MANAGEMENT OF PATIENTS WITH DECOMPENSATED LIVER DISEASE PRE-TRANSPLANTATION AND AT END OF LIFE

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Topics

• Epidemiology of cirrhosis in UK
• Cirrhosis overview including symptom management/management of complications
• Case – involvement of palliative care while on the list
• Update on liver transplantation (listing/prognosis/wait length/machine perfusion)
• End of Life care documents
UK CIRRHOSIS EPIDEMIOLOGY
Figure 4: Age-standardised all-cause mortality for people aged 25-44 years in 2016 at small area geographical level for the whole of England.

Bhala et al, BMJ, 2013
Kontopantelis et al, Lancet, 2018
Williams et al, Lancet, 2014
NORMAL LIVER

NAFL

Lipogenesis

Inflammation

NASH

Fibrosis

CIRRHOSIS

- Dyslipidemia
- Insulin Resistance
- Obesity
- Metabolic Syndrome
- Type 2 Diabetes

- Lipid Peroxidation
- Mitochondrial Dysfunction
- Oxidative Stress
- Apoptosis
- Pro-Inflammatory Cytokine Activation

- Advanced Cell Damage
- Scarring
The Obesity Epidemic

Williams et al, Lancet, 2014
Figure 4: Potential years of working life lost (before 65 years of age) estimated with Office for National Statistics mortality data. Data are from references 31 and 32 and were categorised into 5 year bands. NAFLD—non-alcoholic fatty liver disease.

Figure 6: Causes of liver disease in patients on liver transplantation waiting list as of January, 2017.
CIRRHOSIS OVERVIEW
Natural History of Chronic Liver Disease

Risk Factors
- Alcohol
- Obesity / Diabetes
- Viral hepatitis

Scarring

Severe Scarring (Cirrhosis)

Symptoms

Death

5-20 yrs

10%/yr
Late Diagnosis of Cirrhosis

Fig. 1. Survival estimates within 5 years by time-at-risk period. Number at risk is calculated at each point by excluding previous deaths and censored events. Subseq.hospt, subsequent to hospitalisation.

Ratib et al, J Hep, 2014
Cirrhosis

Increased Hepatic Resistance

Mechanical
- Architectural changes
- Fibrosis
- Vascular occlusion

Dynamic
- Endothelial dysfunction
- $\uparrow$ Vascular tone

Increased Portal Pressure

Increased Portal Inflow

Splanchnic vasodilation
- Increased NO, CO, glucagon, endocannabinoids
- Hyperkinetic syndrome

Portal systemic collaterals

Angiogenesis

$\Delta P = \text{Resistance} \times \text{Blood flow}$
Cirrhosis Prognosis (Baveno Stage)

50% 1 year survival following first episode
- Hepatic Encephalopathy
- Spontaneous Bacterial Peritonitis

D’Amico et al, J Hep, 2006
Fleming et al, AP&T, 2010
Complications of Cirrhosis

- Variceal haemorrhage
- Ascites
- Hepatic encephalopathy
- Sarcopenia
- Osteodystrophy
- Sepsis
- Acute kidney injury incl. hepatorenal syndrome
- Disease specific e.g. pruritus
Common Medications

• Hepatitis C
  • Directly acting antiviral drugs
• Hepatitis B
  • Tenofovir/entecavir
• Hepatic Encephalopathy
  • Lactulose/phosphate enemas/rifaximin
• Variceal prevention
  • Carvedilol
• Ascites management
  • Spironolactone (up to 400mg per day)/Furosemide (up to 160mg per day)
  • Ciprofloxacin (prophylaxis for infection)
  • Often off diuretics to protect renal function
Primary Prophylaxis of Varices

1. Diagnosis of cirrhosis
   - Endoscopy
     - No varices
       - Re-endoscopy 2-3 years*
     - Grade I varices
       - Re-endoscopy 1 year*
     - Grade II or III varices (or any varices with red signs)
       - Non cardio-selective beta-blocker
       - Intolerant/contraindications to non cardio-selective beta-blocker or patient choice: Variceal band ligation

