

7.03.14 Hepatitis C Positive Organs for Transplantation to Non-Viremic Patients**Original Policy Date:** August 1, 2019 **Effective Date:** August 1, 2019**Section:** 2.0 Medicine **Page:** Page 1 of 25**Policy Statement**

The transplantation of Hepatitis C Virus (HCV)-viremic solid organs (kidney, lung, heart, liver, small bowel, pancreas) to a HCV non-viremic recipient with a plan to use direct-acting antiviral treatment for HCV is considered **investigational**.

Policy Guidelines

The American Society of Transplantation Consensus Conference on the use of hepatitis C viremic donors in solid organ transplantation concluded that the transplantation of organs from HCV viremic donors into HCV-negative recipients should be conducted only under monitored IRB-approved protocols and studies. (See Supplemental Information)

Coding

The following CPT codes may be used for this transplant:

Kidney Transplant codes

- 50300-50365
- 50547

Pancreas Transplant codes

- 48550-48554

Small Bowel Transplant codes

- 44120-44121
- 44132-44136
- 44715-44721

Liver Transplant codes

- 47133-47147

Lung Transplant codes

- 32850-32856

Heart Lung Transplant codes

- 33930-33935

Heart Transplant codes

- 33940-33945

The following HCPCS codes may be used for this transplant:

Lung Transplant codes

- S2065
- S2053
- S2054-S2055
- S2060-S2061

Description

In patients with end-stage organ failure, donor organ shortage is a growing concern and there is increasing consideration of use of increased infectious risk, as well as otherwise medically marginal, donors. Hepatitis C virus (HCV)-infected donor organs are typically discarded. The availability of direct-acting antiviral agents (DAA) has made it possible to effectively treat most hepatitis C-infected patients including those who develop acute hepatitis infection after receiving an organ transplant from a hepatitis C viremic donor.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Solid organ transplant represents donor and recipient surgical procedures and, as such, is not subject to regulation by the U.S. Food and Drug Administration (FDA).

Direct-Acting Antiviral Treatment

There are multiple drug combinations approved by the FDA for the treatment of chronic HCV infection. Drug regimen choice and duration of treatment are based on the HCV genotype as well as the degree of liver cirrhosis.

The FDA (2016) approved a fixed-dose combination tablet containing sofosbuvir, a drug previously approved in 2013, and valopate which was the first DAA to treat HCV genotypes 1-6. (Epclusa - Gilead Sciences)

In 2017, two pangenotypic products were approved by the FDA. A once-daily single tablet containing the nucleotide analog nonstructural protein NS5B polymerase inhibitor sofosbuvir, the HCV NS5A inhibitor velpatasvir, and pangenotypic HCV NS3/4A protease inhibitor voxilaprevir was approved to treat adults with chronic HCV genotypes 1 through 6 without cirrhosis or with mild cirrhosis. This product is also indicated in patients who have been previously treated with the DAA drug sofosbuvir or other drugs for HCV that inhibit NS5A. (Vosevi - Gilead Sciences)

The combination of glecaprevir and pibrentasvir was approved for the treatment of adults with chronic HCV infection across all genotypes 1-6 without cirrhosis or with compensated cirrhosis, including patients with moderate to severe kidney disease and those who are on dialysis. The products are also approved for patients with HCV genotype 1 infection who have been previously treated with a regimen containing an NS5A inhibitor or an NS3/4A protease inhibitor but not both. (Mavyret - AbbVie)

There is no specific labeling of DAA treatment for post-exposure prophylaxis for persons exposed to HCV blood or contaminated body fluids.

Rationale

Background

Long wait times for solid organ transplant and the high-risk of mortality while on the transplant waiting list for a kidney, thoracic organ, liver, and other solid organs have prompted an investigation into strategies to increase organ allocation and decrease discard rates of potentially viable donor organs. Although organs from HCV-infected donors have historically been transplanted only into recipients with preexisting HCV infection, direct-acting antiviral (DAA) HCV drugs achieve cure rates greater than 95% with well-tolerated side effects, thus enlarging the pool of organs for waitlisted patients who might consider accepting HCV-infected organs.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

RCTs of transplantation of a hepatitis C virus (HCV) viremic solid organ into an HCV non-viremic donor that would exclude the use of direct-acting antiviral (DAA) in a comparator arm would not meet the requirement of clinical equipoise.

Evaluation of published literature on transplantation issues related to HCV-HIV, HCV-HBV or HCV-HIV-HBV co-infections as well as cytomegalovirus transmission or reactivation is beyond the scope of this policy.

There is considerable literature on transplantation of high-risk solid organ donors HCV-infected recipients in the pre-DAA treatment era. This literature is not evaluated in the report except for the consideration of liver transplantation.

Evaluation of the published literature related to choices and/or modification of post-transplant immunosuppression regimens including drug-drug interactions is also beyond the scope of this policy.

Study limitations tables have not been prepared because all of the publications reviewed are acknowledged as either pilot studies, ongoing trials with preliminary results or case reports. Statistical analyses were limited or nonexistent under these circumstances.

Kidney Transplantation

Clinical Context and Therapy Purpose

The purpose of transplanting a kidney from an HCV viremic donor to an HCV non-viremic recipient is to reduce waiting time to transplant and waitlist-associated morbidity and mortality and to reduce the discard of otherwise healthy solid organs. The purpose of using DAAs to treat HCV non-viremic recipients who may become viremic upon receiving a solid organ transplant from HCV viremic donors is to treat or prevent acute HCV infection and thereby prevent associated acute and chronic downstream sequelae of transplant acquired HCV infection.

The purpose of a kidney transplant from an HCV viremic donor to an HCV non-viremic recipient who has end-stage renal disease is to provide a treatment option that is an alternative to or an improvement on existing management.

The question addressed in this evidence review is: Does kidney transplant from an HCV viremic donor to an HCV non-viremic recipient who has end-stage renal disease result in an improvement in net health outcomes?

The following PICO were used to select literature to inform this review.

Patients

The relevant population(s) of interest are individuals who are HCV non-viremic, on the waiting list for a kidney transplant and in whom the benefit of accepting a solid organ transplant from an HCV viremic donor may outweigh the harms in comparison to waiting for a solid organ from an HCV-negative donor.

Interventions

The therapy being considered is kidney transplant from an HCV viremic donor combined with DAA agents for HCV. Recipients would receive guideline-directed therapy for the treatment of acute HCV infection. Solid organ transplant is provided in a tertiary inpatient setting staffed and equipped to perform the surgical procedure and postsurgical intensive care. Treatment of HCV non-viremic recipients would be managed by infectious disease specialists, transplant surgeons, and nephrologists.

Comparators

The following therapies are currently being used to make decisions about kidney transplantation: continued disease management on a waiting list until an HCV non-viremic donor kidney is available for transplant.

Outcomes

The general outcomes of interest are overall survival (OS), disease-specific survival, and change in disease status, treatment-related mortality and treatment-related morbidity.

Specific outcomes include incidence of HCV viremia and sustained virological response (SVR) rates after use of DAA agents in the transplant recipient at 12 weeks after completion of HCV treatment, assessment of transplanted organ function, the incidence of organ rejection, graft survival, OS and time on waitlist.

There is also a potential for harm resulting from increased post-transplant complications associated with HCV allograft infection among those who fail to achieve an SVR with initial treatment with DAAs and are at risk of developing acute HCV infection with fibrosing cholestatic hepatitis (FCH). HCV associated FCH is a well-described complication in association with liver and kidney transplantation. In severe cases, the graft may be lost with a need for another transplant. There are multiple clinical scenarios including relapse of HCV infection in an HCV-negative donor organ and acute HCV infection with the transplantation of an HIV-viremic organ into an HCV-negative recipient. Additional precipitating factors that have been reported

include the use of azathioprine and co-infection with hepatitis B. The effect of highly effective DAA treatment has been hypothesized to decrease the likelihood of FCH.

