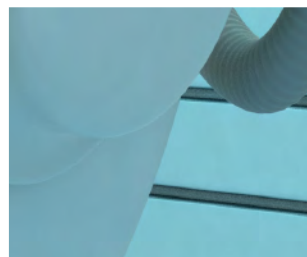
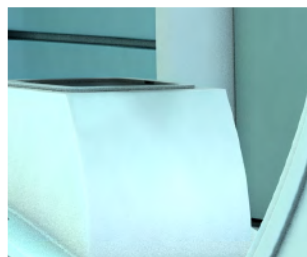
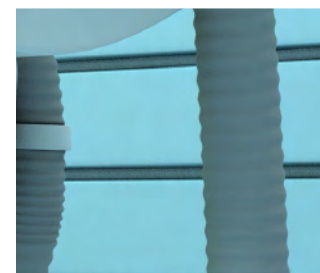
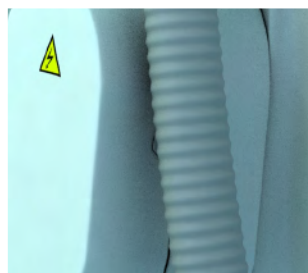
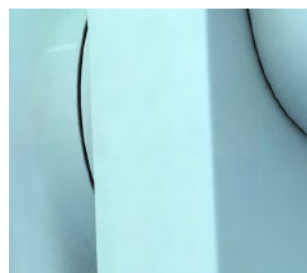
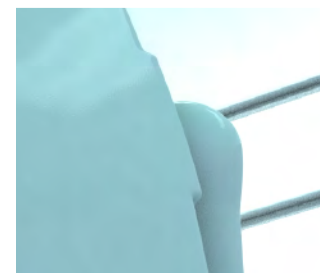


A WEBINAR ON **GLUBRAN®2 IN INTERVENTIONAL RADIOLOGY**

17th and 24th JUNE 2020



with the cooperation of



GLUBRAN[®]2

ENDOVASCULAR

SOLVES.

**Building
the perfect
Embolization**



GEM

**SOLUTION
COMES FROM
EVOLUTION.**



A WEBINAR BY GEM
1° SESSION

17TH JUNE 2020

PRESENTED BY

MASSIMILIANO MATTIOLI

GEM Marketing Manager

ATTENDEES

FRANCESCO GINI MD

Product Specialist

VITTORIO PEDICINI MD

Head of Vascular Interventional Radiology at
Humanitas Hospital

DARIO PORETTI MD

Chief of Oncological and Interventional
Radiology at Humanitas Hospital

EZIO LANZA MD

Diagnostic Radiology PA at Humanitas
Hospital

COMPREHENSIVE SUMMARY

The remainder of this document provides a complete summary of the Webinar held by GEM Italy on 17th June 2020.

Welcome and Introductions

Massimiliano Mattioli

As the webinar commenced, Massimiliano Mattioli welcomed all attendees and introduced the topic at hand.

► For the past ten years, the team at Humanitas has been working with GEM on the use of Glubran®2 in Interventional Radiology. We have programmed two separate sessions of this webinar to illustrate the study and the possible applications of Glubran®2. After each presentation, we will answer questions and leave a few minutes for discussion.

GLUBRAN® 2

Chemical and Physical characteristics, Polymerization Profile and Possible Interactions

Francesco Gini MD

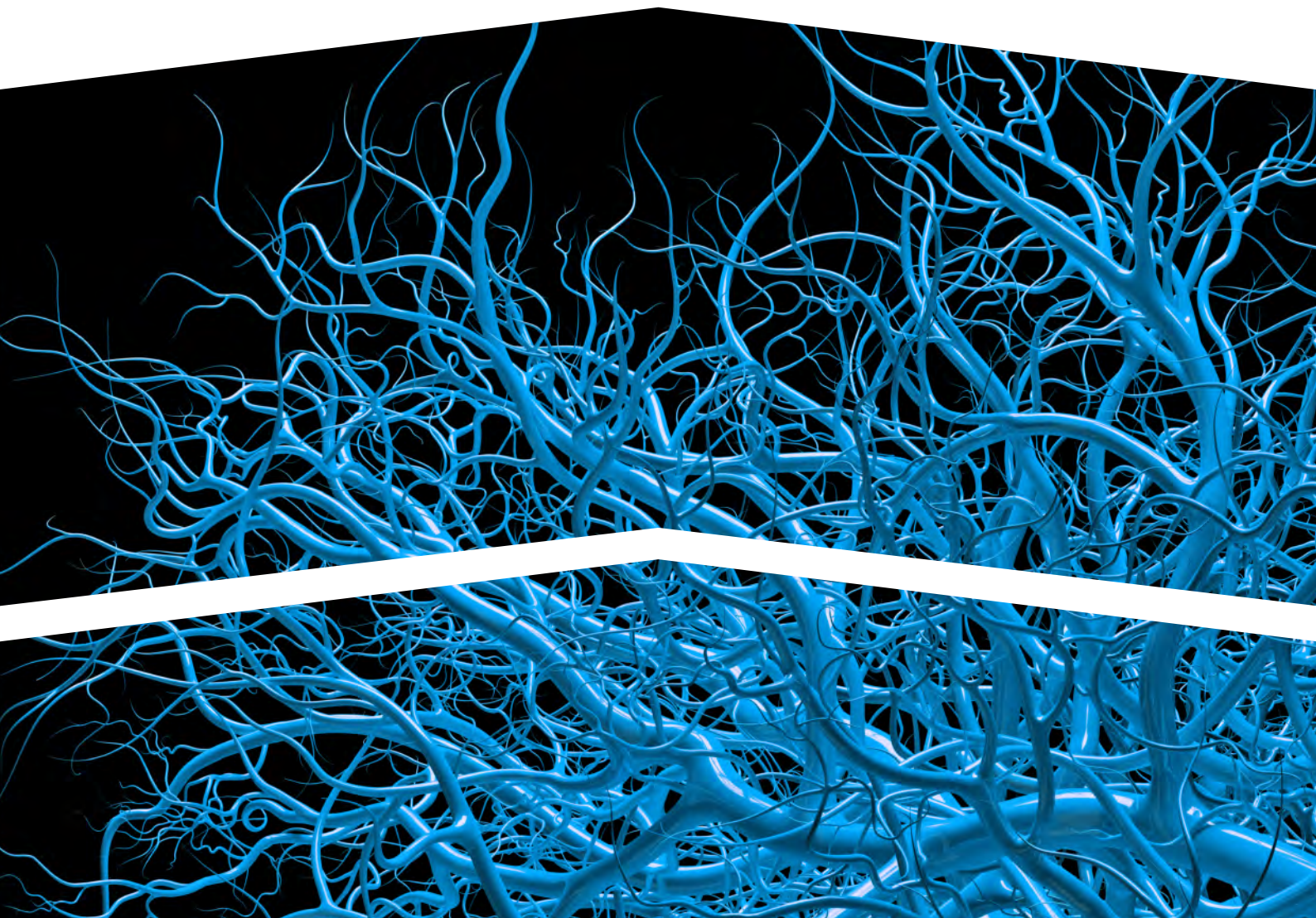
► Welcome everybody, today I am going to give you some basic information about cyanoacrylates in relation to Glubran®2.

Cyanoacrylates are liquid adhesive embolic agents, that allow for permanent occlusion. Some of their characteristics include: liquid state low viscosity, high polymerization rates, and bacteriostatic activity. They are not radiopaque and they need to be mixed with iodized oils, such as Lipiodol. Blood vessels that are subjected to cyanoacrylates injection are embolized via three mechanisms: (1) cast and thrombus formation, (2) the adhesion to the inner vascular wall, and (3) damage to the vascular endothelium caused by an inflammatory response.

► Currently available options include:

- pure NBCA (N-butyl 2 cyanoacrylate), with no CE mark for intravascular use;
- Glubran®2, which is a modified type of cyanoacrylate (N-butyl 2 cyanoacrylate + methacryloxy sulfolane), with CE mark for intravascular use;
- NHCA (N-hexyl 2 cyanoacrylate), with CE mark for intravascular use (only few indications).

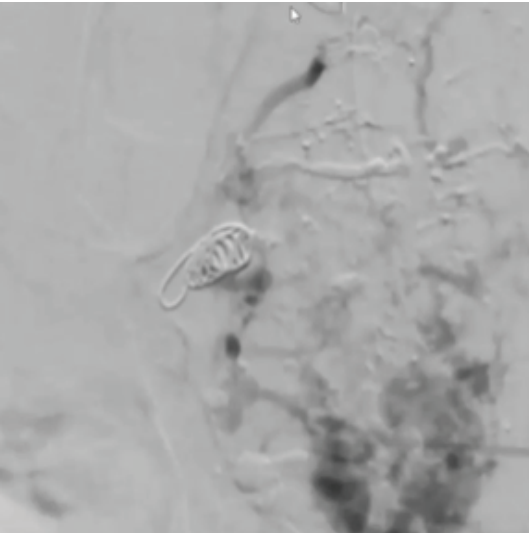
► Compared to pure NBCA, Glubran®2 presents a lower polymerization temperature (max 45° C), a slower polymerization rate, and a milder inflammatory reaction. It is also pliable and therefore more elastic. It is a Class III surgical medical device, widely used in surgery and certified with a CE mark for internal and endovascular use. The packaging includes 10x1ml vials, contained in foil blisters. Physical-chemical characteristics: it appears clear and transparent, with a typical cyanoacrylate smell and water-like density. The polymerization process starts when the product comes into contact with wet environments, such as blood, tissues, or any other bodily fluid. When injected in a vein or an artery, it solidifies within seconds, resulting in a stable and permanent occlusion of the vessel, with no recanalization. The mixture with Lipiodol, while increasing viscosity, allows for improved visualization and delays polymerization time. When mixing the products, we need to avoid contact with ionic solutions, such as blood and saline, and use a glucose solution instead (5%-33%). It is important to underline that we talk about tailored dilution, as this practice cannot be standardized and varies according to the specific case. Detailed information about Glubran®2 in Interventional Radiology is available in our new brochure.



Tips and Tricks

Ezio Lanza MD

Today I am going to give you an overview on the different applications of Glubran®2, through some case reports in both elective and emergency settings.



CASE 1 - Gluteal AVM

Woman (50) - 1:4 ratio small “sandwich” boluses

We injected small boluses of mildly diluted glue, using a very small syringe (1ml), alternated with small amounts of glucose, in order to obtain a widespread distribution of the glue without sacrificing the micro-catheter. As you know, these cases require multiple interventions, and the goal is, of course, to maximize embolization in each session, while avoiding severe ischemia.

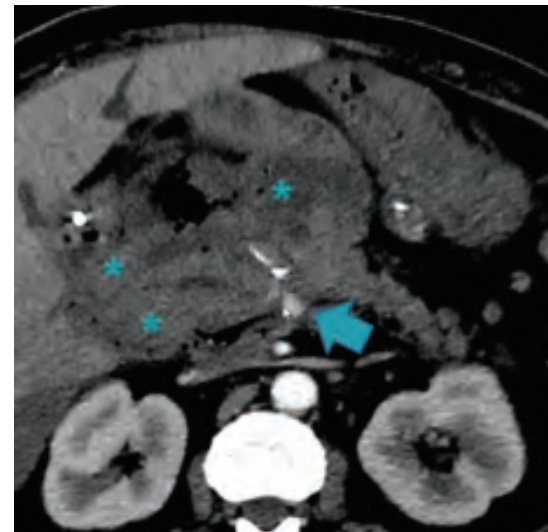
The end result is that the upper part of the AVM has been successfully devascularized, while the lower part will be treated in a subsequent procedure.

CASE 2 - Coeliac Pseudoaneurysm from Superior Mesenteric after Pancreaticoduodenectomy

Man (59) - 1:3 ratio - 0.1 ml focal injection to avoid non-target embolization

In this case, I want to show you which are the metrics we have to get used to when we approach the use of cyanoacrylates: 0.1ml of glue is a reasonable amount and we need to get to terms with the fact that sometimes this is all we need when we are trying to avoid non-target embolization.

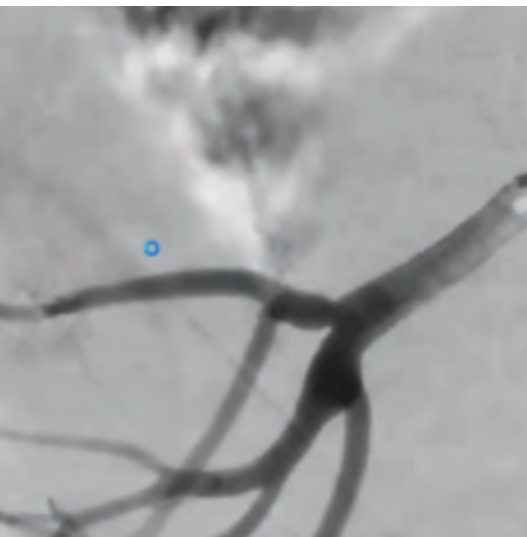
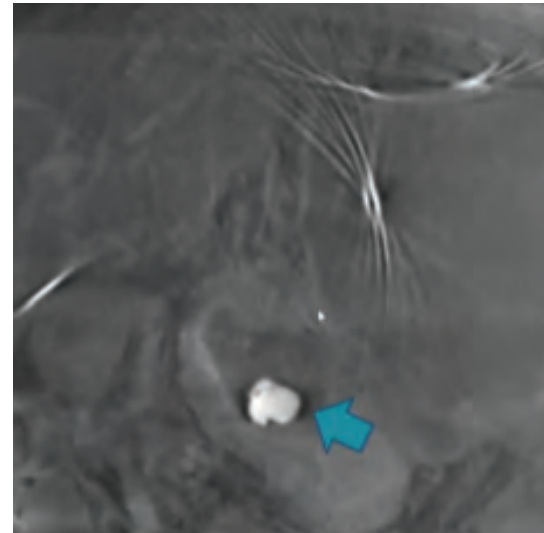
In this case, we have a large coeliac hematoma and a pseudoaneurysm, which is active bleeding from the superior mesenteric artery. This may happen because, as you know, pancreaticoduodenectomy is a very invasive procedure. The difficulty here is that the pseudoaneurysm is pointing upwards in respect to the artery, so the catheterization was quite challenging, however once I managed to place the micro-catheter, the only thing left to do was to inject 0.1ml of glue to create some sort of a balloon, so to completely exclude the pseudoaneurysm.



CASE 3 - Gastric artery bleeding after pancreaticoduodenectomy

Man (80) - 0.15 ml superselective injection - 1:5 ratio

This was a large bleeding from the gastric artery and this patient's haemoglobin levels were rapidly dropping. As you can imagine, in this case, embolizing agents other than liquid would be very difficult to deploy. Medium range of dilution, as 1:4/1:5, allowed for a good deployment of the glue inside the lumen of the bleeding bowel, while achieving the embolization of the vessel to successfully stop the bleeding.



CASE 4 - Adrenal Mass Bleeding

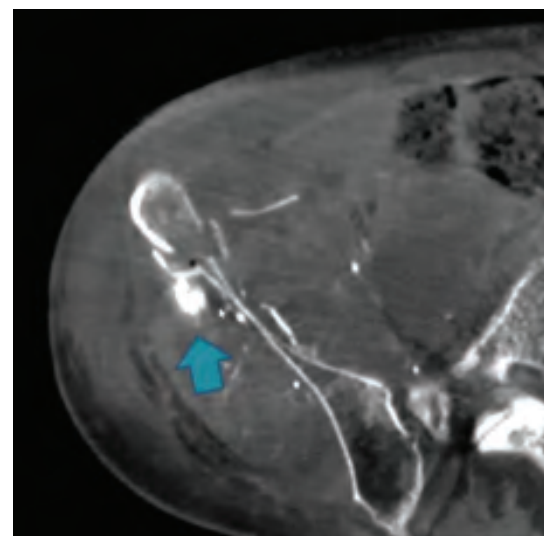
0.1 ml Glubran®2 - 1:3 ratio

This was a very unusual case of adrenal artery bleeding due to a tumour, which was causing a slow decrease of haemoglobin levels. Again, selective catheterization and a very small amount of glue - though in a much denser concentration - allowed to easily stop the bleeding.

CASE 5 - Iliac Bone Comminuted Fracture after RTA

Woman (72) - 1:9 ratio to reach multiple bleeding sites

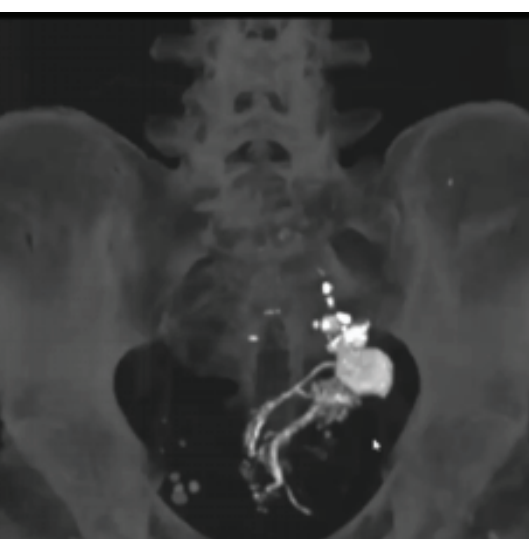
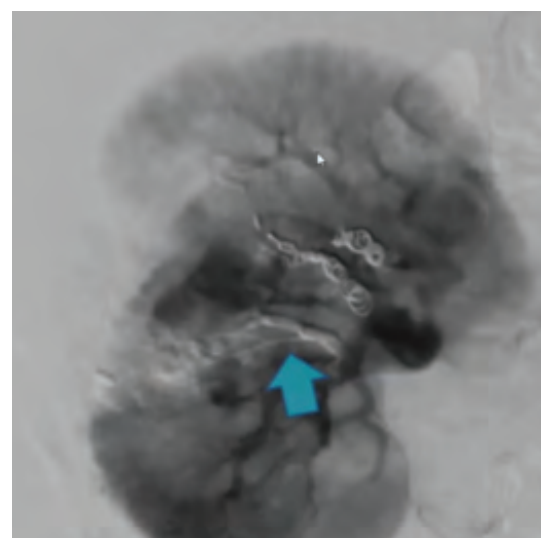
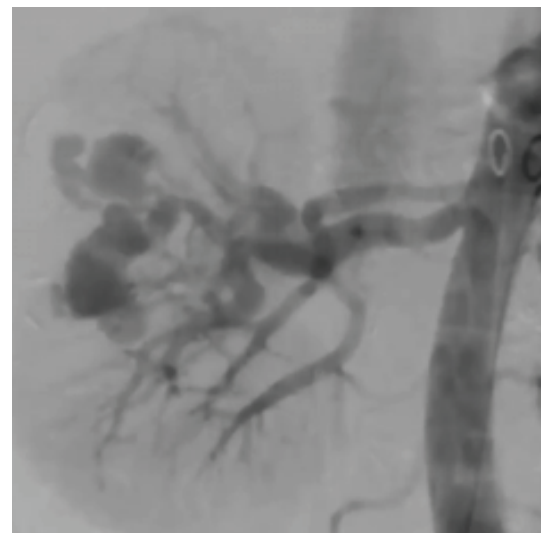
This time we have a very different case, where we adopted a more diluted ratio in order to reach multiple, fast bleeding sites, with a single embolization. This diluted mixture allowed for quick, full and effective embolization of the bleeding spots.



CASE 6 - Robotic Kidney Surgery “when coiling is not enough”

Man (54) - 1:9 ratio - slow controlled injection

We do not normally use glue when it comes to the kidneys because it is a terminal vascularization, but when coiling is not enough you may need different embolic material. This was a particularly difficult case as it presented multiple bleeding, and it just would not stop with simple coiling of the arteries, so I decided to switch to glue. It was important to handle the syringe with care because, when you deal with terminal arteries, it is very easy to get backflow. I used a sandwich technique with a very diluted mixture, inserting small boluses from the tip of the micro-catheter inside the cavity formed by the surgery and the hemorrhage. By handling the syringe with care I was able to inject a block of glue that formed sort of a film from which I could build up and successfully managed to completely embolize the vessel, while avoiding backflow. I could still see some residual bleeding from the coiling technique I had used before, and, although I was confident it would stop sooner or later, which it eventually did, I believe that if I had started with glue rather than coiling, I could have reached the goal much faster.



