

Catheter directed interventions for inferior vena cava thrombosis

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Abstract: Inferior vena cava (IVC) thrombosis, although similar in many aspects to deep venous thrombosis (DVT), has distinct clinical implications, treatments and roles for endovascular management. Etiologies of IVC thrombosis vary from congenital malformations of the IVC to acquired, where indwelling IVC filters have been implicated as a leading cause. With an increasing incidence of IVC thrombosis throughout the United States, clinicians need to be educated on the clinical signs and diagnostic tools available to aid in the diagnosis as well as available treatment options. Untreated IVC thrombus can result in serious morbidity and mortality, both in the acute phase with symptoms related to venous outflow occlusion and embolism, and in the long-term, sequelae of post-thrombotic syndrome (PTS) related to chronic venous occlusion. This manuscript will discuss the clinical presentation of IVC thrombosis, diagnostic and treatment options, as well as the role of endovascular management.

Keywords: Tumor thrombus; thrombolysis; inferior vena cava filter (IVC filter); deep venous thrombosis (DVT); inferior vena cava filter thrombosis (IVC filter thrombosis)

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Introduction

Inferior vena cava (IVC) thrombosis is an underdiagnosed condition associated with a mortality rate approaching twice that of lower extremity deep venous thrombosis (DVT) (1). The lack of a standard diagnostic approach, a sparsity of data, and nonspecific clinical presentation have all hindered in its clinical recognition. The incidence of IVC thrombosis in patients with confirmed DVT is estimated to be between 4–15% (2,3), which is likely an underestimate due to the lack of standard diagnostic protocols for caval thrombus.

Etiology

Thrombosis of the IVC can affect 60–80% of patients with congenital anomalies, especially in cases of IVC hypoplasia

or aplasia (4). These anomalies can remain subclinical for many years due to well-developed collaterals. However, despite these collaterals, blood flow from the lower extremities eventually becomes inadequate, resulting in venous hypertension, stasis, and subsequent thrombosis (*Figure 1*). Congenital anomalies of the IVC are rare and can be associated with other congenital anomalies such as situs inversus, congenital heart diseases, polysplenia and asplenia (5,6).

Thrombotic occlusion related to indwelling IVC filters is the most common cause of acquired IVC thrombosis (7). When anticoagulation is contraindicated or ineffective in patients with or at high risk for venous thromboembolism, an IVC filter device may be considered. In the past, this was performed via surgical ligation of the IVC, which was associated with a high rate of mortality as well as chronic venous insufficiency. In the 1960's, partial interruption of

