Infective Endocarditis White Blood Cell Imaging: Is There an Added Value to the First-Line Imaging?

Darko Pucar, MD, PhD,^a and H. William Strauss, MD^a

^a Section of Nuclear Medicine, Department of Radiology and Biomedical Imaging, Yale University School of Medicine, New Haven, CT

Received Jun 16, 2021; accepted Jun 16, 2021
doi:10.1007/s12350-021-02718-3

See related article, pp. 528–534

Infective endocarditis (IE) is a potentially fatal infection of the endocardial surface. IE may cause valvular vegetations and insufficiency, endocardial and/or myocardial abscess, and congestive heart failure (CHF). IE can be complicated by infected and sterile emboli, sepsis, and immunologic phenomena. To minimize complications IE requires prompt diagnosis and treatment.¹

Depending on the organism(s) causing endocarditis the patient may present with acute symptoms of high-grade fever and CHF or subacute symptoms over weeks or months of low grade fever, fatigue, anorexia, and weight loss. The diagnosis is often difficult, due to the widespread use of antibiotics² (often without blood cultures prior to therapy) and the presence of intravascular devices³ (which can provide an avascular nidus of infection). Overall mortality remains high at 30%.¹ Manifestations of IE are often subtle particularly in patients with underlying conditions or already on antimicrobial therapy. IE is usually divided into 3 categories: (1) native valve endocarditis (NVE; acute and subacute); (2) prosthetic valve endocarditis (PVE); and (3) intravenous drug abuse (IVDA) endocarditis. Acute NVE is often rapidly progressive, caused by virulent organisms (i.e., *Staphylococcus aureus*, *Streptococcus B*) and can occur without underlying valvular

abnormality. Subacute NVE has a protracted course caused by less virulent organisms seeding abnormal valves. PVE (10–20% IE cases) occurs in mechanical or bioprosthetic valves, and can be early or late (less or more than 60 days after valve placement, respectively). PVE can be caused by a wide spectrum of bacterial pathogens and by *Candida*.

IE is usually diagnosed based on the modified Duke criteria which combine clinical, microbiologic, pathologic, and echocardiographic factors (Table 1).⁴ Definitive pathologic IE diagnosis is made by demonstrating microorganisms or IE histology in valvular vegetation or cardiac abscess. Definitive or possible clinical IE diagnosis are rendered based on a combination of major and minor criteria. Major criteria are either positive blood cultures for organisms typical for IE or echocardiographic findings typical for IE. Minor criteria include predisposing factors for IE, fever > 38 °C, vascular phenomena, immunologic phenomena, microbiological evidence not meeting the requirements for a major criterion. IE diagnosis can be rejected based on pathologic, clinical, and echocardiographic evidence. Echocardiography should not be performed for fever or positive blood cultures, in the absence of other symptoms and signs of IE, since vegetations may be sterile in such circumstances. Echocardiography is more accurate for NVE than for PVE, and transesophageal echocardiography (TEE) is superior to transthoracic echocardiography (TTE). Up to 24% of patients with possible IE based on Duke's criteria had IE proven on pathology.⁵ Modified Duke criteria are superior to original Duke criteria, but still fail to provide a definitive diagnosis in 12% of cases.⁶

Planar and SPECT/CT imaging of radiolabeled autologous white blood cells (WBC) or Fluorine-18-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography / computed tomography (PET/CT) can be used to detect both cardiac valve and systemic infection

Reprint requests: Darko Pucar, MD, PhD, Section of Nuclear Medicine, Department of Radiology and Biomedical Imaging, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06511; darko.pucar@yale.edu

J Nucl Cardiol 2022;29:535–9.

1071-3581/\$34.00

Copyright © 2021 American Society of Nuclear Cardiology.

