

Molecular Imaging of Cardiovascular Device Infection: Targeting the Bacteria or the Host–Pathogen Immune Response?

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Learning Objectives: On successful completion of this activity, participants should be able to (1) understand the role of ^{18}F -FDG PET/CT for diagnosis of cardiovascular device infection, as a functional imaging tool for assessing the overall host–pathogen immune response in infection; (2) learn about the strengths and limitations of bacteria-targeting radiotracers for infection imaging, including those based on substances of bacterial maltodextrin transporters, bacterial thymidine kinase, antibiotics, antimicrobial peptides, antibacterial antibodies, bacteriophages, and bacterial DNA/RNA hybrid nucleotide oligomers; and (3) discuss the pros and cons of ^{18}F -FDG versus bacteria-targeting tracers.

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Rapid and accurate diagnosis of cardiovascular device infection remains a challenge in the clinic. Anatomic imaging tools such as echocardiography and cardiac CT or CT angiography are the first-line modalities for clinically suspected endocarditis given their ability to detect vegetation and perivalvular complications. Accumulating data suggest that functional imaging with ^{18}F -FDG PET/CT has unique merits over anatomic imaging and could potentially diagnose early cardiac device infection before morphologic damage ensues and identify infection sources or bacterial emboli in the rest of the body. Although an abnormal finding on ^{18}F -FDG PET/CT was added to the 2015 guidelines of the European Society of Cardiology as a major criterion for the diagnosis of device-related and prosthetic valve endocarditis, that addition has not been incorporated in the U.S. guidelines. Beyond these clinically available imaging tools, attempts have been made to develop bacteria-targeting tracers for specific infection imaging, which include tracers of bacterial maltodextrin transporter, bacterial thymidine kinase, antibiotics, antimicrobial peptides, bacterial antibodies, bacteriophages, and bacterial DNA/RNA hybrid nucleotide oligomers. Most of the tracers have been studied only in experimental animals, except for radiolabeled antibiotics, which have been examined in humans without success in clinical translation for infection imaging. In this article, we compare the roles of anatomic and functional imaging for cardiac device infection and discuss the pros and cons of ^{18}F -FDG and bacteria-targeting tracers. While anticipating continued investigations for bacteria-specific tracers in the future, we recommend that ^{18}F -FDG PET/CT, which represents the host–pathogen immune response to infection, be used clinically for identifying cardiovascular device infection.

Key Words: FDG; PET/CT; bacteria; infection; maltodextrin transporter; cardiovascular device

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Bacterial infection remains a worldwide health problem associated with major mortality and morbidity, yet it is treatable if diagnosed at an early stage. Patients with implanted medical devices, such as electronic or prosthetic cardiac devices, are prone to infection because of their older age and underlying comorbidities (1,2). There has been a continuous increase in the implantation of cardiovascular devices such as pacemakers, defibrillators, prosthetic valves, and left ventricular assist devices (3). Infection is one of the major complications of device implantation, often progresses quickly, and is potentially life-threatening if not diagnosed and treated early (4). On the other hand, overdiagnosis of infection often leads to unnecessary extraction and reimplantation of the device and the associated increase in hospital stays and mortality, imposing a substantial societal and medical burden. Thus, accurate and rapid diagnosis of infected cardiovascular devices is critical for patient management and therapeutic decisions. Clinical diagnosis of cardiac device infection, particularly device-related endocarditis, involves a multidisciplinary team that includes a cardiologist, an infectious disease physician, a microbiology specialist, and imaging specialists (5). Imaging tools play a vital role in localizing and diagnosing cardiovascular device infection and in monitoring treatment response. These tools include anatomically based modalities such as transthoracic echocardiography or transesophageal echocardiography (TEE), electrocardiography-gated cardiac CT or CT angiography (CTA), and functionally based modalities—mainly radionuclide imaging with ^{18}F -FDG PET/CT and ^{111}In - or $^{99\text{m}}\text{Tc}$ -labeled autologous white blood cell (WBC) SPECT/CT. These imaging modalities visualize and diagnose infection on the basis of morphologic and functional changes in the host inflammatory

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immune response to the infectious pathogens. In this article, we examine the roles of these anatomically based (TEE, CT) and functionally based (PET/CT, WBC scan) imaging tools for diagnosing cardiac device infection and discuss the pros and cons of other investigational imaging strategies, such as bacteria-targeted imaging. On the basis of the overall body of articles published, we propose judicious implementation of ^{18}F -FDG PET/CT for evaluating cardiac device infection.

