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# Infective endocarditis: Beyond the usual tests

## ABSTRACT

Infective endocarditis remains a diagnostic challenge. Although echocardiography is still the mainstay imaging test, it misses up to 30% of cases. Newer imaging tests—4-dimensional computed tomography (4D CT), fluorodeoxyglucose positron emission tomography (FDG-PET), and leukocyte scintigraphy—are increasingly used as alternative or adjunct tests for select patients. They improve the sensitivity of clinical diagnosis of infective endocarditis when appropriately used, especially in the setting of a prosthetic valve.

## KEY POINTS

Echocardiography can produce false-negative results in native-valve infective endocarditis and is even less sensitive in patients with a prosthetic valve or cardiac implanted electronic device.

4D CT is a reasonable alternative to transesophageal echocardiography. It can also be used as a second test if echocardiography is inconclusive. Coupled with angiography, it also provides a noninvasive method to evaluate coronary arteries perioperatively.

Nuclear imaging tests—FDG-PET and leukocyte scintigraphy—increase the sensitivity of the Duke criteria for diagnosing infective endocarditis. They should be considered for evaluating suspected infective endocarditis in all patients who have a prosthetic valve or cardiac implanted electronic device, and whenever echocardiography is inconclusive and clinical suspicion remains high.

Dr. Brotman has disclosed consulting for Portola Pharmaceuticals.

doi:10.3949/ccjm.86a.18120

**P**ROMPT DIAGNOSIS of infective endocarditis is critical. Potential consequences of missed or delayed diagnosis, including heart failure, stroke, intracardiac abscess, conduction delays, prosthesis dysfunction, and cerebral emboli, are often catastrophic. Echocardiography is the test used most frequently to evaluate for infective endocarditis, but it misses the diagnosis in almost one-third of cases, and even more often if the patient has a prosthetic valve.

But now, several sophisticated imaging tests are available that complement echocardiography in diagnosing and assessing infective endocarditis; these include 4-dimensional computed tomography (4D CT), fluorodeoxyglucose positron emission tomography (FDG-PET), and leukocyte scintigraphy. These tests have greatly improved our ability not only to diagnose infective endocarditis, but also to determine the extent and spread of infection, and they aid in perioperative assessment. Abnormal findings on these tests have been incorporated into the European Society of Cardiology's 2015 modified diagnostic criteria for infective endocarditis.<sup>1</sup>

This article details the indications, advantages, and limitations of the various imaging tests for diagnosing and evaluating infective endocarditis (Table 1).

## INFECTIVE ENDOCARDITIS IS DIFFICULT TO DIAGNOSE AND TREAT

Infective endocarditis is difficult to diagnose and treat. Clinical and imaging clues can be subtle, and the diagnosis requires a high level of suspicion and visualization of cardiac structures.

Further, the incidence of infective endocarditis is on the rise in the United States,

particularly in women and young adults, likely due to intravenous drug use.<sup>2,3</sup>

### ■ ECHOCARDIOGRAPHY HAS AN IMPORTANT ROLE, BUT IS LIMITED

Echocardiography remains the most commonly performed study for diagnosing infective endocarditis, as it is fast, widely accessible, and less expensive than other imaging tests.

**Transthoracic echocardiography** (TTE) is often the first choice for testing. However, its sensitivity is only about 70% for detecting vegetations on native valves and 50% for detecting vegetations on prosthetic valves.<sup>1</sup> It is inherently constrained by the limited number of views by which a comprehensive external evaluation of the heart can be achieved. Using a 2-dimensional instrument to view a 3-dimensional object is difficult, and depending on several factors, it can be hard to see vegetations and abscesses that are associated with infective endocarditis. Further, TTE is impeded by obesity and by hyperinflated lungs from obstructive pulmonary disease or mechanical ventilation. It has poor sensitivity for detecting small vegetations and for detecting vegetations and paravalvular complications in patients who have a prosthetic valve or a cardiac implanted electronic device.

