# Venous Thromboembolism, an Unusual Complication of Infective Endocarditis Caused by *Moraxella* species: a Case Report

**Meity Ardiana[a], Tita Rif'atul Mahmudah[a], Bambang Herwanto[b], Inna Maya Sufiyah[b]**

[a] *Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Airlangga – Dr. Soetomo General Hospital, Surabaya, Indonesia*
[b] *Medical Faculty of Airlangga University – Dr. Soetomo General Hospital, Surabaya, Indonesia*

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SOUHRN

**Kontext:** Septická embolie je poměrně častá a potenciálně závažná komplikace infekční endokarditidy (IE); nejčastěji se s ní lze setkat v mozku, solidních orgánech (např. ve slezině, ledvinách, plicích) a v dolních končetinách. V tomto článku popisujeme zajímavou akutní příhodu žilní tromboembolie u pacienta s IE a septikemií.
**Popis případu:** Do naší nemocnice byl ze sousedního ostrova v Indonésii odeslán 42letý muž pro IE a septický šok. Při příjmu si stěžoval na dušnost při intenzivnější aktivitě s únavou a horečkou přetrvávajícími po dobu sedmi dní. Uvedl rovněž akutní vznik bolesti v levé horní končetině před třemi dny. Bolest postupem doby zesilovala, při fyzické aktivitě se přidal pocit pálení, a bolest nebylo možné nijak zmírnit. Levá horní končetina byla namodralá, místy jakoby s podlitinami, citlivá a horká na dotek. Laboratorní testy prokázaly leukocytózu (24,7 × $10^9$/l), trombocytopenii (65 × $10^9$/l), zvýšené hodnoty transamináz (AST 3,920 a ALT 1,836), zvýšený sérový kreatinin (4,1 mg/dl) spolu se zvýšenými hodnotami markerů infekce (CRP 5,42 mg/l a prokalcitonin 1,03 µg/l). Echokardiografické vyšetření prokázalo těžkou mitrální regurgitaci (MR) s vegetací na ploše 1,22 × 0,818 cm na zadním cípu, dilataci levé komory a levé síně při normální ejekční frakci. Následně provedené vyšetření horních končetin duplexním ultrazvukem prokázalo trombus v levé podpažní žíle sahající až k levé pažní žíle; na úrovni tepen horní končetiny nebyl žádný trombus nalezen. Nejpravděpodobnější diagnózou byla levostranná IE s akutní příhodou žilního tromboembolismu (VTE) v horní končetině. Proto byla během příjmu empiricky nasazena antibiotika a parenterálně aplikována antikoagulancia. Žilní tromboembolismus jako komplikace levostranné IE se sice vyskytuje vzácně, byl však již popsán v několika případech včetně VTE postihujícího centrální nervový systém, plíce a dolní končetiny.
**Závěr:** Žilní tromboembolické příhody u pacientů s IE jsou sice vzácné, lze se s nimi však setkat při sepsi. U pacientů s potvrzenou diagnózou septické IE a s otoky končetin jako akutními projevy je nutno mít podezření na VTE. Duplexní ultrazvuk je levné, snadno proveditelné a spolehlivé vyšetření v diagnostice VTE, které může pomoci při vedení další léčby, tedy antikoagulační terapie při IE.



ABSTRACT

**Background:** Septic embolism is a relatively common and potentially severe complication of infective endocarditis (IE), and most often are found in the brain, solid organs (e.g. spleen, kidney, lungs), and lower extremity. Interestingly, we found an acute venous thromboembolic event in IE patient with septicemia.
**Case illustration:** A 42-year-old male was referred from neighboring island to our hospital for IE and septic shock. On admission he complained of shortness of breath during heavy activity, with fatigue and fever for seven days. He also presented with acute onset of left upper extremity pain for three days. The pain was increased over time with burning sensation, exacerbated by activity, and there were no relieving factors. The left upper extremity looks bluish with bruising, accompanied by tenderness, and warm to touch. Laboratory examination showed leukocytosis (24.7 × $10^9$/L), thrombocytopenia (65 × $10^9$/L), elevated transaminase (SGOT 3.920 and SGPT 1.836), elevated serum creatinine (4.1 mg/dL), with an elevated infection marker (CRP 5.42 mg/L and procalcitonin 1.03 µg/L). Echocardiography showed severe mitral regurgitation (MR) with

