Siemens has provided me with ARFI software (no funds). I will be discussing unlabeled/unapproved use of propranolol, nadolol and carvedilol.

Natural History of Chronic Liver Disease

- Alcohol
- Hepatitis C / B
- NASH
- Cholestatic
- Autoimmune

Chronic liver disease → Compensated cirrhosis → Decreased portal pressure

- Increasing portal pressure → Variceal hemorrhage
- Ascites
- Encephalopathy

Compensated cirrhosis → Median survival > 12 years

Decompensated cirrhosis → Median survival ~ 2 years

Death

- Portal flow
- β-blockers
- Octreotide
- Resistance
- Simvastatin
- TIPS
- Flow and resistance
- Carvedilol

Natural History of Chronic Liver Disease
In compensated cirrhosis two subpopulations can be identified based on the presence or absence of varices

- No varices (3% mortality)
- Varices (25% mortality)

Variceal hemorrhage can be prevented but this requires screening for the presence / size of varices

- No varices
- Varices (Variceal hemorrhage, Ascites, Encephalopathy, Jaundice)

Non-endoscopic methods to screen for varices

- Platelet/spleen ratio = platelet count (mm$^3$) / spleen diameter (mm)
- >900 rules out varices
- Adding liver stiffness to platelet count and spleen diameter discriminated better than platelet/spleen ratio

Spleen stiffness* discriminates better than liver stiffness* in the diagnosis of varices

Colecchia et al. Gastroenterology 2012;143:646-54. * by transient elastography

Spleen stiffness measurements (by ARFI) were useful to rule out the presence of varices


Cutoff
3.18 m/s

- 23% of patients had decompensated cirrhosis
- No validation cohort
- Has not been combined with platelet/spleen ratio

Non-endoscopic methods to diagnose or exclude varices

- Several methods alone or in combination look promising
  - Spleen stiffness
  - Platelet count/spleen diameter
  - Liver stiffness
- Their main utility is in identifying patients who are unlikely to have varices
- Endoscopy is still gold standard
Risk of first variceal hemorrhage is determined by size of varices, Child class and presence of red wale marks (RWM) on varices

Risk of first variceal hemorrhage is determined by size of varices, Child class and presence of red wale marks (RWM) on varices

AASLD and Baveno recommendations for small varices that have not bled

- High risk (Child C or presence of red wale marks on varices): Should be treated with NSBB to prevent first variceal hemorrhage
- Low risk: May be treated with NSBB although their long term benefit remains to be established

Two treatments reduce the risk of first variceal hemorrhage in pts with medium/large varices:

D’Amico et al., Sem Liver Dis 1999; 19:475

Gluud and Krag, Cochrane Database Syst Rev 2012;8:CD004544

In good quality trials (n=7), no significant differences in bleeding between EVL (17%) and BB (19%)

Baveno V recommendations for pts with medium / large varices that have not bled

- Either NSBB or endoscopic band ligation is recommended in primary prophylaxis
- The choice of treatment should be based on local resources and expertise, patient preference and characteristics, side effects, and contra-indications


Patients with refractory ascites on NSBB may have a poorer survival than those not on NSBB

However, groups were unbalanced with patients in the BB group having a greater number of poor prognostic factors at baseline

Serste et al. Hepatology 2010;52:1017
Patients who develop SBP on NSBB may have a poorer survival than those not on NSBB*

Ascites, no SBP

- Refractory and non-refractory ascites combined
- No differences in MAP

First SBP

- Use of NSBB dose after SBP uncertain
- Other infections or subsequent SBP uncertain
- Lower MAP in those on NSBB (e.g., carvedilol)

*Mandorfer et al. Gastroenterology 2014;146:1680

In patients with large varices that have not bled, a decrease in HVPG >10% improves outcomes

First variceal hemorrhage

- Compared to nonresponders, responders also have a significantly lower risk of developing ascites

Survival


Carvedilol has a higher rate of hemodynamic responders* compared to other NSBB

* HVPG decrease to <12 mmHg or >20% from baseline

25-30 mg/day associated with decrease in MAP and fluid retention

Carvedilol (non-selective, vasodilating β-blocker) was more effective than EVL in preventing first variceal hemorrhage

