Updates in Management of Acute Variceal Bleeding

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Outline

• Significance
• Management
  – Key issues
  – Established therapies
  – Emerging technologies
The Problem

• Gastroesophageal Varices
  ~ 40% in Child’s A cirrhosis
  ~ 85% in Child’s C cirrhosis

• Acute Variceal Bleeding
  – 1-year rate of 1st variceal bleeding ~ 12%
  – 1-year rate of recurrent bleeding ~ 60%
  – 6-week mortality ~ 15 to 20%
The Problem

- Although mortality from variceal bleeding has decreased over the past 2 decades due to:
  - Antibiotic prophylaxis
  - Improved endoscopic therapy and pharmacological therapy

- Still a major potentially lethal complication of cirrhosis

Carbonell N et al. Hepatology 2004
Varices

- Oesophageal
- Duodenal
- Gastric
- Rectal
Management of Acute Variceal Bleeding

- Initial Assessment & Resuscitation
- Pharmacological Therapy
- Endoscopic Therapy
- Rescue / Alternative Therapy
Initial Assessment & Resuscitation

• **Presentation:**

• **Hemodynamic Stability:**
  – ? Shock ? Tachycardia

• **Hemoglobin Level:**
  – ? Target Hb (avoid over-transfusion)
Initial Assessment & Resuscitation

• **Level of Care:**
  – ICU vs general ward

• **Airway Protection:**
  – Consider intubation for patient with significant hepatic encephalopathy
Blood Volume Resuscitation

• Maintain hemodynamic stability
• Avoid over-aggressive transfusion
  – Over-aggressive transfusion
    • → Increase in portal pressure
    • → More re-bleeding & mortality
  – Target Hb ~ 8 g/dL

Castaneda B et al. Hepatology 2001
Restrictive transfusion strategy (Tx if Hb < 7) vs Liberal transfusion strategy (Tx if Hb < 9) in 921 patients with UGIB

In subgroup analysis of 277 patients with cirrhosis

- Reduced rate of re-bleeding & mortality in the restrictive transfusion group in Child’s A or B patients
- No difference in Child’s C patients

Vaillanueva et al. NEJM 2013
Management of Coagulopathy

• FFP and/or Platelets
  – Can be considered in patients with significant coagulopathy and/or thrombocytopenia

• Recombinant Factor VIIa
  – No benefit in cirrhotic patients with UGIB in general
  – But post hoc analysis data shows reduced failure to control variceal bleeding in Child’s B, C patients

Garcia-Tsao G et al. Hepatology 2009
Bosch J et al. Gastroenterology 2004
Pharmacological Therapy

- Vasoactive drugs
- Antibiotic prophylaxis
Vasoactive Drugs

• Somatostatin & Analogues
  – Octreotide & Vapreotide
  – Inhibits vasodilator hormones e.g. glucagon, +/- direct vasoconstricting property
    • Splanchnic vasoconstriction

• Vasopressin & Analogues
  – Terlipressin
  – Non-specific arteriolar vasoconstriction
    • Splanchnic vasoconstriction
## Vasoactive Drugs

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octreotide</td>
<td>IV 50ug bolus, followed by IV infusion of 50ug/h</td>
<td>2 – 5 days</td>
</tr>
<tr>
<td>Terlipressin</td>
<td>2mg IV Q4h x 48h, then 1mg IV Q4h</td>
<td>2 – 5 days</td>
</tr>
</tbody>
</table>
Vasoactive Drugs as 1st line therapy

- A Cochrane meta-analysis of 15 RCTs
  - Sclerotherapy vs
  - Vasoactive drugs is better, controlling bleeding in 83% of patients

