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Updates in Transplantation: Current Challenges in Caring for the Hepatitis C Virus Positive Patient

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Pennsylvania Hospital

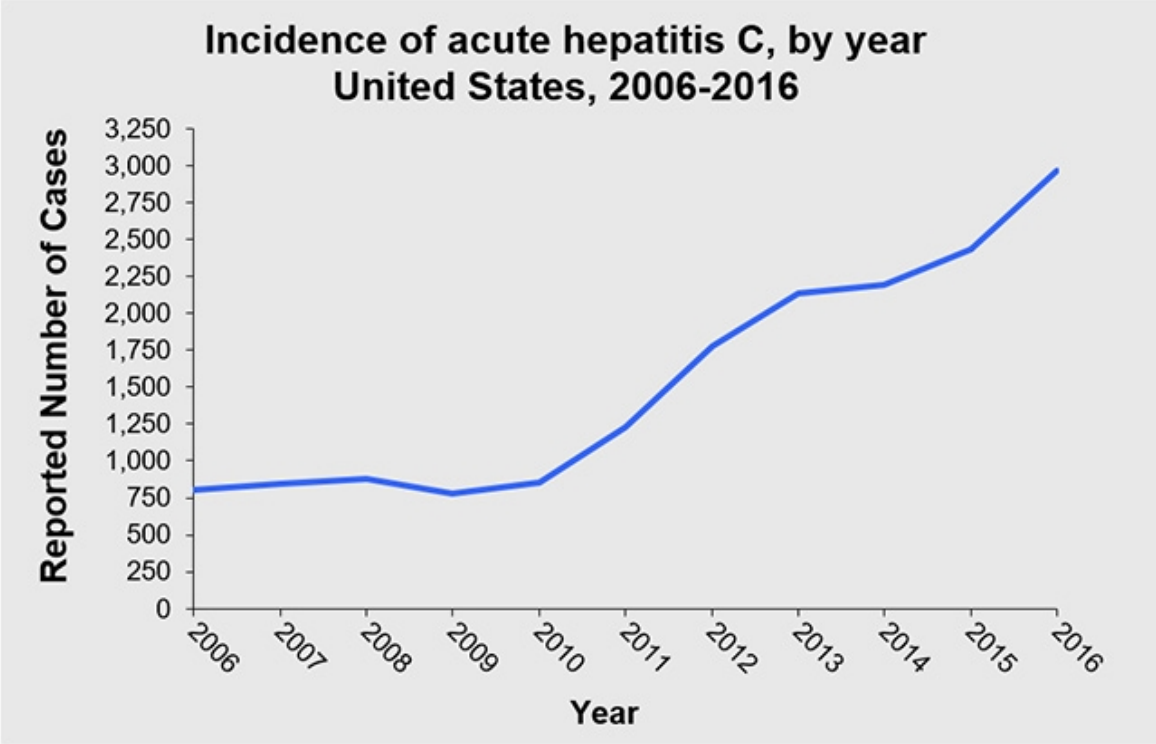
Disclosures

All planners, presenters, reviewers, and ASHP staff of this session report no financial relationships relevant to this activity.

Objectives

- Describe the outcomes of solid organ transplantation in patients with hepatitis C virus (HCV)
- Assess the advantages and disadvantages of initiating treatment for HCV in a pre-transplant candidate
- Select and recommend HCV treatment for a solid organ transplant recipient
- Design an immunosuppression regimen for a transplant recipient with HCV

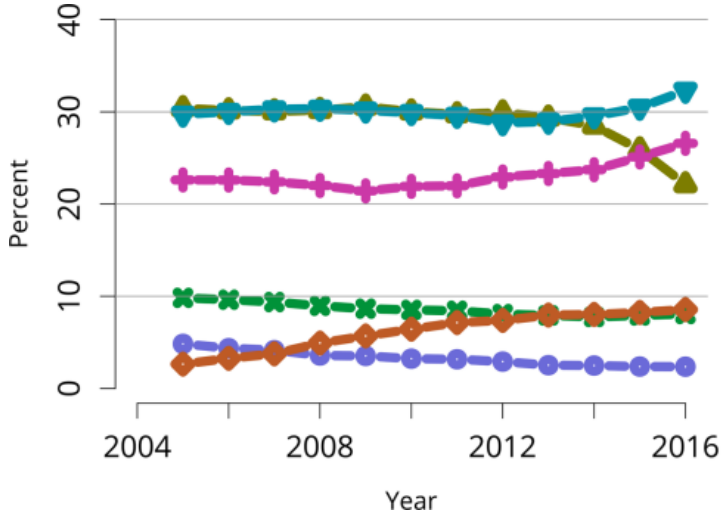
Hepatitis C Virus (HCV) Prevalence



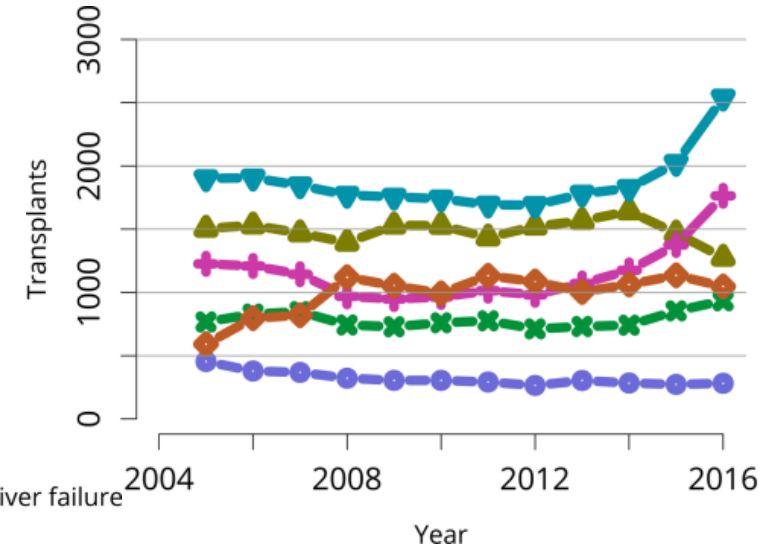
Centers for Disease Control and Prevention. Division of Viral Hepatitis. Statistics and Surveillance

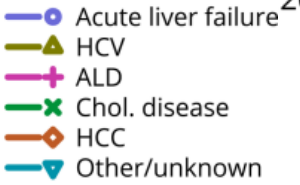
HCV in Transplantation

Liver Transplant Wait-List



Liver Transplants Performed



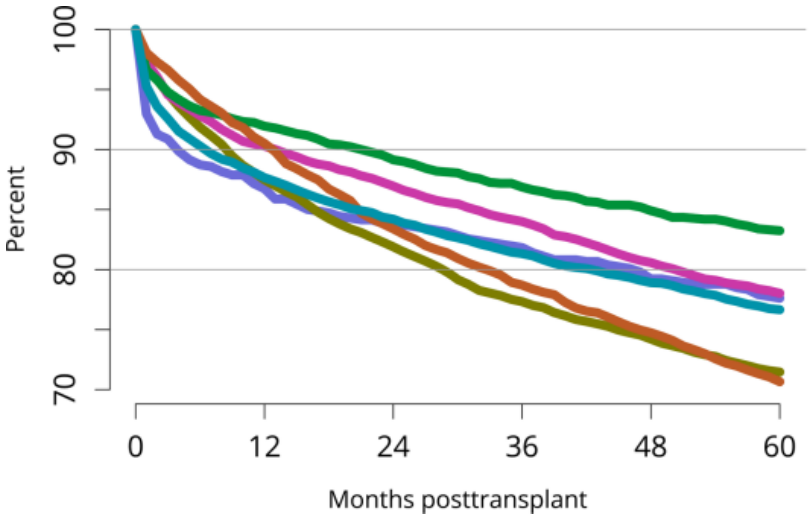


OPTN/SRTR 2016 Annual Data Report: Liver, Volume: 18, Issue: S1, Pages: 172-253,
First published: 02 January 2018, DOI: (10.1111/ajt.14559)

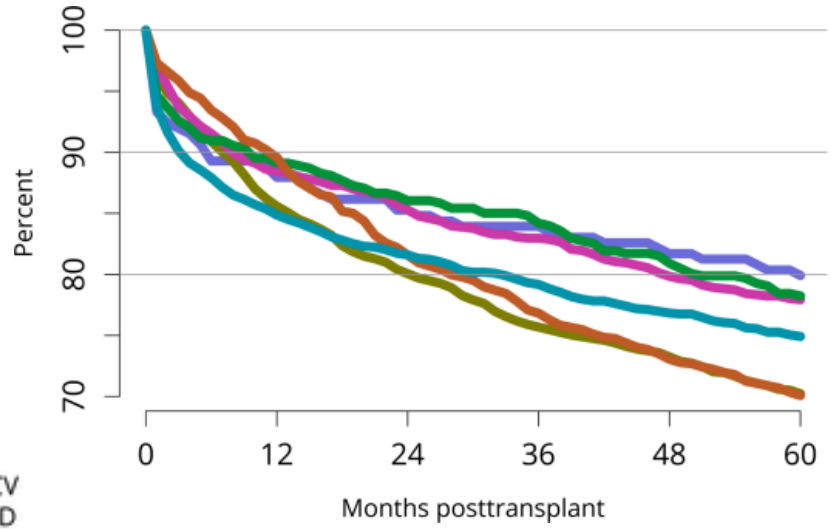
Patient and Graft Survival

Deceased Donor Liver Transplant

Patient Survival



Graft Survival



HCV
ALD
Chol. disease
HCC
Other/unknown

OPTN/SRTR 2016 Annual Data Report: Liver, Volume: 18, Issue: S1, Pages: 172-253, First published: 02 January 2018, DOI: (10.1111/ajt.14559)

Where We Are Now

Organ wait list shortcut: Patients accepting kidneys, hearts infected with hepatitis C

Ken Alltucker, USA TODAY Published 1:52 p.m. ET Sept. 17, 2018 | Updated 4:12 p.m. ET Sept. 17, 2018

Meeting Coverage > EASL

Hepatitis C Treatments Reduce Transplants

— Therapies also appear to reduce liver-related mortality

by Ed Susman, Contributing Writer, MedPage Today
April 15, 2018

New Hepatitis C Drugs Mean More Organs For More Transplants

It's now safe for transplant patients to receive organs from donors with hepatitis C.

08/28/2018 12:09 pm ET | Updated Aug 28, 2018

KEY TAKEAWAYS

1) Patient and graft survival outcomes are expected to greatly improve for transplant recipients with HCV based upon new therapies

2) Over the next decade, HCV is expected to no longer be a top indication for liver transplantation

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To Treat or Not to Treat?
Considerations for Transplant Candidates

Srijana Jonchhe, Pharm.D., BCPS
Clinical Pharmacy Specialist- Liver Transplant
University Hospital New Jersey

Objective

- Assess the advantages and disadvantages of initiating treatment for HCV in a pre-transplant candidate

Patient Case

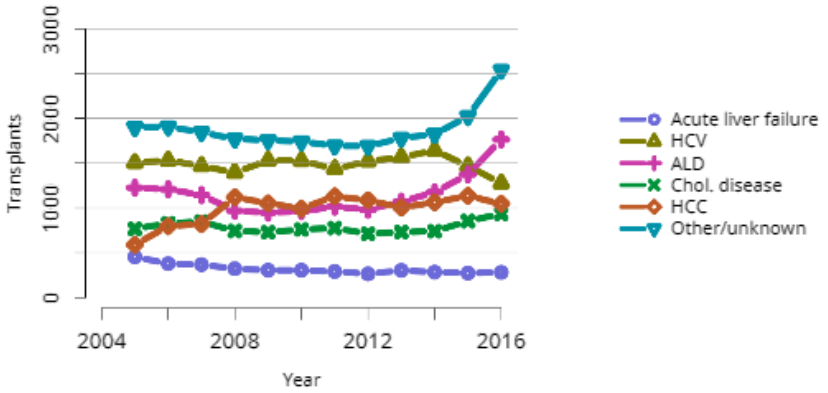
Patient JB is a 52 yo AA male who presents to hepatology clinic for his initial transplant evaluation appointment. He states he was informed of his hepatitis C infection after his primary care physician noted increased LFTs during routine blood work.