CASE 7 - Pelvic CHO type 2 AVM - Large venous backflow

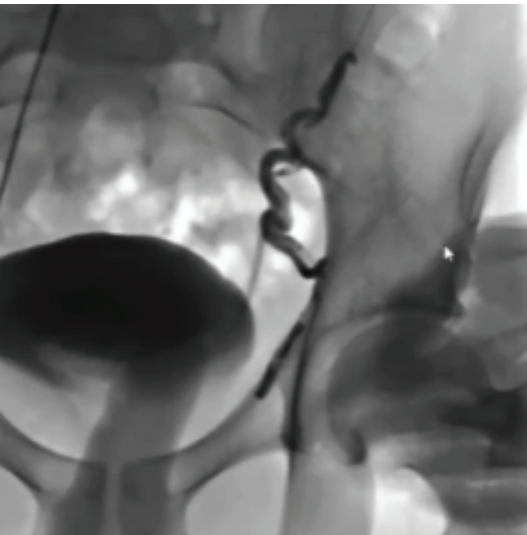
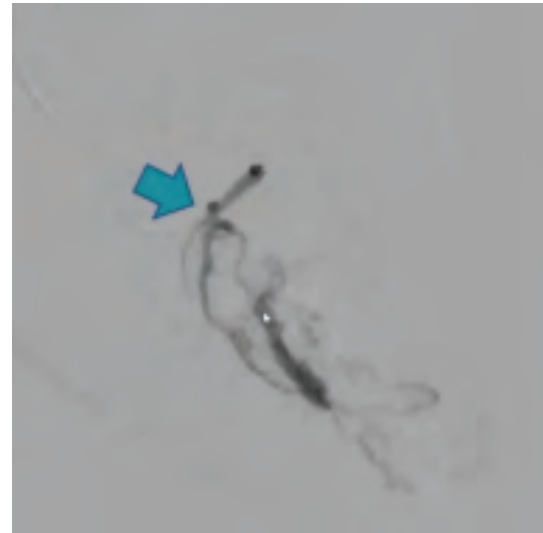
Man (54) - 1:4 ratio Glubran®2 + Amplatzer plug

This was a very unusual and challenging case: a large pelvic malformation with an aneurysmal venous sac. Dario and I got a bit creative and performed a double puncture in order to place three catheters: one inside the artery feeding the AVM, and two inside the draining vein. From the first, we started deploying a 22 mm type 3 Amplatzer plug - to stop the backflow and avoid a pulmonary embolism, - followed by our mixture. The plug successfully stopped the glue, and this allowed us to fill the aneurysmal sac. The final result was very satisfactory and the patient made a complete recovery.

CASE 8 - Forefoot AVM

Woman (35) - 0.1 ml Glubran[®]2 - 1:3 in the posterior tibial

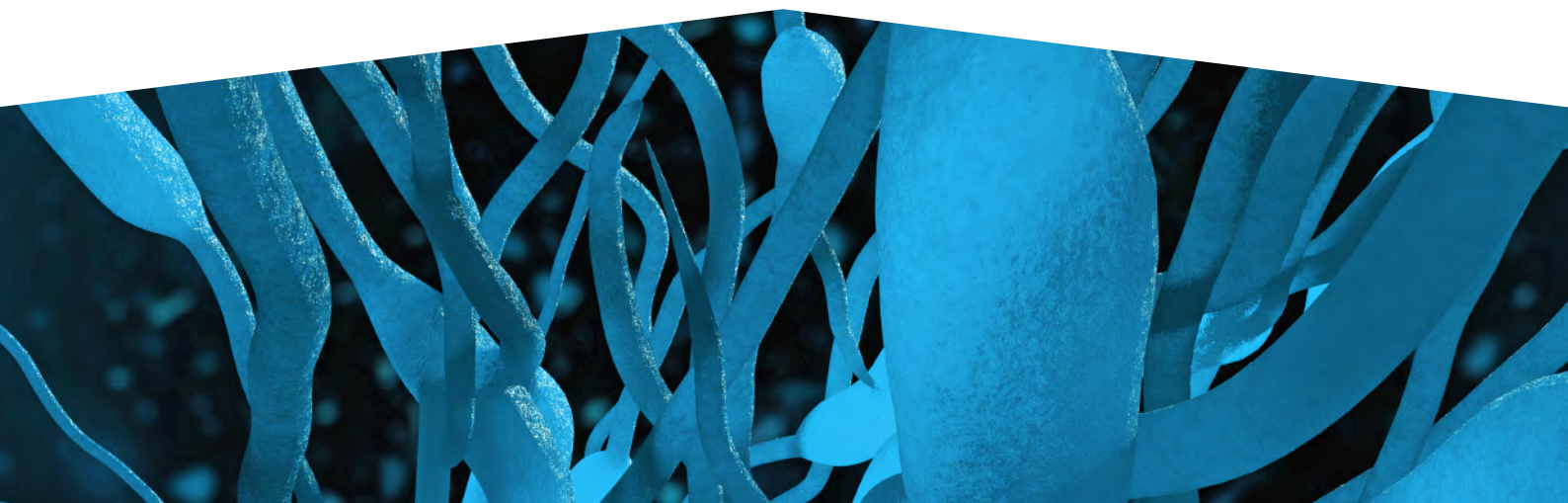
In this case, we applied manual compression of the digital arteries in order to avoid embolization and stop the flow. Again, we used only a small amount of glue, in a highly dense ratio, and the final result was completely satisfactory, with preservation of the digital arteries and no signs of ischemia.



CASE 9 - Varicocele Embolization

Man (20) - 3 ml of Glubran[®]2 - 1:2 ratio

This was a case of very difficult anatomy, as we are talking about many different veins and collaterals, and I could not place the micro-catheter where I wanted to, so my stance was very proximal. I used a very dense mixture while asking the patient to do a strong Valsalva manoeuvre and apply manual compression of the left groin. Using this trick I was able to achieve distal embolization while not being distal at all. The final result was very good and we saw no further complications.



Q&A

Webinar Chat: In CASE 5, could you have opted for gelfoam, instead of glue?

Ezio Lanza, MD: Gelfoam is indeed an option: we use it when we are sure that the patient will be fit enough to undergo surgery, because, as you know, traumatologists will not operate on unstable patients. In that particular case, gelfoam could have meant too proximal an embolization, and I wanted to make sure I could reach the bleeding spots distally, to maximize stability and guarantee a safe surgical procedure. This is not to say that glue is our only option: sometimes it depends on experience and the confidence you have in using different materials, sometimes it depends on the goal.

Dario Poretti, MD: Can you use the micro-catheter multiple times?

Ezio Lanza, MD: If you favor the use of glucose and the sandwich technique, you can save your micro-catheter for multiple uses. So, basically, as long as you flush it with glucose, you can easily eliminate most of the residual glue and use it for up to 3 times (no more than that). In order to flush it effectively, the flow must be free of obstacles. Flushing your micro-catheter in the liver, for example, is perfectly safe, whereas you cannot do this in the kidney, as you would get early backflow. In such a situation, you should quickly extract your micro-catheter, leaving the main catheter in place, and flush it outside, on a towel.

Dario Poretti, MD: Does the glue pose a problem in terms of being able to retrieve your catheter? In other words, is there any risk for the catheter of getting stuck because of the glue?

Ezio Lanza, MD: I know for a fact that glue might cause problems with hydrophilic catheters, as it reacts to water and hydrophilic coating. I do not normally use such catheters, and I never found myself in the position of not being able to retrieve my instrument. You will often find a few centimeters of glue stuck to the tip of the catheter, but a quick and regular movement is all you need to be able to retrieve it.

The role of GLUBRAN[®]2 cyanoacrylate glue in embolization of trauma and spontaneous bleeding

Dario Poretti MD

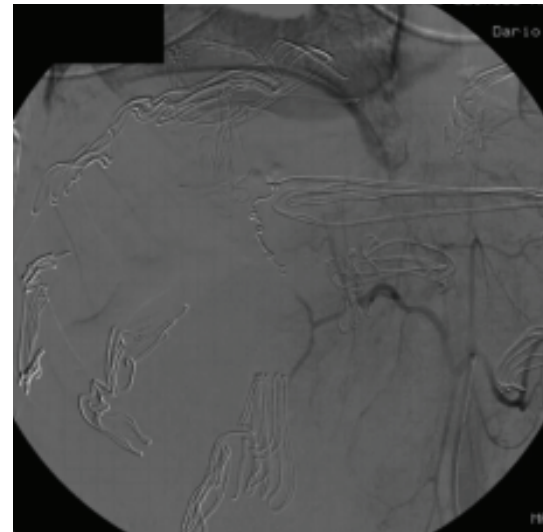
In the past three decades, there has been a growing interest relating to the approach of non-operative management (NOM) in blunt abdominal trauma, so we deal with spleen and liver primarily, but also kidneys and other organs. Non-operative is a definition that actually means non-surgical; in fact, along with observation, it comprises percutaneous, endoscopic, and often endovascular procedures, so the implementation of embolization has been taken into consideration.

Talking about **LIVER INJURIES**, for example, after performing a CT scan to have an overview of the situation of the patient, we proceed to act on both active and non-active bleeding (e.g. a pseudoaneurysm or a fistula).

CASE 1 - Embolization Liver Lesion

44yo male involved in motorvehicle crash Laparotomy at arrival in first ER, liver packing, w/o control of bleeding. Referred to our hospital for ANGIO Tear of peripheral branch or right hepatic artery. Treated by coiling (2005)

So, at the time I used coils, but with with a vastly diffuse vasospasm and intense active bleeding it took me 10-12 minutes to achieve control. Would I use glue today?

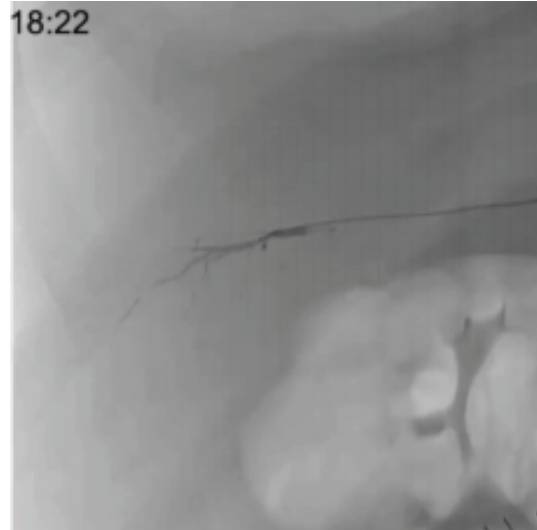
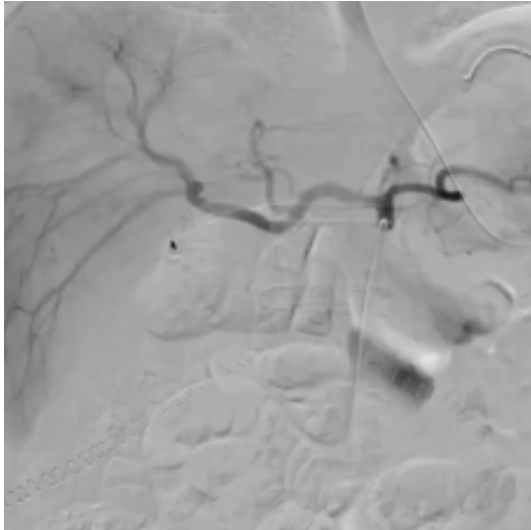


CASE 2 - Embolization Liver Lesion

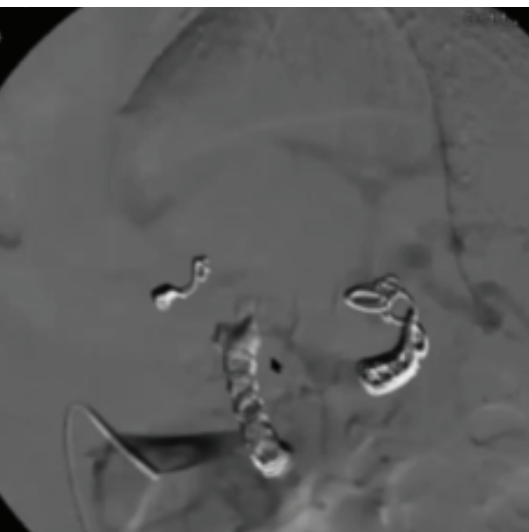
68yo male 12 p.o. day after Whipple procedure. Sent home (9h p.o. day) with anticoagulation and antiplatelet thx (previous ischemic heart dis.) Came back to ER with abd pain and reduction in Hb levels after minor trauma at home. CT reveals hematoma w active bleeding from liver parenchyma in S5. ANGIO identifies bleeding site from peripheral branch or intermediate hepatic artery.

Treated by glue (1:5)

In this case, I used glue, which took me about 2 minutes, so the procedure was much quicker. Additionally, the patient was under anticoagulation and the glue works regardless of the coagulation profile of the patient. This is a very interesting issue as, sometimes, the bleeding is in fact due to the anticoagulation itself. So, we have a product that not only is extremely rapid and effective but also does not revascularize. To answer a previous question, sometimes gelfoam is not ideal: it takes time and does not ensure stability.



The **SPLEEN** is not a setting where embolization has been used extensively. Proximal embolization is the accepted way but, when stopping the bleeding takes time, we can use the glue within the coils. We need to be extremely careful, though, as the following case reports will show. These are not specifically trauma cases, but they will nonetheless elucidate what I am trying to say.



CASE 1 - Embolization Splenic Artery

62yo female pt Aneurysm of mid splenic artery.

Treatment: sandwich coiling + glue filling of proximal coil cluster

In this case, although I used several coils, the bleeding would not stop. I did not want to use too many coils, what I used glue instead, injecting it inside the coil, which completely blocked the flow with no filling of the aneurysm. This is the kind of result we want to achieve.

CASE 2 - Embolization Splenic Artery

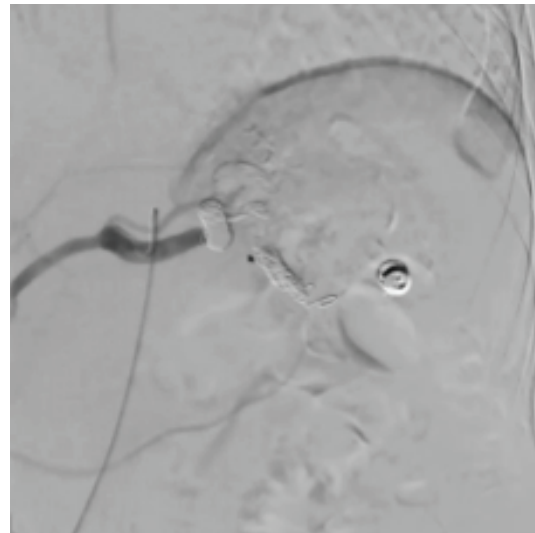
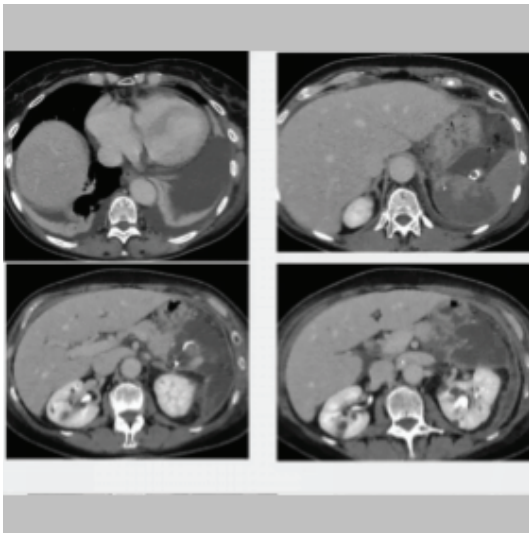
58yo female pt

Double aneurysm of mid and distal splenic artery.

Treatment: sandwich coiling + glue filling of proximal coil cluster

Unintended migration of glue distally, with partial splenic ischemic areas and to non-target vessel, with MAJOR complication.

In this case, we had two aneurysms, close to what I interpreted to be a gastric vessel. I opted for a sandwich coiling technique and applied multiple coils: proximal, distal, and in between. I needed to make sure there would be no flow from any other vessel so I injected some glue which, while perfectly sealing the coils that I had targeted, unexpectedly migrated to reach the tiny vessel, which turned out to be not gastric but a pancreatic anomalous vessel. Consequences were unfortunate, as our patient developed necrotizing pancreatitis and took a while to recover. The point that I am trying to make here is that glue indeed works very effectively, but it does not eliminate mistakes, so we need to be very careful during the diagnostic phase before we proceed to the embolization.



CASE 3 - Embolization Splenic Artery

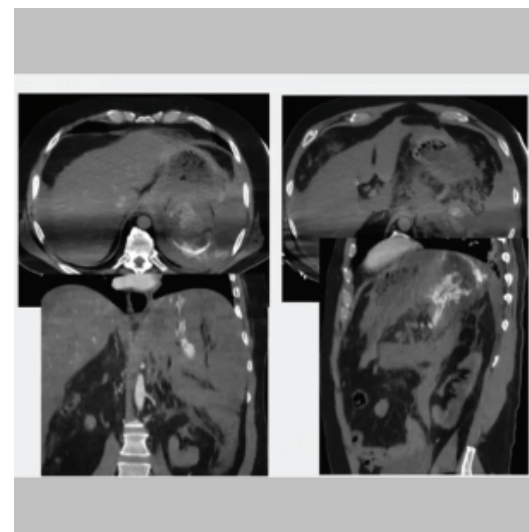
56yo male pt

Fell from stairs at home. Minor head and thoracic trauma.

After 3 hours (already in ER) develops shock state. At CT large retroperitoneal hematoma in LUQ, attributed to rupture of splenic aneurysm Treatment: direct glue filling splenic artery around culprit lesion, associated w distal and proximal coils.

The patient arrived at our hospital with a large hematoma and a very slow flow. We reached the artery beyond the bleeding spot and used coils first, then glue. The glue here not only is blocking the arteries but also navigating the bleeding site. What we want to achieve is distribution both inside and outside of the artery.

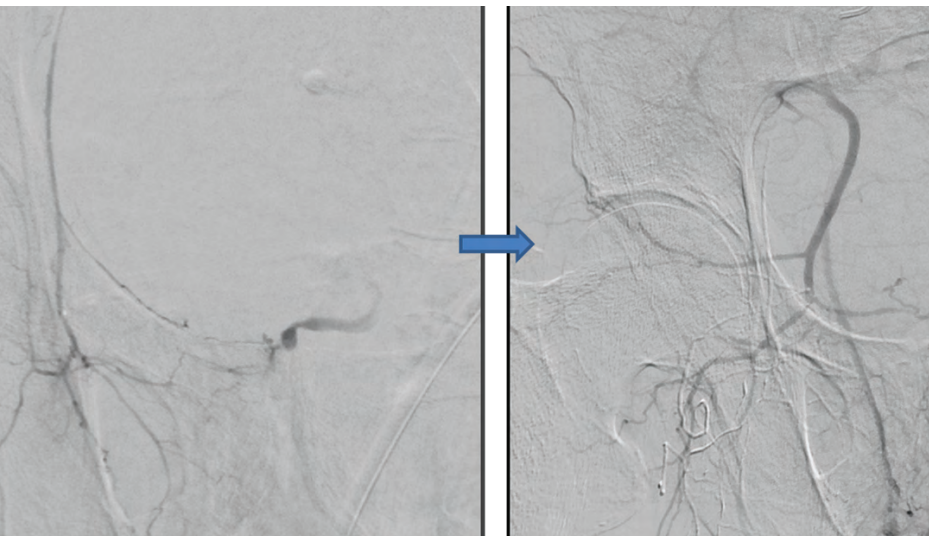
This is a very unfortunate case, that nonetheless proves that glue indeed performs as expected. The patient died due to the prolonged state of shock, but in the



pathologist report we read as follows: "splenic artery filled with hard polymorphous material occupying mid-portion of the vessel and apparently piercing the artery wall and occupying roughly two centimeters of perivascular space". What this means is that the glue hardens and stays in place, doing exactly the job we need it to do.



In trauma settings we also take care of **HIP TRAUMA**, cooperating with surgeons and traumatologists. In some cases, embolization can play an even more important role when dealing with focal fractures.

