ASSESSMENT AND MANAGEMENT OF POTENTIAL LIVER TRANSPLANT CANDIDATES

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HKASLD 30th Annual Scientific Meeting 5th Nov 2017, Hong Kong
Liver Transplantation in Hong Kong (QMH)

<table>
<thead>
<tr>
<th>Date</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 October, 1991</td>
<td>First successful human liver transplant</td>
</tr>
<tr>
<td>28 September, 1993</td>
<td>First paediatric live donor liver transplant</td>
</tr>
<tr>
<td>22 June, 1994</td>
<td>First combined liver and kidney transplant</td>
</tr>
<tr>
<td>12 July, 1994</td>
<td>First adult live donor liver transplant using left liver graft</td>
</tr>
<tr>
<td>10 May, 1996</td>
<td>World's first adult live donor liver transplant using right liver graft</td>
</tr>
<tr>
<td>4 June, 1998</td>
<td>First ABO incompatible liver transplant</td>
</tr>
<tr>
<td>16 January, 2000</td>
<td>Asia first split liver transplant to two adults</td>
</tr>
<tr>
<td>19 February, 2004</td>
<td>First sequential liver transplant</td>
</tr>
<tr>
<td>1 March, 2004</td>
<td>First combined liver and small bowel transplant</td>
</tr>
<tr>
<td>13 January, 2009</td>
<td>First donor interchange live donor liver transplant</td>
</tr>
<tr>
<td>20 August, 2010</td>
<td>First combined heart-liver transplant</td>
</tr>
<tr>
<td>10 November, 2013</td>
<td>First auxiliary liver transplant</td>
</tr>
<tr>
<td>1 October, 2014</td>
<td>First relay liver transplant</td>
</tr>
<tr>
<td>20 July, 2015</td>
<td>First dual right and left liver grafts live donor liver transplant</td>
</tr>
</tbody>
</table>

### Overall recipient cumulative survival

- **Survival:**
  - 1 year: 93%
  - 3 years: 88%
  - 5 years: 86%

### Indications for LT

- 58.6% Hepatitis B virus (HBV)
- 9.8% Hepatitis C virus (HCV)
- 7.8% Alcohol
- 7.8% Primary biliary cirrhosis (PBC)
- 4.6% Graft failure
- 4.6% Wilson's disease
- 3.7% Autoimmune hepatitis (AIH)
- 3.7% Drug-induced liver injury (DILI)
- 1.8% Other
Indications for Liver Transplantation

- Acute liver failure
- Chronic liver failure (noncholestatic)
- Chronic liver failure (cholestatic)
- Chronic liver failure (metabolic)
- Chronic liver failure (vascular)
- Others
- Malignant disease
- Benign tumours
- Pediatric diseases

Hepatitis A/B/E, hepatotoxicity, Wilsons Budd Chiari

Biliary atresia, Alagille’s syndrome, Neonatal hepatitis/AIH, Hepatoblastoma, Byler’s disease
Who To Refer? Is The Patient A Liver Transplant Candidate?

• How severe is the disease and its prognosis for the patient
  • Chronic liver disease
    • Child Pugh score (B/C)
    • MELD score (≥15)
  • Acute liver failure
  • HCC
    • Within Milan or UCSF criteria

Index Complication
  Refractory ascites
  Hepatic encephalopathy
  Portohypertensive bleeding
  Spontaneous bacterial peritonitis
  Hepatorenal syndrome
  Hepatopulmonary syndrome
  Intractable pruritis
  Recurrent cholangitis
Acute/fulminant Hepatic Failure

