Impact of The Opioid Epidemic On Organ Donation and Utilization Of Organs from Hepatitis C-infected Donors

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October 14, 2017
Disclosures

• Consulting: Merck
• Research support: Merck, Intercept
• Will discuss off-label use of an FDA-approved medical product Zepatier
• Despite positive impact on organ donation, would prefer that this talk not have to be given in the future
Objectives

• Identify the current barriers to utilizing hepatitis C infected organs for organ donation.
• Discuss the impact the opioid epidemic has on organ donation.
• Evaluate management strategies to work within and around the identified barriers to better serve potential transplant candidates.
Introduction

• Heroin epidemic a national tragedy
• Ability of organs from these donors might serve as perhaps the only comforting factor among this tragic and unnecessary loss of life.
The Issue: Staggering increase in the number of deceased donors dying from a drug overdose

According to OPTN/UNOS data as of March 15, 2017
Organ specific utilization from donors dying from a drug overdose

According to OPTN/UNOS data as of March 15, 2017
Heroin and opioids

• What is heroin\(^1\)
  – Naturally occurring substance
  – Extracted from seed pod of certain poppy plants

• Heroin types and sources
  – “Pure” heroin
    • White powder can be snorted or smoked
    • Predominantly from South America (lesser SE Asia)
    • US markets east of Mississippi River
  – Black tar heroin
    • Sticky (roofing tar) or hard (like coal)
      – More impurities
      – Must be dissolved, diluted, and injected
    • Predominantly produced in Mexico
    • Sold in US west of Mississippi River

1-National Institute on Drug Abuse; Heroin; https://www.drugabuse.gov/publications/research-reports/heroin/what-heroin
Region of origin of wholesale Heroin seizures from Drug Enforcement Agency

What is fueling opioid epidemic?

• Narcotics frequently prescribed by physicians
  – “Appropriately” used by patients
  – Inappropriately used
    • 10.3 million people used prescription opioids nonmedically in 2014 (not prescribed to them or used high)¹

• National Health and Nutrition Examination Survey²
  – 1999–2006: % of adults ≥20 who used a prescription opioid analgesic in the past 30 days increased from 5.0% ->6.9%
  – 1999-2012: % opioid analgesic users who used opioid analgesic stronger than morphine increased from 17.0% ->37.0%.
  – Opioid analgesic sales (kg/10,000) quadrupled from 1999- 2010

Why is heroin frequently abused?

• Comparatively low cost of heroin
  – Street price Oxycodone: $1/1mg oxycodone
    • $20 for two 10mg/325mg Percocet tablets
    • $30 for 30mg tablet of oxycodone
  – “Bag” of heroin: $5-10
    • Use of 1-5 bags per day

• Rapid onset of action (rapid high or rapid resolution withdrawal symptoms)
  – IV: Peak onset-20 seconds; Duration: 4 hours
  – Smoking: Peak onset-10 minutes; Duration: 5 hours
  – Snorting: Peak onset: 10-30 minutes; Duration: 3-5 hours

1-Bernstein L. Washington Post, 8/27/15; 2-Sapatkin D. Philadelphia Inquirer, 8/6/15
What is fueling epidemic of increased deaths from heroin overdoses?

• Heroin purity
  – Percentage that is heroin versus other additives
  – Chalk, talcum powder, fentanyl
  – Purity can influence lethality
    • Higher percentage inert additives, less lethal
    • 1970s/1980s: 2-5% pure
    • Current era: 85-90% pure in some areas (90% Philly)\(^1\)

• Cutting heroin with fentanyl\(^2\)
  – Heroin natural (poppy seeds)
  – Fentanyl synthetic (4-step process from non-rx ingredients)
    • Cheap, available, and easy to synthesize
    • 100 times stronger than morphine

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Changing prevalence of heroin use disorders since 2001

