Totally Implantable Venous Access Devices
A Review of Complications and Management Strategies

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Objective: Totally implantable venous access devices (portacaths, or "ports"), are widely used for intermittent central venous access especially for cancer patients. Although ports have a superior safety margin compared with other long-term venous access devices, there are a number of complications associated with their use.

Methods: This is a narrative review. We searched PubMed and Google Scholar for articles about complications related to the use of portacaths. "Similar articles" feature of PubMed and reference list of the existing literature were also reviewed for additional relevant studies.

Results: In this review, we provide the latest evidence regarding the most common ones of these adverse events and how to diagnose and treat them. Immediate complications including pneumothorax, hemothorax, arterial puncture, and air embolism as well as late complications such as port infection, malfunction, and thrombosis are covered in detail.

Conclusions: Physicians should be familiar with port complications and their diagnosis and management.

Key Words: totally implantable venous access device, complications, catheter infection, deep venous thrombosis, portacath

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Three decades after their introduction,[1] totally implantable venous access devices (also known as portacaths or "ports") are widely used for long-term access to central venous circulation, especially for cancer chemotherapy.[2–4] Portacaths consist of a reservoir that is implanted subcutaneously via a small incision and a catheter which connects the reservoir to the central venous circulation through a subcutaneous tunnel. The reservoir itself is divided into a chamber and a self-sealing septum which is faced toward the body surface and can be accessed percutaneously by a small noncoring (Huber) needle.

Although ports are considered as the safest way of long-term intermittent central venous access, adverse events can occur. From a pathophysiologic standpoint, early complications occur due to injury to adjacent structures during catheter insertion and reservoir implantation, whereas late complications arise as a result of long-term catheter indwelling and reservoir disintegration due to trauma or improper use (Table 1). It is estimated that 1.68 million new cases of cancer will be diagnosed in 2016 in the United States,[5] many of whom will require IV chemotherapy administration. Therefore, physicians should be able to recognize and manage their complications. This article reviews port complications with a focus on their diagnosis and treatment.

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COMPLICATIONS RELATED TO PORT INSERTION

Technical Considerations

Ports are either single lumen or double lumen. Double lumen ports have 2 parallel catheters and reservoirs that are completely separate, which makes it possible to infuse incompatible solutions at the same time. However, double lumen catheters are less commonly used and have been associated with a slight increase in the risk of infection.[6,7]

There are 2 approaches for placing a port based on how the central vein is accessed.[8] In the surgical cut-down approach either the cephalic vein or, less commonly, the external jugular[9] vein are exposed surgically and the catheter is advanced until the tip is at the junction of the right atrium and superior vena cava (SVC). In the percutaneous approach, the catheter is inserted directly into a central vein using the Seldinger technique. The usual sites for this method are the subclavian vein and the internal jugular vein,[10,11] and the reservoir is placed below the ipsilateral clavicle through an incision.[8,12] Ultrasonography (US) can provide real-time visual guidance for percutaneous catheter insertion and is especially useful for jugular vein catheterization.[13]

Subclavian and internal jugular approaches are both safe and feasible in experienced hands.[14–18] However, subclavian vein cannulation is generally performed more often since ports are typically implanted below the clavicle during the percutaneous approach, and the catheter has to be tunneled over the clavicle to reach the internal jugular vein and at a more acute angle.

Pneumothorax

Pneumothorax is caused by an unintended contact with the lung pleura during insertion of the catheter, permitting air to escape the lung tissue into the pleural cavity.[19,20] It is a cause of morbidity, prolonged hospital stay, and even mortality in some patients. Incidence varies among different studies with most recent studies reporting a rate between 0.5% and 2%.[8,12,21,22]

Percutaneous cannulation of subclavian vein based on anatomic landmarks is widely deemed as an important risk factor for pneumothorax due to anatomic proximity.[8,12,23–25] Therefore, some authors have recommended a cut-down approach as the initial technique of choice to minimize the risk of pneumothorax.[8,12,25] US has been shown to decrease the

TABLE 1. Portacath-related Complications

Early Complications		Late Complications	
Catheter Insertion	**Reservoir Implantation**	**Catheter Related**	**Reservoir Related**
Pneumothorax	Wound dehiscence	Catheter occlusion	Reservoir fracture
Hemothorax	Hematoma	Catheter misplacement	Reservoir rotation
Arterial puncture	Seroma	U-DVT	Drug extravasation
Hematoma	Wound infection	P-BSI	Reservoir membrane disruption
		VTE	
		Pinch-off syndrome	
		Catheter embolization	

P-BSI indicates port-related bloodstream infection; U-DVT, upper extremity deep vein thrombosis; VTE, venous thromboembolism.