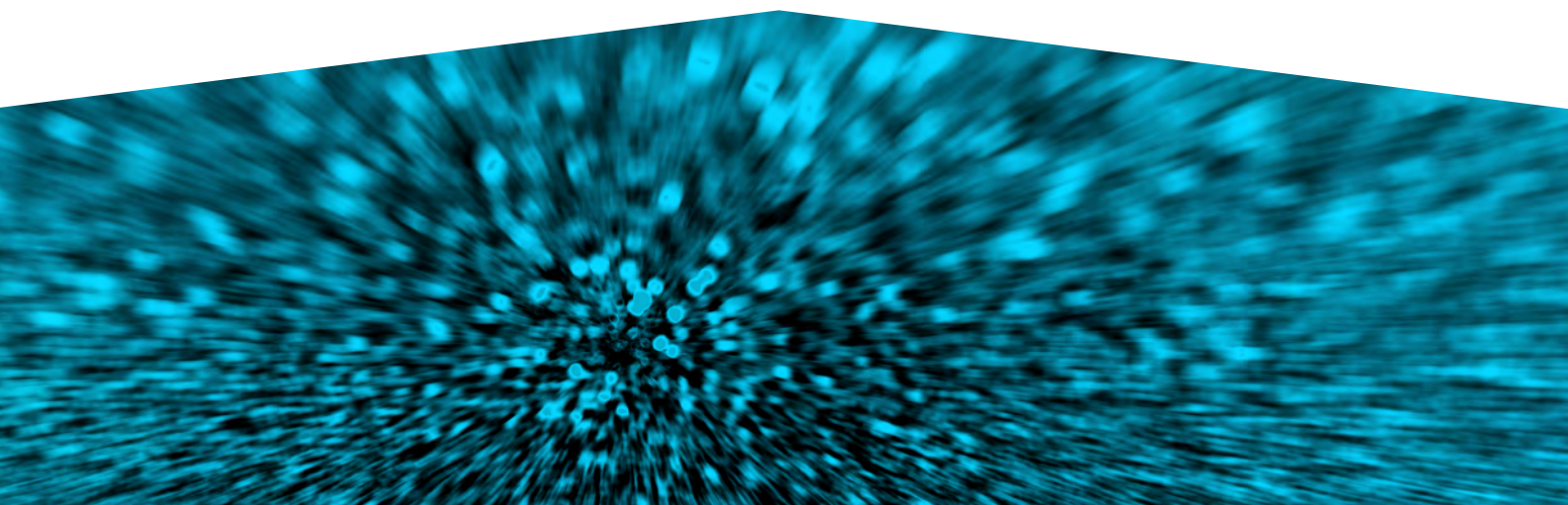


TRAUMA SETTING — HIP

64yo male, vehicle crash. Minimal hip fracture

Pt sent home due to stable conditions. Comes back with enlarging hematoma 48h later.

CT scan reveals bleeding close to the fracture site and, through the angiography, we identify a tiny vessel going to the bleeding spot. I could not reach that tiny vessel so, what I did was getting close to it by slowly injecting diluted glue to freeze all the vessels around the spot, to prevent any possible revascularization. Coils might have left an opening to collaterals and revascularization, and that is why we like to use glue in cases like this.



“IATROGENIC” TRAUMA comprises abdominal surgery and various percutaneous procedures.

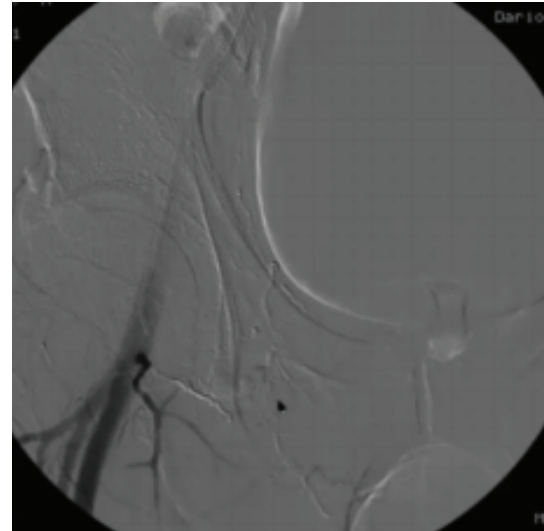
CASE 1

58yo female pt

Endovascular cardio procedure 6 hours before. Progressive pain at the groin and Hg drop. CT scan reveals active bleeding close to CFA.

Treatment: glue filling distally plus coiling of origin of bleeding vessel (branch of profunda femoris)

This patient had undergone a cardiological procedure and, once again, we used coils to reduce the flow and then froze the area with diluted glue.



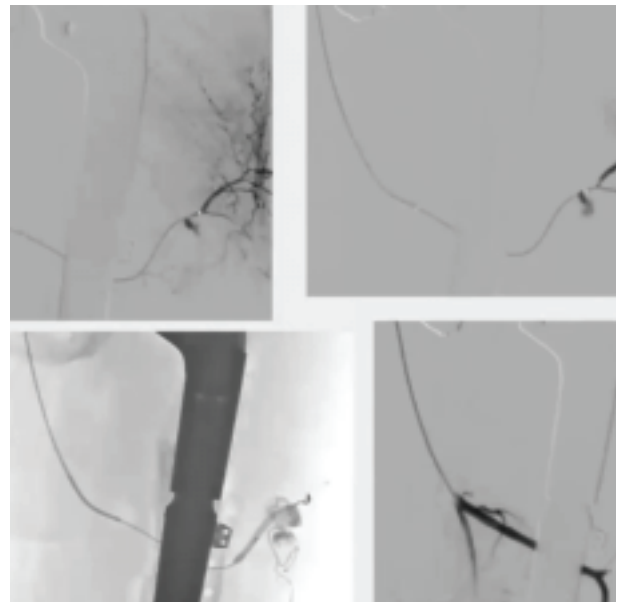
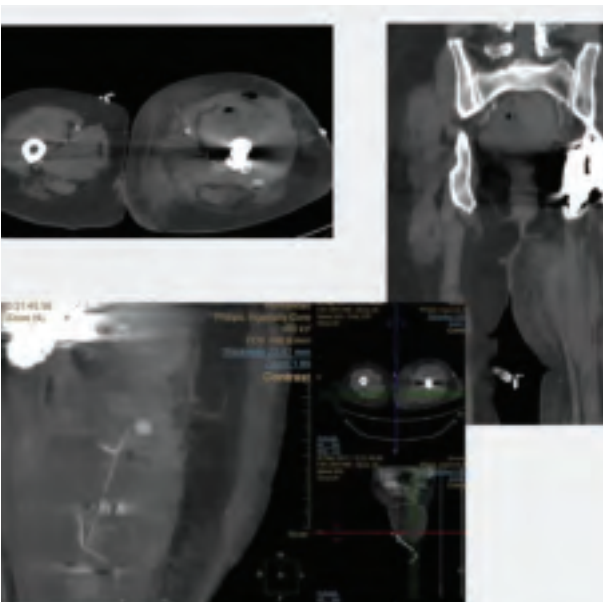
CASE 2 - Embolization Muscular Bleeding Lesion

78yo female pt

Hip surgery 4 days before. Progressive shock and Hg drop. CT scan reveals large hematoma w PSA at left thigh. Treatment: glue filling plus coiling to protect distal branch.

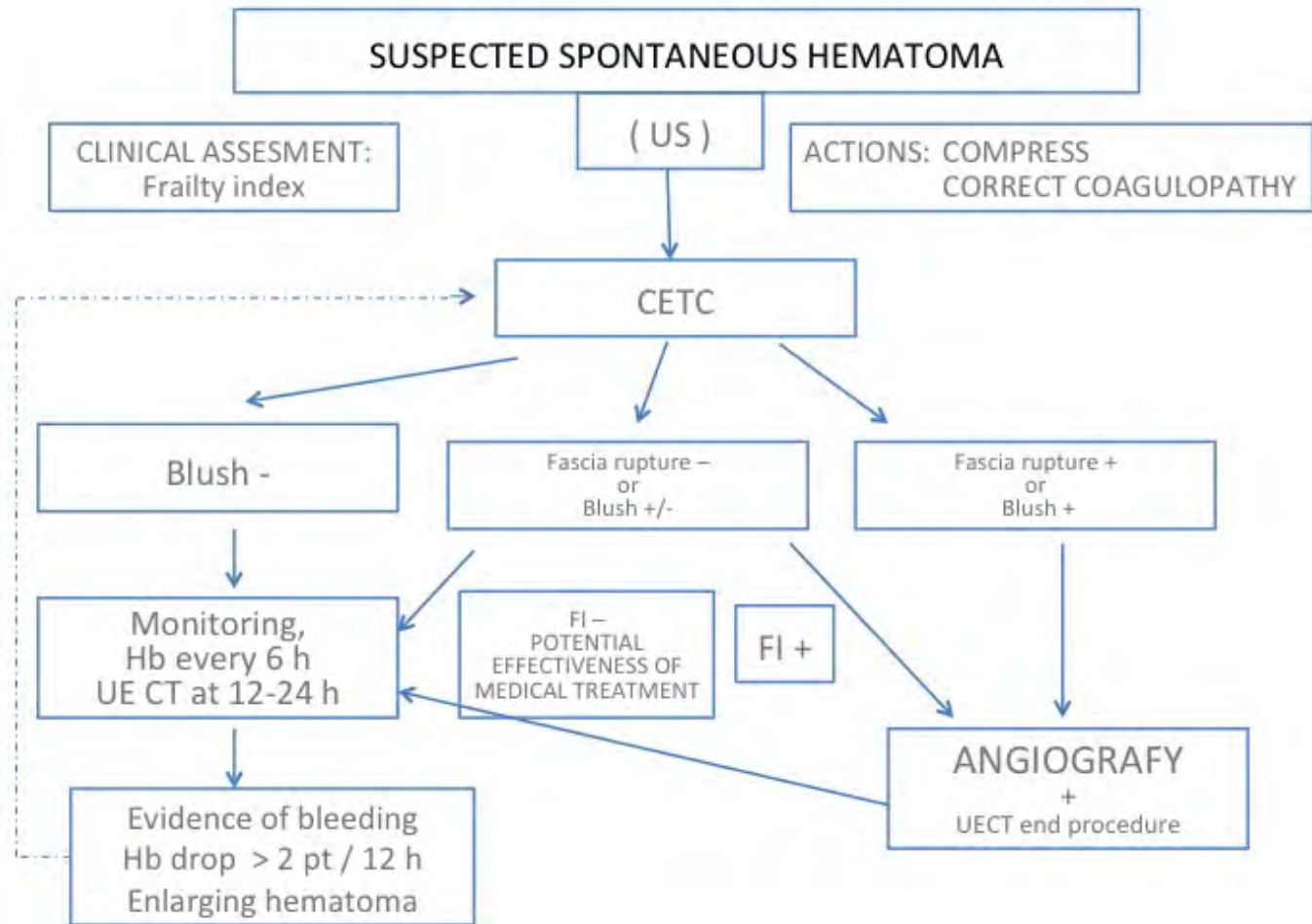
In this case we identified two vessels going out of the injured site, and I wanted to preserve at least the largest. I used coils first and then injected the glue. In this case the coils have been used to prevent devascularization in the peripheral area and there was space left for the glue to fill up the pseudoaneurysm. The injection can be very gentle and slow because there is no risk for the micro-catheter to get stuck with the glue. I injected a continuous flow and left the catheter in place, waiting for the polymerization to complete.

This takes about 10 to 15 seconds, and it is necessary if you want the glue to harden properly, to avoid any unexpected migration. The final result was a perfectly sealed artery, with preservation of the surrounding vessels.



In the past few years, there has been a lot of discussion about **BLEEDING IN ANTICOAGULATED PATIENTS WITH MINOR TRAUMA**. We have been working on an algorithm to lead our decision-making.

FLOW CHART EMORRAGIE SPONTANEE 2.1



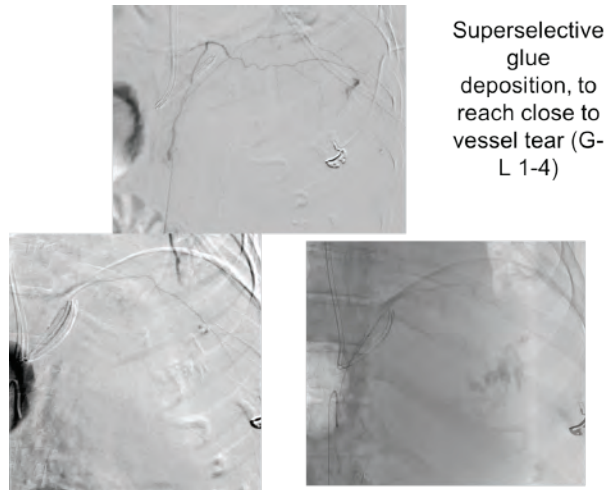
We opt for embolization in case of fascia rupture and active blush. Depending on the amount of blush and on patient frailty, we decide whether to proceed with monitoring or angiography and embolization.

CASE 1

62yo male, major stroke, ARDS, developed large retroperitoneal hematoma, detected by CECT. Referred to ANGIOGRAPHY after transfusion of 2 units of Packed RBC

We detected multiple bleeding sites on the left side and I knew I had to go in the lumbar arteries. I injected a mixture of Lipiodol and Glubran®2 with a 4:1 ratio. I closed the first vessel and flushed the micro-catheter with dextrose: in this way, I was able to use the same catheter 3 times.

Before carrying on with the embolization, I checked a vessel that I thought could be spinal, and only proceeded when I made sure it was safe. I closed all the vessels and the end result was satisfactory but, two days later, the patient came back with a new bleeding site below the diaphragm. Because I had used glue, rather than gelfoam, I was sure the vessels that I had closed could not have opened up again. It had to be a new one, so I started looking until I found a phrenic vessel that I closed with the same mixture.



TAKE HOME MESSAGE

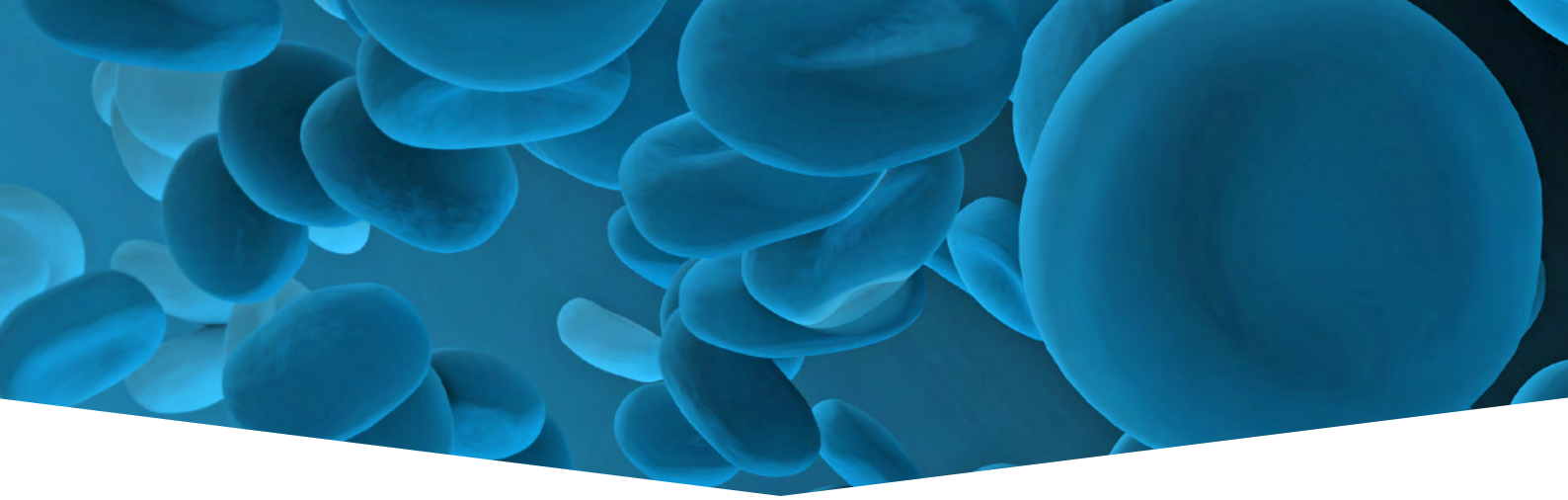
- ▶ After adequate skill development glue can be used with elevated safety profile
- ▶ Beware of noble vessels (spine, pancreas, etc)
- ▶ Microcatheter can be used up to three times (multiple bleeding vessels)
- ▶ Dilution can be changed in order to navigate or seal (1-5 or 1-2)
- ▶ If further bleeding occurs, it has to be a new vessel (no short time recanalization)
- ▶ Vessel occlusion is immediate and independent from coagulation profile

Q&A

Webinar Chat: In the case of the splenic artery, if you had used coils rather than glue, how many would you have needed?

Dario Poretti, MD: Well, it depends on their length but, although we use Glubran®2 to reduce the number of coils, I think you have to base your decision on the speed of the flow, rather than on the amount of metal: if you achieve about 50% of flow reduction but the bleeding is still occurring, you know you are losing precious minutes and wearing out the vessels so, use a high concentration of glue mixture, 1:1 or maybe 1:2, and a small amount within the nest of coils is enough to stop the bleeding. It is very effective.

Vittorio Pedicini MD: You do have alternative tools for muscular bleeding, like particles for example. Due to the aggregation phenomenon, though, you might have an angiogram that shows ceased bleeding but, in fact, you later risk recanalization and further bleeding because of systolic push. This is a risk that you eliminate by using glue.



Use of NBCA in Gastrointestinal Bleeding

Vittorio Pedicini MD

THEORETICAL ADVANTAGES OF NBCA

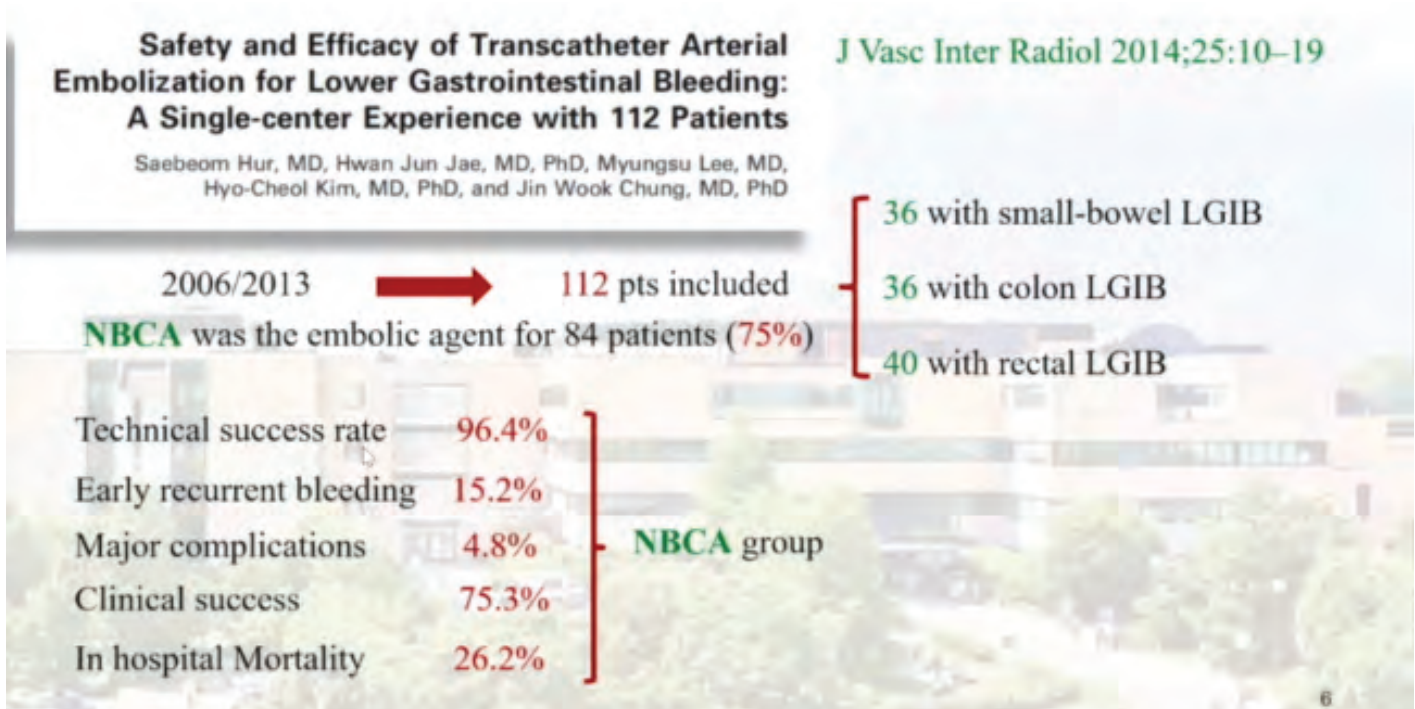
- ▶ Permanent
- ▶ Highly penetrable
- ▶ Occlusive effect does not depend on coagulation parameters - High hemostatic effect
- ▶ Interesting for massive bleeding (very fast - good for emergency procedures)
- ▶ High radiopacity
- ▶ Can reach distal targets (impossible to reach even with micro-catheters)
- ▶ Easy to deliver
- ▶ Best options with very small micro-catheters

When compared to its direct competitor, ONYX, NBCA shows several improved characteristics, as shown in the picture. Even though it is not possible to perform an angiography between injections with NBCA, we know by now that we can flush and re-use the same micro-catheter for up to three times. Due to its peculiar anatomy, the gastrointestinal (GI) tract may present several complications. It is to be noted that the upper and lower tracts are different when it comes to possible risks. The upper tract is rich in collaterals, which allow for harder embolization, and has a lower ischemic risk but, on the other hand, the rebleeding rate is higher, due to the presence of extensive vascular arcades.

