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A Review of the Pathogenesis, Clinical Features and Diagnostic Indicators of the novel condition Vaccine-Induced Thrombotic Thrombocytopenia

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A Review of the Pathogenesis, Clinical Features and Diagnostic Indicators of the Novel Condition Vaccine-Induced Thrombotic Thrombocytopenia

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ABSTRACT

The introduction of vaccination against SARS-CoV-2 infection was a welcome and significant event in the COVID-19 pandemic. While vaccine administration was for the most part successful, it did come with the emergence of a novel condition, Vaccine-Induced Thrombotic Thrombocytopenia (VITT). This condition presents after the administration of adenoviral vector-based vaccines against COVID-19, causing thrombocytopenia and thrombosis in affected individuals. There have been ten suspected cases of VITT in Ireland reported up to March 2022. While its mechanism is not fully understood, the condition is characterised by the presence of Platelet Factor 4 (PF4) antibodies. There are several laboratory indicators which may suggest that a patient has developed VITT, but confirmatory diagnosis requires anti-PF4 ELISA and PF4 Activation Assays. Thrombocytopenia often precedes thrombosis in VITT, so early treatment can aid in preventing the more serious implications of the condition from developing. Early recognition and clear guidelines for diagnosis are imperative in the treatment of VITT.

INTRODUCTION

Vaccine-Induced Thrombotic Thrombocytopenia (VITT) is a novel condition which has been recently identified following the administration of vaccines against the pandemic disease COVID-19. In Europe, four COVID-19 vaccines have been approved for use (EMA, 2021). The mechanism by which these vaccines induce immunity has been well documented. Two mRNA vaccines are in use, the Pfizer/BioNTech and Moderna vaccines. These vaccines work through the administration of mRNA which encodes the production of an antigen. The vaccine mRNA is taken up by cells, which are then prompted to produce the antigen, which in this case is the spike glycoprotein of SARS-CoV-2. The immune system will then launch an immune response against the foreign antigen which has been produced, creating antibodies which attack the spike glycoprotein. This means that on re-infection by SARS-CoV-2, the immune system will quickly recognise and mount an immune response against the spike glycoprotein (Chung, Thone and Kwon, 2021). The spike glycoprotein plays an important role in the entry of SARSCoV-2 into cells, so antibodies against this antigen will block or slow the entry of the virus into the cells (Ortiz-Prado *et al.*, 2020).

The other two vaccines approved for use are the AstraZeneca and Janssen vaccines, which are both adenoviral vector-based. Viral vector vaccines work by replacing a gene responsible for replication with a gene which encodes the required antigen in the viral vector. When administered, this will cause cells to produce the antigen of interest, in this case the spike

glycoprotein of SARS-CoV-2, while also preventing the virus itself from replicating (McGonagle *et al*., 2021). After the production of the spike glycoprotein, the adenoviral vector vaccines work in the same way as the mRNA-based vaccines to promote the immune system to mount a response against the spike glycoprotein. Development of VITT follows the administration of adenoviral-vector vaccines against SARS-CoV-2, although very rare cases of thrombosis following mRNA vaccine administration have also been reported (Elalamy *et al.*, 2021).

VITT has been reported among recipients of the Oxford AstraZeneca ChAdOx1 nCov19 (now Vaxzevria) and Janssen Ad26.COV2.S vaccines (Greinacher, Thiele *et al.*, 2021). VITT is uncommon and affects a low number of vaccine recipients. One of the highest incidence rates was reported in Norway, where VITT developed in 1:22,000 individuals who received an adenoviral vector vaccination. If left untreated the condition can have serious implications and has in some cases caused fatality (Favaloro, 2021). For such reasons, early detection and rapid treatment is of vital importance.

Symptoms of VITT have been seen to develop 4-42 days post vaccination and can include headache, abdominal or back pain, focal changes, petechiae, easy bruising or bleeding, nausea or vomiting and shortness of breath (Kotal *et al.*, 2021). Laboratory indicators suggestive of VITT include a low platelet count, prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT), and elevated d-dimer levels (Favaloro, 2021). If such markers are present in a patient suspected of having VITT, further testing is warranted to confirm the diagnosis.