**Address:** Meity Ardiana, MD, PhD, Department of Cardiology and Vascular Medicine, Faculty of Medicine, Moestopo No.6-8, Surabaya 60132, Indonesia, e-mail: meityardiana@fk.unair.ac.id
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1.22 × 0.818 cm vegetation on the posterior leaflet, dilatation of left ventricle, and left atrium with a normal ejection fraction. The patient then underwent a duplex ultrasound examination of upper extremities and it revealed thrombus in left axillary vein until left brachialis vein, and no thrombus was detected in all upper extremity arteries level. Left sided infective endocarditis with acute venous thromboembolic (VTE) event in upper extremity was the most likely diagnosis. Therefore, empirical antibiotics and parenteral anticoagulant were administered during admission. Venous thromboembolic complication in left-sided IE is rare, but reported in several cases including VTE in central nervous system, pulmonary embolism, and lower extremity.
**Conclusion:** Venous thromboembolic event in patients with IE is rare, but can occur in sepsis condition. In patients with known diagnosis of septic IE with acute presentation of swelling in extremities, VTE event should be suspected. Duplex ultrasound is an inexpensive, feasible, and producible examination for diagnosing VTE, which can direct us to determine further therapy namely anticoagulant therapy in IE.

*Keywords:*
Infective endocarditis,
*Moraxella* species
Venous thromboembolism

## Background

Infective endocarditis (IE) is a life-threatening infection of the heart and predisposes to multiple hearts valve abnormalities, with incident reaching 3–10 out of 100,000 residents each year. Globally, the incidence of IE reached 1.090.530 in 2019, an increase from 478.000 in 1990, with the incidence in men being greater than in woman. It remains a disease with a high mortality rate, namely 25% of all cases, and 66.320 deaths reported in 2019.[1] The diagnosis and therapy of IE have developed rapidly, however, there are large discrepancies in different regions and countries around the world. An unrevealed case may remain undetected in areas that do not have renewed diagnostic technologies like F-FDG PET scan for a patient with implanted devices and prosthetic valves, which have higher diagnostic sensitivity. The risk factors that contribute to IE morbidity are quite diverse, including rheumatic heart disease (RHD), use of prosthetic valves or cardiac devices, use of intravenous drugs, and other blood-borne microbial infections.[1,2]

Rheumatic heart disease and congenital valvular disease have become the most important risk factors in endocarditis, especially at a young age. In developed countries, the epidemiology of IE has undergone significant changes, with more dominant risk factors such as the use of intracardiac devices (especially defibrillators and pacemakers) and degenerative valve disease, which will shift the incidence of IE to older age (> 65 years).[3] Cases of gram-negative infective endocarditis (GNIE) caused by non-HACEK microorganisms (*Haemophilus* species*, Aggregatibacter* species, *Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species) are rare cases, amounting to 2% of all IE cases.[2]

Inflammation of heart valves is characterized by widespread activation of endothelial cells, a degeneration process in the valves, and the emergence of sepsis.[4] Endothelial cells are important regulators of vascular homeostasis with several physiological functions, including vasomotor tone regulation, inflammatory or anti-inflammatory signals, and nutrition carrier. Endothelial cells have glycocalyx made from chondroitin sulfate, heparan sulfate, and transmembrane molecules that act as natural anticoagulant properties. This anticoagulant property influences the fibrinolysis process by urokinase plasminogen activator (uPA) and tissue type plasminogen activator (tPA), which in turn, is a barrier against bacterial invasion.[5]

The vascular endothelial cells undergo a variety of phenomena during sepsis including changes in antifibrinolytic phenotypes, procoagulant, and pro-adhesive as well as cell activation, dysfunction, and cell damage acting as a bridge between the immune system response and the coagulation cascade. This phenotypic shift is the main factor in the emergence of venous thromboembolism in IE patients who experience sepsis.[5,6]

The following article will report a case of man with venous thromboembolism incident of the upper extremity in GNIE caused by *Moraxella* species.

## Case presentation

A 42-year-old male was referred from a regional hospital with infective endocarditis and septic shock. The patients complained of shortness of breath that got worse with moderate to heavy activity, accompanied by weakness and fever that lasted for 7 days. The patient also complained of pain in the left arm for the last 3 days, the pain seems to get worse accompanied by a burning sensation, which was aggravated by movement, and did not decrease with rest. The left arm looked bluish, accompanied by tenderness and felt cold. On physical examination, the sclera was icteric, auscultation of the heart revealed a systolic murmur at the fifth intercostal space left midclavicular line radiating to the axilla. Auscultation of the lungs revealed faint breath sounds at the base of the right lung. There were also ascites and edema in both legs. From the localized status on patient's left arm, edema was found, with signs of bluishness and bruising on the upper and lower left arm, accompanied by bullae that were partially peeled. On arterial pulsation examination, it was found that arterial pulsation of superior extremity was within normal limits, with the saturation of the fingers of the left hand still normal.

