The Management of Other Aspects of Chronic Liver Disease, Including Transplantation

Prof. Timothy M. McCashland, MD
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Omaha NE, USA

Outline

• Management of common complications associated with end stage liver disease
• Preparation for evaluation and listing for liver transplantation
• Listing criteria for liver transplantation
• Management of common medical conditions after liver transplantation

Variceal bleeding

Figure 8—Bleeding varix. Endoscopic imaging showed an active bleeding varix in the stomach.
**Varices increase in diameter progressively**

- No varices
- Small varices
- Large varices

- Risk of bleeding small varices ≈ 10% (3 yrs), large varices ≈ 50% (3 yrs)
- Risk of death, stage 3, decompensation ≈ 20%, stage 4, ≈ 57%

*Merli et al., Hepatology 2003; 38: 205

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**Nonselective beta blocker prevention of first variceal hemorrhage**

<table>
<thead>
<tr>
<th>Bleed rate</th>
<th>Control</th>
<th>Beta blocker</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All varices</td>
<td>25%</td>
<td>15%</td>
<td>-10%</td>
</tr>
<tr>
<td>11 trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large varices</td>
<td>30%</td>
<td>14%</td>
<td>-16%</td>
</tr>
<tr>
<td>8 trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small varices</td>
<td>7%</td>
<td>2%</td>
<td>-5%</td>
</tr>
<tr>
<td>3 trials</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Variceal hemorrhage**

- Acute variceal hemorrhage
- Prophylactic pharmacotherapy and/or endoscopic variceal band ligation

**Recurrent hemorrhage**

- No
- Yes

**Yes**
- Surveillance endoscopy and/or life long pharmacotherapy

**No**
- TIPS/shunt surgery
- Combination treatment

*Garcia-Tsao G. Hepatology 2008; 47: 1764-1772*
Variceal bleeding pearls

- Mortality ↓ 42% to 15% (since 1981)
- Infections SBP 50%, UTI 25%, pneum 25% (ceftriaxone, quinolone 5 days)
- Octreotide bolus 50 μg, 25-50/hr 5 days
- Recombinant factor VII no benefit
- 10-20% unresponsive to endoscopy, 40-50% nonresponders to β-blocker, 20% intolerant
- Gastric varices cyanoacrylate 80% response (dermabond)
- HVPG measurements: who, when and why

Garcia-Tsao G. Hepatol 2008; 47: 1764-72

Ascites

- #1 complication of cirrhosis
- 50% die within 2 yrs of diagnosis (large)
- 50% 10 yr cumulative probability
- Grade 1 (U/S only), grade 2 moderate distension and mild discomfort, grade 3 marked distension and discomfort
- Diagnostic tap
  - Cell count, 250 cell/cu, culture, ALB

Runyon B. Hepatol 2004; 39: 841-56

Ascites management

- Low Na diet (90 mmol/day) (alone 10%)
- Spironolactone 100 mg/d + furosemide 40 mg/d, (increase by 100/40 every 7 days)
- Gynecomastia (amiloride, tamoxifen 20 mg/d)
- Large (paracentesis + diuretics; ALB 8 gm/L)
- Refactory ascites (10%) TIPS vs. paracentesis (bilir > 3, MELD > 18, Cr > 1.5)
- V2 antagonists (satavaptan 5mg, 12.5mg, 25 mg; Na >135 or > 5 ↑; 61%, 55%, 64%, n=73 pt)

Runyon B. Hepatol 2004; 39: 841-56

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Hepatorenal syndrome

- Annual incidence 8%
- Cr >1.5mg/dl, no improvement with volume expansion, absence of kidney disease
- Type 1 - doubling of Cr >2.5 mg/dl (< 2 wks)
  ≈25% of pts with SBP
- Type 2 - moderate slowly progressive rise
  Cr > 1.5 mg/dl (usually with large ascites)
- Imbalance between the activity of the systemic vasoconstriction and renal vasodilators

Arroy V. et al., Sem Liver Dis 2006; 28: 81-95

Hepatorenal survival

Days

Type 1
Type 2
No HRS

Arroy V. et al., Sem Liver Dis 2006; 28: 81-95

HRS treatment

- Octreotide and midodrine
  - 20-40 gm ALB/d, midodrine 7.5, 10, 12.5 tid, octreotide 100 μg tid, 200 tid
  - 3/5 survived vs. 1/8
- TIPS (type 1) 14 pts: 3, 6, 12 m survival (64%, 50%, 20%)
  - 5/7 alive 1 m
  - 10/14 reversal of HRS 1 m