ANATOMIC IMAGING TOOLS

Anatomically based imaging tools are frequently used in diagnosing cardiovascular device infection. Echocardiography and cardiac CT/CTA are currently the first-line imaging studies for device-related and prosthetic valve endocarditis diagnosis, recommended in the 2014 guideline of the American Heart Association/American College of Cardiology (6) and the 2015 guideline of the European Society for Cardiology (7). Results of the recent European Infectious Endocarditis Registry showed that 99.8% of the patients received echocardiography, with TEE being more frequently used in prosthetic valve endocarditis patients (8). Abnormal findings on echocardiography as a major criterion were present in 89.1% of the patients (8). Echocardiography, particularly TEE, can detect valvular vegetation and can also assess perivalvular complications (perforation, pseudoaneurysm, fistulas, and valve dehiscence) with acceptable accuracy (9). TEE findings may also predict embolic events (10). However, TEE may miss up to 30% of valvular prosthetic endocarditis because of the underlying metal ring-related acoustic shadowing artifact (11). Cardiac CT/CTA is a modality of choice for assessing perivalvular complications with a high sensitivity, better than TEE (12). However, both modalities detect late morphologic changes of infection, and findings are often nonspecific and associated with artifacts from the device's foreign material components. TEE is limited to the intracardiac device components and is not able to assess other parts of the device or even the right side of the heart. Although CT can assess infection in the cardiac implantable electronic device pocket and leads, it is not able to evaluate the rest of the body for potential sources of infection or sites of infectious embolism, which are critical for clinical management. Thus, functional ^{18}F -FDG PET/CT and radiolabeled WBC scans have been used and studied for their roles in improving the diagnosis of cardiac device infection. In addition, other strategies such as bacteria-targeting tracers are under active study in experimental animals for their potential translation to the clinic.

FUNCTIONAL IMAGING TOOLS

^{18}F -FDG PET/CT and ^{111}In - or $^{99\text{m}}\text{Tc}$ -labeled WBC SPECT/CT are useful functional imaging techniques for the diagnosis of cardiac device infection. Abnormal findings on ^{18}F -FDG PET/CT or WBC scans have been added as a major imaging criterion for the diagnosis of endocarditis in the European Society for Cardiology guideline though not yet in U.S. guidelines (7). Accumulating data have suggested that ^{18}F -FDG PET/CT could have several merits over TEE and CTA in assessing cardiovascular device infection given its functional and whole-body imaging nature. One merit is the ability to diagnose infection earlier, before TEE- and CTA-detectable morphologic damage ensues. Another is the ability to provide metabolic evidence for a confirmatory diagnosis when TEE and CTA findings are inconclusive or equivocal. A third merit is the ability to diagnose infection in the extracardiac parts

of a device, such as the pacemaker/defibrillator pocket and lead, or the driveline of a left ventricular assist device, which is beyond the TEE and CTA views. A final merit of ^{18}F -FDG PET/CT is the ability to image extracardiac portions of the body in the search for a primary infection source or infectious emboli (13,14). Figure 1 shows 3 examples of infections—in a cardiac implantable electronic device pocket, a prosthetic valve, and a left ventricular assist device—as seen on ^{18}F -FDG PET/CT. A systematic review showed a sensitivity of 73%–100% and a specificity of 71%–100% for ^{18}F -FDG PET/CT in the diagnosis of infection in the pocket of a cardiac implantable electronic device (15). A second metaanalysis showed similar results, with a pooled sensitivity of 87% and specificity of 94% (16). For device-related or prosthetic endocarditis diagnosis, it has been shown that adding ^{18}F -FDG PET/CT-positive findings as a major criterion to the modified Duke criteria increased diagnosis sensitivity from 52%–70% to 91%–97% without compromising specificity (17,18). ^{18}F -FDG PET/CT may change management in up to 35% of clinically suspected endocarditis cases (19). For left ventricular assist device infections, it has been shown that in addition to being able to accurately localize the site and extent of infection along the driveline or central portion of the left ventricular assist device (20), ^{18}F -FDG PET/CT can predict clinical progress and outcome better than CT can (Fig. 2) (21). WBC SPECT/CT is less sensitive for device infection but is more specific than ^{18}F -FDG PET/CT (22), and sequential ^{18}F -FDG PET/CT and WBC scans have been shown to provide a more accurate diagnosis for cardiovascular device infection (23). However, clinical use of ^{18}F -FDG PET/CT is low in the workup of cardiac device infection. For example, the European Infectious Endocarditis Registry data showed that ^{18}F -FDG PET/CT was performed on only 16.6% of patients, with a better sensitivity in prosthetic valve endocarditis (62.5%) than in native (28.0%) and device-related endocarditis (16.3%) (8). The use of ^{18}F -FDG PET/CT in the United States to image cardiac device infection is probably even lower, as such use has not been endorsed in the U.S. guidelines and is not currently reimbursed for infection or inflammation imaging. Although most of the studies using ^{18}F -FDG PET/CT for cardiac device infection are retrospective, current clinical practice and expert consensus support the judicious use of ^{18}F -FDG PET/CT in the workup of cardiovascular device infection (24,25).