Rapid development of encephalopathy, coagulopathy, and jaundice in persons without known pre-existing liver disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Paracetamol (%)</th>
<th>Non-paracetamol (%)</th>
<th>Viral</th>
<th>Unknown (%)</th>
<th>Other (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain 1992–2000</td>
<td>2%</td>
<td>17%</td>
<td>HAV 2%</td>
<td>35%</td>
<td>12%</td>
</tr>
<tr>
<td>Sweden 1994–2003</td>
<td>42%</td>
<td>15%</td>
<td>HBV 32%</td>
<td>11%</td>
<td>25%</td>
</tr>
<tr>
<td>UK 1999–2008</td>
<td>57%</td>
<td>11%</td>
<td>HEV ..</td>
<td>17%</td>
<td>7%</td>
</tr>
<tr>
<td>Germany 1996–2005</td>
<td>15%</td>
<td>14%</td>
<td>Unknown ..</td>
<td>21%</td>
<td>28%</td>
</tr>
<tr>
<td>USA 1998–2001</td>
<td>39%</td>
<td>13%</td>
<td>Other ..</td>
<td>18%</td>
<td>19%</td>
</tr>
<tr>
<td>Australia 1988–2001</td>
<td>36%</td>
<td>6%</td>
<td>Paracetamol ..</td>
<td>34%</td>
<td>10%</td>
</tr>
<tr>
<td>Pakistan 2003–05</td>
<td>0%</td>
<td>2%</td>
<td>HAV 7%</td>
<td>60%</td>
<td>7%</td>
</tr>
<tr>
<td>India 1989–96</td>
<td>0%</td>
<td>1%</td>
<td>HBV 20%</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>Sudan 2003–04</td>
<td>0%</td>
<td>8%</td>
<td>HEV 44%</td>
<td>31%</td>
<td>7%</td>
</tr>
</tbody>
</table>

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not reported. HAV=hepatitis A virus. HBV=hepatitis B virus. HEV=hepatitis E virus.

Bernal W et al. Lancet 2010;376:190-201
Clinical Features of Acute Liver Failure

- Whole body
  - Systemic inflammatory response
  - High energy expenditure and catabolism

- Liver
  - Loss of metabolic function
  - Decreased gluconeogenesis leading to hypoglycaemia
  - Decreased lactate clearance leading to lactic acidosis
  - Decreased ammonia clearance leading to hyperammonaemia
  - Decreased synthetic capacity leading to coagulopathy

- Lungs
  - Acute lung injury
  - Adult respiratory distress syndrome

- Adrenal gland
  - Inadequate glucocorticoid production contributing to hypotension

- Bone marrow
  - Frequent suppression, especially in viral and seronegative disease

- Circulating leucocytes
  - Impaired function and immunoparesis contributing to high risk of sepsis

- Brain
  - Hepatic encephalopathy
  - Cerebral oedema
  - Intracranial hypertension

- Heart
  - High output state
  - Frequent subclinical myocardial injury

- Pancreatitis
  - Particularly in paracetamol-related acute liver failure

- Kidney
  - Frequent dysfunction or failure

- Portal hypertension
  - Might be prominent in subacute disease and confused with chronic liver disease

Bernal W et al. Lancet 2010;376:190-201
**King’s College Criteria for Emergency LT for Acute Liver Failure**

<table>
<thead>
<tr>
<th>Paracetamol</th>
<th>Non-paracetamol</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Arterial pH &lt;7.3 following adequate volume resuscitation</td>
<td>• Any grade encephalopathy and</td>
</tr>
<tr>
<td>• Or combination of</td>
<td>• INR 6.5 or more</td>
</tr>
<tr>
<td>• Encephalopathy (Grade 3 or mo32),</td>
<td>• OR any 3 of the following</td>
</tr>
<tr>
<td>• Creatinine 300 umol/L or more</td>
<td>• INR &gt;3.5</td>
</tr>
<tr>
<td>• INR &gt;6.5</td>
<td>• Br 300 umol/L or more</td>
</tr>
<tr>
<td></td>
<td>• Age &lt;10 or &gt;40 years</td>
</tr>
<tr>
<td></td>
<td>• Unfavourable causes</td>
</tr>
<tr>
<td></td>
<td>• Drug-induced</td>
</tr>
<tr>
<td></td>
<td>• Seronegative disease</td>
</tr>
</tbody>
</table>

Early discussion with the Liver Transplant team is essential
Do not delay until these criteria are met
### Acute on Chronic Liver Failure

**APASL**

a. Acute hepatic insult within 4 weeks with ascites and/or HE
b. Br >5mg/dL and INR 1.5
c. High 28-day mortality

**EASL-CLIF**

Grade 1:

a: Kidney failure
b: Kidney dysfunction (Cr 1.5-1.9 mg/dL) and/or HE + 1 organ failure
c: Kidney dysfunction (Cr 1.5-1.9 mg/dL) and HE

