Esophageal Variceal Bleeding

Wait Expectantly
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Act Prophylactically
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Learning Objectives
1. Accurately assess the risk of variceal hemorrhage in pediatric patients with portal hypertension
2. Develop a treatment strategy for variceal bleeding in children
3. Recognize gaps in evidence-based pediatric management of variceal bleeding

Primary Prophylaxis of varices
- Measurement of portal hypertension
- Guidelines for prophylaxis in adults
- Non-selective β-blockers
- Sclerotherapy
- Endoscopic Band Ligation (EBL)

Measurement of portal hypertension
- Hepato-venous pressure gradient (HVPG)- surrogate marker of portal pressure
- Reduced risk of variceal bleeding: 1-3;
  - HVPG < 20% from baseline or,
  - ≤12 mmHg

Portal Hypertension
- Quantitatively defined as a pressure gradient between portal vein and hepatic veins of greater than 5 mmHg
- Hepatic vein pressure gradient of >10 mmHg strongly predicts development of varices
- Variceal bleeding unlikely with HVPG <12 mmHg
- HVPG now used in adults as HR weakly correlated with portal hemodynamics1,2

Disclosures

Echosens
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Gastroesophageal Varices

- Present in almost half of patients with cirrhosis at the time of diagnosis (increased in CTP Class B and C patients)
- Development and growth of GE varices: 7% per year
- 1-year rate of first variceal hemorrhage is 5% for small varices, 15% for large varices
- Red wale marks on varices, advanced liver disease predict higher risk for hemorrhage
- 1-year rate of recurrent variceal hemorrhage is ≈ 60%
- The 6-week mortality with each hemorrhage episode is close to 0% for CTP class A, ≈ 30% for CTP class C.

Variceal Hemorrhage

- A common presentation of extrahepatic portal vein obstruction
- Significant morbidity and anxiety
- A lethal complication of cirrhosis (ascites, jaundice, previous hemorrhage)
- Three management issues:
  1. Primary prophylaxis
  2. Treatment of acute bleeding episode
  3. Secondary prophylaxis

Risk Stratification

- Not clearly defined
- Cirrhotic vs non-cirrhotic portal hypertension
- Compensated vs decompensated cirrhosis

Rationale to reduce portal pressure

- Varices do not develop until HVPG increases to 10-12 mmHg
- Varices do not bleed until HVPG reaches at least 12 mmHg
- If HVPG decreases below 12 mmHg, either by pharmacologic treatment or improvement in liver disease, variceal bleeding is prevented
- Even if HVPG does not go below 12 mmHg, a 20% decrease in portal pressure from baseline offers marked protection from variceal bleeding
- HVPG decrease is associated with lower risk of developing ascites, DBP, HRS and death

β-Blockers

- Low Cost
- No special expertise
- Prevent other PTHN bleeding
- Lower the risk of ascites
- Lower the risk of SBP
- Relatively common contraindications
- Side effects (fatigue and SOB) that require discontinuation in up to 15-20%
- Pediatrics: dosing guidelines, goal HR not clear

Safety of β-blockers in children

- Now the treatment of choice for infantile hemangiomas – safe and well tolerated
- Used successfully in treatment of dilated cardiomyopathy and some arrhythmias in children, with good safety profile
- Demonstrated value to ameliorate the hyperdynamic, hypermetabolic, hypercatabolic state after large burns in children
- Demonstrated safety and efficacy with chronic use in the prevention of migraines in children

Varices in Children

- Up to 70% of children with biliary atresia or PV thrombosis
- Bleeding from Varices in children:
  - 17-29% in biliary atresia
  - 50% in PV thrombosis
- Mortality from 1st variceal bleed in children:
  - 2-5% with BA
  - 0-2% with PV thrombosis
  - (15-20% in adults)

Effectiveness of beta blockers in primary prophylaxis of variceal bleeding in children with portal hypertension

- Reduced Portal Flow
  - Direct reduction in variceal flow
  - Increased porto-collateral resistance
  - Decreased vascular compliance

Non-Selective β-Blockers

- ↓ the cardiac output- β1 receptors
- Splanchnic vasoconstriction- β2 receptors

Non-Selective $\beta$-Blockers
Are they really as safe as Dr. Jonas tried to tell you?