Most of the information on outcomes associated with the use of an HCV positive donor kidney transplant has been in HCV positive recipients in the pre-DAA era. A decrement in survival has been demonstrated compared to receiving an HCV-negative graft. However, there remains an OS advantage over remaining on dialysis. The use of a high-risk donor also reduces the kidney transplant waiting time. (Kucirka)

Study Selection Criteria

Evidence reviews have used a best available evidence approach. Methodologically credible studies were selected using the following principles:

To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

Studies with duplicative or overlapping populations were excluded.

Goldberg et al (2017) reported preliminary results of the Transplanting Hepatitis C Kidneys into Negative Kidney Recipients (THINKER) trial; an open-label, single-arm trial that transplanted ten patients without HCV with kidneys from HCV-infected donors with positive HCV nucleic acid test (NAT) at the time of transplant.¹ All donors were genotyped prior to transplantation and donated kidneys were restricted to genotype 1 infection and the use of elbasvir-grazoprevir for treatment. All recipients developed viremia within 3 days post-transplant and were then immediately treated with DAA genotype and continued for 12 weeks. All patients had a negative HCV RNA by day 30 of therapy and 100% achieved a durable cure of HCV infection. Elbasvir-grazoprevir, which is approved for patients with any level of baseline kidney function, was well tolerated in the immediate post-transplant period. One patient, who had a prior diagnosis of IgA treated nephropathy, developed focal segmental glomerulosclerosis in the transplanted kidney that was possibly related to DAA therapy.

Reese et al (2018) reported longer follow-up (12 months) of the original THINKER study participants as well as 6-month outcome data for an additional 10 participants.² Additional details on participant inclusion criteria were available in this publication; participants were seronegative for HIV, HCV RNA, and hepatitis B surface antigen and had no acceptable living kidney donor. No substantial evidence of liver disease was detected via FibroScan (Echosens) imaging or hepatic serologic testing. Evaluation by a hepatologist and/or a transplant surgeon had to show no overt contraindication for liver transplant in the unlikely event of acute liver failure after HCV transmission during a kidney transplant.

Five patients in the 20-participant cohort experienced transient aminotransferase levels.

QOL assessment was reported for the first cohort of participants via in-person administration of the RAND-36 questionnaire at enrollment and post-transplant weeks 4, 16, 24, and 52. The Physical Component Summary and Mental Component Summary scores were calculated from the 8 RAND-36 domains and normalized to population standards, with higher scores indicating better QOL. Normalized mean Physical Component Summary scores decreased at 4 weeks and then increased steadily to above pretransplant levels (the mean improvement in Physical Component Summary score from consent to 12 months after transplant was 6.7 [p = 0.012]).

Normalized mean Mental Component Summary scores also decreased at 4 weeks and subsequently returned to baseline and remained stable by 12 months ($p = 0.47$).

Durand et al (2018) reported on the Exploring Renal Transplants Using Hepatitis C Infected Donors for HCV Negative Recipients (EXPANDER) Trial, an open-label nonrandomized study of 10 recipients of HCV-infected kidneys who received HCV treatment at the time of transplant.³ EXPANDER did not restrict transplantation to donors infected with HCV genotype 1 and therefore used elbasvir-grazoprevir supplemented with sofosbuvir for 12 weeks for recipients of kidneys infected with genotype 2 or 3. One participant developed transient asymptomatic transaminase levels greater than 5 times the upper limit of normal which resolved by day 14 without intervention.

The key characteristics and results of these studies are summarized in Tables 1 and 2.

Table 1. Summary of Key Trials: Study Characteristics Transplantation of HCV-Infected Kidney

Study	Study.Type	Country	Dates	Participants	Treatment		Follow.Up
					1	2	
1 Goldberg (2017) ¹ NCT02743897THINKER-1	Pilot Prospective Interventional	US Single site	2016-ongoing	10 HCV non-viremic listed for kidney transplant	HCV genotype1-viremic donor kidney + 12 weeks of GZR-EBR	NA	12 weeks
2 Reese (2018) ² NCT02743897THINKER-2	Pilot Prospective Interventional	US Single site	2016-ongoing	10 HCV non-viremic listed for kidney transplant	HCV genotype1-viremic donor kidney + 12 weeks of GZR-EBR	NANA	12 months
3 Durand (2018) ³ NCT02781649EXPANDER-1	Open-Label Non-Randomized	US Single site	2016-2018	10 HCV non-viremic	Preoperative single dose GZR-EBR + HCV genotype1-viremic donor kidney + 12 weeks of GZR-EBR OR HCV genotype 2 or 3 viremic donor + 12 weeks of GZR-EBR + SOF	NA	12 weeks

4

EXPANDER-1: Exploring Renal Transplants Using Hepatitis C Infected Donors for HCV-negative Recipients; GZR-EBR: grazoprevir/elbasvir; NA: not applicable; SOF: sofosbuvir; THINKER: Transplanting Hepatitis C Kidneys into Negative Kidney Recipients

Table 2. Summary of Key Trials Study Results Transplantation of HCV-Infected Kidney

Study	Primary Outcome1	Primary Outcome2	Primary.Safety.Outcome	X	Secondary Outcome1
1 Goldberg (2017) ¹ NCT02743897THINKER	N(%)				
2	10 (100%)1At 12 weeks	02	1 recipient with FSGS3		
3					4 median 6 month

Study	Primary Outcome1	Primary Outcome2	Primary.Safety.Outcome	X	Secondary Outcome1
					(IQR)Serum Cr: 1.1 mg/dl (0.8 - 1.3mg/dl)GFR: 62.8ml/minute per 1.73 m2 (51.8-83.1)
4 Reese (2018) ² NCT02743897THINKER-1	THINKER-2	10(100%)1At 12 months10(100%)At 12 weeks	0202	0303	
5					
6 Durand (2018) ³ NCT02781649EXPANDER-1		10 (100%)1	02	03	4 median 12 week Serum Cr 1.05 mg/dl (range 0.9-2 mg/dl)GFR: 63.5 ml/minute per 1.73m2 (IQR: 47.8-69.9)

Cr: creatinine; EXPANDER-1: Exploring Renal Transplants Using Hepatitis C Infected Donors for HCV-negative Recipients; FSGS: focal segmental glomerulosclerosis; GFR: glomerular filtration rate; IQR: interquartile range; THINKER: Transplanting Hepatitis C Kidneys into Negative Kidney Recipients Post-treatment sustained virologic response (SVR). The primary analysis based on a calculation of SVR rates (number of subjects with SVR-12; negative HCV RNA 12 weeks after completing HCV therapy) / (number of subjects treated with HCV therapy post-kidney transplantation)2. Major adverse events attributable to HCV therapy (GZR-EBR and SOF if required) in post-kidney transplant patients. 3. Allograft rejection 4 Renal function indices: serum creatinine level (Cr) and glomerular filtration rate (GFR)

Section Summary: Kidney Transplantation

For individuals who are HCV non-viremic who have end-stage renal disease and are candidates for a kidney transplant the evidence for the use of HCV viremic donor organs as an alternative to continuing dialysis or other appropriate treatment and remaining on the transplant wait-list consists of preliminary results of two open-label nonrandomized trials (THINKER and EXPANDER). The primary outcomes were SVR and graft function and survival. Major adverse events attributable to the selected HCV DAA regimen was also assessed. To date, the experience of 30 participants has been reported in the literature. Participants generally had comparable demographic characteristics. The studies differed in whether or not donor kidneys were genotyped in advance of transplantation. Appropriate DAA regimens were chosen to match genotype or pangenotypic was used. There were differences in the timing of administration of the DAA regimen, but all participants were followed to ascertain the need for extension of the original regimen or addition of another drug. All recipients showed evidence of HCV nucleic acid positivity and viral loads were determined in some instances. All recipients had SVR by the completion of the appropriate DAA regimen with the longest follow-up out to 12 months in 10 participants. There were no reports of allograft rejection or renal function abnormalities. Transient elevations in liver transaminases were reported but not in all participants. Assessment of QOL by standard patient-reported measures in the first ten participants of the THINKER cohort indicated that QOL was initially diminished in the early postoperative period. At 12 months, the physical component score of the RAND-36 questionnaire improved beyond baseline but the mental component score returned to baseline. The evidence is insufficient to determine the effects of the technology on health outcomes.

