CLINICAL RESEARCH STUDY

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Peripherally Inserted Central Catheter-associated Deep Vein Thrombosis: A Narrative Review

Nabil Fallouh, MD, MS,[a] Helen M. McGuirk, MPH,[a,b] Scott A. Flanders, MD,[a] Vineet Chopra, MD, MSc[a,b]

[a]*Department of General Medicine, University of Michigan Health System, Ann Arbor;* [b]*Patient Safety Enhancement Program, Hospital Outcomes Program of Excellence and the Center for Clinical Management Research, Ann Arbor VA Medical Center, Ann Arbor, Mich.*

ABSTRACT

BACKGROUND: Although common, little is known about factors associated with peripherally inserted central catheter-related deep vein thrombosis (PICC-DVT). To better guide clinicians, we performed a comprehensive literature review to summarize best practices for this condition.

METHODS: A systematic search of the literature for studies reporting epidemiology, diagnosis, treatment, and prevention of PICC-DVT was conducted. Algorithms for diagnosis and management were compiled using available evidence.

RESULTS: The incidence of PICC-DVT varied between 2% and 75% according to study population, testing modality and threshold for diagnosis. Studies evaluating the diagnostic utility of clinical symptoms suggested that these were neither sensitive nor specific for PICC-DVT; conversely, ultrasonography had excellent sensitivity and specificity and is recommended as the initial diagnostic test. Although more specific, contrast venography should be reserved for cases with high clinical probability and negative ultrasound findings. Centrally positioned, otherwise functional and clinically necessary PICCs need not be removed despite concomitant DVT. Anticoagulation with low-molecular-weight heparin or warfarin for at least 3 months represents the mainstay of treatment. The role of pharmacologic prophylaxis and screening for PICC-DVT in the absence of clinical symptoms is unclear at this time.

CONCLUSIONS: PICC-DVT is common, costly and morbid. Available evidence provides guidance for diagnosis, treatment and prevention of this condition.

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KEYWORDS: Deep vein thrombosis; Diagnosis; DVT; Peripherally inserted central catheter; PICC; Prevention; Thrombosis; Treatment

Over the past decade, use of peripherally inserted central catheters (PICCs) to achieve nonpermanent yet durable venous access has grown dramatically.[1,2] Originally developed in 1975 for delivering total parenteral nutrition,[3] PICCs today serve roles spanning delivery of short- and long-term intravenous antibiotics to invasive hemodynamic monitoring. However, PICCs are also associated with complications, including upper-extremity deep vein thrombosis.[4,5] Peripherally inserted central catheter-related deep vein thrombosis (PICC-DVT) is important because it interrupts venous therapy, increases cost of care, and often leads to sequelae such as phlebitis, vein stenosis, and pulmonary embolism.[5-10]

Despite these facts, little is known about risk factors, diagnostic strategies, treatment, and prevention of PICC-DVT. While a recently published meta-analysis reported that PICCs were associated with a greater risk of thrombosis compared with central venous catheters,[11] factors that may drive this increased risk are not well defined. An overview incorporating the myriad scientific and technical aspects of diagnosis, management, and prevention of PICC-DVT is thus needed. Therefore, we reviewed the literature and synthesized available data to develop evidence-based algorithms for evaluation and treatment of PICC-DVT.

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Requests for reprints should be addressed to Vineet Chopra, MD, MSc, Department of General Medicine, University of Michigan Health System, 2800 Plymouth Road, Building 16, Rm 432W, Ann Arbor, MI 48109.

E-mail address: vineetc@umich.edu

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METHODS

With a medical research librarian, we searched MEDLINE (via PubMed), CINAHL, Embase, and the Cochrane CENTRAL registry for English-language articles with the following keywords: "peripherally inserted central catheter," "PICC," "deep vein thrombosis," and "thrombosis" (Appendix). Boolean operators and medical subject heading terms were used to enhance electronic searches. Additional studies of interest were identified by hand searches of bibliographies. Studies that involved patients <18 years of age, or that were case reports, editorials, or conference proceedings were excluded. The search was last updated August 1, 2014.

Using the retrieved articles, we summarized findings to develop evidence-based algorithms for decision-making in PICC-DVT. To create such algorithms, we first categorized studies by patient-, provider-, and device-related domains according to a published conceptual model (Figure 1).[12] Two authors (VC and NF) then developed workflows in each domain to develop an organizational framework. By determining which factors were modifiable (and consequently, targetable), we developed recommendations for testing and treatment.

CLINICAL SIGNIFICANCE

- Despite increasing recognition, little is known about patient-, provider-, and device-specific risk factors associated with peripherally inserted central catheter-related deep vein thrombosis (PICC-DVT).
- Novel algorithms utilizing these data to guide clinicians in diagnosis and treatment of PICC-DVT are presented.

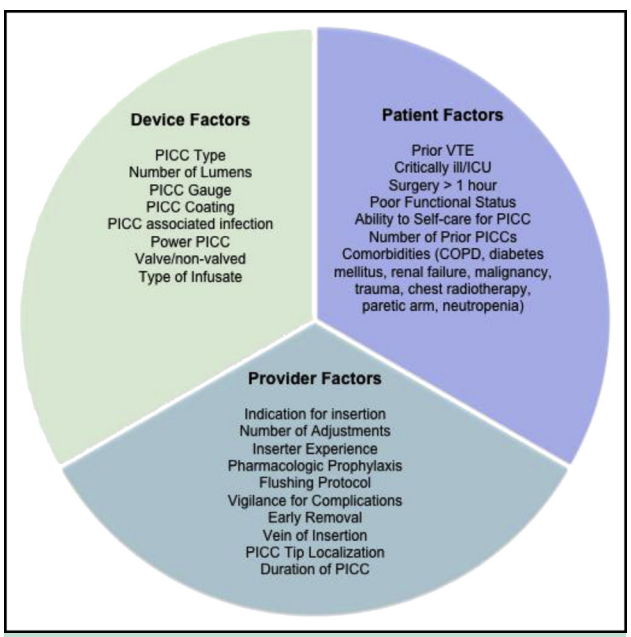

Figure 1 Conceptual model For PICC-DVT. A conceptual model, adapted from a prior submission,[16] displaying patient-, provider-, and device-related characteristics associated with PICC-DVT. COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; PICC = peripherally inserted central catheter; VTE = venous thromboembolism.

RESULTS

A total of 83 articles were included in our review (Figure 2). Studies are presented as follows: (a) epidemiology and risk factors; (b) clinical signs and symptoms; (c) diagnosis, treatment, and prevention of PICC-DVT.

