

Left-sided native valve *Staphylococcus aureus* endocarditis

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ABSTRACT

Despite improved diagnostic tools and expanded treatment options, left-sided native valve endocarditis caused by *Staphylococcus aureus* infection remains a serious and destructive disease. The high morbidity and mortality, however, can be reduced by early recognition, correct diagnosis, and appropriate treatment. In the following article, we discuss the clinical presentation, diagnostic workup and treatment of infective endocarditis, thereby reviewing the current guidelines. Blood cultures and echocardiography are the cornerstones of diagnosis in identifying infective endocarditis but are no substitute for clinical judgement. The modified Duke criteria may facilitate the diagnostic process, but clinical evaluation remains crucial.

KEYWORDS

Endocarditis, mitral valve, *Staphylococcus aureus*

INTRODUCTION

Staphylococcus aureus is the leading cause of left-sided infective endocarditis and is associated with high morbidity and mortality.^{1,2} Infective endocarditis caused by *S. aureus* is usually characterised by an acute presentation in which signs of severe sepsis are predominant and the classic physical findings of infective endocarditis are often absent. Embolism and infarction of various organs are frequently seen on presentation. For this reason (critical care) physicians are frequently confronted with the complications of advanced stages of the disease. We present

a case of a typical presentation of *S. aureus* endocarditis of the mitral valve complicated by multiple systemic arterial embolisations and heart failure. The aim of this report is to discuss the early recognition, diagnostic workup and treatment of patients suspected for infective endocarditis, in particular *S. aureus* endocarditis, in conformity with the current guidelines.¹

CASE REPORT

A 65-year-old man presented to our hospital after two days of fever and coughing. His presenting complaints were acute aphasia and hemiparesis of the right arm. His past medical history was significant for smoking for 40 years, alcohol abuse, and peripheral artery disease resulting in a femoro-popliteal bypass and amputation of his right lower leg.

Physical examination on presentation was significant for normal blood pressure, sinus tachycardia to 116 beats/min and a subfebrile core temperature of 37.9 °C. Auscultation of the heart and lungs revealed no abnormalities. Neurological examination confirmed an aphasia and hemiparesis of the right arm. Laboratory results included a high sedimentation rate (32 mm/h), an elevated white blood cell count of $14.6 \times 10^9/l$ and thrombocytopenia of $82 \times 10^9/l$. Chest X-ray and computed tomography (CT) of the cerebrum were initially normal.

The patient was admitted to the neurology department and antibiotic treatment was initiated (amoxicillin/clavunilate and gentamicin) to treat his fever and haemodynamic deterioration in the absence of a primary focus. Three days later the patient was transferred to the

intensive care unit of our hospital because of progressive sepsis with haemodynamic instability, progressive need for positive inotropic support and deterioration of renal function necessitating renal replacement therapy. Because of declining consciousness (Glasgow Coma Scale <8/15) without sedative medication, the patient was intubated endotracheally and mechanical ventilation was started. On admission to the intensive care, his fingers, toes and legs showed peripheral stigmata of systemic embolism (figures 1A to C). Roth's spots were present on the retina of his right eye (figure not shown). Grade one decubitus wounds were observed on his buttocks. Transoesophageal echocardiography (TEE) detected large vegetations on the mitral valve with valvular perforation of the posterior leaflet (figures 2A and B). No other valvular abnormalities were observed. Left and right ventricular function were normal. On day two of his intensive care admission multiple separate blood cultures were positive for *S. aureus*. Antibiotic therapy was switched to flucloxacillin, dosed in accordance with the endocarditis guidelines (higher dose).¹ The diagnosis was considered 'definitive' according to the modified Duke, meeting two of the major criteria. A new CT scan of the cerebrum showed a left-sided, parieto-temporal-occipital lesion of low density with a midline shift. Emergency valvular surgery was considered but ultimately rejected due to the patient's high risk for intra-cerebral haemorrhage and his sombre prognosis. During his stay in the intensive care unit, the patient deteriorated clinically, requiring increasing inotropic and respiratory support. Because this deterioration occurred despite maximal treatment with no concomitant, treatable or potentially reversible factors, active treatment was suspended five days after ICU admission. The patient died soon afterwards. Autopsy confirmed the diagnosis of endocarditis of the mitral valve. A vegetation of 20 mm was found on the

