Clinical Molecular Imaging of Infection/Inflammation

SNM 2009, CME Session

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Talk Outline

- Introduction
- Anatomic Imaging
- Functional Imaging
  - Review of Current NM Techniques
  - Role of SPECT/CT
  - Emerging Role and Indications for FDG PET/CT
  - Introduce Other Functional Imaging Agents
- Brief Evaluation of optimal modality for Specific Indications to date

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 Role of Imaging in Management of Infections

- **Infection Dx - Clinical signs and symptoms**
  - Ex. Fever, pain, swelling, general malaise and abnormal laboratory results

- **Imaging tests – used to localize or confirm the presence of suspected infection**
  - Anatomic/Morphologic Imaging
    - Radiographs, CT, MRI, Ultrasound
  - Functional Imaging
    - Nuclear Medicine, PET


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“4+1” Cardinal Signs of Inflammation
Signs of Inflammation/Infection

- “4+1” cardinal signs of inflammation
  - Celsus (30BC – 38 AD) and Virchow 1870

- Modern Imaging “detects and localizes” Host Inflammatory Response to Infection
  - Rubor (redness – hyperemia)
  - Calor (increased heat – hyperemia)
  - Tumor (swelling – edema, vascular permeability)
  - Dolor (pain)
  - Functio laesa (loss of function)

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Morphologic/Anatomic Imaging
Edema of acute inflammatory response
  - Example:
    - lung edema – pneumonia
    - replacement of low-density marrow fat with inflammatory edema in acute osteomyelitis

Alteration of anatomy in soft tissue infection
  - swelling and blurring of fat planes from inflammatory edema

Hyperemia and capillary leakage in abscess wall
  - IV contrast enhancement

Palestro CJ et al. Cellular Microbiology 2007

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CT – Pyogenic Microabscesses

Arterial phase contrast-enhanced CT scan
- multiple small hypoattenuating nodules representing pyogenic microabscesses
- faint peripheral enhancement (arrow)
- perilesional edema (arrowhead).

Mortele, K. J. et al. Radiographics 2004;24:937-955
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MRI

- Anatomical imaging test of choice for diagnosing osteomyelitis
  - Signal intensity of the marrow
    - decreases on T1-weighted sequences
    - increases on T2-weighted sequences
    - direct consequence of the free water content (edema) of the inflammatory exudate.
  - These changes can be detected as early as 1–2 days after the onset of infection

- Intravenous gadolinium-containing contrast agents
  - enhancement of any inflamed area
    - due to hyperemia and capillary leakage
    - the enhancement is detected by using T1-weighted images
  - Example:
    - Not required in routine osteomyelitis
    - Useful for soft tissue abscesses and synovial thickening from synovial fluid
      - cellulitis and myositis enhances with contrast vs. 3rd spaced fluid).

Palestro CJ et al. Cellular Microbiology 2007
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MRI - Osteomyelitis

Plain Radiograph  Axial T1-weighted  Axial T2-weighted

Osteomyelitis of 5th proximal phalange

Marcus CD et al. Radiographics 1996
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Ultrasonography

- **Myositis**
  - heterogeneous hypoechoic ‘pock-marking’ of the normal pennate appearance of muscle

- **Abscess**
  - focal collection which is usually hypoechoic but which may have heterogeneous internal echoes due to debris.

- **Suspected septic joint - excellent imaging modality**
  - demonstrates abnormalities sooner than radiography

- **Not well suited for diagnosing osteomyelitis.**
  - acute osteomyelitis can only be diagnosed when a subperiosteal abscess is identified

- **Power Doppler Sonography** can be used to detect hyperemia

Palestro CJ et al. Cellular Microbiology 2007

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Functional Imaging
Functional Imaging

- Imaging utilizes hyperemia or inflammatory infiltrates at sites of infection
- Overlap can exist with sterile inflammatory processes
  - Challenge of differentiating sterile inflammation vs. septic inflammation

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## Nuclear Medicine Techniques

