Endoscopic Therapy for Esophageal and Gastric Varices, Portal hypertensive Gastropathy and GAVE

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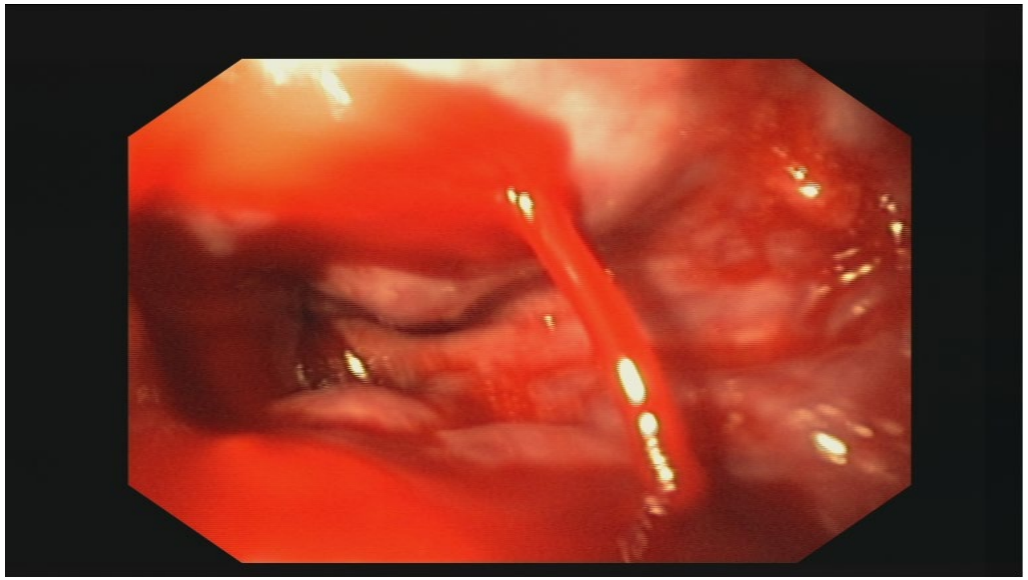
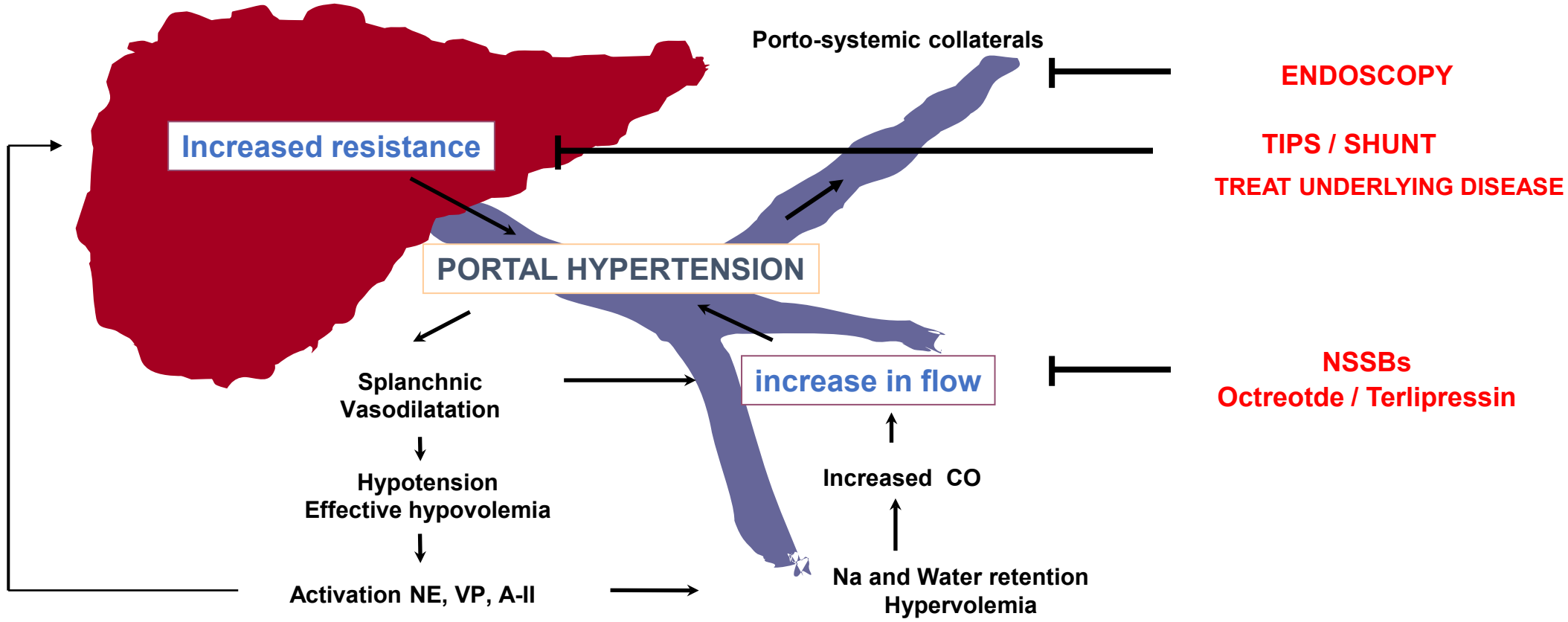
Most common causes of upper gastrointestinal bleeding in cirrhosis

1. Esophageal varices
2. Gastric Varices
3. Portal Hypertensive Gastropathy
4. Ectopic varices
5. Peptic ulcer disease
6. Erosive esophagitis
7. GAVE
8. AVM’s
9. Malignancy
10. Other

85%



Treatment of Portal Hypertension
Rationale



Before endoscopy !

1. IV access and volume expansion
2. Prophylactic antibiotics (*despite this 20% can develop infections*)
3. Vasoactive therapy
4. Do not over-transfuse (Hb ~ 8)
5. Avoid shock (prevents acute kidney injury)
6. IV erythromycin 250 mg (30 min before endoscopy)
7. Avoid the systematic and long-term use of PPI's (i.e omeprazole)
8. Consider intubation
9. No recommendation in regard to coagulopathy
10. Stratify patient- (identifiy those that will re-bleed)

Cardenas .Clin Liv Dis 2014
Baveno VII J Hepatol 2021
Brunner F. Liver Int. 2017
Baiges. Clin Liver Dis . 2021
Martinez. J Hepatol 2021
ESGE Cascade Guideline. Endoscopy International Open 2020;

Orotracheal Intubation?

No clear guidelines

Pros

- Protects airway
- Can administer deep sedation
- Can take longer with the procedure
- May extubate right after

Cons

- Increase rate of cardiopulmonary unplanned events (pneumonia)
- May worsen outcome
- Can cause trauma / more bleeding
- No good data to support intubation

Massive hematemesis or obtunded patient: intubate for procedure

Dig Dis Sci. 2007
Gastrointest Endosc. 2003
Gastrointest Endosc 2017
BANENO VII

Study or subgroup	PI Events	PI Total	No PI Events	No PI Total	Weight	Odds ratio M-H, fixed, 95%CI
Koch *et al*	7	42	0	20	10.7%	8.66 (0.47, 159.62)
Rehman *et al*	9	49	5	49	78.6%	1.98 (0.61, 6.41)
Tang *et al*	4	43	0	26	10.7%	6.04 (0.31, 116.86)
Total (95%CI)		134		95	100.0%	3.13 (1.17, 8.39)
Total events	20		5			

Heterogeneity: $\chi^2 = 1.24$, $df = 2$ ($P = 0.54$); $I^2 = 0\%$

Test for overall effect: $Z = 2.27$ ($P = 0.02$)

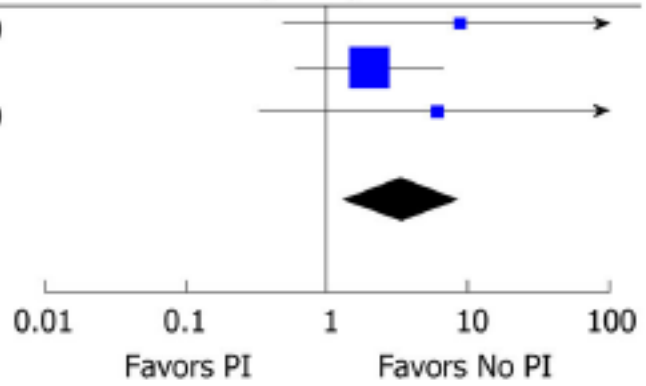


Figure 2 Forest plot demonstrating comparison of prophylactic intubation vs no intubation for patien

PI: Pr

Study or Subgroup	Prophylactic Intubation Events	Total	No prophylactic intubatio Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Abdulsamad 2016	97	264	94	1210	80.3%	6.90 [4.97, 9.56]
Hayat 2017	14	100	2	100	3.8%	7.98 [1.76, 36.10]
Koch 2006	9	42	0	20	1.0%	11.63 [0.64, 210.56]
Lohse 2015	0	2101	0	1479		Not estimable
Perisetti 2013	26	69	4	69	6.8%	9.83 [3.20, 30.14]
Rehman 2009	9	49	5	49	6.2%	1.98 [0.61, 6.41]
Tang 2017	7	65	1	45	1.9%	5.31 [0.63, 44.76]
Total (95% CI)		**589**		**1493**	**100.0%**	**6.58 [4.91, 8.81]**
Total events	162		106			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.84$, $df = 5$ ($P = 0.44$); $I^2 = 0\%$

Test for overall effect: $Z = 12.60$ ($P < 0.00001$)

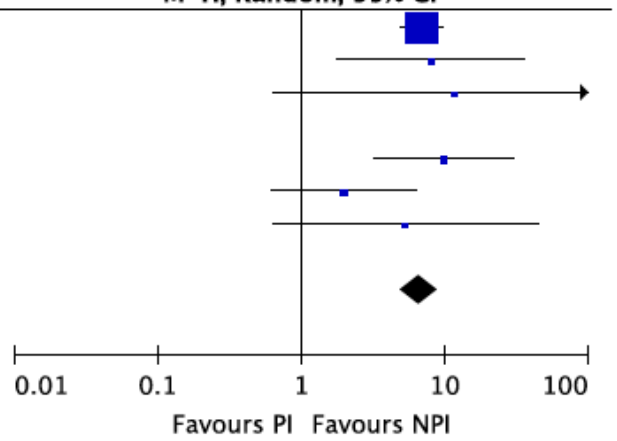


Figure 4 Meta-analysis of rates of pneumonia and prophylactic intubation in upper gastrointestinal bleeding. CI, confidence interval(s); M-H, mantel–Haenszel odds ratio.

Effect of erythromycin before endoscopy in patients with variceal bleeding: a prospective, randomized, double-blind, placebo-controlled trial

TABLE 3. Effects of erythromycin and placebo in the study population

Variables	Erythromycin	Placebo	*P* value
No. of patients	47	43	
Empty stomach, no. (%)	23 (48.9)	10 (23.3)	<.012
Endoscopic score, mean (SD)	12.5 (3.6)	9.8 (4.2)	<.05
Endoscopy duration, min, mean (SD)	19.0 (9.8)	26.0 (13.4)	<.005
Hospital stay, d, mean (SD)	3.4 (2.4)	5.1 (2.9)	<.002
No. of units of blood transfused in 24 h, mean (SD)	3.0 (1.8)	3.6 (2.8)	.64
Transfusion of PRBCs, no. (%) of patients	12 (25.5)	11 (25.6)	.99
Second-look endoscopy, no. (%)	2 (4.3)	4 (9.3)	.33
Aspiration pneumonia, no. (%)	0.0	2 (4.7)	.23
In-hospital mortality, no. (%)	4 (8.5)	6 (13.9)	.41

PRBCs, Packed red blood cells; *SD*, standard deviation.

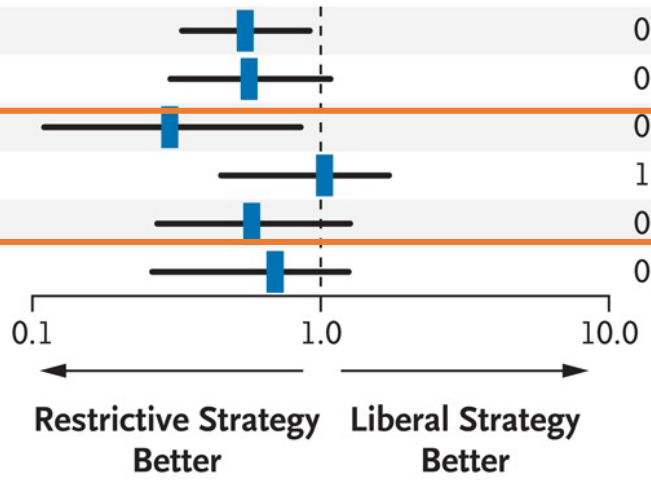
Gastrointest Endosc , 2011 Feb;73(2):245-50

Restrictive *vs* Liberal Transfusion

921 patients with UGI after stabilized were randomized to restrictive transfusion (threshold Hb 7, target 7-9) vs liberal transfusion (threshold Hb 9, target 9-11)

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)	13/109 (12)	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



Villanueva . NEJM 2013 Jan 3;368(1):11-21

Lancet Gastroenterol Hepatol. 2017 May;2(5):354-360

Restrictive *vs* Liberal Transfusion

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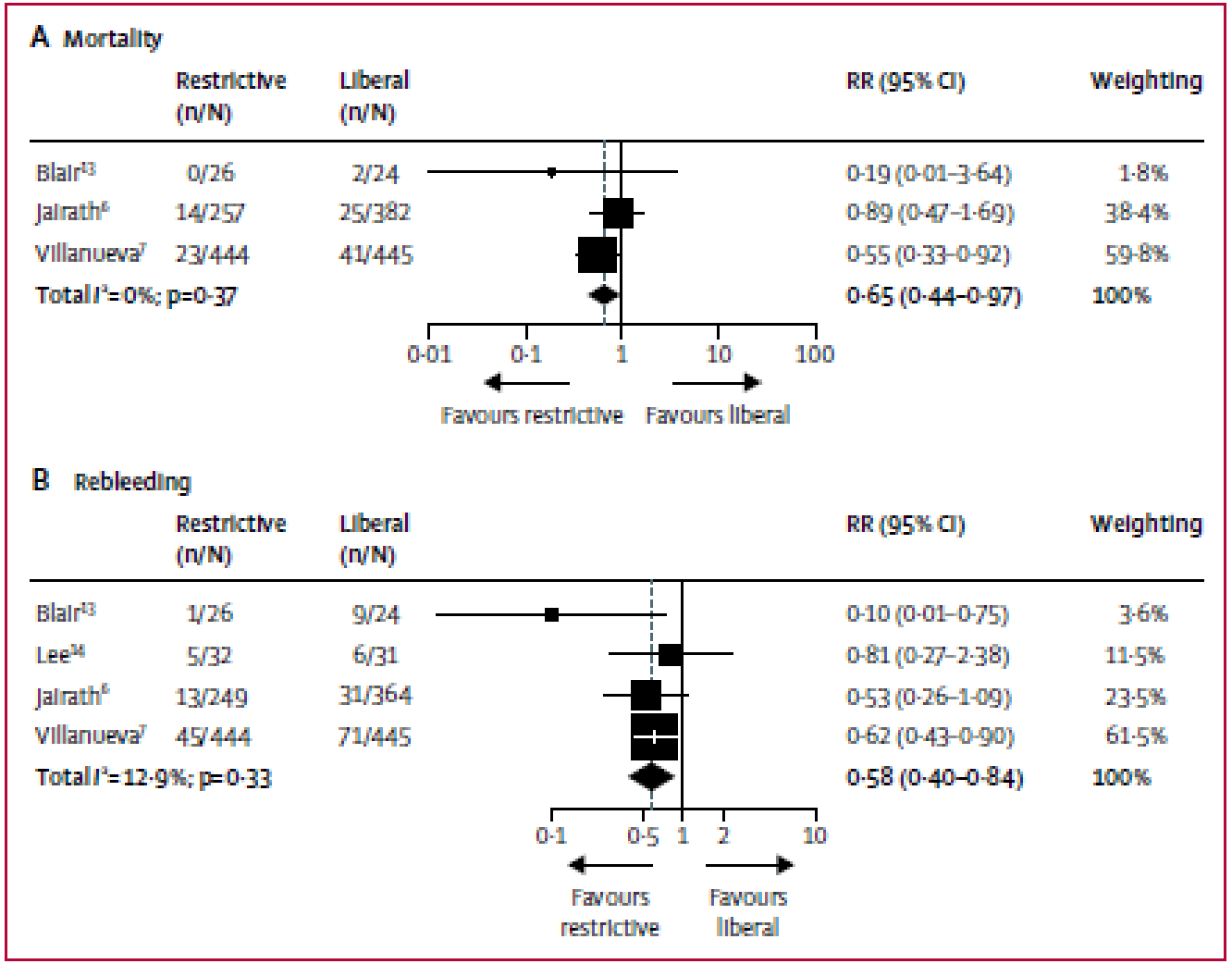
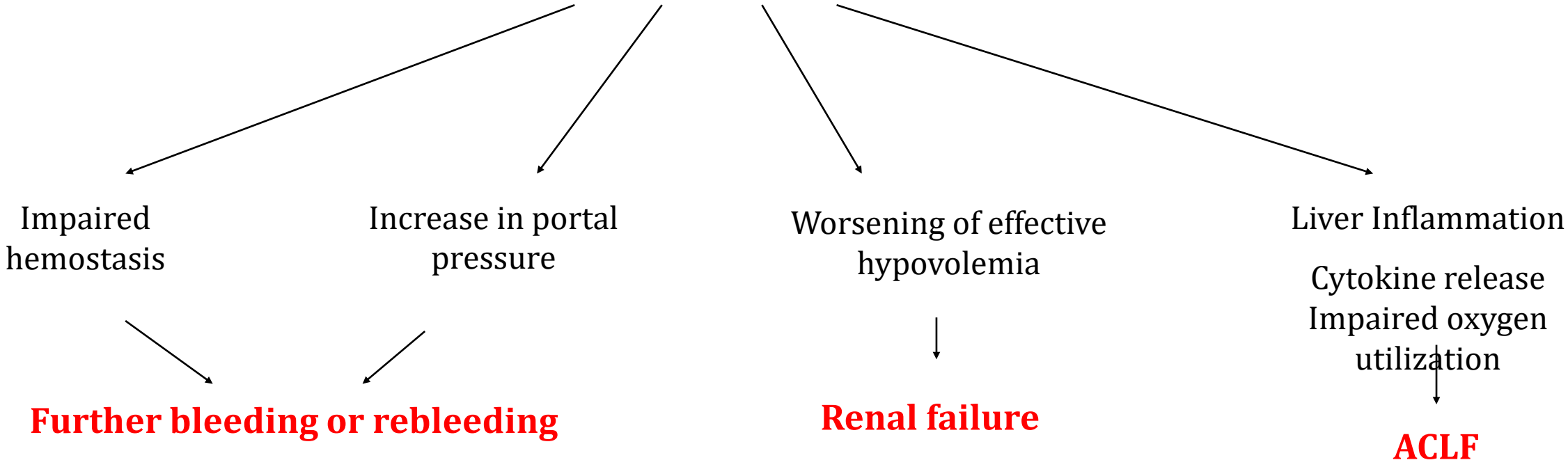


Villanueva . NEJM 2013 Jan 3;368(1):11-21

Lancet Gastroenterol Hepatol. 2017 May;2(5):354-360

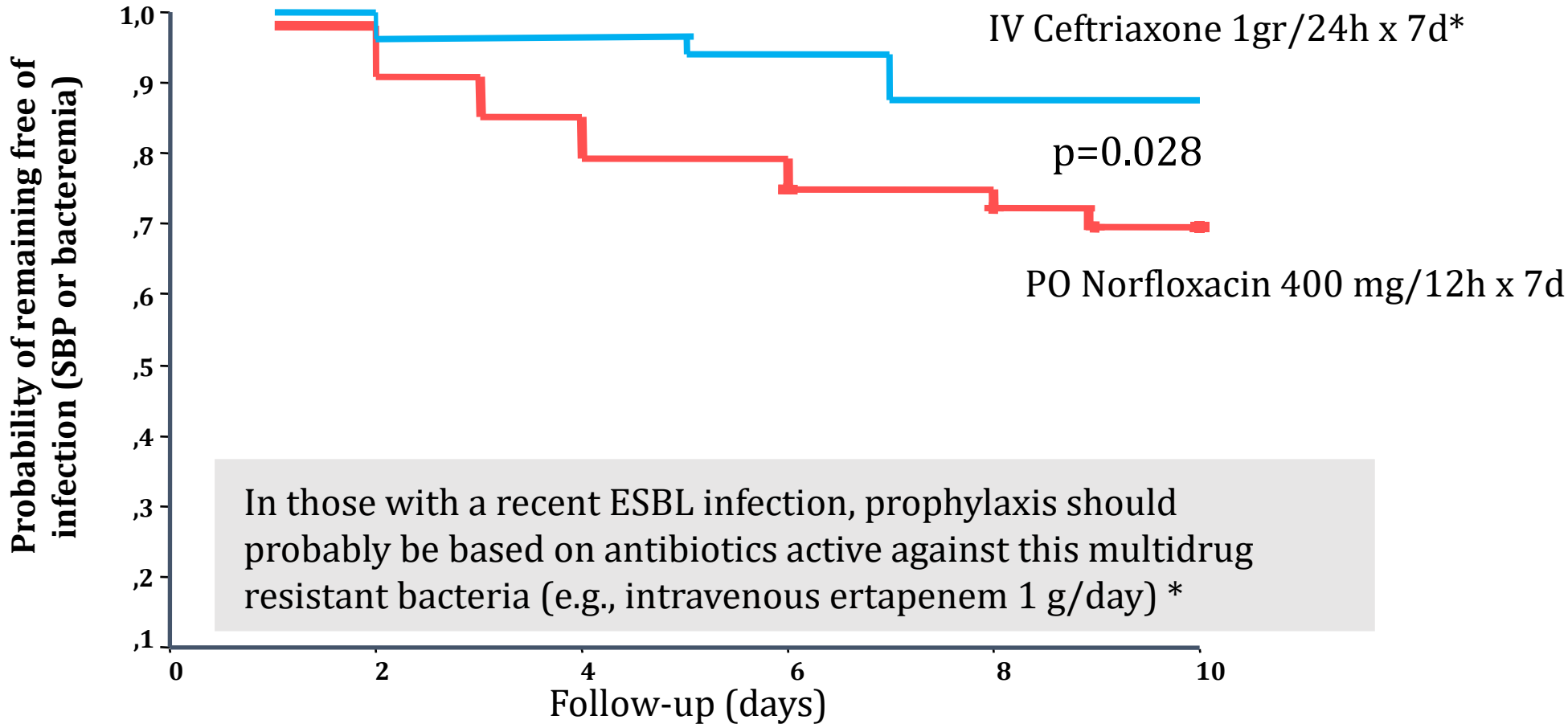
AVB & Infection



Steib, et al. Dig Dis 2015;33(4):570-6

Antibiotic prophylaxis in AVB & advanced cirrhosis

(malnutrition, Bili>3, Ascites, HE, massive bleed)



In those with a recent ESBL infection, prophylaxis should probably be based on antibiotics active against this multidrug resistant bacteria (e.g., intravenous ertapenem 1 g/day) *

Fernández J, Gastroenterology 2006
Fernandez et al. Hepatology 2016; J Hepatol 2018

Bacterial infections in patients with acute variceal bleeding in the era of antibiotic prophylaxis

Journal of Hepatology **2021** vol. 75 | 342–350

Highlights

- Bacterial infections still occur in around one-fifth of patients with cirrhosis and acute variceal bleeding despite antibiotic prophylaxis.
- Respiratory bacterial infections are the most frequent, occurring early after admission.
- Respiratory infections are related to the severity of cirrhosis, presence of severe hepatic encephalopathy and airway manipulation.
- Over 50% of the bacteria isolated in this series were resistant to third-generation cephalosporines.

Bacterial infections in patients with acute variceal bleeding in the era of antibiotic prophylaxis

Journal of Hepatology **2021** vol. 75 | 342–350

Table 3. Multivariate regression analysis of variables associated with development of bacterial and respiratory infection.

	Bacterial infection			Respiratory infection		
Variable	**OR**	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**
Child-Pugh A		Ref.			Ref.	
Child-Pugh B	2.2	1.3–1.7	<0.01			
Child-Pugh C	2.9	1.7–5.0	<0.01	3.1	1.4–6.7	<0.01
Severe (grade III-IV) hepatic encephalopathy	2.3	1.6-3.3	<0.01	2.8	1.8–4.4	<0.01
Nasogastric tube	1.4	1.1–1.8	0.01	1.7	1.2–2.4	<0.01
Orotracheal intubation for endoscopy	2.0	1.5–2.6	0.01	2.6	1.8–3.8	<0.01
Esophageal balloon tamponade				2.4	1.2–4.9	0.02

Conclusion: Bacterial infections develop in almost one-fifth of patients with AVB despite antibiotic prophylaxis. Respiratory infection is the most frequent, is an early event after admission, and is associated with advanced liver failure, severe hepatic encephalopathy and use of nasogastric tube, orotracheal intubation for endoscopy or esophageal balloon tamponade.

Nutrition Risk Assessment Using the Modified NUTRIC Score in Cirrhotic Patients with Acute Gastroesophageal Variceal Bleeding: Prevalence of High Nutrition Risk and its Independent Prognostic Value

Ming-Hung Tsai [1], Hui-Chun Huang [2,3,*], Yun-Shing Peng [4], Yung-Chang Chen [5], Ya-Chung Tian [5], Chih-Wei Yang [5], Jau-Min Lien [1], Ji-Tseng Fang [5], Ming-Chih Hou [2], Chien-Heng Shen [6], Chung-Chi Huang [7], Cheng-Shyong Wu [6] and Fa-Yauh Lee [2,*]

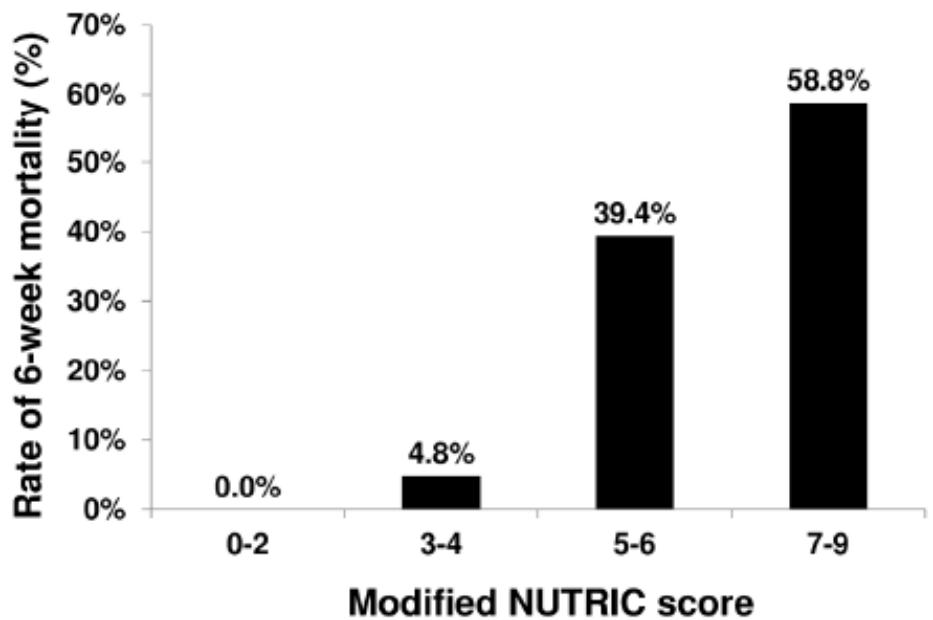
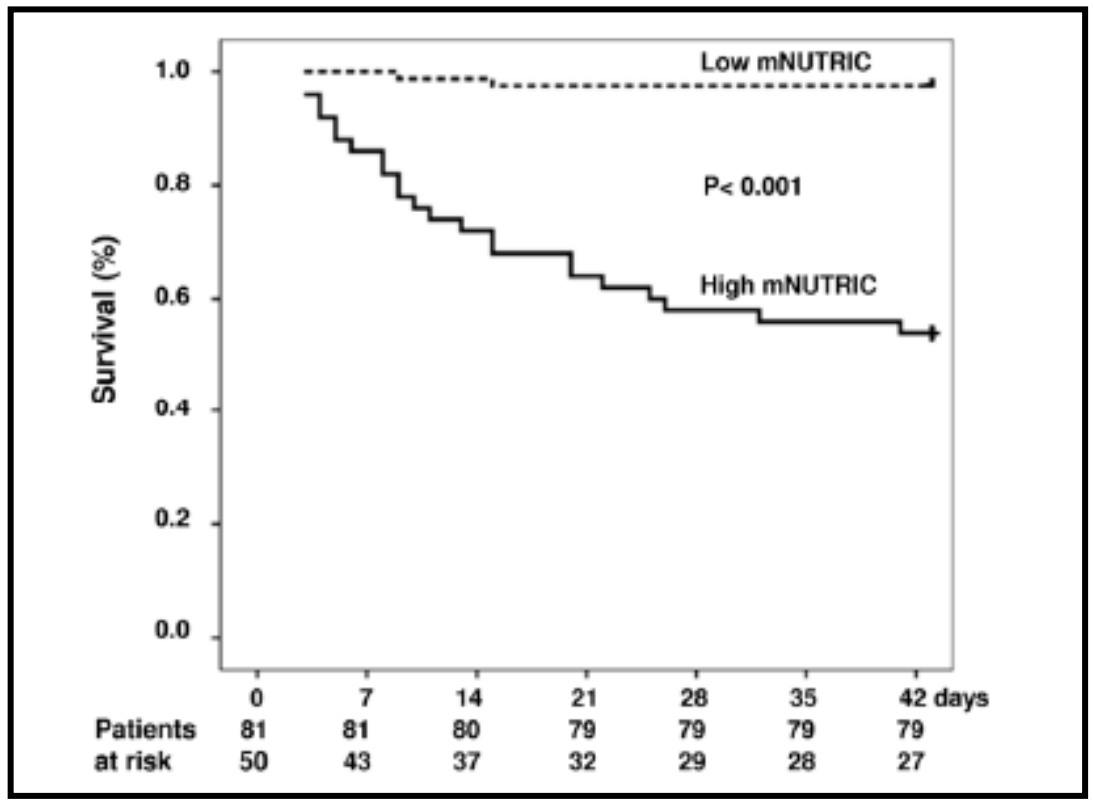


Figure 2. Relationship between 6-week mortality and mNUTRIC score (χ^2 for trend, $p < 0.001$).



Vasoactive Drug Therapy

- In suspected variceal bleeding, vasoactive drugs should be started as soon as possible, before endoscopy.

- Vasoactive drugs (terlipressin, somatostatin, octreotide, vapreotide) should be used in combination with endoscopic therapy and continued for up to 5 days.

AASLD Guidelines, Hepatology 2016
Baveno V. J Hepatol 2015

Vasoactive drugs - ASAP before endoscopy

Drug	Dose		Side effects
Terlipressin	2 mg/4 h for 24–48 h then 1 mg/4 h for up to 5 days	Controls bleeding in 80-90% Decreases mortality	abdominal pain diarrhea Ischemic side effects Hyponatremia
Somatostatin	250 mcg bolus followed by infusion of 250–500 mcg/h	Controls bleeding - 80-90%	nausea, vomiting hyperglycemia tachyphylaxis
Octreotide	50-100 mcg bolus followed by infusion of 50 mcg/h	Control bleeding in 80-90%	tachyphylaxis

EASL Guidellines. J Hepatol 2018

Prospective, multicenter, randomized, noninferiority trial – Terlipressin, Somatostatin,and Octreotide in AVB

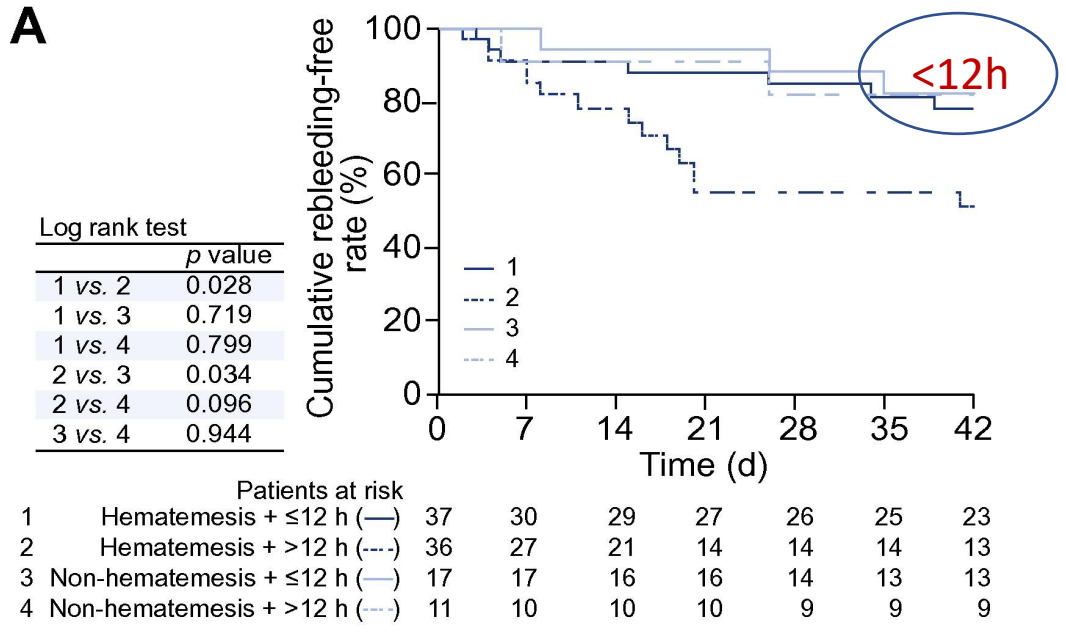
n= 780 patients (all with EBL)- randomized to 3 groups

Treatment Response	All Patients (n = 780)	Terlipressin Group (n = 261)	Somatostatin Group (n = 259)	Octreotide Group (n =2 60)	*P* Value
Control of index bleeding without rescue therapy, n (%)	690 (88.5)	234 (89.7)	227 (87.6)	229 (88.1)	0.752
Time interval from T0 to bleeding control, hours	9.8 ± 10.3	9.6 ± 10.7	10.1 ± 10.1	9.7 ± 10.2	0.839
Time interval from commencement of vasoactive drug to bleeding control, hours	8.0 ± 10.3	7.8 ± 10.6	8.2 ± 10.1	8.1 ± 10.3	0.899
Patients with rebleeding, n (%)*	29 (4.2)	8 (3.4)	11 (4.8)	10 (4.4)	0.739
Time interval from T0 to rebleeding, hours†	66.8 ± 23.6	70.0 ± 27.5	69.0 ± 19.6	61.9 ± 26.0	0.730
Time interval from bleeding control to rebleeding, hours†	62.1 ± 24.4	64.7 ± 26.4	64.2 ± 22.4	57.9 ± 26.8	0.801
Mortality, n (%)	67 (8.6)	21 (8.0)	23 (8.9)	23 (8.8)	0.929
Cause of mortality					0.920
Uncontrolled index bleeding, n (%)***	60 (89.6)	19 (90.5)	20 (87.0)	21 (91.3)	
Uncontrolled rebleeding, n (%)‡	2 (3.0)	1 (4.8)	1 (4.3)	0 (0)	
Liver failure, n (%)‡	3 (4.5)	1 (4.8)	1 (4.3)	1 (4.3)	
Infection, n (%)‡	2 (3.0)	0 (0)	1 (4.3)	1 (4.3)	
5-day treatment success, n (%)	659 (84.5)	225 (86.2)	216 (83.4)	218 (83.8)	0.636

Seo, et al Hepatology 2014;60:954-963

6-week re-bleeding and survival stratified by hematemesis and door-to-endoscopy time (hrs).