Lung Transplantation

Clinical Context and Therapy Purpose

The purpose of transplanting a lung from an HCV viremic donor to an HCV non-viremic recipient is to reduce waiting time to transplant and waitlist-associated morbidity and mortality and to reduce the discard of otherwise healthy solid organs. The purpose of using DAAs to treat HCV non-viremic recipients who may become viremic upon receiving a solid organ transplant from

HCV viremic donors is to treat or prevent acute HCV infection and thereby prevent associated acute and chronic downstream sequelae of transplant acquired HCV infection.

The purpose of lung transplant from an HCV viremic donor to an HCV non-viremic recipient who has end-stage pulmonary disease is to provide a treatment option that is an alternative to or an improvement on existing management.

The question addressed in this evidence review is: Does lung transplant from an HCV viremic donor to an HCV non-viremic recipient who has end-stage pulmonary disease result in an improvement in net health outcomes?

The following PICO were used to select literature to inform this review.

Patients

The relevant population(s) of interest are individuals who are HCV non-viremic, on the waiting list for a lung transplant and in whom the benefit of accepting a solid organ transplant from an HCV viremic donor may outweigh the harms in comparison to waiting for a solid organ from an HCV-negative donor.

Interventions

The therapy being considered is lung transplant from an HCV viremic donor combined with DAA agents for HCV. Recipients would receive guideline-directed therapy for the treatment of acute HCV infection. Solid organ transplant is provided in a tertiary inpatient setting staffed and equipped to perform the surgical procedure and postsurgical intensive care. Treatment of HCV non-viremic recipients would be managed by infectious disease specialists, transplant surgeons, and pulmonologists.

Comparators

The following therapies are currently being used to make decisions about lung transplantation: continued disease management on a waiting list until an HCV non-viremic donor lung is available for transplant.

Outcomes

The general outcomes of interest are OS, disease-specific survival, and change in disease status, treatment-related mortality and treatment-related morbidity.

Study Selection Criteria

Evidence reviews have used a best available evidence approach. Methodologically credible studies were selected using the following principles:

To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

Studies with duplicative or overlapping populations were excluded.

Woolley et al (2019) conducted a trial involving transplantation of HCV viremic hearts and lungs from donors to adults without HCV infection and reported the results on 44 patients.⁴ Donors were not selected on the basis of HCV genotype and DAA with sofosbuvir-velpatasvir was administered preemptively immediately after organ transplant and continuing for four weeks. The DAA regimen provided pangenotypic coverage and is not associated with

immunosuppressive drug interactions. The four-week duration of DAA was used based on the investigator assumption that the HCV viral load transmission would be low at the time of transplantation. The primary outcomes were SVR at 12 weeks (16 weeks after transplantation) and 6-month graft survival. The key characteristics and results of the study are summarized in Tables 3 and 4. An additional exploratory 6-month post hoc analysis was done of transplantation outcomes from a population of 56 trial participants for whom HCV negative donor organs became available. These participants had higher listing Organ Procurement and Transplantation Network status. Acute cellular rejection occurred more frequently in lung transplant recipients of HCV positive donors, but the duration of follow-up is insufficient to determine the effect on long-term graft survival.

The significance of the eclipse period and the sensitivity of available NAT for HCV was assessed by Watson et al (2017).⁵ A single-center retrospective review of a prospectively collected database for lung transplant recipients including HCV Banat- donors sought to ascertain the rate of seroconversion. Between 1/1/17 and 8/9/17, a total of 64 HCV Ab- recipients underwent lung transplantation. The recipients of 13 (20%) HCV Banat- donors underwent protocol NAT at 2 and 12 months and all were NAT- at the time of publication. One recipient developed reactive HCV Ab at six months post-transplant with follow-up HCV RNA undetectable.

Table 3. Summary of Key Trials: Study Characteristics Transplantation of HCV-Infected Heart and Lung

Study	Study.Type	Country	Dates	Participants	Treatment 1	Treatment 2	Follow .Up
1 Wooley (2019) ⁴ NCT03086044DONATE HCV	Pilot Prospective Interventional	US Sing le site	2017-ongoi ng	53HCV non-viremic listed for heart or lung transplant	53 HCV positive donors44 HCV NAT positive(36 lung and 8 heart) + 4 weeks of SOF - VEL	NA	SVR -12 weeks Graft survival -6 months

2

DONATE HCV: Donors of Hepatitis C NAT [nucleic acid amplification test] Positive Thoracic Allografts for Transplantation in Non-HCV Recipients; NA: not applicable; SOF: sofosbuvir; SVR: sustained virologic response; VEL: velpatasvir.

Table 4. Summary of Key Trials Study Results Transplantation of HCV-Infected Heart and Lung

Study	X	X	X	X	X
1 Wooley (2019) ⁴ NCT03086044DONATE HCV					
2	Total participants N=35	Lung transplant recipientsN= 28	Heart transplant recipientsN=7		
3	n(%)	n(%)	n(%)		
4 HCV Ab +: 1 week HCV Ab+: 6 months	27(77)17(49)				
5 SVR 12 weeksSVR 24 weeks	35 (100)35 (100)				
6 Acute cellular rejection requiring treatment		15(54)	3(43)		
7 Graft survival 1 month 6 months		28(100)28(100)	7(100)7(100)		
8 Adverse Events DAAs HCV infection	00				

DAA: direct-acting antiviral; HCV Ab+: hepatitis C antibody positive; SVR: sustained virologic response.

Section Summary: Lung Transplantation

For individuals who are HCV non-viremic who have end-stage pulmonary disease and are candidates for lung transplant the evidence for the use of HCV viremic donor organs as an alternative to continuing appropriate medical treatment and remaining on the transplant wait-list consists of preliminary results of a single open-label nonrandomized trial of 36 HCV viremic lung transplants treated with 4 weeks of pangenotypic DAAs. The primary outcomes were SVR and graft function and survival. SVR at 12 weeks and graft survival at 6 months was available for 28 participants and both rates were 100%. The evidence is insufficient to determine the effects of the technology on health outcomes.

Heart Transplantation

Clinical Context and Therapy Purpose

The purpose of transplanting a heart from an HCV viremic donor to an HCV non-viremic recipient is to reduce waiting time to transplant and waitlist-associated morbidity and mortality and to reduce the discard of otherwise healthy solid organs. The purpose of using DAAs to treat HCV non-viremic recipients who may become viremic upon receiving a solid organ transplant from HCV viremic donors is to treat or prevent acute HCV infection and thereby prevent associated acute and chronic downstream sequelae of transplant acquired HCV infection. The purpose of a heart transplant from an HCV viremic donor to an HCV non-viremic recipient who has end-stage cardiac disease is to provide a treatment option that is an alternative to or an improvement on existing management.

