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# openheart Embolic risk management in infective endocarditis: predicting the 'embolic roulette'

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### ABSTRACT

Life-threatening complications of infective endocarditis

(IE.) are heart failure, uncontrolled infection and embolic

risks. EE from vegetation rupture are frequent, occurring

in more than 50% of patients and can lead to ischaemic

stroke and systemic organ infarctions, contributing to poor

patient outcomes. Early identification and characterisation

of embolic risk factors, including vegetation size, mobility

modalities like CT and MRI in detecting silent emboli and

consideration of surgical options to mitigate embolic risks.

In this regard, embolic vascular dissemination-including

imaging-has been introduced as a new minor criterion

Depending on the location and severity of the embolism.

the embolic risk can either escalate or alternatively.

complicate and delay cardiac surgery. The decision

to proceed with surgery should not hinge solely on

the occurrence of an embolic event, although current quidelines often emphasise this criterion. Therefore, future

perspectives should focus on identifying high-risk profiles

for EE and investigating whether early surgical intervention

benefits these patients, even if they respond favourably to

antibiotic therapy. This review explores current literature

on echocardiographic and biomarker predictors of EE in

embolic complications and improving patient outcomes.

IE, aiming to enhance clinical strategies for mitigating

guiding therapeutic interventions, including the timely

asymptomatic cases detected through multimodality

and echogenicity assessed through transthoracic and

transoesophageal echocardiography, but also certain

pathogens and biomarkers are important for guiding

clinical decisions. The latest European Guidelines

recommendations emphasise the role of imaging

events (EE), which pose significant morbidity and mortality

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### INTRODUCTION

for the diagnosis of IE.

Infective endocarditis (IE,) is a rare, highly morbid disease with 1.5–11.6 cases per 100 000 persons per year, being associated with poor outcomes and high annual mortality rates of up to 40%.<sup>1</sup> Despite improvements in its management, IE remains a life-threatening condition associated with severe complications.

One of the most common complications of IE is embolic events (EE) (21–50%) caused

by the migration of cardiac vegetation.<sup>1</sup> Up to 25% of IE patients exhibit embolic complication at the time of their initial diagnosis.<sup>2</sup> EE originating from the left heart can lead to major peripheral artery embolism, affecting the hepatic, renal or splenic areas, as well as causing ischaemic stroke, cerebral abscess and mycotic aneurysm. These episodes are classified based on their timing relative to the initiation of antibiotic treatment. EE are considered symptomatic if the patient shows local symptoms, or silent and asymptomatic if they are detected only by CT scan.<sup>1</sup>

The brain and spleen emerge as the predominant embolism sites in left-sided IE. Stroke, a severe complication, is associated with increased morbidity and mortality.<sup>3</sup> Notably, EE can be completely silent in 20-50% of IE patients, particularly those affecting the splenic or cerebral circulation. In such cases, non-invasive imaging techniques are crucial for accurate diagnosis.<sup>4</sup> Despite the widespread use of whole-body CT imaging during the preoperative work-up (ie, the chest, abdomen and pelvis), these investigations rarely alter the diagnosis or treatment plan.<sup>9</sup> However, cerebral CT can significantly influence clinical decision-making and outcomes when surgery is being considered.<sup>67</sup>

Embolic risk is highest during the first days of antibiotic therapy, being 10–20 times greater on the day before and the day after starting antibiotics compared with 2 weeks before and after.<sup>8</sup> Consequently, the frequency of EE decreases steadily during the first 2 weeks of antibiotic treatment. Therefore, the benefits of surgery to prevent embolism are likely greatest in the early stages of therapy when the embolic risk is at its peak.<sup>7</sup>

In the revised diagnostic algorithm for IE, as outlined in the 2023 European Society of Cardiology (ESC) guidelines, embolic vascular dissemination, including asymptomatic cases detected only through imaging, has been added as a minor criterion.<sup>7</sup> As a





result, brain and whole-body imaging (CT, fludeoxyglucose F18 positron emission tomography[18F-FDG-PET]/CT and/or MRI) are now Class I indications for patients with embolic complications and Class IIb indications for patients without symptoms.<sup>7</sup>

Henceforth, septic metastatic complications can either impede or expedite the treatment of IE. Importantly, these complications require themselves specialised management, highlighting the need for a multidisciplinary approach. For instance, the transient ischaemic attack prompts cardiac surgery, while the haemorrhagic stroke postpones it for at least 4 weeks.<sup>7</sup> A splenic abscess requires splenectomy at the same operative time as cardiac surgery. Modern treatment of IE involves active screening for these complications. However, it is crucial to recognise that they can occur at any point during the disease course, posing an unresolved clinical challenge due to the lack of effective risk score models over time. The recently updated ESC 2023 guidelines acknowledge the critical role of embolic risk and introduce the concept of a 'high risk of embolism' or 'established embolism' as exclusive indications for urgent surgery, even in stable patients. For this reason, embolic risk 'calculators' were created, primarily using six parameters: age, diabetes, atrial fibrillation, previous embolism, vegetation length and Staphylococcus aureus infection. However, these scores are most accurate in fatal or critical cases and are less reliable in patients who appear stable.<sup>9</sup> Therefore, it is imperative to thoroughly explore what constitutes 'high risk of embolism' and identify independent predictive factors.