Figure 2A. Transoesophageal echocardiography showing vegetations of the mitral valve

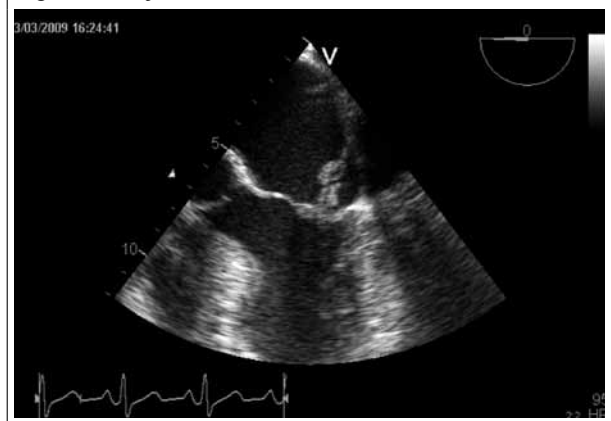
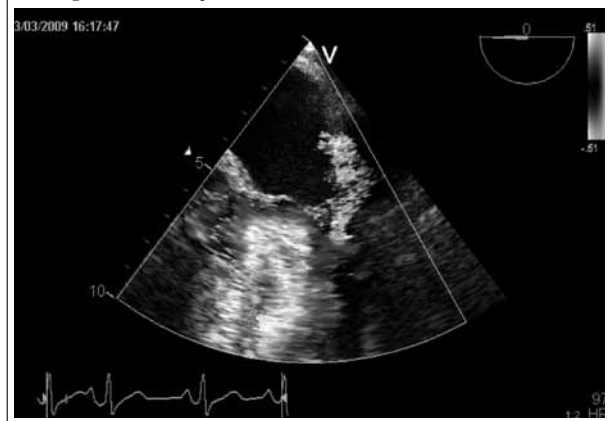


Figure 2B. Transoesophageal echocardiography showing mitral valve regurgitation due to perforation of the mitral valve posterior leaflet



mitral valve (figure 3A). Light microscopy of the mitral valve showed an acute infection with Gram positive cocci (figure 3B and 3C). Septic emboli were observed by light microscopy in the left hemisphere, the spleen and kidneys.

Figure 1A. Janeway spots (fingers)

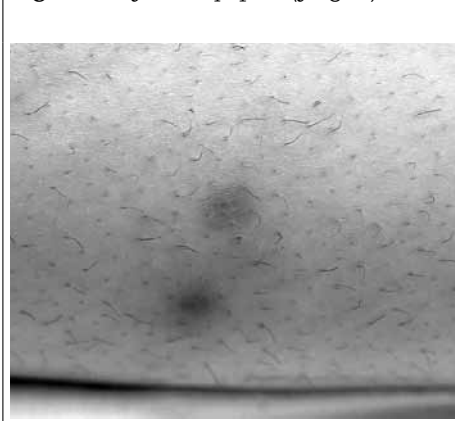


Figure 1B. Embolic lesion (finger)

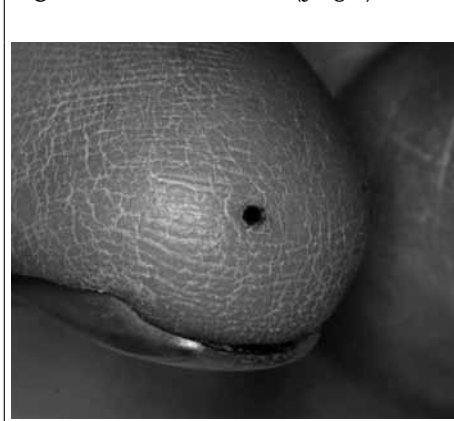


Figure 1C. Splinter haemorrhages (toe)



