VARICEAL BLEEDING

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MANAGEMENT OF ESOPHAGEAL VARICEAL BLEEDING

• Acute Bleeding Episode
  – Vasoactive medication (e.g., octreotide)*
  – Antibiotics*
  – Endoscopic ligation
  – Consider TIPS in high-risk patients

• Prevention of Recurrent Bleeding
  – Endoscopic ligation
  – β-blocker

* Begin before EGD

Garcia-Tsao et al. Hepatology 2008:47:1764;
de Franchis J Hepatol 2010:53:762
MANAGEMENT OF ACUTE VARICEAL BLEEDING

FRESH FROZEN PLASMA FOR PROLONGED PROTHROMBIN TIME?
PT IS NOT A RELIABLE INDICATOR OF COAGULATION STATUS IN CIRRHOSIS

- PT measures procoagulant activity only
  - Cirrhosis: parallel ↓ in pro- and anti-coagulant factors
    - Thrombin generation in cirrhotics ≈ healthy subjects
- Elevated PT or INR not predictive of peri-procedural bleeding in SR of 25 studies
- Procoagulants (e.g., rFVII) shorten prolonged PT, but fail to prevent bleeding


FRESH FROZEN PLASMA FOR PROLONGED PROTHROMBIN TIME
INITIAL MEDICAL THERAPY

ANTIBIOTIC PROPHYLAXIS IN CIRRHOTIC PATIENTS WITH UGI BLEEDING
Meta-Analysis of 12 RCTs (N=1241) vs. Placebo/No Antibiotic

- Bacterial infection: 13% vs. 36%; RR=0.43 (0.19-0.97)
  - Bacteremia: 0.25 (0.15 - 0.40)
  - Pneumonia: 0.45 (0.27 - 0.75)
- Death: 19% vs. 22%; RR = 0.79 (0.63 - 0.98)
- Rebleeding: 24% vs. 45%; RR = 0.53 (0.38 - 0.74)
- Quinolones or ceftriaxone
  - Oral quinolones first line unless
    - Area of high quinolone use, known resistance
    - Advanced cirrhosis
PHARMACOLOGIC THERAPY FOR ACUTE VARICEAL BLEEDING

- Splanchnic artery vasoconstriction
  - Vasopressin, terlipressin
  - Somatostatin and analogs
    - Somatostatin, octreotide, vapreotide

VASOACTIVE MEDICATIONS

Placebo-Controlled RCTs without Endoscopic Therapy

- Somatostatin/Octreotide (3 DB RCTs)
  - Decreased further bleeding in 1; no benefit in 2
  - No benefit in mortality in any trial
- Terlipressin (4 DB RCTs*)
  - Benefit in bleeding control in 4
  - Benefit in mortality in 2
- Terlipressin not superior in head-to-head RCTs

* Terlipressin + NTG patch in 1 RCT

VASOACTIVE DRUGS PRE-EGD FOR SUSPECTED VARICEAL BLEEDING
Three Double-Blind Placebo-Controlled Trials

• Less active bleeding at EGD in 2 trials
  – 13% vs. 25% at mean 4 hrs
  – 31% vs. 46% at mean 3 hrs
• Improved bleeding control at 12 hrs in 3rd trial
  – 71% vs. 47%
• Did not compare to vasoactive drugs started at time of EGD in placebo group
  – Later endpoints don’t reflect utility of pre-EGD drugs


ENDOSCOPIC THERAPY
**SCLEROTHERAPY FOR ACTIVE ESOPHAGEAL VARICEAL BLEEDING**

Subgroup Analysis of RCT of Sclerotherapy vs. Sham Sclerotherapy

<table>
<thead>
<tr>
<th></th>
<th>Sham (N=43)</th>
<th>Sclerotherapy (N=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemostasis</td>
<td>26 (60%)</td>
<td>40 (91%)*</td>
</tr>
<tr>
<td>Rebleed in hospital</td>
<td>22 (51%)</td>
<td>9 (20%)*</td>
</tr>
<tr>
<td>Bleeding episode source**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophageal varices</td>
<td>21</td>
<td>4*</td>
</tr>
<tr>
<td>Esophageal ulcer</td>
<td>0</td>
<td>6*</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>8 units</td>
<td>4 units*</td>
</tr>
<tr>
<td>Mortality</td>
<td>21 (49%)</td>
<td>10 (23%)*</td>
</tr>
</tbody>
</table>