### Approved Radiopharmaceuticals

- $^{67}$Ga-citrate
- $^{111}$In-Oxine to label leukocytes in vitro
- $^{99m}$Tc-HMPAO (Ceretec) to label leukocytes in vitro
- $^{99m}$Tc-anti-NCA-90 Fab’ (LeukoScan) anti-granulocyte antibody
- $^{99m}$Tc-anti-SSEA-1 IgM (LeuTech) to label leukocytes in vivo
- $^{99m}$Tc-ciprofloxacin (Infecton)
- $^{18}$F-FDG

### Investigational Radiopharmaceuticals

- $^{111}$In-DTPA-human IgG (HIG)
- $^{99m}$Tc-HYNIC-IgG (HIG)
- $^{99m}$Tc-anti-NCA-95 IgG (BW 250/183)
- $^{111}$In-F(ab)$_2$-anti-E-selectin antibody
- $^{99m}$Tc-Interleukin-8 (IL-8)
- $^{99m}$Tc-labeled chemotactic peptides
- $^{99m}$Tc-labeled nanocolloids
- $^{18}$F-Fluorodeoxyglucose (FDG)
- $^{18}$F-FDG-Leukocytes (labeled in vitro)
Mechanisms of Radiopharmaceutical Localization

- Vascular permeability and Hyperemia
- Leukocyte Migration to site of infection
- Metabolic Trapping in Leukocyte at infection site
General Nuclear Medicine – Infection Imaging
67Ga-Citrate - Mechanism

- 67Ga-transferrin complex is highly stable at normal pH
- 67Ga dissociates at low pH environment of anaerobic metabolism
- Dependent on leaky blood vessels to enter extracellular space
- At low pH free 67Ga binds to other iron-binding molecules intracellularly at low pH (lactoferrin, siderophores)

Goldsmith SJ and Vallabhajosula S. Sem NM 2009

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Clinical Indications:

- High Sensitivity for Acute and Chronic Infection
  - Previous gold-standard
  - $^{18}$F-FDG PET is comparable and replacing these indications
- Non-infectious Inflammation
- Not dependent on immunocompetent patient

Limitations:

- Low specificity due to physiologic bowel excretion
- Uptake also seen in malignancy and bone healing
- Delayed imaging up to 3 days for improved signal/background

Current Clinical Use:

- vertebral osteomyelitis
  - $^{67}$Ga imaging appears to be more sensitive than labeled leukocytes, probably related to the chronic nature of the infection.

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The uptake of 99mTc-MDP is related to blood flow and to the rate of new bone formation.

Osteomyelitis
- invasion of the bone by microorganisms, as well as accumulation of leukocytes and secretion of powerful cytokines and chemokines
- results in an inflammatory reaction with destruction of the involved bone with osteoblastic formation

Hyperperfusion, hyperemia and accelerated new bone formation are not unique to osteomyelitis,
- 3 phase bone scintigraphy, though sensitive, is not specific for osseous infection.
111In and 99mTc-labeled Leukocytes

**Mechanism**

- Developed in the 1970’s, first introduced by McAfee and Thakur.

- In clinical studies, a mixed leukocyte population is isolated and labeled in vitro with 111In-oxine or 99mTc-HMPAO.
  - Normal differential of circulating leukocytes
  - 59% neutrophils, 34% lymphocytes, 2% monocytes

- Principle mechanism of uptake at the site of infection is
  - Cellular migration
  - Target specific localization.
Chemokine Regulation of Leukocyte Movement

- Chemokines (chemotactic cytokines) are secreted at sites of inflammation and infection.
- Chemokine concentration gradient surrounds the inflammatory stimulus
  - Also on the surface of the overlying endothelium.
- Leukocytes rolling on the endothelium adhere and extravasate into the extravascular environment.

Luster AD. NEJM 1998

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Complex Network of Chemokines in Inflammation

The Scientist 2000

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Clinical Indications:
- FUO
- Inflammatory bowel disease
- Osteomyelitis,
- Follow-up of patients with vascular or orthopedic prostheses

Leukocyte imaging provides high sensitivity for both acute infection (90%) and chronic infection (86%).