Grade 2:

a: ≥2 additional failed organ

Grade 3:

a: ≥3 additional failed organ

**WGO**

a. Acute hepatic decompensation
b. Jaundice and coagulopathy
c. ≥1 extrahepatic organ failure
d. Increased (28d and 3m) mortality from onset

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Rahimi RS, Rockey DC. Curr Opin Gastroenterol 2016;32:172-181
Liver Transplantation for HCC

Usually occurs on the background of liver cirrhosis (except CHB)
Liver Transplantation for Hepatocellular Carcinoma

Eligible HCC patients for LT

- Within criteria
  - Milan (1 lesion ≤5cm, or ≤3 lesions each ≤3 cm)
  - USCF (1 lesion ≤6.5cm, or ≤3 lesion each ≤4.5cm, with total ≤8 cm)
- No evidence of extra-hepatic disease
- No evidence of vascular invasion

- Bridging therapy may be given while on waiting list to prevent tumour progression and drop-outs from waiting list
  - TACE: transarterial chemoembolization
  - SBRT: stereotactic body radiation therapy
  - HIFU: high intensity focal ultrasound

~15% recurrence rate after LT (intra and extrahepatic)
Patients with liver disease referred to QMH for liver transplant

Attend QMH liver clinic (Medical)

Attend QMH liver transplant clinic (Surgical)

Attend QMH paediatric surgical/paediatric clinic (Paediatric)

If indicated

Admit to medical ward for liver transplant work-up

Admit to liver transplant ward for liver transplant work-up

Admit to relevant paediatric ward for liver transplant work-up

Transplant surgeon
Transplant hepatologist
Anaesthetist
Cardiology
Respiratory
Clin. Psychology
Dental
## Evaluation of Potential LT Recipient

<table>
<thead>
<tr>
<th>Evaluation Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Financial screening</td>
<td>Secure approval for evaluation</td>
</tr>
<tr>
<td>Hepatology evaluation</td>
<td>Assess disease severity and prognosis, confirm diagnosis and optimize management</td>
</tr>
<tr>
<td>Surgical evaluation</td>
<td>Confirm need for transplant, identify technical challenges (e.g. prior abdominal surgery, portal vein thrombosis etc.), discuss donor options (deceased, living, extended)</td>
</tr>
<tr>
<td>Laboratory testing</td>
<td>Assess hepatic synthetic function, serum electrolytes, renal function, viral serologies, markers of other causes of liver disease, tumor markers, ABO-Rh blood typing, creatinine clearance, urinalysis and urine drug screen</td>
</tr>
<tr>
<td>Cardiac evaluation</td>
<td>Initial non-invasive evaluation with echocardiography. Noninvasive stress testing and cardiology evaluation if cardiac risk factors are present (hyperlipidemia, hypertension, diabetes, cigarette consumption, age &gt;60 years)</td>
</tr>
<tr>
<td>Hepatic imaging</td>
<td>Ultrasonography with Doppler to document portal vein patency, triple-phase computed tomography or gadolinium magnetic resonance imaging for tumor diagnosis and staging</td>
</tr>
<tr>
<td>General health assessment</td>
<td>Chest film, Pap smear and mammogram (women), colonoscopy if patient is age 50 years or older or has primary sclerosing cholangitis</td>
</tr>
<tr>
<td>Dental assessment</td>
<td>Identify dental caries, buried roots and dental abscesses. Coordinate dental extractions if necessary with hepatology</td>
</tr>
</tbody>
</table>
# Evaluation of Potential LT Recipient

<table>
<thead>
<tr>
<th>Evaluation Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anesthesia evaluation</td>
<td>Required if unusually high operative risk, i.e., patient has portopulmonary hypertension, hypertrophic obstructive cardiomyopathy, previous anesthesia complications</td>
</tr>
<tr>
<td>Psychiatry, psychology or mental health professional consultation</td>
<td>Determine if history of substance abuse, psychiatric illness, or adjustment difficulties (e.g. behavioral or adherence problems)</td>
</tr>
<tr>
<td>Social work evaluation</td>
<td>Address potential psychosocial issues, adequacy of support, and possible effect of transplantation on patient’s personal and social system</td>
</tr>
<tr>
<td>Financial and insurance counseling</td>
<td>Itemize costs of transplantation and posttransplantation care, review insurance coverage, help develop financial management plans</td>
</tr>
<tr>
<td>Nutritional evaluation</td>
<td>Assess nutritional status and patient education</td>
</tr>
<tr>
<td>Infectious disease</td>
<td>Identify infectious processes that require intervention prior to transplant (e.g. latent TB or posttransplant e.g. CMV naïve recipient)</td>
</tr>
</tbody>
</table>
Assessment for Liver Transplantation

