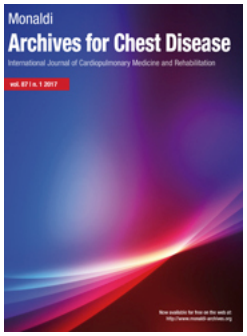

Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

Monaldi Arch Chest Dis 2025 [Online ahead of print]

To cite this Article:
Celeski M, Scalia L, Gatto L, et al. **The enigma of timing for cardiac surgery in aortic valve infective endocarditis with cerebrovascular complications: a case report**. Monaldi Arch Chest Dis doi: 10.4081/monaldi.2025.3500

Submitted: 5-04-2025
Accepted: 3-06-2025

The enigma of timing for cardiac surgery in aortic valve infective endocarditis with cerebrovascular complications: a case report

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Contributions: MC, FGB, conceived and designed the article; MC, LS, FGB, collected data and wrote the first draft of the manuscript; LG, BS, MV, contributed to the writing of the manuscript; MC, prepared the figures; FGB, MV, FP, made a critical revision of the review; FGB, made the final revision of the manuscript. All the authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors have no conflicts of interest to declare.

Ethics approval and consent to participate: not applicable.

Patient consent for publication: informed consent was obtained.

Availability of data and materials: all data underlying the findings are fully available.

Funding: this research received no external funding.

Abstract

Despite considerable improvements in therapeutic opportunities, infective endocarditis (IE) still suffers from a high morbidity and mortality rate, with septic embolism from valvular vegetations being one of its most dreadful complications. In complicated cases, early cardiac surgery can represent the greatest opportunity to improve the patient's prognosis, yet it encounters many issues that limit its indication. Herein, we present a case of an 80-year-old woman with native valve IE causing embolic ischemic stroke, delaying early cardiac surgery, and requiring complex multidisciplinary management. The case summarizes the pros and cons of the delayed surgery approach, which may allow a longer duration of antibiotic therapy and reduced risks of neurologic worsening but may enhance the risk of valve destruction, heart block, embolic complications, and death. This case reveals many critical aspects indicating early intervention despite very high surgical risk, providing insights into knowledge gaps and clinical needs for future research on this topic.

Key words: infective endocarditis, aortic insufficiency, ischemic stroke, endocarditis complications, cardiac surgery.

Introduction

Infective endocarditis (IE) constitutes a substantial public health burden, with an estimated annual incidence of approximately 13.8 cases per 100,000 individuals and accounting for approximately 66,300 deaths globally [1]. It remains one of the most challenging entities in modern medicine due to its multisystemic presentation, high mortality, and paucity of randomized studies regarding surgical management [1]. Embolism to the central nervous system (CNS) complicates up to 40% of cases of IE and has been shown to be an important predictor of outcome [2]. The spectrum of CNS complications includes ischemic infarction, intracerebral hemorrhage, meningitis, brain abscess and mycotic aneurysm. According to the European Society of Cardiology (ESC) guidelines for the management of endocarditis [1], surgical treatment should be considered in patients with signs of heart failure, severe valve dysfunction, prosthetic valve endocarditis, invasion with paravalvular abscess or cardiac fistulas, recurrent systemic embolization, large mobile vegetations, and persistent sepsis despite adequate antibiotic therapy [1]. However, a therapeutic dilemma arises when IE is complicated by a neurologic event. Despite evidence of improved survival in IE patients with earlier surgical treatment [2,3], a significant proportion of patients with IE and neurological complications in everyday clinical practice either undergo delayed surgery or do not have surgery at all. Therefore, physicians and surgeons are caught in a common conundrum where the urgency of the cardiac surgery intervention must be balanced against the real or perceived risks of neurological exacerbation and cardiovascular deterioration.

