Liver Transplantation – a non transplant centre perspective

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HOW AM I QUALIFIED TO DO THIS?

• Don’t work in a transplant centre
• Never worked in a transplant centre
• Not “really” a hepatologist
• But…. therefore, I:
  - Am in awe of transplant centres
  - Talk to them
  - Do what they tell me to

LIVER TRANSPLANTATION: RULE 1

• Communicate with Transplant centre
  (currently, they are being monitored, not you!)
• Wide open portal - letters/phones/e mails….
• Seamless electronic access to imaging
• Shared protocols
• Educational meetings
• If possible - attend MDT in transplant centre
  - combined clinics

SUMMARY

• When to refer (and when not to?)
• Care pre-transplant
• Care post- transplant
• Organisational issues

LIVER TRANSPLANTATION

• Rate in Europe lower than that in USA
• Diminishing supply or organs (less RTAs)
• More restricted indications
• Increasing time and mortality on waiting list
• Options:
  “Marginal” donors (old, fatty livers, virus infected…
  Increased donation after cardiac death (DCD)
  Living donor (?diminishing enthusiasm)
  Split livers (increased biliary complications)

TRANSPLANT REFERRAL; STAGED ALERT SYSTEM

• Stage 0: Don’t even think about it!
• Stage 1: Not now but may need in 5-15 years
• Stage 2: Not right now but will need soon (so, should you refer ?)
• Stage 3: a Now (elective)
  b Now (emergency)
S1: NOT NOW, MAYBE IN 5-15 YEARS

- Significant fibrosis (eg stage 3+) AND
- Cannot halt the cause ("going nowhere")
  - HCV with unsuccessful treatment
  - NAFLD
  - PBC: young or fail to normalise enzymes on URSO
  - PSC
  - AIH who are not in full remission
- Focus (with GP) on general health (CV risk factors...)
- Consider screening for HCC
- Hepatitis A, B vaccination

S2: NOT RIGHT NOW, BUT SOON
(so ideally, need a decision)

- MELD <15; UKELD < 49 but...
- Impending decompensation:
  - Falling serum albumin (eg <32 for > 4 weeks)
  - Raised bilirubin and/or prothrombin time
  - Episode of encephalopathy
  - Ascites/oedema, even if easily treated
  - Large variceal bleed (esp if gastric)
  - Poor nutrition
- Getting old?
  Blood group O – will wait longer

S3: WOULD BENEFIT FROM TRANSPLANT NOW

- MELD approaching 15
- UKELD approaching 49
- HCC
- Encephalopathy; failed treatment
- Refractory ascites or variceal bleeding (? TIPS)
- Episode of SBP
- Fulminant liver failure: refer immediately

BASIS OF ORGAN ALLOCATION

- Principle: ? Need, utility or benefit
- MELD score - based on creatinine, bilirubin, INR
  - extensively validated
  score: <15: outlook no better with transplant
  >30: ? poorer post transplant outcome
- Disadvantages: small women
  HCC, HPS, itching, cystic disease...
- Variants: MELD-Na, UKELD (now used in UK)

HCC “sign” – arterial flush, venous washout

TRANSPLANTATION FOR HCC - Criteria

- Milan: 1 < 5 cm or 3 < 3 cm
  and no portal vein, extrahepatic involvement
  5 yr survival 65-78%, 5-20% recurrence
  Externally validated; widely used
- Others: San Francisco: 1<6.5 or <3 <4.5 cm
  “Up to 7” cm
  Total tumour volume (TTV) <115 cm³
TRANSPLANTATION FOR HCC – Allocation system

• “Exception” MELD points allocated:
  eg: HCC < 5 cm: 19-22 points;
  1-3 extra every 3 months
• Waiting list still 6-10 months
• 10-30% “de-listed” (esp if outside “Milan”)

“NICHE “ INDICATIONS

• Hepato-pulmonary syndrome; PaO2 <60 mmHg
• Polycystic liver disease
• Familial amyloidosis
• Severe symptoms: Pruritus
  Encephalopathy
  Fatigue (no longer)

S2/3: WORK-UP FOR REFERRAL DECISION (1)