6-week re-bleeding

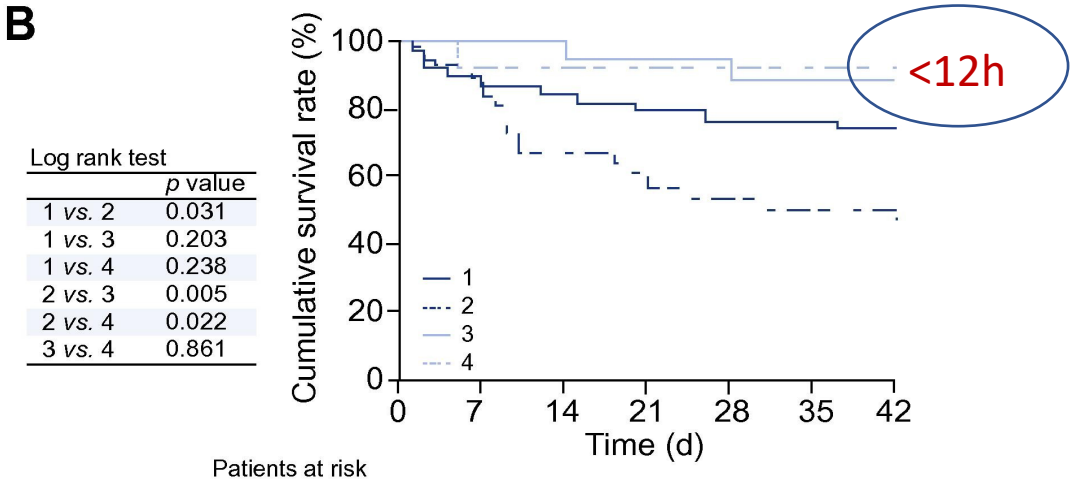


Log rank test	*p* value
1 *vs.* 2	0.028
1 *vs.* 3	0.719
1 *vs.* 4	0.799
2 *vs.* 3	0.034
2 *vs.* 4	0.096
3 *vs.* 4	0.944

Patients at risk

1	Hematemesis + ≤12 h (—)	37	30	29	27	26	25	23
2	Hematemesis + >12 h (- - -)	36	27	21	14	14	14	13
3	Non-hematemesis + ≤12 h (—)	17	17	16	16	14	13	13
4	Non-hematemesis + >12 h (- - -)	11	10	10	10	9	9	9

6-week survival



Log rank test	*p* value
1 *vs.* 2	0.031
1 *vs.* 3	0.203
1 *vs.* 4	0.238
2 *vs.* 3	0.005
2 *vs.* 4	0.022
3 *vs.* 4	0.861

Patients at risk

1	Hematemesis + ≤12 h (—)	37	32	31	29	28	28	27
2	Hematemesis + >12 h (- - -)	36	30	24	20	19	18	16
3	Non-hematemesis + ≤12 h (—)	17	17	16	16	15	15	15
4	Non-hematemesis + >12 h (- - -)	11	10	10	10	10	10	10

Chen P. et al J Hepatol 2012 Dec;57(6):1207-13

6-week re-bleeding and survival stratified by hematemesis and door-to-endoscopy time (hrs).

6-week survval

Timing of Endoscopy for Acute Upper Gastrointestinal Bleeding
Lau JW et al N Engl J Med 2020; 382:1299-1308

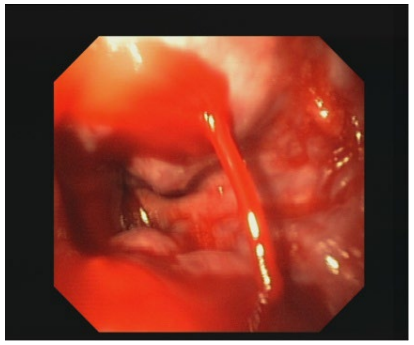
- *Endoscopy should be performed between 6 and 24 hours*
- *516 patients (only 10% with esophageal or gastric varices)*
- *< 6 hours was not associated with lower 30-day mortality*
- *Emphasises the importance of adequate resuscitation and medical optimisation before endoscopy*

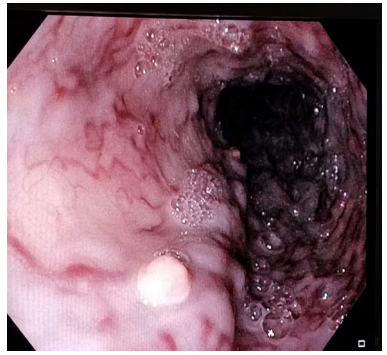
Chen P. et al J Hepatol 2012 Dec;57(6):1207-13

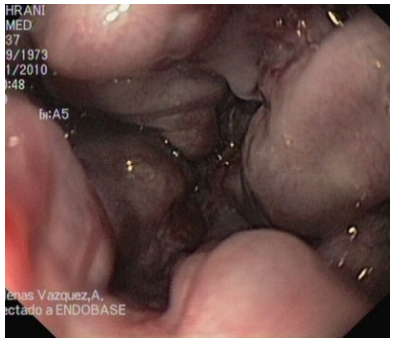
Endoscopy

Diagnosis and therapy

- When?
  - At least within the first 12 hours of admission.
  - Actively vomiting blood / unstable ?
    - *As soon as safely possible*
  - EBL preferred over sclerotherapy
- Diagnosis ?
  - Active blood spurting or oozing from a varix
  - White nipple or clot adherent to a varix
  - Varices without other potential sources of bleeding

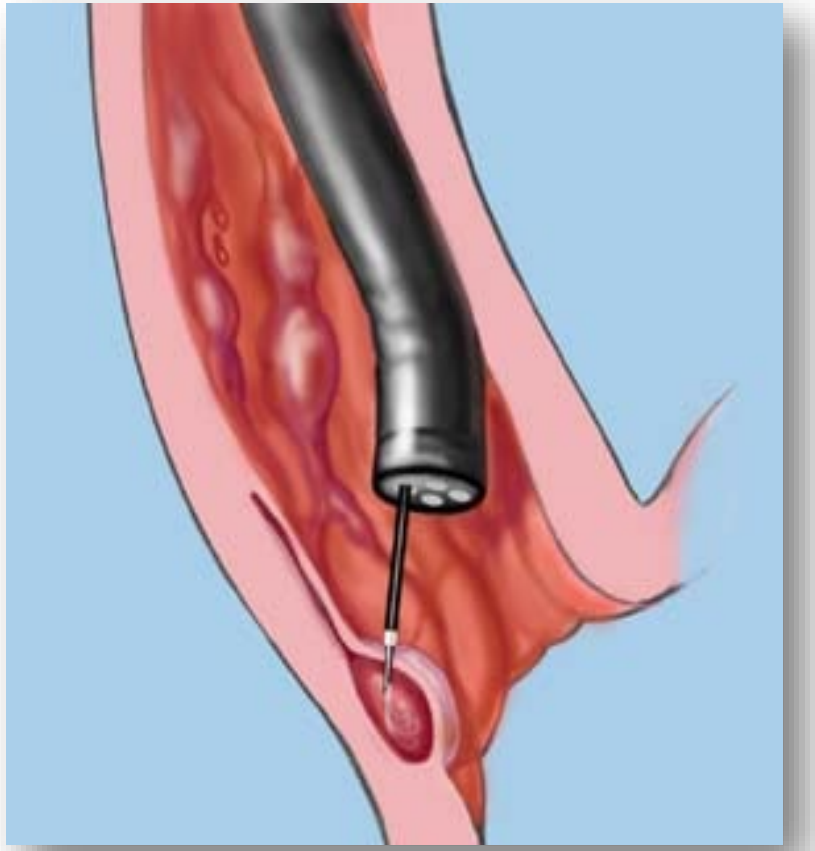




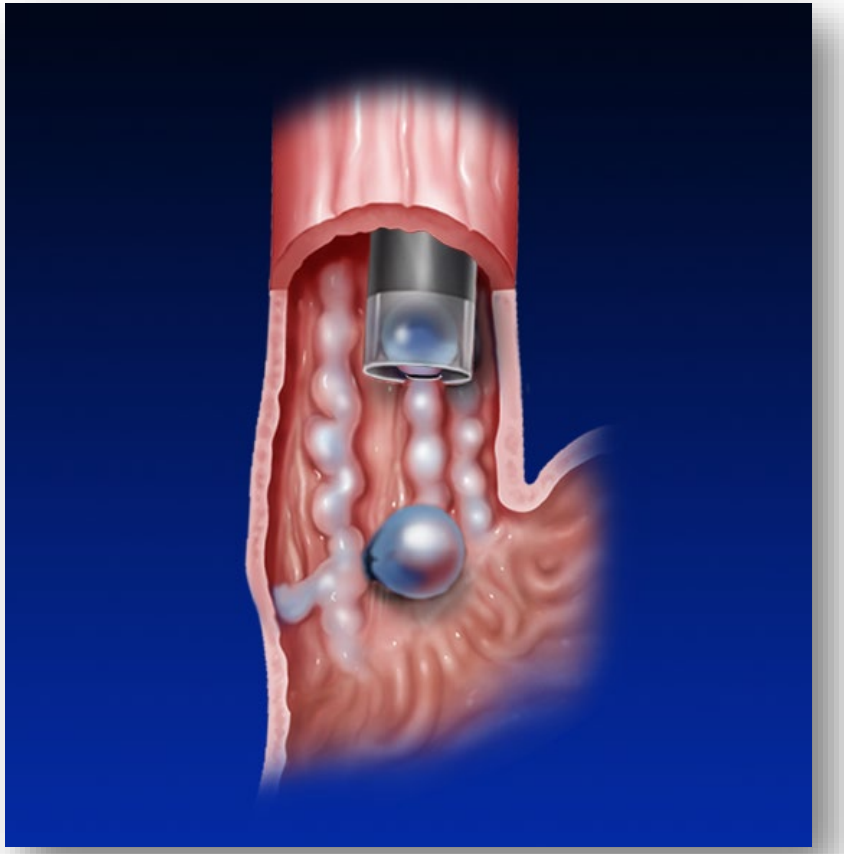


Chen, et al J Hepatol 2012 Dec;57(6):1207-13.
Cardenas Clin Liv Dis 2014
Garcia-Tsao, et al, AASLD Guidance 2017
Endosc Int Open. 2019 Nov;7(11):E1503-E1514
Baveno VII

Endoscopic therapy



Sclerotherapy



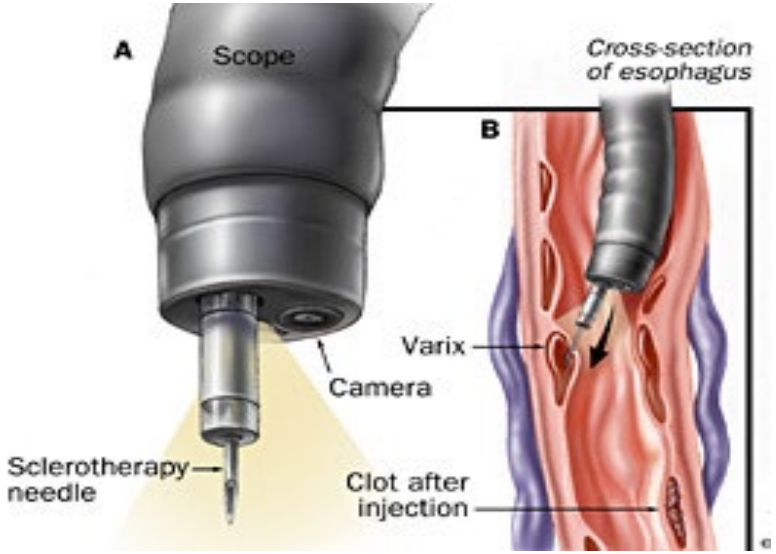
Endoscopic band ligation

Sclerotherapy

- Injection of sclerosant into variceal lumen
- Thrombosis / inflammation of mucosa → scar
- 1st injection (1-2ml) at bleeding site, then target other varices
- Up to 10-15ml
- Effective in 80%

Sclerosants

- Europe - Ethanolamine oleate (5%) or polidocanol (1-2%)
- USA- sodium morrhuate (5%)



Sclerotherapy

Pros

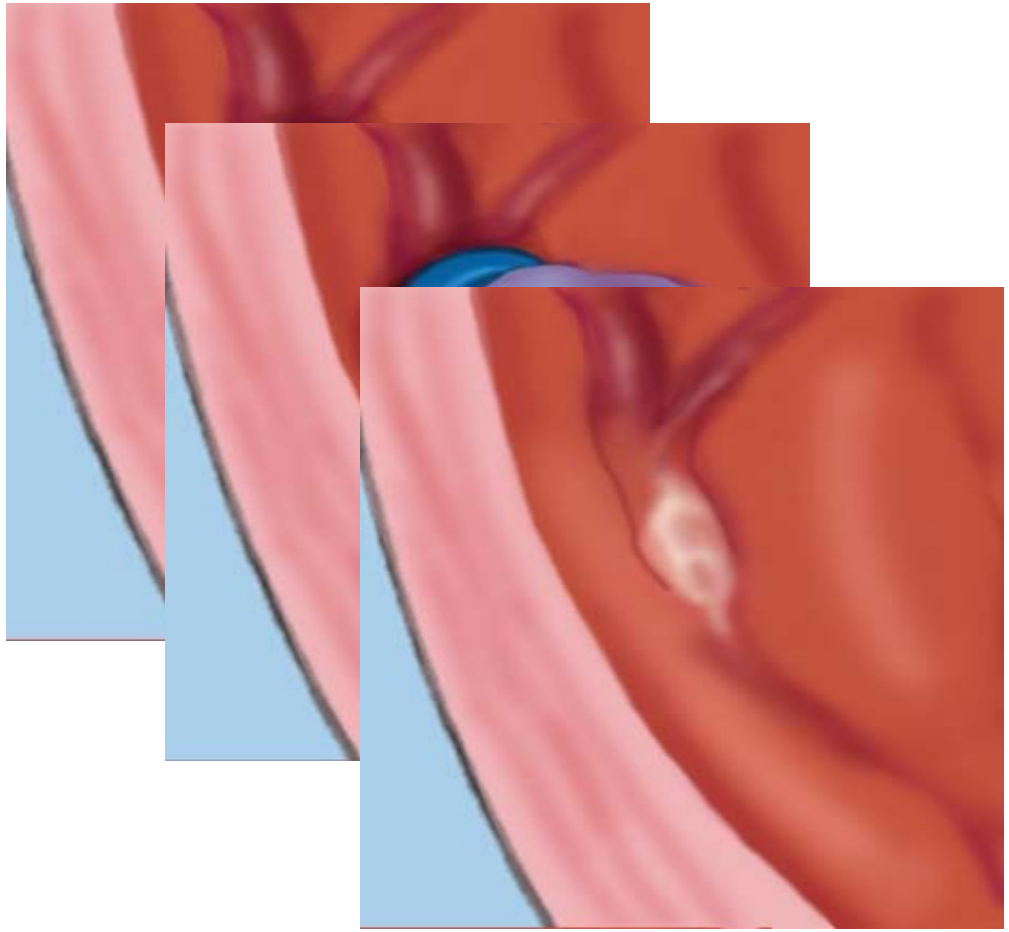
- Easy to use
- Cheap
- Catheter is quickly assembled
- No 2nd second oral intubation
- Rapid formation of a thrombus

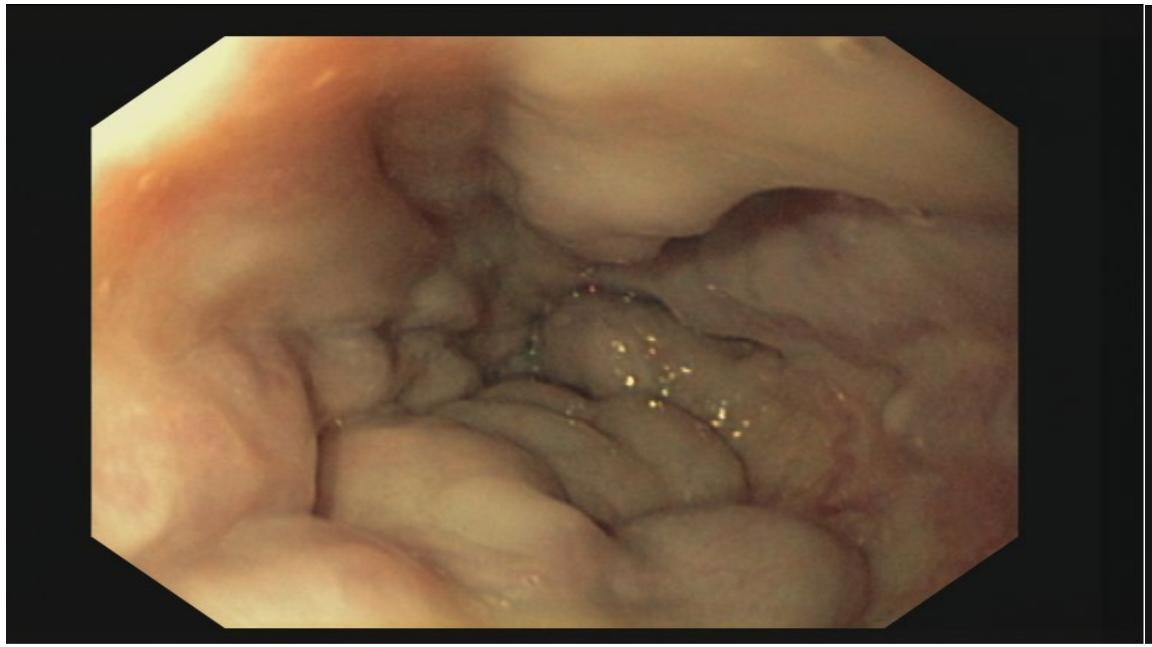
Cons

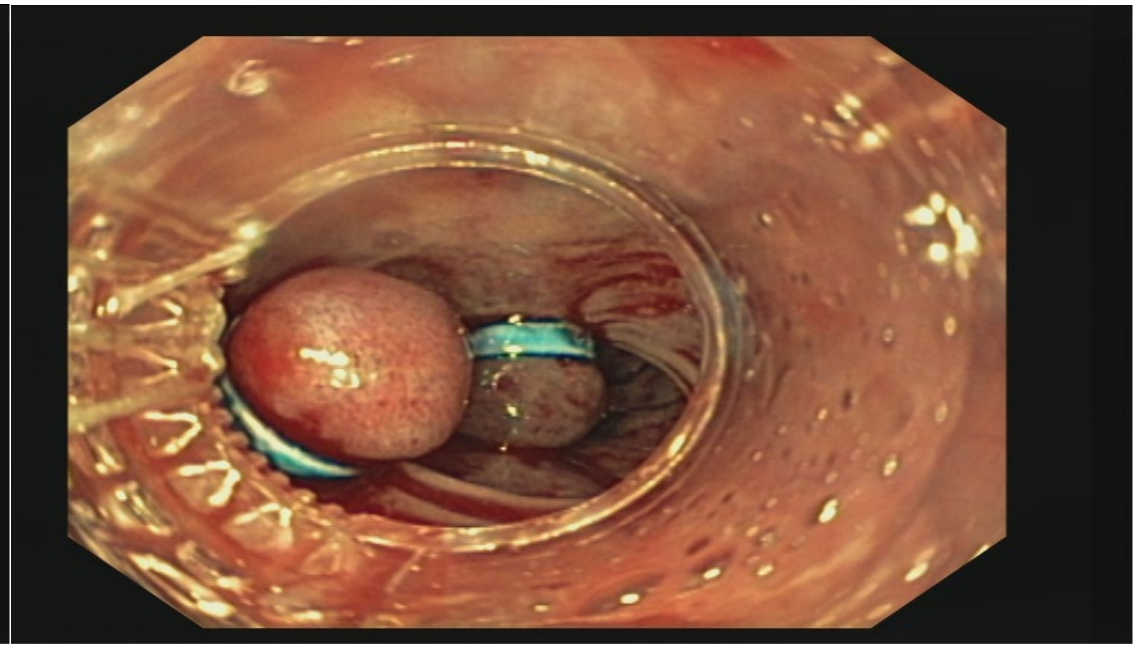
- Ulcers, substernal chest pain, fever, dysphagia,
- Bacteremia , SBP, esophageal strictures, perforations
- Mediastinitis, pericarditis, effusions

Endoscopic band ligation

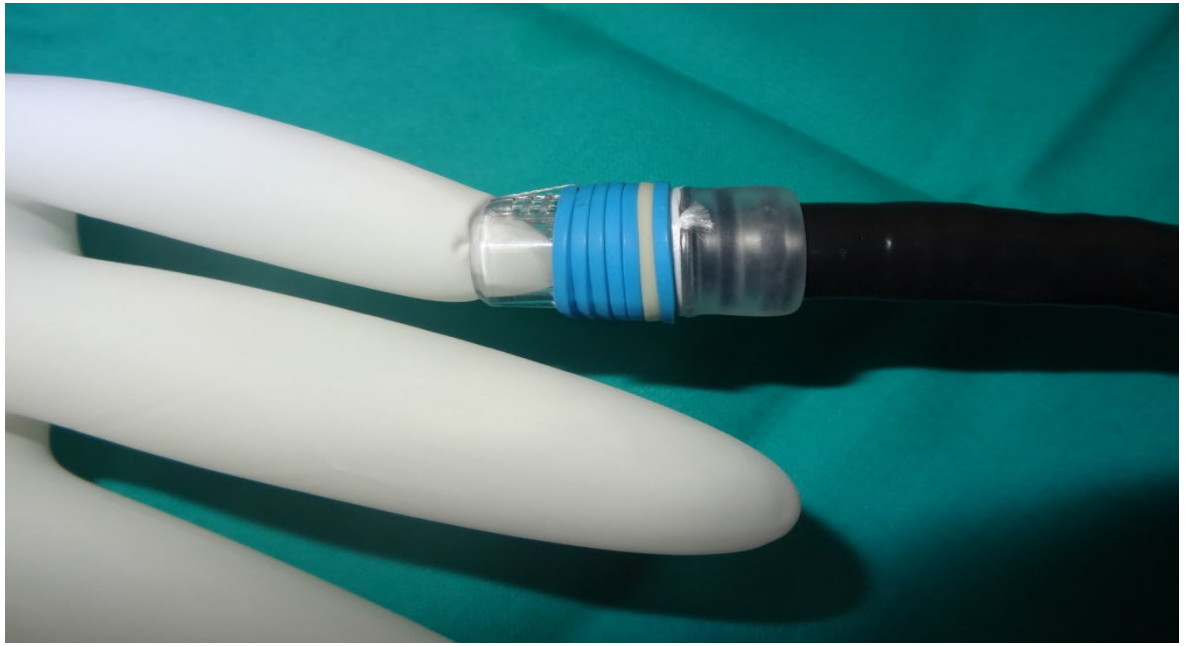
- Placement of elastic bands on the varices – occludes the varix and causes thrombosis
- Leads to necrosis of the mucosa and the bands eventually fall off in a few days leaving a superficial mucosal ulceration that heals and eventually scars

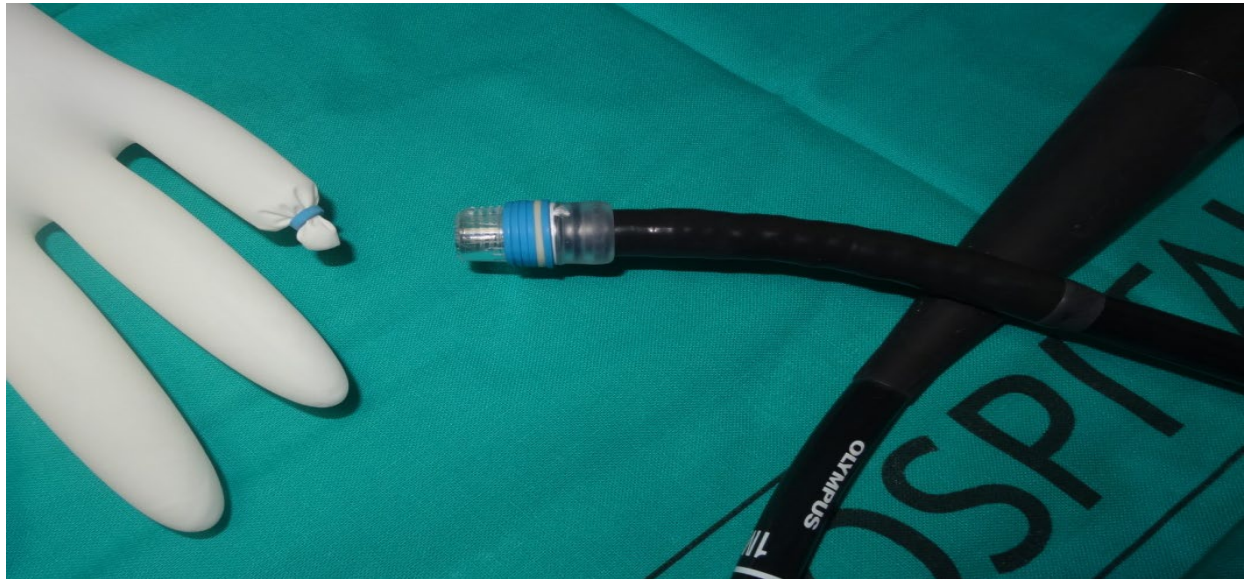


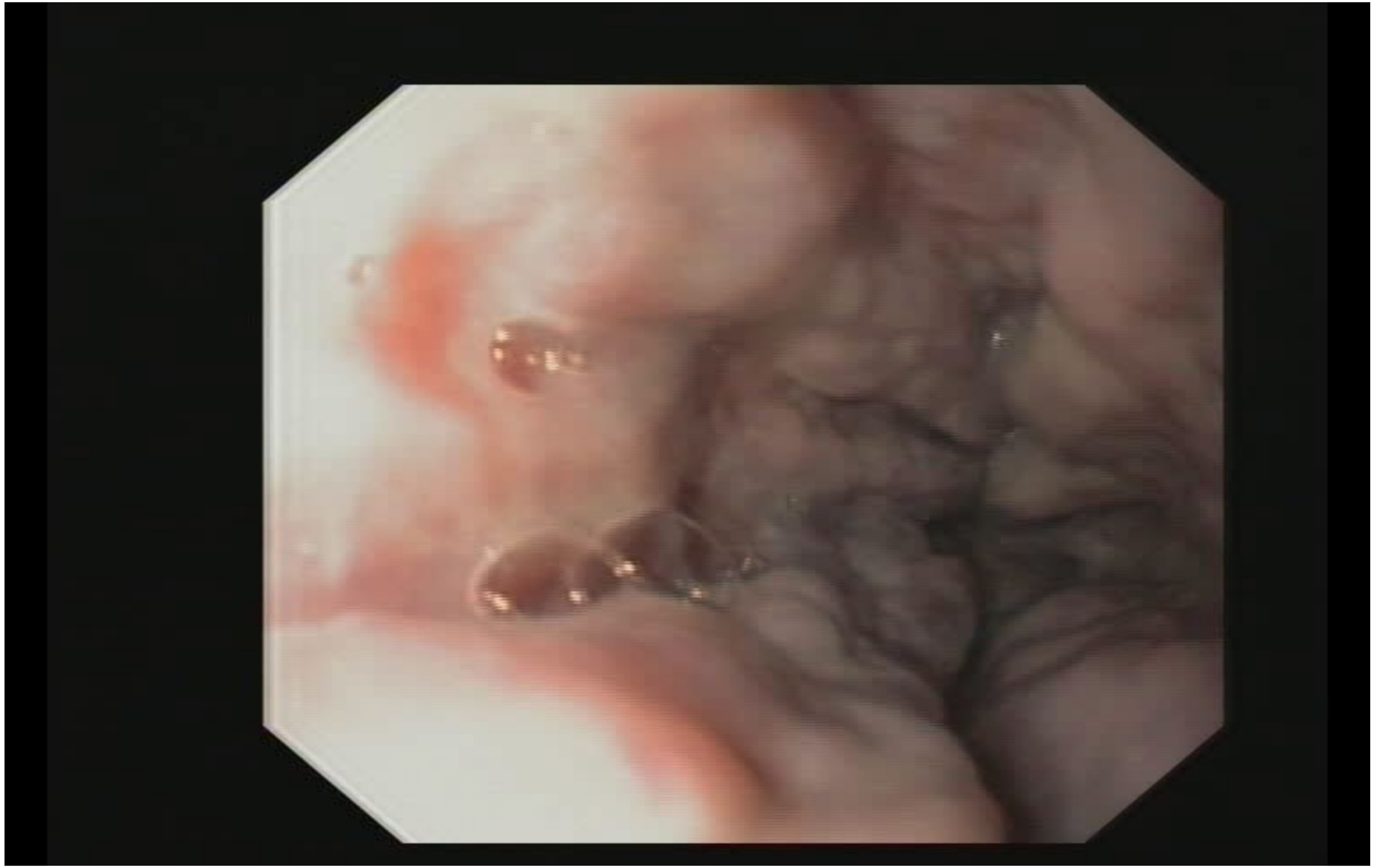





SEVEN
SUPER
7




OLYMPUS



Endoscopic Variceal Band Ligation

- The tip is pointed towards varix and continuous suction applied so it can fill the cap.
- Wait for “red out” sign and fire band.
- Start at most distal portion near the GE junction.
- Apply in spiral pattern progressing up to mid esophagus

- <u>Complications –</u>
- Transient dysphagia / chest pain, ulcers, bleeding (3-7%)
- Compared with sclerotherapy:
  - *Less rebleeding*
  - *Lower mortality*
  - *Fewer complications*
  - *Fewer treatment sessions*

Cardenas A. Clin Liv Dis. 2014

Endoscopic ligation plus pharmacological therapy is better & safer than endoscopic sclerotherapy in acute variceal bleeding

Rx FAILURE	SMT + ES (n=89)	SMT + EBL (n=90)
Overall	21 (24%)	9 (10%)
Child A/B	14/68 (21%)	3/66 (4%)
Child C	7/21 (33%)	6/24 (25%)
Active bleeding	5/21 (24%)	3/17 (18%)
Shock	12/26 (46%)	6/32 (19%)
COMPLICATIONS		
Overall	25 (28%)	13 (14%)
Major side effects	12 (13%)	4 (4%)

