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Monitoring Response to Therapy

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Monitoring response to treatment is a key element in the management of infectious diseases, yet controversies still persist on reliable biomarkers for noninvasive response evaluation. Considering the limitations of invasiveness of most diagnostic procedures and the issue of expression heterogeneity of pathology, molecular imaging is better able to assay in vivo biologic processes noninvasively and quantitatively. The usefulness of ^{18}F-FDG-PET/CT in assessing treatment response in infectious diseases is more promising than for conventional imaging. However, there are currently no clinical criteria or recommended imaging modalities to objectively evaluate the effectiveness of antimicrobial treatment. Therapeutic effectiveness is currently gauged by the patient's subjective clinical response. In this review, we present the current studies for monitoring treatment response, with a focus on *Mycobacterium tuberculosis*, as it remains a major worldwide cause of morbidity and mortality. The role of molecular imaging in monitoring other infections including spondylodiscitis, infected prosthetic vascular grafts, invasive fungal infections, and a parasitic disease is highlighted. The role of functional imaging in monitoring lipodystrophy associated with highly active antiretroviral therapy for human immunodeficiency virus is considered. We also discuss the key challenges and emerging data in optimizing noninvasive response evaluation.
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Introduction

Despite new antimicrobial drugs licensed in recent years, infection remains among the leading causes of death, taking the life of 10-15 million people every year.[1] This is further exacerbated by the syndesmosis of human immunodeficiency virus (HIV) and tuberculosis (TB), leading to the majority of fatal cases occurring in the developing world.[2]

Even in developed countries, treatment of patients with infections is becoming increasingly difficult because of rising rates of antimicrobial drug resistance. The evolution of antimicrobial resistance is exacerbated by the overuse and inappropriate use of antimicrobials, and complicated by the evolutionary capacity of infectious pathogens to adapt to new ecological niches created by human endeavor.[1] Complicating matters is the unpredictability of infectious diseases in general and their potential for explosive global effect, as exemplified by the current pandemics of HIV and TB. Hence, this back-and-forth struggle between human ingenuity and microbial adaptation is a perpetual challenge.[3-5] As such, our response to these challenges must also be perpetual and able to circumvent the adaptations of these microbial agents. Chief among a number of approaches to meet this ever-present challenge is to optimize monitoring of response to therapy.

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Biomarkers for Monitoring Response to Therapy

The World Health Organization defines a biomarker as an objectively measured characteristic used as an indicator of a normal or pathologic biologic process or a pharmacologic response. As such, an ideal biomarker for infection must possess diagnostic, prognostic, and follow-up therapy characteristics.[6] Furthermore, biomarkers should be both sensitive and specific, measurable with good precision and reproducibility, readily available, affordable, responsive to minor changes, and provide timely results.[7] However, in clinical practice, there is a considerable overlap of biomarker values between different infectious (bacterial, viral, parasitic) and noninfectious etiologies. These limitations have been demonstrated on both commonly used biomarkers such as procalcitonin (PCT), C-reactive protein (CRP), white blood cell, or neutrophil count, and the still experimental and not commercially available biomarkers such as soluble urokinase-type plasminogen

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activator receptor, soluble triggering receptor expressed on myeloid cells, and macrophage inhibitory factor.[8] Some of the reasons why these biomarkers cannot be expected to become isolated "magic bullets" are the relevant causes of false-positive and false-negative results of these biomarkers. For instance, the CRP response is blunted in fulminant hepatic failure, but overall the clinical relevance of renal dysfunction, chronic liver insufficiency, and corticosteroid treatment on PCT and CRP seems to be negligible.[9] PCT levels in the absence of bacterial infections are higher in patients with chronic kidney disease than in those without, and levels decrease after renal replacement therapy with either transplant renal graft or hemodialysis. The magnitude of these differences in PCT levels depends on the method used to assay the biomarker.[10] Microbiological markers such as blood cultures and PCR methods still have relatively low sensitivity and lack accurate prognostic rules. Thus, there is an ongoing unmet need for biomarkers that can reliably distinguish between responders and nonresponders and help to optimize antimicrobial treatment decisions. The consequences of this unmet need include an increase in multiresistant pathogens, high costs for inpatient care, and potential adverse outcomes. Hence, available evidence needs to be better incorporated into clinical decision-making, including imaging.

Imaging as a Biomarker for Monitoring Response to Therapy

Given the complexities of the infection response, no 1 biomarker will be sufficient to diagnose and monitor infection. Combinations of biomarkers are needed, and molecular imaging is gaining prominence in this regard.

MRI and conventional nuclear medicine tests can be employed to assess response to therapy. However, these approaches may become accurate only months after complete eradication of the infection and therefore cannot be used to provide an early assessment of therapeutic efficacy.[11] As a result of the limitation of these imaging modalities coupled with the expression heterogeneity by pathology, molecular imaging with PET/CT is better able to assay in vivo biologic processes noninvasively and quantitatively. Molecular imaging has been a particularly attractive tool for monitoring treatment in clinical cancer practice. The radiotracer ^{18}F-FDG is widely used in clinical medicine for noninvasive imaging, staging, and monitoring treatment responses of neoplastic diseases.[12,13] ^{18}F-FDG has also been used to image infection and inflammation, because detection is proportional to the glycolytic activity of the cells that trap it.[14-16]

The accumulation of ^{18}F-FDG in inflammatory and infectious diseases is based on the high uptake in activated leukocytes, which use glucose as an energy source only after activation during the metabolic burst. Transport of ^{18}F-FDG across the cellular membrane is mediated by the glucose transporter proteins, which have increased expression on the cell membrane of inflammatory cells.[17,18] Rabkin et al showed that although hyperglycemia led to a higher false-negative rate in patients with cancer it had, in contrast, no significant effect on the detectability rate of infectious foci.[19] There is currently a lack of approved guidelines for monitoring response with ^{18}F-FDG-PET/CT; however, rapidly growing data appear to show ^{18}F-FDG-PET/CT is valuable for therapy monitoring in some infectious and inflammatory diseases. The data indicate that ^{18}F-FDG-PET/CT could even play a pivotal role in the management of infections, leading to better drug dosage, confirm the usefulness of the treatment, and early modification of the therapeutic strategy. Moreover, recent interesting findings by Kagna et al[20] demonstrate that antibiotic treatment appears to have no clinically significant impact on the diagnostic accuracy of ^{18}F-FDG-PET/CT performed for the assessment of known or suspected infectious processes, despite the long duration of appropriate antimicrobial treatment. This means that in spite of the appropriateness of the administered antibiotics, if there is poor, delayed, or lack of response, ^{18}F-FDG-PET will remain positive. Importantly, Kagna et al[20] recommended that further prospective well-designed studies are needed to determine whether serial maximum standardized uptake value (SUVmax) ^{18}F-FDG measurements will indeed be able to demonstrate therapy control and define response to antibiotics in various infectious processes.

Quantifying Response

Determining an accurate and repeatable means of evaluating response to therapy remains a challenge in patients with infection. An objective assessment of response of the primary site of infection and any metastatic foci is necessary to measure therapeutic effect. One such method makes use of SUVmax.[21]

Some problems associated with quantifying response in infection include:

- In clinical practice, a baseline study is unlikely to have been done
- Limited data and poor correlation between serum biomarkers and imaging biomarkers
- SUV cutoff value (threshold) not established
- Delta SUVmax between 2 studies (baseline and follow-up) not established
- Time point during the course of treatment when the follow-up scan must be done
- Definition of the region of interest is more difficult than with solid tumors
- No clear guidelines on interpretation of mixed response (especially in TB)
- General and technical issues of quantification of SUV

Most studies have focused on changes in SUV between baseline and follow-up scans. Treatment response is considered as decrease in SUVmax between the baseline and the follow-up studies. In a study of 38 patients with spondylodiscitis, the delta-SUVmax had a higher sensitivity for early identification of responders than CRP levels.[22] In another study, the response to antibiotic treatment was defined by a significant reduction in SUVmax between baseline and post-treatment PET/CT studies in 15 patients with infectious

discitis.[23] ^{18}F-FDG-PET/CT was also a useful tool in monitoring therapy results in 25 patients with prosthetic vascular graft infections, defining partial response as a decrease in SUVmax of more than 20%.[24] On the contrary, Riccio et al found quantification of activity could not reliably differentiate patients with active infection from those without active infection and those who had had a successful response to therapy. They rather relied on the pattern of activity as critical to accurate interpretation.[21]

TB and Monitoring of Response to Therapy

Perhaps we need to ask several questions with regard to TB:

(1) What is the role of PET/CT, and does it improve outcome?
(2) For which patients or groups of patients should PET/CT be used?
(3) What is the optimal duration of therapy?
(4) What is the role of biomarkers (eg, CRP or PCT) in determining duration of therapy and their correlation with ^{18}F-FDG-PET/CT?

Although great progress has been made with relatively effective chemotherapy for TB, the host-pathogen interaction is incompletely understood. Therefore, treatment of TB involves administration of multiple drugs with the recommended regimen for drug-sensitive TB (isoniazid and rifampicin for 6 months, together with pyrazinamide and ethambutol for the first 2 months) being highly effective. Unfortunately, this regimen's main drawback is the duration of therapy. This is supported by the proportion of patients defaulting therapy increased linearly after 4 weeks and varied between 7% and 53.6% in a systematic review.[25] One key explanation for this long duration of treatment is based on the findings that during the first 2 months of effective therapy, viable bacteria in sputum samples from patients show a characteristic biphasic kill curve (Fig. 1).[26,27] This indicates that there are at least 2 bacterial subpopulations that differ in their intrinsic drug susceptibility:

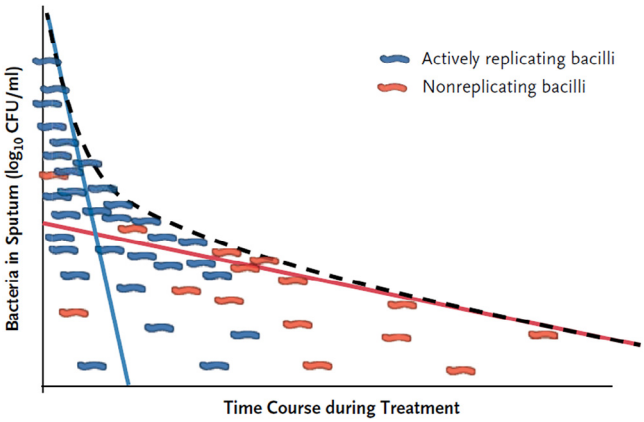

Figure 1 Graph showing the effect of anti-TB therapy on subpopulations of *Mycobacterium tuberculosis* present in sputum over time. Adapted from Horsburgh et al[26] with kind permission of the authors.

1 subpopulation is rapidly killed, and the other responds more slowly. The bacilli in this second and slowly replicating or nonreplicating subpopulation have been classified as persistent.

The effectiveness of combination TB chemotherapy regimens has been theorized to be the result of the differential effectiveness of the individual agents against these discrete bacterial subpopulations.[11] However, there are still unexplained observations in the sense that after the first 2 months of therapy, most patients no longer have bacilli in their sputum that can be cultured, but many must still complete an additional 4 months of treatment to avoid relapse.

