

New Treatments for Upper Gastrointestinal Bleeding

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- Clinical focus: ERCP, EUS, Endo-Hepatology
- Research focus: Endo-Hepatology, GI Procedural and Device Innovation

DISCLOSURES

- EnteraSense- founder, consultant
- Boston Scientific- consultant, research support
- Cook Medical- consultant, research support
- Olympus- consultant, research support
- Fuji- consultant
- GI Windows Surgical- founder, consultant
- Creo Medical- research support



OBJECTIVES

- Review initial management of:
 - Acute Non-Variceal Upper GI Bleed
 - Acute Variceal Upper GI Bleed
- Highlight new GI treatments



INITIAL STRATEGY

- Resuscitation
- Restrictive transfusion strategy (Hgb 7-9 g/dL)
- Anticoagulation reversal / correcting coagulopathy
- Multidisciplinary help: GI, IR, Surgery
- Determine location: upper vs lower GI bleed
 - CT Angiography can be helpful



ETIOLOGIES OF UPPER GI BLEED

NON-VARICEAL (80-90%)

Peptic ulcer (30-56%)
Mallory-Weiss tear (15-20%)
Erosive gastritis, duodenitis (10-15%)
Esophagitis (5-10%)
Arteriovenous malformation (AVM) (5%)
Dieulafoy (2%)
Neoplasm (1-2%)
Other (5%)

VARICEAL (10-20%)



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CHECKLIST FOR NON-VARICEAL UPPER GI BLEED

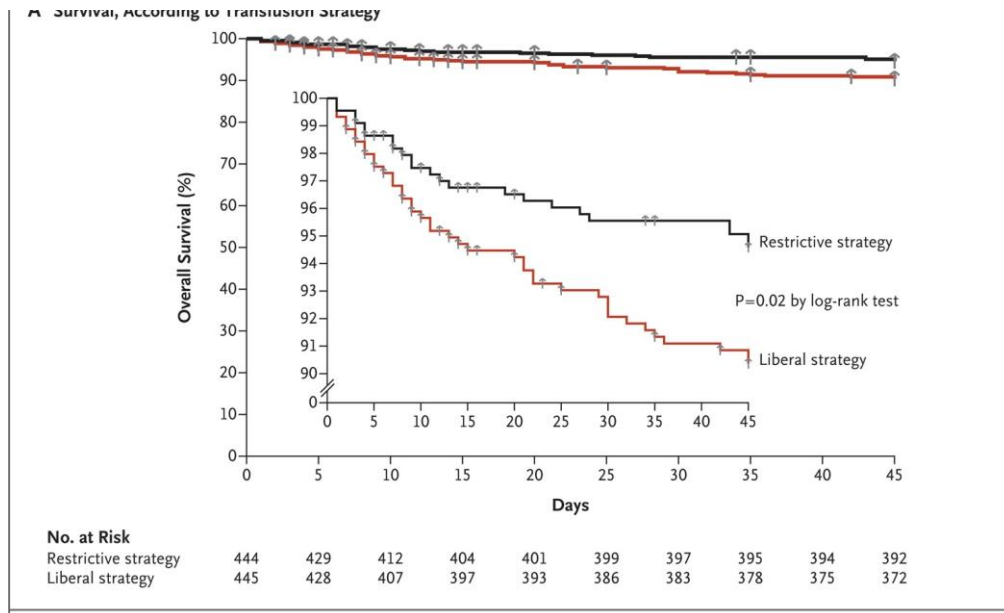
- PPI: 80 mg IV bolus, 8 mg/h or IV BID
- Give IV erythromycin 250 mg IV 30-45 min before EGD
- EGD within 24 hours
- Risk stratification
 - Rockall Score
 - Glasgow Blatchford Score
 - AIMS65



RESTRICTIVE TRANSFUSION STRATEGY

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 Muñoz, M.D., and Carlos Guarner, M.D.

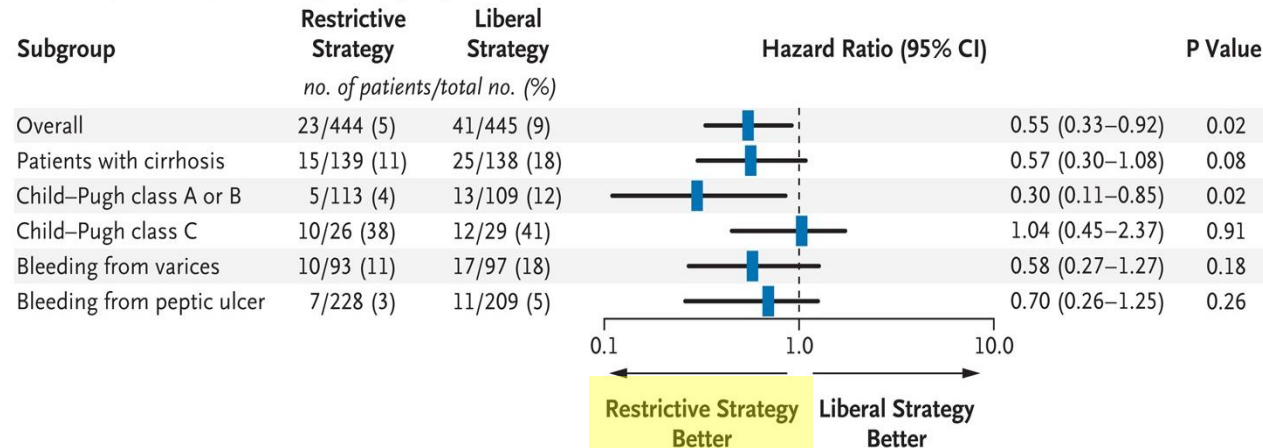


- 921 pts with acute UGIB randomized to
 - Restrictive strategy (transfuse for < 7g/dL)
 - Liberal strategy (transfuse for < 9g/dL)
- 30% had cirrhosis; Mean Rockall score 5.3; Mean admission HgB 9.5 g/dL
- 51% of restrictive strategy vs 14% of liberal strategy did not receive transfusions
- 6 week survival significantly improved in restrictive-strategy group (95% vs 91%, P=0.020)
- Rate of further bleeding was significantly lower in restrictive strategy (10%) vs liberal strategy (16%)



RESTRICTIVE TRANSFUSION STRATEGY

B Death by 6 Weeks, According to Subgroup



- Subgroup analysis showed restrictive strategy was superior to liberal strategy for:
 - Peptic ulcer bleeding
 - Cirrhosis (Child-Pugh class A or B (not C))
 - Variceal bleeding
- Portal pressure gradient increased significantly in patients assigned to liberal strategy (P=0.03) but not restrictive strategy
- TRIGGER study- UK multicenter study showed no evidence of worse outcomes with restrictive strategy



MANAGEMENT OF ANTITHROMBOTICS

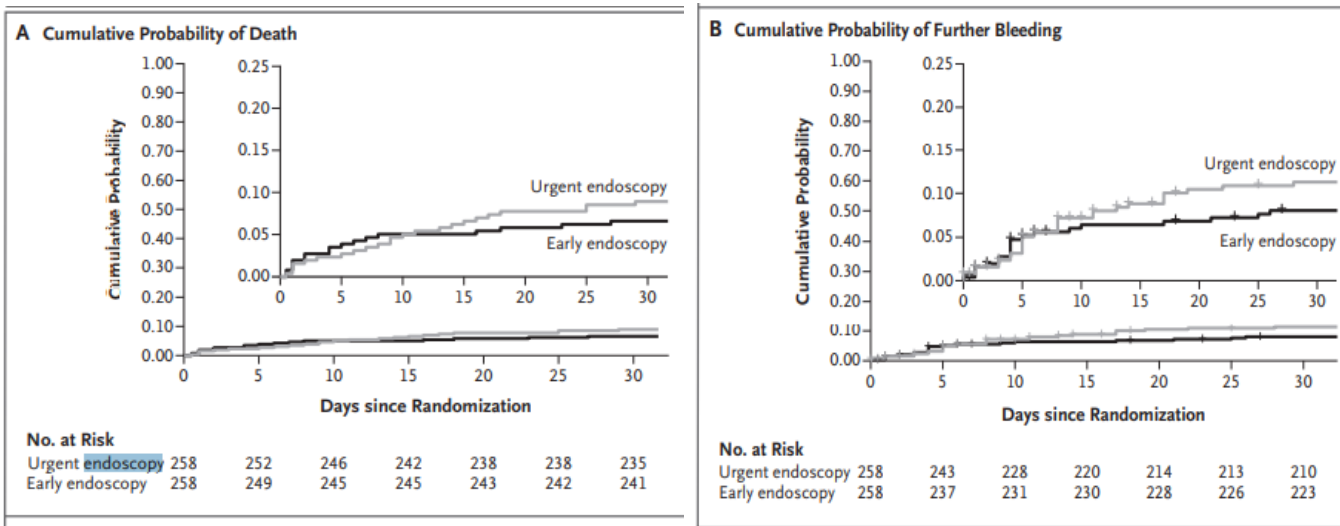
- Low dose ASA for secondary cardiovascular prophylaxis should not be interrupted
- For dual antiplatelet therapy (DAPT) for secondary cardiovascular prophylaxis, ASA should not be interrupted but second antiplatelet should. Suggest consulting cardiology.
- Routine platelet transfusions, tranexamic acid not advised
- For vitamin K antagonists, if patient is unstable, low dose Vitamin K supplemented with IV prothrombin complex concentrate (PCC), or FFP if PCC not available
- For direct oral anticoagulants (DOAC), use of reversal agent or IV PCC should be considered with severe ongoing bleeding