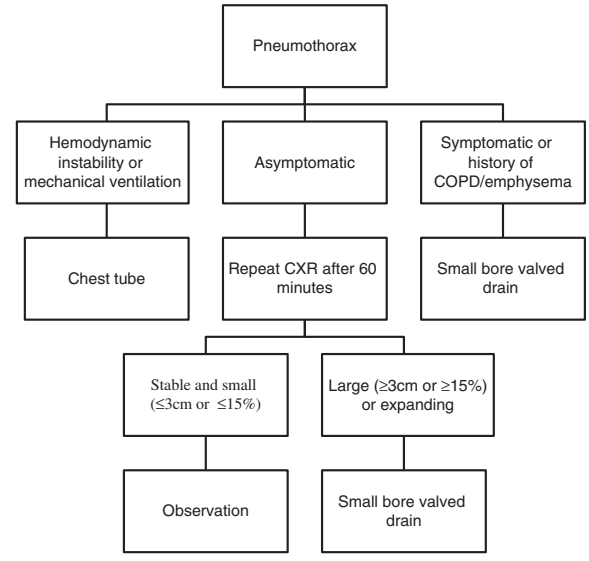

FIGURE 2. Management of pneumothorax.[20] CXR indicates chest x-ray. COPD indicates chronic obstructive pulmonary disease.

risk of failures and is believed to decrease the risk of pneumothorax associated with internal jugular vein cannulation.[13]

Diagnosis

Postoperative chest radiography (CXR) has been traditionally seen as a necessary complement to any central venous access to screen for complications and is the current standard of care. However, some recent studies have questioned their value after seemingly uncomplicated central venous catheterizations, especially if intraoperative fluoroscopy was used to confirm the position of the catheter tip.[24,26,27] Also, pneumothoraces may still develop days after the procedure and go undetected by routine postoperative CXR[28,29] (Fig. 1).

Treatment

Unstable patients should be treated with large bore standard chest tubes.[30] Patients with radiologic evidence of pneumothorax, who are otherwise asymptomatic, could be discharged if the pneumothorax is small in size (< 3 cm from the apex to cupola or <15%), and the size has not increased on a subsequent CXR taken within a few hours of the initial test.[20,30,31] However, patients with a prior diagnosis of emphysema and those who are expected to undergo mechanical ventilation for any reasons should be treated more aggressively regardless of the size of the pneumothorax. Symptomatic patients and patients with pneumothoraces ≥ 3 cm or $\geq 15\%$ should be treated with a small bore (≤ 16 Fr) chest tube (Fig. 2).[20,32,33]

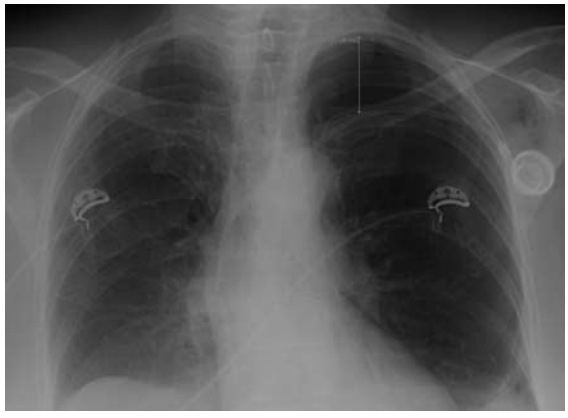

FIGURE 1. Chest x-ray (PA) of a patient with pneumothorax following port insertion.

Hemothorax

Hemothorax occurs rarely after inadvertent puncture of intrathoracic arteries or laceration of veins during percutaneous central venous catheterization.[19,34,35] Each hemithorax could easily accommodate 2 to 3 L of blood, enough to cause hypovolemic shock if the bleeding is not controlled. Right internal jugular cannulation has been associated with subclavian artery puncture, as well as brachiocephalic vein laceration.[34,35] Although the anatomy of the internal jugular vein on the right side is more favorable for advancement of the catheter into the SVC, there is concern that a hemothorax is more probable on the right due to anatomic proximity.[35] Subclavian artery injury can also occur during subclavian vein cannulation.[36]

Diagnosis and Treatment

Hemothorax should be suspected when sudden onset dyspnea and hypotension are encountered during or soon after the operation. US can detect as little as 50 mL of blood in pleural cavities, whereas a CXR, especially when taken supine, could easily miss 300 mL or more of blood.[37] Treatment starts with chest tube placement and volume resuscitation. However, if the initial volume of drained blood exceeds 1500 mL or if the continued bleeding is over 200 to 300 mL in the first 2 to 3 hours, surgical exploration is indicated.[34,35]An alternative management strategy via arterial embolization by interventional radiology has also been described.[38]

Arterial Puncture

The internal carotid artery is punctured in $\sim 3\%$ of internal jugular vein cannulations, whereas subclavian artery

injury is less common and complicates around 0.5% of subclavian vein catheterizations.[39] Arterial punctures are very unlikely during a cut-down procedure. Although subclavian artery injury is less probable compared with the internal carotid artery, it can be more problematic since it is situated deep to the clavicle and is not easily compressible. Although bleeding can be self-limited with no major sequelae,[22] complications such as massive hematoma,[40] airway compromise,[41] pseudoaneurysm with possible pressure on the brachial plexus,[42] and arteriovenous fistula[43] may occur.

Prevention, Diagnosis, and Treatment

The key to avoiding serious complications of arterial puncture includes attention to anatomic landmarks, high index of suspicion for arterial puncture, and rapid pressure. US-guided cannulation is encouraged for the internal jugular vein,[13] particularly in obese patients.[44] However, even with US guidance, inadvertent arterial puncture is still possible.[19] Although an arterial needle stick might respond to compression and be self-limited, repeated injury or insertion of a larger-bore introducer-dilator will certainly require vascular repair to avoid major complication. Direct manual pressure should be applied if arterial blood is withdrawn to minimize the risk of bleeding. Acute management is mostly supportive with tracheal intubation (for expanding hematoma) and fluid resuscitation as the mainstay of treatment.