Thus, the 6-month standard course of therapy for drug-susceptible disease is clearly longer than is necessary for some patients.[28-31] Unfortunately, it has proven extremely challenging to identify which patients can be successfully treated for a shorter time. A clinical trial of shorter treatment for patients without cavities on baseline chest films and with negative sputum cultures at 2 months was unsuccessful.[32] This highlights the need for a combination of biomarkers that includes molecular imaging to optimize treatment duration, taking into consideration that we should avoid multidrug resistance (MDR) TB. The recommended MDR TB regimen is toxic, poorly tolerated and prolonged (up to 24 months), and not based on data from controlled trials. Treatment success rates in many countries are only around 50%, needless to mention about the emergence of incurable TB (failures and resistance beyond XDR TB), totally drug-resistant TB, to which there is no solution.[33,34]

The lack of reliable surrogate markers of drug efficacy hampers efforts to develop new drugs, shorten the treatment time, and reduce extensively drug-resistance (XDR) TB the disease burden. The events that occur in the lungs and other tissues to eliminate *Mycobacterium tuberculosis* during drug treatment are poorly understood, especially at the lesional level. There is evidence that specific lesion types, particularly cavities, are associated with poor treatment outcomes,[35,36] but for the many pathologies present in patients with TB, we currently have little understanding of the kinetics of resolution by different drugs.[37,38] Assessing which lesions respond most slowly and optimizing regimens to resolve them offer a rational route forward to shortening the duration of treatment; this is the ultimate goal for ongoing research with molecular imaging. Currently, response to anti-TB treatment in patients with bacillus-positive TB is monitored principally by serial bacteriologic examinations, whereas responses in patients with bacillus-negative TB, including smear-negative pulmonary and most cases of extrapulmonary TB, are usually monitored clinically or radiographically. Patients with noncavitary tuberculomas usually have no symptoms, and their cultures are usually negative. After 3 and 12 months of treatment for pulmonary tuberculomas, however, only 40% and 76%, respectively, of tuberculomas decreased in size.[36,39]

^{18}F-FDG-PET/CT as a Biomarker for Monitoring Infection

Based on the findings of several investigators (Tables 1 and 3), PET/CT technology could be used in clinical trials of

investigational drugs or diagnostics to predict the efficacy of a treatment regimen early on, potentially shortening the duration of a trial and saving resources.

Metabolic activity as studied on ^{18}F-FDG-PET/CT can be taken as a reliable marker for serial quantification of activity in infectious disease process like TB or invasive fungal infection (IFI). The changes in glycolytic activity within the inflammatory lesion as measured by ^{18}F-FDG uptake correlates well with the clinical markers of response and possibly provide more objective evidence of response rather than the nonspecific biochemical markers such as erythrocyte sedimentation rate. This may translate into a potential clinical role for ^{18}F-FDG as an imaging biomarker for noninvasive response evaluation infection and for guiding modulation of therapy.

^{18}F-FDG-PET or PET/CT for Monitoring Response in TB

Early work with ^{18}F-FDG-PET showed different time activity curves for FDG uptake in acute, healing, and chronic lesions caused by different infective etiologies including TB.[40] This suggested a role for monitoring therapy of anti-TB chemotherapy with ^{18}F-FDG-PET that was explored by different authors in evaluating response to anti-TB chemotherapy in both pulmonary and extrapulmonary TB (Table 1).

Preclinical Assessment of Response to TB Therapy With ^{18}F-FDG-PET/CT

In TB, the usefulness of ^{18}F-FDG-PET and PET/CT has been explored in the preclinical setting in various animal models.

Mouse Model

Metabolic activity in the lungs of mice with TB on ^{18}F-FDG-PET was found to correlate with the bactericidal activity of anti-TB chemotherapy in BALB/c and C3HeB/FeJ mice in 1 study.[61] Mice strains such as BALB/c show little evidence of necrosis and do not reflect human disease accurately. The C3HeB/FeJ on the other hand form necrotic lesions after infection with *M tuberculosis* and develop heterogeneous pulmonary lesions reflecting human pulmonary TB more closely.[45] The C3HeB/FeJ model has been used in combination with ^{18}F-FDG-PET/CT to test new anti-TB drugs.[61,64] In 1 study, ^{18}F-FDG-PET/CT was evaluated in C3HeB/FeJ mice that were infected with TB and subsequently treated.[64] This study demonstrated that ^{18}F-FDG-PET/CT was able to accurately follow the evolution of TB granulomas over time. ^{18}F-FDG-PET detected new TB lesions over the time course over which mice were studied, suggesting that dormant *Mycobacterium bacilli* may reside outside TB lesions and may explain the differential response with the development of new TB lesions in previously uninvolved sites while on treatment. ^{18}F-FDG-PET in mice can potentially help explain TB pathogenesis and complex human response treatment. Evaluation of anti-TB therapy in mice for instance, pyrazinamide and clofazimine demonstrated only moderate bacterial killing in C3HeB/FeJ mice but were highly effective in BALB/c mice without necrotic lesions in necropsy studies.[65,66] ^{18}F-18 FDG-PET studies in mice present a useful tool in investigating therapeutic efficacy.[45]

Rabbit Model

A study using rabbits determined that changes in metabolic uptake in the lungs of rabbits with TB could be observed as early as 1 week after starting anti-TB therapy.[52] Metabolic changes preceded morphologic changes. The rabbit model of TB reflects different aspects of human disease including fibrotic granuloma with caseous necrosis foci that harbor small persisting mycobacterial subpopulations that have adapted to the harsh microenvironment.[45] The different disease states and disease progression that can be induced in rabbits allow monitoring of anti-TB drugs at the lesional level with ^{18}F-FDG-PET/CT.[45,67]

Nonhuman Primates

A reduction in ^{18}F-FDG avidity in the lung of cynomolgus macaques with active TB on anti-TB treatment correlated with reduced bacterial load at necropsy of these animals.[51] In this study, changes in SUV from baseline to end of treatment of about 8-12 weeks were compared for isoniazid and rifampicin monotherapy. Isoniazid-treated animals demonstrated a transient increase in metabolic activity of TB lesions, whereas there was a net decrease in rifampicin-treated animals. Animals treated with the 4 standard first-line TB drugs showed greater metabolic reduction than those treated with individual drugs. The study suggests ^{18}F-FDG-PET/CT may provide an early correlate that can be used to test novel combination of drugs before translating drug combinations into humans. In another study, ^{18}F-FDG-PET/CT findings early in the course of anti-TB therapy predicted the outcome of treatment in nonhuman primates.[47] These findings were translated to humans, and ^{18}F-FDG-PET/CT was used in monitoring multidrug resistant patients.[46]

Clinical Assessment of Response to TB With ^{18}F-FDG-PET/CT

In clinical studies, several authors demonstrated the ability of ^{18}F-FDG-PET or PET/CT to monitor response of TB in pulmonary and extrapulmonary sites.[42,43,62] Table 1 summarizes the findings that have been reported. Figure 2 shows a patient who had serial ^{18}F-FDG-PET/CT scans to monitor therapy. Some authors reported the changes of FDG being apparent in some sites as early as 3 days although most authors reported on changes after 1 month or longer.[54,59]

Pulmonary TB

In pulmonary TB, ^{18}F-FDG provided a noninvasive method of following up TB lesions. This enabled real-time assessment

Table 1 Original Articles of ^{18}F-FDG-PET or PET/CT in Monitoring Response in TB

Author	Journal	Type of Study and Subjects	Comment or Conclusion
Lefebvre et al[41]	Nucl Med Biol 2017	Clinical—patients with TB lymphadenitis	SUVmax follow-up is a potential tool for monitoring response
Stelzmueller et al[42]	Clin Nucl Med 2016	Clinical—pulmonary and EPTB	May be useful for the establishment of individual treatment regimens
Arbind et al[43]	Indian J Nucl Med 2016	Clinical—EPTB	PET/CT is a powerful tool in monitoring therapy in TB
Malherbe et al[69]	Nat Med 2016	Clinical—HIV-negative patients	Patients with durable clinical cure may have metabolic uptake, which may persist in the post-therapeutic period
Maruwski et al[64]	J Nucl Med 2014	Preclinical—C3HeB/FeJ mice	Suggested dormant *Mycobacterium tuberculosis* bacilli were present outside TB lesions in normal lung tissue
Chen et al[46]	Sci Transl Med 2014	Clinical—MDR TB patients	Quantitative changes in SUV at 2 months were associated with long-term outcomes
Coleman et al[47]	Sci Transl Med 2014	Clinical and preclinical—MDR TB patient and cynomolgus macaques	TB treatment was associated with reduction in FDG activity in the lung
Santhosh et al[48]	Indian J Nucl Med 2014	Clinical—Pancreatic tuberculosis	Noninvasively evaluated therapeutic response in peripancreatic TB
Ghesani et al[49]	Am J Respir Crit Care Med 2014	Clinical—latent TB (LTBI)	Monitored response in patient treated for LTBI
Dureja et al[50]	Eur Spine J 2014	Clinical—Extrapulmonary (vertebral) TB	SUVmax was found to be a quantitative marker of response to therapy
Lin et al[51]	Antimicrobial Agents Chemother 2013	Preclinical—cynomolgus macaques	Efficacy of a single anti-TB or multidrug regime could be identified within 1 or 2 months of treatment
Via et al[52]	Antimicrob Agents Chemother 2012	Preclinical—rabbits	Significant reduction in FDG avidity of TB lesions seen as early as 1 week, whereas CT features (size and density) changed more slowly with anti-TB therapy
Martinez et al[53]	Int J Tuberc Lung Dis 2012	Clinical—EPTB	Allows early evaluation of anti-TB therapy especially in EPTB
Yadla et al[54]	Indian J Nucl Med 2012	Clinical—EPTB	Useful in early assessment of anti-TB therapy suggested response in some sites of TB as early as 3 days
Park et al[55]	Nucl Med Mol Imaging 2012	Clinical—EPTB	Useful for estimating patient's therapeutic response to anti-TB
Sathekge et al[56]	EJNMMI 2012	Clinical—Lymph nodes of TB-HIV coinfected patients evaluated at 4 months	Useful in discriminating responders to anti-TB therapy from nonresponders by the metabolic uptake in the lymph nodes
Sathekge et al[57]	J Nucl Med 2011	Clinical—TB burden at before therapy in TB-HIV coinfected patients evaluated	Useful in predicting patients likely to fail treatment after 4 months (prognosis)
Tian et al[58]	Acta Radiol 2010	Clinical—EPTB	Useful in monitoring response in EPTB
Harisankar et al[59]	J Postgraguate Med 2010	Clinical—EPTB	Demonstrated response to anti-TB therapy as early as 8 weeks
Demura et al[60]	EJNMMI 2009	Clinical—pulmonary mycobacteriosis	Useful in monitoring response to both TB and nontuberculous myocobateria
Davis et al[61]	Antimicrobial Agents Chemother 2009	Preclinical—BALB/c and C3HeB/FeJ mice	Correctly identified bactericidal activity of anti-TB therapy
Park et al[62]	Clin Nuc Med 2008	Clinical—pulmonary tuberculomas	Useful for monitoring response in tuberculoma
Hofmeyr et al[63]	Tuberculosis (Edin) 2007	Clinical—EPTB	Useful to monitor therapy and may guide duration of treatment
Ichiya et al[40]	Ann Nucl Med 1996	Clinical—TB and other infections such as fungal and bacterial	Identified patterns for time activity curves of FDG uptake suggesting a role in monitoring therapy

