

## **DEEP VEIN THROMBOSIS: A literature review.**

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### Abstract

*Background:* Deep vein thrombosis is a common and clinically relevant condition with important rates of recurrence and mortality. In particular, it may present the physician with diagnostic and therapeutic challenges. *Methods:* A review of articles was conducted by searching the databases of Pubmed, Medline and Medscape, using the following terms: deep vein thrombosis, pulmonary embolism, and venous thromboembolism. Related articles were also searched. *Conclusions:* Hospitalized patients have a significantly raised risk of venous thromboembolism, which may be compounded by other risk factors. A clinical model using risk stratification of patients may aid in diagnosis, as well as reducing the number of investigations required. Duration of treatment varies according to the patient's risk of recurrent DVT. Despite adequate therapy, DVT is associated with significant morbidity and mortality.

### Introduction

Deep vein thrombosis and pulmonary embolism, are collectively known as venous thromboembolism (VTE), a common disorder that can affect apparently healthy as well as hospitalized patients. The actual incidence and prevalence of this disease are difficult to estimate because of its often silent nature. The clinical relevance of VTE is highlighted by the important rates of recurrence and mortality (1). Virtually every physician who is involved in patient care (eg, specialist physician, GP, orthopaedic surgeon, gynaecologist, urologist, pulmonologist or cardiologist) encounters patients who are at risk of venous thromboembolism.

The causes of venous thromboembolism can be hereditary or acquired. A risk factor for thrombosis can often be identified in over 80% of patients, but usually more than one factor is at play in a patient (2).

### Epidemiology

The incidence of VTE is similar in men and women, and lower in Asians than it is in Caucasians or Africans (3). The overall age- and sex-adjusted incidence of VTE in the United States, including both pulmonary embolism (PE) and deep vein thrombosis (DVT), is 117 cases per 100 000 person-years (4).

These rates mask a considerable variation according to defined populations, such as elderly people, rising from fewer than 5 cases per 100 000 children aged less than 15 years to 450-600 cases per 100 000 adults aged 80 (2). After 40 years of age the incidence about doubles with each decade (3).

VTE is therefore predominantly a disease of older age, with the incidence rising sharply after age 60 in both men and women, with PE accounting for the majority of the increase (4). Over half of the episodes of VTE are deep vein thrombosis, and three quarters are first episodes (3). Compared to residents in the community, hospitalized patients have more than a 100-fold increased incidence of acute venous thromboembolism (5). In the United Kingdom, a report from the House of Commons Health Committee published in 2005 stated that each year over 25 000 people in England die from venous thromboembolism developing during hospitalization (6).

Reports on the frequency of DVT in general medical patients in the absence of prophylaxis vary from 10 to 26 %, depending on the methods used for diagnosis of DVT and the patient population studied (7,8).

Data from several studies show that DVT developed in approximately 55% of patients with stroke, and in 24% of patients with myocardial infarction (2,7). In general medical patients, congestive heart failure, respiratory distress and/or underlying chest infections appeared to increase the risk of VTE. The frequency of VTE in patients with congestive heart failure has been reported to be as high as 40% (7).

Approximately 24-30% of all general surgical patients without any DVT prophylaxis have been shown to develop DVT (5,9). Lower limb DVT has been documented in half of all major orthopaedic operations carried out without antithrombotic prophylaxis (2).

### Pathophysiology

A triad of factors that lead to the pathogenesis of venous thrombosis were described by Virchow in the 19<sup>th</sup> century: venous stasis, injury to the intima, and changes in the coagulation properties of blood.

Venous thrombi are formed by stasis and are mainly composed of red blood cells intertwined with fibrin. As very few platelets are involved, drugs that affect platelet function are less effective for DVT prophylaxis (9).

The red fibrin thrombus may either break off and embolize, or result in total occlusion of the vein. The endogenous thrombolytic system leads to partial dissolution, then the thrombus becomes organized and is incorporated into the venous wall.