Air Embolism

Air embolism is an exceedingly rare but devastating complication of port insertion. Intrathoracic pressure falls by a few mm Hg during normal inspiration, which creates suction on the central veins in the thorax and helps with venous return. Since central veins, especially the subclavian veins are supported by the surrounding connective tissue and do not collapse easily, any decrease in the intravascular volume is rapidly translated into decreased intravascular pressure. An air embolism occurs when central venous pressure falls below the atmospheric pressure and a negative pressure gradient is created. The amount of air required to cause a circulatory collapse is estimated to be 3 to 5 mL/kg.[45] The time needed for such a volume to be entrained across a 14-G needle is 2 to 3 seconds if as little as a -3.5 mm Hg pressure gradient is present.[46]

Diagnosis

The resulting symptoms are mostly a function of the volume of the entrained air, and range from decreased oxygen saturation, sudden onset dyspnea and apprehension, to total circulatory collapse and death. Paradoxical emboli to the brain may also occur as a result of a patent foramen oval and increased right heart pressure with severe neurologic consequences.[47–49] EKG may show signs of right heart strain such as peaked P-waves and ST segment changes.[45] If the air current is turbulent enough a sound might be noticed; however, many cases present without such warning. Transesophageal echocardiography is the most sensitive diagnostic modality and should be considered in equivocal cases.[45]

Prevention

Prevention is of utmost importance and includes methods to maintain a positive pressure gradient, such as putting the patient in Trendelenburg position and administering preoperative fluid load.[45] Nitrous oxide should be avoided if sedation is necessary as the gas causes significant preload reduction. Also, since more peripheral veins have higher pressures and are collapsible, cut-down techniques have a much lower risk for air embolism. Additional precautions that may be helpful in preventing an air embolism include: the Valsalva maneuver, avoiding having the needle or sheath open to air, and using sheaths with 1-way valves.

Management

Management should be focused on immediate recognition and termination of air entrainment as the most effective intervention.[45,47,50] Supplemental oxygen should be given to prevent pulmonary vascular collapse and facilitate reabsorption of the entrapped air. Patients should be repositioned to Trendelenburg with left lateral head down tilt to keep the air bubble away from the right ventricular outflow.[45–49,51] Aspiration could be tried if the catheter is in the right heart; however, success rate is low and human studies are lacking.[10,50,51] Cardiopulmonary support with inotropes may be necessary to maintain perfusion. In the event of a cardiac arrest, cardiopulmonary resuscitation is encouraged to dislodge the air lock from the right ventricular outflow tract. Hyperbaric oxygen supplementation may also be considered especially for cerebral emboli.[45,47]

Arrhythmias

Arrhythmias occur as a result of entry of the guidewire or the catheter into the heart and mechanical irritation of the endocardium. Although most cases are benign atrial arrhythmias that are readily reversible by retraction of the catheter or the guidewire, instances of serious and life-threatening dysrhythmias such as complete heart block and asystole have been reported.[52–54] Ideally, the port catheter and guidewire should not enter the right atrium; however, overadvancing the catheter or the guidewire beyond the RA-SVC junction happens commonly because of the anatomic variations and minor measurement errors. Generally, the guidewire should not be advanced >18 cm, especially on the right side and the catheter tip position should be 1 to 3 cm away from the RA-SVC junction to accommodate for the movement of catheter with the patient's change of position.[53,55] Real-time electrocardiography (ECG) monitoring should be used while advancing the guidewire or the catheter to detect arrhythmias as soon as they arise and pull back the catheter to prevent more serious ventricular arrhythmias. Especial attention should be paid to patients with preexisting cardiac rhythm abnormalities such as bundle branch blocks and those with arrhythmogenic preexisting conditions such as uremia and electrolyte abnormalities.[52,56] Moreover, ports should only be inserted at facilities, where cardioversion and cardiopulmonary resuscitation are readily deployable in an event of serious cardiac arrhythmia.

COMPLICATIONS RELATED TO RESERVOIR INSERTION AND INDWELLING

Wound Dehiscence

Wound dehiscence can occur after port implantation because of technical error or secondary to impaired wound healing due to immunocompromise from cancer, malnutrition, or ongoing chemotherapy. Reservoirs should not be implanted under irradiated skin, previous mastectomy incisions or thin flaps, and the incision should be tension free.[57] An important recently observed nontechnical risk factor for wound dehiscence is bevacizumab therapy.[58,59] Bevacizumab is a humanized monoclonal antibody that inhibits angiogenesis by inhibiting vascular endothelial growth factor. The risk of nonhealing is greatest if the time interval between port insertion and bevacizumab administration is <14 days. Wound

dehiscence is usually managed by port extraction and allowing for wound closure by secondary intention.[58,59] It is advised to implant the port more deeply in patients with thin skin or those who are expected to become cachectic after chemotherapy to prevent late-onset skin necrosis and externalization of the reservoir.[57]

Local Extravasation

Extravasation of chemotherapeutic agents from the ports has been reported in 0.1% to 6% of patients.[57,60] Extravasation could occur if the infusate escapes from the port into the surrounding tissues either because of catheter fracture or disconnection, or disintegration of the reservoir septum. Port septa should withstand hundreds of punctures with proper use of noncoring (Huber) needles. However, if alternative needles are used or left in place for extended periods of time, the septum might deteriorate and allow leaks.[60,61]