ONYX vs NBCA	
Onyx	NBCA
precipitates	polymerizes (exothermic)
cohesive	adhesive
slow injection	fast injection
low thrombogenicity	high thrombogenicity
spongy cast	hard cast
1.3 Fr compatible microcatheter not truly flow-directed	compatible w/ 1.2 Fr flow-guided microcatheters
only 2 concentrations available, unable to mix	Ethiodol/NBCA ratio up to the operator's discretion
angiography btwn injections of the same pedicle	no angiography btwn injections of the same pedicle

The lower tract presents terminal branches and vasa recta. It has a potential higher ischemic risk but lower rebleeding rate. Many papers have been published about the use of NBCA for GI bleeding.

In 2014, AJR (American Journal of Roentgenology) published a study performed on one hundred patients, titled "Clinical Outcome of Transcatheter Arterial Embolization With N-Butyl-2-Cyanoacrylate for Control of Acute Gastrointestinal Tract Bleeding", which concluded that *TAE with NBC-A with or without other embolic agents showed high technical and clinical effectiveness*. In the picture below, we can see the figures from another study from 2014, with high technical success rate and low major complication rate. The conclusions were that *"Transcatheter arterial embolization is a safe and effective treatment for LGIB. NBCA could be used as a primary embolic agent for this procedure."*



Published in 2017 by JVIR (Journal of Vascular and Interventional Radiology) with the title **"Transcatheter Arterial Embolization of Gastrointestinal Bleeding with /V-Butyl Cyanoacrylate: A Systematic Review and Meta-Analysis of Safety and Efficacy"**, an evaluation on 15 studies, performed on a total of 440 patients and including both upper and lower GI tracts, showed high technical and clinical success with very low major complications and only 3 bowel resections.

Characteristics of Included Studies		Technical Success		Clinical Success		Major Complications		Repeat Intervention		30-d Mortality	
Positive Angiography		UGIB	LGB	UGIB	LGB	UGIB	LGB	UGIB	LGB	UGIB	LGB
7 (100)	-	7 (100)	-	6 (85.7)	-	0	-	1 (14.3)	-	0	-
5 (100)	-	5 (100)	-	3 (60.0)	-	0	-	2 (40.0)	-	2 (40.0)	-
32 (100)	-	32 (100)	-	29 (90.6)	-	0	-	3 (9.4)	-	6 (18.8)	-
16 (100)	-	15 (93.8)	-	13 (86.7)	-	0	-	1 (6.7)	-	1 (6.7)	-
-	14 (100)	-	14 (100)	-	10 (71.4)	-	0	-	2 (14.3)	-	1 (7.1)
18 (90.0)	-	20 (100)	-	17 (85.0)	-	0	-	2 (10.0)	-	9 (45.0)	-
-	27 (100)	-	27 (100)	-	23 (85.2)	-	0	-	3 (11.1)	-	12 (44.4)
5 (100)	-	5 (100)	-	4 (80.0)	-	0	-	1 (20.0)	-	1 (20.0)	-
18 (85.7)	-	21 (100)	-	21 (100)	-	0	-	0	-	0	-
15 (100)	-	15 (100)	-	15 (100)	-	0	-	0	-	0	-
7 (50.0)	20 (100)	14 (100)	20 (100)	13 (92.9)	19 (95.0)	3 (21.4)	3 (15.0)	0	1 (5.0)	1 (7.1)	1 (5.0)
49 (100)	-	48 (98.0)	-	30 (62.5)	-	1 (2.1)	-	11 (22.9)	-	15 (31.2)	-
-	84 (95.5)	-	84 (95.5)	-	74 (88.1)	-	4 (4.8)	-	8 (9.5)	-	18 (21.4)
72 (100)	30 (100)	72 (100)	30 (100)	54 (75.0)	26 (86.7)	1 (1.4)	1 (3.3)	10 (13.9)	3 (10.0)	18 (25.0)	2 (6.7)
5 (100)	-	5 (100)	-	5 (100)	-	0	-	0	-	1 (20.0)	-
249 (95.4)	175 (97.8)	259 (99.2)	175 (97.8)	210 (81.1)	152 (86.9)	5 (1.9)	8 (4.6)	31 (12.0)	17 (9.7)	54 (20.8)	34 (19.4)

A very interesting point emerged as follows: "Coagulopathy is an independent predictor of clinical failure, and the site of bleeding, coagulopathy, and clinical failure are independent predictors of 30-day mortality."

Conclusions: "Transcatheter arterial embolization with NBCA is safe and effective for the treatment of GI bleeding."

RESULTS

Upper GI bleeding		Lower GI bleeding
Technical success 93 %		Technical success 95 %
Clinical success 67 %		Clinical success 76 %
Rebleeding rate 33 %		Rebleeding rate 24 %

Weldon DT, Burke SI, Sun S, Mimura H, Golzarian J (2008) Interventional management of lower gastrointestinal bleeding [review]. *Eur Radiol* 18(5):857-867 Epub 2008 Jan 8

Funaki B (2004) Microcatheter embolization of lower gastrointestinal hemorrhage: an old idea whose time has come [review]. *Cardiovasc Intervent Radiol* 27(6):591-599

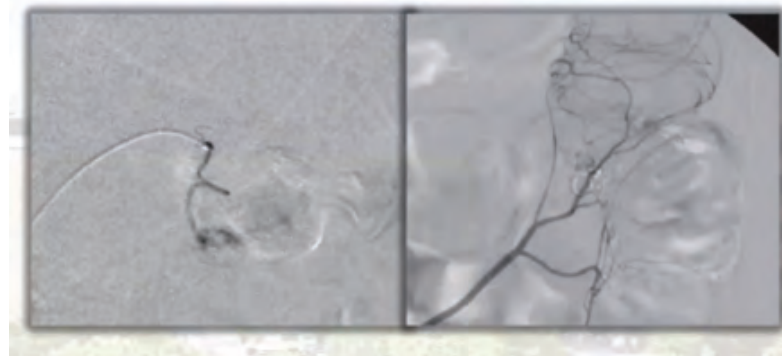
As the data show, employing glue in GI procedures is indeed very effective, but we always need to carefully plan in advance: gastroduodenal bleeding may appear to be easy to treat, but if you miscalculate your ratio and use a high-density embolizing material, the risk is that a procedure that looks successful could present later complications, such as ischemic damage and subsequent perforation.

GASTRODUODENAL BLEEDING

Emb. with glue

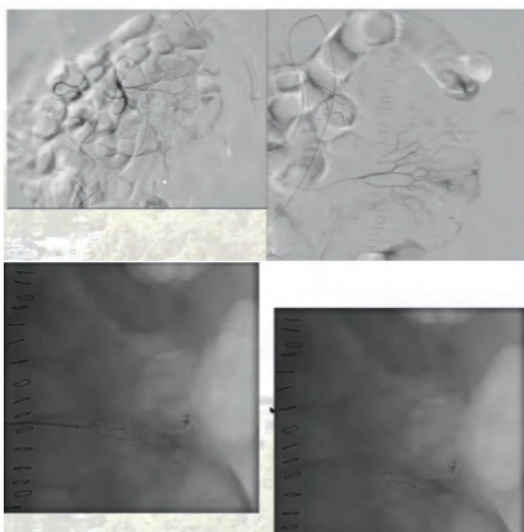
In the picture is a successful example of distal embolization with a thin, 1.3 micro-catheter.

Left colon embolized with glue: bleeding diverticulum

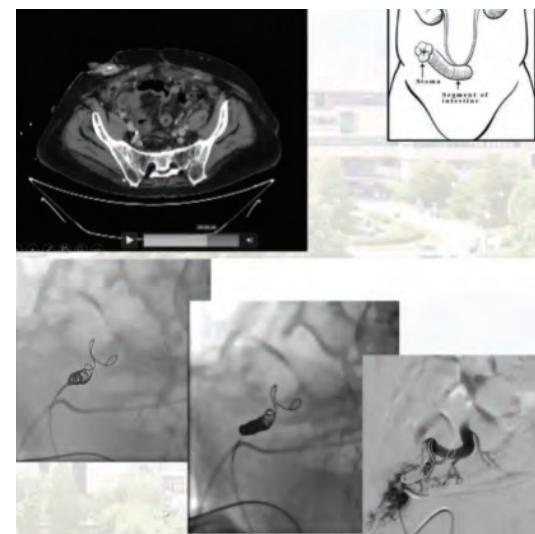


ANGIODYSPLASIAS has also been treated successfully with Glubran®2. Vasodilators can represent a useful aid tool to help locate the bleeding site and experience is always crucial when navigating the vessels, but a distal injection will most certainly lead to complete embolization of this kind of arteriovenous malformations.

On the top left is an example of an angiodysplasia of the ileum that presented distal damage of small vessels. Again, we went distally and used a 1:3 ratio Glubran®2/Lipiodol mixture. The photographs at the bottom show the final “stamp”.

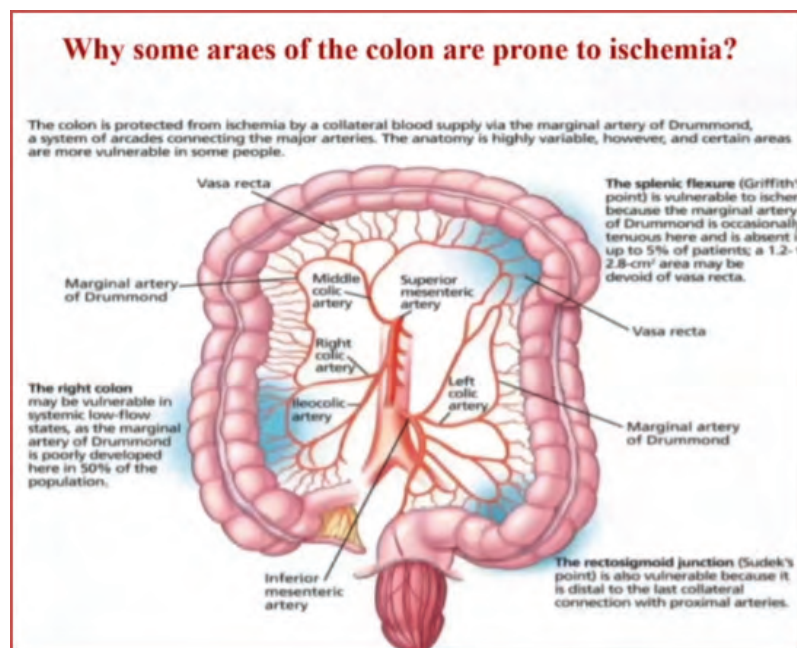


Here we have a case of **VARICEAL BLEEDING** in a patient with multiple pathologies: multifocal hepatocellular carcinoma (HCC) with a portal venous thrombosis, portal hypertension, and portal varices. He had a Bricker bladder due to urothelial carcinoma. We inserted the catheter in the ureters and traveled to the bowel. While the patient was bleeding, the urine in the catheter appeared clear, which suggested that the source of the bleeding might be the bowel, so we decided to approach the varices with an ultrasound-guided percutaneous procedure- We used a micropuncture set, exchanging it for a 5-French. We performed an angiogram and opted for coils first, to avoid migration of the glue to non-targeted distal vessels, then injected an extremely diluted (1:9) mixture near the puncture site, which completely stopped the flow.



To summarize, we have shown that embolization can be successfully performed on the GI tract, as long as we keep in mind the weak points of its anatomy, like the vasa recta, the splenic flexure, the right colon and the Sudeck's point, which is a high risk area due to the lack of collateral circulation. If we pay attention, though, glue can be a very good tool in this difficult area.

Variceal bleeding is also a setting where we can obtain good results.



TAKE HOME MESSAGE

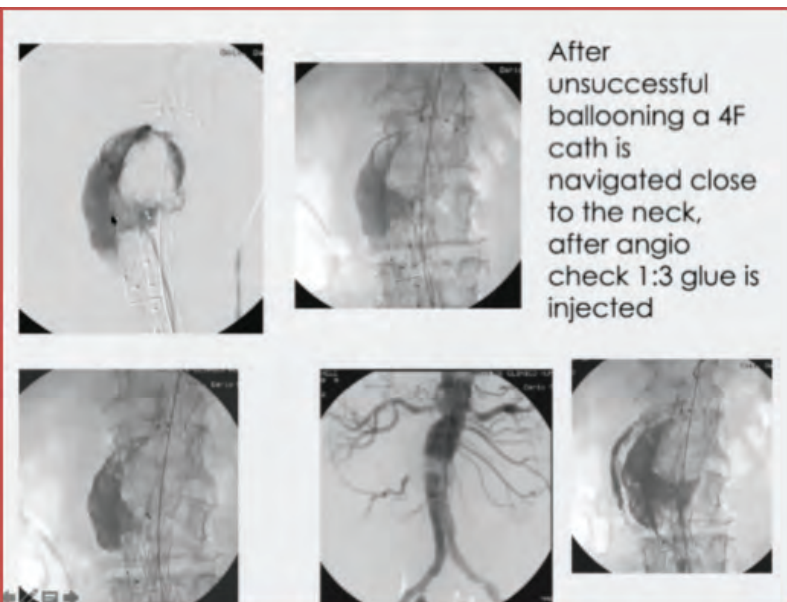
In our experience arterial embolization using NBCA in well-trained hands is effective and safe in controlling bleeding from the GI tract and does not cause more ischemic complications than other embolic agents.

Should you require training on the matter, please be aware that our team from Humanitas regularly provides training sessions and workshops in collaboration with GEM.

The role of GLUBRAN[®]2 cyanoacrylate glue in embolization of Endoleak

Dario Poretti MD

As we all know, endoleak treatments are probably the most difficult part of an EVAR procedure. They currently represent the majority of the complications (10-50%) after EVAR, and the main reason for reintervention (Golzarian J et al., Tech Vasc Interv Radiol 2005). We mainly deal with Type II endoleaks (caused by retrograde branch flow) however also sometimes we treat Type I endoleaks, which treatment options include proximal cuff or extension endograft, as well as balloon angioplasty with large balloons (25 to 30 mm) or large stent placement. Some use coils in the aneurysmal sac and, very occasionally, we have used glue.



TYPE I ENDOLEAK

In this case, we had a very angulated neck, firstly treated unsuccessfully with balloons. We proceeded to insert the catheter outside the graft and inside the aneurysmal sac and checked through aggressive angiography that no flow would leak out of the sac. We injected the glue and completely froze the leak. It is a procedure that requires extreme care, but in a complex case such as this, it proved reliable. Considering hyperdensity, follow up images should preferably be taken through MR scanning, rather than CT. It is to be noted, though, that glue has less hyperdensity, compared to other embolizing materials.

TYPE II ENDOLEAK

The endoleak cavity acts as an “arteriovenous malformation nidus” thrombosing the nidus is the key for a successful embolization.

(Baum RA, Endovascular Today, 2003)

The nidus theory has been investigated: this study involved 29pts to compare outcomes of type II endoleak embolization involving: endoleak nidus only - vs - nidus and branch vessels.

Embolization of nidus and branch vessels is not superior to embolization of only the nidus in terms of occlusion of type II endoleak and change in sac size despite requiring longer procedure time and resulting in greater patient radiation exposure.

(Hyeon Yu. J Vasc Interv Radiol. 2017 Feb;28(2):176-184)

In terms of **embolization routes**, we have:

- ▶ Transarterial (leading to the nidus site);
- ▶ Direct puncture (translumbar or transabdominal);
- ▶ Transcaval (which we have never used).

In terms of **embolizing materials**, we consider:

- ▶ Coils
- ▶ Glue
- ▶ Onyx

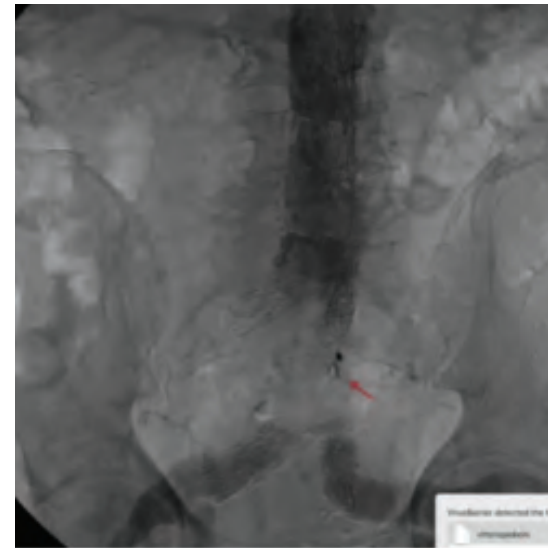
TYPE II ENDOLEAK Transarterial (case I)

Navigation between graft and arterial wall

Here we have a tiny aneurysmal sac along the left side of the inferior aorta, which we decided to treat by positioning a straight graft. Before that, we preemptively close the inferior mesenteric artery with a plug, in order to prevent possible backflow or endoleak. When we found out that the sac was in conjunction with a lumbar artery, though, we first unsuccessfully tried to stop the bleeding with a balloon, then decided to navigate the catheter to reach the sac. In this case, we did not need the typical telescopic that we normally use to deliver the glue, because we had the wall of the aorta and the grafter creating sort of a sheath around the catheter so there was no risk of migration beyond the graft. We injected the glue inside the aneurysmal sac with good final results.

TYPE II ENDOLEAK Transarterial (case II)

In this case, the patient developed a large endoleak after receiving a graft. Again, we decided to navigate between the limb of the graft and the artery and enter the aneurysmal sac. The angiogram revealed two lumbar arteries with no external flow so we injected the glue. The result would have been very satisfactory as we found no further endoleaks, except for the fact that I was not thorough enough to detect a vessel, so the following day the patient developed symptoms of pain in the pelvis and had an ischemic reaction of the sigmoid colon, which was treated with pneumatic dilation and took several months to resolve.