Laboratory results showed leukocytosis (24.7 × $10^9$/L), thrombocytopenia (65 × $10^9$/L), increased transaminase enzymes (SGOT 3,920 and SGPT 1,836), increased serum creatinine (4.1 mg/dL), and increased infection markers (CRP 5.42 mg/L and procalcitonin 1.03 µg/L). Echocardiography showed vegetation on the posterior mitral leaflet of 1.22 × 0.818 cm with severe mitral regurgitation (MR), accompanied by dilatation of the left ventricle and left atrium, with a normal left ventricular ejection fraction (65.9%).

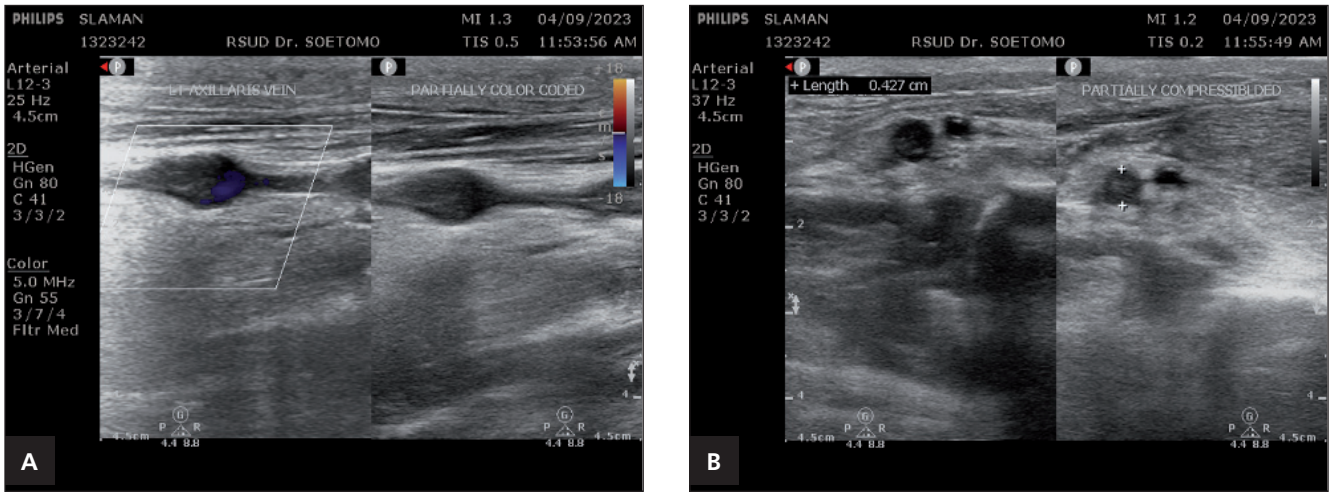


**Fig. 1 – Partially color-coded image on the DUS of the left axillary vein (A), and thrombus is visualized on the axial section of left superior axillary vein (B).**

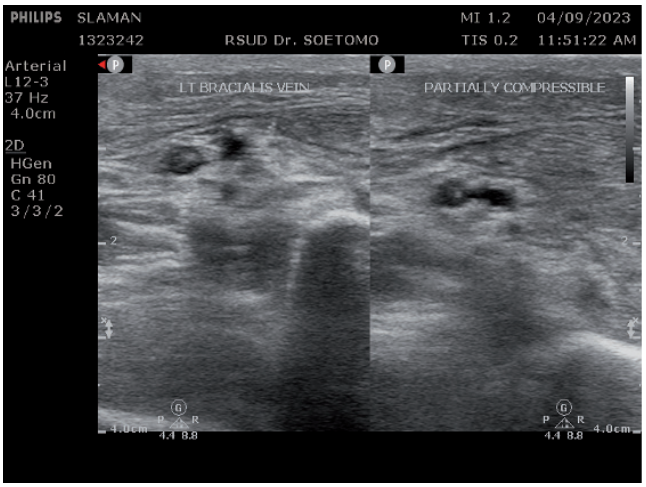


**Fig. 2 – Image of a thrombus on the axial section of left brachial vein.**

The patient also underwent a 2-dimensional vascular duplex ultrasound (DUS) examination of the arteries and veins of upper extremities. On examination of the arteries, no thrombus was visible, and multiphasic waveforms were seen at all levels of the left superior extremity arteries. From the results of duplex venous ultrasound in the left superior extremity, there were thrombi found in the left axillary vein and left brachial vein, with partially compressible in both veins (**Figs 1, 2**).