• Martins S, et al. *JAMA Psychiatry* 2017
• Survey data from National Epidemiology Survey on Alcohol and Related Conditions (NESARC) in 2001-2002 and 2012-2013
  – 2001-2002: 43,093 respondents
  – 2012-2013: 36,209 respondents
• Face-to-face household surveys in households and group quarters
• Heroin use: binary yes/no for ever use
• Abuse/dependence: Single disorder
Lifetime heroin use by demographics: Changes from 2001-2013

A) Sex
- Men vs. Women
- 2001-2002 NESARC vs. 2012-2013 NESARC-III

B) Race
- Non-Hispanic white vs. Nonwhite
- 2001-2002 NESARC vs. 2012-2013 NESARC-III

C) Age
- 18-29 y, 30-44 y, ≥45 y
- 2001-2002 NESARC vs. 2012-2013 NESARC-III

D) Marital status
- Married or living as married, Widowed, separated, or divorced, Unmarried
- 2001-2002 NESARC vs. 2012-2013 NESARC-III

E) Educational level
- Less than high school, High school, Some college or more
- 2001-2002 NESARC vs. 2012-2013 NESARC-III

F) Poverty level
- <100% FPL, 100-200% FPL, >200% FPL
- 2001-2002 NESARC vs. 2012-2013 NESARC-III

JAMA Psychiatry. Published online March 29, 2017. doi:10.1001/jamapsychiatry.2017.0113
Lifetime heroin use disorders by demographics: Changes from 2001-2013
# Donors dying from a drug overdose compared to other donors: Data from 2005-2016

<table>
<thead>
<tr>
<th>Mechanism of death</th>
<th>Number</th>
<th>Median age (IQR)</th>
<th>HCV “positive”</th>
<th>Diabetes</th>
<th>“Increased-risk” designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICH/stroke</td>
<td>46,028</td>
<td>51 (41-59)</td>
<td>3.5%</td>
<td>12.9%</td>
<td>6.9%</td>
</tr>
<tr>
<td>Blunt injury</td>
<td>22,638</td>
<td>28 (19-45)</td>
<td>3.4%</td>
<td>4.2%</td>
<td>11.8%</td>
</tr>
<tr>
<td>CV disease</td>
<td>14,000</td>
<td>47 (33-55)</td>
<td>3.8%</td>
<td>20.1%</td>
<td>11.7%</td>
</tr>
<tr>
<td>Gunshot wound</td>
<td>9,028</td>
<td>26 (20-37)</td>
<td>3.3%</td>
<td>2.7%</td>
<td>16.3%</td>
</tr>
<tr>
<td>Drug overdose</td>
<td>5,666</td>
<td>31 (24-39)</td>
<td>16.3%</td>
<td>4.5%</td>
<td>52.7%</td>
</tr>
<tr>
<td>Asphyxiation</td>
<td>4,621</td>
<td>25 (14-39)</td>
<td>2.8%</td>
<td>4.3%</td>
<td>19.1%</td>
</tr>
<tr>
<td>Seizure</td>
<td>882</td>
<td>29 (18-44)</td>
<td>1.6%</td>
<td>9.2%</td>
<td>8.4%</td>
</tr>
</tbody>
</table>

According to OPTN/UNOS data as of March 15, 2017
What defines an “increased risk organ donor”

### 2013 Guideline (All Ages)

- People who have had sex with a person known or suspected to have HIV, HBV, or HCV infections in the preceding 12 months
- MSM in the preceding 12 months
- Women who have had sex with a man with a history of MSM behavior in the preceding 12 months
- People who have had sex in exchange for money or drugs in the preceding 12 months
- People who have had sex with a person who had sex in exchange for money or drugs in the preceding 12 months
- People who have had sex with a person that has injected drugs by IV, IM, or subQ route for nonmedical reasons in the preceding 12 months
  - **People who have injected drugs by IV, IM, or subQ route for nonmedical reasons in the preceding 12 months**
- People who have been in lockup, jail, prison, or a juvenile correctional facility for $\geq$ 72 hours in the preceding 12 months
- People who have been newly diagnosed with or have been treated for syphilis, gonorrhea, Chlamydia, or genital ulcers in the preceding 12 months
- People who have been on hemodialysis in the preceding 12 months (RISK FOR HCV ONLY)