**Transesophageal echocardiography** (TEE) is the recommended first-line imaging test for patients with prosthetic valves and no contraindications to the test. Otherwise, it should be done after TTE if the results of TTE are negative but clinical suspicion for infective endocarditis remains high (eg, because the patient uses intravenous drugs). But although TEE has a higher sensitivity than TTE (up to 96% for vegetations on native valves and 92% for those on prosthetic valves, if performed by an experienced sonographer), it can still miss infective endocarditis. Also, TEE does not provide a significant advantage over TTE in patients who have a cardiac implanted electronic device.<sup>1,4,5</sup>

Regardless of whether TTE or TEE is used, they are estimated to miss up to 30% of cases of infective endocarditis and its sequelae.<sup>4</sup> False-negative findings are likelier in patients who have preexisting severe valvular lesions, prosthetic valves, cardiac implanted electron-

ic devices, small vegetations, or abscesses, or if a vegetation has already broken free and embolized. Furthermore, distinguishing between vegetations and thrombi, cardiac tumors, and myxomatous changes using echocardiography is difficult.

### ■ CARDIAC CT

For patients who have inconclusive results on echocardiography, contraindications to TEE, or poor sonic windows, cardiac CT can be an excellent alternative. It is especially useful in the setting of a prosthetic valve.

Synchronized (“gated”) with the patient’s heart rate and rhythm, CT machines can acquire images during diastole, reducing motion artifact, and can create 3D images of the heart. In addition, newer machines can acquire several images at different points in the heart cycle to add a fourth dimension—time. The resulting 4D images play like short video loops of the beating heart and allow noninvasive assessment of cardiac anatomy with remarkable detail and resolution.

4D CT is increasingly being used in infective endocarditis, and growing evidence indicates that its accuracy is similar to that of TEE in the preoperative evaluation of patients with aortic prosthetic valve endocarditis.<sup>6</sup> In a study of 28 patients, complementary use of CT angiography led to a change in treatment strategy in 7 (25%) compared with routine clinical workup.<sup>7</sup> Several studies have found no difference between 4D CT and preoperative TEE in detecting pseudoaneurysm, abscess, or valve dehiscence. TEE and 4D CT also have similar sensitivities for detecting infective endocarditis in native and prosthetic valves.<sup>8,9</sup>

Coupled with CT angiography, 4D CT is also an excellent noninvasive way to perioperatively evaluate the coronary arteries without the risks associated with catheterization in those requiring nonemergency surgery (**Figure 1A, B, and C**).

4D CT performs well for detecting abscess and pseudoaneurysm but has slightly lower sensitivity for vegetations than TEE (91% vs 99%).<sup>9</sup>

Gated CT, PET, or both may be useful in cases of suspected prosthetic aortic valve en-

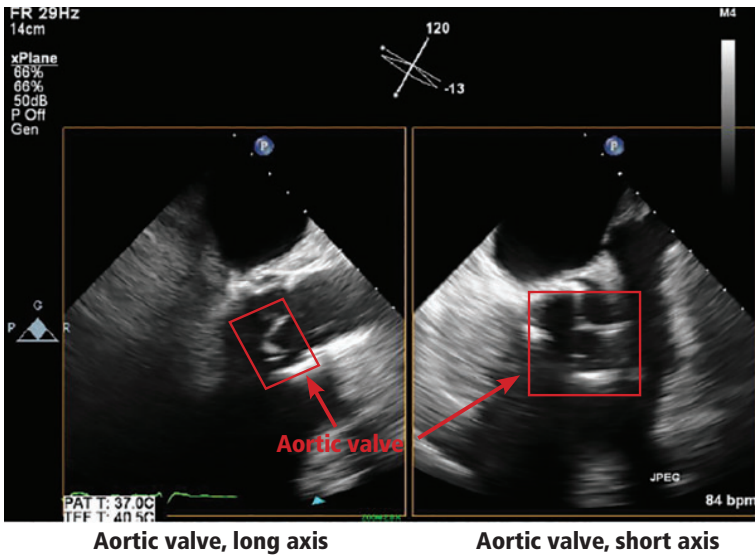
**Consequences of missed or delayed diagnosis are often catastrophic**