Epidemiology and Risk Factors for PICC-DVT

The incidence of PICC-DVT varies by patient population. Studies involving critically ill populations, those with cancer, and hospitalized patients report higher rates of PICC-DVT (5%-15%) than ambulatory populations (2%-5%).[4,5,11,13,14] Correspondingly, estimates of the frequency of PICC-DVT often relate to epiphenomena such as population studied, method of diagnosis, and diagnostic testing thresholds.[11] Studies that utilize screening techniques (eg, testing in the absence of clinical signs or symptoms) demonstrate a pooled frequency of PICC-DVT that is substantially greater than studies where testing is prompted by clinical symptoms (24.2%; 95% confidence interval [CI], 17.9-50.4 vs 4.3%; 95% CI, 3.4-5.2).[11] In a recent study, screening for PICC-DVT was associated with thrombosis in 75% of devices, with the majority of these being asymptomatic.[15]

Patient-related Risk Factors. Several patient-specific characteristics influence the risk of PICC-DVT. For instance, prior venous thromboembolism is associated with greater risk of PICC-DVT.[7,16,17] Critically ill patients and those with a cancer diagnosis are also at a substantially greater risk of PICC-DVT.[4,18,19] Additionally, higher rates of PICC-DVT have been reported in patients with end-stage renal disease, potentially due to the prothrombotic state associated with this condition.[20] Inherited thrombophilias such as protein C or protein S deficiency also fall into this category.[21] Specific comorbidities (eg, diabetes mellitus, obesity, and chronic obstructive pulmonary disease) may be associated with greater risk of PICC-DVT according to a number of observational studies.[4,14,20,22,23] Notably, surgery with a PICC in situ is an important factor associated with this outcome and should be avoided whenever clinically feasible.[7]

Device-related Risk Factors. Blood flow in peripheral veins is hampered by PICC placement; the caliber of the catheter and degree of cross-sectional area occupied by the PICC correlates with reduction in venous flow.[24] In a retrospective cohort study of 966 unique PICC placements, 5- and 6-French PICCs were more likely to develop PICC-DVT compared with 4-French PICCs (hazard ratio [HR] 3.56; 95% CI, 1.31-9.66, and HR 2.21; 95% CI,

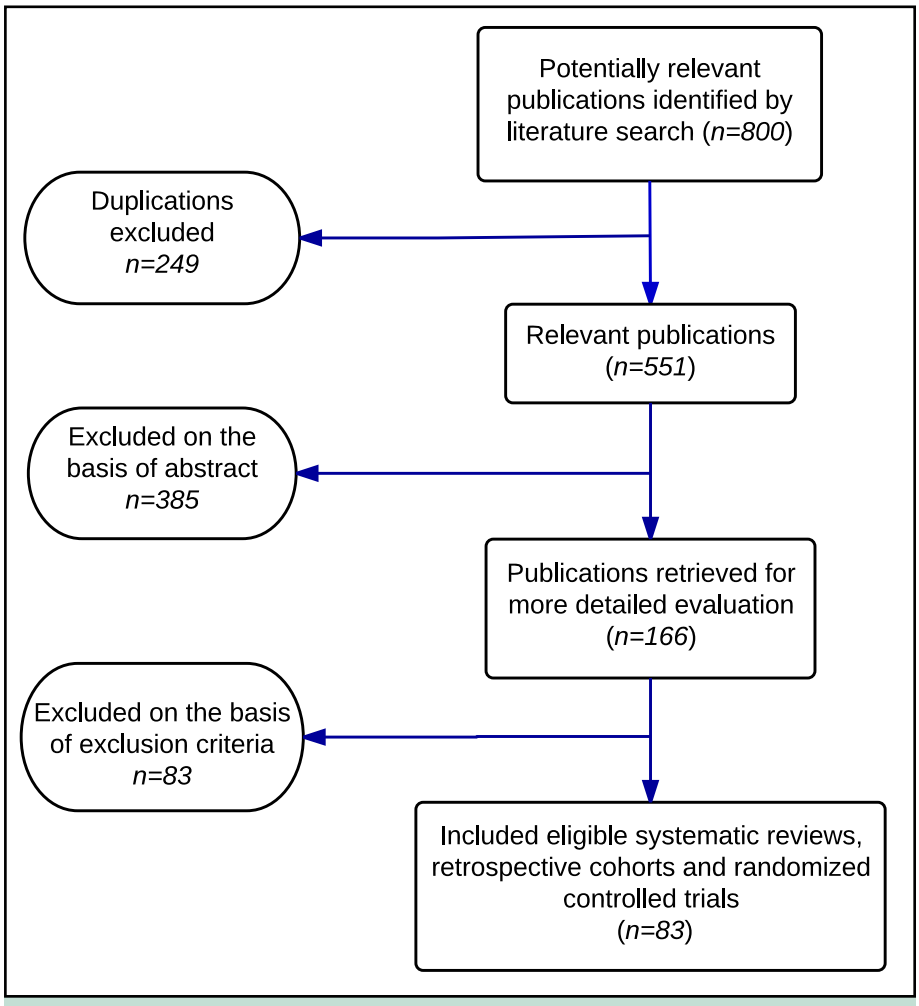

Figure 2 Study flow diagram.

1.04-4.70, respectively).[25] Thus, greater PICC gauge is an important, modifiable device-related risk factor for PICC-DVT.[7,16,25,26]

Some studies suggest that power-capable PICCs (specialized devices that can withstand high pressures associated with contrast injection machines) might be associated with greater risk of PICC-DVT.[27] However, recent data challenge this finding.[16] Additionally, the nature of the infusate administered through the PICC may influence thrombotic risk and confound this association. For instance, administration of antibiotics such as vancomycin, ceftriaxone, and metronidazole are associated with increased rates of PICC-DVT.[5,20] In a study of neurosurgical intensive care unit patients, infusion of mannitol and vasopressors through the PICC was associated with PICC-DVT.[28] The use of erythropoietin-stimulating agents or infusion of specific chemotherapeutic agents (eg, fluorouracil and capecitabine) may also increase the risk of PICC-DVT.[29,30] Collectively, extremes of pH ($\leq$5 or $\geq$9), osmolarity, and concentration of infusates (alone or in combination) may predispose to intimal damage, inflammation, and subsequent thrombosis.[31] Of note, whether the pH of an intermittently delivered medication influences risk of thrombosis or phlebitis has been called into question recently.[32-34]

In a study involving cancer patients, catheter dysfunction (eg, inability to flush the PICC or infuse therapeutics) was noted to herald or accompany DVT in 25% of patients.[35] However, formation of fibrin sheaths composed of platelets, collagen, and smooth muscle elements may also impair PICC performance, as would precipitation of crystals or minerals from infusions and extraluminal factors such as coiling or kinking.[36-38] Thus, although problematic from a clinical perspective, dysfunction is not a reliable predictor of PICC-DVT.[39]

In a randomized trial of 326 patients, Ong et al[40] reported a lower rate of phlebitis and infection associated with proximal-valved PICCs than distal-valved devices. However, other studies, including a recent randomized controlled trial, failed to identify any clinical advantage to valved, compared with nonvalved PICCs.[41,42] Antimicrobial-coated or anti-thrombotic catheters, although promising, are yet to prove effective in preventing PICC-related thrombosis.[43]

