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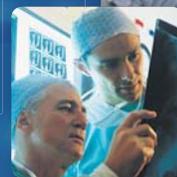
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HEALTH TECHNOLOGY ASSESSMENT RAPID REVIEW

HTA
June 2008

**FDG-PET to Assess Infections:
A Review of the Evidence**



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CADTH
600-865 Carling Avenue
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Tel. (613) 226-2553
Fax. (613) 226-5392
E-mail: pubs@cadth.ca

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Canadian Agency for Drugs and Technologies in Health

FDG-PET to Assess Infections: A Review of the Evidence

Eva Tsakonas, BA MSc¹
Kristen Moulton, BA²
Carolyn Spry, MLIS³

June 2008

¹ Independent Consultant

² Research Assistant, HTA, Canadian Agency for Drugs and Technologies in Health, Ottawa, Ontario

³ Information Specialist, HTIS, Canadian Agency for Drugs and Technologies in Health, Ottawa, Ontario



Canadian Agency for
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HEALTH TECHNOLOGY INQUIRY SERVICE (HTIS)

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The Health Technology Inquiry Service (HTIS) provides Canadian health care decision makers with HTA information, based on the best available evidence, in a quick and efficient manner. Inquiries related to the assessment of health care technologies (drugs, devices, diagnostic tests, and medical and surgical procedures) are accepted by the service. Information provided by the HTIS is tailored to meet the needs of decision makers, taking into account the urgency, importance, and potential impact of the request.

Consultations with the requestor of this HTIS assessment indicated that a review of the literature would be beneficial. The research question and selection criteria were developed in consultation with the requestor. The literature search was carried out by an information specialist using a standardized search strategy. The review of evidence was prepared by one researcher. The draft report was internally reviewed and externally peer-reviewed by two or more peer reviewers. All comments were reviewed internally to ensure that they were addressed appropriately.

Reviewers

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These individuals kindly provided comments on this report:

Peter Hollett, FRCP(C) Nuclear Medicine, ABNM MD Divisional Chief, Nuclear Medicine Department of Medical Imaging Eastern Health St. John's, Newfoundland and Labrador	Steven Kymes, PhD MHA Research Assistant Professor Washington University School of Medicine St. Louis, Missouri
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EXECUTIVE SUMMARY

Title: FDG-PET to Assess Infections: A Review of the Evidence

Date: June 2008

Context and Policy Issues

Fluorodeoxyglucose-positron emission tomography (FDG-PET) is a nuclear medicine imaging technology whose use in the detection and evaluation of infections is an emerging indication. FDG-PET is currently used in the diagnosis and management of cancers, heart conditions, and neurological conditions. Patient groups with infection that could potentially benefit from the use of FDG-PET include patients with skeletal or soft-tissue infections, immunosuppressed (HIV) patients, cancer patients, and patients requiring monitoring of therapeutic response. This technology could have important implications for disease management and patient outcomes if its use leads to earlier and more precise diagnosis, potentially preventing morbidity and mortality in a wide variety of conditions.

Because this technology may have wide application in infection, the potential addition to the current patient base could be significant. At the same time, the cost of operating this technology is relatively high compared with other diagnostic methods. A Canadian study estimated the average per-service costs to be between \$1,231 and \$7,869 (depending on annual throughput), and Alberta and British Columbia charge about \$1,250 and \$1,500, respectively, per scan for out-of-province residents.

There is no Canadian guidance on the use of FDG-PET in infections at the present time. The purpose of this report was to research and critically appraise the recent evidence on the effectiveness, safety, cost-effectiveness, and clinical impact of FDG-PET compared with other imaging methods in the diagnosis and management of infection, with the objective of

informing guidance and policy on the use of FDG-PET for this indication.

Research Questions

1. What is the evidence for the safety and clinical effectiveness of FDG-PET compared to other imaging techniques for the detection, characterization, or management of infections?
2. What is the cost-effectiveness of FDG-PET compared to other imaging techniques for the detection, characterization, or management of infections?
3. What is the evidence that FDG-PET alters or improves treatment of patients with infection?

Methods

Published literature was obtained by cross-searching Ovid's MEDLINE and EMBASE databases. Web sites of regulatory agencies, and health technology assessment and related agencies, were also searched, as were specialized databases such as those of the University of York's Centre for Reviews and Dissemination and The Cochrane Library (Issue 1, 2008). The Google™ search engine was used to search for a variety of information on the Internet.

Results include English language articles published between 2003 and March 2008 for systematic reviews and health technology assessments, and between 2005 and March 2008 for randomized controlled trials, observational studies, and economic evaluations.

The Centre for Evidence-Based Medicine (CEBM) tools for critical appraisal of systematic reviews and of diagnostic studies were used to evaluate the studies in this review.

Summary of Findings

Evidence identified for the clinical effectiveness of FDG-PET compared with other imaging techniques included two meta-analyses and seven prospective observational diagnostic studies. One retrospective observational study reported on the impact of FDG-PET in altering

the treatment of patients with infection. Studies addressing safety issues and cost-effectiveness were not identified.

a) Evidence for Clinical Effectiveness of FDG-PET in Infections

For osteomyelitis, FDG-PET was suggested to be superior to several other imaging techniques in one meta-analysis, while less effective than MRI in one observational study, and useful only in the follow-up of patients in another observational study comparing it to single photon emission computed tomography (SPECT). Meta-analyses of FDG-PET in peripheric bone and prosthetic joint implants, and in infections of the vertebral column suggested superior accuracy of FDG-PET compared with other imaging methods. An observational study also found superiority of FDG-PET in detecting periprosthetic hip infection, compared with scintigraphy. FDG-PET was found to be superior to MRI in the differentiation of Charcot's neuropathic arthropathy. Conclusions differed in two studies of FDG-PET in patients with multiple infection indications, with each study using different imaging methods as comparators.

