Imaging infection
Prof John Buscombe
Inflammation and Infection

**inflammation** in·flam·ma·tion (ĭn'flə-mā'shən)

*n.*
A localised protective reaction of tissue to irritation, injury or infection, characterized by pain, redness, swelling, and sometimes loss of function.

**infection** in·fec·tion (ĭn-fěk'shən)

*n.*
Invasion by and multiplication of pathogenic microorganisms in a bodily part or tissue, which may produce subsequent tissue injury and progress to overt disease through a variety of cellular or toxic mechanisms.

The American Heritage® Stedman's Medical Dictionary
Inflammation: General Features

- Defensive **host response** to invading foreign bodies and necrotic tissue
- Capable of causing tissue damage.

- **Components**: vascular reaction and a **cellular** response
- Both activated by mediators derived from plasma proteins and various inflammatory cells.

- The steps of the **inflammatory response** can be remembered as the five *Rs*:
  - ✓ recognition of the injurious agent
  - ✓ recruitment of leukocytes
  - ✓ removal of the agent
  - ✓ regulation (control) of the response
  - ✓ resolution (repair)
Smooth muscle
VESSEL
Endothelium
Basement membrane

Elaboration of microbes, dead tissue

Source of mediators (histamine, others)

Mast cell

Immune response

Macrophage

Source of mediators (cytokines, others)
Role in immune response

Elimination of microbes, dead tissue

Polymorphonuclear leukocyte

Plasma proteins

Lymphocyte

Monocyte

Platelets

Source of mediators (nitric oxide, cytokines, others)

Elaboration of microbes, dead tissue

Complement: mediators of inflammation, elimination of microbes
Clotting factors and kininogens: mediators of inflammation

Fibroblasts

Extracellular matrix proteins and cells

Repair
Vascular permeability

Increasing vascular permeability leads to the movement of protein-rich fluid and even blood cells into the extravascular tissues.

A. NORMAL

B. TRANSUDATE
   (low protein content, few cells)

C. EXUDATE
   (high protein content, and may contain some white and red cells)
Leukocyte recruitment

The sequence of events in the recruitment of leukocytes from the vascular lumen to the extravascular space consists of:

- margination and rolling along the vessel wall;
- firm adhesion to the endothelium;
- transmigration between endothelial cells;
- migration in interstitial tissues *toward a chemotactic stimulus*
ACUTE INFLAMMATION
- Vascular changes
- Neutrophil recruitment
- Mediators

RESOLUTION
- Clearance of injurious stimuli
- Clearance of mediators and acute inflammatory cells
- Replacement of injured cells
- Normal function

INJURY
- Infarction
- Bacterial infections
- Toxins
- Trauma

Progression

INJURY
- Viral infections
- Chronic infections
- Persistent injury
- Autoimmune diseases

Healing

CHRONIC INFLAMMATION
- Angiogenesis
- Mononuclear cell infiltrate
- Fibrosis (scar)

FIBROSIS
- Loss of function

Healing

Pus formation (abscess)
Acute or chronic inflammation

Acute inflammation is **rapid in onset** and of short duration, lasting from a few minutes to as long as a few days, and is characterized by fluid and plasma protein exudation and a predominantly **neutrophilic leukocyte accumulation**.

Chronic inflammation may be more insidious, is of **longer duration** (days to years), and is typified by influx of **lymphocytes and macrophages** with associated vascular proliferation and fibrosis (scarring).

<table>
<thead>
<tr>
<th>Feature</th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Fast: minutes or hours</td>
<td>Slow: days</td>
</tr>
<tr>
<td>Cellular infiltrate</td>
<td>Mainly neutrophils</td>
<td>Monocytes/macrophages and lymphocytes</td>
</tr>
<tr>
<td>Tissue injury, fibrosis</td>
<td>Usually mild and self-limited</td>
<td>Often severe and progressive</td>
</tr>
<tr>
<td>Local and systemic signs</td>
<td>Prominent</td>
<td>Less prominent; may be subtle</td>
</tr>
</tbody>
</table>
Infection: microbial pathogenesis

- Infectious diseases are causes of death among the **every young, the elderly**, people with **AIDS** or **chronic diseases** and patients receiving **immunosuppressive drugs**.