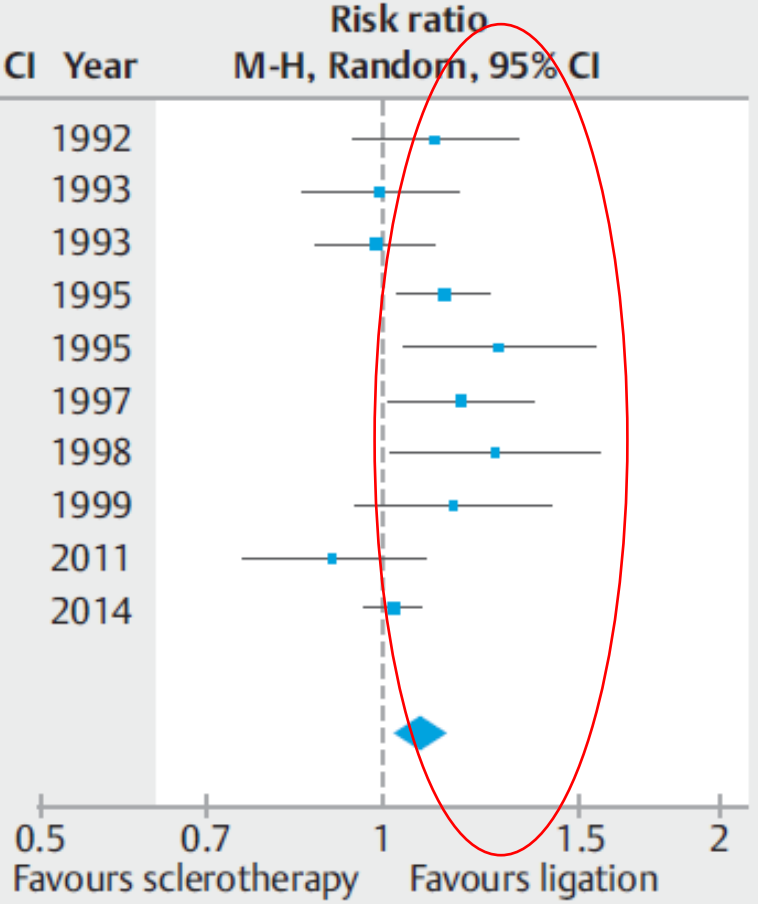
Villanueva J Hepatol 2006;45:560-67

Endoscopic therapy AVB - Meta-analysis of ligation vs sclerotherapy

Study or subgroup	Ligation Events	Ligation Total	Sclerotherapy Events	Sclerotherapy Total	Weight	Risk ratio M-H, Random, 95% CI	Year
Stiegmann 1992	55	64	50	65	8.4 %	1.12 [0.95, 1.32]	1992
Gimson 1993	34	38	35	39	9.3 %	1.00 [0.86, 1.16]	1993
Laine 1993	49	54	45	49	12.1 %	0.99 [0.88, 1.11]	1993
Lo 1995	67	67	59	67	15.0 %	1.13 [1.03, 1.24]	1995
Hou 1995	36	37	26	34	6.8 %	1.27 [1.05, 1.54]	1995
Lo 1997	57	61	47	59	9.8 %	1.17 [1.01, 1.36]	1997
Shafqat 1998	27	28	23	30	6.0 %	1.26 [1.02, 1.55]	1998
de la Peña 1999	37	42	35	46	6.7 %	1.16 [0.95, 1.41]	1999
Luz 2011	39	50	43	50	7.2 %	0.91 [0.75, 1.09]	2011
Sahu 2014	107	111	97	103	18.7 %	1.02 [0.96, 1.09]	2014
Total (95 % CI)		**552**		**542**	**100.0 %**	**1.08 [1.02, 1.15]**	
Total events	508		460				

Heterogeneity $Tau^2 = 0.00$, $Chi^2 = 17.59$, $df = 9$ ($P = 0.04$); $I^2 = 49$ %

Test for overall effect: $Z = 2.59$ ($P = 0.010$)



Endosc Int Open. 2019 Nov;7(11):E1503-E1514

Post-EVL ulcer bleed and predictors

First author (year)	N with EVL	N with bleeding	Time from EVL (days)	Deaths	Clinical predictors of bleeding
Yang (2007)	96	19 (20%)	Within 14		Child C, bacterial infection
Da Rocha (2009)	150	11 (7.4 %)	9.4	-	Child C
Vanbiervliet (2010)	605	21 (3.4%)	13.5	11/21 (52%)	APRI score Prothrombin index*
Xu (2011)	342	26 (7.6)	8.0	7/26 (27%)	Ascites, Prothrombin time**
Sinclair (2015)	347	21(2.8%)	.	5(28%)	Reflux MELD
Blasi /Cardenas (2018)	1472	33(2.2%)	10-14	-	MELD

Key points I

- Be gentle with intubation!
- During an acute episode there may be a limited view –
  - *Try continous flushing & apply suction*.
- A band should be fired at the actively bleeding site if seen
- Torrential bleeding- can´t see ?
  - *Start EBL at GE junction and then move upwards*.
- How many bands ?
  - *Up to 10 but more than 6-7 bands per session does not improve patient outcome, prolongs procedure time and increases the misfire rate*

Ramirez FC, Am J Gastroenterol. 2007 Jul;102(77):1372-6
Cardenas et al Clin Liv Dis 2014

Key points II

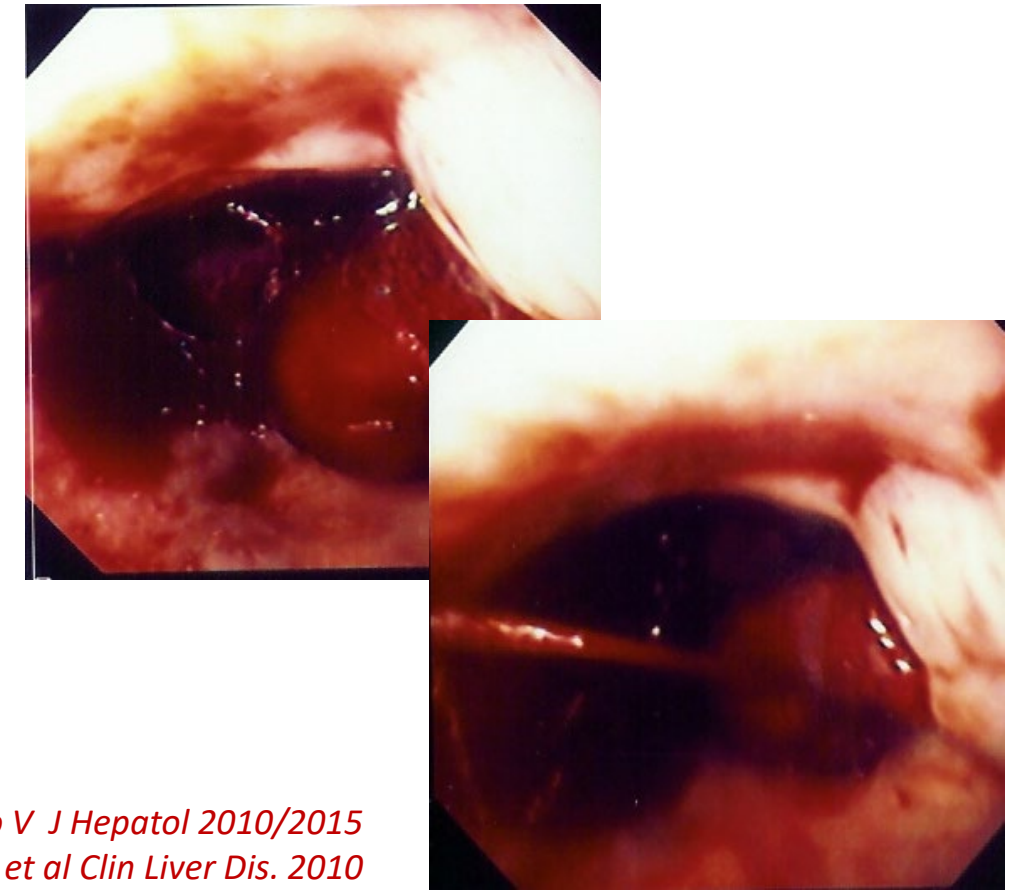
- Try to place 5-7 bands
- Administer analgesia immediately after EGD - tylenol
- Always !! make sure to re-schedule in 2-3 weeks
- Erradication requires between 3-4 sessions
- Pantoprozole 40 mg / day (reduces ulcer size, not bleeding)
  - *Only use during banding period*
- After erradication- follow up in 3 months!!
- Then 6 months , then 1 year

Cardenas, Clin Liv Dis 2014

Refractory bleeding

The time frame for AVB is 5 days

- In 10-15 % of cases, patients are not controlled with therapy
- There are two types:
  - Patients bleed profusely despite EBL
  - Fresh hematemesis >2 hr after therapy, hypovolemic shock, or 3 g drop in Hb
- Left untreated mortality rates > 50%
- Several approaches
  - *Repeat EGD*
  - *Tamponade (balloon or stent)*
  - *TIPS*

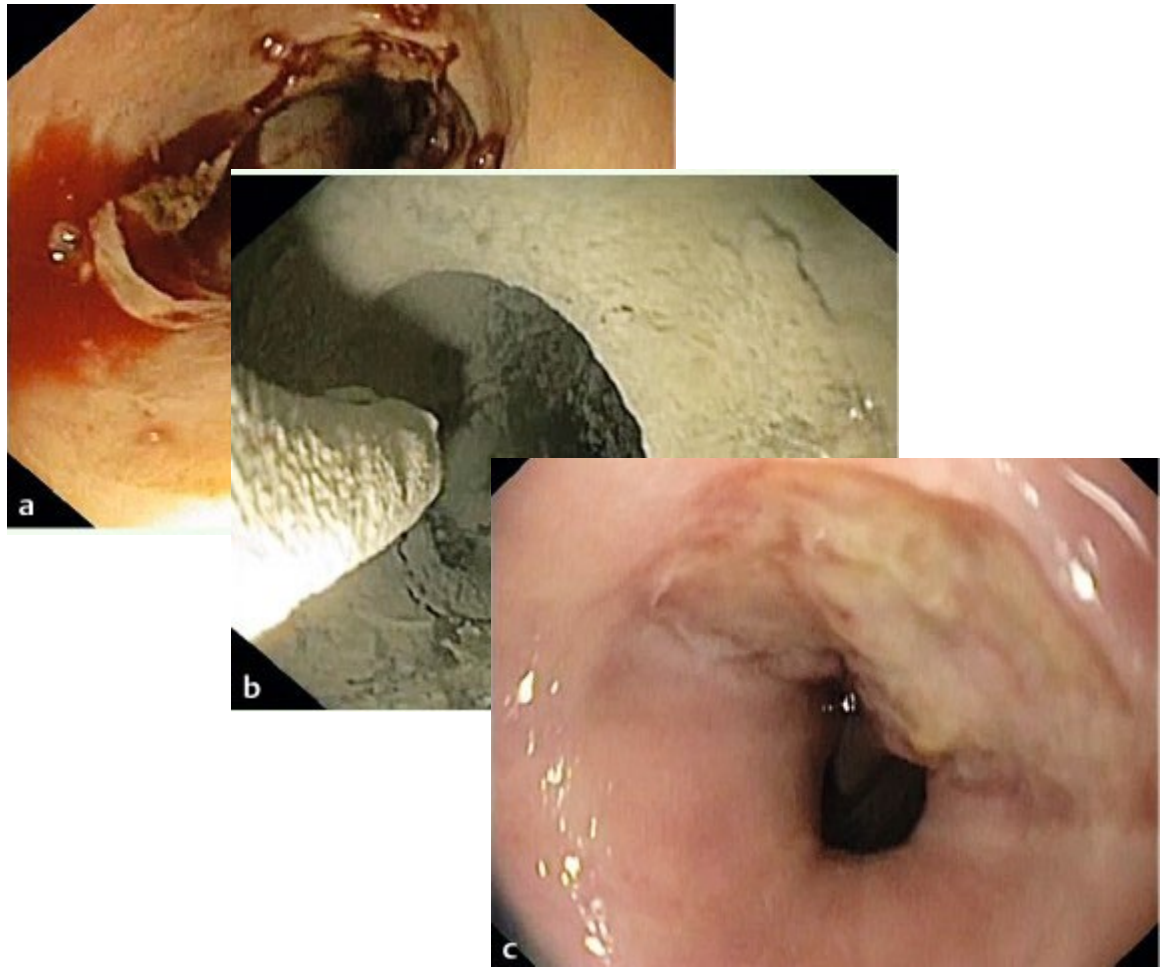


Baveno V J Hepatol 2010/2015
D'Amico M , et al Clin Liver Dis. 2010
Ibrahim. Gastroenterology. 2018

Hemostatic powder

Acute bleeding and/or post EBL ulcers

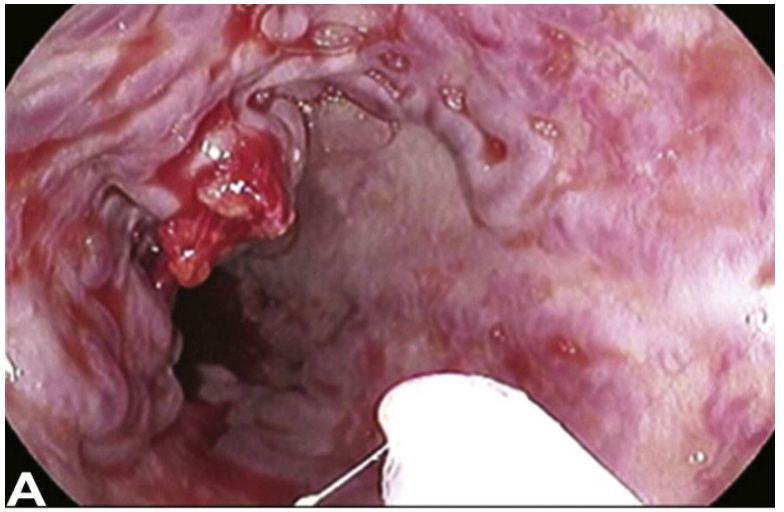
- Hemostatic powder *(Hemospray)*
  - Easy to apply , forms cohesive barrier, non-contact method,
- No controlled studies
- Has been used for AVB and recurrent AVB
  - *Scarce data, but promising in recurrent bleeding*
- Follow-up requires EBL or TIPS



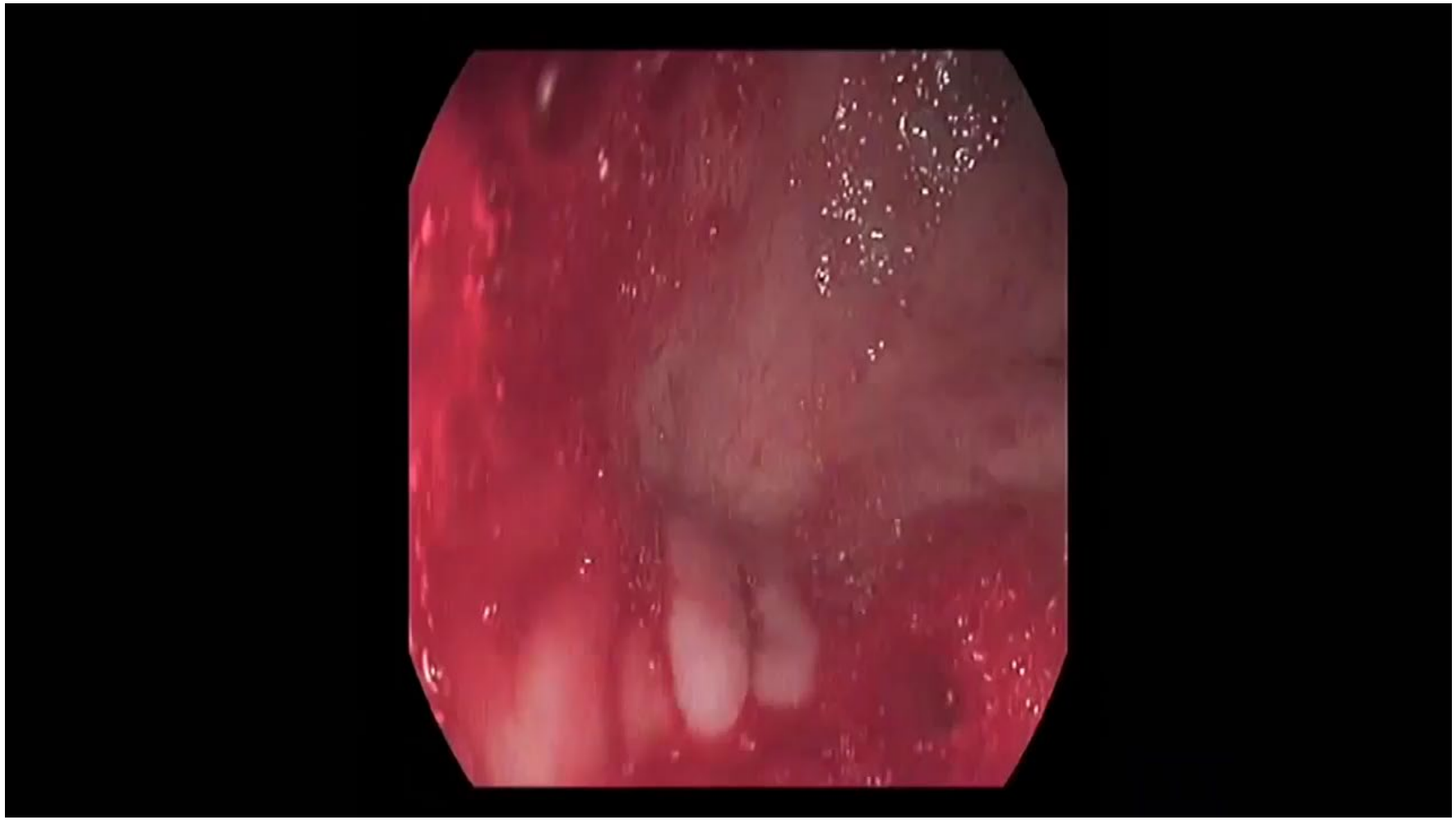
Endoscopy 2014;46 Suppl 1
Clin Exp Hepatol. 2018 Mar;4(1):46-48

Hemospray for post EBL ulcers

- Hemostatic powder
  - Easy to apply , forms cohesive barrier, non-contact method,
- No controlled studies
- Case reports
- Successfully stopped bleeding in all after 1 attempt
- Follow-up requires EBL or TIPS



Endoscopy 2014;46 Suppl 1
Clin Exp Hepatol. 2018 Mar;4(1):46-48



ORIGINAL ARTICLE

Early application of haemostatic powder added to standard management for oesophagogastric variceal bleeding: a randomised trial

- 86 patients
  - 43 hemospray (immediate within 2hr- followed by EGD at 12-24 hr)
  - 43 control (EBL at 12-24 hrs)
- Major limitations
  - No TIPS performed.
  - Control group
    - No EGD for > 12 hrs
    - 13 patients (30%) bled waiting

Table 2 Summary of efficacy measurements

Variable	Study group (n=43)	Control group (n=43)	P values
Composite endpoint (clinical haemostasis+endoscopic haemostasis*), no. (%)†	38/43 (88) (95% CI 87.52 to 88.48)	27/43 (63) (95% CI 61.94 to 64.06)	0.0057
Clinical haemostasis, no. (%)	38 (88) (95% CI 87.52 to 88.48)	30 (70) (95% CI 69.04 to 70.96)	0.034
Haemostasis after Hemospray application at 2 hours endoscopy, no. (%)	39 (91) (95% CI 90.63 to 91.37)	NA	NA
Endoscopic haemostasis at 12 hours endoscopy*, no. (%)†	38/38 (100)	27/30 (90) (95% CI 89.41 to 90.59)	0.0466
Treatment failure at 5 days, no. (%)‡	5 (12) (95% CI 11.52 to 12.48)	16 (38) (95% CI 36.93 to 39.07)	0.006

Ibrahim, et al Gut 2018

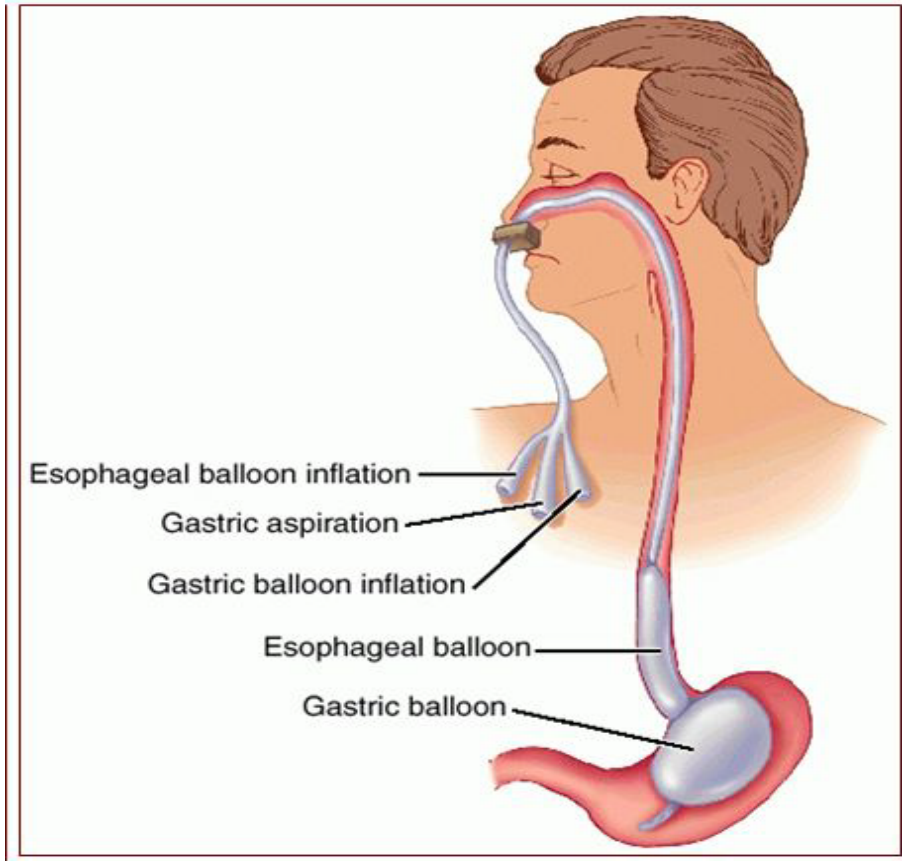
Not recommended as first line therapy. BAVENO VII

Rescue therapies: Tamponade

- 10-15% fail initial hemostasis
- Widely available
- Cheap

- Severe bleed → Balloon tamponade as bridge

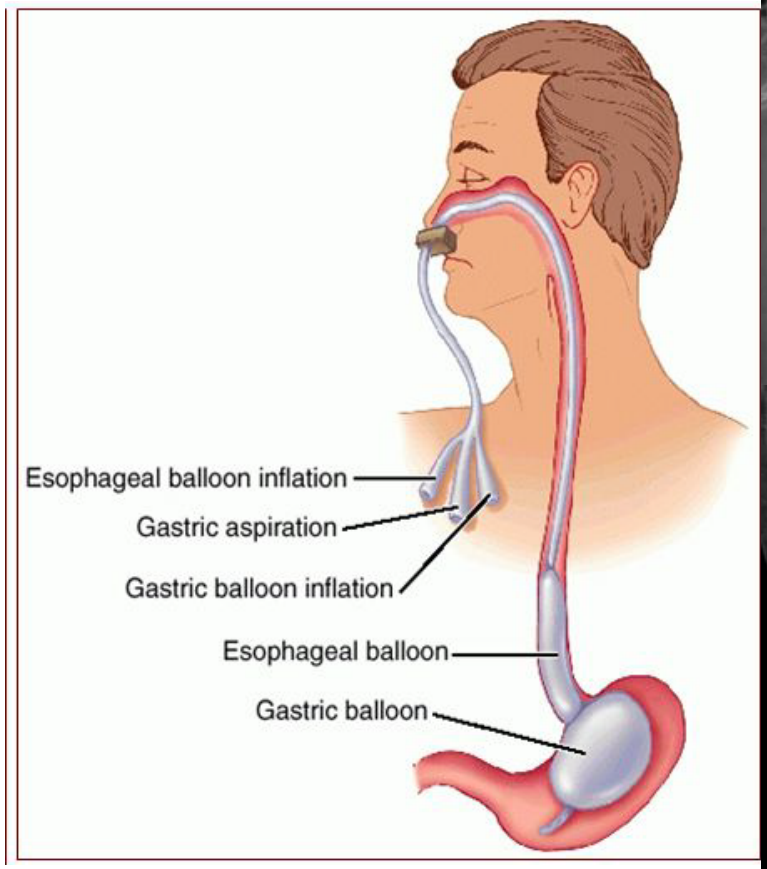
  - Severe side effects 30-50%
  - Mortality 10-40%

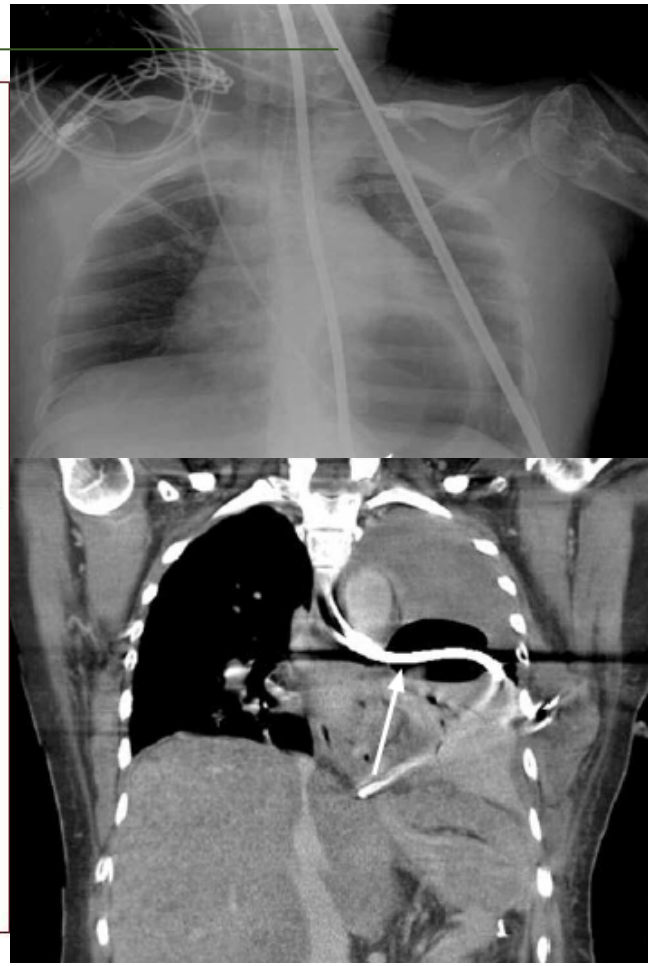


Liver Int. 2018 Mar;38(3):477-483
Choi Korean J Intern Med. 2017 Nov 10. In press

Tamponade

- Balloon tamponade
  - Inflate gastric balloon first
  - Esophageal balloon (if bleeding perisists)
  - Intubation required
- Temporary ‘‘bridge’’ (for a maximum of 24 -48 h)
- Beware of complications!
  - Perforation ~ 5-10%
  - Aspiration neumonia ~25 -35%
  - Ulcers / necrosis ~ 10 -15%

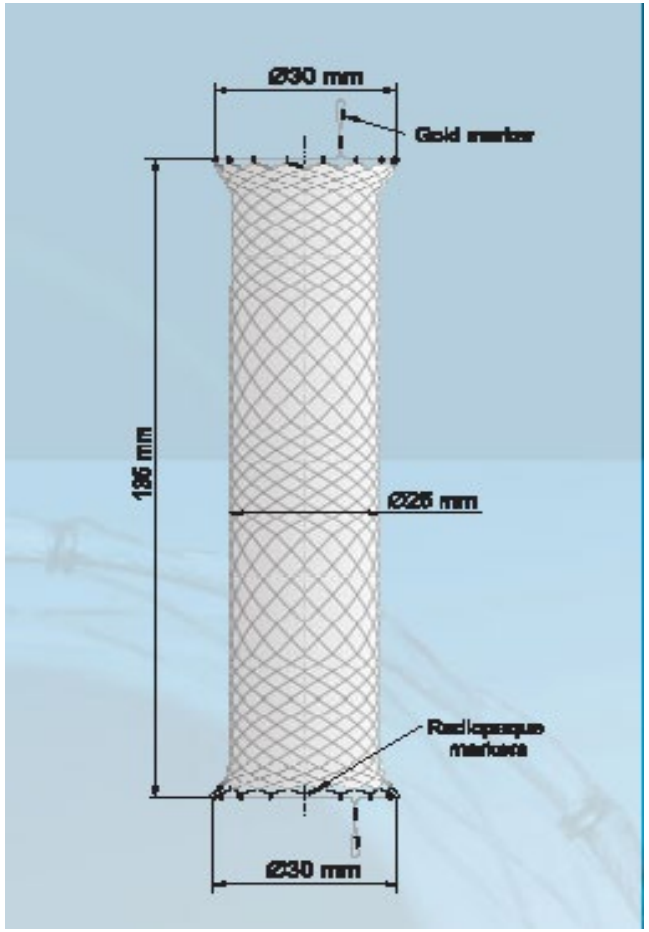




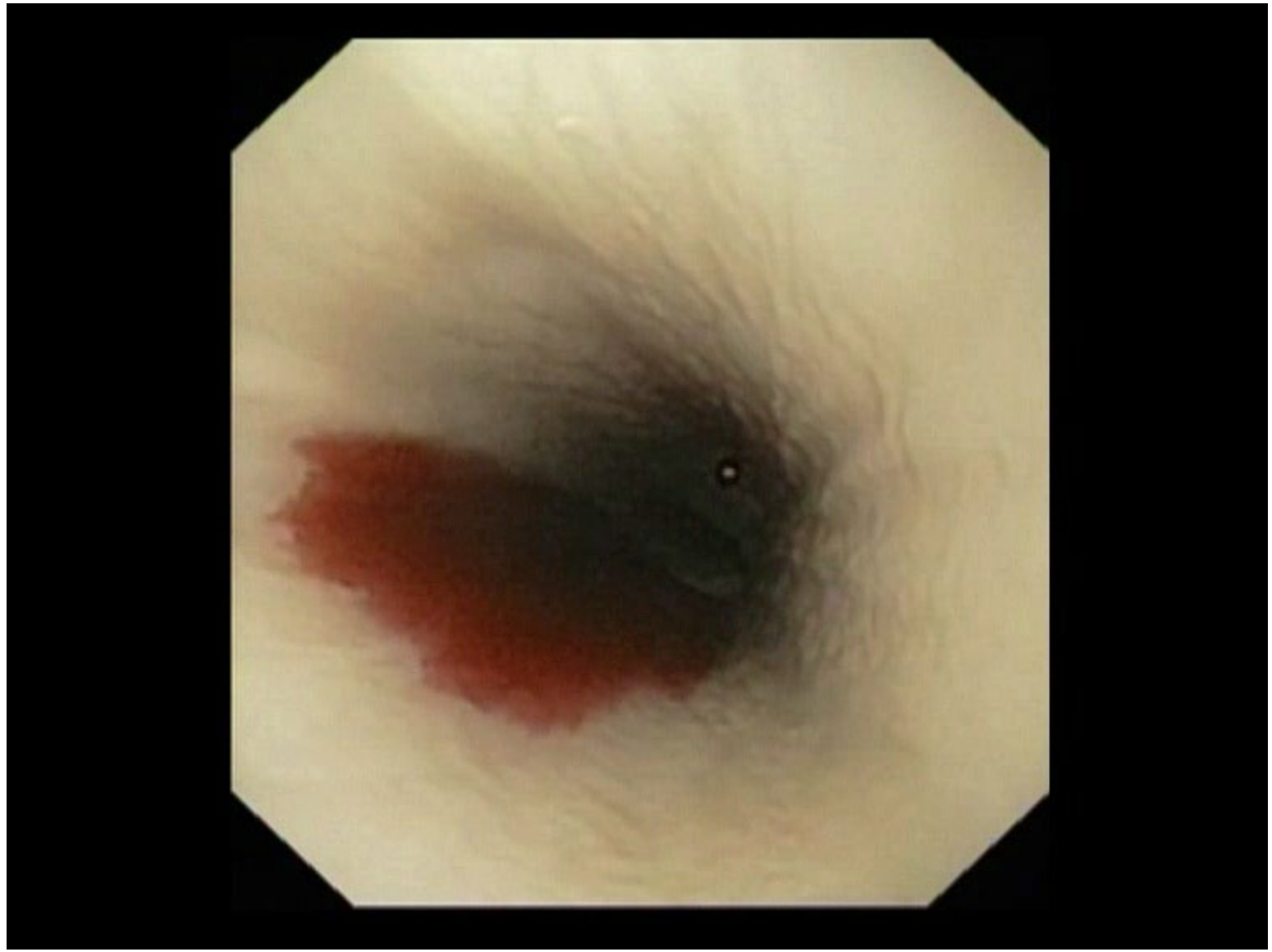
Choi . Korean J Intern Med. 2018 Jul;33(4):696-704
Nadler, et al J Emerg Med 2017 Oct;35(10):1500-1502

Fully covered expandable esophageal metallic stents

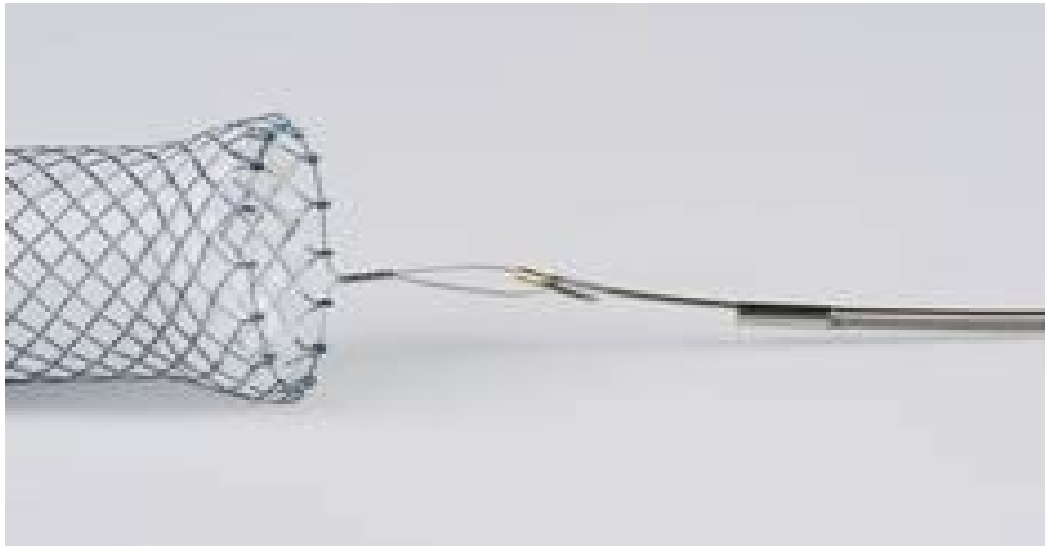
- Easily implanted
- With or without endoscopy
- Direct compression of varices
- Non-traumatic edges
- Highly effective and safe
- Oral intake soon afterwards
- Remove after 7 days
- BRIDGE TO TIPS OR LT