PMH: HCV cirrhosis c/b portal hypertension, history of IV drug abuse (last used 2009), anxiety, hyperlipidemia
Ht: 5'10"
Wt: 94 kg

Labs: **Pending**
HCV genotype: 1b
HCV viral load (7/2018): 62,240 copies/mL

Liver Transplant Candidates

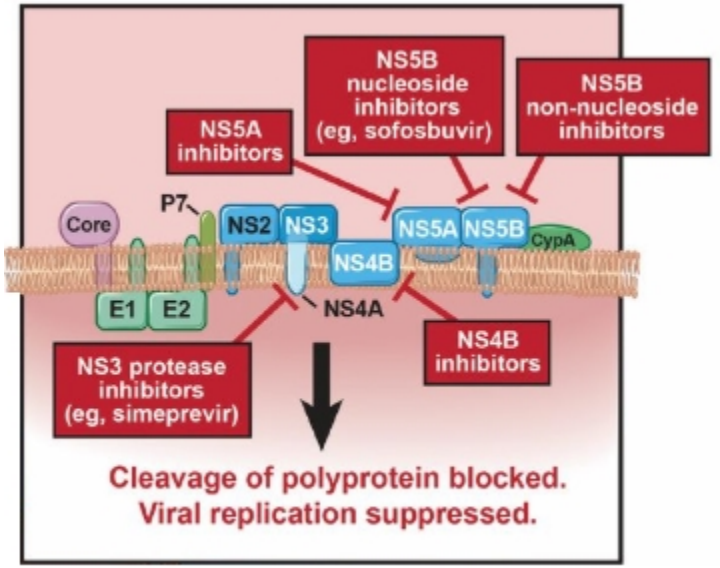
- Up to 85 % with acute HCV infection develop chronic HCV infection
  - Approximately 15-30 % progress to cirrhosis over 20 years
- HCV-related cirrhosis risks:
  - End stage liver disease
  - Hepatocellular carcinoma (HCC)
- Chronic HCV infection is a leading indication for liver transplant (LT)



OPTN/SRTR Annual Data Report 2016
Center for Disease Control 2018

A New Era: Direct Acting Antivirals (DAA)

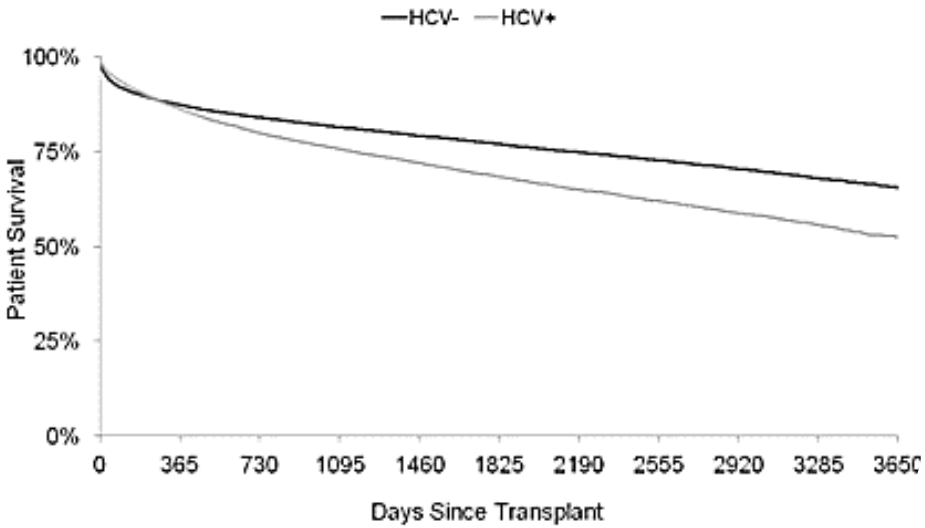
- ✓ Better safety /tolerability than interferon-based regimens
- ✓ Shorter treatment duration
- ✓ Improved efficacy
- ✓ Fewer drug-drug interactions
- ✓ Growing literature in transplant



Cleveland Clinic Journal of Medicine, 81 (3): 159-172

Drug	Brand name	Year Approved
Glecaprevir/Pibrentasvir	Mavyret	2017
Sofosbuvir/Velpatasvir/Voxilaprevir	Vosevi	2017
Sofosbuvir/Velpatasvir	Epclusa	2016
Elbasvir/Grazoprevir	Zepatier	2016
Daclatasvir	Daklinza	2015
Ombitasvir/Paritaprevir/ritonavir + Dasbuvir	Viekira pak	2014
Ledipasvir/Sofobuvir	Harvoni	2014
Sofosbuvir	Sovaldi	2013
Simeprevir	Olysio	2013

Post-transplant HCV



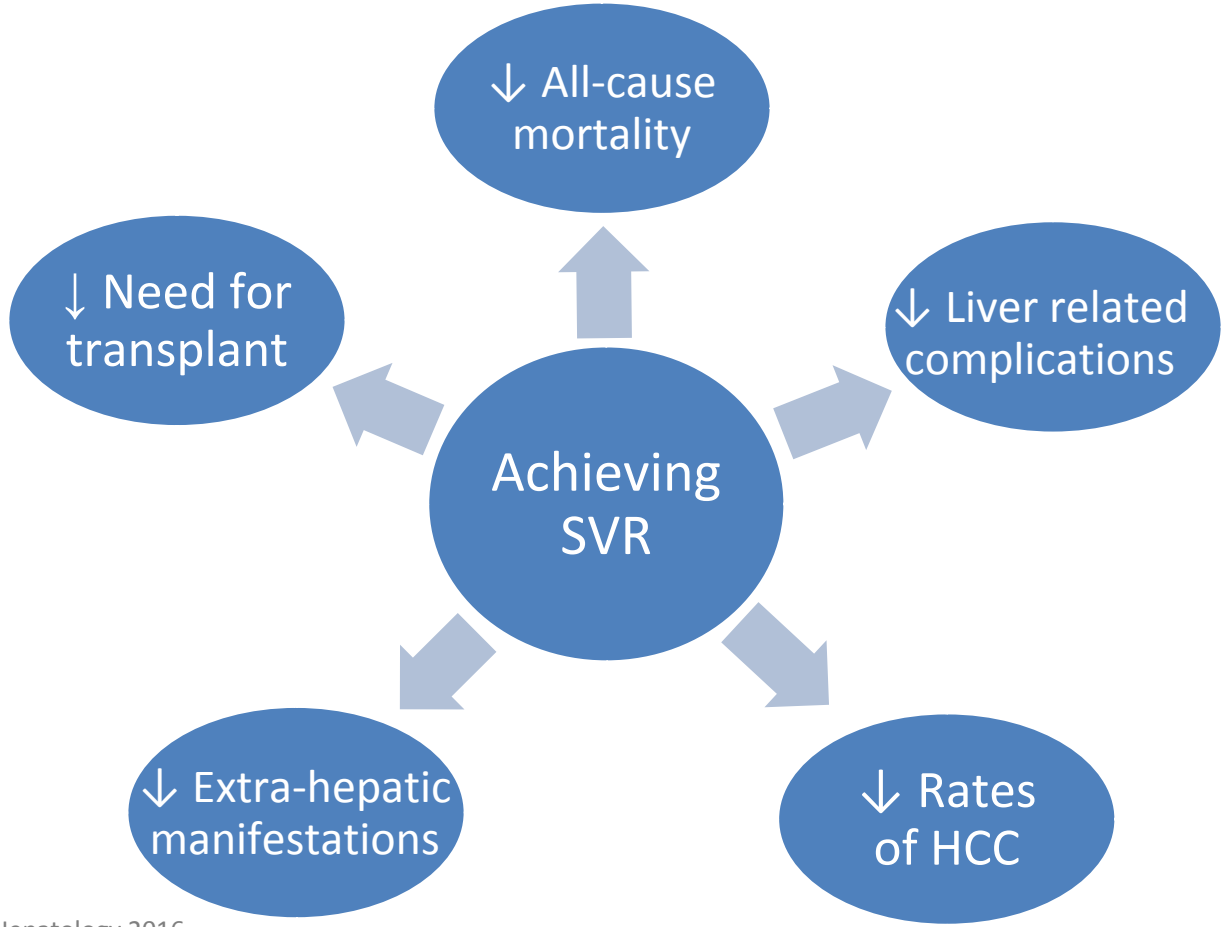
- Universal HCV recurrence
- Rapid progression to cirrhosis
- Fibrosing cholestatic hepatitis (FCH)
- Worse graft and patient survival

Thuluvath PJ. Am J Transplant 2010
Forman LM. Gastroenterology 2002

Outcomes of DAA Treatment Pre-Transplant

Study	Design	Intervention	Results	Comments
Curry et al. Gastroentero logy 2015	Phase 2, open label study of 61 HCV/HCC patients awaiting liver transplant	Up to 48 weeks of SOF/RBV before transplant	N= 43 transplanted with HCV RNA < 25 IU/ml at time of transplant Post-transplant virologic response at 12 weeks = 75%	Recurrence (10%) inverse to number of days undetectable HCV RNA before transplant MELD exception points
Charlton et al. Gastroentero logy 2015 (SOLAR-1)	Phase 2, multicenter, open label study including patients with decompensated cirrhosis	12 vs. 24 weeks of ledipasvir/SOF + RBV in patients with moderate and severe hepatic impairment	N= 108 SVR rate = 87-89% MELD and CTP scored decreased	Lack of long-term follow up Adverse effects mostly related to ribavirin

SOF: sofosbuvir; RBV: ribavirin



Lee MH. J Infect Dis. 2012
Van der Meer. Journal of Hepatology 2016
Mahale P et al Gut. 2018

Patient Case

JB returns to hepatology clinic 3 months later after recently being discharged from the hospital. He states his abdomen was “swelling like a balloon.” Therapeutic paracentesis was performed (3 L removed)

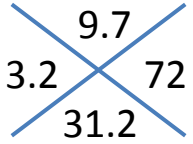
PMH: HCV (1a) cirrhosis c/b portal hypertension and **ascites**, history of IV drug abuse (last used 2009), anxiety, hyperlipidemia

Patient Case

Home Medications:

- Hydroxyzine 25 mg PO QHS
- Bupropion 100 mg PO daily
- Furosemide 40 mg PO daily
- Propranolol 10 mg PO BID
- Omeprazole 20 mg PO daily
- Spironolactone 100 mg PO daily