Table 1 compares anatomic (TEE and CT/CTA) and functional (^{18}F -FDG PET/CT, WBC scanning) imaging modalities for evaluation of cardiovascular device infection.

BACTERIA-TARGETING TRACERS

In an effort to specifically image bacterial infection, attempts have been made to develop tracers that directly target bacterial pathogens in a suspected infection site, which include bacterial metabolic substances (e.g., carbohydrates and nucleosides), antibiotics, antimicrobial peptides, bacterial antibodies, bacteriophages, and bacterial DNA/RNA hybrid nucleotide oligomers. Among these classes of tracers, radiolabeled antibiotics, particularly $^{99\text{m}}\text{Tc}$ -ciprofloxacin, have been extensively studied in clinical trials, without success for clinical translation. Others, such as maltodextrin-based tracers, are still mainly in experimental stages of investigation, with variable clinical promise.

Bacterial Metabolic Substances

Carbohydrates. Different from glucose (and its ^{18}F -labeled analog of FDG), which can be used by both mammalian cells and microbes, certain types of polysaccharides such as maltodextrins can be taken

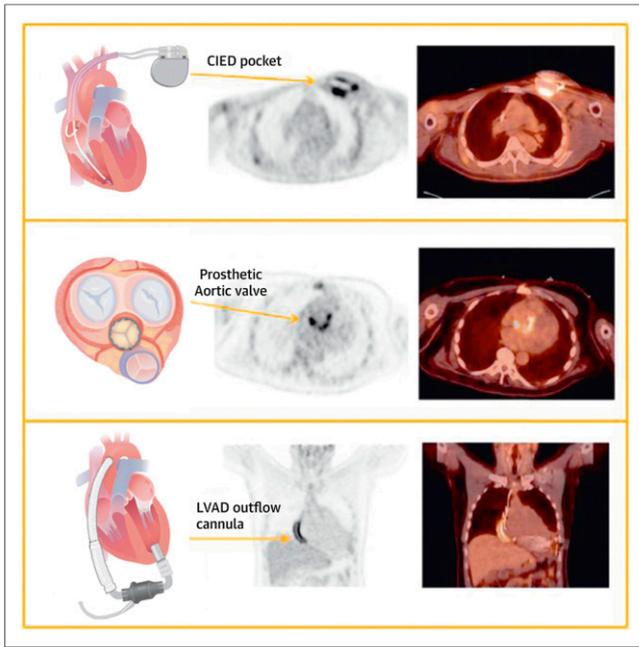


FIGURE 1. Examples of cardiac device infections: illustration of devices (left), PET scans (middle), and ^{18}F -FDG PET/CT scans. (Top) Cardiac implantable electronic device (CIED). There is intense ^{18}F -FDG uptake beneath left upper chest wall CIED pocket, compatible with deep pocket infection. (Middle) Cardiac prosthetic valve. There is intense ^{18}F -FDG uptake along prosthetic aortic valve, compatible with prosthetic valve endocarditis. (Bottom) Left ventricular assist device (LVAD). There is intense ^{18}F -FDG uptake along outflow cannula of LVAD in mediastinum, compatible with central LVAD infection. (Reproduced with permission of (14).)

up and used only by bacteria via maltodextrin transporter (26). Maltodextrin transporter belongs to a family of adenosine triphosphate-binding cassette transporters, which is expressed only in bacteria, not in mammalian cells (26), making it an attractive target for specific bacterial infection imaging. Bacterial maltodextrin transporter can transport maltodextrins with glucose units from 2 (maltose) up to 7 (maltoheptaose) (27). The nonreducing end of a maltodextrin is required for initial binding to the transporter, whereas the reducing end is required for intrabacterial transport (28). Labeling can be performed at the reducing end because bacterial maltodextrin transporters can generally tolerate structure modifications and substitutions at the reducing end (29). Meanwhile, both the nonreducing and the reducing ends of maltodextrins are susceptible to degradation by plasma α -glucosidase and α -amylase, respectively (29), which can result in low tracer stability in the blood with a short imaging window. This restriction should be considered when a maltodextrin-based tracer is being designed for imaging. Certain types of maltodextrin, for example, maltotriose, have been found to be natively resistant to the α -amylase, whereas others, such as maltopentaose, are quickly degraded by the enzyme (29).