Diagnosis

Symptoms are largely related to the toxicity and volume of the leaked medication; while irritant drugs cause mostly pain and inflammation, vesicant agents can cause severe necrosis, and ulceration.[57,62–64] Common early symptoms are swelling, redness, pain and burning, as well as slowing of infusion rate and difficulty aspirating blood from the port.[62,64,65] Extravasation injury from anthracyclines is slowly progressive over weeks and may be missed initially.[64]

Prevention

Ports should be checked routinely before each injection for patency and integrity. If blood cannot be aspirated even after alteration of the patient's position, the port should not be used. Caregivers should also flush the port with saline using a 10 mL syringe before injection, checking for pain. Contrast studies should be done in suspected cases of extravasation (Fig. 3).[60] Furthermore, ports should not be placed under bra lines or where a car seatbelt is expected to pass.[66]

Management

Management begins with rapid recognition and termination of any further infusion. The needle should be removed only after liberal aspiration of the infusate. Heat should be applied to increase the local circulation, except for anthracyclines where cooling of the skin is thought to improve the outcome.[65] There are a number of antidotes available for certain vesicants (Table 2). Hyaluronidase decreases tissue concentration of extravasated vinca alkaloids by breaking down hyaluronic acid, a major extracellular matrix molecule.[65] Intravenous dexrazosane is the antidote of choice for anthracycline extravasation and should be injected at a site other than the site of extravasation.[68] Topical 99% dimethyl sulfoxide is a solvent with antioxidant properties and is used for treating cisplatin, mitomycin C, and anthracycline extravasations.[67] Local or systemic corticosteroids are not recommended in vesicant extravasation.[67] Surgical debridement and reconstruction with full thickness flaps should be reserved for cases with extensive necrosis despite the use of antidotes.

COMPLICATION RELATED TO THE INDWELLING CATHETER

Port Malfunction

The definition of port malfunction varies considerably across different studies as does its incidence, which ranges from 0% to 47%.[69] Nonetheless, port malfunction usually refers to difficulty using the device for blood aspiration or drug injection or both.[69,70] Thrombotic occlusion is considered as the most common underlying mechanism for port malfunction. Fibrin sheaths are common and wrap the catheter tip as soon as the first 24 hours after catheter insertion. Fibrin sheaths are usually asymptomatic; however, they can create a 1-way valve structure where they collapse with negative pressure preventing aspiration, while permitting injection. Intraluminal clots, central venous mural thrombi and deep venous thromboses (DVTs) are the other thrombotic complications. For the purpose of this review, intraluminal thrombotic occlusions and DVTs are discussed separately; however, DVTs could also present as catheter occlusion. Catheter kinking, secondary malposition, pinch-off syndrome and fracture of the catheter can mechanically obstruct the port. Moreover, lipids from total parenteral nutrition (TPN) solutions and some drugs or incompatible drug combinations can precipitate inside the catheter lumen and cause obstruction.[71–73]

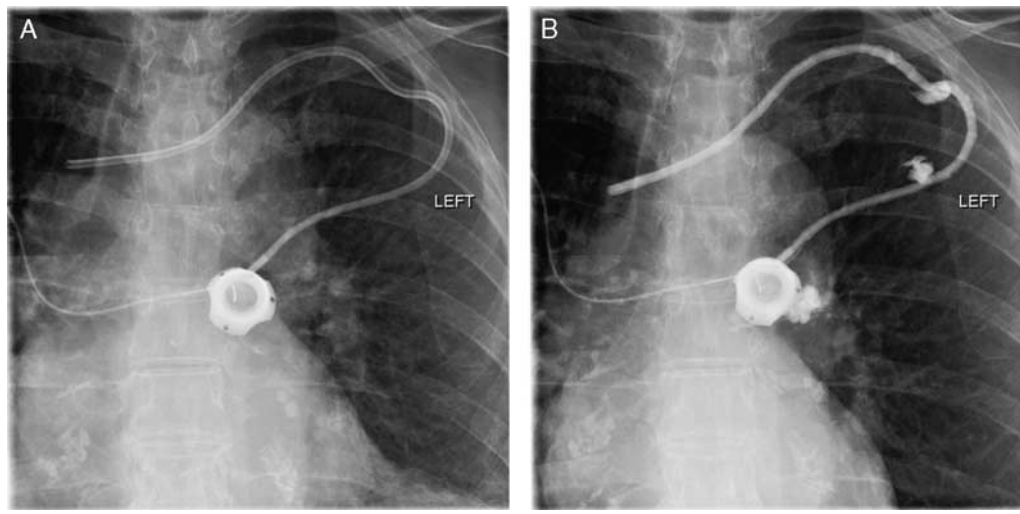

FIGURE 3. Extravasation from a port; before (A) and after (B) contrast injection. Case courtesy of Dr Dayu Gai (Radiopaedia.org, rID: 43440) (http://radiopaedia.org/cases/extravasation-of-contrast-from-portocath).

TABLE 2. Vesicant Drugs and Specific Antidotes[67]

Vesicants	Antidotes
Anthracyclines(nonliposomal preparations) Daunorubicin Doxorubicin Epirubicin Idarubicin	Dexrazoxane if not available within 6 h give DMSO; apply ice
Mechlorethamine; cisplatin (large volumes)	Sodium thiosulfate
Mitomycin	DMSO
Vinca alkaloids Vinblastine Vincristine Vindesine Vinorelbine	Hyaluronidase, local heat

DMSO indicates dimethyl sulfoxide.