TIMING OF ENDOSCOPY

Timing of Endoscopy for Acute Upper Gastrointestinal Bleeding

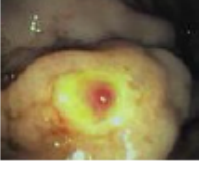
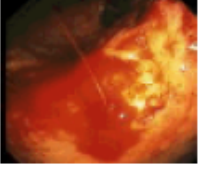
James Y.W. Lau, M.D., Yuanyuan Yu, Ph.D., Raymond S.Y. Tang, M.D., Heyson C.H. Chan, M.B., Ch.B., Hon-Chi Yip, M.B., Ch.B., Shannon M. Chan, M.B., Ch.B., Sally W.Y. Luk, M.B., Ch.B., Sunny H. Wong, Ph.D., Louis H.S. Lau, M.B., Ch.B., Rashid N. Lui, M.B., Ch.B., Ting T. Chan, M.B., Ch.B., Joyce W.Y. Mak, M.B., Ch.B., Francis K.L. Chan, M.D., and Joseph J.Y. Sung, M.D.



- RCT: 516 pts with overt acute UGIB and GBS>12 randomized to:
 - Urgent EGD (within 6h)
 - Early EGD (**6-24h**)
- 30d mortality 8.9% (Urgent) vs 6.6% (Early)
- Further bleed within 30d occurred in 10.9% (Urgent) vs 7.8% (Early)
- No improved mortality for urgent EGD



STIGMATA OF ULCERS

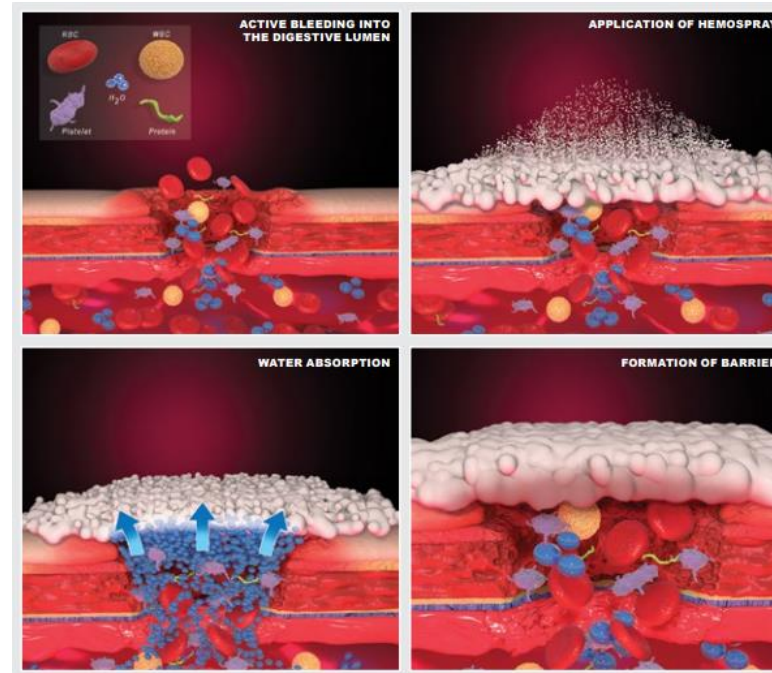
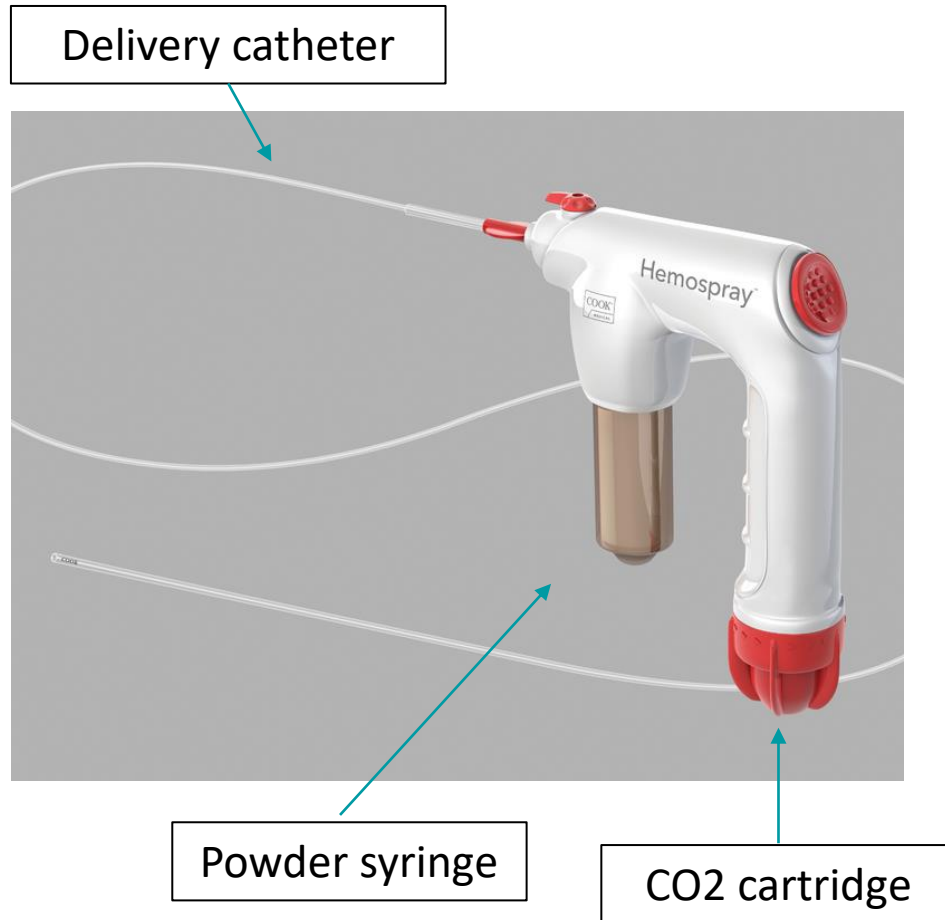
	Endoscopic stigmata	% Rebleed	
	Clean-based ulcer	<3%	Low risk
	Pigmented flat spot	<8%	
	Adherent clot	20%	High risk
	Nonbleeding visible vessel	40%	
	Active bleeding	55%	

Laine et al. NEJM 1994;33:717.