- In developing countries, unsanitary living conditions and malnutrition contribute to a **massive burden** of infectious diseases that kills more than 10 million people each year.

- **Infectious agents** belong to a wide range of classes and vary greatly in size, ranging from prion protein aggregates of under 20 nm to 10 m tapeworms.

<table>
<thead>
<tr>
<th>Taxonomic Category</th>
<th>Size</th>
<th>Propagation Site(s)</th>
<th>Example(s)</th>
<th>Disease(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prions</td>
<td>&lt;20 nm</td>
<td>Intracellular</td>
<td>Prion protein</td>
<td>Creutzfeldt-Jacob disease</td>
</tr>
<tr>
<td>Viruses</td>
<td>20–300 nm</td>
<td>Obligate intracellular</td>
<td>Poliovirus</td>
<td>Poliomyelitis</td>
</tr>
<tr>
<td>Bacteria</td>
<td>0.2–15 μm</td>
<td>Obligate intracellular</td>
<td><em>Chlamydia trachomatis</em></td>
<td>Trachoma, urethritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Extracellular</td>
<td><em>Streptococcus pneumoniae</em></td>
<td>Pneumonia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Facultative intracellular</td>
<td><em>Mycobacterium tuberculosis</em></td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Fungi</td>
<td>2–200 μm</td>
<td>Extracellular</td>
<td><em>Candida albicans</em></td>
<td>Thrush</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Facultative intracellular</td>
<td><em>Histoplasma capsulatum</em></td>
<td>Histoplasmosis</td>
</tr>
<tr>
<td>Protozoa</td>
<td>1–50 μm</td>
<td>Extracellular</td>
<td><em>Trypanosoma gambiense</em></td>
<td>Sleeping sickness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Facultative intracellular</td>
<td><em>Trypanosoma cruzi</em></td>
<td>Chagas disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Obligate intracellular</td>
<td><em>Leishmania donovani</em></td>
<td>Kala-azar</td>
</tr>
<tr>
<td>Helminths</td>
<td>3 mm–10 m</td>
<td>Extracellular</td>
<td><em>Wuchereria bancrofti</em></td>
<td>Filariasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intracellular</td>
<td><em>Trichinella spiralis</em></td>
<td>Trichinosis</td>
</tr>
</tbody>
</table>
Chronic (mononuclear cell-mediated) inflammation

Acute (granulocyte-mediated) inflammation
Inflammation is part of the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants.

Infection is the invasion of a host organism's bodily tissues by disease-causing organisms, their multiplication, and the reaction of host tissues to these organisms and the toxins they produce.

Imaging “inflammation, in nuclear medicine, means to image all those non specific chemical, vascular and cellular phenomena associated to inflammatory diseases.

Imaging “infection” in nuclear medicine, means to specifically detect the presence of pathogens.

Nuclear medicine techniques aim at differentiating “sterile inflammation” from “infection” and the two terms cannot be used as synonyms

Signore A. EJNMMI Research 2013;3:8
## Radiopharmaceuticals

### Targeting the host immune system

<table>
<thead>
<tr>
<th>HIG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labelled White Blood Cells</td>
</tr>
<tr>
<td>Monoclonal Antibodies against Granulocytes</td>
</tr>
<tr>
<td>IL-8 (acute)</td>
</tr>
<tr>
<td>IL-1, IL-2, Monoclonal Antibodies against TNF α (chronic)</td>
</tr>
<tr>
<td>(^{18})Fluorodeoxyglucose (FDG) (images the hypermetabolic state)</td>
</tr>
<tr>
<td>(^{67})Gallium Citrate, (^{68})Gallium Citrate</td>
</tr>
</tbody>
</table>

### Targeting the infectious agent

<table>
<thead>
<tr>
<th>(^{67})Gallium Citrate, (^{68})Gallium Citrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labelled anti-microbials</td>
</tr>
<tr>
<td>Labelled vitamins</td>
</tr>
<tr>
<td>Labelled antimicrobial peptides</td>
</tr>
</tbody>
</table>
Single photon imaging of infection

• Success depends on number of factors
• Understanding the clinical background of the patient immunocompetent vs immunodeficient
• Understanding when a sensitive test is needed and when a specific agent is needed
• Being pragmatic, look at availability, cost and time
• Always do the best study you can for a specific clinical problem and situation in 2016 that means SPECT/CT or PET/CT
• Some infections only seen by some techniques
• Every patient is different
Is there a role for fusion imaging in infection/inflammation?

