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REVIEW

Embolics Review: Current Options and Agents in the Pipeline

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Abstract

As the specialty of interventional radiology has progressed, endovascular embolization has become a cornerstone of the specialty, used in a wide range of clinical indications. Advancements in materials technology since the 1970s have led to an exponential increase in the range of embolic agents available. Fundamental knowledge of the various categories of embolics, including the advantages and shortcomings of each option, is vital for interventional radiologists to determine the optimal embolic for each clinical need. This review aims to provide a brief overview of embolic agents currently available with a focus on new and upcoming options and their associated strengths and weaknesses.

Introduction

As the specialty of interventional radiology has progressed, endovascular embolization has become a cornerstone of the specialty, used in a wide range of clinical indications including vessel occlusion in acute hemorrhage, cancer and benign tumor treatment, vascular malformations, variceal obliteration, and endoleak management.[1] Since the 1970s, significant advancements in materials to address specific clinical applications and respond to failures of natural analogues have led to an exponential increase in the range of available embolic agents. Fundamental knowledge of the various categories of embolics, including characteristics of each option, is vital for interventional radiologists in determining the optimal embolic for each clinical need.

This review aims to provide a brief overview of embolic agents currently available with a focus on new and upcoming options and their associated strengths and weaknesses.

Embolic Agents

Most available embolic agents can be organized into four major categories: particles, liquids, coils, and plugs, though some newer embolics are pushing this paradigm as will be discussed below (**Figure**).[2] Each category can be further categorized based on the characteristics of the embolic in question.

