission after transplant. This section defines donor HCV profiles and discusses factors to consider when assessing potential donors and recipients, with special attention to concomitant HBV.

Interpretation of donor HCV profiles

HCV donor profiles with associated interpretations are outlined in Table 3. A positive nucleic acid test (nucleic acid testing [NAT]+) result indicates viremia and an active infection in the donor. As HCV Ab may take up to 2 to 3 months to develop following virus exposure, donors who test Ab−/NAT+ are presumed to have recent infection.[40] A NAT− result suggests absence of active infection; in the setting of an Ab+/NAT− donor, this could mean successfully treated or spontaneously resolved HCV infection. However, there is an eclipse period in which the virus may be inoculated and transmitted but still undergoing a lag or early replication phase too low to be detected, even by the most sensitive methods such as NAT. As NAT may take 5 to 8 days to become detectable following infection acquisition, there may be false negatives if infection developed in the 5 to 8 days before testing.[41–43]

Table 3 Interpretation of Donor HCV Test Results and Considerations at Time of Organ Offer

Donor **HCV** test results	Interpretations and considerations
Ab + / NAT +	• Active infection present
Ab − / NAT +	• Active infection present; donor in serologic window period suggestive of recent exposure, or • Consider false-positive NAT result
Ab + / NAT −	• Donor exposed to HCV but active infection NOT present because of current or prior treatment or spontaneous clearance, or • Consider false-positive Ab result
Ab − / NAT −	• In most cases, no exposure or infection present • In donors with recent risk factors for HCV infection (PHS IRDs) who may be in an eclipse period, consider possibility of hyperacute infection and follow guidelines for post-transplantation infectious disease surveillance

Abbreviations: Ab, antibody; HCV, hepatitis C virus; NAT, nucleic acid testing; PHS, Public Health Service.

Eclipse period for donor viral infections

Currently, deaths related to anoxia (usually related to intravenous drug use or opioid overdose) account for 65% of HCV NAT+ donors in the USA,[21] and up to 90% of these are considered to be increased risk donors (IRDs).[44] IRDs with negative NAT for HCV, HBV, or human immunodeficiency virus (HIV) may be in an eclipse period for these infections. Thus, IRD donors who are HCV Ab−/NAT− at time of organ donation should have close monitoring for infection acquisition not only for HCV but also for HBV and HIV. Currently, Public Health Service guidelines in the US recommend testing for such infections between 1 and 3 months post-transplant and again at 12 months following transplant from IRDs.[45] These guidelines are being updated and may shorten the period considered to be at risk of infection acquisition from an IRD.[46]

Donor and recipient selection: General considerations

Studies suggest that the risk of HCV transmission from Ab +/NAT− cardiothoracic donors is negligible, with the positive Ab conferring minimal to no additional risk.[30,47,48] These donors should be considered routinely for all waitlisted candidates. Conversely, the risk of HCV transmission from NAT+ donors, regardless of Ab status, is nearly 100%.[27–30] As treatment is complex and expensive and long-term outcomes unclear, this strategy should be undertaken only after education and informed consent of potential recipients and in collaboration with providers who have expertise in treating HCV. For patients who develop donor-derived HCV infection, ensuring timely and guaranteed access to DAAs is imperative, and centers that accept NAT+ donors should have established protocols in place for recipient testing and treatment. Additionally, because data suggest that HCV treatment failure is more likely in patients with advanced liver fibrosis,[49,50] for patients who are listed for heart or lung transplant alone (as opposed to dual heart-liver or dual lung-liver), caution should be exercised in accepting viremic donors in the setting of pre-existing significant liver disease. Published data demonstrate excellent short-term outcomes in patients that undergo combined heart-kidney transplantation from HCV NAT+ donors[29]; data regarding other combined organ transplants are lacking.

Donor and recipient selection: Recommendations specific to HBV

Although guidelines regarding HBV testing and treatment apply to all patients undergoing cardiothoracic transplantation, they merit special attention in patients for whom HCV-infected donors are considered. As described in prior International Society for Heart and Lung Transplantation guidelines,[51] all transplant candidates should be tested for HBV at time of transplant evaluation, and non-immune individuals should be vaccinated before transplant whenever possible. Interpretation of HBV serologic markers is detailed in Table 4. Recipients with evidence of chronic active HBV infection (i.e., HBV surface antigen + or HBV NAT+) have a higher risk of reactivation while on DAA therapy[52]; consideration of avoiding HCV NAT+ organs should be made, and they should be placed on HBV antiviral suppression.[53,54]