Arroy V. et al., Sem Liver Dis 2006; 28: 81-95
Vasoconstrictors and HRS

<table>
<thead>
<tr>
<th></th>
<th>Martin-Liahi et al.</th>
<th>Sanyal et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td># pts</td>
<td>23/23</td>
<td>56/56</td>
</tr>
<tr>
<td>Terlipressin</td>
<td>1 mg/4 hr-2 mg/4 hrs</td>
<td>1 mg/6 hr-2 mg/6 hrs</td>
</tr>
<tr>
<td>ALB</td>
<td>1 g/kg-40 g/d</td>
<td>100 g-25 g/d</td>
</tr>
<tr>
<td>CVP</td>
<td>10-15</td>
<td>9</td>
</tr>
<tr>
<td>Type 1</td>
<td>61%/87%</td>
<td>100%</td>
</tr>
<tr>
<td>EtOH</td>
<td>61%/83%</td>
<td>51%/52%</td>
</tr>
<tr>
<td>MELD</td>
<td>36/28</td>
<td>33/33</td>
</tr>
<tr>
<td>Cr</td>
<td>3.1/3.6</td>
<td>3.9/3.9</td>
</tr>
</tbody>
</table>

West Haven classification

<table>
<thead>
<tr>
<th>Stage</th>
<th>Consciousness</th>
<th>Personality &amp; intellect</th>
<th>Neurologic</th>
<th>Ammonia level</th>
<th>EEG findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subclinical</td>
<td>Normal</td>
<td>Normal</td>
<td>Impaired psychomotor testing</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Stage 1</td>
<td>Euphoria, disturbed sleep pattern</td>
<td>Forgetfulness, agitation</td>
<td>Tremor, constructional apraxia, incoordination</td>
<td>?</td>
<td>Slightly abnormal</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Lethargy</td>
<td>Disorientation, bizarre behavior</td>
<td>Asteria, ataxia</td>
<td>? ?</td>
<td>Slowing of triphasic waves</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Somnolence, but patient may be arousable</td>
<td>Disorientation, aggression</td>
<td>Asteria, hypertensive, positive Babinski’s reflex</td>
<td>? ?</td>
<td>Slowing of triphasic waves</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Coma, unresponsive</td>
<td>Coma</td>
<td>Deteriorate posture</td>
<td>? ? ?</td>
<td>Slow waves (2 to 3 cycles per second)</td>
</tr>
</tbody>
</table>

Precipitants of HE

Rifaximin vs. nonabsorbable disaccharides

- 4 clinical studies comparing rifaximin (1200 mg/day) vs. lactulose\textsuperscript{1-4}
- 1 clinical study comparing rifaximin (1200 mg/day) vs. lactitol\textsuperscript{5}

- Overall results:
  - Rifaximin was at least as effective as lactulose and lactitol
  - For some endpoints, rifaximin produced more rapid and significant effects
  - Rifaximin was better tolerated than the nonabsorbable disaccharides

5. Mas A. et al., J Hepatol. 2003; 38: 51-54

Hepatopulmonary syndrome

- 10-15% of cirrhotics
- Arterial pO\textsubscript{2} < 70 mm Hg
- Screen with pulse oximetry < 97%

Kosaka SU. Semin Liver Dis 2006; 26: 265-72

Fallon MB. et al., Gastro 2008; 135: 1168-75
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HPS: outcome with OLT

<table>
<thead>
<tr>
<th>Type</th>
<th>#</th>
<th>Mortality</th>
<th>PaO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talle</td>
<td>23</td>
<td>30%</td>
<td>51.4</td>
</tr>
<tr>
<td>Arguelas</td>
<td>24</td>
<td>29%</td>
<td>43</td>
</tr>
<tr>
<td>Swanson</td>
<td>24</td>
<td>21%</td>
<td>41</td>
</tr>
<tr>
<td>Schenk</td>
<td>7</td>
<td>42%</td>
<td>66</td>
</tr>
<tr>
<td>Collison</td>
<td>R</td>
<td>50%</td>
<td>57.2</td>
</tr>
<tr>
<td>Schiffer</td>
<td>9</td>
<td>33%</td>
<td>60</td>
</tr>
</tbody>
</table>

Portopulmonary hypertension

- PAS > 30 mmHg
- Hyperdynamic state 30%
- Volume overload 30%
- PPHTN 30%
- False + echo 10%

PPHTN: liver transplantation

Survival

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Evaluation/preparation for liver transplantation

• Once decompensated cirrhosis develops consider referral to a transplant center (20-50% 5 yr mortality rate)
• Special considerations:
  – Alcohol
  – HBV
  – HCV pre treatment
  – NASH (BMI, metabolic syndrome)

Alcohol and transplantation

• Public perception of liver transplantation for alcoholic cirrhosis remains low
• Most programs require a 6 months documented abstinence (relapse drinking, 41% < 6 months, > 6 months, 13%)
• OR 7.8 comparing those who did and did not drink and were documented/in alcohol treatment for recurrent alcohol use post transplant
• Long term follow-up drinking after transplantation:
  – 71% abstainers, 16% minimal, 7% escalating drinking