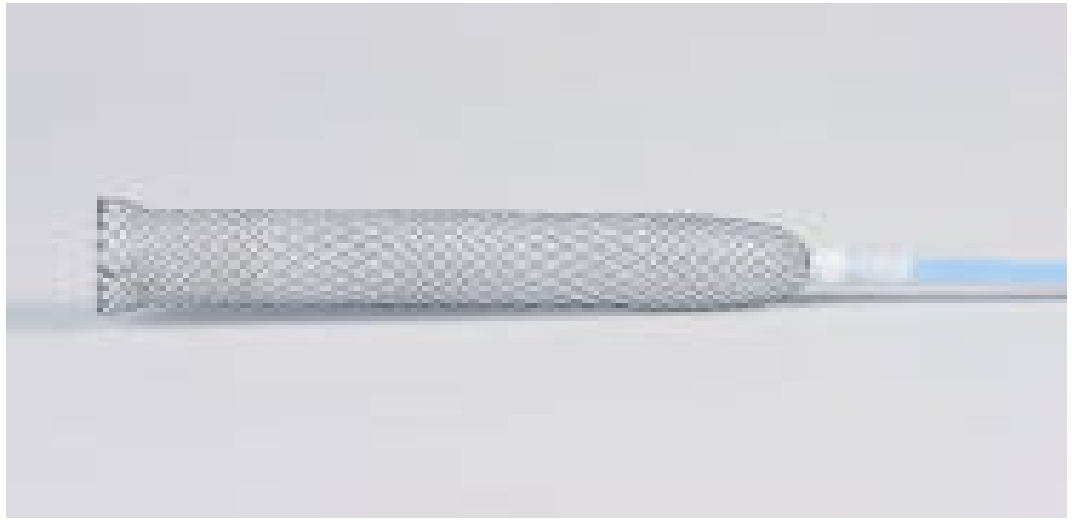


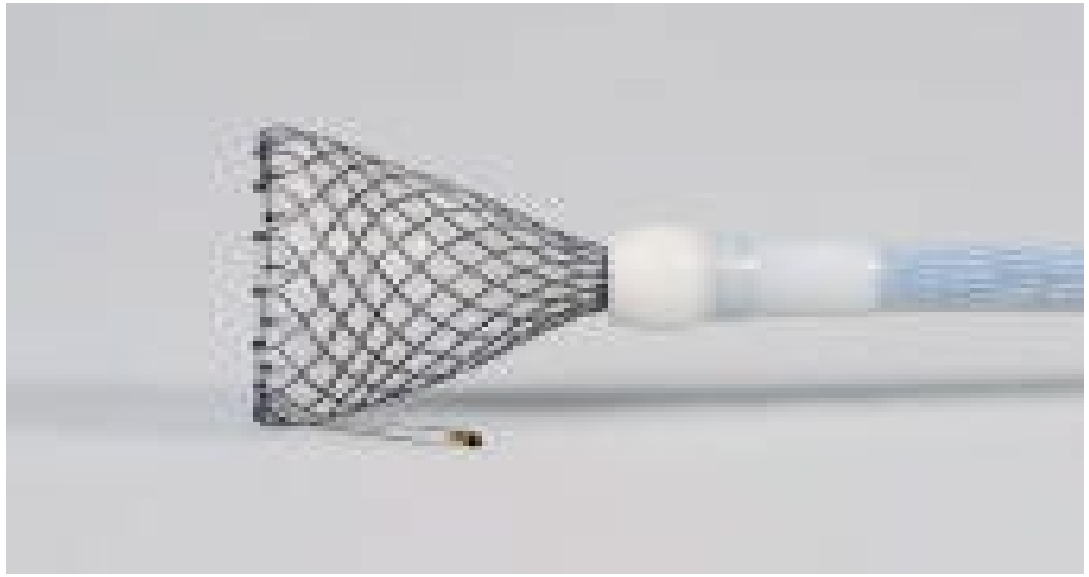
Rodrigues, Cardenas, Escorsell, Bosch. Semin Liv Dis 2019



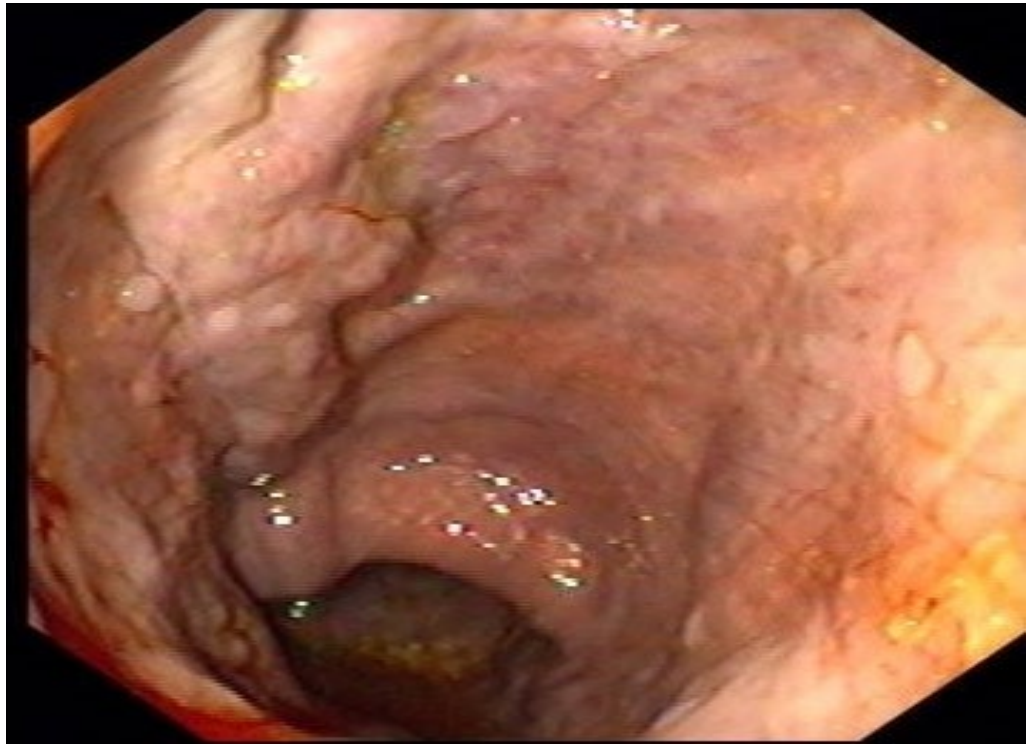
Extraction – Overtube system

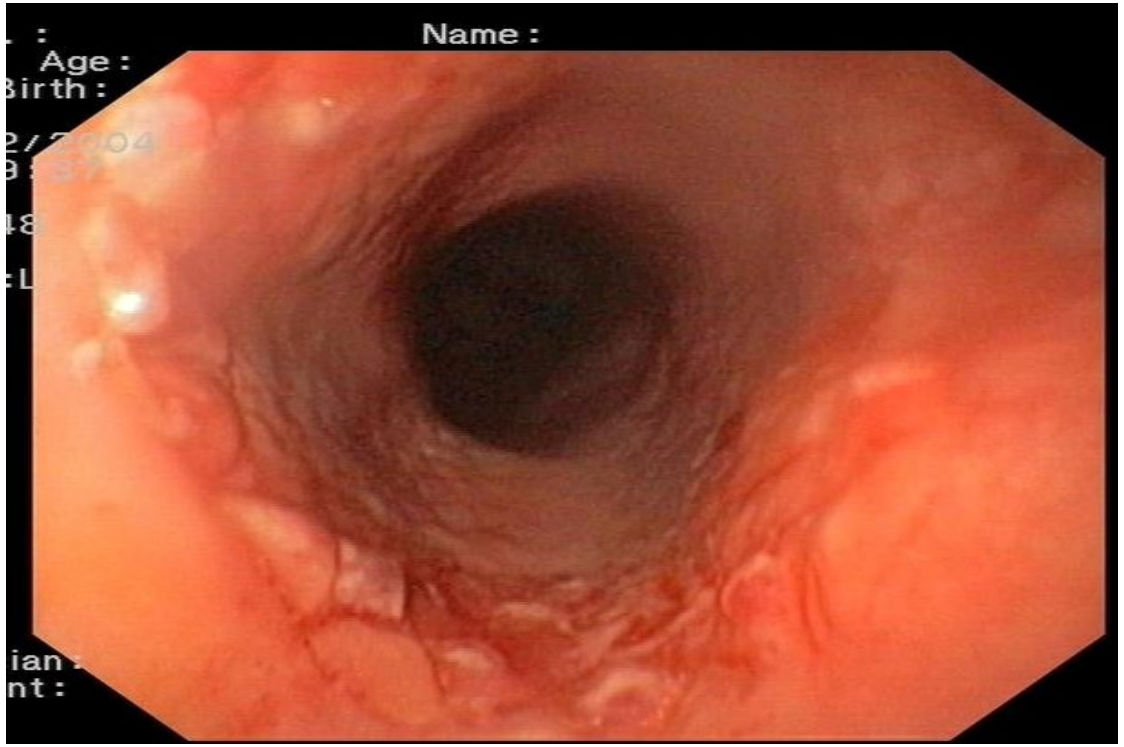






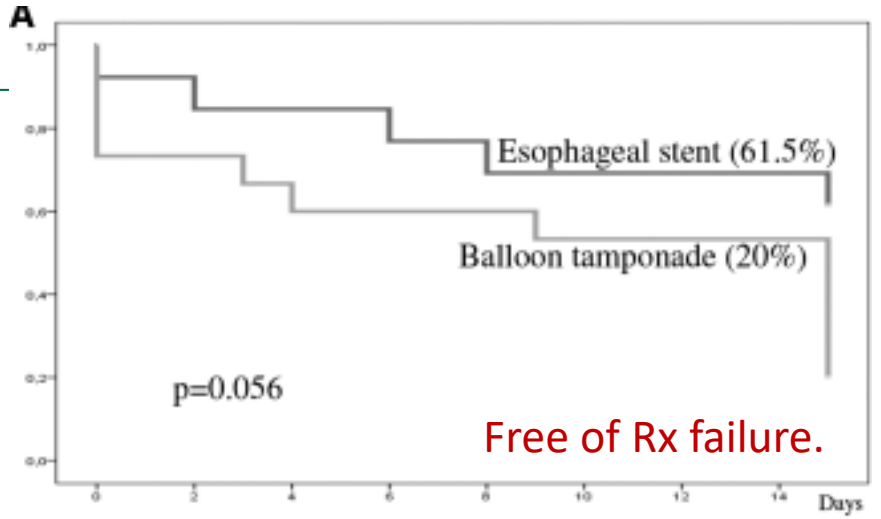
Extraction – Overtube system

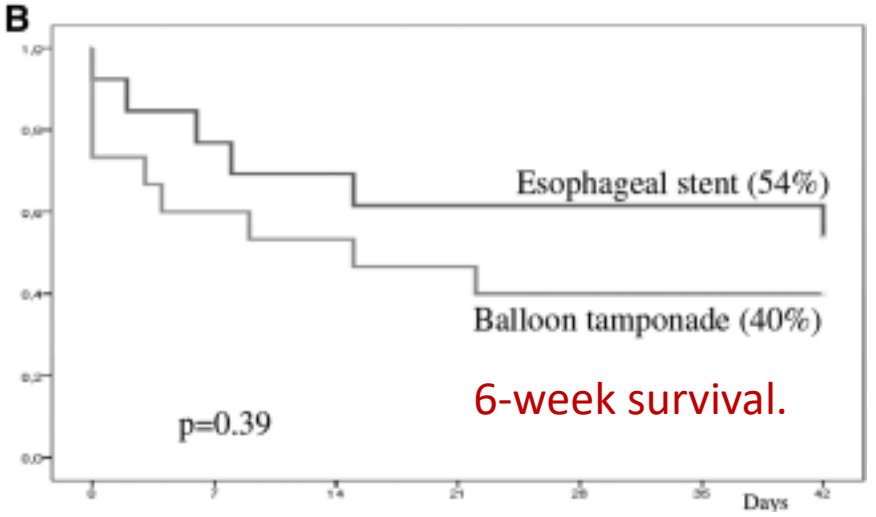




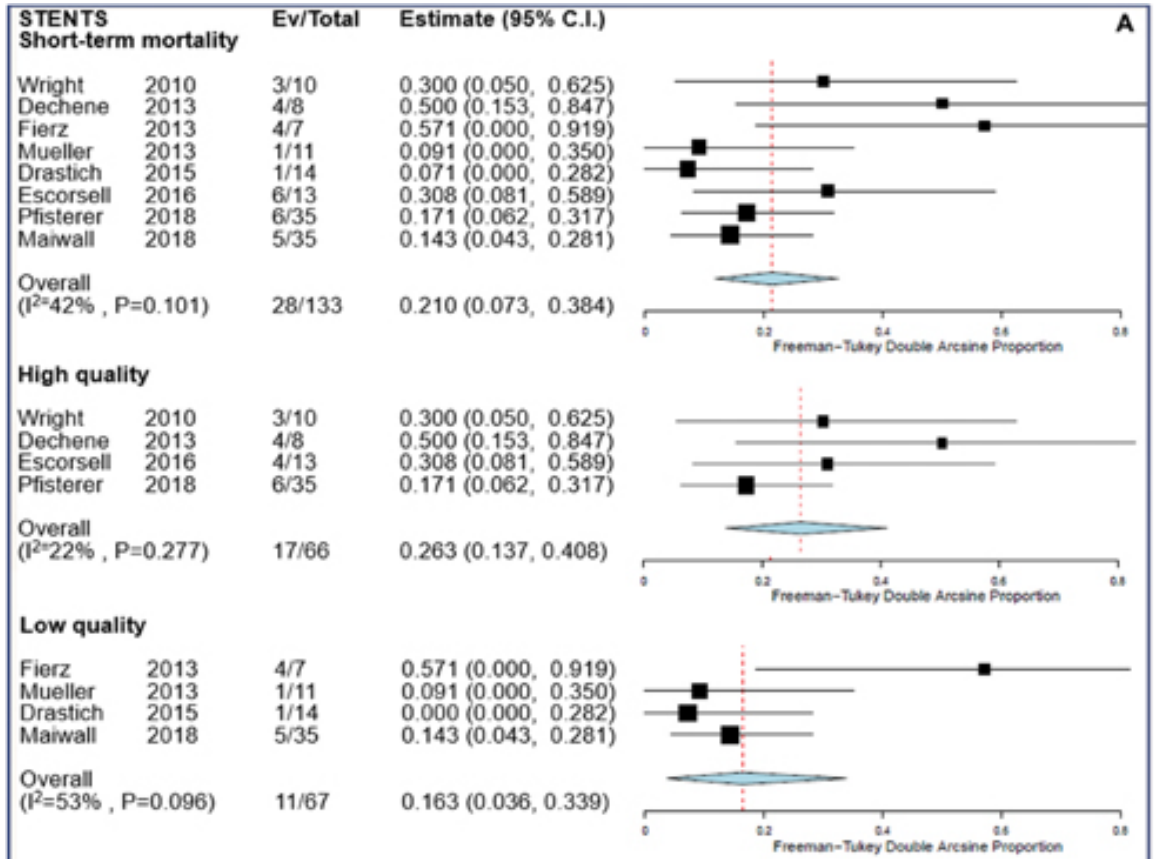
Self-Expandable Esophageal Metal Stent vs Balloon Tamponade in Esophageal Variceal Bleeding Refractory to Medical and Endoscopic Treatment: A Multicenter RCT

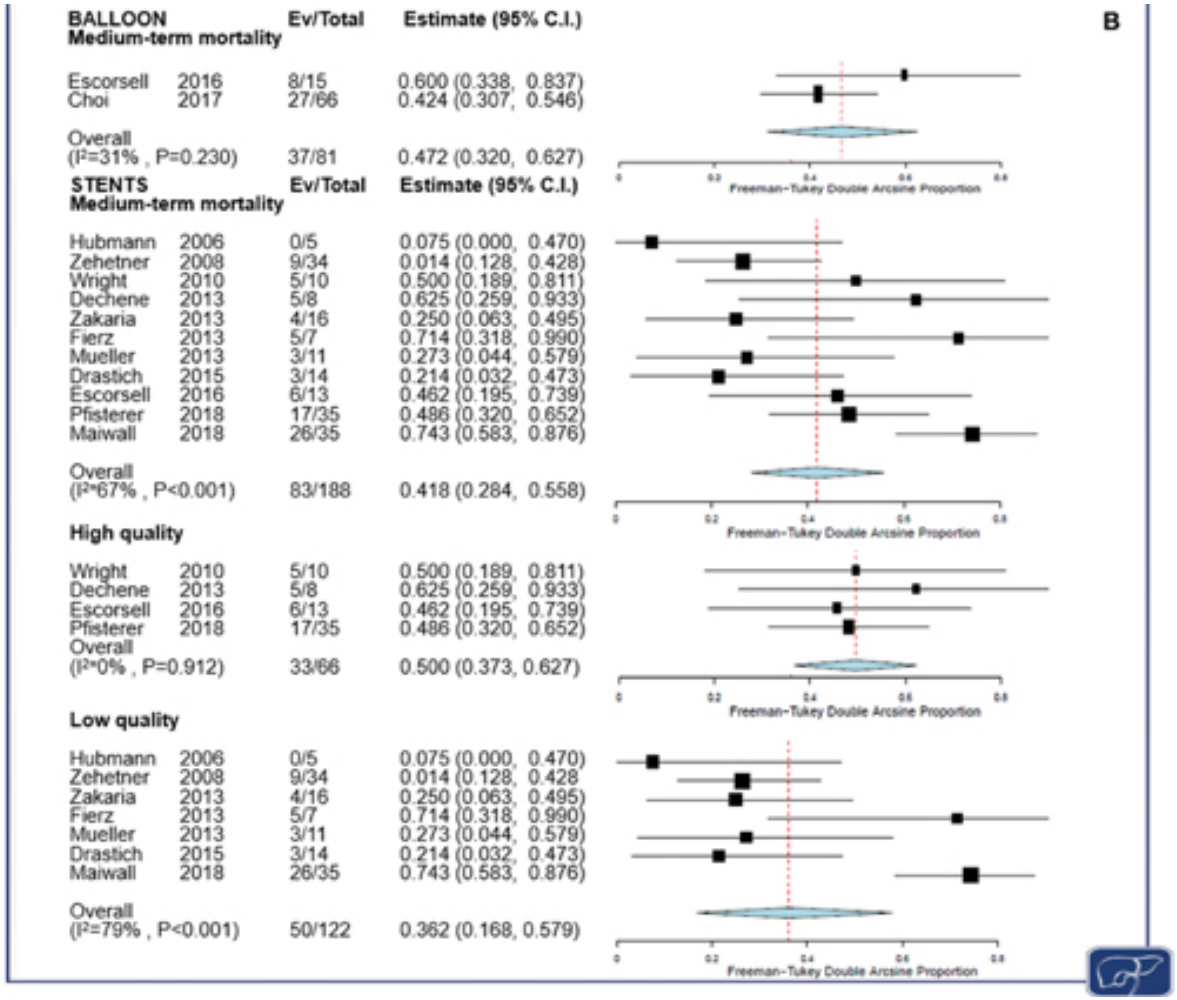
	Stent n : 13	Balloon n: 15	P value
Success of therapy	66%	20%	0.025
Control of bleeding	85%	47%	0.037
Transfusion	2 PRBC	6 PRBC	0.037
Adverse events	15%	47%	
TIPS	4	10	0.07





Escorsell, Pavel, Cardenas, et al Hepatology. 2016 Jun;63(6):1957-67





Rodrigues, Cardenas, Escorsell, Bosch. Semin Liv Dis 2019

RECCOMMENDED BY BAVENO VII

Rescue TIPS in Treatment Failures

Author	*N* pts	% Pugh's C	Immediate control (%)	Previous endoscopic therapy	% rebleeding	Interval of rebleeding (days)	Site of rebleeding[a]	Mortality (%)
LaBerge et al. [3]	32	NG	97	Sclerotherapy	NG	NG	NG	NG
Haag et al. [4]	19	68	100	NG	11	10	SU	26 (30 days)
Helton et al. [5]	23	78	NG	Sclerotherapy	NG	NG	NG	56 (in hospital)
Le Moine et al. [6]	4	NG	NG	Sclerotherapy	NG	NG	NG	75 (30 days)
Rubin et al. [7]	12	NG	75	Sclerotherapy Band ligation	NG	NG	NG	NG
Jalan et al. [8]	19	68	100	Sclerotherapy	15.6	30	V-SU	42 (30 days)
Jabbour et al. [9]	25	48	96	Sclerotherapy	NG	NG	V-SU-DU	44 (30 days)
Sanyal et al. [10]	30	73	100	Sclerotherapy	7	14	V-GU	40 (6 weeks)
Perarnau [11]	48	56	92	Sclerotherapy	8.5	NG	NG	25 (30 days)
Banares et al. [12]	56	41	95	Sclerotherapy	14	30	V	15 (30 days)
Gerbes et al. [13]	11	64	91	Sclerotherapy Band ligation	27	14	NG	27 (30 days)
Chau et al. [2][b]	112 EV 84 GV 28	71 EV 75 GV 61	96	Sclerotherapy	13 EV 14 GV	7	EV-GV-SU	37 (30 days) EV 34 GV 42
Barange et al. [14][c]	32	47	90	Sclerotherapy	14		NG	25 (30 days)
Bizollon et al. [15]	28	61	96	Sclerotherapy Band ligation	8	14	V-SU	25 (40 days)
Azoulay et al. [1]	58	81	90	Sclerotherapy	6	14	V-GU	29 (30 days)

Should high risk patients have a *preemptive* TIPS?

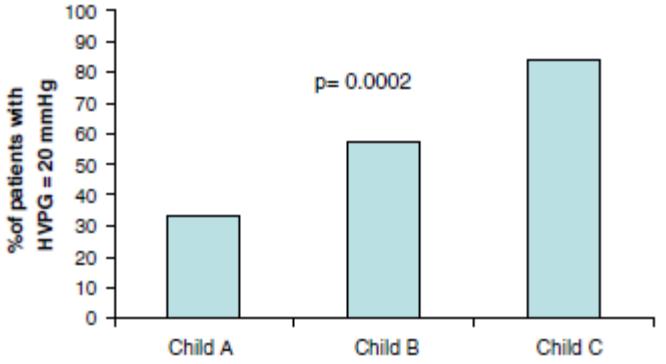
Vangeli et al . J Hepatol. 2002 Nov;37(5):703-4

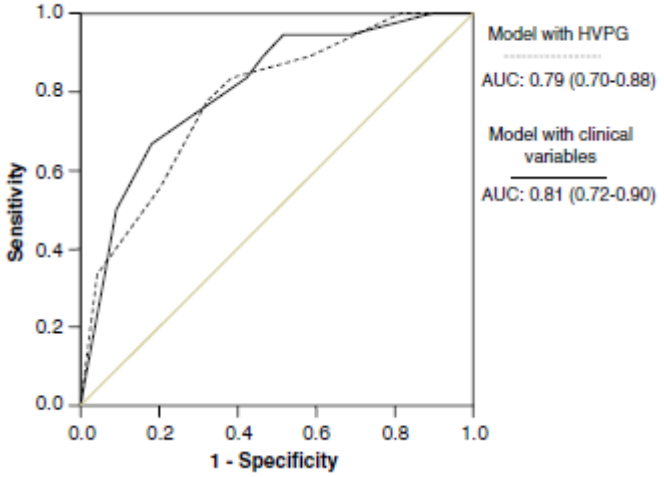
High Risk Criteria for therapeutic failure- Stratification

- 117 patients with AVB in whom HVPG was measured within 48 h of admission
- Multivariate analysis identified three variables independently associated with 5-day failure:

Mutivariable models for 5-day failure

	OR (90% CI)
Model with all variables	
HVPG ⩾20 mm Hg	5.44 (1.67–17.69)
Systolic blood pressure <100	4.94 (1.88–13.02)
Non-alcoholic etiology	4.96 (1.73–14.27)
Model excluding HVPG	
Child class	
Child B vs A	6.41 (1.01–40.75)
Child C vs A	17.61 (2.37–130.89)
Systolic blood pressure <100	5.54 (2.03–15.17)
Non-alcoholic etiology	6.66 (2.00–22.17)





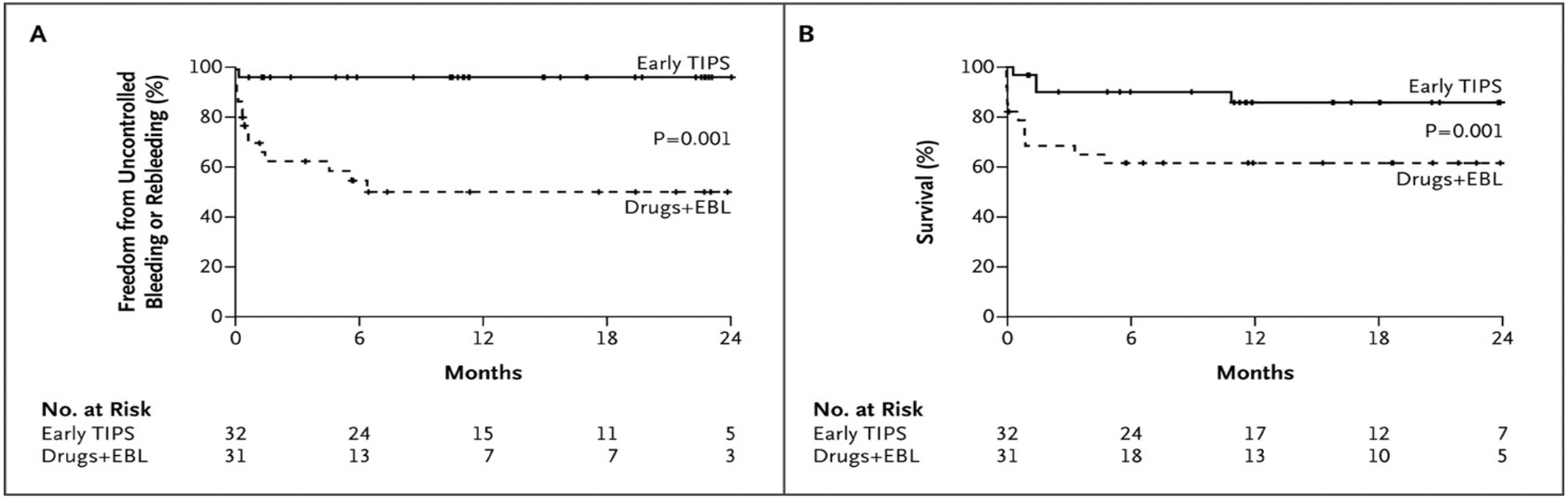
Abraldes. J Hepatol 2008;48:229-236

Multicenter RCT of Early TIPS (1st 72 hrs) vs Band Ligation In Patients with Acute Variceal Bleeding

(Child B with active bleed and Child C ≤ 13)

Primary end-point

Survival



García-Pagán JC et al. N Engl J Med 2010;362:2370-2379.

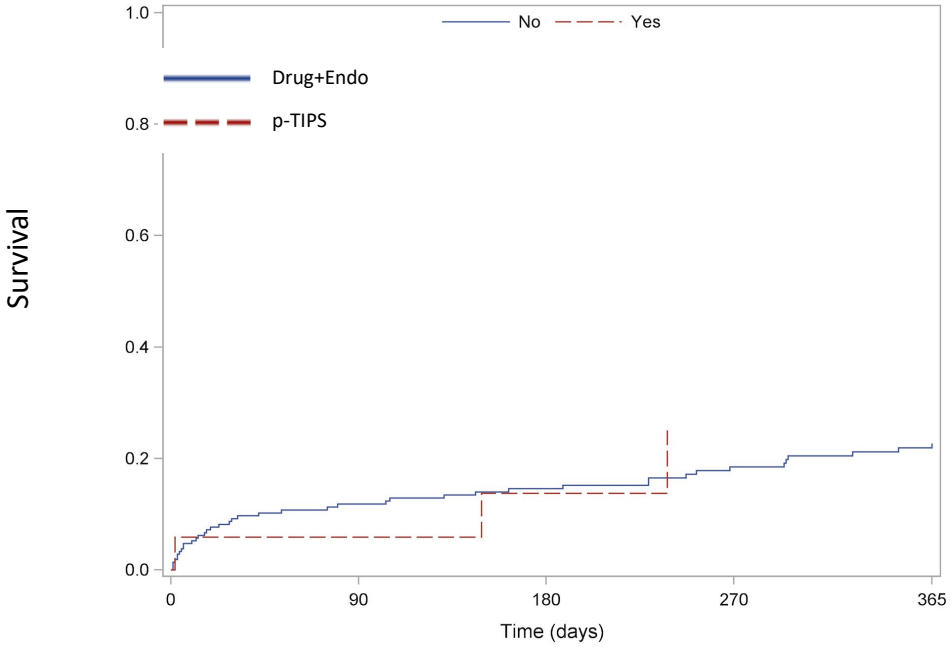
Preemptive-TIPS improves outcome in high-risk variceal bleeding:

(Propensity score matched analysis)

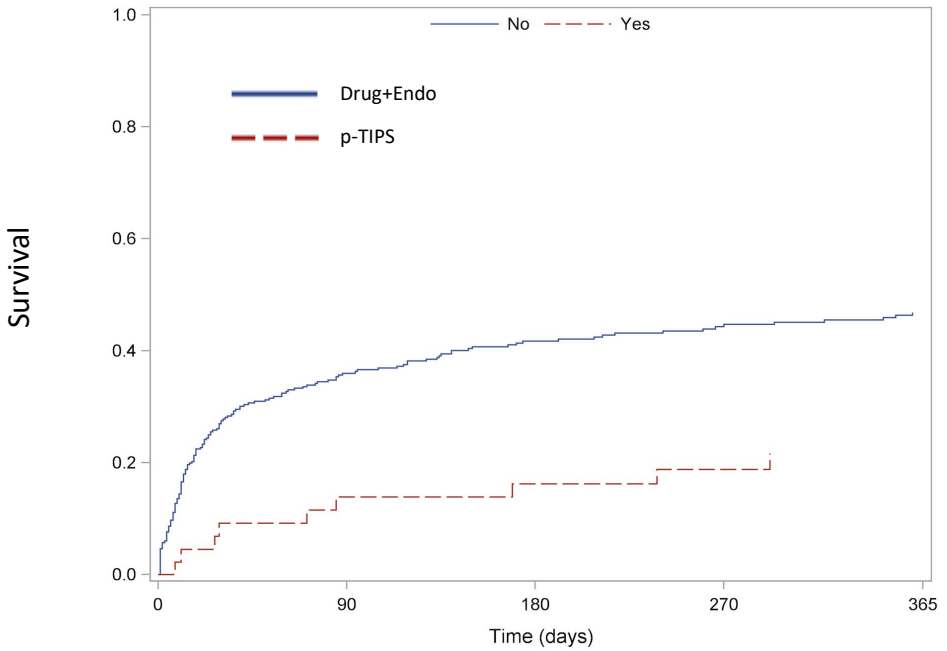
Multicenter, international study in 34 centers (April 2013 – 2015)

66 Early TIPS vs 605 Drugs and EBL

Child-Pugh B + Active Bleeding



Child-Pugh C



Early TIPS is associated with improved survival in patients with MELD ≥19 or Child-Pugh C cirrhosis but not in patients with MELD ≤11 or Child-Pugh A cirrhosis.

MELD 12-18 or Child-Pugh B ? We need future studies

Lv et al Gut. 2019 Jul;68(7):1297-1310.

Hernandez-Gea et al. Hepatology 2018.

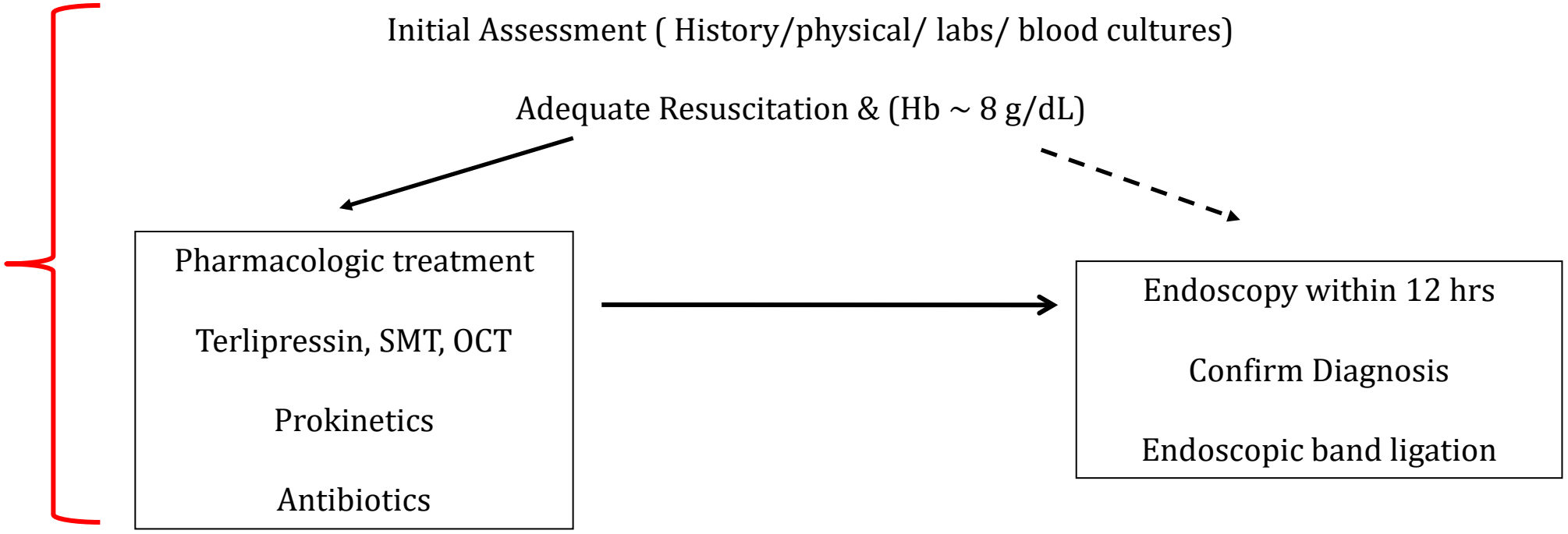
TIPS / Indications

1. Rescue therapy for the 10 – 15 % of patients that fail standard therapy
2. Early TIPS within 72h should be considered in patients at high-risk of treatment failure.
    1. Child-Pugh class C ≤13 points
    2. Child class B with active bleeding?