Donors that die from drug overdose have increased rates of HBV infection along with HCV.[12] One study noted that 20% of HCV NAT+ donors were also positive for HBV core Ab but with negative HBV viremia.[29] This report demonstrated successful outcomes when HCV NAT+ donors that are also concomitantly positive for HBV core Ab (but HBV NAT−) were used for heart transplantation regardless of HBV immune status of the recipient.[29] In this setting, serial monitoring for HBV in the recipient using HBV quantitative viral load and surface antigen should be performed every 3 months for the first post-transplant year.[55] If the recipient is not immune to HBV infection (immunity is determined by HBV surface antibody ≥10 mIU/ml), antiviral prophylaxis with lamivudine, entecavir, tenofovir disoproxil fumarate (TDF), or tenofovir alafenamide (TAF) may be considered.[55] If the recipient is immune to HBV, no prophylaxis is needed in the case of the donor being HBV core Ab+ and HCV NAT+.[55] If HBV viremia is detected in the recipient, appropriate antiviral therapy should be initiated as per guidelines.[55] At this time, there are no data reporting outcomes in cardiothoracic transplant recipients utilizing donors that are simultaneously viremic with both HBV and HCV; both viruses are hepatotoxic, and we do not recommend accepting such organ offers outside of a clinical trial.

Recipients with cleared HBV infection (HBV core Ab+ but surface antigen and NAT−) have a low risk of reactivation but should be monitored closely with HBV quantitative viral load testing every 3 months for the first year. In the setting of transplantation from an HCV NAT+ donor to a recipient that has prior evidence of HBV infection as manifested by a positive HBV core Ab, antiviral prophylaxis with lamivudine, entecavir, TDF, or TAF for the duration of DAA therapy can be considered and surveillance strategy pursued.

Table 4 Interpretation of HBV Serologic Markers

Serologic tests	Interpretation
HBV surface antigen−negative and HBV core antibody negative and HBV surface antibody negative	Not infected and not immune
HBV surface antigen−negative and HBV core antibody positive and HBV surface antibody positive	Previous HBV infection, now cleared (i.e., no viremia) and leading to natural immunity
HBV surface antigen−negative and HBV core antibody negative and HBV surface antibody positive	Successful HBV vaccination leading to immunity
HBV surface antigen positive and HBV core antibody positive (IgM) and HBV surface antibody negative	Acute active HBV infection
HBV surface antigen positive and HBV core antibody positive (IgM negative, IgG positive) and HBV surface antibody negative	Chronic active HBV infection
HBV surface antigen−negative and HBV core antibody positive and HBV surface antibody negative	Four possibilities: 1. Resolved infection and immune (most common) 2. False positive 3. Occult chronic infection 4. Resolving acute infection

Abbreviation: HBV, hepatitis B virus; IgG, immunoglobulin G; IgM, immunoglobulin M; IRD, increased risk donor

Adapted from Mast EE, Margolis HS, Fiore AE, Brink EW, Goldstein ST, Wang SA, Moyer LA, Bell BP, Alter MJ; Advisory Committee on Immunization Practices (ACIP). A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: immunization of infants, children, and adolescents. MMWR Recomm Rep. 2005;54:1-31.

Management of patients with donor-derived HCV infection

A variety of protocols to detect HCV infection following transplantation from HCV NAT+ donors have been described.[23,26−29,44,56−58] The time to detection of HCV viremia in the recipient using quantitative polymerase chain reaction (PCR) in these studies has ranged from 1 to 14 days. For centers planning on DAA therapy only after confirmation of HCV infection, we recommend weekly quantitative HCV PCR for 4 weeks or until detection. Once detected, we recommend genotyping (although this may not be needed if pan-genotypic drugs are employed, it may be needed from a payer perspective); resistance testing can be considered as well (it may be needed for certain insurance payers and if planning to use elbasvir/grazoprevir for genotype 1a). Weekly monitoring of liver and renal function until initiation of DAAs is recommended with weekly serum and urine testing (the latter for proteinuria). Concern for worsening transaminitis related to increasing HCV viremia, fibrosing cholestatic hepatitis, membranous glomerulopathy, or other potential HCV-related adverse events should lead to prompt DAA initiation.[59,60] For those