Case Report

An 80-year-old woman, with hypertension and no significant history of heart disease, presented to the emergency department with dysarthria, mild ataxia and mild right upper limb weakness that appeared 2 days before the admission. She had no chest pain, dyspnea or palpitations complaints and there were not any signs for distress. Her blood pressure was 110/60 mmHg, heart rate 80 bpm, peripheral oxygen saturation 99% in room air, and body temperature 36.5 °C. On physical examination there were no signs of fluid overload and no ankle swelling. During heart auscultation there was an early diastolic murmur at the left third intercostal space. During neurological examination a pronation of the right upper limb in the Mingazzini test and right alteration at the finger-to-nose test was observed. An electrocardiogram (ECG) showed sinus rhythm with single ventricular ectopic beat, no

conduction disorders and non-specific repolarization abnormalities (Figure 1A). Chest-X ray showed diffuse thickening of the bronchial walls, more evident in the bi-basal area, with no clear signs of fluid overload (Figure 1B). Routine laboratory analysis showed low hemoglobin levels (7.9 g/dl), neutrophilic leukocytosis, high pro-BNP values (1213 pg/ml) and elevation of hs TnI (1734 ng/ml). A second and third determination of hs TnI were 4439 and 15757 ng/ml, respectively. Moreover, liver enzymes, renal function and electrolytes were within the normal range. However, high C-reactive protein (9.8 mg/dl) and procalcitonin levels 2.54 ng/ml (normal range < 0.05) were found. A trans-thoracic echocardiography (TTE) was performed showing a slightly dilated ventricle with left ventricular inferior wall akinesia (left ventricular ejection fraction 40%). Furthermore, there was a 24 mm mobile vegetation on the aortic valve causing a moderate to severe aortic valve regurgitation (Figure 2B and C). Few hours after, there was a worsening of the previously mentioned neurological symptoms and new onset of right lower limb weakness. Therefore, the patient was referred for urgent cerebral computed tomography (CT) that evidenced presence of right cerebellar hypodense area (Figure 2A). An empiric antibiotic therapy with vancomycin 500 mg twice a day and ceftriaxone 2 gr were initiated. She was treated with 2 units of blood transfusion with correction of Hb levels (9.6 mg/dl). In addition, acetylsalicylic acid 100 mg was prescribed. She was admitted to the cardiac intensive care unit (CICU) with suspected endocarditis complicated by ischemic stroke for further evaluation. Three days after the admission there was further elevation of C-reactive protein (12.7 g/dl) and reduction of the hsTnI levels (10229 ng/ml). Moreover, blood cultures were positive for Enterococcus faecalis. Therefore, we switched to more specific antimicrobial therapy with Ampicillin 12 gr/day and Ceftriaxone 2 gr twice a day. A control TTE and a transesophageal echocardiography (TEE) confirmed the presence of 10 mm (vs. 24 mm) vegetation on the right coronary cuspid of the aortic valve with moderate-severe aortic regurgitation. A cardiac surgery consultation has been requested for an urgent procedure. However, the request for urgent surgery was denied because of the increased risk of cerebral hemorrhage in the actual clinical condition of the patient. In addition, on ECG telemetric monitoring frequent episodes of non-sustained ventricular tachycardia (NSVT) were recorded. However, 5 days after the admission the patient developed a high-grade atrio-ventricular block (AVB). Considering the presence of sepsis and IE, insertion of an active fixation transvenous pacing lead through a subcutaneous tunneled approach was performed. A control TEE did not reveal any perivalvular complications and confirmed the presence of 10 mm aortic valve

vegetation with severe aortic regurgitation. Neurological status remained unchanged compared to that at admission. The next days there was a reduction of the C-reactive protein (7.79 mg/dl) and procalcitonin (0.59 ng/mL) level. Nevertheless, there was a new episode of acute pulmonary edema treated with 60 mg of diuretic therapy, methylprednisolone 40 mg and non-invasive ventilation. In addition, there was a new-onset acute renal insufficiency not requiring dialytic therapy, which needed an adjustment of antibiotic dose-therapy. Due to a poor diuretic response with furosemide 125 mg i.v. x 4, we opted for sequential nephron blockade using metolazone 5 mg with partial benefit. Thus, a new request for urgent cardiac intervention was denied due to patient's poor clinical conditions and worse prognosis. After 11 days the patient developed a multiple organ failure characterized by acute lung failure, acute liver, kidney failure and cardiogenic shock, with subsequent pulseless electrical activity and patient's death.

