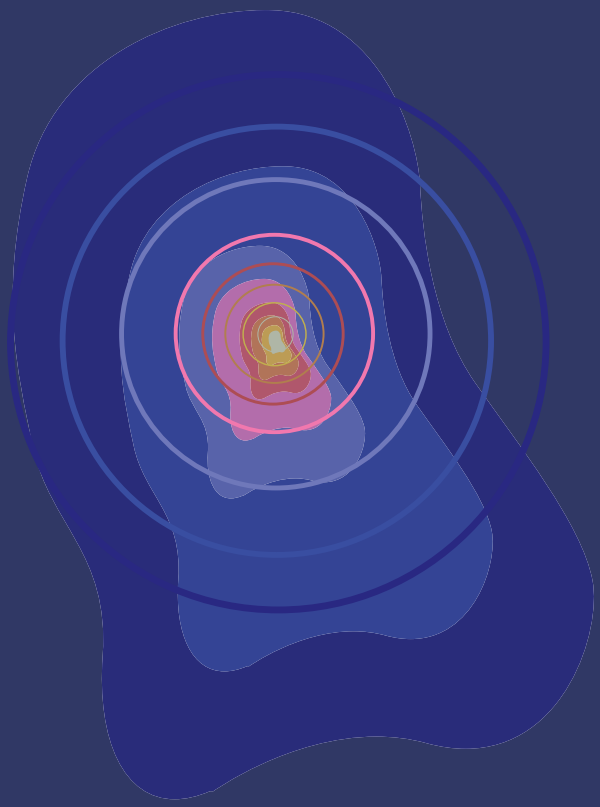
CHAPTER 11

Limitations and pitfalls of FDG-PET/CT in infection and inflammation



Jordy P. Pijl, Pieter H. Nienhuis, Thomas C. Kwee, Andor W.J.M. Glaudemans, Riemer H.J.A. Slart, Lars C. Gormsen

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ABSTRACT

White blood cells activated by either a pathogen or as part of a systemic inflammatory disease are characterized by high energy consumption and are therefore taking up the glucoseanalogue PET tracer FDG avidly. It is therefore not surprising that a steadily growing body ofresearch and clinical reports now supports the use of FDG PET/CT to diagnose a wide rangeof patients with non-oncological diseases. However, using FDG PET/CT in patients withinfectious or inflammatory diseases has some limitations and potential pitfalls that are notnecessarily as pronounced in oncology FDG PET/CT. Some of these limitations are of a gen-eral nature and related to the laborious acquisition of PET images in patients that are oftenacutely ill, whereas others are more disease-specific and related to the particular metabolismin some of the organs most commonly affected by infections or inflammatory disease. Bothinflammatory and infectious diseases are characterized by a more diffuse and less pathogno-monic pattern of FDG uptake than oncology FDG PET/CT and the affected organs also typi-cally have some physiological FDG uptake. In addition, patients referred to PET/CT withsuspected infection or inflammation are rarely treatment naïve and may have received varyingdoses of antibiotics, corticosteroids or other immune-modulating drugs at the time of theirexamination. Combined, this results in a higher rate of false positive FDG findings and also insome cases a lower sensitivity to detect active disease. In this review, we therefore discussthe limitations and pitfalls of FDG PET/CT to diagnose infections and inflammation takingthese issues into consideration. Our review encompasses the most commonly encounteredinflammatory and infectious diseases in head and neck, in the cardiovascular system, in theabdominal organs and in the musculoskeletal system. Finally, new developments in the fieldof PET/CT that may help overcome some of these limitations are briefly highlighted.

INTRODUCTION

Over the past decades, the use of nuclear imaging for diagnosing infectious and inflammatory diseases has rapidly expanded. One of the most commonly used nuclear imaging techniques is positron emission tomography (PET). PET can be used to visualize processes of interest by utilizing the properties of specific molecules labeled with positronemitting isotopes.

Stand-alone PET was clinically introduced in the 1970s, primarily to diagnose brain tumours[1]. After technological developments in detector materials such as increased scintillator density and improvements in scintillation material led to an increase in the resolution of PET imaging, the first modest application of PET for imaging infection and inflammation started in the mid-1990s[2,3]. After the introduction of hybrid imaging of PET combined with computed tomography (CT), which significantly improved anatomical localization, and the release of the first commercially available PET/CT scanner in 2001, the application of PET/CT for infectious and inflammatory diseases rapidly increased, such as in fever of unknown origin and osteomyelitis[4,5]. Now, PET/CT is the most commonly used nuclear imaging technique for diagnosing a large number of infectious and inflammatory diseases[6].

While various radiotracers are available, the most commonly used PET tracer for evaluating infectious and inflammatory diseases is 2-deoxy-2-[18F]fluoro-D-glucose (FDG). Because white blood cells and other inflammatory cells that are recruited to infected and inflamed tissue have a high glucose metabolism compared to other cells, many infectious and inflammatory diseases are often readily visible on FDG-PET/CT. Additionally, inflammatory mediators may also cause a local upregulation of glucose transporters as[7].

Although FDG-PET/CT has been demonstrated to yield acceptable diagnostic accuracy in a number of infectious and inflammatory diseases and in the appropriate clinical setting, it can also present important limitations. In particular, the often less than perfect specificity of FDG PET/CT may result in unnecessary biopsies or even treatments with known adverse effects that are not always justified by the suspected underlying disease. In this review, we will first discuss the most important general limitations of FDG-PET/CT that affect the diagnosis of most infectious and inflammatory diseases, and how to address these. Then, we will zoom in on the most commonly diagnosed infectious and inflammatory diseases subdivided by body region, and we will mention several disease-specific limitations of FDG-PET/CT that need to be taken into account. Finally, we will discuss the latest technological developments in PET/CT that may further increase its diagnostic value and overcome some of the limitations described in this review.

General limitations of FDG-PET/CT in infection and inflammation

Non-specificity of elevated FDG uptake

As most human cells metabolize glucose for ATP synthesis, physiologic FDG uptake occurs throughout the body. The purpose of FDG-PET/CT is to detect an abnormal elevation of FDG uptake that may indicate ongoing infection or inflammation. Because both infection and inflammation cause elevated FDG uptake, the distinction between the two can present a diagnostic challenge. Additionally, cancer cells also display elevated FDG uptake, which further challenges the discrimination between different diseases[8]. As part of hybrid imaging, concurrently performed CT can often provide important anatomical information to discriminate between infection, inflammation, or cancer. For example, the formation of gas bubbles can point in the direction of abscess formation, while high heterogeneity of nodular lesions may be more suspect for malignancy[9]. Elevated FDG uptake in multiple similar regions may point in the direction of a systemic inflammatory disease. For example, increased FDG uptake in multiple large vessels throughout the body may indicate a disease such as large vessel vasculitis. Therefore, to correctly interpret locally elevated FDG uptake, it is important to evaluate the whole patient. It is even more important that clinical physicians who request FDG-PET/CT for their patients provide relevant clinical information that can aid in determining the correct diagnosis. For example, a clinician might request FDG-PET/CT for a patient with high fever of unknown origin, thereby only providing 'high fever, focus?' as additional information. Because fever is such a nonspecific symptom, additional information can be of great help to narrow the differential diagnosis and point nuclear medicine physicians in the right direction. When did the fever start, was the patient previously diagnosed with a malignancy, is there any pain or other localizing symptoms, were blood cultures positive for microorganisms? As this kind of information leads to a better interpretation of elevated FDG uptake on FDG-PET/CT and a higher chance of determining the correct diagnosis, treating physicians should provide this information about their patient and nuclear medicine physicians should request it.