- Who?
- Child Score ≤ 13
- Age ≤ 75-80
- No significant cardiac disease
- No pulmonary hypertension or CHF
- No central HCC
- No extensive portal vein thrombosis

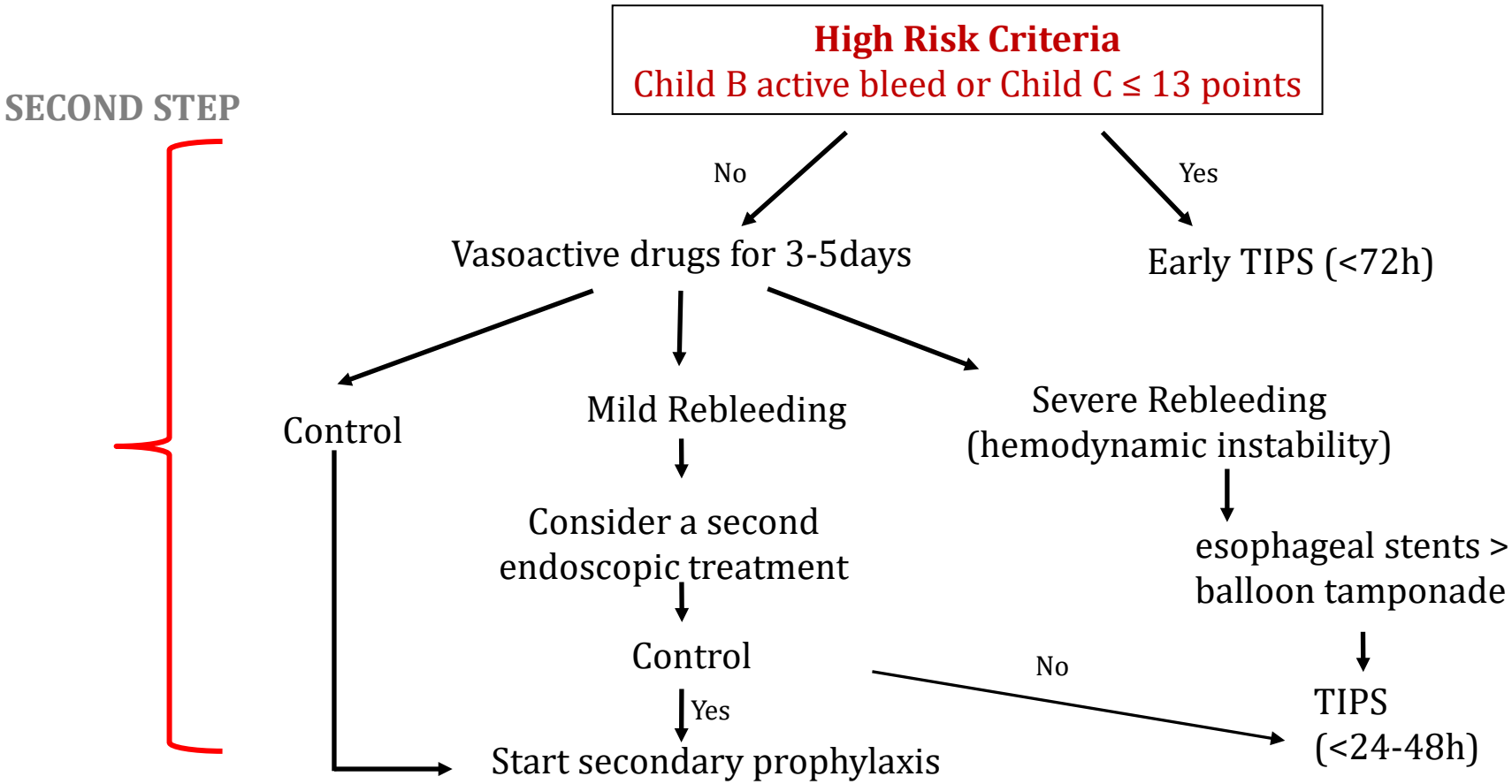
SUMMARY - ACUTE VARICEAL BLEEDING IN CIRRHOSIS

FIRST STEP



AASLD Guidance, Hepatology 2017
EASL Guidelines, J Hepatol 2018
BAVENO VII

SUMMARY- ACUTE VARICEAL BLEEDING IN CIRRHOSIS



AASLD Guidance, Hepatology 2017
EASL Guidelines, J Hepatol 2018
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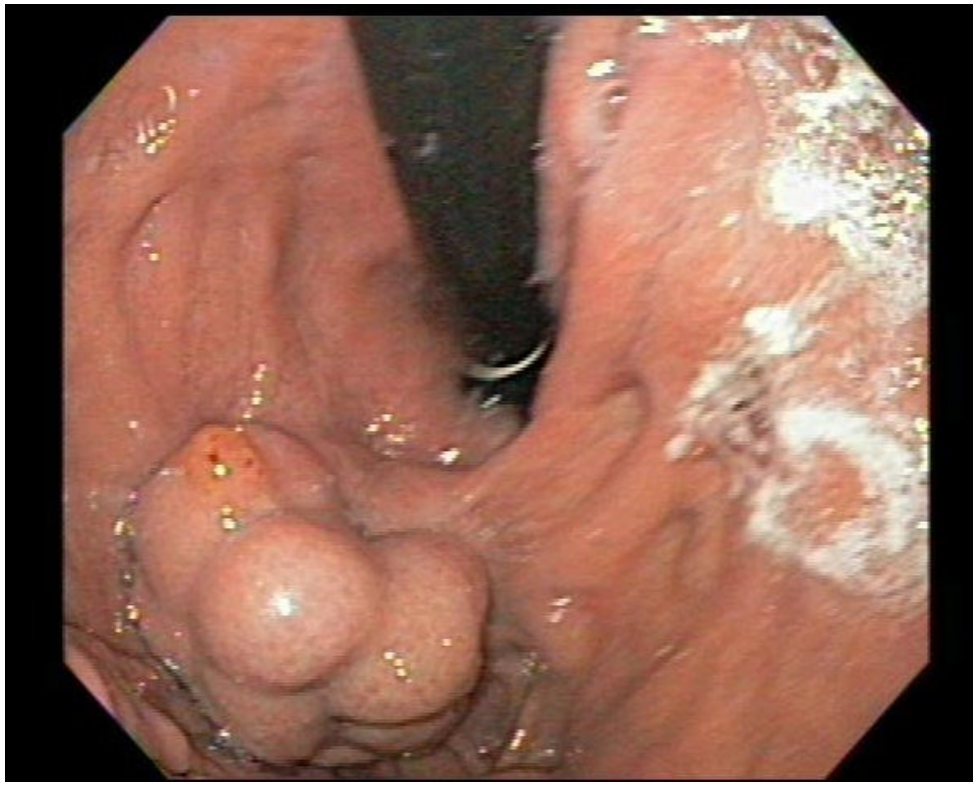
GASTRIC VARICES

CASE

- 62 yr old man with alcoholic cirrhosis – Child B, previous esophageal varices and ascites
- Found drunk and vomiting blood in the street.
- On exam- BP 85/55, HR 92, lung –bilateral rales, grade 2 ascites, + flap
- Hb 6.8, plt 102,000, INR 1.8, creat -2.1



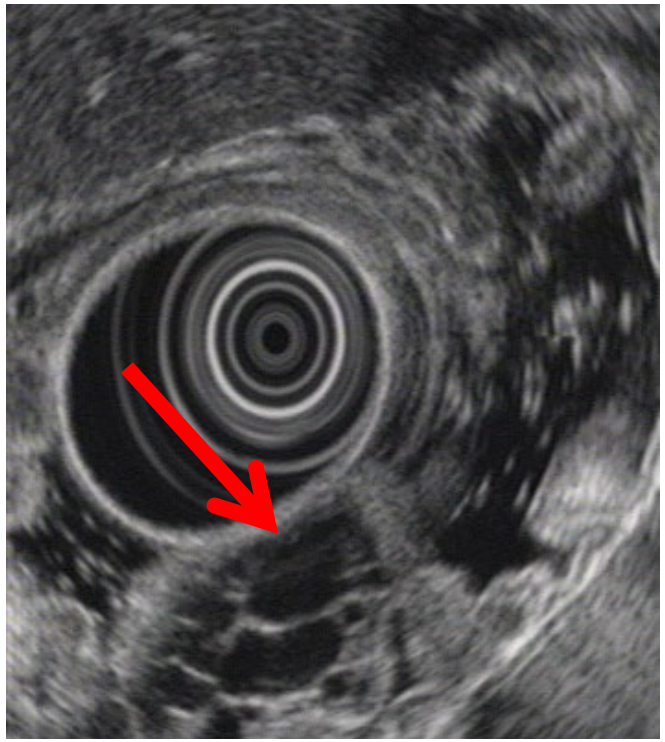
Gastric Varices

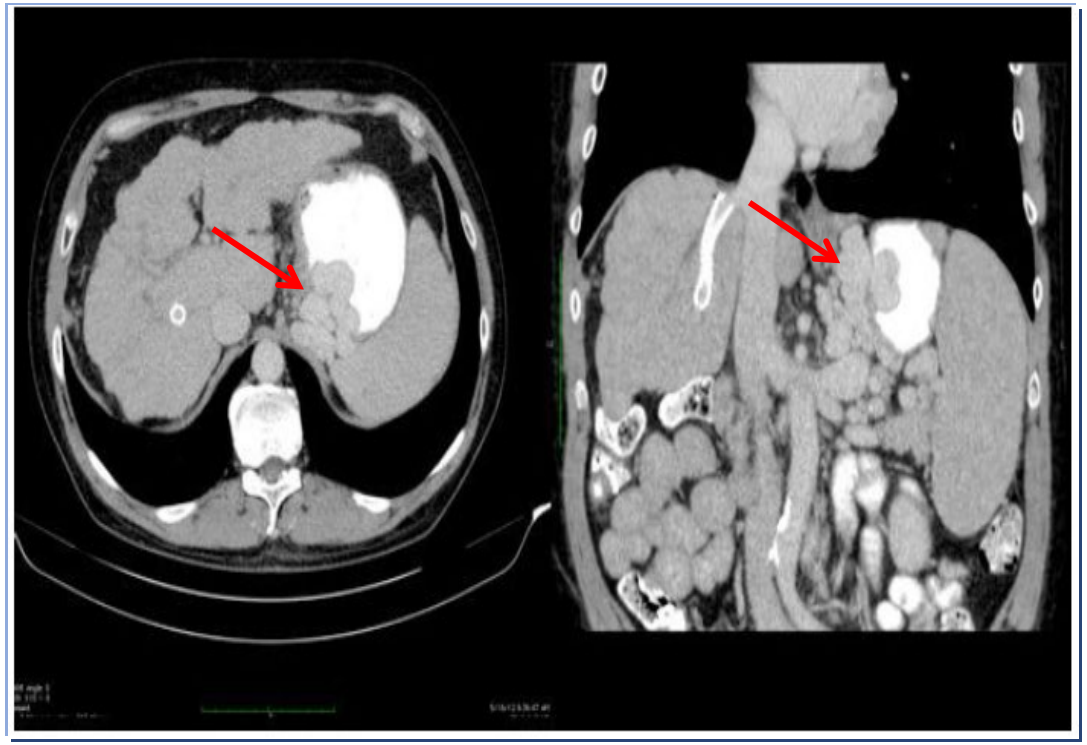
- Present in 5-30% of patients with cirrhosis
- Account for 10-15% of variceal bleeding episodes
- Risk factors: location, size, Child class, presence of red spots, HCC
- Bleed less but more severe
- Therapy can be challenging

Tripathi D, Aliment Pharmacol Ther. 2006
Irani S, J Clin Gastroenterol, 2011
Bazarbashi AN, Ryou M. Curr Opin Gastroenterol. 2019

Diagnosis

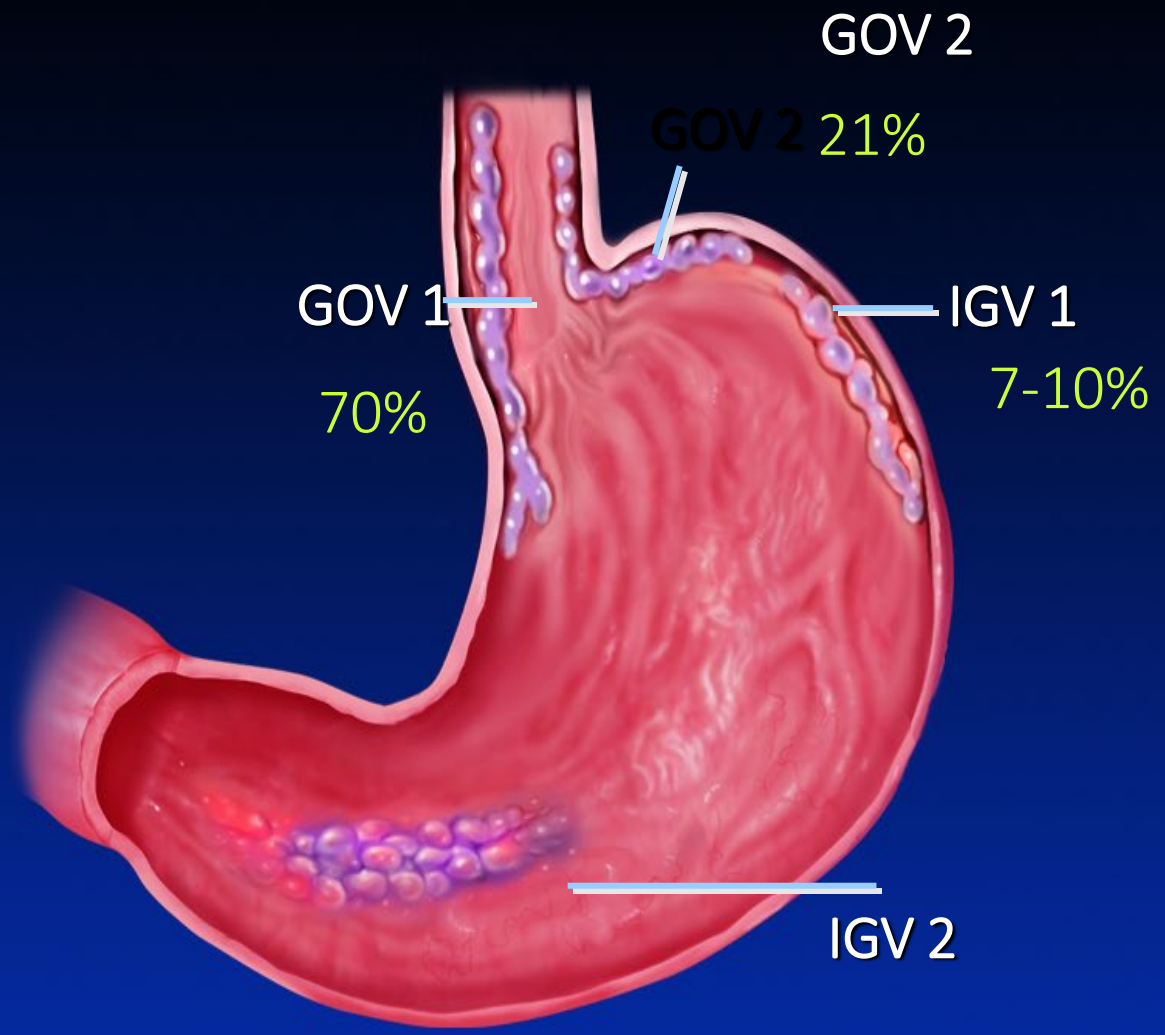
- Diagnosis: endoscopy, CT scan or EUS
- Maybe difficult to detect by endoscopy in some cases (small and isolated).
- Endoscopic ultrasound may help confirm diagnosis and direct therapy





Romero- Castro, GIE 2007,2014
Binmoeller , Endoscopy 2011

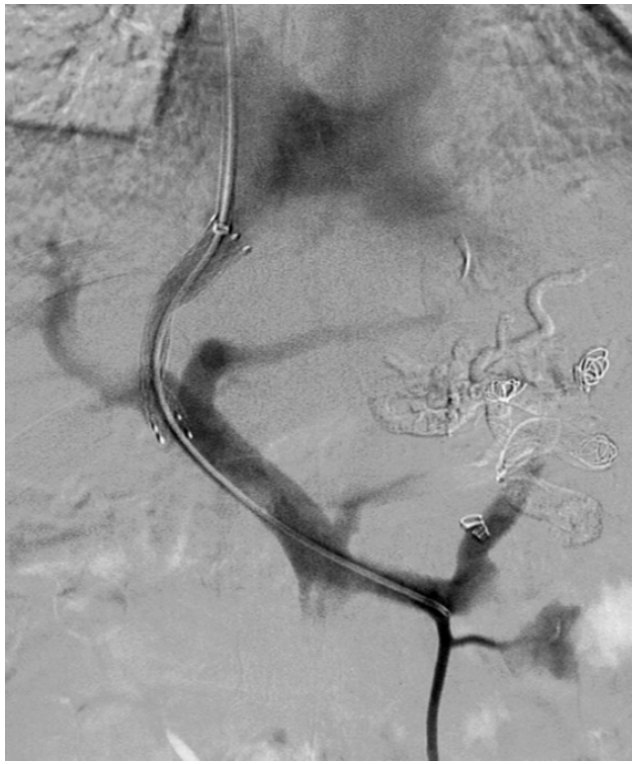
Classification of Gastric Varices



GOV1 (some GOV2) can be treated in the same way as esophageal varices

Sarin et al, Am J Gastro 1989; 84:1244

Treatment Options GV bleeding



Treatment options of GV

Treatment of acute GV bleeding

Endoscopy – first choice

- Cyanoacrylate injection (free hand):
  - 90-98% control of bleeding
- Thrombin injection:
  - 92-100% control of bleeding
- EUS – Guided glue +/- coils
  - Promising, rates similar to endo-glue therapy
- BRTO & TIPS:
  - 95% control of bleeding

Rios-Castellanos. Cochrane Database Syst Rev. 2015 May 12;(5):CD010180.
Bhurwal A et al. Dig Dis Sci. 2021 Mar 17. doi: 10.1007/s10620-021-06915-5.
Lo GH et al Endoscopy. 2020 Jul;52(7):548-555.
Mohan BP et al . Endoscopy. 2020 Apr;52(4):259-267
Sallout D. Frontline Gastroenterol. 2022 Jun 17;13(6):535-542.
Luo X, Hernández-Gea V. Liver Int. 2022 Jun;42(6):1250-1258.

Cyanoacrylate

- A variety of cyanoacrylate are available - they are not the same.

	n-Butyl-2 cyanoacrylate	n-Butyl-2-cyanoacrylate Mixed with Lipiodol	2-Octyl cyanoacrylate
Trade name	Histoacryl, Indermil, Glubran 2, Liquiband, Skin Link		Dermabond, SurgiSeal
Setting time	**Fast**	**Slower**	**Slower**

- We and c

References on straight glue injection: Mishra S, Sarin SK et al. Gut 2010; 59:729-35.
Mishra , Sarin et al. J of Hepatology (2011); 54: 1161-1167
Sarin -- Personal communication 1/2012
Reddy -- Personal communication 1/2012

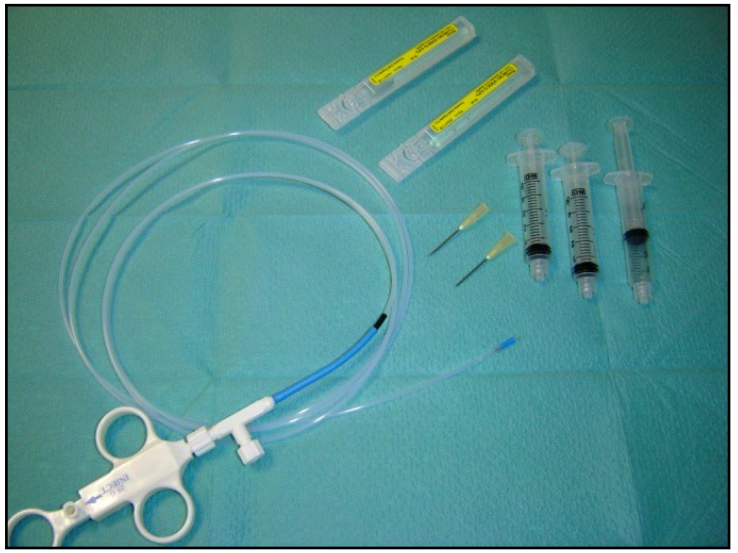
Cyanoacrylate

- Rapidly undergoes polymerization upon contact with any type of tissue.
- Hardens into a solid mass within the varix
- Occludes flow

- Varix hardens after injection
- *Europe / Asia: N-butyl 2 cyanoacrylate (Histoacryl / Glubran)*
- *USA: 2-octyl cyanoacrylate (Dermabond)*

Cyanoacrylate / Histoacryl®

Used with / without lipiodol
Mix 0.5 ml : 0.5 ml (prepare 3-4 ml)
Use distilled water
Limit 1 ml per injection
Use 5 ml luer-lock syringes
Gloves and eye protection for preparation

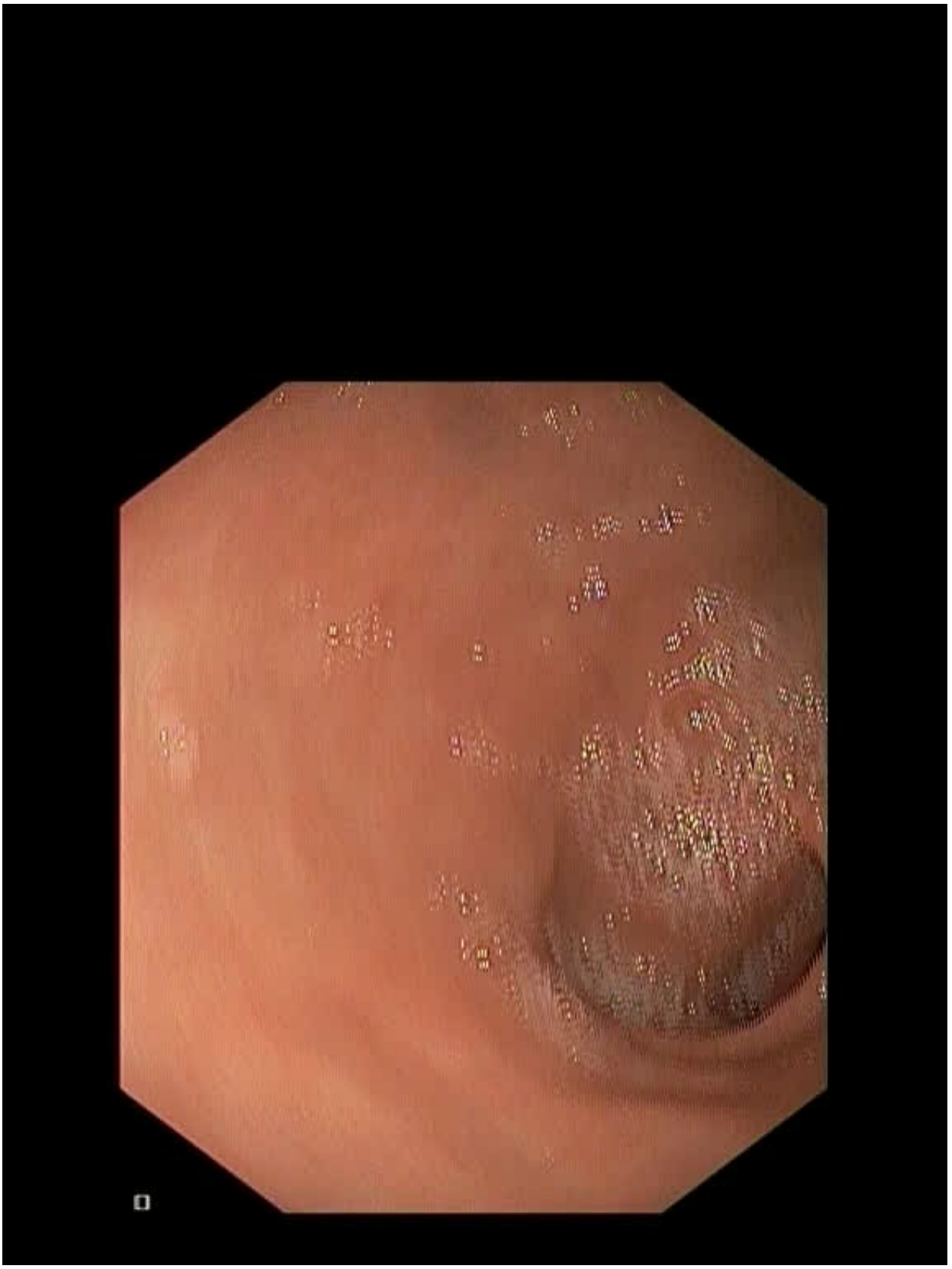


1. Prime Sclero needle (21 gauge) with distilled water, and coat tip needle and gastroscope with lipiodol.

2. Prime the mix [lipiodol/cyanoacrylate] into needle / aprox 1ml

3. Puncture varix and push the mix with distilled water.

4. Repeat as needed finally flush needle with water. Limit injection to 1 or 2 ml per site.



Studies (last 15 yrs) evaluating endoscopic cyanoacrylate injection for acute gastric (cardiofundal) variceal (GOV2, IGV1) hemorrhage

.

Author	N	Hemostasis (%)	Rebleeding (%)	Mortality (%)
Lo GH 2020	35	97.1%	5.7	2.9
Chandra 2018	57	100%	3.5	NA
Singh 2016	30	100%	6.7	none
Monsanto 2012	98	96	14	9.3
Kang 2011	127	98.4	18	NA
Rajoriya 2011	31	100	10	23
Hou 2009	47	90	30	NA
Seewald 2008	131	100	11.1	6.1
Belletrutti 2008	34	94	12	18
Fry 2008	33	88	15	18
Marques 2008	48	87	20.5	NA
Cheng 2007	635	95	8.0	7

Guidelines recommend endoscopic cyanoacrylate injection for acute gastric (cardiofundal) variceal (GOV2, IGV1) hemorrhage.

1. *Henry Z,. AGA Clinical Practice Update on Management of Bleeding Gastric Varices: Expert Review. Clin Gastroenterol Hepatol. 2021 Jun;19(6):1098-1107.e1.*
2. *Baveno VII. J Hepatol. 2022 Apr;76(4):959-974. doi: 10.1016/j.jhep.2021.12.022*
3. *European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2022 Sep 29. doi: 10.1055/a-1939-4887*

Systematic Review

Efficacy and safety of endoscopic ultrasound-guided therapy versus direct endoscopic glue injection therapy for gastric varices: systematic review and meta-analysis

EUS-guided management of bleeding gastric varices combining injection of coils and cyanoacrylate may be used in centers with expertise and familiarity with this technique

23 studies (851 patients) evaluating EUS-guided therapy were included

▶ **Table 1** Pooled results of outcomes.

Intervention/outcomes, pooled rate, % (95%CI, I^2)	All EUS modalities	EUS-glue	EUS-coil	EUS-coil/glue	END-glue (comparator group)
Treatment efficacy	93.7 (89.5–96.3, 53.7) 29 cohorts	91 (80–96.2, 40) 9 cohorts	84.2 (54.5–96, 6.5) 3 cohorts	96.7 (93–98.5, 55) 14 cohorts	91.4 (82.8–95.9, 97) 28 cohorts; $P=0.4$
Obliteration of gastric varices	84.4 (74.8–90.9, 77) 21 cohorts	90 (71.3–97, 0) 5 cohorts	N/C	86.2 (75.5–92.7, 74) 12 cohorts	62.6 (42.6–79.1, 97); 13 cohorts; $P=0.02$
Recurrence of gastric varices	9.1 (5.2–15.7, 32) 16 cohorts	15 (8.8–24.5, 0) 5 cohorts	N/C	5.2 (2.6–9.8, 0) 6 cohorts. $P=0.01$	18 (11.4–27.2, 89) 8 cohorts; $P=0.06$
Early rebleeding	7 (4.6–10.7, 0) 20 cohorts	6 (3.1–11.1, 0) 8 cohorts	N/C	7.7 (3.9–14.9, 46) 7 cohorts	5 (3.3–7.4, 72) 23 cohorts; $P=0.7$
Late rebleeding	11.6 (8.8–15.1, 22) 26 cohorts	16.3 (9.7–26.1, 65) 8 cohorts	16.8 (7.3–34.1, 0) 3 cohorts)	9.2 (6.4–13, 0) 12 cohorts	17 (12.3–22.9, 92) 27 cohorts; $P=0.1$

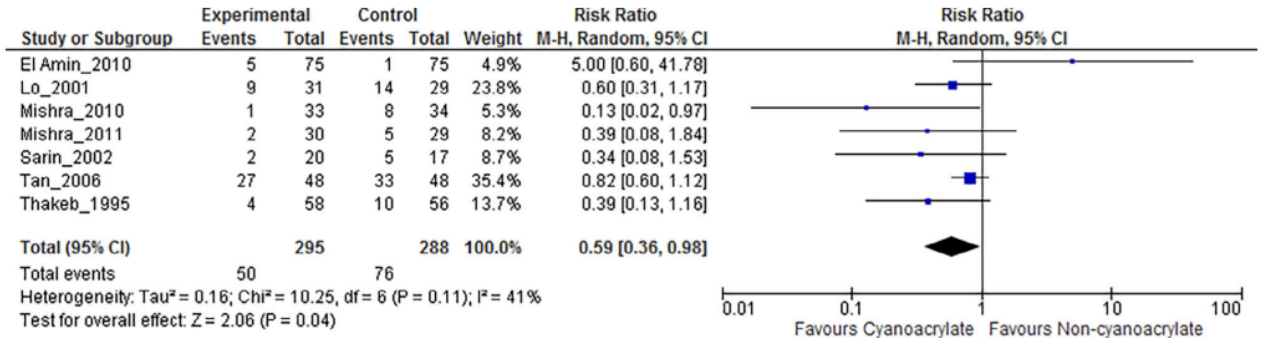
Mohan BP et al . Endoscopy. 2020 Apr;52(4):259-267

Safety and efficacy of endoscopic cyanoacrylate injection in the management of gastric varices: A systematic review and meta-analysis

Seven RCT (six for secondary prophylaxis and one for primary prophylaxis)

Studies	Primary endpoint	Comparison	Characteristic of studied patients		Duration of follow up
			Type of GOV (*n*)	Etiology of PTN	
Mishra (2011)	Primary prophylaxis	Propranolol	GOV2 (51) IGV1 (8)	Cirrhosis	26 months (3–34)
Lo (2001)	Secondary prophylaxis	Band ligation	GOV1 (37) GOV2 (13) IGV1 (5)	Cirrhosis	14 months (GVO) 9 months (GVL)
Tan (2006)	Secondary prophylaxis	Band ligation	GOV1 (53) GOV2 (25) IGV1 (19)	Cirrhosis	610 ± 603.04 days (GVL) 680.67 ± 710.54 days (GVO)
El Amin (2010)	Secondary prophylaxis	Band ligation	GOV1 (150)	Cirrhosis and non-cirrhotic	6 months
Mishra (2010)	Secondary prophylaxis	Propranolol	GOV2 (54) IGV1 (10)	Cirrhosis	26 months (3–34)
Thakeb (1995)	Secondary prophylaxis	Ethanolamine	GOV1 (14) GOV2 (10) IGV1 (3)	Cirrhosis	1 year
Sarin (2002)	Secondary prophylaxis	Alcohol	GOV2 (28) IGV1 (9)	Cirrhosis and non-cirrhotic	15.4 ± 3.7 months

GOV, gastroesophageal varices; GVL, gastric varices ligation; GVO, gastric varices obliteration; IGV, isolated gastric varices; n/a, not available; PTN, portal hypertension.