Labs: sCr 1.3, bilirubin 1.9, INR 1.4



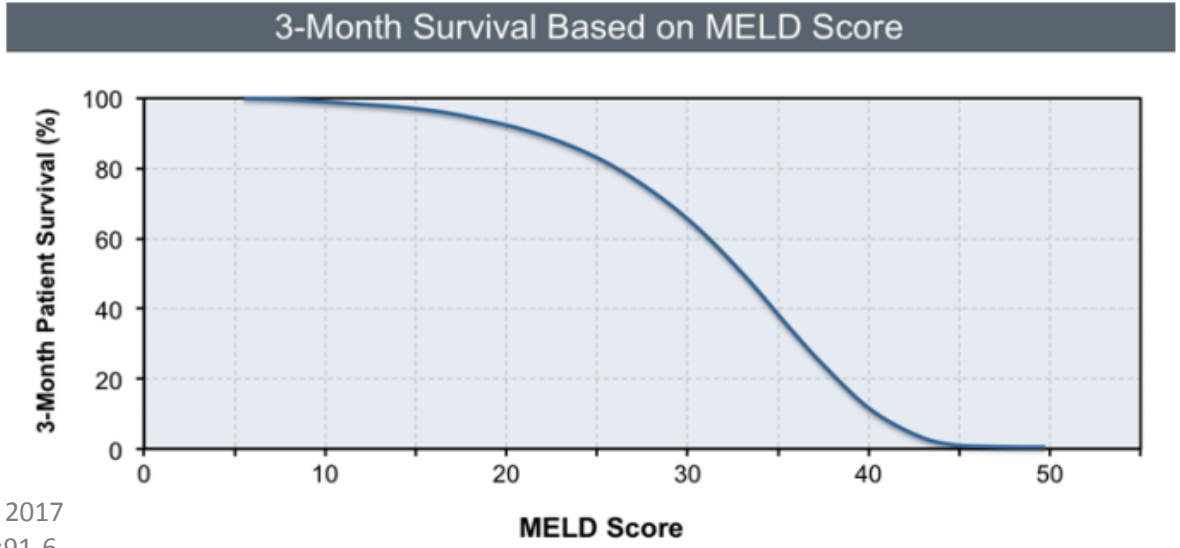
AST: 52
ALT: 47
Alk Phos: 109

Transplant status: listed
MELD score = 17
CTP score = A

MELD: Model of End Stage Liver Disease; CTP: Child-Turcotte Pugh

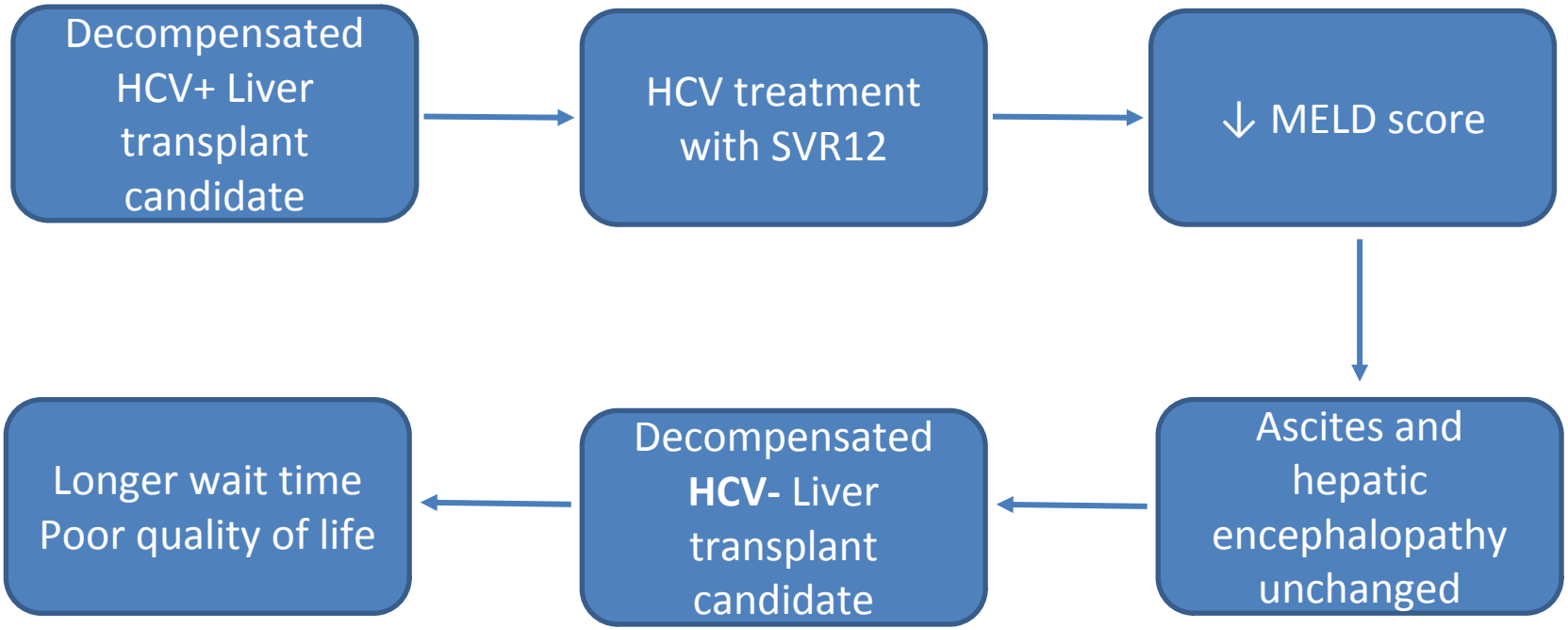
Organ Allocation: Liver Transplant

- Model of End Stage Liver Disease (MELD) score
  - Used to allocate livers to adult transplant recipients
  - Affected by: bilirubin, INR, serum creatinine and sodium



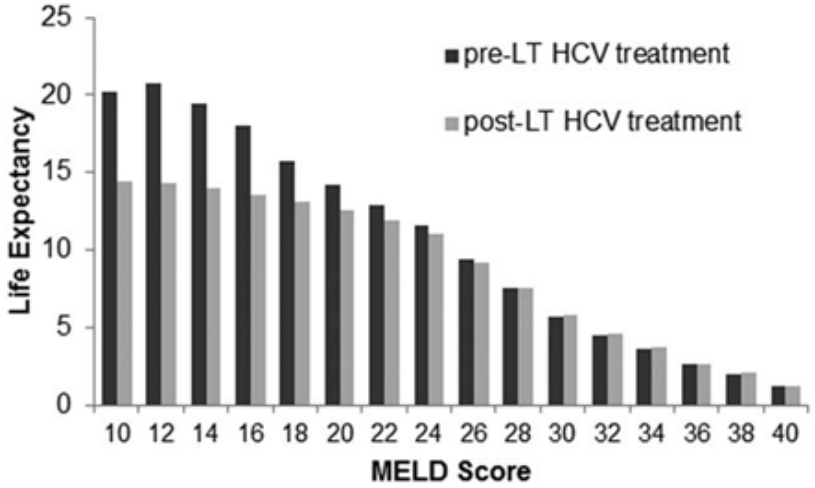
UNOS Liver Allocation Policy 2017
Gastroenterology. 2003;124:91-6

"MELD Purgatory?"



UNOS Liver Allocation Policy 2017
Gastroenterology. 2003;124:91-6

HCV Treatment Pre Vs. Post Liver Transplant



Chhatwal et al. Hepatology 2017

- Optimal MELD threshold
- Cost-effectiveness
- Quality of life-years

Flemming J. Hepatology 2017
Samur S et al. Clin Gastroenterol Hepatol 2018

The ongoing debate…

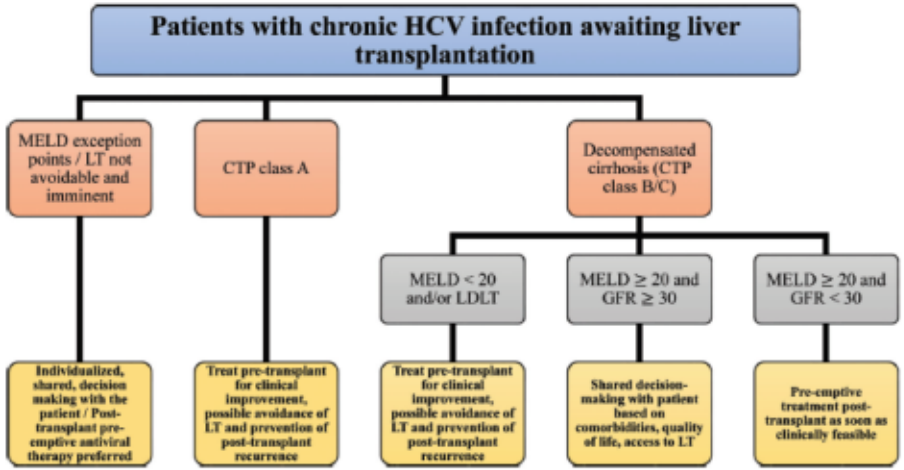
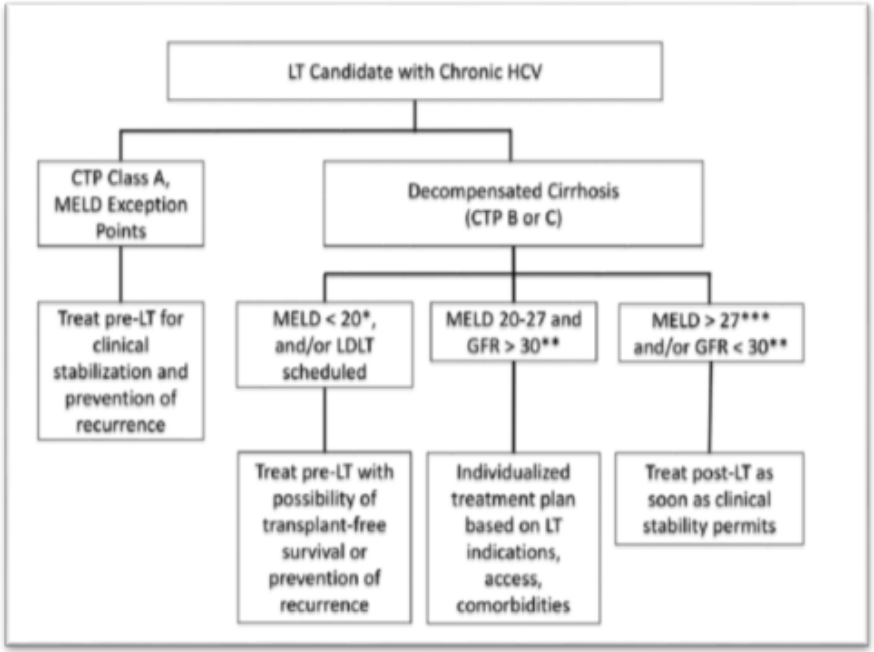


Fig. 1. Algorithm for treatment of HCV-infected liver transplant candidates.

Abbreviations: MELD, model for end-stage liver disease; LT, liver transplantation; CTP, Child-Turcotte-Pugh; LDLT, living donor liver transplantation; GFR, glomerular filtration rate.

Cholankeril G et al. J Clin Transl Hepatol 2017



Verna EC. Hepatology 2017

Special Considerations

	Drug Class	Decompensated cirrhosis	CKD Stage 4 or 5	Genotype	Rating
Elbasvir/Grazoprevir	NS5A NS3/4A	X	12 weeks	1a, 1 b, 4	I B
Glecaprevir/Pibrentasvir	NS5A NS3/4A	X	8-16 weeks	1-6	I B
Ledipasvir/ Sofobuvir	NS5A NS5B	12 weeks (RBV) 24 weeks (no RBV)	X	1,4,5,6	I A
Daclatasvir/Sofosbuvir	NS5A NS5B	12 weeks (RBV) 24 weeks (no RBV)	X	1-4	I/II, B II C
Velpatasvir/Sofosbuvir	NS5A NS5B	12 weeks (RBV) 24 weeks (no RBV)	X	1-6	I A

AASLD/IDSA HCV guidelines- updated 9/2017

Patient Case

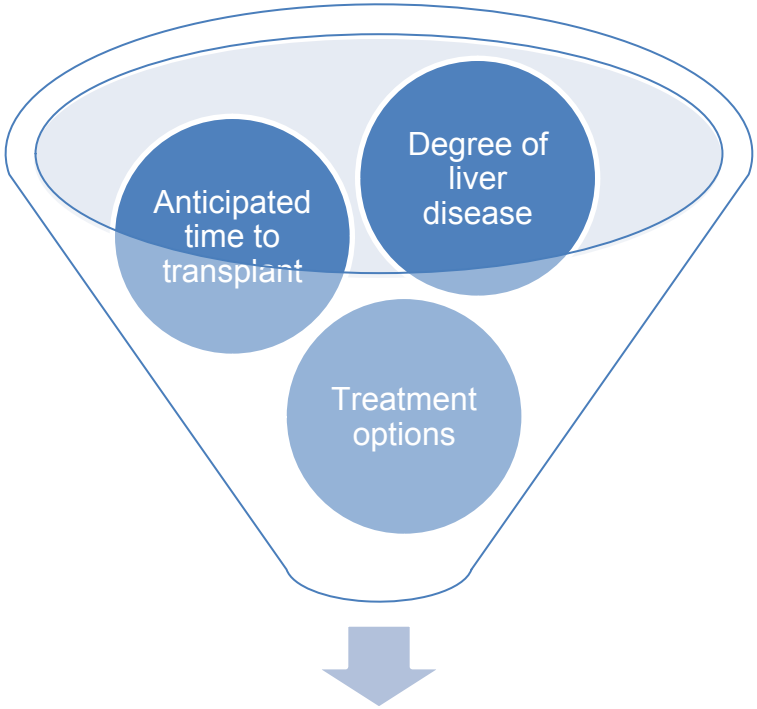
What would be an appropriate treatment strategy for patient JB's HCV?