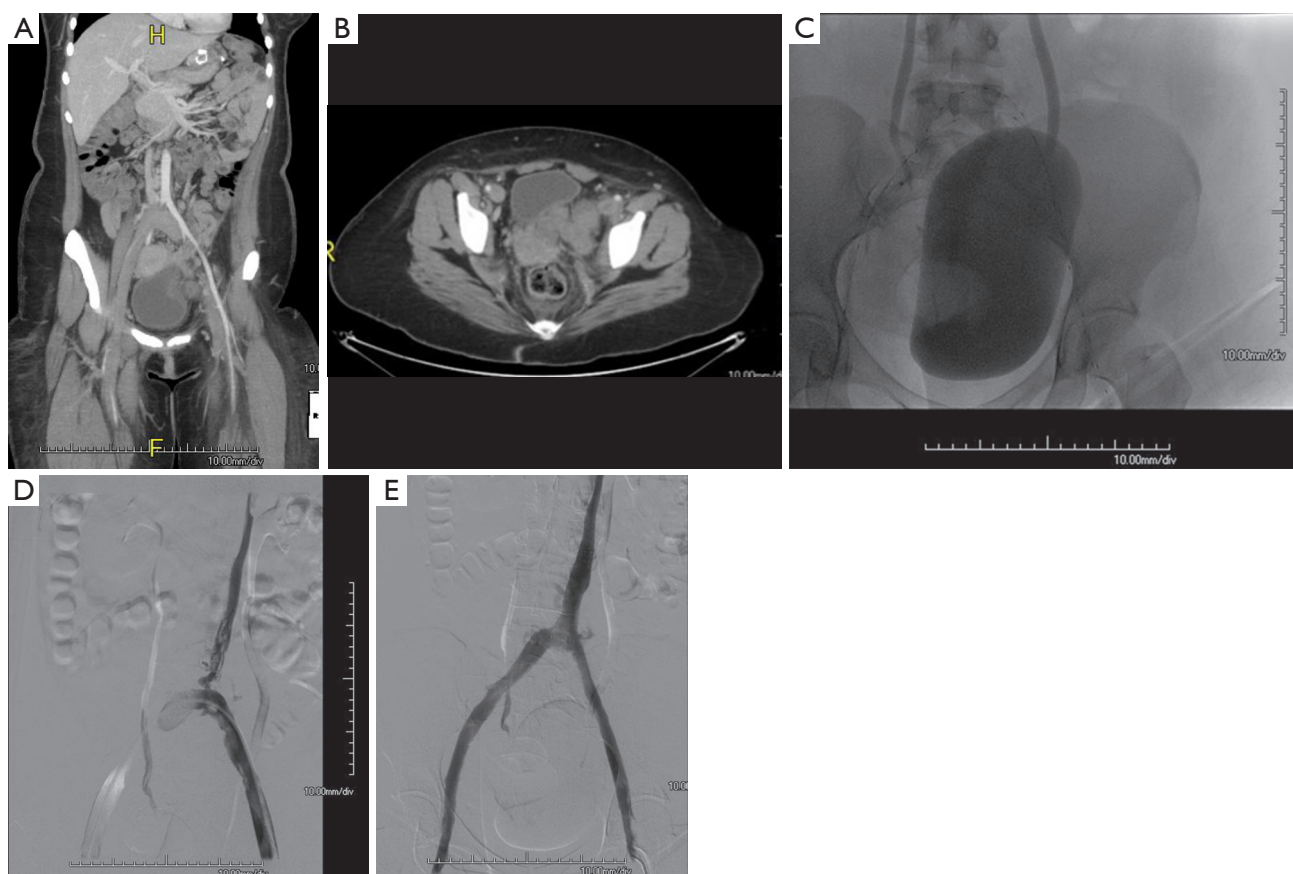


Figure 1 Twenty one years old female with a medical history significant for premature birth with prolong hospital stay. She has chronic mild bilateral lower limb swelling. Patient recently started birth control and her limb swelling became acutely worse. (A) CT images demonstrate bilateral iliofemoral thrombus with diminutive inferior vena cava (IVC); (B) large pelvic venous collaterals which compensated for atretic IVC are thrombosed; (C) bilateral EKOS ultrasound (US)-assisted lysis catheters were placed from popliteal approach for overnight lytic infusion; (D) following thrombolysis, stenotic IVC is demonstrated on venography; (E) angioplasty and stent reconstruction of stenotic IVC was performed resulting in unimpeded central venous flow and rapid improvement in patient's symptoms.

the IVC was introduced using suture and caval clips, though associated IVC occlusion rates remained unacceptably high. The Mobin-Uddin umbrella device was developed in 1967, which partially interrupted flow in the IVC but was also associated with a high percentage of caval thrombus due to inadequate flow. The Greenfield filter was introduced in 1971, followed by the percutaneous Greenfield filter in 1981, which allowed for more blood flow while filtering and lowering the rate of caval thromboses (8).

Thrombotic complications remain the most common adverse event related to IVC filter placement. IVC occlusions occur in up to 2.7% of cases in 6–24 months after placement (9). The increased incidence of deep-vein thrombosis in patients with vena cava filters may

be related to the thrombotic occlusion of those filters leading to venous stasis in the legs. In the PREPIC study, a randomized controlled trial examining efficacy of IVC filters, 26 of 57 patients with deep-vein thrombosis in the IVC filter arm experienced filter thrombosis (10). Despite the increased incidence of thrombus in patients with IVC filters, the presence of a filter alone is not considered an indication for long-term anticoagulation (11). Results of the PREPIC study suggested that an IVC filter is beneficial during the early course of an acute DVT in patients that can't be anticoagulated. Later on the filter is more likely to cause thrombosis of the cava than to prevent a pulmonary embolus (PE). These data have led to the increased use of optional filters that can be removed when the filter is no

longer deemed necessary. Currently, approximately 50% or less of retrievable filters placed are ever removed (12). It is unclear what the true risk of thrombus over time is, however, as with any chronic implant, the risk would be expected to increase with length of implantation. In 2010 the FDA released a safety communication, with a follow-up in 2014, detailing possible complications of long-term indwelling IVC filters. This release encouraged all physicians involved in the treatment, and follow-up of these patients, to consider removing filters when it is no longer needed (13). Increased vigilance in retrieving unnecessary filters may decrease associated long-term complications. The PRESERVE study is a large scale multi-specialty prospective trial evaluating IVC filter use with long-term follow-up. This study is currently enrolling subjects in the United States and may provide further data about IVC filter complications (14).