ENDOSCOPIC THERAPIES



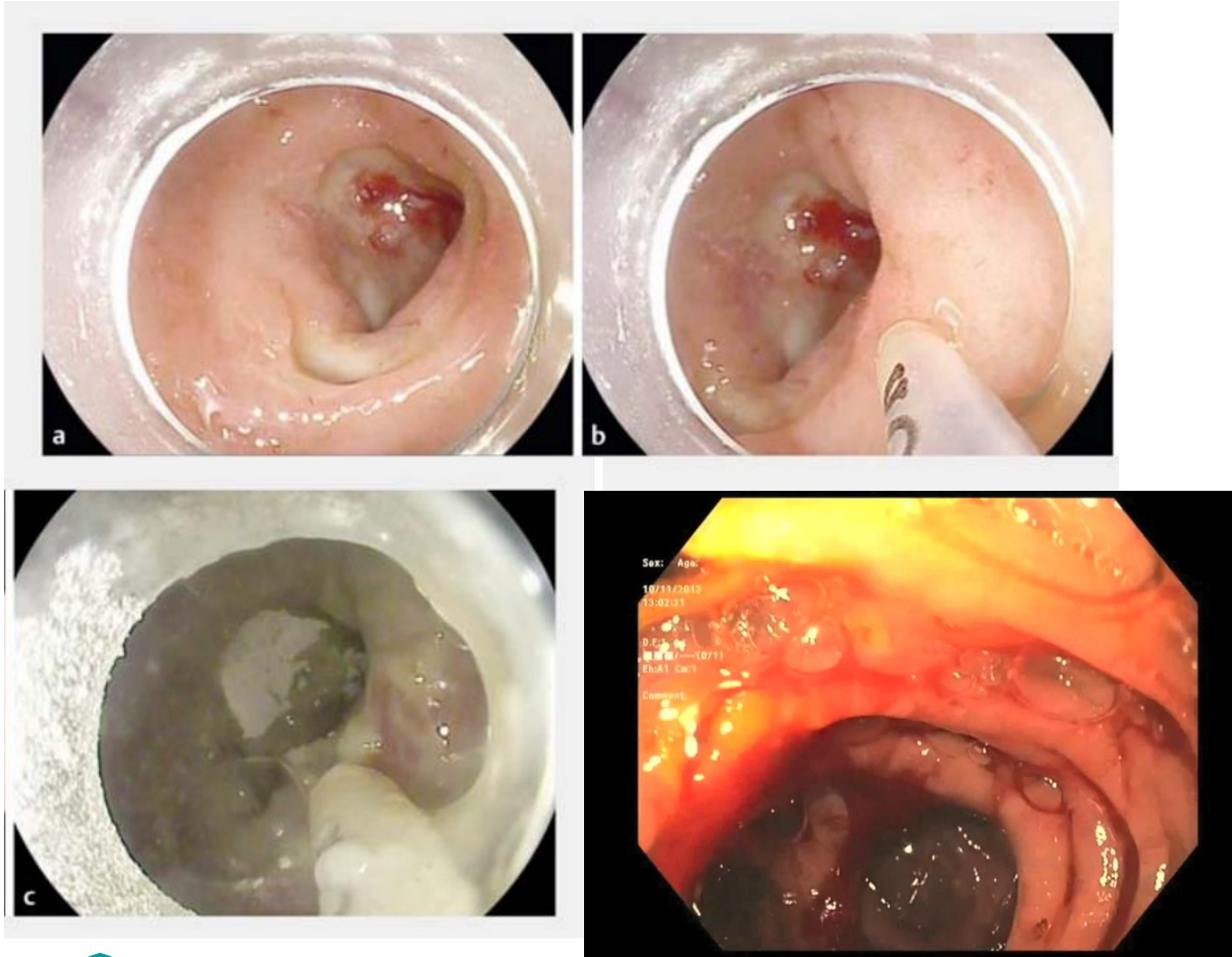
SPOTLIGHT: HEMOSTASIS POWDER SPRAY



- Non-contact modality
- Can be applied diffusely
- TC-325 (HemoSpray) absorbs water (dessicant) from blood
- Acts both cohesively and adhesively, forming mechanical barrier over bleeding site
- Does not affect clotting cascade



TC-325 (HEMOSPRAY)



- Particularly useful for diffuse bleeding, difficult localization, or poor visualization
- In most instances should be used as rescue therapy and not primary hemostasis
- Need for relook EGD is unclear

TC-325 (HEMOSPRAY)

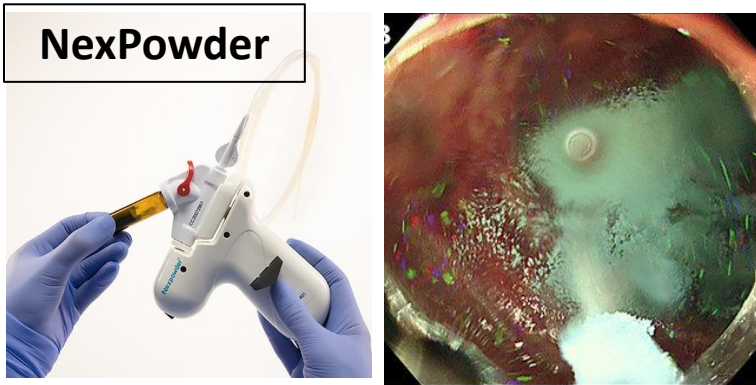
Table 2. Clinical Outcomes Within 30 Days of Endoscopic Therapy

Outcome	TC-325 Group (n = 111)	Standard Treatment Group (n = 113)	Odds Ratio (95% CI)
Primary outcome			
Control of bleeding within 30 d, n (%)*	100 (90.1)	92 (81.4)	8.7 (0.95)†
Secondary outcomes			
Further bleeding in subgroups, n	11	21	0.51 (0.25-1.05)
Peptic ulcer, n/N (%)	8/68 (11.7)	11/68 (16.2)	-
Gastrointestinal tumor, n/N (%)	3/29 (10.3)	6/13 (46.2)	-
Dieulafoy lesion, n/N (%)	0/6 (0.0)	3/16 (18.7)	-
Other lesion, n/N (%)	0/8 (0.0)	1/16 (6.3)	-
Forrest Ia, n/N (%)	1/9 (11.1)	5/12 (41.6)	-
Forrest Ib, n/N (%)	10/102 (9.8)	16/101 (15.8)	-
Failed initial endoscopic control, n	3	11	0.26 (0.07-0.95)
Recurrent bleeding within 30 d, n	9	10	0.91 (0.37-2.22)
Treatment for further bleeding, n (%)	10 (9.0)	12 (10.6)	0.83 (0.34-2.02)
Endoscopic treatment, n‡	8	10	-
Angiography, n	2	4	-
Surgery, n	1	0	-
Median units of red blood cells transfused (range)	3 (1-77)	2 (1-23)	-
Patients with peptic ulcer	2 (1-29)	2 (1-21)	-
Patients with cancer	4 (1-77)	3 (1-14)	-
Patients with other lesion	7 (1-26)	3 (1-23)	-
Median length of hospitalization after randomization (range), d	6 (1-90)	6 (1-107)	-
Intensive care unit admission, n (%)	5 (4.5)	2 (1.8)	2.62 (0.50-13.79)
Death from any cause within 30 d, n (%)	14 (12.6)	14 (12.4)	1.02 (0.46-2.25)
Mean procedure time (SD), min	17.6 (12.0)	18.7 (17.2)	-
Mean visual analogue scale score (SD)	4.49 (2.47)	5.09 (2.25)	-

- Chinese multicenter RCT
- 224 patients with acute NVUGIB randomized to:
 - TC-325 hemostatic powder monotherapy
 - Standard treatment (epi inject plus heat/coag or clipping OR APC for AVMs/tumor)
- Primary endpoint: Control of bleeding within 30 days
- **90.1% of TC-325 vs 81.4% of Standard treatment** achieved bleeding control within 30 days
- Conclusion: TC-325 is noninferior to standard treatment in endoscopic control of NVUGIB