A non-comparative retrospective study evaluated the use of FDG-PET in the diagnosis and management of invasive mould infections in 16 patients, and found this technology to be helpful in the clinical management of 10 (~60%).

b) Quality Assessment

The meta-analysis in osteomyelitis reported methodological shortcomings with the studies it

included in its analysis. In addition, the meta-analysis of peripheric post-traumatic and prosthetic infection, and of infections of the vertebral column, had limitations with its methodology. A critical appraisal of the seven diagnostic observational studies included in this report indicated appropriate methods in the majority of attributes in most studies; however, there exists an overall potential bias in ascertaining the reference standard.

c) Limitations

In spite of the wide range of potential indications for FDG-PET in infection and the numerous possible comparators, very few studies were retrieved within the parameters set for this review. There was no evidence on the safety of FDG-PET, and little evidence on this technology's ability to affect treatment and outcome in patients with infections. Despite the relative cost of FDG-PET and its potential patient base, economic data were lacking.

Conclusions and Implications for Decision or Policy Making

Although suggestive of relative effectiveness in some indications, there is a lack of high-level evidence regarding the effectiveness of FDG-PET across indications and within a range of comparators. More intensive studies or systematic reviews and analyses of specific indications are needed, as well as evidence for this technology's potential to alter patient treatment and outcomes. Assessments of cost-effectiveness and of the possible impact on resource allocation and wait times are also required.

1 CONTEXT AND POLICY ISSUES

Fluorodeoxyglucose-positron emission tomography (FDG-PET) is a nuclear medicine imaging technology that allows detailed diagnostic measurement of physiological and biochemical bodily processes.¹ F18-fluorodeoxyglucose, a radioactive sugar molecule, is injected into the bloodstream and a PET scanner is then used to detect high rates of glucose metabolism, which can be linked to many different diseases.^{2,3} This technology is commonly used to detect and evaluate different types of cancer, to examine brain function, or to assess coronary conditions.² The detection and evaluation of infections is an emerging indication for FDG-PET.

There are several patient groups with infection that could potentially benefit from the use of FDG-PET.^{4,5} Included are patients with abdominal and chest infections; skeletal infections such as chronic osteomyelitis, diabetic foot disease, Charcot's foot; and infected prostheses. Also included are patients with soft-tissue infections such as vascular graft infections, or infections that may be the underlying cause of fever of unknown origin (FUO). Other applications include the differentiation of central nervous system lymphomas from toxoplasmosis in immunosuppressed (HIV) patients, as well as the monitoring of infection in hematological cancers, and the monitoring of therapeutic response in the treatment of infections.

If FDG-PET leads to earlier and more precise diagnosis, as well as better monitoring of infections, this would have important implications for disease management and patient outcomes. Early detection of diabetic foot infection is important as infection can progress rapidly,⁶ and 16% of cases of osteomyelitis of the diabetic foot will require amputation.⁷ Prompt diagnosis of osteomyelitis, in general, helps to prevent sepsis, chronic infection, and deforming bone damage.⁸ Early diagnosis and treatment are also important in vascular graft infection because of relatively high rates of amputation and death.⁹ Accurate and prompt identification of the

underlying cause of FUO may significantly improve patient management.⁵ Differentiation of septic from aseptic painful joint prostheses is challenging, but key, as the treatment of the two conditions is very different and proper identification has implications for patient management and outcome.¹⁰

Given the wide application that this technology may have in the diagnosis and monitoring of infection, the potential patient base in which it might be used could be significant in the aggregate. The annual rate of diabetic foot infection is estimated at 36.5 per 1,000 patients with diabetes in settings with good access to health care,⁶ and approximately 15% of patients with diabetes will develop foot osteomyelitis during the course of their disease.¹¹ Among 58,351 patients undergoing hip and knee replacement surgery in Canada in 2005 to 2006, 780 (1.3%) were diagnosed with infection of the joint within one year of surgery. This estimate, however, reflects only patients who were hospitalized and not those managed at home or in other settings.¹² In addition, this does not represent the number of patients presenting with painful joints due to loosening prostheses that would also require evaluation with FDG-PET in order to determine the cause of symptoms. Many patients with leukemia and non-Hodgkin's lymphoma could develop infection during the course of their disease; there were an estimated 11,000 new cases of leukemia and non-Hodgkin's lymphoma in Canada in 2007.¹³ Fever of unknown origin is a common reason for presentation in emergency rooms and for hospital admissions. Infection is estimated to account for 20% to 30% of cases of FUO.¹⁴