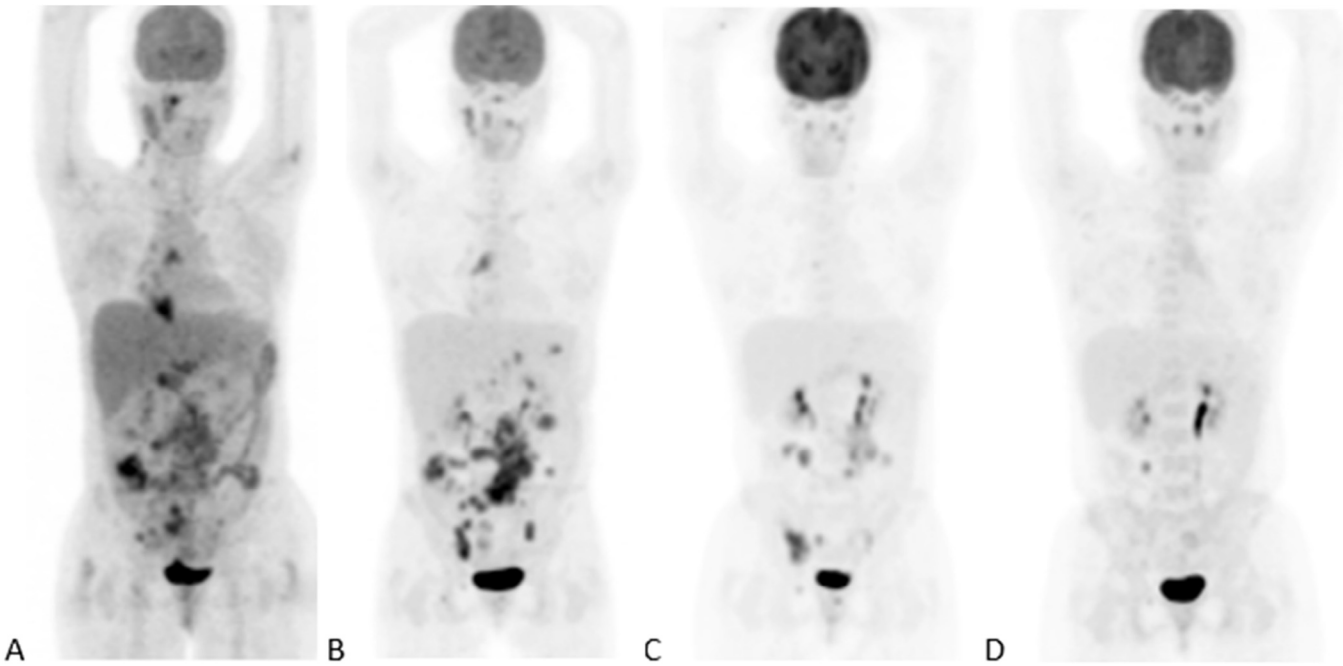

Figure 2 Maximum intensity projection ^{18}F-FDG-PET images in a 30-year-old woman with TB-HIV coinfection on TB therapy at baseline (A), 2 months (B), 6 months, and (D) 9 months. CD4 count was 86, and viral load was 122 copies per mL at baseline.

(A) Baseline study shows abnormal ^{18}F-FDG accumulation in cervical, mediastinal abdominal, and pelvic nodes because of TB. There were also lung lesions that are not demonstrated on the MIP.

(B) Disease activity in the pelvic and mesenteric nodes increased, whereas the cervical and mediastinal nodes showed decreased ^{18}F-FDG activity after 2 months of anti-TB treatment (differential response of lesions to therapy).

(C) Significant disease activity is still noted in the abdominal and mediastinal nodes after 6 months of TB treatment. There is complete resolution of cervical and mediastinal nodes

(D) TB Therapy was extended for a further 3 months. At the end of 9 months of TB treatment, there is complete resolution of all the lesions.

of pulmonary TB lesions over time. In 1 study, 47 patients with pulmonary mycobacteriosis were evaluated. ^{18}F-FDG-PET/CT was used to monitor treatment in 14 of these patients. All 14 patients showed a decrease in metabolic uptake during treatment, demonstrating the usefulness of FDG-PET/CT in monitoring therapy of pulmonary TB and *Mycobacterium avium*-intracellulare complex.[60] Other studies have demonstrated ^{18}F-FDG-PET/CT is useful for monitoring pulmonary TB and may be useful for establishing individual treatment regimens.[42,43] Figure 3 shows ^{18}F-FDG-PET/CT used to monitor therapy in a 21-year-old woman with pulmonary TB. The ^{18}F-FDG-PET/CT scan during anti-TB therapy at 2 months demonstrates decrease in size and metabolic activity compared with baseline, indicating that patient is most likely going to respond to her current drug regimen. Figure 4 demonstrates the use of ^{18}F-FDG-PET/CT to monitor therapy in a 20-year-old female with TB-HIV coinfection at baseline, at 2 months of therapy, and at the end of therapy at 6 months. There is independent response of TB lesions to anti-TB chemotherapy with improvement of the pulmonary lesions but development of new abdominal TB lymphadenitis on the subsequent (2-month follow-up) study. This is consistent with the concept that different TB lesions respond or progress differently within the same patient.[45]

Extrapulmonary TB

In extrapulmonary TB, several studies have demonstrated the use of ^{18}F-FDG-PET/CT in monitoring therapy at various sites.[41,48,50] The role of ^{18}F-FDG-PET/CT in these sites is particularly important, as there may be no pulmonary disease component, thus precluding the use of monitoring disease with serial bacteriologic sputum assessment. Again, the site of the disease may be unsuitable for repeated biopsy such as in the skeleton[50] or the pancreas,[48] where the risk of complications from repeated biopsies is high and morbidity is severe if complications develop. The duration of treatment for extrapulmonary disease is variable, and monitoring with ^{18}F-FDG-PET/CT may help in determining the appropriate time to stop therapy.[63] 18F-FDG-PET/CT allows early noninvasive evaluation of therapy at extrapulmonary sites and is particularly helpful when there is multisite involvement as is usually the case in TB.[53,55,58]

Prognosis and Prediction of Outcome

The burden of infection before initiating anti-TB treatment as assessed by ^{18}F-FDG-PET/CT was found to predict outcome

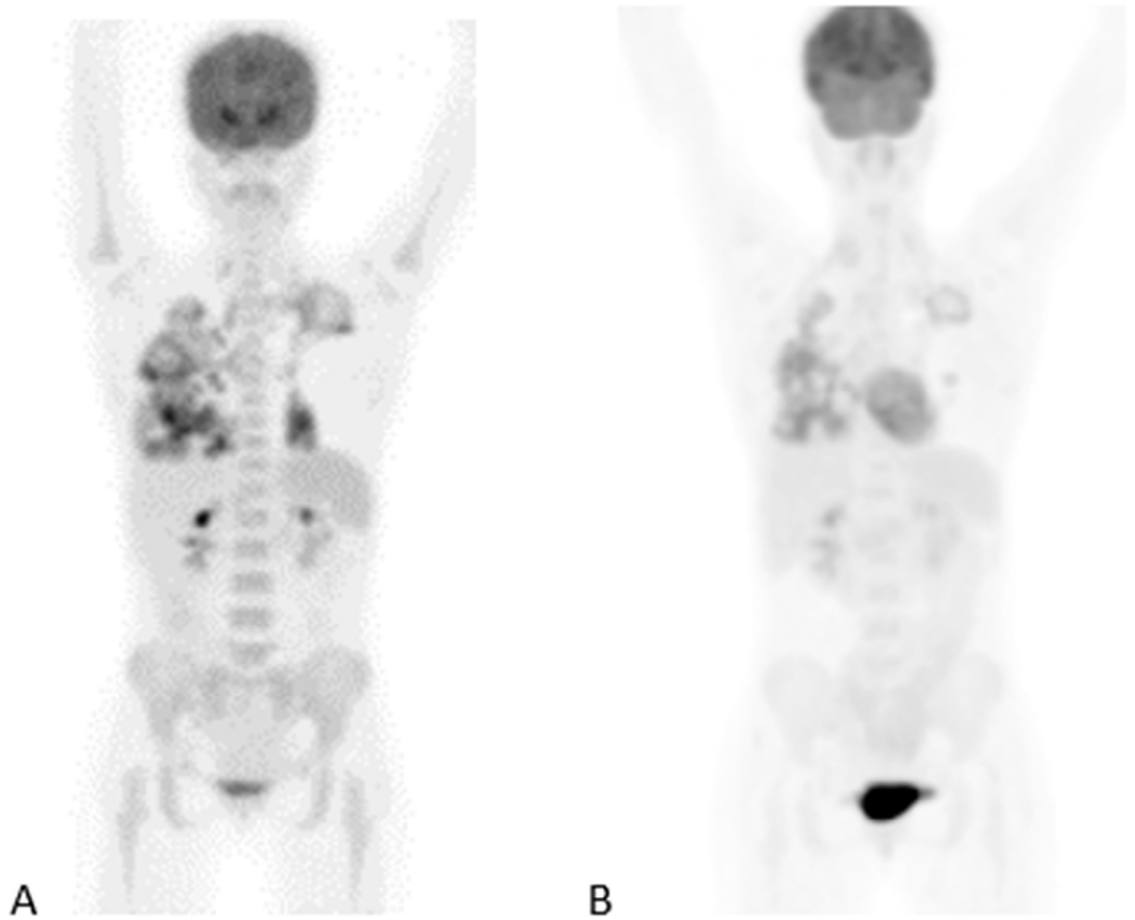

Figure 3 Extensive pulmonary cavitation demonstrated on the MIP images that show response to anti-TB therapy after 2 months in a 21-year-old woman with pulmonary TB.

(A) Baseline study with multiple cavities bilaterally the most intense lesions has an SUVmax of 13.5 and 10.97 in the right and left lungs, respectively.

(B) Two-month follow-up study still has active disease in the lungs bilaterally but less extensive and much less ^{18}F-FDG avid compared with the baseline study SUVmax of the most intense pulmonary lesions have reduced to 9.3 and 7.91 in the right and left, respectively.

of therapy. Using a cutoff SUVmax of 8.15, this prediction could be made with a sensitivity of 88% and a specificity of 81%.[57] This is a very important finding, revealing the ability of ^{18}F-FDG-PET/CT to provide prognosis before the start of therapy. ^{18}F-FDG-PET/CT, however, is expensive and cannot be recommended in all patients with TB before therapy is started. To make this finding relevant, another study evaluated the ability of ^{18}F-FDG-PET/CT to distinguish responders from nonresponders by evaluating the lymph nodes of patients at 4 months into treatment. In this study, 20 patients with HIV-TB coinfection were evaluated. Responders could be discriminated from nonresponders with a sensitivity of 88% and a specificity of 85% using a cutoff SUVmax of 4.5 for lymph nodes.[56] The findings from this study enable ^{18}F-FDG-PET/CT evaluation to be limited to patients who are already on treatment and suspected to be resistant to their current anti-TB regimen. Figure 5 shows a patient with high disease burden at baseline with intense uptake in lymph node basin, that has been found to be a predictor of poor outcome to treatment. Using the 4-month follow-up scan without the baseline study, the intense uptake in the lymph nodes would have identified the patient as a nonresponder.

