Issues and controversies in Liver Transplantation: The Medical Side

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Medical Director, Liver Transplantation;
Chief of Hepatology
The Justification for OLT is Obvious
The Issue is Known
The Treatment is Effective

Two-year Survival
The Questions

- Selection of best candidates?
- Outcomes and follow up after OLT?
- Pushing the envelop (emerging indications)
The First Step: Building The Dream Team
It is A Team Approach!

On List Management

Dropout

Surgical Expertise

Surgery and Post-OLT

Anesthesia ICU

Hepatology Care

Protocols

Donor management

Hepatology Care

Location

Financial Coordinator

Social Services

Outcome

Wait time

Cleveland Clinic
First Issue to Face

• There is an ever increasing gap between the number of organs needed and supply.
Evolution of New Concepts

If you would understand anything, observe its beginning and its development.
1963…A very special year

First human liver transplant -
Dr. Thomas Starzl
(University of Colorado)
LIVER TRANSPLANTATION

THE FIRST PATIENT:

Three year old boy with biliary atresia;

he died on the table

Reactions!!

- Most scientists and the public believed that Starzel was reckless and some accused him of being unethical.
Ethics Of OLT

• While OLT is now an accepted therapy for those with liver failure, its ethics will continue to be debated as we expand indications to those with no liver disease…
History Repeats Itself
April 8, 1886 at 3:42 PM

• The first human appendectomy was performed at the Zurich Hospital by Dr. R. KRÖNLEIN and a team of 6 specialists. The patient was a 17 year old female (Ms Gluck). Twenty-three nurses were assigned exclusively for the care of this patient.
History Repeats Itself
April 9, 1886

• A nationwide media conference was held, during which it was announced that the patient passed gas on day 1 post-operatively.
History Repeats Itself: May 14, 1886

• An international commission formed that included army officers, clergymen and lawyers to study the deep moral and ethical issues raised by the operation.

  — Dr. Mondrian Kantor (USA): favors limiting the procedure to newborn infants
  — Dr. Hector Gomez (Venezuela): favors partial appendectomies
  — Sir Osler Worthington (UK): felt that since the appendix is the seat of the soul, it should not be tampered with under any circumstance
Liver Transplantation Milestones

• 1967 Use of azathioprine + steroids + antibodies
• 1967 1st pediatric patient survived > 1yr
• 1978 Introduction of cyclosporine
• 1983 NIH consensus conference
• 1989 Introduction of tacrolimus
• 1984 - National Organ Transplant Act
Survival after OLT Before and After CYS

% Survival vs. Months after OLT for:
- AZA Child
- CYA Child
- AZA Adult
- CYA Adult
Liver transplantation is accepted as a therapeutic modality by NIH Consensus Conference.
“The operation itself is but one incident, no doubt the most dramatic, yet still only one in the long series of events which must stretch between illness and recovery”

Sir Berkeley Moynihan
OLT
Indications

Accepted
Emerging
Liver Transplantation

Liver transplantation should be reserved to those that have exhausted standard medical and surgical therapies.

Liver transplantation is a form of treatment, and as such was designed for those with life threatening complications of end stage liver disease.
## Complications of Liver Cirrhosis

<table>
<thead>
<tr>
<th>Portal hypertension</th>
<th>Cardiovascular dysfunction</th>
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</thead>
<tbody>
<tr>
<td>Esophageal varices</td>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td>Ascites</td>
<td>Hyperdynamic circulation</td>
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<tr>
<td>Splenomegaly</td>
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<table>
<thead>
<tr>
<th>Pulmonary dysfunction</th>
<th>Synthetic dysfunction</th>
</tr>
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<tbody>
<tr>
<td>Arterial hypoxemia from pulmonary shunts</td>
<td>Coagulopathy</td>
</tr>
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<td>Pulmonary hypertension</td>
<td>Hypoalbuminemia</td>
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<table>
<thead>
<tr>
<th>Renal dysfunction</th>
<th>Neurologic dysfunction</th>
</tr>
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<tbody>
<tr>
<td>Hepatorenal syndrome</td>
<td>Hepatic encephalopathy</td>
</tr>
<tr>
<td>Platelet dysfunction and coagulopathy</td>
<td></td>
</tr>
<tr>
<td>Electrolyte disturbances</td>
<td></td>
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<table>
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<tr>
<th>Excretory dysfunction</th>
<th>Risk of malignancy</th>
</tr>
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<tbody>
<tr>
<td>Jaundice</td>
<td></td>
</tr>
<tr>
<td>Pruritis</td>
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- Electrolyte disturbances
- Neurologic dysfunction
- Excretory dysfunction
- Risk of malignancy