Table 1. Modified Duke Criteria for Infective Endocarditis (IE)

DIAGNOSTIC STATUS of IE

Definite IE

Pathologic Criteria

Microorganisms demonstrated by culture or histology of valvular vegetation, embolized vegetation, or cardiac abscess

Pathologic lesions (vegetation, cardiac abscess) confirmed by histologic examination showing active endocarditis

Clinical Criteria

2 major criteria

1 major criterion + 3 minor criteria

5 minor criteria

Possible IE

Clinical Criteria

1 major criterion + 1 minor criterion

3 minor criteria

Rejected IE

Pathologic Criteria

No pathologic evidence of IE at surgery or autopsy, with antibiotic therapy for <4 days

Clinical Criteria

Firm alternative diagnosis explaining the findings of IE

Resolution of symptoms and signs after ≤ 4 days of antimicrobial therapy

Does not meet clinical criteria for possible IE as above

DEFINITION OF CLINICAL CRITERIA for IE

Major Criteria

Blood Culture positive for IE

Two positive blood cultures for organisms typical of IE > 12 hours apart

All of 3 or a majority of ≥ 4 positive blood cultures (at least 1 h between first and last culture)

Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titer > 1 : 800

Evidence of endocardial involvement on echocardiogram

Oscillating intracardiac mass on a heart valve, on supporting structures, in the path of regurgitant jets, or on implanted material without another anatomic explanation

Cardiac abscess

New partial dehiscence of prosthetic valve

Echocardiogram positive for IE, abscess, new partial dehiscence of prosthetic valve, new valvular regurgitation (worsening or changing of pre-existing murmur NOT sufficient)

Minor Criteria

Predisposing heart condition or injection drug use

Fever, temperature > 38 °C

Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway's lesions

Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor

Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE

Adapted from Li et al⁴

sites. Nevertheless, the American College of Radiology (ACR) appropriateness criteria ⁷ rate WBC and FDG PET scans 3/9 for both modalities. Neither modality is considered appropriate as an initial IE imaging study. However, WBC (rating 5/9) and PET (rating 6/9) scans

may be appropriate in selected patients when Duke criteria including first-line imaging (echocardiography (rating 9/9) and dedicated CT for heart function and morphology with IV contrast (rating 7/9)) are equivocal or suspected to be false negative. They are usually more

helpful in the setting of possible PVE versus possible NVE.

The American Heart Association (AHA) 2015 Scientific Statement on IE indicated that more research is needed to define the utility of FDG PET/CT in the diagnosis and management of IE.⁸ WBC scans were not mentioned. The 2020 ACC/AHA Guideline for the Management of Valvular Heart Disease stated that FDG PET/CT is a reasonable adjunct diagnostic imaging procedure for possible IE on Modified Duke criteria; still with no reference to WBC scans.⁹ 2015 European Society of Cardiology (ESC) Guidelines for the management of infective endocarditis indicated that WBC SPECT/CT and FDG PET/CT are evolving as important supplementary methods for suspected IE.¹⁰ According to ESC, the main added value of these techniques is the reduction in misdiagnosed IE, classified in the possible IE category using the Duke criteria, and the detection of peripheral embolic and metastatic infectious events.^{11,12} For WBC scans, this ESC recommendation was largely based on the landmark study by Erba et al.¹¹ Erba studied 131 consecutive patients with suspected IE assessed by modified Duke criteria and WBC scans between 2005 and 2010. The patients had a final diagnosis based on a combination of parameters including a 12-month follow-up. IE was confirmed in 51 of 131 patients, in 24/28, 25/55, 2/48 of the cases in which IE had been classified as definite, possible, or rejected, respectively, according to the Duke criteria. Whole body, planar spot, and SPECT/CT ^{99m}Tc-HMPAO WBC scans at 4–6 hours and 24 hours were performed in all patients. WBC scans were highly accurate for IE (sensitivity 90%, specificity 100%, positive predictive value (PPV) 100%, negative predictive value (NPV) 94%). ESC also stated that WBC scans are preferred to PET scans in all situations that require enhanced specificity based on Rouzet et al. (Hyafil's group).¹² In this study, investigators compared FDG PET (sensitivity 93%, specificity 71%, PPV 64%, NPV 94%, accuracy 80%) and WBC (sensitivity 64%, specificity 100%, PPV 100%, NPV 86%, accuracy 86%) in 39 consecutive patients with suspected PVE and inconclusive echocardiography results, with final Duke classification after 3 months follow-up used as reference standard.¹² Interestingly, ACR scored this study¹² in its IE appropriateness criteria as category 3 (1—well designed and accounts for common biases; 2—moderately well designed and accounts for common biases; 3—important study design limitations; 4—not useful as primary evidence), likely due to retrospective nature, absence of multiple readers, absence of systematic recruitment, and dependance of reference standard on index test.⁷ In a retrospective study of 42 patients with suspicion of PVE and inconclusive TEE, Hyafil et al. showed impact on

management in 12 patients (29%), with intense positive uptake indicating the need for cardiac surgery, and mild positive uptake and negative uptake suggesting the safety of medical management.¹³

Other WBC studies of IE showed less consistent results,^{14,15} with one small study of 7 patients from 2004 showing 0% sensitivity,¹⁵ which negatively influenced ACR appropriateness criteria.⁷ Due to small sample size and less advanced WBC imaging in these studies, their continued clinical relevance is doubtful.