This review aims to analyse existing literature on the management of embolic risk and the identification of predictive echocardiographic and biological risk factors for EE.

### ECHOCARDIOGRAPHIC PARAMETERS IN EMBOLIC RISK PREDICTION

The individual patient embolic risk and the moment of the EE remain difficult to assess. Transthoracic and transoesophageal echocardiography (TEE) play an essential role in evaluating the embolic risk of patients with  $\mathrm{IE}$ .<sup>8 10–12</sup>

Vegetations have the following cardinal features on echocardiography: isoechoic tissue, independent movement, preferentially congregate on the leading edge of the valve, on the lower-pressure side of the valve (most common location of mitral valve involvement would be the anterior leaflet of the mitral valve on the atrial side). In prosthetic valves, however, they will most commonly be located at the junction between the sewing ring and the valvular annulus. Vegetations are also associated with valvular regurgitation, the vast majority cause failure of leaflet coaptation and may also perforate the valve, which will appear as an endocardial discontinuity (often results in multiple, aliased regurgitant jets on the high-pressure side of the affected valve). If regurgitation jet is not present, usually it argues against IE.

The size of the vegetation, increased mobility, the inhomogeneous appearance with reduced echogenicity are predictive factors of embolic risk.<sup>13</sup>

The description of the dimensions and shape is much more detailed using TEE, being the essential imaging method in this context.<sup>13</sup> TEE enhances the sensitivity of TTE to about 85–90% for the diagnosis of vegetation and the additive value of TEE is even more important for the diagnosis of abscess and other forms of perivalvular extension.<sup>14</sup> In a study by Pérez-García *et al*, major diameter measured by real-time three-dimensional (3D)-TEE had better embolic predictive performance than twodimensional (2D)-TEE.<sup>15</sup> In another study of 119 subjects with *S. aureus* bacteraemia receiving both TTE and TEE, IE was diagnosed in 29 (24%), for whom endocardial involvement was evident in 25 (86%) by TEE, versus only 6 (21%) by TTE (p<0.001).<sup>16</sup>

Several echocardiographic characteristics, including vegetation size and mobility, location on the mitral valve, the response under antibiotic therapy (increasing or decreasing in size vegetation) and multivalvular IE, have been linked to an increased risk of embolism.<sup>8 11 12 17-22</sup> Additionally, a range of other clinical and humoral factors collectively contribute to a spectrum of scenarios that significantly elevate the embolic risk of IE (figure 1, central figure).

Among these, vegetation size and mobility are the most powerful independent indicators of a new EE.  $^{4\,23}$ 

### Size

Infective vegetations are amorphous, mobile masses with various sizes ranging from millimetres to centimetres.<sup>24</sup> The maximum length of vegetation represents the most important echographic parameter in embolic risk assessment. The risk of embolism is increased in patients with vegetations >10 mm in length (figure 2), and it is significantly higher in individuals with larger (>15 mm) and mobile vegetations, particularly in staphylococcal IE that affects the mitral valve.<sup>48</sup>

In a large meta-analysis of 21 studies with more than 6500 cases of IE and more than 5000 measured vegetations, the vegetation size greater than 10 mm had a higher risk of EE (OR, 2.28; 95% CI 1.71 to 3.05; p<0.001) and mortality (OR, 1.63; 95% CI, 1.13 to 2.35; p=0.009) compared with those with a vegetation size less than  $10 \text{ mm.}^{13}$ 

Another study of 142 patients with definite IE and TEE imaging available, vegetation length 10mm (OR 1.21 (95% CI 1.02 to 1.43), p=0.03) and vegetation area 50 mm<sup>2</sup> (OR 1.21 (95% CI 1.03 to 1.43) p=0.02) were significantly associated with increased risk of valve destruction. Vegetation area 50 mm<sup>2</sup> was associated with a trend towards significance (OR 1.18 (95% CI 1.00 to 1.39), p=0.05). In a subgroup analysis of patients with left-sided IE, vegetation area remained significantly associated with severe





valve damage (OR 1.26 (95% CI 1.07 to 1.51), p,0.01) along with age (0.99 (95% CI 0.99 to 0.99), p=0.03).<sup>25</sup>

The consequence of vegetation size on hard clinical outcomes is disputed. The length of vegetation has been correlated with a higher risk of mortality at 1 year, but a recent report from the International Collaboration on Endocarditis-Plus registry suggests this relationship may be restricted to medically managed patients only.<sup>26</sup>

The Class I indication pertains to persistent vegetations larger than 10 mm on the native valve (mitral or aortic) or prosthetic valve, accompanied by more than one embolic episode despite appropriate antibiotic therapy. The second Class I indication applies to vegetations exceeding 10 mm in the presence of another surgical indication. Lastly, the Level IIb recommendation involves vegetations over 10 mm without valvular destruction, clinical signs of embolic episodes and in cases of low surgical risk.<sup>7</sup>

TEE plays a key role in identifying vegetations more prone to embolise. Cabezón Villalba *et al* investigated the

interobserver variability in vegetation diameter assessment and its impact on surgical indication when using guideline cut-off points. Based only on the measurement of the length of the vegetation, the surgical indication varied in 43% of the patients. The authors accurately concluded that the variability of measuring vegetation diameter by TEE is significant, and so the IE surgical indication based on a cut-off vegetation diameter should be used with caution and requires a multiparametric approach.<sup>27</sup>

