OVERVIEW AND UPDATES ON THE MANAGEMENT OF ESOPHAGEAL VARICEAL HEMORRHAGE

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Disclosures

I have no disclosures

Clinical Case

A 52-year-old male presented to the ED with hematemesis

Patient has a history of alcohol use disorder and alcoholic liver disease. No prior history of GI bleeds. No prior endoscopy

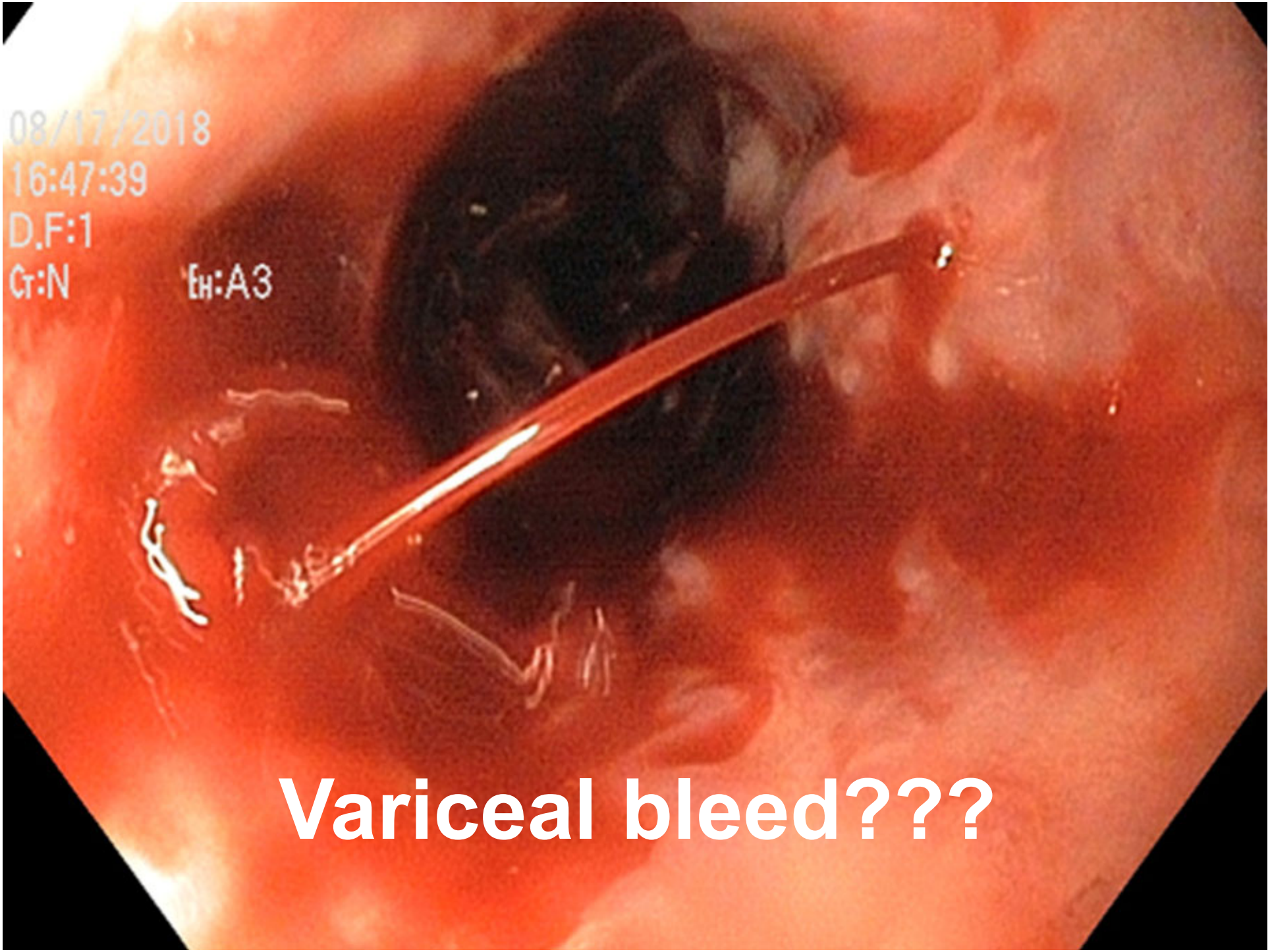
In the ED he is pale, diaphoretic, and ill-appearing. He appears jaundiced

HR 112, BP 90/62, RR 20, O2 Sat 100%

Abdomen is soft, non-tender, but distended

HgB 8.2 g/dl, Platelets 100,000, WBC 11,000

AST 220 ALT 107, T. bili 12.6, ALK phos 145, INR 1.3, Albumin 3.1


08/17/2018
16:47:39
D.F:1
CT:N
EH:A3
Variceal bleed???