A Canadian study that estimated the costs of operating a PET centre found average per-service costs ranged from \$1,231 to \$7,869, depending on the range of annual throughput (with a larger number of scans resulting in lower average costs). Marginal costs range from \$263 to \$332 per service, again depending on throughput.¹⁵ Alberta and British Columbia charge about \$1,250 and \$1,500, respectively, per FDG-PET scan for out-of-province residents, and private Canadian facilities charge approximately twice this amount.³ In comparison, the cost of

magnetic resonance imaging (MRI) at a private Canadian facility is approximately \$750, and a bone scan is approximately \$600. The Ontario Health Insurance Plan reimburses \$151 for a bone scintigraphy with single photon emission computed tomography (SPECT).¹⁶

As of November 2007, there were 22 centers performing publicly funded PET scans in seven Canadian provinces.¹⁷ Approximately 31,600 PET scans will be publicly funded in Alberta, British Columbia, Manitoba, New Brunswick, Nova Scotia, and Quebec in 2008, with 21,000 of these scans being conducted in Quebec.¹⁷ PET scanning is currently not an insured health service in Ontario, however, Ontario provides funding for PET scans through clinical trials, registry studies, and the Ontario PET Access Program.^{17,18} There is no Canadian guidance for the use of FDG-PET in infections at the present time.

FDG-PET has several comparators in the assessment of infections. Other imaging technologies currently being used or studied in the diagnosis of infection include radiographs, ultrasound, SPECT, and MRI.^{8,19,20} Nuclear imaging methods may use different types of intravenous radioactive tracers, including 99m technetium compounds, labelled leukocytes, and gallium.^{2,21}

Given FDG-PET's emergence in the assessment of infections and the potential number of patients in which this technology may be used, an assessment of the existing evidence is required as a step towards informing policy. The purpose of this report is to research and critically appraise the recent evidence on the effectiveness, safety, cost-effectiveness, and clinical impact of FDG-PET compared with other imaging methods in the diagnosis and management of infection, with the objective of informing guidance and policy on the use of FDG-PET in this indication.

2 RESEARCH QUESTIONS

1. What is the evidence for the safety and clinical effectiveness of FDG-PET

- compared to other imaging techniques for the detection, characterization, or management of infections?
2. What is the cost-effectiveness of FDG-PET compared to other imaging techniques for the detection, characterization, or management of infections?
3. What is the evidence that FDG-PET alters or improves treatment of patients with infection?

3 METHODS

Published literature was obtained by cross-searching Ovid's MEDLINE and Ovid's EMBASE databases. Web sites of regulatory agencies, and health technology assessment and related agencies, were also searched, as were specialized databases such as those of the University of York's Centre for Reviews and Dissemination and The Cochrane Library (Issue 1, 2008). The Google™ search engine was used to search for a variety of information on the Internet.

Regular alerts were established on MEDLINE and EMBASE, and information retrieved via alerts is current to April 22, 2008. Results include articles published between 2003 and March 2008 for systematic reviews and health technology assessments, and between 2005 and March 2008 for randomized controlled trials, observational studies, and economic evaluations. The results are limited to English language publications only. Filters were applied to limit the retrieval to systematic reviews and health technology assessments, randomized controlled trials, observational studies, and economic evaluations.

Studies were screened and selected for inclusion by two independent reviewers (ET, KM). Any differences in the selection of papers were resolved by discussion and consensus.

The Centre for Evidence-Based Medicine (CEBM)²² tools for critical appraisal of systematic reviews and of diagnostic studies were used to evaluate the studies included in this review.

4 SUMMARY OF FINDINGS

The initial screening criteria allowed any observational studies, randomized controlled trials, HTAs, reviews and meta-analyses, and economic evaluations of FDG-PET in infection to be considered for further screening. A total of 28 papers were retrieved for further consideration for inclusion in this review. Reasons for final exclusion of papers were: reviews that were not systematic, lack of a comparator, an indication other than infection, case reports, FDG-PET was not evaluated, or the publication was outside of the retrieval date range.

Evidence found for the clinical effectiveness of FDG-PET compared with other imaging techniques included two meta-analyses (one of which conducted a systematic review) and seven prospective observational diagnostic studies. Studies addressing safety issues were not identified. No health technology assessments or randomized controlled trials were retrieved, nor were studies evaluating the cost-effectiveness of FDG-PET compared with other imaging techniques. One retrospective observational study reported on the impact of FDG-PET in altering the treatment of patients with infection.

4.1 Evidence for the Clinical Effectiveness of FDG-PET in Infections

4.1.1 Systematic review and meta-analyses

A systematic review and meta-analysis that reported on the accuracy of diagnostic imaging for the assessment of chronic osteomyelitis was published in 2005 by Termaat *et al.*²¹ A total of 126 studies published from 1975 to 2003 were considered for the review. The search was restricted to primary studies that were written in English and involved adults who were at least 19- years-old. A study was eligible for inclusion if it was a clinical investigation that evaluated the

specific diagnostic tests in defined chronic osteomyelitis, if the study group included ten or more patients, if the study used a valid reference test, and if study details permitted the reconstruction of the results of the index tests by disease status. The 23 studies included in the report summarized findings on the diagnostic accuracy of radiography (2), magnetic resonance imaging (5), computed tomography (1), bone scintigraphy (7), leukocyte scintigraphy (13), gallium scintigraphy (1), combined scintigraphy (9), and FDG-PET (4). A total of 1,269 diagnostic evaluations were included for patients with (n=687) and without (n=582) chronic osteomyelitis. All of the included studies had a level-of-evidence rating of III (non-consecutive study or study without consistently applied reference standards), with the reference test not being applied independently or blindly in nineteen. In the four studies where an independent blind comparison was performed, it was done in either non-consecutive patients or in a narrow spectrum of patients.