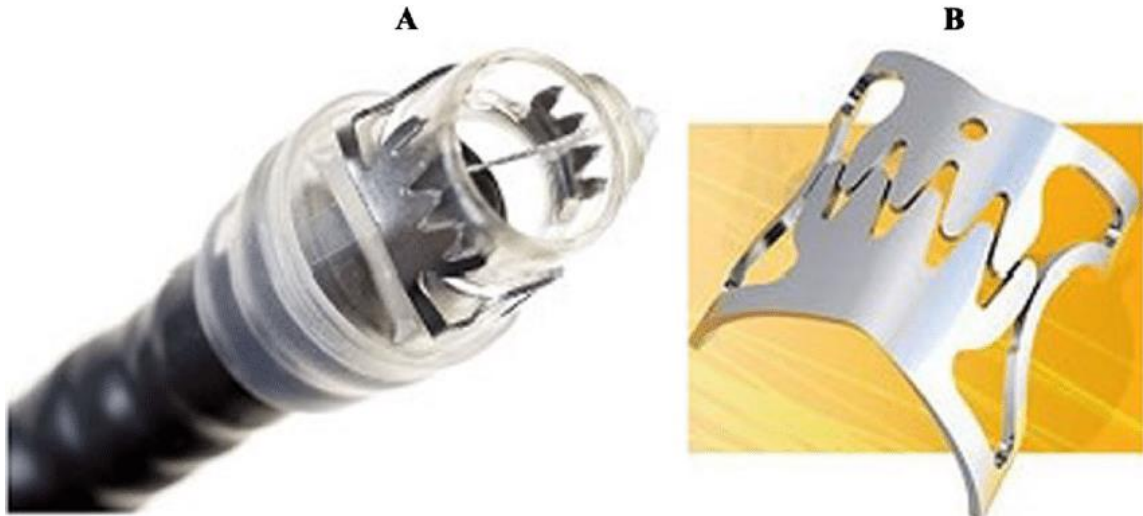


OTHER TOPICAL HEMOSTATIC AGENTS



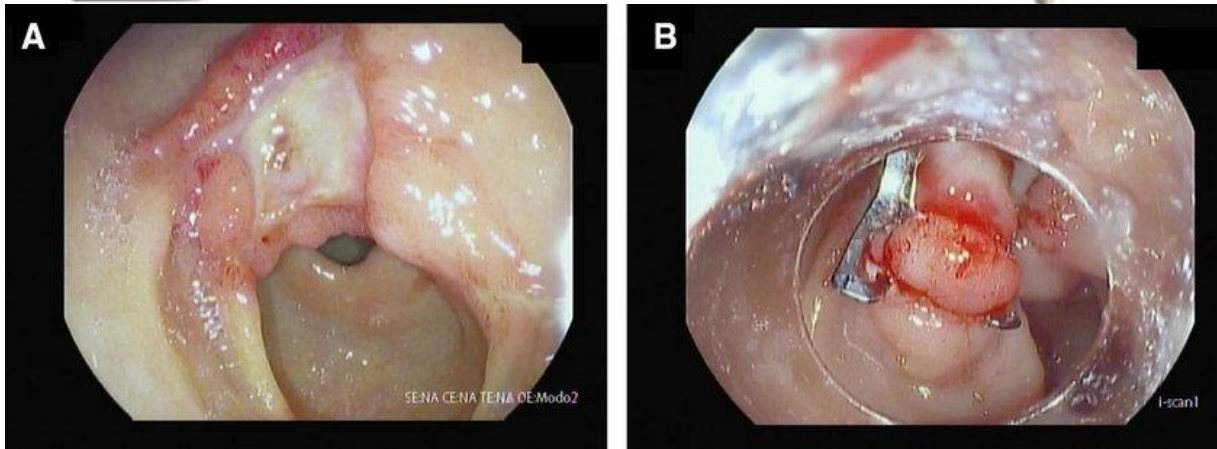
- **EndoClot:** hemostatic powder derived from plant starch which absorb water. White powder turns to clear gel. Uses air compressor.
- **NexPowder:** hemostatic powder (succinic anhydride and oxidized dextran), forms adhesive gel after contacting water or blood
- **PuraStat:** topical gel; synthetic crosslinking polypeptide for intraprocedural hemostasis, bleeding prevention, and wound healing

SPOTLIGHT: OVER-THE-SCOPE CLIP (OTSC)

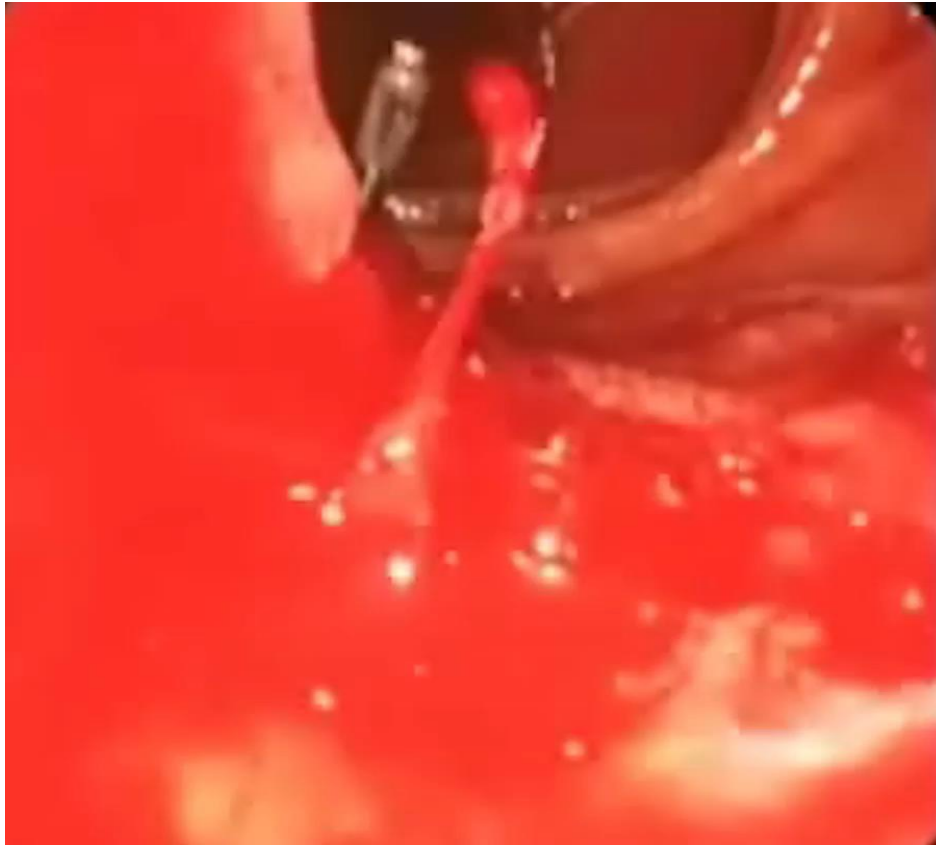


Compared to traditional hemoclips, OTSC can:

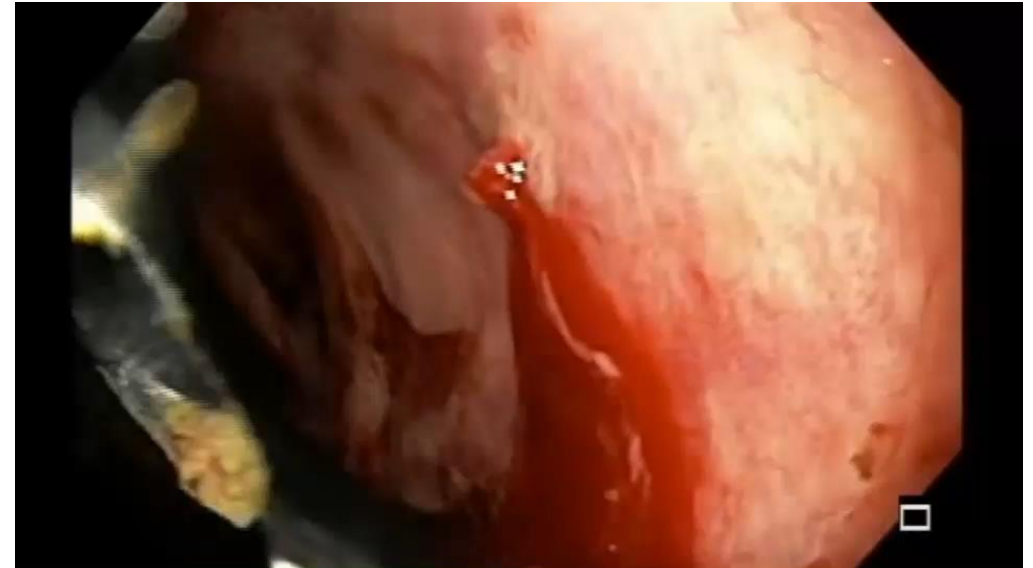
- Handle bigger ulcers
- Treat deeper (and probably larger) vessels
- Close perforations at the same time



SPOTLIGHT: OVER-THE-SCOPE CLIP (OTSC)



Over-the-Scope Clip (OTSC)



Through-the-Scope (TTS) Clip

OTSC FOR HIGH-RISK BLEEDING LESIONS

Over-the-scope-clips versus standard treatment in high-risk patients with acute non-variceal upper gastrointestinal bleeding: a randomised controlled trial (STING-2)

Table 2 Endoscopic therapy and 7 days outcome

Endoscopic therapy	Standard (n=52)*	OTSC (n=48)†	P value	Absolute difference (%)
Clinical success‡, n (%)	38 (73.1)	44 (91.7)	0.019	18.6
Endoscopic therapy				
No of OTSC, n (range)	–	1 (1–1)	–	–
No of haemoclips, median (range)	2 (2–6)	–	–	–
Use of thermal therapy, n (%)	1 (1.9)	–	–	–
Volume of injection (diluted epinephrine), ml, median (range)	10 (1–30)	5 (1–10)	<0.001	–
Procedure time, min, median (range)	28 (15–95)	27 (15–75)	0.593	–
Persistent bleeding, n (%)	6 (11.5)	0 (0)	0.027	–11.5
Recurrent bleeding, n (%)	8 (15.4)	4 (8.3)	0.362	–7.1

*Application of at least two haemoclips (or haemostasis with a thermal method) plus injection of diluted epinephrine.
†Injection of diluted epinephrine was allowed before OTSC application but not mandatory.
‡Successful endoscopic haemostasis without evidence of recurrent bleeding.
OTSC, over-the-scope-clips.