- Portal hypertension
- Esophageal varices
- Ascites
- Splenomegaly
- Cardiovascular dysfunction
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- Electrolyte disturbances
- Neurologic dysfunction
- Hepatic encephalopathy
- Excretory dysfunction
- Jaundice
- Pruritis
- Risk of malignancy
Indications for LTX

- Chronic end-stage liver disease
  - Chronic Hepatitis B and C
  - Alcoholic liver disease
  - Autoimmune hepatitis
  - PBC
  - Secondary biliary cirrhosis
  - PSC
  - Biliary atresia
  - NASH
Indications for LTX

• Metabolic liver disease
  – Wilson’s disease
  – Alpha-1 antitrypsin deficiency
  – Hemochromatosis
Emerging Indications

Malignant Disease

Recurrent Disease

Uncommon Disease

HCV
NASH
AIH
PSC/PBC

Amyloidosis
Oxylosis
Cystic Fibrosis
Metabolic Diseases

[Graph showing the incidence of HCC from 1976 to 1995 for Black men, White men, Black women, and White women, with an increasing trend over the years.]
Hepatocellular Carcinoma: Incidence Time Trends

(Age-adjusted rates of death for HCC per 100,000 of population)

USA: 2.3, 7.0
France: 4.8, 10.2
Italy: 10.9
Japan: 19.0, 40.0

Death rate per 100,000

H. El Serag and A. Mason, NEJM, 1999
Trends in OLT for hepatic malignancies in USA

UNOS Database
Milan Criteria: 1996

- One lesion less than 5 cm, OR
- Up to 3 lesions each less than 3 cm
HCC and the Milan Criteria

Expanded Criteria For OLT in the setting of HCC

- **UCSF:**
  - Single tumor up to 6.5 cm
  - $\leq$ 3 tumors each up to 4.5 cm but with cumulative diameter up to 8 cm.
**TTV < 35.8 cm³ in patients BEYOND Milan criteria**

**Recurrence**

- **Within Milan**
- **Beyond Milan/TTV <35.8**
- **Beyond Milan/TTV ≥35.8**

*p-value <0.001*

**Survival**

- **Within Milan**
- **Beyond Milan/TTV <35.8**
- **Beyond Milan/TTV ≥35.8**

*p-value <0.002*

- *n = 15 pts*
- *n = 14 pts*
- *n = 92 pts*
Transplant For Recurrent Disease (HCV)
Retransplantation for recurrent HCV

• Hepatitis C is the most common indication for liver transplantation in most countries.
• Re-infection of liver allografts is virtually universal and occurs at reperfusion
• HCV liver injury is believed to be more aggressive in transplant recipients compared to non-transplant patients.
Recurrent HCV

• HCV is currently responsible for at least 40% of all re-tx in the U.S. and the number is anticipated to rise.
Patterns Of HCV Recurrence

Severe Fibrosing Cholestatic HCV Recurrence

Chronic Hepatitis

Linear Rate Of Fibrosis Progression

Delayed Onset Progression

* At 5 years follow-up
# Factors With Impact On Recurrent HCV

<table>
<thead>
<tr>
<th>Viral Factors</th>
<th>Host Factors</th>
<th>Iatrogenic</th>
<th>Donor Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-OLT RNA</td>
<td>Immune status</td>
<td>Immunosuppressive drugs (steroids, MMF)</td>
<td>Donor age</td>
</tr>
<tr>
<td>Post-OLT RNA</td>
<td>Non-Caucasian race</td>
<td></td>
<td>Steatosis</td>
</tr>
<tr>
<td>Genotype 1b</td>
<td>Female gender</td>
<td>Ischemic time</td>
<td>Iron load</td>
</tr>
<tr>
<td>Genetic diversity</td>
<td></td>
<td></td>
<td>CMV status</td>
</tr>
</tbody>
</table>

Cleveland Clinic
Treatment of Recurrent HCV

• Using Pg IFN and RBV combination therapy (5 studies/~150 pts):
  – SVR 26%-40% (average 23%)
  – High withdrawal due to side effects (7%-43% mostly due to anemia)
Results of Re-tx for HCV

Survival %

<table>
<thead>
<tr>
<th></th>
<th>1 year</th>
<th>2 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV +</td>
<td>80</td>
<td>40</td>
</tr>
<tr>
<td>HCV -</td>
<td>100</td>
<td>90</td>
</tr>
</tbody>
</table>
Predictors of poor outcome after re-tx

• Time: Later is better

• Renal function
Current Recommendations

• For selected patients with recurrent HCV after initial OLT, re-tx is an appropriate option