The patient then underwent blood culture examination at 3 different times, and was given empiric antibiotics and parenteral anticoagulants. An aerobic bacterium is detected from the blood culture, namely *Moraxella* species, which is a gram-negative coccus bacterium, was found in one of the three blood samples examined. Based on these findings above, it was concluded that the patient met the criteria for definite IE, with 1 major criterion (intracardiac vegetation), and three minor criteria (vascular phenomena detected on imaging, fever, predisposing heart condition, suspected glomerulonephritis, and minor positive blood culture results), with complications of sepsis and venous thrombosis.

Despite prompt initial medical treatment and empiric antibiotics, the patient's condition deteriorated rapidly, with unremitting septic shock. Unfortunately, the patient died on the second day of treatment due to septic shock and multi-organ failure.

## Discussion

### *Diagnosis of infective endocarditis with Gram-negative bacteria (GNIE)*

The clinical history of IE is very varied, depending on the causative microorganism, the presence of previous heart disease, and the presence or absence of a prosthetic valve or cardiac device in the patient. Fever symptoms appear in up to 90% of patients and are often associated with systemic symptoms such as chills, reduced appetite, and weight loss. In patients with fever, the suspected diagnosis of IE can be supported by laboratory results indicating infection, such as increased C-reactive protein (CRP) or increased erythrocyte sedimentation rate (ESR), leukocytosis, anemia, and microscopic hematuria. However, none of the laboratory results above can be used to confirm the diagnosis of IE (**Table 1**).[7]

The diagnosis of IE is made based on clinical manifestations, blood culture, and cardiac imaging. So far the modified Duke criteria are still used to diagnose IE (**Table 2**).[7]

IE which is caused by gram-negative bacteria that are not included in the HACEK group is a rare infection, accounting for around 2% of IE cases, and is characterized by high mortality.[8] *Moraxella* species are gram-negative coccus of the *Moraxellaceae* family, which also includes *Psychrobacter* and *Acinetobacter*. Initially, this microorganism was found in the upper respiratory tract as normal human flora but since 1970s there have been evidences to show that this microorganism is an important pathogen and often appears in respiratory diseases.[9,10]

The microorganisms that cause IE are dominated by gram-positive bacteria such as *Streptococci*, *Enterococci*,

**Table 1 – The diagnostic criteria for infective endocarditis are based on the terms used in the European Society of Cardiology 2015 modified criteria for the diagnosis of infective endocarditis**

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|---|
| **Major criteria** |
| 1. Blood culture positive for IE<br>a. Microorganisms consistent with IE from 2 different blood cultures:<br>• Viridans *Streptococci, Streptococcus gallolyticus* (*Streptococcus bovis)*, HACEK group, *Staphylococcus aureus*; or<br>• Community-acquired *Enterococci*, without the presence of primary focus; or<br>b. Microorganisms consistent with IE from persistently positive blood cultures<br>c. One positive blood culture for *Coxiella burnetii* or titration phase I IgG antibodies titre > 1 : 800 |
| 2. Imaging positive for IE<br>a. Echocardiogram positive for IE<br>• Vegetation<br>• Abscess, pseudoaneurysm, intracardiac fistula<br>• Valvular perforation or aneurysm<br>• New partial dehiscence from prosthetic valve<br>b. Abnormalities around the site of prosthetic valve implantation detected by F-FDG PET/CT (only if implantation > 3 months) or radiolabelled leukocytes SPET/CT<br>c. Definitive paravalvular lesion by cardiac CT |
| **Minor criteria** |
| 1. Predisposition such as predisposing heart condition or injection drug use<br>2. Fever, defined as a temperature >38 °C<br>3. Vascular phenomena: major arterial embolism, septic pulmonary infarcts, infectious (mycotic) aneurysm, intracranial hemorrhage, conjunctival hemorrhage, and Janeway's lesions<br>4. Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor<br>5. Microbiological evidence: positive blood culture, but does not fulfil major criteria above, or serological evidence of active infection with organism consistent with IE |