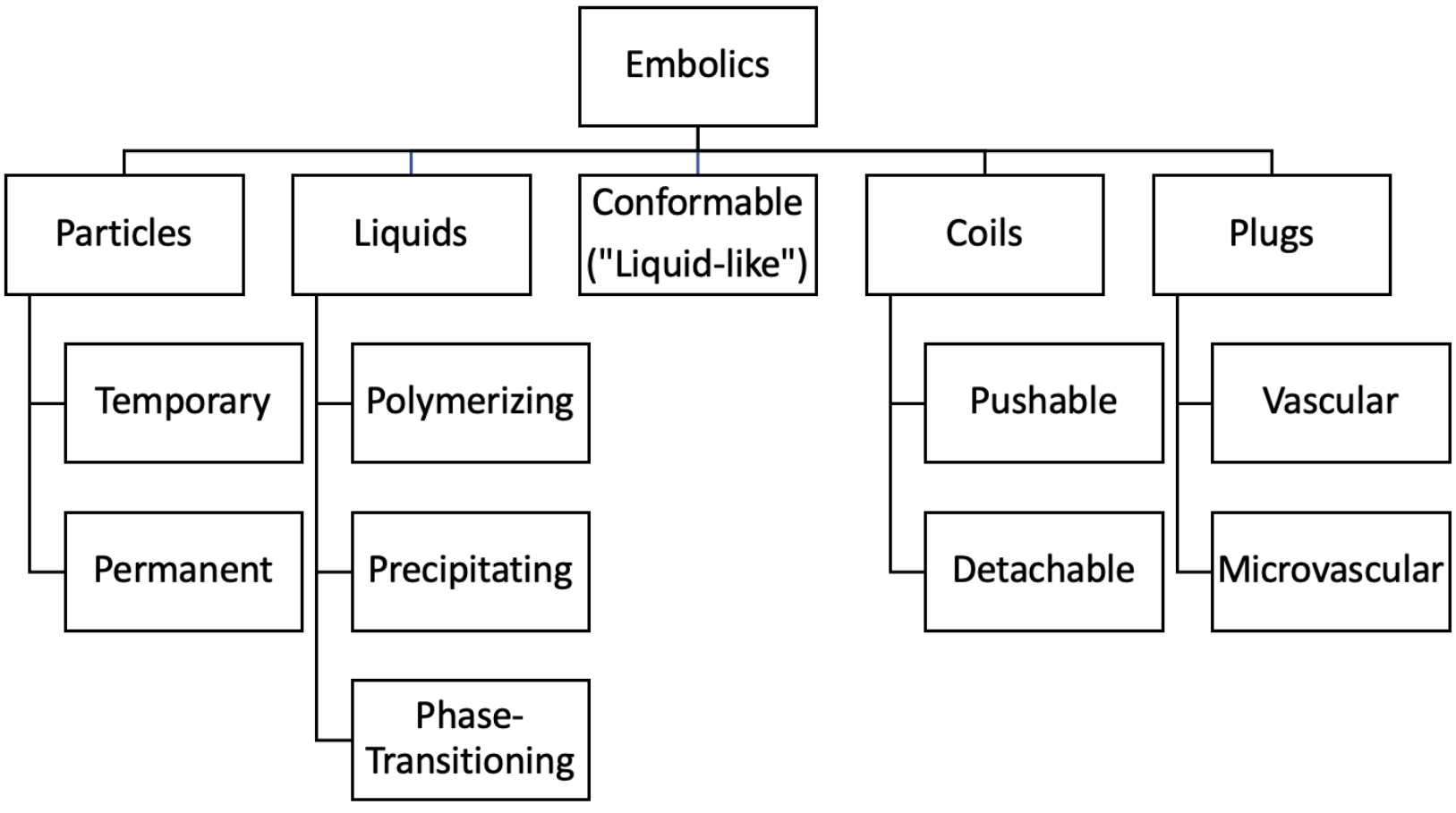

Figure. Major categories of embolic materials.

Particles

Particles comprise the first historically described embolic agents and continue to be one of the most ubiquitous in use today.[3] Particle embolics are usually categorized into temporary/resorbable or permanent, although they can also be categorized based on shape (spherical vs nonspherical) or function (radioembolics or drug-eluting particles for oncologic interventions).[2,4]

Temporary Particles

Temporary (or resorbable) particles are made of biodegradable materials and function to temporarily occlude vessels. These can be useful in cases of acute hemorrhage, allowing injured vessels to heal before recanalization, or immediately before scheduled surgical resections of tumors to minimize intraoperative blood loss. The most used temporary embolics include: 1) Gelfoam (Pfizer), a porous, water-insoluble gelatin made from pork skin, which acts as a spongy scaffolding that can absorb high amounts of blood and allow it to thrombose;[4-7] and 2) autologous blood clots. Gelfoam has a reported recanalization time in the range of 2 weeks to 3 months, though there have been reports of recanalization as early as 3 days or as long as 4 months.[5]Gelfoam most often comes as a dry gelatin sponge, which can be cut into small pieces measuring 1 mm or larger and mixed with contrast and/or saline to form a foam slurry to be used for endovascular embolization in cases of acute hemorrhage, or be cut into strips and be used as torpedoes in biopsy or access tract embolization. It is also available in the form of powder, with particle sizes ranging from 50 to 450 μm. Advantages of Gelfoam include its extremely low cost, ease of use, and wide availability, with its disadvantages being inconsistent duration until recanalization. Since its function relies on the blood's ability to coagulate, its effectiveness can also be hindered in coagulopathic patients. Autologous blood clots are perhaps the cheapest and most widely available as they are derived directly from the patient. The inherent weakness of the clot is its short recanalization time in the range of hours, which limits its use to a few specific scenarios. These include percutaneous organ access tract closure, epidural blood patch to occlude cerebrospinal fluid leaks, and high-flow priapism.[4,8,9]

Permanent Particles

In comparison to temporary particles, permanent particles are not resorbed by the body and thus lead to permanent occlusion of vessels, which can be desirable in cases such as tumor embolization, uterine artery embolization, and prostate artery embolization. Permanent particles can also be divided based on other characteristics, such as shape (spherical or nonspherical) or function (functional as opposed to nonfunctional or "bland" particles).

An example of nonspherical permanent particle is nonspherical polyvinyl alcohol (PVA), available as Contour (Boston Scientific). Nonspherical PVA is created from PVA foam, with particles passed through filters to achieve a size range from 100 to 1100 μm.[4] As PVA particles are not uniform in shape, the exact level of arterial occlusion can be difficult to predict.[10-12] Nonspherical PVA particles are inexpensive compared with spherical particles, but due to their propensity to aggregate or clump, can also more easily clog microcatheters.[2]

Unlike nonspherical PVA, spherical particles are precisely sized and come in 200 to 300 μm increments, ranging from 40 to 1200 μm. They avoid particle aggregation and may even compress to fit through delivery microcatheters. Compared with nonspherical PVA, spherical particles achieve more predictable vessel occlusion.[13] Examples of common spherical particles include spherical PVA (Bead Block [Boston Scientific]), trisacryl-gelatin (Embosphere [Merit Medical]), and polymethylmethacrylate with polyzene-F coating (Embozene [Varian]).