\(^{111}\)In-leukocytes are more stable in vivo and are better for infection imaging
- Lower resolution due to \(^{111}\)In label
- Higher radiation dose to patient
- Radiation exposure is an issue in pediatric patients

\(^{99m}\)Tc-leukocytes may provide early diagnosis (2-4 hours) but physiological \(^{99m}\)Tc activity in the abdominal area may be seen and results in false positive images.
Specific Indications for Radiolabeled Leukocyte Imaging

- **Diabetic foot**
  - Labeled leukocyte imaging is the radionuclide procedure of choice for evaluating diabetic pedal osteomyelitis.
    - Sensitivity 72% and 100%
    - Specificity 67% and 98%

- **Prosthesis Infection**
  - $^{99m}$Tc-MDP – Sen 100% but a very low Spec 30%
  - Radiolabeled Leukocyte – improves Spec to 86%
Utility of SPECT/CT in Infection/Inflammation Imaging

- Incremental Value of SPECT/CT in musculoskeletal infections
- $^{99m}$Tc-MDP Bone Scintigraphy
- $^{99m}$Tc-HMPAO–labeled white cell scintigraphy – planar vs. SPECT/CT
  - SPECT/CT provided an accurate anatomic localization of all positive foci.
  - With regard to the final diagnosis, SPECT/CT added a significant clinical contribution in 10 of 28 patients (35.7%).

- Filippi L and Schillaci O. JNM 2006
SPECT/CT with $^{67}$Ga or $^{111}$In-WBC scintigraphy

- SPECT/CT provides anatomical localization of functional imaging
- SPECT/CT made an incremental contribution to GS and WBC in 48% of patients with suspected infections, by improving
  - Localization
  - Improved Diagnosis
  - Definition of extent of disease
- Bar-Shalom R et al. JNM 2006.
Hx:
- SPECT/CT for suspected bone infection
  - 1 mon post spinal surgery

Imaging:
- $^{67}$Ga uptake in paravertebral soft tissue abscess.
- Negative for osteomyelitis; confirmed on 1 month followup CT.

Bar-Shalom R et al. JNM 2006

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Contribution of SPECT/CT to Diagnosis and Localization of Infection: Patient-Based Analysis

<table>
<thead>
<tr>
<th>Scintigraphy</th>
<th>Clinical indication</th>
<th>Total no. patients</th>
<th>Contributory SPECT/CT no. patients</th>
<th>$P$</th>
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<tr>
<td>GS</td>
<td>Osteomyelitis</td>
<td>21</td>
<td>10 (48)</td>
<td>NS*</td>
</tr>
<tr>
<td></td>
<td>Soft-tissue infection</td>
<td>13</td>
<td>3 (23)</td>
<td>NS*</td>
</tr>
<tr>
<td></td>
<td>FUO</td>
<td>13</td>
<td>4 (31)</td>
<td>NS*</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>47</td>
<td>17 (36)</td>
<td></td>
</tr>
<tr>
<td>WBC</td>
<td>Vascular graft infection</td>
<td>24</td>
<td>16 (67)</td>
<td>NS*</td>
</tr>
<tr>
<td></td>
<td>Osteomyelitis</td>
<td>11</td>
<td>0 (55)</td>
<td>NS*</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>35</td>
<td>22 (63)</td>
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<tr>
<td>Total</td>
<td></td>
<td>82</td>
<td>39 (48)</td>
<td>&lt;0.05†</td>
</tr>
</tbody>
</table>

*Comparison between different clinical indications for same scintigraphic method.
†Comparison between GS and WBC.
NC = nonsignificant.
Numbers in parentheses are percentage of total number of patients with this indication.

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20 year-old male with history of JRA, common variable immunodeficiency, asplenia, and inflammatory bowel disease.
- Persistent left ankle pain.
- MRI of bilateral ankles 6 days ago showed neuropathic osteoarthropathy changes but was indeterminate for osteomyelitis.

Planar $^{111}$In-Leukocyte scan with $^{99m}$Tc – SC dual isotope imaging of ankles.