- Potential for better localisation
- Potential for improved specificity
- Is time taken justified
- Will use of machines be taken up by more "trendy" topics such as cancer/endocrine
- Will it be worth the effort
Gallium-67 citrate

- No cell labelling
- 90keV, 190keV, 300keV, 394keV gammas med energy collimator
- Poor dosimetry limits activity that can be given
- Indications now limited
  - Sarcoid
  - Spinal infections
  - Immunocompromised
- FDG PET-CT can do some of these
- SPECT-CT of suspect areas at 24 or 48 hours
Ga-67 in sarcoid

Panda sign, lacrimal and salivary glands

Lamba sign mediastinum and hilar nodes

Diffuse lung uptake

Lymphadenopathy (symmetrical)

Joints

Liver-diffuse
More specific agents; In-111 WBCs

- In-111 WBC
  - Limited access, needs cell labelling
  - 174 keV and 247 keV needs medium energy collimator
  - Poor dosimetry limits activity to 20MBq
  - Gold standard good specificity
  - All but spinal infections
  - Imaging 4 and 20 hours p.i.
  - SPECT/CT at 24 hours
Tc-99m HMPAO labelled WBCs

- **Tc-99m HMPAO WBC**
  - Needs cell labelling
  - Max 200MBq but lower radiation dose
  - Theoretically less specific than In-111 WBC but no real evidence in skilled hands
  - All but spinal infections
  - Imaging normally 30 mins and 3-4 hours
  - Can perform late imaging at 24 hours
  - SPECT-CT normally at 3-4 hours
Infected knee
Tc-99m HMPAO WBCs
Antibodies

- Tc-99m granuloscint
  - Anti-CD66 on granulocytes
  - No cell labelling
  - Use similar to Tc-99m HMPAO WBC
  - Widely used in Europe
- Tc-99m leucoscan
  - No cell labelling
  - Mechanism not clear
  - No Fc on antibody so can do repeat scanning
  - Mainly in bone/joint infection
- Both agents imaging normally 1 and 4 hours (sometimes 24 hours)
- SPECT-CT normally at 24 hours
A. PET/CT whole body MIP projection showing high $^{18}$F-FDG uptake around the peritoneal part and cutaneous exit of the driveline (red arrow) and in the LVAD pocket (green arrow).

B. CT scout view showing LVAD pocket and driveline.

C. Anterior planar scintigraphy 24 hours after injection of the Tc $^{99m}$-anti-leucocyte antibodies showing uptake along the driveline.

Images from Dr A Boubaker
Why spend $600,000 on this
SPECT-CT in infection imaging should be our standard method.

- Roach et al 2006 NMC
- Looked at 50 scans including bone and Ga-67 SPECT-CT
- 16% of patients had minor change 11% major change c/w SPECT alone
- Almost all to do with localisation and improved specificity
- Specificity itself improved by 26%
Specific results identifying infection

- Inquie et al J Comp Assist Tom 2007
- 16 patients (11 In-111 WBC and 6 Ga--67)
- SPECT/CT images yielded "added value" for anatomical localization in 65%, diagnostic confidence in 71%, and altered interpretations in 47% of cases
WBC SPECT-CT showing an infected iliac graft Bar Shalom et et JNM 2006 48% more accurate than planar WBC imaging
Ga-67 citrate in an infected renal transplant; Nowosinska et al
Other use of Ga-67 is discitis

- 85 year old man
- Severe back pain
- CRP 250
- Gram positive rods in blood
- Pacemaker
Ga-67 citrate