Another subset of permanent particles are functional particles, whereby therapeutics are “loaded” onto particles so the therapeutic and particles can be delivered together, potentially improving the efficacy and safety profile of the therapeutic treatment. Examples include drug-eluting beads (DEBs), created by combining a chemotherapeutic agent with nonresorbable beads, and radioembolics, created by attaching Y-90 radioisotope to nonresorbable beads.[1,6,12,14] A more detailed discussion of the strengths and weaknesses of DEBs based on chemotherapy types and mechanics of bead sizes, as well those of radioembolization particles based on glass or resin-based materials, particle size, and differing levels of radioactivity, is outside the scope of this review. Some DEBs currently available include DC Bead (Boston Scientific), HepaSphere (Merit Medical), and Oncozene (Varian), while the 2 radioembolics currently available in the United States include TheraSphere (Boston Scientific) and SIR-Spheres (Sirtex).

New and Upcoming Particles

One of the overall weaknesses of particle embolics is lack of visibility, as most agents currently available, whether biodegradable or not, are radiolucent and thus must be mixed with intravenous contrast or lipiodol for visibility during administration.[6] Although lipiodol can remain visible within the body for a relatively short period of time in limited clinical scenarios, such as in conventional transarterial chemoembolization for hepatocellular cancer, long-term monitoring after embolic treatments is difficult due to rapid clearance of contrast material and eventual clearance of lipiodol by the body. This has led to the development and investigation of intrinsically radiopaque particle embolics, created via polymerization of radiopaque moieties onto particles, thus retaining the physical properties of calibrated microspheres while potentially reducing physiologic toxicities associated with iodinated contrast material or other radiopaque materials.[6,15-17] An available example of imageable particles is LC Bead LUMI (Boston Scientific), available in calibrated size ranges from 40 to 90 μm to 500 to 700 μm.[18,19] Although it still requires contrast to be seen fluoroscopically, it is easily visible on post-treatment computed tomography (CT).

Another new development in particle embolics is calibrated microspheres that are resorbable, combining the benefits of resorbable embolics with more consistency in small vessel occlusions.[20-23] These biodegradable spheres can be made of natural polysaccharides, including starch-based, dextran-based, and calcium alginate microspheres, or synthetic polymers, such as polylacticoglycolic acid (PLGA) microspheres.[24-28] Examples of resorbable particles currently available or under investigation include Gel-Bead (Teleflex), available in size ranges from 100 to 300 μm to 700 to 1000 μm with reported recanalization time between 4 to 12 weeks, and Occlusin (IMBiotechnolgies Ltd.), calibrated to 150 to 212 μm size range.[29,30] Some limitations of currently available resorbable calibrated microspheres are that they have restricted compressibility and have been known in in vivo experiments to have relatively shorter resorption periods of less than 10 days.[31-33]

Liquids

Liquid embolics cause vessel embolization via polymerization, inflammation, or phase transitions and thus can function independent from a patient’s clotting functions, unlike certain particles, coils, or plugs. As a flow-directed embolic, liquids can also obstruct blood flow to distal/small vessels that could not otherwise be reached by microcatheters. However, liquids pose a high risk of nontarget embolization so can require high levels of experience and understanding from the interventional radiologist for safe and effective deployment. Liquid embolics can be further categorized into precipitating or polymerizing agents, although newer agents are expanding outside of this classic paradigm as will be described below.[2]