- Colon activity - colitis
- Uptake in the bilateral ankles
  - matched
  - neuropathic osteoarthropathy
- Soft tissue vs. osteomyelitis of right tibia?
SPECT/CT

$^{111}$In-Leukocyte

$^{99m}$Tc-SC

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\(^{18}\text{F-FDG PET/CT} – \text{Infection Imaging}\)
FDG in Inflammation

Activated Leukocyte

Adapted from: Kapoor, V. et al. Radiographics 2004;24:523-543

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Molecular Basis of FDG Uptake in Infection and Inflammation

- *Activated* inflammatory cells metabolized glucose as energy source
- Neutrophils, Macrophages, and Lymphocytes
  - a postmigratory event of activated cells and not dependent on an ongoing chemotactic stimulus
- Mainly GLUT-1 and GLUT-3
  - intracellular GLUT-1 pool can be translocated to the cell membrane
  - (> 24 h) increase in 18F-FDG uptake by gene dependent de novo synthesis of GLUT-1
  - neutrophils and macrophages - overproduction of the hexokinase II enzyme during the respiratory burst
- Meller J et al. JNM 2007
FDG PET
Inflammation/Infection – Pros/Cons

- **Advantage**
  - Higher Resolution
  - Quantitative
  - Logistically easy, now widely available
  - Uptake in both chronic and acute inflammation
  - High sensitivity (but suffers from low specificity)
  - High Negative Predictive Value
  - PET/CT offers anatomical localization

- **Disadvantage**
  - FDG may diffuse out of cells with increased glucose-6-phosphatase
  - Nonspecific for tumor vs. inflammation vs. infection
  - No applicable to patients with active malignancy

- Currently not reimbursed by CMS
FDG PET Inflammation/Infection – Clinical Indications

- FUO
- Osteomyelitis
- Sarcoidosis
- Vasculitis
- HIV
- Lung Inflammation
- Atherosclerosis (carotid and coronary)
- *In vitro* 18F-FDG-labelled leukocytes
FDG PET –
Chronic Osteomyelitis

FDG PET most accurate; Leukocyte scintigraphy similar accuracy axially

Termaat MF et al. The Journal of Bone and Joint Surgery 2005
FDG PET – Chronic Osteomyelitis

- Highly Sensitive (96%: 88-99% [95%CI])
- Greater Specificity versus other modalities:
  (91%: 81-95% [81-95%])
  - 67Ga-Citrate
  - Radiolabeled Leukocyte scintigraphy
  - Bone Scintigraphy
  - MRI

Termaat MF et al. The Journal of Bone and Joint Surgery 2005
FDG PET/CT –
Chronic Osteomyelitis Case

Back pain s/p spinal hardware for unstable L2 fracture
Osteomyelitis and adjacent soft tissue infection

Hartmann A et al. EJNMMI 2007
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FDG PET –
Diabetic Foot Infection

- Limited number of studies to date
- Differential Diagnosis:
  - Osteomyelitis vs.
  - Acute Neuropathic Osteoarthropathy (Charcot Neuroarthropathy) vs.
  - Cellulitis
- Useful complement to MRI for detection of neuropathic joints
- Potentially difficult to differentiate cellulitis from osteomyelitis due to tight anatomical space
- Blood Glucose may complicate studies
  - Reportedly quality for infection imaging was not affected by serum glucose levels

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FDG PET – Diabetic Foot Infection

- Mean SUVmax uptake pattern
- More focal and intense uptake in osteomyelitis
- FDG PET
  - Sen 100%, Spec 93.8%
- MRI
  - Sen 76.9%, Spec 75%
(Basu S et al. Nuc Med Comm 2007)

<table>
<thead>
<tr>
<th></th>
<th>Sen</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDG-PET</td>
<td>78%</td>
<td>93%</td>
<td>78%</td>
<td>93%</td>
</tr>
<tr>
<td>MRI</td>
<td>95%</td>
<td>78%</td>
<td>56%</td>
<td>98%</td>
</tr>
<tr>
<td>Plain Films X-ray</td>
<td>57%</td>
<td>85%</td>
<td>57%</td>
<td>85%</td>
</tr>
</tbody>
</table>

- Preliminary Data of a prospective study (Nawaz A et al. JNM 49:123P, 2008 (suppl 1)
- FDG PET vs. MRI vs. plain film radiographs for detection of osteomyelitis
- FDG PET has high specificity – useful compliment to MRI scan

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FDG PET/CT – Diabetic Foot Infection Case

Osteomyelitis at head of 4th metatarsal bone

Cellulitis and negative for osteomyelitis


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FDG PET – Prosthesis Infection

- Differentiate mechanical loosening vs. superimposed bacterial infection
- Incidence of infection with Hip arthroplasty:
  - 1-4% initially
  - 25% after revision
- High negative predictive value
FDG PET – Prosthesis Infection – Literature Review