D'Amico G et al. Gastroenterology 2003
## Early use of Vasoactive Drugs

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment</th>
<th>Control</th>
<th>Timing</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Levacher</td>
<td>Terlipressin+</td>
<td>Nil</td>
<td>At home</td>
<td>Rebleeding</td>
</tr>
<tr>
<td>Lancet 95</td>
<td>TNG</td>
<td></td>
<td></td>
<td>Mortality</td>
</tr>
<tr>
<td>Averginos</td>
<td>Somatostatin</td>
<td>Placebo</td>
<td>Before endoscopy</td>
<td>Rebleeding</td>
</tr>
<tr>
<td>Lancet 97</td>
<td></td>
<td></td>
<td></td>
<td>Mortality</td>
</tr>
<tr>
<td>Cales</td>
<td>Vapreotide</td>
<td>Placebo</td>
<td>&lt;6h before endoscopy</td>
<td>Survival &amp; control of bleeding</td>
</tr>
<tr>
<td>NEJM 01</td>
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</table>
Endoscopic Variceal Ligation (EVL) vs Octreotide + EVL

- Control of bleeding: EVL alone 94%, EVL + octreotide 96%
- Rebleeding: EVL alone 38%, EVL + octreotide 9%

*P = 0.0007*

Antibiotic Prophylaxis

• Cirrhotic patients with UGIB $\rightarrow$ high risk of bacterial infection
  $\rightarrow$Higher risk of recurrent variceal bleeding
  $\rightarrow$Higher mortality

• Antibiotic prophylaxis x 5 – 7 days
  –Ceftriaxone, Quinolones
  –Reduced bacterial infections (with or without ascites)
  –Increased survival

Garcia-Tsao G et al. Hepatology 2009
Timing of Endoscopy

- OGD within 12 hours of admission in cirrhotic patients with suspected variceal bleeding

- Vasoactive drugs should be given before endoscopy if variceal bleeding is highly suspected

Garcia-Tsao G et al. Hepatology 2009
Endoscopic Therapy

- Banding Ligation
- Injection Sclerotherapy
- Cyanoacrylate Obturation
Endoscopic Therapy + Pharmacological Therapy

Meta-analysis of 8 trials

- Improve initial & 5-day hemostasis
- No difference in mortality or severe adverse events

Bañares R et al. Hepatology 2002
Oesophageal Varices (OV)
Endoscopic Banding Ligation (EBL) vs Injection Sclerotherapy

- Data from RCTs and Meta-analysis support EBL as the preferred therapy:
  - Better initial control of bleeding
  - Less adverse events
  - Improved mortality

Lo G et al. Hepatology 1997
Villanueva et al. J Hepatol 2006
Endoscopic Banding Ligation (EBL) vs Injection Sclerotherapy

• Sclerotherapy can be used in patients in whom EBL is not feasible

Lo G et al. Hepatology 1997
Villanueva et al. J Hepatol 2006
Endoscopic Banding Ligation (EBL) vs Cyanoacrylate Obturation

• Conflicting data from 1 small prospective case series & 2 small randomized studies
  – Ljubicic et al reported no significant difference in terms of acute OV bleeding control, re-bleeding rate, and mortality
  – Santos et al reported more minor complications, OV recurrence, and a trend towards more re-bleeding in Cyanoacrylate group

Cipolletta L et al. Dig Liver Dis 2009
Ljubicic N et al. Hepatogastroenterology 2011
Santos M et al. Eur J Gastroenterol Hepatol 2011
Gastric Varices (GV)
Gastric Varices (GV)

- Present in 20% of patients with cirrhosis
  - Isolated or in combination with OV

- More severe bleeding than OV bleeding

- Higher mortality than OV bleeding

Garcia-Tsao G et al. Hepatology 2009
Classification of GV

- **GOV1:**
  - GV is a continuation of OV along lesser curve
  - Same treatment as OV

- **IGV1:**
  - If this is from splenic vein thrombosis, then splenectomy
Cyanoacrylate Obturation

- Tissue adhesive
  - N-butyl-cyanoacrylate
  - Isobutyl-2-cyanoacrylate
  - Thrombin

- Acute fundal GV bleeding
  - Better initial control of bleeding
  - Lower re-bleeding rate

Sarin S et al. Am J Gastro 2002
Lo G et al. Hepatology 2001
Cyanoacrylate Obturation vs Endoscopic Banding Ligation (EBL)

