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REVIEW

Peripherally inserted central catheter (PICC)-related thrombosis in critically ill patients

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ABSTRACT

Background: **Peripherally inserted central catheters (PICC) are being increasingly used in critical care setting. However, PICCs are associated with a number of complications, particularly upper extremity venous thrombosis (UEVT), leading to post-thrombotic syndrome, pulmonary embolism and increased risk of catheter-related infection.**

Objective: **To review the literature surrounding PICCs and highlight the epidemiology, pathophysiology, diagnosis and management of PICC-related thrombosis in critically ill patients.**

Data sources and extraction: **We performed an electronic literature search of the databases PubMed, EMBASE and Google scholar using set search terms, from their commencement date to the end of January 2014.**

Summary of review: **It has been shown that PICCs may double the risk of deep venous thrombosis compared with centrally inserted venous catheters, in critically ill patients. However, the incidence of PICC-related thrombosis in critically ill patients has not been quantified. Ultrasonography is the preferred diagnostic imaging modality. There are no randomized controlled trials (RCTs) on the best treatment of PICC-related thrombosis in the intensive care unit (ICU) setting and in most cohort studies, anticoagulation strategies with or without PICC removal have been used.**

Conclusions: **Decision to insert a PICC should be taken after careful risk stratification. There is lack of high-quality evidence assessing prevention strategies and management of PICC-related thrombosis in the ICU. Well-designed RCTs are required to estimate the prevalence of UEVT in ICU patients with PICCs and evaluate the efficacy and magnitude of clinical benefit and cost-effectiveness of therapeutic strategies.**

Key words: Critical illness, PICC, Upper extremity thrombosis

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INTRODUCTION

Peripherally inserted central catheters (PICC) are non-tunneled medium- to long-term vascular access devices which are usually inserted into the deep veins of the upper extremities (1, 2). PICCs are being increasingly utilized in the intensive care unit (ICU), because of the safe insertion, ease of use, lower risk of mechanical injury (such as pneumothorax and vascular injury) and perceived lower incidence of infectious complications with longer duration of use, when compared to centrally inserted venous catheters (CIVCs) (1-3). In many hospitals, there are now dedicated vascular access teams available to undertake PICC placement (3).

ICU patients are at high risk of deep venous thrombosis (DVT) with its associated morbidity and mortality (4-6).

METHODS

We searched electronic databases PubMed, EMBASE and Google scholar, for articles reporting on use of PICCs in the ICU and PICC-related thrombosis, from their commencement date to the end of January 2014. Only English language articles were searched for, using various combinations of the following search terms: peripherally inserted central catheters, PICC, pulmonary embolism, PE, deep venous thrombosis, upper extremity thrombosis, venous

thromboembolism, critical illness, intensive care unit, mechanical ventilation, PICC management, vascular access, anticoagulation. A total of 65 articles were included in the review.

An overview of the epidemiology, pathophysiology, risk factors, diagnostic and management strategies of PICC-related thrombosis among critically ill patients is provided in the current review article. Our recommendations are based on physiological principles, published reports and personal experience.

EPIDEMIOLOGY

The incidence of PICC-related symptomatic upper extremity venous thrombosis (UEVT) ranges from 3% to 20% and the rate of asymptomatic thrombosis has been reported to be as high as 61.9% (3, 7-13). A prospective study by Itkin et al showed an overall thrombosis rate of 71.9%, on ultrasound of upper extremity veins, in patients with 5F double-lumen PICCs (14). In a descriptive retrospective study of 479 consecutive PICCs placed in neurocritically ill patients, the incidence rate of PICC-related large vein thrombosis was 8.1% (15).

Bonizzoli et al showed that in patients discharged from the ICU with a PICC in situ, the rate of DVT/1,000 catheter days was 7.7 and the estimated incidence rate of PICC-related thrombosis, 27.2% (16). One prospective trial which had aimed to recruit 167 ICU patients with triple-lumen 6F PICCs was stopped prematurely after recruiting only 50 patients due to the unacceptable number of symptomatic (20%) and asymptomatic (58%) UEVTs detected (3). Of note is the fact that in the above studies large-bore PICCs (5F and 6F) were used, without taking into account the caliber of the vein and therefore these results may be biased (3, 16).