Figure 3A. Macroscopy. Detail of vegetation of the mitral valve with valvular perforation (arrows)

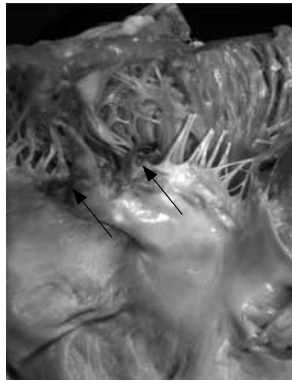


Figure 3B. Microscopy. General view of vegetations of the mitral valve (Haematoxylin and Eosin staining)

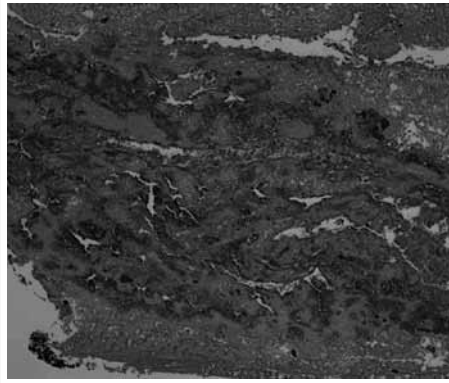
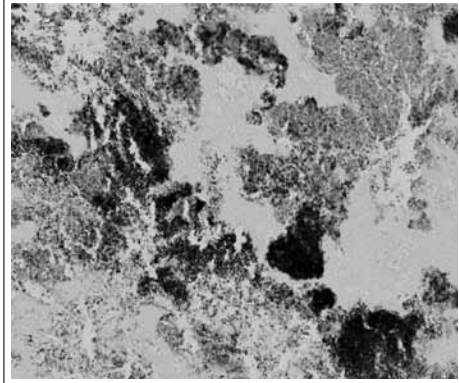


Figure 3C. Microscopy. Bacterial colonies on mitral valve (Gram staining)



DISCUSSION

Early recognition/ diagnosis

S. aureus endocarditis is a serious infection that is associated with high morbidity and mortality even in patients without risk factors for infective endocarditis.¹ Signs and findings which demand consideration of infective endocarditis are summarised in *table 1*. Our patient demonstrated the typical presentation of *S. aureus* endocarditis of the mitral valve with fever, systemic arterial embolisation to various organs, sepsis and heart failure.

Table 1. Clinical presentation of infective endocarditis

Infective endocarditis, in general, must be suspected in the following situations:

- New regurgitant heart murmur
- Embolic events of unknown origin
- Sepsis of unknown origin
- Fever: the most frequent sign of infective endocarditis

Infective endocarditis must be suspected if fever is associated with:

1. Intracardiac prosthetic material (e.g. prosthetic valve, pacemaker, implantable defibrillator, surgical baffle / conduit)
2. Previous history of infective endocarditis
3. Previous valvular or congenital heart disease
4. Other predisposition for infective endocarditis (e.g. immunocompromised state)
5. Predisposition and recent intervention with associated bacteraemia
6. Evidence of congestive heart failure
7. New conduction disturbance
8. Positive blood cultures with typical infective endocarditis causative organism or positive serology for chronic Q-fever
9. Vascular or immunological phenomena: embolic event, Roth's spots, splinter haemorrhages, Osler's nodes, Janeway lesion
10. Focal or non-specific neurological symptoms and signs
11. Peripheral abscesses (renal, splenic, cerebral, vertebral) of unknown cause

Embolism and infarction in various organs are frequently seen as first presentations of infective endocarditis. Systemic emboli involving the spleen and kidneys are mostly seen in cases of left-sided endocarditis.³ Systemic embolisation in our patient was documented in cerebrum (resulting in cerebral infarction), spleen, and both kidneys. Peripheral embolic lesions were found in the right eye, fingers and toes.