Acquired IVC thrombosis can also result from cranial extension of DVT into the IVC, spontaneous thrombosis of the cava, venous stasis in the setting of external compression, or thrombosis secondary to a thrombogenic diseased or injured vessel wall (15). Spontaneous thrombosis is typically related to Virchow's triad of hypercoagulability, stasis and endothelial injury. Pro-thrombotic factors include: thrombophilia, malignancy, oral contraceptives, smoking, obesity, pregnancy, hormonal replacement therapy and nephrotic syndrome. External compression may be a sequelae of renal cell tumors, uterine fibroids, hematoma, or compression from other vascular structures such as an abdominal aortic aneurysm or an iliac artery such as in May-Thurner syndrome (16).

Clinical presentation

The clinical presentation of IVC thrombosis varies according to the anatomical level of thrombosis, the degree of occlusion and chronicity of the thrombus. Acute IVC thrombosis is generally accompanied by a sudden onset of symptoms, while chronic IVC thrombosis, presents with a more gradual onset, secondary to thrombotic IVC occlusion with already established venous collateralization or gradual narrowing of the IVC (15). As with DVT, the typical presentation of IVC thrombosis may present with pain, swelling, and cramping of the lower extremities. In addition, and more specific to IVC thrombosis, back and pelvic pain are generally the earliest symptoms. In cases that have renal vein involvement, symptoms may involve hematuria and flank pain whereas bilateral renal

venous thrombosis can result in acute renal failure (17). Pulmonary embolism, which is reported in up to 12% of patients with IVC thrombosis, can present with chest pain and shortness of breath (18). Chronic occlusion can have varied presentations depending on the extent of the collateral venous drainage. Patients can present with bilateral lower extremity pain and edema; skin changes such as pigmentation and venous ulcers; back pain; inguinal, abdominal and thoracic varicosities. Rarely, chronic IVC thrombosis can present with compromised kidney or liver function (Budd-Chiari syndrome) if the venous outflow from these organs are obstructed (*Figure 2*). In addition, patients with chronic thrombosis can present with severe lumbar radicular pain, sciatica, or cauda-equina symptoms secondary to compression from paraspinal collaterals (19). With chronically untreated IVC thrombosis, patients are at risk of developing post-thrombotic syndrome (PTS) as a result of chronic venous hypertension and stasis. Presenting symptoms range from minor leg heaviness to debilitating leg claudication.

Diagnosis

Although no specific diagnostic guidelines for IVC thrombosis exist, non-invasive imaging modalities such as ultrasound (US), contrast enhanced computer tomography (CECT), and magnetic resonance venography (MRV) have resulted in higher and more accurate diagnostic rates of IVC thrombosis. Invasive venography is generally reserved for intent to treat or, in rare cases, a problem solver when other modalities are inconclusive.

Duplex US is often the first-line diagnostic imaging modality, providing a rapid, readily available, non-ionizing, and non-invasive method. US may also detect pathology causing thrombosis such as extrinsic compression of the IVC or anomalies of the IVC itself. However, it suffers from inter-user variability due to its operator-dependent nature. Accurate visualization of the IVC on US can also be limited by overlying bowel gas and patient body habitus (20).

CECT has excellent contrast resolution, allowing visualization of venous structures as well as the ability to depict secondary abdominal or pelvic pathology (21). CECT also has the ability to differentiate between bland and tumor thrombus by observing for enhancement during the arterial phase of injection. CECT is also advantageous in patients with venous stents compared with MRI which may be prone to susceptibility artifact in these areas. CECT is prone to over diagnosing IVC thrombosis, due to the merging of