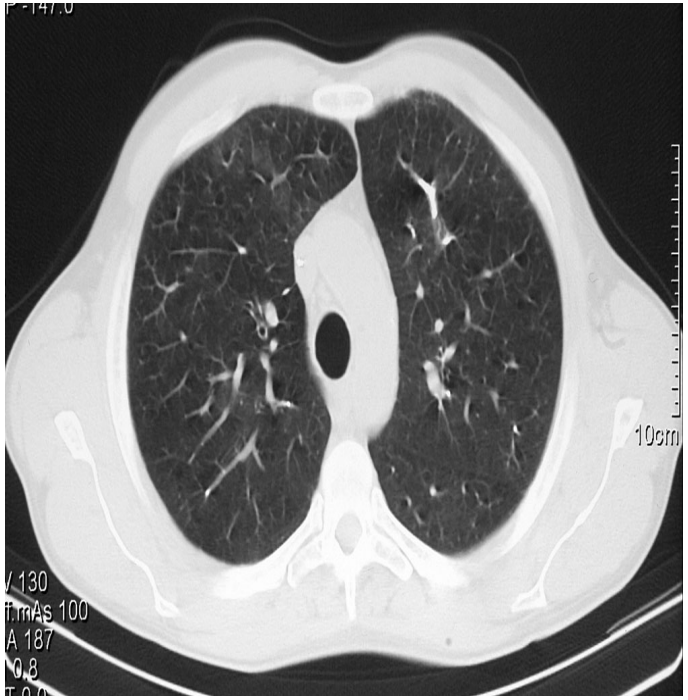


Mortality between the cyanoacrylate injection and non-cyanoacrylate therapy

Chirapongsathorn et al. JGH Open. 2021 Jul 30;5(9):1047-1055

Complications

- Total rate aprox 4-6%
- Pulmonary embolism (0.6-3%)
- Mesenteric /portal vein embolism
- Bacteremia, Infection
- Stroke
- Ulcers
- Splenic infarction



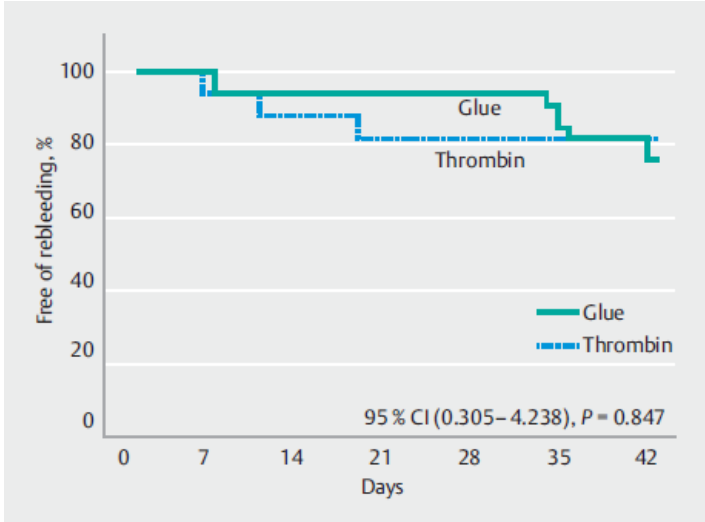
Cheng et al Clin Gastroenterol Hepatol. 2010

Thieme

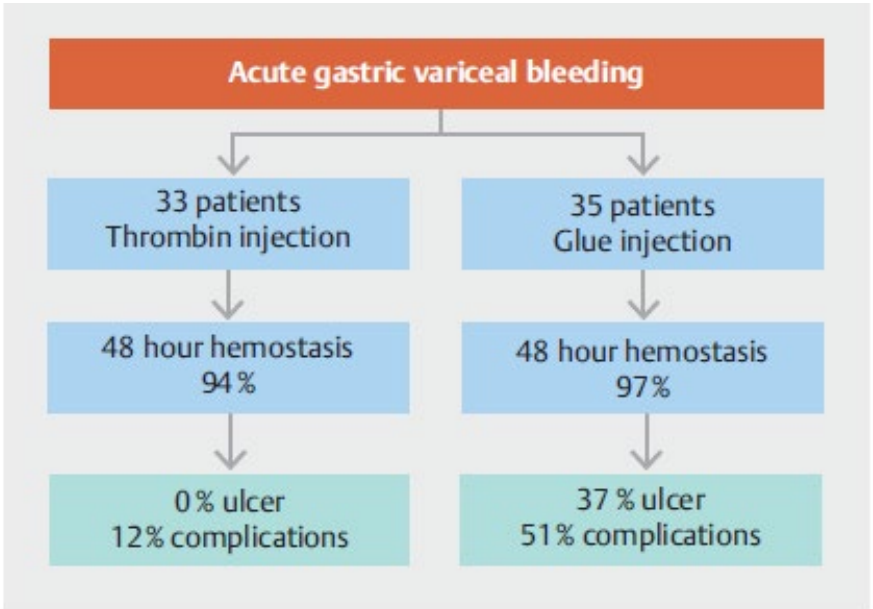
A prospective, randomized trial of thrombin versus cyanoacrylate injection in the control of acute gastric variceal hemorrhage

▶ **Table 2** Main outcomes in the two treatment groups.

	Thrombin (n = 33)	Glue (n = 35)	*P*
Volume, mL			
▪ Mean (SD)	5.1 (0.5)	1.8 (0.2)	
▪ Range	5.0 – 10.0	1.5 – 3.0	
Hemostasis of active bleeding, n/N (%)	9/10 (90.0)	10/11(90.9)	0.58
▪ GOV1	2/2	3/3	
▪ GOV2	6/6	5/6	
▪ IGV1	1/2	2/2	
Initial hemostasis for 48 hours, n (%)	31 (93.9)	34 (97.1)	0.60
Very early rebleeding (3–5 days), n	0	1	> 0.99
Treatment failure (5 days), n (%)	2 (6.0)	2 (5.7)	> 0.99
▪ GOV1	0/15 (0)	0/17 (0)	
▪ GOV2	2/12 (16.7)	1/14 (7.1)	
▪ IGV1	0/6 (0)	1/4 (25)	
Rebleeding between 6 – 42 days, n	3	4	0.67



▶ **Fig. 2** Probability of being free of rebleeding from gastric varices.



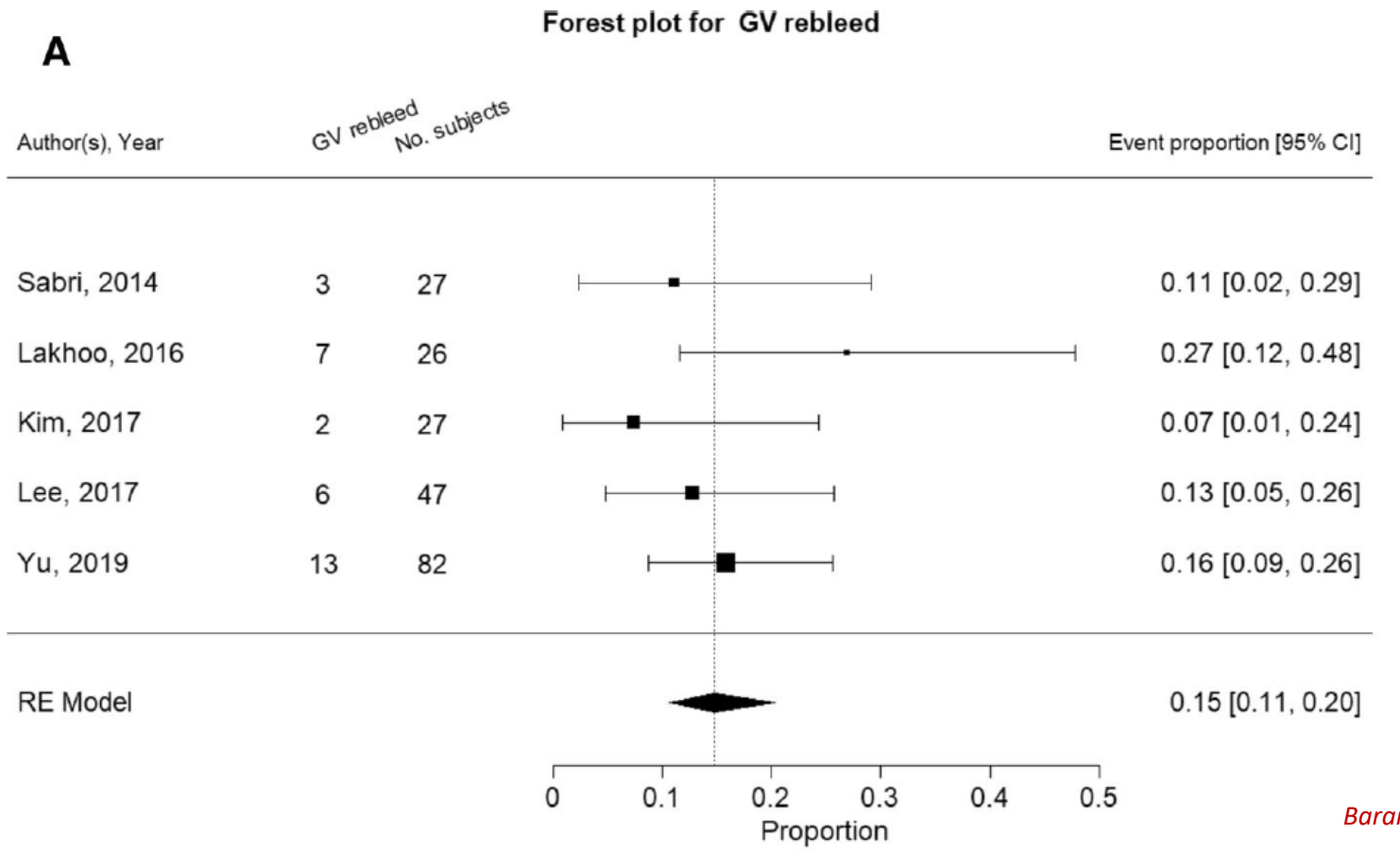
Lo GH et al Endoscopy. 2020 Jul;52(7):548-555.

TIPS for Gastric Varices

- 1st line therapy in some centers (including USA)
- Recommended as 2nd line therapy
  - If glue not available
- Hemostasis rates >95%
- Few studies specifically evaluating IGV1 or IGV2
- Rebleeding rates up to 15%-
  - Meta-Analysis of Clinical Outcomes

Barange et al Hepatology. 1999; 30: 1139-1143
Lo G et al. Endoscopy. 2007; 39: 679-685
Procaccini et al. Gastrointest Endosc. 2009; 70: 881-887
Henry Z et al. Clin Gastroenterol Hepatol. 2021 Jun;19(6):1098-1107.e1
Alqadi M et al. Cardiovasc Intervent Radiol (2021) 44:1231–1239

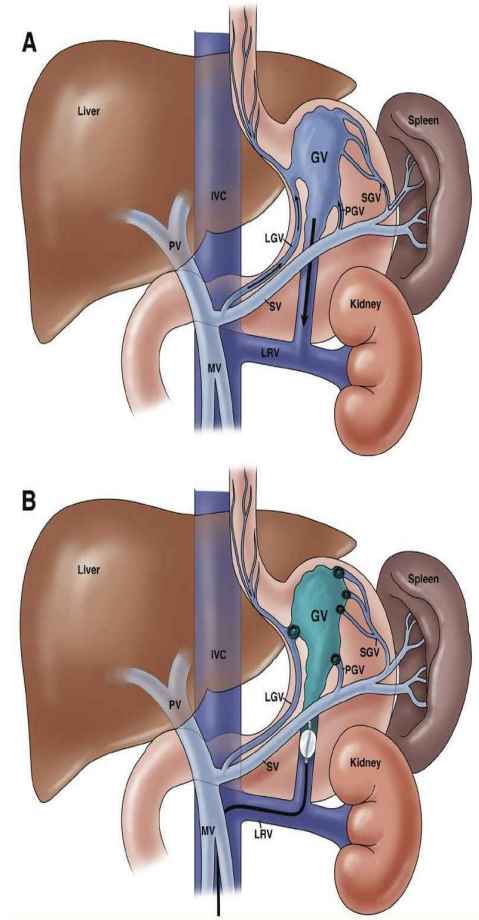
TIPS for Gastric Varices

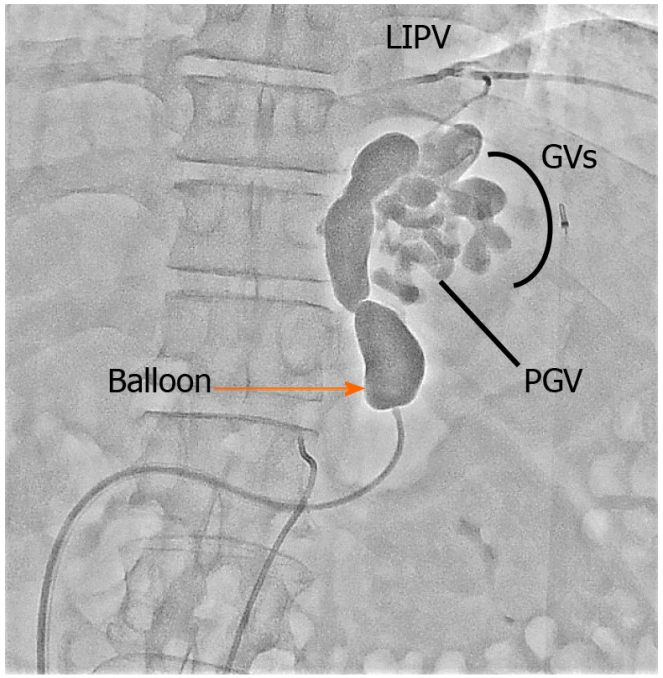


Barange et al Hepatology. 1999; 30: 1139-1143
Lo G et al. Endoscopy. 2007; 39: 679-685
Procaccini et al. Gastrointest Endosc. 2009; 70: 881-887
Henry Z et al. Clin Gastroenterol Hepatol. 2021 Jun;19(6):1098-1107.e1
Alqadi M et al. Cardiovasc Intervent Radiol (2021) 44:1231–1239

Balloon-occluded retrograde transvenous obliteration (BRTO) for Gastric Varices

- BRTO could be considered as an alternative to endoscopic treatment or TIPS
- Occlusion of blood flow with balloon catheter with instillation of a sclerosant proximal to the site of balloon occlusion.
- In the case of gastric varices, there frequently is a spontaneous gastrorenal shunt
- Hemostasis 95%, comparable to TIPS
- Very limited high-level data (e. g. RCTs) comparing TIPS and BRTO for cases where endoscopic hemostasis has failed and/or early recurrent gastric variceal bleeding occurs





J Clin Gastroenterol 2020; 54: 655-660

Yu Q, et al. J Clin Gastroenterol. 2021 Feb 1;55(2):147-158.

Balloon-occluded Retrograde Transvenous Obliteration Versus Transjugular Intrahepatic Portosystemic Shunt for Gastric Varices A Meta-Analysis

5 RCT and retrospective cohort studies. BRTO (n: 308) and TIPS (n:127)

TABLE 10 - Pooled Immediate Bleeding Control Rate of BRTO Versus TIPS

References	IBC of BRTO	Total BRTO	IBC of TIPS	Total TIPS
Choi et al[7]	8	8	7	7
Lee et al[9]	95	95	47	47
Gimm et al[11]	153	159	16	19
Total	256	262	70	73
Success rate	256/262	97.7%	70/73	95.9%

BRTO indicates balloon-occluded retrograde transvenous obliteration; IBC, immediate bleeding control; TIPS, transjugular intrahepatic portosystemic shunt.

1. *Similar technical success rates (91.4% vs. 89.7%, P=0.995)*
2. *BRTO -> lower likelihood of rebleeding (10.6% vs. 18.7%, P=0.027) and HE (0.00% vs. 23.1%, P<0.001)*
3. *BRTO more likely to aggravate ascites (22.4% vs. 4.3%, P=0.009).*

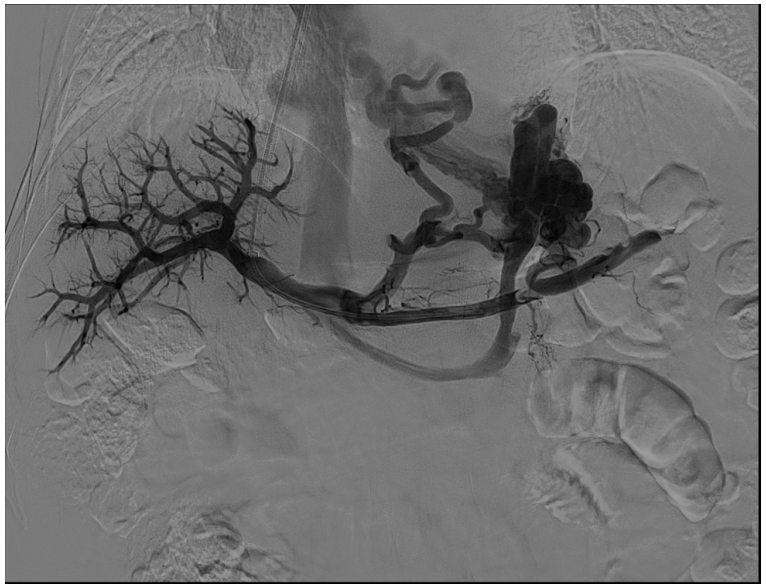
Yu Q, et al. J Clin Gastroenterol. 2021 Feb 1;55(2):147-158

BRTO and Gastric Varices

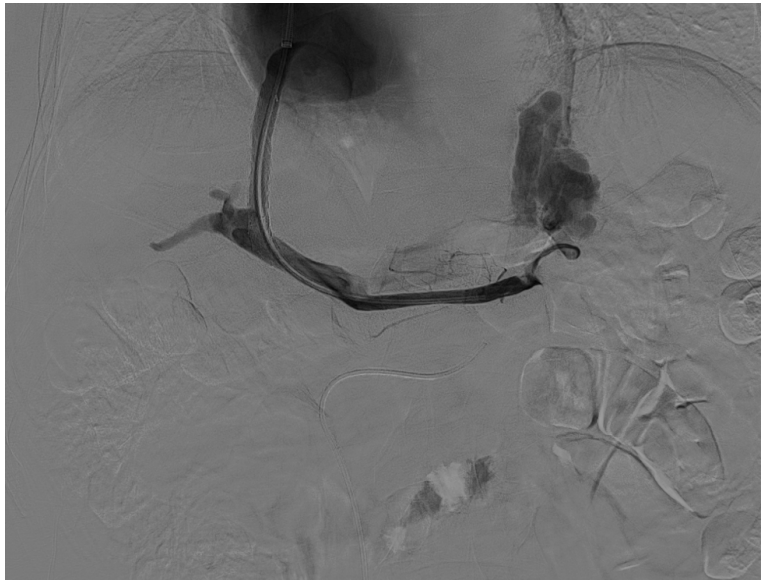
- In patients with GOV2 or IGV1, BRTO could be considered first-line (alternative to endoscopic treatment or TIPS), in centers with significant expertise, as it has been shown to be safe and effective
- Urgent rescue TIPS or BRTO are the best options for acute GV bleeding when there is a failure of endoscopic hemostasis or early recurrent bleeding.
- BRTO and TIPS have similar technical success rates and AE rates.
- Patient selection is important; however, given the limited quality of comparative data, specific selection criteria are not currently available

J Clin Gastroenterol 2020; 54: 655-660
Yu Q, et al. J Clin Gastroenterol. 2021 Feb 1;55(2):147-158
Baveno VII. J Hepatol. 2022 Apr;76(4):959-974. doi: 10.1016/j.jhep.2021.12.022

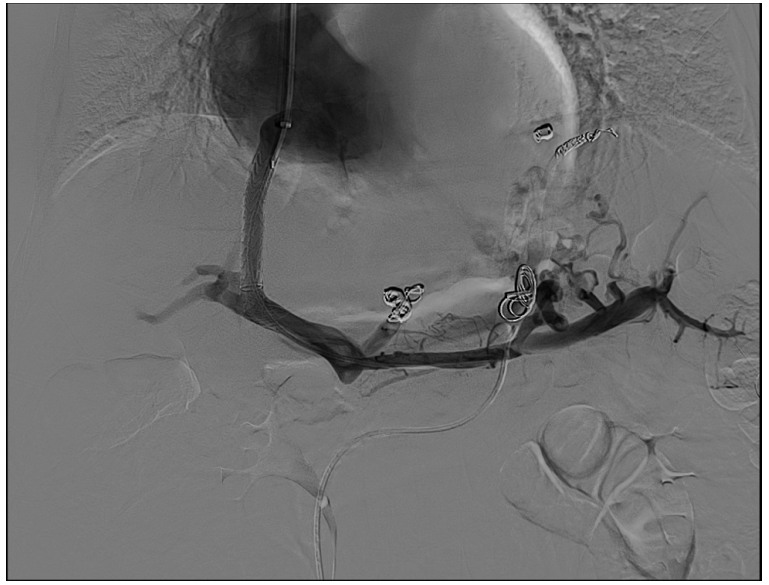
Combined TIPS &BRTO versus TIPS Alone for the Management of Gastric Varices



Pre-TIPS



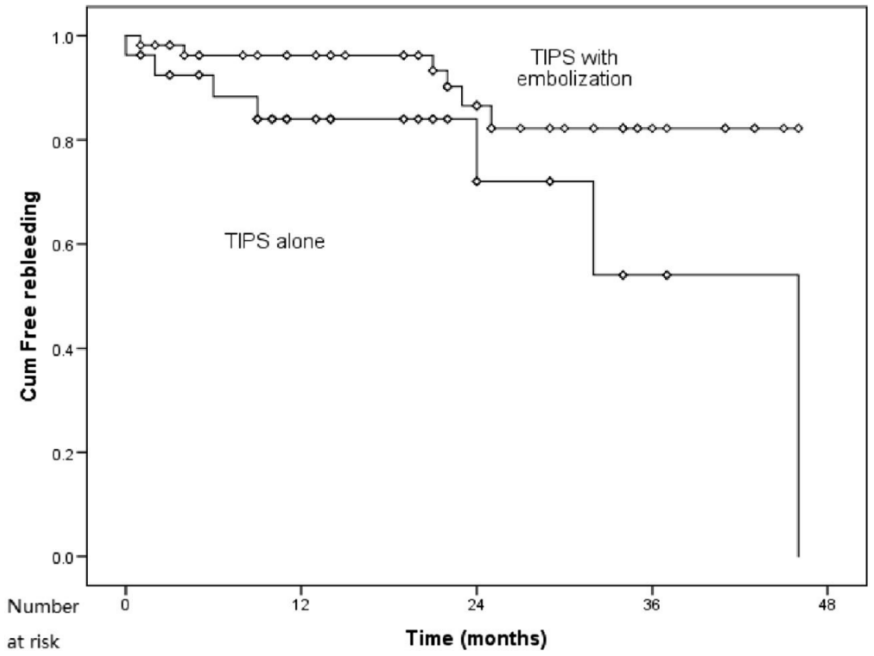
Post-TIPS



Post-TIPS+embolization

Combined TIPS & Obliteration versus TIPS Alone for the Management of Gastric Varices

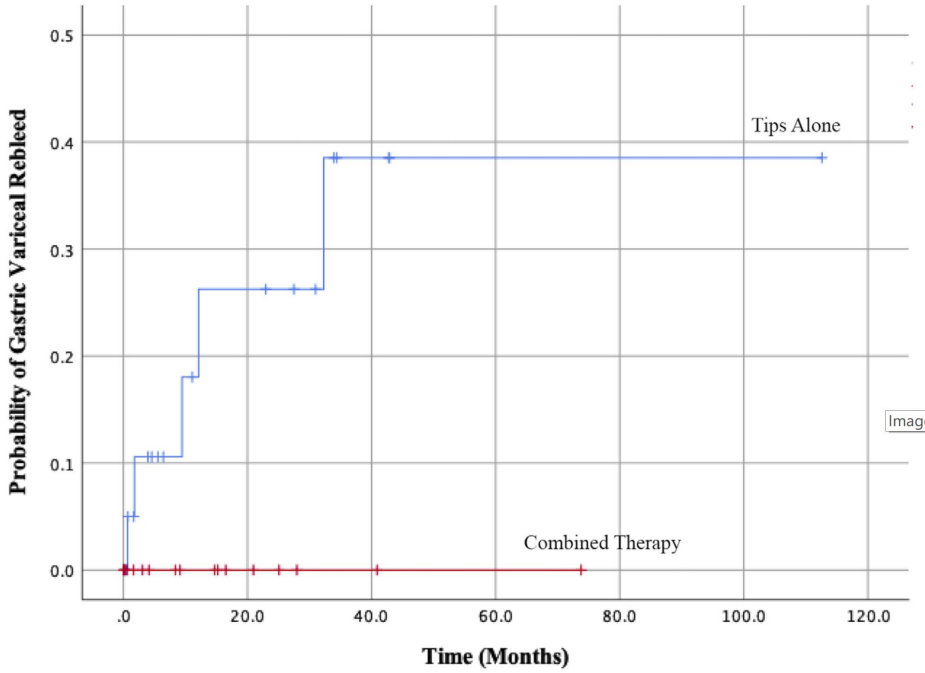
TIPS+ Emb (n=55) vs TIPS (n=26)

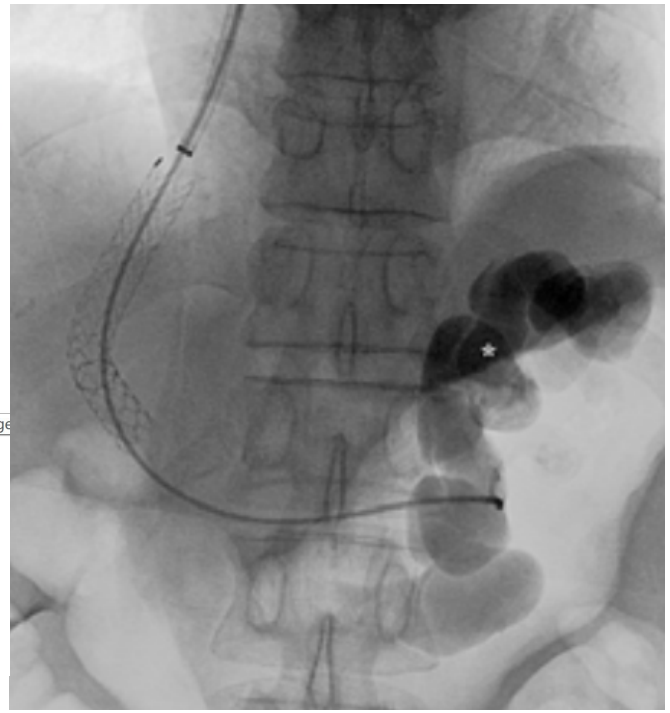


1 yr re-bleeding rate

3.8% vs 13%, P =.041

TIPS+ BRTO (n=18) vs TIPS (n=22)





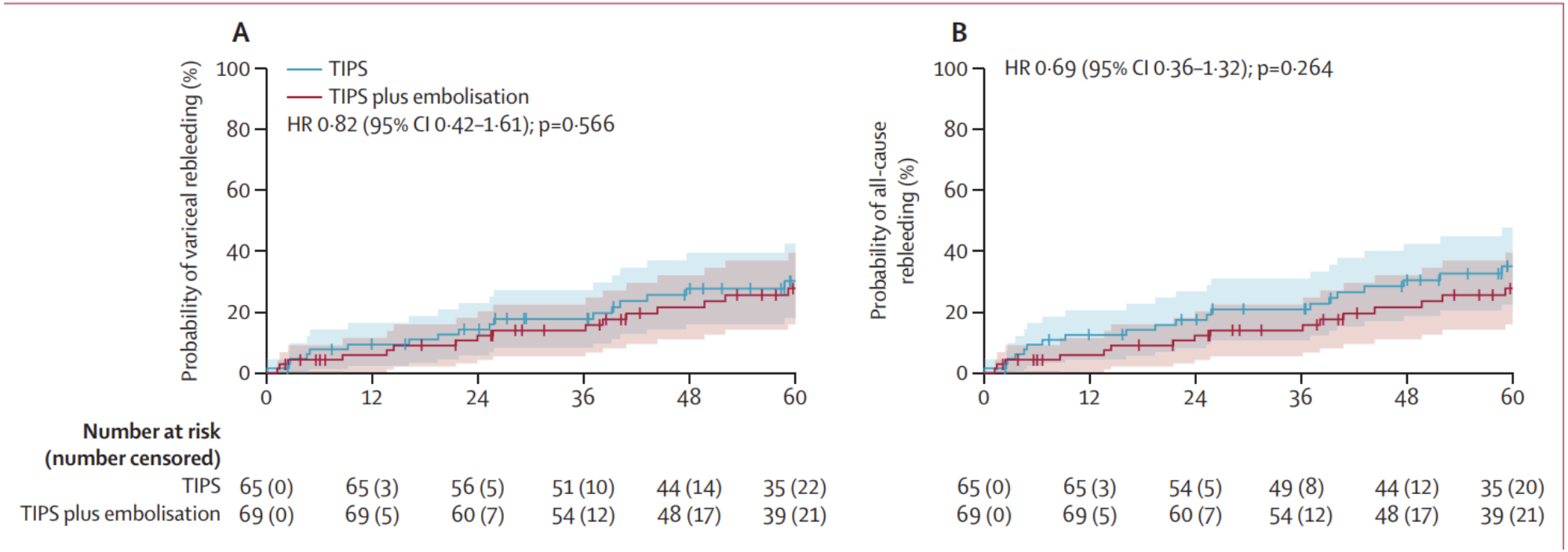
0% vs 23%, P =.056

Shah K et al J Vasc Interv Radiol. 2021 Feb;32(2):282-291.e1
Yu et al. Eur Radiol. 2019 Feb;29(2):699-706.

Transjugular intrahepatic portosystemic shunt with or without gastro-oesophageal variceal embolisation for the prevention of variceal rebleeding: a randomised controlled trial

Open label – TIPS alone (n:65) Vs TIPS + Emb (n:69), all successfully placed

GOV 1: 49%, GOV2: 17%, EV: 33%



No IGV's!

Lv Y. Lancet Gastroenterol Hepatol. 2022 Aug;7(8):736-746.

Combined TIPS & Embolization
Management of Gastric Varices

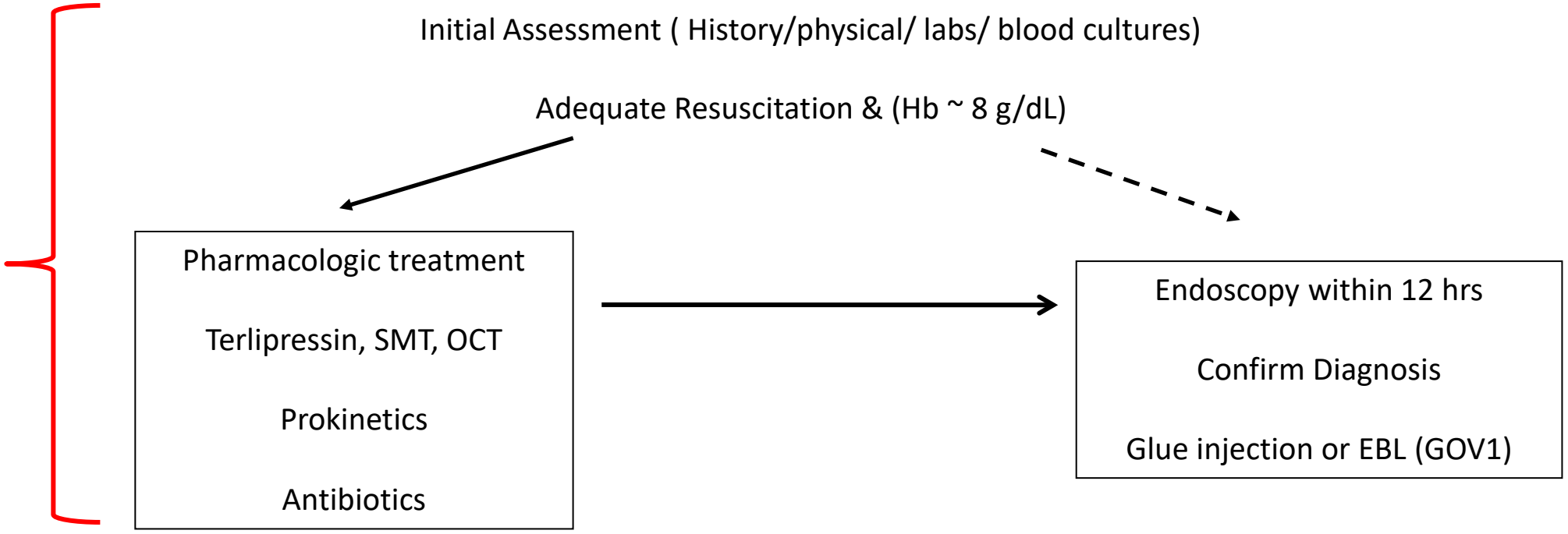
TIPS may be combined with embolization to control bleeding or to reduce the risk of recurrent variceal bleeding from gastric or ectopic varices (mainly large IGV's), particularly in cases when, despite a decrease in portosystemic pressure gradient, portal flow remains diverted to collaterals.

Lv Y. Lancet Gastroenterol Hepatol. 2022 Aug;7(8):736-746
Shah K et al J Vasc Interv Radiol. 2021 Feb;32(2):282-291.e1
Baveno VII. J Hepatol. 2022 Apr;76(4):959-974. doi: 10.1016/j.jhep.2021.12.022
Yu et al. Eur Radiol. 2019 Feb;29(2):699-706.