Precipitating

Precipitating embolics consist of a polymer agent suspended in a carrier solution; the polymer precipitates and solidifies when it comes into contact with certain aqueous environments.[2,4] The most commonly used precipitating agent is n-butyl-cyanoacrylate/nBCA (glue), which comes as a clear, thin liquid at room temperature, commonly injected via a 5% dextrose solution, and solidifies in ionic environments such as blood or saline. nBCA is commonly mixed with lipiodol, an oil-based liquid agent that is often used alone as an embolic due to its viscous nature. Higher lipiodol:glue ratios increase the polymerization time of glue, allowing for more distal embolization. nBCA is commonly available commercially as Histoacryl (B. Braun) and TruFill (Cordis). Onyx (Medtronic) is another precipitating liquid embolic agent, comprised of an ethylene vinyl alcohol (EVOH) copolymer dissolved in dimethyl sulfoxide (DMSO), mixed with tantalum powder for fluoroscopic visualization.[34,35] After the solution is delivered via a DMSO-compatible microcatheter, the DMSO solvent dissipates and the EVOH polymer precipitates into a nonadhesive solid embolus. Although Onyx was originally developed for neurointerventional indications such as arteriovenous malformation embolization, it has been successfully used in other peripheral interventions including endoleak embolization after endovascular aneurysm repair, post-trauma embolization, and organ bleeding. Being a nonadhesive, Onyx provides a more controlled delivery with less risk for gluing of the delivery microcatheter; however, it is more expensive than nBCA glue.

Other precipitating agents are in various levels of development.[36-39] Squid (Emboflu), another EVOH/DMSO system with micronized tantalum powder that remains in suspension longer than in Onyx, allowing for longer time windows during administration. Squid is also available in varying viscosities, which can be chosen based on indication. The delivery, mechanism of action, and limitations are otherwise identical to those of Onyx. Precipitating hydrophobic injectable liquid (PHIL [Terumo Medical]) is another polymer that uses DMSO as solvent; however, instead of visualization from tantalum powder, PHIL polymers are bound to iodine moieties that provide inherent radiopacity to the material itself and limit streak artifacts on subsequent CT scans as seen with Onyx or Squid. PHIL is also available in differing viscosities. Additional agents include Easyx (Antia Therapeutics AG), and Lava (BlackSwan Vascular, Inc.).[37-39]

Polymerizing

Polymerizing liquid embolics combine an initiating agent with monomers to create solidified polymers.[2] The introduction of an initiating agent can be done outside the body before delivery, in which case the time to solidification must be known and consistent, making such agents difficult to use in clinical settings. Alternatively, the initiating agent and monomer solution can be introduced concurrently into the target vessel, allowing for polymerization within the body. A relatively new polymerizing agent currently available is the Embrace Hydrogel Embolic System (Instylla), which uses 2 coaxial microcatheters to instill the initiator and monomer solution, causing embolization within the target vessel. This product currently only has approved indication for embolization of hypervascular tumors.[40]

Phase-Transitioning

Another category of liquid embolics encompasses the phase-transitioning agents, which function via external stimulus to transition from liquid to gel. In patients, this could be temperature, pH, or salt concentrations in blood. Two products belonging to this category in the pipeline include GPX (Fluidx Medical Technology) and PuraMatrix (3-D Matrix).[41-43]

Conformable

A separate new "liquid-like" embolic is considered by some to belong in its own "conformable" category of embolic agents—Obsidio (Boston Scientific). Obsidio begins as solid material designed with a "shear-thinning" technology that allows it to become liquid or gel-like when shear-stress is applied, such as the pressure from microcatheter injection. Once the embolic enters the vessel and the shear stress ceases, the embolic becomes a solid. Obsidio is currently approved for embolization of hypervascular tumors and peripheral vascular bleeding, but ongoing multicenter clinical trials are taking place to expand its indications.[44]

Coils

Coils provide permanent occlusion by slowing blood flow and providing increased surface area for thrombogenesis. As such, the function of coils depends on the patient's intact coagulation cascade. Coil selection is based on several characteristics, and as such there are many types of coils available on the market designed for different clinical scenarios (**Table 1**).[6] Perhaps the 2 most important characteristics in coil selection are thrombogenicity and packing density.[4,45,46] Since coils rely on thrombosis to cause occlusion, coil development has focused on creating improved ways to cause thrombogenesis. Apart from attachment of thrombogenic fibers, as seen in many early-generation platinum coils like Nester and Tornado coils (Cook Medical), newer coils have been developed with hydrogel coating that expands to fill in spaces after coil delivery like the Azur CX HydroCoil (Terumo), or making the coils so soft that they pack more efficiently, such as the Ruby coils (Penumbra).[4,45,47,48] Advantages of coils overall include their wide availability, relatively low cost compared with some other embolics, and extensive experience and data on their use throughout the years. However, due to their metallic composition, coils can lead to significant imaging artifacts, including beam-hardening/scatter on CT and susceptibility on magnetic resonance imaging.