Outline

- Management of acute esophageal variceal bleeding in cirrhosis
  - Pre-endoscopic management
  - Endoscopic management
  - Post endoscopic management
  - Braveno VII updates (practicing personalized care)
- Medical therapy and prophylactic Interventions
  - Future Strategies

Variceal Hemorrhage

- VH is the second most common cause of decompensation in cirrhosis
- Varices form at a rate of 5-15%/ year
- 30% will bleed at some point
- Bleeding if Portal Pressure ≥ 12mmHg
- Mortality of acute variceal bleed is 15-20%
- In hospital mortality: continuous bleed, rebleed, infection, HRS and advanced disease

Goals of Therapy:

- Restore and maintain hemodynamic stability
- Maintain tissue oxygenation
- Control bleeding
- Prevent recurrent bleeding and mortality

Karstensen et al. Endoscopy International Open 2020; 08: E990-E997

Pre-Endoscopic Management

- Manage in intensive care or intermediate care units
- Volume resuscitation
  - *Volume expansion – crystalloids*
  - *Conservative RBC transfusion (target Hgb 7- 9 mg/dL)*
- Intubation if AMS or actively vomiting
- Use of NGT should be performed with caution
- Vasoactive agents should be started as soon as possible and continued for 2-5 days

J Hepatol. 2022 Apr;76(4):959-97
Garcia-Tsao J. Hepatology 2017

Pre-Endoscopic Management

- Consider PPI (1/3 non-variceal source)
- Anticoagulants should be discontinued until hemorrhage is under control
- IV ceftriaxone (1g/24 hours) should be considered in patients with advanced cirrhosis (continue up to 7 days)
- Pre-endoscopy erythromycin (250 mg IV 30-120 minutes prior)

J Hepatol. 2022 Apr;76(4):959-974
Garcia-Tsao J. Hepatology 2017

PRBC Transfusion

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 3, 2013 VOL. 368 NO. 1

Transfusion Strategies for Acute Upper Gastrointestinal Bleeding

Càndid Villanueva, M.D., Alan Colomo, M.D., Alba Bosch, M.D., Mar Concepción, M.D., Virginia Hernandez-Gea, M.D., Carles Aracil, M.D., Isabel Graupera, M.D., María Poca, M.D., Cristina Alvarez-Urturi, M.D., Jordi Gordillo, M.D., Carlos Guarner-Argente, M.D., Miquel Santaló, M.D., Eduardo Muñiz, M.D., and Carlos Guarner, M.D.

PRBC transfusion threshold = Hgb <7g/dl
Higher threshold in CV disease = Hgb <9g/dl

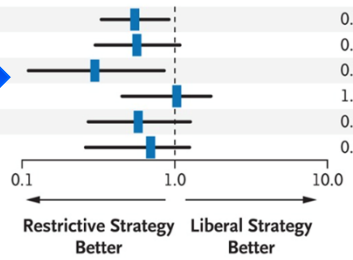
Restrictive versus liberal blood transfusion for gastrointestinal bleeding: a systematic review and meta-analysis of randomised controlled trials

Lancet Gastroenterol Hepatol

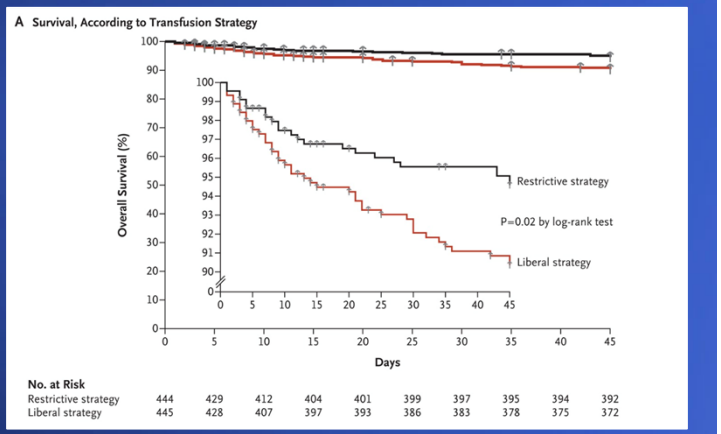
Ayodele Odutayo, Michael J R Desborough*, Marialena Trivella, Adrian J Stanley, Carolyn Dorée, Gary S Collins, Sally Hopewell, Susan J Brunskill, Brennan C Kahan, Richard F A Logan, Alan N Barkun, Michael F Murphy, Vipul Jairath*