Real-time (RT) 3D-TEE enables for more accurate vegetation description dimension, morphology, consistency, oldness, than 2D-TEE, which might lead to a better prediction of the embolic risk in patients with IE.<sup>27 28</sup>

The cut of value of vegetation length for increased embolic risk was  $\geq 16.4$  mm, respectively  $\geq 9.5$  mm, measured by RT 3D TEE and 2D TEE.<sup>27 29</sup>

RT 3D TEE has enabled an 'enface' view as a surgical view and shows the wide spectrum of the image more precisely (figure 3). $^{3031}$ 



Figure 2 TEE vegetation on the mitral valve, with maximum length >10 mm with high embolic risk (arrows). TEE, transoesophageal echocardiography.



**Figure 3** Three-dimensional transoesophageal echocardiography enface view—vegetation (arrows) on the posterior mitral valve (scallop P2).

However, a recent study found that vegetation size only predicted worse outcomes when it was combined with additional indication for surgery, such as heart failure or an uncontrolled infection.<sup>7 32</sup>

Verhoeven *et al* discovered that patients with very large vegetations (>30 mm length) were at a higher risk of neurological complications.<sup>33</sup>

### Mobility

Mobile vegetation shows an increased risk compared with fixed vegetation. Larger and mobile vegetation can break up into smaller pieces that are transported to other blood vessels until its path is narrowed and further transportation is impossible. When large and mobile, vegetations are prone to embolism and less frequently to valve or prosthetic obstruction. In a subgroup of 14 patients with new cerebral embolism from a multicentre prospective European study, vegetation length was >10 mm in all 14 patients and vegetation mobility was severe in 12 patients (85%).<sup>34</sup>

The vegetation has a mobility that is independent of the adjacent valves. Tissue colour Doppler imaging using TEE was proven to distinguish unique motion patterns in floating vegetations.<sup>13</sup> This is beneficial for distinguishing between various native valvular features that could be misinterpreted as infective vegetations.<sup>30 35</sup>

### Shape

The globular shape of vegetation is associated with a higher risk of embolisation than the non-globular shape (figure 4).<sup>2</sup> A globular vegetation is defined as having a difference of <30% between the length and width as recorded on TEE.

In a transvenous lead extraction study, the shape of the vegetation was a significant predictor of worse outcomes. When compared with the non-globular group, patients with globular vegetations had a considerably greater mortality due to the occurrence of pulmonary embolism (33% vs 0%, p=0.002).<sup>2 36</sup> Interestingly, the non-globular (fingerlike) vegetations had a risk of mortality due to pulmonary embolism associated with percutaneous extraction no higher than in the small vegetation group. Moreover, the same study found that methicillin-sensitive *Staphylococcus epidermidis* and methicillin-resistant *S*.



**Figure 4** Transoesophageal echocardiography vegetation on the mitral valve with globular shape (orange arrow) and hipoecogenicity complicated with annular abscess (blue arrow).

*epidermidis* were the predominant pathogens found in the globular subset of vegetations.<sup>36</sup> The hypothesis would be that the elongated vegetations are more adherent to the adjacent structures, while the globular, bulky ones are heavier and can detach more easily.

### Echogenicity

In the initial stages of the IE, there is an increase in echogenicity and thickness of the valve, with the leaflet displaying an irregular contour due to the biofilm initiating the infection.

Vegetation in the acute phase is often soft and friable on echocardiography, however, in the subacute or chronic stages, it can become partially or completely calcified ('healed') and attached to the underlying structure.<sup>24</sup>

Typically, the tissue density or grey scale of vegetations is similar to the myocardium with a tendency to increase density with chronicity. The echogenicity of the vegetation increases during the period of the healing process after antibiotic therapy. Therefore, hypoechogenic and inhomogeneous vegetations are more exposed to embolisation. Valvular abscesses are predominantly hypoechoic with hyperechoic debris.

In prosthetic valve endocarditis, sewing ring and support structures of mechanical and bioprosthetic valves are strongly echogenic and may prevent vegetation detection within the valve apparatus or its shadow.<sup>37</sup>

### Number

The more vegetations there are, the more likely blood arteries will become obstructed and embolisation will occur.<sup>2</sup> They can be located on the same valve, as illustrated in figures 5 and 6, or they can be found on different valves. Special attention should be paid to multivalvular IE, which, although rare, represents an independent risk factor affecting survival.<sup>38</sup> Moreover, patients undergoing multivalvular surgery have a mortality rate of up to 25%.<sup>38</sup> A strong positive correlation was also found between multiple vegetations and the risk of stroke.<sup>39</sup>

### Location

### Mitral valve

The risk of embolism can be influenced by the location of vegetations, with those situated on the mitral valve posing a greater risk of embolisation in comparison to vegetations on the aortic valve. A meta-analysis of 23 studies found that IE patients with vegetations on the mitral valve had a greater risk of EE than those with vegetations on the aortic valve.<sup>40 41</sup>