- Differentiation of infection vs. loosening
- 5 prospective studies with total of 209 pts
  - 2001 - 2005
  - 223 Hips and 36 Knee prostheses
- Sensitivity = 82.8% (33 – 94%)
  - the result is influenced by one study with outlier sensitivity of 33%
  - Exclusion of outlier, Sensitivity = 92%
- Specificity = 92% (77.8 – 96.6%)
  (Zoccali C et al. Int Ortho (SICOT) 2009)
FDG PET –
Prosthesis Infection –
2nd Literature Review and MetaAnalysis

• ROC plot with pooled sensitivity and specificity
• 11 studies collected (to 27 May 2008)
• Sensitivity 82.1% (68 – 90.8%)
• Specificity 86.6% (79.7 – 91.4%)
Presently, combined leukocyte/marrow imaging, with approximately 90% accuracy, is the radionuclide imaging procedure of choice for diagnosing prosthetic joint infection.

Comparison to gold standard leukocyte imaging

- Varying data – no definite conclusion
- Pill et al. J Arthroplasty 2006(Suppl 2)
  - Comparable specificity (93% FDG, 95.1% LS)
  - FDG-PET had high sensitivity (95.2% vs 50%)
  - Both with 100% Sensitivity
  - Poor FDG-PET specificity (73% vs 93%)
- More Studies Needed
Femur head region uptake – nonspecific
Left hip prosthesis shaft linear uptake - considered strongly suggestive of periprosthetic infection.
The periprosthetic infection was confirmed by subsequent surgery.

Femur head region uptake – nonspecific
Left hip prosthesis shaft linear uptake - considered strongly suggestive of periprosthetic infection.
The periprosthetic infection was confirmed by subsequent surgery.

Zhuang H et al. RCNA 2007
Limited number of prospective studies indicate that FDG PET has the potential to play a central role as a second-line procedure in the management of patients with FUO.

In these studies, the PET scan contributed to the final diagnosis in 25% - 69% of the patients.

Miller J et al. JNM 2006
Types of FDG uptake in FUO

- **Infectious diseases**
  - focal abdominal, thoracic, or soft-tissue infection
  - chronic osteomyelitis
  - Negative findings on 18F-FDG PET essentially rule out orthopedic prosthetic infections.

- **Noninfectious inflammatory diseases**
  - large-vessel vasculitis
  - Inflammatory bowel disease
  - sarcoidosis
  - painless subacute thyroiditis.

- **Oncology**
  - Hodgkin’s disease
  - aggressive non-Hodgkin’s lymphoma
  - colorectal cancer
  - sarcoma.
FDG PET – FUO

- Identified the underlying cause of the fever in 46% of patients.
- Contributed to the diagnosis or exclusion of a focal pathologic etiology of the febrile state in 90% of patients.
- Uptake in 27 of 48 total patients.
  - In 22 of these 27 positive studies (81%), PET/CT identified the underlying disease
    - Infection in 9 patients
    - Inflammatory process in 10 patients
    - Malignancy in 3 patients
- FDG PET/CT has a high negative predictive value (100%) for assessment of FUO.
- Keidar Z et al. JNM 2008
A 78-y-old woman presented with 6 wk of fever, night sweats, and weight loss. Intense linear 18F-FDG uptake along walls of major vessels c/w arteritis:
• thoracic aorta
• Brachiocephalic and subclavian arteries

Giant cell arteritis was diagnosed on temporal artery biopsy.

41-y-old woman presented with 3 wk of fever. CT demonstrated small amounts of pleural, pericardial, and peritoneal fluids and 2-cm hypodense lesion in left pelvis adjacent to uterus.

Diagnosis of right ovarian abscess and left ovarian cyst was confirmed at surgery.

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FDG PET – Vascular Graft

Among the various assessed parameters only focal FDG uptake and an irregular graft boundary were significant predictors of VPI.