Splinter haemorrhages, Janeway lesions, Osler's nodes and Roth's spots are uncommon findings (*figure 1*).^{3,4} The origin of these findings remains a source of debate. Some authors have reported that microorganisms are directly involved in the genesis of these lesions and that the microorganisms can be cultured from these lesions. Others argue that the lesions result from immune-mediated vasculitis, irrespective of (local presence of) the microorganism.^{1,3}

Embolic risk is higher in *S. aureus* endocarditis than in endocarditis caused by other microorganisms. It is also seen more frequently in left-sided endocarditis and with (mobile) vegetations >15 mm on echocardiography.⁵ Cerebral embolism is seen most frequently (up to 18% of the patients, as reported by Nadji *et al.*)⁶ The combination of embolisation to the central nervous system and to peripheral organs is seen in 10% of the patients.³ More than half of these patients will not survive. Mortality is significantly higher in patients who have a neurological event compared with those who do not have any neurological events.

Blood cultures and echocardiography are the cornerstones in the diagnosis infective endocarditis. Confirming the diagnosis of 'infective endocarditis' clinically remains a difficult process and is a challenge for the (critical care) physician. The diagnostic process may be facilitated by the Duke criteria (*table 2*), which are based on strict clinical, microbiological and echocardiographic parameters.

Table 2. Modified Duke criteria for diagnosis of infective endocarditis¹

Major criteria

Blood cultures

- ≥ 2 positive for typical infective endocarditis micro-organisms (*Streptococcus viridans* spp., *Streptococcus bovis*, HACEK group, *Staphylococcus aureus* or *Enterococci*) in absence of primary focus
- Persistently positive blood culture (2 sets drawn >12 hours apart, or ≥ 3 of 4 sets with first and last separated by >1 hour)
- 1 positive for *Coxiella burnetii* or IgG titre against phase 1 $>1:800$

Endocardial involvement

- Positive TTE or TEE, i.e.:
 - Discrete, echogenic, oscillating intracardiac mass on valve or supporting structure, in the path of regurgitant jets, or on implanted material, in the absence of an alternative anatomic explanation (vegetation)
 - Periannular abscess or
 - New partial dehiscence of prosthetic valve
- New valvular regurgitation (worsening of or change in pre-existing heart murmur)

Minor criteria

Broader clinical findings

- Predisposing cardiac condition or intravenous drug use
- Fever ($\geq 38^\circ\text{C}$)
- Vascular phenomena (major arterial emboli, septic pulmonary infarct, mycotic aneurysm, intracranial haemorrhage, conjunctival haemorrhage, Janeway lesions)
- Immunological phenomena (glomerulonephritis, Osler's nodes, Roth's spots, positive rheumatoid factor);
- Microbiological findings of positive blood cultures not meeting major criteria or serological evidence of active infection with plausible microorganisms

TTE = transthoracic echocardiography; TEE = transoesophageal echocardiography.

Table 3. Diagnosis¹

Definite	• Pathology or bacteriology of vegetations, major emboli, or intracardiac abscess specimen, or • 2 major criteria, or • 1 major and 3 minor criteria, or • 5 minor criteria
Possible	• 1 major and 1 minor criterion, or • 3 minor criteria
Rejected	• Firm alternative diagnosis, or • Resolution of syndrome after ≥ 4 days' antimicrobial therapy, or • No pathological evidence at surgery or autopsy after ≤ 4 days of antimicrobial therapy, or • Does not meet definite or possible criteria

is challenged to diagnose and treat the disease before autopsy is necessary to prove infective endocarditis as the final diagnosis. In the current guidelines the role of echocardiography is emphasised and well defined (table 4).¹ The modified Duke criteria may facilitate the diagnostic process, as discussed earlier (tables 2 and 3). Echocardiographic findings and the anatomically representative structures, are summarised in table 5. Of these, vegetation, abscess and dehiscence of a prosthetic valve