Preparation time for FDG-PET/CT

Before FDG-PET/CT can be performed, patients have to be prepared according to preparation guidelines. Amongst other things, patients should fast for at least 4 to 6 hours before FDG-PET/CT to reduce background FDG uptake, increase FDG uptake of infectious or inflammatory lesions and subsequently generate a higher lesion-to-background ratio, which is vital to distinguish physiologic from pathologic FDG uptake.

Apart from the preparation time, performing FDG-PET/CT itself also takes longer than standalone CT. First, the FDG has to be synthesized by nuclear lab technicians. Due to the short half-life of FDG, which is 110 minutes, FDG cannot be synthesized far in advance. After intravenous FDG injection, patients have to lie still for one hour to allow biodistribution of FDG throughout the body and prevent FDG uptake of skeletal muscle caused by voluntary movement. Performing whole-body PET/CT on a patient of 180 cm long takes approximately 30 minutes[10]. Patients who must be nursed in isolation due to multi resistant microorganisms or contagious disease such as COVID-19 may also significantly delay the process.

These time restrictions may cause clinical physicians to refrain from FDG-PET/CT and opt for other diagnostic procedures such as stand-alone CT, especially in critically ill patients where a diagnosis has to be established as soon as possible or where constant monitoring is necessary. This can be the case in patients who are receiving vasopressors or are undergoing mechanical ventilation.

FDG-PET/CT after invasive procedures

Patients who have undergone surgery or invasive procedures, such as coronary angioplasty with stenting, are prone to infection. Diagnosing infection with FDG-PET/CT shortly after surgery can be challenging. After surgery, wound healing occurs which involves formation of granulation tissue in large part consisting of inflammatory cells and fibroblasts.

Within weeks to months, the granulation tissue is replaced with scar tissue, which initially is also rich in inflammatory cells such as macrophages. This causes an elevation of FDG uptake in the surgical bed, which gradually subsides after a couple months[11]. Therefore, it can be difficult to distinguish physiologic post-surgical FDG uptake from infection.

A suspected foreign body infection, such as vascular graft or prosthetic hip infection, is also a common reason to perform FDG-PET/CT. Although FDG-PET/CT presents a high sensitivity and specificity for diagnosing foreign body infections, several limitations need to be taken into account. For vascular graft infections, for example, it is recommended to perform CT instead of FDG-PET/CT in early graft infections (within 2 months after placement) due to elevated FDG uptake caused by post-surgical inflammation[12]. Of interest, some vascular grafts consist of materials that elicit a significant inflammatory response reflected by avid FDG uptake several years following the surgical procedure, most notably Dacron based prostheses[13]. Implanted foreign materials can also be subject to sterile inflammation which may lead to elevated FDG uptake[14]. This may be difficult to distinguish from lowgrade infections. The location of elevated FDG uptake may be of use to make the distinction, as focally elevated FDG uptake is generally more suspect for infection than diffusely elevated FDG uptake[15].

Effect of medical drugs

Because FDG and glucose compete for the same glucose transporters and hexokinase, it is recommended that FDG-PET/CT is performed in patients with a blood glucose level <11 mmol/L[16,17]. This can be challenging in patients with diabetes, especially when they are dependent on insulin treatment. Because insulin causes cells to take up glucose (and therefore FDG as well, resulting in elevated FDG uptake in physiologic tissue), use of insulin before FDG-PET/CT should be restricted. Rapid-acting insulin should not be given within 4 hours of FDG-PET/CT, short-acting insulin not within 6 hours of FDGPET/CT, and intermediate or long-acting insulin should not be used on the day FDG-PET/CT is performed[16]. Metformin, another commonly used glucose-regulating drug, can also affect FDG-PET/CT outcome. As metformin increases intestinal glucose uptake, patients who are using metformin display high intestinal FDG uptake on FDG-PET/CT[18,19]. This may obscure pathologic FDG uptake due to infection or inflammation.

Patients with a suspected or proven infection often receive antibiotic treatment. A longer duration of antibiotic treatment may be associated with a lower chance of finding an infection focus on FDG-PET/CT, but literature on this topic is conflicting[20,21].
Patients with a suspected or proven inflammatory disease may receive immunosuppressive medication during FDG-PET/CT. Use of corticosteroids significantly reduces the sensitivity of FDG-PET/CT for diagnosing inflammatory disease. This has been demonstrated in several diseases, including large vessel vasculitis, rheumatoid arthritis, and polymyalgia rheumatica[22–24]. As such, it is recommended to delay the commencement of corticosteroid treatment until FDG-PET/CT is performed, unless there is a risk of severe complications such as ocular ischemia in temporal arteritis[25,26].
Of interest, the use of checkpoint inhibitors in patients with cancer is increasing. Because this may cause an elevated inflammatory response in tumors, increased FDG avidity of tumor lesions can indicate both disease progression and good response to treatment[27].
Additionally, checkpoint inhibitors may cause inflammation and elevated FDG uptake in other organs as well leading to nonspecific findings on FDG-PET/CT such as possible arthritis or colitis[28].

Effect of kidney and liver failure
FDG is primarily eliminated through the kidneys. In patients with kidney failure, urinary FDG excretion may be reduced, resulting in higher background activity and lower lesion-to-background ratios[29]. However, the exact impact of kidney function on FDG biodistribution and its clinical implications remain unclear, as some studies also report that kidney function does not significantly affect FDG biodistribution[30,31]. Patients with liver failure may show diffusely increased hepatic FDG uptake, but it remains unclear whether this also affects FDG biodistribution and background-to-lesion ratios[32].

DISEASE-SPECIFIC LIMITATIONS

Apart from the previously described general limitations of FDG-PET/CT, various diseasespecific and organ-specific limitations may also affect its diagnostic value for infectious and inflammatory disease. We will briefly discuss the most common infectious and inflammatory diseases diagnosed with FDG-PET/CT and potential pitfalls in diagnosing these diseases.