Tripathi et al, Gut, 2015
Ascites

Diuretic sensitive ascites

Diuretic resistant ascites

Hyponatraemia

Hepato-renal failure

Ciprofloxacin reduces risk of further episodes often used as secondary prophylaxis
Primary Prophylaxis of SBP

- Number of studies have demonstrated that low protein in ascitic fluid (<10-15g/L) increases risk of SBP development (although overall still <20% at one year)
  
- RCT of PO norfloxacin vs. placebo
- 68 patients with Childs B/C cirrhosis and jaundice, renal failure or hyponatraemia (<130)
- Ascitic albumin <15g/L

Fernandez, Gastro, 2007
Overt Hepatic Encephalopathy

• Present in:
  • 30-40% cirrhotics at some time in their clinical course
  • 16-21% point prevalence in patients with decompensated cirrhosis
  • 10-50% 1 year incidence in patients with cirrhosis and TIPSS stent

<table>
<thead>
<tr>
<th>Portal Hypertension Complication</th>
<th>One Year Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic Encephalopathy</td>
<td>64%</td>
</tr>
<tr>
<td>Variceal Haemorrhage</td>
<td>20%</td>
</tr>
<tr>
<td>Ascites</td>
<td>29%</td>
</tr>
<tr>
<td>Ascites and Variceal Haemorrhage</td>
<td>49%</td>
</tr>
</tbody>
</table>

Bernel, Lancet, 2015
EFFECTS OF LACTULOSE

- Decreased pH
- Lactic acid
- Lactulose
- Urease-producing bacteria
- Increase cathartic effect
- NH$_3$
- NH$_4^+$
Rifaximin

Results:
- Rifaximin group 31/140 (22.1%)
- Placebo group 73/159 (45.9%)
- NNT 4

- Rifaximin group 19/140 (13.6%)
- Placebo group 36/159 (22.6%)
- NNT 9

Bass et al, NEJM, 2010
What Causes Malnutrition in CLD?

- Accelerated starvation (proteolysis)
- Dysgeusia incl. salt restricted food
- Anorexia of chronic disease
- Impaired gut motility/protein losing enteropathy
- Inappropriate dietary protein restriction
- Hospitalisation
- Fasting for diagnostic/therapeutic procedures
Strategies to Optimise Nutrition

• Avoid long periods of fasting
  • Regular snacks during the day and late evening protein snack

• Optimise energy intake (>35kcal/kg/day)
• Optimise protein intake (1.2-1.5g/kg daily)
• Salt restriction (ascites) – 80mmol sodium (5g salt) daily
• Consider micronutrient deficiencies
  • Vitamin D
  • Zinc
  • Selenium
• Resistance exercise
Hepatic Osteodystrophy

- Prevalence of osteoporosis approximately 30% in cirrhosis, greatest in decompensate cirrhosis/those awaiting OLT

Montomoli et al, Clinical Epidemiology, 2018
• Vitamin D – 800iu/day or load 50,000iu weekly for 6 weeks then maintenance
• Avoid bisphosphonates in patients with oesophageal varices – consider intravenous bisphosphonates/denosumab

EASL Clinical Practice Guidelines, 2018
AKI In Cirrhosis

- 20% of hospitalised cirrhotics
- Commonest precipitants:
  - Sepsis (esp. SBP)
  - GI Bleeding (AKI in 26% cirrhotics)
  - Medications
  - Large volume paracentesis without albumin cover

- The majority are NOT hepatorenal syndrome

Garcia-Tsao et al, Hepatology, 2008
Belcher et al, CGH, 2013
**Investigations:**
- Septic screen
  - Chest X-ray
  - Urine dipstick/biochemistry
  - Diagnostic ascitic tap
  - Blood cultures
- Renal imaging (US)
• Multicentre prospective cohort study
  • 192 patients with cirrhosis meeting AKIN criteria
  • Assessment of Stage of AKI diagnosis and AKI progression contributing to risk of mortality

