What’s New in EASL Guidelines for the Management of DECOMPENSATED CIRRHOSIS

JAMES Y.Y. FUNG
Liver Transplant Center, Queen Mary Hospital
Department of Medicine, The University of Hong Kong
State Key Laboratory for Liver Research
Decompensated Cirrhosis

- Decompensation marked by development of **overt** clinical signs, the most frequent of which are ascites, bleeding, encephalopathy, and jaundice.
Pathogenesis of Decompensated Cirrhosis

- **Liver Disease Aetiology**
  - (1) Treat primary liver disease
  - (2) Targeting key pathogenic events
  - (3) Targeting specific complications

- **Cirrhosis**
  - Portal hypertension
    - Bacterial translocation (PAMPs)
      - Pathogen Associated Molecular Patterns (PAMPs)
    - Activation of innate pattern recognition receptors
    - Release of pro-inflammatory molecules (ROS/RNS)
      - \( \uparrow \) NO, \( \uparrow \) CO, \( \uparrow \) prostacyclin, \( \uparrow \) endocannabinoids

- **Splanchnic arteriolar vasodilation and cardiovascular dysfunction**

- **Liver injury**
  - Damaged cells (DAMPs)
  - Beta-blockers, Relaxin, Statins, Albumin

- **Classical Pathway**
  - Adrenal dysfunction
    - GI bleeding, Infections
  - ACLF
  - Hyponatremia
  - HE
  - Cardiomyopathy
  - Kidney dysfunction
  - HRS
  - PPHT
  - Jaundice, Ascites

- **Other potential mechanisms**

- **Ultimate treatment goal**
  - Regression of fibrosis/cirrhosis
Ascites Development

- 5-10% of compensated cirrhosis per year

<table>
<thead>
<tr>
<th>Grade 1.</th>
<th>Mild ascites: it is only detectable by ultrasound examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2.</td>
<td>Moderate ascites: it is manifest by moderate symmetrical distension of abdomen</td>
</tr>
<tr>
<td>Grade 3.</td>
<td>Large or gross ascites: it provokes marked abdominal distension</td>
</tr>
</tbody>
</table>

- 5-yr survival drops from 80% to 30%

- Hyponatremia
- Low arterial pressure
- GFR
- Low renal sodium excretion

Consider LT as an option

Diagnostic paracentesis

Hospitalized for worsening ascites or any complications of cirrhosis

Neutrophil counts
Culture
Total protein conc.
SAAG
Cytology

Uncomplicated Ascites

Infected
Refractory
HRS
Complicated Ascites
Management of Uncomplicated Ascites

- **Grade 1 (Mild)** – no data on treatment for progression

- **Grade 2 (Mod)**
  - **Salt restriction**
  - **Diuretics**
  - Moderate (80-120mmol)
    - 4.6-6.9g salt
      - (No added salt)
  - Anti-mineralocorticoid
    - (100mg → 400mg/d)
    - Stop if hyper-K (>6)
    - +/-
    - Frusemide
      - (40mg → 160mg)
    - Stop if hypo-K (<3)
  - Max weight loss/day
    - 0.5kg (w/o oedema)
    - 1 kg (with oedema)
  - Stop if Na <125,
    - AKI, worsening
    - HE, worsening
    - cramps
  - Baclofen 10mg/d,
    - weekly increase
    - up to 30mg/d for cramps
  - Reduced to lowest effective dose
    - after ascites resolves

- **Grade 3 (severe)** – LVP
  - Safe even if INR >1.5 and platelet count <50
  - No data supporting prophylactic use of FFP or platelets
  - Minimum dose of diuretics needed to prevent re-accumulation
  - LVP can be performed if needed in AKI/SBP

**Contraindications**
- Uncooperative patient
- Abdominal skin infection at the proposed puncture sites
- Pregnancy
- Severe coagulopathy (accelerated fibrinolysis or disseminated intravascular coagulation)
- Severe bowel distension
Post-Paracentesis Circulatory Dysfunction (PPCD)

- Reduction of effective blood volume after LVP
  - Renal failure
  - Dilutional hyponatremia
  - Hepatic encephalopathy
  - Decreased survival