The question addressed in this evidence review is: Does heart transplant from an HCV viremic donor to an HCV non-viremic recipient who has end-stage cardiac disease result in an improvement in net health outcomes?

The following PICO were used to select literature to inform this review.

Patients

The relevant population(s) of interest are individuals who are HCV non-viremic, on the waiting list for a heart transplant and in whom the benefit of accepting a solid organ transplant from an HCV viremic donor may outweigh the harms in comparison to waiting for a solid organ from an HCV negative donor.

Interventions

The therapy being considered is heart transplant from an HCV viremic donor combined with DAA agents for HCV. Recipients would receive guideline-directed therapy for the treatment of acute HCV infection. Solid organ transplant is provided in a tertiary inpatient setting staffed and equipped to perform the surgical procedure and postsurgical intensive care. Treatment of HCV non-viremic recipients would be managed by infectious disease specialists, cardiothoracic surgeons, and cardiologists.

Comparators

The following therapies are currently being used to make decisions about heart transplantation: continued disease management on a waiting list until an HCV non-viremic donor heart is available for transplant.

Outcomes

The general outcomes of interest are OS, disease-specific survival, and change in disease status, treatment-related mortality and treatment-related morbidity.

Study Selection Criteria

Evidence reviews have used a best available evidence approach. Methodologically credible studies were selected using the following principles:

To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

Studies with duplicative or overlapping populations were excluded.

The report by Woolley et al (2019) described above and summarized in Tables 3 and 4, included 8 heart transplant recipients; 7 of whom survived to assess the primary outcomes of SVR at 12 weeks and graft survival at 6 months.⁴ Both rates were 100%. The eighth recipient died of bacterial sepsis that was not judged to be related to either DAAs or acute HCV infection.

McLean et al (2019) reported a pilot trial, Using Hepatitis c positive hearts for negative Recipients (USHER), that was intended to determine the safety and efficacy of transplanting 10 hearts from HCV-viremic donors into HCV negative patients followed by treatment with elbasvir/grazoprevir treatment upon detection of HCV viremia (NCT03146741; sponsor: Merck).⁶ The cobas HCV Test, for use on the 6800/8800 Systems (Roche Diagnostics Systems, Inc.) with an analytic sensitivity of approximately 15 IU/mL of plasma was used for HCV viral load surveillance in recipients. The investigators report that they did not use an “on-call” to the operating room treatment protocol for the following reasons; post-transplant treatment on day three increased the likelihood that patients were clinically stable at the time of treatment initiation with a reduced likelihood of treatment interruption for transplant complications; to better reflect a real-world scenario where DAA therapy might not be available at the time of transplantation due to hospital formulary policies; and to provide data on the HCV transmission rates via transplantation. Key study characteristics and results are summarized in Tables 5 and 6.

Table 5. Summary of Nonrandomized Trial Study Characteristics-Heart Transplant

Study	Study.Type	Country	Dates	Participants	Treatment	X Follow.U p
1 McLean (2018) ⁶ NCT03146741USHER	Pilot Single Arm Interventional	USSingle site	2017-2018	20 adult HCV-negative patients enrolled 10 transplanted at time of publication	Genotype 1 HCV-viremic donors + EBR-GZR treatment upon detection of HCV viremia	6-12 months
2						

EBR-GZR = elbasvir-grazoprevir; HCV: hepatitis C virus; USHER: Using Hepatitis c positive hearts for negative Recipients.

Table 6. Summary of Nonrandomized Trial Study Results- Heart Transplant

Study	X	X	X	X
1 McLean (2018) ⁶ NCT03146741USHER	N=10			
2				
3 Viral load Day 3Viral load undetectable week 4 EBR-GZR SVR 12 weeksNS5A resistance in genotype 1a	25 IU/ml - 40 million IU/ml9/1010/1019/10; negative1/10; indeterminate			
4 Grade 2R ACRSevere AMR resulting in death	2/101/10			
5				
6				

ACR: acute cellular rejection; 2R: moderate rejection; AMR: antibody mediated rejection; EBR-GZR = elbasvir-grazoprevir; SVR: sustained virologic response;1 EBR-GZR treatment was empirically extended to 16 weeks with the addition of oral ribavirin in 1 heart recipient based on the non-responder viral load status of a kidney recipient from the same donor. Ribavirin was discontinued secondary to anemia.

Case reports and series are summarized in Tables 7 and 8. Gottlieb et al (2017) reported a single case of an HCV Ab- adult female patient with biventricular heart failure, Organ Procurement and Transplantation Network status 1A and who was not a candidate for the bridge to transplant mechanical ventricular assist.⁷ An HCV Ab and NAT+ donor heart was transplanted. An unanticipated post-transplant management issue was reported given that there was an insufficient donor sample to perform HCV genotyping. The recipient developed an HCV viral load sufficient to perform genotyping by day 13 after transplant. At that time, DAA with sofosbuvir-velpatasvir was initiated. HCV genotype 3a was identified and the patient completed 12 weeks of DAA treatment with last dose on post-transplant day 96. HCV viral titers were negative by post-transplant day 23 and remained negative.

Radzi (2019) provided the only identified experience with pediatric heart transplantation of HCV-antibody positive patients by inquiry of the United Network for Organ Sharing, the U.S. private nonprofit organization that administers the Organ Procurement and Transplantation Network.⁸ Post-transplant survival was the only outcome available for three infants who received an HCV Ab+ donor heart.

Table 7. Summary of Key Case Reports and Series Characteristics - Heart Transplant

	Study	Country	Participants	Treatment.Delivery	Follow.Up
1	Gottlieb (2017) ⁷	USSingle site	Patient 1 HCV-seronegativefemale	HCV NAT-positive donor + SOF-VEL 12 weeks	1 year
2	Jawad (2018) ⁹	GermanySingle site	Patient 1 HCV-seronegativemale	HCV seropositive donorYear 4: SOF+DCV	5 years
3	Moayed (2018) ¹⁰	USSingle site	Patient 1 HCV-seronegativemalePatient 2 HCV-seronegativeFemale with LVAD	HCV NAT-positive donor + SOF-VEL 12 weeks initiated at 2 weeks post-transplantHCV NAT-positive donor + SOF-VEL 12 weeks initiated at 2 weeks post-transplant	12 weeks
4	Radzi (2019) ⁸	US registry	3 HCV-seronegative infants < 1year of age with CHD	HCV seropositive donor	0.38 to 5.91 years

CHD: congenital heart disease; DCV: daclatasvir; HCV: hepatitis C virus; LVAD: left ventricular assist device; NAT: nucleic acid testing; SOF: sofosbuvir; VEL: velpatasvir.

Table 8. Summary of Key Case Reports and Series Results - Heart Transplant

	Study	Treatment	Outcome.1SVR	Outcome.2Graft.survival	Outcome.31
1	Gottlieb (2017) ⁷	HCV NAT-positive donor + SOF-VEL 12 weeks	Sustained at 1 year	No rejection episodes	No renal or hepatic AEsNo hospitalization
2	Jawad (2018) ⁹	HCV seropositive donorYear 4: SOF+DCV	Sustained at 6 months	No rejection episodes	Progression of CAVPreservation of LVEF (60%)
3	Moayed (2018) ¹⁰	HCV NAT-positive donor + SOF-VEL 12 weeks initiated at 2 weeks post-transplant	SVR at 12 weeks in patients 1 and 2	NR	NR
4	Radzi (2019) ⁸	HCV seropositive donor	No HCV treatment reported	2 alive at 5.91 and 1.91 years1 dead at .38 years due to respiratory failure	NR

AEs: adverse events; CAV: cardiac allograft vasculopathy; DCV: daclatasvir; HCV: hepatitis C virus; LVEF: left ventricular ejection fraction; NAT: nucleic acid testing; NR: not reported; SOF: sofosbuvir; SVR: sustained virologic response; VEL: velpatasvir. 1secondary outcomes as indicated.