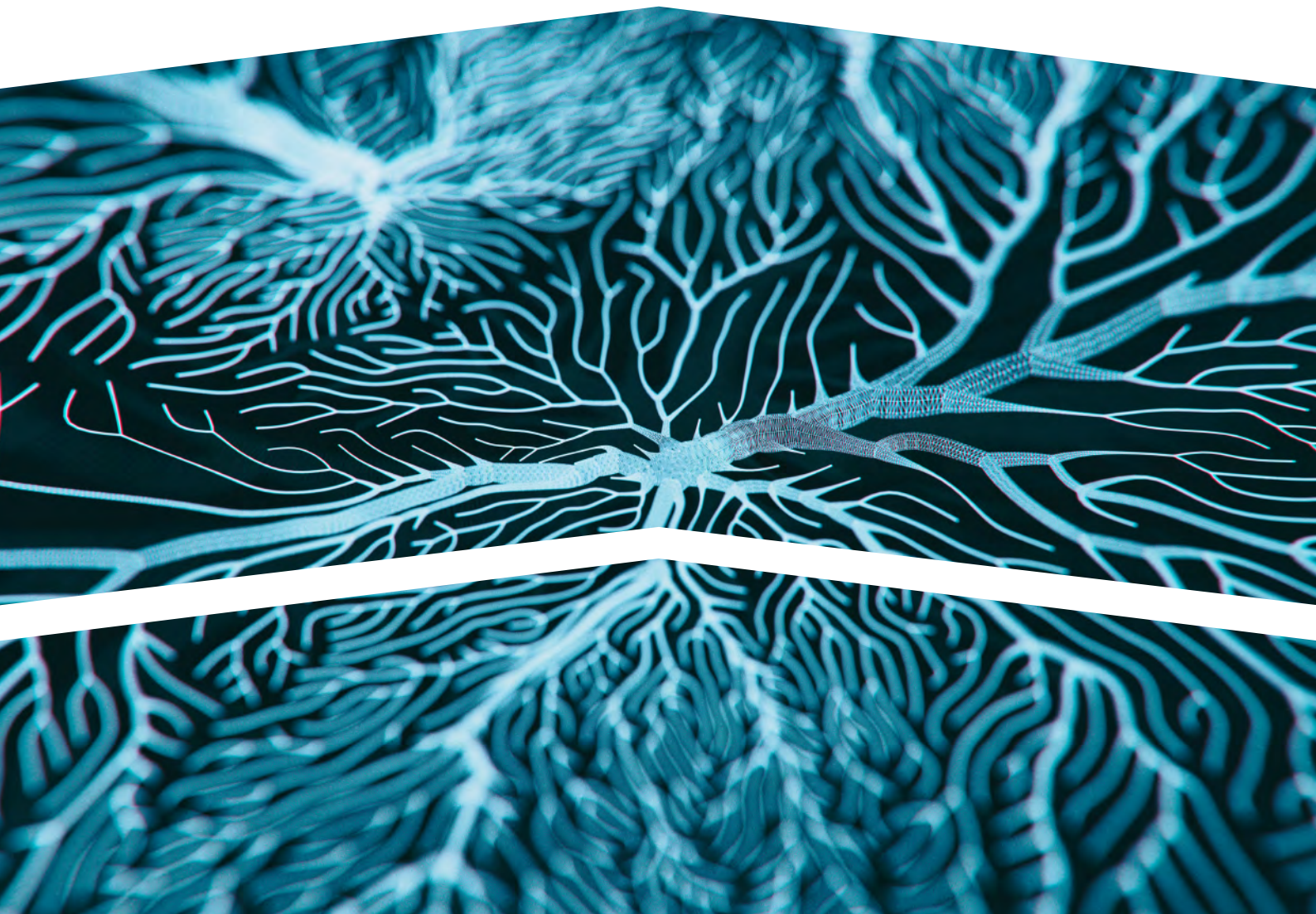
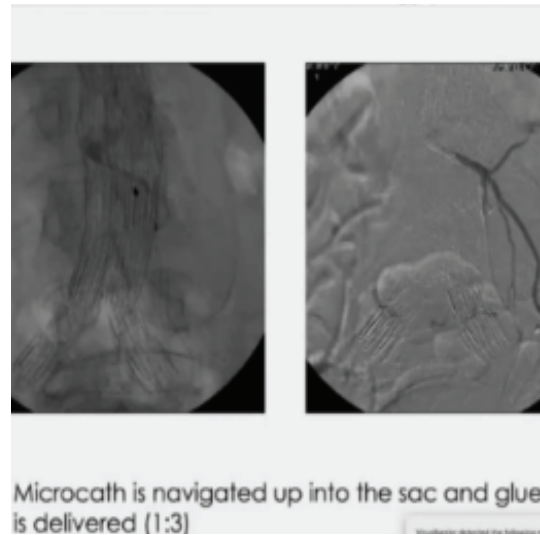
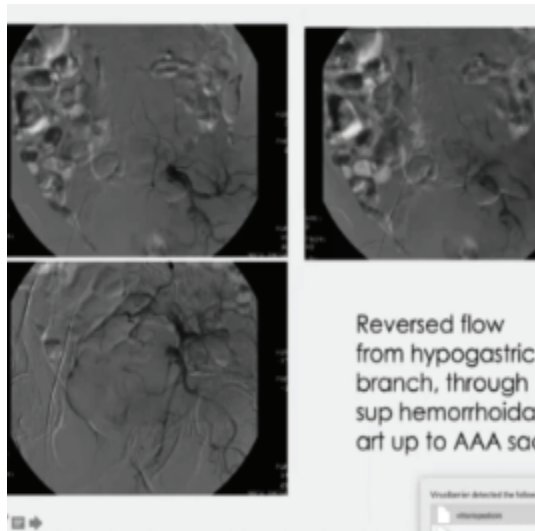


TYPE II ENDOLEAK

Transarterial (case III)

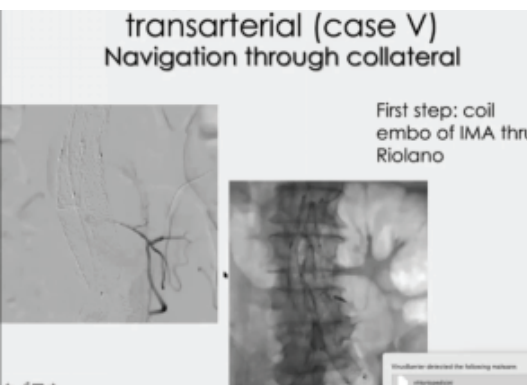
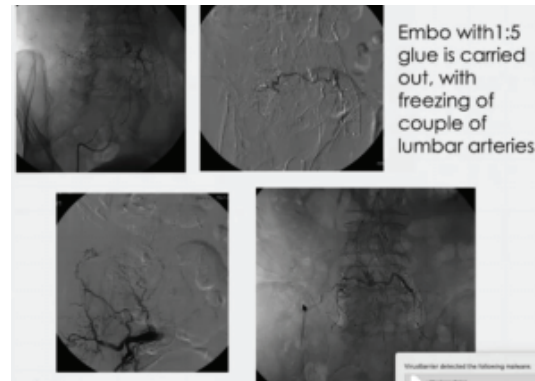
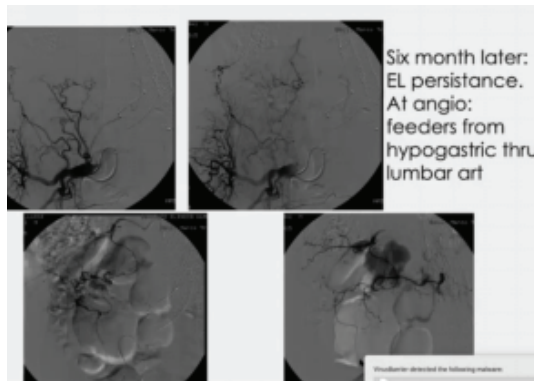
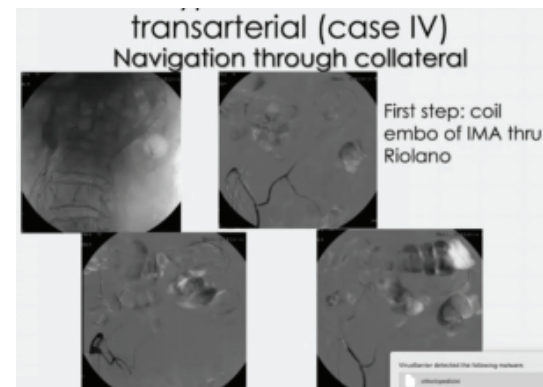
Navigation through collateral

In this other case, we followed the endoleak flow all the way back up into the aneurysm, to deploy the glue into the sac. The injection was very careful and slow and included the first part of the inferior mesenteric artery and preserving the flow of the various branches, in order to avoid any possible ischemic complication.



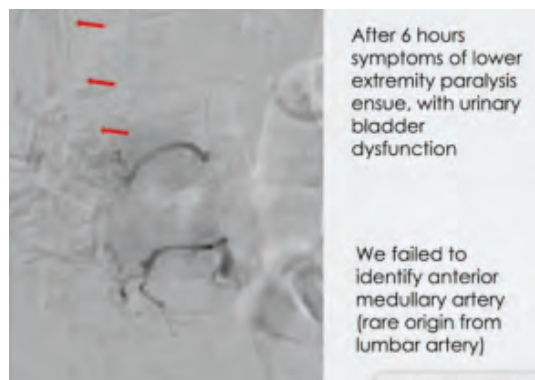
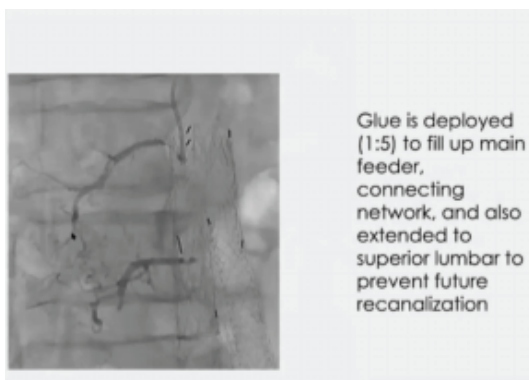
TYPE II ENDOLEAK Transarterial (case IV) Navigation through collateral

Here we first opted for coils, but six months later, we realized the leak was still there. We navigated through a large network of collateral branches and injected a glue that was diluted enough to navigate even further, along the lumbar arteries, close to the aorta. In this way, starting from one single spot on the right side, we were able to reach both sides, right and left.



TYPE II ENDOLEAK Transarterial (case V) Navigation through collateral

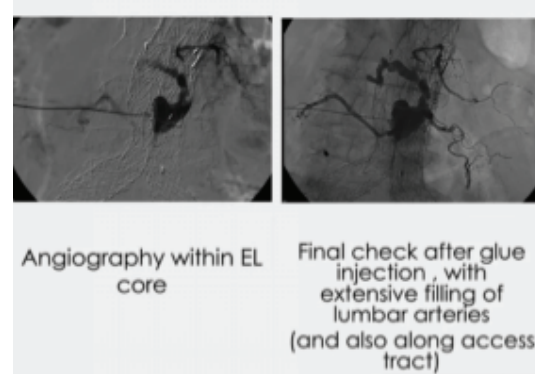
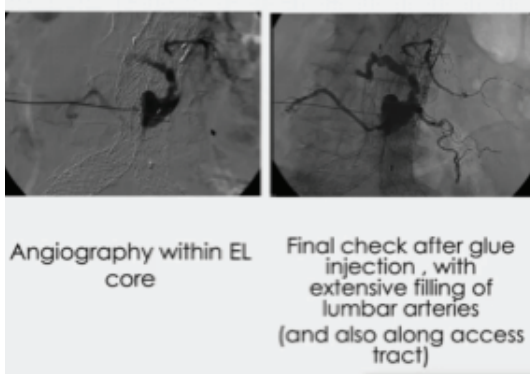
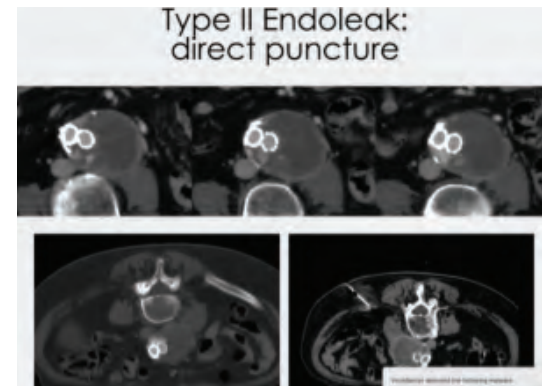
In this case, we started closing the upflow from the mesenteric artery, and later we found a collateralized lumbar artery reaching the nidus, went as close as we could, and injected a 1:5 glue mixture. I decided to push harder, in order to prevent any possible comeback. Unfortunately, I missed the anterior medullary artery. This is quite rare an occurrence, as the origin is usually around T9. The point, though, is that the mistake was not due to the glue, which performed exactly as expected.



TYPE II ENDOLEAK

Direct puncture

The direct puncture technique requires you to aim exactly at the nidus site. If you get in the thrombus, you are not going to achieve your result. You need to insert a wire and the catheter, then, through the angiography, identify the vessels involved, control any possible risk and inject the glue, thus creating a stamp of the nidus and of the initial part of each collateral vessel. We usually leave some glue along the tract injection, in order to safeguard the walls of the aorta.



TAKE HOME MESSAGE

- ▶ Reach the nidus and fill it up completely
- ▶ Safeguard peripheral branches of IMA
- ▶ Watch out for spinal vessels
- ▶ Do not be afraid of glue coming into contact with graft fabric



A WEBINAR BY GEM
2° SESSION

24TH JUNE 2020

PRESENTED BY

MASSIMILIANO MATTIOLI

GEM Marketing Manager

ATTENDEES
HUMANITAS RESEARCH
HOSPITAL TEAM

VITTORIO PEDICINI MD

Head of Vascular Interventional Radiology

DARIO PORETTI MD

Chief of of Emergency Radiology Unit

EZIO LANZA MD

Diagnostic Radiology PA

FELICE D'ANTUONO MD

Oncological and Interventional Radiology PA

RICCARDO MUGLIA MD

Senior Radiology Resident

COMPREHENSIVE SUMMARY

The remainder of this document provides a complete summary of the Webinar held by GEM Italy on 24th June 2020.

Welcome and Introductions

Massimiliano Mattioli - Vittorio Pedicini MD - Dario Poretti MD

As the webinar commenced, Massimiliano Mattioli welcomed all attendees and Vittorio Pedicini made a brief introduction, underlining the importance of sharing information about the use of NBCA, as a new material to be used in the ER.

Dario Poretti listed the topics presented by each attendee:

- ▶ **Felice D'Antuono** - Portal Vein Embolization
- ▶ **Vittorio Pedicini** - TAE: Hepatocellular Carcinoma
- ▶ **Ezio Lanza** - AVMs
- ▶ **Felice D'Antuono** - Varicocele
- ▶ **Riccardo Muglia** - Enterocutaneous Fistulas

PORTAL VEIN EMBOLIZATION - PVE

Felice D'Antuono MD

Over the past decades, perioperative care and surgical techniques improvement have led to an increased number of candidates for major liver resection.

One of the limiting factors for surgery is the share of residual parenchyma, FLR (future liver remnant); in particular, high-risk patients for perioperative liver failure are those whose liver is removed:

- ▶ >80% (HEALTHY LIVER)
- ▶ >60% (CHRONIC HEPATOPATHY).

In literature, post-surgical liver failure reaches 30% and is still the leading cause of death after major liver resections. It appears directly related to FLR (future liver remnant).

Most surgical teams consider the minimum share of FLR / TLV as = 20%

However, FLR / TLV = 40% in case of chronic liver disease

FLR / TLV = 30% when CT is present in high doses

Preoperative Portal Embolization (PVE) is a technique developed to compensate for insufficient FLR volume by embolizing the portal branches of the parenchyma to be resected and direct the flow to the FLR branches.

As an example, here is a successful case from literature: a patient with intrahepatic cholangiocarcinoma in the right lobe, who underwent extended right hepatectomy.

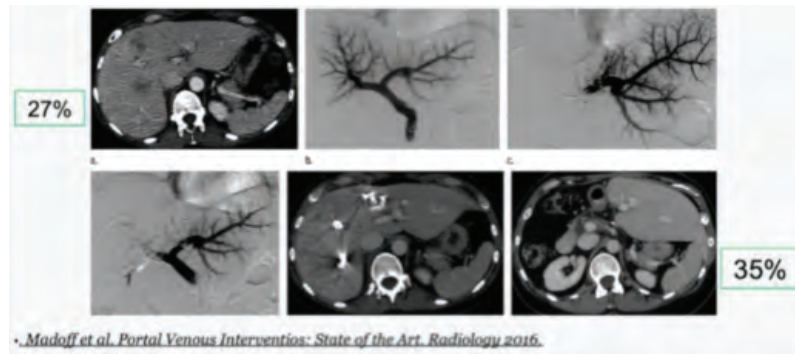
sFLR/TLV starts at just 27% but a CT scan 2 weeks after right PVE shows hypertrophy with sFLR/TELV at 35%.

PVE can be also used as a **STRESS TEST**: it is shown that a modest hypertrophic response to PVE is strongly correlated with postsurgical liver failure. In other words, an insufficient hypertrophic response can be considered an indicator of reduced regenerative capacity, and surgery should be avoided.

Liver regeneration properties have been well known since ancient Greece. In the 1920s, two French surgeons studying rabbit liver demonstrated that the ligation of the right lobe induced its atrophy while causing hypertrophy of the left one.

Today we know why that is: PVE triggers a membrane-and-cytoplasmic signaling cascade and the production of growth factors and cytokines, which increase the mitotic activity of the liver, thus causing its hyperplasia.

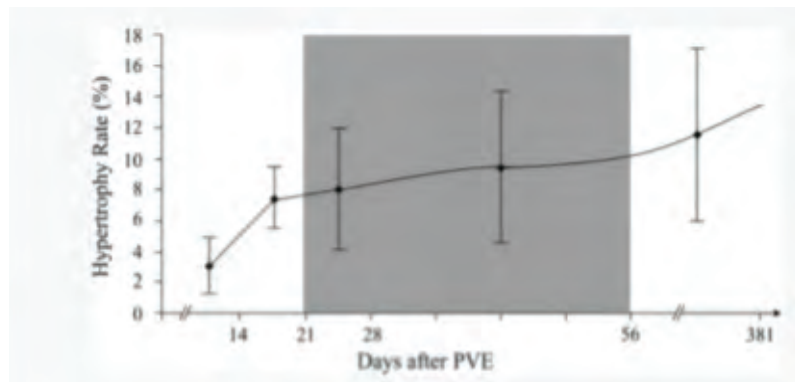
This answer is generally very rapid: the graph on the left shows a fast-growing hypertrophy rate over the first two weeks and the subsequent plateau phase. During this phase, CT scans are performed to evaluate liver volume in order to assess patient fitness for surgery.



Madoff et al. Portal Venous Interventions: State of the Art. Radiology 2016.



Kim et al. Liver Regeneration and the Atrophy-Hypertrophy Complex. Sem Int Radio 2008



Kim et al. Liver Regeneration and the Atrophy-Hypertrophy Complex. Sem Int Radio 2008

PVE PROCEDURE

- ▶ Percutaneous transhepatic approach has become the standard choice (a trans-ileocolic approach is also an option)
- ▶ Broad-spectrum antibiotic prophylaxis
- ▶ Procedure most frequently performed with local anesthesia and analgo-sedation
- ▶ Preliminary CT study to evaluate vascular anatomy - **procedure planning is a crucial step**

PV ANATOMY & APPROACH

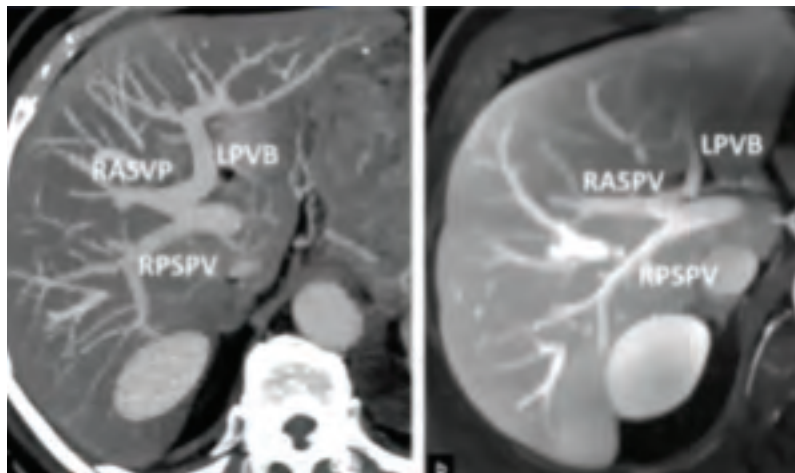
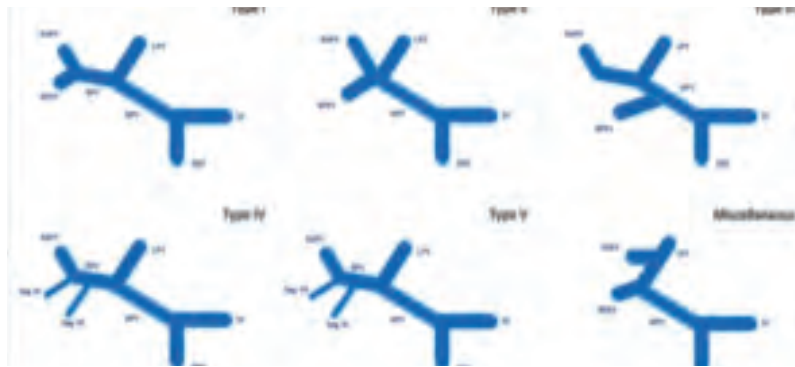
As standard anatomy can only be observed in about 30% of patients, we need to assess the case at hand before performing a portography. The picture shows an example of Type 3 or “Z” anomaly, where the left PV and the right anterior PV share a common trunk. If we approach the procedure with this information we can plan a selective categorization of the branches and perform a fast and safe embolization using glue, as in this case.

In order to reduce the risk of later FLR-related problems such as thrombosis, dissection, or hematoma, we usually prefer [ipsilateral access](#), however, studies have shown that a [contralateral approach](#) presents a similar kind and rate of possible complications.

At any rate, it is very important to avoid lesions, to reduce the risk of dissemination and subcapsular hematoma.

A safe puncture technique is extremely important: we use ultrasound guidance with a 21/22 gauge Chiba needle to puncture a peripheral PV (usually segment 5/6), then we place a 4/5 Fr vascular sheath and proceed to do a preliminary portography before we advance our diagnostic catheter. Multiple projections (anterior, posterior, oblique) are needed to confirm vascular anatomy and plan the embolization, which must include the branches of S4 whenever surgical planning involves its resection. Cone-beam CT is also an option: the anatomic details are excellent and we can obtain a volumetric 3D reconstruction.

After thorough and correct planning, we can proceed to select the vessels and insert a coaxial catheter. Another option is to exploit the venous flow to treat multiple branches at the same time.



EMBOLIC AGENTS

Although in this setting, we have tested all the embolic agents currently available in our interventional radiology department, from this systematic review we can clearly see the advantages of using glue from an FLR increase perspective.