Heterogeneous Response of TB Lesions to Anti-TB Medication

TB lesions are very complex and dynamic, with both spatial and temporal heterogeneity occurring within the same patient. TB lesions have divergent trajectories occurring independently of other lesions in the same host. In untreated patients, these dynamic temporal changes have been imaged with ^{18}F-FDG-PET/CT.[45] A study compared disparate imaging response to anti-TB therapy with results from deep genome sequencing of serial sputum culture in MDR TB. The study demonstrated clear evidence of branched microevolution of *M tuberculosis* in vivo and suggested these complex subpopulations contribute to the different lesion responses.[44] ^{18}F-FDG-PET/CT has the advantage of following up these lesions with differential response over time and can detect at an early point in time a TB lesion that may not respond.

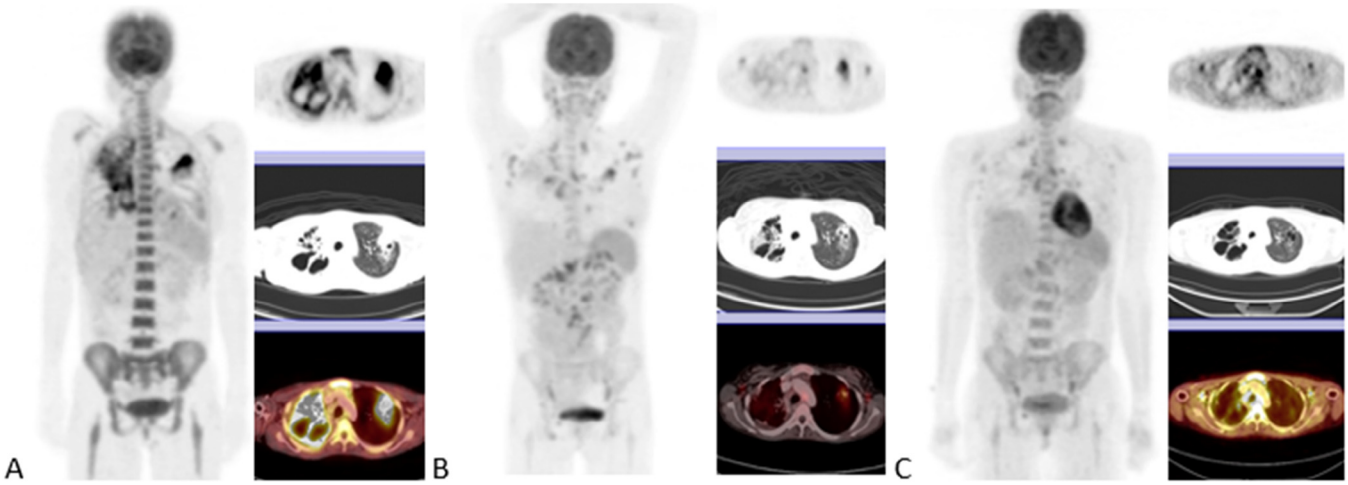

Figure 4 Twenty-year-old woman with TB-HIV coinfection defaulted treatment present with smear-positive pulmonary TB.

(A) Baseline MIP, PET, CT, and fused PET/CT showing bilateral upper lobe cavitation. SUVmax of the left lung lesion is 18.34.

(B). After 2 months, marked improvement seen in pulmonary lesions with SUVmax of left lung lesion now 8.52. New cervical, axillary, and abdominal nodes with SUVmax of 7.3 are noted. Cervical and axillary nodes are most likely reactive lymphadenopathy due to HIV because of symmetrical pattern.

(C) Six months end of therapy scan shows marked improvement in the pulmonary and abdominal lymphadenopathy. Left lung lesion with an SUV of 1.5; abdominal node was 3.3. Patient had been sputum negative from month 2, was gaining weight, and ESR and CRP were decreasing. Therapy stopped, and patient showed no evidence of disease after a year of follow-up.

Figures 2 and 4 demonstrate the phenomenon of differential response in TB that occur frequently in follow-up of anti-TB treatment with ^{18}F-FDG-PET/CT. Differential response to anti-TB on ^{18}F-FDG-PET/CT may be because of TB. However, heterogeneous response may also occur when TB coexists with another pathology, and careful evaluation of the findings and histology may be useful in making the distinction. A similar phenomenon has also been noted when ^{18}F-FDG-PET/CT

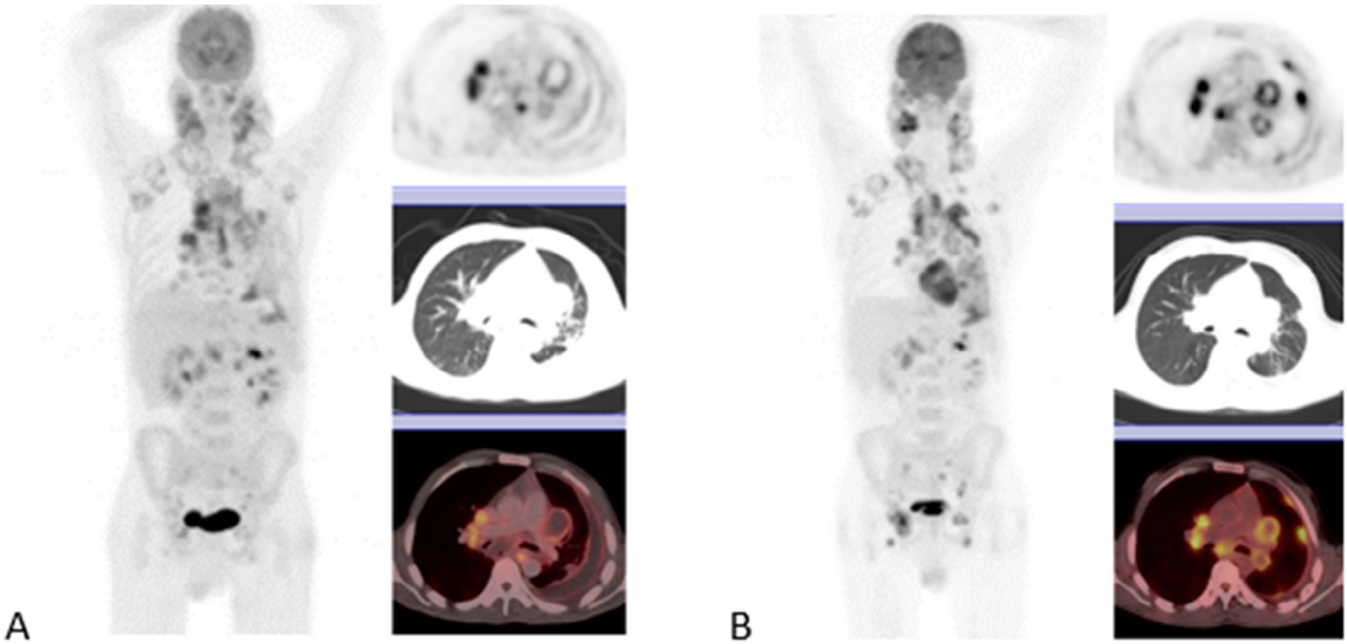

Figure 5 Poor response to anti-TB treatment: MIP, PET, CT, and fused images showing increasing FDG avidity over time in a 37-year-old man.

(A) Baseline study demonstrates extensive TB involving the lung parenchyma and cervical, clavicular, and mediastinal nodes. SUVmax right cervical 9, left cervical 9.4, and mediastinal nodes 12.

(B) Follow-up study after 2 months of anti-TB shows more avid lesions, with SUVmax of the right cervical left cervical and mediastinal nodes being 20.8, 13.9, and 18.1, respectively. More avid and larger inguinal nodes also present on the follow-up study.

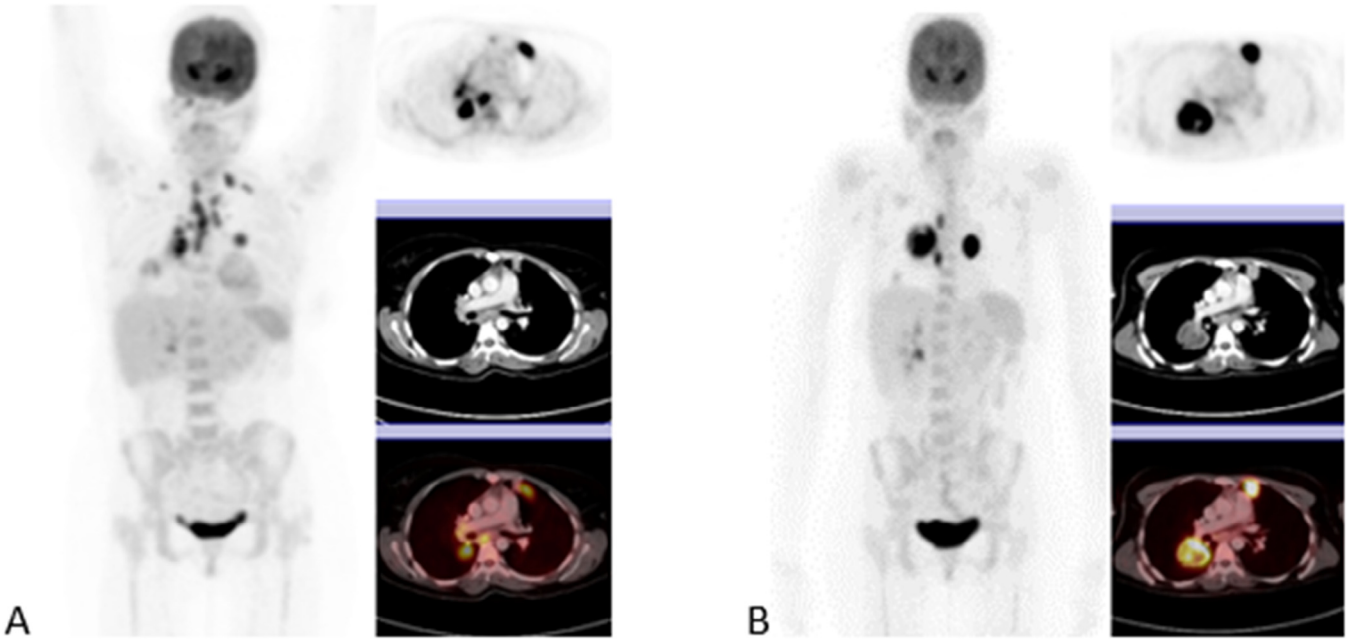

Figure 6 MIP, PET, CT, and fused images in a 41-year-old woman with TB, demonstrating a heterogeneous response.

(A) Baseline study demonstrating ^{18}F-FDG-avid cervical and mediastinal nodes. SUVmax of the intense right hilar lesion is 14.81. A pleural-based lung lesion is noted anteriorly on the left.

(B) Follow-up scan demonstrates complete resolution of cervical, paratracheal, and subcarinal nodes with increase in size and avidity of the right hilar lesion, with SUVmax of 16.78. The right pleural-based lesion also increased in size. Biopsy of the lung lesion noted showed granulomatous and necrotic tissue with no evidence of malignant cells and no acid-fast bacilli present.

is used in monitoring cancer. In 1 report, there was a heterogeneous radiological response that was suspected to be caused by tumor heterogeneity, but biopsy of the persistent metabolic lesion diagnosed TB.[68] Figure 6 demonstrates a case of differential response on the follow-up study where the ^{18}F-FDG-PET/CT findings demonstrated both progression and regression of the different lesions present.