B Death by 6 Weeks, According to Subgroup

Subgroup	Restrictive Strategy	Liberal Strategy	Hazard Ratio (95% CI)	P Value
	no. of patients/total no. (%)			
Overall	23/444 (5)	41/445 (9)	0.55 (0.33–0.92)	0.02
Patients with cirrhosis	15/139 (11)	25/138 (18)	0.57 (0.30–1.08)	0.08
Child–Pugh class A or B	5/113 (4)	13/[illegible]	0.30 (0.11–0.85)	0.02
Child–Pugh class C	10/26 (38)	12/29 (41)	1.04 (0.45–2.37)	0.91
Bleeding from varices	10/93 (11)	17/97 (18)	0.58 (0.27–1.27)	0.18
Bleeding from peptic ulcer	7/228 (3)	11/209 (5)	0.70 (0.26–1.25)	0.26



Restrictive RBC transfusion lower all - cause mortality lower re-bleeding rates



Transfusion of other blood products

- No evidence that platelet count is correlated with likelihood of controlling bleeding
- In the case of failure to control bleeding, decision to correct hemostatic abnormalities should be considered on a case-by-case basis
- The following transfusion thresholds for management of active bleeding or high-risk procedures may optimize clot formation in advanced liver disease:

hematocrit ≥25%, platelet count >50,000,
and fibrinogen >120 mg/dL

Gastroenterology Volume 157, Issue 1, July 2019, Pages 3
43.e1
J Hepatol. 2022 Apr;76(4):959-974

Transfusion of other blood products

- Transfusion of FFP not recommended
  - Will not correct coagulopathy
  - Volume overload and worsening portal pressures
- Recombinant factor VII not recommended
- Prothrombin complex concentrate (Kcentra)
  - Limited experience in liver disease
  - No clear consensus with regards to safety and role in patients with liver disease

Gastroenterology Volume 157, Issue 1, July 2019, Pages 34-43.e1
J Hepatol. 2022 Apr;76(4):959-974

Vasoactive agents

Vasoactive Drugs	Recommended Dose	Duration
Terlipressin (VP analogue)	Initial 48 hours: 2mg IV every 4 hours until control of bleeding Maintenance: 1mg IV every 4 hours to prevent rebleeding	2-5 days
Octreotide (SMT analogue)	Initial IV bolus of 50 µg (can be repeated in 1st hr if ongoing bleeding) Continuous IV infusion of 50 µg/hr	2-5 days
Somatostatin	Initial IV bolus 250 µg (can be repeated in 1st hr if ongoing bleeding) Continuous IV infusion of 250-500 µg/h	2-5 days
Vasopressin	Vasopressin Continuous IV infusion: 0.2-0.4 U/min; can be increased to 0.8 U/min It should always be accompanied by IV nitroglycerin at a starting dose of 40 µg/min, which can be increased to a maximum of 400 µg/min, adjusted to maintain a SBP 90mm Hg	24 hrs

The use of vasoactive agents in acute VH is associated with lower 7-day all cause mortality and lower transfusion requirements

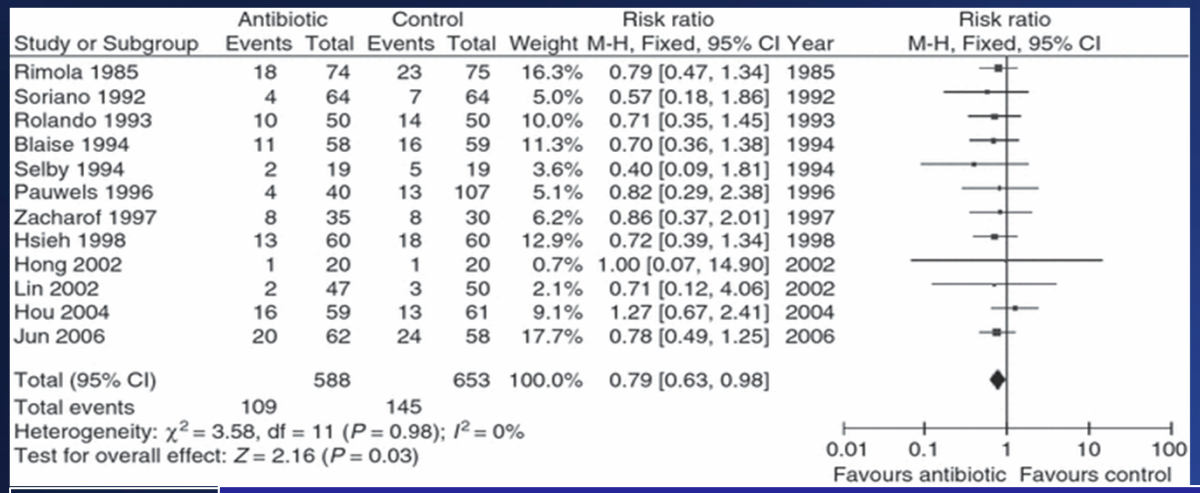
Vasoactive agents should be started as soon as possible, together with antibiotics and before the diagnostic endoscopy