**Table 2 – Definition of infective endocarditis according to the modified Duke criteria[7]**

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|---|
| **Definite IE** |
| Pathological criteria<br>• Detected microorganisms by blood culture or histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or<br>• Pathological lesions: vegetation or intracardiac abscess confirmed by histological examination showing active endocarditis<br>Clinical criteria<br>• 2 major criteria; or<br>• 1 major criterion and 3 minor criteria; or<br>• 5 minor criteria |
| **Possible IE** |
| • 1 major criterion and 1 minor criterion; or<br>• 3 minor criteria |
| **Rejected IE** |
| • Firm alternate diagnosis; or<br>• Resolution of symptom suggesting IE with antibiotic therapy for ≤4 days; or<br>• No pathological evidence of IE at surgery or autopsy, with antibiotic therapy for ≤4 days; or<br>• Does not fulfil criteria for possible IE |

and *Staphylococci*. IE caused by gram-negative bacteria can be difficult to treat, due to a lack of clinical experience with this entity, and as a result there is little data and guidelines regarding its therapy.[8,9] From a literature review by Ioannou et al., it was stated that the most common location of endocarditis in *Moraxella* spp infections. are mitral (58%) and aortic (50%) valves, and involve multiple valves in 8.3% of patients.[9] The duration of symptoms varies greatly; however, 17 of 23 (82.6%) patients with available data had a symptom duration of 4 to 30 days (mean symptoms 14 days). Symptoms of fever appeared in 87.1% (27 of 31 patients), heart failure in 19.4% (6 of 31 patients), immunological phenomena occurred in 19.4% (6 of 31 patients), sepsis in 65.4% (17 of 26 patients), embolic phenomena in 22.6% (7 of 31 patients), and septic shock in 10% (3 of 30 patients). Furthermore, 19.4% (6 of 31 patients) had paravalvular abscesses.[9]

The recommended therapy for non-HACEK species associated IE is early surgical therapy plus long-term antibiotic therapy (minimum 6 weeks), namely a combination of beta-lactams and Aminoglycosides, and can also be supplemented with quinolone or cotrimoxazole therapy.[7] Overall, the mortality rate during hospitalization was 13.8%, with a cumulative mortality rate at one year of 30.6%.[8]

### *Venous thromboembolism as complications of IE*

In IE caused by Moraxella species, the most frequent clinical presentations are fever, sepsis, and embolic events.[9] Septic embolism is a complication that can be fatal in IE. Septic embolism is often described as consisting of a combination of inflammatory cells, colonized infectious organisms, platelets, and fibrin, which can result from hematogenous spread from any anatomical location, with the most common location originating from the heart valves.[11] Septic embolism in IE can occur throughout the body, starting from the central nervous system/brain, eyes, coronary circulation, thoracic aorta, pulmonary circulation, abdominal organs (spleen, liver, pancreas, kidney, intestinal), to embolism in the extremities and other systems. Musculoskeletal[11] septic embolism has a wide range of clinical presentations, ranging from asymptomatic to severe clinical presentations with high mortality. Pulmonary embolism and deep vein thrombosis (DVT) are included, under the broad umbrella of VTE. A combination of inherited and acquired risk factors can trigger VTE in IE.[12]

During sepsis, the vascular endothelial cells undergo a variety of phenomena including changes in antifibrinolytic phenotypes, procoagulant, and pro-adhesive as well as cell activation, dysfunction, and cell damage acting as a bridge between the immune system response and the coagulation cascade. This phenotypic shift is the main factor in the emergence of venous thromboembolism in IE patients who experience sepsis.[5,6]

Sepsis caused by gram-negative bacteria results in endotoxemia, which is characterized by the release of lipopolysaccharide (LPS, endotoxin). LPS has a major role and directly induces significant changes in the structure of the fibrin network, and LPS has been shown to bind directly to fibrinogen. It is known that small amounts of LPS can significantly affect fibrinogen and coagulation

processes, which indicates that the involvement of very small amounts of inactive bacteria can induce inflammation and disease progression.[13]

A healthy venous endothelial lining can prevent and limit the coagulation process through the expression of tissue factor pathway inhibitor (TFPI), tissue-type plasminogen, activator (tTPA), prostacyclin, nitric oxide (NO), and heparin sulfate. The process of VTE starts from activation of the venous endothelium in response to injury, experiencing a shift to a prothrombotic surface layer. There was an increase in the expression of tissue factor (TF), angiopoietin2 (Angpt2), and leukocyte adhesion molecules (P- and E-selectin) as well as down regulation of the leukocyte adhesion receptor tyrosine kinase with Ig and EGF homologous domains (Tie2). These changes are associated with decreased expression of antithrombotic molecules and loss of vascular integrity, cytokine production, and increased expression of procoagulants such as complement effectors, and the coagulation factors thrombin, VIIa, and Xa. This mechanism is what underlies the formation of VTE in inflammatory and infectious processes, especially the incidence of septicemia in patients.[6,14]

**Conflict of interest**
There is no conflict of interest in this case.

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**Informed consent**
The patient gave written, informed consent for the publishing of this case study and any related photos.

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