### 2013 Guidelines (Pediatric Ages)

- A child $\leq$ 18 months of age and born to a mother known to be infected with, or at increased risk for HIV, HBV, or HCV infections
- A child breastfed within the preceding 12 months and the mother is known to be infected with, or at increased risk for HIV

### 2013 Guidelines (Laboratory Findings)

- Any evidence of hemodilution

**NOTA precludes the use of HIV+ donors – now waived for research due to HOPE Act**

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*Seem et al. Public Health Reports. 2013; 128: 247-344*
Residual Risk: *Impact of Donor Screening*

Viremia Exposure

Nucleic acid testing

Serologic conversion

Serologic testing

**SEROLOGIC WINDOW**

**NAT WINDOW**

_Eclipse Period_

<table>
<thead>
<tr>
<th>Virus</th>
<th>Serology</th>
<th>NAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>22 days</td>
<td>5-9 days</td>
</tr>
<tr>
<td>HBV</td>
<td>44 days</td>
<td>22 days</td>
</tr>
<tr>
<td>HCV</td>
<td>66 days</td>
<td>5-7 days</td>
</tr>
</tbody>
</table>


Courtesy of Michael Ison, MD
## OPTN-Defined Increased Risk Donors: Residual Risk

<table>
<thead>
<tr>
<th>Risk per 10,000 donors</th>
<th>HIV ELISA</th>
<th>HIV NAT</th>
<th>HCV ELISA</th>
<th>HCV NAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Window Period</td>
<td>22 days</td>
<td>5-7 days</td>
<td>66 days</td>
<td>5-7 days</td>
</tr>
<tr>
<td>IV Drug Users</td>
<td>12.1</td>
<td>4.9</td>
<td>300.6</td>
<td>32.4</td>
</tr>
<tr>
<td>Prostitutes</td>
<td>6.6</td>
<td>2.7</td>
<td>114.9</td>
<td>12.3</td>
</tr>
<tr>
<td>Partner with the above</td>
<td>0.7</td>
<td>0.3</td>
<td>114.9</td>
<td>12.3</td>
</tr>
<tr>
<td>Men who have sex with men</td>
<td>10.2</td>
<td>4.2</td>
<td>32.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Blood product exposure</td>
<td>1.5</td>
<td>0.6</td>
<td>4.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Incarceration</td>
<td>2.3</td>
<td>0.9</td>
<td>7.2</td>
<td>0.8</td>
</tr>
</tbody>
</table>


Courtesy of Michael Ison, MD
Organ utilization and organ quality of donors dying from a drug overdose from 2005-2016

<table>
<thead>
<tr>
<th>Mechanism of death</th>
<th>Number</th>
<th>Organs transplanted per donor, mean ±SD</th>
<th>Overall KDPI, median (IQR)</th>
<th>KDPI of transplanted kidneys, median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICH/stroke</td>
<td>46,028</td>
<td>2.6 ± 1.6</td>
<td>61% (37-82%)</td>
<td>51% (31-72%)</td>
</tr>
<tr>
<td>Blunt injury</td>
<td>22,638</td>
<td>3.7 ± 1.7</td>
<td>30% (12-56%)</td>
<td>27% (11-50%)</td>
</tr>
<tr>
<td>CV disease</td>
<td>14,000</td>
<td>2.3 ± 1.5</td>
<td>64% (42-84%)</td>
<td>54% (34-72%)</td>
</tr>
<tr>
<td>Gunshot wound</td>
<td>9,028</td>
<td>4.4 ± 1.9</td>
<td>26% (12-41%)</td>
<td>24% (11-38%)</td>
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<tr>
<td>Drug overdose</td>
<td>5,666</td>
<td>3.1 ± 1.6</td>
<td>34% (19-51%)</td>
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<td>Seizure</td>
<td>882</td>
<td>3.3 ± 1.7</td>
<td>44% (24-65%)</td>
<td>38% (21-58%)</td>
</tr>
</tbody>
</table>