Different types of fluorescence- and ^{18}F -labeled maltodextrin tracers have been synthesized and tested on animals for their potential clinical translation for bacteria-specific infection imaging. These tracers include fluorescence-maltohexaose (30), ^{18}F -maltohexaose (31), ^{18}F -maltose (32), ^{18}F -maltotriose (33), ^{18}F -sorbitol (34), and ^{18}F -trehalose (35).

Work in this field was initiated by Ning et al., who first synthesized fluorescence- and ^{18}F -labeled maltohexaose for optical and PET

imaging of bacterial infection, respectively (30,31). Both tracers could visualize bacterial infection in rat thigh, with very low activity in the contralateral thigh with lipopolysaccharide-induced inflammation, indicating potential to distinguish between bacterial infection and sterile inflammation. A subsequent study of cardiac pocket infection in a rat model showed that both tracers accumulated in the cardiac pocket infection sites but not in sterile inflammation sites induced by turpentine oil. In contrast, ^{18}F -FDG uptake was observed in both the infection and the inflammation sites (Fig. 3) (36). ^{18}F -maltohexaose uptake could also be detected in a biofilm model, indicating its potential use for biofilm infection (36). The fluorescence tracer was found mainly in the liver, with very low counts in the kidneys, indicating its primary hepatobiliary excretion (36). Although ^{18}F -maltohexaose showed significant excretion in the urine at early time points (36), the stability of the fluorescence- and ^{18}F -maltohexaose tracers in the blood was not reported. In addition to having different plasma amylase activities, humans and rats may also have different tracer pharmacokinetics. To our knowledge, no clinical human studies with these 2 tracers have yet been reported.

A new tracer, ^{18}F -labeled maltotriose, was recently shown to have a superior pharmacokinetic feature for infection imaging, with urinary clearance (33). Mouse PET imaging showed that ^{18}F -maltotriose accumulated in bacteria-induced muscle infection but not in lipopolysaccharide-induced inflammation, indicating its specificity for bacterial infection. Although maltotriose has previously been shown to be natively resistant to α -amylase (29), ^{18}F -maltotriose stability in the blood was not reported, and a human study is also lacking.

In addition to the above-mentioned tracers, other maltodextrin-based tracers have also been developed and tested on animal models, but with certain limitations. For example, ^{18}F -maltose can also accumulate in inflammation sites, raising concerns of nonspecificity (32). The radio-pharmacokinetics of the ^{18}F -maltose tracer was suboptimal, with predominant hepatic excretion. Another tracer, ^{18}F -sorbitol, can target only gram-negative Enterobacteriaceae-specific infection, as sorbitol can be metabolized only by gram-negative

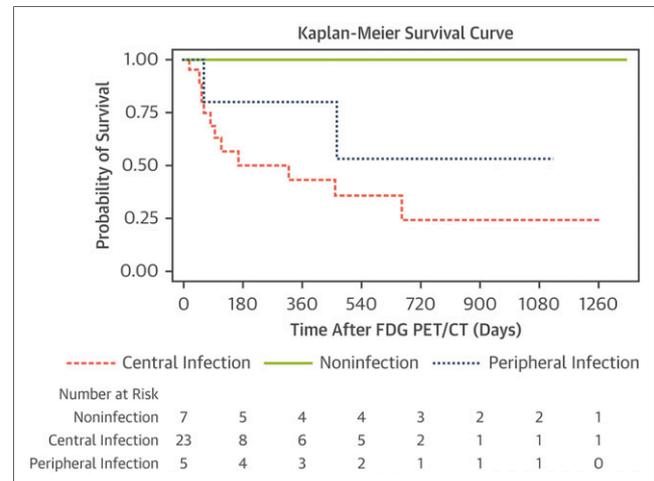


FIGURE 2. Kaplan–Meier survival curves in patients with left ventricular assist device (LVAD). Patients are grouped according to noninfection of LVAD, peripheral infection, and central infection, on basis of diagnosis on ^{18}F -FDG PET/CT. There was significantly higher mortality in ^{18}F -FDG-avid central vs. peripheral infection group. No uninfected patients died ($P < 0.03$, log-rank test). (Reproduced from (27).)