Drug Res. 2019 Sep;69(9):487-495.
Aliment Pharmacol Ther. 2012 Jun;35(11)1267-78

AP&T Alimentary Pharmacology and Therapeutics

Meta-analysis: antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding – an updated Cochrane review

N. C. Chavez-Tapia*, T. Barrientos-Gutierrez†, F. Tellez-Avila‡, K. Soares-Weiser§, N. Mendez-Sanchez*, C. Gluud¶ & M. Uribe*



Study or Subgroup	Antibiotic Events	Antibiotic Total	Control Events	Control Total	Weight	Risk ratio M-H, Fixed, 95% CI	Year
Rimola 1985	18	74	23	75	16.3%	0.79 [0.47, 1.34]	1985
Soriano 1992	4	64	7	64	5.0%	0.57 [0.18, 1.86]	1992
Rolando 1993	10	50	14	50	10.0%	0.71 [0.35, 1.45]	1993
Blaise 1994	11	58	16	59	11.3%	0.70 [0.36, 1.38]	1994
Selby 1994	2	19	5	19	3.6%	0.40 [0.09, 1.81]	1994
Pauwels 1996	4	40	13	107	5.1%	0.82 [0.29, 2.38]	1996
Zacharof 1997	8	35	8	30	6.2%	0.86 [0.37, 2.01]	1997
Hsieh 1998	13	60	18	60	12.9%	0.72 [0.39, 1.34]	1998
Hong 2002	1	20	1	20	0.7%	1.00 [0.07, 14.90]	2002
Lin 2002	2	47	3	50	2.1%	0.71 [0.12, 4.06]	2002
Hou 2004	16	59	13	61	9.1%	1.27 [0.67, 2.41]	2004
Jun 2006	20	62	24	58	17.7%	0.78 [0.49, 1.25]	2006
Total (95% CI)		588		653	100.0%	0.79 [0.63, 0.98]	
Total events	109		145				

Heterogeneity: $\chi^2 = 3.58$, df = 11 ($P = 0.98$); $I^2 = 0\%$
Test for overall effect: $Z = 2.16$ ($P = 0.03$)

Figure 2: Fores

Prophylactic antibiotics significantly reduce:

- Overall mortality
- Mortality secondary to bacterial infections

Low risk in child's A cirrhosis

Ceftriaxone (1g/24h) being the first choice

Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year
Rimola 1985	1	74	7	75	37.3%	0.14 [0.02, 1.15]	1985
Soriano 1992	1	64	2	64	10.7%	0.50 [0.05, 5.38]	1992
Pauwels 1996	1	40	4	107	11.7%	0.67 [0.08, 5.80]	1996
Lin 2002	0	47	2	50	13.0%	0.21 [0.01, 4.31]	2002
Hou 2004	2	59	2	61	10.6%	1.03 [0.15, 7.10]	2004
Jun 2006	2	62	3	58	16.6%	0.62 [0.11, 3.60]	2006
Total (95% CI)		346		415	100.0%	0.43 [0.19, 0.97]	
Total events	7		20				

Heterogeneity: $\chi^2 = 2.43$, df = 5 ($P = 0.79$); $I^2 = 0\%$
Test for overall effect: $Z = 2.02$ ($P = 0.04$)

Figure 3: Forest plot of comparison: antibiotic vs. placebo/no intervention. Outcome: mortality due to bacterial infections.

Aliment Pharmacol Ther, Volume: 34, Issue: 5, Pages: 509-518, First published: 27 June 2011

Pre-endoscopy Management:

Erythromycin

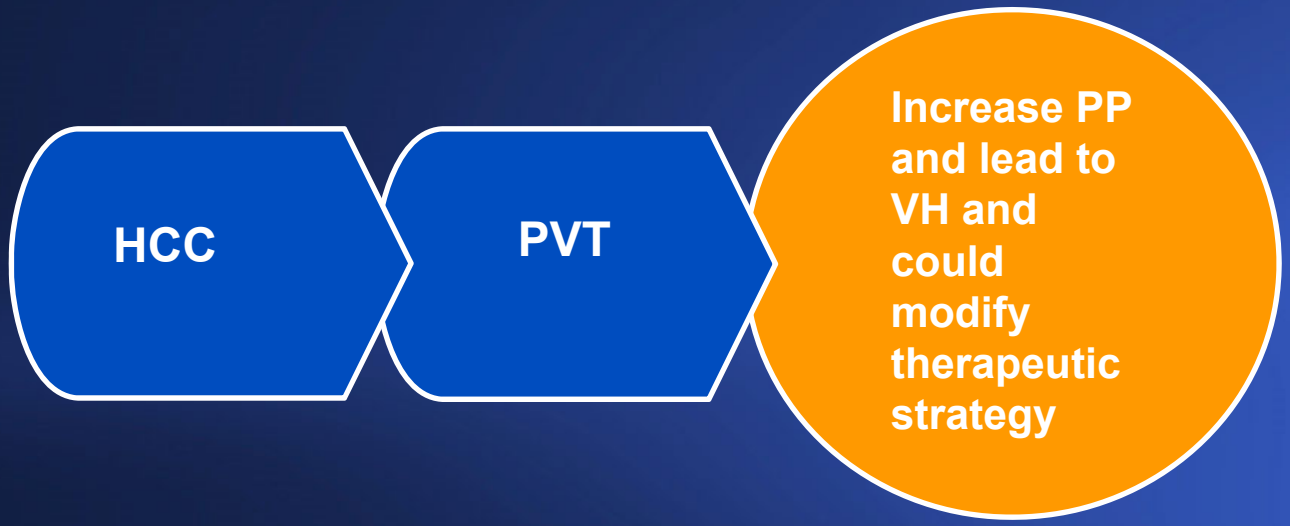
- Suspected ongoing bleeding or suspected blood in stomach
- 250 mg IV 30 – 120 minutes prior to endoscopy
- Contraindications:
  - *Prolonged QTc*
  - *Macrolide allergy*

J Hepatol. 2022 Apr;76(4):959-974

Pre-endoscopy Management:

Imaging

- All patients with acute variceal bleed should undergo abdominal imaging
  - *Cross sectional imaging with CT or MRI*



J Hepatol. 2022 Apr;76(4):959-974

Endoscopic Management:

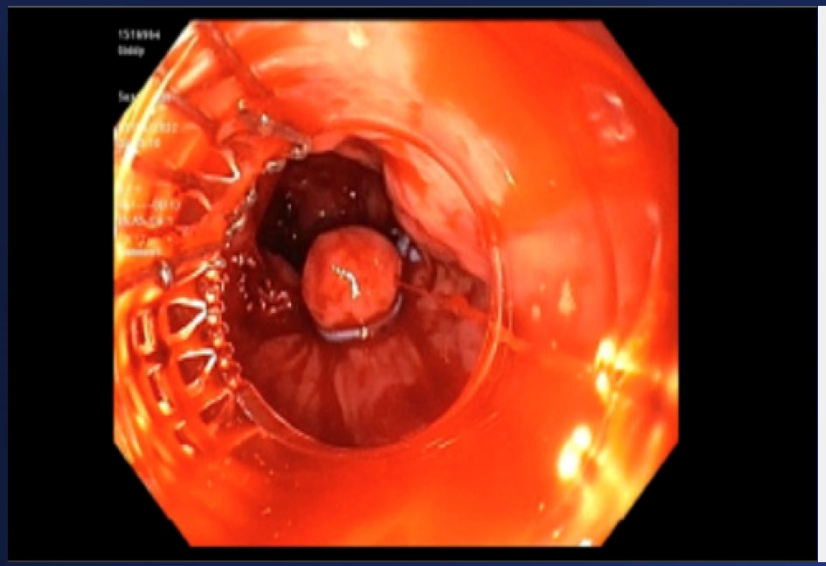
Patient with a suspected variceal bleed should undergo endoscopy within 12 hours after adequate resuscitation

Goals of endoscopic Therapy:

- Stop bleeding
- Prevent early re-bleeding (50% within the first 5 days)
- Prevent late re-bleeding (after 6 weeks) and variceal eradication

Garcia-Tsao et al. Hepatology 2017
Garcia-Pagan et al. CGH 2014

Endoscopic Variceal Ligation:

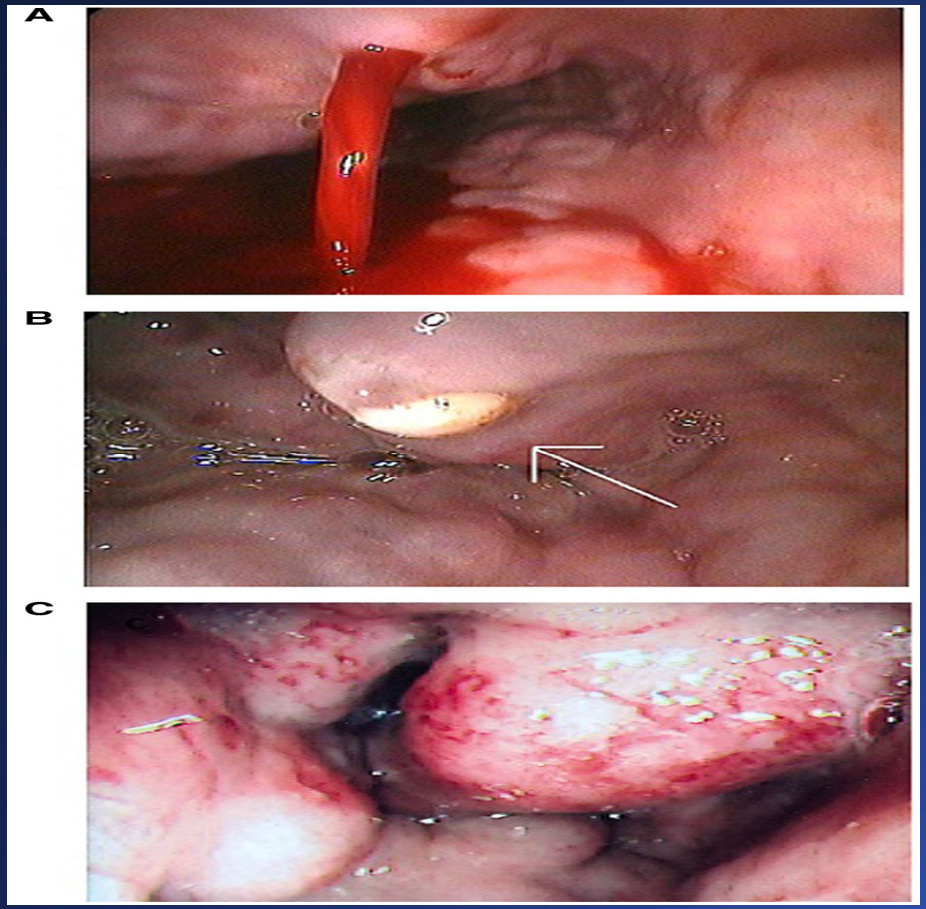


With the use of vasoactive agents, most patients will have stopped bleeding by the time of endoscopy

Active bleeding

Nipple sign

Red wale signs



Risk factors for endoscopic failure and/or rebleeding:
high CTP, high MELD (18 or above), high risk stigmata, HVPG over 20 mmHg

Clinical Liver Disease, Volume: 18, Issue: 4, Pages: 179-183, First published: 27 October 2021
Case Rep Gastroenterol 2011;5:386- 390

Technical recommendations for EV ligation:

- Diagnostic size gastroscope
- Adequate suction
- Water jet capabilities
- Apply first band to site of active or suspected bleeding/nipple sign
- Ideally achieve “red out” of screen
- Apply further bands to other variceal columns in a proximal spiral fashion

Age:
Birth:
01/2000
53:31
A3/4
r:N

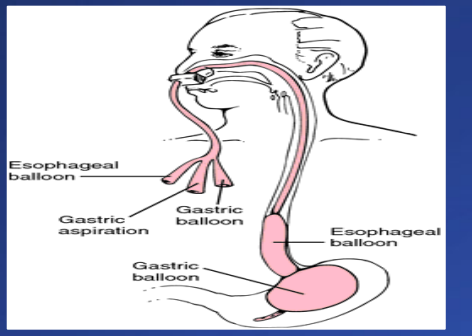
Additional Therapies:

- Sclerotherapy
  - e.g ethanolamine, Na murrhaute, polidocanol, Na tetradecyl, hypertonic dextrose
  - Increased risk of complications
- Hemostatic powder/ Hemospray e.g TC-325
  - cannot be recommended as first line endoscopic therapy
  - Use is off-label
- Endoscopic clipping, argon plasma coagulation, and microwave ablation: No established role

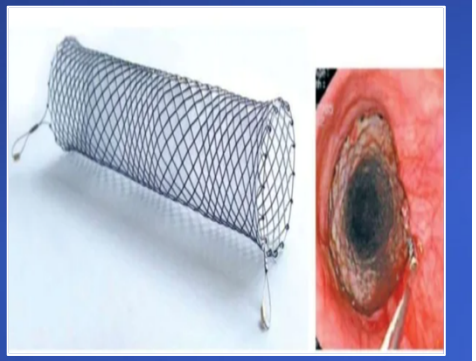
United European Gastroenterol J 2015;**3**:277-283
Escorsell À, Pavel O, Cárdenas A, et al. *Hepatology* 2016;63:1957-1967

Bridge to Definitive Therapy: (Refractory Bleeding)

- Balloon tamponade:
  - Sengstaken-Blakemore tube (SBT)
  - 90% hemostasis rate
  - 20% to 60% complication rate
  - Xray post insertion



- Esophageal stents: SEMS
  - As efficacious as balloon tamponade
  - A safer option (lower serious adverse events)
  - Reduced TIPS utilization
  - Complications: ulceration, migration, rebleeding at 48 hours, and re-bleeding after removal
  - Stent retrieval should be done within 7 days of placement



Hepatology. 2016Jun;63(6):1957-67

Post endoscopy Management:

- Oral nutrition should be started as soon as possible
  - Within 4 hours vs. within 72 hours – Safe, decreased risk of infection, improved nutrition
- Proton Pump inhibitors should be stopped after procedure unless a strict indication to continue
  - To reduce the size of post-EVL ulcers
  - The duration of PPI treatment in a patient with cirrhosis after ulcer bleeding remains unresolved
- Duration of discontinuation of oral anticoagulants should depend on strength of indication

Dig Endosc 2019;31:646-652
J Gastroenterol Hepatol 2011 Jun;26(6):996-1003
De Francis et al. Jo of Hepatology 2022

Post endoscopy Management:

- Repeat EGD with EVL every 2-8 weeks until eradication to prevent further variceal bleeding
- Lowering portal pressures and risk of further decompensation (associated with higher mortality)
  - Non-selective beta blockers (NSBB) or carvedilol
  - Treating the primary cause
  - If re-bleeds despite dual therapy ➔TIPS
- Oral lactulose or enemas to prevent HE and rapid removal of blood for GI tract

Post endoscopy Management:

First line therapy for prevention of recurrent variceal bleed is the combination of NSBBs or Carvedilol and EVL

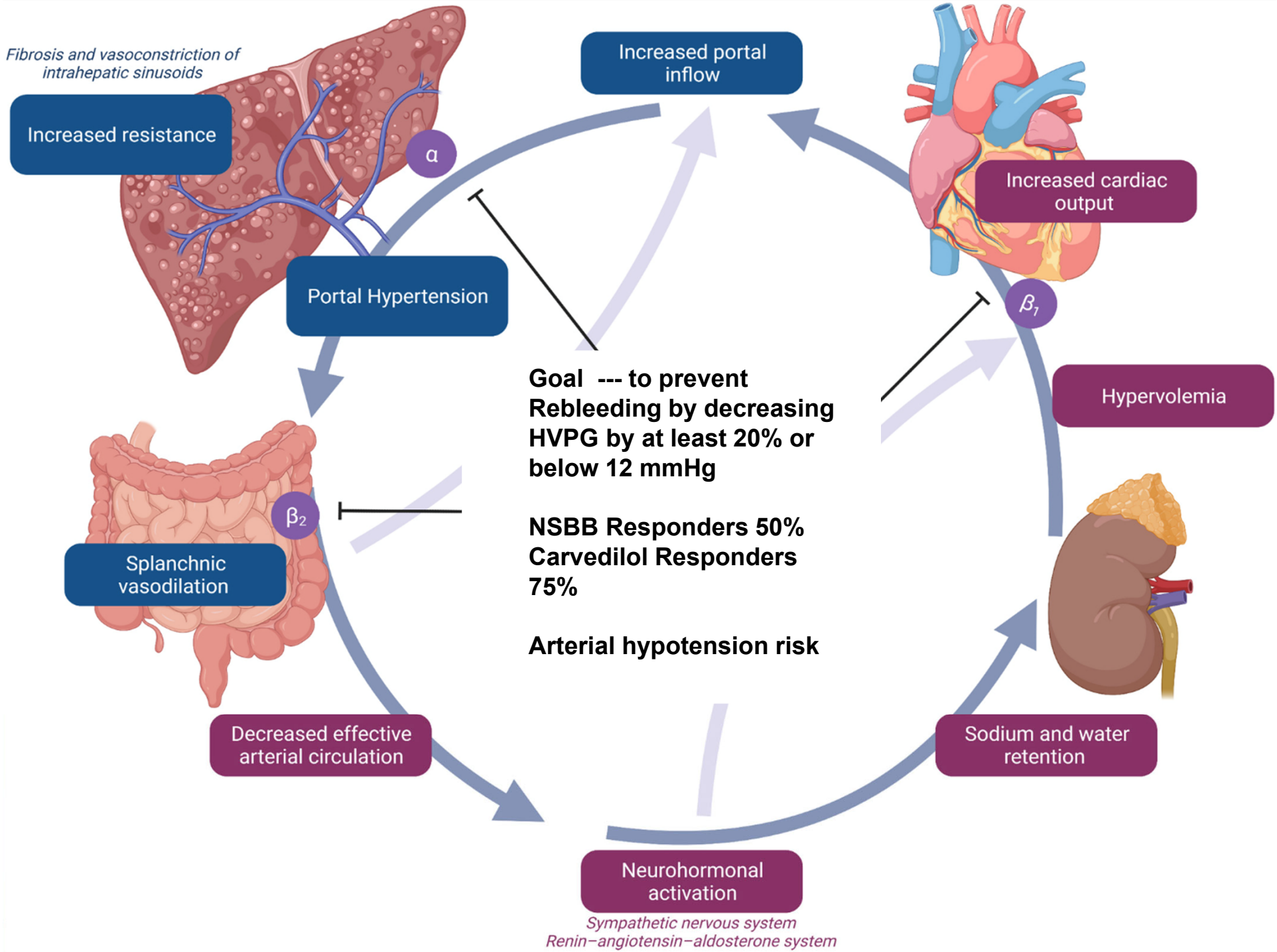
NSBBs have been shown to be the key component of the combination therapy and drive the majority of the benefit