Transplant Work-up Completed

Case submitted to Joint Liver Transplant Meeting for discussion
Liver transplant surgical team
Transplant hepatologist / hepatologist
Anaesthetic team
Paediatric team (if applicable)

Accepted for transplant
Case enter into the liver transplant waiting list in ORTS
Outcome of the meeting documented on patient’s file by Liver Transplant Coordinator

Not accepted for transplant
Further evaluation, may re-discuss later; or Continue follow up in liver transplant clinic
Continue follow up in liver clinic; or Discuss alternative treatments; or Referred back to regional hospital for follow up
# Contra-indications to Liver Transplantation

<table>
<thead>
<tr>
<th>Absolute Contraindications</th>
<th>Relative Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active alcohol &amp; substance abuse</td>
<td>Psychosocial conditions</td>
</tr>
<tr>
<td>HCC with macrovascular invasion or extrahepatic spread</td>
<td>Advanced age</td>
</tr>
<tr>
<td>Uncontrolled systemic infections/sepsis outside the hepatobiliary system</td>
<td>Severe obesity/malnutrition</td>
</tr>
<tr>
<td>Uncontrolled extrahepatic malignancy</td>
<td>Many of the “contraindications” to transplantation are relative or correctable, so these should probably not prevent referral of patients, particularly without discussion with the transplant center</td>
</tr>
<tr>
<td>Uncontrolled/limiting medical conditions</td>
<td></td>
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<tr>
<td>Technical and/or anatomical surgical barriers</td>
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<tr>
<td>Brain death</td>
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</table>
Artificial Liver Support Devices as Treatment Option for Liver Failure

- MOLECULAR ADSORBENT RECIRCULATING SYSTEM (MARS)
  - MARS® Flux (non-permeable to albumin)
  - Secondary closed circuit
  - Hemodialysis unit
  - Low flux
  - Activated charcoal
  - Anion exchange resin

- FRACTIONATED PLASMA SEPARATION AND ADSORPTION (PROMETHEUS)
  - AlbuFlow® (permeable to albumin)
  - Secondary FP5A circuit
  - High flux
  - Hemodialysis

Remove protein-bound & water-soluble toxins
- bilirubin, ammonia, creatinine

Beneficial effects on survival not proven
- ?Bridge to transplant
Wait-Listed Patients

- Prioritize according to MELD score
  - MELD = 9.57 \times \log_e(\text{creatinine}) + 3.78 \times \log_e(\text{total bilirubin}) + 11.2 \times \log_e(\text{INR}) + 6.43
- MELD-exception criteria (eg. HCC, genetic & metabolic diseases)
- Listed according to blood group
Chronic Hepatitis B and Liver Transplantation

- CHB remains the most common (~60%) primary liver disease for liver transplantation
  - Cirrhosis with decompensation
  - Hepatocellular carcinoma
  - Severe acute flares

- All CHB patients waitlisted for liver transplantation should be on antiviral therapy
  - Nucleoside analog - entecavir
  - Nucleotide analog – tenofovir-based
  - Although undetectable viral load is desirable at the time of transplant, it is not essential
Antiviral Prophylaxis after Liver Transplantation for Chronic Hepatitis B

• Long term antiviral prophylaxis is required to prevent graft hepatitis and graft loss from HBV reactivation after LT
  
  Fung J. World J Hepatol. 2015 Jun 8;7(10):1421-6
  Fung J. World J Gastroenterol. 2014 Nov 21;20(43):16053-61

• Oral nucleoside/nucleotide analogues alone without HBIG is highly effective after LT for CHB patients, with excellent long term survival
  