Monitoring Response on Completion of TB Therapy

An international study involving 113 HIV-negative patients was conducted with ^{18}F-FDG-PET/CT scans done at different time points before, during, and after anti-TB therapy.[69] On completion of therapy, the study found that patients who had achieved a clinical cure had different patterns of ^{18}F-FDG uptake when compared with baseline study. In some patients, there was complete resolution of metabolic activity in lesions that were seen at baseline; in others, most of the lesions resolved, with a few just above background or reference structure. In others, however, some lesions were more intense than the baseline scan or new lesions appeared in patients who achieved and sustained a clinical cure. These new TB lesions may be because of differential response of the various TB lesions and microevolution in subpopulations of *M tuberculosis* in patients. These bacilli may be contained by the host or give rise to active disease. This presents a challenge in interpretation of end-of-treatment ^{18}F-FDG scans. The finding of ^{18}F-FDG uptake alone in the absence of clinical data to suggest active disease after a patient has completed chemotherapy may not be because of active disease but may represent the host response to replicating bacilli, which are well contained by the immune system.[70] ^{18}F-FDG-PET findings must be carefully correlated with clinical data when interpreting end-of-therapy scans. Figure 7 shows a baseline and end-of-treatment scan in a patient with HIV-TB coinfection. There is still uptake in the mediastinal nodes at the end of therapy. The patient clinically was cured and was followed up for a year, with no evidence of active TB.

Monitoring Response in Treated Patients With Latent TB With FDG-PET/CT

^{18}F-FDG-PET/CT has also been evaluated for its usefulness in monitoring therapy in patients with latent TB who received anti-TB preventive therapy latent infection. This study included 5 asymptomatic subjects with no radiological evidence of disease who had positive QuantiFERON tests. A decrease in metabolic activity was noted in the thoracic lymph nodes at the end of treatment in most lesions; however, the authors were unable to determine whether the findings were the result of treatment or the natural history of latent TB.[49] They concluded that ^{18}F-FDG-PET/CT might be useful for studying early events in latent TB.

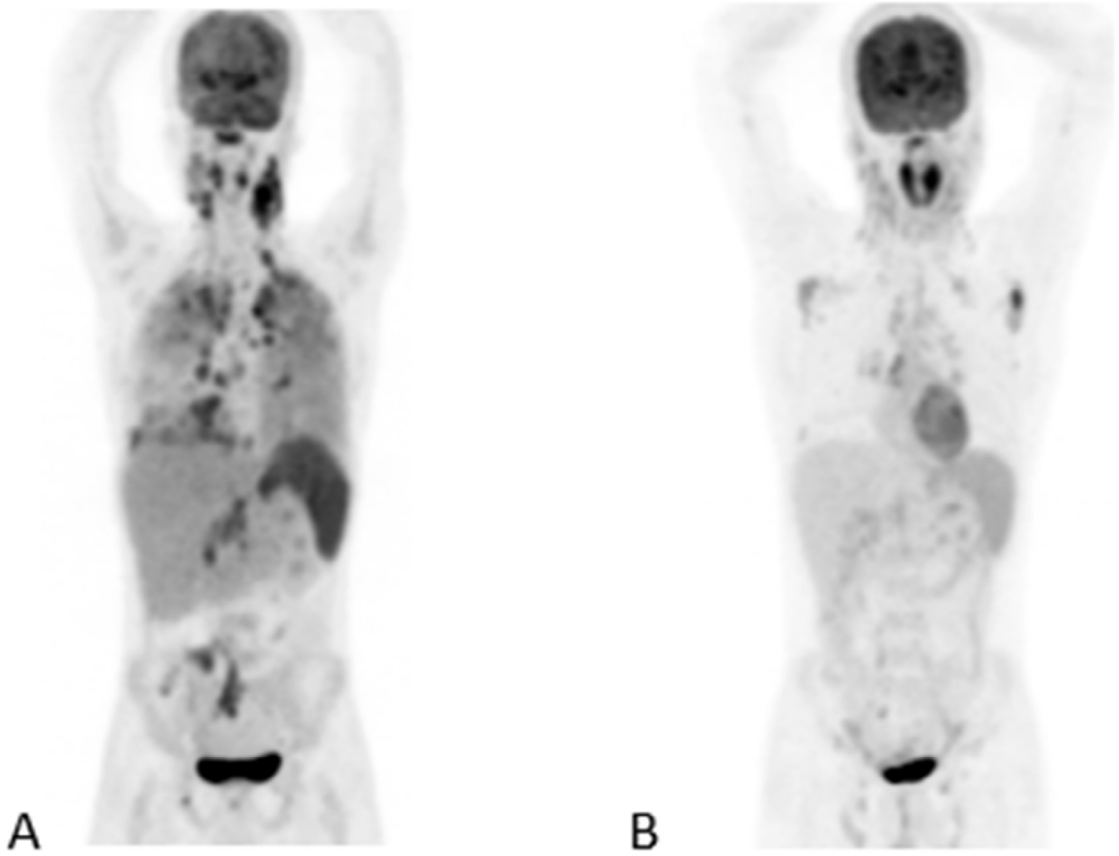

Figure 7 Baseline (A) and end of TB therapy (B) maximum intensity projection images in a 27-year-old man with TB-HIV coinfection showing good response to therapy.

(A) Baseline study shows diffuse FDG accumulation in the lung parenchyma. Widespread ^{18}F-FDG-avid lymph nodes because of TB lymphadenitis demonstrated in the cervical mediastinal, abdominal, and pelvic nodes. There is also diffuse intense splenic uptake noted on the baseline study.

(B) Following 6 months of TB treatment, there is complete resolution of the parenchymal lung lesions and marked reduction of FDG accumulation in the lymph nodes. The spleen is still more intense than the liver but much less intense than baseline study. The symmetrical axillary and inguinal uptake on the end of treatment study is most likely because of HIV-associated lymphadenopathy.

Review Papers on TB and FDG

Several authors have highlighted the role of ^{18}F-FDG in monitoring response to anti-TB medication in various review articles (Table 2). Some of these reviews focus on certain special issues such as TB in children, extrapulmonary TB, role of ^{18}F-FDG as a biomarker in TB, and multidrug-resistant TB.[2,71-73] Other reviews emphasize the response assessment as being the most important role of ^{18}F-FDG-PET/CT in TB image with the ability to assess disease activity over time with semiquantitative measures.[14,74-79]

Monitoring Therapy in Patients With HIV-TB Coinfection

Patients with TB and HIV coinfection may present with atypical patterns of disease. The presentation of pulmonary disease depends on the extent of immunosuppression.[1,14] Patients with suppressed viral loads and high CD4 count may present as typical TB, but as the immunity is depressed, lung cavitation occurs less frequently and TB lesions may involve lung apices less commonly.[76,77] Monitoring with ^{18}F-FDG-PET/CT is very useful as these patients are more frequently sputum negative and they present with extrapulmonary disease more often. On ^{18}F-FDG-PET/CT, HIV-related lymphadenopathy may show metabolic uptake that may be difficult to distinguish from TB lymphadenitis.[78] These nodes very often may not be apparent on the baseline study but usually present on follow-up scans (Fig. 7). HIV lymphadenopathy frequently involves the cervical, axillary, and inguinal nodes and is frequently bilateral.[79,80] The appearance of these peripheral nodes in a patient with HIV-TB coinfection on anti-TB being monitored with ^{18}F-FDG-PET/CT should not be mistaken for differential response. Patients with TB-HIV may be started on anti-TB therapy and then later started on antiretroviral therapy. This can cause increased inflammation in existing TB lesions because of immune reconstitution and may be misinterpreted as poor response. A careful history, viral load CD4 count, and time of initiation of antiretroviral therapy are necessary

Table 2 Review Articles Where Monitoring Response With ^{18}F-FDG-PET/CT Highlighted

Author	Journal	Comment
Pelletier-Galarneau et al[71]	Semin Nucl Med 2017	Role of monitoring therapy in children highlighted
Gambhir et al[72]	Int J Infect Dis 2017	Role of monitoring therapy in EPTB underscored
Rockwood et al[73]	Expert Rev Respir Med 2016	Discusses ^{18}F-FDG-PET/CT as one of the biomarkers for monitoring TB therapy
Ankrah et al[14]	Clin Trans Imaging 2016	Highlights role of FDG and other PET tracer in monitoring therapy
Skoura et al[74]	Int J Infect Dis 2015	^{18}F-FDG-PET/CT is the preferred modality for assessing treatment response
Bomanji et al[75]	Cold Spring Harb Perspect Med	Highlights the role of ^{18}F-FDG in monitoring therapy
Vorster et al[76]	Curr Opin Pulm Med 2014	FDG monitoring of therapy is discussed as potentially the most important role of ^{18}F-FDG-PET in TB management
Sathekge et al[2]	Semin Nucl Med 2013	Emphasizes role in monitoring therapy especially in context of MDR and XDR
Sathekge et al[77]	Nucl Med Commun 2012	The role of ^{18}F-FDG-PET/CT and other nuclear medicine techniques in monitoring response is discussed

to give the correct interpretation of an ^{18}F-FDG-PET/CT used to monitor anti-TB.

Invasive Fungal Infections

IFIs are relatively uncommon but have a worldwide distribution, although certain species and are endemic in certain geographical areas. IFIs have a high morbidity and mortality if diagnosis and early initiation of appropriate therapy are delayed. Monitoring IFI therapy is extremely important as duration of therapy is not well established in some cases and given over long periods. Again, antifungal agents frequently have side effects, and resistance by fungi may develop.[81] Furthermore, IFIs frequently occur in patients with hematologic malignancies, and solid tumors, and in patients who have undergone organ transplant who are being considered for treatment or are already on therapies that would depress their immune system.[82] If IFIs are not properly treated before institution of such therapy, the infection may disseminate, resulting in high morbidity or even mortality in these patients.[16] In some IFIs, the fungi localize to the tissue after clearing from blood such as chronic disseminated candidiasis. In such cases, the conversion of blood culture from positive to negative may not indicate infection is cleared, and other biomarkers such as imaging will be important to determine the elimination of the IFI.

^{18}F-FDG-PET or PET/CT in Monitoring Antifungal Therapy in IFIs

FDG-PET has been used to monitor IFI usually correlating with clinical outcome.[83] In 1 case, ^{18}F-FDG-PET/CT was more accurate than MRI in showing disease progression when MRI findings remained unchanged.[84] In the literature, ^{18}F-FDG-PET/CT was useful to monitor therapy in different sites including lungs, skeleton, central nervous system, adrenals, and prosthetic heart valves.[85-89] ^{18}F-FDG-PET/CT has been used to determine duration of therapy led to cessation of antifungal therapy at a time when there was no resolution of the morphologic imaging.[90,91] ^{18}F-FDG-PET/CT also detected poor response to antifungal therapy, leading to a change of therapy with favorable outcome after the switch.[91-94] IFIs can be caused by a wide array of fungi, and FDG-PET/CT was useful in monitoring disease across a broad spectrum. Table 3 summarizes the relatively few studies available in literature on monitoring response with ^{18}F-FDG-PET or PET/CT in IFIs.