- German multicenter RCT
- 100 pts with acute NVUGIB and Rockall >7 randomized to
 - OTSC (Clip)
 - Standard therapy (almost all hemoclip)
- OTSC 91.7% clinical success vs Standard Rx 73.1%
- OTSC appears superior to standard Rx with clips for primary therapy of NVUGIB with high risk of rebleed



NEWER MODALITIES: KEY TAKE-AWAYS

Hemostatic Sprays

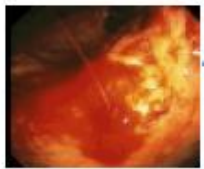
- Good evidence for rescue therapy; emerging evidence for primary therapy
- Easy to use but has a learning curve
- Good for diffuse bleeding (e.g. tumor), difficult localization, difficult visualization

OTSC clips:

- Good evidence for rescue therapy but emerging evidence for initial therapy of NVUGIB at high risk for rebleeding
- Good for fibrotic bases
- Requires familiarity with device



POST EGD MANAGEMENT OF NON-VARICEAL UGIB



Feed and discharge
PO PPI QD with GI f/u
Check H. pylori

Watch 72h

IV PPI BID x 72 h, then PO BID x 14d, then PO QD x14d

- H pylori ulcer:
 - Treat H. pylori & stop PPI
- NSAID-induced ulcer:
 - Only continue PPI if continuing NSAID
- Idiopathic ulcer:
 - Continue PPI indefinitely
- If anemic, IV iron one dose or PO iron x 3 months



IF ENDOSCOPIC THERAPY FAILS...

- Repeat endoscopic therapy is usually recommended (efficacy >75%)
- IR angiographic embolization if 2nd endoscopy fails (efficacy >60%)
- Surgery as last resort (efficacy >80% but SAE >30%)



SUMMARY: NON-VARICEAL UPPER GI BLEED

- Start PPI
- Following hemodynamic resuscitation, early EGD (<24h) should be performed; <12h does not lead to improved outcomes
- In hemodynamically stable patients with acute UGIB, restrictive transfusion strategy (goal Hgb>7 g/dL)*
- Stopping antithrombotic and possibly giving reversal agent is warranted in severe bleeding
- For active bleeding or ulcers with stigmata, endoscopic therapy is warranted
- For bleeding refractory to standard hemostasis modalities, newer modalities (hemospray or OTSC clips) are available
- If failed 2nd endoscopic attempt or severe bleeding, consider angiographic embolization +/- surgery



ETIOLOGIES OF UPPER GI BLEED

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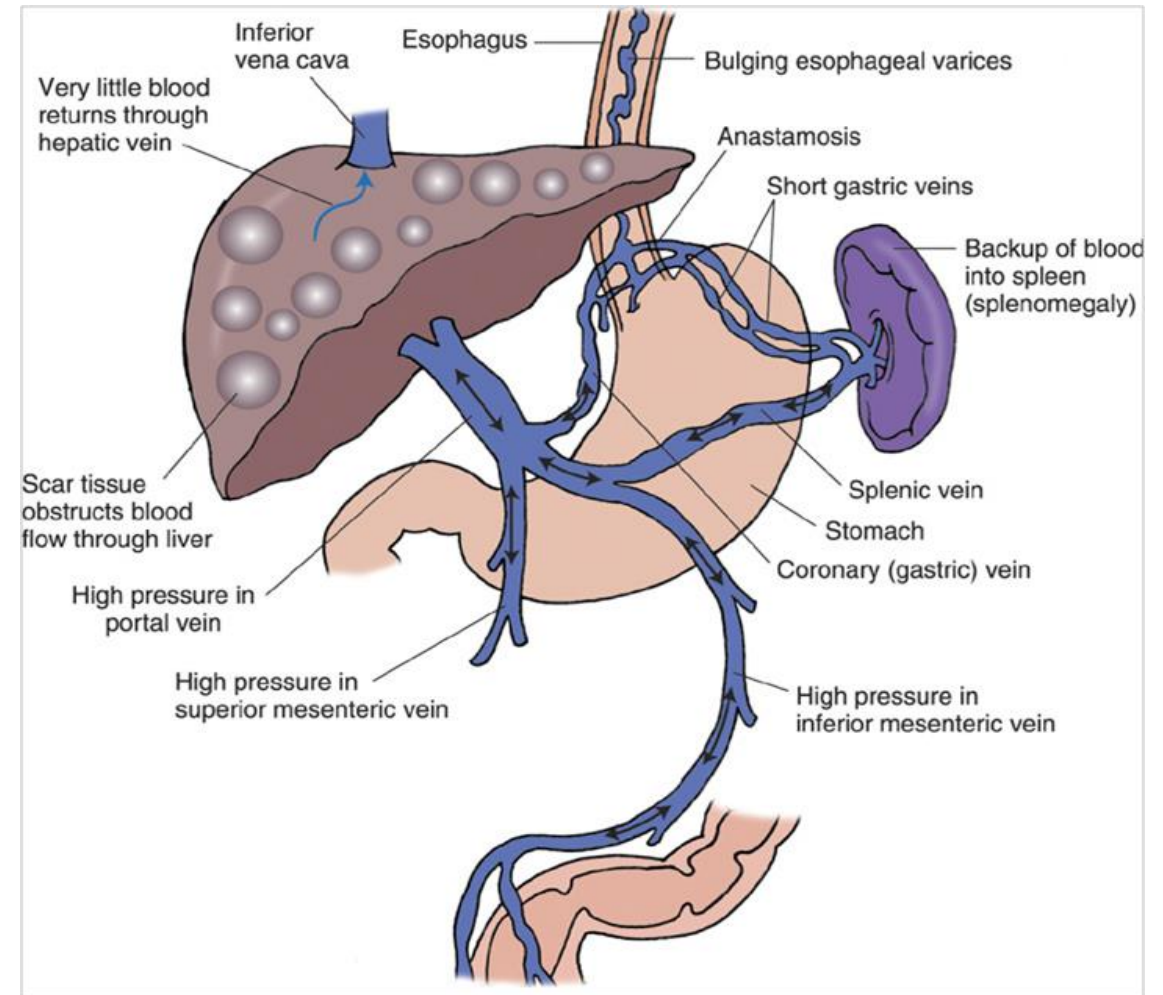
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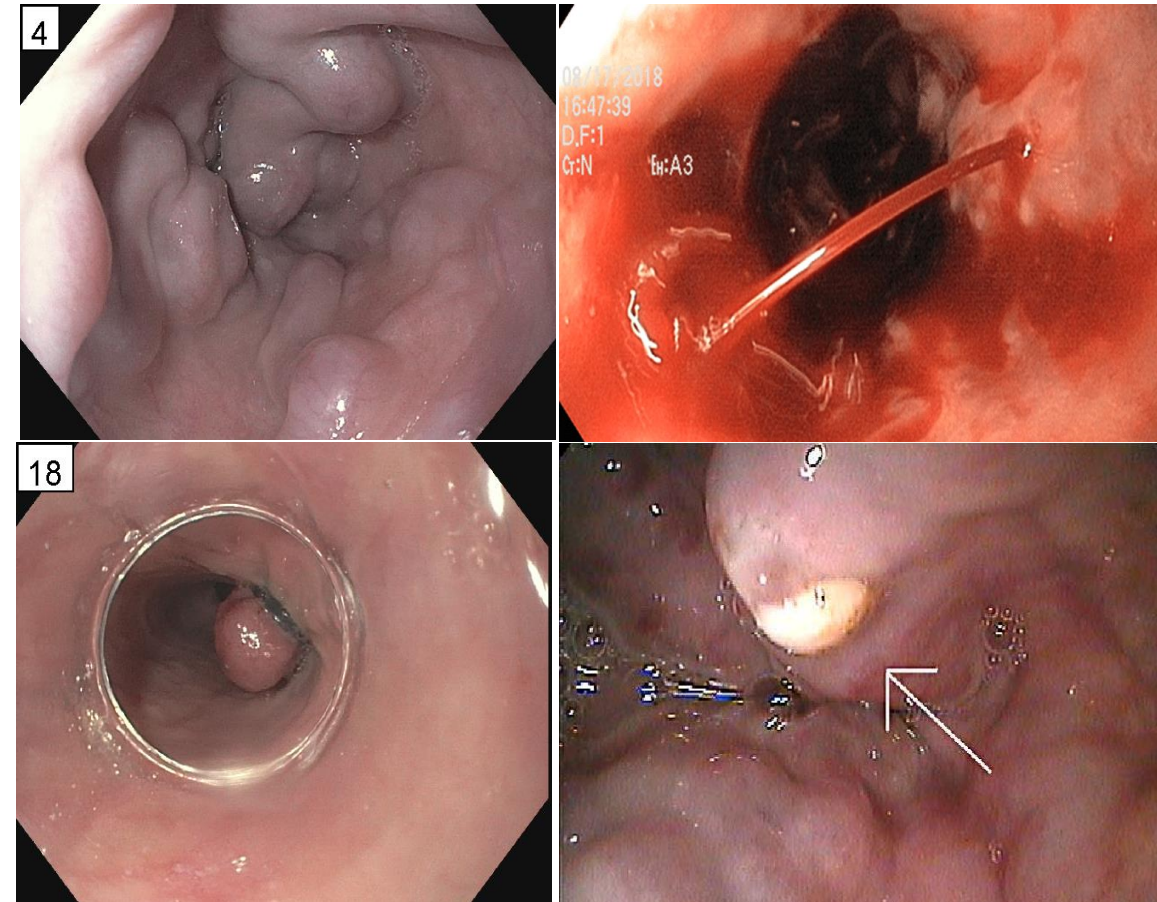
ESOPHAGEAL VARICES (EV)