Prevention

Ports should be flushed monthly and after each use, to prevent fibrin or drug particle accumulation and to create a fluid lock. Heparin has been the agent of choice for the lock solution; however, recent studies have shown that normal saline is equally effective in preventing port malfunction.[74,75] Although the dose of heparin needed to lock a port is around 500 to 1000 IU and does not typically increase the bleeding risk, heparin-induced thrombocytopenia may still occur through immune mechanisms.[76,77] Furthermore, there is insufficient data to support prophylactic use of fibrinolytic agents such as urokinase for prevention of catheter-related thrombosis.[18,78]

Diagnosis and Management

Successful management of port malfunction depends on the accurate diagnosis of the underlying mechanism (Fig. 4). Mechanical obstruction of the catheter should be ruled out first by imaging studies such as a CXR, especially if the obstruction is positional. Small doses of contrast agents could be injected for improved visualization. Some cases of mechanical obstruction are amenable to radiologic interventions, which should be considered before port removal and reimplantation.[79] Several mechanisms of occlusion and their specific management are discussed below.

Pinch-off Syndrome. Pinch-off syndrome is an uncommon mechanical complication of infraclavicular subclavian port placement, and is caused by catheter impingement between the first rib and the clavicle (Fig. 5).[80] If the impingement is not relieved, the catheter can break and embolize to the right heart or pulmonary arteries. The hallmark of pinch-off syndrome is a positional occlusion of the port where the system regains patency with abduction of the ipsilateral arm.[81] Therefore, a CXR should be taken with the patient's arms by their sides and not abducted as is the case with a routine upright or supine CXR.[82,83] If pinch-off syndrome is diagnosed, the port should be removed and implanted at another site.

Drug Precipitation. Treatment of intraluminal drug precipitation depends on the suspected agent. For TPN solutions, 70% ethanol have been used to dissolve the fat,[78] whereas hydrochloric acid (0.1 mol/L) has been used for clearing calcium phosphate crystals or acidic drug particles.[72,84] Sodium hydroxide (0.1 mol/L) and sodium bicarbonate (1 mol/L) are used to salvage catheters infused with alkaline drugs.[85,86]

Intraluminal Catheter Thrombosis. Intraluminal catheter thrombosis is usually treated empirically with thrombolytic agents if mechanical obstruction is ruled out, since the intervention is both effective and safe. Urokinase, alteplase, reteplase, and tenecteplase are tissue plasminogen activator analogs and act by plasmin activation, whereas alfimeprase is a newer generation agent and directly lyses the clot by targeting α-chain of fibrin molecules.[72,78,87–89] Reteplase is an alteplase analog, but it lacks several domains of alteplase and therefore has a longer half-life and penetrates deeper into the clot[78]; however, primary studies in cancer patients with ports are lacking.[72,78,90,91] Preliminary studies suggest that alfimeprase has a more rapid onset of action and is readily deactivated by plasma α-2 macroglobulin, which theoretically minimizes the risk of systemic adverse events.[88,92]

CATHETER MIGRATION AND EMBOLIZATION

Catheters can be dissected by mechanical stress as a result of pinch-off syndrome or external force such as rapid deceleration against a seatbelt, friction against tight clothing, forceful flushing with small syringes (< 10 mL) or with no identifiable reason.[66,93,94] Patients whose ports are in use usually present with port malfunction or symptoms of extravasation before complete dissection occur; however, some only present after the catheter is transected and embolized most commonly with palpitations and arrhythmias.[93] Diagnosis is readily confirmed with posteroanterior and lateral CXRs. Ports should be inserted deep enough especially if patients are expected to have significant weight loss. Furthermore, catheter should not be placed over bony prominences and should have as straight a course as technically possible. The port should be removed and the catheter fragments retrieved by interventional radiology usually through the femoral vein to prevent further complications.[95–97]

DVT

Patients with ports often have multiple risk factors for development of DVT, most notably cancer-related hypercoagulability and indwelling catheters.[98] Upper extremity DVT (U-DVT) is seen in ~5% of the implanted ports and could be complicated by venous thromboembolism in around 5% of untreated cases; however, the risk of venous thromboembolism is lower in U-DVT than lower extremity DVT.[98–100] Other complications include postthrombosis syndrome and chronic venous insufficiency.[72]

Diagnosis

Unilateral pitting edema, pain, and varicosity of the superficial veins of upper limbs, head or neck are strong indicators of an U-DVT in a patient with a port; nevertheless, these symptoms are nonspecific and many cases remain asymptomatic.[101,102] Symptoms are more likely if the thrombus is proximal to the axillary vein.[102] Ultrasound (compression or color Doppler) is the main modality used for U-DVT diagnosis; however, it is neither specific nor sensitive enough to guide management when used alone.[100,103–106] If the initial US establishes the diagnosis of DVT, no further testing would be necessary. Conversely, if the US is normal or inconclusive, the next steps are less clear (Fig. 6). Although some support serial US for patients with inconclusive tests,[100] others suggest magnetic resonance venography, CT-angiography, or conventional venography.[105,107] As the main indication for port implantation is cancer chemotherapy, almost every patient with the device and signs of U-DVT would have