Alveolar Echinococcosis

Alveolar echinococcosis (AE) is a zoonotic parasitic infection caused by the larval stages (metacestode) of the *Echinococcus multilocularis* tapeworm found in the gut of carnivores. AE although a parasite, behaves like a malignancy and metastasizes or extends from the liver where infection usually begins. Complete surgical resection of hepatic AE offers the best prospect for cure; however, most patients have unresectable disease by the time of diagnosis.[96] Patients are thus subjected to lengthy and sometimes life-long antimicrobial treatment. Benzimidazoles are the only established drugs effective against AE. These drugs may produce significant and sometimes severe side effects and have a very high cost in terms of public health and the quality of life of the patient.[97] Attempts to interrupt life-long therapy require an accurate biomarker that is able to determine that there would be no recurrence on stopping the antiparasitic agent. Morphologic imaging modalities including ultrasound, CT, and MRI have not been useful for follow-up because neither the reduction in size of the lesion nor the presence of calcification is a reliable predictor of parasitic activity.[98,99]

^{18}F-FDG-PET/CT has been shown to be useful in monitoring patients with unresectable AE. It has been proposed as a surrogate marker for parasitic activity especially when combined with *E multilocularis*-specific serological testing by the expert consensus group for the diagnosis and management of cystic and AE in humans.[96] ^{18}F-FDG-PET/CT causes perilesional metabolic uptake in the AE lesions. Follow-up scans with FDG found rapid resolution of this metabolic uptake. Relapse of infection occurred in some patients with

Table 3 Original Articles of Monitoring Response in IFIs With ^{18}F-FDG-PET or PET/CT

Author	Journal and Year	Type of IFIs Evaluated	Comment
Franzius et al[85]	Clin Nucl Med 2001	*Aspergillus sp.*	Resolution of metabolic activity in pulmonary lesions on completion of therapy
Chamilos et al[95]	Med Mycol 2008	*Aspergillus* and *Zygomycosis spp.*	Metabolic resolution of infection when morphologic lesions persisted was a frequent finding
Teyton et al[91]	Clin Nucl Med 2009	*Candida sp.*	Detected poor response to antifungal therapy with resolution of IFI after therapy was changed
Avet et al[92]	Eur J Nucl Med Mol Imaging 2009	*Candida sp.*	Detected poor response to antifungal therapy with resolution of IFI after therapy was changed
Xu et al[93]	Clin Nucl Med 2010	*Candida sp.*	Detected poor response to antifungal therapy with resolution of IFI after therapy was changed, it also helped to determine duration of therapy
Hot et al[86]	Clin Microbiol Infect 2011	*Aspergillus, Candida, Coccidioidomycosis, Mycetoma, Phomopsis* and *Scedosporium spp.*	Useful in monitoring therapy in pulmonary and extrapulmonary sites of IFI including bones and joints. Helped determine duration of therapy. There was persistent metabolic uptake of unknown significance in a case of *Aspergillus sp.*
Miyazaki et al[90]	Ann Hematol 2011	Unidentified yeast-like fungi	Demonstrated metabolic response to antifungal when findings on morphologic imaging were unchanged
Wallner et al[89]	Herz 2013	*Candida sp.*	Demonstrated metabolic response in a bioprosthetic aortic valve
Liu et al[94]	Clin Nucl Med 2013	*Zygomycosis sp.*	Antifungal therapy was appropriately modified as a result of serial ^{18}F-FDG-PET/CT studies
Tsai et al[83]	Clin Imaging 2013	*Histoplamosis sp.*	Clinical outcome correlated with response demonstrated by ^{18}F-FDG-PET/CT
Dubbioso et al[87]	J Neurol Sci 2013	*Cryptococcus sp.*	Useful in monitoring intracranial IFI
Altini et al[84]	Clin Nucl Med 2015	*Zygomycosis sp.*	Metabolic uptake demonstrated increase uptake in keeping with worsening clinical disease when MRI did not show worsening of the rhino-orbito-cerebral IFI
Kasaliwal et al[88]	Clin Nucl Med 2014	*Histoplamosis sp.*	Metabolic disease activity in adrenal gland and nodes correlated with clinical outcome

rapid metabolic resolution whose treatment was stopped based on PET/CT findings alone.[100] One study evaluated the role of delayed imaging in the follow-up of patients with AE. The study evaluated 120 scans performed on 70 patients. PET/CT imaging was acquired at 3 hours after tracer injection instead of the conventional 1 hour. In 57 scans that were considered false negative on the 1-hour scan, definite lesions were identified in 22.8%, and in a further 10.8% such scans were considered indeterminate. Almost all the scans that had been reported as indeterminate on the 1-hour follow-up scan were positive on the delayed 3-hour imaging. In another study, the outcome of discontinuing long-term benzimidazole therapy in patients with unresectable AE with ^{18}F-FDG-PET/CT and anti-EmII/3-10 was evaluated in 34 patients. None of the 11 patients who had negative ^{18}F-FDG-PET/CT scan and anti-EmII/3-10 and were discontinued developed recurrent disease after they were followed up for a median of 70.5 months.[101] These studies indicate that a combination of 3-hour delayed ^{18}F-FDG-PET/CT and AE-specific serology provide the best in vivo biomarker for assessment of parasitic activity of AE.

Metabolic Dysfunction Associated With Antiretroviral Therapy in HIV

Antiretroviral therapy used in HIV usually is taken for life and given in combination, and side effect may occur. Lipodystrophy, a side effect that is associated commonly with antiretroviral drugs, has been described in up to 70% of patients.[102] HIV infection itself contributes to hypertriglyceridemia, insulin resistance, and other metabolic abnormalities that are not completely reversed by antiretroviral therapy.[103] Newer antiretroviral agents appear to have a better effect on lipid profile but are not completely devoid of these deleterious dyslipidemic effects.[104] The synergistic effect of these metabolic changes by both the infection and the antiretroviral therapy may pose higher risk

of comorbidities especially in aging HIV-infected patients.[103] It is important to detect these effects early and address the problems associated with the metabolic dysfunction.

Preliminary data suggest ^{18}F-FDG-PET/CT may be useful to monitor lipodystrophy in patients with HIV on antiretrovirals. In a prospective study that included a total of 39 patients with HIV, 11 patients with lipodystrophy were compared with 28 patients without lipodystrophy. Mean SUVmax for the subcutaneous tissue was higher in lipodystrophy patients and also correlated with the duration of HIV treatment.[105] In another study, extremity subcutaneous adipose tissue ^{18}F-FDG uptake was increased in association with reduced extremity fat. The study also found subcutaneous adipose ^{18}F-FDG uptake correlated to lipoatrophy present and positively associated with insulin resistance in patients with HIV with lipodystrophy.[106] These studies suggest ^{18}F-FDG may be a useful biomarker for lipodystrophy in patients with HIV; however, larger studies are needed to validate this.

FDG Monitoring in Other Conditions

The role of ^{18}F-FDG-PET in monitoring skeletal infections such as spondylodiscitis and vascular graft infection has already been discussed.[21-24]

Other PET Tracers

Preliminary data suggest a role for monitoring for other PET tracer such as Ga68 citrate, F18 ethylcholine, and C11 methionine.[107-109] In preclinical studies, ^{68}Ga labeled with triacetylfusarinine C and ferrioxamine E and [^{64}Cu] DOTA labeled *Aspergillus fumigatus*-specific monoclonal antibody are Aspergillus-specific tracers that may have a role in monitoring infections.[110,111] In TB, a tracer trehalose, a non-mammalian disaccharide is at the very early stage of development and has shown promise in TB imaging.[112] It has the potential of being used in monitoring response.

SPECT Tracers

In the past, tracers such as Ga67 citrate, thallium, and Tc-99m MIBI have been used in assessing response in fungal infections, osteomyelitis, and even TB.[113-115] New tracers that may be specific to organisms have been evaluated in their role for monitoring response such as Tc-99m-labeled fluconazole or Tc-labeled chitin or chitinase.[116-118] A SPECT tracer, Tc-99m ubiquicidin, that localizes to infection and not inflammation has been tested in humans and potentially has a role in therapy response.[119-121]

Conclusion and Future Perspectives

Molecular imaging allows in vivo, noninvasive, and quantitative assessment of biologic process, marking it a useful biomarker for infectious process over time. ^{18}F-FDG-PET/CT is the most commonly used PET radiotracer and is a useful biomarker for monitoring bacterial, fungal, parasitic, and side effects of viral treatment. ^{18}F-FDG-PET/CT has been found to be useful for monitoring infections that have complex and long therapies. Monitoring infection with FDG allows early detection of treatment failure, allowing a change of therapy. It has been shown to provide prognostic information by pretherapeutic evaluation or distinguishing responders from nonresponders. It is useful to provide a whole-body assessment of infection, allowing differential response of different lesions to be determined. Guidelines for the use of FDG in monitoring infection are generally lacking, but evidence for its use is mounting. Data are continuously emerging on the role of PET in assessing response. New tracers have been tested at preclinical and clinical level and are likely to dominate the field of assessing response and providing individualized therapy in the future.[122] Pathogen-specific tracers for both PET and SPECT at various stages of development would potentially play a role beyond the current role played by the nonspecific FDG tracer, including new serum biomarkers and drug development.

Conflict of Interest

No conflicts of interests.

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References

1. Weis S, Rubio I, Ludwig K, et al: Hormesis and defense of infectious disease. Int J Mol Sci 18:2017, E1273 [pii]
2. Sathekge M, Maes A, Van de Wiele C: FDG-PET imaging in HIV infection and tuberculosis. Semin Nucl Med 43:349-366, 2013
3. Morens DM, Folkers GK, Fauci AS: Emerging infections: A perpetual challenge. Lancet Infect Dis 8:710-719, 2008
4. Lederberg J: Infectious history. Science 288:287-293, 2000
5. Morens DM, Folkers GK, Fauci AS: The challenge of emerging and re-emerging infectious diseases. Nature 430:242-249, 2004, Erratum, Nature, 463 (2010), p. 122.
6. Albrich WC, Harbarth S: Pros and cons of using biomarkers versus clinical decisions in start and stop decisions for antibiotics in the critical care setting. Intensive Care Med 41:1739-1751, 2015
7. Shehabi Y, Seppelt I: Pro/Con debate: Is procalcitonin useful for guiding antibiotic decision making in critically ill patients? Crit Care 12:211, 2008
8. Kofoed K, Andersen O, Kronborg G, et al: Use of plasma C-reactive protein, procalcitonin, neutrophils, macrophage migration inhibitory factor, soluble urokinase-type plasminogen activator receptor, and soluble triggering receptor expressed on myeloid cells-1 in combination to diagnose infections: A prospective study. Crit Care 11:R38, 2007
9. Kutz A, Grolimund E, Christ-Crain M, et al: Pre-analytic factors and initial biomarker levels in community-acquired pneumonia patients. BMC Anesthesiol 14:102, 2014
10. Grace E, Turner RM: Use of procalcitonin in patients with various degrees of chronic kidney disease including renal replacement therapy. Clin Infect Dis 59:1761-1767, 2014