- 5%-15% of cirrhotic pts per year develop EV
- EV correlate with severity of liver disease
 - 40% of Childs A; 85% of Child C
- 6-week mortality among patients with index variceal bleeding is 20%
- Risk of rebleeding without endoscopic intervention is 60%
- In cirrhotic pts, assume it's EV bleeding until proven otherwise



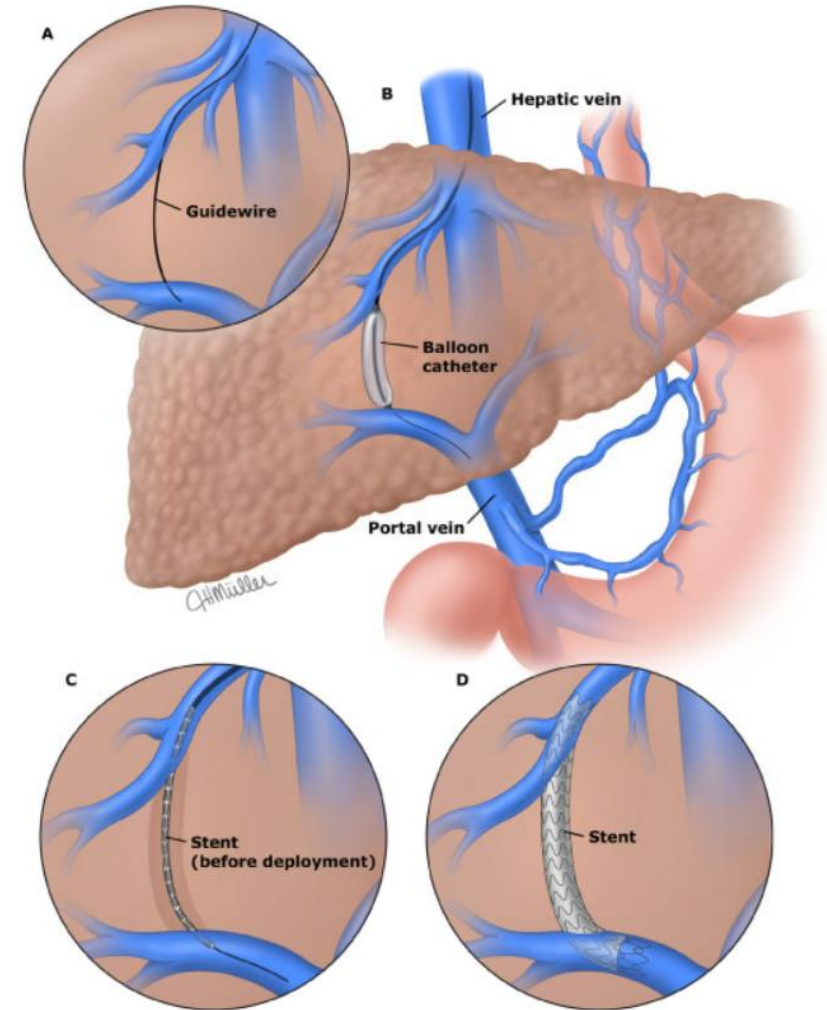
MANAGEMENT OF ACUTE EV BLEEDING

- Hgb goal 7-9 g/dL (restrictive)
- Ceftriaxone 1 g daily → max of 7 days
- Octreotide for 2-5 days (Terlipressin not available in US)
- EGD within 12 hours
- Endoscopic variceal band ligation (EVL) if active bleeding or stigmata
- No role for recombinant factor VIIa, FFP, or Plt transfusion

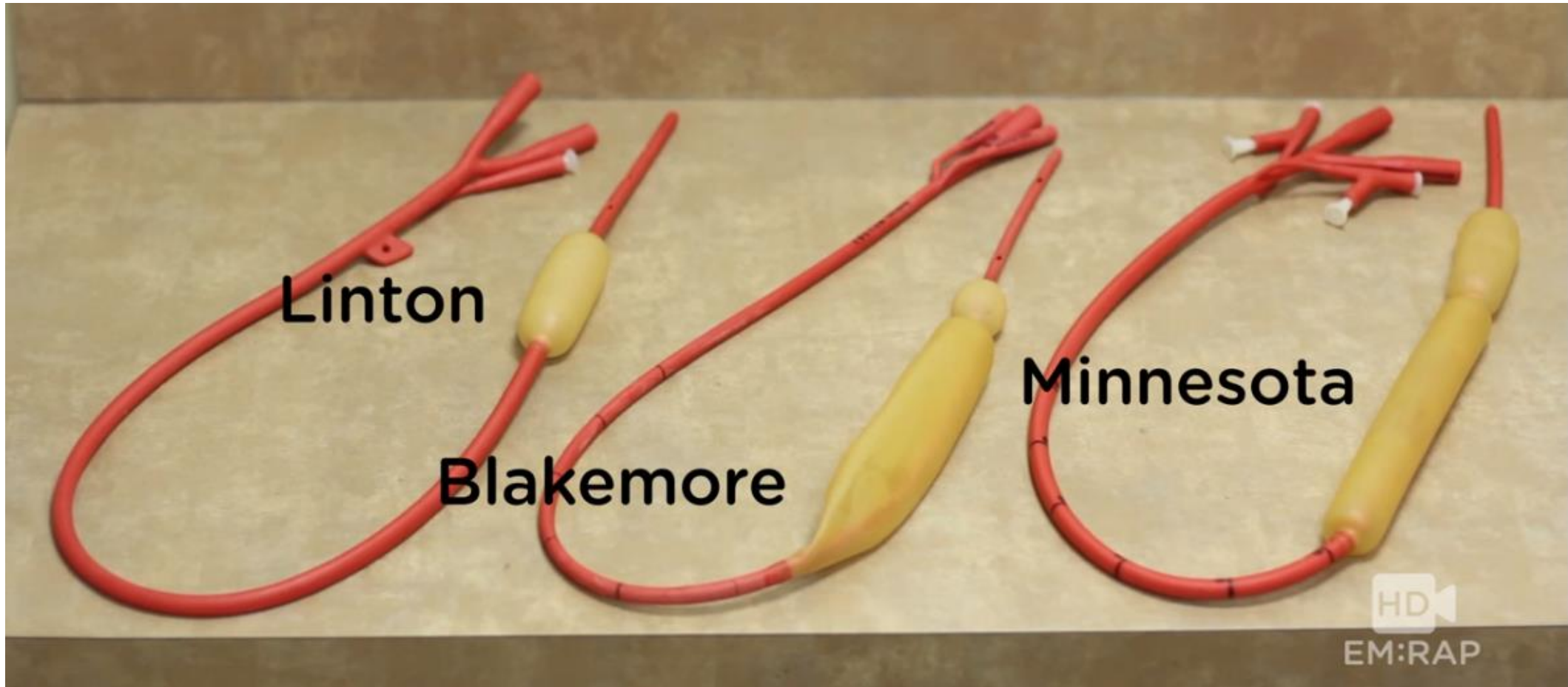


MANAGEMENT OF ACUTE EV BLEEDING

- Transjugular Intrahepatic Portosystemic Shunt (TIPS)
 - “Early” within 72 hrs in select patients → recommended if no contraindications and deemed high risk with:
 - HVPG > 20 mm Hg
 - CTP Class C or B with active bleeding
 - Or if bleeding recurs despite endoscopic variceal band ligation + vasoactive drugs