Figure 2 Patient with hypercoagulable disorder and remote history of inferior vena cava (IVC) thrombosis presents with abdominal ascites requiring frequent paracentesis. She was referred for consultation for TIPS procedure. (A) CT images demonstrates a diminutive IVC with large abdominal ascites related to a suprahepatic venous obstruction (Budd Chiari); (B) venogram reveals extensive collateral flow and hepatic venous congestion; (C) angioplasty of the retrohepatic and suprahepatic IVC was performed; (D) venography post angioplasty demonstrates unobstructed flow from the IVC to the right atrium with resolution of flow through collaterals; (E) CT performed 1 month after angioplasty reveals interval resolution of abdominal ascites, large collateral veins are no longer visualized.

contrast enhanced blood with unenhanced venous return from the lower body (22). Longer delays in imaging after contrast injection make opacification more homogeneous. Peak opacification time ranges from 93–147 seconds while scanning at 210 seconds results in more homogenous opacification which is most likely optimal (23).

MRV evaluation of the IVC can be performed with or without gadolinium enhanced sequences. MRV is advantageous as it does not use ionizing radiation, provides more accurate delineation of thrombus, as well as accurate

visualization of IVC anomalies. It can be used to follow morphological changes of thrombus after therapy as well (24). In patients with an existing IVC filter or venous stent, susceptibility artifact may limit accurate assessment of adjacent veins. In addition, availability and cost are other limitations to routinely using MRV.

Treatment

If left untreated, most patients with IVC thrombus

develop some sequelae of PTS (25). The cornerstone of treatment centers on systemic anticoagulation therapy to reduce thrombus propagation and minimize the risk of pulmonary embolization while alleviating lower extremity symptoms. The open vein hypothesis of DVT (26) would seem to translate to patients with IVC thrombosis as well, in that long term outcomes would improve with more aggressive endovascular treatment involving thrombolysis or thrombectomy.

Patients with IVC thrombosis have a large thrombus burden and thus are at significant risk of thrombosis-related morbidity and mortality. In addition, they often have a correctable risk factor for rethrombosis. Simultaneously addressing both these factors, results in rapid symptom relief with improved patency and lower incidence of PTS (27).

In chronic IVC thrombus, the removal of the occlusion allows for less impeded venous flow, thereby decreasing venous hypertension and improving associated symptoms.

Acute thrombosis

Endovascular techniques in treating acute IVC thrombus are similar to those described in treating acute iliofemoral DVT, though significant differences exist due to the larger clot burden in the cava. Caval thrombi carry a greater risk of lethal pulmonary embolism and can also involve the renal veins. Although placement of IVC filter for endovascular treatment of iliofemoral vein thrombosis may not be indicated (28), consideration for placing a filter should be made when treating IVC thrombus given the more extensive and possibly free floating clot (*Figure 3*). In addition, catheter directed lytic therapies in the IVC may require longer lysis times because of the large thrombus burden and mechanical thrombectomy devices would need to have a larger radial reach to treat pockets of thrombus in the larger caliber vessel.

Catheter directed thrombolysis (CDT) delivers thrombolytics directly into the thrombus, thereby providing a safer alternative to systemic thrombolysis. A multiple sidehole infusion catheter is positioned within the thrombus and thrombolytic agent is infused directly into the thrombus. This is routinely performed from a femoral or popliteal vein approach, depending on the extent of the clot. Venography can be repeated at 12–24 hours, and if there is significant residual clot, CDT may be continued. However, lengthy thrombolysis increases the rate of bleeding complications (16).

US assisted thrombolysis (EKOS) (BTG, UK) entails

technology in which high frequency US disrupts the fibrin matrix of the thrombus, thereby exposing more binding sites for the thrombolytics (29,30). Compared with CDT, EKOS displays similar efficacy and potentially shorter treatment duration (31) which may be advantageous, specifically in the setting of large thrombus burden (32).

In light of the bleeding risks associated with prolonged thrombolytic infusions to treat extensive thrombus, percutaneous mechanical thrombectomy (PMT) devices can be used as an adjunct or alternative. The AngioJet rheolytic thrombectomy device (Boston Scientific, Marlborough, MA, USA) utilizes high-pressure pulsatile saline jets to create localized low-pressure zones for thrombus maceration and aspiration. Effectiveness of the device may be limited in large spaces such as the vena cava, in that the diameter of the action of thrombectomy does not reach the entire diameter of the cava, and will often create a channel through the clot. A spiral technique can be utilized in which the AngioJet is placed within a curved sheath to direct it towards pockets of thrombi as the catheter is withdrawn. With large IVC clots, care must be taken in the amount of time thrombectomy is performed with AngioJet, as the rheolytic mechanism causes hemolysis. This may precipitate acute renal failure (33) in patients at risk, as well as a drop in hemoglobin levels. The device also allows for a power pulse spray feature in which thrombolytics can be infused with a high pressure spray directly with deep penetration of the lytic agent into the thrombus. After allowing the thrombus to bathe in thrombolytics, the catheter can then be switched to the thrombectomy setting to reduce residual clot. Combining power-pulse with thrombectomy can reduce the amount of hemolysis (34). A recently introduced more powerful 8 F AngioJet catheter named the ZelanteDVT is likely to be more effective in large spaces such as the IVC, although experience is currently limited.