• Do they want one?
• How long will they live with a new liver?
• History of “major” disease (cancer, vascular..)
• Performance status (run for bus, stairs..)
• Clinical examination: heart, chest, breasts, testes, prostrate.
• Other factors: smoking, alcohol
  compliance, clinic attendance
  psycho-social

S2/3: WORK-UP FOR REFERRAL DECISION: INVESTIGATIONS (establish what local centre expects)

• CT/MRI liver
  - ? Tumour
  - ? Portal vein patent
  - Both, if HCC
• Tumour markers
• Consider liver biopsy
• Chest X ray, ECG, oximetry
• Echocardiogram +/– myoview; need cardiology access
• Spirometry, transfer factor
• CT/MRI head if any cognitive impairment
• BUT if S3, do not delay unduly before referring

S2/3: WHEN MIGHT YOU NOT REFER?

• Doesn’t want one (early mortality about 5%)
• Alcohol related disease; continued drinking
• Active illicit drug abuse
• Extra-hepatic cancer (within 3 years
  5 yr survival <50+%)
• Advanced “biological” age
  “invalidity”
• Severe heart/lung/brain/psychiatric disease
• Extensive portal/SMV thrombosis (but should discuss)
• Persistent non-compliance
  non-attendance

WHAT ABOUT MARGINAL CASES?

• Always ask
• Don’t be afraid to be the patient’s “advocate”
  - You know patient better
  - They (not you!) must balance resource and demand
• Occasionally worth a second opinion
• Which centre? – consider patient’s views
**REFERRAL “ETIQUETTE”**

- Avoid cold-calling with a new referral (even if urgent)
- Send (post/fax) detailed referral letter, based on a records summary and including:
  - Diagnosis (and basis for)
  - Liver function
  - Complications
  - Co-morbidity
  - Social/Psychological
- Then, phone (or leave a contact number)
- Ensure electronic access to imaging

**TRANSPLANT CENTRE: OPTIONS**

- Reject
- Suggest further tests
- For future consideration, if deterioration
- See in clinic
- Admit electively
- Transfer urgently
- May repeat “all the tests” – that’s OK!

**JOURNEY TOWARDS TRANSPLANT: THINGS TO WATCH (1)**

- Nutrition Be pro-active
  - Vitamins (A D K in cholestatic disease)
    - Exclude thyroid, coeliac, pancreatic disease
- Repeated paracentesis: consider TIPSS
- Antibiotic prophylaxis following SBP episode
- Serum sodium (<126, may be suspended)
- Encephalopathy...? Rifaximin
  - Safe to drive

Critical event: always phone transplant centre

**JOURNEY TOWARDS TRANSPLANT: THINGS TO WATCH (2)**

- HAV, HBV immunisation
- Bone health: Calcium and Vitamin D
  - DEXA scanning +/- bisphosphonates
- Screening: HCC, varices
- Lifestyle: cigarettes
  - alcohol
  - clinic attendance
- Psyche

**POST TRANSPLANT: CAUSES OF LATE DEATH**

- Graft failure (23% HCV, 12% PSC..)
- Cardiovascular (3 fold increase)
- Cancer (3 fold increase overall; up to 30% of late deaths)
- Renal failure
- Infection

![Life expectancy by age at transplant](from Barber Gut 2007)
POST TRANSPLANT CARE; BASICS

- Eventual shared care (transplant and referring centre)
- GPs may not want to get too involved
- Roles of referring centre:
  - 2-4 monthly monitoring:
    - weight, BP, medications, compliance
    - U+E, LFTs, FBC, HbA1c, lipids, drug levels
    (communicate blood results, complete proformas)
  - Rapid access blood results (+ultrasound if needed)
  - Often, drug prescriptions - avoid patient running out.