11. Nanni C, Boriani L, Salvadori C, et al: FDG PET/CT is useful for the interim evaluation of response to therapy in patients affected by haematogenous spondylodiscitis. Eur J Nucl Med Mol Imaging 39:1538-1544, 2012
12. Lodge MA: Repeatability of SUV in oncologic 18F-FDG PET. J Nucl Med 58:523-532, 2017
13. Vallabhajosula S: (18)F-labeled positron emission tomographic radiopharmaceuticals in oncology: An overview of radiochemistry and mechanisms of tumor localization. Semin Nucl Med 37:400-419, 2007
14. Ankrah AO, van der Werf TS, de Vries EF, et al: PET/CT imaging of *Mycobacterium tuberculosis* infection. Clin Transl Imaging 4:131-144, 2016
15. Glaudemans AW, de Vries EF, Galli F, et al: The use of (18)F-FDG-PET/CT for diagnosis and treatment monitoring of inflammatory and infectious diseases. Clin Dev Immunol 623036, 2013
16. Ankrah AO, Sathekge MM, Dierckx RA, et al: Imaging fungal infections in children. Clin Transl Imaging 4:57-72, 2016
17. El-Haddad G, Zhuang H, Gupta N, et al: Evolving role of positron emission tomography in the management of patients with inflammatory and other benign disorders. Semin Nucl Med 34:313-329, 2004
18. Kubota R, Kubota K, Yamada S, et al: Microautoradiographic study for the differentiation of intratumoral macrophages, granulation tissues and cancer cells by the dynamics of fluorine-18-fluorodeoxyglucose uptake. J Nucl Med 35:104-112, 1994
19. Rabkin Z, Israel O, Keidar Z: Do hyperglycemia and diabetes affect the incidence of false-negative 18F-FDG PET/CT studies in patients evaluated for infection or inflammation and cancer? A comparative analysis. J Nucl Med 51:1015-1020, 2010
20. Kagna O, Kurash M, Ghanem-Zouabi N: Does antibiotic treatment affect the diagnostic accuracy of FDG PET/CT studies in patients with suspected infectious processes? J Nucl Med 2017, doi:10.2967/jnumed.117.19206, In press
21. Riccio SA, Chu AK, Rabin HR, et al: Fluorodeoxyglucose positron emission tomography/computed tomography interpretation criteria for assessment of antibiotic treatment response in pyogenic spine infection. Can Assoc Radiol J 66:145-152, 2015
22. Kim SJ, Kim IJ, Suh KT, et al: Prediction of residual disease of spine infection using F-18 FDG PET/CT. Spine 34:2424-2430, 2009
23. Niccoli Asabella A, Iuele F, Simone F, et al: Role of (18)F-FDG PET/CT in the evaluation of response to antibiotic therapy in patients affected by infectious spondylodiscitis. Hell J Nucl Med 18:17-22, 2015 (suppl 1)
24. Husmann L, Sah BR, Scherrer A, et al: (18)F-FDG PET/CT for therapy control in vascular graft infections: A first feasibility study. J Nucl Med 56:1024-1029, 2015
25. Kruk ME, Schwalbe NR, Aguiar CA: Timing of default from tuberculosis treatment: A systematic review. Trop Med Int Health 13:703-712, 2008
26. Horsburgh CR, Barry CE, Lange C: Treatment of tuberculosis. N Engl J Med 373:2149-2160, 2015
27. Mitchison D, Davies G: The chemotherapy of tuberculosis: Past, present and future. Int J Tuberc Lung Dis 16:724-732, 2012
28. Gillespie SH, Crook AM, McHugh TD, et al: Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. N Engl J Med 371:1577-1587, 2014
29. Merle CS, Fielding K, Sow OB, et al: A four-month gatifloxacin-containing regimen for treating tuberculosis. N Engl J Med 371:1588-1598, 2014
30. Jawahar MS, Banurekha VV, Paramasivan CN, et al: Randomized clinical trial of thrice-weekly 4-month moxifloxacin or gatifloxacin containing regimens in the treatment of new sputum positive pulmonary tuberculosis patients. PLoS ONE 8:2013, e67030
31. Jindani A, Harrison TS, Nunn AJ, et al: High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. N Engl J Med 371:1599-1608, 2014
32. Johnson JL, Hadad DJ, Dietze R, et al: Shortening treatment in adults with noncavitary tuberculosis and 2-month culture conversion. Am J Respir Crit Care Med 180:558-563, 2009
33. Dheda K, Migliori GB: The global rise of extensively drug-resistant tuberculosis: Is the time to bring back sanatoria now overdue? Lancet 379:773-775, 2012
34. Mattila JT, Beaino W, Maiello P, et al: Positron emission tomography imaging of macaques with tuberculosis identifies temporal changes in granuloma glucose metabolism and integrin $\alpha4\beta1$-expressing immune cells. J Immunol 199:806-815, 2017
35. Pratt PC: Pathology of tuberculosis. Semin Roentgenol 14:196-203, 1979
36. Lee HS, Oh JY, Lee JH, et al: Response of pulmonary tuberculomas to anti-tuberculos treatment. Eur Respir J 23:452-455, 2004
37. Rom WN, Garay SM: Tuberculosis. New York, Little, Brown and Company, 1996, pp 373-412
38. Khan MA, Kovnat DM, Bachus B, et al: Clinical and roentgenographic spectrum of pulmonary tuberculosis in the adult. Am J Med 62:31-38, 1977
39. Culver GJ, Concannon JP, McManus JE: Pulmonary tuberculomas: Pathogenesis, diagnosis, and management. J Thorac Surg 20:798-822, 1950
40. Ichiya Y, Kuwabara Y, Sasaki M, et al: FDG-PET in infectious lesions: The detection and assessment of lesion activity. Ann Nucl Med 10:185-191, 1996
41. Lefebvre N, Argemi X, Meyer N, et al: Clinical usefulness of ^{18}F-FDG PET/CT for initial staging and assessment of treatment efficacy in patients with lymph node tuberculosis. Nucl Med Biol 50:17-24, 2017
42. Stelzmueller I, Huber H, Wunn R, et al: 18F-FDG PET/CT in the initial assessment and for follow-up in patients with tuberculosis. Clin Nucl Med 41:e187-e194, 2016
43. Arbind A, D'souza M, Jaimini A, et al: Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography imaging in response monitoring of extra-pulmonary tuberculosis. Indian J Nucl Med 31:59-61, 2016
44. Liu Q, Via LE, Luo T, et al: Within patient microevolution of *Mycobacterium tuberculosis* correlates with heterogeneous responses to treatment. Sci Rep 5:17507, 2015
45. Lenaerts A, Barry CE, Dartois V: Heterogeneity in tuberculosis pathology, microenvironments and therapeutic responses. Immunol Rev 264:288-307, 2015
46. Chen RY, Dodd LE, Lee M, et al: PET/CT imaging correlates with treatment outcome in patients with multidrug-resistant tuberculosis. Sci Transl Med 6:265ra166, 2014
47. Coleman MT, Chen RY, Lee M, et al: PET/CT imaging reveals a therapeutic response to oxazolidinones in macaques and humans with tuberculosis. Sci Transl Med 6:265ra167, 2014
48. Santhosh S, Bhattacharya A, Rana SS, et al: Pancreatic tuberculosis: Evaluation of therapeutic response using F-18 fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography. Indian J Nucl Med 29:257-259, 2014
49. Ghesani N, Patrawalla A, Lardizabal A, et al: Increased cellular activity in thoracic lymph nodes in early human latent tuberculosis infection. Am J Respir Crit Care Med 189:748-750, 2014
50. Dureja S, Sen IS, Acharya S: Potential role of F18 FDG PET-CT as an imaging biomarker for noninvasive evaluation in uncomplicated skeletal tuberculosis: A prospective clinical observational study. Eur Spine J 23:2449-2454, 2014
51. Lin PL, Coleman T, Carney JP, et al: Radiologic responses in cynomolgus macaques for assessing tuberculosis chemotherapy regimens. Antimicrob Agents Chemother 57:4237-4244, 2013
52. Via LE, Schimel D, Weiner DM, et al: Infection dynamics and response to chemotherapy in a rabbit model of tuberculosis using [(18)F]2-fluoro-deoxy-d-glucose positron emission tomography and computed tomography. Antimicrob Agents Chemother 56:4391-4402, 2012
53. Martinez V, Castilla-Lievre MA, Guillet-Caruba C, et al: (18)F-FDG PET/CT in tuberculosis: An early non-invasive marker of therapeutic response. Int J Tuberc Lung Dis 16:1180-1185, 2012
54. Yadla M, Sivakumar V, Kalawat T: Assessment of early response to treatment in extrapulmonary tuberculosis: Role of FDG-PET. Indian J Nucl Med 27:136-137, 2012