Provider-related Risk Factors. To minimize thrombosis, insertion into appropriately sized veins and localization of the catheter tip at the cavoatrial junction are vital.[44-46] The rationale for the latter recommendation relates to blood velocity in these regions compared with other sites. PICC tips that lie outside of the superior vena cava are more likely to develop thrombosis; conversely, placement of the PICC tip at the cavoatrial junction substantially reduces such risk.[5,11,18,47] Early findings of novel technology to improve positioning of PICC tips (eg, electromagnetic and electrocardiogram-based PICC-tip systems) suggest reduced thromboses with use of these modalities.[48-50]

Vein and arm of insertion may be an important factor associated with PICC-DVT.[20,51] In their study, Liem et al[14] reported that PICCs placed in the basilic vein were associated with twice the risk of DVT compared with nonbasilic vein placements (3.1% vs 1.5%, $P = .05$).[14] While PICCs placed in the left arm may be associated with greater risk of thrombosis (perhaps due to insertion challenges leading to endothelial damage),[20] Sperry et al[52] examined 798 consecutively placed PICCs and found that laterality was not associated with symptomatic DVT. Thus, available evidence does not support preferential insertion of the PICC in one arm over the other; patient preferences should influence this decision.[53] Rather than avoidance of a specific vein or arm, ascertainment of an appropriate catheter-to-vein ratio and avoidance of smaller forearm veins are important to prevent PICC-DVT.[24,54,55]

A summary of publications relevant to patient-, provider-, and device-related factors associated with PICC-DVT is presented in **Table 1**.

Clinical Signs and Symptoms of PICC-DVT

When symptomatic, PICC-DVT often presents with signs of impaired venous outflow (eg, arm pain, swelling, or distention of the veins in the arm, neck, and chest). Manifestations related to superficial thrombophlebitis may also be observed.[56,57] Characterized by erythema, redness, and warmth along the vein of entry, thrombophlebitis may become painful or infected (eg, septic thrombophlebitis) so as to necessitate PICC removal.[58]

Although less frequent than embolization from deep veins of the leg,[9,57,59] PICC-associated pulmonary embolism is more common in those that are critically ill or afflicted with cancer.[11] In studies involving critically ill patients, pulmonary embolism accounts for 13%-20% of all thrombotic events related to PICCs.[8,28-30] Interestingly, unlike the lower extremities, the frequency of postthrombotic syndrome following upper-extremity DVT is highly variable, potentially due to the differences in venous pressure between the limbs. Therefore, whether PICC-DVT increases risk of postthrombotic syndrome is unclear at this time.[30,60,61]

It is important to emphasize that most PICC- and catheter-related DVTs are often clinically silent,[62] and diagnosis is hampered by low specificity.[56,63] While a risk score to assess probability of catheter-related DVT has been proposed, the mere presence of an indwelling venous catheter moves the probability of DVT from low to intermediate.[64] An unmet need for a clinical risk prediction tool that offers high specificity for PICC-DVT thus exists.

Diagnosis of PICC-DVT

Owing to noninvasiveness, radiation, and contrast-free properties, compression ultrasonography is the initial modality for diagnosis of PICC-DVT. Ultrasound confirmation of PICC-DVT is often based on (a) the presence of visible thrombus in the vein, (b) noncompressibility of the affected vein, or (c) absence of venous flow on Doppler or color ultrasound.[63,65] Early systematic reviews reported sensitivity and specificity of ultrasound for catheter-associated DVT of 56%-100% and 94%-100%, respectively.[66] Of note, because compression of the veins to confirm thrombus requires access to the segment involved, sensitivity and specificity of ultrasound diminish with proximal involvement (eg, brachiocephalic, subclavian, or innominate veins).[67,68] However, a systematic review of 17 studies and 793 patients concluded that ultrasonography is an acceptable alternative to venography given summary sensitivity and specificity estimates of 97% and 96%, respectively.[63]

Contrast venography is an invasive and a more technically challenging procedure that should be reserved for cases where ultrasound is not confirmatory but alternative diagnoses are unlikely. While venography performed by computed tomography or magnetic resonance imaging has emerged as a less invasive alternative, the diagnostic accuracy of these modalities in upper-extremity or catheter-related thrombosis is unclear.[68,69] No studies have directly compared these with ultrasound for catheter or PICC thrombosis.

Compared with lower-extremity DVT, plasma biomarkers have a limited role in diagnosis of catheter DVT.[70-72] In a Swiss study of 52 consecutive patients, D-dimer was highly sensitive (100%) but not specific (14%) in patients with suspected arm DVT.[73] The diagnostic utility of D-dimer is also weakened by the coexistence of conditions such as cancer or infection, both of which confound PICC use and D-dimer elevation. Novel biomarkers not affected by these factors (eg, P-selectin) may be of greater utility.[74] For example, Ramacciotti et al[75] found that the combination of soluble P-selectin and Wells score was the strongest predictor of catheter DVT among a number of candidate markers. More evidence regarding such markers in upper-extremity DVT is needed.

Integrating the available evidence, an algorithmic approach for diagnosis of PICC-DVT is presented in **Figure 3**.

Treatment and Management

Treatment and management of PICC-DVT centers on 3 principles: 1) therapeutic systemic anticoagulation; 2)

Table 1 Epidemiology, Risk Factors and Evidence for Catheter-Associated Thrombosis

Risk Factor	Study/Citation (First Author)	n	Design/Population	Results/Effect Size (95% Confidence Interval)	Comments
Patient-related					
Surgery ≥1 h	Evans, 2010[7]	1728	Prospective cohort study of hospitalized patients at a single health system	OR 1.66 (0.91-3.01)	Avoiding PICC insertion in those undergoing elective surgery may prevent thrombosis
	Wilson, 2012[28]	431	Retrospective cohort study of critically ill neurological intensive care unit patients	OR 3.26 (1.48-7.17)	Neurological ICU patients who underwent surgery for 1 h or more had higher risk of PICC-DVT
COPD	Aw, 2012[4]	340	Retrospective cohort of patients with cancer who received PICCs for outpatient chemotherapy	OR 2.67 (0.65-11)	Following adjustment, COPD remained associated with higher risk of PICC-DVT
Diabetes mellitus	Yi, 2013[22]	81	Prospective cohort of hospitalized patients with cancer and PICCs who underwent screening Doppler sonography every 3 d for the first month	OR 3.01 (1.01-9.5)	Diabetes mellitus was associated with higher risk of PICC-related thrombosis
	Aw, 2012[4]	340	Retrospective cohort of patients with cancer who received PICCs for outpatient chemotherapy	OR 3.18 (1.06-9.53)	Diabetes increased the risk of developing PICC-DVT in patients receiving chemotherapy
Prior CVCs	Lee, 2006[35]	444	Prospective cohort of patients with cancer undergoing CVC insertion for outpatient chemotherapy	OR 3.8 (1.4-10.4)	History of prior CVC use/ insertion was associated with higher risk of thrombosis
History of DVT	Lobo, 2009[17]	777	Retrospective cohort of patients who required PICCs during their hospitalization	OR 10.83 (4.89-23.95)	Avoiding PICCs in patients who have prior history of DVT may prevent thrombosis
	Evans, 2010[7]	1728	Prospective cohort study at a single health system of hospitalized patients	OR 9.92 (5.08-21.25)	Patients with a history of DVT are at increased risk for developing PICC-DVT
	Wilson, 2012[28]	431	Retrospective cohort study of critically ill neurosurgical intensive care unit patients	OR 6.66 (2.38-18.62)	A history of venous thromboembolism was associated with the development of PICC-related large vein thrombosis
Renal failure	Marnejon, 2012[20]	400	Case-control study of consecutive patients post PICC insertion at a single hospital	OR 2.095 $P = .010$	Patients with renal failure were at greater risk of thrombosis following adjustment for other confounders
Malignancy or metastatic cancer	Verso, 2008[18]	310	Retrospective analysis of thrombosis risk factors from a randomized controlled trial targeting outpatient chemotherapy	OR 9.36 (1.53-57.05)	Along with prior history of DVT, active malignancy and, particularly, metastatic cancer are factors that were most associated with increased risk of catheter-related thrombosis