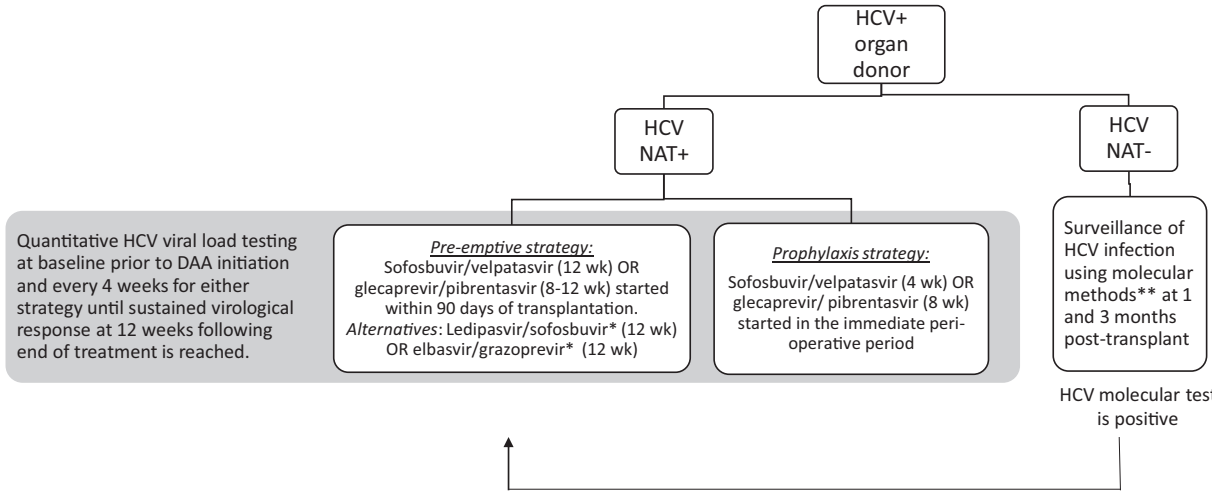

Figure 1 Algorithm depicting flow of events when utilizing HCV-positive organs for cardiothoracic transplantation into HCV-negative recipients. *Based on appropriate genotype as per manufacturer recommendations. **Molecular methods include NAT and quantitative RNA PCR and/or viral load. DAA, direct-acting antiviral; HCV, hepatitis C virus; NAT, nucleic acid test; PCR, polymerase chain reaction; wk, week.

patients with negative HCV PCR in the first 4 weeks, absence of infection should be confirmed at 3 months.

Recent studies investigating the use of HCV Ab+/NAT− donors for HCV− solid organ recipients conducted HCV surveillance using molecular methods (quantitative PCR or NAT).[47,48,61,62] Whereas cardiothoracic organ recipients did not develop active HCV infection,[47,48] 10% of liver transplant recipients and 1.9% of kidney transplant recipients have developed HCV viremia by the third month of follow-up.[61,62] We recommend surveillance of HCV infection following transplant by using molecular methods at 1 and 3 months following transplantation. We do not believe that prophylactic DAA is warranted in this setting.

A variety of DAAs have been used successfully for HCV treatment after organ transplantation from HCV NAT+ donors. There is a trend in favor of using pan-genotypic drugs, which obviate the need for resistance testing, and therapy can be initiated before availability of genotype testing results (genotype results are rarely available at the time of organ offer).[23,27−31,44,56,58]

Based on published data, we recommend 1 of 2 approaches to the management of donor-derived HCV infection in transplant recipients (Figure 1). A prophylaxis approach aims to prevent transmission of HCV from the NAT+ donor to the recipient by starting DAA therapy in the immediate pre- or post-transplant period (i.e., within hours of transplant surgery). A pre-emptive approach aims to start treatment of acute HCV infection after HCV transmission to the recipient has occurred and is verified by means of quantitative PCR.[1] In either setting, a successful outcome is based on the demonstration of SVR12, that is, absence of HCV viremia at a time point 12 weeks following the end of DAA therapy (regardless of the duration of DAA).

Prophylaxis strategy

The goal is to prevent transmission of HCV from the NAT+ donor to the recipient by DAA therapy. Recent clinical trials demonstrate 100% SVR12 when DAA therapy is initiated pre-operatively or just hours after transplant.[24,27,28] Two of these trials used a full course of DAA: 12 weeks of elbasvir/grazoprevir for genotype 1, with addition of sofosbuvir for genotype 2 and 3 for kidney transplants, and 8 weeks of glecaprevir/pibrentasvir for heart transplants. One study noted 100% SVR12 with a short 4-week course of sofosbuvir/velpatasvir following heart and lung transplantation from HCV-viremic donors.[27] Benefits of such an approach include a potentially shorter duration of DAA that is cost saving, prevention of the onset of HCV latency, and prevention of HCV-related adverse events such as hepatitis and extrahepatic manifestations, including allograft-related complications. Critically ill transplant recipients may provide challenges to early initiation of DAA therapy, including factors such as the inability to take oral medications, need for prolonged feeding tube requiring DAAs to be crushed, onset of renal failure requiring hemodialysis influencing DAA exposure and clearance, cardiogenic shock requiring mechanical circulatory support such as extracorporeal membrane oxygenation, and other percutaneous mechanical cardiac support devices with unclear volume of distribution of DAAs. Additionally, access to the drug or insurance payer denial may pose barriers for some centers as well.