Belcher et al, Hepatology, 2013
Pruritus (i.e. PSC/PBC)

- **Pruritus**
  - Cholestasis present? NO → Investigate other causes
  - YES →
    - Pregnant? YES → Specific management
    - NO →
      - Bile duct obstruction? (US, ERCP or MRCP)
        - YES → Specific management
        - NO →
          - Cholestyramine (up to 4g qds) BENEFIT → Continue
            - Monitor fat sol. vitamins
          - Rifampicin 150 mg daily → Continue
            - Monitor serum liver tests
          - Increase stepwise to max 600mg daily (every other week)
            - NO BENEFIT/INTOLERANT → NO BENEFIT
          - Naltrexone (up to 50mg daily) → Continue
            - NO BENEFIT/INTOLERANT → NO BENEFIT
          - Sertraline (up to 100mg daily) → Continue
            - NO BENEFIT/INTOLERANT → NO BENEFIT
          - Consider experimental approaches → Continue
            - NO BENEFIT/INTOLERANT → Consider transplant

EASL Guidelines, Cholestatic Liver Diseases, 2009
CASE STUDY
Cirrhosis Rollercoaster

Sudden Unpredictable Deteriorations

May improve dramatically

Particularly with encephalopathy

Hard for family and can make palliation a challenge

Alcohol big modifier in non transplant listed patients
Case

52 yr old man

Below knee amputation complicated by osteomyelitis and a blood transfusion (1980)
Hepatitis C Cirrhosis (2008)
Treatment with boceprevir and Interferon for 40 weeks in 2013
Relapsed and developed ascites

Referred liver transplant assessment March 2014
Ascites (on spironolactone 100mg/furosemide 40mg) and UKELD score 55
Albumin 28 g/l and Bilirubin 28 micmol/

First Ascitic Drain April 2014

\[ \text{UKELD score} = (5.395 \times \ln(INR)) + (1.485 \times \ln(\text{creatinine})) + (3.13 \times \ln(\text{bilirubin})) - (81.565 \times \ln(\text{Na})) + 435 \]

Chronic Hepatic encephalopathy

Listed for liver transplantation July 2014
2014

April

2015

Ascitic Drain

Listed transplant

Oral HCV treatment - 3 months Successful (regular visits)

Ascitic drain

Hepatic Encephalopathy*

Drain

* Enemas added to rifaximin

Confusion and ascites (prosthetic leg)

No treatment (on rifaximin and lactulose)

Palliative care**

Confusion

Ascitic drain

Subdural Haematoma Craniotomy

Liver Transplant
Palliative Care - assessment Feb 2015

’Hard to live with uncertainty….. Mind is spinning’
‘Unable to do much due to fatigue and poor mobility’
“Poor sleep due to pain and anxiety (also sleep/wake cycle in HE)
‘Urinary urgency and okay incontinence’
‘Pain in left leg and lower back- no current pain relief’
‘Erratic bowel action-wife giving phosphate enemas’
‘ March 2015 –told number 1 on the waiting list at Roayl Free---- “ 1 am brilliant””

“ I am in NO MANS LAND”
LIVER TRANSPLANTATION
Indication for listing: Why I am I been considered for a transplant?

• Worsening liver function +/- complication of cirrhosis
  • UKELD > 49 with decompensating episode
• Ascites uncontrolled by diuretics
• Recurrent hepatic encephalopathy
• Hepatocellular carcinoma
  • Size criteria/number/AFP criteria
  • Bridging therapy e.g. chemoembolisation while on waiting list
• Rare other indications
  • Hepatopulmonary syndrome
  • Intractable itch/recurrent cholangitis (PSC)
### Indications for Liver Transplantation