Head and neck
Due to the complex anatomy of the head and neck region, special attention must be given to correct anatomic localization of FDG avid regions[33]. This necessitates precise fusion of the PET image with the CT image, which may prove more challenging in the head and neck due to patient motion between PET and CT image acquisition. Similarly, anatomic localization may be complicated by scatter on CT from dental prosthetics[34].
FDG uptake by primary malignancies or malignant spread are important to differentiate from infectious or inflammatory causes. Reactive, inflammatory lymph nodes are a common cause of increased nodal FDG uptake in the head and neck region. Clinical characteristics may help prevent misclassification of reactive nodes as metastatic disease. The intensity of FDG uptake

is not a good indicator for distinguishing benign from malignant disease[35]. For FDG-PET/CT imaging of the thyroid, diffuse and symmetric uptake is characteristic of benign diseases, such as thyroiditis, or may be regarded as physiologic uptake. Focal FDG uptake increases the likelihood of malignancy up to 25% and may warrant additional investigation with ultrasound and cytology[36]. Furthermore, FDG uptake in the lower cervical nodal stations may sometimes be difficult to distinguish anatomically from focal uptake in the thyroid.

Increased salivary gland FDG uptake may have several inflammatory causes, such as infection, granulomatous disease (granulomatosis with polyangiitis), and autoimmune disorders (Sjögren's disease, Ig-G4-related disease). Low-grade, symmetrical, and diffuse uptake may also be physiological and is frequently observed in the parotid glands[37].

Especially in young children, brown fat can also affect the diagnostic value of FDG-PET/CT (**Figure 1**). Brown fat displays higher metabolic activity than white fat, and is primarily located in the neck, shoulders and paravertebrally[38]. FDG avid brown fat may be mistaken for active lymph nodes or malignancy. As being exposed to cold can induce brown fat activation, it is important to keep patients warm prior to FDG-PET/CT[39]. (Low-dose) CT can aid in distinguishing elevated FDG uptake in brown fat from lymph nodes, but may prove difficult when brown fat activation is extensive.

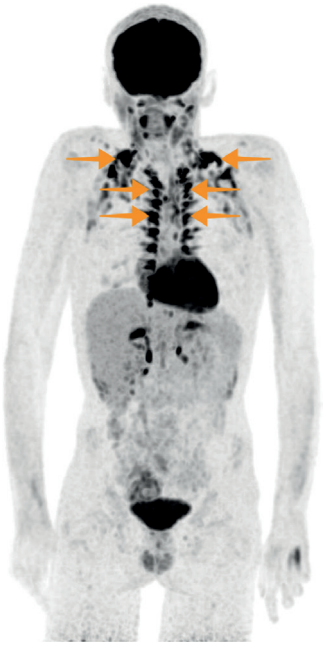

Figure 1 |
A 17-year-old boy with Staphylococcus aureus bacteremia underwent FDG-PET/CT to identify the primary infection focus and potential septic emboli. While the infection focus was not identified on FDG-PET/CT, extensive brown fat activation (maximum intensity projection, orange arrows) was noticed, which may have obscured the infection focus. Due to high FDG uptake of the myocardium, the presence or absence of endocarditis could not be determined.

Cardiovascular system

Cardiovascular infections are associated with high morbidity and mortality[40]. FDGPET/CT can be used for a number of cardiovascular infections including vascular graft infections and endocarditis.

Interpretation of these pathologies may be complicated by high FDG uptake in the myocardium. To limit this effect, patients should be started on a carbohydrate-low diet 24 hours prior to FDG administration[41]. This causes the cardiac myocytes to switch from glucose to fatty-acid metabolism. Additionally, a single-dose injection of heparin administered 15 minutes before FDG-PET/CT can help suppress physiologic FDG uptake of the myocardium. Heparin stimulates hydrolysis of circulating triglycerides releasing more cardiac oxidative substrate in the form of fatty acids and also reduces cellular surface expression of glucose transporter 4 (GLUT4) which mediates cardiac glucose uptake. By contrast, insulin-independent and less fluctuating GLUT1 and GLUT3 mediate the increased glucose consumption of inflammatory cells[42,43].

For endocarditis, it is important to realize that FDG-PET/CT only presents a high sensitivity of 73 to 100% for diagnosing *artificial* valve endocarditis, but a low sensitivity of approximately 14% for native valve endocarditis even after appropriate dietary precautions[44]. This discrepancy is likely caused by the different sites of infection in artificial valve vs. native valve endocarditis: infections are typically located at non-moving surgical anchor points in the artificial valves, whereas the infection is located in valvular and thus moving vegetations in native valve endocarditis. Imaging moving objects has never been a strong feature of PET.

Of interest, the sensitivity for diagnosing focal cardiac infection and inflammation may be improved by ECG-gated cardiac FDG-PET acquisition. As the heart is constantly beating, this can help to obtain FDG-PET and CT images 'in sync'[45].

Cardiac sarcoidosis (CS) is also increasingly imaged with FDG-PET/CT. The diagnosis is inherently difficult to ascertain by right sided catheterization and biopsy, where sensitivity may be as low as ~30 % due to the patchy nature of myocardial sarcoid lesions[46]. In a clinical context, CS is therefore most often diagnosed when patients fulfill a set of criteria originally set up by the Japanese Ministry of Health and Welfare and modified by others to include a certain pattern of myocardial FDG uptake[47]. A pattern of patchy and focal FDG uptake with predilection for the septum and involvement of the right ventricle is highly suggestive of CS if the patient has undergone preparations to suppress physiological FDG uptake. However, correctly identifying patchy FDG uptake may be difficult. In some – often younger - patients, physiological FDG uptake is not completely suppressed despite adequate preparations, and a pattern of FDG uptake mimicking CS may be reported. Variants of physiological uptake in the myocardium is a basal ring spanning the entire base of the left ventricle, and FDG uptake at the aortic ostium[48] (**Figure 2**). Also, in patients with insulin treated diabetes, an 18 hour fast is most often not desirable. In these cases, alternative macrophage tracers such as 68Ga-DOTATOC may be considered[49].