Pre-emptive strategy

This approach aims to start treatment of acute HCV infection after HCV transmission to the recipient has occurred

[1]The prophylaxis term was unanimously agreed upon by the working group and the pre-emptive term by most members. We chose these terms because transplant professionals are familiar with this terminology when dealing with cytomegalovirus infection in the transplant recipient where donor and recipient serologies are an indicator of infection risk and inform management strategies as well (although we acknowledge the overall different outcomes in these two viral infections).

and is verified by means of quantitative PCR. Pan-genotype DAA regimens can be started once the patient has recovered from transplant surgery. There are data demonstrating the feasibility and success of this approach from both cardiothoracic and abdominal transplantation.[23,27−31,44,56,58] We recommend sofosbuvir/velpatasvir (12 weeks) or glecaprevir/pibrentasvir (8−12 weeks) within 90 days of transplantation. Alternatives include ledipasvir/sofosbuvir (12 weeks) or elbasvir/grazoprevir (12 weeks). The benefits of such an approach include knowledge of genotype (and resistance testing if indicated) before the start of DAA therapy, lower chance of treatment interruption if started after the patient has recovered from the immediate transplant period, less variability in drug absorption and kidney function, and potential cost difference based on the lower costs of outpatient initiation of DAA therapy than in-hospital use. Potential caveats of this approach include adverse events related to untreated early establishment of HCV infection, including hepatoxicity, extrahepatic manifestations, and unknown long-term effects on the allograft. In general, most centers utilizing this approach for cardiothoracic transplant initiate DAA at a median of 21 to 125 days.[29,57,58] We believe that as early an initiation as possible should always be preferable and recommend initiating DAA within 90 days of transplant (although this recommendation is unsubstantiated). Pan-genotypic drugs are preferred for this reason because they can be started before receiving results of an HCV genotype. Close monitoring for HCV-related adverse events is recommended.

Induction immunosuppression

Recent studies do not note a difference in SVR12 outcomes based on induction strategy consisting of anti-thymocyte globulin, basiliximab, or no induction in the cardiothoracic transplant setting.[27−29,57,58] Outcomes of alemtuzumab induction in the setting of donor-derived HCV infection have not been reported. Most recent studies report maintenance immunosuppression regimens consisting of tacrolimus, prednisone, and mycophenolate mofetil.

Patient education

In patients with donor-derived HCV infection, potentially hepatotoxic exposures should be avoided or minimized. Patients should be educated regarding recognition of potential hepatotoxic symptoms such as jaundice, right upper quadrant pain, persistent nausea, and vomiting. HCV is a highly infectious blood-borne pathogen; sexual transmission is extremely low and mainly described in men who have sex with men or those coinfected with HIV.[33,63] Patients should be educated that, during the period they are viremic, safe practices include cautious use and disposal of sharps including glucometer lancets and insulin syringes; careful dressing changes of open wounds performed by the patient or gloved care-takers; no sharing of toothbrushes or razors; safe sexual practices using barrier precautions; and bleach-cleaning of all household surfaces contaminated with blood from the HCV-infected individual.[33]

Ethical considerations and informed consent

Ethical considerations

Expansion of the donor pool by using organs from HCV+ donors benefits both the individual recipient and, by extension, other patients on the wait list (by reducing competition for organs). The magnitude of this benefit is proportional to the prevalence of HCV+ donors and also based on the estimated advantage for the recipient of not having to wait for the next HCV− organ offer, an advantage that would be particularly large for clinically unstable patients. Although there is available evidence to help determine the degree of urgency for both heart and lung wait list candidates,[64−66] it is important to note that such individual predictions are highly uncertain. A longer than usual expected wait time for recipients coupled with a high prevalence of HCV infection among available donors would increase the benefit of accepting such organs. Furthermore, increasing the donor pool and shortening wait times also benefits health care providers and payers, as time on the wait list may be associated with significant cost. In thoracic transplantation, this is particularly relevant for the growing cohort of candidates who are bridged to transplant with device-based support that requires prolonged hospitalization in critical care units.

