Tropical Biomedicine 42(2): 220-225 (2025)
https://doi.org/10.47665/tb.42.2.015

CASE REPORT

Innocuous to insidious: an unpredictable diagnosis of *Streptococcus sanguinis* infective endocarditis in a young adult

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ARTICLE HISTORY

Received: 22 August 2024
Revised: 3 April 2025
Accepted: 10 April 2025
Published: 30 June 2025

ABSTRACT

Streptococcus sanguinis is a commensal oral flora and an opportunistic pathogen prevalently implicated in native valve infective endocarditis (IE). However, in developing nations, infective endocarditis is currently affecting young healthy adults. In this case report, we presented a case of a 26-year-old male with *Streptococcus sanguinis* endocarditis without obvious aetiology, which was initially diagnosed and treated for dengue fever. A full medical history, physical examination, procedures such as transoesophageal echocardiography and electrocardiogram, and laboratory tests of full blood count and blood cultures were obtained to diagnose infective endocarditis based on the modified Duke criteria. The patient underwent mitral valve replacement with antibiotic therapy and currently presents no further complications. This article underscores the significance of thorough clinical assessment on patients and the hidden, life-threatening complications of *Streptococcus sanguinis* infective endocarditis if left untreated.

Keywords: infective endocarditis; streptococcus sanguinis; mitral valve regurgitation; anterior mitral valve prolapse; mitral valve replacement.

INTRODUCTION

Infective endocarditis (IE) is an inflammation condition of the endocardium, typically caused by bacterial infection. In Malaysia, native valve IE contributed to 94% of total cases, with left-sided involvement being predominant (Sunil *et al*., 2019). While *Staphylococcus aureus* is the leading aetiological agent of native valve IE in Malaysia, Viridans group streptococci such as *Streptococcus mitis*, *Streptococcus sanguinis*, *Streptococcus godonii*, *Streptococcus mutans*, *Streptococcus oralis*, *Streptococcus angiosus*, and other uncategorised species (Sunil *et al*., 2019; Yang *et al*., 2022). Arguably, streptococci species continue to be clinically relevant pathogens, as they were still prevalently isolated from IE patients (Miao *et al*., 2024).

Streptococcus sanguinis, which belongs to the Viridans group streptococci, is identified as a commensal biofilm-producing bacteria that is found ubiquitous in human saliva, as well as surfaces of teeth, oral gingiva, and dental implants (Zhu *et al*., 2018). *S. sanguinis* plays a significant role in sustaining oral flora equilibrium, thereby preventing cavities and periodontitis (Zhu *et al*., 2018). However, it is simultaneously an opportunistic pathogen that typically causes mitral or aortic valve IE in the elderly via haematogenous spread from the oral cavity (Chamat-Hedemand *et al*., 2020). Case reports implied that dental procedures increase the risk of pathogens entering the bloodstream and colonising the endocardial tissue (Birlutiu *et al*., 2018; Rahman *et al*., 2023; Singu *et al*., 2024). As the pathogens adhere to the valvular tissue, they produce a biofilm that leads to the aggregation of platelets and thrombosis, thereby forming a dense vegetative lesion on the cardiac valve and eventually resulting in valvular dysfunction (Martini *et al*., 2020). With that, patients with IE often exhibit clinical manifestations of murmurs and constitutional symptoms of infection comprising fever, chills, fatigue, weight loss, and night sweats, which may overlap with other infectious diseases (Chamat-Hedemand *et al*., 2023; Pillai *et al*., 2005; Rahman *et al*., 2023; Singu *et al*., 2024). Therefore, it is repetitively emphasised that prompt diagnosis and interventions should be initiated to avoid misdiagnosis leading to severe systemic complications of IE. This report discusses an intriguing case of a 26-year-old healthy young male initially treated for dengue fever but later diagnosed with *S. sanguinis* IE.