Moreover, the location of the vegetation on the anterior mitral valve represents an embolic risk factor. This issue is explained due to the rapid and forceful movement of the anterior cusp of the mitral valve and the fact that the anterior cusp is larger than the posterior and the vegetation is more mobile in this condition with a higher embolic risk.<sup>17 42</sup>

A recent multicentre study including 3899 consecutive patients with isolated aortic or mitral valve IE found that vegetation was more frequently observed in patients with mitral valve IE compared with those with aortic valve IE (66.6% vs 57.1%; p<0.001). The incidence of cerebral EE was higher in mitral valve IE patients (25.4%) compared with aortic valve IE patients (17.7%; p<0.001). This higher occurrence of vegetation and cerebral EE correlated with an increased rate of preoperative stroke (28.2% vs 19.3%; p<0.001). More importantly, patients with mitral valve IE had a higher 1-year mortality rate (35.3% vs 29.0%; p<0.001).<sup>43</sup>

### Aortic valve

In the aforementioned study, aortic valve endocarditis was found to have a higher incidence of perivalvular invasion compared with mitral valve endocarditis. The infection more commonly involves the surrounding valve tissue, making embolisation less likely.<sup>43</sup> Moreover, prosthetic valve endocarditis was more common in the atrioventricular-IE group (33.4% vs 16.6%; p<0.001).<sup>43</sup>



**Figure 5** Transoesophageal echocardiography multiple vegetations on the mitral valve that increase the embolic risk; right panel: zoomed-in image with three detailed vegetations (arrows).



### Timeline

Whatever risk factors are seen in a specific patient, it must be highlighted that the risk of new embolism is highest during the first days after starting antibiotic therapy and rapidly reduces subsequently, especially after 2 weeks. Some embolic risk continues indefinitely as long as vegetations exist, particularly very large ones.<sup>44</sup> As a result, the advantages of surgery to prevent embolism are greatest during the first 2weeks of antibiotic medication, when embolic risk is the highest.<sup>4</sup> The occurrence of EE following the commencement of antibiotic treatment has been approximated to range from 6% to 21% in earlier research. This variability is primarily attributed to variations in selection criteria and the frequency of valve surgery, which differ among different centres. This observation likely highlights the positive impact of antibiotics on endocarditis risk by altering the biological composition of vegetations and lends support to earlier uncontrolled studies.<sup>14</sup>

Several studies have shown a markedly decreased risk of EE in the second week after initiation of targeted antimicrobial therapy. Thus, prompt initiation of an appropriate antibiotic therapy is the most effective known method to reduce EE. Even though the risk of cerebral embolism in general is high, the risk of recurrence seems to be lower than initially suspected. In the vast majority, the first embolic episode occurs before the initiation of antibiotic treatment.<sup>31 45 46</sup>

### **PATIENT CHARACTERISTICS**

When evaluating embolic risk, several factors need to be taken into consideration. In a recent study, the 6-month incidence of new embolism was 8.5% among 847 patients with IE.<sup>47</sup> An 'embolic risk calculator' was developed using six parameters that were linked to an increased risk of embolism: age, diabetes, atrial fibrillation, prior embolism, vegetation length and *S. aureus* infection.<sup>4</sup>

Systemic embolism occurred more frequently in younger patients (figure 7). The authors expected that younger IE patients would react more powerfully to an inflammatory trigger, such as bacteraemia, predisposing them to more  $\text{EE.}^{48}$ 

Recurrent IE has been linked to a decreased incidence of embolic consequences, including central nervous system and systemic embolism.<sup>49</sup>



**Figure 7** Infective endocarditis in a 40 years old patient with blood cultures positive for methicillin-sensitive *Staphylococcus aureus* and multiple systemic embolic abscesses (brain, splenic, liver): (A) vegetation at TEE imaging of the anterior mitral valve in the cleft area (arrow). (B) TEE colour Doppler—severe mitral regurgitation (arrow). (C) TEE abscess on the right side of the atrial surgical patch with echo lucent area (arrow). (D) CT-large splenic abscess (arrow) (E) CT-liver structure with multiple subcapsular peripheral areas, imprecisely delimited with low contrast uptake—budding abscesses (yellow arrows), renal abscess (blue arrow) (F) CT-brain abscesses—ring enhancing lesions with slightly perilesional oedema (arrow). TEE, transoesophageal echocardiography.

One study found that IE-related cerebral emboli were more common in patients with skin symptoms, such as Osler's nodes, Janeway lesions, purpura and oral and conjunctival haemorrhages. More extracerebral emboli were also linked to Janeway lesions. In light of this, the existence of these cutaneous lesions may be a sign of an ongoing embolic process that is causing systemic consequences.<sup>50</sup> This was later confirmed by Lovelock *et al* who found that signs of embolic phenomena in the limbs were established as an independent predictor of mortality.<sup>51</sup>

Patients with cardiac conduction abnormalities had a considerably greater probability of EE versus patients without this complication.<sup>52</sup> While invasive infections, including perivalvular complications, were linked to conduction abnormalities cases, establishing a definitive connection between systemic embolism and conduction abnormalities remains challenging. The same study demonstrated that C-reactive protein (CRP) level was higher in patients with conduction abnormalities compared with those without conduction abnormalities—this actually showing a more active disease in these patients, potentially elucidating the higher rate of embolism.<sup>52</sup>

Prosthetic valve endocarditis is more prone to dehiscence than vegetation formation, however, related septic embolism dramatically raises mortality and morbidity (figures 8 and 9). Ivanovic *et al* studied embolic risk in patients with prosthetic valve endocarditis and established that the incidence of stroke in a group of 111 patients was found to be 23%.<sup>53</sup> Additionally, haemorrhagic transformation occurred in 42% of prosthetic valve endocarditis patients, perhaps as a result of the anticoagulant medication that is routinely used in these circumstances.