VITT is characterised by the presence of Platelet Factor 4 (PF4) antibodies in individuals who have recently received a vaccine. The presentation and mechanism of VITT is thought to be closely like that of heparin-induced thrombotic thrombocytopenia (HIT), another condition which is characterised by the presence of anti-PF4 antibodies (Klok *et al.*, 2021). PF4 Anti IgG ELISA testing and Platelet Factor 4 Induced Platelet Activation Assays (PIPA) can be used to confirm the presence of PF4 antibodies, which will confirm the diagnosis of VITT (Lavin *et al.*, 2021). Since this is a newly emerging condition, little is known about what proportion of vaccine recipients develop VITT or how the vaccine triggers the thrombotic thrombocytopenic response seen in VITT. This review assimilates and analyses what has been reported about VITT and discusses laboratory investigation of the condition and current treatment so far.

REPORTED INCIDENCE OF VITT

Variation in the incidence of VITT has been reported between different countries and different age groups. In the UK, the incidence is reported as being 1:100,000 for patients over the age of 50, and 1:50,000 for patients under the age of 50 (Pavord *et al.*, 2021). Norway has reported a much higher incidence rate, with 1:22,000 of all individuals vaccinated developing VITT (Wiedmann *et al.*, 2021). It has been suggested that VITT is less prevalent in Asian populations, as is the case with HIT. In South Korea after the administration of 7.9 million doses of adenoviral vector-based vaccines there had only been ten cases of VITT, giving an incidence of 1:790,000, much lower than rates reported in Europe (Kim *et al.*, 2021). Although literature on the incidence of VITT in Ireland has so far been minimal, it has been reported that there have been ten suspected cases of VITT in the country to date (March 2022) with no associated deaths. Nine of the cases occurred following vaccination with the AstraZeneca vaccine, and one case following the Janssen vaccine (Swan *et al.*, 2021).

The first publications of VITT reported fatality rates was of 55-60% (Klok *et al.*, 2021). A more recent publication in the UK reported a fatality rate of 23%, which is still very significant (Pavord *et al.*, 2021). This difference in reported rates may be due to the underreporting of cases when the condition was first described. Most cases where VITT has resulted in fatality have been cases where extensive thrombosis has been present (Swan *et al.*, 2021). The highest mortality rate is associated with cases where the platelet count is below $30x10^9$/L and intracranial haemorrhage is reported (Pavord *et al.*, 2021).

It has been shown that 54% of individuals affected by VITT are female (Pavord *et al.*, 2021). There appears to be a higher risk for younger age groups, with 85% of VITT patients being under 60 years of age (Klok *et al.*, 2021). Following the emergence of VITT, many countries including Ireland, the UK, Germany, and Austria stopped the administration of the AstraZeneca vaccine to younger age groups (Elalamy *et al.*, 2021). The majority of VITT cases occur after the first dose of a two-dose vaccine, and it has been recommended that any patients who develop VITT after their first dose should receive an mRNA vaccine for their second dose (Klok *et al.*, 2021).

CLINICAL PRESENTATION AND GUIDELINES FOR DIAGNOSIS OF VITT

A wide range of symptoms have been reported to be associated with VITT, with the most common including headache, nausea, visual disturbances, easy bruising, petechiae and acute pain (Elalamy *et al.*, 2021). On laboratory investigation, thrombocytopenia and elevated Ddimer levels are common. Coagulation tests such as the prothrombin time (PT) and activated partial thromboplastin time (aPTT) may be prolonged, and hypofibrinogenemia has also been noted in numerous cases (Lavin *et al.*, 2021). VITT is associated with thrombosis at unusual sites, such as cerebral venous sinus thrombosis (CVST), splenic venous thrombosis (SVT) and ophthalmic vein thrombosis (McDonnell *et al.*, 2021), as well as more common presentations of thrombosis such as deep-vein thrombosis (DVT) and pulmonary embolism (PE). Venous thrombosis is also commonly present at multiple sites in VITT patients (Kotal *et al.*, 2021). Different publications have reported different time ranges for when the symptoms of VITT can appear, with the widest range being 4 – 42 days post vaccination. VITT is an immune response so any adverse reactions to a vaccination seen before 4 - 5 days post vaccination are not because of VITT (Kotal *et al.*, 2021).