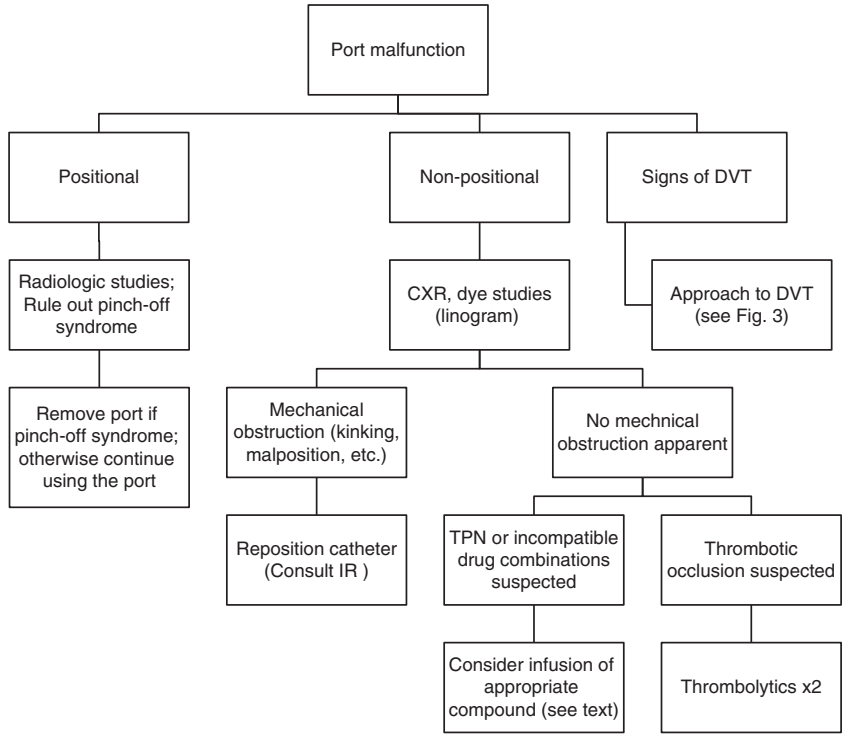

FIGURE 4. Management of port malfunction.[72] CXR indicates chest x-ray; DVT, deep venous thrombosis; IR, interventional radiology; TPN, total parenteral nutrition.

a high pretest probability for U-DVT. Therefore, negative results should be confirmed by other modalities such as serum D-dimer before U-DVT is ruled out.[105]

Prevention

Prophylaxis for U-DVT in cancer patients with indwelling catheters remains controversial. A recent systematic review and meta-analysis reported a reduction in symptomatic and asymptomatic DVTs with heparin and warfarin (vitamin K antagonist), respectively.[108] However, many of the primary studies that were used for the analysis were rated by the authors to be of low quality.[108,109] Moreover, most of the reports that showed a large effect size were from earlier studies with high event rates. Recent randomized clinical trials (RCT) have reported the risk of U-DVT in general oncologic population with indwelling catheters to be ~4% to 6%,[108,110,111] with no benefit for warfarin or heparin. Therefore, the current consensus is that prophylaxis with anticoagulants does not provide additional benefit and should not be routinely administered.[18,107]

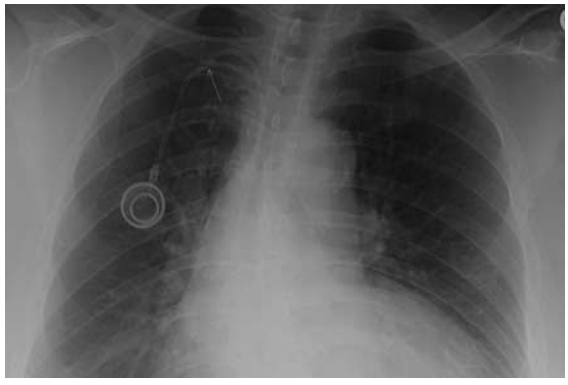

FIGURE 5. Grade 2 pinch-off sign resulting from compression of the catheter between the clavicle and the first rib (arrow).

Management

Ports can still be used in most patients despite a U-DVT; however, if the device is not needed it should be removed (Fig. 6).[72,102,107] If the port is needed, low molecular weight heparin and fondaparinux are preferred over unfractionated heparin for acute management. Fibrinolytic therapy is not routinely added to anticoagulants for U-DVTs; however, they may reduce the risk of postthrombosis syndrome in extensive or refractory cases.[102,107] Anticoagulation should be continued for at least three months or until the catheter is in place, whichever is longer, regardless of thrombolytic use.[102,107]

INFECTION

Infection is the most common cause of premature port removal,[112–114] affecting 5.6% to 8% of devices at a rate of 0.2/1000 catheter days.[115,116] Risk factors include frequent access, neutropenia, TPN, hematologic malignancy as compared with solid tumors, chronic steroid use, thrombosis, and metastatic disease.[116–119]

Bacteriologically, the most common causative agents are coagulase-negative *Staphylococci* (CoNS), gram-negative Bacilli (*Enterobacteriaceae*), *Staphylococcus aureus*,