The paucity of evidence regarding long-term outcomes following use of HCV+ donors in the DAA era introduces some uncertainty. Among the ethical issues that require consideration is the potential risk of disease transmission to the recipient's partner, caregiver, or other health care providers. Another issue relates to the need to guarantee access to treatment in cases where costs of antiviral therapy are not covered by payer systems. In such cases, it is unclear if the transplanting center has an ethical obligation to assume the costs of treatment.

Informed consent

According to current policy in the USA, recipients must be informed and must consent to receiving an organ from IRDs (specific surveillance is required for such recipients, not addressed in this document) and must additionally consent to the recipient of an organ from a viremic (NAT+) HCV donor.[43,45] There is no policy mandating consent or specific surveillance for HCV Ab+/NAT− donors. Most centers in the USA obtain consent at the time of listing and then again upon organ offer. The recipients may decline such organs at any time. In the United Kingdom, guidelines issued by the National Health Service include a wider range of putative risks, although HCV infection is not specifically addressed.[67] In these guidelines, the right to decline organs perceived to be associated with certain risks is clearly expressed, as is the need to reconfirm the consent while the patient is on the waitlist. In many other countries (such as in Scandiatransplant and in some Eurotransplant countries),

there is no specific guideline for informed consent in organ transplantation, and it is handled by the rules that would guide any other medical procedure. In such allocation systems, there is no system for granting a recipient the option to decline particular categories of organs, leaving the candidate with an all-or-nothing choice. Given unique challenges related to the use of HCV NAT+ cardiothoracic organs, we recommend HCV-specific informed consent of waitlisted patients before organ offer. In countries where recipients cannot be selective to organ offers, patients should be informed regarding the specific risks associated with HCV NAT+ donors and about the risks associated with declining the offer such as clinical deterioration. Given minimal risk of infection transmission, we do not believe that informed consent specific to HCV Ab+/NAT− donors is necessary, although it may be implemented based on local center preferences.

Granting the recipient a right to be selective, however, may raise certain dilemmas. There is concern, for example, that giving candidates choices about donor organ acceptance will favor those who are stable and can afford to wait for a more desirable organ, whereas those who are critically ill are compelled to accept higher risk organs.[68] This may be considered poor distributive justice because those who are more sick do not have the opportunity to exert complete choice. Moreover, encouraging the use of high-risk organs for high-risk recipients may potentially result in worse outcomes, although this has not been demonstrated in current literature for HCV-infected organs.[69] Finally, in organ procurement systems with low volumes and long estimated wait times, granting a candidate the right to be selective may simply not be feasible.

Communication of risk

Communication barriers may make it difficult to adequately discuss comparison of alternatives and their risks.[70] The qualitative comparison of these risks depends on the candidate's individual beliefs and preferences. Based on data from National Health Service and the Organ Procurement and Transplantation Network, we present a tool to help explain the implications of accepting an organ from a HCV NAT+ donor, designed to be incorporated in discussions for consent (Table 5).[43,67] It is important to carefully parse out that granting the recipient a right to decline donors of perceived risk may convey the erroneous message that an organ transplant could be risk-free.

For the quantitative risk comparison, both the risk and inconvenience of acquiring HCV and the risk of death on the wait list should be discussed. Whether perceived risk and inconvenience of receiving an organ from an HCV NAT+ donor is more or less preferable to the patient than an increased wait time depends on the anticipated wait time and on how this increase would affect the individual candidate's prospects of a successful transplant. Thus, both qualitative and quantitative risk comparisons should be discussed with the candidate, and the decision should be documented according to local requirements.

Table 5 Relevant Considerations during Shared Decision Making between the Transplant Team and the Patient and Their Caregivers

Questions
From the patient's perspective
What is HCV infection?
What are my risks of acquiring HCV infection?
Will the antiviral treatment work?
How will the team determine which therapy to use and when to start the therapy?
How will the cost of antiviral therapy be covered? Will insurance cover my therapy?
What could happen if antiviral therapy is not started immediately after transplant? What are the potential risks associated with transient/brief viral infection?
What are the side effects of the medications?
What happens if the antiviral therapy fails to cure my HCV infection?
Is there a risk for others whom I care about?
How much longer will I have to wait for an organ if I decline this type of organ?
How much will my chances of a successful transplant decrease if I decline this organ and have to wait longer?
From the transplant team's perspective
What is the prevalence of HCV-viremic donors available to waitlisted candidates at our center?
What is the estimated wait time for this particular patient, taking into account the local waitlist, the local organ supply, and the current allocation system?
What is the prognosis of this patient within the estimated wait time?
Will this particular patient tolerate antiviral medication?
Will the peri- and post-transplant follow-up of an HCV-infected recipient require changes in our protocols or practice?
How should we communicate with the patient and caregivers?
Based on national organ allocation policies, is it desirable and feasible to grant patients the option to refuse organs from HCV-viremic donors at our center?
What are the legal and administrative requirements at our center for obtaining informed consent, and do we have such consent?