CASE PRESENTATION

A 26-year-old Chinese male who worked as an aircraft maintenance engineer with no travel history and no significant trauma history or notable injury that might be a risk of sepsis, presented at the Emergency Department with a chief complaint of persistent pyrexia and worsening headache for 10 days. One week before the admission, he visited a general practitioner clinic with a sudden onset of low-grade fever (37.6°C), chills, fatigue, arthralgia, and severe

generalised headache (pain scale: 8/10). He did not experience nausea, vomiting, bleeding tendency, dyspnoea or chest discomfort. The systems review indicated anorexia and night sweats. The patient reported no notable past medical history but has a documented allergy to Amoxicillin, characterised by mild acute urticaria upon administration. To alleviate fever and headache, he consumed the over-the-counter tablet paracetamol (1g) 3 times per day. He also revealed that his residing area was a dengue yellow zone. The patient often consumed meals outside home and previously had spicy numbing meals. Full blood count results showed thrombocytopenia (Table 1), dengue combo NS1 and IgG/IgM antibodies rapid test was only IgG antibodies positive, and SARS-CoV-2 rapid antigen test was negative. Further laboratory investigations for Zika and Chikungunya virus infection returned negative results. Hence, a tentative diagnosis of dengue fever was provided. The patient was prescribed paracetamol and oral rehydration salts as symptomatic treatment for dengue fever and returned home for monitoring.

Nonetheless, the symptoms manifested intermittently throughout the week despite taking the prescribed medications. On day 10, the patient had worsening headache, lethargy and arthralgia with increased night sweats frequency. Upon admission to the hospital, the patient appeared conscious and responsive but occasionally drowsy, and generally erythematous. The evaluated vital signs included blood pressure (122/75mmHg), heart rate (112bpm), and oxygen saturation (100%). A palpable thrill in the mitral area was detected during physical examination. Upon precordial auscultation, a grade V to VI pansystolic murmur was best heard in the mitral area and radiating to the axilla. The pansystolic murmur was accentuated with inspiration. Apart from precordial examination, a dental examination resulted in no obvious odontogenic cause of infection in the oral cavity. A complete blood count was indicative of mild leucocytosis (11.2×10^9/L). Inflammatory marker tests suggested moderate inflammation due to increased C-reactive protein (91.6mg/L), erythrocyte sedimentation rate (45mm/hr), and procalcitonin level (0.67ng/mL). Blood culture also identified a Gram-positive cocci bacteria via the Gram stain method (Figure 1). Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry, VITEK 2 system, and prokaryote DNA barcoding (Siew *et al*., 2024) were performed to identified and confirmed the cocci bacteria as a *Streptococcus sanguinis*. The broth microdilution method was used for the antibiotic susceptibility test of *Streptococcus sanguinis*, which was sensitive to penicillin, tetracycline, clindamycin, and vancomycin (Table 2). A lumbar puncture was also conducted to rule out meningitis by examining the cerebrospinal fluid. The cerebrospinal fluid analysis confirmed no growth of microorganisms, and computed tomography of the head showed no mass effect, acute intracranial haemorrhage or established territorial infarct.

Subsequently, a 12-lead electrocardiogram (ECG) revealed sinus tachycardia, possibly with left atrial dilation (Figure 2). The first transoesophageal echocardiography (TOE) reported a thickened, sail-like anterior mitral valvular leaflet (AMVL) with bulky posterior annulus of the mitral valve, which implied possible posterior mitral annulitis and early abscess formation. (Figure 3, Figure 4). An aneurysmal A3 segment of AMVL was also observed along with ruptured materials (Figure 5). The second performed TOE depicted a prolapsed AMVL with severe mitral regurgitation at the coaptation point between the anterior and posterior mitral valvular leaflet. The left ventricular ejection fraction was 65%. Remarkably, the AMVL appeared extremely mobile which is suggestive of chordae tendineae rupture.