The AngioVac system (AngioDynamics, Latham, New York, USA) consists of a 22 F cannula with an expandable tip that opens to 48 F and creates a suction vortex allowing en-bloc removal of a large amount of thrombus while maintaining flow during extracorporeal circulation. By using the AngioVac to aspirate caval thrombus, the use of thrombolytics can be avoided in patients who may be at risk of bleeding while also avoiding the hemolysis associated with rheolytic devices. The suction vortex can pull in the walls of the vein to be able to reach the clot in a large vessel such as the IVC (35). Limitations include the large size and rigidity of the cannula precluding passage of the device into leg veins, thereby necessitating other techniques or devices

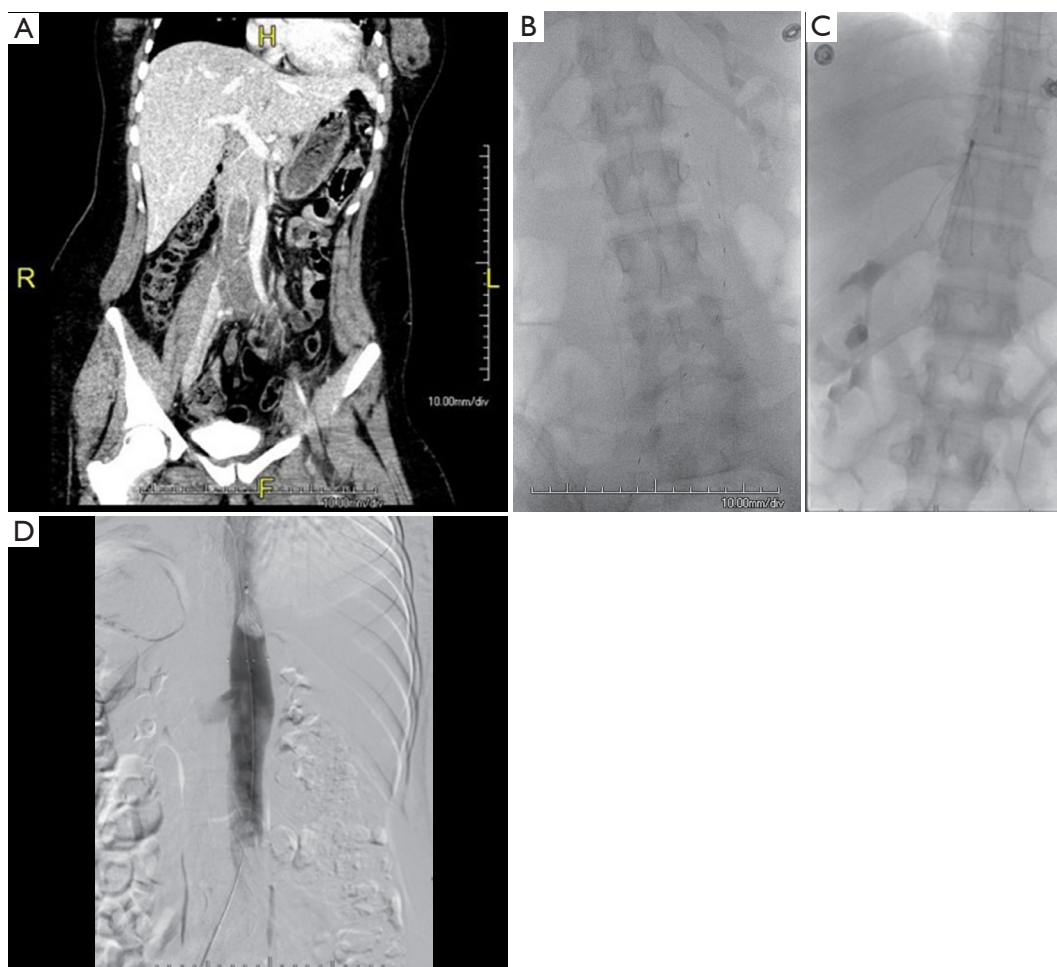


Figure 3 Seventeen years old female who recently started oral contraceptive pills with 3 days history of left lower extremity pain and swelling presents with acute shortness of breath. (A) CT demonstrates large thrombus extending from the left iliac vein to the inferior vena cava (IVC) up to the level of the renal veins. CT images of the chest (not shown) demonstrated pulmonary embolus (PE); (B) catheter directed thrombolysis (CDT) was performed with EKOS lysis catheter (patient is in prone position); (C) a retrievable filter placed in the suprarenal IVC in lieu of large thrombus burden; (D) patient was found to have iliac vein compression which was treated with angioplasty and stent placement. Venogram demonstrated embolized thrombus in the filter cone. After 2 months of anticoagulation therapy, venogram was performed confirming resolution of thrombus allowing the filter to be safely removed (not shown).

to treat the inflow. In addition, these procedures must be performed with perfusionists as well as under general anesthesia.

Other thrombectomy devices successfully used to treat caval thrombus utilize rotating sinusoidal wires to macerate the clot (36,37). These devices can be used in conjunction with thrombolytic agents for better dispersal throughout the clot. The CleanerXT/Cleaner15 (Argon Medical Devices, Athens, TX, USA) is comprised of a single unit rotating S-wire and the drive motor with a side port which allows

infusion of thrombolytics or contrast media. While effective at clearing thrombus, this device potentially can cause emboli and insertion of IVC filter should be considered when using this device to treat DVT (36). The Trellis device (Medtronic, Dublin, Ireland) also utilizes rotating sinusoidal wires but has proximal and distal occluding balloons which allow the infusion of thrombolytic agents to the isolated thrombosed vascular segment and protect clot from embolizing. However, in the large caliber IVC, the balloons may not always be capable of being occlusive. The