Abbreviation: HCV, hepatitis C virus.

Economic implications of using HCV-infected donors

The enthusiasm for DAA therapies has been tempered by challenges patients and clinicians face with drug access, largely because of cost implications. When introduced, these drugs were high in cost, and currently significant barriers for obtaining approval through insurance payers may be encountered. Such barriers create uncertainty and delays in therapy initiation. When DAA therapies were initially introduced, cost of a typical single 12-week course of ledipasvir/sofosbuvir was approximately USD $94,500.[71] The most recent entrant on the market, glecaprevir/pibrentasvir, was priced at USD $26,400 for an 8-week treatment course.[72] Additionally, the actual cost for use may be significantly lower than the recorded wholesale acquisition cost because of a variety of factors, such as negotiated rates between payers and drug companies, generic formulations, and presence of rebates; these prices vary geographically across world regions.

The costs for waitlisted cardiothoracic transplant patients, particularly those who are sick enough to require intensive care within specialized units and/or mechanical circulatory support devices, can be exceedingly high and resource intensive.[73] Thus, accelerating access to organs could serve to provide a significant reduction in health resource use and decrease the morbidity (and even mortality) during this waiting period. The use of HCV NAT+ organs can reduce the waitlist time and potentially improve waitlist survival.[57,74–76] Formal cost-effectiveness analyses that assess the incremental cost-effectiveness ratio for cardiothoracic transplantation using HCV NAT+ donors are still unavailable as of this writing. However, this approach has been found to be cost effective in the setting of kidney transplantation.[75] The use of a prophylactic DAA strategy among recipients from HCV NAT+ donors could shorten the duration of therapy and be potentially even more cost saving.[27,77] However, in such a case, the cost will likely be absorbed by the transplant center.

Consensus statements

The following consensus statements summarize the principal recommendations by the working group:

Consensus #1: The donor HCV profile should be characterized by the presence or absence of HCV viremia as detected by NAT and the presence or absence of anti-HCV antibodies as determined by serologic testing. In the case of HCV Ab−/NAT− donors that are considered Public Health Service IRDs, risk factors for HCV acquisition should be taken into account to help guide post-transplant surveillance.

Consensus # 2: Suitable organs from HCV Ab+/NAT− donors should be routinely accepted for cardiothoracic transplant given the negligible risk of HCV transmission to recipients without need for specific informed consent (unless required under local laws). Suitable organs from NAT+ donors should be considered for consented waitlisted candidates undergoing transplant at centers with established protocols, teams, and resources to manage donor-derived HCV.

Consensus #3: Given unique challenges related to the use of HCV NAT+ cardiothoracic organs, we recommend HCV-specific informed consent of waitlisted patients before organ offer. In countries where recipients cannot be selective to organ offers, patients should be informed regarding the specific risks associated with HCV NAT+ donors and those associated with declining the offer.

Consensus #4: At the time of transplant or within 12 months preceding organ offer from an HCV+ donor (as well as anytime there is concern for exposure), the transplant recipient should be tested for pre-existing HCV, HBV, and HIV infection using molecular methods and serology.

Consensus #5: For centers planning on DAA therapy only after confirmation of HCV infection following transplant from an HCV NAT+ donor, the recipient should be tested for acquisition of donor-derived HCV infection within the first post-operative week using quantitative HCV RNA testing. Once positive, HCV genotyping and resistance testing may be performed, based on whether pan-genotypic DAA will be used or not as well as payer requirements. If quantitative PCR is negative at 1 week post-transplant, serial testing should be performed weekly until infection is confirmed. In those patients who fail to develop viremia by 1 month following transplant, absence of infection should be confirmed by repeat testing at 3 months following transplant. Weekly assessment of liver and renal function for potential adverse events until DAA initiation is recommended as well.

Consensus #6: Following transplant from an HCV Ab +/NAT− donor, the recipient should undergo quantitative HCV RNA testing at 1 and 3 months for surveillance.