<table>
<thead>
<tr>
<th>Focal FDG uptake</th>
<th>Graft boundary</th>
<th>n</th>
<th>Probability of VPI</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quantitative assessment (%)</td>
<td>Subjective assessment</td>
</tr>
<tr>
<td>Not present</td>
<td>Smooth</td>
<td>31</td>
<td>4.5</td>
<td>Very low</td>
</tr>
<tr>
<td>Inhomogeneous</td>
<td>Smooth</td>
<td>9</td>
<td>28.2</td>
<td>Ambiguous-low</td>
</tr>
<tr>
<td>Not present</td>
<td>Irregular</td>
<td>1</td>
<td>30.4</td>
<td>Ambiguous-low</td>
</tr>
<tr>
<td>Intense</td>
<td>Smooth</td>
<td>4</td>
<td>76.5</td>
<td>Ambiguous-high</td>
</tr>
<tr>
<td>Inhomogeneous</td>
<td>Irregular</td>
<td>0</td>
<td>78.3</td>
<td>Ambiguous-high</td>
</tr>
<tr>
<td>Intense</td>
<td>Irregular</td>
<td>42</td>
<td>96.8</td>
<td>Very high</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>96</td>
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</table>

Spacek M et al. EJNMMI 2009

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Vascular Graft Case

True-positive findings.
There is a high focal FDG uptake and irregularity of the boundary of the distal portion of the left femorotibial bypass 6 months after grafting. (+)MRSA

True-negative finding.
Mild homogeneous FDG uptake without any focal accumulation in the course of the right iliofemoral bypass 23 months after grafting.
A further 18 months of clinical follow-up did not reveal any infection.
High FDG uptake was found in aortovascular grafts
- 10 of 12 grafts in the patients who underwent open surgery
- 1 of 4 grafts in patients who underwent endovascular aneurysm repair.

On the basis of biochemical and clinical data
- Only 1 of the 16 patients had a graft infection at the time of investigation.
  - *Infected* Graft SUVmax / BP SUVmean Ratio = 5.7
  - *Uninfected* ratio 1.3 to 3.7

Wassélius J et al JNM 2008
Another Vascular Graft Case

64 year old fever of unknown origin 5 yr after uneventful open surgery and postoperative recovery.
FDG accumulation close to bifurcation corresponding to soft-tissue mass seen on CT ventral to graft (arrowheads)
FDG PET – Infectious Indications

- **FUO**
  - High negative predictive value
  - Localize site of suspected infection or inflammation or malignancy
  - Low specificity

- **Joint Replacement – Loosening vs. infection**
  - Inflammation in both situations
  - Labeled leukocytes more accurate and imaging of choice currently
  - Ongoing studies

- **Chronic Osteomyelitis**
  - Accurate diagnosis
  - Likely will replace gallium for vertebral osteomyelitis

- **Diabetic Foot osteomyelitis**
  - Incomplete data to date
  - Useful complement to MRI

- **Vascular Graft Infection and Fistula**
  - Pattern and level of uptake is crucial to differentiate normal uptake versus infection
18F-FDG PET/CT – Inflammatory Conditions
FDG PET – Vasculitis

- Current imaging modalities show only anatomical changes in vessel lumen and cannot detect early stage inflammation when structural changes have not developed yet.

- FDG PET/CT
  - Large vessel vasculitis, GCS, TA
  - Sensitivity 77 – 92%
  - Specificity 89 - 100%
  - SUV does not seem to correlate with disease activity
    - BUT can be used to evaluate response to therapy

- Ben-Haim S et al. Sem NM 2009
Vasculitis Case

72-year-old-female patient with fever of unknown origin and a history of lymphoma - increasing inflammatory markers, clinically suspected recurrence

FDG PET:
- increased FDG uptake along the walls of the ascending and descending thoracic aorta
- the aortic arch
- the abdominal aorta and iliac arteries
- great vessels extending from the arch of the aorta into the subclavian and common carotid arteries bilaterally.

These findings are consistent with large vessel arteritis

Biopsy diagnosed Takayasu arteritis.

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FDG PET – HIV

- Scharko AM et al. Lancet 2003
- HIV-1 progression was evident by distinct FDG lympoid anatomical
  - Head and neck during *acute disease*
  - Generalised peripheral lymph-node activation at *mid-stages*
  - Involvement of abdominal lymph nodes during *late disease*

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Healthy HIV-positive patients with suppressed viral loads and HIV-negative individuals
- no or little FDG nodal accumulation or any other hypermetabolic areas

Viraemic individuals with early and advanced HIV disease
- increased FDG in the peripheral nodes
- indicates that FDG potentially identifies areas of HIV replication.