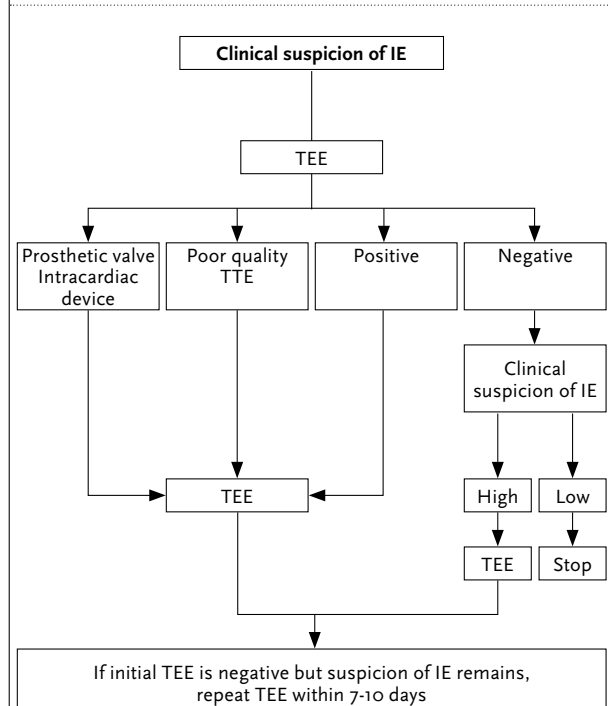
According to these criteria the diagnosis of infective endocarditis can be classified as definite, possible or rejected (table 3). It is to be noted, however, that these criteria were originally developed to compare clinical studies, yielding the highest possible specificity for infective endocarditis (but never 100%). This implies that sensitivity is not 100%. The criteria, therefore, may not be used to definitively exclude the diagnosis of 'infective endocarditis'.

In *S. aureus* bacteraemia a routine echocardiographic evaluation is justified because of the aspecific presentation of *S. aureus* endocarditis and the potentially devastating effects of intracardiac infection.⁷ As in our case, acute valvular dysfunction due to perforation (figure 2A and B) results in acute severe heart failure. It is the most common cause of death in *S. aureus* endocarditis, especially in cases in which surgery is not, or can not be performed.

Echocardiography

Echocardiography plays an important role in the diagnostic workup of patients in whom infective endocarditis is suspected (figure 4). It must be noted, however, that the diagnosis of 'infective endocarditis' is not based solely on echocardiographic findings. Endocarditis is strictly a pathological-anatomical diagnosis in which the clinician

Figure 4. Echocardiographic workup algorithm for patients suspected for infective endocarditis



IE = Infective endocarditis; TTE = Transthoracic echocardiography; TEE = Transoesophageal echocardiography

Table 4. Role of echocardiography in infective endocarditis¹

Recommendations for echocardiography	Class	Level
A Diagnosis		
1. TTE is recommended as the first-line imaging modality in suspected infective endocarditis	I	B
2. TEE is recommended in patients with high clinical suspicion of infective endocarditis and a normal TTE	I	B
3. Repeat TTE / TEE within 7-10 days is recommended in the case of an initially negative examination when clinical suspicion of infective endocarditis remains high	I	B
4. TEE should be considered in the majority of adult patients with suspected infective endocarditis, even in cases with positive TTE, owing to its better sensitivity and specificity, particularly for the diagnosis of abscesses and measurement of vegetation size	IIa	C
5. TEE is not indicated in patients with good quality negative TTE and low clinical suspicion of infective endocarditis	III	C
B Follow-up under medical therapy		
1. Repeat TTE and TEE are recommended as soon as a new complication of infective endocarditis is suspected (new murmur, embolism, persisting fever, heart failure, abscess, atrioventricular block)	I	B
2. Repeat TTE and TEE should be considered during follow-up of uncomplicated infective endocarditis, in order to detect new silent complications and monitoring vegetation size. The timing and mode (TTE or TEE) of repeat examination depend on the initial findings, type of micro-organism, and initial response to therapy	IIa	B
C Intra-operative echocardiography		
Intra-operative echocardiography is recommended in all cases of infective endocarditis requiring surgery	I	C
D Following completion of therapy		
TTE is recommended at completion of antibiotic therapy for valuation of cardiac and valve morphology and function	I	C

TTE = transthoracic echocardiography; TEE = transoesophageal echocardiography.