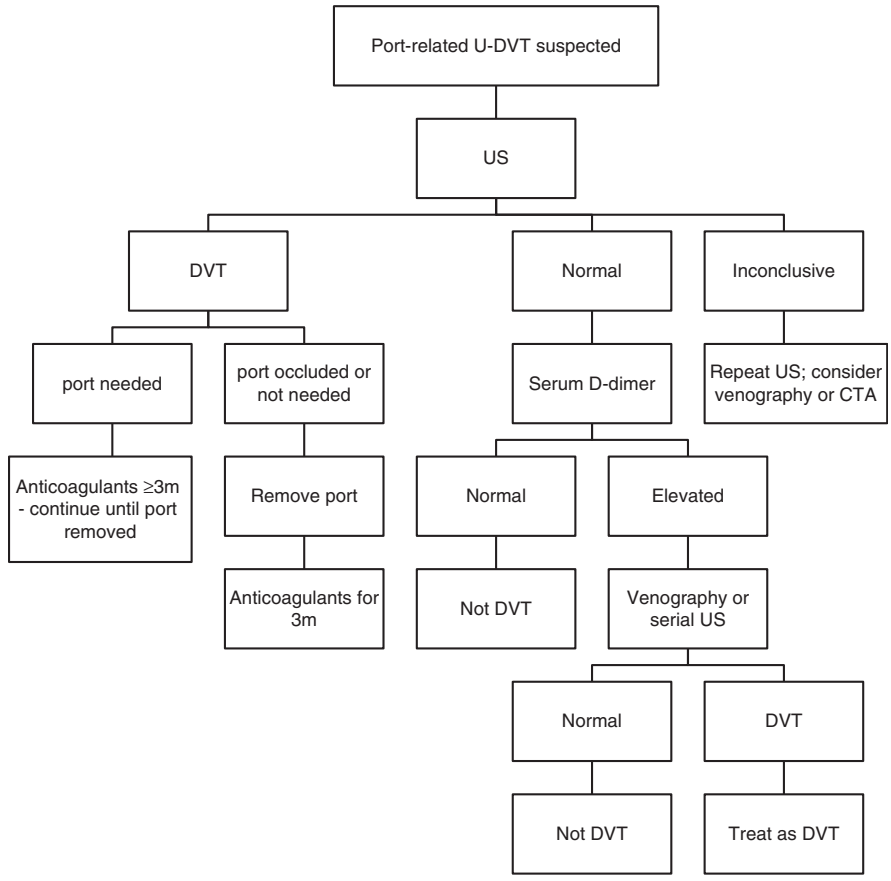

FIGURE 6. Approach to port-related DVT.[102,105] CTA indicates computed tomography angiography; DVT, deep venous thrombosis; U-DVT: upper extremity deep venous thrombosis; US: ultrasound.

Pseudomonas aeruginosa, and *Candida* species.[115] CoNS are normally present on the skin and are introduced into the body during port implantation or during subsequent access, whereas *Enterobacteriaceae* and *Candida* species cause infection when neutropenia permits bacteria and fungi to invade the mucosa and cause opportunistic bloodstream infections. Therefore, with intensification of antiseptic methods on one hand and more aggressive chemotherapy on the other, CoNS are becoming relatively less common.[115,116,118] *Staphylococcus aureus* infection is associated with severe complications such as endocarditis and septic emboli.[115]

Prevention

Strict adherence to sterile technique during implantation as well as each subsequent access is believed to be the most effective preventive measure. Chlorhexidine alcohol was shown to prevent more infections than povidone iodine alcohol in patients who needed central venous access in intensive care units.[120] A randomized controlled trial has demonstrated that percutaneous (subclavian or internal jugular veins) and cut-down approaches (cephalic vein) are equally safe in relation to infection rates.[16] Ideally, ports should not be used for continuous infusions, but if they are, needles should be changed at least every 7 days to prevent infection.[116,118] Antibiotic-coated catheters are shown to prevent infection in short-term central venous catheters; however, their efficacy is not well documented for ports.[121,122] Intravenous antibiotics are not effective for prophylaxis and should not be used.[123,124]

Diagnosis

Diagnostic workup is guided by the clinical presentation and should ideally identify the responsible organism (Fig. 7). The majority of patients with port-related bloodstream infections (P-BSIs) present with an isolated fever. The diagnostic workup should begin by quantitative culture of paired blood samples drawn from the port and a peripheral vein. The samples should be taken aseptically by experienced staff before any empiric antibiotic therapy is initiated.[125] To prove that the ports is the source of sepsis without removing the device, it is necessary to document either higher colony counts (≥ 3 times) or earlier times to culture positivity (≥ 2 h), in the sample drawn from the port compared with the peripheral blood sample.[125–127] If these criteria are not met, other sources of infection such as urinary tract infection should be considered and ruled out.

Local signs of reservoir or tunnel infection are highly specific; however, only 3% of port-related infections present with local signs.[116] As localized infections are not amenable to antibiotic treatment, ports along with any necrotic surrounding tissue should be removed using sterile technique and sent for culture. The distal 5 cm of the catheter and the reservoir septum have the highest yields for culture; however, only quantitative techniques should be used for these samples.[125] A