REFRACTORY EV BLEEDING: BALLOON TAMPONADE

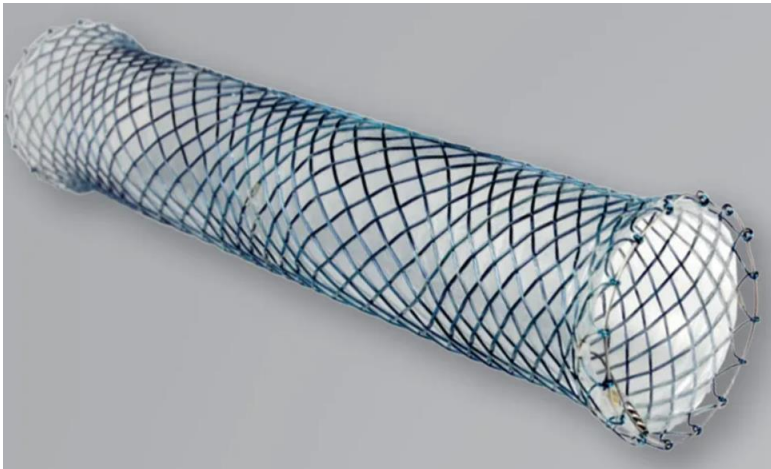
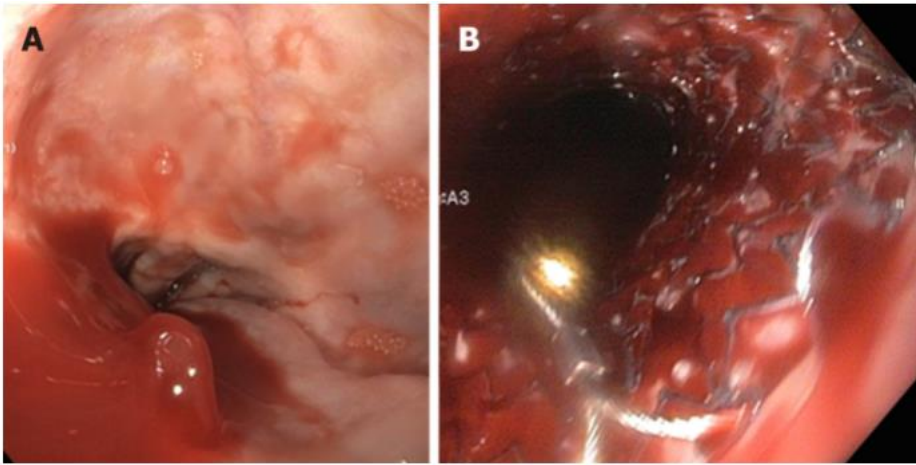


REFRACTORY EV BLEEDING: BALLOON TAMPONADE



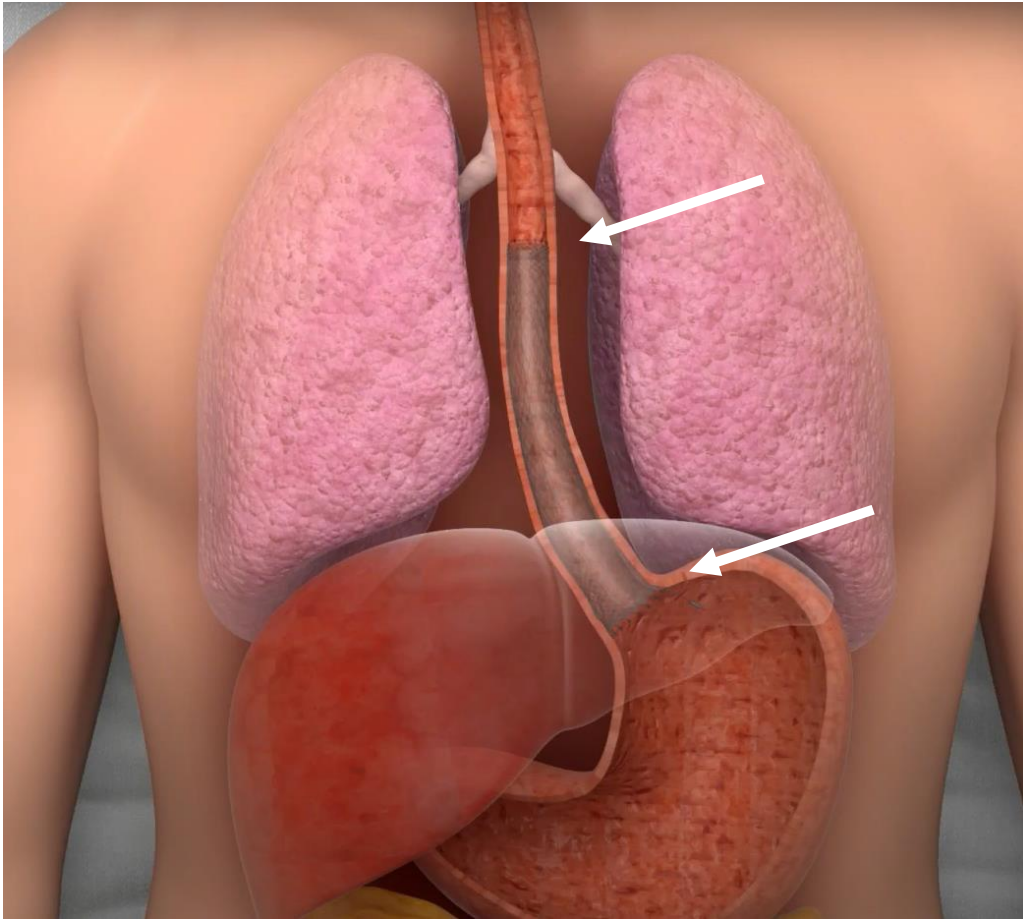
[Placement of a Blakemore Tube for Bleeding Varices - YouTube](#)

SPOTLIGHT: STENT FOR REFRACTORY EV BLEEDING



- Self expanding esophageal metal stents exert a radial force on esophageal wall
- RCT: in refractory acute EV bleeding, self-expandable esophageal covered metal stents (SEMS) had greater efficacy (66%) and less serious adverse events (15%) compared to balloon tamponade therapy (efficacy 20%, SAE 47%)
- This particular stent is currently unavailable in the US, although other through-the-scope esophageal stents are being used
- Some expert centers now favor esophageal stents over balloon tamponade therapy for refractory variceal bleeding