* p < 0.05; ** Patients may have >1 bleeding episode

Hartigan et al. GIE 1997;46:1

**SCLEROTHERAPY VS. LIGATION FOR ACUTE VARICEAL BLEEDING**

- **Population:** Active Bleeding
- **Endpoint:** Persistent bleeding: 3 days

Lo (N=71)

- **Population:** Acute bleeding: EGD ≤ 6 hrs (SMT)
- **Endpoint:** Further bleeding: 5 days

Villanueva (N=179)

* P < 0.05

EMERGENT LIGATION VS. SOMATOSTATIN FOR ACUTE ESOPHAGEAL VARICEAL BLEEDING
RCT with EGD Within 12 Hrs of Presentation

<table>
<thead>
<tr>
<th>Results at 48 hrs</th>
<th>Ligation (N=62)</th>
<th>Somatostatin (N=63)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure</td>
<td>3 (5%)</td>
<td>20 (32%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Units transfused</td>
<td>4.7</td>
<td>6.9</td>
<td>0.03</td>
</tr>
<tr>
<td>Hospital days</td>
<td>7.7</td>
<td>10.2</td>
<td>0.07</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>2 (3%)</td>
<td>4 (6%)</td>
<td>&gt; 0.2</td>
</tr>
<tr>
<td>Mortality</td>
<td>0</td>
<td>0</td>
<td>----</td>
</tr>
</tbody>
</table>

SMT: 250 µg bolus, 250 infusion  
COMBINED ENDOSCOPIC PLUS MEDICAL THERAPY VS. ENDOSCOPIC THERAPY

LIGATION ± OCTREOTIDE FOR ACUTE VARICEAL BLEEDING

* P < 0.001

TIPS FOR ACUTE VARICEAL BLEEDING

EARLY TIPS AS PRIMARY THERAPY FOR ACUTE VARICEAL BLEEDING

- 2 RCTs of TIPS within 24-72 hrs
- High-risk patients
  - HVPG ≥ 20 mm Hg
  - Childs C (score 10-13); Child B + active bleeding
- Significant decreases in further bleeding and mortality

EARLY TIPS VS. LIGATION + MEDICAL THERAPY
RCT for Acute Variceal Bleeding in High-Risk Patients*

Child C or B with active bleeding; randomized within 24 hrs of admission; coated TIPS within 72 hrs of randomization

Garcia-Pagan, et al. NEJM 2010;362:2370

EARLY TIPS AS PRIMARY THERAPY FOR ACUTE VARICEAL BLEEDING

- 2 RCTs of TIPS within 24-72 hrs
- High-risk patients
  - HVPG ≥ 20 mm Hg
  - Childs C (score 10-13); Child B + active bleeding
- Significant decreases in further bleeding and mortality
  - Non-significant decreases in encephalopathy
    - 31 vs. 35%; 25 vs. 39%

FAILURE OF ENDOSCOPIC AND MEDICAL THERAPY: ACUTE VARICEAL BLEEDING

FAILURE OF THERAPY FOR ACUTE VARICEAL BLEEDING

- Defined as persistent or recurrent bleeding in first 5 days despite endoscopic and pharmacologic therapy
- Repeat endoscopic therapy or TIPS
  - TIPS if persistent bleeding or severe rebleeding
  - Covered esophageal stents: initial reports promising

SELF-EXPANDING METAL STENT FOR ESOPHAGEAL VARICEAL HEMORRHAGE


FAILURE OF THERAPY FOR ACUTE VARICEAL BLEEDING

- Defined as persistent or recurrent bleeding in first 5 days despite endoscopic and pharmacologic therapy
- Repeat endoscopic therapy or TIPS
  - TIPS if persistent bleeding or severe rebleeding
  - Covered esophageal stents: Initial reports promising
    - Bleeding stopped without recurrence in 34/34
    - Stent migration to stomach in 7 patients
      - Repositioned with EGD at 24-48 hrs
    - Stent extraction at mean of 5 days (1-14)

PREVENTION OF RECURRENT VARICEAL BLEEDING

ENDOSCOPIC THERAPY
## LIGATION VS. SCLEROTHERAPY

Meta-Analysis of 7 Trials (N=547)

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
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<tbody>
<tr>
<td>Rebleeding</td>
<td></td>
</tr>
<tr>
<td>Due to varices</td>
<td>0.5 (0.4 - 0.7)</td>
</tr>
<tr>
<td>Due to Rx-induced ulcers</td>
<td>0.5 (0.3 - 0.8)</td>
</tr>
<tr>
<td></td>
<td>0.6 (0.3 - 1.1)</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.7 (0.5 - 0.98)</td>
</tr>
<tr>
<td>Esophageal stricture</td>
<td>0.1 (0.03 - 0.3)</td>
</tr>
</tbody>
</table>