Section Summary: Heart Transplantation

For individuals who are HCV non-viremic who have end-stage cardiac disease and are candidates for heart transplant the evidence for the use of HCV viremic donor organs as an alternative to continuing appropriate medical treatment and remaining on the transplant wait-list consists of preliminary results of 2 single-arm, open-label nonrandomized trials that total 17

HCV viremic heart genotype 1 transplants. The primary outcomes were SVR and graft function and survival. Trial protocols differed in the timing of administration and duration of DAA with elbasvir/grazoprevir. All recipients achieved an SVR including when the extension of treatment was required. Each trial reported a death; one unrelated to DAA or HCV infection and the other due to antibody mediated graft rejection in a patient who had a positive cross-match. Several case reports have published outcomes for four adults and three infants less than one year of age. The results for the pediatric cases were derived from the national transplant registry and only included graft and OS. The evidence is insufficient to determine the effects of the technology on health outcomes.

Liver Transplantation

Clinical Context and Therapy Purpose

The purpose of transplanting a liver from an HCV viremic donor to an HCV non-viremic recipient is to reduce waiting time to transplant and waitlist-associated morbidity and mortality and to reduce the discard of otherwise healthy solid organs. The purpose of using DAAs to treat HCV non-viremic recipients who may become viremic upon receiving a solid organ transplant from HCV viremic donors is to treat or prevent acute HCV infection and thereby prevent associated acute and chronic downstream sequelae of transplant acquired HCV infection.

The purpose of a liver transplant from an HCV viremic donor to an HCV non-viremic recipient who has end-stage liver disease is to provide a treatment option that is an alternative to or an improvement on existing management.

The question addressed in this evidence review is: Does liver transplant from an HCV viremic donor to an HCV non-viremic recipient who has end-stage liver disease result in an improvement in net health outcomes?

The following PICO were used to select literature to inform this review.

Patients

The relevant population(s) of interest are individuals who are HCV non-viremic, on the waiting list for a liver transplant and in whom the benefit of accepting a solid organ transplant from an HCV viremic donor may outweigh the harms in comparison to waiting for a solid organ from an HCV negative donor.

Interventions

The therapy being considered is a liver transplant from an HCV viremic donor combined with DAA agents for HCV. Recipients would receive guideline-directed therapy for the treatment of acute HCV infection. Solid organ transplant is provided in a tertiary inpatient setting staffed and equipped to perform the surgical procedure and postsurgical intensive care. Treatment of HCV non-viremic recipients would be managed by infectious disease specialists, transplant surgeons, and hepatologists.

Comparators

The following therapies are currently being used to make decisions about liver transplantation: continued disease management on a waiting list until an HCV non-viremic donor liver is available for transplant.

Outcomes

The general outcomes of interest are OS, disease-specific survival, and change in disease status, treatment-related mortality and treatment-related morbidity. HCV associated FCH is a well-described complication in association with liver and kidney transplantation. In severe cases, the graft may be lost with a need for another transplant. There are multiple clinical scenarios including relapse of HCV infection in an HCV negative donor organ and acute HCV infection with the transplantation of an HIV-viremic organ into an HCV negative recipient. Additional precipitating factors that have been reported include the use of azathioprine and co-infection

with hepatitis B. The effect of highly effective DAA treatment has been hypothesized to decrease the likelihood of FCH.

Study Selection Criteria

Evidence reviews have used a best available evidence approach. Methodologically credible studies were selected using the following principles:

To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

Studies with duplicative or overlapping populations were excluded.

Luckett et al (2019) reported a prospective review of all HCV nonviremic liver transplant patients who had received HCV Ab+/NAT- donor organs during a 1 year period.¹¹ The recipients were compared to a group from the same center who had received a U.S. Public Health Service increased-risk HCV Ab-/NAT- donor liver. The only baseline difference was in the MELD score at the time of transplantation indicating a higher status on the transplant list for those who received the HCV Ab and NAT- organs. The study explored the potential for viremia to be observed in the HCV Ab+ and NAT- population of 53 patients; 2 patients in the original population of 55 died before HCV testing was carried out. A positive HCV NAT was found in five recipients; four of whom underwent HCV anti-viral treatment with subsequent SVR. The fifth recipient died of unrelated causes. This finding raised the possibility of a false-negative NAT in the donor but with low probability due to the high sensitivity of currently available NAT testing. The authors discussed the possibility of a reservoir of occult HCV infection of the liver; however, no tissue was available for analysis in either donors or recipients. The key characteristics and results of this study are summarized in Table 9 and 10.

Table 9. Summary of Key Observational Comparative Study Characteristics - Liver Transplant

Study	Study.Type	Country	Dates	Participants	Group.1	Group.2	Follow.Up	
1	Luckett (2018) ¹¹	Prospective	USsingle site	2016-2018	112	Recipient of HCV Ab+ /NAT-donor liver n=55	Recipient of HCV Ab-/NAT- donor livern=57	1 year

2

HCV Ab+: hepatitis C antibody positive; HCV Ab-: hepatitis C antibody negative; NAT-: nucleic acid test negative

Table 10. Summary of Key Observational Comparative Study Results-Liver Transplant

Study	X	X	X	X	X
1	Luckett (2018) ¹¹				
2		HCV Ab+/NAT-Recipientn=55	HCV Ab-/NAT-recipientn=57		
3	PHS increased-risk criteria, n (%)	43 (78)	57 (100)		
4	Donor HCV NAT performed in eclipse period, n (%)	51 (93)	56 (98)		
5	HCV viremia detected in recipient n (%)	5 (9.3%)	0		
6					
7	Graft loss, n/N (%) 3 months 1 year Overall	2/55 (3.6)5/37 (13.5)8/55 (14.5)	3/57 (5.3)4/42 (9.5)7/57 (12.3)		

Study	X	X	X	X	X
8 Mortality, n/N (%) 3 months 1 year	2/55 (3.6)4/36	3/57 (5.3)4/42			
Overall	(11.1)7/54 (13.0)	(9.5)6/56 (10.7)			

HCV Ab+: hepatitis C antibody positive; HCV AB-: hepatitis C antibody negative; NAT-: nucleic acid test negative; PHS: U.S. Public Health Service.

A total of 12 patients have been identified in case reports and case series who were transplanted with HIV Ab + or NAT+ liver donors. The majority of the patients had prior HCV infection, were treatment experienced and HCV NAT- at the time of transplantation. All patients were found to be NAT+ after transplantation and received DAA at a wide range of time periods after identification of seroconversion. DAA treatment was provided on the basis of genotype with an appropriate drug combination and duration consistent with the products available at the time. Additional details of key characteristics and results of the case reports are summarized in Table 11 and Table 12.