- Prevented by use of plasma volume expansion
  - Albumin infusion 8g/L of ascites removed
Refractory Ascites

- Ascites that cannot be mobilized or the early recurrence of which cannot be satisfactorily prevented by medical therapy
  - **Diuretic-resistant ascites** - lack of response to Na restriction and diuretic treatment
  - **Diuretic-intractable ascites** – development of diuretic-induced complications that preclude the use of an effective dose

- Poor prognosis → median survival ~6m
Management of Refractory Ascites

• **Repeated LVP + albumin (8g/L) – 1st line**
• Diuretics should be discontinued for those who do not excrete >30 mmol/day Na
• NSBB use is controversial – avoid high doses
• TIPS considered for those with recurrence or with ineffective LVP (loculation)
  • Improves survival and control of ascites
  • Use small-diameter PTFE-covered stents
    • Lowers risk of TIPS dysfunction and HE
• Needs **careful selection of patients in experienced centre**
  • Br >3mg/dL. Plt <75, HE grade 2, chronic HE, active infection, progressive renal failure, severe systolic/diastolic dysfunction, pulmonary hypertension
The Role of Beta-Blockers in Cirrhosis

Early Cirrhosis
- NSBB: no effect on survival
- May increase adverse events

Decompensated Cirrhosis (Medium-large varices)
- NSBB improves survival
- Reduces variceal bleeding
- Reduces gut bacterial translocation

End-stage Cirrhosis (Refractory Ascites)
- NSBB reduces survival
- Negative impact on cardiac reserve during stress and precipitation of HRS/AKI
Portal Hypertension & Transjugular Intrahepatic Portosystemic Shunt (TIPS)

Architectural distortion of liver secondary to fibrotic tissue and regenerative nodules
Increase resistance to flow

Active intra-hepatic vasoconstriction
Decrease in endogenous nitrous oxide production
Increase intra-hepatic resistance

Increase portal flow
Splanchnic arteriolar vasodilatation
Variceal Haemorrhage in Cirrhosis

- Prevalence of GOV correlated with cirrhosis severity
  - Child’s A: ~40%
  - Child’s B/C: ~70%

- De novo development 7-8%/year in decompensated cirrhotics

- Risk of variceal haemorrhage ~5-15%/year
  - Variceal size
  - Severity of liver dysfunction (Child’s B/C)
  - Presence of red wales

- Re-bleeding ~60-70% without secondary prophylaxis
- Mortality with VH ~15-25%

Decompensated cirrhotics should have OGD for variceal screening

For those without varices on screening, OGD should be repeated every year if still decompensated/etiological factor persists.
Prophylaxis of Variceal Haemorrhage

Decompensated Cirrhosis

OGD screening

No/low risk varices

High risk varices

Small varices + red wales

Small varices + CPC

Medium/large varices

NSBB*

NSBB*/ EBL

Primary Prophylaxis

Secondary Prophylaxis

* Cautious use in cases of severe/refractory ascites (avoid high doses)
* Discontinue if hypotensive (sys BP<90), bleeding, sepsis, SBP, AKI (can retry after recovery)
* EBL for those with NSBB intolerance/contraindication
Management of Acute GI Bleeding in Cirrhosis

Acute gastrointestinal bleeding + portal hypertension

Initial assessment (history, physical & blood exam, cultures) & resuscitation

Immediate start of drug therapy (somatostatin/terlipressin)
Antibiotic prophylaxis (ceftriaxone or norfloxacin)

Early diagnostic endoscopy (<12 h)
Confirm variceal bleeding
Endoscopic therapy (band ligation)

+ maintain vasoactive drug therapy 3-5 days and antibiotic prophylaxis (ceftriaxone or norfloxacin)

Control (~85% of cases)
Consider early TIPS in high-risk

Further bleeding (~15% of cases)
Rescue with TIPS

Airway
Breathing
Circulation
- Volume replacement with crystalloids (or colloids)
- Restrictive transfusion
  Hb threshold of 7 g/dl & target of 7-9 g/dl

Somatostatin
Naturally occurring endogenous peptide
Inhibits vasodilatory peptides (eg. VIP, glucagon)
Short half life (bolus = infusion)

Octreotide
Synthetic peptide with longer half life
Lower dose for bolus + infusion
Less side effects