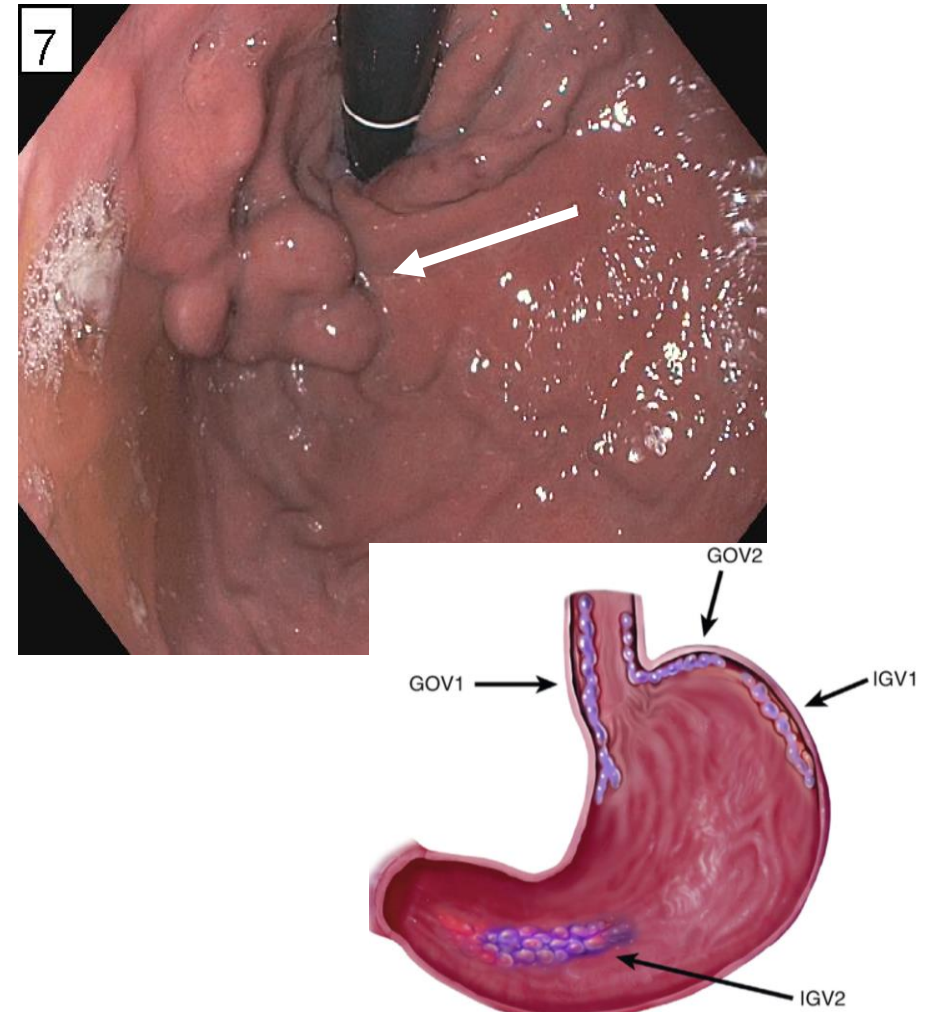
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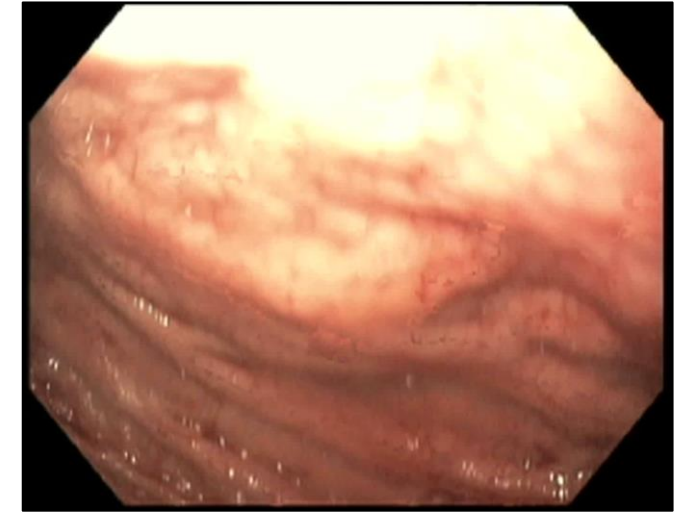
ACUTE GASTRIC VARICEAL (GV) BLEED

- 10-20% of all variceal bleeding
- Higher risk of bleeding and more severe bleeding
- High mortality rates
- Fewer well-established guidelines
- Most common cause: Portal Hypertension, although can occur with portal/splenic venous thrombosis



ACUTE GV BLEED MANAGEMENT

- HgB goal 7-9 g/dL (restrictive)
- Ceftriaxone 1g daily → max 7 days
- Octreotide → data not available
- **Endoscopy within 12h** to diagnose and potentially treat
- Traditional endoscopic Rx = glue injection (rebleed rate > 30%, embolic complications)
- However, if offered, endoscopic ultrasound (EUS) guided injection therapies is preferred endoscopic therapy
- If recurrent bleeding and/or HD unstable → IR (TIPS or BRTO)

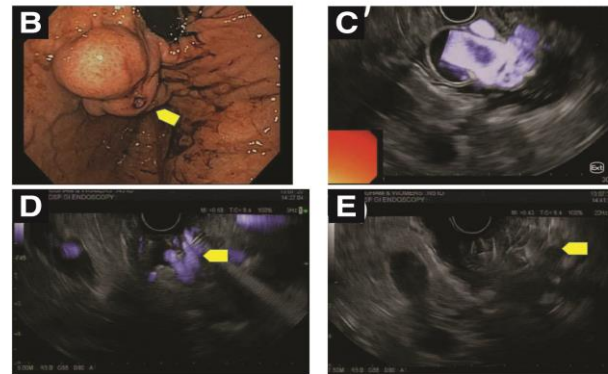
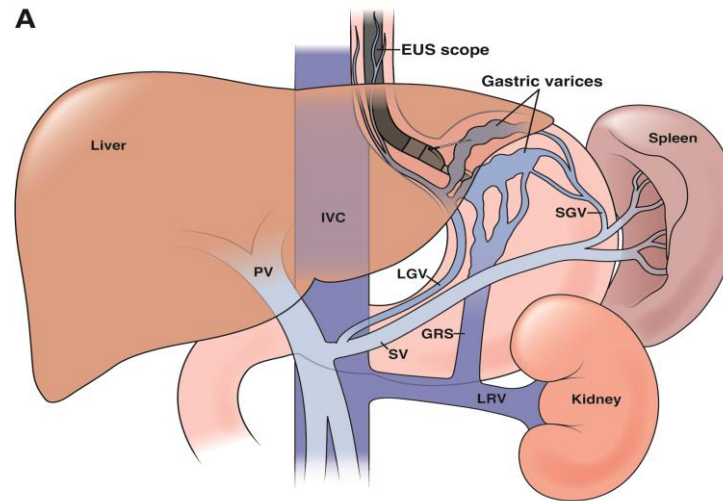


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Bazarbashi AN, Ryou M. Current Opinions in Gastroenterology 2019.
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SPOTLIGHT: ENDOSCOPIC ULTRASOUND COIL INJECTION

- Endoscopic ultrasound allows direct intravariceal injection of hemostatic agents
- Hemostatic coils can now be injected
- Doppler provides real-time hemostasis feedback
- Durable efficacy >95%
- AEs <10%



SUMMARY: ACUTE VARICEAL GI BLEED

- Antibiotics, vasoactive medications, careful replacement of volemia
- Endoscopy within 12 hours
 - For EV, band ligation is preferred
 - For GV, glue injection is gold standard but endoscopic ultrasound guided injection therapies (where available) may be superior
- For refractory bleeding:
 - For EV, esophageal stent (where available) is preferred over balloon as bridge to TIPS
 - For GV, IR therapy (BRTO or TIPS depending on anatomy)



PRACTICE QUESTION 1:

A 56 year-old man with history of cirrhosis is admitted to the ICU with large-volume hematemesis. Do all of the following EXCEPT:

- A) Give antibiotics (e.g. Ceftriaxone)
- B) Call GI for urgent endoscopy
- C) Start vasoactive medication (e.g. octreotide)
- D) Administer FFP to reverse INR
- E) Transfuse for goal Hgb 7-9 g/dL (restrictive transfusion strategy)



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PRACTICE QUESTION 2:

The following bleeding etiologies are correctly paired with endoscopic and endovascular therapies EXCEPT:

- 1) Peptic ulcer bleed and Over-the-Scope Clip
- 2) Peptic ulcer bleed and Hemospray
- 3) Esophageal variceal bleed and Esophageal Stent
- 4) Gastric variceal bleed and Over-the-Scope Clip
- 5) Esophageal variceal bleed and Endoscopic Band Ligation



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- 4) Gastric variceal bleed and Over-the-Scope Clip**
- 5) Esophageal variceal bleed and Endoscopic Band Ligation



MOC REFLECTIVE STATEMENT (BRIEF TAKE HOME NOTES FOR REFERENCE)

- For non-variceal upper GI bleeding (NVUGIB), endoscopy within 24 hours is warranted after resuscitation
- Newer endoscopic modalities (over-the-scope clips and topical hemostatic agents) are available for NVUGIB
- For variceal bleeding, endoscopy within 12 hours is warranted after resuscitation
- Newer endoscopic therapies (esophageal stenting and endoscopic-ultrasound guided coil therapy) are available for variceal bleeding



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