A. Hold HCV treatment until after patient receives a liver transplant
B. Start treatment with ledipasvir/sofobuvir/ribavirin for 12 weeks. Extend therapy to 24 weeks if unable to tolerate ribavirin
C. Start treatment with sofosbuvir 400 mg/ribavirin 600 mg daily for up to 48 weeks prior to transplant
D. Inform patient he will not benefit from DAA therapy due to severe decompensated cirrhosis

Pre-Transplant Treatment

- Improved graft outcomes
- Reduce all-cause mortality
- Alleviate need for transplant
- Less drug interactions- no immunosuppression

- Longer wait time without HCV donor pool
- Risk of reinfection
- Treatment failure/resistance
- Limited treatment options
- Potential peri-transplant treatment concerns



Decision to treat

- Renal
- Heart
- Lung
- Other: small bowel, pancreas

Renal Transplant Candidates

- HCV is independently associated with chronic kidney disease
  - 5-10 % in HD units
  - Higher mortality

- HCV in renal transplant recipients increases risk of:
  - ↑ Graft loss
  - ↑ Liver-related complications (cirrhosis, FCH, HCC)
  - ↑ Infection, Diabetes
  - ↑ Death

Fabrizi F. Am J Transplant. 2014
Finelli L. Semin Dial 2005

Renal Transplant Candidates

- KDIGO guidelines recommend evaluating *all* chronic kidney disease patients for HCV treatment

- Treatment pre-transplant was previously limited by genotype due to lack of safety data in ESRD
  - C-SURFER
  - EXPEDITION-4

KDIGO Clinical Practice Guideline 2017
Roth D. Lancet 2015
Gane E. NEJM 2017

Renal Transplant Candidates

- KDIGO guidelines recommend evaluating *all* chronic kidney disease patients for HCV treatment

- Treatment pre-transplant was previously limited by genotype due to lack of safety data in ESRD
  - C-SURFER
  - EXPEDITION-4

- ***Kidney transplant candidates with HCV are also eligible to receive HCV positive organs, shortening the wait time significantly in some regions***

KDIGO Clinical Practice Guideline 2017
Roth D. Lancet 2015
Gane E. NEJM 2017

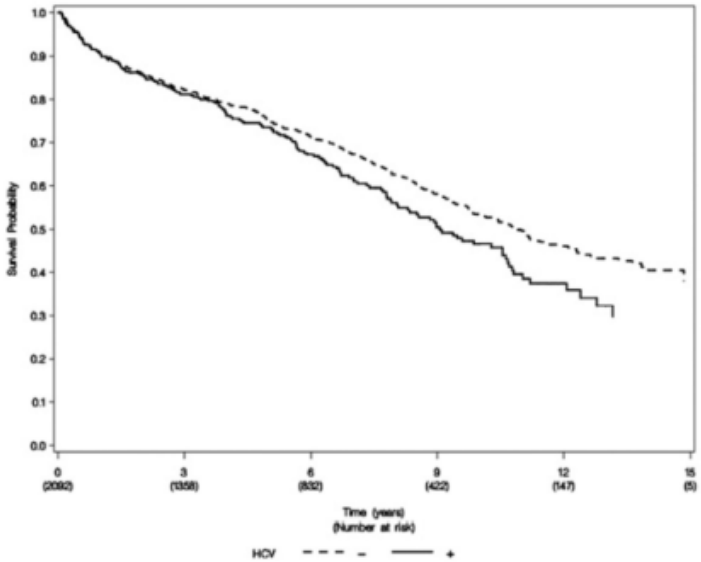
Special Considerations

	Drug Class	Decompensated cirrhosis	CKD Stage 4 or 5	Genotype	Rating
Elbasvir/Grazoprevir (Zepatier ®)	NS5A NS3/4A	X	12 weeks	1a, 1 b, 4	I B
Glecaprevir/Pibrentasvir (Mavyret ®)	NS5A NS3/4A	X	8-16 weeks	1-6	I B
Ledipasvir/ Sofobuvir (Harvoni ®)	NS5A NS5B	12 weeks (RBV) 24 weeks (no RBV)	X	1,4,5,6	I A
Daclatasvir/Sofosbuvir (Daklinza ®)	NS5A NS5B	12 weeks (RBV) 24 weeks (no RBV)	X	1-4	I/II, B II C
Velpatasvir/Sofosbuvir (Epclusa ®)	NS5A NS5B	12 weeks (RBV) 24 weeks (no RBV)	X	1-6	I A

AASLD/IDSA HCV guidelines- updated 9/2017

Cardiac Transplant Candidates

- Prevalence of HCV appears to be similar to general population (~2%)



Lee et al. J Heart Lung Transplant 2011
Gasinki et al. JAMA 2006

2016 ISHLT listing criteria for heart transplantation:

- Contraindicated if signs of cirrhosis, portal hypertension, or HCC
- Liver biopsy should be performed
- Anti-viral treatment should be considered

Lung Transplant Candidates

- Prevalence of HCV appears to be similar to general population (~2%)

Study	Design*	Results	Comments
Fong TL et al. Transplantation 2011	Retrospective, multi-center, lung transplant recipients from 2000-2007	Similar patient survival rate in HCV Ab+ vs. HCV Ab- recipients 1 yr: 84.7% vs 82% 3 yr: 63.9% vs 65% 5 yr: 49.4% vs 51.4%	Most HCV+ patients were probably not viremic
Englum BR. J Heart Lung Transplant 2016	Retrospective, multicenter, lung transplant recipients from 1994-1999 and 2000-2011	Overall survival lower in HCV+ during the early era but not in recent era Median: 1.7 vs 4.5 years; p=0.004 4.4 vs 5.4 years; p = 0.100	Recent era based on improved HCV treatment options

* Both studies utilized OPTN/UNOS database

ISHLT CONSENSUS

A consensus document for the selection of lung transplant candidates: 2014—An update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation

David Weill, MD (Committee Chairs),[a] Christian Benden, MD (Committee

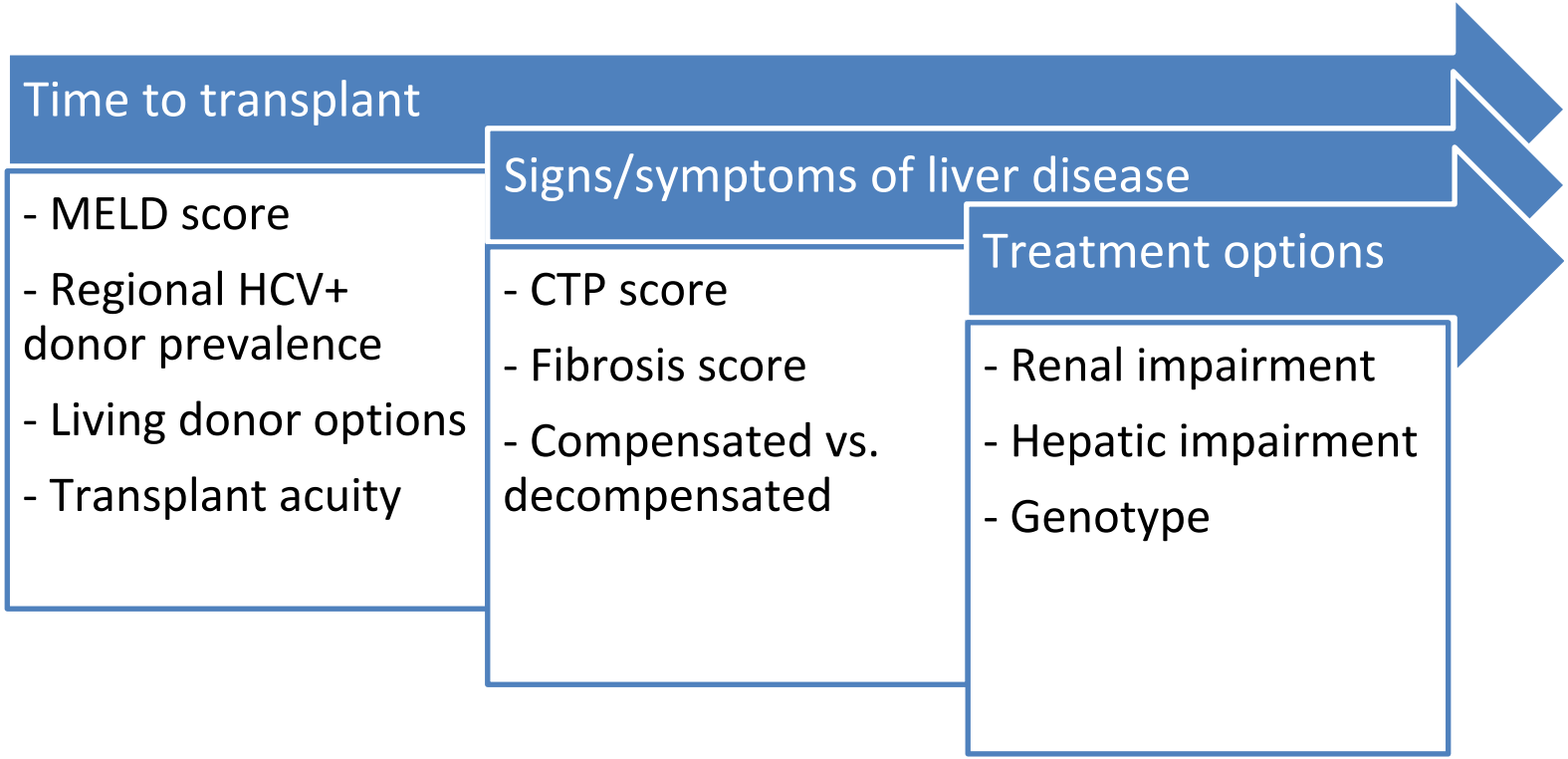
Relative Contraindication:
"Lung transplant can be considered in patients without significant clinical, radiologic, or biochemical signs of cirrhosis or portal hypertension and who are stable on appropriate therapy."