Evans et al showed that when large (6F triple-lumen) PICCs were phased out in a large center over a 2-year period, and with the correct clinical education, PICC-related thrombosis decreased from 3% to 1.9%. The study also demonstrated that PICC-associated thrombosis prolongs a patient stay by 4.6 days and costs $15,973 (7).

In a preliminary retrospective analysis, Pittiruti et al evaluated 89 patients in whom ultrasound-guided insertion of multilumen PICCs was performed and found two cases (2.2%) of symptomatic thrombosis (however, not routinely screened for) (17).

It has been shown that the cumulative incidence of PICC-related symptomatic DVT, in neurological ICU patients, is 8.4% (2). In the same cohort of neurological ICU patients, centrally inserted central venous catheters appeared (CICVCs) to have a better risk profile compared to PICCs, with a decreased risk of catheter-related thrombosis (18). In a recent meta-analysis, Chopra et al demonstrated that the frequency of PICC-related DVT is higher in critically ill patients (13.91%; 95% CI, 7.68%-20.14%) and patients with malignancy (6.67%; 95% CI, 4.69%-8.64%). Main limitations of this meta-analysis lie in the fact that no randomized controlled trials (RCTs) were included in the study and about a third of the studies included were published in abstract form only. In addition, during the evaluation process, the authors did not consider the PICC size, a major component that could potentially affect the robustness of the conclusions (19). The prevalence of PICC-associated DVT among critically ill patients is unknown.

RISK FACTORS

Thrombus formation needs the three components described as Virchow's triad: abnormal flow, endothelial damage and altered blood composition (20). At particular DVT risk are trauma and neurosurgical patients (21). ICU-acquired risk factors for DVT include immobility, sedatives and paralytic drugs, end-stage renal failure, platelet transfusion, sepsis and the use of vasopressors (6, 22).

Mechanical ventilation (MV) has been identified as an independent ICU-acquired DVT risk factor (6). MV and positive-end expiratory pressure tend to reduce right and left ventricular preload, increase right ventricular afterload and decrease left ventricular afterload. The sum of these effects is that the cardiac output may fall, especially in the presence of hypovolemia or in those with impaired cardiovascular reflexes. Consequent exacerbation of venous stasis could potentially increase the DVT risk (23).

There are numerous studies highlighting the risk factors for the development of PICC-related thrombosis (1-3, 7, 8, 24, 25). In this narrative review we sought to highlight those risk factors which were determined from large population sizes and regression modeling with a p-value of <0.05 (Tab. I).

PICC caliber/number of lumens and thrombotic risk

There is an association between larger PICC diameter and higher rate of thrombosis. Evans et al observed that increasing catheter size is associated with increased DVT risk (0.4% symptomatic thrombosis rate for 4F PICCs and an 8.8% symptomatic thrombosis rate for 6F PICCs), with an incidence of 0.6% with single-lumen catheters, compared with 2.9% with double lumen and 8.8% with triple lumen (7). These results were recently confirmed in a 3-year, prospective, observational study, which showed that an increase in the use of single-lumen PICCs combined with use of smaller 5F triple-lumen PICCs was associated with significant decrease in the rate of PICC-related thrombosis (26).