Embolization materials	No. of patients	(%)	Embolization material	Article	No. of patients	% Increase FRL
PVA particles + coils [14, 27, 30, 47, 48, 51]	250	14.7	PVA + coils/vascular plug	Esschert [30]	10	26.1
PVA + alcohol [25]	3			Libicher [40]	10	26.4
PVA + Amplatzer vascular plug [40]	10			Covey [14]	100	24.3
Gelatin sponge + lipiodol [11, 35–37, 49, 52]	130	26.3	Gelatin sponge	Fujii [11]	30	17.8
Gelatin sponge + coils [44, 50, 70]	71			Imamura [33]	84	30.7
Gelatin sponge + thrombin + urografine [12, 33]	102			Kakizawa [35]	14	23.8
Gelatin sponge + urografine [20, 22]	120			Kim [37]	17	27.0
Gelatin sponge + povidocanol [36]	8			Kusaka [12]	18	21.2
Gelatin sponge + amplatzer [45]	41		Makuuchi [20]	54	37.9	
Fibrin glue/Beriplast + lipiodol [15, 36, 39, 54]	177	9.9	N-butyl cyanoacrylate	Nanashima [49]	30	29.4
N-butyl cyanoacrylate + lipiodol [5, 9, 16, 17, 24–27, 29, 31, 36, 41, 42, 47, 53, 57]	554	32.5		Sugawara [22]	66	35.8
N-butyl cyanoacrylate + gelatin sponge [23]	11			Baere [16]	107	57.8
N-butyl cyanoacrylate + Amplatzer vascular plug [26, 42]	18			Barbaro [24]	26	53
Embol-78 [38]	51	2.8		Capussotti [9]	31	48.5
Ethanol + lipiodol [15, 34]	159	10.2		Elias [29]	68	59.1
Ethanol + gelfoam + lipiodol [43]	24			Giraud [17]	146	41.7
Ethoxysclerol/air-foam [28, 32]	30	1.8	Sirichindakul [53]	29	27.5	
Ethibloc + lipiodol [46, 48]	33	1.8	Broering [57]	17	69.4	
			Fibrin glue	Liem [54]	15	31.4
				Nagino [15]	105	27.4

van Lienden KP, van den Esschert JW, de Graaf W, et al. Portal vein embolization before liver resection: a systematic review. *Cardiovasc Intervent Radiol.* 2013;36(1):25-34. doi:10.1007/s00270-012-0440-y

From researches comparing different embolic agents we can gather more results, like those emerging from a 1996 study by De Baere, run on 31 patients, which reports:

“Hypertrophy of the FRL was 90% +/- 52% after 30 days with cyanoacrylate, 53% +/- 6% after 43 days with Gelfoam, and 44% +/- 30% after 35 days with coils.”

de Baere T, Roche A, Elias D, Lasser P, Lagrange C, Bousson V. Preoperative portal vein embolization for extension of hepatectomy indications. *Hepatology.* 1996;24(6):1386-1391. doi:10.1053/jhep.1996.v24.pm0008938166

Another interesting study by De Baere was run on animals in 2009 and compared embolized and non-embolized liver ratio. Glue and small PVA gave the best response:

Hydrophilic gel vs NBCA vs small PVA vs large PVA

N=20 pigs - left and median PVE
(5 for each embolic agent)

Embolized liver /Non-embolized liver

- Hydrophilic gel = 1.65

- NBCA = 2.19

- PVA 50 -150 = 1.57

de Baere T, Denys A, Paradis V. Comparison of four embolic materials for portal vein embolization: experimental study in pigs. *Eur Radiol.* 2009;19(6):1435-1442. doi:10.1007/s00330-008-1277-2

Another interesting study in the clinical setting which does not only show a higher FLR increase with NBCA but also a lower volume of the iodinated contrast used during the procedure:

NBCA vs Spherical Microparticles + Coils

N=34 (NBCA 20; SM + COILS 14)

FLR increase after 1 month

- NBCA = 74%± 69%
- SM + COILS = 23% ± 14%

Contrast Medium used

- NBCA = 162 ± 24 ml
- SM + COILS = 264 ± 43 ml

Guiu B, Bize P, Gunthern D, Demartines N, Halkic N, Denys A. Portal vein embolization before right hepatectomy: improved results using n-butyl-cyanoacrylate compared to microparticles plus coils. *Cardiovasc Intervent Radiol.* 2013;36(5):1306-1312. doi:10.1007/s00270-013-0565-7

This comparative study on NBCA vs Ethanol, while showing little difference in hypertrophic stimulus, reported a higher rate of major adverse events in patients treated with ethanol:

NBCA vs Absolute Ethanol

N=61 (NBCA 34; Ethanol 27)

NELV increase after 1 month

- NBCA = 116 ml
- Ethanol = 129.4 ml

ELV decrease after 1 month

- NBCA = 99.2 ml
- Ethanol = 191.9 ml

Sugawara S, Arai Y, Sone M, et al. Retrospective Comparative Study of Absolute Ethanol with N-Butyl-2-Cyanoacrylate in Percutaneous Portal Vein Embolization. *J Vasc Interv Radiol.* 2019;30(8):1215-1222. doi:10.1016/j.jvir.2018.12.020

A 2018 systematic review and meta-analysis aimed at evaluating the safety and effectiveness of NBCA in PVE, reported the following data:

“The literature search yielded **18 relevant articles**. **Six hundred and seven patients** (383 men, 220 women; mean age 60.7 years) with procedures describing PVE utilizing NBCA were reviewed. The most common underlying hepatic malignancies were **colorectal metastases** (n = 348), followed by **cholangiocarcinomas** (n = 92), and **hepatocellular carcinomas** (n = 89).

Technical success was reportedly achieved in 603/607 patients, for a **success rate of 99.3%**. Fixed effects meta-analysis of the relative hypertrophy rate of the FLR among studies resulted in an aggregate rate of 49.4±1.3%. Of the patients who underwent attempted PVE, 461/607 (75.9%) eventually underwent surgical resection. **Major complications following PVE occurred in 19 patients (3.13%)**, while minor complications following PVE occurred in 38 patients (6.26%).”

Wajswol E, Jazmati T, Contractor S, Kumar A. Portal Vein Embolization Utilizing N-Butyl Cyanoacrylate for Contralateral Lobe Hypertrophy Prior to Liver Resection: A Systematic Review and Meta-Analysis [published correction appears in *Cardiovasc Intervent Radiol.* 2018 Nov;41(11):1811]. *Cardiovasc Intervent Radiol.* 2018;41(9):1302-1312. doi:10.1007/s00270-018-1964-6

TAKE HOME MESSAGE

PVE is a very safe procedure and shows even better results when used in combination with NBCA, due to its ability to generate great hypertrophic stimulus without any increase in complication rate.

Q&A

Dario Poretti, MD: Considering the risk of misembolization, the dilution rate is a key element in this procedure. We have been working on it for the past six years and we adjusted our technique as we progressed because it can be a game-changing factor. Can I ask you to elaborate on this subject?

Felice D'Antuono, MD: Although in literature the matter of dilution has been explored extensively, it is still handled quite differently from one place to another. In France, for example, it is common to use lower glue concentration, with a 1:10 ratio, whereas we settled around 1:4/1:5. This is due to different techniques: we first use PVA particles to reduce distal flow, and this allows for better control of the glue in the proximal part. It is very important to identify the target with pinpoint accuracy in order to maintain PV patency, as well as to keep in mind that using a denser mixture calls for a slow and careful injection. enough to stop the bleeding. It is very effective.

Massimiliano Mattioli: Let's also underline that when we talk about glue, here, we are not talking about standard, pure NBCA. As we all know, our Glubran®2 new formula includes methacryloxy sulfolane, which lowers polymerization temperature by half, taking it down to about 45°. This is a very important property, that makes it different from other embolic agents,

Webinar chat: Would you consider alternatives to Lipiodol to dilute glue?

Dario Poretti, MD: We have no experience on this matter, nor have I read of other teams using alternative dilution agents, so at this moment in time my answer is no.

Webinar chat: Could you elaborate on the use you make of balloons?

Dario Poretti, MD: Our experience using balloons is related to inflow/outflow vessels during arteriovenous malformation embolization, in order to be able to control the flow within the AVM (or in the area of interest). Balloons can, in fact, be used as an aid to manage glue movements, in order to prevent it from hitting unintended spots.

Balloons are also currently used to exclude visceral aneurysms, such as renal artery aneurysm, more specifically with Onyx, but nevertheless with liquid embolic agents. You can inflate the balloon in the artery to exclude the aneurysm and then fill it up with glue, so that, when you extract it, the glue will stay in place. We have no experience with that and I would personally rather use a stent.

BLAND EMBOLIZATION: NBCA IN HEPATOCELLULAR CARCINOMA (HCC)

Vittorio Pedicini MD

As we all know, bland embolization is the best treatment for HCC: our goal, in this case, is to induce ischemic damage to the tumor. This is also done by means of Transarterial Chemoembolization (TACE), a treatment that delivers the drugs, through a blood vessel, straight into the tumor.

As of today, though, no evidence suggests that TACE is more effective than simple embolization (TAE).

Pertaining literature started with a 2002 paper published on The Lancet. This was a randomized study run by the Barcelona-Clinic team on 112 patients, divided into three groups and assigning 37 pts to TAE (gelatin sponge), 40 to TACE (gelatin sponge plus doxorubicin) and 35 to control treatment. While the resulting interpretation was that "*Chemoembolisation improved survival of stringently selected patients with unresectable hepatocellular carcinoma*," the difference between TACE and TAE appeared insignificant. Llovet JM, Real MI, Montaña X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet. 2002;359(9319):1734-1739. doi:10.1016/S0140-6736(02)08649-X

Several pieces of research followed suit, and the validity of chemoembolization as a treatment for HCC has been well established since. However, as far as optimal schedules are concerned, or whether embolization alone can yield the same results, the data is yet inconclusive.

A 2007 systematic review was conducted to delve into the topic, using additional elements such as PVA particles. The research concluded that: "No chemotherapeutic agent appears better than any other. There is no evidence for benefit with Lipiodol. Gelatin sponge is the most used embolic agent, but PVA particles may be better. **TAE appears as effective as TACE.** New strategies to reduce the risk of post-TACE complications are required."

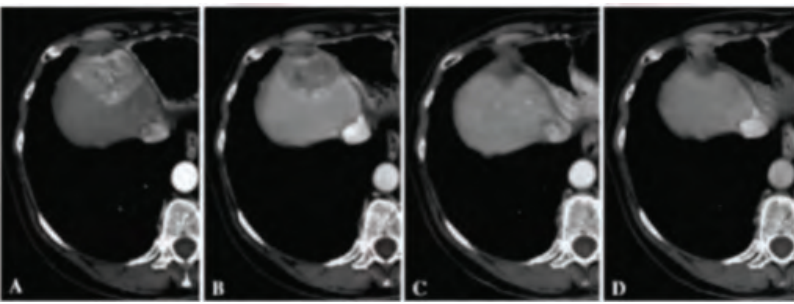
Marelli L, Stigliano R, Triantos C, et al. Transarterial therapy for hepatocellular carcinoma: which technique is more effective? A systematic review of cohort and randomized studies. Cardiovasc Intervent Radiol. 2007;30(1):6-25. doi:10.1007/s00270-006-0062-3

The PRECISION V study, run by Professor Johannes Lammer, Medical University of Vienna, in 2009, aimed at investigating the safety and efficacy of chemoembolization with DC Bead loaded with doxorubicin (PRECISION TACE with DC Bead). The results were extremely positive but might have been affected by the size of the particles employed for the embolization.

Lammer J, Malagari K, Vogl T, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol. 2010;33(1):41-52. doi:10.1007/s00270-009-9711-7

In fact, due to the liver's unique dual blood supply, the smaller the particles, the stronger the ischemic effect: the optimal strategy could be to disrupt vascularization where the portal vein and hepatic artery converge, at the sinusoids - which we know are about 10–15 µm in diameter. When you use particles that can fit this size, you can achieve impressive results in terms of ischemia and consequent effects on your target lesion.

This was the theory at the base of a study that our team ran on >50 pts in 2009, whose purpose was "to report on the feasibility, local response, and 1-year clinical outcome of bland transarterial embolization (TAE) with 40 and 100 µm Embozene microspheres in patients affected by unresectable hepatocellular carcinoma (HCC)."



Local control results were extremely positive: in the picture, we can observe a case treated over a 12-month period, showing progressive lesion shrinking and eventually complete response.

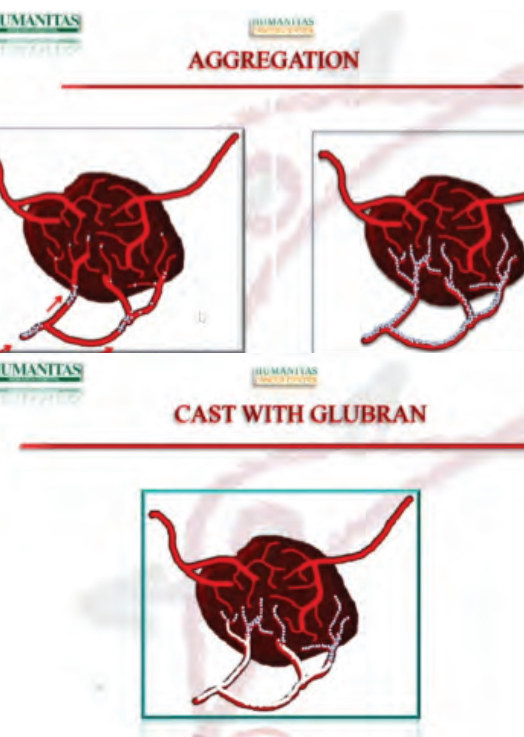
At the time, local results were assessed according to RECIST criteria.

The complete response rate might be higher today, using mRECIST criteria.

Bonomo G, Pedicini V, Monfardini L, et al. Bland embolization in patients with unresectable hepatocellular carcinoma using precise, tightly size-calibrated, anti-inflammatory microparticles: first clinical experience and one-year follow-up. *Cardiovasc Intervent Radiol.* 2010;33(3):552-559. doi:10.1007/s00270-009-9752-y

In 2016, a randomized trial was run by the Memorial Sloan Kettering Cancer Center to compare "the outcome of embolization using microspheres alone with chemoembolization using doxorubicin-eluting microspheres." The study concluded that "there was no apparent difference between the treatment arms. These results challenge the use of doxorubicin-eluting beads for chemoembolization of HCC."

Brown KT, Do RK, Gonen M, et al. Randomized Trial of Hepatic Artery Embolization for Hepatocellular Carcinoma Using Doxorubicin-Eluting Microspheres Compared With Embolization With Microspheres Alone. *J Clin Oncol.* 2016;34(17):2046-2053. doi:10.1200/JCO.2015.64.0821



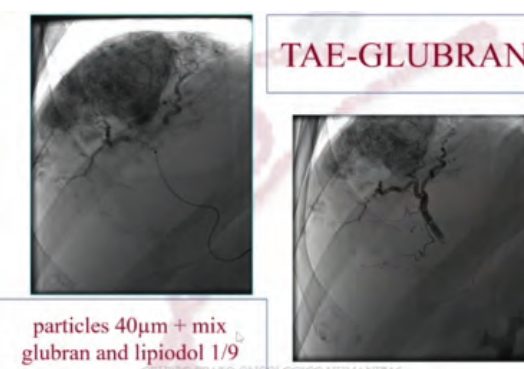
It was around this time that we started to employ Glubran®2 in our treatments.

When we inject the particles in the arterial flow, we aim at ideal distribution, which sometimes fails to happen due to the aggregation of the particles in the vessel. This aggregation usually occurs in the proximal side of the artery, and, when it does, the distal bed is difficult to reach.

Probably due to this phenomenon, sometimes the contrast media will stop in the arterial flow and then start to revascularize after a few minutes. We can hope for the systolic pressure to do its job, and push the particles into place, but we cannot be sure.

This heterogeneous distribution could very likely affect the patient response, as the difference between complete and partial response might well depend on lesion coverage.

Reinforcing our treatment with glue helps us to obtain the perfect embolization of our target.



CASE 4 - CAPSULATED HCC

In this case we had a capsulated, partially exophytic lesion, which we treated with TAE-Glubran®2 (1:9 ratio).

In the picture, we can see the embolization, with the same characteristics as the previous case.

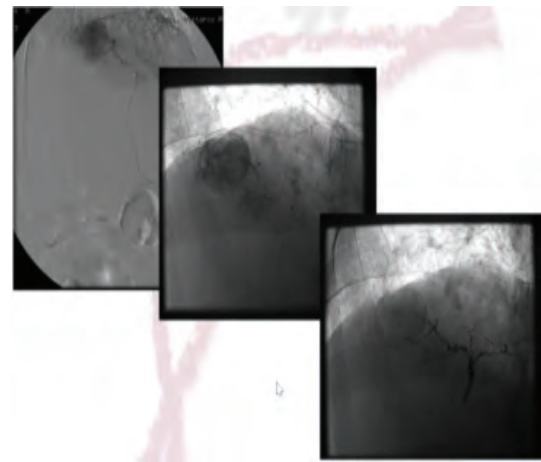
3 months later, we could observe a complete devascularization of the lesion.

CASE 4 - Adrenal Mass Bleeding

77 yo man with chronic hepatitis (esotoxic)

Varices F2, AFP 800

This case presented a small HCC lesion on segment 8, which we embolized selectively, first with particles and then with glue. We could notice some non-target embolization in another small vessel, with ischemic damage of the dorsal territory. At follow-up, 1 month later, control showed a lesion without vascularization.



In January 2020, we published our “Survival analysis of 230 patients with unresectable hepatocellular carcinoma treated with bland transarterial embolization”, describing our experience with TAE on HCC patients over a period of 7 years. We reported high survival rates of 85% at 1-year and 59% at 2-years. These results are in line with comparative literature on chemoembolization, however, no clinical trial with the same number of patients bore such high figures.

Table 3. Survival rates at different time points grouped by BCLC stage and history of percutaneous treatment.

SURVIVAL RATES																
BCLC	baseline		1 year		2 yrs		3yrs		4 yrs		5 yrs		6 yrs		7 yrs	
	1	0,4%	1	0,4%	1	0,4%	1	0,4%	1	0,4%	1	0,4%	1	0,4%	1	0,4%
I	23	10,0%	19	8,3%	17	7,4%	12	5,2%	9	3,9%	7	3,0%	2	0,9%	0	0,0%
A	95	41,3%	83	36,1%	60	26,1%	39	17,0%	28	12,2%	18	7,8%	6	2,6%	1	0,4%
B	111	48,3%	92	40,0%	57	24,8%	36	15,7%	27	11,7%	17	7,4%	6	2,6%	1	0,4%
no PT	141	61,3%	112	48,7%	72	31,3%	44	19,1%	31	13,5%	19	8,3%	7	3,0%	2	0,9%
PT	89	38,7%	83	36,1%	63	27,4%	44	19,1%	34	14,8%	24	10,4%	8	3,5%	1	0,4%
TOTAL	230	100%	195	84,8%	135	58,7%	88	38,3%	65	28,3%	43	18,7%	15	6,5%	3	1,3%

BCLC = Barcelona Clinic Liver Cancer stage, PT = patients who received a Percutaneous Treatment. The percentages are referred to the whole cohort (n = 230)

Lanza E, Muglia R, Bolengo I, et al. Survival analysis of 230 patients with unresectable hepatocellular carcinoma treated with bland transarterial embolization. PLoS One. 2020;15(1):e0227711. Published 2020 Jan 14. doi:10.1371/journal.pone.0227711

TAKE HOME MESSAGE

- ▶ In HCC treatment, the addition of NBCA to microparticles appears to improve devascularization of the embolized target, allowing for better local control
- ▶ The strong effects of this treatment call for a selective approach, in order to avoid nontarget embolization and subsequent damage to unaffected parts of the liver.

GLUBRAN®2: AVM

Ezio Lanza MD

We are now going to look at some case reports concerning the use of Glubran®2 in Arteriovenous and Venous Malformation, a wide area that Park and Young, among others, have successfully managed to classify in a chapter of their book "Congenital Vascular Malformations: A Comprehensive Review of Current Management".

Park, Kwang & Do, Young. (2017). *Angiographic Classification: Arteriovenous Malformation and Venous Malformation*

The need for a systematic classification arises from the notion that different AVM types behave differently in terms of response, thus attempts have been made to standardize treatment according to AVM type.