Garcia-Tsao G, Abraldes JG, Berzigotti A, et al. Portal hypertensive bleeding in cirrhosis: risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. *Hepatology* 2017;**65**:310-335

Prognostic Value of HVPG in Patients with Chronic Liver Disease

Measurement	Significance
1-5 mm Hg	Normal
≥ 6 mm Hg	Risk of disease progression in persons with HCV recurrence after liver transplantation
≥ 10 mm Hg	Clinically significant portal hypertension
≥ 12 mm Hg	Increased risk for rupture of varices
≥ 16 mm Hg	Increased risk of mortality
≥ 20 mm Hg	Treatment failure and mortality in acute variceal bleeding

Bochnacova, CLD 2021


Fibrosis and vasoconstriction of intrahepatic sinusoids
Increased resistance
α
Portal Hypertension
Increased portal inflow
Increased cardiac output
β1
Hypervolemia
Sodium and water retention
Neurohormonal activation
Sympathetic nervous system
Renin–angiotensin–aldosterone system
Decreased effective arterial circulation
Splanchnic vasodilation
β2
Goal --- to prevent Rebleeding by decreasing HVPG by at least 20% or below 12 mmHg
NSBB Responders 50%
Carvedilol Responders 75%
Arterial hypotension risk

Therapy	Route	Initial Dose	Maximum Dose	Maintenance
Carvedilol*	Oral	6.25 mg once daily	• 12.5 mg once daily (unless persistent hypertension) • Hypertension or hypotension?	• Maintain systolic blood pressure > 90 mm Hg
Propranolol	Oral	20-40 mg twice daily	• 160 mg/day for patients with ascites • 320 mg/day for patients without ascites	• Resting heart rate at 55-60 beats per minute • Maintain systolic blood pressure > 90 mm Hg
Nadolol	Oral	20-40 mg once daily	• 80 mg/day for patients with ascites • 160 mg/day for patients without ascites	• Resting heart rate at 55-60 beats per minute • Maintain systolic blood pressure > 90 mm Hg

Discontinue or reduce if refractory ascites and: SBP <90 mmHg, MAP <65 mmHg, hyponatremia and/or AKI/HRS-AKI

Adapted from AASLD and EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis
Lancet. 2019;393(10181):1597–608
JHEP Rep. 2019 Dec 20;2(1):100063
Clinical liver Disease, VOL 19, NO 3, March 2022

Preemptive TIPS:

- Once endoscopy and EVL have been performed, “early” (preemptive) TIPS within 72 hours of admission can be considered
- Associated with significantly lower treatment failure and mortality rates in carefully selected patients

HVPG > 20 mmHg

CTP C with a score of 10-13

CTP B with active bleeding on endoscopy despite intravenous vasoactive therapy

N Engl J Med. 2010 Jun 24;362(25):2370-9
Hepatology. 2017 Jan;65(1):310-335

Future Direction:

- Focus on prevention of bleeding and hepatic decompensation
- Use of noninvasive testing for assessing presence of CSPH
- Noninvasive tests are sufficiently accurate to define CSPH
- Treatment with NSBB or Carvedilol should be considered for the prevention of decompensation in patients with CSPH
- We are in a new era of NSBB management

De Francis et al. Jo of Hepatology 2022
Hepatology. 2017 Jan;65(1):310-335

Patient Update:

- Resuscitated and underwent endoscopy within 12 hours
- Endoscopy demonstrated multiple large non-bleeding varices.
- EVL was performed with the successful placement of a total of 6 ligation bands
- Discharged 3 days later on NSBB and scheduled for repeat endoscopy 2 weeks later

De Francis et al. Journal of Hepatology 2022
Hepatology. 2017 Jan;65(1):310-335

Summary:

- Management of VH should include resuscitation then timely endoscopy within 12 hours
- EVL effectively treats VH, however, does not treat the portal hypertension
- EVL should be coupled with secondary prophylaxis with non-selective beta blockers and treatment of the primary disease
- Consider temporary SEMS placement or Balloon tamponade in refractory bleeding and as a bridge to rescue TIPS
- High risk individuals should be considered for preemptive TIPS
- Patients that do not undergo TIPS should undergo scheduled endoscopy to ensure eradication and prevention of recurrent VH
- A personalized approach to care should be used to determine a patient's ideal therapeutic intervention to prevent bleeding

THANK YOU