Pulmonary emboli usually arise from the thrombi originating in the deep venous system of the lower extremities. However, rarely they may originate in the pelvic, renal or upper extremity veins and right heart chambers (4). In addition to physical obstruction, acute PE leads to the release of pulmonary artery vasoconstrictors and hypoxemia, with a subsequent increase in pulmonary vascular resistance and right ventricular (RV) afterload (4). The abrupt increase in RV afterload can cause RV dilatation and hypokinesis, tricuspid regurgitation, and ultimately RV failure (4). RV pressure overload can also lead to interventricular septal flattening and deviation towards the left ventricle (LV) in diastole, thereby impairing LV filling (4). Patients with RV failure may rapidly progress to systemic arterial hypotension and cardiac arrest (4).

### Risk Factors

Risk factors for VTE may be inherited or acquired. Thrombophilias include inherited reductions in plasma natural anticoagulants (eg antithrombin, protein C, or protein S). Impaired downregulation of the procoagulant system (eg activated protein C resistance, Factor V Leiden), increased plasma concentrations of procoagulant factors (eg factors I [fibrinogen], II[prothrombin], VIII, IX, and XI), increased basal procoagulant activity, and impaired fibrinolysis have been added to the list of inherited or acquired disorders predisposing to thrombosis (thrombophilia) (3,4,5). Antiphospholipid antibody syndrome as well as hyperhomocysteinemia are also associated with an increased risk of VTE (4,5).

Age, obesity, cardiovascular disease, atherosclerotic disease, smoking, recent surgery, cancer, hormone replacement therapy (HRT) or oral contraceptive use, trauma or hospitalization, central venous lines, immobility, long distance travel, pregnancy or post partum, and history or family history of previous VTE are all commonly mentioned in the literature as being associated with an

increased risk for VTE (1,2,3,4,5). Ischaemic heart disease, heart failure and cerebrovascular disease have been associated with an increased risk of PE, but not with DVT (10). In cancer patients, the risk varies for different types of cancer. The risk appears to be higher in pancreatic cancer, lymphoma, malignant brain tumours, liver cancer, leukaemia, lung, colorectal and breast cancer (5,11).

Among surgery patients, the risk varies according to age, type of surgery (eg major orthopaedic surgery, elective neurosurgery, multiple trauma or acute spinal cord injury being associated with higher risk), presence of cancer, and presence of other risk factors for VTE (eg a history of previous DVT, hypercoagulable state) (2,5). Major abdominal surgery, hip or knee replacement surgery also carry higher risk of VTE (2,12). Laparoscopic surgery has been shown to have a lower incidence of VTE compared to open surgery (13).

Women taking hormone replacement therapy (HRT) have a 2- to 5-fold increased risk of venous thrombosis compared with non-users (14). The increase in risk varies with duration of use (the risk being greatest during the first year of use), the type of preparation used (estrogen-progestin HRT has significantly greater risk of VTE than estrogen-only HRT), higher doses have a higher risk, and transdermal HRT has a lower risk of VTE than oral preparations (14). The use of oral contraception increases the risk of venous thromboembolism as well as arterial thrombosis. Third-generation pills seem to increase the risk of VTE compared with second generation pills. This effect seems to be reversed or absent for the risk of arterial thrombosis (15). An obese patient using oral contraceptives has been shown to have a 2.4-fold increased risk of VTE compared to oral contraceptive users of normal body mass index, and a 24-fold increased risk of VTE compared to non-users of oral contraceptives who had normal BMI (16).

A 30-year population-based study found the relative risk of VTE among pregnant or post-partum women was 4.29 and the overall incidence of VTE (absolute risk) was 199 per 100 000 woman-years. The annual incidence was 5 times higher among postpartum women than pregnant women, and the incidence of DVT was 3 times higher than that of pulmonary embolism (5,17). Pulmonary embolism was relatively uncommon during pregnancy versus the postpartum period (17). During pregnancy, the risk of DVT begins in the first trimester, and more commonly involves the right lower limb (18,19).