FDG biodistribution was similar between early and advanced disease.

Brust D et al. AIDS 2006
FDG PET – HIV on ART

- FDG PET in HIV patients on ART
- PET images revealed different patterns of FDG uptake.
  - All ART-treated patients with either suppressed (<50 copies/mL; Group A) or high viremia (group B)
    - showed a normal pattern of FDG uptake.
  - ART-naïve subjects with high viraemia (group C)
    - multiple foci of FDG avid lymph nodes
    - viremia below 100,000 copies/mL
      - upper torso mainly in the axillary nodes bilaterally
    - viremia higher than 100,000 copies/mL,
      - FDG uptake also observed in the inguinal lymph nodes.
FDG PET – HIV on ART

<table>
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<th>GROUP</th>
<th>A</th>
<th>B</th>
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<tr>
<td>ART</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
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<tr>
<td>Viremia (copies/ml)</td>
<td>&lt;50</td>
<td>8892</td>
<td>20243</td>
<td>122983</td>
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</table>
FUO - CMV(IgM+) Case

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FDG PET – Sarcoidosis

- Considering only the 12 patients who underwent both scintigraphic examinations, overall sensitivity of:
  - $^{67}$Ga scintigraphy = 58%
  - FDG PET/CT = 79%

- After excluding all sites of skin involvement, sensitivity improved to:
  - $^{67}$Ga scintigraphy = 67%
  - FDG PET/CT = 86%

- Braun JJ et al. EJNMMI 2008
FDG PET – treatment monitoring in sarcoidosis

66-year-old woman with multisystemic biopsy-proven sarcoidosis at primary staging (a) and after corticosteroid treatment
Other Functional Imaging Agents
**99mTc-Labeled AntiGranulocyte Abs**

- **Advantage** – fast, logistically easier, better imaging resolution
- **99mTc-anti-NCA-90 Fab’ fragments**
  - (Sulesomab, LeukoScan; Immunomedics GmbH, Darmstadt, Germany)
  - Rapid localization of soft tissue and bone infections
  - Clinical Results have been variable
- **99mTc-labeled antistage specific embryonic antigen-1**
  - Known as 99mTc-fanolesomab (NeutroSpec™)
  - (anti-SSEA-1) monoclonal IgM class antibodies, known as LeuTech (Mallinckrodt, Hazelwood, MO)
  - Binds preferentially to CD-15 on activated neutrophils
  - 99mTc-fanolesomab approved for clinical use in the USA in 2004, accurately diagnosed appendicitis osteomyelitis, and vascular graft infection
  - In December 2005 it was withdrawn from the US market because of reports of serious and life-threatening cardiopulmonary events, including two fatalities, shortly after administration.
  - Future of this agent is uncertain
- **Radiolabelled interleukin-8 (IL-8), a chemokine that binds with high affinity to the CXC1 and CXC2 receptors present on neutrophils**
  - Significant localization in animal models of infection and clinical trial.
  - No significant side effects in 20 patients

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99mTc-Labeled Interleukin 8 - Case

4 and 24 hour; liver abscess

4 hour; calcaneus osteomyelitis

Bleeker-Rovers CP et al. JNM 2007

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Apoptosis Imaging

- 99mTc-Recombinant Human Annexin V Imaging
  - Differential Diagnosis of
    - Aseptic Loosening vs. Low-Grade Infection
    - Hip and Knee Prostheses
  - Only 1 false positive of 7 patients
  - Lorberboym M et al. JNM 2009

Example

MDP BS

Ant

Post

Annexin V

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Direct Bacterial Infection Imaging

- $^{124}$I - FIAU –Bacterial Thymidine Kinase

Images show various infections:
- Septic Arthritis
- Osteomyelitis
- Cellulitis
- Necrotizing Septic Arthritis

Diaz LA et al. PLoS One 2007

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Recommended References

- Seminars in Nuclear Medicine
  - 2 part series - The Role of Nuclear Medicine Techniques in the Evaluation of Infectious Disease
    (January and March 2009)
Thank You


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