### **BIOLOGICAL MARKERS**

Easily acquired blood biomarkers, indicative of the underlying biological processes (particularly inflammation or immune response), also have promising prospects as predictors. The presence of an EE in IE patients can be predicted by mean platelet volume, which is related to platelet function and activation. An effective independent predictor of EE is a mean platelet volume greater than 8.6 fL.<sup>2</sup>

Serum CRP is a key inflammatory marker. Elevated CRP levels indicate the presence of embolism risk. CRP elevation (>40 mg/L) is an independent predictor of EE. The increased friability may explain the association between elevated CRP and EE in IE patients.<sup>54</sup> The systemic immune-inflammation index is also a promising



**Figure 8** IE in a 50 years old patient with mechanical mitral prosthesis and recurrent IE with blood culture positive for *Staphylococcus hominis* spp MR: (A), (B) vegetation at transoesophageal echocardiography on the atrial side of mitral mechanical prosthesis with embolic risk (arrows) CT abdomen with contrast, section in (C) coronal, (D) axial and (E) sagittal planes, highlighting splenic infarcts (arrows). IE, infective endocarditis.

predictor for EEs in patients with IE. A recent study showed that higher systemic immune-inflammation indexes were independently and strongly associated with EEs, and patients with high index values (>1960.945) had a higher risk of EEs and ischaemic stroke.<sup>55</sup>

A higher D-dimer level may be an indicator of embolism due to faster fibrin turnover. Recent studies have reported that higher plasma D-dimer levels were linked with the occurrence of ischaemic stroke in patients with IE and a higher mortality during follow-up.<sup>56 57</sup> However, it is important to note that elevated D-dimer levels are not specific to endocarditis and can be observed in various other conditions, such as deep vein thrombosis or disseminated intravascular coagulation, and their role in the context of IE is not well defined.

The neutrophil-to-lymphocyte (NLR) ratio can be used to predict the severity of cardiovascular disease. A retrospective research found that an NLR greater than 3.045 on admission had a 73.3% sensitivity and a 51.9% specificity for predicting embolisation.<sup>58</sup>

Troponin I (TnI) levels are typically increased in IE due to microbial infection and inflammation. Significant statistical correlations were observed between elevated TnI levels and adverse outcomes, such as central nervous system events and severe arterial embolism.<sup>59</sup> The same study suggests that the incidence of elevated TnI in IE

patients with embolism may be related also to coronary septic embolisation. Nevertheless, it is important to note that severe infection or sepsis can also result in elevated TnI levels.<sup>59</sup> Therefore, further investigation is warranted to explore the relationship between TnI and embolism.

Other possible biomarkers were reported in the literature, such as matrix metalloproteinases, anti- $\beta$ 2-glycoprotein I antibodies, the calcium-binding protein S100A11, aquaporins, cellular adhesion molecules or interleukins were linked to EE in IE, however, the gold standard for diagnosing IE still relies on a combination of clinical presentation, the results of blood culture and echocardiography.<sup>2 60</sup>

Systemic bacterial infections can independently increase the risk of EE, even without cardiac involvement. Inflammation-induced changes that promote blood clotting and the activation of endothelial cells seem to play significant roles in this context. Additionally, there is evidence indicating that the formation of infection-related antiphospholipid antibodies (APAs)—which occur independently of primary APA syndrome or any identifiable autoimmune disease—might influence the likelihood of EE.<sup>61</sup>

In a group of 26 patients who experienced EE, larger vegetations were significantly more common in those with elevated APA levels (averaging  $1.6\pm0.4$  cm)



Figure 9 Three-dimensional transoesophageal echocardiography prosthetic mitral valve endocarditis enface view vegetation on the ring (orange arrow), annular dehiscence (blue arrow) and paraprosthetic leak (red arrow).

compared with patients with normal APA levels (averaging  $1.1\pm0.4$  cm) (p=0.002). By setting an arbitrary cutoff for vegetation size at 1.3 cm, there were noticeable differences in the occurrence of EE among patients with elevated APA levels (p=0.002). Patients with IE and positive for APA showed a significantly higher incidence of structural valve abnormalities: sclerosis, stenosis, leafletprolapse, leaflet-aneurysm and leaflet-perforation (7 out of 13; 54%) compared with those without APA (15 out of 78; 19%) (p=0.01).<sup>61</sup>

### **MICROBIOLOGICAL CHARACTERISTICS**

Particular microorganisms especially *S. aureus, Streptococcus gallolyticus* and *Candida* spp are associated with the risk of EE.<sup>11 62 63</sup>

This is of particular importance especially since the incidence of *S. aureus* IE is increasing.<sup>64–66</sup> Moreover, more severe lesions are caused by *S. aureus*, coagulase-negative staphylococci and non-HACEK bacteria (HACEK = Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, and Kingella). Moreover, real-life observational studies showed that *S. aureus* and non-HACEK bacteria were independent predictors of a large vegetation, which can further increase the embolic risk.<sup>67</sup>