Discussion

Septic embolism from valvular vegetations is a very frequent complication of IE [1,2]. In our case, two major Duke criteria including echocardiogram positive for aortic valve 24 mm-vegetation and blood cultures positive for community acquired Enterococcus faecalis permitted the diagnosis of IE and CT confirmed right ischemic cerebellar infarction. In this case, several points should be considered.

Embolic risks

The reduced dimensions of the vegetation (10 mm vs 24 mm) individuated on control TTE, subsequently confirmed on TEE, and the in-hospital onset of new motor function deficits, confirmed the suspected embolic stroke due to IE. Chronological timeline of the patient's clinical course is illustrated in Figure 3. The rise and fall pattern of hs TnI and the wall motion abnormalities on echocardiography suggested a concomitant presence of non-ST elevation myocardial infarction. As it is widely known, in case of embolization of vegetation fragments into the coronary artery the resulting myocardial ischemia can be the substrate for the onset of tachy-arrhythmias [1]. In our case there were frequent episodes of NSVT during ECG telemetric monitoring. We hypothesized a concomitant presence of coronary embolism. Nevertheless, because of the previously mentioned conditions (IE and stroke) and no need for urgency, a

coronary angiography was not performed. Due to the high creatinine level, coronary CT was not performed as well.

Timing of surgery and neurological deterioration

Existing ESC and ACC/AHA guidelines have defined the indications for surgery, but risk stratification and timing, especially in the setting of recent ischemic stroke are less well defined [1,3,4]. Early surgery should be considered in patients with IE and valvular-associated heart failure or uncontrolled infection (highly resistant organisms, perivalvular extension or persistent bacteremia despite appropriate antibiotics). Guidelines suggest considering early surgery for patients with large vegetations (>10 mm) and at least one embolic episode or severe valve stenosis or regurgitation and low operative risk [1,4]. Nevertheless, ideal timing for surgery in IE with preoperative neurological events remains controversial. About 20%-40% of patients present with a clinical stroke or other neurological event [1,2]. Although the most common neurological insult is an ischemic stroke from septic emboli, other sequelae might include subarachnoid hemorrhage, brain abscesses, mycotic aneurysms, and meningitis [2]. Prior ESC guidelines generally favored deferral of surgical intervention for 1–2 weeks in patients with non-hemorrhagic stroke and for 3 to 4 weeks in patients with hemorrhagic stroke or complex stroke (causing coma) unless a delay in surgery puts the patient at immediate risk of death [1]. In contrast, transient ischemic attack or silent embolism should not delay surgery that is indicated for other reasons. Neither ESC nor ACC/AHA guidelines recommend routine brain imaging prior to surgery in the absence of signs of neurologic complications. On the other hand, ACC/AHA guidelines recommend no delay in indicated surgery in the setting of stroke without evidence of intracranial hemorrhage or extensive neurologic damage; in the setting of hemorrhagic stroke or extensive neurologic damage, guidelines advise that surgery should be delayed ≥ 4 weeks [3,5].

However, in patients with IE and ischemic stroke there is an increased risk of neurological deterioration in the perioperative period, potentially due to hemorrhagic extension or transformation induced by anticoagulation that is required for cardiopulmonary bypass, or exacerbation of ischemia in the setting of intraoperative hypotension. The likelihood of hemorrhagic transformation may be related to the timing of surgical intervention and the severity of cerebral infarction. Furthermore, possibly the antithrombotic therapy with acetylsalicylic acid and heparin enhances the propensity to bleeding ischemic and