Table 1 Continued

Risk Factor	Study/Citation (First Author)	n	Design/Population	Results/Effect Size (95% Confidence Interval)	Comments
	Liem, 2012[14]	690	Retrospective cohort study comparing patients with PICC-related symptomatic thrombosis to those without thrombosis	OR 4.1 (1.9-8.9)	Concurrent or recent malignancy was associated with the development of DVT in patients with PICCs
	Tran, 2010[19]	498	Retrospective single-center analysis of patients with hematological malignancies with PICCs and symptomatic UEDVT	7.8%	High incidence of DVT associated with PICCs in patients receiving myelosuppressive chemotherapy; central IJ PICCs were associated with low incidence of thrombosis
	Chopra, 2013[11]	64	Systematic review and meta-analysis of 64 studies including 29,503 patients	OR 2.24 (1.01-4.99)	In patients with a malignancy, PICCs were associated with a higher risk of DVT as compared with CVCs
Recent trauma	Marnejon, 2012[20]	400	Case-control study of consecutive patients post PICC insertion at a single hospital	OR 2.76 $P = .011$	History of trauma was associated with higher risk of thrombosis
Chest radiotherapy	Verso, 2008[18]	310	Retrospective analysis of thrombosis risk factors from a randomized controlled trial targeting outpatient chemotherapy	OR 7.01 (1.42-34.66)	Prior chest radiotherapy was highly associated with increased risk of thrombosis
Paretic arm	Wilson, 2012[28]	431	Retrospective cohort study of critically ill neurosurgical intensive care unit patients	OR 9.85 (4.42-21.95)	Providers should avoid placing PICCs in paretic arms
Critically ill and hospitalized	Chopra, 2013[11]	64	Systematic review and meta-analysis of 64 studies including 29,503 patients	OR 4.04 (2.17-7.07)	Critically ill patients with PICCs are more likely to develop DVT than those who receive acute CVCs
High BMI	Moran, 2014[23]	1444	Case control analysis of adult inpatients who underwent PICC placement at a single hospital	BMI >30 OR 1.98 (1.09-3.61)	Providers should pay attention to patients with PICCs and a BMI >30 in order to reduce the risk of PICC-associated complications
Device-related					
Larger catheter diameter	Evans, 2010[7]	1728	Prospective cohort study at a single health system of hospitalized patients	Double-lumen 5-Fr vs single-lumen OR 7.54 (1.61->100) Triple-lumen 6-Fr vs single-lumen OR 19.5 (3.54->100)	Smaller catheters and correspondingly, catheters with a lower number of lumens were associated with lower risk of thrombosis
	Evans, 2013[10]	5018	Prospective observational study at a Level I trauma and tertiary referral hospital for 3 years with smaller-diameter PICCs used more during the third year of the study	Double-lumen 5 Fr vs single-lumen 4Fr OR 2.24 (1.16-4.31) Triple-lumen 6 Fr vs single-lumen 4 Fr OR 6.35 (2.78, 14.52)	Clinicians should select the smallest-diameter PICC necessary for the patient's care to reduce risk of thrombosis from PICCs

Table 1 Continued

Risk Factor	Study/Citation (First Author)	n	Design/Population	Results/Effect Size (95% Confidence Interval)	Comments
	Liem, 2012[14]	690	Retrospective cohort study comparing patients with PICC-related symptomatic thrombosis to those who did not develop thrombosis	OR 3.9 (1.1-13.9)	Catheters with a large diameter ($\geq$5 Fr) were associated with the development of UEDVT compared with smaller size devices
	Nifong, 2011[24]	N/A	Experimental study that used fluid mechanics to calculate relative flow rates as a function of the ratio of the catheter to vein diameters	Linear relationship between the relative flow rate and the catheter to cylinder diameter ratio was found with a correlation of $r^2 = 0.90$	PICCs may substantially decrease venous flow rates by as much as 93%
PowerPICCs	Baxi, 2013[27]	1652	Retrospective cohort of patients who received PICCs during their hospitalization at a single medical center	OR 2.3 (1.08-4.91)	PowerPICCs were associated with both venous thrombosis and central line-associated bloodstream infection
Catheter-associated infection	Ahn, 2013[29]	237	Retrospective cohort study of patients with cancer at a single medical center	OR 2.46 (1.03-5.86)	Higher rate of PICC-DVT observed when catheters were infected compared with those that were not.
	Del Principe, 2013[106]	71	Prospective cohort study of patients with acute myeloid leukemia; sepsis associated with PICC-DVT	HR 4.12	Patients with sepsis had higher rates of catheter thrombosis than those without this condition.
Number of lumens	O'Brien, 2013[25]	1328	Quasi experiment (pre-post) study in a Canadian teaching hospital. Intervention consisted of screening all PICC orders and placing only single-lumen PICCs unless more lumens were warranted	Rates of thrombosis was reduced from 1.22% with double lumen catheters to 0% with single lumen catheters	A hospital-wide effort to decrease the insertion of multi-lumen PICCs without an appropriate rationale for the same can decrease overall rates of PICC-DVT
Vancomycin infusion	Marnejon, 2012[20]	400	Case-control study of consecutive patients post PICC insertion at a single medical center	OR 3.44 $P = .001$	Because vancomycin has a low pH, endothelial irritation and thrombosis is possible, although this is controversial and likely also influenced by duration of treatment
Amphotericin B infusion	Chemaly, 2002[5]	2063	34-month retrospective chart review of patients who had a PICC placed at the Cleveland Clinic Foundation	OR 10.0 (2.04—49.05)	Association of UEDVT with antifungal AmB likely relates to thrombogenicity from irritation of the venous intima
Chemotherapy	Yi, 2013[22]	81	Prospective cohort of hospitalized patients with cancer and PICCs who underwent Doppler sonography every 3 days for the first month	OR 2.77 (1.01-9.5)	Chemotherapy was associated with higher risk of PICC-related thrombosis
Mannitol infusion	Wilson, 2012[28]	431	Retrospective cohort study of critically ill neurosurgical intensive care unit patients	OR 3.27 (1.27-8.43)	Mannitol use in critically ill neurosurgical patients was associated with increased risk of thrombosis