S. aureus represents the most pathogenic and virulent bacterium in IE that causes severe tissue valve destruction and it is associated with the high risk of emboli and mortality. On the other hand, MRSA (methicillin-resistant Staphylococcus aureus) isolates, have been thought to be a poor predictor of embolism. One theory is that the mecA gene caused methicillin resistance, which altered the functional surface expression of fibrinogen and fibronectin adhesins. Furthermore, embolism was related to the specific clonal complex, CC30 and the absence of the plasmid-borne enterotoxin-encoding genes, sed, sej and ser.<sup>68</sup>

Compared with the more 'aggressive' *S. aureus*, *Streptococcus viridans* is associated with a higher incidence of mitral endocarditis.

Pergola *et al* discovered that EE was more common in *Streptococcus bovis* infections than in other pathogens.<sup>63</sup>

A recent systematic study of fungal endocarditis found a significant embolic rate in fungi-infected patients.<sup>69</sup> In a review of 270 subjects with fungal endocarditis, peripheral arterial embolisation occurred in 45% of patients.<sup>70</sup> A case report of an extremely rare black fungi (dematiaceous mould) that involved the prosthetic aortic valve, root and graft in an immunocompetent patient was diagnosed through severe embolic manifestations in the renal, mesenteric and cerebral districts.<sup>71</sup> Finally, Aspergillus is a highly embolic fungi, with an embolisation rate of 54% in the GAMES (*Grupo de Apoyo al Manejo de la Endocarditis Infecciosa en España*) registry,<sup>72</sup> and 53% in a review of 53 cases of Aspergillus endocarditis.<sup>73</sup>

### EMBOLISM MANAGEMENT IN INFECTIVE ENDOCARDITIS

The surgical extraction of potentially embolic material from the heart can effectively prevent new or additional EE. It is important to recognise that septic emboli may affect any organ system or anatomic location. While certain patterns of involvement tend to be more prevalent, variations exist. Insufficiently known pathophysiological mechanisms represent a barrier to the management of IE and EE.<sup>2</sup> Emboli to different anatomic regions may require distinct plans and different timing in terms of surgical intervention.

As a general rule, any septic embolism to end organs or associated arterial aneurysms necessitates immediate surgical evaluation and prompt intervention. According to the latest ESC guideline, vegetations higher than or equal to 10mm and an EE despite adequate antibiotic treatment represent a Class I indication for urgent surgery (within 3-5 days). Vegetations over 10mm and the presence of severe valvulopathies (not necessarily related to endocarditis) are also Class I indications for urgent surgery, this recommendation is different from the previous guidelines from 2015.<sup>7</sup> The indications are downgraded to Class IIb if no embolism occurs but the vegetation exceeds 10mm. In other cases, such as residual vegetation smaller than 10mm after an embolism or vegetation under 10mm without complications, the guidelines recommend antibiotic therapy alone.<sup>4</sup> Surgical removal of the vegetation from the infected native valve or prosthetic valve insertion when repair of the native valve is not feasible may preclude new or additional EE.<sup>7</sup>

In patients with cerebral haemorrhage and unstable clinical status due to heart failure, uncontrolled infection or persistent high embolic risk, urgent or emergency surgery should be considered, assessing the possibility of a meaningful neurological outcome.<sup>7</sup>

In a prospective randomised trial in a low-risk young patient group with large vegetation and streptococcal IE early surgical removal of vegetation was linked with significantly reduced EE. On the other hand, all-cause mortality at 6 months was not different between the early surgery and conventional treatment groups.<sup>74</sup>

In a non-randomised study patients at higher risk also demonstrated that early surgery may be beneficial in patients with a high risk of embolisation<sup>75–78</sup> and that initial conservative treatment is related to increased mortality.<sup>79 80</sup>

In contrast, the ACC/AHA (American College of Cardiology/American Heart Association) guideline suggests considering early surgery (during initial hospitalisation

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and before completion of antibiotic therapy) as a Class IIb recommendation for left-sided, mobile vegetation >10 mm, without respect to valve lesion severity or operative risk.<sup>81 82</sup>

Prosthetic dehiscence represents another indication of early surgery in patients with *S. aureus* IE.<sup>10</sup> To balance the risk of surgery, which is also influenced by preoperative neurological events or other comorbidities, individualised decision-making is essential.<sup>83 84</sup>

Neurological complications after cerebral embolism like stroke, brain abscess and infectious aneurysms are associated with excess mortality, as well as long-term morbidity, particularly in the case of stroke.<sup>85</sup> Major causes of stroke are embolism by migration of vegetation fragments into the cerebral circulation, and mycotic aneurysm rupture.<sup>3 85</sup>

Prompt antibiotic therapy introduction and immediate diagnosis are very important for avoiding neurological complication. Urgent cardiac surgery in high-risk patients is essential for preventing vegetation embolisation.<sup>74 86</sup>

Anticoagulant or thrombolytic therapy is not useful in this condition.<sup>86–88</sup> Mechanical thrombectomy may be considered within time limits in selected cases.