• Those with early and severe recurrence of HCV or those with a significant renal dysfunction, re-tx is associated with poor outcome and should be avoided.
Disease Recurrence post OLT: NASH vs. HCV


[Graph showing disease recurrence over time for HCV and NASH]
The Impact of Steroids on Disease Recurrence

Survival post OLT: NASH vs. HCV

## Cause of Death post OLT: NASH vs. HCV


<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>NASH</th>
<th>Hepatitis C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular events</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Recurrence of Liver disease</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Others</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
Familial Amyloidosis Polyneuropathy

- FAP is an autosomal-dominant inherited systemic disease
  - Neuropathy (peripheral and autonomic)
  - Cardiomyopathy
  - Nephropathy
  - Malnutrition

- A mutant protein is produced by the liver and deposited in various tissues.
Familial Amyloidosis Polyneuropathy

- OLT is the only definitive therapy for FAP
- Worldwide experience include > 550 patients transplanted in 54 centers
Familial Amyloidosis Polyneuropathy

- One year and 5 years survival are 90% and 82%, respectively.
- Abnormal Amyloid protein becomes undetectable and most patients has no further progression of neuropathy or cardiac disease.
- 30% of patients may even improve.
Domino liver transplantation – the Concept

Metabolic liver disorder

Deceased or live donor

Pathology

Domino recipient
Ethics Of OLT
Waitlist death (%)
The First Assumption

More transplants =

1. Lower waitlist mortality
2. Lower MELD at OLT
3. Better post-OLT outcome
4. Improved financial state
It has been suggested that increasing OLT volume by using marginal organs may lead to lower outcome, raising ethical dilemmas: Going Against Conventional Wisdom!!!
Changing Philosophy?

• **Donors:** Greater use of extended criteria donors and DCD

• **Recipients:** More liberal listing of:
  – Obese patients
  – Patients with multi-organ dysfunction
  – HCC beyond Milan
  – Sicker patients who were not able to complete chemical dependency treatment after approval by the Ohio Solid Organ Transplant Consortium
Increasing the Volume
Looking at the Outcome

• Assess intention-to-transplant outcome following a change in our program philosophy associated with a significant increase in OLT volumes and the use of marginal donors.

- Volume of OLT
- Average MELD at the time of OLT
- Waitlist death
- 1-year Graft survival
- 1-year Patient survival
Volumes

* P<0.0001

00-04

05-07
Severity of illness

50% increase in patients with MELD > 21

P<0.0001
Waitlist death (%)
1-year graft survival (%)

P = 0.96

00-04

05-07
1-year patient survival (%)
Pre- and post-transplantation outcome following a change from program-centered to patient-centered selection committee decision making

Zein NN, Miller C, Bennett R, Smith M, Humberson A

Presented at the OLT ethics conference in Chicago, 2008
Conclusion

• Changing our program philosophy resulted in:
  – Greater OLT volumes
  – Decrease in waitlist death
  – No compromise of graft or patient survival

• These findings may have implications in the era of continued shortage of organs.
The First Step: Building The Dream Team
Current Outcomes: US Transplant Scientific Registry (CCF, July 07-June 08)  
Data Published in January 2009
Current Numbers: US Transplant Scientific Registry (CCF, July 07-June 08)

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<thead>
<tr>
<th>Item</th>
<th>Observed</th>
<th>Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Graft Survival</td>
<td>84</td>
<td>82</td>
</tr>
<tr>
<td>Adult Patient Survival</td>
<td>91</td>
<td>88</td>
</tr>
<tr>
<td>Peds Graft Survival</td>
<td>100</td>
<td>93</td>
</tr>
<tr>
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<td>100</td>
<td>93</td>
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## US Transplant Scientific Registry (CCF, 3-year survival)

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<tbody>
<tr>
<td>Adult Graft Survival</td>
<td>75.4</td>
<td>72</td>
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<tr>
<td>Adult Patient Survival</td>
<td>80</td>
<td>77</td>
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<tr>
<td>Peds Graft Survival</td>
<td>87.5</td>
<td>82</td>
</tr>
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Conclusions

• Recent advances in knowledge has led to expanded list of indications for OLT.

• The risk/benefit ratio and its ethics will continue to be evaluated as we move forward with “non-traditional” indications for organ transplantation.
Thank you for participating in our webinar today!

Market and Network Services Access Line

A new, one-stop, easy to use service dedicated for Case Managers, Medical Directors and Corporate Leaders who need assistance in referring patients to Cleveland Clinic, Main Campus. This line is open from 7am – 11pm, seven days a week.

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