device is currently off the market due to a class I FDA recall as of February 2015, due to mislabeling of balloon inflation ports. Both of these devices are also limited for treating clot within a thrombosed filter.

Chronic thrombosis

Acute soft thrombi begin to undergo fibrotic transformation within 2 weeks of clot formation. While catheter based thrombectomy can be very effective in the treatment of soft acute thrombus, the chronic fibrotic component remains more difficult to treat. Chronic DVT can cause luminal stenosis, stasis and predispose to recurrent DVT. The current treatment of choice for chronic, symptomatic ilio caval thrombosis is endovascular angioplasty combined with stenting.

Surgical reconstruction of central venous occlusion is associated with significant morbidity and marginal results. Gloviczki *et al.* reported limited patency of IVC reconstructions following surgical reconstruction in 28 patients with SVC or ilio caval obstruction (38). Long-term patency of angioplasty alone in the setting of chronic occlusion is limited due to venous recoil, low flow, and thrombogenicity of the lumen (39). Stents have the potential to improve patency in large veins by preventing recoil and allowing sufficient flow to maintain patency. The literature supports stenting and angioplasty in the IVC with improvement of symptoms and good patency (40). When chronic IVC obstruction cannot be recanalized via endovascular means, stenting to collateral drainage, possibly to the ascending lumbar vein, has been advocated with improvement in symptoms and good patency.

Choice devices for stenting the cava currently include WallStent (Boston Scientific Marlborough, MA, USA), and Gianturco-Rosch tracheobronchial Z stents (Cook, Bloomington, IN, USA) (41). Both have adequate radial force and are available in appropriate sizes. Z stents have the advantage of having large interstices that can be deployed across veins without compromising inflow. Z stents have a greater radial force than Wallstents and do not foreshorten upon deployment, making precise placement easier. The disadvantages of Z stents include large caliber sheaths, which are necessary for delivery, as well as the stabilizing barbs which although decrease the risk of migration, carry a theoretical predisposition to perforation.