Large infective aneurysms should be treated by neurosurgery or endovascular therapy, particularly if there is persistent growth despite receiving optimal antibiotic therapy or when they have ruptured.<sup>89</sup>

Endovascular therapy for infective aneurysms is highly successful and has a low morbidity rate when compared with microsurgical and conventional therapy, and may be considered prior to cardiac surgery, even if no rupture is documented.<sup>90 91</sup>

Regarding anticoagulant treatment in patients with a pre-existing indication it is recommended to continue the anticoagulant treatment, which does not seem to increase the risk of stroke or cerebrovascular haemorrhage. Heparin treatment instead of oral anticoagulant is recommended for those with haemorrhagic stroke and indication for early surgery.<sup>92</sup>

After a stroke, the risk of haemorrhagic transformation of uncomplicated ischaemic lesion is reduced and most studies recommend early cardiac surgery given the increased risk of recurrent embolism even under optimal antibiotic treatment.<sup>7</sup> In patients who have experienced a transient ischaemic attack, the risk associated with surgery is typically low and the procedure should be carried out promptly. For individuals with an ischaemic stroke, numerous observational data support a non-delayed (urgent) intervention, unless the neurological status is severely compromised (eg, coma or extensive stroke leading to a poor functional prognosis).<sup>93 94</sup> Consulting with an expert in neurology or neurosurgery can aid in risk assessment discussions. If the stroke is haemorrhagic but the bleeding presents with favourable features (intracranial haemorrhage volume <30 mL or National Institutes of Health Stroke Scale Score <12), the new ESC guidelines recommend urgent surgery, otherwise delaying the surgery for at least 1 month is

recommended.<sup>7</sup> However, the timing of surgery following intracranial haemorrhage is a subject of controversy and represents an area in need of urgent further evidence.

ACC/AHA guidelines recommend no delay in indicated surgery in the setting of stroke without evidence of intracranial haemorrhage or extensive neurological damage; in the setting of haemorrhagic stroke or extensive neurological damage, guidelines advise that surgery should be delayed  $\geq$ 4 weeks.<sup>82</sup> Both recommendations have a Class IIb status and are based on observational data which found similar survival and neurological outcome in operated patients without cerebral haemorrhage or major neurological impairment.<sup>3 95</sup> The ESC guideline is consistent with these recommendations for surgery after a stroke in IE.

These recommendations are in line with a recent study that showed no statistically significant difference in postoperative stroke between patients with versus without preoperative stroke (4 out of 98 (4.1%) vs 10 out of 558 (1.8%); p=0.148). However, the rate of postoperative haemorrhagic strokes was higher in the preoperative stroke group (3.1% vs 0.5%, p=0.016). Lastly, for patients with preoperative stroke, early surgery within 72 hours (38 out of 98 (38.8%)) did not correlate with an increased risk of stroke (2.6% vs 5.0%, p=0.564).<sup>96</sup> These recent findings underscore the viability of an early valve surgery approach for acute endocarditis in the context of acute stroke, demonstrating a comparable postoperative stroke risk.

Splenic complications related to IE range from asymptomatic infarction to abscess formation.<sup>97</sup> Splenic infarcts are frequent and often asymptomatic (20% of patients in the European Infective Endocarditis [EURO-ENDO] registry) but 5% of splenic infarcts can progress to abscess formation.<sup>98</sup> For splenic infarction, conventional treatment with appropriate antibiotics is indicated and for large splenic abscess that does not respond to treatment, splenectomy performed before valve surgery is recommended to avoid spreading the infection to the new prosthesis. In patients with significant surgical risk, percutaneous drainage and/or laparoscopic surgery may be considered as alternatives to open splenectomy.<sup>99 100</sup>

Vaccination against encapsulated bacteria (*Streptococcus pneumoniae*, *Neisseria meningitidis* and *Hemophilus* spp) is advised following splenectomy.<sup>7</sup>

A study suggests that residual vegetation is frequently observed in patients who did not undergo surgery at the completion of antibiotic treatment for IE. Approximately half of the patients with non-operated valvular IE who presented with vegetation at admission continued to exhibit residual vegetation at the end of their antibiotic treatment.<sup>101</sup>

The natural progression of vegetation under antibiotic treatment remains unclear. While antibiotics can eradicate bacteria, vegetation might continue to grow due to fibrin or platelet deposition. Moreover, a reduction in vegetation size might result from micro embolism. Some antibiotics might alter platelet function, potentially

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contributing to vegetation size reduction.<sup>102</sup> In theory, even if bacteria are eradicated, the thrombotic framework may persist.

To summarise, the collective knowledge of IE has undergone significant changes since its early characterisation by Sir William Osler.<sup>103</sup> The characterisation of vegetation has evolved, influencing therapeutic decisions. The patient's clinical presentation, along with the anatomy of the vegetation, determines whether treatment extends beyond antibiotic therapy. In addition to sterilising septic foci, the treatment must address the prevention of equally significant embolic complications. The heterogeneity of septic embolisation adds complexity to treatment but should not result in delays. To provide a comprehensive overview, figure 10 attempts to integrate all embolic complications of IE and connect them with the related treatment approaches.