Organs transplanted per donor among donor dying from a drug overdose
- PHS-IR: 2.97 ± 1.64
- Not PHS-IR: 3.22 ± 1.64

According to OPTN/UNOS data as of March 15, 2017
Why are not all donors with a drug overdose deemed PHS-IR

- PHS-IR criteria for drug use: “People who have injected drugs by IV, IM, or subQ route for nonmedical reasons in the preceding 12 months”

Recipient follow-up of PHS IR donors

• 1 month
  – HCV RNA
  – HIV antibody
  – HIV RNA
  – HBV DNA
  – Hepatitis B core antibody
  – Hepatitis B surface antigen

• 1 year
  – HBV DNA
  – Hepatitis B core antibody
  – Hepatitis B surface antigen
HCV seropositivity in deceased donors dying from a drug overdose since 2011
Geographic differences in number of HCV-positive donors

Number of positive deceased donors in 2015-2016

- <50
- 50-99
- 100-200
- >250

*HCV positive donors based on a donor having a positive serologic test (HCV antibody) and/or detectable HCV RNA nucleic acid testing (NAT)
Non-hepatic organs from HCV-infected donors frequently discarded

- Liver: Historically HCV+ recipients > HCV+ donors
- Kidney: Donors > recipients
  - 5% of patients on HD with HCV
  - 1.8% of waitlisted kidney patients agree to receive kidneys from HCV-infected donors
    - Increased-risk behaviors
    - Viewed as ‘lower quality’ in KDPI
- Heart and lung: Few patients with HCV listed
  - 2006 JAMA study on worse outcomes in heart recipients
Two-thirds of kidneys from HCV+ donors discarded
Discarded hearts from HCV+ donors mirrors waitlist removals for death/clinical deterioration

* HCV+ based on a positive HCV Ab. Data on HCV RNA not uniformly collected until 2015
Pilot trial of transplanting kidneys from HCV-positive deceased donors into HCV-negative patients

Key considerations
- Recipients ages 40-65
- ≤548 days of waiting time
- No major contraindications to liver transplantation
- Genotype 1 donors
- Pre-emptive HCV treatment with Zepatier

ClinicalTrials.gov Identifier: NCT02743897
Do these studies need to be formal clinical trials

- AST Consensus Conference, January 30-31, 2016
  - Experimental with unknown safety and efficacy
  - “The Consensus Conference participants felt strongly that until the practice of transplanting organs from HCV-viremic donors into HCV-negative patients is shown to be safe and efficacious, all centers performing such transplants should have formal IRB-approved research protocols that have been vetted for safety and appropriate review of the informed consent process with an acceptable risk/benefit profile.”

Do clinical trials need to be able to guarantee HCV therapy for patients?

- I would argue yes
- Others argue no
- Potential options for treatment
  - Pharmaceutical support
  - Large research grant
  - Arrangement with insurer
  - Prior authorization on patient-by-patient basis
  - Apply on a case-by-case basis
- Logistical and financial considerations
- Ethically not needed but if not available
  - IRB approve risk-benefit profile
  - Patients counseled on risks of insurance denial and/or delay
Why we have been genotyping for the THINKER and USHER trials