IE was first described by Lazaire Riviere on autopsy specimens in a 1674 publication “Opera Medica Universa.” Even after numerous publications over several centuries described details of the pathophysiology the diagnosis of IE remains challenging.¹⁶ In this issue of the Journal, Kooshi et al. describe a retrospective analysis of preoperative ^{99m}Tc labeled autologous white blood cell images in patients with suspected IE. The surgical results were considered the definitive outcome. ^{99m}Tc-HMPAO WBC scans were performed in 36 consecutive patients suspected of PVE.¹⁷ Antimicrobial therapy was administered in 23 patients prior (3–96 days) to WBC scans. The patients underwent surgery 12 ± 8 days after WBC scans. Based on Modified Duke Criteria applied preoperatively, 16, 18, and 2 patients were classified as definite, possible, and rejected IE, respectively. WBC scans were classified as 20 positive and 16 negative for PVE. Based on intraoperative findings, 23 patients were positive, while 13 patients were negative for PVE. WBC scans demonstrated excellent performance (sensitivity 87%, specificity 100%, PPV 81%, NPV 92%). WBC scans re-classified 9 of 18 patients with possible PVE based on modified Duke criteria to definitive PVE, indicating added value for the indication currently supported by guidelines. The three patients with falsely negative WBC scans had longer duration of antibiotic treatment before imaging and no perivalvular abscess. Importantly, 13 of 16 patients with negative WBC scans did not have PVE on surgery, indicating that WBC may also be helpful in avoiding surgery in patients with high operative risk.

Positivity on the WBC scan was defined as focal uptake that increased on 24 hour images relative to 4 hour images. Intensity of uptake based on 24 hour images was classified as moderate and intense relative to reference uptake in the liver. The scan was negative if uptake at 4 hours disappeared at 24 hours. Inter-observer variability between 2 readers was strong (kappa 0.82) in 23 of 36 patients who had both planar and SPECT images available. All 11 patients with abscess at surgery had intense uptake. The prevalence of abscess in patients with intense and moderate uptake was 83% and 12%, respectively. Thus, intense uptake, greater than liver

reference, is helpful in predicting the presence of abscess.

The present study shows excellent accuracy of WBC scans for PVE with surgical pathology as the reference standard. The study has similar limitations as other prior studies in this field, including: small sample size, retrospective design, and dependence of reference standard on index test. The authors minimized selection bias by including consecutive patients; however, WBC scan results biased a decision to perform the surgery (absence of systematic recruitment). The study collected data over 13 years, with WBC technology changing over time. Thus, inter-observer variability could be determined in only 23 of 36 patients. The study is single institutional without an independent validation set.

Although there is no doubt that WBC scans are accurate for IE, it remains unresolved if they add value to first-line imaging. Despite nuclear medicine community enthusiasm for WBC and FDG PET scans in IE, radiology and cardiology guidelines consider these modalities as optional (maybe appropriate) for possible IE based on Duke criteria.^{7–10} At present, echocardiography is the only universally accepted first-line imaging for IE. This is unlikely to change; however, better design of nuclear medicine studies may upgrade PET and WBC scans from optional to appropriate as second or third-line imaging. Considering the high morbidity and mortality of IE, a prospective trial with randomization to groups with and without utilization of PET and WBC scans, is not ethical. However, the quality of evidence can be improved by conducting prospective IE multi-institutional studies with harmonization of acquisition, processing, and interpretation. Prospective design will allow systematic recruitment aimed to answer a specific question and impact on management determination. For example, % of change in management after performance PET and WBC scans in patients with possible IE based on modified Duke criteria. Multi-institutional design will allow data acquisition within a reasonably short time frame. Inclusion and exclusion criteria could be strictly applied since the study will not be limited by a low number of patients meeting these criteria in a single institution. Separate prospective trials for NVE and PVE will be likely the best approach. In addition to IE diagnosis, prospective trials utilizing favorable response to antimicrobial therapy on PET and WBC scans to avoid surgery in high operative risk patients may be considered.