TABLE I - RISK FACTORS FOR THE DEVELOPMENT OF PICC-RELATED UEVT

Study	Risk factor	Odds ratio (95% confidence interval)	Population size/ type of study
Evans et al (2010) (7)	Previous DVT	9.92 (5.08-21.25)	1728/Prospective
Evans et al (2010) (7)	Triple- vs single-lumen PICC	19.50 (3.54-100)	1728/Prospective
Evans et al (2010) (7)	Surgery >1 hour	1.66 (0.91-3.01)	1728/Prospective
Wilson et al (2012) (2)		3.01 (1.50-6.06)	431/Retrospective
Wilson et al (2012) (2)	Mannitol use	3.27 (1.27-8.43)	431/Retrospective
Wilson et al (2012) (2)	History of venous thromboembolism	6.66 (2.38-18.62)	431/Retrospective
Wilson et al (2012) (2)	Placement in a paretic arm	9.85 (4.42-21.95)	431/Retrospective
Wilson et al (2012) (2)	Heart failure	2.62 (1.01-6.83)	431/Retrospective
Liem et al (2012) (8)	Malignancy	4.10 (1.90-8.90)	690/Retrospective
Liem et al (2012) (8)	Diabetes mellitus	2.50 (0.98-6.30)	690/Retrospective
Yi XL et al (2013) (24)		1.12 (0.89-4.57)	89/Prospective
Liem et al (2012) (8)	PICC caliber (>5F)	3.90 (1.10-13.90)	690/Retrospective
Ahn et al (2013) (25)	Erythropoietin	10.60 (2.25-50.5)	237/Retrospective
Ahn et al (2013) (25)	Hospitalization	2.38 (1.05-2.39)	237/Retrospective
Ahn et al (2013) (25)	PICC infection	2.46 (1.03-5.85)	237/Retrospective
Marnejon et al (2011) (1)	Left-sided PICC	Not stated	400/Retrospective
Marnejon et al (2011) (1)	Basilic placement	Not stated	400/Retrospective
Marnejon et al (2011) (1)	Trauma	Not stated	400/Retrospective
Marnejon et al (2011) (1)	Renal failure	Not stated	400/Retrospective
Yi XL et al (2013) (24)	Chemotherapy	3.19 (1.07-9.77)	89/Prospective
Marnejon et al (2011) (1)	Antibiotic infusion	Not stated	400/Retrospective
Marnejon et al (2011) (1)	Total parenteral nutrition	Not stated	400/Retrospective

In a retrospective analysis, Grove et al showed no thrombosis for PICCs <3F and 9.8% rate of thrombosis for 6F PICCs (27).

PATHOPHYSIOLOGY

There is a fine balance between anticoagulant and procoagulant factors in the body that prevents the explosive production of thrombin when the clotting cascade is activated (28). Several preclinical studies and one clinical study in healthy subjects suggest that pulmonary fibrin turnover is altered by MV (29). Haitsma et al demonstrated that injurious MV increased pulmonary coagulopathy in an animal model of *Streptococcus pneumoniae* pneumonia, which resulted in a systemic coagulopathy. Coagulation dysfunction with both defective inhibition of coagulation and attenuation of fibrinolysis could potentially contribute to the development of UEVTs in patients with a PICC in situ (30).

According to Virchow's triad the development of UEVTs can be explained by taking into consideration the risk factors mentioned previously. Other clinical risk factors can also be considered to play a major role. Infusion of therapeutic drugs which alter the pH (vancomycin, chemotherapy) or osmolality (total parenteral nutrition) of blood can directly affect venous endothelium and increase the likelihood of thrombosis (1, 31).

It has been shown that UEVT can be a response to the introduction of the PICC itself. Nifong et al created an experimental model of the upper limb vasculature taking into consideration the caliber of the upper limb venous system and explored the effect of PICC to vein caliber ratio on venous flow. They determined that the introduction

of a PICC resulted in a decrease in laminar flow within the center of the vessel lumen by as much as 93% and an increase in turbulent flow due to the obstruction caused by the device (32). Therefore, the larger the PICC, the less the central flow and greater the turbulence and the subsequent risk of UEVT (23). Flow within upper extremity veins can be reduced by up to 93% with large PICCs (32). This decrease in flow can have a direct effect on venous stasis, which can result in thrombosis; however, the exact flow reduction required for stasis is still unknown (32). Besides the effect of stasis, direct trauma from insertion or rigidity of the PICC can cause thrombosis as it distorts the vein architecture. The inflicted venous trauma results in an inflammatory response which can precipitate thrombosis. An additional risk factor is the introduction of a foreign material (the PICC itself), which the body quarantines by forming an encompassing biofilm (32, 33). The biofilm production includes the accumulation of platelets and fibrin. This, coupled with low flow and venous stasis, disrupts the balance in favor of thrombosis.

COMPLICATIONS OF PICC-RELATED THROMBOSIS

PICC-related thrombosis is associated with complications such as pulmonary embolism, colonization in areas of clot and systemic sepsis, loss of intravenous access, post-thrombotic syndrome and recurrent venous thrombosis (34).

Pulmonary embolism

In a retrospective study, Fletcher et al found that among neurological ICU patients with PICCs, PE occurred in 1.3% of line placements and 15% of symptomatic DVTs (incidence rate of PICC-associated thrombosis = 8.1%) (35). The incidence of PE secondary to UEVT, in patients with central venous catheters (PICCs and CICVCs), thrombotic states and previous DVT, can be greater than 35%, with asymptomatic PE in a substantial proportion of patients, and it is associated with high mortality (36).