TABLE 1

**Imaging tests for assessment of infective endocarditis**

Imaging test	When to consider	Advantages	Limitations
<b>Transthoracic echocardiography (TTE)</b>	Suspected infective endocarditis in patients with risk factors	Widely available Relatively fast Provides hemodynamic information Noninvasive	Decreased sensitivity for abscesses Can miss small vegetations Limited sensitivity for prosthetic valve infective endocarditis Operator-dependent
<b>Transesophageal echocardiography (TEE)</b>	Suspected infective endocarditis despite negative or inconclusive TTE Suspected infective endocarditis in patients with prosthetic valves	Higher sensitivity than TTE for native-valve infective endocarditis, especially mitral valve infection Higher sensitivity than TTE in the presence of prosthetic valves or cardiac implanted electronic device (CIED) No radiation involved	Patients must fast before test Cannot be used if oropharyngeal or esophageal structural abnormalities are present Sensitivity still decreased if prosthetic valve or CIED is present Anesthesia-associated risk Operator-dependent
<b>4-dimensional computed tomography (4D CT), with or without coronary angiography</b>	Suspected infective endocarditis in patients with negative or inconclusive TTE and contraindications to TEE Perioperative assessment of coronary vasculature and aortic tree in patients with known infective endocarditis	Can detect local extension of infection, including abscess, fistula, and pseudoaneurysm Can incidentally detect pulmonary emboli Alternative to coronary catheterization for preoperative evaluation	Can miss small valvular vegetations and perforations Iodinated contrast may exclude patients with renal dysfunction or iodine sensitivity Radiation exposure Arrhythmia reduces sensitivity due to motion artifact
<b>Fluorodeoxyglucose positron emission tomography (FDG-PET)</b>	Suspected infective endocarditis in patients with prosthetic valve or cardiac implanted electronic devices and negative or inconclusive echocardiography Patients with persistent bacteremia and negative CT to identify nidus of infection for source control	Identifies metastatic sites of infection Increases sensitivity of Duke criteria, especially in patients with cardiac implanted electronic devices Can identify source of bacteremia Better than echocardiography at diagnosing intracardiac abscesses and pseudoaneurysms	False positives, particularly $\leq 3$ months after cardiac surgery or with vasculitis, tumors, foreign bodies, postsurgical inflammation False-negatives with antibiotics for several days Limited diagnostic precision in native valve infective endocarditis Limited ability to evaluate infection in brain, gingiva, kidneys Dietary carbohydrate restriction 12–24 hours before study Expensive, limited availability
<b>Leukocyte scintigraphy</b>	Same as for FDG-PET	More specific than FDG-PET	Long study duration Expensive, limited availability Radiation exposure
<b>Cerebral magnetic resonance imaging (MRI)</b>	Assess for mycotic aneurysm in patients otherwise deemed candidates for surgical intervention Assess for cerebral hemorrhage, which may affect management (surgery, anticoagulation)	More sensitive than CT for detecting intracranial lesions Can lead to reclassification of patients (by adding a minor criterion), especially in those without neurologic symptoms	Difficult in unstable patients Contraindicated in patients with noncompatible metal hardware Cannot be done with gadolinium enhancement in patients with contraindications (acute renal failure, chronic kidney disease with glomerular filtration rate $< 30$ mL/min/1.73 m <sup>2</sup> , dialysis)
<b>Cardiac MRI</b>	Quantify valvular regurgitation in patient with poor echocardiography images Assess intracardiac spread of disease in patient unable to receive contrast and with poor echocardiography images	May be more sensitive than echocardiography for detecting vegetations	Unclear if better than CT Contraindicated in patients with noncompatible metallic hardware

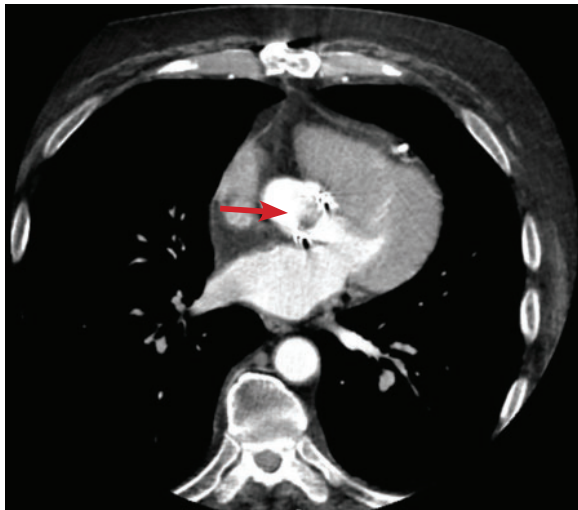
Suspected prosthetic aortic valve infective endocarditis