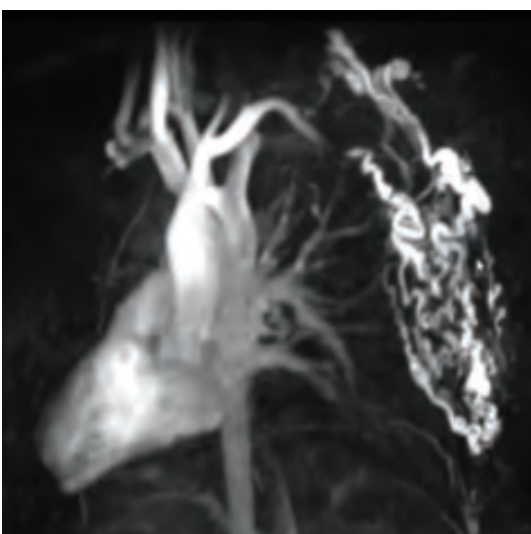
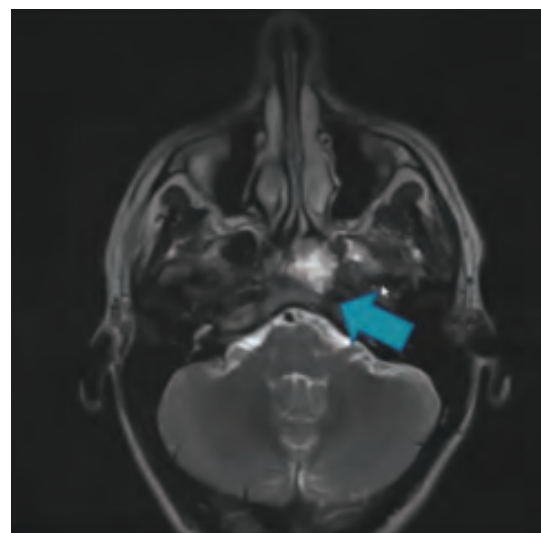
CASE 1 - RHINOPHARYNX AVM

24 yo man - 1:4 ratio, 0.2ml boluses

A very young man with a small, oval-shaped malformation of the rhinopharynx located right behind the ethmoid bone, which rendered it inoperable.

We saw we could gain direct access through the external carotid artery, performed a selective angiography, and then proceeded to distally place a micro-catheter and injected 0.2 ml of standard glue mixture, thus achieving full exclusion.

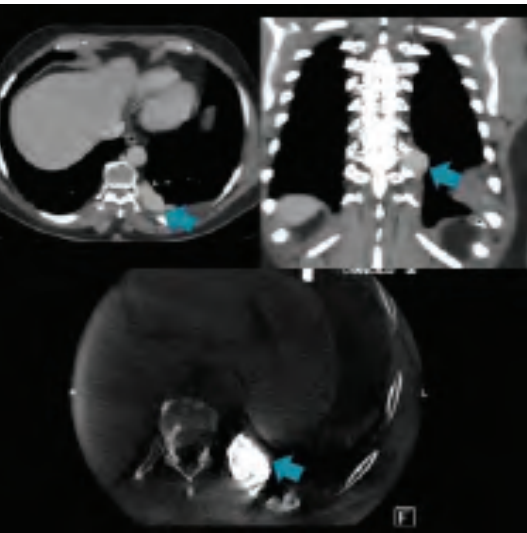
As these kind of malformations are mostly congenital and do not tend to grow much over time, the successful result was confirmed at 2-years follow up.



CASE 2 - RIGHT THORACIC WALL AVM

28 yo man - multiple treatments

Such a large AVM usually requires multiple treatments: we started with selective catheterization of a malformed vessel arising directly from the right subclavian artery and made multiple attempts at using a high-density glue mixture to embolize different parts of the malformation. In these cases, surgery would be very invasive and the AVM would just grow back, so liquid embolic agents are our only option. The goal is to reduce the symptoms, do as little harm as possible, and go back at a later time when symptoms resurface. In our case, we treated the patient again after one year.



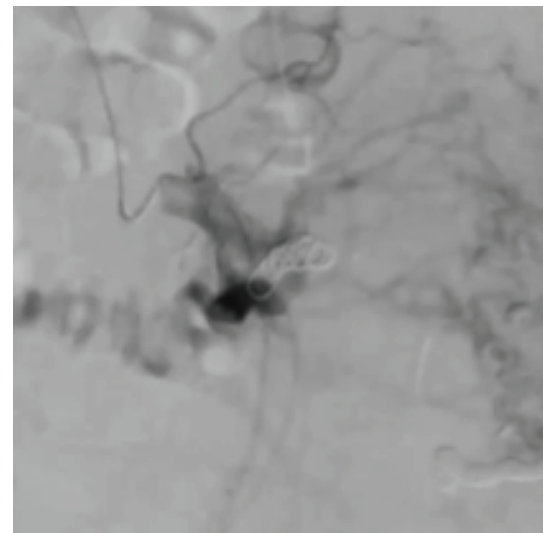
CASE 3 - LEFT THORACIC WALL

60 yo man

This is a very interesting case that goes to show how things do not always go as planned. The patient had a very symptomatic AVM with high-risk bleeding that was also eroding part of the bone cortex. A previous embolization with coils had produced no significant results. We performed an angiography of the left intercostal artery and used selective catheterization to enter the sac, then glued distally, creating a blockage. We kept injecting glue until there was a very low residual flow from the malformation. As shown in the bottom left picture, the result was very satisfactory, however, we later discovered that some glue had migrated to a spinal artery, thus provoking ischemia of the spinal cord. Luckily, using the small bolus technique meant that only a reduced amount of glue had migrated, and the damage was not severe. At follow up, a month ago, the patient exhibited only mild symptoms.

CASE 4 - GLUTEAL AVM

Another large AVM that we treated with coils first, then with glue. Because such cases need to be treated repeatedly, communication with the patient becomes very important: we create a relationship and monitor symptoms regularly so that we decide together with the patient when it is time to intervene again.



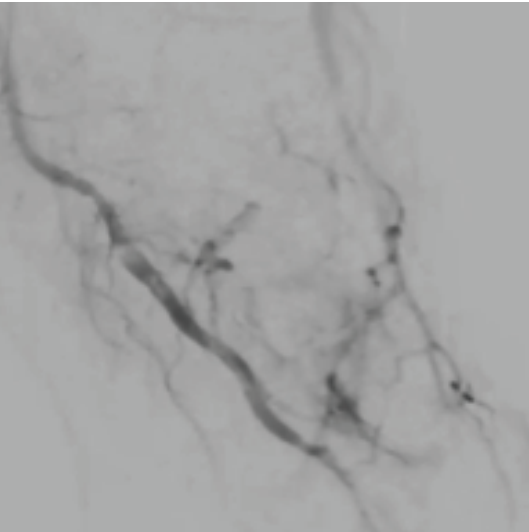
CASE 5 - PELVIC CHO TYPE 2 AVM

54 yo man - Large venous outflow

1:4 Glubran + Amplatzer plug

In this case, we needed to block the outflow from a large venous sac, so we used triple access (one arterial and two venous), placing a 32 mm Amplatzer plug on the large venous outflow of the AVM, This way we could operate with no risk of non-target embolization. We injected small amounts of glue, some of which gathered in high-density concentration just below the plug, which effectively stopped it from migrating into the pulmonary circulation system. This is also called the "Pressure Cooker Technique" , which can be used with liquid embolic agents. As the bottom picture shows, the final result was excellent.

severe. At follow up, a month ago, the patient exhibited only mild symptoms.



CASE 6 - FOREFOOT AVM

Woman (35) - 0.1 ml Glubran®2 1:3 in the posterior tibial
Manual compression of the digital arteries

This was a wide AVM, similar to a sponge, which we embolized with a very dense mixture through a distally placed catheter while applying manual compression to the digital arteries. As you can see in the picture, digital circulation has been preserved.

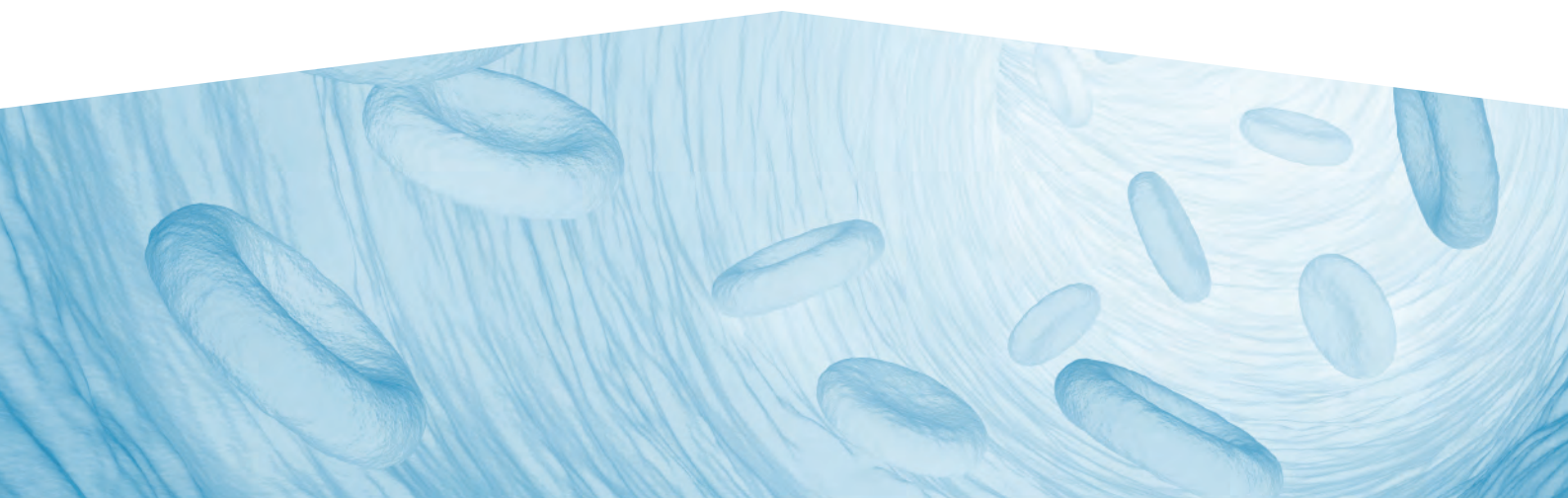
The result was satisfactory even though we noticed that a small part of the malformation appeared still vascularized. In treating AVMs, in fact, it is important to focus on the symptoms rather than on the image: striving for perfection will likely lead to nontarget embolization and its consequences.

CASE 7 - EMERGENCY EMBOLIZATION LARGE FACIAL AVM BLEEDING

This is a case of large AVM arising from the external carotid artery, which was bleeding into the mouth and therefore required emergency treatment. Nontarget embolization occurred, with some glue migrating to the internal carotid artery and displacing into the brain, provoking stroke-like symptoms. Thanks again to the sandwich technique and the glue having been injected in small boluses, the symptoms disappeared within a week. And at 3-months follow up, the signs of the non-target embolization had disappeared.

For those of you wishing to learn from our mistakes, we have published an open-access full report on this case, under the following title: *"Full recovery after non-target cerebral embolization."*

Lanza E, Gennaro N, Poretti D, et al. Full recovery after non-target cerebral embolization of n-butyl-cyanoacrylate occurred during emergency treatment of a facial arteriovenous malformation. *CVIR Endovasc.* 2019;2(1):20. Published 2019 Jun 29. doi:10.1186/s42155-019-0063-3



Q&A

Webinar Chat: In CASE 7: where did the glue migrate to?

Ezio Lanza, MD: We are not completely sure, however, our opinion is that the bright spots we detected were mostly composed of Lipiodol, rather than glue. Even though there are not many reports available to clear this subject, we know that Lipiodol is resolvable, so our guess is that there was a substantial mismatch between the CT image and what was actually happening inside the brain.

To validate this theory is also the fact that, if the stroke had been as severe, the symptoms would have been permanent.

Vittorio Pedicini, MD: We know there is some concern around the use of glue in AVM treatment. Some authors claim that glue induces an inflammatory reaction in the vessels, creating some sort of neoangiogenesis. I do not personally remember any such case. Can you share your experience on this subject?

Ezio Lanza, MD: Most of these claims are not based on in vivo studies but rather on lab research. As of today, we have no evidence that alternative embolic agents such as Onyx or Squid do not facilitate AVM re-growth just the same. What we know is that AVMs tend to grow back and that, sooner or later, we will have to treat the patient again. The important thing here is that we have an agent that spreads easily and is effective. Costs also need to be factored in: depending on the agent of choice, some embolization procedures can add up to 50k, which, clearly, can be an issue. At any rate, nobody has yet proven that neoangiogenesis is caused by the agent and not, for instance, by the embolization itself, as a procedure.

To validate this theory is also the fact that, if the stroke had been as severe, the symptoms would have been permanent.

VARICOCELE

Felice D'Antuono MD

VARICOCELE IN MEN

A varicocele is a vascular lesion characterized by dilatation and tortuosity of the spermatic veins. It is commonly found in adolescents and young adults. Varicocele is found in approximately 15% of adult males, but the incidence could go as high as 40% in patients attending infertility clinics and up to 80% in those with secondary infertility. Varicoceles predominantly affect the left side (90% of cases) with bilateral varicoceles present in 10% of patients. Varicoceles can be primary or secondary to increased pressure on the spermatic veins. Secondary varicocele is usually manifested on the right side.

Mohammed A, Chinegwundoh F. Testicular varicocele: an overview. *Urol Int.* 2009;82(4):373-379. doi:10.1159/000218523

Sarteschi's classification of varicocele

Supine & standing positions

Grade 1	Reflux in inguinal channel only during Valsalva Scrotal varicosity not evident in standard US study
Grade 2	Small varicosities extend to superior pole of testis Diameters increase & venous reflux seen only during Valsalva
Grade 3	Vessels enlarged at inferior pole of testis only in standing position No enlargement detected in supine position Reflux observed only during Valsalva
Grade 4	Vessels appear enlarged in supine position Dilatation increased in upright position & during Valsalva Testicular hypotrophy common at this stage
Grade 5	Venous ectasia even in prone decubitus and supine positions Reflux at rest & does not increase during Valsalva

Sarteschi LM. *G Ital Ultrasonologia* 1993 ; 4 : 43 – 9.

Radiologists can not only perform diagnoses with ultrasounds, thus classifying the condition as Grade 1 or 2, which is all but asymptomatic, but can also treat it when it becomes symptomatic. It can cause pain and infertility and it can be treated either surgically or with embolization.

Embolization is a widely accepted treatment for varicocele: the first reported attempt dates as back as 1978 when Lima et al. induced sclerosis by catheterization of the internal spermatic veins with the injection of a 75% hypertonic glucose solution.

Later, in 1981, Formanek et al describe bilateral embolization using a transjugular approach.

Treating varicoceles using an endovascular, percutaneous approach is quite easy: we usually prefer to puncture the right femoral vein (whereas other colleagues would rather enter the jugular or the basilic vein), then perform a phlebography and catheterize the left testicular vein. Our target is the anterior pampiniform plexus, which is drained by the internal spermatic vein because this is where the pathology originates. Correct treatment will avoid relapses. We select the left renal vein with a 6-Fr guiding catheter, then perform a renal phlebography and easily locate the left spermatic vein. With a hydrophilic guidewire and a 4-Fr sheath, we select the vein. Due to the wide range of anatomical variances, the phlebography plays an important role in this procedure: we need to ascertain whether we have one or two collectors, for instance, or if there is evidence of anastomosis involving the lumbar vein. Distal catheterization is usually performed with a 4-Fr catheter or, in particularly difficult cases, with a microcatheter. We inject the glue gently, making sure it does not migrate to the plexus because this might cause thrombophlebitis.

Alternative ways to treat varicocele percutaneously include coils, sclerosants, or other embolic agents, and the available literature on the use of glue in this setting is still insufficient. Nevertheless, an interesting 2017 systematic review from the UK analyzed the different materials and reported the following conclusions: "Despite the heterogeneity of the included studies, preliminary evidence supports the safe and effective use of the various embolic materials currently used for the management of varicoceles. At 1 year, glue appears to be the most effective in preventing recurrence with coils being the second most effective. The addition of sclerosants to the coil embolization did not appear to have an impact on recurrence rates. Further research is required to elucidate the cost-effectiveness of these approaches. Advances in knowledge: Varicocele embolization appears to be a safe and effective

technique regardless of the embolic agent. Addition of a sclerosant agent to coil embolization does not appear to improve outcomes.”

Makris GC, Efthymiou E, Little M, et al. Safety and effectiveness of the different types of embolic materials for the treatment of testicular varicoceles: a systematic review. *Br J Radiol.* 2018;91(1088):20170445. doi:10.1259/bjr.20170445

Our team at Humanitas also ran a study to report a 3-year experience in varicocele embolization using n-butyl-cyanoacrylate-methacryloxy sulfolane (NBCA-MS).

We retrospectively collected data from 47 procedures [mean age = 27.9 years, SD=8.3], selecting candidates according to the following criteria:

Inclusion Criteria:

Diagnosis of Varicocele:

- ▶ Urological or Radiological Diagnosis (Clinical Visit and Color-Doppler US)

Exclusion Criteria:

Pain from:

- ▶ Testicular torsion
- ▶ Epididymis
- ▶ Orchitis
- ▶ Inguinal hernia
- ▶ Recent trauma

OUTCOME MEASURES:

- ▶ Length of Procedure (through electronic records)
- ▶ Impact on groin pain (4-point scale through telephonic contact)
- ▶ Complications (CIRSE Classification System)
- ▶ Recurrence Rate
- ▶ Patient Satisfaction (4-point scale through telephonic contact)
- ▶ Spermogram Changes (sperm count; percentage of motile or normal morphology sperm)

Pain improvement was evaluated using a 4-point scale:

1. Mild pain
2. Considerable pain
3. Severe pain
4. Unbearable pain

RESULTS

- ▶ 43/47 left-side
- ▶ 3/47 bilateral
- ▶ 1/47 right-sided
- Procedures were technically successful in all cases
- Mean length of procedure was 42 minutes
- Follow-up was 18 months (range=1-83, SD=17)
- 40/47 (85.1 %) patients completed the questionnaire regarding late post-procedural pain and overall satisfaction towards the procedure

RESULTS - Pain improvement

- ▶ 26/40 (65%) patients were symptomatic before the intervention
- 08/40 (20%) patients felt discomfort (1 point)

- 05/40 (13%) patients felt mild pain (2 points)
- 10/40 (25%) patients felt considerable pain (3 points)
- 03/40 (7.5%) patients reported unbearable pain (4 points)

- ▶ Pain score decreased significantly from an initial mean of 1.5 (SD=1.4) to 0.4 (SD=0.5) $p = 0.0001$ (mean reduction 73%)
- 16/26 (62%) patients reported complete disappearance of varicocele-related symptoms
- 9/26 (35%) patients reduced or halved the initial pain
- only 1 patient reported a pain decrease <50%

RESULTS - Spermogram changes

- ▶ 34/47 (72%) patients underwent varicocele embolization after a baseline spermogram
- ▶ only 18/40 (45%) patients underwent a spermogram after the procedure
- ▶ 16/18 (89%) patients reported an improvement in spermogram values either in sperm count or in motile/normal morphology sperm percentage

Two patients (11%) did not report any improvement.

Post-procedural spermograms results were stable in one case, worse in the other.

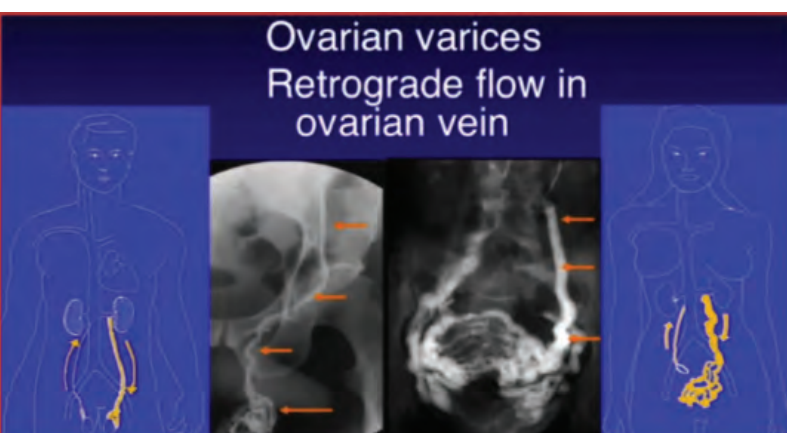
RESULTS - Complications

No major complications were observed.

- ▶ Scrotal pain was observed in 3/40 (8%) patients immediately after the procedure.
At 1-month follow-up, pain had disappeared completely

One patient (27yo) with severe bilateral varicocele suffered from a small, non-target embolization in the left pulmonary artery. However, the incident had no consequences and the patient was completely asymptomatic for the entire time.