Pre-Transplant Treatment

- Improved graft outcomes
- Reduce all-cause mortality
- Alleviate need for liver transplant
- Less drug interactions- no immunosuppression

- Longer wait time without HCV donor pool
- Risk of reinfection
- Treatment failure/resistance
- Limited treatment options
- Potential peri-transplant treatment concerns

Decision to Treat Pre-transplant



KEY TAKEAWAYS

1) With the advent of DAAs, treatment of HCV in pre-transplant candidates can reduce liver-related complications, improve patient survival and prolong graft survival

2) The benefits of achieving SVR pre-transplant should be weighed against the potential disadvantages of a longer wait time for non-HCV organs, especially in patients where liver transplant is required to improve quality of life

3) Treating HCV early may alleviate the need for transplant in select liver candidates, allowing for more effective utilization of organs while providing long term cost benefits

Resources for HCV treatment

- AASLD/IDSA guidelines: https://www.hcvguidelines.org
- World Health Organization Guidelines for Hepatitis C (July 2018)
- KDIGO Clinical Practice Guideline (February 2017)
- Drug interactions: https://www.hep-druginteractions.org

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Updates in Transplantation: Current Challenges in Caring for the Hepatitis C Virus Positive Patient

Vicky Kuo, Pharm.D.
Clinical Pharmacist, Solid Organ Transplantation
University of California, San Francisco

Objectives

- Compare the risks and benefits of utilizing HCV positive organ donors

HCV Positive Organ Donor Utilization (2010-2014)

Donated HCV + Organ Donors

1812 HCV + donors
Age < 40
Donated at least 1 organ

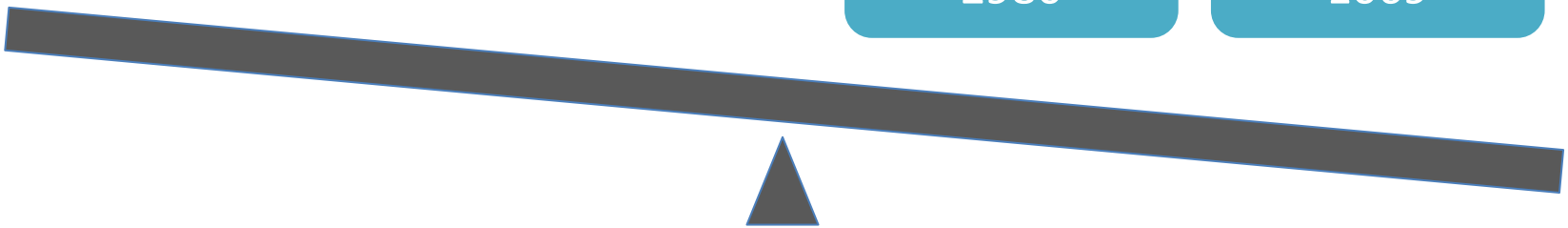
Discarded HCV + Organ Donors

Kidneys
2075

Livers
382

Lungs
2980

Hearts
1069



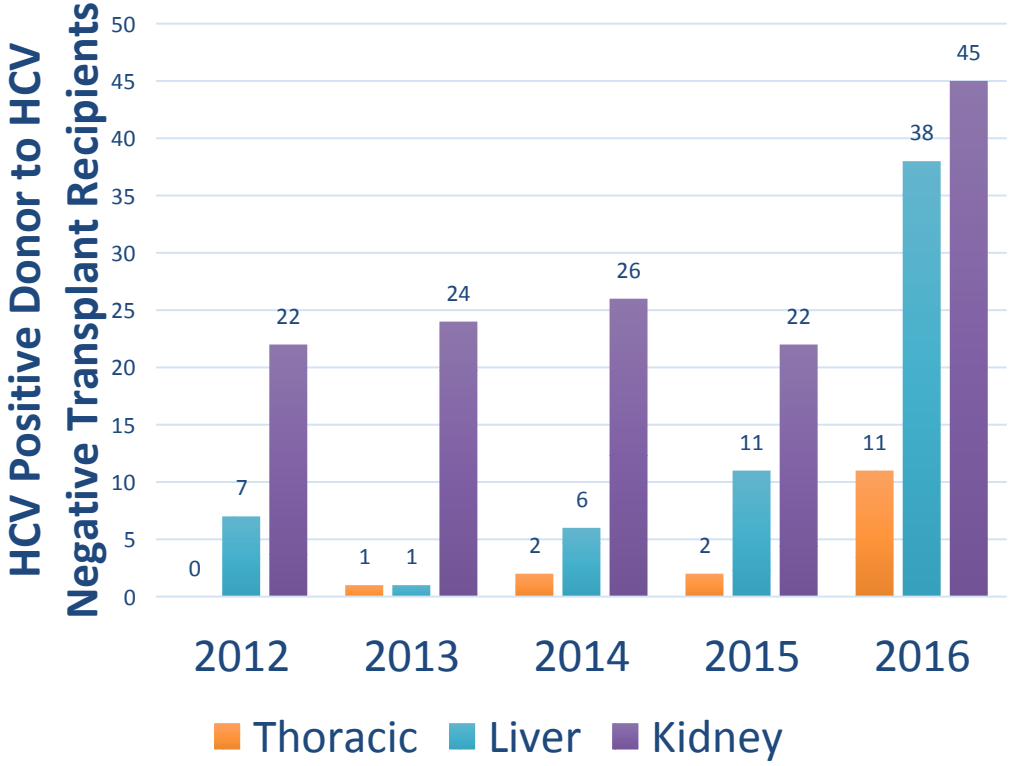
Goldberg DS et al. Am J Transpl 2016; 16: 2836-41.
Sibulesky L et al. Clin Transpl 2015; 29: 724-7.

Concerns with Utilizing HCV Positive Organ Donors Pre-DAA Era

Disease Transmission → Complications

- Reduced patient and graft survival
- Rapid progression of liver fibrosis
- Increased risk of acute rejection, graft complications
- HCV treatment failure

Use of HCV Positive Organs in HCV Negative Transplant Recipients



Adapted from Gonzalez SA et al. Hepatology 2018; 67: 1600-08.

Opioid Epidemic

Population	• Persons who inject drugs • Young (age 20-40), white race with few other medical comorbidities
Increase in Deaths	• 3 fold increase in drug overdose related deaths • In 2014, 47,000 deaths related to drug overdose
Increase in Donor Pool	• 17% increase per year in overdose death donors • Resulting in 13% of donor pool

Gonzalez SA et al. Hepatology 2018;67:1600-08.
Durand CM. Ann Intern Med 2018;168:702-711.
Goldberg DS et al. Am J Transpl 2016; 16:2836-41.
Kurcika LM et al. Am J Transpl 2010;10:1238-46.

HCV "Positive" Donor

- HCV seropositive, NAT negative (nonviremic)
  - Spontaneous clearance of HCV
  - Successfully treated infection
  - False positive antibody

Does not result in HCV transmission and is deemed safe to use

NAT = nucleic acid testing

Levitsky J et al. Am J Transpl 2017; 17: 2790-802.

Quality of HCV Nonviremic Organs

Methods	**Retrospective case-control analysis of UNOS data** Organ donors from DDRTs performed Dec 2014-2016
Donor Characteristics	**Recipient Characteristics**
• Younger • lower SCr, hypertension, diabetes, DCD • White race, PHS increased risk designation	• Older, male, black race, HCV+, diabetic, previous transplant • Lower PRA, reduced days on dialysis and waitlist

SCr = serum creatinine, DCD = donation after cardiac death, PHS = Public Health Service, PRA = panel-reactive antibody

Sibulesky L et al. Am J Transpl. 2018; 18: 2465-72.

Quality of HCV Nonviremic Organs

Methods	**Retrospective case-control analysis of UNOS data** Organ donors from DDRTs performed Dec 2014-2016	
Findings	**HCV Ab-, NAT- (N=19,633)**	**HCV Ab+, NAT- (N=205)**
Patient Survival Acute Rejection	No difference	
Graft Survival	92.2 $\pm$ 0.1% (P=0.08)	96 $\pm$ 0.02%
Incidence of DGF	33.9% (P< 0.0001)	19%

Sibulesky L et al. Am J Transpl. 2018; 18: 2465-72.

HCV "Positive" Donor

- HCV seropositive, NAT positive (viremic) = active infection
- HCV seronegative, NAT positive (viremic) = acute infection
  - Within 2 months of exposure

Potentially providing 300-500 donation opportunities per year

Levitsky J et al. Am J Transpl 2017; 17: 2790-802.

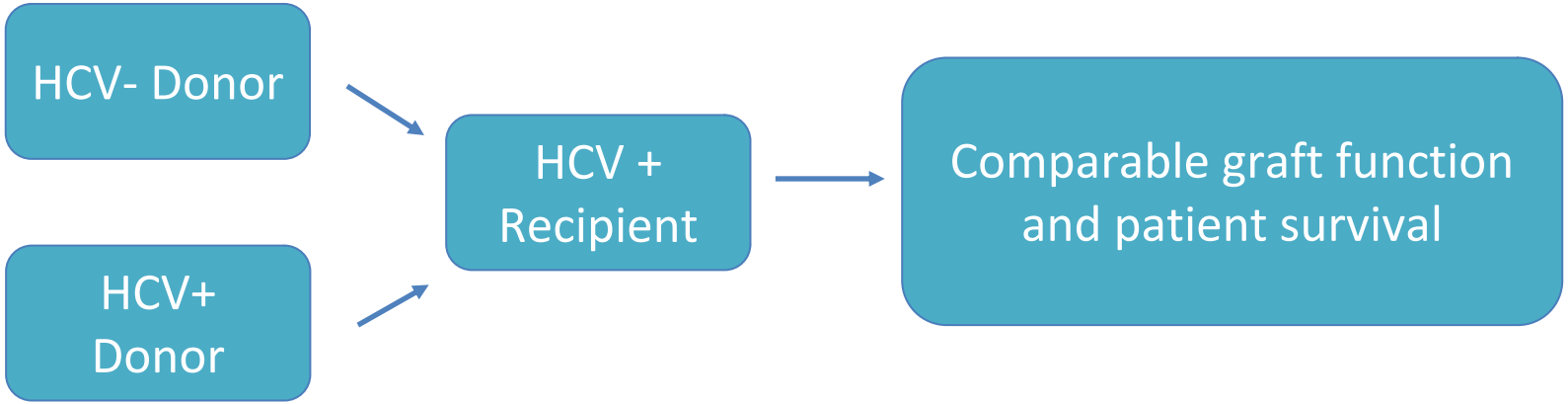
HCV Positive Transplant Recipients

Patient and graft survival is lower in those who receive HCV positive donors when compared to those who receive HCV negative donors

A TRUE

B FALSE

Liver Transplant



- Older donor age and donors with significant fibrosis were found to have faster HCV recurrence

Bushyhead D et al. Curr Hepatol Rep 2017; 16: 12-17.
Marroquin CE et al. Liver Transpl 2001; 7:762-8.
Gane EJ et al. Am J Tranpl 2012; 12: 531-38.
Stepanova M et al. BMC Gastroenterol 2016; 16:137-42.
Northup PG et al. Transpl Intl 2010;23:1038-44.
Lai JC et al. Liver Transpl 2012; 18: 532-8.
Berenguer et al. J Hepatol 2013; 58: 1028-41.
Khapra AP et al. Liver Tranpl 2006; 12: 1496-503.

Renal Transplant

Methods	Observational, two-centers Transplanted 1990-2007 (N=468 HCV+ recipients) Group 1 HCV+ donors (N=162); Group 2 HCV- donors (N=306)		
Findings*		Patient Survival	Graft Survival (P=0.006)
	5 year (Group 1 vs. 2) 10 year (Group 1 vs. 2)	84.8% vs. 86.6% 72.7% vs. 76.5%	58.9% vs. 65.5% 34.4% vs. 47.6%
	Acute rejection 42% vs. 37%; NODAT 21% vs. 12.4% (P= 0.03); HCV-related glomerulonephritis 6.8% vs 7.2%		

*Donor HCV + serology did not significantly increase risk of death, graft loss, decompensated liver disease, or incidence of NODAT

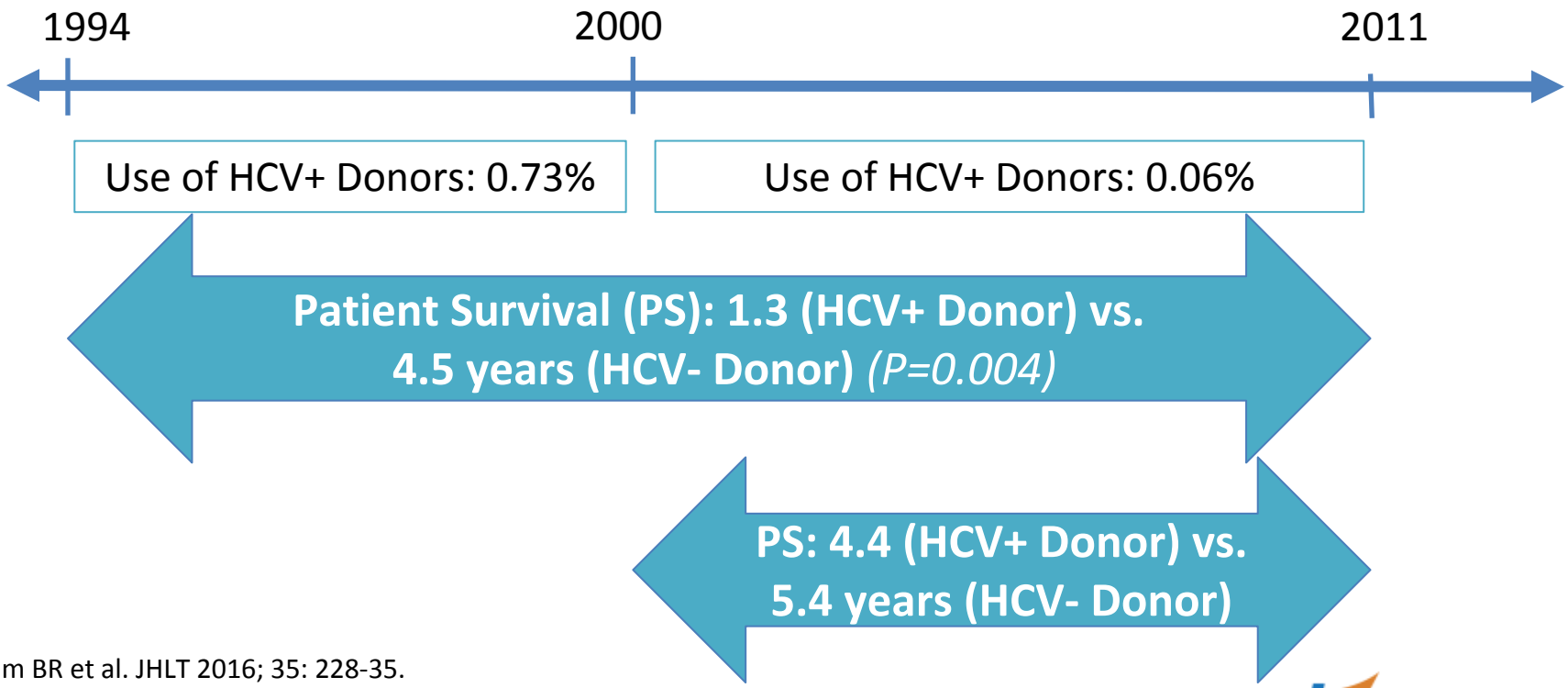
Morales JM et al. Am J Transpl 2010; 10: 2453-62.