- In PCKD residual infection can occur in native cysts
- Ga-67 after 24 hours has no normal renal uptake
- Therefore focal uptake in cyst infection
- Helped by SPECT-CT
Tc-WBC scintigraphy vs conventional radiological imaging in management of late, low-grade vascular prosthesis infections

Erba et al, EJNMMI 2014

55 patients, susp. late & low grade graft infection
- Tc-WBC (planar +SPECT/CT)
- 47 graft infection, 8 extra-graft infectious foci
- Tc-WBC positive: 90% (43/47, 20/43 also extra-graft)
- SPECT/CT: reduced # FP in 37% patients

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPECT</td>
<td>85%</td>
<td>63%</td>
</tr>
<tr>
<td>SPECT/CT</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>US</td>
<td>34%</td>
<td>75%</td>
</tr>
<tr>
<td>CT</td>
<td>49%</td>
<td>83%</td>
</tr>
<tr>
<td>Clinical criteria</td>
<td>68%</td>
<td>63%</td>
</tr>
</tbody>
</table>
In-WBC imaging of infected vascular grafts

Two different clinical cases. Sometimes uptake is obvious in the heavily pretreated patient it can be subtle.

NB. The specificity of In-111 WBCs and the 24 hour image can be advantageous.
In-111 WBC SPECT-CT in infected THR

Though planar image was positive the SPECT-CT images allow for good localisation of the labelled WBCs and show where the infection is sited so drainage and anti-biotics used
The Diabetic Foot – the Value of WBC-SPECT/CT

WBC scan:
• Pros: Diagnosis of infection
• Cons: not good enough [poor] for localization (to soft tissues and/or bone)

Solved with SPECT/CT!
• Single study
• Accurate spatial localization
  • extremities are less prone to motion
  • close proximity of structures in a small anatomic region
• Decreased radiation exposure; lower cost
Skin ulcer, pus secreting, tenderness & swelling 1st right toe

Infected soft tissue ulcer, plantar aspect 1st right toe

No evidence of osteomyelitis 5 months follow up
WBC Scan in Diabetic Foot Potential Pitfalls

Tc-WBC uptake in hyperdense foreign body secondary to soft tissue infection – no OM!
44 year old male diabetic since aged 6 Had carpet changed pain in heel
## WBC Imaging of the Diabetic Foot

### Summary of Literature

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Agent/Technique</th>
<th>Pts/sites</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fillippi</td>
<td>2009</td>
<td>Tc-WBC/SPECT/CT</td>
<td>17/19</td>
<td>Contribution of SPECT/CT: 53%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heiba</td>
<td>2010</td>
<td>BS &amp; In-WBC (SPECT/CT) ± BM</td>
<td>213/?</td>
<td>95%</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>Erdman</td>
<td>2012</td>
<td>Tc-WBC / SPECT/CT</td>
<td>77/100</td>
<td>Composite severity index: prediction of outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capriotti</td>
<td>2006</td>
<td>WBC</td>
<td>Meta-analysis</td>
<td>90%</td>
<td>81%</td>
<td></td>
</tr>
<tr>
<td>Dinh</td>
<td>2008</td>
<td>In-WBC</td>
<td>Meta-analysis</td>
<td>74%</td>
<td>68%</td>
<td></td>
</tr>
<tr>
<td>Palestro</td>
<td>2009</td>
<td>Review</td>
<td>72-100%</td>
<td>67-98%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asli</td>
<td>2011</td>
<td>Tc-IgG / planar</td>
<td>18/23</td>
<td>100%</td>
<td>69%</td>
<td>83%</td>
</tr>
</tbody>
</table>
When specificity is needed

- Routine use of In-111 WBC SPECT-CT
- 4 year old female with multiple problems
- Temp after bilateral cochlear implants
- ?infected
- 24 hr SPECT/CT only
- Retropharyngeal abscess
Glucose uptake into tumours