Table 1 Continued

Risk Factor	Study/Citation (First Author)	n	Design/Population	Results/Effect Size (95% Confidence Interval)	Comments
ESA administration	Ahn, 2013[29]	237	Retrospective cohort study of patients with cancer at a single medical center	OR 10.7 (2.3-50.0)	Concomitant administration of ESAs while a PICC is in situ was the strongest predictor of thrombosis
Catheter dysfunction	Lee, 2006[35]	444	Prospective cohort of patients with cancer undergoing CVCs insertion for outpatient chemotherapy	OR 14.7 (5.5-40)	Catheter blockage is significantly associated with catheter-related thrombosis
Spontaneous dislodgement	Qiu, 2014[44]	510	Prospective cohort of oncology patients with PICCs followed until catheter removal or spontaneous dislodgment	RR 17.46 (8.29-36.82)	Catheter-related thrombosis was observed to be strongly associated with spontaneous dislodgement of PICCs
Provider-related					
Decision to screen	Itkin, 2014[15]	332	Prospective randomized, controlled trial in a single center comparing 2 types of PICCs and symptomatic vs nonsymptomatic screening	Symptomatic: 4.3% and 3.6% Asymptomatic: 65.2% and 69.1%	Asymptomatic PICC-DVT is far more common than symptomatic DVT. At-risk patients may need to be screened regularly in order to detect this event
	Chopra, 2013[11]	64	Systematic review and meta-analysis. 533 citations, 64 studies with 29,503 patients	Asymptomatic screening: OR 3.22 (1.67-6.18) Symptomatic testing: OR 2.37 (1.18-4.76)	PICC-DVT might be more prevalent than clinically perceived and more evident when screened for than when clinically recognized
Site other than cavoatrial junction/ noncentral PICC tip	Lobo, 2009[17]	777	Retrospective cohort of patients who required PICCs during hospitalization	OR 2.61 (1.28-5.35)	Verifying the cavoatrial junction placement of PICCs is protective against PICC-DVT
US guidance during insertion	Gong, 2012[54]	180	Prospective cohort of patients with cancer who were divided to receive PICC using ultrasound or traditional method	Thrombosis upon removal of the catheter was noted in 7.5% of the traditionally placed PICCs vs 0% of the US guided	PICCs placed using the ultrasound were less likely to have thrombotic complications
Basilic vein placement	Marnejon, 2012[20]	400	Case-control study of consecutive patients post PICC insertion at a single hospital	OR 2.95	Providers should avoid basilic vein PICCs placement
	Bonizzoli, 2011[13]	239	Prospective cohort of patients admitted to a teaching hospital's intensive care unit in Florence, Italy who were (i) discharged with CVCs (during the first 4 mo) or PICCs (during the last 4 mo) and (ii) serially underwent Doppler studies	OR 2.18 (1.122-4.244) if placed in left basilic vein	Found a higher risk of DVT development related to sex (female) and site access (left basilic vein)
	Liem, 2012[14]	690	Retrospective cohort study comparing the characteristics of patients with PICC-related symptomatic thrombosis to the ones of patients who did not develop thrombosis	Basilic 3.1% Non-basilic 1.5%	Basilic vein PICCs were associated with a higher incidence of UEDVT, however, there is no significant evidence that cephalic veins should be used for PICCs

Table 1 Continued

Risk Factor	Study/Citation (First Author)	n	Design/Population	Results/Effect Size (95% Confidence Interval)	Comments
Cephalic vein placement	Allen, 2000[51]	119	Retrospective study on patients who had (i) normal findings during initial venography, (ii) PICC placement, and (iii) underwent repeated venography	Cephalic 57% Basilic 14% Brachial 10%	Relatively high rate of venous thrombosis associated with PICCs placed in the cephalic vein

BMI = body mass index; COPD = chronic obstructive pulmonary disease; CVC = central venous catheter; DVT = deep vein thrombosis; ESA = erythropoiesis-stimulating agents; Fr = French; IJ = internal jugular; OR = odds ratio; PICC = peripherally inserted central catheter; UEDVT = upper-extremity deep vein thrombosis; US = ultrasonography.

removal of PICCs that are no longer necessary; and 3) thrombolysis or interventional procedures.

Systemic Anticoagulation. No randomized controlled trials of systemic anticoagulation for PICC-DVT exist. Available recommendations are thus extrapolated from lower-extremity DVT and studies of recurrent venous thromboembolism in patients with cancer.[9,76,77]

Weight-based low-molecular-weight heparin (eg, fondaparinux or enoxaparin) is recommended over intravenous unfractionated heparin infusion as the initial therapeutic strategy for PICC-DVT in patients with cancer.[76,78,79] Warfarin dosed to achieve an international normalized ratio of 2-3 is acceptable for noncancer patients or those who cannot receive low-molecular-weight heparins due to medical or cost constraints. At minimum, 3 months of anticoagulation are recommended (Grade 2B evidence). Should the affected PICC be clinically needed beyond 3 months, prolonging systemic anticoagulation to match the duration of catheter use is