TABLE 1
Comparison of Anatomic and Functional Imaging Modalities for Imaging Cardiovascular Device Infection

Modality	Pros	Cons
TEE/TTE	Provides first-line imaging for infective endocarditis	Shadows artifacts/misses lesions
	Detects vegetation and perivalvular complications	Cannot differentiate infectious from noninfected vegetation
	Assesses valvular function	Cannot evaluate right-side heart and chest wall CIED pocket and leads
	Predicts embolic risk	
Cardiac CT	Provides first-line imaging for infective endocarditis	Has metallic artifacts, nonspecific findings
	Detects large vegetation	Is less sensitive for small vegetation
	Is better than TEE for perivalvular complication evaluation	Is not for extrathoracic evaluation
	Detects chest wall CIED infection	
¹⁸ F-FDG PET/CT	Has high imaging sensitivity	Provides false-positive findings for inflammation
	Provides earlier diagnosis	Is less sensitive for small vegetation
	Assesses extracardiac infection	
	Provides a signal of host immune response	
WBC scan	Has high specificity	Has moderate sensitivity
	Assesses extracardiac infection	Is labor-intensive

TEE/TTE: Transesophageal/transthoracic echocardiography; CIED: Cardiac implantable electronic device.

Enterobacteriaceae (34). In addition, ¹⁸F-trehalose might be a specific tracer for mycobacteria-specific imaging (35).

In summary, whereas maltodextrin-based tracers such as ¹⁸F-maltohexaose and ¹⁸F-maltotriose are promising for bacterial infection imaging, published studies thus far are limited to experimental animal models, and translational clinical data are lacking. More studies are needed to address issues such as tracer stability in the blood and, more importantly, the pharmacokinetics of the tracers, before they are applied in human subjects.

Nucleoside. Fialuridine-5-iodouracil (FIAU) is an analog of a nucleoside substrate for bacterial thymidine kinase but is not phosphorylated by the human kinase (37). ¹²⁴I labeled FIAU (¹²⁴I-

FIAU) has proven capable of visualizing infection in mice induced by a wild-type strain of *E. coli*, but not by a thymidine kinase-deficient mutant strain, indicating its bacterial thymidine kinase specificity (37). However, not all bacteria have an FIAU-binding thymidine kinase. For example, *P. aeruginosa* and *Nocardia* species do not take up FIAU because of lack of the kinase (38), thus limiting the use of ¹²⁴I-FIAU for imaging a broad bacterial infection. A pre-clinical human study with ¹²⁴I-FIAU for assessing prosthetic joint infection showed that the tracer lacks specificity, likely related to host mitochondrial thymidine kinase metabolism (39), leading to a high background activity, particularly muscle uptake, and limiting its use clinically.

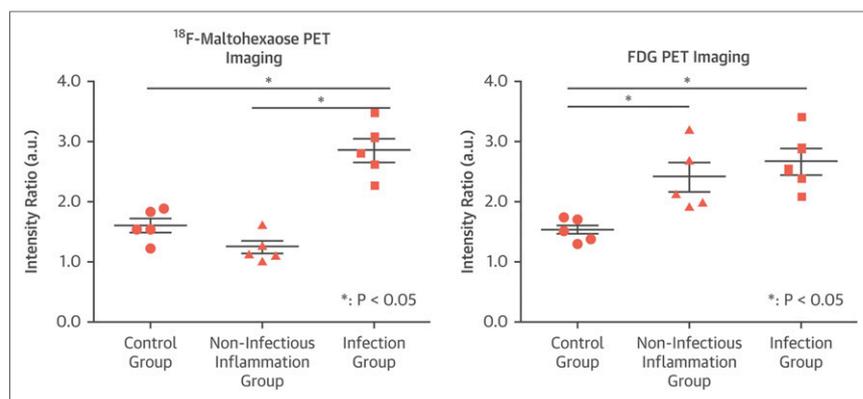


FIGURE 3. ¹⁸F-maltohexaose PET and ¹⁸F-FDG PET in mouse infection models. On ¹⁸F-maltohexaose PET scan, infection mice showed significant increase in tracer intensity compared with control and noninfectious inflammation mice. In contrast, with ¹⁸F-FDG PET imaging, both infection and noninfectious inflammation groups had similar significant increases in intensity compared with control group, demonstrating lack of specificity. a.u. = arbitrary units. (Reproduced from (36).)

Antibiotics

Antibiotics have been radiolabeled for their potential use in bacterial infection imaging given their specific binding and uptake in bacteria. Among the different groups of radiolabeled antibiotics that have been tested for almost 2 decades (40), ^{99m}Tc-labeled ciprofloxacin is the most extensively studied and has been assessed in large clinical trials for use in bacterial infection imaging. Ciprofloxacin is an analog of quinolone, a broad-spectrum antibiotic that inhibits bacterial DNA synthesis by binding to bacterial DNA gyrase. An early clinical study showed that compared with radiolabeled WBC scanning, ^{99m}Tc-ciprofloxacin was the preferred imaging tracer for infection, but it had a fairly high false-negative rate (41). A later large multicenter clinical trial showed that ^{99m}Tc-ciprofloxacin