If prophylaxis is indicated, it should therefore be initiated early in pregnancy (18). Among trauma patients, injury severity, operative intervention, spinal cord injury, lower extremity fracture, and certain thoracic injuries were significant in VTE development (20). Minor injuries of the leg are also associated with a higher risk of VTE (21).

Nephrotic syndrome is a risk factor for VTE, and is more apparent among young adults (22,23). Risk of VTE was at its highest during the first six months after onset (24). The metabolic syndrome may contribute to the development of VTE, and is associated with a two-fold increased risk of VTE (25,26).

Recent studies have indicated an increased risk of venous thrombosis after air travel (27,28,29,30). In fact, the risk of venous thrombosis after travel has been found to be moderately increased for all modes of travel (28). Duration of travel (more than 6-8 hours), and clinical risk (higher risk travelers compared to those with lower risk) were significantly related to VTE rate (27,31). Long distance travel increases the risk of VTE approximately 2- to 4-fold, with a quantitative risk of lower limb venous thrombosis in high-risk subjects of about 5% per flight (29,30). Even individuals of low to moderate risk were found to have an increased incidence of VTE (32).

There is evidence that an additional mechanism to that of immobilization may lead to activation of coagulation after air travel (30,33). Hypoxia and dehydration have been amongst those postulated as possible mechanisms, although these hypotheses were not supported in experimental models (34,35). Incidence of VTE has been shown to be unrelated to class (business or economy) flown (36). Asymptomatic thrombi of uncertain clinical significance were more common than symptomatic VTE (31). This data may be influenced by the duration of surveillance of the participants after their flights.

More than 10% of passengers have been shown to develop raised levels of D-dimers, with its inherent risk of thrombosis (36). However, short-haul cockpit crews had no evidence of sub-clinical thrombotic events (37).

Prolonged seated immobility at work may also represent a risk factor for VTE (38,39). Even long term exposure to particulate air pollution has been associated with altered coagulation function and DVT risk (40).

### Diagnosis

The clinical diagnosis of deep vein thrombosis is unreliable, but clinical prediction rules based on signs and symptoms do facilitate the categorization of patients into high, low, or medium risk categories (41,42). A clinical model has been devised (table 1) and validated in numerous studies, and has been used in diagnostic algorithms to reduce the number of diagnostic tests required on patients with suspected deep vein thrombosis (42,43). Patients with a low pretest probability can have DVT safely excluded on the basis of a single negative ultrasound result (43,44). The use of plasma D-dimer tests in diagnostic algorithms can identify patients who do not require ultrasonography (43,45).

Table 1: Clinical model for predicting pretest probability of deep vein thrombosis (DVT).

<i>Clinical characteristic</i>	<i>Score</i>
Active cancer (treatment ongoing, administered within previous 6 months, or palliative)	1
Paralysis, paresis or recent plaster immobilization of the lower extremities	1
Recently bedridden > 3 days or major surgery within previous 12 weeks requiring general or regional anaesthesia	1
Localized tenderness along distribution of the deep venous system	1
Swelling of the entire leg	1
Calf swelling > 3 cm larger than asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
Alternative diagnosis at least as likely as DVT	-2

A score of 3 or higher = high probability.

A score of 1 or 2 = moderate probability.

