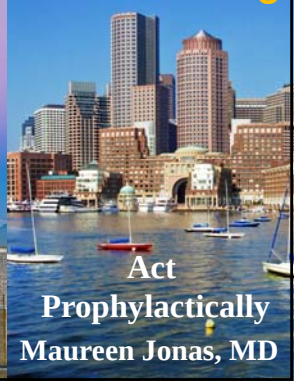
Esophageal Variceal Bleeding

Wait Expectantly

Karen Murray, MD



Act Prophylactically

Maureen Jonas, MD

Disclosures

Echosens

Maureen Jonas, MD

No relevant financial relationships

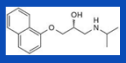
Karen Murray, MD

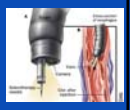
Learning Objectives

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

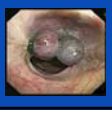
Primary Prophylaxis of varices

- Measurement of portal hypertension
- Guidelines for prophylaxis in adults
- Non-selective β-blockers





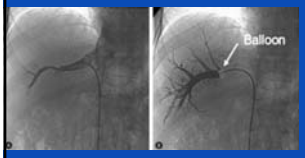
- Sclerotherapy



- Endoscopic Band Ligation (EBL)

Measurement of in 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

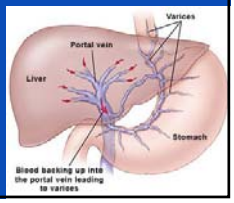


A: Free hepatic venous pressure
B: Wedged hepatic venous pressure
B-A=HVPG

[1] *J Hepatol* 2003;38:S54-68; [2] *Lancet* 1995;346:1056-9; [3] *J Hepatol* 2010;53:762-8

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 is adults as HR ***weakly*** correlated with portal hemodynamics[1, 2]



[1] Bosch et al. Hepatology 1984;4:1200-5
[2] Garcia-Tsao et al. Hepatology 1986;6:101-6

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 o[illegible]all varices, 15% for large var[illegible]
- Red wale ma[illegible]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.

Adult Data!!!

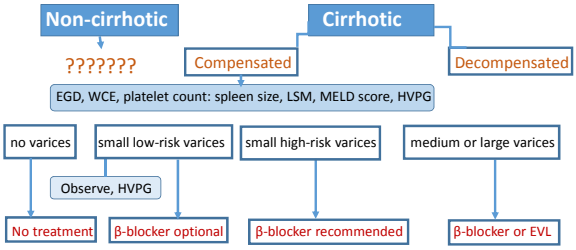
Variceal Hemorrhage

- A common presentation of extrahepatic portal vein obstruction
  - Significant morbidity and anxiety
- A lethal complication of cirrhosis
  - Especially in patients with decompensated 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

Risk Stratification



β-Blocker EVL

- Equivalent efficacy
- No differences in survival

Rationale to reduce portal pressure

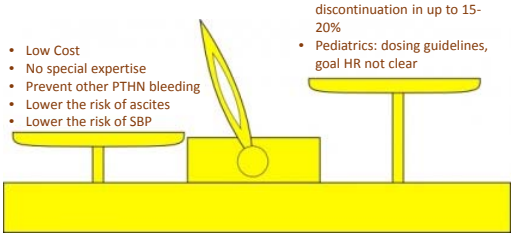
- Varices do not develop until HVPG increases to 10-12 mmHg
- Varices do not bleed until HVPG reaches at least 12 mmHg
- If HBPG decreases below 12 mmHg, either by pharmacologic treatment or improvement in liver disease, variceal bleeding is prevented
- Even if HVPG does not go below 12 mmHg, a 20% decrease 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

D'Amico et al. Hepatic vein pressure gradient reduction and prevention of variceal bleeding in cirrhosis: a systematic review. Gastroenterology 2006;131:1611
Abraldes et al. Hemodynamic response to pharmacological treatment of portal hypertension and long-term prognosis of cirrhosis. Hepatology 2003;37:902

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



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

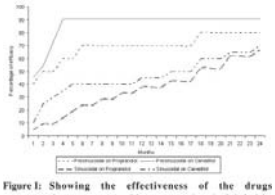


Figure 1: Showing the effectiveness of the drugs (in percentages) with respect to the scheduled visits in the 4 groups

Samanta T et al. Trop Gastroenterol 2011;32:299

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

Boston Baked Beans

Seattle Coffee Beans

Varices in Children

- Up to 70% of children with biliary atresia or PV thrombosis[1,2]
- Bleeding from Varices in children[2]:
  - 17-29% in biliary atres
  - 50% in PV thrombosis **2-6%/year**
- Mortality from 1st variceal bleed in children:
  - 2-5% with BA[3]
  - 0-2% with PV thrombosis[4]
  - (15-20% in adults)

[1]*Gastroenterology* 2010;139:1952-60; [2]*J Pediatr* 2000;136:805-8; [3]*JPGN* 2013;56:537-43; [4]*J Pediatr* 2001;139:291-6

Non-Selective β-Blockers

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

↓

Reduced Portal Flow

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

Ann Gastroenterol 2014;27(1):20-6

Non-Selective β-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[1]
  - Meta-analysis of acute NSBB exposure reveals a mean change in FEV1 of -10.2% (95% CI, -14.7 to -5.6)[2]

[1]Arch Dis Child 2009;94:968–969
[2]Chest 2014 Apr;145(4):779-86

Non-Selective β-Blockers

Use in Children with Portal Hypertension

- HVPG now used is adults as HR ***weakly*** correlated with portal hemodynamics[1, 2]
  - HVPG measurement is safe[3], 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 pre-sinusoidal disease and the presence of veno-venous intrahepatic collaterals