The sensitivity and specificity estimates from the FDG-PET studies were homogeneous ($Q_{sens}=0.23$, $Q_{spec}=0.51$, $df=3$). (See Appendix 3 for definitions of terms.) Pooled sensitivity of FDG-PET was significantly higher than that of other tests ($p<0.05$), estimated at 96% (95% CI: 88% to 99%). Pooled specificity of FDG-PET (91%, 95% CI: 81% to 95%) was significantly higher than that of leukocyte scintigraphy, bone scintigraphy, and MRI, but not significantly different from combined bone and leukocyte scintigraphy, and combined bone and gallium scintigraphy. Pooled sensitivities and specificities from this meta-analysis are provided in Table 1. While the results of this study suggested that FDG-PET has a comparatively high accuracy in osteomyelitis, they must be interpreted with care, primarily because many of the studies included in this analysis contained methodological flaws, including lack of a valid reference test, non-independent selection of patients for the reference test, non-independent comparison of the index test, and no accounting for reproducibility of the imaging technique.

Table 1: Meta-analysis of diagnostic imaging in osteomyelitis, Termaat (2005)²¹

Diagnostic Tests	Sensitivity (95% CI)	Specificity (95% CI)
FDG-PET	96% (88-99%)	91% (81-95%)
BS	82% (70-89%)	25% (16-36%)
LS	61% (43-76%)	77% (63-87%)
BS+LS	78% (72-83%)	84% (75-90%)
BS+Gallium scintigraphy	55% (25-80%*)	75% (50-95%*)
MRI	84%, (69-92%)	60% (38-78%)

BS=bone scintigraphy; CI=confidence interval; FDG-PET= fluorodeoxyglucose-positron emission tomography; LS=leukocyte scintigraphy; MRI=magnetic resonance imaging

*Not explicitly reported, estimated from graphs

Two meta-analyses were published in a single report in 2006 by Prandini *et al.*²³ The authors summarized the findings of studies of numerous nuclear medicine imaging methods on peripheral post-traumatic and prosthetic infection, and on infections of the vertebral column. Pooled test characteristics reported in the two meta-analyses by Prandini *et al.* are provided in Tables 2 and 3.

The meta-analysis relating to peripheral bone and prosthetic infections considered 89 studies that were published between 1984 and 2004. Six of the studies were on FDG-PET. Approximately 8,180 lesions were studied. Among the technologies considered were bone scintigraphy, scintigraphy with mixed white blood cells or granulocytes, radionuclide imaging of granulocytes labelled by monoclonal antibodies or gallium, polyclonal human immune globulin, and MRI. Sensitivity values for the imaging test methods ranged from 70.1% (gallium) to 95.2% (polyclonal human-immune globulin), with FDG-PET sensitivity being 94.1%. Specificity estimates ranged from 75.2% (bone scan) to 89.1% (scintigraphy with white blood cells), with FDG-PET specificity being 87.3%. FDG-PET had the highest accuracy (91.9%) of all methods and the lowest accuracy was bone scintigraphy (75.5%).

In their analysis of infections of the vertebral column, the authors evaluated thirty papers published between 1984 and 2004. Information on 1,373 patients was considered in the meta-analysis. Several of the imaging technologies reported on in the first meta-analysis were also considered here, in addition to x-rays and computed tomography (CT) scans. FDG-PET

had the highest sensitivity and accuracy (100% and 90%, respectively) of all the test methods considered.

The results of these analyses are favourable for FDG-PET in peripheral bone and prosthetic infections and infections of the vertebral column, however, as with the previous meta-analysis, these results must be interpreted with caution. Information on the inclusion and exclusion criteria for studies was not systematic or clear, and no information was provided regarding included study methods or quality. Methods used for the meta-analysis were not given, ranges or confidence intervals for test characteristics were not provided, statistical comparisons between diagnostic tests were not conducted, and homogeneity of test characteristics between studies was not considered.

4.1.2 Observational studies

A study of 63 patients was conducted to assess the ability of FDG-PET to differentiate uncomplicated Charcot's neuropathic arthropathy from osteomyelitis and soft-tissue infection, compared with MRI.²⁴ Four patient groups were assessed: 17 patients with Charcot's foot (a progressive degenerative condition that affects the joints of the feet and that is associated with nerve damage), 21 patients with uncomplicated diabetic foot, 20 non-diabetic patients with normal lower extremities, and five patients with proven osteomyelitis secondary to complicated diabetic foot. Final diagnosis in patients with Charcot's foot was determined either by surgical and histopathological findings, or through long-term

follow-up, depending on whether the patients underwent surgery. Ranges for maximum standard uptake values (SUVmax) differentiated Charcot's foot from the other patient groups (ANOVA $p < 0.01$) using FDG-PET. The

sensitivity and accuracy of FDG-PET in Charcot's foot were 100% and 93.8%, respectively. For MRI, sensitivity and accuracy were 76.9% and 75.0%, respectively.