<table>
<thead>
<tr>
<th></th>
<th>EVL</th>
<th>Carvedilol*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>75</td>
<td>77</td>
</tr>
<tr>
<td>Median follow-up (mos)</td>
<td>25.5</td>
<td>26.2</td>
</tr>
<tr>
<td>First variceal hemorrhage</td>
<td>23%</td>
<td>10%</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>37%</td>
<td>35%</td>
</tr>
<tr>
<td>Bleeding-related mortality</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Treatment discontinuation due to intolerance</td>
<td>12%</td>
<td>16%</td>
</tr>
</tbody>
</table>

Tripathi et al.  Hepatology 2009;50(3):825-33

*12.5 mg/day

Carvedilol has a higher rate of hemodynamic responders* compared to other NSBB

<table>
<thead>
<tr>
<th></th>
<th>No drugs (3 studies)</th>
<th>NSBB (18 studies)</th>
<th>Carvedilol (3 studies)</th>
<th>NSBB Carvedilol (6.5-12.5 mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HVPG decrease to &lt; 12 mmHg or &gt;20% from baseline</td>
<td>19/116 (16%)</td>
<td>197/527 (37%)</td>
<td>32/70 (46%)</td>
<td>38/87 (57%)</td>
</tr>
</tbody>
</table>

Milano and Garcia-Tsao, Gastro Clin N Am 2010;39:681

Reiberger et al. Gut 2012 [Epub ahead of print]

Propranolol and carvedilol hemodynamic responders* have a lower probability of variceal bleeding and decompensation than EVL

Variceal Bleeding

<table>
<thead>
<tr>
<th></th>
<th>EVL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up [months]</td>
<td></td>
</tr>
</tbody>
</table>

Decompensation

<table>
<thead>
<tr>
<th></th>
<th>EVL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up [months]</td>
<td></td>
</tr>
</tbody>
</table>

Reiberger et al. Gut 2012 [Epub ahead of print]

* HVPG decrease to < 12 mmHg or >20% from baseline
Reduction in MAP in patients with cirrhosis is more marked with carvedilol than with propranolol

Propranolol

Carvedilol

Stratifying patients with cirrhosis and varices who have not bled

Child A

Small

Large

Monitor

1) NSBB or 2) Carvedilol (if intolerant to NSBB?)

Child B

Small

Large

NSBB optional, unless red marks present

Child C

Small

Large

NSBB

NSBB or EVL

NSBB or NSBB

NSBB = non-selective beta-blockers; EVL = endoscopic variceal ligation

Management of acute variceal hemorrhage

Chronic liver disease

Compensated cirrhosis

Decompensated cirrhosis

Death

Variceal hemorrhage

Ascites

Encephalopathy
Survival after variceal hemorrhage has improved in the last decades

Survival is better in patients with GI hemorrhage subjected to a restrictive transfusion strategy

In Child A/B cirrhosis, mortality was significantly decreased with restrictive transfusion strategy
In Child A/B cirrhosis, rebleeding was significantly decreased with restrictive transfusion strategy

<table>
<thead>
<tr>
<th>Further bleeding — no. of patients/total no. (%)</th>
<th>Restrictive strategy</th>
<th>Liberal strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>45/144 (32)</td>
<td>71/145 (49)</td>
</tr>
<tr>
<td>Patients with cirrhosis</td>
<td>10/139 (7)</td>
<td>22/135 (16)</td>
</tr>
<tr>
<td>Child—Child class A or B</td>
<td>15/137 (11)</td>
<td>25/139 (18)</td>
</tr>
<tr>
<td>Child—Child class C</td>
<td>4/14 (3)</td>
<td>8/16 (5)</td>
</tr>
</tbody>
</table>


- HVPG increased with liberal transfusion strategy (n=77)
- HVPG did not change with restrictive transfusion strategy (n=74)

Prophylactic Antibiotics Improve Outcomes in Cirrhotic Patients with GI Hemorrhage

Do we need to stratify patients with cirrhosis and GI hemorrhage for antibiotic prophylaxis?
Do we need to stratify patients with cirrhosis and GI hemorrhage for antibiotic prophylaxis?