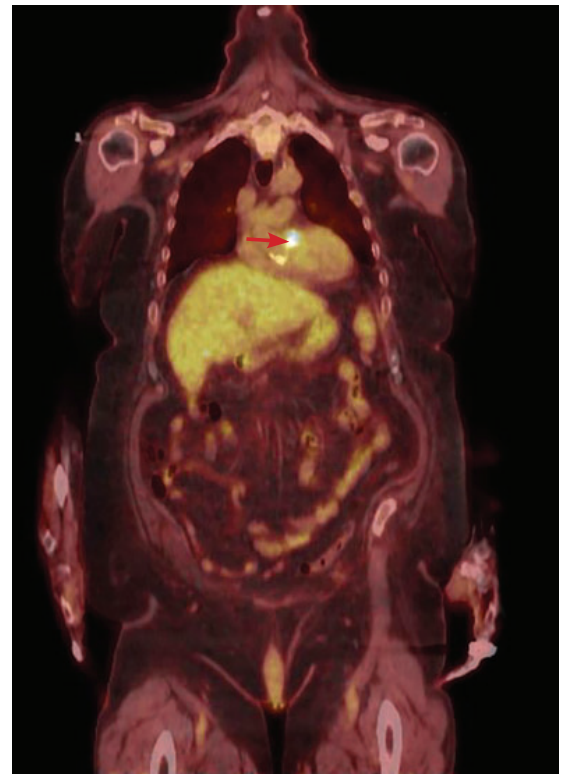
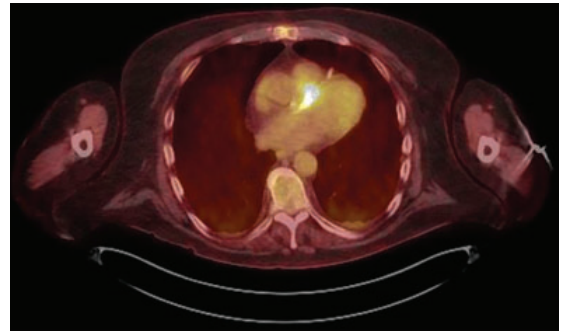
Aortic valve, long axis

Aortic valve, short axis

**Figure 1A.** Transesophageal echocardiography in a 73-year-old man with a bioprosthetic aortic valve who presented with 2 months of fevers, chills, and night sweats. He had several negative blood cultures and 2 negative transesophageal echocardiograms over 1 month. No mass, vegetation, paravalvular abscess, or significant valve dysfunction was noted.



**Figure 1B.** Cardiac computed tomographic (CT) angiography with iodinated contrast, including 4D reconstruction, in the same patient, however, shows an 11-mm vegetation on the bioprosthetic aortic valve leaflets (arrow).



**Figure 1C.** Fluorodeoxyglucose positron emission tomography (FDG-PET) in the same patient confirms the diagnosis, showing a 13-mm hypermetabolic focus on the prosthetic valve (arrow), yielding the diagnosis of infectious endocarditis.



docarditis when TEE is negative. Pseudoaneurysms are not well visualized with TEE, and the atrial mitral curtain area is often thickened on TEE in cases of aortic prosthetic valve infective endocarditis that do not definitely involve abscesses. Gated CT and PET show this area better.<sup>8</sup> This information is important in cases in which a surgeon may be unconvinced that the patient has prosthetic valve endocarditis.

### Limitations of 4D cardiac CT

4D CT with or without angiography has limitations. It requires a wide-volume scanner and an experienced reader.

Patients with irregular heart rhythms or uncontrolled tachycardia pose technical problems for image acquisition. Cardiac CT is typically gated (ie, images are obtained within a defined time period) to acquire images during diastole. Ideally, images are acquired when the heart is in mid to late diastole, a time of minimal cardiac motion, so that motion artifact is minimized. To estimate the timing of image acquisition, the cardiac cycle must be predictable, and its duration should be as long as possible. Tachycardia or irregular rhythms such as frequent ectopic beats or atrial fibrillation make acquisition timing difficult, and thus make it nearly impossible to accurately obtain images when the heart is at minimum motion, limiting assessment of cardiac structures or the coronary tree.<sup>4,10</sup>

Extensive coronary calcification can hinder assessment of the coronary tree by CT coronary angiography.

Contrast exposure may limit the use of CT in some patients (eg, those with contrast allergies or renal dysfunction). However, modern scanners allow for much smaller contrast boluses without decreasing sensitivity.