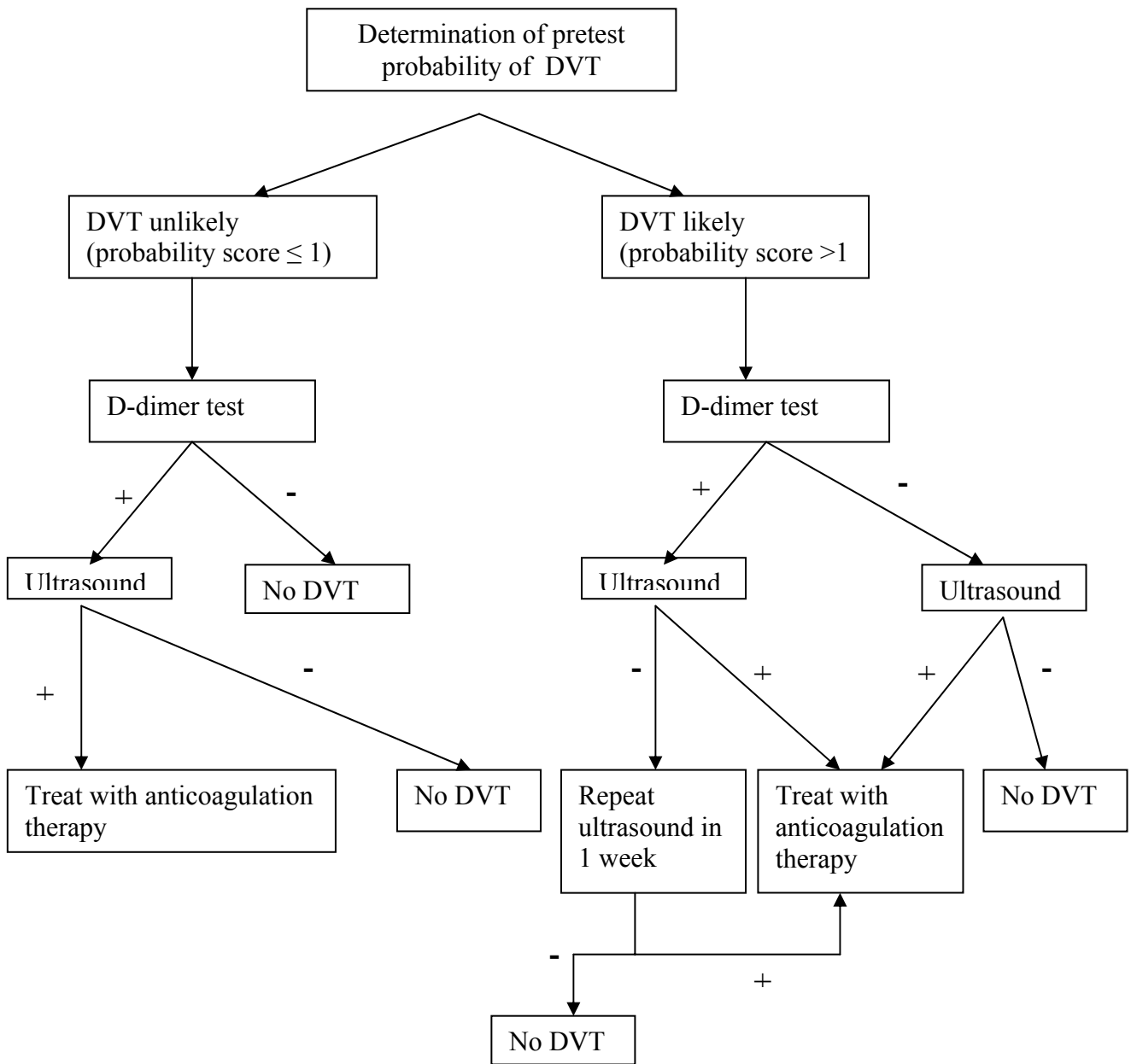
A score of 0 = low probability.

*Adapted from Journal of the American Medical Association. 1998 Apr 8; 279(14):1094-9.*

Compression ultrasonography is the imaging test of choice to diagnose deep vein thrombosis (42,43). It shows an average sensitivity and specificity of 97% for proximal deep vein thrombosis, but the sensitivity for symptomatic calf vein thrombosis has been reported as low as 75% (42). Ultrasonography therefore cannot be relied on to diagnose calf vein thrombosis (42). Diagnostic strategies that combine clinical probability, D-dimer testing, and repeat ultrasound after one week have been used to improve diagnosis (42,43). In compression ultrasound, the most simple ultrasonic criterion for diagnosing venous thrombosis is non-compressibility of the vascular lumen under gentle probe pressure.