**Normal Glycolytic Flux**
- Differentiated Tissue
  - \( \text{O}_2 \) absent
  - \( \text{GLUCOSE} \)
  - \( \rightarrow \) \( \text{PyKM1} \)
  - \( \rightarrow \) \( \text{PYRUVATE} \)
  - \( \rightarrow \) \( \text{LACTATE} \)
  - \( \rightarrow \) \( \text{CO}_2 \)

**Warburg-effect**
- Proliferative Tissue / Tumor
  - \( \text{GLUCOSE} \)
  - \( \rightarrow \) \( \text{PyKM2} \)
  - \( \rightarrow \) \( \text{FBP} \)
  - \( \rightarrow \) \( \text{O}_2 \)
  - \( \rightarrow \) \( \text{PYRUVATE} \)
  - \( \rightarrow \) \( \text{LACTATE} \)

\( \text{PyKM1} \) and \( \text{PyKM2} \) represent different enzymes involved in glucose metabolism. The presence of \( \text{O}_2 \) in differentiated tissue indicates normal metabolism, while its absence in tumours indicates the Warburg effect, where tumours rely on anaerobic glycolysis regardless of oxygen availability.
FDG and inflammation or infection

- Increased uptake of FDG occurs when lymphocytes activated. Ishimori JNM 2002
- Uptake not just related to perfusion but active uptake when FDG increased compared to FLT where no increased uptake van Gaarde JNM 2004
- Uptake of FDG related to hypoxia and presence of cytokines Matsui JNM 2009
Uptake and cytokines - Matsui

JNM

A

Macrophages

\[
\begin{array}{c}
\text{Control} & \text{TNF}\alpha & \text{IL-1} & \text{IL-6} \\
\end{array}
\]

B

Neutrophils

\[
\begin{array}{c}
\text{Control} & \text{TNF}\alpha & \text{IL-1} & \text{IL-6} & \text{PMA} \\
\end{array}
\]

C

Fibroblasts

\[
\begin{array}{c}
\text{Control} & \text{TNF}\alpha & \text{IL-1} & \text{IL-6} \\
\end{array}
\]

D

\[
\begin{array}{c}
\text{Control cells} & \text{TNF}\alpha \text{ stimulated cells} \\
\end{array}
\]
Imaging inflammation

• Most inflammatory diseases can be imaged using scintigraphic technique
• Some techniques are blood flow dependent such as 2 phase bone and Tc-99m HIG
• Some methods dependent on bone turnover such as Tc-99m bone scintigraphy and F-18 NaF
• Other methods image inflammation more directly eg Labelled WBCs, and F-18 FDG
• All can be quantified so useful in research
Sarcoid

• Disseminated inflammatory disease
• Characterised by granuloma
• Various patterns
  – Salivary/lacrimal glands
  – Lymph nodes
  – CNS
  – Skin
  – Joint
  – Pulmonary- the most dangerous
Imaging in sarcoid

- Normally diagnosis clinical followed by biopsy
- 50% of patients have raised serum ACE
- If lymph nodes involved may see symmetrical enlarged mediastinal/hilar nodes the lambda pattern
- Since 1966 Ga-67 citrate used
  - Not very trendy
  - High radiation dose
Use of F-18 FDG

- Lymphocytes very FDG avid
- Much improved resolution
- Lower radiation dose (5mSv vs 18mSv)
- Confirm sites of active disease esp in the abdomen
- Quantify uptake which may be useful in treatment monitoring
FDG vs Ga-67

- Nishiyama et al. JNM 2006
- 18 sarcoid patients imaged with Ga-67 and FDG.
- Pulmonary disease Ga-67 81%, FDG 100% - mean SUVmax 7
- Extra-pulmonary disease Ga 48%, FDG 90% mean SUVmax 5

A= Ga-67
B= F-18 FDG
C= F-18 FDG post therapy
## Radiotracer utilisation in RA

<table>
<thead>
<tr>
<th>Indication</th>
<th>MDP Bone Scan</th>
<th>Sodium Flouride PET/CT</th>
<th>IgG (HIG) imaging</th>
<th>FDG PET/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmation of suspected diagnosis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Probably</td>
</tr>
<tr>
<td>Depiction of joints involved</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Extra-articular disease</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Therapy response assessment</td>
<td>Maybe</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Suitability for radiosynovectomy</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Bone scintigraphy in arthritis