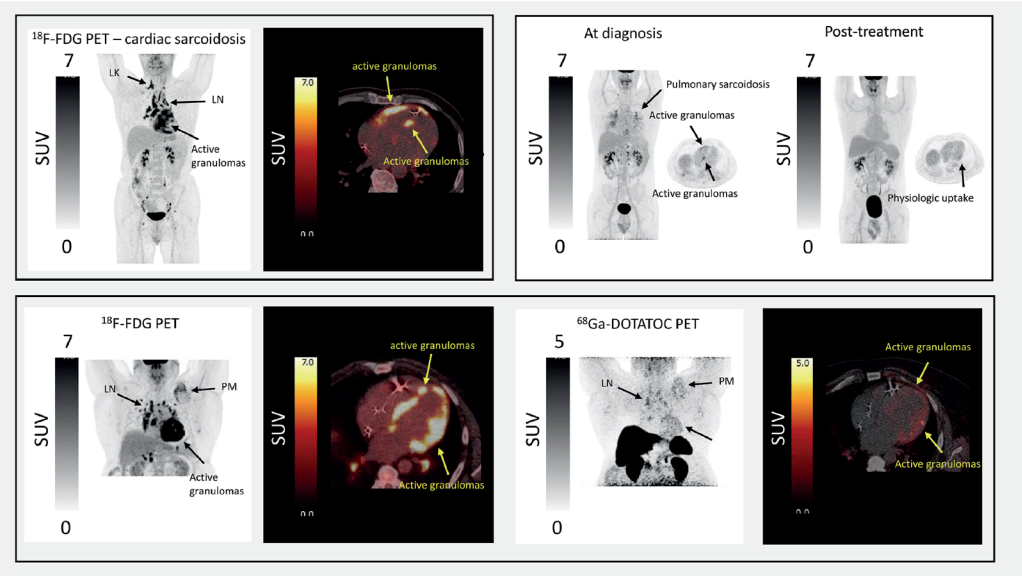

Figure 2 **|**
Examples of patients with CS. In the upper left column, avid FDG uptake is observed in the mediastinal and hilar lymph nodes. In addition, myocardial FDG uptake is focal with patchy lesions in the septum and right ventricle. Such a pattern is highly suggestive of CS. In the right upper column, pre- and post-therapy FDG PET/CT of a patient with pulmonary and CS is presented. As seen, some physiological FDG uptake persisted in the basal and lateral parts of the left ventricle despite good response to corticosteroid therapy. In the lower column, matching FDG and 68Ga-DOTATOC scans of a patient with CS clearly reveal that the signal-to-noise ratio of 68Ga-DOTATOC may be less than that of FDG.

Involuntary movements of the feet and legs during image acquisition may cause motion artifacts and may impede precise anatomic localization of cardiovascular infections. In case of suspected vascular graft infections, the pattern of FDG uptake should always be taken into account to differentiate acute infection from chronic inflammation. Diffuse uptake may represent chronic inflammation and may persist years after surgery. Acute inflammation in infected vascular grafts is generally characterized by focal and intense FDG uptake. When evident abscesses are noticed around the graft, a vascular graft infection may easily be diagnosed. Sometimes, however, hematomas and seromas may appear similar to abscess formation[13,50].

Besides endocarditis and vascular graft infections, FDG-PET/CT is also frequently used to diagnose infection of cardiac implantable electronic devices and left ventricular assist devices[51]. While pocket infections can sometimes even be diagnosed on physical

examination, infection of the leads is often more difficult to diagnose. It is important to establish infection as certainly as possible, as the treatment consists of surgical removal of the infected device which also poses important risks[52]. FDG-PET/CT presents a high sensitivity for diagnosing cardiac implantable devices. The specificity for infection is low within two months after surgical placement due to postsurgical inflammation, but moderate when this has subsided[52].

FDG-PET/CT is now a main imaging technique in the diagnosis of large vessel vasculitis (LVV) with impressive diagnostic accuracy, in particular when including the cranial vessels[53]. The main pitfall of FDG-PET/CT imaging in LVV is the effect of glucocorticoids (e.g. prednisone) on the ability to assess vessel wall inflammation. Glucocorticoid treatment strongly decreases the FDG uptake in the vessel wall and, therefore, renders FDG-PET/CT imaging unable to diagnose LVV. Ideally, FDG-PET/CT imaging should be performed prior to glucocorticoid treatment[25] (**Figure 3**). Diagnostic accuracy is maintained if FDG-PET/CT imaging is performed within 3 days of starting glucocorticoid therapy[54]. Moreover, FDGPET/CT interpretation of LVV is often based on comparison of the vascular uptake intensity to hepatic FDG uptake Therefore, factors increasing liver uptake such as glucocorticoid treatment may cause an underestimation of vascular FDG uptake[55].

Atherosclerotic lesions in the vessel wall may also cause increased uptake on FDG-PET/CT. This way, atherosclerosis may mimic LVV, and both diseases may also overlap. Several factors may be taken into consideration when trying to distinguish atherosclerosis and LVV.

First, the pattern of FDG uptake in atherosclerosis is generally focal whilst vasculitis most frequently presents with diffuse and circumferential uptake along a large segment of the artery. Second, a patient with suspected LVV and increased uptake at arterial junctions should be interpreted with caution because atherosclerotic plaques are often localized there. Third, (low-dose) CT imaging may reveal arterial atherosclerotic calcifications. Patients with suspected LVV and widespread calcifications should warrant careful evaluation of FDG uptake.

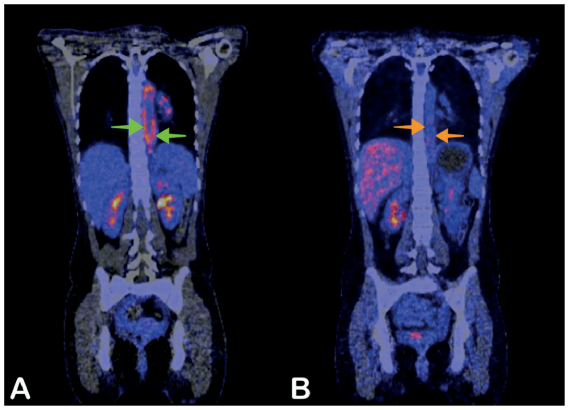

Figure 3 **|**
A 16-year-old girl underwent FDG-PET/CT because of general malaise for two months and elevated inflammatory markers. Fused coronal PET/CT showed elevated FDG uptake of the thoracic aortic wall (A, green arrows), suggestive of Takayasu arteritis. After corticosteroid treatment was started, FDG-PET/CT was performed 3 months later during follow-up showing resolved FDG avidity of the thoracic aorta (B, orange arrows). This illustrates that a diagnosis such as Takayasu arteritis can be missed when patients already blindly receive corticosteroid treatment when an unknown immune-mediated disease is suspected.

Lungs

While pulmonary infections are very common, FDG-PET/CT is rarely the first imaging modality of choice to diagnose these infections. A plain thoracic X-ray or (when clinically indicated) high-resolution CT are usually performed first to detect potential infectious anomalies. In patients with parapneumonic pleural effusions, however, FDG-PET/CT may be used to detect abnormal FDG uptake suggestive of persisting infection or render this less likely due to normalized FDG uptake. Likewise, FDG-PET/CT can also be used to distinguish benign pleural effusion from malignant pleural effusion[56].

Especially in cancer patients with suspected infection, it can be challenging to distinguish pulmonary metastases from septic emboli, as both can feature multiple small FDG avid nodules[57]. Additionally, due to the relatively low spatial resolution of 4 to 6 millimeters of FDG-PET/CT and partial volume effect, small lesions may not be detected[58,59].