Migration of the stent into the right heart or pulmonary arteries is one of the most dreaded complications. Thus, stenting the suprarenal IVC must be done cautiously,

as there is a higher risk for stent migration in this region (42). Wallstents in particular may undergo unpredictable foreshortening upon expansion and may not adequately fix to the caval wall (43). Palmaz stents have been utilized to treat short segmental occlusions (44). However, they are not an ideal choice for lesions at the IVC/right atrial junction given reports of stent migration at this location (45). Deploying self expanding IVC stents from a right internal jugular vein approach, especially when the vessel is structured, may be advantageous as it allows the stent to first fix to the caudal part of the cava below the stricture. If however, it fixes to the cranial portion first, the stent may “watermelon seed” and migrate. In addition, if the stent jumps forward upon deployment, it will extend caudally, as opposed to towards the heart.

The data regarding placing stent grafts in the IVC is limited. Due to the nature of covered stents, the orifice of collateral veins which may have developed to compensate, may be covered, possibly exacerbating symptoms. In addition, if the grafts are oversized, any redundancy in the material which may not be fully expanded can serve as a nidus for thrombus in a low pressure venous system.

A specific technical problem is encountered in the setting of an occluded IVC filter. The obstruction needs to be relieved in order to assure adequate outflow. Angioplasty and stenting through the filter to restore flow has been shown to be safe with good patency both in patients with acute thrombosis after thrombolysis (46) and in patients with chronic IVC occlusion with indwelling IVC filter (47) (*Figure 4*).

Tumor thrombus

Tumors of the IVC are rare, with surgical resection generally the only alternative for cure or palliation of symptoms (48). Malignancies can be primary, such as leiomyosarcomas, or secondary, such as retroperitoneal soft tissue hepatic tumors or pancreaticoduodenal cancers. Other malignancies, such as renal cell carcinoma, pheochromocytoma, adrenocortical carcinoma, uterine sarcomas and germ cell tumors, also cause tumor thrombi.

The role for endovascular treatment is limited in certain cases, it may be difficult to discern between bland and tumor thrombus and the interventionalist may be consulted to evaluate for treatment. Demonstrating enhancement of thrombus on CT or MRI can help make the diagnosis of tumor thrombus. In addition, if histologic tissue diagnosis is helpful for treatment planning, a core needle biopsy can be obtained intravenously using a transjugular liver

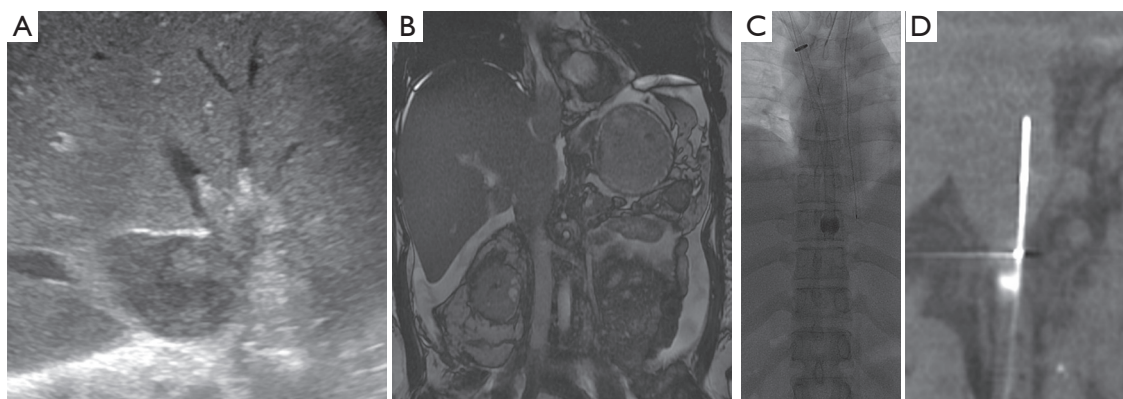


Figure 4 Forty years old female presents with increasing abdominal ascites. (A) Abdominal ultrasound (US) image demonstrates expansile inferior vena cava (IVC) thrombus extending to the hepatic veins; (B) MRI demonstrates an expanded IVC with thrombus and abdominal ascites in the setting of hepatic vein outflow obstruction (Budd-Chiari). Contrast was withheld due to patient's acute renal azotemia; (C) thrombectomy for presumed acute thrombus was attempted with AngioVac device which was unable to aspirate any thrombus; (D) intravenous biopsy of the mass was obtained with transjugular liver biopsy set. Cone beam CT images acquired during biopsy confirm needle within the mass. Pathology came back as leiomyosarcoma.