Table 2: Meta-analysis of diagnostic techniques in infections of peripheric bone and of prosthetic joint implants, Prandini (2006)²³

Technique	Lesions	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
¹⁸ FDG-PET	413	94.1	87.3	91.9	86.9	94.2
⁶⁷ Gallium	569	70.1	81.8	78.2	50.0	89.5
¹¹¹ In-WBCs	2147	82.8	83.8	84.6	60.9	92.4
^{99m} Tc-WBCs	1453	89.0	89.1	89.1	75.1	91.6
^{99m} Tc-BS	1527	85.4	75.2	75.5	62.9	95.8
^{99m} MoAb BW 250/183	258	81.7	80.1	83.2	79.9	88.5
^{99m} MoAb MN3	129	92.0	86.0	86.0	NA	NA
^{99m} Tc-HIG and ¹¹¹ In-HIG	537	95.2	78.7	86.0	72.7	96.1
^{99m} Tc-nanocolloid	154	89.0	80.5	80.7	33.0	90.0
MRI	95	88.2	84.7	88.7	69.0	100.0
Aspiration	786	50.7	93.9	88.4	91.3	55.5

BS=bone scintigraphy; FDG-PET= fluorodeoxyglucose-positron emission tomography; HIG=human polyclonal immune globulin; In=indium; Tc=technetium; MoAb=monoclonal antibodies against granulocyte antigens; MRI=magnetic resonance imaging; NA=not available; NPV=negative predictive value; PPV=positive predictive value; WBCs=labelled white blood cells and granulocytes (See Appendix 3 for definition of terms.)

Table 3: Meta-analysis of diagnostic techniques in infections of the vertebral column, Prandini (2006)²³

Technique	Patients	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
¹⁸ FDG-PET	147	99.9	87.9	90.0	NA	100.0
⁶⁷ Gallium	223	86.3	35.8	88.5	66.6	100.0
^{99m} Tc-MoAbs	22	91.9	84.4	88.5	NA	NA
¹¹¹ In-WBCs	163	83.8	54.9	65.5	63.5	86.7
^{99m} Tc-WBCs	26	63.4	100.0	80.1	NA	NA
^{99m} Tc-HDP	324	81.4	40.7	69.3	67.7	80.6
X-rays	115	64.2	37.8	78.2	95.4	66.6
CT	53	82.4	12.8	82.4	80.0	66.7
MRI	300	81.8	57.0	78.8	95.6	80.0

CT=computed tomography; HDP=disodium hydroxymethylene diphosphonate; In=Indium; MoAb=monoclonal antibodies against granulocyte antigens; NA=not available; NPV=negative predictive value; PPV=positive predictive value; Tc=technetium; WBCs=labelled white blood cells and granulocytes

Twenty patients with diabetic foot ulcer and without clinical signs of osteomyelitis were assessed for the presence of clinically unsuspected osteomyelitis using MRI, ^{99m} technetium-labelled monoclonal antigranulocyte antibody scintigraphy (^{99m}Tc-MOAB), and FDG-PET, in a study

published in 2007.²⁵ Seven of the patients were assessed as being osteomyelitis-positive on at least one diagnostic test, and this was confirmed by bone biopsy in all seven. It is not clear whether disease was ascertained in patients with negative diagnostic findings, as confirmation of diagnosis using biopsy was not ethically

possible in all patients. Sensitivities, specificities, and accuracies for the three diagnostic tests were 86%, 92%, and 90%, respectively, for MRI; 29%, 85% and 65%, respectively, for ^{99m}Tc-MOAB; and 29%, 92%, and 70% for FDG-PET.

In 2006, Hakim *et al.* published a study comparing FDG-PET and bone scintigraphy using SPECT in the primary diagnosis and follow-up of 42 patients with chronic osteomyelitis of the mandible.²⁶ Histological confirmation of disease was available for most patients. Patients were followed up to 11 months after diagnosis. In primary diagnosis, sensitivity and specificity for SPECT were 84.0% and 33.3%, and for FDG-PET, they were 64.0% and 77.7%. In the follow-up period, sensitivity and specificity for SPECT were 93.7% and 6.6%, and for FDG-PET, they were 62.5% and 80.0%. The authors concluded that SPECT was superior in initiating treatment, but that it might be replaced by FDG-PET in the follow-up period.

A study published in 2007 examined the value of FDG-PET as part of a structured diagnostic protocol in 70 patients with FUO.²⁷ Upon final diagnosis, twelve of the patients had an infection, five had a neoplasm, sixteen had a non-infectious inflammatory disease, two had other diagnoses, and thirty-five had no diagnosis. A subgroup of 43 patients had an abdominal and chest CT performed. True positive FDG-PET results were confirmed by different means including biopsy, microbiology, serology, accepted clinical criteria, radiology, and clinical course. In the subgroup of 43 patients, abdominal and chest CT had a positive predictive value (PPV) of 48% and a negative predictive value (NPV) of 86%, while the results for FDG-PET were 65% and 90%, respectively. In 70 patients with FUO, sensitivity and specificity for FDG-PET were 88% and 77%, respectively, while PPV was 70% and NPV was 92%. The authors estimated that 33% of all FDG-PET scans conducted in this study contributed to the final diagnosis.