VARICOCELE IN WOMEN



The gonadal veins are paired structures that drain the gonads in males and females. In males it is called the testicular vein (or internal spermatic vein) and in females it is called the ovarian vein. The gonadal veins ascend with the gonadal arteries in the abdomen along the psoas muscle anterior to the ureters. Like the suprarenal veins each side drains differently:

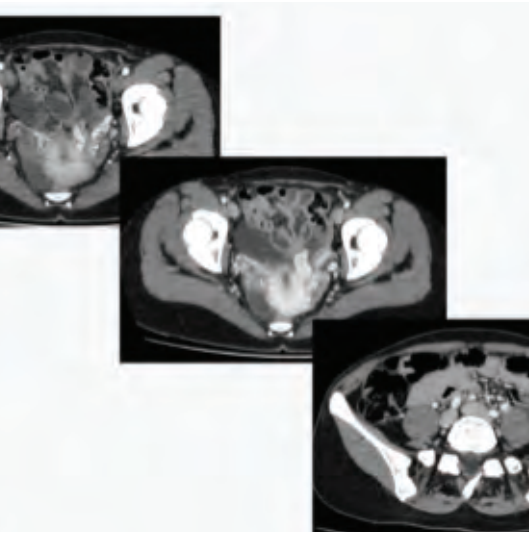
- the left gonadal vein drains into the left renal vein
- the right gonadal vein drains directly into the inferior vena cava. [Gonadal vein-Radiopaedia](#)

Incompetence and retrograde flow in the gonadal veins can result in a varicocele in the male and pelvic congestion syndrome in the female. Venography and therapeutic embolization of incompetent gonadal veins are performed on male and female patients for different clinical situations using similar techniques. [Bittles MA, Hoffer EK. Gonadal vein embolization: treatment of varicocele and pelvic congestion syndrome. Semin Intervent Radiol. 2008;25\(3\):261-270. doi:10.1055/s-0028-1085927](#)

When we talk about varicocele in women, the situation appears completely different:

- ▶ **CCP (Chronic Pelvic Pain):** continuous or intermittent noncyclic pain of 6 or more months' duration
- ▶ **10%** -> general population

- ▶ 30 - 40% -> PCS or PVI (pelvic congestion insufficiency)
- ▶ PCS (Pelvic Congestion Syndrome): when varicose veins develop around the ovaries in a CCP setting, causing pelvic pain with no other identified cause.
- ▶ Sometimes, vulvar/labial/ perineal varicosity
- ▶ **Typical difficult patient:** multipara, 40-50 yo with multiple previous pregnancies, with chronic pain, generally bilateral or left-side prevalent, often exacerbated by prolonged standing, coitus, menstruation, and pregnancy
- ▶ Rarely: hip pain, lower extremity varicose veins, persistent genital arousal



CASE REPORT

- ▶ 47yo woman
- ▶ Non-smoker; previous spontaneous PNX
- ▶ Since November 2018: dysuria then pelvic and perineal pain
- ▶ Antibiotics with no improvement
- ▶ Since January 2020: dysmenorrhea, severe pain before and after menstrual cycle
- ▶ Urological evaluation: negative
- ▶ Gynecological evaluation: negative
- ▶ Suspect PCS

MDCT arterial phase image revealed early opacification of the periuterine plexus and congestion of both left and right gonadal veins. The symptoms were consistent with PCS and the patient was, therefore, eligible for percutaneous treatment. We proceeded as per angiographic evaluation but, when we got to the jugular vein to catheterize the hypogastric axis and the uterine vein to assess the situation, we decided to place an occlusion balloon and gently inject a 2:3 Glubran®2/Lipiodol mixture into the vessels. For the right ovarian vein, we opted for a 1:2 ratio, as the situation appeared more manageable.

- ▶ Glubran®2/Lipiodol 2:3 ratio, 2ml for left ovarian vein
- ▶ Glubran®2/Lipiodol 1:2 ratio, 1 ml for right ovarian vein
- ▶ Procedure length: 55'
- ▶ No complications

Q&A

Webinar Chat: Does the long access route, via the external iliac vein, affect the amount of injected glue?

Felice D'Antuono, MD: No, it does not, as this was the only possible route in this case. When you deal with varicocele in women, it is very important to study both the ovarian and the uterine side of the varices. In the right side, we can sometimes catheterize just the ovarian vein, but when we have communication between the hypogastric and the gonadal veins, we need to use the stop-flow technique to gain complete control of the embolization. This calls for double access, as in this case, and also for perfect detection of the point of injection, because we need forward flow to be able to fill the varices and the vein.

THE ROLE OF NBCA-MS IN ENTEROCUTANEOUS FISTULAS

Riccardo Muglia MD



GASTROINTESTINAL FISTULAS are abnormal communications between two epithelized surfaces. They are most commonly iatrogenic and can be caused by trauma, radiation, IBD, etc., but they can also be spontaneous (75%/25%).

They can occur all along the gastrointestinal tract and they are classified based on their position within the tract.

Foregut Fistulas

- ▶ **Esophageal fistulas** are mainly related to congenital and postsurgical atresia repair. They can be treated surgically, through re-thoracotomy, however, this is a technically challenging procedure, associated with significant morbidity (re-fistulation rate of 10%-32%). Another option is to treat them with glue sealant: this approach involves an endoscopic occlusion with tissue adhesives, which is completely safe and highly effective, with a success rate of 46% to 100%, with 1.3 sessions attempts per patient
- ▶ **Refractory gastric/duodenal fistulas** of iatrogenic etiology can also be treated successfully with sealant, fibrin glue, clipping, metal stents, and biologic plugs. Reported success rate: 57% to 100%
- ▶ **Pancreatic fistulas** treated with sealant report a cumulative success rate of 67% to 100% and 1.2 sessions to definitively close the fistula
- ▶ **Biliary fistulas** report a cumulative success rate of 78% to 100% and 1.2 sessions to definitively close the fistula

Midgut Fistulas

- ▶ Jejunal or ileal postoperative fistulas are the most common. Cumulative success rate with repetitive glue treatment of 67% to 100% and 1.2 sessions to definitively close the fistula
- ▶ Spontaneous fistulas due to Crohn's disease are more difficult to heal

Hindgut Fistulas

- ▶ Colorectal: postoperative - Crohn's disease - rectal cancer. Success rate with adhesive glue: 100%
- ▶ Anorectal: glandular etiology. Success rate with adhesive glue: 68% to 95% and 1.2 sessions to definitively close the fistula. Overall complication rate: 1%

ENTEROCUTANEOUS FISTULAS

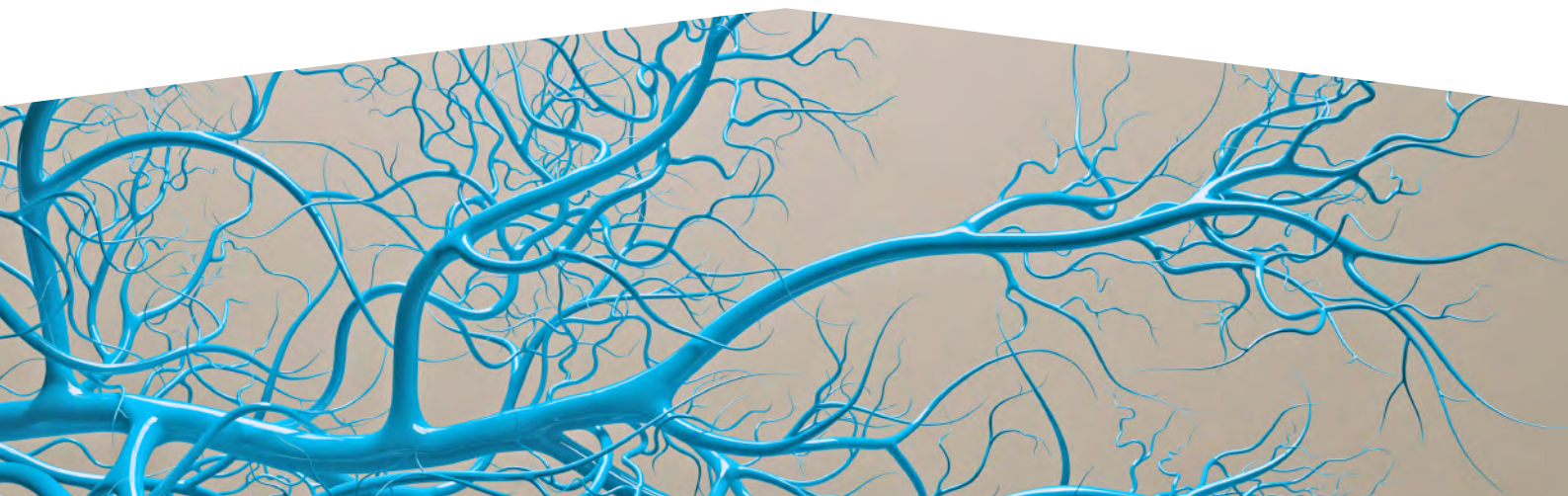
They are a particular kind of fistulas formed through an aberrant connection between a fistula in the GI tract and skin/wound. They are classified in high output > 500 ml/24h and low output < 200 ml/24h and they are mostly iatrogenic (75-85%) with a low incidence of the spontaneous kind (15-25%),

Another classification divides them in Type I (abdominal, esophageal, gastroduodenal), Type II (small bowel), Type III (large bowel), and Type IV (enteroatmospheric, regardless of origin).

Enterocutaneous Fistulas

Favorable	Unfavorable
Surgical etiology	Ileal, jejunal, nonsurgical etiology
Appendicitis, diverticulitis	IBD, cancer, radiation
Transferrin > 200 mg/dL	Transferrin < 200 mg/dL
No obstruction, bowel in continuity, no infection, no inflamed intestine	Distal obstruction, bowel discontinuity, adjacent infection, adjacent active inflammation
Length > 2 cm, end fistula	Length < 2 cm, lateral fistula, multiple fistulas
Output < 200 mL/24 h	Output > 500 mL/24 h
No sepsis, balanced electrolytes	Sepsis, electrolyte disturbances
Initial referral to tertiary care center and subspecialty care	Delay getting to tertiary care center and subspecialty care

A list of variables related to treatment outcome

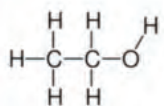
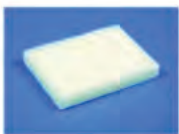


MANAGEMENT

- ▶ **Skin and Sepsis control** is extremely important to manage enterocutaneous fistulas
- ▶ **Nutrition** translates into electrolytes requirements, usually provided in the crystalloid form
- ▶ **Anatomy** of the fistula needs to be thoroughly studied by means of CT or MRI scans
- ▶ **Procedure:**
 1. *Conservative treatment*
 - i. Total parenteral nutrition to improve fluid and electrolyte balance and assure adequate nutritional support
 - ii. Empirical or targeted antibiotic therapy
 - iii. Somatostatin analogues: inhibitory effect on GI secretions
 - iv. Low output fistula with no evidence of sepsis or localized infection: sealant glue
 2. *Image-guided drainage*
 - i. Diagnostic: the injection of contrast medium through the drainage catheter may demonstrate communication with GI lumen
 - ii. Therapeutic: removal of infected collection
 3. *Endoscopy*
 - i. Clip: technology available for acute fistulas and perforations
 - ii. Plugs: more commonly used as an adjunct in the treatment of enteroatmospheric fistula
 - iii. Fibrin glue
 4. *Percutaneous treatments*
 5. *Surgical repair*
 - i. Definitive treatment but increased risk of morbidity
 - ii. Indication: no spontaneous closure by 12 weeks after sepsis control,
 - iii. nutritional optimization and wound care
 - iv. Success rates: 58 to 89%
 - v. Challenging dissections and possibility of recurrence
 - vi. 30-day morbidity rate: up to 82%
 - vii. Mortality rate: 2-5%

Embolic Agents

- Ethanol
- Gelfoam
- Glue



CYANOACRYLATE GLUE

- ▶ Obliteration of fistulous tracts
- ▶ Solidification of the compound within 30 seconds
- ▶ Induction of an inflammatory response that enhances fibrosis and foreign-body granuloma formation
- ▶ Ultimate epithelization
- ▶ Has to oppose to physiologic loads that tend to move tissues away from each other
- ▶ Must guarantee uniform distribution of the loads throughout the affected areas, without compromising the elastic properties of the natural tissues

CASE 1

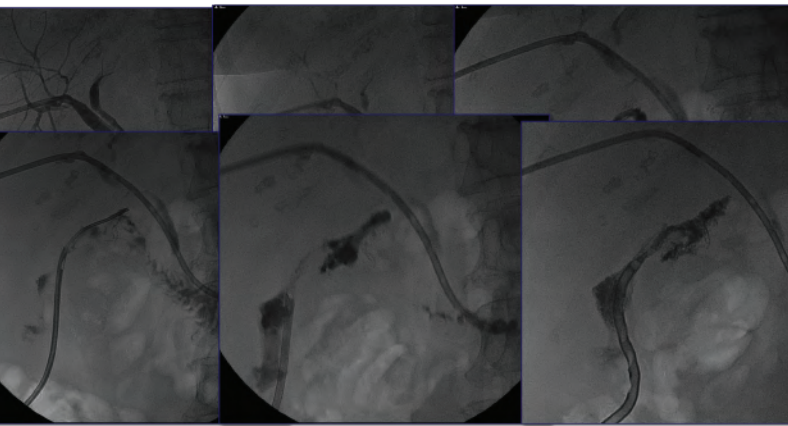
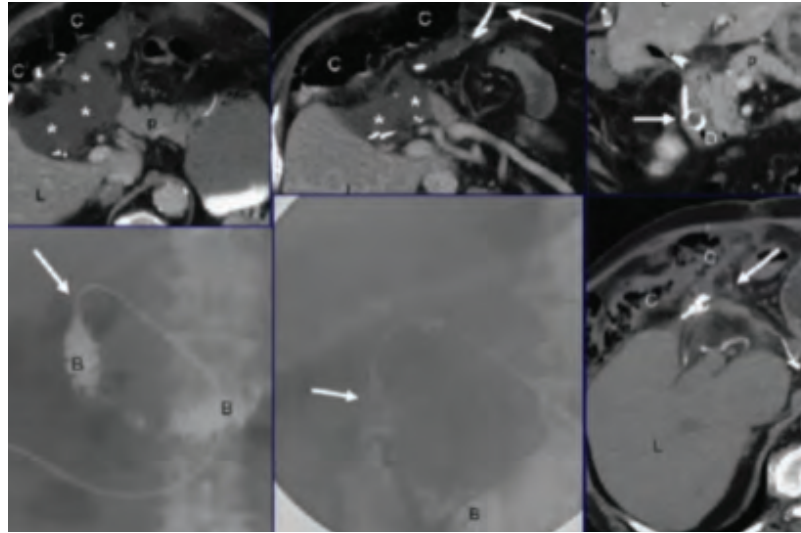
82 yo man

Gastric Resection for Gastric Adenocarcinoma

After surgery, the patient presented with a collection positioned between transverse colon, liver, and pancreas, which we drained successfully and that disappeared after about 2 weeks.

At 10-months follow up, though, we noticed the tip of the catheter inside the duodenum. We went into the lumen to retract the catheter and seal the fistula.

The angiogram shows the radiopaque glue and no collection.



CASE 2

77 yo woman

Gastrectomy for Gastric Cancer

The patient had undergone surgical drainage, which we retraced by means of an angiographic catheter, detecting a fistula connected with the enteric lumen, behind the peritoneum.

We used a hydrophilic guidewire to insert our catheter and sealed with a mix of Glubran®2 and Lipiodol, with successful results.

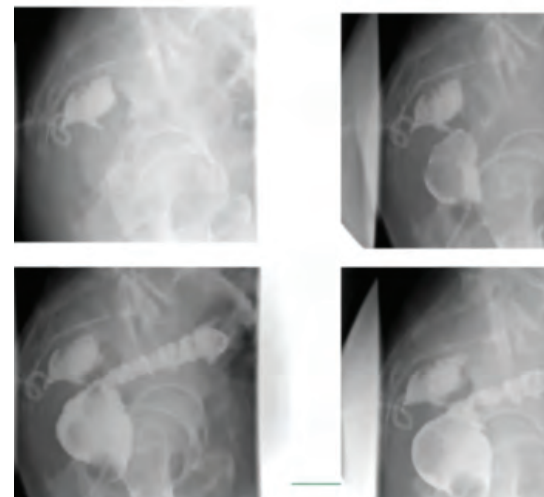
CASE 3

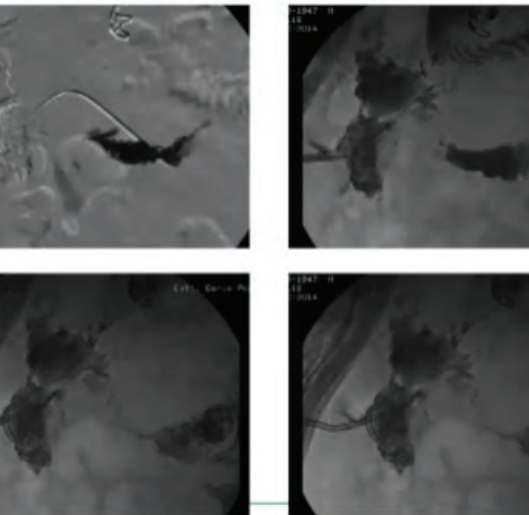
70 yo man

Anterior Resection for Rectal Cancer

This patient developed a collection behind the rectum. After draining it, we detected a fistula between the collection and the lumen of the rectum, which we treated with glue through the usual procedure.

The picture shows the final result, which, as you can see, was extremely good.





CASE 4

72yo man

Duodenal Resection for Perforated Ulcer

This was an unfortunate case of a patient developing an extremely large collection of the right flank. We injected glue to seal the fistula but, unfortunately, the patient had to be treated multiple times as the fistula would not heal. The picture shows the impressive amount of glue we used over time to treat this case.

The patient eventually had to undergo surgery to solve the problem.

This goes to show that the occlusion of fistulas can be performed effectively by using glue, provided that the collection is not too large.



GUIDELINES FOR USING GLUBRAN[®] 2



1. Careful preliminary angiographic examination

Identification of the afferent and collateral vessels and any eventual AV fistulas, with oblique and cranio-caudal projections



2. Selective and superselective catheterisation of the area to be embolised

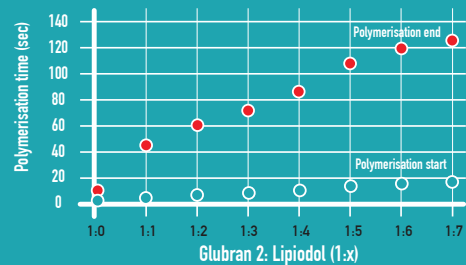


3. Careful hemodynamic evaluation



4. Dilute with Lipiodol[®]:

- To delay the Glubran[®] 2 to polymerisation start time
- To make it radiopaque



5. Mix the two compounds uniformly

Immediately before injection (with a 3-way resistant stopcock or in a steel bowl)



6. Wash the catheter with glucose or dextrose solution



7. Inject slowly

- Microbolus of 0.1-0.3 ml of mixture > push with glucose/dextrose ("sandwich" technique)
- A single injection continuously



8. Remove the catheter

(quickly and immediately after the injection, if it was not performed the "sandwich technique" with glucose)



9. Eventual check with contrast medium at least two minutes later

WARNING: DO NOT USE GLUBRAN[®] 2 WITH POLYCARBONATE OR SILICONE MATERIALS

Advised products & materials

- Glubran[®] 2/Lipiodol[®] Ultra-Fluid
- Glucose or dextrose 5%-33%
- Polyethylene (PE) or polypropylene (PP) syringes with luer lock
- 3-way-stopcocks
- Standard 4F catheter
- Coaxial microcatheter

Glubran[®] 2/Lipiodol[®] dilution ratios⁸⁴

	MICROCATHETER POSITION	CATHETER TIP	INJECTION OF THE MIXTURE	FLOW SPEED	OCCCLUSION	EXAMPLES OF APPLICATIONS
GLUBRAN [®] 2/LIPIODOL [®] Dilution ratio 1:1 to 1:3 ¹⁻⁷	Close to lesion	Wedged	Continuous	High	Proximal	Varicocele, Hypervascularized tumors, Gastro-intestinal bleedings, Peripheral bleedings, Pseudoaneurysms, High-flow AVM
GLUBRAN [®] 2/LIPIODOL [®] Dilution ratio 1:4 to 1:9 ¹⁰⁻¹⁴	Far from lesion	Free	Drop by drop	Low	Distal	Organ-end artery, Portal vein embolization, Low-flow AVM, Tumor devascularization, Venous malformations, Lymphatic leakage



**SOLUTION
COMES FROM
EVOLUTION**

GEM S.r.l.

Via dei Campi, 2 - PO Box 427 55049 Viareggio (LU) ITALY
Phone : +39 0584 389784/391388 Fax : +39 0584 397904

www.gemitaly.it - info@gemitaly.it