As FDG-PET/CT can examine the whole body within a single examination, it can be very helpful in patients with pulmonary diseases that can also be accompanied by extrapulmonary lesions, such as tuberculosis and sarcoidosis[60]. While tuberculosis is associated with caseating granulomas and sarcoidosis with non-caseating granulomas, it may not always be possible to make the distinction with FDG-PET/CT[61] (**Figure 4**).

Nevertheless, FDG-PET/CT can detect the most favorable lesion for diagnostic puncture and subsequent final diagnosis. Additionally, in patients with rheumatoid arthritis, extra-articular pulmonary rheumatoid lesions should also be included in the differential diagnosis[62,63].
Because PET imaging of the lungs takes several minutes, lesion blurring caused by breathing movements frequently occurs. Breath-holding during PET imaging or respiratory-gated PET/CT may reduce this problem, but current literature on the clinical benefits of performing breath-hold or respiratory-gated PET/CT is limited[64,65].

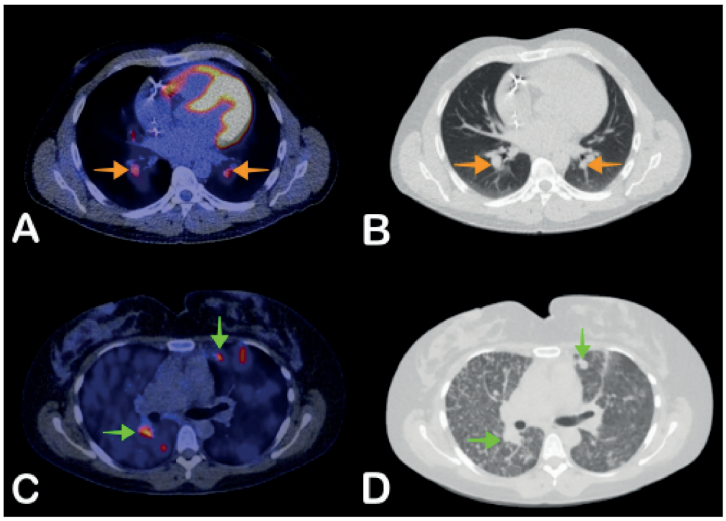

Figure 4 |
Two patients with similar lesions are shown. The first patient, a 41-year-old man, underwent FDG-PET/CT to determine whether his thoracic pain and slightly elevated inflammatory markers were caused by an infected pacemaker. While the pacemaker leads did not show elevated FDG uptake, multiple FDG avid pulmonary lesions were seen on fused axial PET/CT (A, orange arrows), also visible on low-dose CT (B, orange arrows). Biopsy of an extrapulmonary nodule excluded tuberculosis and confirmed the diagnosis of sarcoidosis.
The second patient, a 39-year-old woman, underwent FDG-PET/CT due to fever of unknown origin. Multiple FDG avid pulmonary lesions were detected on fused axial PET/CT (C, green arrows), also visible on low-dose CT (D, green arrows). Molecular testing of respiratory sputum confirmed the diagnosis of active tuberculosis.

Abdomen
FDG-PET/CT can be used to diagnose numerous abdominal infectious and inflammatory diseases. For example, cholecystitis and pancreatitis can often easily be detected, and abscesses can quickly be identified[26,66]. However, FDG-PET/CT is rarely the first diagnostic method of choice in these diseases, as cholecystitis is usually diagnosed with ultrasonography and pancreatitis can be diagnosed based on laboratory work[67,68].

When patients are suspected of cyst infection, however, use of FDG-PET/CT should be strongly considered. Especially in patients with polycystic kidney or liver disease, diagnosing cyst infection can be challenging. Anatomic hallmarks of infection are usually absent and performing percutaneous cyst drainage can result in complications such as contamination of adjacent cysts and bleeding[66].
Because FDG is excreted through the kidneys, the urine in the pyelum will always show high FDG avidity in patients with functioning kidneys. This makes it very difficult to diagnose pyelonephritis based on FDG-PET/CT when other anatomic abnormalities are absent.

Due to ongoing peristalsis, a certain degree of physiologic FDG uptake in the gastrointestinal tract can always be expected. When this is moderate to high, however, it may obscure gastrointestinal disease such as Crohn's disease, ulcerative colitis, enterocolitis, or malignancy[69]. As previously mentioned, use of metformin can also significantly increase gastrointestinal FDG uptake, especially in the colon[70] (**Figure 5**).

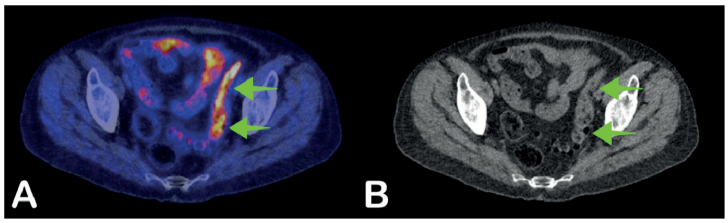

Figure 5 |
A 65-year-old woman with known diffuse large B-cell lymphoma underwent FDGPET/CT because of fever and pain in the left lower abdomen. Fused axial PET/CT showed intense FDG uptake in several parts of the colon, including the sigmoid colon (A, green arrows). This was most likely related to the use of metformin. Diverticulosis of the sigmoid colon was visible on low-dose CT (B, green arrows). Due to the intense FDG uptake of the sigmoid colon, it was difficult to assess the possibility of diverticulitis. The fever remained of unknown origin.

Pelvis
Due to FDG accumulation in the urine bladder, it is usually not possible to diagnose cystitis with FDG-PET/CT. However, this disease is usually easily diagnosed with urinalysis without the need for imaging. In men, increased FDG uptake in the prostate may indicate prostatitis[71]. Because prostate cancer is usually not associated with high metabolic tumor activity, it usually does not cause elevated FDG uptake[72]. In women of reproductive age, physiologic FDG uptake of the uterus may occur during menstruation which can obscure endometritis or be mistaken for endometrial cancer[73] (**Figure 6**). Likewise, pelvic inflammatory disease and ovarian cancer may go unnoticed or may be false positively diagnosed during ovulation[73,74].

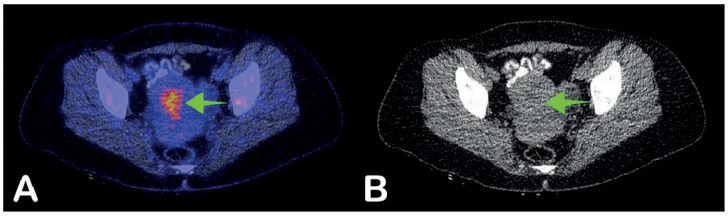

Figure 6 **|**
A 38-year-old woman underwent FDG-PET/CT because of cervical lymphadenopathy and fever. While she was diagnosed with Hodgkin lymphoma, fused axial PET/CT showed increased FDG uptake of the endometrium (A, green arrow), probably due to menstruation. The contrast between the endometrium and myometrium on low-dose CT (B, green arrow) was too low to clearly delineate these separate structures. Follow-up FDGPET/CT showed normalized FDG uptake of the endometrium.