Eighty-nine patients with 92 painful hip prostheses were assessed for periprosthetic infection of the hip using FDG-PET and ^{99m}Tc-sulphur colloid 111-indium-labelled white blood-cell scintigraphy (TcSC-In BM/WBC) in a 2006 study.¹⁰ All 92 painful hip prostheses were assessed with FDG-PET and 51 were assessed using TcSC-In BM/WBC, as patients were given a choice to be evaluated with both tests, or with FDG-PET only. A final diagnosis was given to each patient after surgery, based on interpretation of clinical presentation, as well as on preoperative and intraoperative findings. Sensitivity, specificity, PPV, and NPV for FDG-PET were 95.2%, 93.0%, 80.0%, and 98.5%, respectively. For TcSC-In BM/WBC, these results were 50.0%, 95.1%, 41.7%, and 88.6%, respectively. The authors concluded that FDG-PET may be a promising diagnostic tool for distinguishing between infected and loose hip prostheses.

A 2006 study compared FDG-PET with scintigraphy using ¹¹¹In-oxine-labeled leukocytes in the detection of different types of infections.²⁸ Fifty-one patients suspected of having an infection were included in the study. Reasons for referral included suspicion of various musculoskeletal infections such as osteomyelitis of the pelvis, hands, or of the lower extremities, and infected prosthetic joints (n=47), vascular graft infection (n=3), and FUO (n=1). Forty-three patients were successfully imaged using both methods. Results were assessed as positive or negative for infection by a single blinded reader. Final diagnosis for the 43 patients was ascertained by histopathological findings, microbiological examination, surgical findings, or on the basis of clinical follow-up. Fifteen patients were found to have infection. The authors reported that they found no statistically significant difference between the FDG-PET and ¹¹¹In-oxine-labeled leukocyte scintigraphy with regard to sensitivity (87% versus 73%, respectively), specificity (82% versus 86%), accuracy (84% versus 81%), PPV (72% versus 73%), and NPV (92% versus 86%).

FDG-PET/CT was compared with ^{99m}Tc -fanolesomab for the localization of different infections in a study of 12 patients published in 2007.²⁹ Among the infections assessed were osteomyelitis (1 patient), recurrent urinary tract infection (1 patient), bacteremia (4 patients), graft infection (1 patient), and FUO (6 patients). Three patients were determined not to have infection by either follow-up, culture, or other information provided by the patient. Nine patients were determined to have an infection, and two different types of infection (graft infection and FUO) were assessed in one of these patients. All ten infections were ascertained by culture, and some by aspiration or by surgery. Ten paired studies of infection were conducted in the nine patients, and each of the ten paired studies were determined to have at least one site of infection (seven paired studies had one site of infection, and three had two sites of infection). On a per-paired study basis, the sensitivity, specificity, and accuracy of ^{99m}Tc -fanolesomab were 30%, 100%, and 46%, respectively. On a per-site basis, these results were 23%, 100%, and 38%. The sensitivity, specificity, and accuracy of FDG-PET/CT were all 100%, regardless of whether it was assessed on a per-paired or per-site basis.

A summary of the seven observational studies reviewed for the clinical effectiveness of FDG-PET in infections is provided in Appendix 1.

4.2 Impact of FDG-PET on the Treatment of Patients with Infections

A non-comparative retrospective study published in 2008 evaluated the use of FDG-PET in the diagnosis and management of invasive mould infections (IMIs).³⁰ Twenty-two patients with IMIs were identified, and 16 of these patients had FDG-PET imaging studies conducted. FDG-PET was considered helpful when it resulted in:

- earlier diagnosis of IMI compared with culture, histopathology, or CT imaging
- modification of diagnostic work-up by indication of an occult site of infection, or
- monitoring of anti-fungal treatment.

FDG-PET revealed an occult site of infection in three cases of disseminated IMIs, and was helpful in therapeutic monitoring by shortening the duration of systemic anti-fungal treatment in eight patients with IMI. In seven patients in whom FDG-PET was performed prior to the diagnosis of IMI, the authors found that it was able to detect IMIs earlier than conventional culture and histopathology-based diagnostic methods. Overall, FDG-PET was considered to be helpful in 10 of the 16 eligible patients (60%). The authors concluded that prospective validation of the role of FDG-PET in the diagnosis and management of IMIs is needed.

4.3 Critical Appraisal of Diagnostic Studies

Appendix 2 presents a summary of a critical appraisal of the seven observational diagnostic studies reviewed, using the CEBM criteria for assessing the validity of diagnostic studies.²² Six of the seven studies included a representative spectrum of patients, five conducted independent blind evaluations, all seven presented test characteristics, and five provided sufficient description to permit replication. While all studies ascertained the reference standard, similar methods of ascertainment were not always applied in all patients, as is to be expected in diagnostic studies where some methods of disease ascertainment are invasive and can not be performed unless indicated. Nonetheless, inconsistency in ascertainment may introduce bias in the results.

4.4 Limitations

In spite of the wide range of potential indications for FDG-PET in infection, and the numerous possible comparators, few studies were retrieved within the parameters set for this review.

Two meta-analytic reports were retrieved, both of which had methodological shortcomings, either with the studies that they included in their review, or within their own methodology. Seven observational diagnostic studies were of

reasonable quality in some attributes, but could have been subject to verification bias in their ascertainment of disease status to varying degrees. For example, in the study by Schwegler *et al.*,²⁵ the authors noted that four patients with negative imaging but non-healing ulcers or eventual amputations may have had false-negative results on their diagnostic images, and that it was unclear whether these negative patient outcomes were due to undetected osteomyelitis or some other underlying pathology. Test diagnoses could not be ascertained by biopsy in these four patients because of ethical considerations.