had a compromised specificity likely caused by its accumulation in noninfectious inflammation sites (42). Ciprofloxacin was also labeled with ^{18}F for PET imaging (43), and a study showed that although increased activity was detected in infected tissue, it was subsequently washed out, likely representing increased regional blood flow and vascular permeability instead of specific ciprofloxacin binding to bacteria (43). In addition, emerging bacterial resistance to ciprofloxacin was also a concern because it can lead to false-negative imaging results (44). Besides ciprofloxacin, many other groups of antibiotics have been labeled and tested (40). Unfortunately, no single radiolabeled antibiotic tracer has been shown to be highly specific for bacterial infections. Thus, although radiolabeled antibiotics, particularly $^{99\text{m}}\text{Tc}$ - or ^{18}F -labeled ciprofloxacin, have been extensively studied in both experimental animals and human subjects, they are not used clinically because of their nonspecificity and low sensitivity. In addition, there is no report regarding radiolabeled antibiotics for imaging cardiovascular device infection in either animal models or human subjects.

Antimicrobial Peptides

To overcome the nonspecificity and bacterial resistance of radiolabeled antibiotics, some antimicrobial peptides have been radiolabeled for their potential use in specific bacterial infection imaging. For example, a synthetic peptide, ubiquicidin 29-41, was radiolabeled and studied for use in bacterial infection imaging. Animal studies showed that $^{99\text{m}}\text{Tc}$ -ubiquicidin 29-41 accumulated in bacterial infection sites but not in sterile inflammation sites (45). However, small clinical trials showed a variable specificity of 80%–100% (46,47). Binding of ubiquicidin to bacteria is initiated and mediated by its positive charges, which interact with negatively charged phospholipids in the bacterial walls (48). This mechanism raises concern about ubiquicidin–bacterial binding strength and mechanistic specificity. In addition, ubiquicidin also binds to fungi, and thus $^{99\text{m}}\text{Tc}$ -ubiquicidin 29-41 may not be able to differentiate bacterial infection from fungal infection (49). ^{68}Ga -labeled ubiquicidin 29-41 was also developed for PET imaging and showed similar findings (50). Like radiolabeled antibiotics, radiolabeled antibacterial peptides are less likely to be clinically translatable.

Bacterial Antibodies

Radiolabeled antibodies are one of the first approaches applied for bacterial infection imaging. Early animal studies using radiolabeled (^{111}In and $^{99\text{m}}\text{Tc}$) human immunoglobulin showed that although much higher activity was seen in infection sites, less activity was observed in inflammation sites, likely because of increased vascular permeability and nonspecific Fc fragment binding to immune cells recruited to the site of infection (51). To overcome the nonspecific binding related to Fc region, radiolabeled antibody fragments lacking the Fc region, such as Fab' fragment, were designed, without success (51). As an alternative, antigen-specific monoclonal antibodies were tested (52), but monoclonal antibodies would target only a specific strain or species of bacteria with the same antigen and thus would have only limited use for detecting broad bacterial infections. In addition to the nonspecificity, radiolabeled antibodies are well known for slow blood-pool clearance and poor imaging quality, making them less likely to be useful for the rapid diagnosis of infection that is critical for immediate clinical management. Thus, although different approaches have been attempted, none of the antibody-based tracers has shown desirable radio-pharmacokinetic features for diagnosis of infection.

Bacteriophages and Bacterial DNA/RNA Hybrid Nucleotide Oligomers

Other tracers that have been tested for bacteria-specific infection imaging include $^{99\text{m}}\text{Tc}$ -labeled bacteriophages (53), which are viruses that specifically infect bacteria but not mammalian cells, and radiolabeled bacterial DNA/RNA hybrid nucleotide oligomers that specifically target the bacterial DNA or RNA in the pathogens (54,55). These could be attractive tracers for specific bacterial infection imaging at least in theory; however, studies are in their early stages.