The patient was first treated for meningitis with empirical ceftriaxone, acyclovir, and vancomycin before receiving the cerebrospinal fluid analysis result. However, the following blood culture and sensitivity test with TOE evaluation determined the diagnosis of *Streptococcus sanguinis* IE with severe mitral regurgitation and AMVL prolapse. As mentioned previously, the

Table 1. Full blood count results

Test	Results	Unit	Reference Interval
White Blood Cell	4.460	$\times 10^9$/L	3.400 – 9.600
Lymphocytes	1.030	$\times 10^9$/L	0.940 – 3.080
Monocytes	0.740	$\times 10^9$/L	0.200 – 0.810
Neutrophils	2.68	$\times 10^9$/L	1.27 – 6.20
Eosinophils	0.00	$\times 10^9$/L	0.00 – 0.60
Basophils	0.01	$\times 10^9$/L	0.00 – 0.08
Red Blood Cells	5.260	$\times 10^{12}$/L	4.300 – 5.700
Haemoglobin	16.00	g/dL	12.90 – 17.00
Haematocrit	46.60	%	37.50 – 49.30
MCV	88.60	fl	80.00 – 95.00
MCH	30.40	pg	27.00 – 33.00
MCHC	34.30	g/dL	32.00 – 36.00
RDW	13.00	%	11.40 – 14.80
Platelets	106.0	$\times 10^9$/L	132.0 – 372.0
MPV	11.10	fL	8.70 – 12.20

MCV, mean corpuscular volume; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; RDW, red cell distribution width; MPV, mean platelet volume.

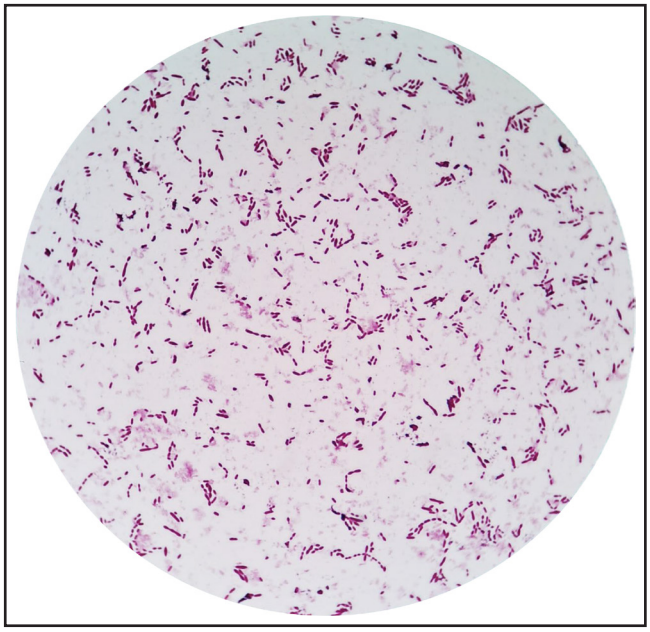

Figure 1. Micrograph of Gram-positive *Streptococcus sanguinis* (Magnification: 1000X). Gram-positive cocci arranged in chains.

Table 2. Microbiology laboratory result

Sample Origin	Blood
Gram Smear	Gram positive cocci in chains
Microorganism Identification (MALDI-TOF MS, VITEK 2, 16S rRNA Sequencing)	*Streptococcus mitis* group (*Streptococcus sanguinis*)
Antibiotics	**Antibiotic Susceptibility**
Penicillin	Sensitive (MIC: 0.047 mg/L)
Tetracycline	Sensitive
Clindamycin	Sensitive
Vancomycin	Sensitive
Erythromycin	Intermediate

MIC, Minimum Inhibitory Concentration.