Coils are commonly categorized into pushable or detachable, each with their own strengths and weaknesses.

Table 1. Common Coils Currently Available			
Coil Name	**Characteristic**	**Delivery Catheter Minimum Inner Diameter (in)**	**Delivery Category**
Cook Medical			
Hilal	Fibered platinum	0.018	Pushable
Tornado	Fibered platinum	0.018 0.035	Pushable
Nester	Fibered platinum	0.018 0.035	Pushable
MReye	Fibered inconel (alloy)	0.035 0.038	Pushable
Retracta	Fibered platinum	0.035	Detachable
MReye Flipper	Fibered inconel (alloy)	0.041	Detachable
Boston Scientific			
Straight-18	Fibered platinum alloy	0.021	Pushable
Figure 8-18	Fibered platinum alloy	0.021	Pushable
VortX-18	Fibered platinum alloy	0.021	Pushable
VortX Diamond-18	Fibered platinum alloy	0.021	Pushable
Multi-Loop-18	Fibered platinum alloy	0.021	Pushable
Complex Helical-18	Fibered platinum alloy	0.021	Pushable
VortX-35	Fibered platinum alloy	0.035	Pushable
Multi-Loop	Fibered platinum alloy	0.035	Pushable
IDC-18	Platinum alloy 2D regular helical Platinum alloy 2D soft helical	0.021 0.021	Detachable Detachable
Interlock-18	Fibered platinum alloy 2D helical Fibered platinum alloy diamond	0.021 0.021	Detachable Detachable
Interlock-35	Fibered platinum alloy cube Fibered platinum alloy 2D helical Fibered platinum alloy diamond	0.035-0.038 0.035-0.038 0.035-0.038	Detachable Detachable Detachable
Embold Fibered	Fibered platinum alloy	0.021-0.027	Detachable
Embold Soft	Non-fibered platinum alloy	0.021-0.027	Detachable
Embold Packing	Non-fibered platinum alloy	0.021-0.027	Detachable
Medtronic			
Concerto Helix	Fibered 2D helical	0.017-0.021	Detachable
Concerto 3D	Fibered framing	0.017-0.021	Detachable
Penumbra			
POD	Soft platinum with anchor tip	0.026-0.027 (lantern)	Detachable
Packing Coil	Soft platinum packing	0.026-0.027 (lantern)	Detachable
Packing Coil LP	Soft Platinum Packing	0.017-0.021	Detachable
Ruby	Platinum 3D packing	0.026-0.027 (lantern)	
Ruby LP	Platinum 3D packing	0.017-0.021	Detachable
Terumo			
Azur Framing Coil	Platinum framing	0.019-0.027 0.041-0.047	Detachable Detachable
Azur CX	Platinum helical with expanding hydrogel core	0.019-0.027 0.041-0.047	Detachable/pushable Detachable/pushable
Azur HydroCoil	Platinum helical with expanding hydrogel coating	0.019-0.027 0.041-0.047	Detachable/pushable Detachable/pushable

Pushable coils

Pushable coils are delivered through a catheter or microcatheter without an attached delivery system. They can be deployed via pusher wire or with saline flush. Unlike detachable coils that are attached to a delivery wire until the wire is detached, once pushable coils are delivered into the microcatheter, there is no way to retract the coil for repositioning. This reduces the relative “control” of pushable coils compared with detachable coils, but pushable coils are much cheaper to use per unit and can be faster to deploy. Pushable coils come in a variety of shapes and sizes for different clinical scenarios, such as the VortX, Straight, and Figure 8 coils (Boston Scientific). The coils’ fibers can be made of various thrombogenic materials, including nylon, polyester, and Dacron, to name a few.[4] Microcoils are deployed via microcatheters and are commonly used for neurointerventions, in controlling bleeds, and in peripheral vascular embolizations, while larger coils can be deployed via angiographic catheters and are often used for large vessel occlusions.[49,50]