CONSIDERATIONS OF ^{18}F -FDG AND BACTERIA-TARGETING TRACERS FOR INFECTION IMAGING

Given the tremendous clinical impact, it is imperative to develop an imaging tool for rapid and accurate diagnosis of cardiovascular device infection with high sensitivity and specificity. ^{18}F -FDG PET/CT has unique merits over anatomic imaging techniques for earlier and more sensitive diagnosis of cardiovascular device infection. In addition, ^{18}F -FDG PET/CT can identify extracardiac infection sources or infectious emboli, which are critical for patient management. Thus, ^{18}F -FDG PET/CT has been recommended by the European Society for Cardiology for the diagnosis of cardiac device-related and prosthetic valve endocarditis (7). Although ^{18}F -FDG is criticized for its nonspecific accumulation in inflammation sites (56,57), differentiation between infection and inflammation can be reasonably achieved by recognizing the ^{18}F -FDG uptake pattern: ^{18}F -FDG uptake in an infection site is generally heterogeneous, with focal increased activity, whereas the distribution of ^{18}F -FDG in an inflammatory area is more homogeneous and mild (58,59). In addition, clinical information such as about the device material (metal or bioprosthesis) and surgical technique (use of adhesion glue or anticalcification material) is also useful for the differentiation. For example, like application of surgical adhesive to a mechanical prosthesis (60), application of anticalcification treatment with α -amino oleic acid to a bioprosthetic tissue can cause a characteristic pattern of ^{18}F -FDG uptake: low shortly after surgery but intensely homogeneous at 6 mo and persisting up to 1 y or even longer (61). A recent study showed that the diagnostic accuracy of ^{18}F -FDG PET/CT for prosthetic endocarditis can be significantly improved after adjusting clinical cofounders (62). If infection and inflammation can be reasonably differentiated on the basis of ^{18}F -FDG uptake pattern and surgical information, then the nonspecific ^{18}F -FDG uptake may actually represent a unique feature of ^{18}F -FDG for infection diagnosis: its high sensitivity for infection with a low rate of missing an infection (low false-negative rate).

^{18}F -FDG signal in an infection site represents the overall host-pathogen immune response and thus the underlying severity of infection. In addition, the ^{18}F -FDG uptake and distribution pattern in the liver, spleen, and bone marrow seen on whole-body scans provides information on the activation status of the reticuloendothelial system, representing the body's systemic response to the infection. Thus, findings on ^{18}F -FDG PET/CT represent the severity of the infection and the body's overall immune response, which are more critical for decisions on patient management than on the accuracy for diagnosis per se (63). ^{18}F -FDG PET/CT findings thus may in fact be more reliable in guiding patient management and predicting outcome. A negative ^{18}F -FDG PET/CT finding, which represents either no infection (true-negative) or mild infection (but false-negative based on standard diagnosis), may warrant conservative antibiotic treatment without device extraction. A positive

¹⁸F-FDG PET/CT finding (when inflammation is excluded on the basis of uptake pattern and surgical history) confirms infection and necessitates complete device extraction. In other words, ¹⁸F-FDG PET/CT may have the potential to quantify the severity of infection and accordingly guide patient management beyond its capacity in cardiac device infection diagnosis. This hypothesis is supported by several prior studies, though with small numbers of patients (64,65).

On the other hand, bacteria-targeting tracers detect only the specific bacteria itself, without providing information on the severity of the infection and the body's immune response to it. Although the primary goal of developing bacteria-imaging tracers is to provide a specific diagnosis of infection, unexpectedly, many of these assumed bacteria-specific tracers also show nonspecific accumulation in inflammation sites with undesirable radio-pharmacokinetic features for infection imaging. There are also additional limitations associated with each group of the tracers.

Antibiotics and antimicrobial peptides kill or inhibit bacteria at a low concentration. Thus, antibiotics and antimicrobial peptide-based tracers lack signal amplification with low intrabacterial accumulation, limiting their signal sensitivity. Although their binding to bacteria is specific, these tracers also show activity in inflammation sites due to increased vascular permeability and decreased washout (43). Pre-antibiotic treatment could also significantly decrease bacterial viability and loading, further decreasing the sensitivity (41). Finally, bacterial antibiotic resistance can potentially lead to a false-negative findings (44). Thus, these tracers have not made—and are not expected to make—their final inauguration in the clinic for specific bacterial infection imaging.

Antibody-based tracers are studied mainly in oncology imaging. Radiolabeled antibodies suffer from low target accumulation, non-specific binding (related to Fc segment), high blood-pool retention due to slow excretion, and poor imaging quality. The same issues exist in radiolabeled bacterial antibodies for infection imaging (51,52).

Bacterial thymidine kinase targeting FIAU can also be phosphorylated by mammalian cell mitochondrial kinase, raising concerns about nonspecificity and being less likely to be clinically translatable (38,39). Tracers based on bacteriophages and bacterial DNA/RNA hybrid nucleotide oligomers are in their early stages of development and are conceptually attractive (53,55).

