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Q: Should you use compression duplex ultrasonography to detect deep vein thrombosis to evaluate unexplained fevers?

An 84-year-old female was admitted for pyelonephritis complicated by septic shock and *Klebsiella pneumoniae* bacteremia. She was treated with antibiotics and she clinically improved. However, she later developed daily fevers with temperatures up to 39°C (102.2°F) with a negative repeat workup for infectious disease. Should you consider venous thromboembolism (VTE) as a potential cause of her fevers?

A: The hospitalized patient with unexplained fever is a commonly encountered diagnostic challenge. These patients constitute a heterogeneous group that shares broad differential diagnoses and often the need for extensive and expensive testing.

Venous thrombosis of the extremities has been traditionally taught to be a cause of occult fevers, and its diagnosis can be reliably made using a noninvasive test, compression duplex ultrasonography (CDUS). Hence, the use of CDUS in the workup of unexplained fever has increased despite the paucity of evidence on safety and cost-effectiveness in this clinical context.^{1,2}

Although CDUS is essentially a risk-free procedure that can be performed on virtually any patient, clinical reasoning based on the outcome of this test could lead to substantial harm. The most important risks are stopping the diagnostic process prematurely if CDUS identifies an incidental thrombus, and the unlikely, but possible, risk of false-positive results leading to inappropriate anticoagulation therapy. Given these potential risks and the substantial financial cost associated with CDUS, ordering this as an initial test is not advisable. We reviewed the literature

to provide clinicians with recommendations on when to order CDUS of the extremities in the evaluation of hospitalized patients with unexplained fever.

■ VENOUS THROMBOEMBOLISM AND FEVERS: CAUSATION VS MERE ASSOCIATION?

Thrombosis involves endothelial activation and inflammation, which has been hypothesized to be pyrogenic.³ However, VTE risk factors (eg, malignancy, infection, recent surgery, autoimmune diseases) are associated with fevers even in the absence of thrombosis, possibly acting as confounding variables in the association between VTE and fevers.^{4,5} Hence, it is important to revisit the traditional teaching that venous thrombosis of the extremities causes fevers.

The association between VTE and fevers has been frequently described in case series. The estimated prevalence is highly variable and ranges between 4.9% and 33.3% in recent studies (Table 1).⁶⁻¹¹ This wide range is likely related to different temperature cutoffs, sites of measurement, measurement timing and frequency, scope of investigation (venous thrombosis of extremity alone vs pulmonary embolism), and the extent to which patients were evaluated for other causes of fevers before attributing the fever to VTE.

Despite the attempt to rule out alternative causes of fever in some series, the possibility of unidentified etiologies threatens the claim that thromboembolic events are causally related to fevers. Two studies emphasized this concern after finding similar temperatures in patients diagnosed with VTE and unmatched patients

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TABLE 1
Fever characteristics in case series of VTE

Study	Sample size (n)	VTE site	Temperature for fever definition	Frequency of fever/VTE-related fever ^a	Exclusion of other causes ^b	Fever grade
Barba et al, 2011 ⁶	14,814	DVT	≥ 38.0°C	4.9%	No	
Stein et al, 2000 ⁷	363	PE	≥ 37.8°C	26.2%/11.8%	Yes	> 38.9°C was seen in 1.4%
Saad et al, 2018 ⁸	245	PE	≥ 38.0°C	25.7%/24.1%	Yes	
Kazmers et al, 2000 ⁹	175	DVT	≥ 37.8°C	9.1%	No	> 38.3°C was seen in 4.6%
Calvo-Romero et al, 2004 ¹⁰	154	PE	≥ 37.0°C	18.2%/18.2%	Yes	> 39.0°C was seen in 0.6%
Kokturk et al, 2005 ¹¹	117	PE	≥ 37.2°C	53.0%/33.3%	Yes	> 37.9°C and > 39°C were seen in 13.7% and 4.3%

^aWhen no attempt was made to exclude alternative causes, only the total frequency of fever is listed.

^bThis was done in varied ways, including querying discharge documentation, review of culture/radiographic data, and careful review of the entire chart.

DVT = deep vein thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism

who had negative testing.^{4,12} In a prospective study evaluating computed-tomography angiography, Stein et al reported temperatures greater than 38.5°C (101.3°F) in 2% of patients with both positive (n = 191) and negative (n = 632) testing for pulmonary embolism.¹²

In a study by Kazmers et al,⁹ oral temperatures were measured in 1,847 patients referred for venous doppler ultrasonography of the lower extremities. Fever [defined as temperature > 37.8°C (100.4°F)] was present in 9.5% of the 175 patients diagnosed with acute deep vein thrombosis (DVT) and 7.5% of the remaining 1,678 patients. This difference was not statistically significant. When temperature was analyzed as a continuous variable, the authors detected a statistically significant but clinically small difference between patients with and without thrombosis (mean temperatures of 37.0 ± 0.6°C and 36.9 ± 0.6°C, respectively; *P* < .02).⁹

The main limitation of these studies is that the study groups may have differed in characteristics other than the presence of thrombosis. For example, patients referred for CDUS who did not have DVT may have had a higher rate of cellulitis as an alternative cause of their symptoms. Despite the limitations, the results of the study by Kazmers et al⁹ suggest that body temperature may be elevated by acute thrombosis, though this seems to happen only to a mild degree or only in occasional patients, given the similar mean temperature across both groups.

YIELD OF COMPRESSION DUPLEX ULTRASONOGRAPHY IN EVALUATING UNEXPLAINED FEVERS

Two studies investigated the yield of venous doppler ultrasonography in patients being evaluated for unexplained fevers.^{1,2} AbuRahma et al² retrospectively reviewed 89 patients undergoing a fever workup who had their lower extremities assessed for venous thrombosis. Acute DVT was diagnosed in 7 patients (7.9%), though only 5 patients (5.6%) met the study criteria to ascribe the fever to the thrombotic event.