4D CT involves radiation exposure, especially when done with angiography, although modern scanners have greatly reduced exposure. The average radiation dose in CT coronary angiography is 2.9 to 5.9 mSv<sup>11</sup> compared with 7 mSv in diagnostic cardiac catheterization (without angioplasty or stenting) or 16 mSv in routine CT of the abdomen and pelvis with contrast.<sup>12,13</sup> In view of the morbidity and mortality risks associated with infective endocarditis, especially if the diagnosis is delayed, this small radiation exposure may be justifiable.

### Bottom line for cardiac CT

4D CT is an excellent alternative to echocardiography for select patients. Clinicians should strongly consider this study in the following situations:

- Patients with a prosthetic valve
- Patients who are strongly suspected of having infective endocarditis but who have a poor sonic window on TTE or TEE, as can occur with chronic obstructive lung disease, morbid obesity, or previous thoracic or cardiovascular surgery
- Patients who meet clinical indications for TEE, such as having a prosthetic valve or a high suspicion for native valve infective endocarditis with negative TTE, but who have contraindications to TEE
- As an alternative to TEE for preoperative evaluation in patients with known infective endocarditis.

Patients with tachycardia or irregular heart rhythms are not good candidates for this test.

### ■ FDG-PET AND LEUKOCYTE SCINTIGRAPHY

FDG-PET and leukocyte scintigraphy are other options for diagnosing infective endocarditis and determining the presence and extent of intra- and extracardiac infection. They are more sensitive than echocardiography for detecting infection of cardiac implanted electronic devices such as ventricular assist devices, pacemakers, implanted cardiac defibrillators, and cardiac resynchronization therapy devices.<sup>14-16</sup>

The utility of FDG-PET is founded on the uptake of <sup>18</sup>F-fluorodeoxyglucose by cells, with higher uptake taking place in cells with higher metabolic activity (such as in areas of inflammation). Similarly, leukocyte scintigraphy relies on the use of radiolabeled leukocytes (ie, leukocytes previously extracted from the patient, labelled, and re-introduced into the patient) to allow for localization of inflamed tissue.

The most significant contribution of FDG-PET may be the ability to detect infective endocarditis early, when echocardiography is initially negative. When abnormal FDG uptake was included in the modified Duke criteria, it increased the sensitivity to 97% for detecting infective endocarditis on admission,

**Echocardiography misses the diagnosis in almost 1/3 of cases**

leading some to propose its incorporation as a major criterion.<sup>17</sup> In patients with prosthetic valves and suspected infective endocarditis, FDG-PET was found in one study to have a sensitivity of up to 91% and a specificity of up to 95%.<sup>18</sup>

Both FDG-PET and leukocyte scintigraphy have a high sensitivity, specificity, and negative predictive value for cardiac implanted electronic device infection, and should be strongly considered in patients in whom it is suspected but who have negative or inconclusive findings on echocardiography.<sup>14,15</sup>

In addition, a common conundrum faced by clinicians with use of echocardiography is the difficulty of differentiating thrombus from infected vegetation on valves or device lead wires. Some evidence indicates that FDG-PET may help to discriminate between vegetation and thrombus, although more rigorous studies are needed before its use for that purpose can be recommended.<sup>19</sup>

### Limitations of nuclear studies

Both FDG-PET and leukocyte scintigraphy perform poorly for detecting native-valve infective endocarditis. In a study in which 90% of the patients had native-valve infective endocarditis according to the Duke criteria, FDG-PET had a specificity of 93% but a sensitivity of only 39%.<sup>20</sup>

Both studies can be cumbersome, laborious, and time-consuming for patients. FDG-PET requires a fasting or glucose-restricted diet before testing, and the test itself can be complicated by development of hyperglycemia, although this is rare.

While FDG-PET is most effective in detecting infections of prosthetic valves and cardiac implanted electronic devices, the results can be falsely positive in patients with a history of recent cardiac surgery (due to ongoing tissue healing), as well as maladies other than infective endocarditis that lead to inflammation, such as vasculitis or malignancy. Similarly, for unclear reasons, leukocyte scintigraphy can yield false-negative results in patients with enterococcal or candidal infective endocarditis.<sup>21</sup>

FDG-PET and leukocyte scintigraphy are more expensive than TEE and cardiac CT<sup>22</sup> and are not widely available.