Detachable coils

Detachable coils are delivered while attached to a delivery wire and stay attached until the wire is manually “detached.” This characteristic allows the operator to retract the coil and re-deliver if the initial deployment site is suboptimal. Detachable wires are thus considered to have better control, although tend to be more expensive to use per unit. The process of coil detachment also adds an additional step to coil delivery, and the occasional detachment failure can occur, which can add procedural time. Examples of detachable coils include Concerto (Medtronic) and the newer Embold (Boston Scientific) coils. The Embold family of coils include: 1) the fibered coil, which is comprised of a fibered segment and a nonfibered segment; 2) the soft coil, a more flexible helical coil that can track and deploy easily in more peripheral vessels; and 3) the packing coil, which, similar to the Penumbra packing coils (discussed below), acts as “liquid metal” to occlude target vessels more thoroughly. Some strengths of the Embold coils include the ability to deploy through a wide range of microcatheters, both normal and high flow, deployment via a nitinol introducer wire that prevents kinking during microcatheter advancement, and ease of deployment without a separate detachment handle.

Coil deployment in the case of detachable coils is often seen as a process consisting of 3 steps: anchoring, framing, and packing. When complete occlusion is desired at a specific location in a vessel, anchoring allows for a backstop to be created so that additional coils can be placed more proximally with less risk of unexpected distal coil migration leading to nontarget embolization. Anchoring can be achieved with a specifically designed coil that is stiff enough to stay in place but soft enough to form a pack within the vessel lumen without travelling distally. An example of a coil designed for this purpose is the POD coil (Penumbra), which requires the use of specific microcatheters with inner diameters larger than 2.5F. Additional ways to create anchoring is to allow a detachable coil tip to start coiling within a vessel branch. After anchoring, the coil pack can be “framed” to create a scaffold through which soft packing coils can be used to pack the vessel space. Framing coils are commonly used in situations of arterial aneurysms. An example includes the Azur framing coil (Terumo). Lastly, packing coils have specific characteristics that can help “fill in” the vessel space. The Azur HydroCoil, for instance, has a hydrogel coating that expands and fills in the spaces between coiling loops over time. The Ruby and Packing coils (Penumbra) are examples of soft coils that allow for high-density packing.

Vascular Plugs

Vascular plugs were developed to address the issue of the need to sometimes deliver multiple coils to achieve complete vascular occlusion.

The Amplatzer vascular plug (AVP) (Abbott) was the first vascular plug available on the market and has been made into 4 different shapes (although the AVP III is not currently available).[51-54] All AVP designs are made of a nitinol mesh and are detachable systems, with a microcoil holding the device to the delivery wire. Although the theoretical advantage of using plugs is that a single plug can be enough to occlude the target vessel, downsides of AVPs are that they require fairly large catheters or sheaths for delivery, which limits the caliber of vessels the plugs can be deployed into, and in some cases the plug takes a long time to achieve vessel occlusion or does not occlude the vessel sufficiently such that additional coils or plugs must be used to achieve satisfactory occlusion.

The MVP microvascular plug (Medtronic) was developed to address the downsides of the AVP in terms of deliverability and vessel occlusion.[2,55-57] The MVP can be delivered via microcatheters and thus can be used in vessels as small as 1.5 mm. It is made of nitinol like the AVP, but also uses a polytetrafluoroethylene (PTFE) covering instead of simple mesh to cause vascular occlusion. The AVP comes in a detachable system via a microscrew and has excellent trackability and deliverability. However, in certain high-flow situations, the MVP has been reported to migrate as its PTFE covering can act as a sail pushed by antegrade blood flow.[57]

Additional plugs have been designed and produced due to continued perceptions of unmet needs. These include the Azur Vascular Plug (Terumo) and LOBO device (Okami Medical), as well as ones in the pipeline such as the Hourglass (Malin), Pillow Occluder (AndraTec), and Impede (Shape Memory Medical).[2,58,59]

Conclusion

As the specialty of interventional radiology has progressed, endovascular embolization has become vital to a wide range of clinical indications, and as such, the number of different embolic agent options is profound and continues to grow. Each embolic agent has its own advantages and shortcomings; thus, depending on the clinical indication, no “ideal” embolic exists. It is important for the interventional radiologist to understand the strengths and weaknesses of each agent to be able to select the correct option for each clinical need. One must note that this review is only meant to serve as a brief summary of basic embolization principles with a focus on select new and upcoming embolic agents. It is not meant to be an exhaustive list or a comprehensive discussion of embolization. ■

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