Treatment of Acute GV Bleeding

Baveno VII (2022), AASLD Guidance (2017)

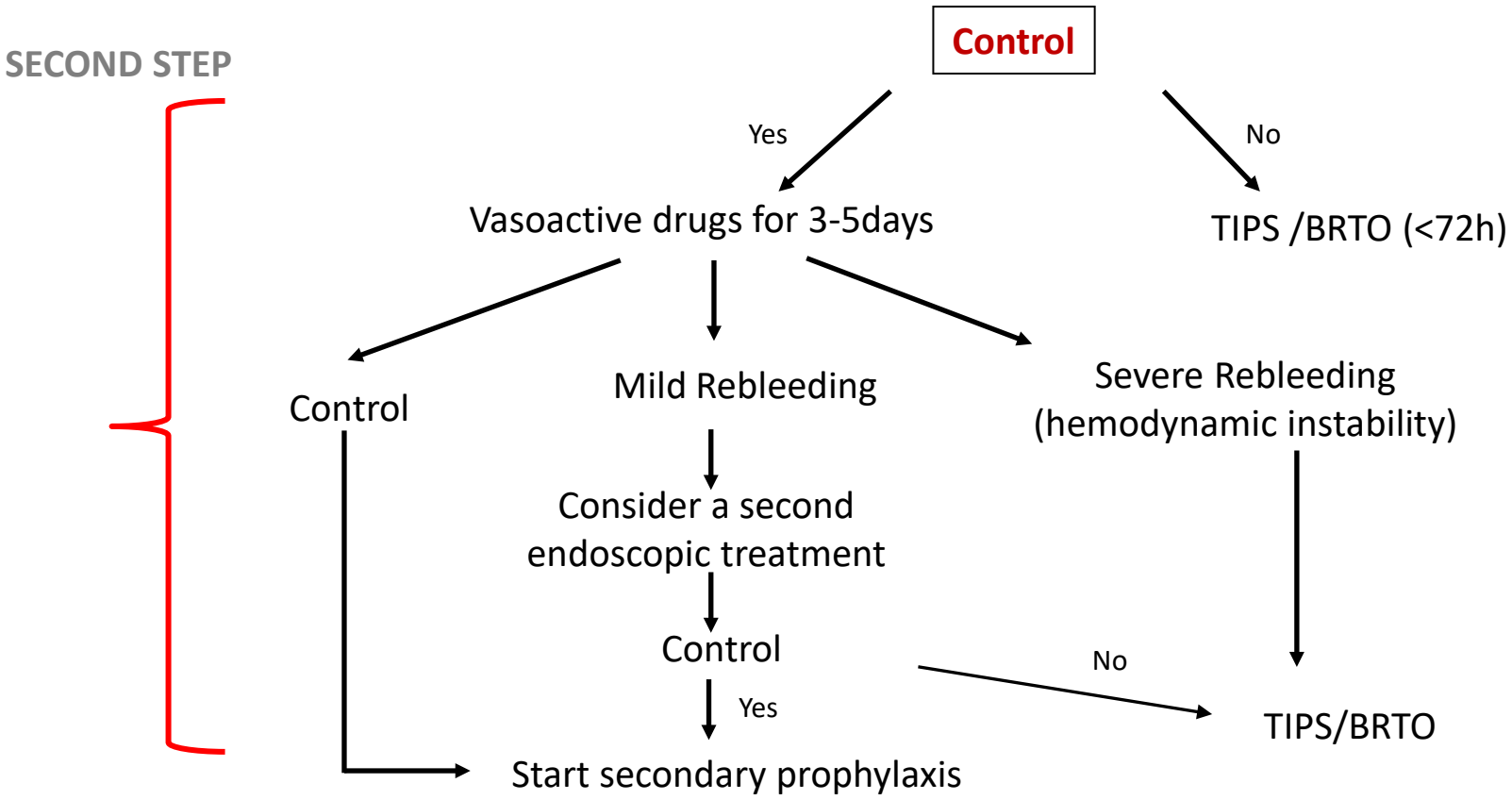
FIRST STEP



Baveno VII. J Hepatol. 2022 Apr;76(4):959-974. doi: 10.1016/j.jhep.2021.12.022

Treatment of Acute GV Bleeding

Baveno VII (2022), AASLD Guidance (2017)



Baveno VII. J Hepatol. 2022 Apr;76(4):959-974. doi: 10.1016/j.jhep.2021.12.022

PORTAL HYPERTENSIVE GASTROPATHY AND GAVE

Portal Hypertensive Gastropathy (PHG) Definition

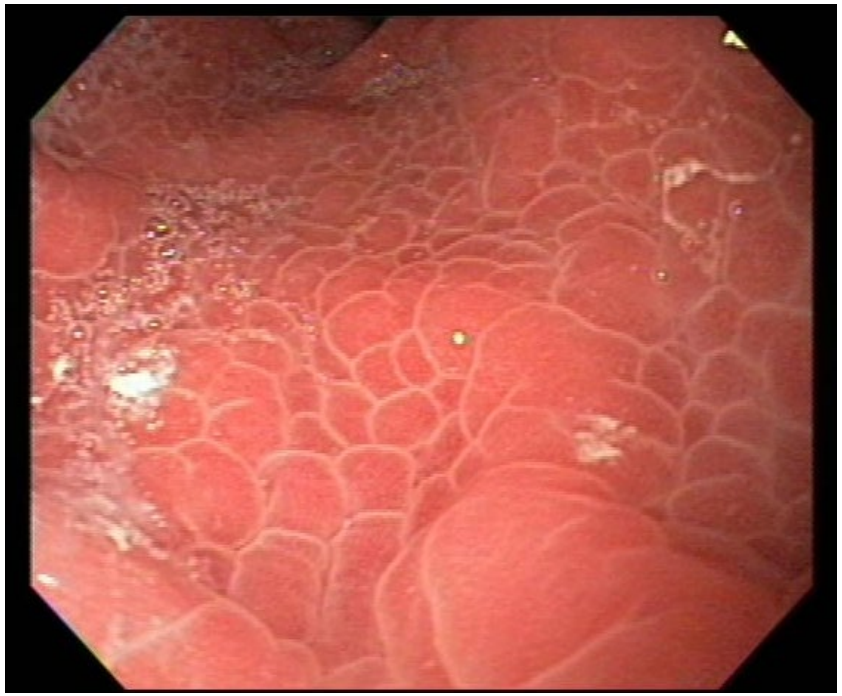
- Macroscopic changes of the stomach associated with mucosal and submucosal vascular dilation

- Endoscopy:
  - Mosaic pattern
  - Red spots

McCormack T, Gut 1985
Ripoll C, Garcia-Tsao, Clin Liv Dis 2010

Portal Hypertensive Gastropathy (PHG) Characteristics

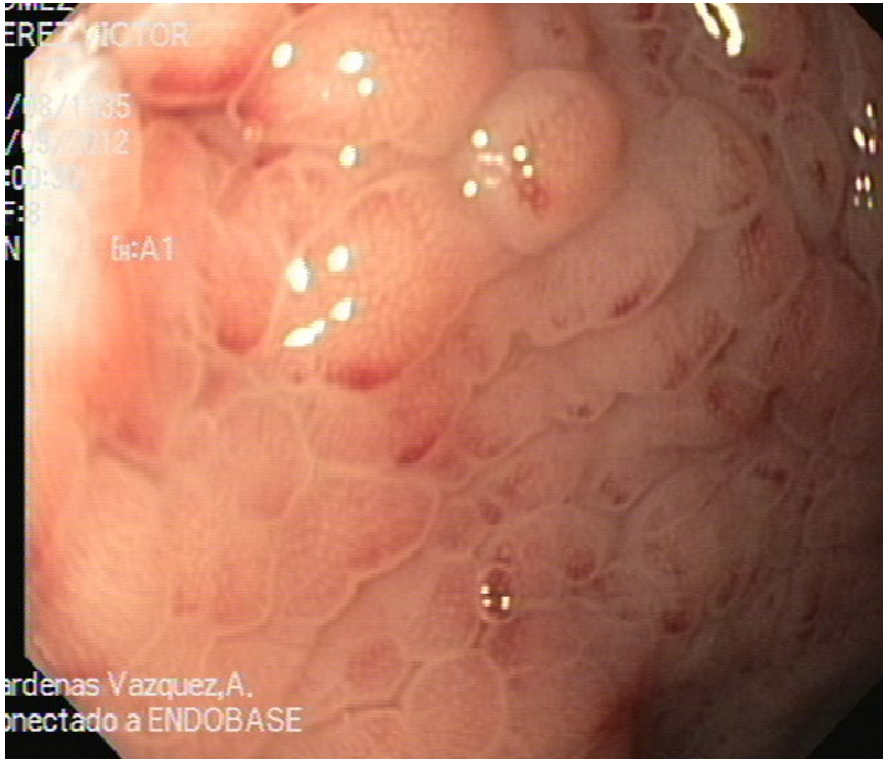
- Mild or severe
- Characterized by a cobblestone / snakeskin appearance
- Distribution – fundus and body
- Bleeding responds to measures that reduce portal hypertension



Kalafateli M et al, Dig Dis Sci 2012
Patwardhan VR, Cardenas A.Aliment Pharmacol Ther. 2014

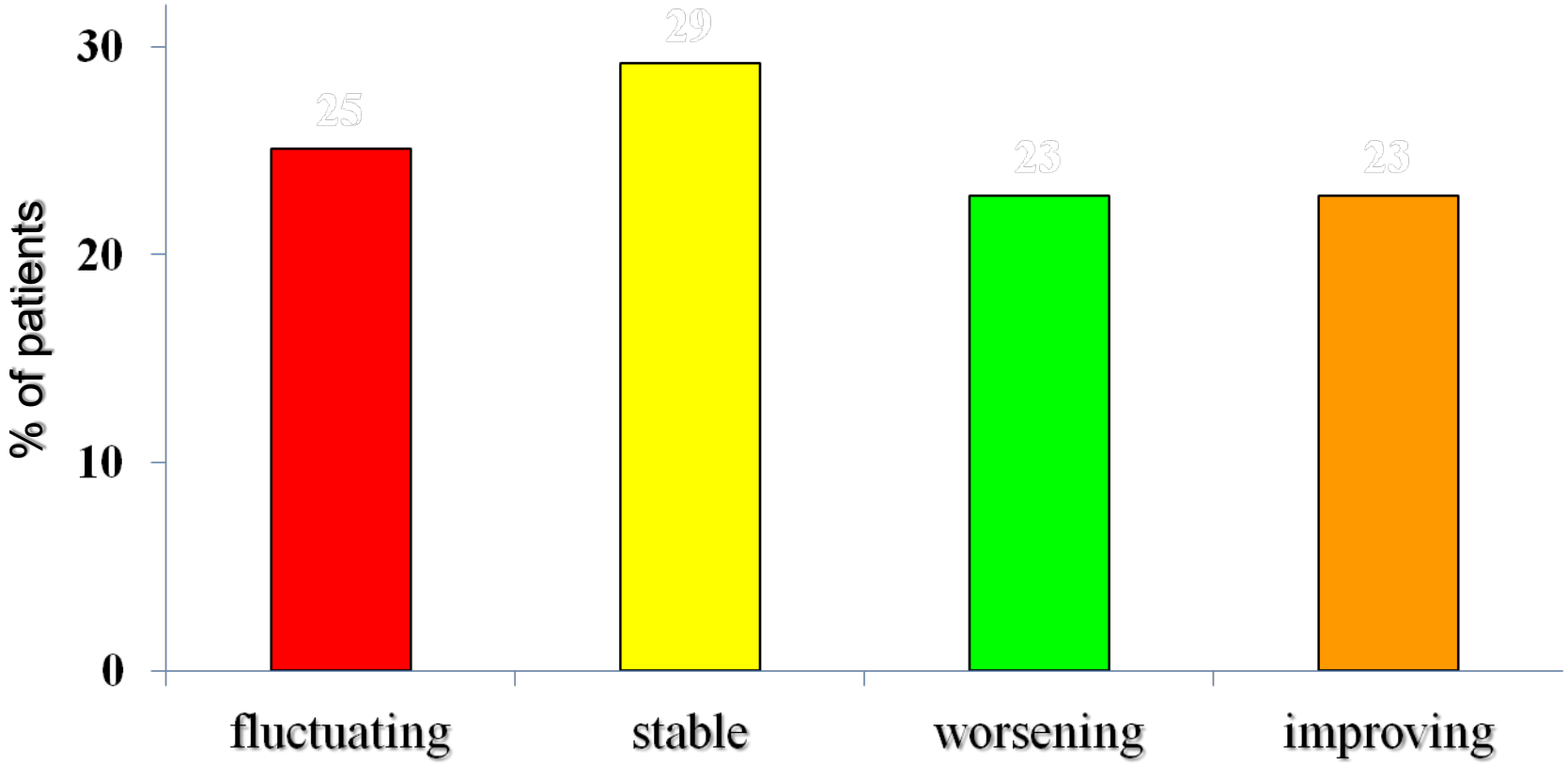
Portal Hypertensive Gastropathy (PHG) Prevalence

- Overall prevalence 20%-98%
- Highest prevalence in advanced cirrhosis and those with varices
- Prevalence seems to increase with EV obliteration



Primignani M, Gastroenterology 2000
Merli M, Am J Gastroenterol 2004

PHG: Natural History



N= 373 / 3 yr follow up

Primignani M, Gastroenterology 2000

Portal Hypertensive Gastropathy
Natural history

- HALT C study → 1017 patients with bridging fibrosis/compensated cirrhosis were analyzed

- 37% had PHG
  - 34% mild changes, 3% severe changes.
  - *Mosaic pattern - 33%, red marks – 15%, GAVE - 3%*

- More prevalent in advanced disease and large EV

4 yr follow up → new onset PHG - 13% / yr
worsening PHG - 7% / yr

Fontana R, Am J Gastroenterol 2006
Fontana R, Am J Gastroenterol 2011

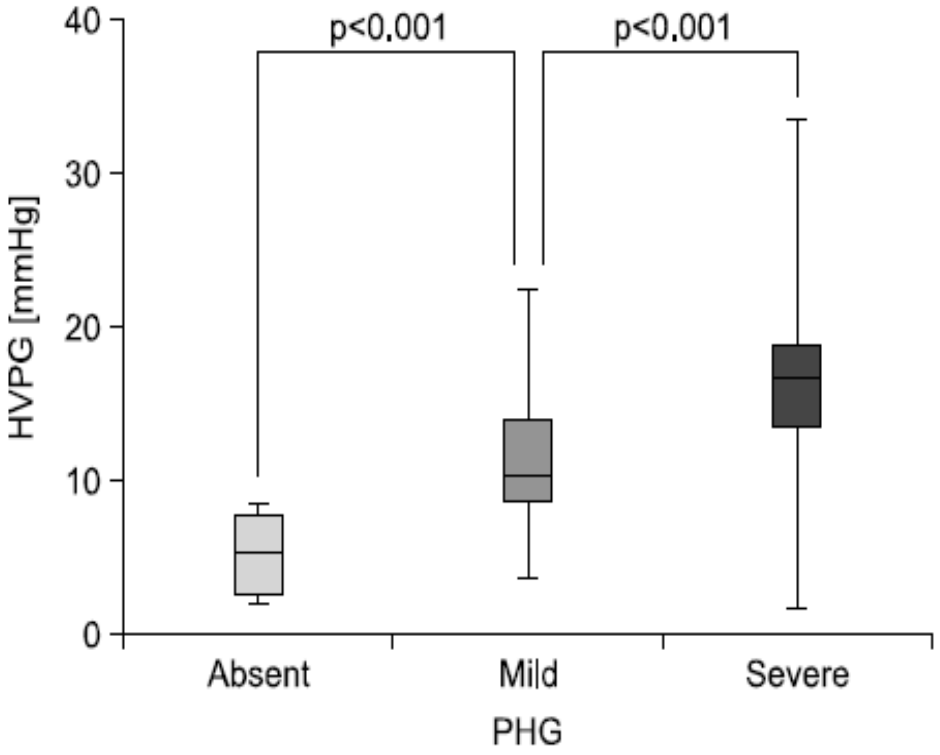
Portal Hypertensive Gastropathy Pathophysiology

1. Increased portal pressure > 12mm Hg
2. Abnormal gastric mucosal blood flow
   Congestion → may lead to hypoxia
3. Mucosa susceptible to injury
   Impaired healing and mucosal defense
4. Local factors : overproduction of NO, endotoxemia and prostaglandins
   Role in microcirculatory changes

Kumar K et al, J Clin Gastroenterol 2010
Perini R, Nat Clin Pract Gastroenterol Hepatol 2009
Patwardhan VR, Cardenas A. APT 2014

Portal Hypertensive Gastropathy Pathophysiology

Degree of PHG is associated with severity portal hypertension



Kim et al Dig Dis Sci 2010

Portal Hypertensive Gastropathy Classification

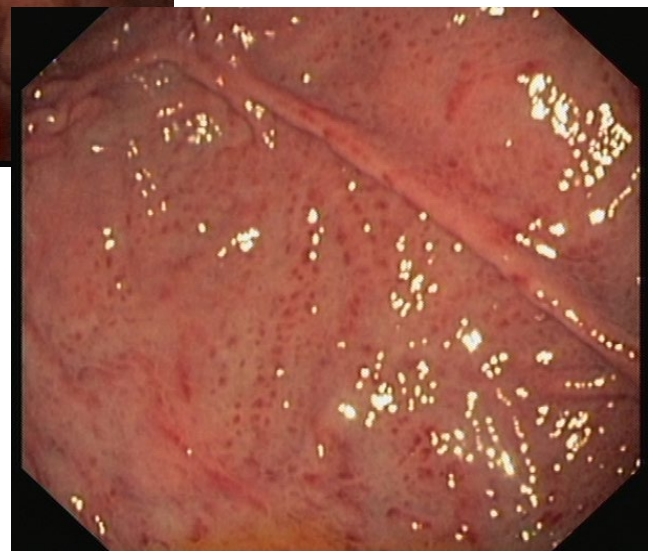
New Italian Endoscopic Club for the Study and Treatment of Esophageal Varices
MILD - Mosaic like pattern
Mild : diffusely pink areola
Moderate: flat red spot in center of pink areola
Severe: diffusely red areola
SEVERE - Red marks
Red lesions of variable diameter, flat or slightly protuding
Discrete or confluent

Spina GP, et al.. J Hepatol 1994

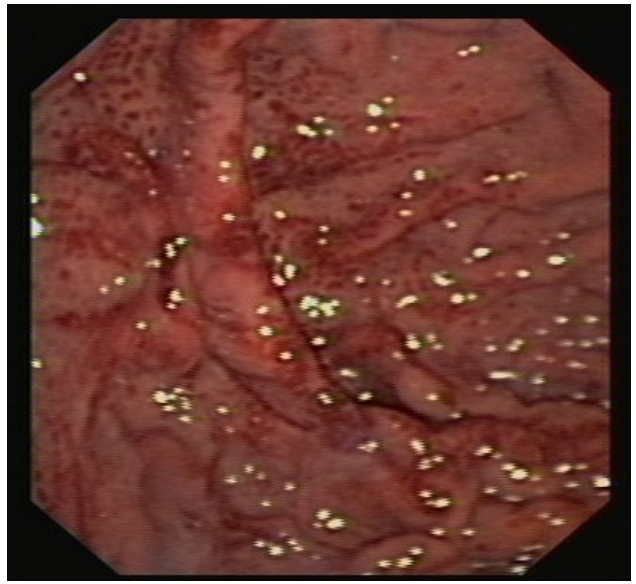
Mosaic like pattern

Mild

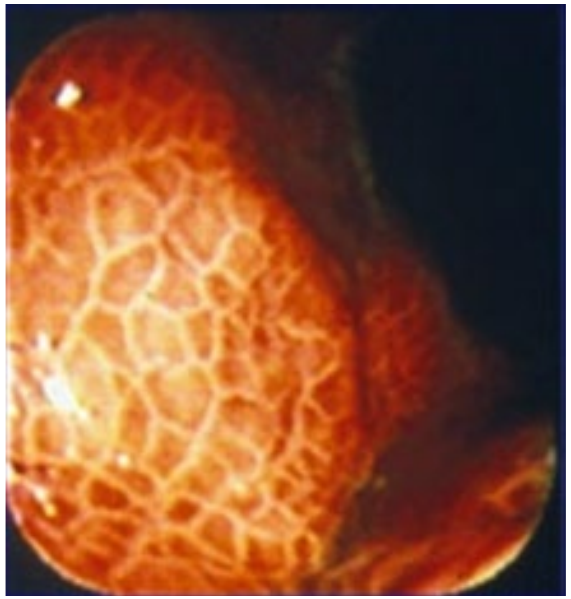
Moderate

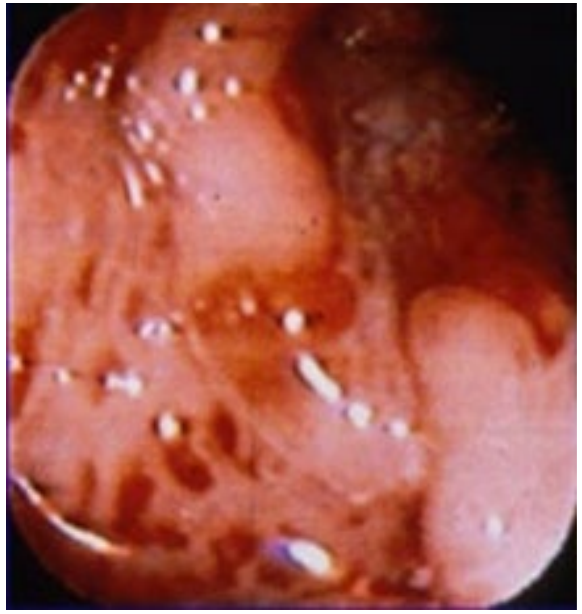


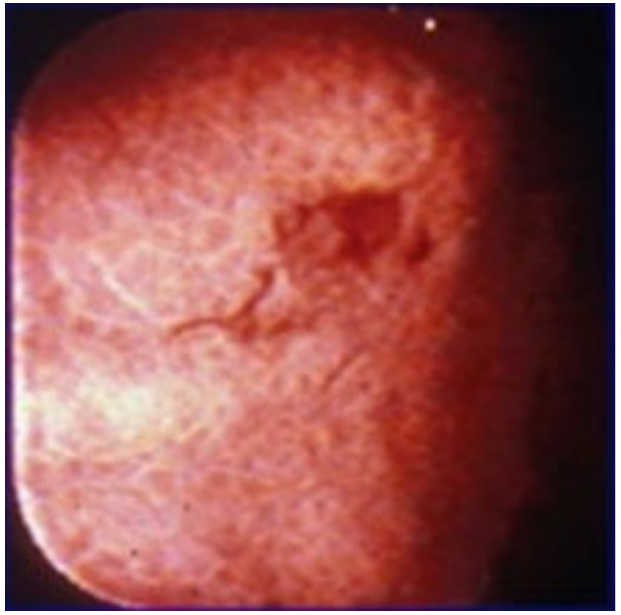
Severe



Red marks (severe)







Management

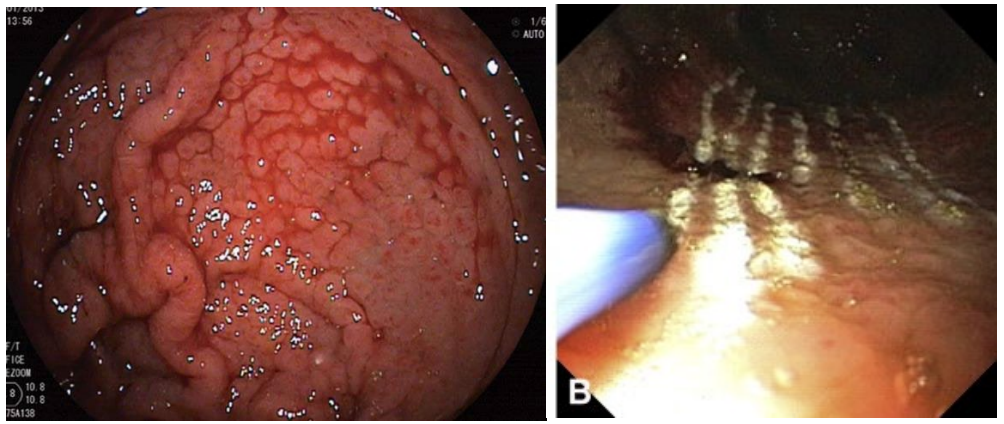
Asymptomatic patients- no therapy !!

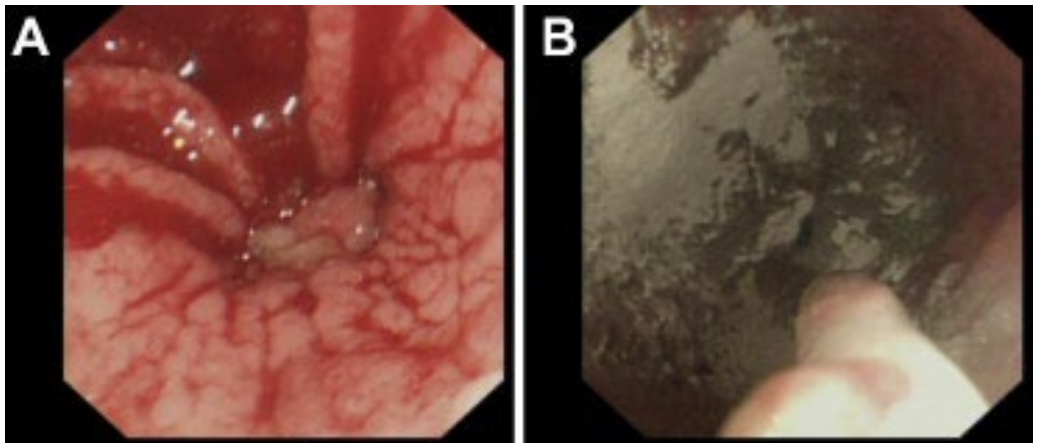
Therapy	Intervention
Reduction of portal pressure	Beta blockers
	Somatostatin/octreotide
	Terlipressin
	TIPS
Local therapy	Argon Plasma coagulation
Underlying liver disease	Liver transplantation

Patwardhan VR, Cardenas A. APT 2014

Treatment of portal hypertensive gastropathy
Acute bleeding

- *Acute bleeding – occurs in 2-12% of cases*
- *Severe PHG and advanced liver disease*
- *Therapy –*
  1. *IV vasoconstrictors & antibiotics*
  2. *TIPS*
  3. *Endoscopic therapy- scarce data!*
     1. *Argon plasma coagulation*
     2. *Hemostatic powder*





J Hepatol. 2014 Feb;60(2):457-60.
Gastrointest Endosc. 2008 Sep;68(3):440-6.

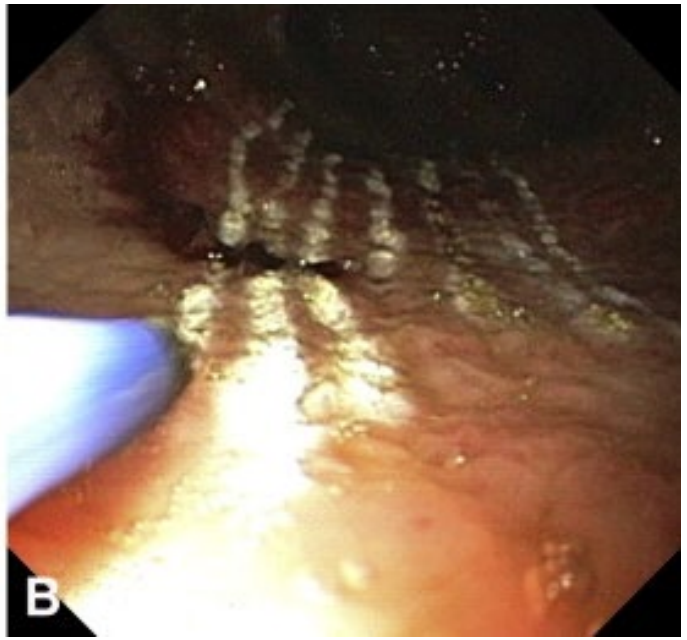
Argon Plasma Coagulation (APC)

Noncontact thermal coagulation -applies high-frequency electric current that is passed through argon gas.

Scarse data in PHG and active bleeding

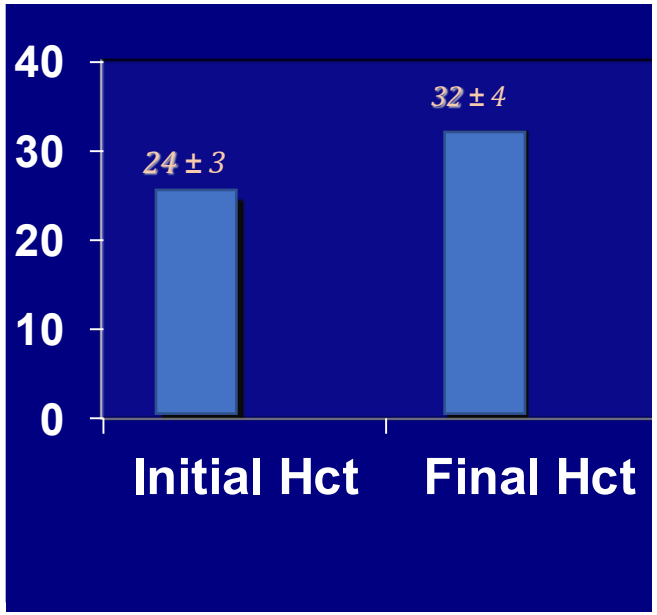
APC aimed to ablate specific lesions and /or the majority of mucosa at least 80% in diffuse lesions.

APC is administered at 40-60W and 1–2 L/min of flow



APC in PHG

- 11 patients with acute bleeding from PHG were treated with APC-(mean 2 -3 sessions)
- 81% of the patients stopped bleeding or reduced transfusion requirements



Who?

Suboptimal control with IV vasoconstrictors

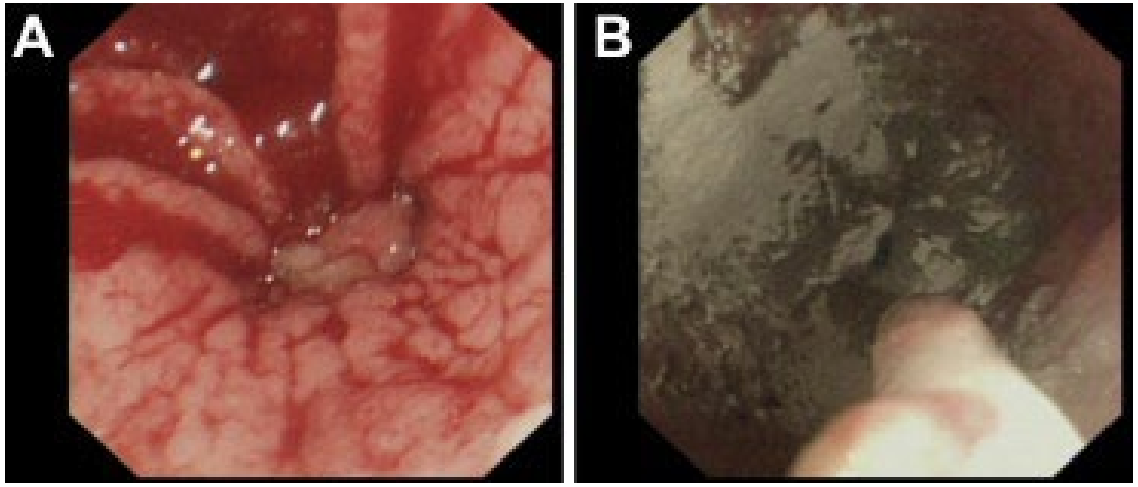
Poor candidates for TIPS

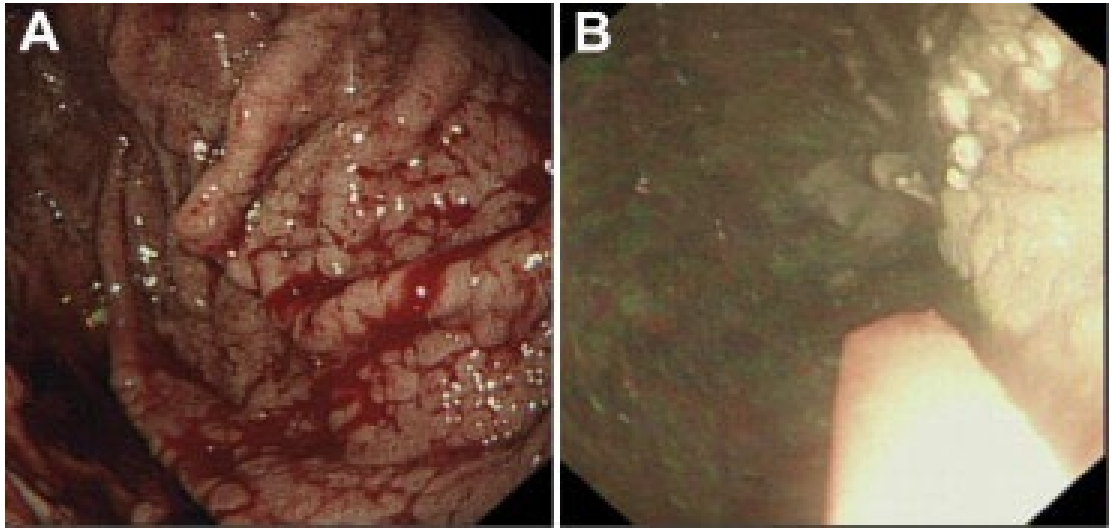
Herrera S, Gastrointestinal Endoscopy 2008

Hemospray

- Hemostatic powder licensed for endoscopic hemostasis (Europe and Canada).
- Easy to apply, non-contact method, which can cover large areas of mucosa, may benefit in acute bleeding from portal hypertensive gastropathy in case reports.
- No controlled studies