Renal Transplant

Methods	Scientific Registry of Transplant Recipients (SRTR) HCV+ recipients transplanted between 1995-2009 (N=6830) Receiving HCV+ vs. HCV- donors	
Findings	Patient Survival	HR 1.29 (p<0.001) 1% difference at 1 year survival 2% difference at 3 year survival
	Graft Survival	HR 1.18 (p=0.007) No difference at 1 year survival 3% difference at 3 year survival
	Accepting HCV+ donor ↓ average waitlist time by 395 days	

Kucirka LM et al. Am J Tranpl 2010; 10: 1238-46.

Lung Transplant



Englum BR et al. JHLT 2016; 35: 228-35.

HCV Positive Organ Donors in HCV Positive Recipients

Liver	• Similar patient and graft survival • Use of HCV+ organs is acceptable
Kidney	• Improved survival compared with waitlist mortality • Use of HCV+ organs is generally acceptable
Thoracic	• Limited data from pre-DAA era • Reduced patient and graft survival compared to HCV- organs, variability in complications • HCV+ organs discarded at high rates

HCV Negative Transplant Recipients

HCV negative recipients receiving HCV positive organ donors have a higher risk of acute rejection and reduced patient and graft survival

A TRUE

B FALSE

Liver Transplant

- No available data on the use of HCV + livers in HCV - recipients
  - Concern for risk of rapidly progressive fibrosis and HCV-related disease

- Modeling Study:
  - Projecting a possible benefit in reduced wait time by accepting HCV + organ in HCV - recipients with MELD > 20
  - Highest benefit observed at MELD of 28
  - Model analysis can help inform future trial study design

Chhatwal J et al. Hepatology 2018; 67: 2085-95.

Renal Transplant Key Trial: THINKER

Methods	Prospective, open-label, single center Recipients: HCV NAT -, age 40-65 (N=20) Donors: HCV NAT+, genotype 1a or 1b
Findings	• All recipients achieved SVR12 • No treatment related adverse events • Excellent allograft function • No cases of acute rejection at 6- and 12- month follow-up • Time to transplant: 57 days (12-91 days)

DAA used: elbasvir/grazoprevir

Goldberg DS et al. NEJM 2017;376;24:2394-5.
Reese PP et al. Ann Intern Med 2018;169:273-281.

Renal Transplant Key Trial: EXPANDER

Methods	Prospective, open-label, single center Recipients: HCV NAT -, age ≥ 50 (N=10) Donors: HCV NAT+, all genotypes
Findings	• Median KDPI: 45% (41-50%) • No treatment related adverse events • No acute rejection at 6 month follow-up • Median time to transplant: 1 month (0.7-2 months)

DAA used: elbasvir/grazoprevir; addition of sofosbuvir if donor was genotype 3

Durand GM et al. Ann Intern Med 2018;168:533-540.

Cardiac Transplant

Methods	Retrospective case series, single-center N=13, n=9 treated; 6 month follow-up
Findings	• Mean donor age: 29 ± 6 years • Waitlist time: 11 ± 12 days (total time 256 ± 583 days) • Mean time to DAA initiation: 47 days (26-95 days) • 4 of 13 did not develop HCV infection • 8 of 9 achieved SVR12, 1 died of pulmonary embolism • No SAEs, drug interactions or delays in obtaining DAA medication noted

DAA used: ledipasvir/sofosbuvir; velpatasvir/sofosbuvir if donor genotype 3
SAEs = serious adverse events

Schlendorf KH et al. JHLT 2018; 37:763-9.

Lung Transplant

Methods	Case report, genotype 1a	Case series, genotype 1, 2 (N=5)
Time to transplant	Not reported	51 days (24-94)
Time to DAA initiation	6 weeks post transplant	24-94 days post transplant
Safety	No SAEs or acute rejection	No SAEs or acute rejection

DAA used: ledipasvir/sofosbuvir; ledipasvir/sofosbuvir or velpatasvir/sofosbuvir

Khan B et al. Am J Transpl 2017; 17:1129-31.
Abdelbasit A et al. Am J Respir Crit Care Med 2018; 197: 1492-6.

HCV Negative Recipients

- Further studies needed to assess use in HCV negative liver recipients
- Short term data with DAA treatment show high rates of HCV cure (SVR12) with good graft function and minimal side effects
- Further studies needed to assess long term data on graft and patient survival, risk of rejection, in addition to complications associated with HCV infection

Considerations for Utilizing HCV Positive Organ Donors in HCV Negative Recipients

- Risk of clinical deterioration while waiting for HCV- organ offer
- Age
- Prolonged waitlist time
- No available living donors
- No substantial risk for liver disease
- Clinical trial opportunities

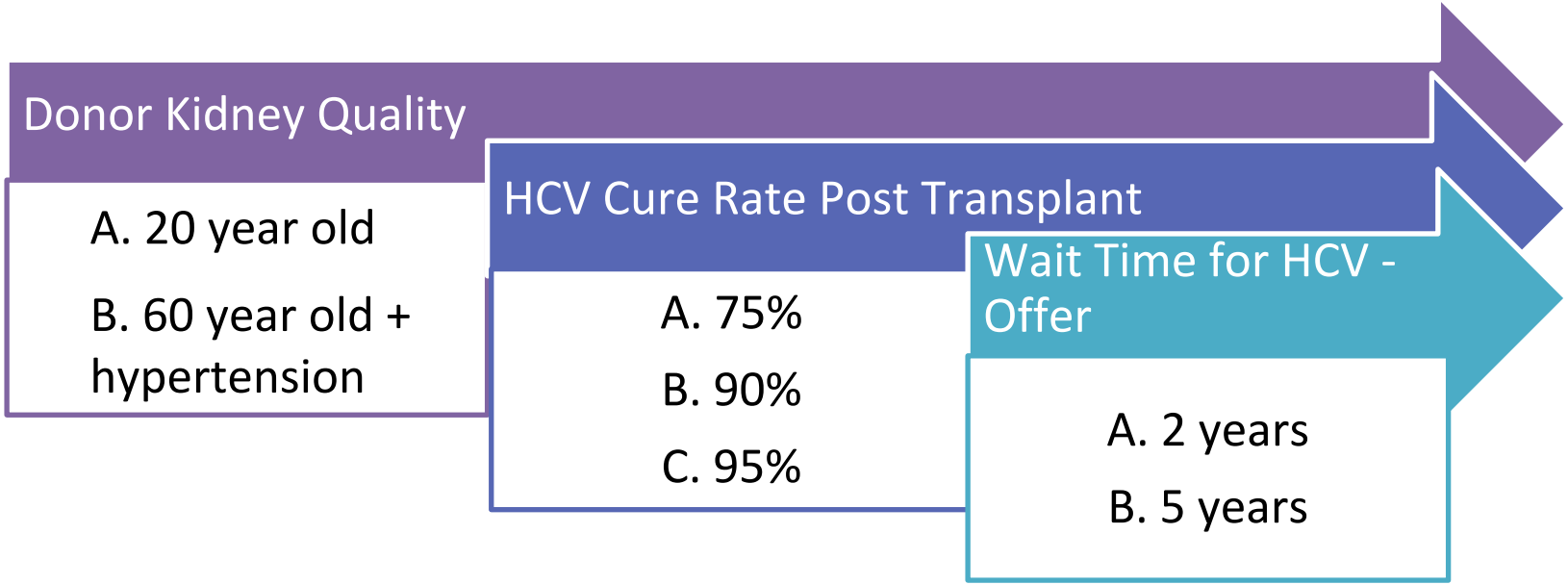
Ethical Perspective

- Mismatch between organ supply and demand
- Patient willingness
- Multistep informed consent process
- Cost and obtaining DAA medication

Levitsky J et al. Am J Transpl 2017; 17: 2790-802.

Patient Willingness to Accept HCV Positive Organs

- Survey with different scenarios from each category



McCauley M et al. Transplantation 2018; 102: e163-70.

Patient Willingness to Accept HCV Positive Organs

- Willingness to accept HCV positive organ
  - Under all circumstances: 53%
  - At least one circumstance: 82%
  - 18% refused all offers
- Participants highly influenced by anticipated HCV cure rate and better allograft quality
- Participant attributes associated with willingness to accept offer
  - Age > 60, transplant reevaluation, prior transplant recipient
- Most patients acknowledged limited understanding of HCV

McCauley M et al. Transplantation 2018; 102: e163-70.

Multi-step Patient Consent Approach

Describe HCV, risk of HCV, and possible complications

Potential Benefits: Reduced wait time vs. risk of death or health deterioration on wait list

Communicate possible adverse consequences: Treatment or graft failure risks, side effects

Cost: inform possibility of high cost or insurance approval for DAA therapy not guaranteed

McCauley M et al. Transplantation 2018;102:e163-70.
Reese PP et al. Ann Intern Med 2018;169:273-281.

Medication Approval and Cost Considerations

- Hepatology consult
- Obtaining appropriate documentation to initiate HCV treatment request
  - Requested information may vary based on insurance plan
- Cost to the patient
  - Financial counseling
  - Patient assistance programs, contingency plan vs. patients pay out of pocket
  - Insurance plan formulary

Goldberg DS et al. NEJM 2017;376;24:2394-5.
Reese PP et al. Ann Intern Med 2018;169:273-281.
Levitsky J et al. Am J Transpl 2017;17:2790-802.

Utilization of HCV + Donors

Advantages	Disadvantages

• Increase donor pool
• Better donor quality
• Decrease time on waitlist
• Decrease waitlist mortality
• High cure rate with DAA treatment
	• Disease transmission
	• Treatment cost and availability
	• Concern for
	  • treatment failure
	  • DAA resistance
	  • HCV associated complications
	  • increased morbidity & mortality
	• Societal barriers

Levitsky et al. Am J Transpl 2017;17:2790-2802.
Goldberg DS et al. Am J Transpl 2016; 16: 2836-41.