55. Park YH, Yu CM, Kim ES, et al: Monitoring therapeutic response in a case of extrapulmonary tuberculosis by serial F-18 FDG PET/CT. Nucl Med Mol Imaging 46:69-72, 2012
56. Sathekge M, Maes A, D'Asseler Y, et al: Tuberculous lymphadenitis: FDG PET and CT findings in responsive and nonresponsive disease. Eur J Nucl Med Mol Imaging 39:1184-1190, 2012
57. Sathekge M, Maes A, Kgomo M, et al: Use of 18F-FDG-PET to predict response to first-line tuberculostatics in HIV-associated tuberculosis. J Nucl Med 52:880-885, 2011
58. Tian G, Xiao Y, Chen B, et al: FDG PET/CT for therapeutic response monitoring in multi-site non-respiratory tuberculosis. Acta Radiol 51:1002-1006, 2010
59. Harisankar C, Mittal BR, Bhattacharya A, et al: FDG-PET/CT in diagnosis and early response evaluation of extra-pulmonary tuberculosis in a patient with aplastic anemia. J Postgrad Med 56:219-221, 2010
60. Demura Y, Tsuchida T, Uesaka D, et al: Usefulness of 18F-fluorodeoxyglucose positron emission tomography for diagnosing disease activity and monitoring therapeutic response in patients with pulmonary mycobacteriosis. Eur J Nucl Med Mol Imaging 36:632-639, 2009
61. Davis SL, Nuermberger EL, Um PK, et al: Noninvasive pulmonary [18F]-2-fluoro-deoxy-D-glucose positron emission tomography correlates with bactericidal activity of tuberculosis drug treatment. Antimicrob Agents Chemother 53:4879-4884, 2009
62. Park IN, Ryu JS, Shim TS: Evaluation of therapeutic response of tuberculoma using F-18 FDG positron emission tomography. Clin Nucl Med 33:1-3, 2008
63. Hofmeyr A, Lau WF, Slavin MA: *Mycobacterium tuberculosis* infection in patients with cancer, the role of 18-fluorodeoxyglucose positron emission tomography for diagnosis and monitoring treatment response. Tuberculosis (Edinb) 87:459-463, 2007
64. Murawski AM, Gurbani S, Harper JS, et al: Imaging the evolution of reactivation pulmonary tuberculosis in mice using 18F-FDG PET. J Nucl Med 55:1726-1729, 2014
65. Driver ER, Ryan GJ, Hoff DR, et al: Evaluation of a mouse model of necrotic granuloma formation using C3HeB/FeJ mice for testing of drugs against *Mycobacterium tuberculosis*. Antimicrob Agents Chemother 56:3181-31895, 2012
66. Irwin SM, Gruppo V, Brooks E, et al: Limited activity of clofazimine as a single drug in a mouse model of tuberculosis exhibiting caseous necrotic granulomas. Antimicrob Agents Chemother 58:4026-4034, 2014
67. Kjellsson MC, Via LE, Goh A, et al: Pharmacokinetic evaluation of the penetration of antituberculosis agents in rabbit pulmonary lesions. Antimicrob Agents Chemother 56:446-457, 2012
68. Ryu JS, Kim L, Kim WC, et al: Interpretation of a heterogeneous radiological response as tumor heterogeneity or a non-tumor diagnosis: A case report. Oncol Lett 10:2953-2956, 2015
69. Malherbe ST, Shenai S, Ronacher K, et al: Persisting PET-CT lesion activity and *M. tuberculosis* mRNA after pulmonary tuberculosis cure. Nat Med 2:1094-1100, 2016
70. Heysell SK, Thomas TA, Sifri CD, et al: 18-Fluorodeoxyglucose positron emission tomography for tuberculosis diagnosis and management: A case series. BMC Pulm Med 13:14, 2013
71. Pelletier-Galarneau M, Martineau P, Zuckier LS, et al: 18F-FDG-PET/CT imaging of thoracic and extrathoracic tuberculosis in children. Semin Nucl Med 47:304-318, 2017
72. Gambhir S, Ravina M, Rangan K, et al: Imaging in extrapulmonary tuberculosis. Int J Infect Dis 56:237-247, 2017
73. Rockwood N, du Bruyn E, Morris T, et al: Assessment of treatment response in tuberculosis. Expert Rev Respir Med 10:643-654, 2016
74. Skoura E, Zumla A, Bomanji J: Imaging in tuberculosis. Int J Infect Dis 32:87-93, 2015
75. Bomanji JB, Gupta N, Gulati P, et al: Imaging in tuberculosis. Cold Spring Harb Perspect Med 5:a017814, 2015
76. Vorster M, Sathekge MM, Bomanji J: Advances in imaging of tuberculosis: The role of ^{18}F-FDG PET and PET/CT. Curr Opin Pulm Med 20:287-293, 2014
77. Sathekge M, Maes A, D'Asseler Y, et al: Nuclear medicine imaging in tuberculosis using commercially available radiopharmaceuticals. Nucl Med Commun 33:581-590, 2012
78. Ankrah AO, Glaudemans AW, Klein HC, et al: The role of nuclear medicine in the staging and management of human immune deficiency virus infection and associated diseases. Nucl Med Mol Imaging 51:127-139, 2017
79. Mhlanga JC, Durand D, Tsai HL, et al: Differentiation of HIV-associated lymphoma from HIV-associated reactive adenopathy using quantitative FDG PET and symmetry. Eur J Nucl Med Mol Imaging 41:596-604, 2014
80. Sathekge M: Differentiation of HIV-associated lymphoma from HIV-reactive adenopathy using quantitative FDG-PET and symmetry. Eur J Nucl Med Mol Imaging 41:593-595, 2014
81. Ankrah AO, Klein HC, Span LF, et al: The role of PET in monitoring therapy in fungal infections. Curr Pharm Des 2017, in press
82. Signore A, Glaudemans AW, Gheysens O, et al: Nuclear medicine imaging in pediatric infection or chronic inflammatory diseases. Semin Nucl Med 47:286-303, 2017
83. Tsai YJ, Lin YH, Hsu CH, et al: 18F-fluorodeoxyglucose positron emission tomography for the initial evaluation and monitoring of therapeutic response in bilateral adrenal histoplasmosis. Clin Imaging 37:791-793, 2013
84. Altini C, Niccoli Asabella A, Ferrari C, et al: (18)F-FDG PET/CT contribution to diagnosis and treatment response of rhino-orbital-cerebral mucormycosis. Hell J Nucl Med 18:68-70, 2015
85. Franzius C, Biermann M, Hülskamp G, et al: Therapy monitoring in aspergillosis using F-18 FDG positron emission tomography. Clin Nucl Med 26:232-233, 2001
86. Hot A, Maunoury C, Poiree S, et al: Diagnostic contribution of positron emission tomography with [18F]fluorodeoxyglucose for invasive fungal infections. Clin Microbiol Infect 17:409-417, 2011
87. Dubbioso R, Pappatà S, Quarantelli M, et al: Atypical clinical and radiological presentation of cryptococcal choroid plexitis in an immunocompetent woman. J Neurol Sci 334:180-182, 2013
88. Kasaliwal R, Malhotra G, Bukan A, et al: 18F-FDG PET as a monitoring tool to assess treatment response in bilateral adrenal histoplasmosis. Clin Nucl Med 39:576-578, 2014
89. Wallner M, Steyer G, Krause R, et al: Fungal endocarditis of a bioprosthetic aortic valve. Pharmacological treatment of a *Candida parapsilosis* endocarditis. Herz 38:431-434, 2013
90. Miyazaki Y, Nawa Y, Nakase K, et al: FDG-PET can evaluate the treatment for fungal liver abscess much earlier than other imagings. Ann Hematol 90:1489-1490, 2011
91. Teyton P, Baillet G, Hindié E, et al: Hepatosplenic candidiasis imaged with F-18 FDG PET/CT. Clin Nucl Med 34:439-440, 2009
92. Avet J, Granjon D, Prevot-Bitot N, et al: Monitoring of systemic candidiasis by 18F-FDG PET/CT. Eur J Nucl Med Mol Imaging 36:1900, 2009
93. Xu B, Shi P, Wu H, et al: Utility of FDG PET/CT in guiding antifungal therapy in acute leukemia patients with chronic disseminated candidiasis. Clin Nucl Med 35:567-570, 2010
94. Liu Y, Wu H, Huang F, et al: Utility of 18F-FDG PET/CT in diagnosis and management of mucormycosis. Clin Nucl Med 38:e370-e371, 2013
95. Chamilos G, Macapinlac HA, Kontoyiannis DP: The use of 18F-fluorodeoxyglucose positron emission tomography for the diagnosis and management of invasive mould infections. Med Mycol 46:23-29, 2008
96. Brunetti E, Kern P, Vuitton DA, et al: Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. Acta Trop 114:1-19, 2010
97. Torgerson PR, Schweiger A, Deplazes P, et al: Alveolar echinococcosis: From a deadly disease to a relatively well-controlled infection. Relative survival and economic analysis in Switzerland over the past 35 years. J Hepatol 48:72-77, 2008
98. Ehrhardt AR, Reuter S, Buck AK, et al: Assessment of disease activity in alveolar echinococcosis: A comparison of contrast enhanced ultrasound, three-phase helical CT and [^{18}F] fluorodeoxyglucose positron emission tomography. Abdom Imaging 32:730-736, 2007

99. Caoduro C, Porot C, Vuitton DA: The role of delayed 18F-FDG PET imaging in the follow-up of patients with alveolar echinococcosis. J Nucl Med 54:358-363, 2013
100. Reuter S, Buck A, Manfras B, et al: Structured treatment interruption in patients with alveolar echinococcosis. Hepatology 39:509-517, 2004
101. Ammann RW, Stumpe KD, Grimm F, et al: Outcome after discontinuing long-term benzimidazole treatment in 11 patients with non-resectable alveolar echinococcosis with negative FDG-PET/CT and anti-EmII/3-10 serology. PLoS Negl Trop Dis 9:e0003964, 2015
102. Fiorenza CG, Chou SH, Mantzoros CS: Lipodystrophy: Pathophysiology and advances in treatment. Nat Rev Endocrinol 7:137-150, 2011
103. Calvo M, Martinez E: Update on metabolic issues in HIV patients. Curr Opin HIV AIDS 9:332-339, 2014
104. Srinivasa S, Grinspoom SK: Metabolic and body composition effects of newer antiretrovirals in HIV infected patients. Eur J Endocrinol 170:R185-R202, 2014
105. Sathekge M, Maes A, Kgomo M, et al: Evaluation of glucose uptake by skeletal muscle tissue and subcutaneous fat in HIV-infected patients with and without lipodystrophy using FDG- PET. Nucl Med Commun 31:311-314, 2010
106. Torriaini M, Zanni MV, Fitch K, et al: Increase FDG uptake associated with reduced extremity fat in HIV patients. Antivir Ther 18:243-248, 2013
107. D'Souza MM, Sharma R, Jaimini A, et al: Metabolic assessment of intracranial tuberculomas using 11C-methionine and 18F-FDG PET/CT. Nucl Med Commun 33:408-414, 2012
108. Vorster M, Stoltz A, Jacobs AG, et al: Imaging of pulmonary tuberculosis with 18f-fluoro-deoxy-glucose and 18F-ethylcholine. Open Nucl Med J 6:17-21, 2014
109. Vorster M, Maes A, Van de Wiele C, et al: 68Ga-citrate PET/CT in tuberculosis: A pilot study. Q J Nucl Med Mol Imaging 2014, In press
110. Haas H, Petrik M, Decristoforo C: An iron-mimicking, Trojan horse-entering fungi—Has the time come for molecular imaging of fungal infections? PLoS Pathog 11:e1004568, 2015
111. Rolle AM, Hasenberg M, Thornton CR, et al: ImmunoPET/MR imaging allows specific detection of *Aspergillus fumigatus* lung infection in vivo. Proc Nat Acad Sci USA 113:E1026-E1033, 2016
112. Rundell SR, Wagar ZL, Meints LM, et al: Deoxyfluoro-d-trehalose (FDTre) analogues as potential PET probes for imaging mycobacterial infection. Org Biomol Chem 14:8598-8609, 2016
113. Tzen KY, Yen TC, Lin KJ: Value of Ga-67 SPECT in monitoring the effects of therapy in invasive aspergillosis of the sphenoid sinus. Clin Nucl Med 24:938-941, 1999
114. Schuster DM, Alazraki N: Gallium and other agents in diseases of the lung. Semin Nucl Med 32:193-211, 2002
115. Onsel C, Sönmezoglu K, Camsari G: Technetium-99m-MIBI scintigraphy in pulmonary tuberculosis. J Nucl Med 37:233-238, 1996
116. Lupetti A, de Boer MG, Erba P, et al: Radiotracers for fungal infection imaging. Med Mycol 49:S62-S69, 2011 (suppl 1)
117. Siaens R, Eijsink VG, Vaaje-Kolstad G, et al: Synthesis and evaluation of a 99mTechnetium labeled chitin-binding protein as potential specific radioligand for the detection of fungal infections in mice. Q J Nucl Med Mol Imaging 50:155-166, 2006
118. Siaens R, Eijsink VG, Dierckx R, et al: [123]I-Labeled chitinase as specific radioligand for in vivo detection of fungal infections in mice. J Nucl Med 45:1209-1216, 2004
119. Ebenhan T, Zeevaart JR, Venter JD, et al: Preclinical evaluation of 68Ga-labeled 1,4,7-triazacyclononane-1,4,7-triacetic acid-ubiquicidin as a radioligand for PET infection imaging. J Nucl Med 55:308-314, 2014
120. Ebenhan T, Chadwick N, Sathekge MM, et al: Peptide synthesis, characterization and ^{68}Ga-radiolabeling of NOTA-conjugated ubiquicidin fragments for prospective infection imaging with PET/CT. Nucl Med Biol 41:390-400, 2014
121. Lawal I, Zeevaart JR, Ebenhan T, et al: Metabolic Imaging of Infection. J Nucl Med 2017, jnumed.117.191635 [pii]. In press
122. Mahon RN, Hafner R: Applying precision medicine and immunotherapy advances from oncology to host-directed therapies for infectious diseases. Front Immunol 8:688, 2017