hemorrhagic strokes in 25 to 35% of patients with endocarditis. For this reason, the cardiac surgery consultation in our case did not give an indication for cardiac intervention. However, there are several strategies proposed by the ESC guidelines to preserve cerebral damage during extracorporeal circulation [1]. Many studies suggest that in patients with IE and recent stroke but without evidence of intracranial hemorrhage or extensive neurologic damage (such as major deficit in function), surgery may be performed without delay when a surgical indication is present [2,4]. More recent studies suggest that the neurologic risk of early cardiac surgery may not be as high as previously thought. They claim that early surgery is not associated with an increased in-hospital or 1-year mortality and can be even beneficial in non-severe stroke category [6-8]. However, these studies are generally small and retrospective, and evidence for the optimal time interval is conflicting because of a lack of controlled studies. In our case, the decision to defer surgery was influenced by a perceived high neurological risk, but this ultimately led to disease progression and death. Indeed, delaying surgery might lead to possible harm, in certain patient population, due to the occurrence of additional lethal complications. However, endocarditis team including a neurologist that considers the mechanism and severity of hemorrhage, ideally supported by imaging and clinical scores, remains of critical importance. Indeed, serial imaging remains important strategy that permits reassessing surgical timing in delayed cases. On the other hand, age alone should not preclude surgical intervention. Indeed, the multicenter ESC EORP EURO-ENDO [9] registry reported that patients ≥80 years had lower rates of surgical indication and surgery compared to younger patients and higher in-hospital (25.9% vs. 15.8%, $p<0.001$) and 1-year mortality (41.3% vs. 22.2%, $p<0.001$). In addition, multivariable analysis revealed that age alone was not predictive of 1-year mortality and not performing surgery when indicated was strongly associated with increased mortality (HR 2.98 [2.43–3.66]). After matching, surgical mortality in ≥80s was similar to younger patients, highlighting the need for better recognition of surgical indications and increased intervention in the elderly [9]. Thus, a more detailed geriatric assessment including evaluation of functional and nutritional status might contribute in the surgical decision-making process.

Ongoing complications and conduction disorders in IE

On the other hand, delaying surgery might lead to possible harm due to the occurrence of ongoing and additional cardiac and systemic complications including paravalvular abscess or

cardiac fistulas, valve distruction, recurrent systemic embolization, heart failure, persistent sepsis as well as conduction disorders. Indeed, in our case the patient developed a high-degree AVB without evidence of perivalvular abscess on the control TEE. This brought to a more enigmatic situation that is the treatment of AVB due to IE. Firstly, in some cases it could be a regression of the AVB after urgent cardiac surgery. Secondly, as there are no specific guidelines, timing of permanent pacemaker implantation and whether biventricular pacing should be placed are also decisions that need to be evaluated on an individual patient basis [10].

We opted for insertion of an active fixation transvenous pacing lead through a subcutaneous tunneled approach that is demonstrated to be a safe and effective method for bridge pacing in patients with IE. Five days after the admission, the patient developed acute pulmonary edema and acute renal insufficiency with subsequent diuretic resistance. A cardiac surgery was denied again due to the poor clinical conditions, poor prognosis, and the recent stroke event. Unfortunately, our patient developed a multiple-organ failure and died 11 days after the admission in CICU. Earlier surgical intervention might have altered the clinical course, although the benefit in such complex cases remains uncertain.

Conclusions

This case report highlights the importance of a multidisciplinary 'endocarditis team' involving cardiologists, cardiac surgeons, infectious diseases specialists, neurologists, and radiologists. It further underlies that delaying surgery may allow for a longer duration of antibiotic therapy and reducing the risk of worsening neurologic symptoms but enhances the risk of disease progression, heart and systemic complications.

The decision about surgical timing in patients with IE complicated with stroke should be personalized and based on a multidisciplinary approach. Indeed, potential surgical delaying should be carefully justified, considering patient's hemodynamic status, risk of new or recurrent embolization, neurological deterioration, and risk for cardiac complications.

New multimodality imaging methods and improved risk-scoring models for IE may help to clarify the decision-making process in this setting. Larger early versus late surgery randomized controlled trials are required to provide better guidance to clinicians regarding the optimal timing of surgery in IE complicated by neurological injury.