KEY TAKEAWAYS

1) HCV positive organs are currently being underutilized. These donors are otherwise young with minimal or no other medical comorbidities

2) Utilizing HCV positive organs can decrease time on waitlist and possible waitlist mortality. These grafts show good short term outcomes

3) Larger, prospective clinical trials are needed to assess long term data of HCV impact on complications, patient and graft survival, as well as treatment failure

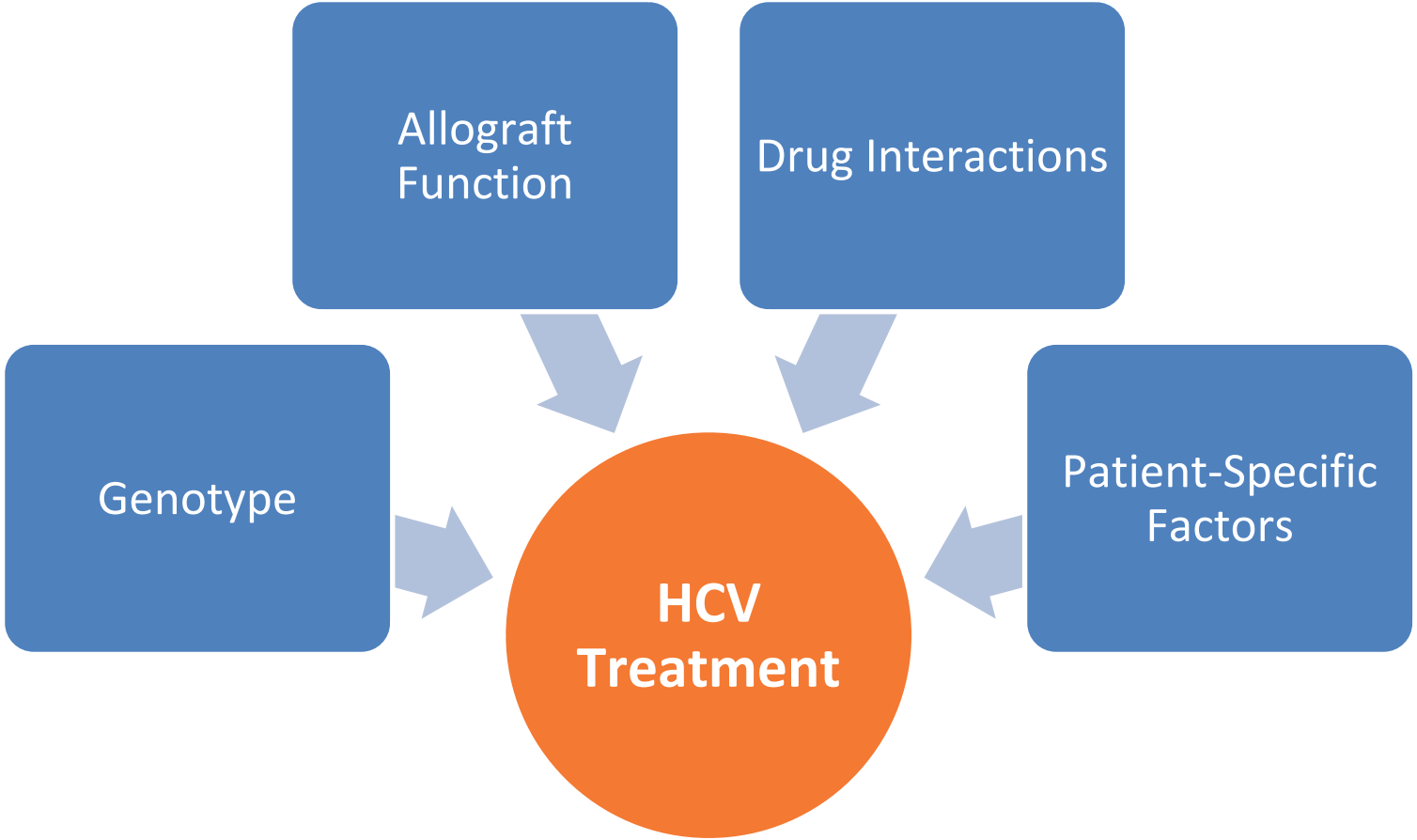
ashp MIDYEAR 2018
Clinical Meeting & Exhibition

Updates in Transplantation: Current Challenges in Caring for the Hepatitis C Virus Positive Patient

Kimberly Boyle, Pharm.D., BCPS
Cardiothoracic Transplant Clinical Pharmacist
Vanderbilt University Medical Center

Objectives

- Select and recommend HCV treatment for a solid organ transplant recipient
- Evaluate pertinent drug interactions relevant to HCV treatment in solid organ transplant patients
- Design an immunosuppression regimen for a transplant recipient with HCV


Allograft Function
Drug Interactions
Genotype
Patient-Specific Factors
HCV Treatment

Therapy Selection: Allograft Function & Genotype

	Genotype	Use in Hepatic Impairment	Use in Renal Impairment
Elbasvir/Grazoprevir (Zepatier ®)	1, 4	Mild	Yes
Glecaprevir/Pibrentasvir (Mavyret ®)	1-6	Mild	Yes
Ledipasvir/ Sofobuvir (Harvoni ®)	1,4,5,6	Yes	CrCl ≥ 30ml/min
Velpatasvir/sofosbuvir (Epclusa ®)	1-6	Yes	CrCl ≥ 30ml/min
Paritaprevir/Ritonavir/Ombitasvir/ Dasabuvir (Viekira Pak®)	1	Mild	Yes

Overview of Drug Interactions

- Absorption Interactions
- Cytochrome P450 & Transporter Mediated Interactions
- Amiodarone
- Immunosuppressant Interactions

Polling Question

- Which of the following drug-drug interactions are contraindicated in a solid organ transplant recipient being treated for HCV?

A Glecaprevir/Pibrentasvir (Mavyret®) and pantoprazole 40mg PO daily

B Ledipsavir/Sofosbuvir (Harvoni®) and omeprazole 20mg PO daily

C Elbasvir/Grazoprevir (Zepatier®) and amiodarone 200mg PO daily

D Velpatasvir/Sofosbuvir (Epclusa®) and amiodarone 400mg PO daily

Overview of Drug Interactions

- **Absorption Interactions**
- Cytochrome P450 & Transporter Mediated Interactions
- Amiodarone
- Immunosuppressant Interactions

Effect of Food on DAA Absorption

With Food

Glecaprevir/Pibrentasvir
(Mavyret®)

Sofosbuvir/Velpatasvir/ Voxilaprevir
(Vosevi®)

Paritaprevir/Ritonavir/Ombitasvir/
Dasabuvir
(Viekira Pak®)

With or Without Food

Ledipasvir/Sofosbuvir
(Harvoni®)

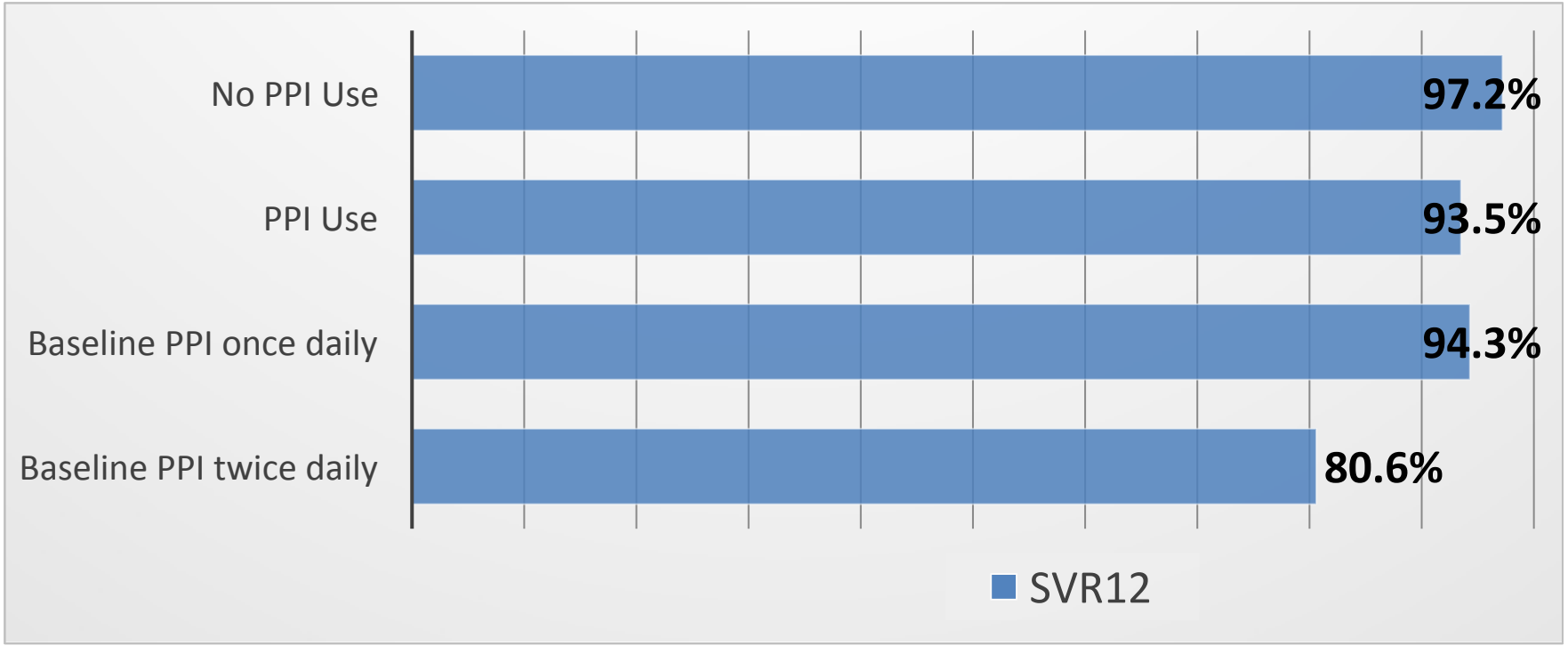
Velpatasvir/Sofosbuvir
(Epclusa®)

Elbasvir/Grazoprevir
(Zepatier®)

Effect of Gastric pH on DAA Absorption

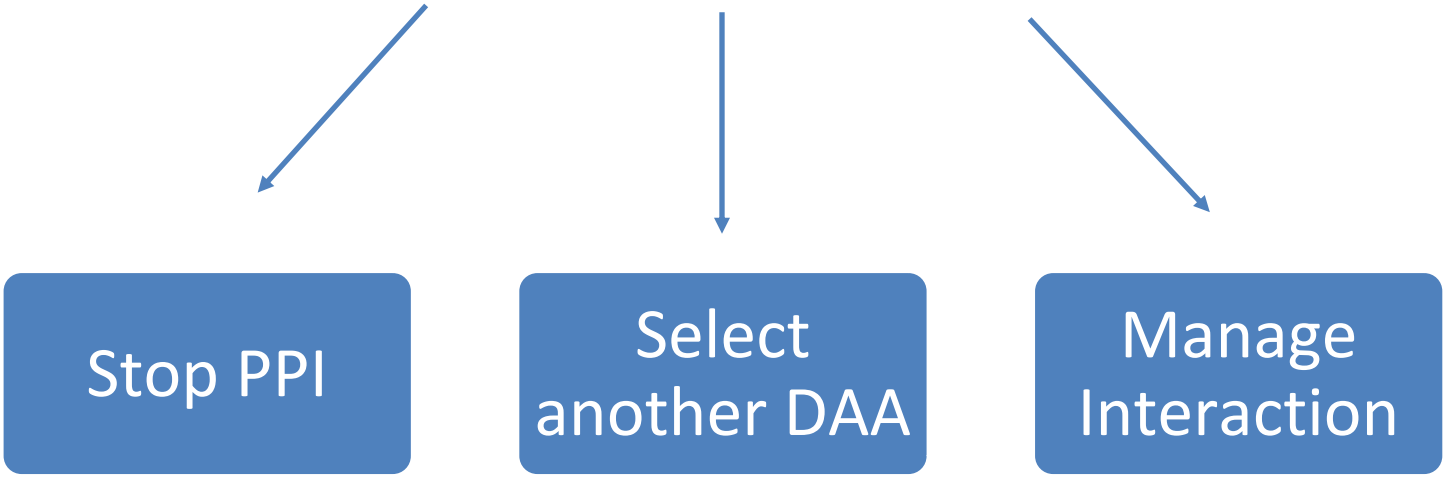
- Some DAAs have gastric pH dependent absorption
- Stress-ulcer prophylaxis is commonly used after transplant
- Acid suppressants can negatively effect DAA absorption risking treatment failure