Bravata DM. Liver Transpl 2001; 7: 191-202
Foster PF, et al., Hepatology 1997; 26: 149-77
Mathurin P, Lucy M. Liver Transpl 2007; 13: S83-S86
Dillman A. Liver Transpl 2007;13: S76-78
Hepatitis B

- Elimination of HBV DNA detection at OLT
  - Reduced recurrence from 90% to 29% (with HBIG)
- Low recurrence risk HBV DNA <10^4 c/mL
- Use nucleos(t)ide analogue treatment
  - Entecavir, tenofovir > adefovir, lamivudine
- Monitor HBV DNA level every 3 months while on list for response and resistance

Lok A. Liver Transpl 2008; 14: S8-14
Anus P. Patterson S. Liver Transpl 2008; 14: S15-22

Hepatitis C treatment prior to transplantation

<table>
<thead>
<tr>
<th>Authors</th>
<th>Treatment</th>
<th>Severity of disease</th>
<th>Virological response G1/4</th>
<th>Virological response G2/3</th>
<th>SVR</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forns</td>
<td>Std inf/PEG-INF (R=600-1200 mg)</td>
<td>CTP=4</td>
<td>50%</td>
<td>83%</td>
<td>61%</td>
<td>13% discontinued</td>
</tr>
<tr>
<td>Forns</td>
<td>Std inf</td>
<td>CTP=4</td>
<td>80%</td>
<td>66%</td>
<td>60%</td>
<td>25% discontinued</td>
</tr>
<tr>
<td>Iacobellis</td>
<td>PEG INF (R=800-1000 mg)</td>
<td>11% CTP=4</td>
<td>30%</td>
<td>63%</td>
<td>64%</td>
<td>25% discontinued</td>
</tr>
</tbody>
</table>

* Treatment not recommended CTP = B, C or MELD >20, prior nonresponders
* Best used for living donation candidates?

Everson G. et al., Hepatology 2005; 42 456-462; Forns X. et al., Hepatology 2004; 40 489; Iacobellis A. et al., J Hepatology 2007; 46 200-212

NASH/metabolic syndrome

- 400 million people BMI >30
- Obese liver transplant recipients 15%-25% (1990-2006)
- Transplant candidate BMI 35-40
- NASH 3.6%-7% (2001-2005)
- 60% steatosis (grade2) 1 yr and 10% develop cirrhosis (5 yrs)
- Close monitoring of weight pretransplant is mandatory

Charlton M. Liver Transpl 2006; 15 583-89
Pagadala M. et al., Liver Transpl 2009; 15 1062-1070
Liver transplantation for HCC:
Milan criteria (stage 1 and 2)

- Single tumor, not > 5 cm
- Up to 3 tumors, none > 3 cm
- Absence of macroscopic vascular invasion, absence of extrahepatic spread


UCSF criteria for HCC

- 1 lesion ≤ 6.5 cm
- 2 to 3, none > 4.5 cm, total diameter ≤ 8 cm
- Absence of macroscopic vascular invasion
- Absence of extra-hepatic spread

Yeo et al., Hepatology 2001; 33: 1304-1403

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Liver allocation MELD score

- Objective variables, not related to duration on the list, ascites, encephalopathy
- MELD score = 0.957 X \( \log_{\text{e}}(\text{creatinine mg/dL}) \) + 0.378 X \( \log_{\text{e}}(\text{bilirubin mg/dL}) \) + 1.12 X \( \log_{\text{e}}(\text{INR}) \) + 0.643
- Highest score "wins"
- HCC upgrade to 22

Mortality risk according to MELD

Change to inactive status
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Biliary endoscopy

• Biliary complication: OLT 15-30%, LRT 30%
• Most common biliary anastomosis strictures, leaks, leak cut edge
• Early complications associated with HAT, prolonged warm ischemia time, prolonged cold ischemia
• Late complications: technical or vascular
• Biliary stones and casts can occur

Thuluvath P. et al., Liver International 2003; 23: 156-162
Thethy S. et al., Clin Transpl 2004;18:647-53
GI related disorders

- Esophageal
  - CMV, HSV, Candida
- CMV (↓ to 15%): high risk (donor + to recipient -)
- PUD (CMV > acid PUD)
- Diarrhea (CMV, C. diff, medications)
  - F/S, stool studies
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Inflammatory bowel disease

- 78 pts PSC and 30 pts AI followed for 7.2 yrs
- 9/25 with IBD flared after OLT
- 6/53 developed IBD after OLT
  - (1 yr 6%, 3 yrs 12%, 5 yrs 20%)
- Aza protective?
- Leave on steroids post transplant