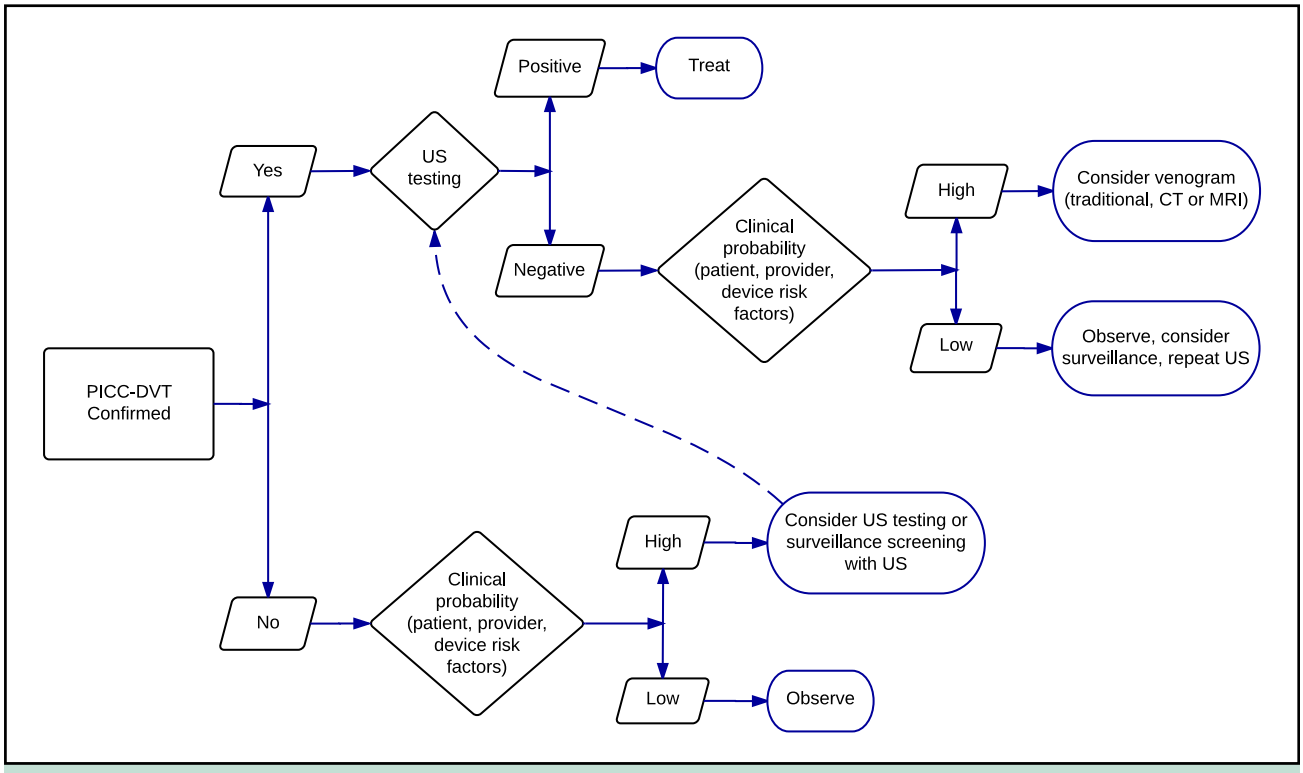

Figure 3 Algorithmic, evidence-based approach to diagnosis of PICC-DVT. The flowchart shows an algorithmic, evidence-based approach to diagnosis of PICC-DVT. CT = computed tomography; MRI = magnetic resonance imaging; PICC-DVT = peripherally inserted central catheter-deep venous thrombosis; US = ultrasonography.

recommended (Grade 1C evidence).[76] However, limited data regarding risks and benefits of prolonged anticoagulation are currently available.

PICC Removal. Because PICCs remain a nidus for propagation of clot, removal should be considered when thrombosis is detected. In this context, 2 questions should be answered: 1) is the PICC still clinically necessary? and if so, 2) is it still well positioned (eg, at the cavoatrial junction) and functional? Existing guidelines do not advocate routine removal of PICCs provided the answer to these questions is affirmative (Grade 2C evidence).[76] However, PICC removal may be unavoidable in settings where anticoagulation is contraindicated or if bloodstream infection coexists. Persistent symptoms such as arm pain or swelling despite several days of anticoagulation may also warrant catheter removal.[80]

Thrombolysis and Interventional Procedures. Few studies have compared thrombolytic or endovascular treatments with anticoagulation alone for catheter-related DVT, let alone PICC-DVT. However, observational data suggest improvement in upper-extremity venous patency with early institution of thrombolytic therapy and anticoagulation, albeit with an increased risk of bleeding.[81-84] Catheter-directed therapy has replaced systemic thrombolytic therapy in upper-extremity DVT.[85-87] Current guidelines recommend that thrombolysis be reserved for patients who present with severe symptoms (eg, phlegmasia or functional impairment of the limb); extensive thrombus burden in the subclavian or axillary veins; symptoms for 14 days; good functional status; life expectancy of at least 1 year; and low risk of bleeding.[76]

Endovascular modalities including thrombectomy and angioplasty reduce the risk of postthrombotic syndrome in the lower extremities, but their role in treating PICC-DVT is unclear.[88,89] Observational studies of endovascular therapies for catheter-related DVT suggest promise of early recanalization.[85,90] Although in use,[91] long-term safety and efficacy data for superior vena cava filters in upper-extremity DVT are not available[92]; thus, use in PICC-DVT cannot be recommended at this time.[76]

An algorithmic approach for managing PICC-DVT that synthesizes the available evidence is presented in **Figure 4**.

Prevention of PICC-DVT

Prevention of PICC-DVT should center on patient-, provider-, and device-related characteristics. Consideration of vascular access devices that are associated with lower risk of thrombosis is therefore a pragmatic and proactive approach.[19,34,93,94] Similarly, use of ultrasound to ensure appropriate catheter-to-vein ratio, verification of tip position, and early removal of PICCs are but a few provider

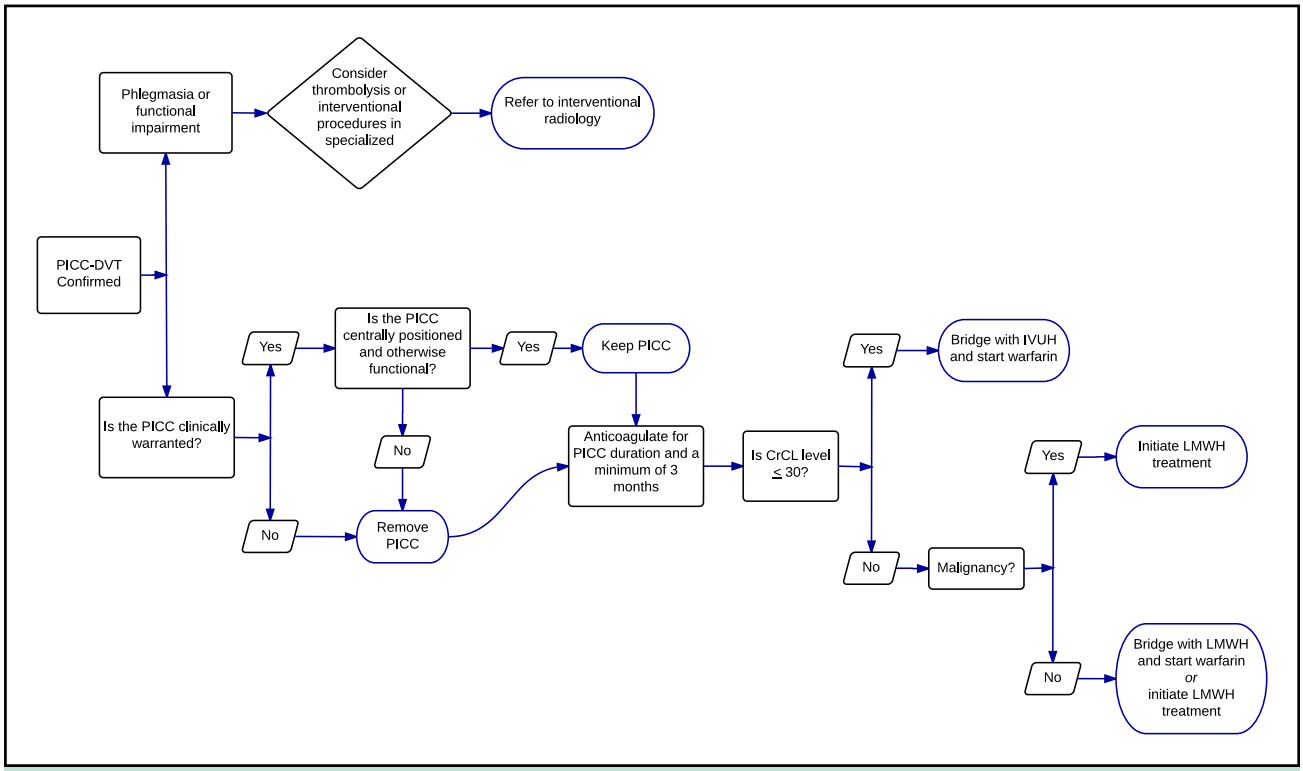

Figure 4 Flowchart showing an algorithmic, evidence-based approach to treatment of PICC-DVT. CrCl = creatinine clearance; LMWH = low-molecular-weight heparin; IVUH = intravenous unfractionated heparin; PICC = peripherally inserted central catheter; PICC-DVT = peripherally inserted central catheter-deep venous thrombosis.