When VITT was first recognised, the varied clinical presentation possible in VITT was not fully appreciated. It was thought that thrombosis, thrombocytopenia, and elevated D-dimer levels were present in all cases, and if a patient presented lacking one of these criteria VITT was not suspected (Klok *et al.*, 2021). One report detailed a case where a patient presented to a hospital with headache, visual disturbance, nausea, thrombocytopenia, and elevated D-dimer levels. Investigation found that there were no signs of thrombosis, so VITT was not suspected, and the patient was discharged. The patient subsequently re-presented three days later with worsening symptoms and the diagnosis of VITT was confirmed (Lavin *et al.*, 2021). This delay in the recognition of VITT can have a significant effect on patient outcome, so it is important to highlight that not all cases will present with all classical signs of VITT.

One factor which may influence why there appears to be a delay between when a patient with VITT first presents and when the diagnosis of VITT is confirmed is the discrepancy between diagnostic guidelines which have been published since the condition emerged. One report used four different sets of guidelines, published by the Society for Thrombosis and Haemostasias

Research in Germany (GTH), UK Expert Haematology Panel (UK EHP), Thrombosis Canada and International Society on Thrombosis and Haemostasis (ISTH), to evaluate case studies of confirmed VITT cases (Lavin *et al.*, 2021). The findings were that there was inconsistency in what were considered diagnostic indicators between the different sets of guidelines. This ambiguity in the recommendations for the diagnosis of VITT is a plausible reason as to why there may have been a delay in recognising the signs of VITT when a patient first presented. Since the identification of VITT some organisations including the UK EHP have updated their guidelines for diagnosis (Pavord *et al.*, 2021), there is now greater consistency between the guidelines available.

Recent publications have suggested defining a new condition, 'pre-VITT'. This condition was suggested on the basis that patients with VITT can present with elevated D-dimer levels, thrombocytopenia and anti-PF4 antibodies before they develop thrombosis (Salih *et al.*, 2021; Makris and Pavord, 2022). Recognition of this condition would allow such patients to be identified and treated quickly, reducing the chance that they will develop thrombosis. In such cases where 'pre-VITT' is present, it is important that the condition is recognised and not mistaken for other thrombocytopenic conditions such as thrombotic thrombocytopenic purpura, immune thrombocytopenic purpura, or catastrophic antiphospholipid syndrome (Makris and Pavord, 2022). Given that SARS-CoV-2 infection can also cause thrombosis, current COVID-19 disease should also be ruled out in a patient presenting with symptoms suggestive of VITT. It should also be determined whether the patient has recently received heparin treatment so as not to mistake the condition for HIT (Elalamy *et al.*, 2021).

RELATIONSHIP BETWEEN COVID-19 DISEASE AND THROMBOSIS

Infection with SARS-CoV-2 has been associated with several cardiovascular complications, including thrombosis. Thrombosis commonly occurs in patients who develop severe COVID19 disease (Zhang *et al.*, 2020). Some research has investigated whether there could be a shared cause for the thrombosis seen in COVID-19 and in VITT, due to the fact that both involve the expression of the spike protein of SARS-CoV-2 (McGonagle *et al*., 2021). In COVID-19 disease, viral RNA is the main cause of thrombosis although research has shown that the spike protein may also be involved in immunothrombotic events. The spike protein acts via the MAPK/ACE2 pathway (Zhang *et al.*, 2020). Research has suggested that vaccination against SARS-CoV-2 can promote the downregulation of ACE2 expression (Angeli *et al.*, 2021), proving it to be unlikely that ACE2 is involved in thrombotic events in VITT. Thus, there is little evidence to support the suggestion that COVID-19 disease and VITT share the same cause of thrombosis.

When it first emerged that there were thrombotic events associated with the administration of the adenoviral vector vaccines, vaccine administration was paused in most countries to allow research to be conducted into the link between the vaccines and thrombosis. Although the AstraZeneca and Janssen vaccine programmes were both continued, the level of vaccine hesitancy associated with the adenoviral vector-based vaccines was greater than that of the mRNA based COVID-19 vaccines (Machingaidze and Wiysonge, 2021). One point which is stressed across numerous research publications is that although there is a risk of thrombosis associated with vaccination, the risk of thrombosis associated with infection by SARS-CoV-2 is far greater. On infection by SARS-COV-2, thrombosis is 100 times more likely to occur in unvaccinated patients than in those who are vaccinated (Elalamy *et al.*, 2021).