The two meta-analytic reports included in this review contained older studies in which the technologies examined may have evolved and changed over time, thus biasing against them. It is difficult to ascertain if this is the case given the presentation of results in these reports.

There may be some limitations in the reporting of test characteristics in the studies reviewed, as none reported likelihood ratios or receiver operating characteristic (ROC) curves, and estimates of PPV and NPV may be biased if patients participating in these studies were from highly selected samples.

Given that the ultimate utility of FDG-PET would depend on this technology's comparative ability to affect the treatment and outcome of patients with infections, there was very little evidence in this regard.

Data on the relative safety of FDG-PET compared with other imaging techniques were lacking; however, this may be due to safety having been evaluated in earlier indications for FDG-PET.

Considering the relative cost of FDG-PET and the potential patient base for this indication, economic data would be pertinent; however, none were retrieved. Higher-quality clinical data would be required to support this type of analysis.

5 CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The findings of this review suggest that FDG-PET is superior to several other imaging techniques in osteomyelitis in one meta-analysis,²¹ while less effective than MRI in one observational study in osteomyelitis,²⁵ and useful only in the follow-up of patients in another observational study comparing it to SPECT in chronic osteomyelitis of the mandible.²⁶ Meta-analyses of FDG-PET in peripheric bone and prosthetic joint implants, and in infections of the vertebral column, also suggest superior accuracy of FDG-PET compared with other imaging methods.²³ An observational study also found superiority of FDG-PET in detecting periprosthetic hip infection, compared with scintigraphy.¹⁰ FDG-PET was found to be superior to MRI in the differentiation of Charcot's neuroarthropathy.²⁴ Conclusions differed in two studies of FDG-PET in patients with multiple infection indications, with each study using different imaging methods as comparators.^{28,29}

Although suggestive of relative effectiveness in some indications, there is a lack of a high level of evidence regarding the effectiveness of FDG-PET across indications and within a range of comparators. This may be, in part, due to the fact that different radiotracers may perform differently in different conditions and may not be fully explored in comparison to FDG-PET. For example, labeled leukocyte imaging may perform relatively well in the diagnosis of prosthetic joint infection, but be of little value in spinal osteomyelitis.¹⁴ More extensive investigations of FDG-PET that focus on specific infection indications may be required. This would necessarily include studies that look at the relative impact of FDG-PET on treatment and patient outcomes.

As was previously noted, the use of FDG-PET in the diagnosis of infection could substantially

increase the current patient base for this technology. This addition to the patient base would have to be estimated, as would resource requirements and the potential impact on wait times. Of interest, a methodology for calculating a country's need for PET scanners has recently been published.³¹ The paper outlines three factors to be considered; specifically, the diagnostic accuracy and clinical effectiveness of PET in different indications (based on an assessment of the level of evidence of the diagnostic studies), the eligible population, and the production capacity of a PET scanner.

The results of this review suggest that FDG-PET may be more effective in diagnosing certain types of infection relative to other imaging techniques, but more intensive studies or systematic reviews and analyses of specific indications are needed, as well as evidence for this technology's potential to alter patient treatment and outcomes. Assessments of cost-effectiveness and of the possible impact on resource allocation are also required.

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APPENDIX 1: SUMMARY OF OBSERVATIONAL STUDIES COMPARING FDG-PET TO OTHER IMAGING TECHNIQUES

Study	Patients	Comparator	Indication	Results and Conclusions
Basu, <i>et al.</i> (2007) ²⁴	63 patients in four patient groups: – Charcot’s neuroarthropathy (17) – uncomplicated diabetic foot (21) – normal (20) – osteomyelitis (5)	MRI	Charcot’s neuroarthropathy	Ranges for SUVmax differentiated Charcot’s foot from the other patient groups (ANOVA $p < 0.01$) with FDG-PET. Sensitivity, accuracy for: FDG-PET: 100%, 93.8%; MRI: 76.9%, 75.0%. FDG-PET is valuable in reliably differentiating Charcot’s neuroarthropathy from osteomyelitis in general, and in the presence of foot ulcer.
Schwegler, <i>et al.</i> (2008) ²⁵	20 diabetic patients with chronic foot ulcer without clinical signs of osteomyelitis, 7 of which had confirmed osteomyelitis	MRI and ^{99m} Tc-MOAB	osteomyelitis	Sensitivity, specificity, accuracy for: MRI: 86%, 92%, 90%; ^{99m} Tc-MOAB: 29%, 85%, 65%; FDG-PET: 29%, 92%, 70%. MRI appears superior in detecting foot ulcer-associated osteomyelitis.
Hakim, <i>et al.</i> (2006) ²⁶	42 patients provisionally diagnosed with chronic osteomyelitis of the mandible	Bone scintigraphy with SPECT	chronic osteomyelitis of the mandible	In primary diagnosis, sensitivity and specificity for: SPECT: 84.0% and 33.3%; FDG-PET: 64.0% and 77.7%. In follow-up, sensitivity and specificity for: SPECT: 93.7% and 6.6%; FDG-PET: 62.5% and 80.0%. Because of high sensitivity, SPECT is superior in initiating treatment, but may be replaced by FDG-PET in the follow-up period.
Bleeker-Rovers, <i>et al.</i> (2007) ²⁷	70 patients with fever of unknown origin, 43 of which had both CT and FDG-PET performed	CT	Fever of unknown origin	In the subgroup of 43 patients: CT, PPV, and NPV: 48% and 86%; FDG-PET, PPV, and NPV: 65% and 90%. In all 70 patients, FDG-PET: Sensitivity: 88%, Specificity: 77%,