Table 11. Summary of Key Case Report and Series Characteristics - Liver Transplant

Study	Country	Participants	Treatment.Delivery	Follow.Up
1 Saberi (2018) ¹²	US	57 year old female, HCV genotype 1a post- HCV DAA SVR with Child-Turcotte-Pugh class A cirrhosis	HCV Ab negative/NAT positive donor + 24 weeks LDV/SOF initiated at postoperative day 25	2 years
2 Campos-Varela (2018) ¹³	US/Spain	64 year old male, HCV genotype 1b, post-interferon based regimen and HCC treated with TACE	HCV Ab positive donor	1 year
3 Kwong (2018) ¹⁴	US	10 adult HCV NAT negative patients Prior HCV treated with DAA (70%)	HCV NAT+ liver donor + DAA based on genotype	17 months
4				

Ab: antibody; DAA: direct-acting antiviral; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; LDV: ledipasvir; NAT: nucleic acid test; SOF: sofosbuvir; SVR: sustained virologic response; TACE: transcatheter arterial chemoembolization

Table 12. Summary of Key Case Series Results - Liver Transplant

Study	Treatment	Outcome.1SVR	Outcome.2Graft.survival	Outcome.3AEs
1 Saberi (2018) ¹²	HCV Ab negative/NAT positive donor + 24 weeks LDV/SOF initiated at postoperative day 25	Achieved at 8 weeks Maintained at 2 years	Functioning graft	NR
2 Campos-Varela (2018) ¹³	HCV Ab positive donor	Achieved at 12 weeks post-interferon containing DAA regimen when genotype 3 was identified	Functioning graft	None identified
3 Kwong (2018) ¹⁴	HCV NAT+ liver donor + DAA based on genotype (n)Genotype!A: (4) 1B: (1) 2B: (1) 3: (4)Days to treatment range (11-84)	All 10 achieved SVR after 12-24 weeks of genotype specific DAA	1 ACR+AMR1 ACR1 AMR Successfully treated	1 ribavirin intolerance

Ab: antibody; ACR: acute cellular rejection; AMR: antibody-mediated rejection; DAA: direct-acting antiviral; HCV: hepatitis C virus; LDV: ledipasvir; NAT: nucleic acid; NR: not reported; SOF: sofosbuvir; SVR: sustained virologic response;

Section Summary: Liver Transplantation

For individuals who are HCV non-viremic who have end-stage liver disease and are candidates for liver transplant the evidence for the use of HCV viremic donor organs as an alternative to continuing appropriate medical treatment and remaining on the transplant wait-list consists of a

report from a single- site prospectively evaluating 55 recipients of HCV Ab+/NAT- donors compared to 57 recipients of HCV Ab-/NAT- donors. Graft function and loss were comparable between groups, as was mortality by one year of follow-up. Seroconversion was detected by NAT in five of the HCV Ab+/NAT- recipients. Four were successfully treated with an appropriate HCV antiviral therapy and subsequent SVR. A fifth recipient died before treatment of non-HCV related causes. Several case reports have published outcomes for a total of 12 adults who received HCV viremic liver transplants. A notable finding in the reports is that the majority of recipients had prior HCV infection and had successfully achieved an SVR using genotype-specific DAA when reinfection was identified. The evidence is insufficient to determine the effects of the technology on health outcomes.

Other solid organ Transplantation

Clinical Context and Therapy Purpose

The purpose of transplanting other solid organs (e.g. small bowel or pancreas) from an HCV viremic donor to an HCV non-viremic recipient is to reduce waiting time to transplant and waitlist-associated morbidity and mortality and to reduce the discard of otherwise healthy solid organs. The purpose of using DAAs to treat HCV non-viremic recipients who may become viremic upon receiving a solid organ transplant from HCV viremic donors is to treat or prevent acute HCV infection and thereby prevent associated acute and chronic downstream sequelae of transplant acquired HCV infection.

The purpose of other solid organ transplants from an HCV viremic donor to an HCV non-viremic recipient who has end-stage organ disease is to provide a treatment option that is an alternative to or an improvement on existing management.

The question addressed in this evidence review is: Does other solid organ transplant from an HCV viremic donor to an HCV non-viremic recipient who has end-stage organ disease result in an improvement in net health outcomes?

The following PICO were used to select literature to inform this review.

Patients

The relevant population(s) of interest are individuals who are HCV non-viremic, on the waiting list for a solid organ transplant such as a small bowel or pancreas transplant and in whom the benefit of accepting a solid organ transplant from an HCV viremic donor may outweigh the harms in comparison to waiting for a solid organ from an HCV negative donor.

Interventions

The therapy being considered is a solid organ transplant from an HCV viremic donor combined with DAA agents for HCV. Recipients would receive guideline-directed therapy for the treatment of acute HCV infection. Solid organ transplant is provided in a tertiary inpatient setting staffed and equipped to perform the surgical procedure and postsurgical intensive care. Treatment of HCV non-viremic recipients would be managed by infectious disease specialists, transplant surgeons, and hepatologists.

Comparators

The following therapies are currently being used to make decisions about solid organ transplantation: continued disease management on a waiting list until an HCV non-viremic donor organ is available for transplant.

Outcomes

The general outcomes of interest are OS, disease-specific survival, and change in disease status, treatment-related mortality and treatment-related morbidity.

Study Selection Criteria

Evidence reviews have used a best available evidence approach. Methodologically credible studies were selected using the following principles:

To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

Studies with duplicative or overlapping populations were excluded.

No publications were identified in the last five years that reported on planned transplantation of HCV -viremic solid organs such as small bowel or pancreas into HCV non-viremic recipients. One earlier publication of outcomes for 16 simultaneous pancreas-kidney transplant recipients from HCV positive donors patients identified in the United Network for Organ Sharing database (2000-2011) reported 4 kidney allograft losses and 6 pancreas allograft losses without a known direct relationship to HCV.¹⁵

Section Summary: Other Solid Organ Transplantation

For individuals who are HCV non-viremic who have end-stage organ disease and are candidates for a solid organ transplant such as for small bowel or pancreas, evidence for the use of HCV viremic donor organs as an alternative to continuing appropriate medical treatment and remaining on the transplant wait-list has not been reported in the last five years in the published literature. The evidence is insufficient to determine the effects of the technology on health outcomes.

Summary of Evidence

For individuals who are HCV non-viremic who have end-stage renal disease and are candidates for a kidney transplant the evidence for the use of HCV viremic donor organs as an alternative to continuing dialysis or other appropriate treatment and remaining on the transplant wait-list consists of preliminary results of two open-label nonrandomized trials (THINKER and EXPANDER). The primary outcomes were SVR and graft function and survival. Major adverse events attributable to the selected HCV DAA regimen was also assessed. To date, the experience of 30 participants has been reported in the literature. Participants generally had comparable demographic characteristics. The studies differed in whether or not donor kidneys were genotyped in advance of transplantation. Appropriate DAA regimens were chosen to match genotype or pangenotypic was used. There were differences in the timing of administration of the DAA regimen, but all participants were followed to ascertain the need for extension of the original regimen or addition of another drug. All recipients showed evidence of HCV nucleic acid positivity and viral loads were determined in some instances. All recipients had SVR by the completion of the appropriate DAA regimen with the longest follow-up out to 12 months in 10 participants. There were no reports of allograft rejection or renal function abnormalities. Transient elevations in liver transaminases were reported but not in all participants. Assessment of QOL by the standard patient-reported measures in the first ten participants of the THINKER cohort indicated that QOL was initially diminished in the early postoperative period. At 12 months, the physical component score of the RAND-36 questionnaire improved beyond baseline but the mental component score returned to baseline. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are HCV non-viremic who have end-stage pulmonary disease and are candidates for lung transplant the evidence for the use of HCV viremic donor organs as an alternative to continuing appropriate medical treatment and remaining on the transplant wait-