PATHOGENESIS OF VITT

VITT is still a relatively new condition, so there are no reports which have definitively detailed the mechanism by which the thrombotic thrombocytopenia is caused. It is likely that VITT has an immunological mechanism like that of HIT. There are two forms of HIT, HIT which is induced by heparin treatment and autoimmune or spontaneous HIT, which is not caused by heparin treatment. VITT resembles autoimmune HIT closely. PF4 and anti-PF4 antibodies play a pathological role in both VITT and HIT (Klok *et al.*, 2021). In HIT, anti-PF4 antibodies bind to platelet receptor FcγRIIA, causing platelet activation and thrombocytopenia (Elalamy *et al.*, 2021). Activation of platelets causes the release of PF4 from platelet alpha granules. Increased levels of PF4 can cause endothelial activation which causes the recruitment of monocytes and neutrophils. Monocyte sidechains can then bind with PF4 to create an immune complex which will activate monocytes, stimulating their pro-coagulant activity. This in turn leads to the expression of tissue factor and generation of thrombin, which further stimulates the activation of platelets (Gaunt and Mabbott, 2021). This inflammatory response also involves the activation of neutrophils, causing a process in which foreign pathogens are trapped, called NETosis. This process releases leukocytic DNA, which promotes the formation of microthrombi (Elalamy *et al.*, 2021). A similar mechanism is predicted to occur in VITT, as depicted in Figure 1. In VITT, the binding of the anti-PF4 antibodies occurs at a different epitope than the binding site in HIT (Huynh *et al.*, 2021). Platelet activation is reported to occur through CD32a, which is a platelet membrane FcγRIIA receptor (Elalamy *et al.*, 2021).