Study	Patients	Comparator	Indication	Results and Conclusions
				PPV: 70%, NPV: 92%. FDG-PET is valuable as part of a diagnostic protocol in the general patient population with FUO and a raised ESR and CRP.
Pill, <i>et al.</i> (2006) ¹⁰	89 patients with painful hip prostheses, 21 cases of infected hip, 36 patients with non-painful prostheses	TcSC-In BM/WBC	Periprosthetic hip infection	Sensitivity, specificity, PPV, NPV, for: FDG-PET: 95.2%, 93.0%, 80.0%, 98.5%; TcSC-Ind BM/WBC: 50.0%, 95.1%, 41.7%, 88.6%. FDG-PET appears promising for distinguishing septic from aseptic painful hip prostheses.
Rini, <i>et al.</i> (2006) ²⁸	43 patients with suspected infection; 15 with infection and 28 without infection	¹¹¹ In-oxine-labeled leukocyte scintigraphy	Multiple indications	Sensitivity, specificity, accuracy, PPV, NPV for: FDG-PET: 87%, 82%, 84%, 72%, 92%; scintigraphy : 73%, 86%, 81%, 73%, 86%. FDG-PET comparable to scintigraphy. Further investigation in larger patient population warranted.
Klingensmith, <i>et al.</i> (2007) ²⁹	12 patients; 10 infections in 9 patients, with the 10 infections being present in one or more sites; 3 patients without infection	^{99m} Tc-fanolesomab	Multiple indications	Sensitivity, specificity, accuracy for ^{99m} Tc-fanolesomab on a per-paired study basis: 30%, 100%, 46%; ^{99m} Tc-fanolesomab on a per-site basis: 23%, 100%, 38%; FDG-PET/CT, regardless of basis of analysis: 100%, 100%, 100%. FDG-PET superior for detecting and localizing sites of infection.

CRP= C-reactive protein; CT=computed tomography; ESR=erythrocyte sedimentation rate; FDG-PET= fluorodeoxyglucose-positron emission tomography; In=indium; Tc=technetium; MoAb=monoclonal antibodies against granulocyte antigens; MRI=magnetic resonance imaging; NPV=negative predictive value; PPV=positive predictive value; SPECT=single photon emission computed tomography; SUVmax=maximum standard uptake values; WBCs=labelled white blood cells and granulocytes (See Appendix 3 for definition of terms.)

APPENDIX 2: OXFORD CENTRE FOR EVIDENCE-BASED MEDICINE (CEBM) DIAGNOSTIC CRITICAL APPRAISAL²²

Study	Representative Spectrum of Patients	Reference Standard Ascertained	Independent Blind Comparison	Test Characteristics Presented	Measures	Sufficient Description to Permit Replication
Basu, <i>et al.</i> (2007) ²⁴	Yes	Yes*	Yes	Yes	Sensitivity Specificity	Yes
Schwegler, <i>et al.</i> (2007) ²⁵	Yes	Partially†	Yes	Yes	Sensitivity Specificity Accuracy	Yes
Hakim, <i>et al.</i> (2006) ²⁶	Yes	Yes‡	Unclear	Yes	Sensitivity Specificity	Unclear
Bleeker-Rovers, <i>et al.</i> (2007) ²⁷	Yes	Yes§	Yes	Yes	Sensitivity Specificity PPV, NPV	Yes
Pill, <i>et al.</i> (2006) ¹⁰	Yes	Yes§	Yes	Yes	Sensitivity Specificity PPV, NPV	Unclear
Rini, <i>et al.</i> (2006) ²⁸	Yes	Yes§	Yes	Yes	Sensitivity Specificity Accuracy	Yes
Klingensmith, <i>et al.</i> (2007) ²⁹	Unclear	Yes§	Unclear	Yes	Sensitivity Specificity Accuracy	Yes

*Positive and negative tests ascertained using different methods

†Describes ascertainment only in patients with a positive diagnostic test

‡Biopsy performed in most patients

§ Ascertained using various methods

APPENDIX 3: GLOSSARY

Maximum standard uptake values (SUVmax): a measure of the intensity of FDG uptake at sites of suspected infection.

Qsens: a chi-square statistic used to evaluate the homogeneity of pooled estimates of test sensitivity.

Qspec: a chi-square statistic used to evaluate the homogeneity of pooled estimates of test specificity.

df (degrees of freedom): an estimate of the number of independent categories in a statistical test.

Test Characteristics

Accuracy: the proportion of correctly diagnosed persons.

Negative Predictive Value (NPV): the proportion of subjects with negative tests who are disease-free.

Positive Predictive Value (PPV): the proportion of subjects with a positive test who have the disease.

Sensitivity: the proportion of correctly identified diseased persons.

Specificity: the proportion of correctly identified disease-free persons.