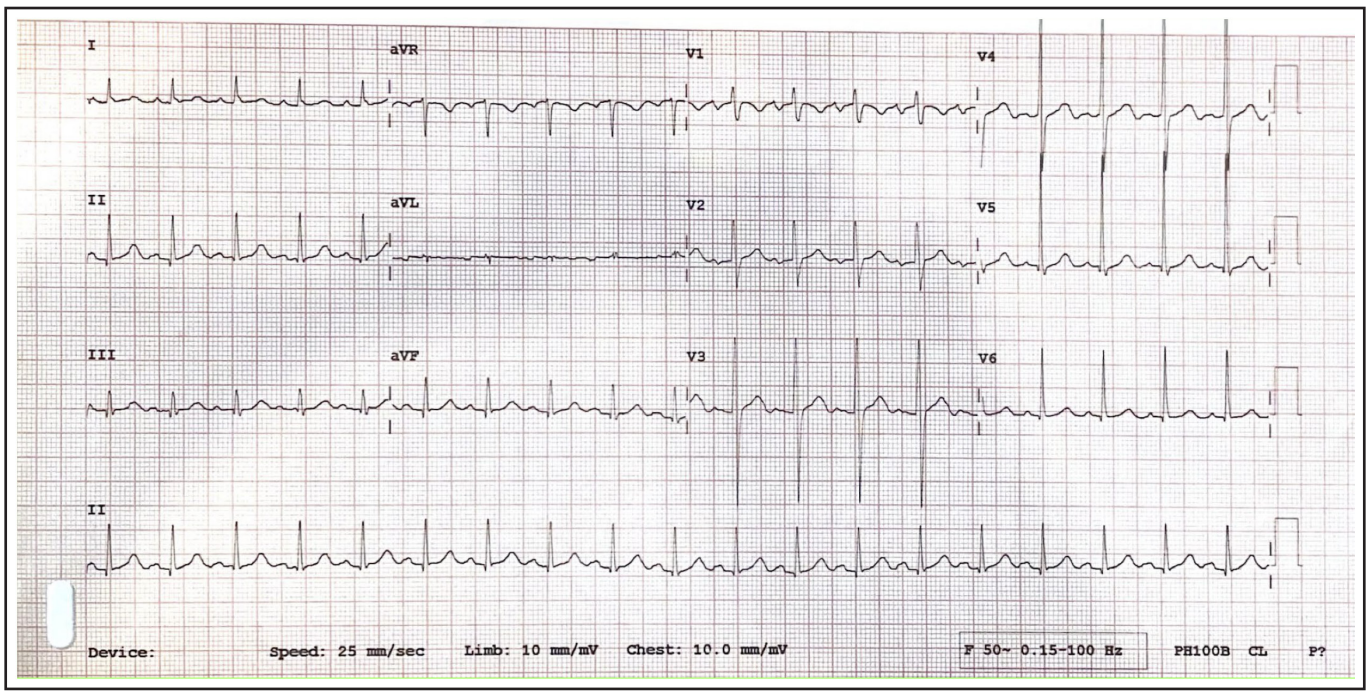

Figure 2. 12-lead ECG results presented sinus tachycardia. The rhythm is regular with a ventricular rate of more than 100bpm. P-wave is seen as positively deflected in lead II and preceding the QRS complex.