Vasopressin
Endogenous peptide hormone
Short half life - infusion
Limited use due to side effects

Terlipressin
Synthetic analog of vasopressin
Longer half life - bolus
Lower circulatory levels of vasopressin
# Meta-Analyses of Terlipressin vs Placebo in Acute Bleeding Oesophageal Varices

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Terlipressin (n/N)</th>
<th>Placebo (n/N)</th>
<th>Risk Ratio (M-H,Fixed,95% CI)</th>
<th>Weight</th>
<th>Risk Ratio (M-H,Fixed,95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 High quality studies (Jadad score 3-5)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Freeman 1989</td>
<td>3/15</td>
<td>4/16</td>
<td></td>
<td>4.8%</td>
<td>0.80 [0.21, 3.00]</td>
</tr>
<tr>
<td>Levacher 1995</td>
<td>12/41</td>
<td>20/43</td>
<td></td>
<td>24.3%</td>
<td>0.63 [0.35, 1.12]</td>
</tr>
<tr>
<td>Patch 1999</td>
<td>22/66</td>
<td>28/66</td>
<td></td>
<td>34.9%</td>
<td>0.79 [0.50, 1.22]</td>
</tr>
<tr>
<td>Sderlund 1990</td>
<td>3/31</td>
<td>11/29</td>
<td></td>
<td>14.2%</td>
<td>0.26 [0.08, 0.82]</td>
</tr>
<tr>
<td>Walker 1986</td>
<td>3/25</td>
<td>8/25</td>
<td></td>
<td>10.0%</td>
<td>0.38 [0.11, 1.25]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>178</strong></td>
<td><strong>179</strong></td>
<td></td>
<td><strong>88.1%</strong></td>
<td><strong>0.61 [0.45, 0.84]</strong></td>
</tr>
<tr>
<td>Total events: 43 (Terlipressin), 71 (Placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Heterogeneity: Chi² = 4.17, df = 4 (P = 0.38); I² = 4%</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.08 (P = 0.0021)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Low quality studies (Jadad score 1-2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brunati 1996</td>
<td>4/28</td>
<td>4/27</td>
<td></td>
<td>5.1%</td>
<td>0.96 [0.27, 3.47]</td>
</tr>
<tr>
<td>Pauwels 1994</td>
<td>6/17</td>
<td>5/14</td>
<td></td>
<td>6.8%</td>
<td>0.99 [0.38, 2.56]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>45</strong></td>
<td><strong>41</strong></td>
<td></td>
<td><strong>11.9%</strong></td>
<td><strong>0.98 [0.45, 2.12]</strong></td>
</tr>
<tr>
<td>Total events: 10 (Terlipressin), 9 (Placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.06 (P = 0.96)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>223</strong></td>
<td><strong>220</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>0.66 [0.49, 0.88]</strong></td>
</tr>
</tbody>
</table>

Ioannou et al. Cochrane Database Syst Rev 2009
Gastric Varices

<table>
<thead>
<tr>
<th>Type</th>
<th>Definition</th>
<th>Relative frequency</th>
<th>Overall bleeding risk without treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOV 1</td>
<td>OV extending below cardia into lesser curvature</td>
<td>70%</td>
<td>28%</td>
</tr>
<tr>
<td>GOV 2</td>
<td>OV extending below cardia into fundus</td>
<td>21%</td>
<td>55%</td>
</tr>
<tr>
<td>IGV 1</td>
<td>Isolated varices in the fundus</td>
<td>7%</td>
<td>78%</td>
</tr>
<tr>
<td>IGV 2</td>
<td>Isolated varices else in the stomach</td>
<td>2%</td>
<td>9%</td>
</tr>
</tbody>
</table>

- Acute gastric VH treated medically like oesophageal VH
- Cyanoacrylate recommended endoscopic therapy for GOV1 or IGV1
- TIPS should be considered in appropriate candidates
Hepatopulmonary Syndrome

- Prevalence of 5-32% of patients evaluated for liver transplantation
  - Mortality rate almost twice with HPS

- Disorder in pulmonary oxygenation caused by intrapulmonary vasodilatation (IPVD)
  - Less commonly pleural and pulmonary AV communications with portal hypertension