Musculoskeletal

Although no physiologic FDG uptake should be seen in cortical bone, increased FDG uptake in the assessment of musculoskeletal infection or inflammation may be difficult to distinguish from malignancies and degenerative changes. Bone marrow FDG uptake may be increased in patients with active inflammation and infection (often described as 'reactive bone marrow'), but hematologic malignancies may also show diffusely increased FDG uptake. On the other hand, focal and intense activity in the bone marrow should always raise suspicion of malignant disease[75]

FDG-PET/CT presents a high diagnostic sensitivity and specificity for osteomyelitis and spondylodiscitis.

In some patients, it may be difficult to distinguish infection from mildly elevated FDG uptake associated with degenerative changes, but the distinction can usually be made based on the exact localization of elevated FDG uptake (i.e. intervertebral disc in case of spondylodiscitis) and clinical presentation[76].

Another important indication for performing FDG-PET/CT can be suspected infection of osteosynthesis material. Especially in patients with non-union fractures, swelling, erythema and hyperthermia can be present in the absence of infection. While healing fractures can also cause elevated FDG uptake, the distinction between fracture healing and infection can usually be made based on the location of elevated FDG uptake, as bone regeneration usually causes elevated FDG uptake along the entire surface of the fracture line, and infection causes focal elevation of FDG uptake[77].

Inflammatory changes manifesting in rheumatic diseases may also be imaged with FDGPET/CT. Increased FDG uptake localized around joints in polymyalgia rheumatica (PMR), rheumatoid arthritis RA), and spondyloarthritis (SpA) may appear similar. Distinguishing these different

pathologies from each other and from degenerative changes may prove difficult. However, the intensity of the periarticular FDG uptake tends to be greater in RA than in PMR and the shape of the increased FDG also tends to be more rounded, reflecting synovitis rather than bursitis (Figure 7). Moreover, symmetrical inflammation of the small joints in the hand is characteristic for RA and rare in PMR[78]. PMR is characterized by FDG uptake in the interspinous bursae, ischiogluteal bursae and sacroiliac joints[23] (**Figure 8**) whereas in SpA, vertebral column FDG avidity is often most pronounced in the zygapophyseal (facet) and sacroiliac joints[79] (**Figure 9**). Thus, in addition to clinical information, the most important differentiating factor may be the pattern of the involved joints[78].

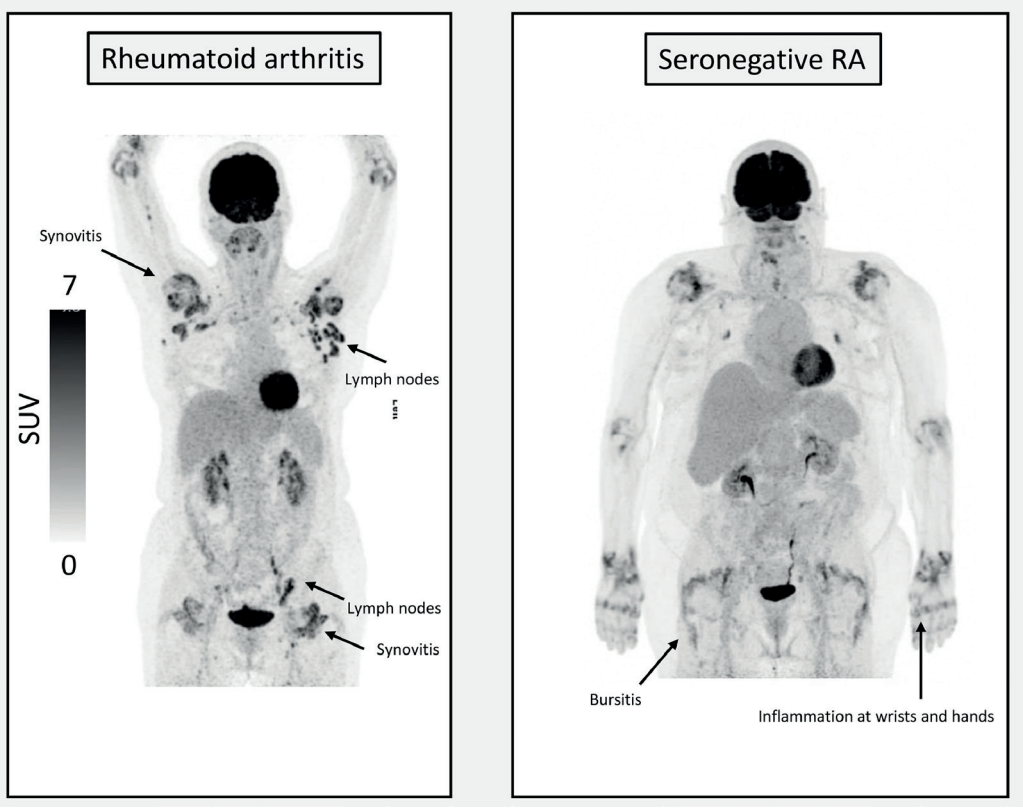

Figure 7 |
In the left column, a 45-year old woman with known RA underwent FDG-PET/CT due to suspected infection. No infectious foci were found, but her RA was clearly active with avid FDG uptake in the shoulders, elbows, and hips. Reactive local lymph nodes were also visible in the axillae and along the pelvic arteries. The right column was a 67-year old man with negative biomarkers for RA. However, FDG uptake was rounded and avid in the shoulder region and both wrists and finger joints were involved indicating a tentative diagnosis of seronegative (or elderly onset) RA.