If no residual lumen is observed the vein is considered to be fully compressible, which indicates the absence of venous thrombosis. In duplex ultrasonography, in addition to vascular lumen compressibility, blood flow characteristics are evaluated by using the pulsed Doppler signal. If flow is seen as continuous (rather than phasic with respiration) the presence of venous outflow obstruction is indicated (42). In colour flow Doppler ultrasonography, Doppler shifts are assigned different colours (red or blue) according to their direction (towards or away from the probe).

Table 2: Diagnostic algorithm using D-dimer testing and ultrasound imaging in patients with suspected DVT.



*Adapted from Canadian Medical Association Journal. 175(9): 1087- 1092*

Other imaging modalities include venography, computerized tomography venography (CTV), magnetic resonance venography (MRV), and radionuclide venography (RNV). Venography is reserved for discrepant non-invasive studies (46).

D-dimer is a degradation product of cross-linked fibrin blood clots, produced when fibrin is degraded by plasmin, so concentrations are raised in patients with venous thromboembolism. However, D-dimer levels may be raised in patients with a variety of other non-thrombotic conditions such as malignancy, pregnancy, trauma, haemorrhage or recent major surgery (42,43). D-dimer assays are generally sensitive but non-specific markers of DVT. Current evidence strongly

supports the use of a D-dimer assay in the clinical algorithm of suspected deep vein thrombosis (43,44,47). A negative D-dimer assay result excludes DVT in a low risk (Wells score <1) patient. A D-dimer assay should not be used to exclude DVT in patients who have a high pretest probability (43).

## Treatment and Prevention

Initial management of deep vein thrombosis is to prevent extension of thrombus and pulmonary embolism. Long-term management is to prevent recurrent events. Traditionally patients were admitted to hospital for treatment with intravenous unfractionated heparin (UFH), but over time this has been replaced with low molecular weight heparin (LMWH).

The current standard of care is to administer weight-adjusted LMWH once daily for 5-7 days as initial treatment (138). However, extended post-discharge prophylaxis with LMWH for 28 days should be considered for hospitalized medical patients with high risk for VTE (eg reduced mobility, older than age 75, cancer diagnosis, or history of VTE) (48). Simultaneous initiation of therapy with oral anticoagulants such as warfarin is required because of the time required for the therapeutic international normalized ratio to be stable between 2 and 3.

LMWH is the preferred anticoagulant, given its ease of administration and efficacy. LMWH is superior to UFH for treating DVT, with less recurrent venous thromboembolism, and particularly for reducing mortality and the risk for major bleeding (43,49,50). In prevention of DVT and PE in patients with acute ischaemic stroke, indirect comparison of low and high doses of UFH and LMWH suggests that low-dose LMWH have the best benefit/ risk ratio by decreasing the risk of both DVT and pulmonary embolism, without a clear increase in intra- or extra-cranial haemorrhage (51). Heparin-induced thrombocytopenia is possible with both therapies, although LMWH is less likely to cause antibody formation for this condition (49,52).

Additional advantages of LMWH are that it offers a more reliable dose-response relation, has a longer half-life, and so permits once daily subcutaneous administration without the need to monitor activated partial thromboplastin time. It remains unclear whether it is better to administer LMWH once or twice daily. A meta-analysis showed that once daily treatment with LMWH is as effective and safe as twice daily treatment with LMWH, however the 95% confidence interval implies that there is a possibility that the risk of recurrent VTE might be higher when patients are treated once daily (53).

LMWH is predominantly renally excreted, and therefore more dependant on renal function than UFH, where bioaccumulation of LMWH may cause bleeding. Consequently, care should be employed when LMWH is administered to patients with impaired renal function, particularly those with severe renal impairment (creatinine clearance below 30 ml/min) (54). In these patients, UFH would be the more suitable therapy.

In pregnancy, LMWH is preferred over UFH, although around the time of delivery UFH, with its shorter half-life, is easier to manage (55).