list consists of preliminary results of a single open-label nonrandomized trial of 36 HCV viremic lung transplants treated with 4 weeks of pangenotypic DAAs. The primary outcomes were SVR and graft function and survival. SVR at 12 weeks and graft survival at 6 months was available for 28 participants and both rates were 100%. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are HCV non-viremic who have end-stage cardiac disease and are candidates for heart transplant the evidence for the use of HCV viremic donor organs as an alternative to continuing appropriate medical treatment and remaining on the transplant wait-list consists of preliminary results of 2 single-arm, open-label nonrandomized trials that total 17 HCV viremic heart genotype 1 transplants. The primary outcomes were SVR and graft function and survival. Trial protocols differed in the timing of administration and duration of DAA with elbasvir/grazoprevir. All recipients achieved an SVR including when the extension of treatment was required. Each trial reported a death; one unrelated to DAA or HCV infection and the other due to antibody mediated graft rejection in a patient who had a positive cross-match. Several case reports have published outcomes for four adults and three infants less than one year of age. The results for the pediatric cases were derived from the national transplant registry and only included graft and OS. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are HCV non-viremic who have end-stage liver disease and are candidates for liver transplant the evidence for the use of HCV viremic donor organs as an alternative to continuing appropriate medical treatment and remaining on the transplant wait-list consists of a report from a single- site prospectively evaluating 55 recipients of HCV Ab+/NAT- donors compared to 57 recipients of HCV Ab-/NAT- donors. Graft function and loss were comparable between groups, as was mortality by one year of follow-up. Seroconversion was detected by NAT in five of the HCV Ab+/NAT- recipients. Four were successfully treated with an appropriate HCV antiviral therapy and subsequent SVR. A fifth recipient died before treatment of non-HCV related causes. Several case reports have published outcomes for a total of 12 adults who received HCV viremic liver transplants. A notable finding in the reports is that the majority of recipients had prior HCV infection and had successfully achieved an SVR using genotype-specific DAA when reinfection was identified. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are HCV non-viremic who have end-stage organ disease and are candidates for a solid organ transplant such as for small bowel or pancreas, evidence for the use of HCV viremic donor organs as an alternative to continuing appropriate medical treatment and remaining on the transplant wait-list has not been reported in the last five years in the published literature. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements

The American Society of Transplantation (2017) convened a consensus conference of experts to address issues related to the transplantation of hepatitis C virus (HCV) viremic solid organs into HCV non-viremic recipients.¹⁶ Key findings and recommendations are summarized in Table 13.

Table 13. American Society of Transplantation Consensus Conference - Use of HCV Viremic Donors

	Content.Area	Key.Point
1	Definition of HCV positive	HCV –viremic reflecting a positive NAT should be adopted
2	Data interpretation	HCV antibody status alone limits interpretation of outcomes of transplantation of HCV “positive” organs
3	Transmission and Treatment	Highest risk for unexpected HCV transmission is associated with organ donation from a person who injected drugs within the eclipse or pre-viremic period

	Content.Area	Key.Point
4	OPTN policy	No current policies prevent transplantation of HCV-viremic organs into HCV non-viremic recipients
5	Ethical considerations	Transplantation of HCV-viremic organs into HCV non-viremic recipients should be conducted under site specific IRB approved protocols with multi-step informed consent.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in April 2019 identified some currently unpublished trials that might influence this review. (Table 14).

Table 14. Summary of Key Trials

	NCT.No.	Trial.Name	Planned.Enrollment	Completion.Date
1	Ongoing-Kidney			
2	NCT02669966	Live Kidney Donors With Positive Anti-HCV Antibody, But Negative HCV PCR	6	Jun 2020
3	NCT02945150	Preemptive Treatment With Grazoprevir and Elbasvir for Donor HCV Positive to Recipient HCV Negative Kidney Transplant	40	Sept 2020
4	NCT02743897	Open-Labeled Trial Of Zepatier For Treatment Of Hepatitis C-Negative Patients Who Receive Kidney Transplants From Hepatitis C-Positive Donors (THINKER)	75	Dec 2021
5	NCT02781649	An Open-label Pilot Study to Determine the Tolerability and Efficacy of Fixed-dose Grazoprevir/Elbasvir Treatment in Hepatitis C Uninfected Recipients of Renal Transplants From Hepatitis C Infected Deceased Donors		
6	NCT03801707	An Open Label, Prospective, Interventional, Proof of Concept Study to Evaluate the Feasibility and Safety of Kidney Transplant From HCV Positive Donors Into HCV Negative Recipient Using Sofosbuvir/Velpatasvir as a Treatment for Post-Transplant HCV Transmission	25	Jan 2022
7	Ongoing-Thoracic			
8	NCT03523871	A Single-center Pilot Study of the Use of Hepatitis C Positive Donors for Hepatitis C Negative Lung Transplant Recipients With Post-transplant Treatment With Mavyret	20	Jun 2020
9	NCT03625687	Pan-genotypic Direct Acting Antiviral Therapy in Donor HCV-positive to Recipient HCV-negative Lung Transplant	25	Apr 2021
10	NCT03222531	Expanding the Pool in Orthotopic Heart Transplantation: The Use of Hepatitis C Positive Donor Hearts in Hepatitis C Negative Recipients	20	Jul 2019
11	NCT03382847	A Single-center Pilot Study of the Use of Hepatitis C Positive Donors for Hepatitis C Negative Heart Transplant Recipients With	10	Oct 2019

	NCT.No.	Trial.Name	Planned.Enrollment	Completion.Date
		Post-transplant Treatment of Hepatitis C Viremia With Mavyret		
12	NCT03146741	Open-Labeled Trial Of Zepatier For Treatment Of Hepatitis C-Negative Patients Who Receive Heart Transplants From Hepatitis C-Positive Donors	20	Dec 2020
13	NCT03086044	Transplanting Thoracic Organs From Hepatitis C Positive Donors to Hepatitis C Uninfected Recipients	100	Dec 2021
14	NCT03208244	Pan-genotypic Direct Acting Antiviral Therapy in Donor HCV-positive to Recipient HCV-negative Heart Transplant	30	Apr 2022
15	Unpublished-Lung			
16	NCT03112044	Lung Transplantation Using Hepatitis C Positive Donors to Hepatitis C Negative Recipients: A Pilot Study Donor lungs will be subjected to normothermic Ex vivo Lung Perfusion (EVLP) for 6 hours for organ assessment and reduction of viral load prior to transplantation.	20	Dec 2018
17	Ongoing-Liver			
18	NCT03208127	Pan-genotypic Direct Acting Antiviral Therapy in Donor HCV-positive to Recipient HCV-negative Liver Transplant	10	Sep 2020

NCT: national clinical trial.

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

IE

The following services may be considered investigational.

Type	Code	Description
CPT®	32850	Donor pneumonectomy(s) (including cold preservation), from cadaver donor
	32851	Lung transplant, single; without cardiopulmonary bypass
	32852	Lung transplant, single; with cardiopulmonary bypass
	32853	Lung transplant, double (bilateral sequential or en bloc); without cardiopulmonary bypass
	32854	Lung transplant, double (bilateral sequential or en bloc); with cardiopulmonary bypass
	32855	Backbench standard preparation of cadaver donor lung allograft prior to transplantation, including dissection of allograft from surrounding soft tissues to prepare pulmonary venous/atrial cuff, pulmonary artery, and bronchus; unilateral
	32856	Backbench standard preparation of cadaver donor lung allograft prior to transplantation, including dissection of allograft from surrounding soft tissues to prepare pulmonary venous/atrial cuff, pulmonary artery, and bronchus; bilateral
	33930	Donor cardiectomy-pneumonectomy (including cold preservation)