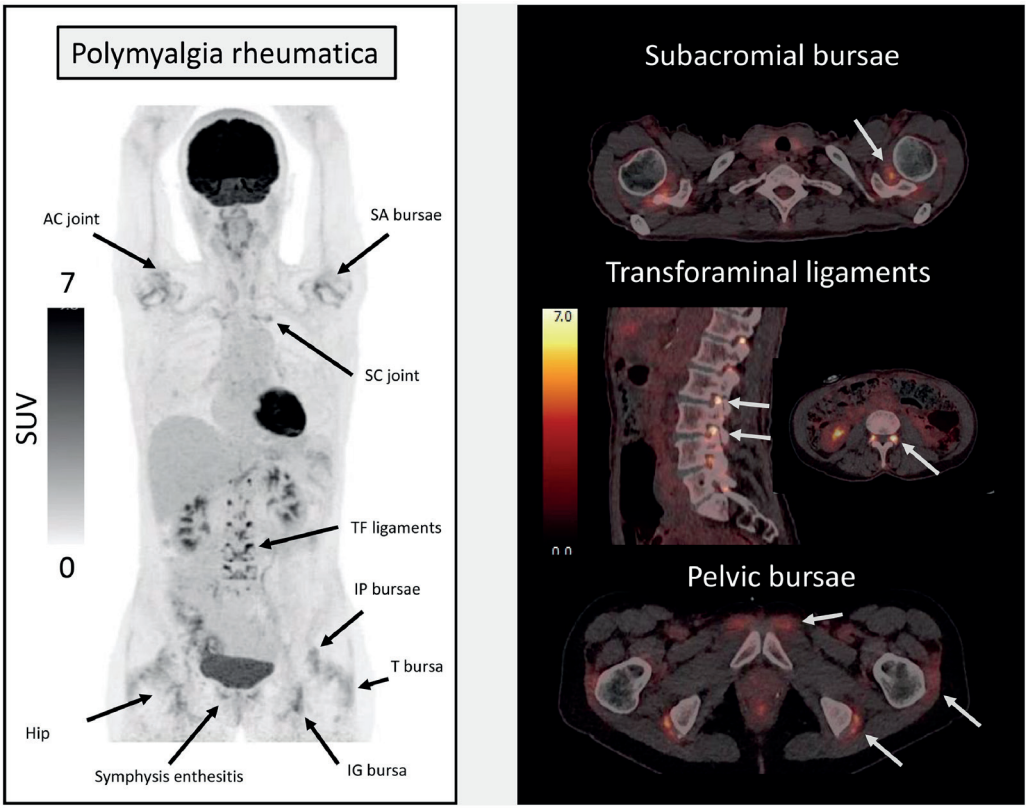

Figure 8 |
Typical pattern of FDG uptake in a 73-year old PMR patient with joint, shoulder, and hip pain, elevated CRP and unintended weight loss. FDG uptake is more blurry and less avid than in RA patients. In addition, interspinous ligaments, ischiogluteal bursae and sternoclavicular joints are almost always involved.

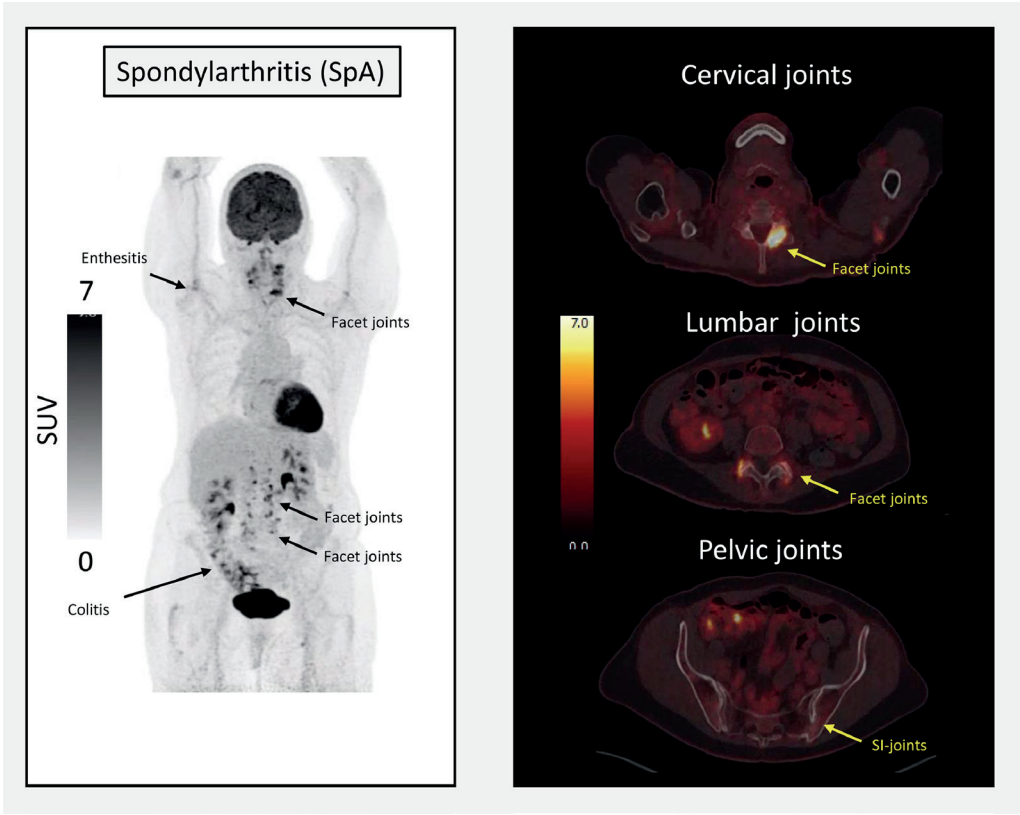

Figure 9 |
A 42-year old woman with lumbar pain was referred due to suspicion of spondylodiscitis. FDG-PET/CT revealed avid uptake in the zygapophyseal joints of the neck and lumbar region as well as some enthesitis. Inflammation of the vertebral spine was subsequently confirmed by MRI.

Physiologic FDG uptake in skeletal muscle should be limited as much as possible by instructing the patient to refrain from strenuous exercise 24 hours prior to FDG-PET/CT. However, involuntary muscle movements from cold or stress may also contribute to increased skeletal muscle uptake.

Elevated FDG uptake due to movement can usually be distinguished from inflammatory myositis because the majority of patients with inflammatory myositis show multiple muscle lesions on FDG-PET/CT (Figure 10). Focal lesions may be used to localize the most suitable lesion for diagnostic biopsy[80]. Malignancies such as sarcoma or muscular lymphoma can often be diagnosed based on CT or MRI due to evident anatomic abnormalities.