Unlike the above-mentioned types of tracers, uptake of the maltodextrin tracers is actively mediated by the bacterial maltodextrin transporter, similarly to ¹⁸F-FDG, which is mediated by the glucose transporter. Maltodextrin tracers can reach high intrabacterial activity because there is continuous internalization through the transporters, facilitating highly sensitive detection (29). Meanwhile, there is efficient and rapid renal excretion of some of the maltodextrin tracers, such as ¹⁸F-maltotriose (33). However, not all maltodextrin transporter-targeting tracers show efficient excretion and ideal radio-pharmacokinetic features. For example, ¹⁸F-maltose is excreted mainly by the hepatobiliary pathway, with minimal renal excretion, making it an undesired tracer for infection imaging (32). Among the current reported maltodextrin transporter-targeting tracers, ¹⁸F-maltotriose holds the most promise for clinical translation based on an animal study (33). However, different from ¹⁸F-FDG, which is trapped inside the cell as FDG-6-P, the metabolism of ¹⁸F-maltotriose inside the

TABLE 2
Comparison of ¹⁸F-FDG and Bacteria-Targeting Tracers

Tracer	Target	Studies on...		Main findings
		Animals	Humans	
¹⁸ F-FDG	Glut	Y	Y	Early and sensitive diagnosis of infection in cardiac and extracardiac portions; may guide management based on severity
MDT targeting tracers				
¹⁸ F-maltotriose	MDT	Y	N	Tested on rat cardiac device infection model; differentiates infection from inflammation
¹⁸ F-maltohexaose	MDT	Y	N	Tested on mouse muscle infection model; differentiates infection from inflammation
¹⁸ F-maltose	MDT	Y	N	Suboptimal radiopharmaceutics in mice
¹⁸ F-trehalose	MDT	Y	N	Limited to mycobacteria
¹⁸ F-sorbitol	MDT	Y	N	Limited to gram-negative bacteria
¹²⁴ I-FIAU	TK	Y	Y	Nonspecific uptake in inflammation; not clinically translated
Antibiotics (^{99m} Tc-ciprofloxacin)	DNA gyrase	Y	Y	Low sensitivity, nonspecific uptake; not clinically translated
Antimicrobial peptides (^{99m} Tc-UBI29-41)	Innate immune	Y	Y	Low sensitivity, nonspecific uptake; not clinically translated
Antibodies	Antigen	Y	Y	Slow blood pool clearance; nonspecific uptake, poor imaging quality; not clinically translated

Glut = glucose transporter; MDT = maltodextrin transporter; TK = thymidine kinase.

bacteria is unknown. It remains unclear whether ^{18}F is trapped inside the bacteria or whether it will efflux or diffuse out of the cell after ^{18}F -maltotriose degradation. In addition, its stability in the blood is unknown either. More studies are needed to explore its potential for clinical translation. Table 2 summarizes and compares the main findings of ^{18}F -FDG and other bacteria-targeting tracers.

TECHNICAL CHALLENGES FOR BACTERIA-TARGETING PET TRACERS

In addition to the inherent limitations of the bacteria-targeting tracers, other challenges for direct PET imaging of infection with these tracers include the complex clinical setting of infection (including empiric antibiotic treatment and biofilm formation) and the technical capability of the current PET camera for detecting small lesions or lesions with low counts. Empiric antibiotic therapy is generally started for any case of suspected cardiac device infection before a definite diagnosis is made. The treatment may greatly decrease bacterial signal, much more significantly than the host immune response signal as revealed by ^{18}F -FDG. In addition, cardiac device infection is frequently associated with biofilm formation, which limits permeation of tracers such as antibiotics and antibodies (66). Although preliminary animal work showed that ^{18}F -maltotriose could potentially penetrate the biofilm (33), detailed work is lacking. Most of the current PET camera may not be able to detect a small lesions with low counts given the limited spatial resolution. In addition, these tracers cannot access intracellular bacteria when they are phagocytosed by immune cells. Cardiac and respiratory motion during data acquisition would impose a further technical challenge. These issues need to be addressed when these bacteria-targeting tracers are being translated to the clinic (67).

CONCLUSION

Direct bacteria-targeted tracers have been assumed to be more specific than ^{18}F -FDG for imaging bacterial infection. However, it turns out that most of the bacteria-targeted tracers also show non-specific accumulation at inflammation sites. Moreover, most of the bacterial tracers suffer from low sensitivity due to no intrabacterial signal amplification, prior antibiotic treatment, and the impermeability of biofilm. One exception could be maltodextrin-based tracers such as ^{18}F -maltotriose, which shows specificity for bacteria with high sensitivity due to signal amplification from continuous intrabacterial accumulation by the maltodextrin transporter. However, current data are limited to early experimental studies on animals, and it is unclear whether successful translation into the clinic will be possible. On the other hand, ^{18}F -FDG PET/CT is sensitive for early diagnosis of infection, and ^{18}F -FDG findings represent the overall severity of infection and the body's immune response to the infection—capabilities that are more reliable for making decisions on patient management. Accumulating clinical data support the use of ^{18}F -FDG PET/CT for imaging cardiovascular device infections.

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