- Current landscape of HCV therapy
  - Pan-genotypic
    - Two sofosbuvir-based regimens
      - Kidney/heart transplants: Contraindicated if eGFR<30mL/min
      - Heart transplants: Cardiac toxicity and amiodarone interactions
    - Glecaprevir/Pibrentasvir (Mavyret): Just approved in 8/2017
  - Grazoprevir/Elbasvir (Zepatier)
    - Only FDA approved for GT 1 and 4
    - Can be used at any level of renal function
    - No reported cardiac toxicity
    - No significant amiodarone interaction
    - Can be used with NG tube
What we didn’t know or still don’t know yet

• Will patients know about HCV and understand risks
• Which patients should be considered for such organs?
• Will all patients develop HCV?
• Will drugs work as well in the acute setting?
• What are the risks of severe acute HCV?
• Importantly
  – Risks need to be balanced against risks of not doing transplant
  – Must consider other things done in transplant
    • Immunosuppression withdrawal trials
    • Routine exposure to CMV and EBV (both incurable)
Overall aim: To determine the safety and efficacy of transplanting kidneys from HCV+ donors into HCV- patients on the kidney transplant waitlist.

• Other aims
  – To determine SVR (cure) rates
  – To evaluate safety of treating acute HCV
  – To determine 1-year graft survival rates
  – To evaluate rates of spontaneous HCV clearance
Rationale for inclusion and exclusion criteria

- Patients with longer than average expected waiting time
  - Provide earlier access to lifesaving kidney transplant
- Identify patients without significant waiting (HD) time accrued
  - Increased waiting time $\rightarrow$ increased probability of transplant
  - Increase dialysis time $\rightarrow$ increased CV complications
- Intermediate age patients
  - Increasing age $\rightarrow$ more co-morbidities
  - Increasing age $\rightarrow$ more aggressive HCV in acute setting
- Patients who could be OLT candidates if ALF develops
  - Age
  - Screening echocardiogram
  - Evaluation by liver transplant surgeon and transplant hepatologist
In-depth multi-stage informed consent process

1. Principal Investigator contacts patient on phone to introduce study
2. Patient attends group educational session
3. One-on-one discussion following group session
4. At least 24 hour waiting period before informed consent can be signed
THINKER Enrollment

Enrollment
- Preliminarily eligible and invited to educational session (n=38)
  - Declined to participate (n=16)
  - Attended Educational Session (n=22)
    - Activated for HCV+ kidneys on Waitlist (n=17)
      - Declined to participate (n=2) Screen Fail (n=3) Due to liver evaluation
      - Transplanted (n=10)
        - Awaiting Transplant (n=7)
    - Lost to follow-up (n=0)
      - Analysed (n=10)
Why patients declined to attend education session

- Concerns about HCV
  - Didn’t want an additional medical problem
  - Social stigmas and/or know someone with HCV
- Concerns about research
  - Don’t want to participate in experimental
- Outside pressures
  - Social support
  - Nephrologist or other physicians
Genotyping: Non-Genotype 1 was common

THINKER, N=40
- Genotype 1a: 45.0%
- Genotype 1b: 19.0%
- Genotype 2b: 16.0%
- Other: 5.0%

NHANES, N=63
- Genotype 1a: 44.0%
- Genotype 1b: 16.0%
- Genotype 2b: 19.0%
- Other: 15.0%

KPNC, N=10,256
- Genotype 1a: 42.3%
- Genotype 1b: 27.6%
- Genotype 2b: 16.2%
- Other: 11.8%
Sustained virologic response (cure) in 10/10 patients

Figure 1. Hepatitis C Viral Load in 10 Kidney-Transplant Recipients.
The hepatitis C viral load was measured by means of polymerase chain reaction. Each curve represents a transplant recipient.