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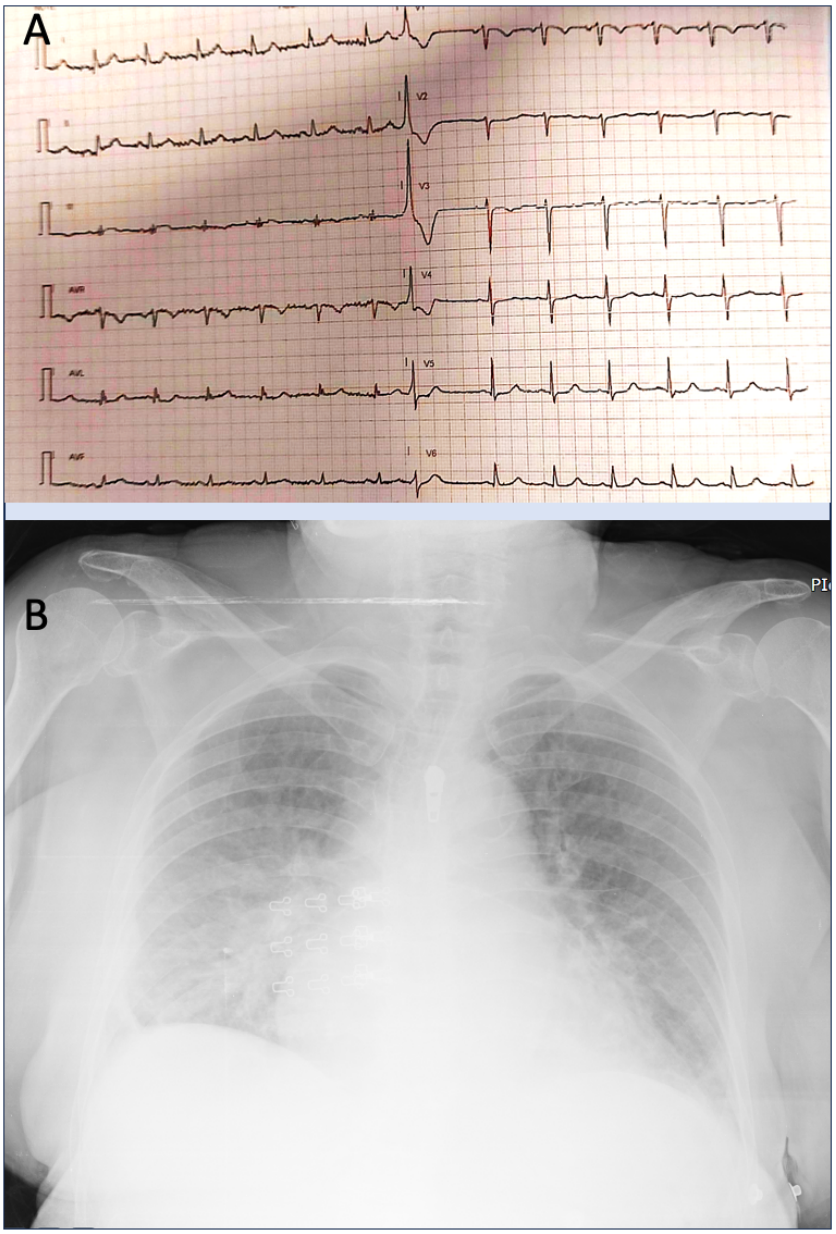

Figure 1. EKG (A) and chest X-ray (B) of the patient.