Type	Code	Description
	33933	Backbench standard preparation of cadaver donor heart/lung allograft prior to transplantation, including dissection of allograft from surrounding soft tissues to prepare aorta, superior vena cava, inferior vena cava, and trachea for implantation
	33935	Heart-lung transplant with recipient cardiectomy-pneumonectomy
	33940	Donor cardiectomy (including cold preservation)
	33944	Backbench standard preparation of cadaver donor heart allograft prior to transplantation, including dissection of allograft from surrounding soft tissues to prepare aorta, superior vena cava, inferior vena cava, pulmonary artery, and left atrium for implantation
	33945	Heart transplant, with or without recipient cardiectomy
	44120	Enterectomy, resection of small intestine; single resection and anastomosis
	44121	Enterectomy, resection of small intestine; each additional resection and anastomosis (List separately in addition to code for primary procedure)
	44132	Donor enterectomy (including cold preservation), open; from cadaver donor
	44133	Donor enterectomy (including cold preservation), open; partial, from living donor
	44135	Intestinal allotransplantation; from cadaver donor
	44136	Intestinal allotransplantation; from living donor
	44715	Backbench standard preparation of cadaver or living donor intestine allograft prior to transplantation, including mobilization and fashioning of the superior mesenteric artery and vein
	44720	Backbench reconstruction of cadaver or living donor intestine allograft prior to transplantation; venous anastomosis, each
	44721	Backbench reconstruction of cadaver or living donor intestine allograft prior to transplantation; arterial anastomosis, each
	47133	Donor hepatectomy (including cold preservation), from cadaver donor
	47135	Liver allotransplantation, orthotopic, partial or whole, from cadaver or living donor, any age
	47140	Donor hepatectomy (including cold preservation), from living donor; left lateral segment only (segments II and III)
	47141	Donor hepatectomy (including cold preservation), from living donor; total left lobectomy (segments II, III and IV)
	47142	Donor hepatectomy (including cold preservation), from living donor; total right lobectomy (segments V, VI, VII and VIII)
	47143	Backbench standard preparation of cadaver donor whole liver graft prior to allotransplantation, including cholecystectomy, if necessary, and dissection and removal of surrounding soft tissues to prepare the vena cava, portal vein, hepatic artery, and common bile duct for implantation; without trisegment or lobe split
	47144	Backbench standard preparation of cadaver donor whole liver graft prior to allotransplantation, including cholecystectomy, if necessary, and dissection and removal of surrounding soft tissues to prepare the vena cava, portal vein, hepatic artery, and common bile duct for implantation; with trisegment split of whole liver graft into 2 partial liver grafts (i.e., left lateral segment [segments II and III] and right trisegment [segments I and IV through VIII])
	47145	Backbench standard preparation of cadaver donor whole liver graft prior to allotransplantation, including cholecystectomy, if necessary, and dissection and removal of surrounding soft tissues to prepare the

Type	Code	Description
		vena cava, portal vein, hepatic artery, and common bile duct for implantation; with lobe split of whole liver graft into 2 partial liver grafts (i.e., left lobe [segments II, III, and IV] and right lobe [segments I and V through VIII])
	47146	Backbench reconstruction of cadaver or living donor liver graft prior to allotransplantation; venous anastomosis, each
	47147	Backbench reconstruction of cadaver or living donor liver graft prior to allotransplantation; arterial anastomosis, each
	48550	Donor pancreatectomy (including cold preservation), with or without duodenal segment for transplantation
	48552	Backbench reconstruction of cadaver donor pancreas allograft prior to transplantation, venous anastomosis, each
	48554	Transplantation of pancreatic allograft
	50300	Donor nephrectomy (including cold preservation); from cadaver donor, unilateral or bilateral
	50320	Donor nephrectomy (including cold preservation); open, from living donor
	50323	Backbench standard preparation of cadaver donor renal allograft prior to transplantation, including dissection and removal of perinephric fat, diaphragmatic and retroperitoneal attachments, excision of adrenal gland, and preparation of ureter(s), renal vein(s), and renal artery(s), ligating branches, as necessary
	50325	Backbench standard preparation of living donor renal allograft (open or laparoscopic) prior to transplantation, including dissection and removal of perinephric fat and preparation of ureter(s), renal vein(s), and renal artery(s), ligating branches, as necessary
	50327	Backbench reconstruction of cadaver or living donor renal allograft prior to transplantation; venous anastomosis, each
	50328	Backbench reconstruction of cadaver or living donor renal allograft prior to transplantation; arterial anastomosis, each
	50329	Backbench reconstruction of cadaver or living donor renal allograft prior to transplantation; ureteral anastomosis, each
	50340	Recipient nephrectomy (separate procedure)
	50360	Renal allotransplantation, implantation of graft; without recipient nephrectomy
	50365	Renal allotransplantation, implantation of graft; with recipient nephrectomy
	50547	Laparoscopy, surgical; donor nephrectomy (including cold preservation), from living donor
HCPCS	S2053	Transplantation of small intestine and liver allografts
	S2054	Transplantation of multivisceral organs
	S2055	Harvesting of donor multivisceral organs, with preparation and maintenance of allografts; from cadaver donor
	S2060	Lobar lung transplantation
	S2061	Donor lobectomy (lung) for transplantation, living donor
	S2065	Simultaneous pancreas kidney transplantation
ICD-10 Procedure	02YA0Z0	Transplantation of Heart, Allogeneic, Open Approach
	0BYC0Z0	Transplantation of Right Upper Lung Lobe, Allogeneic, Open Approach
	0BYC0Z1	Transplantation of Right Upper Lung Lobe, Syngeneic, Open Approach
	0BYD0Z0	Transplantation of Right Middle Lung Lobe, Allogeneic, Open Approach

Type	Code	Description
	0BYD0Z1	Transplantation of Right Middle Lung Lobe, Syngeneic, Open Approach
	0BYF0Z0	Transplantation of Right Lower Lung Lobe, Allogeneic, Open Approach
	0BYF0Z1	Transplantation of Right Lower Lung Lobe, Syngeneic, Open Approach
	0BYG0Z0	Transplantation of Left Upper Lung Lobe, Allogeneic, Open Approach
	0BYG0Z1	Transplantation of Left Upper Lung Lobe, Syngeneic, Open Approach
	0BYH0Z0	Transplantation of Lung Lingula, Allogeneic, Open Approach
	0BYH0Z1	Transplantation of Lung Lingula, Syngeneic, Open Approach
	0BYJ0Z0	Transplantation of Left Lower Lung Lobe, Allogeneic, Open Approach
	0BYJ0Z1	Transplantation of Left Lower Lung Lobe, Syngeneic, Open Approach
	0BYK0Z0	Transplantation of Right Lung, Allogeneic, Open Approach
	0BYL0Z1	Transplantation of Left Lung, Syngeneic, Open Approach
	0BYL0Z1	Transplantation of Right Lung, Syngeneic, Open Approach
	0BYM0Z0	Transplantation of Bilateral Lungs, Allogeneic, Open Approach
	0BYM0Z1	Transplantation of Bilateral Lungs, Syngeneic, Open Approach
	0DY80Z0	Transplantation of Small Intestine, Allogeneic, Open Approach
	0FSG0ZZ	Reposition Pancreas, Open Approach
	0FSG4ZZ	Reposition Pancreas, Percutaneous Endoscopic Approach
	0FY00Z0	Transplantation of Liver, Allogeneic, Open Approach
	0FY00Z1	Transplantation of Liver, Syngeneic, Open Approach
	0FYG0Z0	Transplantation of Pancreas, Allogeneic, Open Approach
	0FYG0Z1	Transplantation of Pancreas, Syngeneic, Open Approach
	0TY00Z0	Transplantation of Right Kidney, Allogeneic, Open Approach
	0TY00Z1	Transplantation of Right Kidney, Syngeneic, Open Approach

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
08/01/2019	BCBSA Medical Policy adoption	Medical Policy Committee

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.