Malinoski et al demonstrated that among trauma and surgical ICU patients (including mechanically ventilated patients and patients with PICCs), the rate of PE after CVC-associated UEVT was 1.3%, despite thromboprophylaxis (37).

PICC-related thrombosis and infection

There has been ongoing controversy regarding the bidirectional relationship between CVC-related thrombosis and infection. It has been demonstrated that fibrin sheath formation around the external portion of the catheter and within the CVC lumen promotes colonization and enhances CVC infection and persistent bacteremia (38). There is a convincing body of evidence supporting the relationship between coagulation and inflammation at the level of platelet activation, fibrin formation and physiological anticoagulant pathways (38-40). Timsit et al in a prospective multicenter study showed that in critically ill patients with CVCs, colonization rates are almost double (32 vs 19.4) in CVCs with thrombosis and CVC-related septicemia almost triples in patients with CVC thrombosis (11.6 vs 3.6). Although the study did not include any patients with PICCs, it confirms the relationship between CVC thrombosis and CVC-related sepsis, which confers significant mortality (up to 35%) in the ICU setting (41, 42).

Post-thrombotic syndrome

Postthrombotic syndrome is characterized by pain, venous hypertension, swelling of the limb and limitation of activity and causes severe morbidity. The incidence of postthrombotic syndrome in patients with UEVT without CVC is 36-50% (9). In a retrospective study, Ong et al demonstrated that functionally significant postthrombotic symptoms are uncommon following PICC-associated thrombosis (43). A systematic review by Elman et al showed that catheter-associated UEVT may be associated with a decreased risk of postthrombotic syndrome (44). There is paucity of definitive data regarding the incidence of postthrombotic syndrome and recurrent UEVT in ICU patients with PICC-related thrombosis.

DIAGNOSIS

A 4-item prediction score (CVC or pacemaker +1; unilateral edema +1; pain +1, alternative diagnosis –1) for calculating clinical probability of UEVT was designed by Constans and colleagues. However, 13% of patients with low clinical probability score (<0) were found to have UEVT, which suggests that this clinical model is insensitive and probably unreliable (45).

There is no validated diagnostic algorithm for UEVT that determines pretest probability, and imaging confirmation, in the ICU patient population (46).

Clinical evaluation

The clinical diagnosis of PICC-related UEVTs is often difficult in ICU patients. Symptomatic UEVTs exhibit a number of clinical signs, such as unilateral arm swelling, arm pain (which may be exacerbated by movement) and erythema. Other features include superficial venous engorgement, discoloration of the arm and unexplained systemic inflammatory response syndrome (47, 48). Despite the typical signs of UEVT, the clinical evaluation and diagnosis of UEVT has been found to have a low specificity (30%-64%) (47).

A significant proportion of PICC-related DVTs may be totally asymptomatic or complications such as PE are the presenting clinical features of PICC-related thrombosis (2).

In the context of PE, prominent clinical findings include small volume arterial pulse, tachycardia, clinical right ventricular failure, a gallop rhythm at the left sternal edge and accentuated second heart sound (often difficult to ascertain on ventilated patients with ongoing physiological derangement) (49).

Laboratory testing

The use of D-Dimers has not been validated in the ICU setting (48).

Imaging modalities

Ultrasound

The most commonly used diagnostic imaging modality for UEVT detection is ultrasonography (compression and duplex).

Depending on suspected location of the thrombus, compression or duplex ultrasonography can be used and can characterize the level of occlusion. Compression ultrasonography determines the compressibility of the vein, with normal veins being easily compressed and lack of normal compression and areas of variable echogenicity corresponding with an area of thrombus. This method is preferred in peripherally located thrombi and has been stated to have a sensitivity of 97% and specificity of 96% in the diagnosis of UEVT (47, 48).

Duplex ultrasonography determines differences in flow across a venous segment and its variability with certain maneuvers, for example, Valsalva maneuver, with the absence of flow suggesting thrombus. Duplex ultrasonography is used in the diagnosis of more centrally located thrombi due to their difficult access for compression ultrasonography (47, 48).