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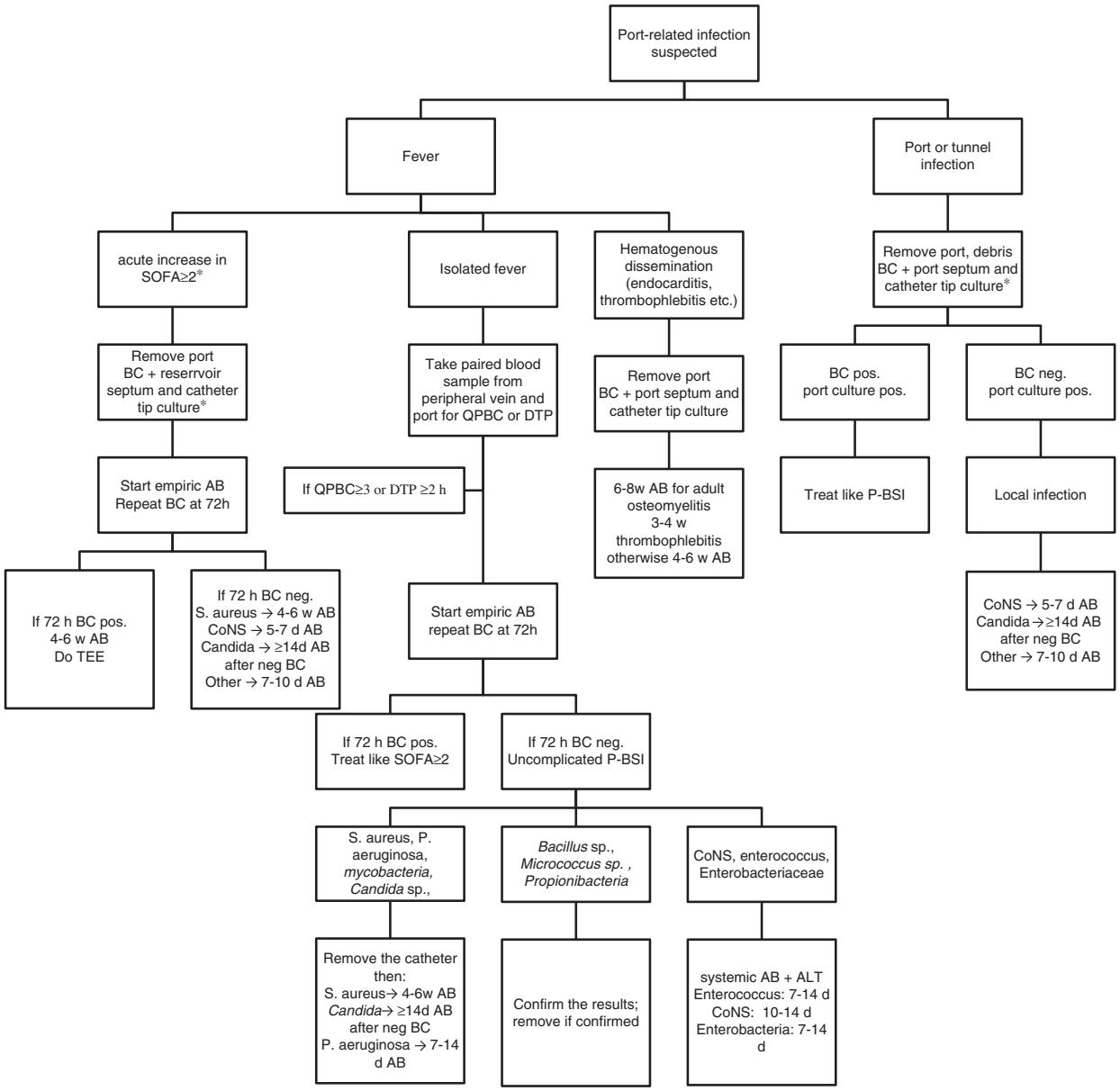

FIGURE 7. Approach to port-related infections.[125] AB indicates antibiotics; ALT, antibiotic lock therapy; BC, blood culture; CoNS, coagulase-negative *Staphylococci*; DTP, differential time to positivity; P-BSI, port-related bloodstream infection; QPBC, quantitative-paired blood culture; SOFA, Sequential Organ Failure Assessment Score; TEE: transesophageal echocardiography.

separate peripheral blood culture should also be performed to rule out concomitant P-BSI.

Management

Management begins with appropriate empirical antibiotics. Vancomycin should be used to cover gram-positive cocci with daptomycin reserved for centers where methicillin resistant *S. aureus* have minimal inhibitory concentrations (MIC) $\geq 2\,\mu g/mL$ for vancomycin.[128] Gram-negative bacilli should be covered as well, based on local susceptibility data and patient's condition.[125] *Candida* infections are common with TPN and should be covered with echinocandins such as caspofungin rather than fluconazole.[125] Antibiotic coverage should be deescalated once the culture results are available. If the patient has sequential organ failure score ≥ 2,[129] or has endocarditis, osteomyelitis, suppurative thrombophlebitis, or any other hematogenous dissemination, the port should be removed and long-term antibiotics be given based on the culture sensitivity results.[116] Moreover, if the causative agents are *Candida* species or *S. aureus* the catheter needs to be removed in most cases.[125] Otherwise antimicrobial lock therapy combined with systemic antibiotics should be tried to salvage the port (Fig. 7).[116,125]

Antimicrobial lock therapy has shown great promise in treating P-BSI at the source. As lock solutions only fill the port, and do not enter the systemic circulation, they can be administered at doses 1000 times above the MICs, contain antiseptic compounds such as ethylenediaminetetraacetic acid (EDTA) or

have a pH significantly above or below that of the plasma.[116,130,131] Of note, ethanol has been used as a lock solution at different concentrations (25% to 60%) in combination with ethylenediaminetetraacetic acid or as monotherapy against *Candida* as well as other microorganisms; however, its use has been associated with thrombosis.[132,133]

CONCLUSIONS

Despite their general safety and tolerability, ports are associated with a number of potentially severe early and late complications. Although many of these adverse events are preventable with proper implantation and maintenance techniques, physicians should be prepared to spot and manage the complications as they arise.

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