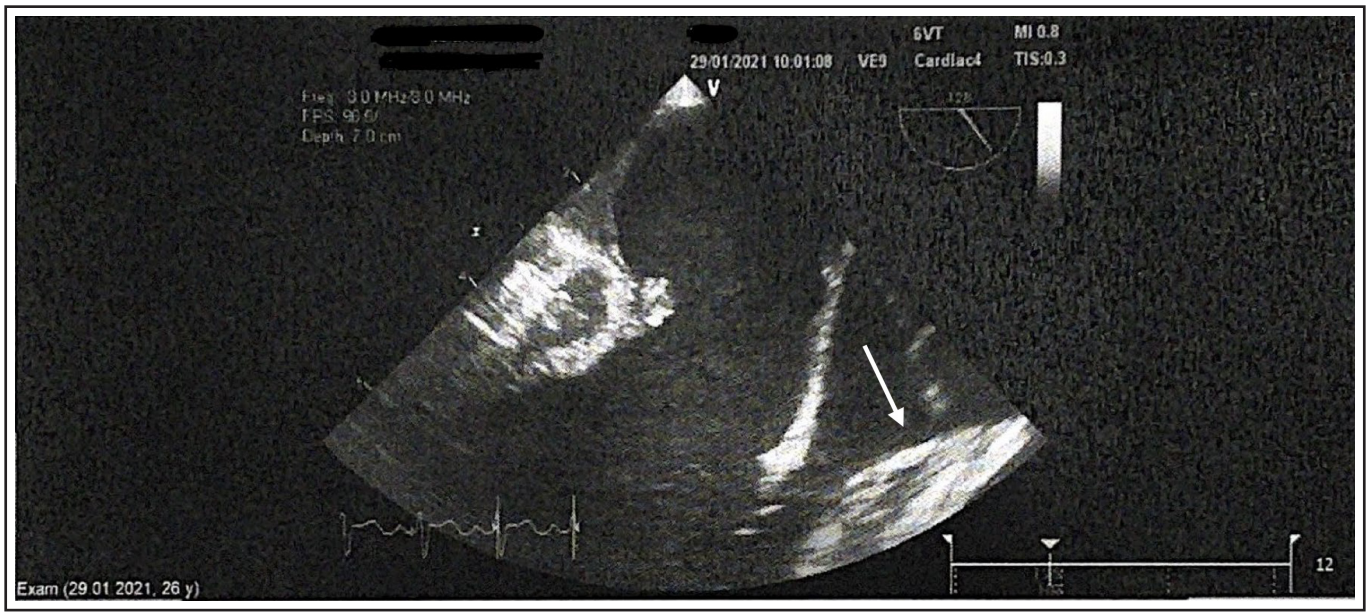

Figure 3. 2-D TOE imaging with mid-oesophageal long-axis view. A bulky posterior annulus of the mitral valve is indicated on the white arrow. TOE, transoesophageal echocardiography.

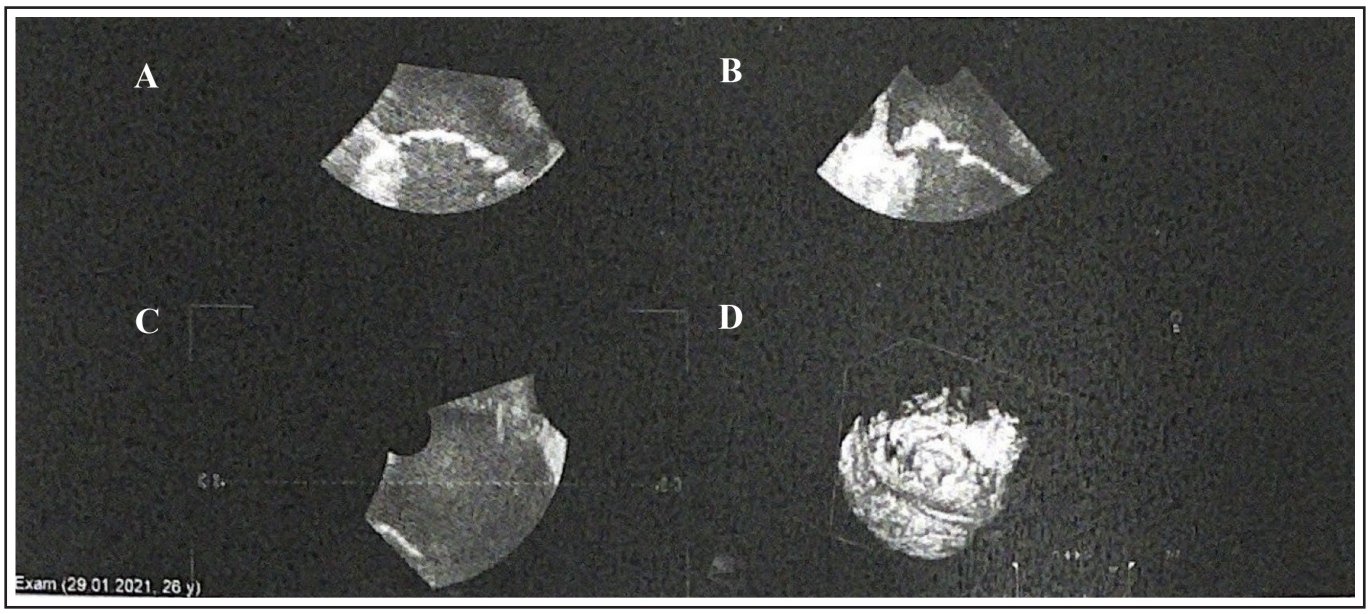

Figure 4. 2-D TOE imaging with mid-oesophageal long axis view (Figure 4A, Figure 4B, and Figure 4C) and trans-gastric left ventricular short axis view (Figure 4D). The images show mitral valve vegetations in different viewing axes. TOE, transoesophageal echocardiography.