# MORE QUESTIONS THAN ANSWERS—YOU CANNOT PREDICT A ROULETTE

Despite new guidelines and new data, the question of how the presence of vegetations affects the decision regarding valve surgery in IE remains controversial. Large vegetations (>10 mm), persistent vegetation(s) after systemic embolisation and at least one EE during the first 2 weeks of antimicrobial therapy are consistently cited as 'accepted' indications for valve surgery in IE.

The reality and practicality of managing vegetations in IE is a complex and multifaceted issue. In the absence of additional complications that necessitate surgical intervention, physicians and surgeons are often hesitant to subject patients with IE to valve surgery solely due to the presence of vegetations. This reluctance is further amplified in cases of acute cerebral EE, as cardiac surgeons frequently delay valve surgery to mitigate the risk of cerebral bleeding during intraoperative heparinisation. While 'uncomplicated, nonhemorrhagic embolic stroke' is associated with favourable outcomes following valve surgery, the presence of cerebral haemorrhage prior to surgery significantly increases perioperative mortality.<sup>96</sup>

Basic research looking at the interplay between microbes, vegetations and host highlights additional 'invisible' variables that may influence the natural history and complications of IE. Some of these hypotheses have been clinically studied with mixed outcomes. For instance, the adherence of oral streptococci to non-bacterial thrombotic endocarditis lesions and their capacity to cause IE may depend on the production of dextran, an extracellular polysaccharide. Experimental studies show that ongoing dextran synthesis correlates with larger vegetation size and increased resistance to antimicrobial therapy.<sup>104 105</sup> Platelets also play a significant role in the pathogenesis of IE, contributing to vegetation formation and propagation. Interactions between certain pathogens, platelets and the endothelium enhance the likelihood of IE. Strains of streptococci and staphylococci that aggregate platelets more actively are more likely to cause



Figure 10 Proposed treatment algorithm for embolic complications in infective endocarditis.

IE compared with less aggressive strains. These findings suggest that platelet inhibition might be a promising strategy to prevent vegetation growth and embolisation.

Despite progress in understanding IE, numerous critical questions remain unanswered:

- 1. Does vegetation size truly matter? If so, what is the 'exact' size beyond which embolisation becomes more likely?
- 2. Is vegetation mobility an independent factor contributing to EE, beyond vegetation size?
- 3. Should large and mobile vegetations alone warrant surgical intervention, particularly if detected early in the course of IE? We know that the risk of embolisation decreases during the first 2weeks of effective antimicrobial therapy, therefore it is very challenging to decide the timing of surgery prior to embolisation. Additionally, considerations such as the risks of openheart surgery, patient comorbidities and the necessity of lifelong anticoagulation with mechanical valves must be carefully weighed. The new ESC guidelines have already given partial answers to this question.
- 4. Does an initial 'major' embolisation increase the likelihood of recurrence? If so, can valve surgery prevent

further emboli? As previously discussed, most surgeons avoid immediate cardiac surgery following an embolic stroke, especially if haemorrhage is present. It remains unclear whether all IE patients with major embolisation benefit from urgent valve surgery or only those with persistent vegetations after an EE. The new ESC guidelines have already given partial answers to this question.

- 5. Do 'asymptomatic' emboli increase the risk of subsequent 'major' emboli? If so, should serial imaging studies (eg, CT scans) be performed to detect such emboli, and should surgical intervention be considered if they are identified?
- 6. Is it necessary to perform serial echocardiograms to monitor vegetation evolution? Enlarging vegetations may indicate an increased embolisation risk, but vegetations often persist following the completion of antimicrobial therapy. Conversely, diminishing vegetation size during treatment could represent either resolving infection or asymptomatic embolisation of part of the vegetation.

- 7. Does the choice of antimicrobial therapy influence vegetation size and density based on its 'vegetational penetrability' and affect the risk of complications?
- 8. Is there a role for antiplatelet therapy in IE management? If so, should it be initiated prophylactically in patients at high risk of future IE?

Our current ability to predict complications and outcomes based on macroscopic vegetation characteristics remains a gamble indeed. Given the heterogeneity of IE presentations and outcomes, management decisions will likely continue to rely on individualised, case-by-case assessments.

### CONCLUSION

The management of embolic complications in IE continues to be difficult due to insufficiently understood pathophysiological mechanisms. Echocardiographic parameters, in particular the size and mobility of the vegetation are high risk factors for embolisation. Among the biological factors, infection with S. aureus, S. gallolyticus and Candida spp increases the risk of embolisation. Early diagnosis and targeted antibiotic treatment is the first step in reducing the risk of embolism. According to the latest recommendations surgical removal of the vegetation is strongly indicated only in the case of symptomatic EE despite optimal antibiotic therapy. Urgent surgery may be considered if the vegetation exceeds 10mm (without any severe valve dysfunction or without clinical evidence of embolism) if the surgical risk is low. Overall, studies supporting early surgery for patients with IE-related stroke predominate in the present literature. To completely predict the 'embolic roulette' remains impossible, but through collaborative efforts, physicians can continually improve the treatment of these 'lowfrequency, high-impact' events. The contributions of pathogen-associated virulence factors and host-derived immune responses to the (already-known) morphological characteristics of vegetation represents a key focus for the future. A 'heart team' strategy comprising of cardiologists, cardiac surgeons, microbiologists and neurologists is highly advised.

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