Table 2 Diagnosis, Treatment, and Prevention of Catheter-Associated Thrombosis

Method Used	Study/Citation (First Author)	N	Design/Population	Sensitivity/Specificity (95% Confidence Interval)	Comments
Diagnosis					
US and contrast venography	Di Nisio, 2010[63]	17 articles 793 patients	Retrospective systematic review assessing diagnostic accuracy of tests for clinically suspected UEDVT and to evaluate replacement of venography up to June 2009	Compression US: 97% (90%-100%)/ 96% (87%-100%) Doppler US: 84% (72%-97%)/94% (86%-100%) Doppler US with compression: 91% (85%-97%)/93% (80%-100%) Phleborheography: 85% (72%-99%)/87% (71%-100%)	Compression US may be an acceptable alternative to venography Color Doppler does not seem to improve the accuracy of UEDVT diagnosis
	Mustafa, 2002[66]	6 articles 170 patients	Prospective review of duplex US for diagnosis of UEDVT from 1980-2000	56%-100%/94%-100%	Doppler evaluation alone is less sensitive and less specific than real-time imaging or duplex UEDVT diagnosis. US for clinically suspected UEDVT needs further study
	Baarslag, 2002[67]	126	Prospective study of duplex US compared with venography at one teaching hospital	Duplex US: 82% (70%-93%)/82% (72%-92%) 50% of isolated flow abnormalities were thrombosis-related	Duplex US may be used for initial diagnosis Contrast venography should be performed in patients with isolated flow abnormalities
	Kim, 2003[69]	18	Prospective study following patients who underwent CT and MR venography	Spearmen rank correlation coefficient: Reader 1: $Rs = 0.58$ ($P < .01$) Reader 2: $Rs = 0.56$ ($P < .01$)	CT and MR venography are correlated; CT venography accurately depicted benign venous obstruction; more studies are needed
Plasma biomarkers	Merminod, 2006[73]	52	Preliminary data on D-dimer testing in clinically suspected UEDVT	100% (78%-100%)/14% (4%-29%) PPV: 32% (19%-47%) NPV: 100% (47%-100%)	There is doubt that D-dimer can be used as a diagnostic test for UEDVT; further study is needed
	Ramacciotti, 2011[75]	178	Prospective study to evaluate diagnosis of DVT with a combination of soluble P-sel, D-dimer and clinical Wells score	P-sel: 28%/96% P-sel + Wells score: Establish diagnosis of DVT 33%/95%, PPV: 100% Rule-out DVT 99%/33%, NPV: 96% D-dimer: 98%/29% PPV: 40%, NPV: 80% P-sel + D-dimer: 43%/81% PPV: 58%, NPV: 81%	P-sel in combination with Wells score could be useful in DVT diagnosis
	Rectenwald, 2005[74]	73	Prospective study to evaluate diagnosis of DVT with a combination of D-dimer, soluble P-sel, and total microparticles	73%/81%	Plasma biomarkers, specifically P-sel, can be developed to achieve moderate sensitivity and specificity to diagnose DVT
Treatment					
Systemic anticoagulation	Akl, 2008[78] and Akl, 2014[104]		Review and systematic meta analysis of heparin (UFH or LMWH) and warfarin on DVT treatment	Heparin RR 0.43 (0.18-1.06) Mortality RR 0.74 (0.40-1.36) Infection RR 0.91 (0.36-2.28) Major bleeding RR 0.68 (0.10-4.78) Thrombocytopenia RR 0.85 (0.49-1.46)	Heparin (UFH or LMWH) was the only therapy associated with a reduction of symptomatic DVT

Table 2 Continued

Method Used	Study/Citation (First Author)	N	Design/Population	Sensitivity/Specificity (95% Confidence Interval)	Comments
				Warfarin RR 0.62 (0.30-1.27)	
Thrombolysis and other interventions	Sabeti, 2002[82]	95	Prospective study of inpatients with subclavian-axillary vein thrombosis treated either with thrombolysis and subsequent oral anticoagulation, or with anticoagulation only	60% reduced risk for a thrombosis (0.2 to 0.9)	Systemic thrombolysis was useful in treating subclavian-axillary vein thrombosis as compared with anticoagulation alone; high rate of complications during thrombolysis may exceed the harm of thrombosis
	Horne, 2000[81]	18	Small prospective study of patients diagnosed with lower-extremity thrombosis treated with intraclot administration of urokinase substitute, rtPA	Venous patency achieved in 10 of the 18 patients with axillary-subclavian thrombosis after 1 or 2 treatments	No observation of uncontrolled bleeding, however, more studies are needed to evaluate use of rtPA
	Maleux, 2010[85]	68	Retrospective case review of patients with active cancer and without cancer between 1997 and 2009 who underwent CDT	91% ($P = .68$)	CDT may be a feasible and effective intervention for catheter-related thrombosis in patients without cancer
	Enden, 2009[88]	103	Multicenter randomized controlled trial where patients with ilia-femoral patency received either additional CDT or standard treatment alone	Iliofemoral patency: RR 28.2% (9.7%-46.7%) Venous obstruction: RR 29.1% (20.0%-38.0%)	Additional CDT may increase iliofemoral patency; lysis or angioplasty did not correlate significantly with 6-month patency
Prevention					
Patient-, provider-, and device-related characteristics	Pikwer, 2012[94]	12	Review of studies comparing complications of CVCs or PICCs	Catheter tip malposition 9.3% (CVC) vs 3.4% (PICC) Thrombophlebitis 78 vs 7.5 per 10,000 indwelling days Catheter dysfunction 78 vs 14 per 10,000 indwelling days	Risks of tip malposition, thrombophlebitis, and catheter dysfunction are more common in CVCs as compared with PICCs
Institution-wide limits to PICC gauge	Evans, 2013[10]	5018	Prospective observational study at a level I trauma and tertiary referral hospital for 3 years with smaller-diameter PICCs were more used during the 3rd year of the study	Double-lumen 5-Fr vs single-lumen 4-Fr OR 2.24 (1.16-4.31)	The use of significantly ($P < .0001$) more single-lumen PICCs in 2010 (compared with 2008-2009) was a major contributor to the decrease in PICC-associated DVTs
	O'Brien, 2013[25]	1328	Quasi experiment (pre-post) in a Canadian teaching hospital consisted of screening all PICC orders by a nurse and	Triple-lumen 6-Fr vs single-lumen 4-Fr OR 6.35 (2.78-14.52) Triple-lumen 6-Fr vs single-lumen 4-Fr OR 6.35 (2.78-14.52)	A significant increase in the use of single-lumen and smaller PICCs was associated with a significant decrease in PICC-DVT