Figure 5. 2-D TOE imaging with mid-oesophageal long-axis view. An aneurysmal A3 segment of the mitral valve is labelled with a cyan arrow and a ruptured chordae tendineae is indicated by a white arrow. TOE, transoesophageal echocardiography.

patient developed mild acute urticaria upon taking Amoxicillin, therefore the antibiotic regime given was IV Ceftriaxone as an alternative instead of Benzylpenicillin. This prompted the antibiotic treatment of IV Ceftriaxone (2g) for eight weeks, as the patient has a non-severe allergy to penicillin, and gentamicin (160mg) for 2 weeks. Consequently, a mitral valve replacement surgery was planned for the patient with post-operation treatment of long-term warfarin. On the day of discharge, a final echocardiography report indicated normal left atrial and ventricular size, functional prosthetic mitral valve, and no mitral regurgitation with a left ventricular ejection fraction of 68%. The patient was finally discharged with intravenous ceftriaxone (2g) for the remaining one week. He was also advised to follow up at the cardiology clinic every eighth week. In a total follow-up duration of 3 years, the patient had no complaint of complications or any pertinent adverse effects.

DISCUSSION

It is reported that elderly individuals or patients who have a history of valvular pathologies are more susceptible to acquiring *Streptococcus sanguinis* IE (Chamat-Hedemand *et al*., 2020). Conversely, several studies have suggested that the prevalence of IE is shifting towards the younger population, with a minimum age of 19 years. (Birlutiu *et al*., 2018; Kassis *et al*., 2010; Kim *et al*., 2016; Rahman *et al*., 2023; Sunil *et al*., 2019), thus highlighting the necessity for additional epidemiological studies on streptococcal IE in young adults. Nevertheless, this uncommon case of *Streptococcus sanguinis* IE in a young, healthy male adult was diagnosed incidentally with no apparent aetiology as the patient did not undergo dental procedures, unlike the recently reported cases. However, the bleeding tendency induced by dengue virus infection leads to gingival bleeding during

toothbrushing. Thus, it is hypothesised that *Streptococcus sanguinis* could potentially enter the blood circulation from the oral cavity due to a previous dengue infection.

Based on the clinical presentation of the patient, there were no significant signs and symptoms that would immediately indicate IE. On the contrary, an acute onset of fever, headache, and arthralgia with thrombocytopenia heightens suspicion of dengue fever rather than IE, especially given that the patient was living in a tropical region with frequent dengue cases (Pajor *et al*., 2024). Additionally, the dengue combo test produced results of positive IgG antibodies with negative IgM antibodies, which are likely indicative of secondary dengue infection (Chong *et al*., 2020). As a result, dengue infection was diagnosed provisionally, and less attention was initially paid to assessing the cardiovascular system. Upon visiting the hospital, the vital signs of the patient were within normal range, except for tachycardia, without cardiac failure or shock symptoms. A primary assessment of the cardiovascular system in the Emergency department unexpectedly uncovered a high-grade murmur with palpable thrill felt in the mitral area. It is fascinating to acknowledge that despite severe valvular regurgitation, vital signs of IE patients in the Emergency Department often presented normal with a mean blood pressure of 126/71mmHg and an average heart rate of 100bpm (Jingushi *et al*., 2017). It may be possible that the normal vitals are due to compensation mechanisms that prevent low tissue perfusion to vital organs. In addition, IE is also associated with low platelet count as it is believed to correlate with increased platelet consumption for the formation of valvular vegetation (Ferrera *et al*., 2015).

To date, the modified Duke criteria serve as a standard clinical guideline to diagnose IE (Table 3). According to the current case report, a total of two major criteria and one minor criterion have been fulfilled, leading to a definitive diagnosis of *Streptococcus sanguinis* IE, in correlation with the blood culture results (Fowler *et al*., 2023). Seo *et al*. (2023) discovered that isolation of *Streptococcus sanguinis* from blood is strongly associated with IE and suggested performing TOE as a routine examination to diagnose IE. It is of paramount importance to note that TOE is a gold standard diagnostic technique for IE to visualise the abnormal morphology of valvular structures and detect the severity of valvular dysfunction.