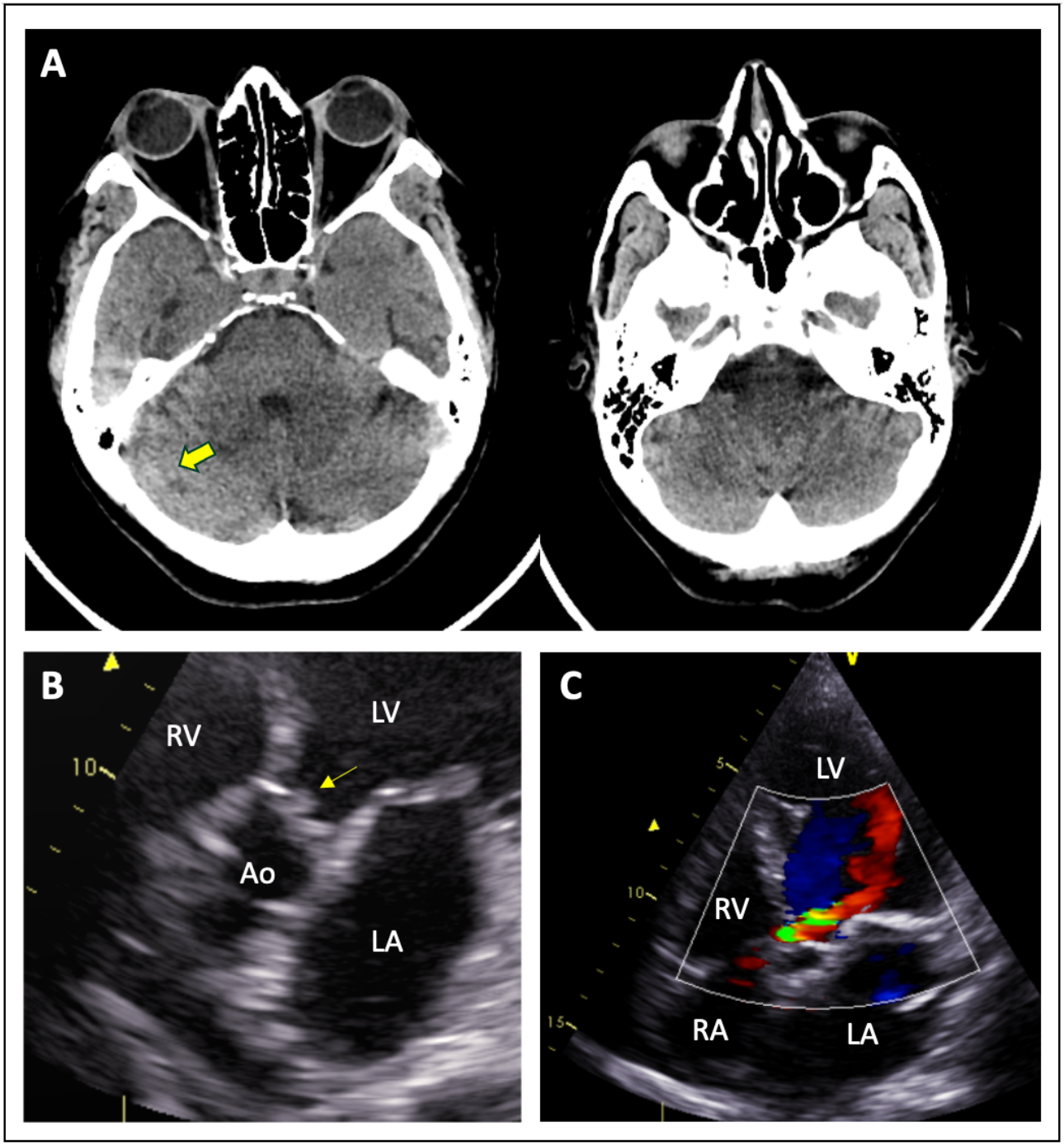

Figure 2. A) Computer tomography showing right cerebellar hypodense area (yellow arrow); B) trans-thoracic echocardiography showing vegetation of the right coronary cusp (yellow arrow); C) trans-thoracic echocardiography showing severe eccentric aortic regurgitant jet. Ao, aortic root; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