- Adverse effects: bradycardia, hypotension, conduction disorders, bronchospasm, hypoglycemia.
- Response to shock: tachycardia due to relatively fixed stroke volume
- Hypoglycemia from beta-blockers now recognized as cause of syncope, seizures, or altered consciousness in young children
- Meta-analysis of acute NSBB exposure reveals a mean change in FEV1 of -10.2% (95% CI, -14.7 to -5.6)

1. Arch Dis Child 2009;94:968–969

Non-Selective $\beta$-Blockers
Use in Children with Portal Hypertension

- HVPG now used is adults as HR weakly correlated with portal hemodynamics
- HVPG measurement is safe, but it is very invasive
- How pediatric HVPG correlates to variceal development not yet established
- Portal pressure may be underestimated in pediatric liver disease due to presinusoidal disease and the presence of veno-venous intrahepatic collaterals


NSBB in Children with Portal Hypertension

- Pediatric case-series of NSBB show 10-35% bleeding over 3-5 years of follow-up
- Overall bleeding noted in these case series was 2-11% per year of follow-up
- Natural history of similar population is 2-9% per year of follow-up

1. Ling S. Clin Liver Dis 2012;1(5):139-142

Carvedilol: is it a better NSBB?

- Additional vasodilation properties hence decreasing the hepatic vascular resistance of cirrhosis:
  - Anti-$\alpha_1$ adrenergic activity
  - Enhances release of nitric oxide
  - Potentially more hypotension
- Results in adults mixed
- Pediatrics:
  - Not FDA approved for pediatric use
  - Long-term efficacy for preventing variceal bleeding comparable to propranolol


Carvedilol vs Propranolol

- 62 children (<12 years) followed for 2 years post NSBB
- 4.83% bled over the 2 years


Endoscopic Variceal Ablation

Sclerotherapy
Band Ligation
Endoscopic Variceal Ablation

Risks...in a non bleeding child

- Anesthesia
- Post-procedure pain
- Bleeding - immediate and with ulceration
- Stricture formation
- Infection
- Cost

Primary Sclerotherapy in Biliary atresia

1987-2009 Finland

- 47 consecutive children with BA post-Kasai
- Yearly endoscopy starting ≤ 12 months of age
- Prophylactic sclerotherapy for Grade 2/3 varices
  - Sessions every 2-4 weeks; 2 sites (1-7) injected/session
  - Yearly endoscopy if grade 0/1 varices
- Median follow-up 1.7 years (0.5-18.9 years)

Primary Sclerotherapy in Biliary atresia

- 60% with varices, median age 11 months (6-165 months)
- 34 patients had 2-30 endoscopies (median 4)
- Sclerotherapy sessions: 1-19 (median 2)
- Bili > 40µmol/L 6 months post portoenterostomy was the only variable significant for developing varices (OR 7.9, 95% CI 1.2-53, P=0.046)
- Bili > 40µmol/L 3 months post portoenterostomy = risk for bleeding (OR 17, 95% CI 1.7-175, P=0.017)

Overall 2-year survival 71%

*Transplant-free survival not influenced by varices*

Sclerotherapy and Band Ligation

- 36 children underwent primary prophylaxis with Sclerotherapy (44%; <8 kg or esoph. <11 mm), EBL (41%), or both (14%)
- Mean age 22 months (5-75 months)
  - Mean bili > 10 mg/dl
  - 20% with ascites

4.2 (1-10) sessions required to eradicate the varices

8.8 months (1.7-18.6)

within 14 months
Endoscopic ligation of esophageal varices for prophylaxis of first bleeding in children and adolescents

• 31 subjects, 4-17 years of age (9.5 ± 4.4)
• Mixed group: cirrhosis and PVT
• Grade II or more varices at BL, enlargement by at least 1 grade after 6 months of non-intervention
• Eradication achieved in 28 children (90.3%) after 2 EVL sessions at 3 month intervals
• No bleeding
• Recurrence of varices in 3 children after 12, 13 and 28 months


Bleeding-free survival in 36 children with biliary atresia and major endoscopic signs of portal hypertension who underwent primary prophylaxis

• 36 children (mean age 22 months) with either grade 3 EV or grade 2 EV with red wale markings and/or GV
• Mean # sessions to eradicate = 4.2
• Varices reappeared in 37%
• 97% 3-year survival

Duché M et al. Gastroenterology 2013;145:801