- For local issues 2-phase imaging is useful though not good for axial skeleton
- Can image whole body for same radiation dose – 2mSv
- Normally extra images of hands and feet
- Pattern may be useful
- Personal view SIJ quant not very helpful
Whole Body Bone Scan in RA

PALM VIEW to depict small joints
Dual Phase Imaging-
seronegative

Early blood pool imaging to capture inflammatory process
FDG - psoriatic arthritis
\(^{18}\text{F} \) FDG PET/CT-staging a little like cancer

Extra-articular disease

Atlantoaxial synovitis
Using FDG in RA

- Beckers et al JNM 2004
- 21 patients with active RA
- FDG imaging with views of knees and hands
- FDG positive in 68% joints though 75% of joints swollen and 79% painful
- Good correlation with increased blood flow on Doppler ultrasound
FDG uptake in RA
Beckers et al JNM 2004

Normal

Patient with RA
Monitoring response

• Vijavant et al WJR 2012. 17 newly diagnosed RA and 11 newly diagnosed sero-neg arthropathy
• Good correlation between symptoms and sites of increased uptake of FDG
• Change in SUVmax correlated well with clinical response and change in CRP
FDG before and after Tx
Vijavant et al WJR 2012
F-18 FDG in RPF

- Small volume of published work
- Concentrates on the use of F-18 FDG in following inflammation in RPF
- 26 patients with iRPF 20 positive with FDG PET correlated with high initial CRP
- F-18 FDG reduction correlated with reduction in inflammatory markers not CT thickness of RPF
F-18 FDG Imaging to monitoring treatment of unilateral RPF

Jan 09  Jan 10  Oct 10  Oct 11
on steroids  off steroids  on steroids  on steroids

Case of Prof A Signore
F-18 FDG in vasculitis

• Walter et al EJNMMI 2005 used F-18 FDG imaging in 26 patients with giant cell arteritis
• Good correlation with wall thickness on CT, ESR and CRP
• Papathanasiou et al from UCL BJR imaged 16 patients with GCA before and after their first dose of steroids
• Mean SUVmax dropped from 3.38 to 2.32 with treatment
Giant cell arteritis
Aortitis
Physiologic FDG uptake

- oropharynx, vocal cords
- Cervical muscle, fat uptake (vs. LN)
- GIT (focal or segmental)
- Ureter
- Salivary glands, lymphoid tissue
- LN proximal to tissue injection
- Skin folds & sweat gland in axilla
- Bone marrow uptake
- Ovarian & endometrial uptake
- Brown Fat
- Lactating Breasts

Benign FDG uptake & artifacts

- **Artifacts** (e.g. injection, AC, contamination, metallic devices)
- Benign bone lesions (fracture, degenerative changes)
- Uptake in **foreign body** aseptic reaction (e.g. implants, grafts, stents)
- **After treatment** (e.g. healing scar, chemo/radiation & distorted anatomy)
- Uptake in [un]known malignancies
FDG Imaging of Infection

Pitfalls Associated with Administration of Drugs

• Antibiotics - thought to lower FDG uptake in infection (no studies confirming this)

• Metformin (antihyperglycemic) - associated with intense diffuse FDG uptake in small & large bowel, could mask infectious/inflammatory lesions (=FN) or be misinterpreted as severe colitis (=FP). Resolved by 2 days discontinuation.

• Steroids - may result in FN, should be avoided or on low dose if possible. Potential mechanisms:
  – resolution of inflammation
  – Inhibition of peripheral glucose uptake (reduce GLUT expression on cell surface)
  – effect on liver uptake with lower FDG availability
FDG Imaging of Infection

M, 67, advanced parotid ca
s/a total parotidectomy &
radiotherapy (1y)
FUO

Focal FDG uptake in lt. maxilla

Dental abscess
PET and FUO

- Bleeker-Rovers et al. EJNMMI 2004
- Nijmegen group
- 35 patients with FUO imaged
- Diagnosis conformed in 19
- 37% of scans clinically useful
- 65% of the positive scans clinically useful
- PPV 87%, NPV 95%
Peritonitis
FDG in infective discitis
F-18 FDG in neutropaenic patients