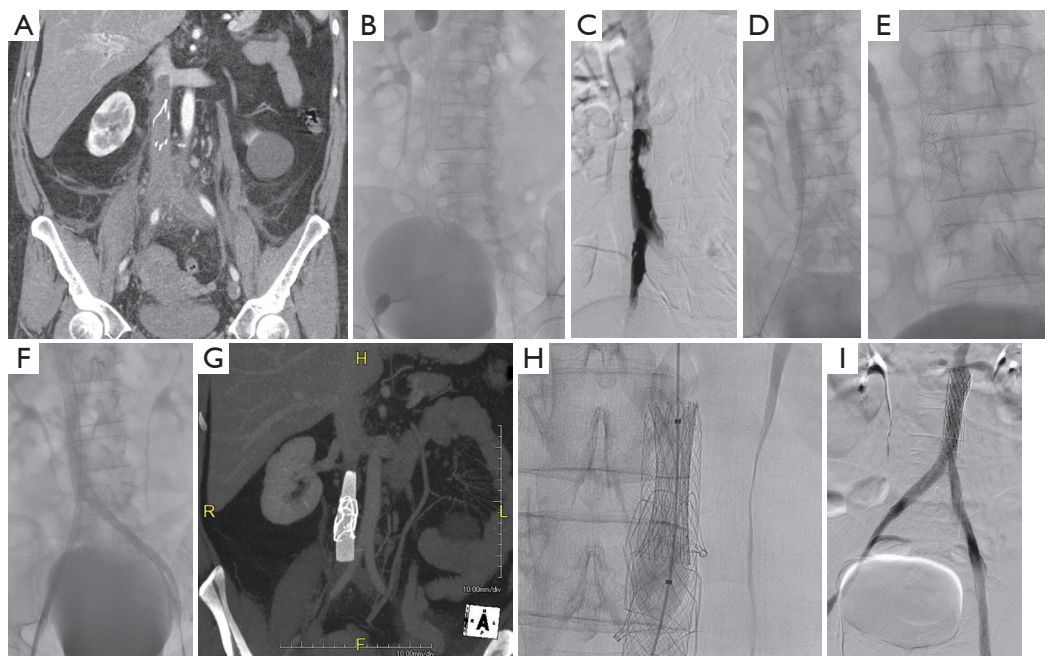


Figure 5 Fifty six years old woman with permanent inferior vena cava (IVC) filter placed 3 years ago for chronic pulmonary embolus (PE) presents with acute lower limb swelling and back pain. (A) CT demonstrates extensive ilio caval thrombus that extends cranial to the filter up to the renal veins; (B) thrombolysis of IVC clot was performed with Trellis device; (C) chronic partially obstructing thrombus remained in filter despite trellis, catheter directed thrombolysis, and AngioJet attempts at removal; (D,E) exclusion of IVC filter was achieved with balloon maceration followed by placement of a large caliber Wallstent; (F) venogram following stent placement demonstrates unobstructed antegrade IVC flow; (G) patient returns 4 months later with caval rethrombosis secondary to stent collapse at the cranial end of the Wallstent; (H) following thrombolysis, the collapsed stent was buttressed with balloon-expandable Palmaz stents to provide hoop strength; (I) venogram following restenting demonstrated restoration of central venous flow. On 2-year follow-up the IVC remains patent and the patient is asymptomatic.

biopsy system (*Figure 5*). In instances where a mobile tumor thrombus protrudes into the right atrium and the risk for embolization or tricuspid valvular damage exists, AngioVac can be used for removal (49,50).

Conclusions

IVC thrombosis can be associated with significant morbidity if left untreated. As no standardized diagnostic guidelines exist, clinicians must maintain a high index of suspicion across a wide range of different clinical presentations to expeditiously and effectively treat this under-recognized condition. US, CECT, MRV, and invasive venography are all modalities at our disposal for further workup and characterization. Endovascular techniques can rapidly and safely remove IVC thrombi, thereby treating possible underlying venous occlusions, alleviating symptoms, and reducing the likelihood of complications with chronic thrombus such as PTS.

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None.

Footnote

Conflicts of Interest: Y Golowa involved in a clinical trial with the AngioVac (Angiodynamics). The other authors have no conflicts of interest to declare.

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