Consensus #7: We recommend pan-genotypic DAAs for treatment of donor-derived HCV infection in cardiothoracic transplant recipients; genotype-specific DAAs may be used as an alternative. Drug interactions must be carefully evaluated before initiation of DAAs to avoid decreased efficacy of HCV treatment and thereby potential treatment failure.

Consensus #8: We recommend 1 of 2 approaches to the management of donor-derived HCV infection in transplant recipients:

1. Prophylaxis strategy: Pan-genotypic DAA regimen is initiated pre-operatively or within a few hours following cardiothoracic transplantation from an HCV NAT+ donor with 4 weeks of sofosbuvir/velpatasvir or 8 weeks of glecaprevir/ pibrentasvir.
2. Pre-emptive strategy: After HCV infection acquisition is confirmed, DAA regimen can be started once the patient has recovered from surgery, ideally within 90 days of transplantation. We recommend sofosbuvir/velpatasvir (12 weeks) or glecaprevir/pibrentasvir (8−12 weeks). Alternatives include ledipasvir/sofosbuvir (12 weeks) or elbasvir/grazoprevir (12 weeks) for specific genotypes as per manufacturer recommendations.

Consensus #9: Quantitative HCV RNA testing should be performed at initiation of DAA, every 4 weeks while on treatment, and following end of treatment until SVR12 is achieved. DAA therapy should not be discontinued or interrupted if HCV viral load is not performed.

Consensus #10: Induction and maintenance regimens for immunosuppression should be based on local center guidelines. Currently, there is no evidence to suggest that immunosuppression regimens need to be altered when accepting an HCV NAT+ donor.

Consensus #11: If the recipient has evidence of pre-existing HBV infection (core Ab−positive, PCR-negative, and surface antigen−negative), we recommend periodic HBV PCR and surface antigen surveillance every 3 months for the first year following transplant with consideration of concomitant HBV secondary prophylaxis with lamivudine, entecavir, TDF, or TAF for the duration of DAA therapy.

Consensus #12: If an HCV NAT+ donor is concomitantly positive for HBV core Ab (but HBV NAT−), serial monitoring for HBV in the recipient using HBV quantitative PCR and surface antigen should be performed every 3 months for the first post-transplant year. If the recipient is not immune to HBV infection (as determined by HBV surface antibody ≥10 mIU/ml), antiviral prophylaxis with lamivudine, entecavir, TDF, or TAF may be considered. If the recipient is immune to HBV, no prophylaxis is needed in the case of donor being HBV core Ab+.

Consensus #13: Specific patient and care provider education and counseling (as outlined in the consensus document) is recommended for the promotion of medication adherence, recognition of potential adverse events, and prevention of HCV transmission to others.

Ongoing areas of research

Donors with HCV represent an increasing source of organs for both patients infected and uninfected with HCV awaiting cardiothoracic transplantation. Although preliminary results are encouraging, a number of issues merit further exploration and research. Ideally, research should be multicentric and prospective; heart and lung transplants should initially be studied separately as it is likely that there are organ-specific nuances that will affect outcomes. Data regarding outcomes with combined multiple organ transplants are minimal, as is the use of such donors for patients with a prior transplant (retransplantation). Because long-term outcomes are unknown, it is imperative that research elucidates whether allograft and patient survival is similar to that found in recipients of HCV-uninfected donor organs at diverse short- and long-term time points after transplantation. In particular, the incidence of primary graft dysfunction and acute and chronic rejection, including transplant vasculopathy for heart and chronic lung allograft dysfunction for lung transplants, must be determined. Additionally, other manifestations of immune activation, specifically the risk of coinfections with other infectious pathogens, and the development of other comorbidities, including cirrhosis and post-transplant diabetes mellitus, must be assessed. In vitro studies of immune responses may inform clinical findings.

It is possible that the mere presence or absence of HCV infection in the donor is not the sole determinant of recipient outcome; other factors are likely to be important as well. For example, viral load and genotype may play a role. Preliminary data suggest that multiple viral genotypes may be transmitted concurrently; whether this has an impact on outcomes is unknown.[29,78] Additionally, duration of HCV infection as well as prior HCV treatment and/or treatment failure in the donor may have an impact on outcomes in the recipient following transplantation. The impact of other donor features, including demographics, substance abuse, unknown downtime, and prolonged cardiopulmonary resuscitation should also be evaluated.