IMMUNOSUPPRESSIVE STRATEGY

- Steroids - 1st few months (can sometimes avoid)
- Azathioprine/Mycophenolate - 1st year
- Calcineurin Inhibitors – long-term; gradual dose reduction
- Sirolimus if CNI-induced renal dysfunction

CALCINEURIN INHIBITORS

- Cyclosporin (trough level 50-150 ng/ml) or Tacrolimus (trough level 5-10 ng/ml)
- Cause: hypertension, renal impairment, hyperlipidaemia, diabetes, cancer...
- Levels may depend on formulation
- Levels increased: antifungals, macrolides, diltiazam, verapamil
- Levels reduced: antiepileptics, rifampicin
- Inhibit Cyp-450
- NSAIDS, ACE inhibitors may worsen renal damage

POST TRANSPLANT PROBLEMS

- Infection
- Liver dysfunction
- Hypertension
- Renal impairment
- Metabolic syndrome
- Cancer

CMV INFECTION

- Usually in first 3 months
- Used to be 25% if donor CMV+, recipient –
- Much rarer with valgancyclovir prophylaxis
- Px: systemic, oesophagitis, colitis, hepatitis...
- Increases rejection, mortality
- May have late onset if donor+, even if prophylaxis
- Rx: Reduce immunosuppression
  - IV gancyclovir till PCR negative

EBV INFECTION AND PT LYMPHOPROLIFERATIVE DISORDER

- Uncontrolled proliferation of transformed EBV-infected B lymphocytes
- Incidence 2% in adults (more in children)
- Associations: EBV at transplant, EBV DNA level
- Symptoms: fever, lymphadenopathy
- Rx Reduce immunosuppression
  - Rituximab (anti B cell)
  - Surgery/DXR for local disease
  - Prevent by EBV DNA surveillance
LIVER DYSFUNCTION (>6 months)

- Rejection: 20% acute, 2% chronic
- Biliary strictures – esp. if early vascular injury
- Disease recurrence: Autoimmune disease 20-40%
  - HCV - usually
  - NAFLD - 20-30%
- Infection (CMV….)
- Portal/Hepatic vein thrombosis

LIVER DYSFUNCTION: WORKUP

- Clinical: Rigors/jaundice
  - Immunosuppression gap (or interaction)
  - Ascites, adenopathy?
- Ultrasound with Doppler
- MRCP if suspected biliary problem
- CT if suspected PT Lymphoproliferative Disorder
- Full viral screen (incl. PCR for EBV, CMV)
- Autoantibodies
- Liver biopsy (discuss first)

HYPERTENSION AND RENAL DYSFUNCTION

- BP >130/80 in 75%; GFR <30 ml/min in 25% (10 yr)
- Causes: Calcineurin inhibitors
  - HCV
  - Diabetes
- Approaches: Minimise steroids
  - Lower CNI dose, unless levels low
  - Change Cyc. to Tac. or Sirolimus
  - Calcium channel blocker: Amlodipine
  - ACE inhibitor. if proteinuria
  - Doxazosin

METABOLIC PROBLEMS

- Diabetes:
  - Late incidence 25%
  - Associations: steroids, HCV, Tacrolimus
  - Poorer outlook
  - Rx: Metformin (creatinine<130), insulin
- Hyperlipidaemia:
  - Incidence 50%
  - Associations: steroids, Cyclosporin, Sirolimus
  - Rx: Pravastatin (not Cyp450 metabolised)

POST TRANSPLANT MALIGNANCY

- Relative Risk
  - Overall 2-4
  - Non melanoma skin cancer 20-70
  - Lymphoma 10-30
  - Colorectal 3-12 (30 if IBD)
  - Head and neck 4-7 (25 if ALD)
  - Kaposi sarcoma 100

POST TRANSPLANT MALIGNANCY

- Risk factors: age, smoking
  - EBV infection
  - ALD (oropharyngeal)
- May be lower with sirolimus
- Annual dermatology review, avoid sunlight
- Colonoscopy screening (PSC)
### TRANSPLANT PATIENTS

**ORGANISATIONAL ISSUES**

- Should be cared for by:
  - Hepatologists or 1-2 designated Gastroenterologists
- Need:
  - Specialist Nurse
  - System for blood monitoring
  - Rapid access ultrasound
- See in liver clinics; access to other clinics:
  - Dermatology
  - Renal
  - Diabetic

### TRANSPLANT MEDICINE - STAYING IN TOUCH

- Read "Liver Transplantation" occasionally
- Attend EASL/AASLD postgraduate courses
- Attend Transplant Centre Educational events
- If possible: Attend MDTs
  - Combined clinics