Clinical Effect of PPI Interaction



Gastroenterology 2016 Dec;151(6):1131-1140

Management of PPIs and DAAs



Management of PPIs and DAAs

Ledipasvir

- PPI: Give together with ≤ 20mg omeprazole once daily on empty stomach
- With or 12 hours apart at dose that ≤ 40mg BID famotidine
- Antacids: separate by 4 hours

Velpatasvir

- PPI: ≤ 20mg omeprazole 4 hours after velpatasvir with food
- With or 12 hours apart at dose that ≤ 40mg BID famotidine
- Antacids: separate by 4 hours

Overview of Drug Interactions

- Absorption Interactions
- **Cytochrome P450 & Transporter Mediated Interactions**
- Amiodarone
- Immunosuppressant Interactions

DAA Metabolism

	Substrate		Inhibitor		Other
DAA Agent	**CYP3A4**	**P-gp**	**CYP3A4**	**P-gp**	
Glecaprevir/ Pibrentasvir (Mavyret®)	x	x	x	x	BCRP, OATP
Paritaprevir/ ritonavir/ Ombitasvir/ Dasabuvir (Viekira Pak®)	x	x	x		BCRP, OATP
Elbasvir/Grazoprevir (Zepatier®)	x		x		OATP
Voxilaprevir	x	x		x	BCRP, OATP
Ledipasvir		x		x	--
Velpatasvir	x	x		x	BCRP, OATP
Sofosbuvir		x			BCRP

BCRP: breast cancer resistance protein; OATP: organic anion transporting polypeptide

Potential Drug Interactions

Inducers

- St John's Wort
- Rifampin/ Rifabutin
- Carbamazepine
- Phenytoin
- Phenobarbital
- Efavirenz

Inhibitors

- Azole antifungals
- Protease Inhibitors
- Erythromycin/Clarithromycin

Statins and DAAs

	Rosuvastatin	Atorvastatin	Pitavastatin	Simvastatin	Pravastatin	Lovastatin	Fluvastatin
Glecaprevir/ Pibrentasvir	Max 10mg	NR	Use lowest dose	NR	↓ dose by 50%	NR	Use lowest dose
Ledipasvir/ Sofosbuvir	NR	Monitor closely	--	--	--	--	--
Velpatasvir/ Sofosbuvir	Max 10mg	Monitor closely	--	--	--	--	--
Elbasvir/ Grazoprevir	Max 10mg	Max 20mg	--	Use lowest dose	--	Use lowest dose	Use lowest dose
Sofosbuvir/ Velpatasvir/ Voxilaprevir	NR	Use lowest dose	NR	Use lowest dose	Max 40mg	Use lowest dose	Use lowest dose
Paritaprevir/ Ritonavir/ Ombitasvir/ Dasabuvir	Max 10mg	--	--	--	Max 40mg	--	--

NR: not recommended, Per Package Labeling

Overview of Drug Interactions

- Absorption Interactions
- Cytochrome P450 & Transporter Mediated Interactions
- **Amiodarone**
- Immunosuppressant Interactions

Amiodarone-Sofosbuvir Induced Bradycardia

- Post-marketing reports of life-threatening bradycardia
- May occur within first few hours up to 2 weeks
- Exact mechanism unknown

Toxicol Sci. 2016;154(1):174-182.
https://www.fda.gov/Drugs/DrugSafety/ucm439484.htm

Management of Amiodarone and Sofosbuvir

- Avoid coadministration
- When discontinuing amiodarone prior to starting sofosbuvir, consider long half-life of amiodarone
- If coadministration is unavoidable
  - Counsel patients about risk of serious symptomatic bradycardia
  - Cardiac monitoring in an in-patient setting for first 48 hours of coadministration followed by daily heart rate monitoring

https://www.fda.gov/Drugs/DrugSafety/ucm439484.htm

Overview of Drug Interactions

- Absorption Interactions
- Cytochrome P450 & Transporter Mediated Interactions
- Amiodarone
- **Immunosuppression Interactions**

Cyclosporine and DAAs

- Cyclosporine is an inhibitor of CYP3A4 (weak), P-glycoprotein, OATP1B1, and BCRP

Glecaprevir/ Pibrentasvir	Elbasvir/ Grazoprevir	Sofosbuvir/ Velpatasvir/ Voxilaprevir
• Use not recommended in patients requiring >100mg cyclosporine per day	• Cyclosporine may increase risk of ALT elevations due to OATP inhibition	• Cyclosporine increases Voxilaprevir concentrations • Use not recommended

Calcineurin Inhibitor Dose Adjustments

	Cyclosporine		Tacrolimus	
DAA Therapy	**AUC**	**Dosing**	**AUC**	**Dosing**
Ritonavir-boosted	↑482%	1/5 total daily dose	↑5613%	0.5mg every 7 days
Elbasvir/ Grazoprevir	--	--	↑43%	Monitor levels closely

Hepatology 2016;63:634-643

https://www.hcvguidelines.org/unique-populations/post-liver-transplant

Polling Question

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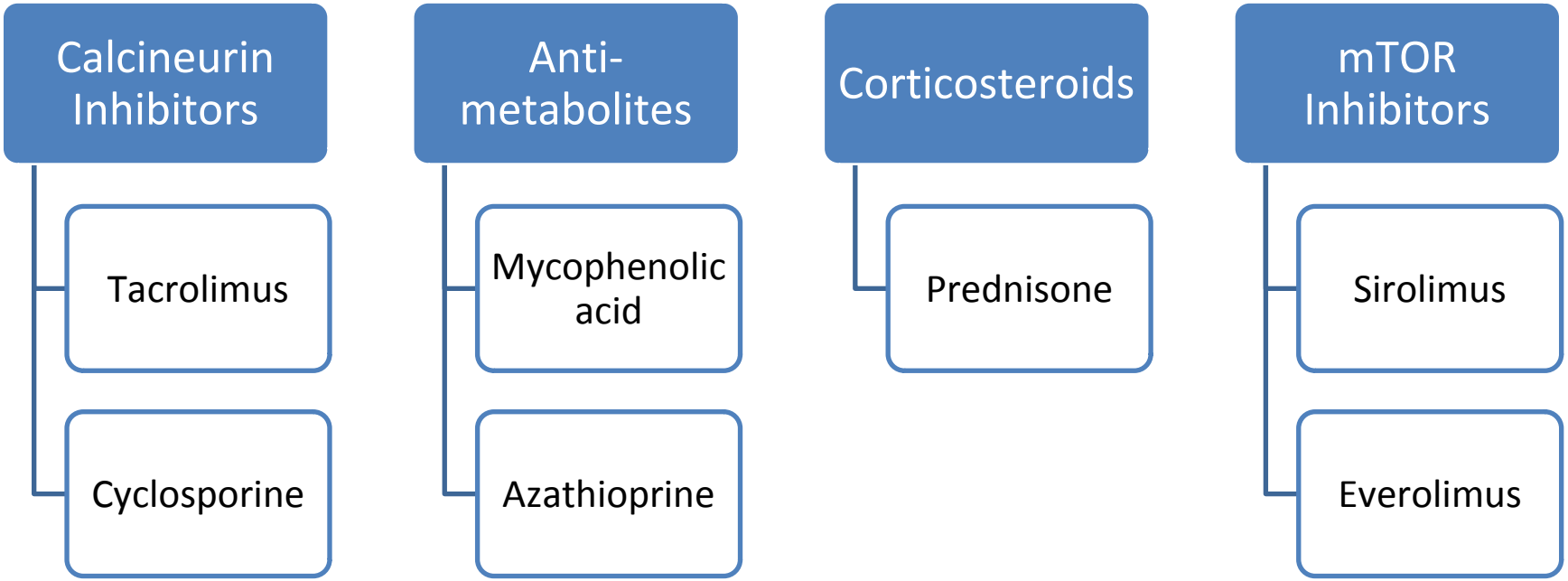
D Velpatasvir/Sofosbuvir (Epclusa®) and amiodarone 400mg PO daily

Common Adverse Effects

- Fatigue
- Headache
- Nausea
- Diarrhea
- Skin reactions (rare)

Overview Maintenance Immunosuppression



Cyclosporine vs Tacrolimus

	Levy et al.	Liu et al.
Design	Prospective, randomized, open label, 356 liver txp recipients for HCV	Meta-analysis of 9 randomized and quasi-randomized controlled trials
Intervention	Tacrolimus vs Cyclosporine	Tacrolimus vs Cyclosporine
Outcome	<u>Fibrosis ≥ stage 2 @ 12months</u> FK vs CyA 67.5% vs 71.6% (P=0.759) <u>HCV Viral Load @ 12 months</u> FK vs CyA 3.13 U/µL vs 3.17 U/µL (P=0.866)	No difference found in: -mortality -graft loss -histological HCV recurrence

Am J Transplant. 2014;14(3):635-46; PLoS ONE. 2014;9(9):e107057

Steroid Withdrawal

	Segev et al.
Design	Meta-analysis of 30 publications (19 RCT)
Intervention	Steroid-free vs Steroid-based
Outcome	↓ HCV recurrence with steroid avoidance (RR 0.90, P=0.03)

Liver Transpl. 2008 Apr;14(4):512-25

mTOR Inhibitors

	McKenna et al.	Soliman et al.
Design	Single center, retrospective, 455 liver txp recipients with HCV	Single center, open-label, prospective, 25 renal txp recipients with HCV
Intervention	Sirolimus within 7 days of txp vs Non-sirolimus	Conversion to Sirolimus vs Cyclosporine
Outcome	<u>Fibrosis on biopsy</u> SRL vs Non-SRL 1 year: 15.3% vs 36.2% (p<0.0001) 2 year: 30.1% vs 50.5% (p=0.001)	<u>HCV PCR @ 6 months:</u> SRL 700,000 → 400,000 IU/mL (P<0.001) CyA 680,000 → 660,000 IU/mL (P=NS)

Am J Transplant. 2011 Nov;11(11):2379-87, Exp Clin Transplant. 2013 Oct;11(5):408-11

Patient Case Discussion

RH is a 54yo male with ICM now s/p OHT 6 weeks ago from a HCV positive donor. His post-op course was complicated by persistent afib. He presents to clinic for a routine cardiac biopsy and to see hepatology for initiation of hepatitis C therapy.

PMH GERD, gout, and hypothyroidism

Medications

- Tacrolimus 3mg PO q12h
- Mycophenolate mofetil 1000mg PO q12h
- Prednisone 15mg PO daily
- Valganciclovir 450mg PO daily
- Nystatin Swish and swallow 5mL TID
- Bactrim DS qMWF
- Rosuvastatin 5mg PO qhs
- Aspirin 81mg PO daily
- Pantoprazole 40mg PO BID
- Levothyroxine 88mcg PO daily
- Allopurinol 300mg PO daily
- Amiodarone 200mg PO daily

Pertinent Labs

Serum Cr: 2.1	LFTs: WNL	Hepatitis C PCR: 2 million
CrCl = 45ml/min	TFTs: WNL	HCV Genotype: 1

Patient Case Discussion

RH is a 54yo male with ICM now s/p OHT 6 weeks ago from a HCV positive donor. His post-op course was complicated by persistent afib. He presents to clinic for a routine cardiac biopsy and to see hepatology for initiation of hepatitis C therapy.

- What are some patient-specific issues to consider in selecting his hepatitis C therapy?
- Which DAA would you select? Are there any changes you would recommend to his other medication therapy?

Challenges of Hepatitis C Therapy After Transplant

- Compliance with Complicated Medication Regimens
- Complex Drug Interactions involving DAAs and transplant medications
- Side Effect Management
- Cost

Key Takeaways

- There are a variety of drug interactions with DAAs that require careful consideration of patient-specific factors, especially after solid organ transplant

- In the current era of DAAs, standard immunosuppression should be used post-transplant for patients receiving hepatitis C positive donors

Acknowledgements

- ASHP Section of Clinical Specialists and Scientists

- American Society of Transplantation Transplant Pharmacist Community of Practice Education Workgroup