[1]Hepatology 1984;4:1200-5; [2]Hepatology 1986;6:101-6; [3]JPGN 2013;57(5):634-637

NSBB in Children with Portal Hypertension

- Pediatric case-series of NSBB show 10-35% bleeding over 3-5 years of follow-up[1]

TABLE 3: Studies of Primary Prophylaxis of Variceal Bleeding in Children

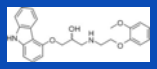
Study	Treatment	Design	n	Follow-Up	Bleeding (%)
Jhashidhar (1999)[9]	Beta-blocker	Case series	17	3 years	35
Zaraylu (2000)[8]	Beta-blocker	Case series	45	5 years	16
Erkan (2003)[10]	Beta-blocker	Case series	10	5.2 years	10

- 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-α1 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*

*Samanta et al. Trop Gastroenterol 2011;32:299-303

Carvedilol vs Propranolol

- 62 children (<12 years) followed for 2 years post NSBB

Table 2: Shows the details of distribution of gradation of varices at the start of treatment and after 2 years of continuous pharmacotherapy along with number of breakthrough bleeders in each group

Groups	IV (n)	III (n)	IIA (n)	IIB (n)	Total (n)
At the time of initiation of therapy					
Gradation of oesophageal varices					
• IV	-	-	-	-	-
• III	2	2	1	1	6
• II	6	5	3	4	18
• I					38
GOV					9
PHG					4
At the time offend of study period					
Gradation of oesophageal varices					
• IV	1	1	-	-	2
• III	2	1	-	1	4
• II	2	3	1	-	6
• I	5	5	3	1	14
• No varices	11	10	6	9	36
GOV	2	2	1	1	6
PHG	1	1	1	1	4
Bleeders following pharmacotherapy	1	1	-	1	3

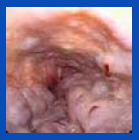
IIA= Sinusoidal on propranolol, IIB= Sinusoidal on carvedilol, IIA= Presinusoidal on propranolol, IIB= Presinusoidal on carvedilol n = number of patient

4.83% bled over the 2 years

Samanta et al. Trop Gastroenterol 2011;32:299-303

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)

Lampela et al. *JPGN* 2012;55(5):574-9

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)

Lampela et al. *JPGN* 2012;55(5):574-9

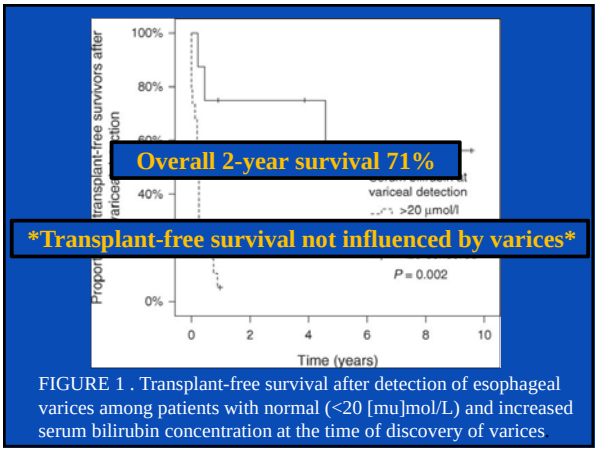
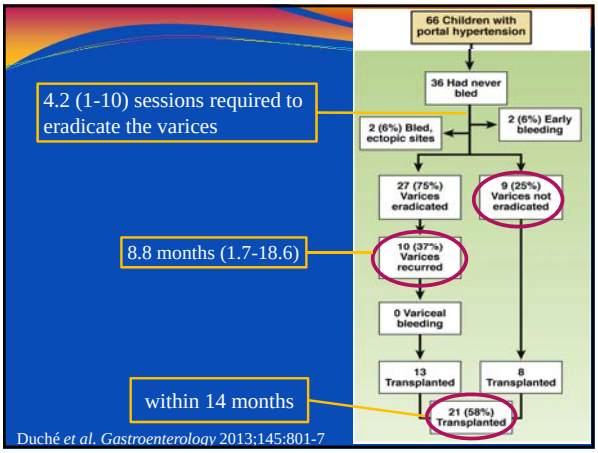


FIGURE 1 . Transplant-free survival after detection of esophageal varices among patients with normal (<20 [mu]mol/L) and increased serum bilirubin concentration at the time of discovery of varices

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

Duché et al. *Gastroenterology* 2013;145:801-7

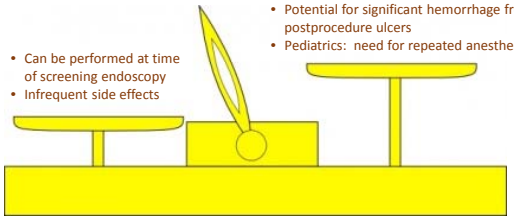


Duché *et al. Gastroenterology* 2013;145:801-7

EVL

- Can be performed at time of screening endoscopy
- Infrequent side effects

- Specific expertise necessary
- More costly
- Potential for significant hemorrhage from postprocedure ulcers
- Pediatrics: need for repeated anesthesia



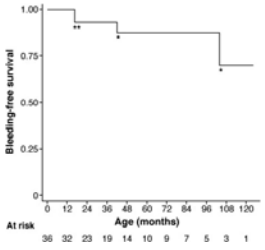
Endoscopic ligation of esophageal varices for prophylaxis of first bleeding in children and adolescents

- 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

Celińska-Cedro et al. J Pediatr Surg 2003:38:1008

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