In a systematic review assessing the accuracy of diagnostic tests for clinically suspected UEVT, the summary estimates of sensitivity (95% CI) were 97% (90%-100%) for compression ultrasonography, 84% (72%-97%) for Doppler ultrasonography and 91% (85%-97%) for Doppler ultrasonography with compression. The corresponding summary estimates of specificity were 96% (87%-100%), 94% (86%-100%), 93% (80%-100%), respectively. The reference modality used was mostly contrast venography (49, 50).

Contrast venography

Though venography is considered the reference imaging modality for the diagnosis of UEVT, due to its invasiveness, cost and risks associated with contrast media (contrast-induced nephropathy, hypersensitivity reactions, phlebitis), it has been replaced by ultrasonography (47). However, venography may be indicated in cases where there is high clinical suspicion for UEVT and ultrasonography is nondiagnostic, inconclusive or difficult to obtain. An intraluminal filling defect is diagnostic (47, 48). In the context of critical illness, contrast venography poses a risk of acute kidney injury and complications of transportation to radiology.

Other imaging modalities

Other imaging techniques that may be used are computed tomography (CT) venography (sensitivity: 95.9%, specificity: 95.2%) or magnetic resonance (MR) venography (sensitivity: 91.5%, specificity: 94.8%) (51-53). The accuracy of the above diagnostic imaging modalities has not been tested in critically ill mechanically ventilated patients. Besides, CT and MR environment carries significant risks to patients during transportation and prolonged periods in the scanner. High cost and need for expertise further limit the use of CT and MR venography.

PREVENTION

Despite universal thromboprophylaxis, critically ill patients remain at risk for DVT. Ibrahim et al showed that 5% of mechanically ventilated medical ICU patients receiving thromboprophylaxis developed CIVC-related UEVT (5). In a prospective observational cohort study, patients with a PICC in situ who received prophylactic anticoagulation had a 22.9% incidence of thrombosis, which was significantly less ($p<.05$), than for those who did not receive thromboprophylaxis (61.9%) (54).

A retrospective analysis of adult patients with PICCs, in the acute care setting, demonstrated that ensuring PICC tip is lying in the distal third of the superior vena cava, on a postprocedure chest X-ray and using ultrasound guidance for PICC placement were effective in reducing PICC-related UEVT incidence, from 4.8% to 2.9%. In addition, careful evaluation of vein diameter in their native state, by ultrasound, further decreased the incidence of PICC-induced DVT from 2.9% to 1.4% (55, 56). Strategies for prevention of PICC-related thrombosis in the critically ill are summarized in Figure 1.

ACUTE MANAGEMENT OF PICC-RELATED THROMBOSIS IN THE ICU

The aim of therapy is to alleviate the symptoms of UEVT, prevent progression of the thrombus and compli-

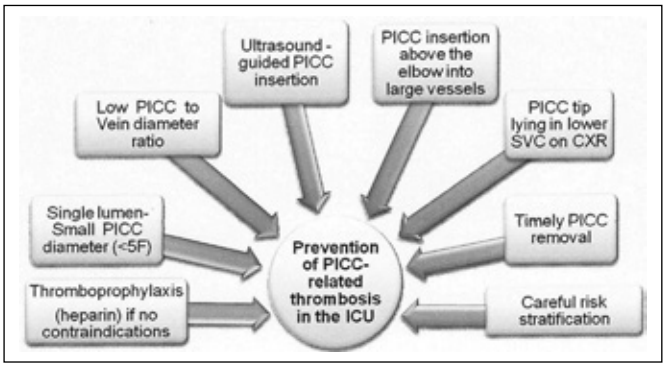

Fig. 1 - *Strategies for prevention of PICC-related thrombosis in the ICU (5, 54-56).*

cations associated with UEVT (PE, early recurrence and postthrombotic syndrome). Prevention of DVT complications in critically ill mechanically ventilated patients with limited cardiopulmonary reserve is imperative. There are no data from RCTs comparing different treatment strategies in ICU patients with PICC-induced thrombosis (48).

Routine catheter removal, in cases of PICC-associated thrombosis, is not recommended, especially if the catheter is functional and there is an ongoing need for catheter use (Grade 2C) (57). Removal is recommended when there is catheter malfunction and it is no longer needed, in cases of catheter-related sepsis and when anticoagulation treatment is contraindicated (48, 58, 59).

Anticoagulation

The cornerstone of UEVT management is anticoagulation, unless there are absolute contraindications owing to bleeding risk. There have been no large-scale studies looking at the management of UEVTs secondary to PICCs in the ICU. The paucity of information has resulted in the extrapolation of management protocols from lower limb DVT studies (25, 48).