Table 5. Anatomic and echocardiographic definitions¹

	Surgery / necropsy	Echocardiography
Vegetation	Infected mass attached to an endocardial structure, or on implanted intracardiac material	Oscillating or non-oscillating mass on valve or other endocardial structures, or on implanted intracardiac material
Abscess	Perivalvular cavity with necrosis and purulent material not communicating with the cardiovascular lumen	Thickened, non-homogenous perivalvular area with echodense or echolucent appearance
Pseudoaneurysm	Perivalvular cavity communicating with the cardiovascular lumen	Pulsatile perivalvular echo-free space, with colour-Doppler flow detected
Perforation	Interruption of endocardial tissue continuity	Interruption of endocardial tissue continuity traversed by colour-Doppler flow
Fistula	Communication between two neighbouring cavities through a perforation	Colour-Doppler communication between two neighbouring cavities through a perforation
Valve aneurysm	Saccular outpouching of valvular tissue	Saccular bulging of valvular tissue
Dehiscence of a prosthetic valve	Dehiscence of the prosthesis	Paravalvular regurgitation identified by TTE / TEE, with or without rocking motion of the prosthesis

TTE = transthoracic echocardiography; TEE = transoesophageal echocardiography.

are major Duke criteria. TTE has a low sensitivity for the detection of cardiac vegetations, and a negative TTE cannot exclude infective endocarditis in patients with *S. aureus* bacteraemia or in patients with a high clinical suspicion for infective endocarditis.⁸ TEE, however, is useful in detecting even small vegetations as well as cardiac complications such as (small) abscess formation, pseudoaneurysm, fistula and valvular perforations and is, therefore, indicated when suspicion is high or in patients with prosthetic valves or intracardiac devices (*figure 4*).¹

Treatment

The therapy of infective endocarditis consists of elimination of the infection focus, antimicrobial treatment and, if necessary and if possible, early surgical treatment.

Antiplatelet and antithrombotic therapy are extremely controversial, should be individualised, and should be discontinued when infective endocarditis is complicated by cerebral embolism, infarction or haemorrhage.^{9,10}

Antimicrobial therapy

The optimal antibiotic therapy for a methicillin-susceptible *S. aureus* is intravenous flucloxacillin, preferably given continuously.^{1,11} No randomised controlled trials have determined the optimal duration of therapy, but based on current literature left-sided endocarditis should be treated for at least six weeks. Based on *in vitro* and animal study evidence of synergistic bactericidal activity, combination therapy is used widely. In *S. aureus* endocarditis, animal and human studies suggest that flucloxacillin, when

combined with a cell-wall active agent such as an aminoglycoside during the initial three to five days of therapy, can lead to a shortened duration of bacteraemia, although mortality and morbidity remained unchanged.^{12,13} In right-sided *S. aureus* endocarditis, however, addition of aminoglycosides did not result in additional benefit.¹⁴ Additional administration of low-dose aminoglycosides in left-sided infective endocarditis, even when given for a short duration, was found to result in a significantly higher incidence of nephrotoxicity.¹⁵

Before admission to the intensive care unit, our patient had been treated with gentamicin for three days, and we therefore continued flucloxacillin monotherapy.

The port of entry or focus from which the infective endocarditis originates is generally not obvious. Our patient only had minimal signs of decubitus wounds which might have been the source for his bacteraemia.

Surgical therapy

Surgical therapy, even in the early active phase, should be a treatment consideration in order to avoid progressive heart failure, to control infection or to prevent (further) systemic embolism (table 6). Age per se is not a contraindication to surgery. Early consultation with the cardiothoracic surgeon is recommended to secure the optimal therapeutic approach, especially in *S. aureus* endocarditis.