![Diagram showing normal and HPS alveoli](image)

- Anatomic/functional shunt
- Impaired V/Q ratio
- Hypoxaemia
- Dyspnoea / Platypnoea (increase when upright)
Pathogenesis of Hepatopulmonary Syndrome

- Hepatic injury/failure
- Portal hypertension

Increased release of ET-1

- ET_{A} receptor
- Increased expression and activity of eNOS
- Increased release of NO

vasodilation

Endothelial cell

Endothelial activation of CX3CL1

Endothelial cell

Increased adherence of macrophages/monocytes to endothelial cells

Angiogenesis

Increased expression and activity of iNOS and HO

Increased release of NO and CO

vasodilation

Systemic inflammation

Recruitment of macrophages in the lungs

Macrophage

Vascular capillary

Genetic factors

Endothelial cell proliferation

Increased release of VFG-A

HEPATOPULMONARY SYNDROME
Diagnosis of Hepatopulmonary Syndrome

**Screening (Adults)**
- Pulse Oximetry
  - $SPO_2 < 96\%$

**ABG**
- $PaO_2 < 80\text{mmHg}$ or
- $P[A-a]O_2 \geq 15\text{mmHg}$ ($\geq 20\text{mmHg}$ in age $\geq 65$)

**Contrast (microbubble) echo**
- Recommended

**Contrast Enhanced TOE**
- Can exclude definitively intra-cardiac shunts

**MAA Scan**
- Technetium-99 macro-aggregated albumin
- Can quantify degree of shunting in severe hypoxemia & coexisting intrinsic lung disease, or assess prognosis

**Pulmonary angiography**
- Only in severe hypoxemia poorly responsive to 100% O2, and strong suspicion of AV communications

**Hypoxia**

**Diagnostic Criteria**

**Pulmonary Vascular Defect**
Severity & Management of HPS

- Mild: PaO2 ≥ 80 mmHg
- Moderate: PaO2 60-79 mmHg
- Severe: PaO2 50-59 mmHg
- Very Severe: PaO2 < 50 mmHg

- Spontaneous resolution uncommon
- No established medical therapy
- TIPS not recommended
- Long term O₂ therapy for severe hypoxemia
- LT—significant improvement/complete reversal > 85%
  - PaO2 < 60 mmHg should be evaluated for LT (MELD exception)
  - 6-monthly ABG to monitor
Portopulmonary Hypertension

Asymptomatic ↔ SOBOE / RHF

3-10% of those worked up for LT
Higher in females, pre-existing autoimmune liver diseases

Exact pathophysiology unknown
Severity of Portopulmonary Hypertension

No association between severity of liver disease/portal hypertension and development of severe PPHT

- **Mild**
  - mPAP ≥ 25 and < 35 mmHg

- **Moderate**
  - mPAP ≥ 35 and < 45 mmHg

- **Severe**
  - mPAP ≥ 45 mmHg

Mortality after liver transplantation
Evaluation of Portopulmonary Hypertension

Screening for PPHT (echocardiography)

Threshold for RHC unclear (RVSP >50mmHg or RVH)

Right Heart Catheterization

No PPHT
- No contraindication to LT (listed)

mPAP <35mmHg
- RV function preserved
- LT considered

mPAP ≥35 mmHg
- PVR <240 or mPAP <35 + PVR <400
- Medical therapy

mPAP ≥45 mmHg
- Absolute contraindication to LT

No PPHT

Endothelin receptor antagonists (Bosentan) – caution with advanced liver dysfunction
Phosphodiesterase-5 inhibitors (Sildenafil) – caution with variceal bleeding
Prostacycline analogies – caution with thrombocytopenia/splenomegaly

- Beta-blockers should be stopped
- TIPS should not be used
EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis

European Association for the Study of the Liver

- Ascites
- AKI & Hepatorenal Syndrome
- GI Bleeding
- Adrenal Insufficiency
- Cirrhotic Cardiomyopathy
- Bacterial Infections SBP, UTI, Pneumonia, Cellulitis
- Hepatic Hydrothorax
- Acute on Chronic Liver Failure
- Hepatopulmonary Syndrome
- Portopulmonary Hypoertension
- Hyponatremia

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