<table>
<thead>
<tr>
<th>Cause (2013/14)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocellular carcinoma**</td>
<td>25</td>
</tr>
<tr>
<td>Alcohol related cirrhosis</td>
<td>23</td>
</tr>
<tr>
<td>Chronic viral hepatitis B and C*</td>
<td>12</td>
</tr>
<tr>
<td>Primary sclerosing cholangitis</td>
<td>11</td>
</tr>
<tr>
<td>Primary biliary cholangitis</td>
<td>9</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>7</td>
</tr>
</tbody>
</table>

** complicates 1% of cirrhotics/year; small tumours curable with liver transplant
Risk reduces if treat cause of cirrhosis i.e. hepatitis C and B but not abolished

Number of patients being listed for liver transplant for HCC is increasing

* 21% on list HCV or HCV related HCC

# Liver Function Severity

<table>
<thead>
<tr>
<th></th>
<th>Clotting (INR)</th>
<th>Bilirubin</th>
<th>Creatinine</th>
<th>Sodium</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKELD</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>MELD</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MELD-Na</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Child-Pugh</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>Albumin/ascites/hepatic encephalopathy</td>
</tr>
</tbody>
</table>

UKELD > 49  1 year mortality > 5%
UKELD Score

UKELD 55 – 20% mortality at 1yr
Bilirubin 45
INR 1.2
Creatinine 80
Sodium 133

UKELD 60 – 50% mortality at 1yr
Bilirubin 60
INR 1.7
Creatinine 80
Sodium 132

Barber at al Transplantation 2011; 92: 469
Liver Transplant Activity

- 1003 transplants /year
- 7 liver transplant centers
- Limited by donor numbers
- Most transplants from deceased donors
  - Brain Dead (DBD)
  - Cardiac Death (DCD)
- Increasing number of living donor transplants in UK

Figure 2.5 Total number of liver transplants by donor type, 1 April 2009 - 31 March 2019

- 2009-2010: 580 DBD, 576 DCD, 607 Living, 793 Donor
- 2010-2011: 39 DBD, 100 DCD, 132 Living, 737 Donor
- 2011-2012: 136 DBD, 132 DCD, 648 Living, 727 Donor
- 2012-2013: 153 DBD, 136 DCD, 665 Living, 665 Donor
- 2013-2014: 28 DBD, 38 DCD, 206 Living, 737 Donor
- 2014-2015: 3 DBD, 36 DCD, 209 Living, 813 Donor
- 2015-2016: 29 DBD, 200 DCD, 188 Living, 793 Donor
- 2016-2017: 31 DBD, 209 DCD, 188 Living, 793 Donor
- 2017-2018: 31 DBD, 200 DCD, 188 Living, 793 Donor
- 2018-2019: 29 DBD, 200 DCD, 188 Living, 793 Donor
UK Waiting Lists

SUPER-URGENT
10% of transplants
Acute Liver Failure e.g. paracetamol
Strict Listing Criteria
1st available organ
Organ needed within 24-48hrs

ELECTIVE
90% of transplants
End stage chronic liver disease (cirrhosis)

Organ become available retrieved and patient rung to come in for transplant next morning – sometimes organ not suitable once retrieved and transplant cancelled
Transplant Waiting List

**Figure 2.1** Patients on the active liver transplant list at 31 March

![Graph showing the number of patients on the active liver transplant list from 2010 to 2019. The number of patients fluctuates from 371 in 2010 to 611 in 2015, before declining to 432 in 2019.](image-url)
How long is the wait?

• Median wait 99 days
  • Can wait 1-2 years

• Dependent on
  • Severity of liver disease (UKELD)
    • Priority
    • Needing a good liver graft
  • Blood group/matching
  • Size

• National allocation as of 2017

<table>
<thead>
<tr>
<th>Blood group</th>
<th>Wait length (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>182</td>
</tr>
<tr>
<td>A</td>
<td>92</td>
</tr>
<tr>
<td>B</td>
<td>239</td>
</tr>
</tbody>
</table>

Johnson. Transplantation 2015; 97; supp1S: p1-27
Getting On The Waiting List

Local Referral

Seen at transplant centre

Listed

Up to 3 months

Need to be able to fit enough to walk into outpatients’