Haagsma EV. et al., Aliment Pharmacol Ther 2003;18: 33-44

Colon cancer, IBD, PSC and transplantation

- 100 pts with IBD and PSC, (1986-2000)
- Colon cancer 8/100 (8%) vs. 7/1184 (0.6%)
- Cumulative risk of CRC: 14% (5 yrs) and 17% (10 yrs)
- Risk factors: dysplasia, duration of IBD > 10 yrs, pancolitis
- Yearly colonoscopy


Annual examinations

- Annual history and physical required
- Eye
- Dental
- Skin (SPF > 30)
- Obesity
- Pap smears/mammograms
- Colonoscopy

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Vaccination

- Pre transplant: HAV, HBV, pneumococcal
- Influenza yearly, response rates 50-95%
- No live vaccines
- Varicella-zoster: varivax 19 ped patients
- 4/19 had rashes, 4/19 fever
- 87% developed humoral and cellular immunity
  (Weinberg, et al., AM J Transpl 2006; 6: 565-568)
- Human papilloma virus no studies

Obesity

- Common: 70% of patients will gain weight after transplantation at yrs 1 and 3 post transplant 24% and 31% of patients had BMI > 30
- Predictors: prednisone, BMI > 25, age > 50, NASH?
- Restriction of OLT with BMI > 40
- Dietary control and exercise still best first options

Bone disease

- BMD returns to pre transplant ~ 85 months
- 15% developed symptomatic fx within 2 yrs
- 38% vertebral fx within 6 months
- Alendronate/Ca/Vit D, 75% stable, 10% improved
- Zolendronic acid prevents bone loss
  (4 mg., 1, 5, 6, 9 months post transplant)
  - 1 yr post transplant, 3% difference in treatment groups
- Avascular necrosis in 5%

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Bone disease recommendations

- Yearly DEXA, normal every 2 yrs
- Ca, Phos, Vit D yearly
- Treat if T-score > -1.5 (Ca, Vit D, biphosphonates)

Cardiovascular

- Hypertension 17-85%
- 58% on single agent, 29% on two agents
- Hyperlipidemia 5-30% (types 2a, 2b, 4)
- Statins OK to use (↓ chole 21%)

Cardiovascular recommendations

- Fasting lipid profile yearly
- Chole < 200 mg/dl, LDL < 130 mg/dl, normal triglycerides
- Weight loss and statins
- HTN: <140/90, diuretics, beta blocker, calcium channel blocker, ACE inhibitor
Diabetes

- Pre transplant DM ≈ 13%
- Immunosuppressants are diabetogenic tacrolimus > cyclosporine
- HCV greater likelihood of DM
- New onset DM after transplantation ≈ 10%
- Treat the same
- Outcomes worse

Marroni C. et al., Transpl Proc 1999; 31: 3046
Yoo H. et al., Transplant 2002; 74: 1007-1012

Patient and graft survival in patients with or without DM (IDDM or NIDDM)

- Patients in graft survival and those who have type I and NIDDM have a worse outcome compared to patients who have no DM
- The longer the days post survival the worse survival in patients who have IDDM

Yoo H. et al., Transplant 2002; 74: 1007-1012

Chronic renal failure after solid organ transplantation

Relative risk of death with CRF 4.55; P < 0.001

Ojo AO. et al., NEJM 2003; 348: 931-40

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Renal disease

- Risk factors: calcineurin inhibitors, HCV, DM, advanced age, ARF
- Survival profoundly worse (27% vs. 71% with ESKD at yr 6 post transplant)
- HRS, and predictable as early as 4 weeks post transplant
- What to do?
  - Avoid high levels of CNI, conversion and induction therapy?

Pawarode A. et al., Liver Transpl 2003; 9: 741-47

De novo malignancy

- 3-15% with cancer rates 3-5X > general population
- Similar rates of colon, breast, lung, prostate
- Lymphoma (B-cell) 5-44%, skin 12-57%, head and neck 6-26%, kidney 3-14%

Haagsma E. et al., J Hepat 2001; 34: 84-91

Long-term causes of death

- Malignancy 17%
- Recurrent disease 30%
- Cardiovascular 20%
- Infection 6%
- Chronic rejection 5%

Voght D. et al., Surgery 2002; 132: 775-90
Common drug interactions in transplantation medications

• Drugs that increase levels of cyclosporine, tacrolimus and sirolimus
  - Diltiazem, Nicardipine, Verapamil
  - Ketoconazole, clotrimazole, itraconazole, intracnazole
  - Rifampin, clarithromycin, erythromycin
  - Metrocilompril
  - Dnaptazl

• Drugs that decrease levels of cyclosporine, tacrolimus and sirolimus
  - Rifampin
  - Phenytoin
  - Phenobarbital
  - Carbamazepine

Next decade?

• Molecular diagnostics?
• Recurrent disease/renal failure (are we on the Titanic?)
• One size fits all for immunosuppression
• Living related (how low can you go?)

Thank you for your attention!