Both tests entail radiation exposure, with the average dose ranging from 7 to 14 mSv. However, this is less than the average amount acquired during percutaneous coronary intervention (16 mSv), and overlaps with the amount in chest CT with contrast when assessing for pulmonary embolism (7 to 9 mSv). Lower doses are possible with optimized protocols.<sup>12,13,15,23</sup>

### Bottom line for nuclear studies

FDG-PET and leukocyte scintigraphy are especially useful for patients with a prosthetic valve or cardiac implanted electronic device. However, limitations must be kept in mind.

A suggested algorithm for testing with nuclear imaging is shown in **Figure 2**.<sup>1,4</sup>

## CEREBRAL MAGNETIC RESONANCE IMAGING

Cerebral magnetic resonance imaging (MRI) is more sensitive than cerebral CT for detecting emboli in the brain. According to American Heart Association guidelines, cerebral MRI should be done in patients with known or suspected infective endocarditis and neurologic impairment, defined as headaches, meningeal symptoms, or neurologic deficits. It is also often used in neurologically asymptomatic patients with infective endocarditis who have indications for valve surgery to assess for mycotic aneurysms, which are associated with increased intracranial bleeding during surgery.

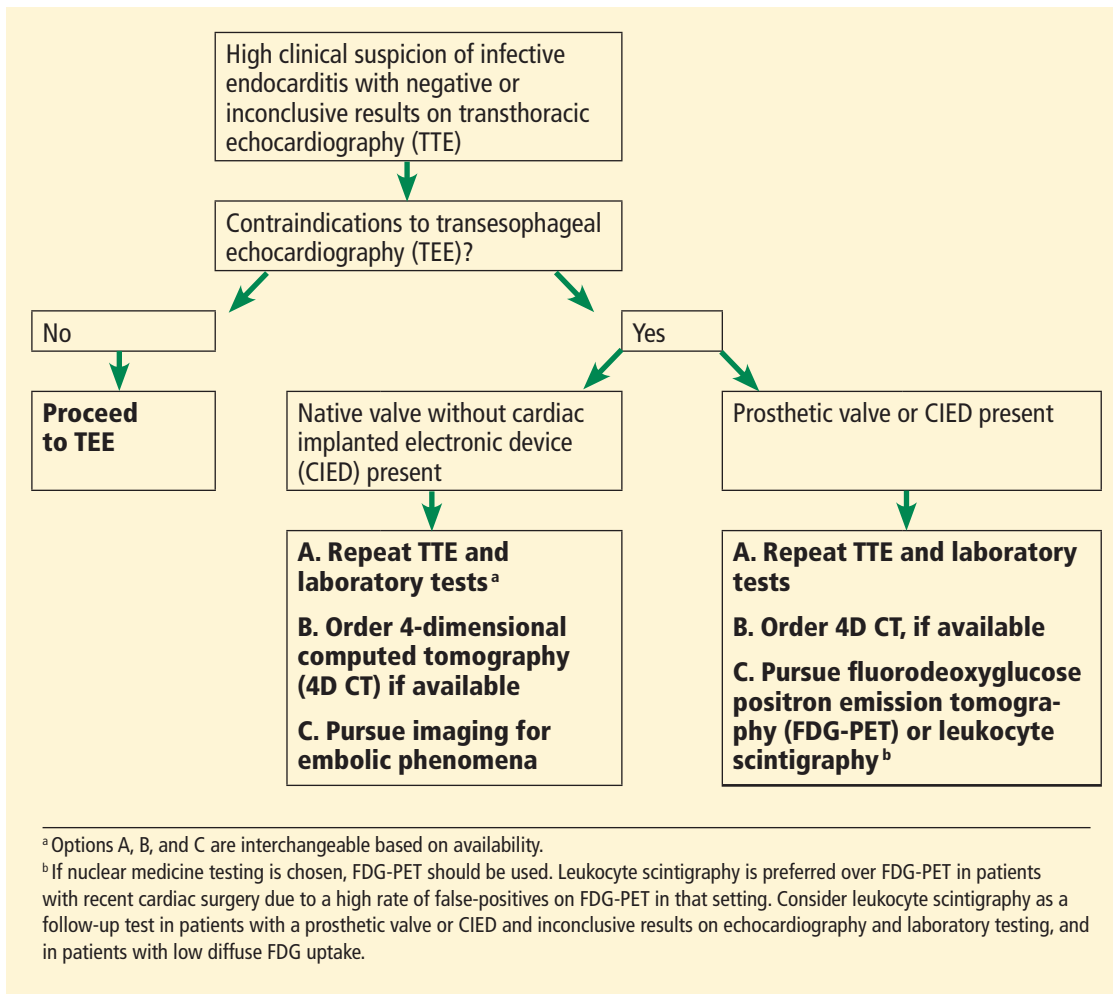
MRI use in other asymptomatic patients remains controversial.<sup>24</sup> In cases with high clinical suspicion for infective endocarditis and no findings on echocardiography, cerebral MRI can increase the sensitivity of the Duke criteria by adding a minor criterion. Some have argued that, in patients with definite infective endocarditis, detecting silent cerebral complications can lead to management changes. However, more studies are needed to determine if there is indeed a group of neurologically asymptomatic infective endocarditis patients for whom cerebral MRI leads to improved outcomes.