6-month post-transplant renal function

- Median creatinine: 1.1 mg/dl (IQR 0.8 - 1.3)
- Median eGFR: 62.8 ml/min/1.73m² (IQR: 51.8-81.3)

## Adverse events

### SERIOUS

<table>
<thead>
<tr>
<th>Category</th>
<th>Event</th>
<th>Related to HCV or HCV therapy*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Procedural Complications</strong></td>
<td>Post-op reintubation (n=2), intra-operative nasal bleeding (n=1)</td>
<td>Unrelated</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic</strong></td>
<td>Pneumonia</td>
<td>Unrelated</td>
</tr>
<tr>
<td><strong>Metabolism and Nutritional Disorder</strong></td>
<td>Hyperkalemia (1 session post-transplant dialysis)</td>
<td>Unrelated</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorder</strong></td>
<td>Partial self-resolved small bowel obstruction</td>
<td>Unrelated</td>
</tr>
<tr>
<td><strong>Renal Disorder</strong></td>
<td>Renal pelvic mass and native nephrectomy</td>
<td>Unrelated</td>
</tr>
<tr>
<td><strong>Metabolism Disorder</strong></td>
<td>Hyperparathyroidism with parathyroidectomy</td>
<td>Unrelated</td>
</tr>
<tr>
<td><strong>Renal disorder</strong></td>
<td>Focal segmental glomerulosclerosis</td>
<td>Possible</td>
</tr>
</tbody>
</table>

Non-serious Adverse events included:
- One patient with transient, new donor specific antibody (1800 MFI)
Thoracic transplant considerations

• Acute kidney injury in the recipient quite common
• Appropriate patient selection
  – Balance of finding patients with poor transplant options but not at highest risk for post-transplant complications
• Organ specific potential drug interactions
  – e.g. antifungals in lung transplant
• Inability to swallow after transplant common
  – Need plan for administering antiviral treatment
• Vascular inflammation/injury
  – Heart transplantation
HCV-Infected Heart Transplants for HCV-negative patients

ClinicalTrials.gov Identifier: NCT03146741
HCV-infected heart transplants for HCV-negative patients

Inclusion Criteria:
• Age 40-65
• Inoperable coronary artery disease with intractable anginal symptoms
• Malignant ventricular arrhythmias unresponsive to medical or surgical therapy
• No evident contraindication to liver transplantation other than the underlying cardiac disorder

Exclusion Criteria:
• Chronic liver disease (excluding non-alcoholic fatty liver disease (NAFLD) with abnormal liver enzymes
• Congenital heart disease
• Fibrosis by liver biopsy or total bilirubin > 2.5 with associated evidence of synthetic dysfunction.
• Severe pulmonary hypertension as evidenced by a fixed pulmonary vascular resistance of greater than 4 Wood units on appropriate medical therapy.
Next steps

• THINKER trial
  – 2\textsuperscript{nd} phase near completion
    • 10 additional transplants
    • 4 cured, 6 awaiting SVR-12
  – 3\textsuperscript{rd} phase underway: Additional 20 transplants

• USHER trial
  – Have performed some transplants
  – Total number=10
Future of utilization of HCV+ organs

• What is needed for standard-of-care
  – Confidence in similar cure rates
  – No additional risks
    • Acute HCV
    • Immunologic complications
  – ‘Similar’ graft outcomes
  – What is correct N?
    • 100->SVR-12 cure rates with narrow CI
Future of utilization of HCV+ organs

• How to operationalize as standard-of-care
  – Should treat like any other infection in terms of risks
    • HBV core Ab->treat post
    • CMV->treat if mismatch (don’t always discuss)
  – Insurers paying for therapy
    • Need to be able to guarantee treatment coverage
    • Similar to CMV
  – Should treat like any other infection in terms of quality
    • Accept 60 year-old CMV kidney
    • Need to ensure no graft issues from chronic infection
      – Chronic GN/immune complex
Conclusions

• Opioid epidemic tragedy but organ donation may be only solace to families
• Deceased dying of a drug overdose fasting growing demographic of organ donors
• Opioid epidemic fueling increase in donor supply
• Combination of heroin + non-prescribed opioids
• Number of organs transplanted per donor dying from a drug overdose lower
• Need to properly educate patients (and providers) on true “increased risks”