6/7 trials required fewer treatment sessions with ligation to achieve variceal obliteration

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## INTERVALS FOR LIGATION THERAPY

AASLD-ACG Guideline Recommendation

- Initial eradication therapy
  - Every 1-2 weeks until variceal eradication
- After variceal eradication
  - 1<sup>st</sup> EGD at 1-3 months
  - Subsequent EGDs at 6-12 month intervals depending on variceal recurrence
**PHARMACOLOGICAL THERAPY**

### β-BLOCKERS FOR PREVENTION OF RECURRENT VARICEAL BLEEDING

- β-blockers superior to placebo, inactive Rx
  - Systematic review of RCTs
    - Rebleeding: ARR = 21% (13 to 30%)
    - Mortality: ARR = 7% (2 to 12%)
- Adding ISMN may further decrease HVPG
  - Not documented to decrease rebleeding
    - Meta-analysis: decreased variceal rebleeding but not overall rebleeding

## CARVEDILOL VS. NADOLOL + ISMN FOR 2° PREVENTION OF VARICEAL BLEEDING
Open-Label RCT at 5 Days of Stability after Emergency EVL (No Serial EVL)

<table>
<thead>
<tr>
<th></th>
<th>Carvedilol (N=61)</th>
<th>Nadolol + ISMN (N=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rebleeding</td>
<td>37 (61%)</td>
<td>37 (62%)</td>
</tr>
<tr>
<td>Blood transfusions</td>
<td>3.1 u</td>
<td>3.3 u</td>
</tr>
<tr>
<td>Mortality</td>
<td>15 (25%)</td>
<td>17 (28%)</td>
</tr>
<tr>
<td>Side effects→D/C of drug</td>
<td>0</td>
<td>18 (30%)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(15 ISMN, 3 nadolol)</td>
</tr>
</tbody>
</table>

Median F/U: 30 mos


## COMBINED ENDOSCOPIC PLUS MEDICAL THERAPY VS. EITHER THERAPY ALONE
### LIGATION + MEDICAL THERAPY VS. LIGATION OR MEDICAL THERAPY ALONE

**Meta-Analysis of 9 Secondary Prevention RCTs**

<table>
<thead>
<tr>
<th></th>
<th>Combination vs. Ligation (6 trials)</th>
<th>Combination vs. Medical Therapy (3 trials*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophageal variceal rebleeding</td>
<td>0.65 (0.40-0.93)</td>
<td>0.60 (0.43-0.84)</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.71 (0.45-1.11)</td>
<td>1.08 (0.73-1.60)</td>
</tr>
</tbody>
</table>

Medical therapy = β-blocker ± isosorbide mononitrate
* β-blocker + isosorbide mononitrate

Thiele, et al. APT 2012;35:1155

### FAILURE OF ENDOSCOPIC AND MEDICAL THERAPY IN PREVENTION OF RECURRENT VARICEAL BLEEDING
RECURRENT VARICEAL BLEEDING DESPITE 2° PROPHYLACTIC THERAPY

• TIPS*
  – If well-compensated liver disease may consider surgical decompression
    • Similar clinical outcomes
    • Fewer re-interventions (TIPS shunt dysfunction)

*PTFE-coated preferred to decrease shunt dysfunction, recurrent bleeding


GASTRIC VARICES
N-BUTYL-CYANOACRYLATE (BCA) FOR GASTRIC VARICEAL BLEEDING

- BCA superior to ligation
  - Active bleeding in 1 of 3 RCTs
  - Less further bleeding in 3 of 3 RCTs
- BCA superior to β-blockers
  - Lower rebleeding and mortality in 1 RCT
- TIPS superior to BCA
  - Less rebleeding (11 vs. 38%) in 1 RCT
    - No significant difference in mortality, complications
      - More encephalopathy with TIPS (26 vs. 3%)


MANAGEMENT OF ESOPHAGEAL VARICEAL BLEEDING

- Acute Bleeding Episode
  - Vasoactive medication (e.g., octreotide)*
  - Antibiotics*
  - Endoscopic ligation
  - Consider TIPS in high-risk patients
- Prevention of Recurrent Bleeding
  - Endoscopic ligation
  - β-blocker (?β-blocker + ISMN; carvedilol)
- TIPS if failure of medical/endoscopic therapy
  - ?surgical decompression if well-compensated

* Begin before EGD

Garcia-Tsao et al. Hepatology 2008;47:1764;
de Franchis, J Hepatol 2010;53:762