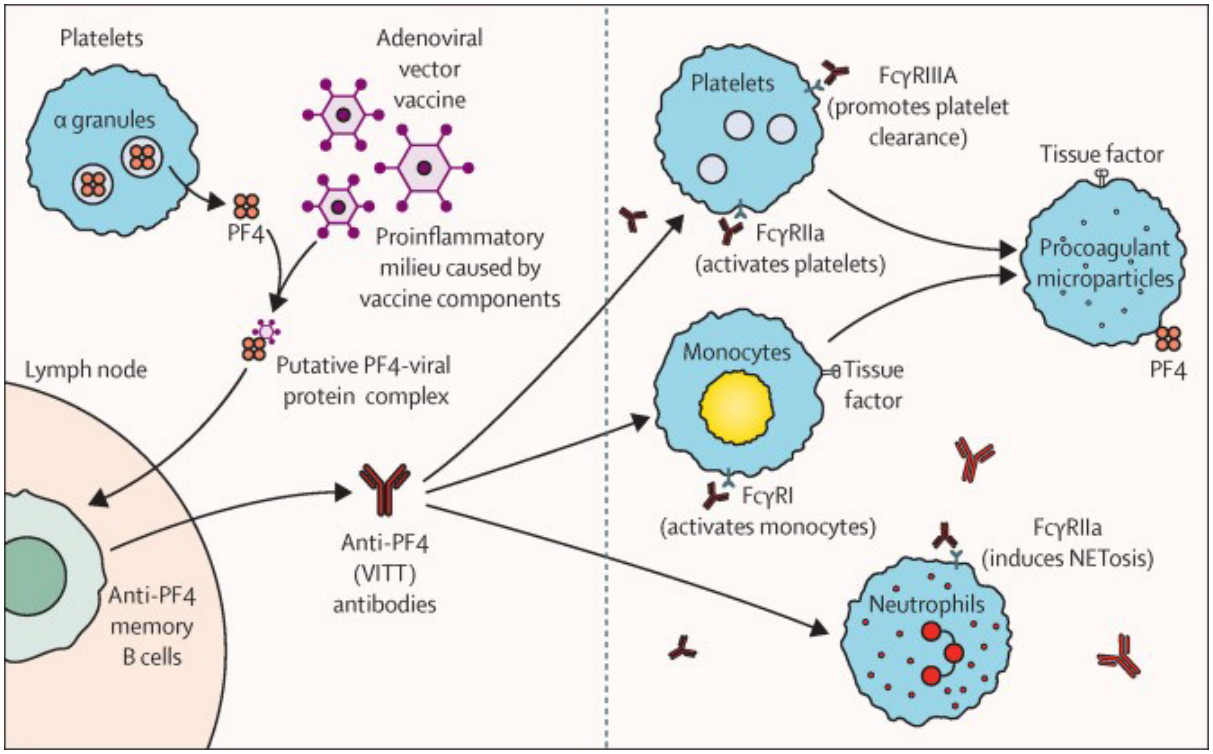

Figure 1 – Proposed pathogenesis of VITT (Klok et al., 2021).

In addition to the spike protein, vaccine components such as the adenoviral vector itself, the viral capsid, free DNA, vaccine impurities, EDTA and other human proteins contained within the vaccine have all been suggested as potential triggers for the response seen in VITT (Klok *et al.*, 2021). It has been shown that in the case of the AstraZeneca vaccine, the viral capsid can

bind to spaces between the hexon proteins in PF4, allowing interaction between viral components and PF4 (Baker *et al.*, 2021). Before the emergence of VITT it was already known that DNA can form complexes with PF4 which can bind to antibodies found in patients with HIT (Greinacher, Thiele, *et al.*, 2021). VITT appears to have an immune response involvement, which may be triggered by EDTA, or other human proteins used in the vaccine (Greinacher, Selleng, *et al.*, 2021).

LABORATORY CONFIRMATION OF VITT

Reports on the laboratory indicators of VITT have been consistent since the condition was identified. Indicators include thrombocytopenia, raised D-dimer levels, and in some cases low fibrinogen levels and prolonged PT and aPTT. Platelet counts of $\leq 107 \times 10^9$/L, D-dimer levels of ≤142mg/L and fibrinogen levels ≤2g/L are commonly observed in VITT patients (Greinacher, Thiele, *et al.*, 2021). Although these results are indicative of VITT, further testing is required for diagnosis. VITT is characterised by the presence pf anti-PF4 antibodies, so antiPF4 ELISA is commonly used as a diagnostic test. Anti-PF4 anti bodies have also been found outside of VITT, with 5-7% of blood donors having detectable levels of anti-PF4 antibodies (Elalamy *et al.*, 2021). Considering this, further testing is required to confirm that the anti-PF4 antibodies detected in the suspected VITT patient are the cause of the platelet activation and aggregation observed (Swan *et al.*, 2021). Functional platelet activation assays are often used for VITT confirmation after a positive anti-PF4 ELISA result is received (Klok *et al.*, 2021).

Anti-PF4 ELISA is commonly used for the detection of HIT antibodies but can be used for the detection of VITT antibodies also (Kotal *et al.*, 2021). The principle of the ELISA assay involves the formation of PF4 and polyvinyl sulfonate (PVS) complexes, which are immobilised on the surface of microwells. Anti-PF4 antibodies will bind to sites on the PF4/PVS complexes, allowing their detection. The concentration of the anti-PF4 antibodies is reported as an optical density (Mcfarland *et al.*, 2012). Commonly used anti-PF4 ELISA tests include Immucor, Hyphen and Stago assays, which have reported sensitivities of 100%, 92% and 91% respectively when used for the detection of anti-PF4 antibodies in known positive VITT patients (Swan *et al.*, 2021).

Following a positive anti-PF4 ELISA result, a functional platelet activation assay should be performed. Functional platelet activation assays for VITT have been developed based on assays which are used for HIT diagnosis, including heparin-induced platelet activation (HIPA) assays, and serotonin release assays (SRA) (Swan *et al.*, 2021). The HIPA assay principle involves the detection of platelet aggregation in the presence of heparin. The assay involves the visual assessment of platelet aggregation within the reaction mixture, and a positive result is indicated by the change in appearance from turbid to transparent. The SRA is based on the principle that serotonin is released by the dense granules of platelets on activation by HIT antibodies. The SRA involves the detection and quantification of serotonin released by patient platelets in the presence of heparin (Minet, Dogné and Mullier, 2017). The utility of functional platelet activation assays in the diagnosis of HIT has been well researched and documented.