Pauwels et al. Hepatology 1996;24:802-806

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Child A patients with acute variceal hemorrhage have a low risk of infection and death

Tandon et al. AASLD 2013 #1627. Submitted

Retrospective database (1996-2009); 252 patients who had not received antibiotic prophylaxis
**Variceal Hemorrhage – Standard of Care**

*Garcia-Tsao et al. AASLD / ACG Guidelines; Hepatology 2007; Garcia-Tsao, Bosch NEJM 2010.*

**Variceal Hemorrhage Suspected**

- Resuscitation (maintain hemoglobin ~ 8 g/dL)
- Antibiotic prophylaxis (quinolones, ceftriaxone)
- Safe vasoactive drug

Endoscopy (within 12 hours): variceal hemorrhage confirmed

Perform EVL (sclerotherapy if EVL not possible)

Continue vasoactive drug and antibiotics

Failure of combination drug/endoscopic therapy

Child C patients are the most likely to fail

*Abraldes, J Hepatol 2008  Am J Gastro 2012*

**Multicenter RCT of early TIPS in high-risk patients with variceal hemorrhage**

- 63 patients: Child C (10-13 points) or Child B with active bleeding (on vasoactive drugs)
- TIPS within 72 hours of admission vs. standard therapy
- Median follow-up 16 months

<table>
<thead>
<tr>
<th>TIPS (n=32)</th>
<th>Std (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endpoint</td>
<td></td>
</tr>
<tr>
<td>- Failure to control bleed</td>
<td>1 (3%)*</td>
</tr>
<tr>
<td>- Early rebleed (&lt;6 wks)</td>
<td>1</td>
</tr>
<tr>
<td>- Late rebleed (6 wk-1 yr)</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>4 (12%)*</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>8 (25%)</td>
</tr>
</tbody>
</table>


**Acute Variceal Hemorrhage – New Standard?**

**Variceal Hemorrhage Suspected**

- Resuscitation (maintain hemoglobin ~ 8 g/dL)
- Antibiotic prophylaxis (quinolones, ceftriaxone)
- Safe vasoactive drug

Endoscopy (within 12 hours): variceal hemorrhage confirmed

Perform EVL (sclerotherapy if EVL not possible)

Not high risk (Child A/B)

Continue vasoactive drug (2-5 days)

TIPS if bleeding persists or recurs

High risk patients: Child C (10-13 points)

Early TIPS (ideally within 24 hours) should be considered
Ligation + drugs* are preferred therapy to prevent recurrent variceal hemorrhage

Rebleeding rates:
- Untreated
- β-blockers
- Sclerotherapy
- Sclerotherapy + ISMN
- Ligation
- Ligation + drugs*

* non-selective β-blockers ± nitrates


TIPS is indicated in patients who fail combined therapy with drugs + EVL

Rebleeding rates:
- Untreated
- β-blockers
- Sclerotherapy
- Sclerotherapy + ISMN
- Ligation
- Ligation + drugs*

* non-selective β-blockers ± nitrates


Lowest Rebleeding Rates are Observed in HVPG Responders*

Rebleeding rates:
- Untreated
- NSBB
- Sclerotherapy
- NSBB + ISMN
- Ligation
- Ligation + drugs*
- TIPS

* HVPG <12 mmHg or >20% from baseline

Bleeding and death are significantly lower in HVPG responders*

Variceal hemorrhage

Death

Feu (1995)
Villanueva (1996)
Mc Cannich (1996)
Markel (2000)
Eversen (2000)
Villanueva (2001)
Bureau et al. (2002)
Patch (2002)
Turnes (2003)
Abraldes (2003)
Villanueva (2004)

0.17 (0.09-0.33)

0.39 (0.19-0.81)

Variceal hemorrhage

Feu (1995)
Villanueva (2001)
Bureau (2002)
Abraldes (2003)
Villanueva (2004)
Turnes (2006)

Less bleeding in responders
169
More bleeding in responders

Less death in responders
More death in responders

0.01

* HVPG to <12 mmHg or >20% from baseline

Future

- Refine stratification strategies
  - New “recalibrated” MELD? (<11, low risk; >19 high risk
  - Investigate non-invasive indicators of hemodynamic response
  - Develop therapies or combination of therapies that will increase the proportion of “responders”

Abraldes et al. EASL 2013.
Child A patients with acute variceal hemorrhage have a low risk of infection

- Retrospective database (1996-2009)
- Selected 252 patients with cirrhosis who had not received antibiotic prophylaxis
- 51 (20%) developed infection
  - Child A: 5%; Child B: 16%; Child C: 34%
- Child A patients had a 6-week mortality rate of only 2% (one died of HCC)

Tandon et al. AASLD 2013 #1627