In our patient surgery was considered immediately because of the presence of haemodynamically significant left-sided valvular regurgitation with perforation, the large and highly mobile vegetation, and the evidence of systemic

embolisation.¹⁶ Appropriately timed and performed surgical therapy of the infected heart valve substantially reduces early and late mortality.¹⁷ However, as evidenced by CT-scan evaluation, our patient already had severe neurological complications at the time of diagnosis. As valve replacement is relatively contraindicated in the presence of large cerebral embolic events, additional diagnostic imaging examinations are necessary to determine the cause, location and extent of the lesion.³ Most surgeons would like to delay operative intervention for at least 7-14 days to lessen likelihood of, or worsening of, the neurological deficit with the knowledge that subsequent anticoagulant therapy, during and after surgery, is usually necessary. Also, in the early stages of endocarditis the infected heart tissue is soft, making surgical repair technically difficult ('like sewing in butter'). Delaying surgery, on the other hand, also entails high risks. The decision to operate in cases of infective endocarditis, therefore, depends on the clinical situation and should be individualised.

In this case CT scanning showed a large lesion of the left parieto-temporal-occipital region which was why surgery was postponed. In the following days the patient deteriorated haemodynamically due to his sepsis and progressive heart failure. Because of this clinical course, in combination with a poor neurological prognosis, it was decided to suspend further treatment.

Prognosis

The six-month mortality rate of complicated left-sided native valve endocarditis is approximately 25%, but

Table 6. Indications and timing of surgery in left-sided native valve infective endocarditis¹

	Timing	Class	Level
A Heart failure			
• Aortic or mitral infective endocarditis with severe acute regurgitation or valve obstruction causing refractory pulmonary oedema or cardiogenic shock	Emergency	I	B
• Aortic or mitral infective endocarditis with fistula into a cardiac chamber or pericardium causing refractory pulmonary oedema or cardiogenic shock	Emergency	I	B
• Aortic or mitral infective endocarditis with severe acute regurgitation or valve obstruction and persisting heart failure or echocardiographic signs of poor haemodynamic tolerance (early mitral closure or pulmonary hypertension)	Urgent	I	B
• Aortic or mitral infective endocarditis with severe regurgitation and no heart failure	Elective	IIa	B
B Uncontrolled Infection			
• Locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation)	Urgent	I	B
• Persisting fever and positive blood cultures >7-10 days	Urgent	I	B
• Infection caused by fungi or multiresistant organisms	Urgent / elective	I	B
C Prevention of embolism			
• Aortic or mitral infective endocarditis with large vegetations (>10 mm) following one or more embolic episodes despite appropriate antibiotic treatment	Urgent	I	B
• Aortic or mitral infective endocarditis with large vegetations (>10 mm) and other predictors of complicated course (heart failure, persistent infection, abscess)	Urgent	I	C
• Isolated very large vegetations (>15 mm)	Urgent	IIb	C

patients with infective endocarditis comprise an extremely heterogeneous group.¹⁰

Hasbun and colleagues derived a prognostic classification system for patients with infective endocarditis.¹⁸ Five clinical features were significantly associated with six-month mortality: i.e. abnormal mental status, moderate to severe heart failure, causative organism other than *Streptococcus viridans* spp., medical therapy without valve surgery and increased Charlson comorbidity score (in which the one-year mortality risk is based on 19 categories of comorbidities). A weighted scoring system was made by use of these prognostic features. Patients were classified into four groups with progressively increasing six-month mortality risks, ranging from 5 to 59%.¹² In our patient all five prognostic features of this scoring system were present, resulting in a calculated six-month mortality risk of (at least) 59%.

CONCLUSION

The presented case illustrates the acute presentation of *S. aureus* endocarditis of the mitral valve in which the signs of severe sepsis, systemic embolisation and heart failure were predominant. Blood cultures and echocardiography are cornerstones of diagnosis in infectious endocarditis but clinical judgement remains crucial. The modified Duke criteria facilitate the diagnostic process, but do not replace clinical evaluation. Early recognition, diagnosis and treatment according to current guidelines, remain extremely important to reduce morbidity and mortality in this disease.

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