Yoo et al¹ reviewed orders for 4-extremity venous Doppler ultrasonography in their vascular imaging laboratory. Out of 188 orders, 101 had fevers listed as the indication. Of these 101 orders, acute DVT was diagnosed in 11 patients (10.9%), though a more likely etiology for the fevers was found in 10 patients, leaving only 1 patient (1.0%) to have fever attributed to the DVT. These findings highlight the risk of premature closure if fever workup is terminated after identifying the presence of VTE.

UPPER-EXTREMITY COMPRESSION DUPLEX ULTRASONOGRAPHY

If CDUS is ordered to screen for DVT in patients with unexplained fevers in the absence of signs of venous thrombosis in any extremity, the question of which extremities to scan remains. In the study by

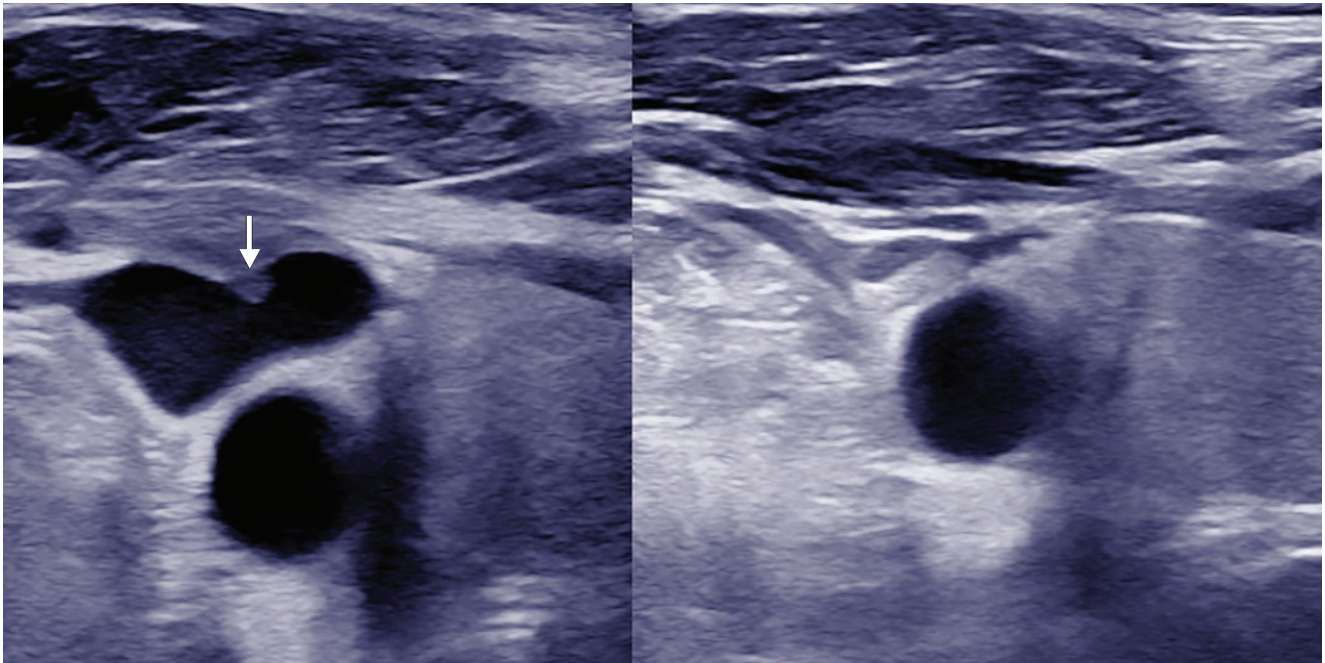


Figure 1. The left panel shows the right internal jugular vein with a scant amount of thrombus adherent to the anterior wall of the vessel (arrow). The right panel shows essentially complete compression of the right internal jugular vein on compression duplex ultrasonography.

Yoo et al,¹ which evaluated 188 orders for 4-extremity CDUS performed for various indications, 31 patients had acute DVT. Of the total number, 16 cases were only in the lower extremities, 11 were only in the upper extremities, and 4 were in both the upper and lower extremities. All 15 patients with upper-extremity DVT had a central venous catheter in place.¹ Furthermore, several studies suggest that central venous catheters and active cancer markedly increase the odds of upper-extremity DVT.^{13,14} These findings suggest that upper-extremity Doppler ultrasonography in asymptomatic limbs should only be considered in individuals with increased pretest probability of upper-extremity thrombosis, such as those with an indwelling catheter or active cancer.

EVIDENCE SUMMARY

Overall, current evidence suggesting that VTE could cause fevers is weak, and in most cases where these two phenomena coincide, they are not causally related. Moreover, in the population presenting with unexplained fevers, the yield of venous Doppler ultrasonography is low. Hence, given the costs and potential harm associated with its use, we believe that venous Doppler ultrasonography should not be an initial test

and should be ordered only when an exhaustive evaluation has been completed for more common causes of fever in the hospitalized patient. Caution should be taken before ascribing fevers to a venous thrombotic event. Lastly, when a decision has been made to use the test in asymptomatic extremities, we suggest scanning the lower extremities only, unless there are risk factors for upper-extremity venous thrombosis.

CASE CONTINUED

In our 84-year-old patient, CDUS was ordered and showed a small echogenic image suggestive of a venous thrombus where the patient had had an internal jugular vein catheter (**Figure 1**). Given the minuscule size of the thrombus and the presence of an alternative cause of the fever, ie, aspiration pneumonia, the thrombus was thought to have been an incidental finding rather than the true cause of her fevers.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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