Table 2 Continued

Method Used	Study/Citation (First Author)	N	Design/Population	Sensitivity/Specificity (95% Confidence Interval)	Comments
			placing only single-lumen PICCs unless more lumens are indicated		
	Evans, 2013[10]	5018	Prospective observational study at a Level I trauma and tertiary referral hospital for 3 years with smaller-diameter PICCs were more used during the third year of the study	Double-lumen 5-Fr vs single-lumen 4-Fr OR 2.24 (1.16- 4.31) Triple-lumen 6-Fr vs single-lumen 4-Fr OR 6.35 (2.78, 14.52)	A significant increase in the use of single-lumen, smaller gauge PICCs was associated with a significant decrease in PICC-DVT
Use of antiplatelet agents	Ahn, 2013[29]	237	Retrospective cohort study of patients with cancer at a Dallas medical center	OR 10.7 (2.3-50.0)	Use of antiplatelet agents seems to have a protective effect against UEDVT
US screening high-risk patients	Bonizzoli, 2011[13]	239	Prospective cohort of patients admitted to a teaching hospital's intensive care unit in Florence, Italy who were discharged with CVCs (during the first 4 mo) or PICCs (during the last 4 mo) and serially underwent Doppler studies	80% of PICC-DVTs occurred 2 weeks after intensive care unit discharge	Screening during this 2-week period may be of clinical value for prevention of PICC-DVT

CDT = catheter-directed thrombolysis; CT = computer tomography; CVC = central venous catheter; LMWH = low molecular weight heparin; MR = magnetic resonance; NPV = negative predictive value; PICC = peripherally inserted central catheter; PPV = positive predictive value; P-sel = P-selectin; RR = relative risk; rtPA = recombinant tissue plasminogen activator; UEDVT = upper extremity deep vein thrombosis; UFH = unfractionated heparin; US = ultrasonography.

practices that may reduce thrombosis risk.[17,45,49,95] Such efforts may occur at an institutional level by removing PICCs of greater gauge or multiple lumens, both of which have been shown to effectively reduce cost and DVT rates.[10,25]

Early studies of thromboprophylaxis suggested small reductions in rates of catheter thrombosis.[96-99] However, newer studies have rendered the matter controversial, at best.[16,100-103] In a Cochrane review, Akl et al[104] included 12 randomized trials of 3611 cancer patients and found that prophylaxis with heparin was not associated with reduction in symptomatic DVT compared with placebo (relative risk [RR] 0.4; 95% CI, 0.2-1.1). Similarly, anticoagulation with low-dose warfarin did not reduce symptomatic or asymptomatic DVT (RR 0.6; 95% CI, 0.3-1.3).[78] However, a recent update to this review reported a statistically significant reduction of symptomatic DVT with heparin and asymptomatic DVT with warfarin.[104] However, given the risk of important adverse events, existing guidelines do not recommend routine use of pharmacologic prophylaxis to prevent catheter thrombosis.[76] Notably, 2 recent studies involving PICCs have suggested that prophylaxis may prevent PICC-DVT.[23,105] Thus, further PICC-specific studies in this area appear necessary. While some studies have reported that antiplatelet agents such as aspirin and clopidogrel may reduce PICC-DVT,[29] limited large-scale data exist at this time. Screening ultrasonography in patients with PICCs has not been shown to be beneficial to date. Given the uncertainty regarding the clinical significance of asymptomatic thrombi and the natural history of these events, well-designed studies are also needed in this area.

Table 2 summarizes 16 studies relevant to diagnosis, treatment, and prevention of PICC-DVT.

Limitations

Despite a systematic approach, this review has some limitations. First, the existing PICC-DVT literature comprises many observational studies. As such, the quality of the available evidence and inherent risk for bias must be carefully considered. Second, while the algorithms we propose

are evidence based, these should be viewed as informative until better data are available. Third, because many studies do not report the association between catheter-dwell time and risk of PICC-DVT, recommendations regarding an "optimal" window of PICC use cannot be defined. However, early removal of nonessential PICCs is an important aspect in preventing thrombosis and should be encouraged whenever possible.

CONCLUSIONS

This review summarizes the state of the art with respect to diagnosis, treatment, and prevention of PICC-DVT. Despite substantial progress in our understanding of this condition, many questions remain to be answered. Given the clinical consequences (pain, interruption of venous therapy, risk of infection, and pulmonary embolism), potential for chronic debility (venous outflow obstruction, central vein stenosis, postthrombotic syndrome), and challenges associated with treatment and diagnosis of this state, further research would be welcomed. In the interim, a mindful approach that weighs the pros and cons of PICC use may be our most effective approach: an ounce of prevention may thus be our greatest ally in thwarting PICC-DVT.

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APPENDIX

PubMed Clinical Queries

(Etiology/Broad[filter] OR risk) AND ((PICC OR "peripherally inserted central catheter" OR peripherally inserted central catheter) AND (DVT OR "deep vein thrombosis" OR deep vein thrombosis))

Scopus

TITLE-ABS-KEY((etiology OR risk*) AND ((picc OR "peripherally inserted central catheter" OR peripherally inserted central catheter) AND (dvt OR "deep vein thrombosis" OR deep vein thrombosis OR thromboembolism* OR thrombus OR thrombosis)))

CINAHL

(etiology OR risk) AND (picc OR "peripherally inserted central catheter" OR peripherally inserted central catheter) AND (dvt OR "deep vein thrombosis" OR deep vein thrombosis OR thromboembolism* OR thrombus OR thrombosis)

Embase

('etiology'/exp OR etiology OR risk*) AND (picc OR 'peripherally inserted central catheter'/exp OR 'peripherally inserted central catheter' OR (peripherally AND inserted AND central AND ('catheter'/exp OR catheter))) AND (dvt OR 'deep vein thrombosis'/exp OR 'deep vein thrombosis' OR ((deep AND ('vein'/exp OR vein)) AND ('thrombosis'/exp OR thrombosis)) OR thromboembolism* OR 'thrombus'/exp OR thrombus OR 'thrombosis'/exp OR thrombosis)

CCRT

((etiology OR risk*) AND ((picc OR "peripherally inserted central catheter" OR peripherally inserted central catheter) AND (dvt OR "deep vein thrombosis" OR deep vein thrombosis OR thromboembolism* OR thrombus OR thrombosis)))