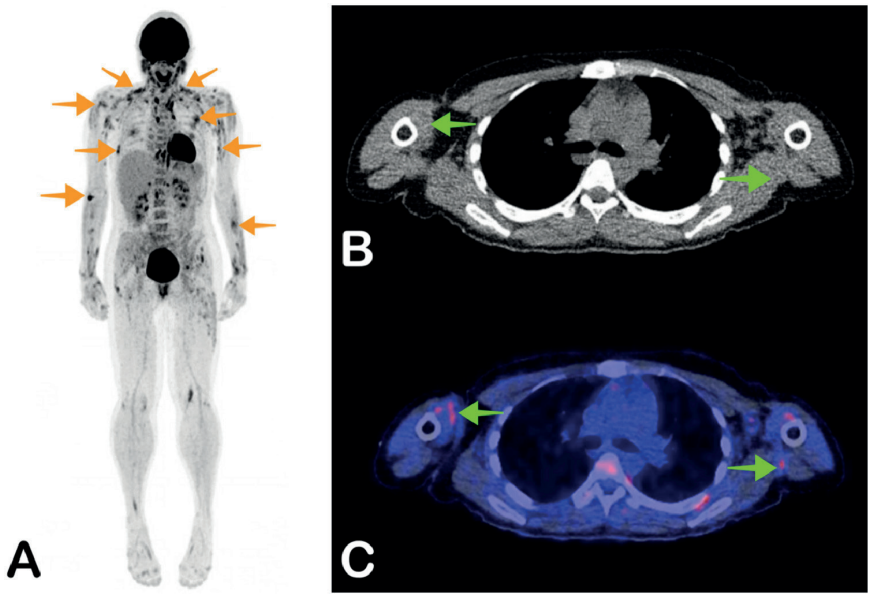

Figure 10 |
A 33-year-old woman underwent FDG-PET/CT because of chronic joint pain, weight loss, high inflammatory markers, and night sweats. Maximum intensity projection PET showed multiple FDG avid lesions in the muscles (A, orange arrows), which were also visible on fused axial PET/CT (C, green arrows). On low-dose CT, no clear anatomic abnormalities corresponding to the high FDG avidity were seen (B, green arrows). Based on PET/CT, the distinction between polymyositis, sarcoidosis or systemic candidiasis could not be made. Repeated biopsies showed myositis, which could not further be specified. The patient responded well to immunosuppressive treatment.

Current technological advances and future developments

Dual time point imaging may aid in distinguishing malignant disease from infection and inflammation. Due to differences in glucose metabolism, FDG uptake tends to remain high for a longer time in malignant lesions than in infection and inflammation, which can be visualized by performing FDG-PET/CT at two different time points. While dual time point imaging can improve the specificity of elevated FDG uptake in some cases, such as chronic inflammatory lesions in sarcoidosis versus malignancy, the distinction can still be difficult to make[81]. Dynamic PET imaging, where PET images are obtained at various time intervals immediately after FDG injection, is closely related to this[82]. As distribution of FDG throughout the body is a dynamic process, differences in glucose metabolism may be more apparent in dynamic imaging than static imaging one hour after FDG injection. The clinical utility of dynamic imaging in patients without a strongly suspected disease may be limited using current PET/

CT systems, as most PET/CT systems operate with a 20 cm wide detector ring, the whole body needs to be assessed, and the region of interest is unclear. However, automated dynamic whole body (D-WB) imaging may become more widely available with the recent introduction of scanner systems and software solutions that capture the input function during the initial 6-minutes of the scan and subsequently make up to 20 passes from the vertex of the skull to the lower extremities covering all areas of interest. We have previously demonstrated that D-WB is feasible in a clinical setting and it is possible that the technique will be of particular interest in e.g. patients with inflammatory diseases such as suspected vasculitis[83].

As previously mentioned, respiratory movements and a beating heart can complicate precise fusion of FDG-PET and CT images. Respiratory-gated or ECG-gated FDG-PET/CT may be used to overcome this problem. While literature on the topic is still relatively limited, performing gated PET/CT may cause a significant increase in diagnostic sensitivity and specificity for infection and inflammation of the heart and lungs, especially in infective endocarditis[45].

An overview of common practical or technical pitfalls and potential solutions is shown in **Table 1**.

Due to the relative non-specificity of elevated FDG uptake, there is an increasing interest in exploring alternative PET radiopharmaceuticals with a higher specificity for infection and inflammation. While most of these novel tracers have currently only been used in a research setting, they may be clinically used in the future to distinguish infection from sterile inflammation. Examples of these novel PET tracers include 89Zr-SAC55 which consists of a monoclonal antibody against Staphylococcus aureus labeled with Zirkonium-89, 68Ga-NOTAUBI which consists of chelated ubiquicidin (an antimicrobial peptide) labeled with Gallium-68, and 2-18F-fluorodeoxysorbitol which consists of sorbitol labeled with Fluorine-18[84–86].

Another interesting development in the field of nuclear medicine is the introduction of total body PET/CT systems. While current PET/CT systems operate with a 20 cm wide detector ring and field of view, total body PET/CT systems contain a detector tube of up to 200 cm long[87]. This could potentially decrease total scanning time to less than a minute, increase sensitivity by a factor of 40, and decrease FDG dosage, partially because much less high-energy photons scatter outside the detector tube and go undetected[88]. While this does not decrease the necessary dietary preparation time for patients and the one hour wait after FDG injection to allow biodistribution to occur, it may allow more flexibility in hospital planning and increase patient capacity. Additionally, a faster scanning procedure may also better allow imaging of critically ill patients. The increase in image resolution may enable a better discrimination between physiologic and pathologic FDG uptake and may also allow the detection of smaller FDG avid lesions. This would also benefit the detection of smaller inflamed vessels such as in Kawasaki arteritis and potentially inflamed cranial vessels in large vessel vasculitis[54,89]. Lastly, it would enable dynamic imaging of (almost the) the whole body, depending on the length of the detector tube.

Table 1 | *Overview of common practical or technical pitfalls and potential solutions*

Challenges in FDG-PET/CT	Consequence	(Potential) solution
Imaging of moving structures such as the heart and lungs.	Reduced diagnostic accuracy of diseases such as endocarditis or pulmonary septic emboli.	Perform ECG-gated or respiratory-gated PET/CT.
High physiologic FDG uptake of the myocardium.	Reduced ability to diagnose cardiac infections, especially endocarditis	Follow adequate dietary precautions. Administer single dose of heparin before FDG-PET/CT.
Inability to distinguish malignant disease from infection or inflammation	Additional testing such as biopsy is necessary for diagnosis.	Dual time point or dynamic PET/CT imaging may be performed.
Suspicion of inflammatory disease while the patient is already receiving immunosuppressive treatment.	Reduced sensitivity to diagnose inflammatory disease, especially vasculitis.	Lower the dosage of immunosuppressive treatment before FDG-PET/CT where the clinical status permits.
Diabetic patients with hyperglycemia.	A serum glucose level above 11 mmol/L may result in low lesion-to-background ratios.	Dietary precautions should be followed and rapid-acting insulin may be given up to 4 hours before FDG-PET/CT.
Extensive brown fat activation.	Extensive FDG avidity in the head and neck region that may mimic active lymph nodes	Keep (young) patients warm before FDG-PET/CT.

CONCLUSION

For many infectious and inflammatory diseases, FDG-PET/CT yields an acceptable diagnostic sensitivity and specificity, when used in the appropriate clinical setting. However, there are various caveats that need to be taken into account when performing FDG-PET/CT and interpreting elevated FDG uptake. The most important limitations of FDG-PET/CT are related to the relative non-specificity of elevated FDG uptake, the ability to distinguish physiologic from pathologic FDG uptake, and time needed for adequate patient preparation including dietary precautions and FDG biodistribution. In the future, these limitations may be (partly) overcome by using radiotracers with a fast blood clearance and a higher specificity for infection or inflammation, and the introduction of new total body PET/CT systems that allow rapid scanning and higher image resolution compared to current PET/CT systems.

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