Streptococcal IE is reported to have an overall mortality of 20% and 18% of IE patients presented complications (Chamat-Hedemand *et al*., 2020, 2023; Seo *et al*., 2023). They cause bacteraemia and disseminate throughout the systemic circulation to the peripheral vascular, pulmonary, renal and central nervous systems, thereby resulting in complications such as arterial pseudoaneurysm, stroke, haemothorax, glomerulonephritis, and brain abscess (Kassis *et al*., 2010; Kim *et al*., 2016; Takahashi *et al*., 2024). Fortunately, the isolated *Streptococcus sanguinis* in this case are susceptible to the first-line antibiotics which are of the beta-lactam group (penicillin). The effective management for *Streptococcus sanguinis* IE involves intravenous antimicrobial therapy with penicillin or ceftriaxone to eradicate pathogens in the circulation, along with surgical replacement of the mitral valve to restore the valvular function (Miao *et al*., 2024). A study by Sunil *et al*. (2019) indicated that surgical intervention contributes to a lower overall mortality rate of IE in developing countries.

Table 3. Brief updated 2023 version of modified Duke criteria

Major Criteria	Minor Criteria	Reference
Microbiology Positive Blood Cultures: 1. Isolated microorganisms that frequently cause IE (*Staphylococcus aureus*, *Staphylococcus lugdunensis*, *Enterococcus faecalis*, all *Streptococcus* spp. (except *S. pneumoniae* and *S. pyogenes*), *Granulicatella* and *Abiotrophia* spp., *Gemella* spp., HACEK group bacteria) from at least 2 separate blood cultures.* **or** 2. Isolated microorganisms that atypically cause IE from at least 3 separate blood cultures.	**Risk Factors** 1. History of previous IE. **or** 2. History of congenital heart disease. **or** 3. History of valvular repairment or installation of intracardiac implantable device. **or** 4. Intravenous drug abuse. **or** 5. History of hypertrophic obstructive cardiomyopathy.	(Fowler *et al*., 2023)
Imaging Echocardiography and/or Computed Tomography (CT) of Heart: 1. Echocardiography and/or cardiac CT show(s) valvular/ leaflet vegetation, perforation, abscess, aneurysm, pseudoaneurysm, or intracardiac fistula.* **or** 2. Echocardiography shows significant new or worsening valvular regurgitation compared to previous imaging.	**Clinical Features** 1. Fever (greater than 38°C). **or** 2. Clinical/imaging report of cerebral/splenic abscess, mycotic aneurysm, intracranial haemorrhage, Janeway lesions, arterial emboli, septic pulmonary infarcts. **or** 3. Immunological signs of positive rheumatoid factor and symptoms of Osler nodes, Roth spots. **Physical Examination** Murmur is heard upon auscultation if echocardiography is not available.*	

CONCLUSION

In summary, the current case report emphasises the challenges and complexities of diagnosing an atypical case of *Streptococcus sanguinis* IE in a young healthy male patient. Albeit dengue fever should be a primary concern in tropical Southeast Asian nations, persistent and non-self-limiting clinical symptoms in a patient may raise attention to an insidious underlying condition. The earlier evidence demonstrated that *Streptococcus sanguinis* IE is a silent killer as patients frequently present with either asymptomatic or non-specific clinical features that can advance to a severe pathological crisis.

Conflict of Interest Statement

The author declares no conflict of interest.

ETHICS STATEMENT & ACKNOWLEDGEMENTS

This case study has been approved by the IMU Joint Committee on Research and Ethics. We thank the patient for gaining full consent for this study. Furthermore, we extend our gratitude to the dedicated cardiologists and medical officers from the Tan Tock Seng Hospital (Singapore) and the University Malaya Medical Centre for providing the medical records, diagnostic images, and laboratory reports that aided the conduct of this study.

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