- Acute GV bleed:
  - Similar initial control of bleeding by both
  - Less re-bleeding in the Cyanoacrylate Obturation group (23% vs 47%)

Transjugular Intrahepatic Portosystemic Shunt (TIPS) for GV

• Can be 1st line therapy for uncontrolled GV bleeding if Cyanoacrylate obturation is not available

• Initial hemostasis success ~ 90%

Garcia-Tsao G et al. Hepatology 2009
TIPS vs Cyanoacrylate Obturation in Prevention of GV re-bleeding

- 35 patients in TIPS group vs 37 patients in Cyanoacrylate group

- Less re-bleeding in TIPS group
  - 4 TIPS patients (11 %) and 14 cyanoacrylate patients (38 %) (P = 0.014)

- No difference in survival or complication rate

Lo G et al. Endoscopy 2007
EUS guided Cyanoacrylate Injection

- Advantages of EUS
  - Allow detection of “deep” varices not seen on luminal view
  - Allow treatment of bleeding varix even if luminal view is obscured by blood clot
  - Ensure intra-variceal injection
  - Allow real-time monitoring of variceal obturation
EUS guided Cyanoacrylate Injection

• Lee YT et al. GIE 2000
  – 54 patients with GV bleeding treated with biweekly Cyanoacrylate injection under EUS monitoring
  – Less recurrent bleeding compared to “on-demand” Cyanoacrylate injection group

• Romero-Castro R et al. GIE 2007
  – 5 patients with GV bleeding successfully treated with EUS-guided FNA needle injection of Cyanoacrylate
EUS guided Cyanoacrylate Injection + Coil Embolization

- Binmoeller K et al. GIE 2011
  - 30 patients with fundal GV bleeding
  - Control of acute bleeding 100%
  - 4 patients had re-bleeding from non-variceal source
  - No distant “glue” embolization
GV Bleeding treated with EUS guided Cyanoacrylate Injection
Rescue / Alternative Therapy

- TIPS
- Shunt Surgery
- Balloon Tamponade
- Self-Expandable Metal Stents
- Balloon-Occluded Retrograde Transvenous Obliteration
- Liver Transplant
TIPS

- Modern covered TIPS stents usually have longer patency

- Usually a bridge to more definitive therapy (e.g. liver transplant)
Early Use of TIPS in Variceal Bleeding

- Garcia-Pagan et al. NEJM 2010
  - 63 patients with Child’s C or Child’s B cirrhosis and persistent variceal bleeding
  - Early TIPS (within 72h) vs EBL + B-blocker, after initial treatment with vasoactive drug + endoscopy
Shunt Surgery

- Child’s A and B cirrhosis with uncontrolled variceal bleeding
- Non-cirrhotic portal hypertension related variceal bleeding
- Effective in preventing re-bleeding, but higher rates of hepatic encelphalopathy

Garcia-Tsao G et al. Hepatology 2009
Balloon Tamponade

- Sengstaken–Blakemore tube
- Minnesota tube
- Linton tube
  - Temporary measure for uncontrolled variceal bleeding
  - Complications:
    - Aspiration, migration, necrosis/perforation of esophagus

Garcia-Tsao G et al. Hepatology 2009
Self-Expandable Metal Stents

• Alternative to Balloon Tamponade or TIPS (contraindications to TIPS) in uncontrolled OV bleeding
• Usually as a temporary measure (removable stents)
• Not very useful for GV bleeding

Wright G et al. GIE 2010
Balloon-Occluded Retrograde Transvenous Obliteration

- For cardiofundal GV with dominant tributaries from the splenic vein or splenic hilum and terminate in the left renal vein (spontaneous splenorenal or gastrorenal shunts)
- GV treated with sclerosants
- However, may aggravate OV, ascites

Caldwell S et al. Am J Gastro 2012
Summary

• Variceal bleeding is still a major potentially lethal complication of cirrhosis
• Early use of vasoactive drugs
• Timely endoscopy
• Tailor endoscopic therapy to the type of varix
• Becoming familiar with benefits and risks of rescue / alternative therapies for uncontrolled variceal bleeding