Fondaparinux, a factor Xa inhibitor, is an alternative agent for the treatment of DVT, with the advantage that heparin-induced thrombocytopenia (HIT) is not seen with this agent. Treatment of HIT involves immediate heparin cessation, and substitution with a non-heparin anticoagulant such as lepirudin (direct thrombin inhibitor) or fondaparinux (factor Xa inhibitor) (56).

Oral therapy with warfarin (a vitamin K antagonist) is used for long-term prevention of recurrent thrombosis. Warfarin has an unpredictable pharmacokinetic profile and a variable dose-response relationship that requires frequent coagulation monitoring and dose adjustments to maintain a target intensity that is both safe and effective. The duration of long-term treatment varies according to the perceived risk of recurrent DVT, and varies from 3-6 months to indefinitely (43,57). In a patient with first DVT in the absence of an identifiable risk factor, six months of anticoagulation would be considered as a minimum duration of therapy (43). At time of anticoagulant discontinuation, D-dimer levels and residual thrombosis have been indicated as predictors of recurrent VTE (57).

Although aspirin has been shown to reduce the risk of VTE in high risk surgical patients, it is not recommended for VTE prophylaxis in the medical patient (58,59). It has no role in the prevention of travel-related thrombosis (58,60).

Development of new anticoagulants, such as the direct thrombin inhibitors (ximelagatran, dabigatran) will offer alternative therapies in the future. Both the anti-factor Xa and antithrombin agents have been developed for oral use, and have shown impressive results in sponsor trials for the post-surgical prophylaxis of venous thrombosis; however safety concerns related to liver enzyme elevations and thrombosis rebound have been reported with their use (61).

Complementary medicines containing fibrinolytic enzymes such as nattokinase have demonstrated significant thrombolytic activity in animal models, and have been shown to reduce venous thrombosis in passengers on long-haul flights (62,63). These may also offer alternative therapies to patients with contra-indications to conventional anti-coagulants, as an add-on to compression stockings, or where oral medication is the only alternative.

Mechanical prophylactic devices include graduated compression stockings and intermittent pneumatic compression. These increase blood flow and may enhance fibrinolysis, leading to reductions in VTE (29,49,64). Inferior vena cava filters are indicated for the prevention of PE in patients in whom anticoagulation is contra-indicated, those who experience recurrent PE despite adequate anticoagulation, and those undergoing open surgical embolectomy. IVC filters are associated with an increased incidence of DVT (64).

## Prognosis

Despite adequate therapy, 1% to 8% of patients in whom pulmonary embolism develops will die; others will experience long-term complications such as post-phlebotic syndrome (40%) and chronic thromboembolic pulmonary hypertension (4%) (43). The overall mortality rate associated with pulmonary embolism exceeds 15% in the first 3 months, and in nearly 25% of patients with PE, the initial clinical manifestation is sudden death (4). The annual number of pulmonary embolism-related deaths in the US may exceed myocardial infarction-related deaths and also stroke-related deaths (5).

Patients with VTE have also been shown to have a substantially increased long-term risk of subsequent arterial cardiovascular events. For patients with DVT the relative risks varied from 1.60 for myocardial infarction to 2.19 for stroke in the first year after the thrombotic event; for patients with PE the relative risks in that year were 2.60 for myocardial infarction and 2.93 for stroke (65).

## Conclusion

Hospitalized patients have a significantly raised risk of VTE, which may be compounded by other risk factors.

The clinical diagnosis of DVT is unreliable, but a clinical model based on risk stratification of patients may aid diagnosis and reduce the number of diagnostic tests required. Compression ultrasonography and D-dimer levels remain the most useful diagnostic tools. Treatment duration with LMWH and oral warfarin varies according to the risk of recurrent DVT. Evidence supports the reduction of risk of VTE by use of compression stockings and proteolytic enzymes; the use of aspirin seems limited to use in surgical patients, but not medical patients or long-distance travelers. Despite adequate therapy, DVT is associated with significant morbidity and mortality.

Potential conflict of interest: The author is a director of Diversal Pharmaceuticals, manufacturer of Nattozimes DVT, a complementary oral medication used in the prevention of DVT.

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