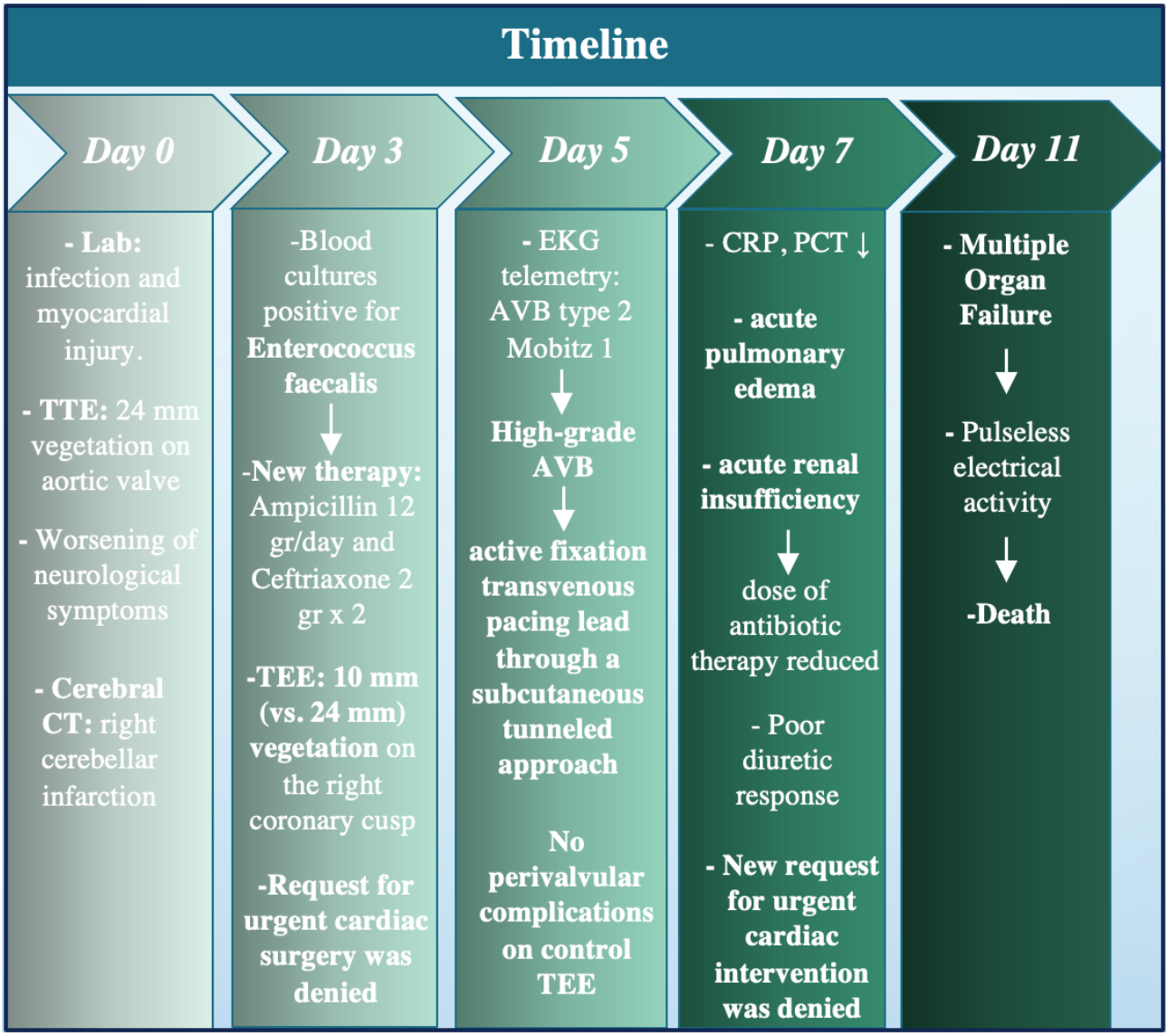

Figure 3. Chronological timeline of the patient's clinical course. AVB, atrio-ventricular block; CT, computed tomography; EKG, electrocardiography; CRP, C reactive protein; Lab, laboratory; PCT, procalcitonin; TEE, Trans-esophageal echocardiography; TTE, trans-thoracic echocardiography.