- Vos et al EJNMMI 2102
- 28 patients neutropaenic following chemotherapy
- 26 patients FDG positive
- 18 in GI Tract
- 9 around CVC lines
- 7 in the lungs
- Found bacterial and fungal disease
Cryptococcus in patient post BMT
Diabetes & Infection

- Diabetics – increased propensity to infections
- Unclear if hyperglycemia is an independent risk factor
- Host-specific factors predisposing diabetics to infection:
  - impairment of immune response induced by hyperglycemia
  - vascular insufficiency (local tissue ischemia)
  - neuropathy (unnoticed, ignored skin ulcers, urinary stasis)
  - skin & mucosa pathogens (Staph, candida)
- Frequent type of infections:
  - Foot
  - Urinary tract
  - Fungal, **malignant otitis externa**
  - Cholecystitis, Pyomyositis, Necrotizing fasciitis
FDG Imaging in Infection
Diabetes & Hyperglycemia, Specific Considerations

Diabetic foot
blood glucose – 10.6 mmol/l
TP study

Diabetic patient, vascular graft
blood glucose – 4.7 mmol/l
FN study

Osteomyelitis 4th metatarsus

Infected surgical wound
### Diagnostic Accuracy of FDG-PET/CT in Hyperglycemia & Diabetes [n=443 Patients]

*Rivkin et al, JNM 2010*

<table>
<thead>
<tr>
<th>Infection &amp; Inflammation</th>
<th>Cancer</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. pts</td>
<td>False negative rate</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>19/123</td>
<td>0/11 (0%)</td>
</tr>
<tr>
<td>Normo-glycemia</td>
<td>104/123</td>
<td>4/54 (7%)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>42/123</td>
<td>2/26 (8%)</td>
</tr>
<tr>
<td>No diabetes</td>
<td>83/123</td>
<td>2/39 (5%)</td>
</tr>
</tbody>
</table>

- Hyperglycemia but not DM affect FDG-PET/CT detection rate of cancer \(p<0.05\)
- Neither DM nor hyperglycemia had a significant impact on false negative rate of FDG imaging in infection
Neither DM nor hyperglycemia had an impact on FN rate of FDG in infection

[High glucose levels but not DM affected FDG detection rate of cancer (p<0.05)]

Different response: ? different intracellular glycogen storage
- inflammatory cells: can mobilize intracellular glycogen when plasma glucose levels are low
- [tumor cells: low storage capabilities, need for extracellular glucose supply]

These data were used as recommendations in the EANM/SNM guidelines for FDG imaging in infection-inflammation
M, 60, Diabetes, non-healing wound lt. foot, susp. osteomyelitis

3-phase Tc-99m MDP Bone Scintigraphy

Early: increased blood pool in region of 3rd left toe
Delayed and Late: Focal uptake in 3rd & 5th left toes
M, 60, Diabetes, non-healing wound lt. foot, susp. osteomyelitis

Tc99m-MDP SPECT/CT

SPECT:
- Focal uptake 2\textsuperscript{nd}, 3\textsuperscript{rd}, 5\textsuperscript{th} lt. metatarsus

CT:
- Wound between 2\textsuperscript{nd} and 3\textsuperscript{rd} toe
- Wound at lateral aspect of the foot
- Bone destruction and periosteal reaction
M, 60, Diabetes, non-healing wound lt. foot, susp. osteomyelitis

Bone SPECT/CT  
FDG

FDG-PET/CT:
Focal FDG uptake 3rd metatarsus
Single site of osteomyelitis

Surgery (2 days later):
Osteomyelitis & fracture 3rd metatarsus
Additional metatarsal fractures
FDG –PET/CT Performance Indices for Vascular Graft Infection

*Keidar et al, JNM 2007, 39 patients*

- Sens: 93%, Spec: 91%, PPV: 88%, NPV: 96%
- Accurate diagnosis of infection
- Differential diagnosis
- Precise localization to soft tissues ± graft