These assays have been modified for use in the diagnosis of VITT by replacing heparin with PF4 in both assays (Lavin *et al.*, 2021). PF4-induced platelet activation (PIPA) assays have been further modified to PF4-induced flow cytometry-based platelet activation (PIFPA) tests, which are both used for the purpose of confirmation of a VITT diagnosis (Favaloro, 2021).

PIPA assays have been reported to detected between 95 to 100% of VITT cases, making PIPA a sensitive indicator of the condition (Lavin *et al.*, 2021). HIPA and PIPA assays can in some circumstances be used for the differential diagnosis of HIT and VITT, as the HIPA assay will return a negative result in most VITT patients and most HIT patients will receive a negative PIPA result (Lavin *et al.*, 2021). The modified SRA has not been reported to show the same sensitivity as the PIPA, with some research suggesting it is only 10% sensitive when used to detect positive VITT cases (Swan *et al.*, 2021). Both Anti-PF4 ELISA and PIPA assays are currently performed by reference laboratories and not offered routinely in hospital laboratories.

TREATMENT OF VITT

The treatment of VITT generally involves two approaches. The patient must be treated for thrombocytopenia, which generally involves intravenous immunoglobulin (IVIG) to recover the platelet count. A form of anticoagulant should also be administered, regardless of whether thrombosis has been identified in the patient or not (Pavord *et al.*, 2021). This will reduce the likelihood that patients who are in the proposed 'pre-VITT' stage will develop thrombosis. The choice of treatment should be determined based on the severity of the symptoms experienced by the patient. In cases of more serious illness, further treatment such as plasma exchange should be considered and has been shown to be beneficial (Elalamy *et al.*, 2021).

IVIG has been widely documented as one of the most common methods of treating thrombocytopenia in VITT patients. IVIG inhibits the binding of anit-PF4 antibodies to the FcγRIIA receptor, which prevents platelet activation and results in a rise in platelet count (Bourguignon *et al.*, 2021). IVIG administration should be combined with anticoagulant treatment, to counteract or prevent thrombosis. Given that it is recommended to avoid heparin, direct oral anticoagulants including fondaparinux, danaparoid and argatroban are commonly used in VITT treatment. Some patients with VITT may experience excessive bleeding due to thrombocytopenia, so different strategies to manage thrombosis should be considered for these patients (Klok *et al.*, 2021). For patients who are experiencing severe thrombocytopenia or extensive thrombosis, plasma exchange should be considered. Mortality rates in VITT patients increases with the presence of CVST and platelet counts of under $30x10^9$/L, but plasma exchange in such cases is associated with a 90% survival rate, making it a very favourable treatment option (Pavord *et al.*, 2021). Steroids and rituximab have also been reported to be beneficial in settings of severe VITT (Klok *et al.*, 2021).

CONCLUSION

While considerable research has been carried out on the clinical presentation and diagnostic markers of VITT, there is still a lack of information on some aspects of the condition, including how the vaccine triggers the thrombotic thrombocytopenia response observed. Initial research reports published about VITT showed considerable variation in findings. Greater consistency is seen in more recent publications, likely due to the accumulation of data about VITT as case numbers of the condition have risen. Guidelines on the diagnosis of VITT have changed since the condition was first recognised, and it is advisable that a set of guidelines which are updated regularly should be used when diagnosing VITT, such as the recommendations set up by the UK EHP.

Recommendations for the treatment and management of VITT have been well-documented. Although many cases of VITT are resolved with appropriate treatment, the fatality rate for the condition is still very significant. This may be in part due to the fast progression of the condition, making it difficult to make a diagnosis and start treatment before a patient becomes considerably ill. The recognition of the proposed 'pre-VITT' stage could improve the overall prognosis of the condition by increasing the chances of treating the patient before they have developed thrombosis, which is the leading cause of fatality in VITT. Further research in this area would be of benefit for the overall management of the condition. Expanding the availability of Anti-PF4 ELISA and PIPA assays to hospital laboratories would lessen the time between patient presentation and confirmation of diagnosis of VITT. Age is a known factor for the condition, but further research into whether certain cohorts of individuals are more susceptible to developing the condition, and the mechanism by which the vaccine triggers the immune response seen in VITT would help in the prevention of serious illness.

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