We have a limited understanding of the virologic factors that may play a role in the success of HCV+ donor to HCV− recipient in cardiothoracic transplantation. It is important to recognize that standard definitions of SVR12 may not accurately predict viral control. Preliminary data suggest that relapses may occur in the setting of lung transplantation.[31] Although these reactivations and/or relapses may be easily controlled, it will be important to evaluate the impact of post-SVR viremia on allograft and patient outcomes. Although this consensus statement is focused on the use of HCV-viremic donors, we do not have sufficient data to accurately determine transmission risk from the HCV Ab+/NAT− donor (although this appears very low) or other issues related to allograft function. A systematic examination of risks associated with these donors, those that are and are not IRDs, should be performed.

Although long-term outcome is the greatest unknown, a number of short-term concerns are worthy of study. Perhaps most pressing are the pharmacologic considerations. The optimal choice of medication may be determined in view of viral load, genotype, and concurrent medications. Whether the timing of DAA initiation (pre-emptive therapy of acute HCV infection vs prophylaxis) and donor viral load should affect duration of treatment is unknown and merits further investigation. The choice of immunosuppression, both induction and maintenance, must be independently considered as it may have an impact on viral clearance as well as allograft function and rejection. Pharmacokinetics of DAAs, including absorption considerations in the early post-transplant period when administration may involve crushing tablets, should be studied. In some cases, drug interactions may dictate other aspects of management, including choice of DAA, lipid lowering therapies, and anti-arrhythmics; these adjustments may have an impact on both viral and organ-specific outcomes and will need to be specifically considered. In addition to rates of SVR, reporting outcomes should include development of HCV-related transaminitis, fulminant hepatic failure, cholestatic hepatitis, extrahepatic manifestations, and other adverse events.

The immunology of donor-derived HCV infection may be an important predictor of short- and long-term outcomes. Past research has demonstrated that donor-derived HCV is a likely cause of immune activation, potentially contributing to accelerated transplant arteriopathy in heart transplant

recipients.[79] Delayed effects of immune activation may not represent the full spectrum of allograft-specific events; it is possible that primary graft dysfunction may be a manifestation of early immune dysregulation and activation. How to best assess immunologic effects in patients receiving induction immunosuppression is unknown. Simple measurements of immune mediators, lymphocyte counts and function, and the development of donor-specific antibody may be insufficient to define the immunologic perturbations specific to donor-derived HCV infection. Preliminary studies in recipients of kidneys from HCV-viremic donors have revealed the development of a de novo Ab, which in some cases has been persistent, suggesting that there is ongoing production of Abs[80]; whether this correlates with allograft function will need further investigation.

Several approaches utilizing ex vivo organ perfusion platforms in the donor organ to minimize or eliminate HCV virus in the organ before transplantation are undergoing evaluation and include the use of photodynamic therapy, ultraviolet light, and methylene blue.[31,81,82] Ultrashort courses of DAA as a prophylaxis strategy have been reported as well from a few centers utilizing glecaprevir/pibrentasvir combined with ezetimibe for a week started in the pre-operative period, as well as a 4-day course of sofusbuvir/velpatasvir for kidney transplantation, and appears promising.[83,84]

At the time of writing, there is a lack of data regarding the use of HCV+ organs for pediatric transplantation, and this will need to be explored further. The impact of regional variation of HCV+ donors on waitlist times may be different in different regions and will need to be assessed as well.

In summary, we believe that the advent of therapies for successful treatment of HCV has allowed the cardiothoracic transplant community to re-explore the use of HCV-positive donors for organ transplantation, with a benefit for many terminally ill patients. The consensus statements provided herein represent the current state of knowledge and expertise in this area, which we expect will continue to rapidly evolve over the next few years.

Disclosure statement

Dr Aslam reports consulting fees from Merck; Dr Grossi reports consulting fees from Merck as an advisory board member and was on the speakers bureau of Gilead; Dr Blumberg reports a research grant from Merck to her institution and an unpaid engagement as an advisory committee member for Merck, a research grant from Hologic and Takeda, consulting fees from Shionogi, and engagement as a data safety and committee member for Bristol Myer Squibb and Glaxo; Dr Mehra reports no direct conflicts pertinent to the development of this consensus document. Other general conflicts include consulting relationships with Abbott, Medtronic, Janssen, Mesoblast, Portola, Bayer, NupulseCV, FineHeart, Leviticus, and Triple Gene. Dr Mehra is also Editor in Chief of the Journal of Heart and Lung Transplantation. The remaining primary authors report no conflicts of interest. The conflicts of other authors and group members are outlined in detail in the accompanying online supplement; this work was commissioned, reviewed, and approved by the International Society for Heart and Lung Transplantation.

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