*Bruggink JL et al, Eur J Vasc Endovasc Surg, 2010, 25 patients*

- FDG sensitivity 93%, specificity 70%, PPV 82%, NPV 88%
- CT 56% 57% 60% 58%

*Spacek et al., EJNMMI, 2009, 76 patients*

Diagnostic criteria *(quantitation lesion/aorta > 1.7)*

- Focal intense uptake + irregular CT boundaries: 97% PPV
- No uptake and regular CT boundaries: 95% NPV
- Inhomogeneous uptake + irregular CT boundaries: 77% PPV
Infected Vascular Graft
Additional Findings on FDG-PET/CT

M, 62, s/a aorto-bifem, fem-fem & bilateral fem-pop graft insertion

FDG-PET/CT uptake of mild intensity in soft tissues of left thigh at the margins of a hypodense soft tissue lesion, with a “cold” center: consistent with post-surgery seroma

Resolution of the findings on the study performed 6 mo later
Warning FDG is not specific

41 year old swinging fever. FDG looks like an abscess but is Hodgkin’s Lymphoma in adrenals. Case supplied by Dr Gnanasegaran.
Guidelines

EANM/SNMIMI Guideline for $^{18}$F-FDG Use in Inflammation and Infection*

Francois Jamar1 (Chair), John Buscombe2, Arturo Chiti3, Paul E. Christian4, Dominique Delbeke5, Kevin J. Donohoe6, Ora Israel7, Josep Martin-Comín8, and Alberto Signore9

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### TABLE 1
Published Studies with More Than 10 Patients Before December 2011

<table>
<thead>
<tr>
<th>Disease</th>
<th>Considered papers</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarcoidosis</td>
<td>7 (173 patients)</td>
<td>93.5% (7 papers)</td>
<td>Data not available</td>
<td>95.5% (1 papers)</td>
<td>9–15</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>8 (287 papers)</td>
<td>94.6% (8 papers)</td>
<td>91.5% (8 papers)</td>
<td>94.5% (6 papers)</td>
<td>16–23</td>
</tr>
<tr>
<td>Spondyloarthritis</td>
<td>5 (136 patients)</td>
<td>100.0% (5 papers)</td>
<td>89.3% (5 papers)</td>
<td>91.0% (4 papers)</td>
<td>24–28</td>
</tr>
<tr>
<td>FUO</td>
<td>15 (758 papers)</td>
<td>90.6% (15 papers)</td>
<td>76.9% (15 papers)</td>
<td>86.4% (10 papers)</td>
<td>29–44</td>
</tr>
<tr>
<td>Vasculitides</td>
<td>12 (283 papers)</td>
<td>80.4% (12 papers)</td>
<td>89.3% (12 papers)</td>
<td>85.0% (3 papers)</td>
<td>45–56</td>
</tr>
<tr>
<td>Diabetic foot</td>
<td>5 (220 papers)</td>
<td>70.6% (5 papers)</td>
<td>84.4% (5 papers)</td>
<td>80.0% (5 papers)</td>
<td>88–92</td>
</tr>
<tr>
<td>Prosthesis (knee + hip)</td>
<td>17 (770 patients)</td>
<td>95.0% (17 papers)</td>
<td>88.0% (17 papers)</td>
<td>78.0% (8 papers)</td>
<td>93–109</td>
</tr>
<tr>
<td>Vascular grafts</td>
<td>5 (189 patients)</td>
<td>88.9% (5 papers)</td>
<td>64.6% (4 papers)</td>
<td>74.5% (4 papers)</td>
<td>110–114</td>
</tr>
</tbody>
</table>
Summary-single photon vs FDG PET

- **Single photon**
  - A choice of agents for different types of patients and infections
  - Immunocompetent
  - SPECT-CT is now our standard
  - Need cell labelling
  - Time to do scan
  - Offers specificity

- **FDG PET-CT**
  - FDG can find infection and inflammation
  - Though more expensive in England paid by NHS England
  - May be quicker to get results
  - Immunocompetent and immunodeficient
  - Sensitivity better, specificity may be an issue