### Limitations of cerebral MRI

Cerebral MRI cannot be used in patients with non-MRI-compatible implanted hardware.

Gadolinium, the contrast agent typically

**Infective endocarditis is on the rise, likely due to intravenous drug use**



**TEE is the recommended first-line study for patients with a prosthetic valve**

**Figure 2.** Suggested algorithm for evaluating suspected infective endocarditis with negative or inconclusive results on echocardiography.

used, can cause nephrogenic systemic fibrosis in patients who have poor renal function. This rare but serious adverse effect is characterized by irreversible systemic fibrosis affecting skin, muscles, and even visceral tissue such as lungs. The American College of Radiology allows for gadolinium use in patients without acute kidney injury and patients with stable chronic kidney disease with a glomerular filtration rate of at least 30 mL/min/1.73 m<sup>2</sup>. Its use should be avoided in patients with renal failure on replacement therapy, with advanced chronic kidney disease (glomerular filtration rate < 30 mL/min/1.73 m<sup>2</sup>), or with acute kidney injury, even if they do not need renal replacement therapy.<sup>25</sup>

Concerns have also been raised about

gadolinium retention in the brain, even in patients with normal renal function.<sup>26–28</sup> Thus far, no conclusive clinical adverse effects of retention have been found, although more study is warranted. Nevertheless, the US Food and Drug Administration now requires a black-box warning about this possibility and advises clinicians to counsel patients appropriately.

**Bottom line on cerebral MRI**

Cerebral MRI should be obtained when a patient presents with definite or possible infective endocarditis with neurologic impairment, such as new headaches, meningismus, or focal neurologic deficits. Routine brain MRI in patients with confirmed infective endocarditis without neurologic symptoms, or

those without definite infective endocarditis, is discouraged.

**■ CARDIAC MRI**

Cardiac MRI, typically obtained with gadolinium contrast, allows for better 3D assessment of cardiac structures and morphology than echocardiography or CT, and can detect infiltrative cardiac disease, myopericarditis, and much more. It is increasingly used in the field of structural cardiology, but its role for evaluating infective endocarditis remains unclear.

Cardiac MRI does not appear to be better than echocardiography for diagnosing infective endocarditis. However, it may prove helpful in the evaluation of patients known to have infective endocarditis but who cannot be properly evaluated for disease extent because of poor image quality on echocardiography and contraindications to CT.<sup>1,29</sup> Its role is limited in patients with cardiac implanted electronic devices, as most devices are incompatible with

MRI use, although newer devices obviate this concern. But even for devices that are MRI-compatible, results are diminished due to an eclipsing effect, wherein the device parts can make it hard to see structures clearly because the “brightness” basically eclipses the surrounding area.<sup>4</sup>

Concerns regarding use of gadolinium as described above need also be considered.

The role of cardiac MRI in diagnosing and managing infective endocarditis may evolve, but at present, the 2017 American College of Cardiology and American Heart Association appropriate-use criteria discourage its use for these purposes.<sup>16</sup>

**Bottom line for cardiac MRI**

Cardiac MRI to evaluate a patient for suspected infective endocarditis is not recommended due to lack of superiority compared with echocardiography or CT, and the risk of nephrogenic systemic fibrosis from gadolinium in patients with renal compromise. ■

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**4D CT is recommended for patients with a prosthetic valve or inconclusive results on echocardiography**



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