• For those without drug resistance, entecavir monotherapy without HBIG is highly effective with no recurrence of HBV-related graft hepatitis and graft loss, and excellent long-term outcome
  
  Fung J et al. Liver Transpl. 2015 Dec;21(12):1504-10

• Even with pre-existing lamivudine-resistant HBV, oral nucleoside/nucleotide analogues without HBIG is highly effective
  
Shifting Paradigm of HBV Prophylaxis after Liver Transplantation

- **1990’s**
  - High dose IV
  - Low dose IV
  - Low dose IM
  - HBIG Withdrawal
  - HBIG Free

- **Oral NAs**
  - Lamivudine
  - Adefovir
  - Entecavir & Tenofovir

- **2017**

**Decreasing HBIG use**
- Needs regular injection
- Expensive
- Resistance Risk

**Higher potency. Lower resistance**
- Daily oral dosing
- Inexpensive
- Resistance Risk
Chronic Hepatitis C in Liver Transplantation

- Less common than HBV - ~0.5% in Hong Kong

- Indications for liver transplantation
  - Cirrhosis with decompensation
  - Hepatocellular carcinoma

- After liver transplantation, recurrence of hepatitis C in the graft is universal
  - If untreated, 20% will have graft cirrhosis by 5 years
Evolution of Antiviral Therapy for HCV after Liver Transplantation

Peg-interferon + ribavirin (2002-2014)

- Poorly tolerated with significant side effects
- Requires weekly injection (IFN) for ~1 year
- High rate of graft cirrhosis, failure, and re-transplantation

95-100%

All oral DAAs 2015-2017

Gane EJ, Agarwal K. Am J Transplant. 2014 May;14(5):994-1002
## Opportunities to Treat Before LT

Prior to the availability of all-oral DAA regimens, treatment while on the LT waiting list was largely contraindicated.

### Advantages

- High SVR rates can be achieved
- Reduce post-transplant recurrence rate
- May reduce decompensation & death on waiting list
- Improve MELD and clinical status on waiting list
- May improve QOL while on waiting list
- May increase likelihood of bridging therapy for HCC

### Disadvantages

- Potentially lower SVR rates in decompensated group
  - MELD purgatory
- Potential greater risk of drug toxicity
  - Restricted regimens
  - ?HCC recurrence
• Expected time to liver transplantation
• MELD score

Some DAA regimens may have significant drug-drug interactions with immunosuppressive agents
Alcoholic Liver Disease and LT

• Indications for liver transplantation
  • Decompensated cirrhosis
  • Severe Alcoholic hepatitis

• Six month abstinent period prerequisite for consideration of liver transplantation for alcoholic liver disease
  • ?Improvement in liver function with stopping alcohol
  • ?Ability to remain abstinent

• Severe alcoholic hepatitis unresponsive to medical therapy—unlikely to survive 6 months without early LT
  • Early LT significant improves survival (77% vs 23% @ 6m)

Early Liver Transplantation for Severe AH

**PROS**
- Living donor available
- Improved survival

**CONS**
- Negative public perception
- Limited organ supply
- Risk of relapse

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**PRO VIEW**
Liver transplantation for severe alcoholic hepatitis—The PRO view

Michael R. Lucey
Liver Int. 2017 Mar;37(3):343-344

**CON VIEW**
Liver transplantation for severe alcoholic hepatitis—The CON view

James Y. Y. Fung¹,²
Liver Int. 2017 Mar;37(3):340-342
Proposed Treatment Algorithm for Severe Alcoholic Hepatitis

Thurz M and Morgan TR. Gastroenterology 2016;150:1823-1834
Summary

• **Timely** referral to the liver transplant center is essential for **eligible** patients
  • If in doubt – discuss with the transplant team

• Evaluation for LT should be considered once a patient with cirrhosis has experienced an index complication such as ascites, hepatic encephalopathy, or variceal hemorrhage or hepatocellular dysfunction results in a MELD Score ≥15

• Patients with acute liver failure (ALF) require immediate discussion with the liver transplant center
Future Direction

Create opportunities and training in transplant hepatology for gastroenterology fellowship

“I am currently in public practice in a city with a population of about 7 million where I am the only formally trained transplant hepatology physician.”

“AASLD MEMBER

HKASLD MEMBER

“7 million”