It has been demonstrated that in non-ICU patients with venous thromboembolism (and no need for thrombolysis or embolectomy), low molecular weight heparin (LMWH) appears to be as effective and safe as unfractionated heparin (UFH) (60). However, ICU patients might not have a reliable relationship between LMWH and antithrombotic response due to potentially impaired absorption following subcutaneous administration, decreased clearance secondary to renal impairment and use of vasopressors (61, 62).

In the ICU setting, where unplanned invasive procedures are very commonly performed, use of LMWH poses a high risk of bleeding complications. Therefore, it must be used with caution and monitoring of anti-factor Xa activity approximately 4 hours after administration would be advisable. Large, well-designed studies assessing anti-factor Xa activity, dosage and the mode of administration of LMWH to attain adequate antithrombotic response in ICU patients with UEVT are needed.

TABLE II - LMWH vs UFH FOR TREATMENT OF DVT IN THE CRITICALLY ILL

	LMWH	**UFH**
Route of administration	Subcutaneous	Intravenous
Absorption	May be impaired in ICU patients	Bioavailability 100%
Elimination half-life	3-6 hour	Dose dependent
Monitoring	Anti-factor Xa activity	Activated partial thromboplastin time (aPTT)
Anticoagulant effect	Protamine reverses <40% of anti-factor Xa activity	Reversed by protamine
Heparin-induced thrombocytopenia	Rare	4% incidence

Stansted News. Zochios VA, Keeshan A. Pulmonary embolism in the mechanically ventilated critically ill patient: is it different? JICS 2013;14(1):36-44. Permission to reproduce granted under Stansted News' general terms (63).

It is recommended that LMWH or UFH is used in UEVT (Grade 1B). Although current guidelines suggest use of LMWH over intravenous UFH for UEVT (Grade 2C), UFH may be a safer treatment option in the ICU, with patients at higher risk of hemorrhage, as it has the advantage of immediate discontinuation and rapid reversal if bleeding complications occur (Tab. II) (57, 63).

Thrombolysis

Catheter-directed thrombolysis is recommended in massive UEVT (severe symptoms and signs) associated with CVC (Grade 2C) (46). Semba et al showed that use of alteplase in patients with CVC-related thrombosis (including patients with PICC-related thrombosis) is safe and effective for restoring flow to occluded CVCs (64). However, there is notable lack of evidence in support of catheter-directed thrombolysis, in critically ill patients with PICC-associated DVT.

Surgical interventions

Surgical procedures such as thrombectomy and angioplasty with endovascular stenting have been reviewed. Their use is generally limited to thrombosis with severe symptoms after initial anticoagulation or thrombolysis treatment and initial massive venous thrombosis (Grade 2C) (47, 48, 65).

CONCLUSIONS

As shown in the literature, PICC lines are far from innocuous as previously believed, and the related risk of thrombosis and its (as yet unquantified) sequelae such as PEs, central vein occlusion and PICC-related infection must be taken into consideration when taking the decision to insert a PICC. Clinicians need to consider a number of factors when considering PICCs, beginning initially with appropriate patient selection and risk stratification, the availability of peripheral access, the intended duration of use, its indicated use and the PICC size and lumen number required. The size and lumen number of a PICC and high catheter to vein diameter ratio is related to thrombosis, with larger lumen PICCs and those with more than one lumen having an increased risk of thrombosis. As of yet, there are limited data available that take all of these into consideration in the context of critical illness.

Measures to reduce the risk of PICC-related DVT, such as thromboprophylaxis, use of ultrasound to ensure adequate vessel size prior to insertion, ultrasound-guided access, insertion of a smaller catheter in a vein with an optimal caliber and adequate position of the PICC tip on a postprocedure chest-X ray, should be considered, as varied ICU patient profiles and lack of robust evidence make it difficult to develop a consistent treatment bundle.

The current management strategies for PICC-associated UEVTs have mostly been developed from lower limb DVT studies and a number of clinically important questions remain unanswered due to lack of robust evidence.

There is a definite need for well-designed prospective trials evaluating the risk factors, prevention strategies and optimal management of PICC-associated thrombosis and comparing clinical outcomes of PICCs versus CIVCs, in critically ill patient populations.

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