J Hepatol 2014 Feb;60(2):457-60





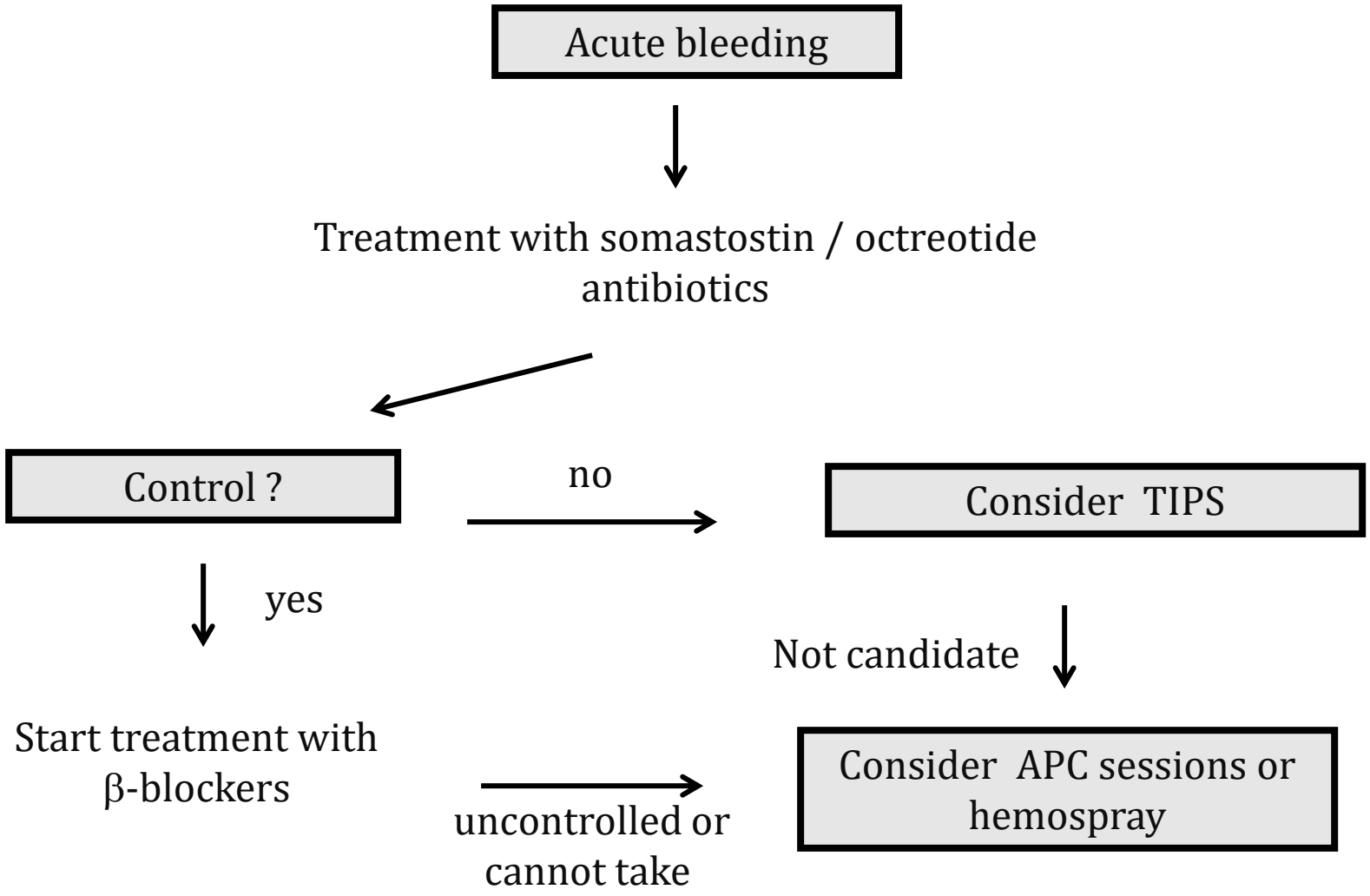
J Hepatol. 2014 Feb;60(2):457-60

Portal Hypertensive Gastropathy
Chronic bleeding

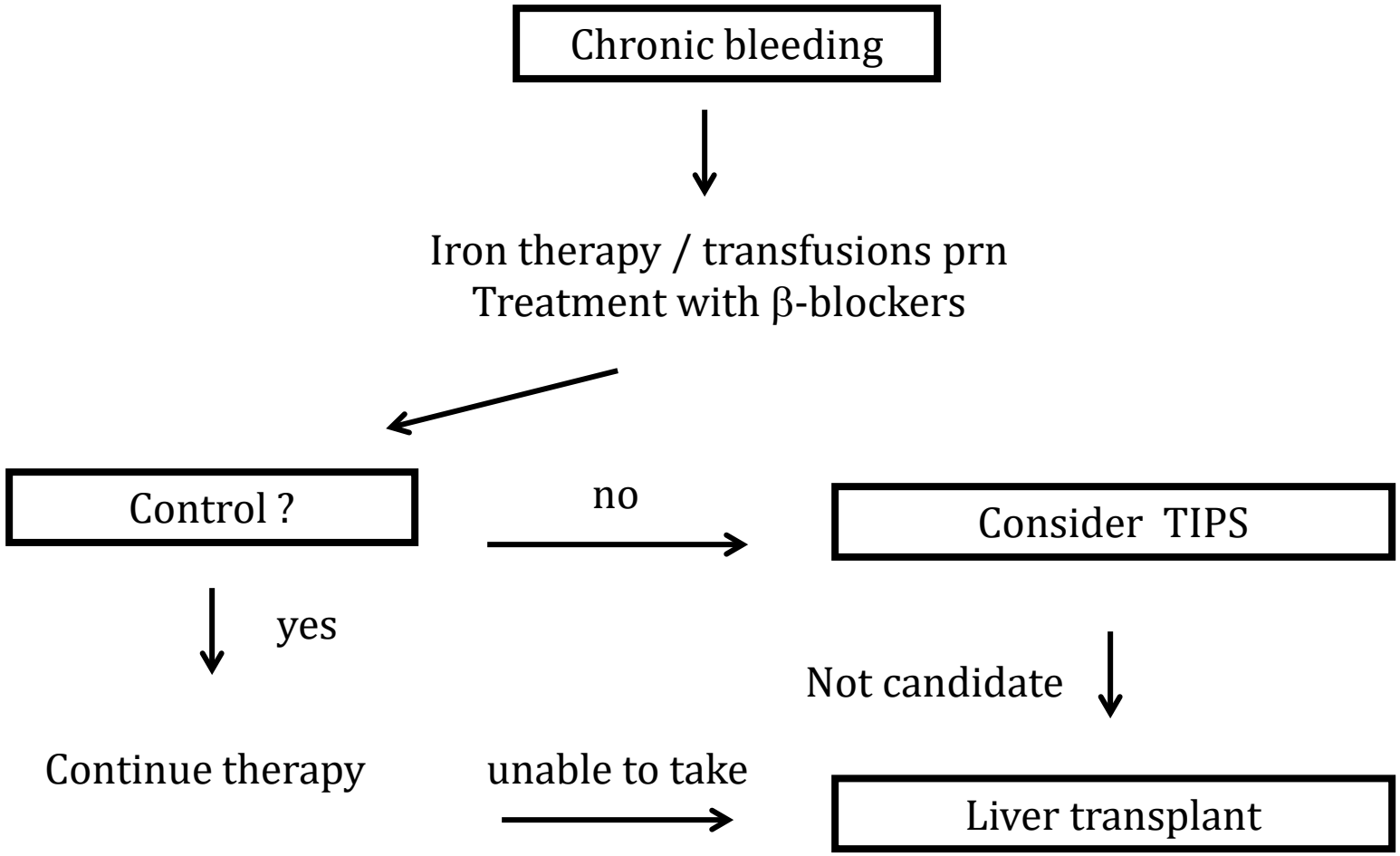
- Obscure / occult GI bleeding and anemia
- Occurs in up to 26% of cases
- Mainstay of therapy :
  - Iron supplementation / transfusions
  - Propranolol (20mg bid) or Nadolol (40 mg qd)
    - Decreases rebleeding ~ 60-80% cases
  - TIPS
    - Refractory cases / cirrhosis (Child < 12 points)

Perez-Ayuso, Lancet 1991
Kamath P, Gastroenterology 2000

PHG Treatment Algorithm



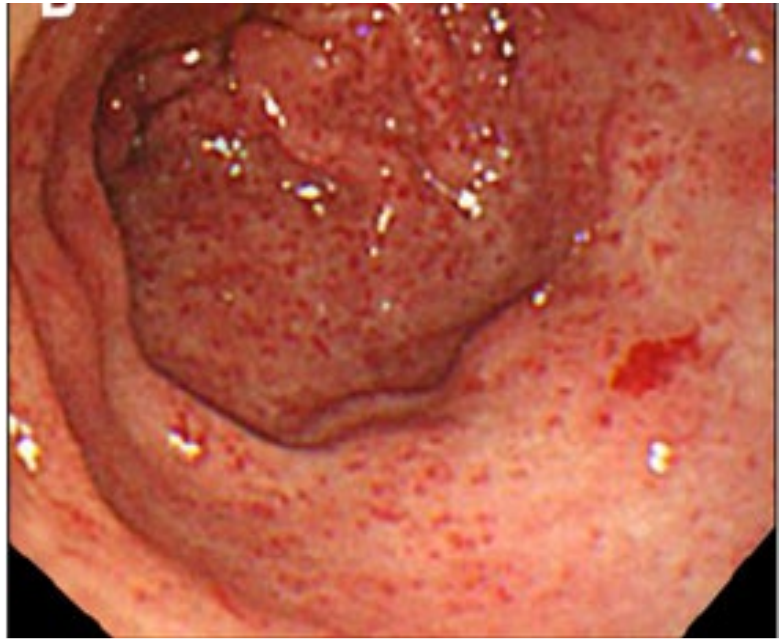
PHG Treatment Algorithm



GAVE

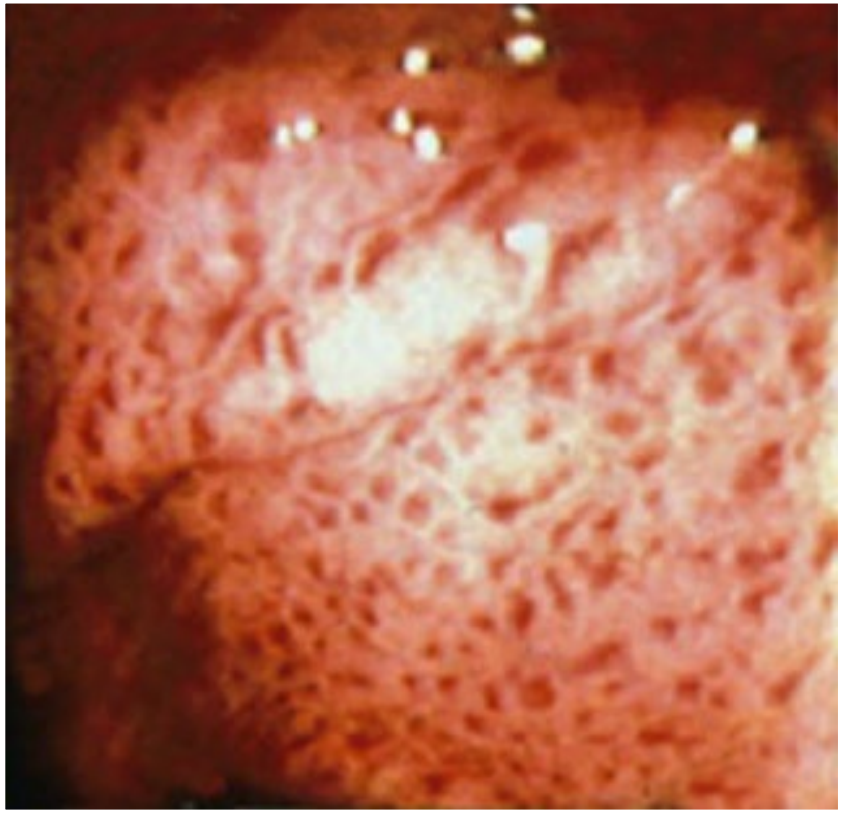
Watermelon Stomach

Diffuse Gastric Vascular Ectasia



Jabbari , Gastroenterol 1984
Ripoll C, Dig Liver Dis. 2011

Severe PHG may be difficult to distinguish from diffuse GAVE



Severe PHG

Diffuse GAVE

How to tease apart?

	PHG	GAVE
Associated with portal hypertension	Yes	No
Distribution in stomach	Proximal	Distal
Mosaic pattern	Present	Absent
Associated with other diseases	No	Yes
Response to therapies directed at decreasing portal pressure	Yes	No
First line therapy	Drugs	Endoscopy
Salvage therapy	TIPS	Other

Patwardhan VR, Cardenas A. APT 2014

Biopsy may help tease apart PHG and GAVE

Correlation between histology and endoscopy

	PHG	GAVE
Biopsy:		
-Thrombi	-	+ + +
- Vascular ectasia		+ + +
- Spindle cell proliferation	+	++
- Fibrohyalinosis	-	+ + +
- Dilated capillaries	+++	+
- Submucosal edema	+++	-
- Thick submucosal vessels	+++	-

Do you really want to do a jumbo biopsy in patients with advanced cirrhosis?

Bella et al Gastroenterol Hepatol. 2018 Nov

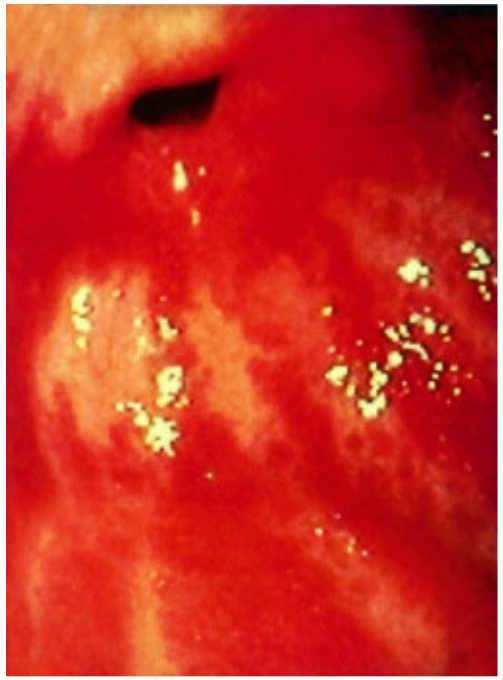
Gastric Antral Vascular Ectasia Characteristics

- GAVE is distinct entity
- Occurs in < 5% of patients with cirrhosis
- Not related to portal hypertension
- Iron deficiency anemia due to chronic GI bleeding
- Other disease states associated with GAVE
  - autoimmune connective tissue disorders
  - systemic sclerosis
  - renal failure
  - bone marrow transplantation

Gostout, J Clin Gastroenterol 1992
Kalafateli M, Dig Dis Sci, 2012

Gastric Antral Vascular Ectasia Pathophysiology

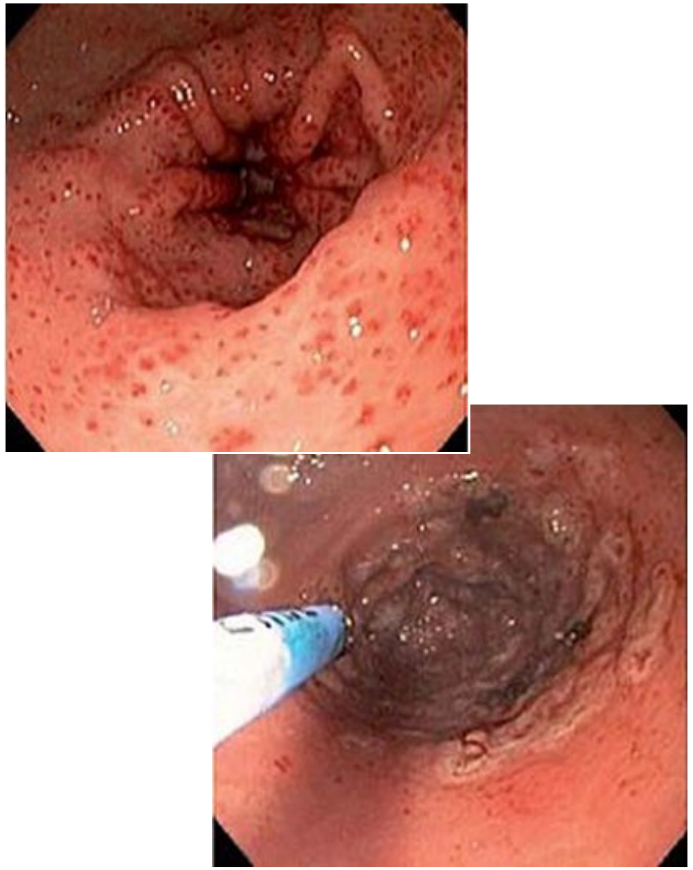
- Mainly unknown
- Related more to liver insufficiency
  - does not respond to BB or TIPS
  - Resolves after LT
- High levels of gastrin and prostaglandin E2 (vasodilators)
- Abnormal antral motility
- Mechanical stress



Quintero Gastroenterology 1987
Sparh, Gut 1999
Selinger, Digestion 2008

Gastric Antral Vascular Ectasia Therapy

- Indicated for bleeding
- Medical treatment ?
  - *Steroids, tranexanemic acid, thalidomide –poor results*
- Endoscopy
  - APC (standard of care)
  - ND:Yag laser (>complications)
  - Band ligation (promising)
  - RFA (refractory cases)



Kwan Am J Gastroenterol 2006
Fuccio Digestion 2008
Wells, Gastrointest Endosc 2008
Sato Digest Endosc 2012

Gastric Antral Vascular Ectasia
APC

- Effective in 85-90%
- Reduces transfusion requirements
- Increases Hb levels (mean 2-3g/L)
- Safe , easily applied
- Widely available

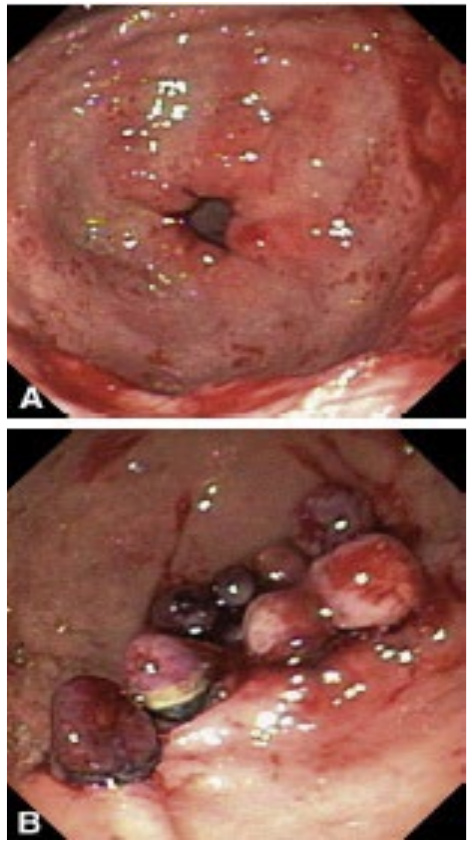
- Large areas can be treated
- Treatment every 2-4 weeks
- Approximately 3-4 sessions

Recurrence in 30-60 %

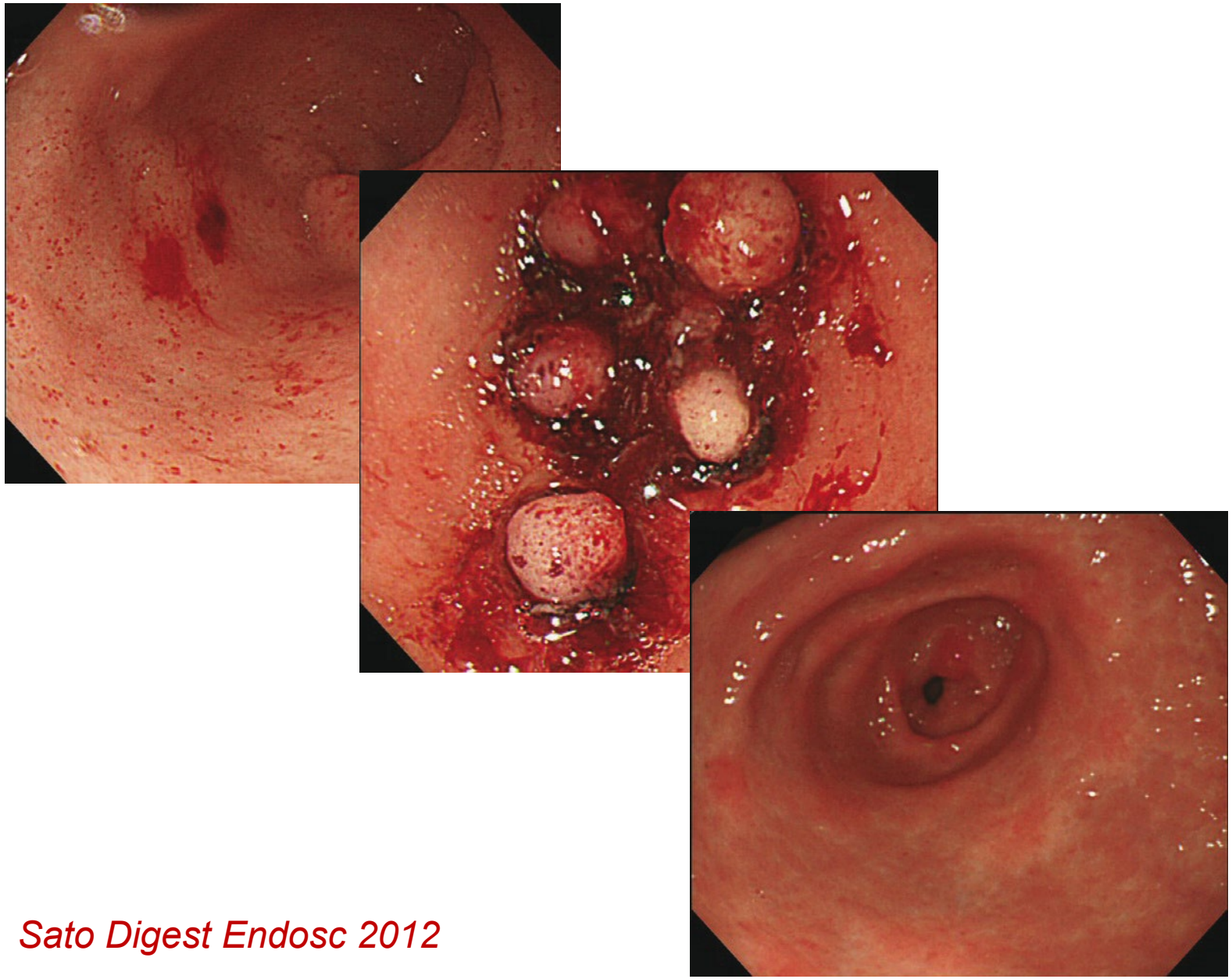
Sebastian S, Dig Liver Dis. 2004
Kwan Am J Gastroenterol 2006
Fuccio, Digestion 2008
Herrera S ,Gastrointest Endosc 2008

Gastric Antral Vascular Ectasia Banding

- Used given safety and efficacy of EBL in obliterating submucosal vascular plexus
- Involves banding a large area of antrum
- Maximum amount of bands placed (mean 7-12)
- Scarse data –
- 2 small studies with promising results



Wells, Gastrointest Endosc 2008
Sato Digest Endosc 2012



Sato Digest Endosc 2012

Gastric Antral Vascular Ectasia
Banding- summary of 2 studies

	APC (n=35)	Banding (n= 21)
Rebleeding	68-70%	8.3 - 33%
Transfusion	2.7-5.7	1-2.5
Cessation of bleed	56%	23%
Treatment sessions	3-4	1-3
Mean Hb level post	10	11
Deaths	33-39%	33-39%
Side effects	bleeding	bleeding, nausea, vomiting

Wells, Gastrointest Endosc 2008
Sato Digest Endosc 2012
Patwardhan, Cardenas APT 2014

Gastric Antral Vascular Ectasia
Prospective study

	Banding (n= 21)
Clinical response	19%
Hb - Before EBL / After EBL	88 (101–118) vs109 (79–97) p<0.001
PRBC (Before EBL / After EBL)	2.85 (2.03–3.6) vs 1.15 (0.3–2)p<0.001
Sessions Bands applied	2.28 (1-6) 16 (6-59)
Side effects	2 Transient abdominal pain

Zepeda – Gomez- Endoscopy. 2015

New approaches for GAVE in cirrhosis

Endoscopic band ligation in the treatment of gastric antral vascular ectasia: a systematic review and meta-analysis

Endoscopic success with EBL for treatment of GAVE

Study name	Event rate	Lower limit	Upper limit	Z-Value	P-Value
Wells et al (2008)	0.9500	0.5251	0.9969	2.0293	0.0424
Sato et al (2013)	0.9615	0.5968	0.9976	2.2319	0.0256
Koehane et al (2013)	0.9444	0.4953	0.9966	1.9469	0.0515
Abdelhalim et al (2014)	0.9500	0.7178	0.9930	2.8699	0.0041
Zepeda-Gomez et al (2014)	0.9048	0.6887	0.9761	3.0284	0.0025
Abd Al-Waab et al (2019)	0.7222	0.4810	0.8794	1.8158	0.9694
Abdel Ghaffar et al (2019)	0.9500	0.7178	0.9930	2.9699	0.0041
Eccles et al (2019)	0.8182	0.6501	0.9160	3.3325	0.0009
Hasan et al (2020)	0.9500	0.7178	0.9930	2.8699	0.0041
	0.8784	0.8025	0.9278	6.7339	0.0000

Event rate and 95% CI

−1.00 −0.50 0.00 0.50 1.00

a

Endoscopic success with EBL vs APC for treatment of GAVE

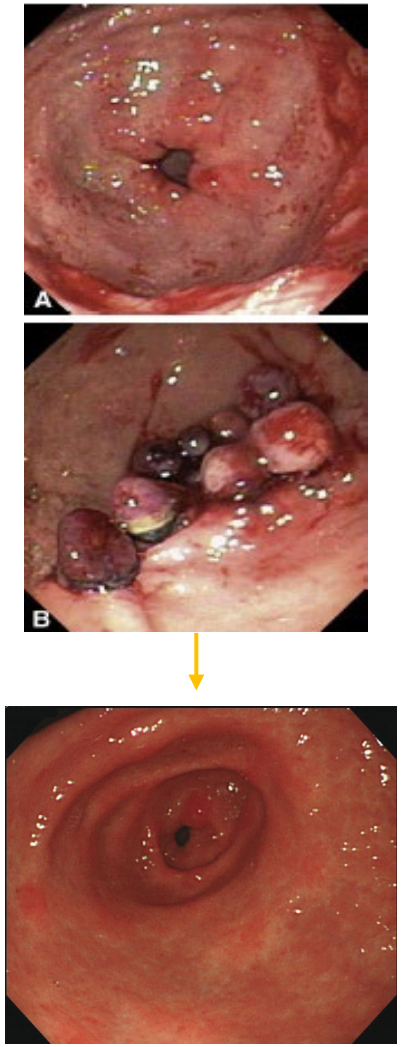
Study name	Statistics for each study: Odds ratio	Lower limit	Upper limit	Z-Value	P-Value
Koehane et al (2013)	19.267	0.944	393.401	1.922	0.055
Abdelhalim et al (2014)	12.667	1.402	114.419	2.561	0.024
Abd Al-Waab et al (2019)	2.080	0.519	8.399	1.034	0.301
Abdel Ghaffar et al (2019)	12.667	1.402	114.419	2.261	0.024
	6.040	1.966	18.557	3.141	0.002

Odds ratio and 95% CI

0.01 0.1 1 10 100

APC EBL

a



McCarty TR et al. Endosc Int Open. 2021 Jul;9(7):E1145-E1157

RFA- HALO

In 6 patients with GAVE, 83% of patients had cessation of bleeding with improvement in haemoglobin after 1–3 treatments.

More recently, in a prospective study of 21 patients with bleeding GAVE refractory to APC, 86% of patients became transfusion independent after radiofrequency ablation (maximum of four treatment sessions)

Gastrointest Endosc 2008; **67**: 324–7
Gastrointest Endosc 2013; **78**: 584–8.

New approaches for GAVE in cirrhosis

Radiofrequency ablation for GAVE

Delivers a uniform depth of ablation over a 3 cm² area, may theoretically allow for more reliable destruction of vascular ectasias and more surface area to be treated in a single session

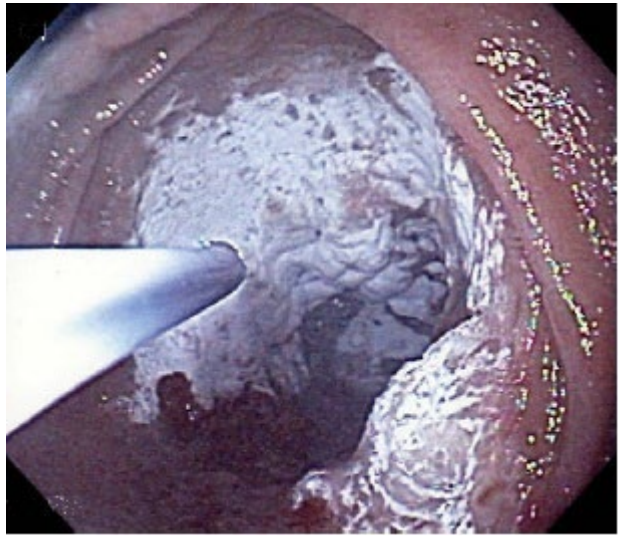
Table 3. Radiofrequency ablation for the treatment of GAVE in patients with cirrhosis

Author, year (ref)	Type of study	Patients included (n)	No. of patients with cirrhosis (n)	Patients refractory to APC (n)	Mean no. of RF sessions	Follow-up (months)	No. of patients transfusion dependent, pre (%)	No. of patients transfusion dependent, post (%)
Gross *et al*. [26], 2008	Prospective single center	6	5[a] (83%)	4 (80%)	NA	2	100%	20%[b]
McGorisk *et al*. [28], 2013[c]	Prospective single center	21	18 (86%)	21/21 (100%)	2	6	100%	14%[d]
Dray *et al*. [25], 2014	Retrospective multicentric	24	11 (49%)	5 (46%)	1.7	6	100%	36%
Raza and Diehl [20], 2015	Prospective single center	9	3 (33%)	3 (100%)	2	11[e]	100%	100%
Jana *et al*. [27], 2015[f]	Prospective single center	7	2 (28%)	7 (100%)	2	5	100%	28%
St Romain *et al*. [29], 2018	Retrospective single center	81	27 (33%)	NA	2.4	NA	Hb: 9.2 g/dL[g]	Hb: 9.2 g/dL[g]

McCarthy TR et al. J Clin Gastroenterol. 2019 Sep;53(8):599-606.
Senzolo M et al . Eur J Gastroenterol Hepatol. 2021 Nov 1;33(11):1414-1419.

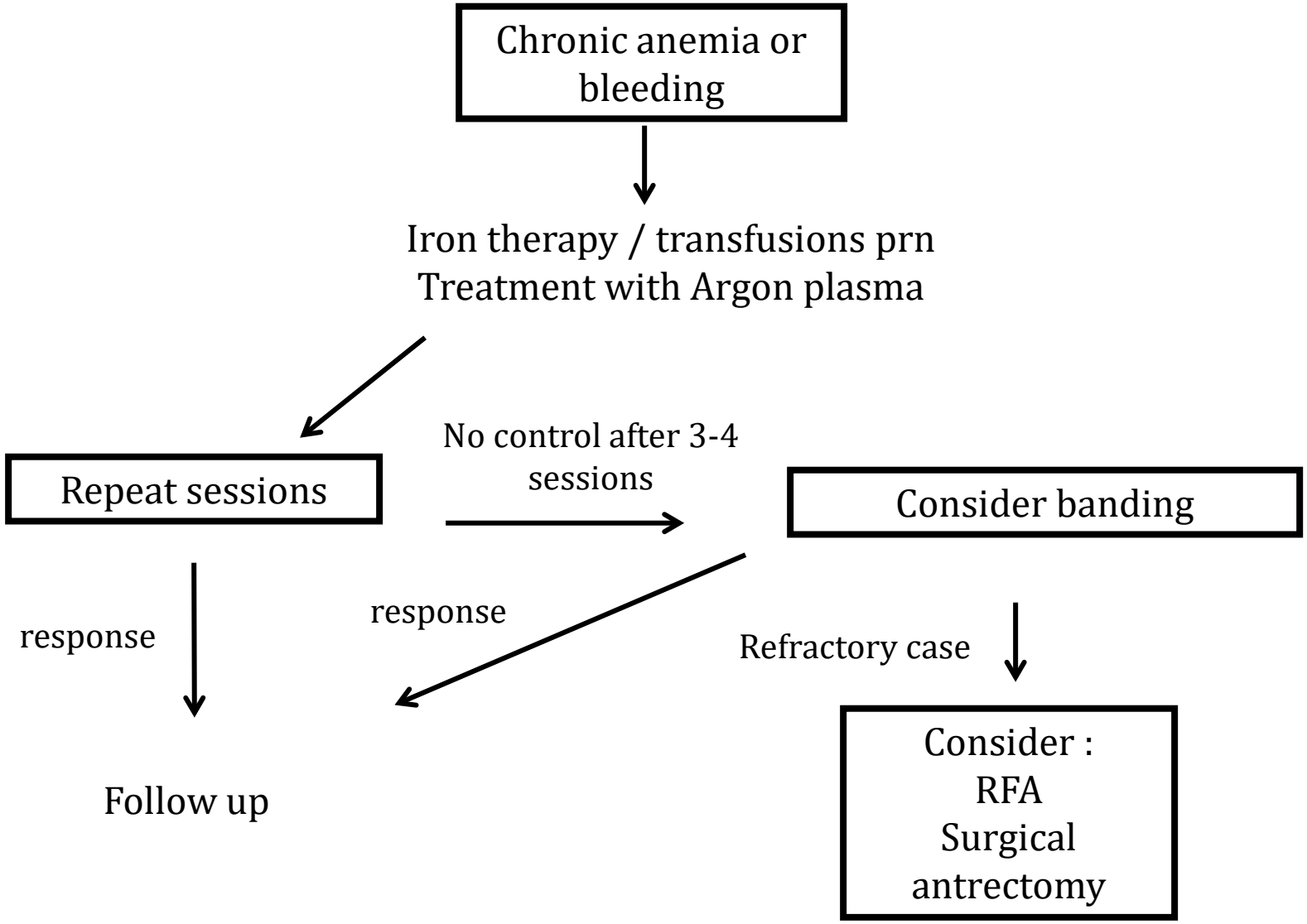
Gastric Antral Vascular Ectasia
Rescue therapy

- Endoscopic cryotherapy is beneficial in some cases
- Surgical antrectomy in selected cases
- TIPS is not effective



Cho, Gastrointest Endosc 2008
Belle JM, Surg Laparosc Endosc Percutan Tech 2009
Kamath PS Gastroenetrology 2000
Gastrointest Endosc. 2013 Oct;78(4):584-8.
Patel United European Gastroenterol J. 2018 Oct;6(8):1155-1160

GAVE Treatment Algorithm



Thank you