Sequencing of PET and WBC scans is another important question that needs to be answered by prospective trials. It is likely that PET scan will be second-line nuclear imaging of choice due to superior logistics over WBC scans.

In summary, Kooshki et al. has contributed a high-quality retrospective study which shows high accuracy of ^{99m}Tc-HMPAO WBC scans with SPECT/CT for the diagnosis of PVE. The study strongly supports utilization of WBC scans in patients with possible PVE based on Duke criteria. However, to upgrade WBC scans from optional to appropriate in patients with equivocal IE diagnosis based on microbiological, echocardiographic and clinical criteria, multi-institutional prospective trials are required.

Disclosures

Darko Pucar: Telix Pharmaceuticals Inc. (speaking fee), Cohere Health (consulting fee) H. William Strauss has nothing to disclose.

References

- Hackett AJ, Stuart J. Infective endocarditis: Identification and management in the emergency department. *Emerg Med Pract* 2020;22:1–24.
- Lerner PI, Weinstein L. Infective endocarditis in the antibiotic era. *N Engl J Med* 1966;274:388–93.
- Cahill TJ, Baddour LM, Habib G, Hoen B, Salaun E, Pettersson GB, et al. Challenges in infective endocarditis. *J Am Coll Cardiol* 2017;69:325–44.
- Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 2000;30:633–8.
- Habib G, Derumeaux G, Avierinos JF, Casalta JP, Jamal F, Volot F, et al. Value and limitations of the Duke criteria for the diagnosis of infective endocarditis. *J Am Coll Cardiol* 1999;33:2023–9.
- Tissieres P, Gervais A, Beghetti M, Jaeggi ET. Value and limitations of the von Reyn, Duke, and modified Duke criteria for the diagnosis of infective endocarditis in children. *Pediatrics* 2003;112.
- Malik S, Hsu J, Hurwitz Kowek L, Ghoshhajra B, Beache G, Brown R et al. ACR Appropriateness Criteria® Infective Endocarditis. <https://acsearch.acr.org/docs/69408/Narrative/>. American College of Radiology. Accessed 6 December 2021.
- Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Tleyjeh IM, Rybak MJ, et al. Infective endocarditis in adults: Diagnosis, antimicrobial therapy, and management of complications: A scientific statement for Healthcare Professionals From the American Heart Association. *Circulation* 2015;132:1435–86.
- Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: Executive summary: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2021;143:e35–71.
- Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J* 2015;36:3075–128.

11. Erba PA, Conti U, Lazzeri E, Sollini M, Doria R, De Tommasi SM, et al. Added value of ^{99m}Tc-HMPAO-labeled leukocyte SPECT/CT in the characterization and management of patients with infectious endocarditis. *J Nucl Med* 2012;53:1235–43.
12. Rouzet F, Chequer R, Benali K, Lepage L, Ghodbane W, Duval X, et al. Respective performance of ¹⁸F-FDG PET and radiolabeled leukocyte scintigraphy for the diagnosis of prosthetic valve endocarditis. *J Nucl Med* 2014;55:1980–5.
13. Hyafil F, Rouzet F, Lepage L, Benali K, Raffoul R, Duval X, et al. Role of radiolabelled leucocyte scintigraphy in patients with a suspicion of prosthetic valve endocarditis and inconclusive echocardiography. *Eur Heart J Cardiovasc Imaging* 2013;14:586–94.
14. Borst U, Becker W, Maisch B, Borner W, Kochsiek K. Clinical and prognostic effect of a positive granulocyte scan in infective endocarditis. *Clin Nucl Med* 1993;18:35–9.
15. McDermott BP, Mohan S, Thermidor M, Parchuri S, Poulouse J, Cunha BA. The lack of diagnostic value of the indium scan in acute bacterial endocarditis. *Am J Med* 2004;117:621–3.
16. Geller SA. Infective endocarditis: a history of the development of its understanding. *Autops Case Rep* 2013;3:5–12.
17. Kooshki N, Grambow-Velilla J, Mahida M, Benali K, Nguyen C, Cimadevilla C, et al. Diagnostic performance of White Blood Cell SPECT imaging against intra-operative findings in patients with a suspicion of prosthetic valve endocarditis. *J Nucl Cardiol* 2021. <https://doi.org/10.1007/s12350-021-02674-y>.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.