‘Need to be able to climb two flights of stairs’
Chance of Receiving Liver Transplant

Figure 2.3  Post-registration outcome for 1023 new elective liver only registrations made in the UK, 1 April 2016 - 31 March 2017

<table>
<thead>
<tr>
<th>Time since listing</th>
<th>Transplanted</th>
<th>Still waiting</th>
<th>Removed</th>
<th>Died/Removed*</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>60</td>
<td>29</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>1 year</td>
<td>73</td>
<td>13</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>2 years</td>
<td>79</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Removals due to condition deteriorating
Age on Waiting List Increasing

Outcomes less good > 65 yrs

Consider selected patients 65-70yrs
Survival Following Liver Transplantation

Unadjusted patient survival (%) post-transplant for first liver transplants

<table>
<thead>
<tr>
<th></th>
<th>One year patient survival (%)</th>
<th>Five year patient survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adult</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elective</td>
<td>94</td>
<td>83</td>
</tr>
<tr>
<td>Super-urgent</td>
<td>88</td>
<td>82</td>
</tr>
<tr>
<td><strong>Paediatric</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elective</td>
<td>97</td>
<td>92</td>
</tr>
<tr>
<td>Super-urgent</td>
<td>94</td>
<td>70</td>
</tr>
</tbody>
</table>

Source: Transplant activity in the UK, 2015-2016, NHS Blood and Transplant
Normothermic Machine Perfusion

- The liver is perfused with oxygenated blood, medications and nutrients at normal body temperature to maintain a physiological milieu.
  - Allows utilisation of donor organ for up to 24 hours after retrieval
  - Increased organ utilisation
  - ‘real-time’ assessment of borderline grafts e.g. DCD, moderate steatosis
- RCT of NMP vs. SCS
  - 50% reduction in organ discard rate (11.7% vs. 24.1%)
  - Reduction in peak AST, early allograft dysfunction

Nasralla et al, Nature, 2018
END OF LIFE CARE
Rocket Drain Insertion

- Allows drainage of ascites at home (district nurse/family member)
- Inserted by Interventional Radiology
- High incidence of bacterial peritonitis (up to 50% at 100 days), therefore antibiotic prophylaxis required
BASL END OF LIFE SIG

Clinical Guideline

SYMPTOM CONTROL AND END OF LIFE CARE IN ADULTS WITH ADVANCED LIVER DISEASE

FOR STAFF: Hospital doctors, GPs, specialist nursing staff and clinical pharmacists

PATIENT GROUP: Adult patients with Child Pugh B or C cirrhosis who are experiencing symptoms which interfere with their quality of life

www.basl.org.uk
<table>
<thead>
<tr>
<th>Itching</th>
<th>Menthol 1% in aqueous cream</th>
<th>Apply 1-2 times daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colestyramine</td>
<td>4-8g PO OD</td>
<td>First line if itching is due to cholestasis (build-up of bile salts). Affects absorption of other medications: take other medications at least 1 hour before or 4-6 hours after colestyramine.</td>
</tr>
<tr>
<td>Antihistamines e.g. chlorphenamine</td>
<td>Second line - sedative effect can be helpful if given at night as patients are woken less frequently by pruritus. Sedating effect can mask or worsen encephalopathy.</td>
<td></td>
</tr>
<tr>
<td>Rifampicin, Naltrexone, SSRIs (e.g. sertraline)</td>
<td>Can all be used for itching secondary to cholestasis, but should not be initiated without Hepatology guidance.</td>
<td></td>
</tr>
<tr>
<td>Colesevelam</td>
<td>Off licence indication and limited evidence for effectiveness therefore not recommended</td>
<td></td>
</tr>
</tbody>
</table>
References

• Changing face of liver disease in UK
  • Lancet report
    • Williams et al. Lancet 2014; 384:1953

• Liver Transplantation
  • www.odt.nhs.uk

• British Association for the Study of Liver Disease (BASL)
  • www.basl.org.uk
ANY QUESTIONS